4-20-2023 2:40 PM

Exploration of Force in Movement and Perception in Parkinson's Disease

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A thesis submitted in partial fulfillment of the requirements for the Master of Engineering Science degree in Electrical and Computer Engineering
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Abstract

Parkinson’s Disease (PD) causes force control deficits in upper and lower limbs. About 50% of patients with advanced PD develop freezing of gait (FOG). There is limited research comparing force control in PD with and without FOG, especially in upper limbs. It has been suggested that motor control deficits in PD are related to deficits in kinesthesia, but there is conflicting evidence whether levodopa alleviates kinesthetic deficits. In this thesis, force control was explored using an upper-and-lower-limb haptics-enabled robot in a reaching task, and kinesthesia was investigated using a haptic device in a force discrimination task while participants were on and off levodopa. Similar significant force control deficits were found in upper and lower limbs in patients with FOG compared to those without FOG. However, no significant kinesthetic deficits were found in patients with PD, independent of medication state, suggesting force control deficits may not be attributable to kinesthetic deficits.
Keywords

Parkinson’s disease, freezing of gait, levodopa, force control, visuomotor control, force perception, kinesthesia, haptics
Parkinson's Disease (PD) is a degenerative neurological disease that causes a range of symptoms, including motor issues such as tremor, rigidity, bradykinesia (slow movement), and gait problems. While levodopa, the gold standard drug for PD, can help with alleviating some symptoms, PD patients experience continuing decline. As PD progresses, patients may develop freezing of gait (FOG), which is when they have trouble initiating or continuing to walk despite the intention to do so. FOG is unpredictable and typically occurs when trying to start walking, turn, or navigate narrow spaces. Levodopa can typically manage FOG, but for some FOG can persist despite treatment (called levodopa-unresponsive FOG). People with PD have measurable motor deficits, specifically in force control, which refers to the magnitude, direction, and speed of force generation. The area of the brain affected by PD is associated with generating both kinesthesia (the body's sense of position, speed, and force) and movements in response to kinesthesia. Because of this, it is thought that PD may also impair kinesthesia, and it is unclear whether levodopa can improve kinesthesia. Recent research has explored the use of haptic devices, which provide force and motion feedback to a user while interacting with a virtual environment to study changes in force control in people with PD with FOG. Not many studies have been done regarding changes in movement in the arms of people with FOG. This study used haptic devices to measure force control in both the arms and legs of people with PD with levodopa-unresponsive FOG, compared to those with PD without FOG and healthy people without PD. The results showed that people with PD and levodopa-unresponsive FOG had greater deficits in force control than those with PD without FOG. However, deficits in kinesthesia were not found in PD patients while on or off levodopa. This suggests that the deficits in force control may not be attributable to deficits in kinesthesia. Although the results presented here are from pilot studies with small numbers of participants, the findings are interesting and warrant further research with larger cohorts.
Co-Authorship Statement

Chapter 2 in the thesis contains materials from a manuscript that is intended to be published. Besides the author of this thesis, other authors of the manuscript include Anish Naidu (A.N.), Mandar S. Jog (M.S.J), Olivia Samotus (O.S.) and Rajni V. Patel (R.V.P.). A.N. was a research associate at CSTAR (Canadian Surgical Technologies and Advanced Robotics) and contributed to the analysis of the data and the results, and the preparation of the paper. M.S.J. was the clinical lead of the project and contributed to interpretation of the results. O.S. was a doctoral student supervised by M.S.J and contributed to the analysis of the data and the results, and the preparation of the paper. R.V.P. was the supervisor of this thesis research project. R.V.P. proposed the research problem, and contributed to the analysis of the data, and the preparation of the paper. Funding in this work was provided from grants awarded to R.V.P. The author conducted an estimated 95% of the work reported in the manuscript.
Acknowledgments

I would like to begin by thanking my family and friends for their support and encouragement to keep pushing and take the time needed to complete my thesis. This is especially true for my partner, who has been very understanding of my time and nothing but supportive in my endeavour to feed the needs of my curiosity. Thank you to those who listened to me talk for hours about my work and giving me the opportunity to better formulate my ideas and become more skilled in explaining my work to others.

My sincerest gratitude is extended to those who participated in my research. I would also like to give my appreciation to the kindness and support of those at CSTAR and the London Movement Disorders Centre who directly and indirectly supported the project and gave ideas and guidance. Thank you to everyone who encouraged me to meet my goals, to remember the bigger picture, and not lose focus on the smaller details. A special thanks to Olivia Samotus, Dina Babiker, Soumya Sharma, and Gala Prado-Miranda, for their direct help with ideas for and data collection for my experiments, and to Yokhesh Krishnasamy-Tamilselvam, Jacky Gulangy, Ale Parra Peña, Yekta Mahdi, Chris Morley, Sara Ab khoft e, Elaheh Arefinia, Kanstantsin Pachkouski, Lukasz Nowakowski, and Anirudh Vajpeyi for assisting with experimental testing. A very special thank you to Anish Naidu for your continual guidance, and for convincing me to see the potential in my work. I would not have achieved what I have without you pushing me to keep going.

I would like to thank Dr. Roy Eagleson for his support in trusting my work and what I’ve accomplished in my research, while always remembering to set goals and continue moving forward. I would like to thank Dr. Mandar S. Jog for his great suggestions regarding this work, the use of his lab to perform my experiments, and his continual guidance to strive to do great work and understand what it means to be a scientist in addition to an engineer. Finally, I would like to give my thanks to my supervisor, Dr. Rajni V. Patel, for his continual guidance, support, and inspiration to be excited about the world, encouraging me to strive to solve problems in my own way, and have a sense of discovery about what we do.
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List of Abbreviations

1RM – one repetition maximum

ANOVA – analysis of variance

APAs – anticipatory postural adjustments

BG – basal ganglia

CI – confidence interval

Dn – Dunn’s post-hoc test

DOF – Degrees of Freedom

Dt - Dunnett’s post-hoc test

fMRI – functional magnetic resonance imaging

FOG – freezing of gait

GABA – gamma-aminobutyric acid

GPe – globus palladus externus

GPi – globus palladus internus

LMS – least mean squares

MDS – Movement Disorder Society

MLR – mesencephalic locomotor region

MoCA – Montreal Cognitive Assessment

MRF – medullary reticular formation

MVC – maximum voluntary contraction

NN – neural network
PD – Parkinson’s Disease

PPN – pedunculopontine nucleus

SMA – supplementary motor area

SNC – substantia nigra pars compacta

SNr – substantia nigra pars reticulata

STN – subthalamic nucleus

UPDRS – Unified Parkinson’s Disease Rating Scale

WF – Weber Fraction
Preface

“If I had an hour to solve a problem, I’d spend 55 minutes thinking about the problem and 5 minutes thinking about solutions.”

- Albert Einstein
Chapter 1

1 Introduction

This chapter provides an overview of Parkinson’s Disease (PD) motor symptoms, and the effects of the current treatment, levodopa. It will also describe a subset of motor problems called Freezing of Gait (FOG) experienced by some with PD. It will examine these issues as primarily a problem of force control.

1.1 Background

Parkinson’s Disease (PD) is one of the most common neurodegenerative disorders, affecting more than 6.1 million people globally [1]. Its prevalence is increasing, having more than doubled since 1990 [1]. PD typically affects elderly populations, with the average age for disease occurring at 60 years [2]; however, the global percentage of people over the age of 85 that have PD is quite high - at 1.7% for men and 1.2% for women [1]. In Canada in particular, people over the age of 85 are among the fastest growing populations, and by 2046, the number is expected to triple to 2.5 million [3].

PD can present with a diverse set and combination of motor symptoms including tremor, bradykinesia (global slowness of movement), rigidity (stiffness), and postural and gait difficulties [4]. These symptoms are caused by the degeneration of dopaminergic neurons located in the basal ganglia (BG) [5], a heavily integrated structure lying within the midbrain, and is most frequently treated with the dopamine precursor levodopa [6]. While levodopa provides effective symptomatic treatment of these motor symptoms, it is not capable of slowing or preventing the progression of the disease [6].

An additional symptom that can occur in the later stages of PD is Freezing of Gait (FOG) [7]. FOG presents as a sudden inability to initiate or continue walking [8]; it is typically considered an issue of correct timing of steps, as it can be mitigated using external cues, such as lines on a floor [9], [10]. FOG is also usually responsive to treatment by levodopa; however, this is not always the case [11]. In addition to this, other regions of the brain that
do not contain dopaminergic neurons, including those responsible for visuomotor processing, are implicated in the pathophysiology of FOG [12]–[14].

To understand how degeneration of neurons in the brain affects motion control in people with PD with and without FOG, a person in motion can be considered as a closed-loop control system; one with inputs (sensory organs), controllers (centres of sensorimotor integration), and outputs (muscles). Due to the dominance of motor symptoms in PD, heavy focus has been placed on these issues in the literature, including force [15], [16], velocity [17]–[19], visuomotor [19], [20], and timing [21]–[23] deficits. While there is some literature on these issues with respect to FOG [24]–[27], it tends to be focused specifically on gait deficits. Therefore, there is not a lot of literature focusing on other potential performance differences between people with PD with and without FOG.

The BG has been implicated as a major centre for sensorimotor integration [28] and may be considered a central component of the motion controller. While it is clear that motion is affected in PD, it is not clear whether this is exclusively an issue of lowered gain from the BG in motor output [29]–[32], or whether a reduced motor command may be the result of improper integration of sensory information [33].

Understanding how the system interprets information and a quantitative analysis of how motion is changed is “the first step to successful management of an individual patient” [34], [35]. This thesis aims to address areas of motor control in PD that are not well understood or where there remains conflicting evidence in the literature, with a focus on the nature of force control in humans with PD. Haptic tools are employed to objectively measure and assess movement and perception in people with PD with and without FOG to understand how the motion control system is impacted by the disease.

1.2 Parkinson’s Disease: Symptomology and Pathophysiology

The symptoms of PD are caused by the loss of dopaminergic neurons of the substantia nigra pars compacta (SNC), a part of the BG, a densely interconnected structure located in the centre of the brain [5]. The loss of these dopaminergic neurons can be due to the
aggregation of a mis-folded protein called alpha-synuclein, and mitochondrial dysfunction [36], [37]. The causes of PD are often multifactorial [38], but “may be influenced by genetic factors” [39]. One theory has suggested that PD can originate from a foreign body entering the digestive tract and ascending the vagus nerve to the brain [40]. However, there is no clear way to determine either cause or combination of causes, and therefore almost all cases of PD are considered idiopathic [41]. Further, there is no definitive diagnosis method available while a patient is alive to make an unequivocal diagnosis; a clinician must use their expertise in identifying symptoms to diagnose PD, sometimes with additional use of brain imaging and drug treatment [41].

While PD can present with a diverse set of symptoms, including behavioural and sleep disorders [42], [43], the focus of this thesis remains on the motor symptoms. These motor symptoms include tremor, bradykinesia (a global slowness of movement), rigidity (stiffness) [28], and postural and gait difficulties [35]. PD presents differently from one person to the next; for example, while most experience tremor, up to 20% of patients may not [37]. Further, a person may present with tremor in one limb, but not in another. However, all people with PD will present with some degree of bradykinesia [37].

As mentioned earlier in this chapter, PD is a progressive disease. Motor symptoms often present initially with lateralization of symptoms to one side of the body [44], but typically progress to include both sides [45]. In later stages, motor symptoms referred to as axial symptoms tend to worsen, which include increased deficits in gait and balance [45]. It is also important to note that levodopa, while an effective treatment for the loss of dopamine in the striatum, does nothing to stop the progression of the disease [6]. There are currently no known treatments to slow, stop, or prevent the progression of Parkinson’s disease [46].

How the loss of these dopaminergic cells affects some aspects of motor control can be determined by understand the pathophysiology. The SNc of the BG lies within the midbrain, and its dopaminergic neurons connect to a structure called the putamen, in the striatum [47], [48]. It does so along two separate pathways, referred to as the direct and indirect pathways [49]. In the direct pathway, the neuronal projections from the SNc to the putamen have an excitatory effect. The putamen’s neurons, which use the neurotransmitter
gamma-aminobutyric acid (GABA), serve to inhibit activity in the globus palladus internus (GPI). GABAergic neurons in the GPI also inhibit activity in the thalamus, which acts to excite the cortex through its glutamatergic neurons. The loop is completed by the glutamatergic neurons in the cortex exciting neuronal activity in the putamen (Figure 1.1 (a)). Ultimately, the direct pathway serves to promote motion [50].

In the indirect pathway, neurons from the SNc inhibit neuronal activity in the putamen, as opposed to promoting activity as in the direct pathway. From here, the putamen inhibits activity in the globus palladus externus (GPe), which in turn reduces neuronal activity in the subthalamic nucleus (STN) through projections of its GABAergic neurons. The glutamatergic projections of the STN act to excite the neurons in the GPI, and in an additional region in the midbrain called the substantia nigra pars reticulata (SNr), which also has GABAergic neurons. Ultimately, as in the direct pathway, both regions then inhibit neuronal activity in the thalamus. As in the direct pathway, this causes projections from the thalamus to promote activity in the cortex, and thus to the putamen (Figure 1.1 (b)). The indirect pathway is thought to suppress motion, behaving like the breaks of the motor control system [50].

The direct and indirect pathways contain more complex pathways within them, which are largely segregated such that each region can be associated with a particular subset of behavioural functions. For example, the postcommissural putamen is associated with sensorimotor integration [47], whereas visuospatial processing is associated with the pericommissural putamen [28].
Figure 1.1: Diagram representing connections between brain regions implicated in (a) the direct and (b) the indirect pathways. The green arrows represent projecting neurons from the tail of the arrow exciting neuronal activity in the region pointed to by the head of the arrow. The red arrows represent projecting neurons from the tail of the arrow inhibiting neuronal activity in the region pointed to by the head of the arrow. The neurotransmitters between the regions are not shown.

In PD, the loss of dopaminergic neurons results in hypoactivation of the direct pathway and hyperactivation of the indirect pathway. In relation to the sensorimotor and visuospatial processing centres, this results in striatal dopamine deficiency in the post- and precommissural putamen, respectively [28]. Through administration of levodopa, the precursor to dopamine capable of passing through the blood brain barrier, typical dopaminergic levels in the striatum can be increased [51]. However, the administration of levodopa can cause an undesirable symptom called dyskinesias, which are involuntary writhing movements [52]. This is thought to be caused by hypoactivation of the indirect pathway, but more prominently, hyperactivation of the direct pathway [47], [52]. Appearance of dyskinesias typically occurs when the disease has developed to a more advanced stage, as higher doses of levodopa are required to treat the motor deficits caused by PD [53].
Clinical discretion and individual needs and wants of the patient must be considered carefully to find the right balance of medication as the disease progresses. While the motor symptoms directly caused by PD can be debilitating, excessive dyskinesias can also be uncomfortable and cause severe disability in advanced cases [53]. Through the use of animal models, it is thought that dyskinesias are due to a change in expression of glutamate receptors in the BG [54]. Typical treatments of dyskinesias include lowering the dose of levodopa (which is not always ideal when motor symptoms are debilitating) or using medications such as amantadine to change the behaviour of these glutamate receptors [55], [56]. This combined treatment allows for higher doses of levodopa to treat PD motor symptoms while reducing the presence of dyskinesias [56].

1.3 Freezing of Gait

1.3.1 Symptoms and Prevalence

As demonstrated in the case of dyskinesias, as PD progresses, it appears that other neurological changes occur in addition to the loss of dopaminergic neurons in the nigrostriatal pathway. For example, some have observed loss of gray matter in the primary and non-primary motor cortices in PD, which is associated with bradykinesia [57]. Other symptoms that sometimes appear in more advanced stages of PD may also be caused by degeneration outside of the BG, including Freezing of Gait (FOG).

FOG is an axial motor symptom (one of posture, balance, and gait) as opposed to an appendicular motor symptom (like tremor and rigidity) [11]. It presents as a “sudden inability to initiate or continue gait” [8]. It is not always clear what causes a FOG event; it seems to be triggered by cognitive and environmental factors, or some combination of them. For example, FOG can be triggered or worsened by turning [58], or by crowded areas and walking through doorways [59]. There are 3 subtypes of FOG: shuffling with small steps, trembling of the leg without it moving forward, or complete akinesia (lack of movement) [60]. However, it is unclear what specific brain mechanisms may be responsible for these types of FOG [60]. Potential changes in the brain in people with FOG will be discussed briefly later.
About 50% of people in the advanced stages of PD can experience FOG [35], [61], [62], and presentation of FOG is correlated with years with PD [62]. It can be debilitating and dangerous [8], resulting in lower quality of life [62], and has a high potential to cause falls and injury relative to other PD symptoms [63].

It is important to note that while freezing episodes seem to be restricted to the lower limb in gait, events that can be categorized as “freezing” have been observed in the upper limbs. For example, one study [61] examined differences in gait and finger tapping in people with PD with and without FOG. The study found events that appeared to be like “freezing” in the upper limbs, and that these were more frequent in people objectively assessed as having FOG symptoms as compared to people with PD without FOG symptoms [61]. They did not find that upper limb freezing was correlated with lower limb freezing, and variability in spatial metrics were not found to be different between the two cohorts [61]. Similarly, Nieuwboer et al. [64] found that freezing-like episodes occurred in the upper limbs in a rhythmic bimanual task. However, the latter study did find that these upper limb freezing events were correlated to FOG scores as assessed by the Freezing of Gait Questionnaire (FOG-Q) [65], a standard subjective clinical method used to assess the history of falls and freezing episodes. Therefore, it is unclear if the mechanisms that may be responsible for freezing are restricted to pathophysiology dedicated to gait.

1.3.2 Response of FOG to Levodopa

As with other symptoms of PD, the symptoms of FOG are typically alleviated by the administration of levodopa [66]. However, sometimes as the disease progresses, FOG will no longer respond to the dopamine precursor [67]. The cause of this phenomenon is complex. For example, it could be that a clinician and their patient determined that their treatment is optimized at a lower dose of levodopa, where PD motor symptoms besides FOG are treated well and effect of dyskinesias is reduced [67]. However, there is evidence that other regions of the brain are implicated in FOG [11], [12], [60].

1.3.3 Pathophysiology of FOG

Gait, while requiring low levels of attention to control in healthy people, is actually a very complex task requiring “automatic movement processes involved in stepping and balance,
Simple gait patterns are generated in the spinal cord and controlled by descending glutamatergic tracts from the medullary reticular formation (MRF) [8]. The MRF is also responsible for “postural tone and stability”, while gait initiation and continuation are controlled by “serotonergic neurons from the parapyramidal region” [8]. The mesencephalic locomotor region (MLR) appears to be responsible for stride length [11] and may also assist in anticipatory postural adjustments (APAs) - forward movements of the trunk to prepare for motion - and stepping [8]. A heavily implicated brain structure that lies within (or may be) the MLR is the pedunculopontine nucleus (PPN) [12], which has a diverse network of neuronal projections to regions such as the “cerebral cortex, multiple BG and limbic areas, the thalamus, the brainstem, the spinal cord, and the cerebellum” [12], [60]. Based on animal studies, it appears that the PPN controls the muscle tone in gait in addition to modulation of the locomotor pattern [60]. The supplementary motor area (SMA) located in the frontal cortex appears to play a role in movement initiation [11], while other regions of the frontal cortex projecting to the brainstem and striatum are “important for both postural control and locomotion” [8].

Ultimately, “corticostriatal activity, facilitated by striatal dopamine, is important in determining which motor programmes are active at any point in time” [8]. In PD, postural and gait instability may occur by the failure of neuronal projections from the GPi to the MLR to suppress motor programmes [8]. It appears that in FOG, other regions of the brain may be affected. Research has shown that abnormalities in “posture and gait [are] induced in monkeys with cholinergic lesions in the PPN” [8]. Human functional Magnetic Resonance Imaging (fMRI) studies have demonstrated that hyperactivity of the MLR and PPN and a decrease in activity in the right GPi and SMA are present in those with FOG [60]. There is also potential for an inability of people with FOG to properly activate the left premotor cortex and SMA [68], which is directly implicated in the execution of motion [69]. In addition to this, while not directly linked to FOG, research has determined that there is “significant degeneration of PPN neurons in patients with advanced PD” [60]. Ultimately, the network dysfunction in people with PD with FOG is complex, demonstrating a combined impact of reduced striatal dopamine levels in the BG in addition to the PPN and other cortical areas.
Interestingly, atrophy of gray matter in posterior cortical regions associated with visuospatial processing has been found to be present in functional magnetic resonance imaging in people with FOG [12]. In addition to this, cholinergic deficits in the right visual thalamus [13], [14] are associated with deficits in the executive-attention network observed in people with FOG [60]. It appears that in FOG, there is also an error of central processing of visuospatial information [11]. In fact, this error of central processing is not restricted to visuospatial information but may involve defective integration of kinesthetic information [11].

1.3.4 Cueing in FOG

The defective integration of information in FOG is theorized to be caused by a competition of processing resources used for sensorimotor integration and an inability to select (or give attention to) relevant information, resulting in a “jamming” of the system [59]. This seems to result in an inability in people with FOG to generate their own motion cues [11].

To overcome these difficulties, external sensory cues have proven to be useful in the alleviation of FOG. For example, the use of auditory rhythmic cues during gait was found to significantly reduce frequency and duration of FOG events, as well as increasing velocity and cadence in people with FOG [70]. Viable cues for alleviating FOG are not restricted to various auditory cues either; there is evidence that visual and haptic cues are effective treatments as well [9], [10], [35]. It is thought that external cueing has the effect of assisting people with FOG in focussing attention on salient information required for gait, and “reducing the interference of salient visual input” [10]. The implications of impaired sensorimotor integration in FOG will be addressed in section 1.6.5.

1.4 Changes in People With PD

It has long been of interest to quantify motor control changes in PD, with a primary interest in understanding “how the disease disrupts normal control processes” [31]. It is particularly interesting because such a vast array of motor symptoms and presentations are caused by the deterioration of the same small region (the SNc) in the brainstem. The study of motor changes can elucidate the effects of BG degeneration on motion planning and sensory
interpretation in the hopes of serving in the development of personalized rehabilitative care [31], [34], [35].

Within this section, review of existing literature will separate knowledge of changes in motor control into subgroups of people with PD and people with PD with FOG, and focus specifically on material relating to force control, additionally subdivided into visuomotor control and timing, as the BG appears to play a central role in these processes.

### 1.4.1 Force Control

When considering how motor patterns change in PD to produce affected output, it is natural to consider it in terms of affected force control, since the way humans move is through the contraction and tensioning of muscles. One way this has been studied in PD is in the control of magnitude of force in isometric tasks (measures of force where muscles remain the same length) and isokinetic tasks (measures of force where muscles contract at the same speed).

In the lower limbs, people with PD have been shown to have lower maximum force output than healthy age-matched controls in both isometric and isokinetic tasks [71]–[73]. While there is evidence that there are some changes of muscle composition in people with PD, it is unknown whether this is a result of the disease or rather a symptom of reduced mobility [72]. In contrast, a discrepancy in maximal force output was not typically found in the upper limbs. For example, a study in the upper limbs measured the exerted force in tasks of precise application of force and found no differences in peak force between controls and people with PD while they were off their dopaminergic medication [74]. Similarly, in tasks where participants were asked to use their grip on an object using either a strategy of power or precision, in both cases, average and peak forces did not differ significantly between people with PD and controls [75], [76]. Overall, evidence surrounding deficits of force output are not unanimous, and it is unclear whether muscle changes could be attributed to PD. There is also a possibility that reduced mobility resultant from PD may be responsible for muscular changes, rather than caused by PD itself [77].

However, there are consistent findings in both the upper and lower limbs that people with PD have lower *rates* of production of force magnitude in tasks [16], [71], [75], [76], [78].
These results seemed to be independent of whether the patients were taking their dopaminergic medication [16]. All of the studies listed demonstrated a specific reduction in rate of force when relaxing from a contracted state [16], and while most of them demonstrated an increase in the time required to obtain a peak force, one study did not [15]. Despite this, it is still clear that people with PD have difficulty turning off their muscle activity, which corresponds to decreased levels of activity in the indirect pathway [15], [16].

Also of interest is that within these studies, the rate of relaxation time after muscle contraction was correlated with the severity of motor impairment caused by PD as assessed using clinical motor scales [15], [16]. This makes sense, as it has been shown that reductions in force and velocity are related to the loss of dopamine in the striatum [57]. It has also been shown in the upper limbs in measures of elbow flexor and extensor strength that levodopa assists in increasing the rate of force output [16], [57], corresponding to the alleviation of symptoms of bradykinesia. It is thought that the release of dopamine from the SNc is therefore responsible for the initiation and continuation of movement [57].

Further, the BG may play a role in evaluation of cost savings in motion. For example, a study on the lower limbs used EMG to measure force output [73]. The study asked people with PD and controls to output their maximum force at their own speed to define a one repetition maximum (1RM), or the maximum force each person was capable of outputting only once. Then, the power of each person’s movement was evaluated at percentages of their own 1RM. The study found that power was still reduced at lower levels of each individual's 1RM, demonstrating a selection of lower rates of contraction even at proportionally low forces [73]. Therefore, people with PD preferentially select lower energy motion compared to healthy age-matched controls.

Despite these changes, it is thought that people with PD are still capable of proportionally scaling their forces. A study in 1988 used EMG to evaluate each subject’s maximum voluntary contraction (MVC) [79]. Then, with visual feedback from a screen, participants from PD and control groups were found to accurately output 25%, 50%, and 75% of their MVC, indicating that there may remain an accurate “internal model” of required force [79].
However, another study in 2001 asked people with PD and controls to accurately output 5%, 25%, and 50% of their MVC in conditions with and without visual feedback in grip force [80]. As found in the 1988 study [79], with visual feedback people with PD could accurately control their force output proportionally. With the removal of visual feedback, the force output was found to be maintained about 2 seconds after visual feedback removal in both people with PD and controls, but to decay faster in subjects with PD than age-matched controls. The study [80] proposed that the best hypothesis to explain this phenomenon is that the memory of the required force output decays more quickly in people with PD.

1.4.2 Visuomotor Control

Given these changes in control of force magnitude in PD, it is then interesting to measure how people with PD change their force output in reaching tasks. It has been observed that people with PD tend to have difficulty performing visuomotor tasks such as reaching for objects [21]. In PD, it appears that there is an inappropriate scaling of dynamic muscle forces to the requirements of the task [57]. For example, Flowers [81] found that in simple reaching tasks in the upper limb, people with and without PD tend to move in two stages: an initial reaching movement, which is then followed by corrective movements to reach a target. In elbow flexion tasks, Hallett and Khosbin [32] also found that initial ballistic movements were smaller, and more recruitment of muscles was required in corrective phases of motion. Also, in reaching tasks, there is shown to be reduced velocity overall [19]. Similar effects have been demonstrated in the lower limbs in gait, where speed and step length are both reduced [82].

These observations also support the hypothesis that the BG plays a role in the computation and storage of cost functions that modulate motor performance [30]. Mazzoni et al. [83] discuss the role of the BG in energetic cost functions further: during simple task completion, people must prioritize speed and accuracy. In bradykinesia in PD, there may be “an implicit decision not to move fast because of a shift in the cost/benefit ratio of the energy expenditure needed to move at normal speed” [83]. These findings ultimately implicate dopamine in the role of assessment of this cost function and may provide a signal for “implicit motor motivation” [83].
Given the potential changes in visuospatial processing in the brain mentioned in section 1.2, it is natural to ask how well people with PD can spatially maneuver their arm or hand in space. In an occluded reaching task, subjects were asked to control the movement of a cursor on a screen between points as quickly as possible [84]. It was found that in the initial movement towards targets, PD and controls had similar initial directional error, although the smoothness (measured by normalized jerk) was reduced in people with PD. Contrary to these findings, a different study asked participants to track and trace targets moving on a screen [20] and found that people with PD had higher directional tracing error than controls. It is possible that given a higher cognitive load in reaching tasks, tracing error emerges, implicating issues of cognitive-executive control [20] as opposed to an explicit inability to control direction.

Though there is a hypothesized link between visuospatial deficits in PD and pathological gait, no studies were found that directly assessed the lower limbs or gait in similar visuomotor tasks. While humans typically use their lower limbs in different ways than the upper limbs and therefore it makes sense that different metrics are applied, it would still be interesting to examine, using similar measures and metrics to the upper limbs, changes in visuospatial metrics such as direction error in the lower limbs to address if there are similar processing changes in the upper and lower limbs in PD. This would allow for similar comparisons between upper and lower limbs to see if there is a difference in performance in gauges of similar tasks.

1.4.3 Timing

A direct result of bradykinesia, given a selection for lower velocities, is increased time to complete tasks in people with PD. It was found in a review by Gauntlett-Gilbert and Brown [22] that in simple reaction time (SRT) tasks (those in which the shortest time to respond to a stimulus is recorded), there are consistent findings in studies that SRT is significantly increased in people with PD compared to controls. In tasks of recording force generation, similar to those presented in the earlier section on force control, levodopa has been found to decrease times to reach the peak of required forces and time taken to relax muscles after contraction [16].
Understanding how force control, visuomotor control, and timing is affected in the lower limbs in typical tasks is more complex, since most motion in the lower limbs is in gait, which as described in section 1.3.1, also involves posture and balance in addition to lower limb movement. In force control in gait, studies have found people with PD have difficulty in transferring weight in preparation for stepping [85]. Measures of gait have found differences in spatiotemporal characteristics in people with PD, such as significant decreases in stride length, stride velocity and increases in time spent in double support (or when both feet are on the ground in between steps) [86]. Typically, significant gait disturbances, such as difficulties in gait initiation, do not occur until later stages of PD, as in the manifestation of FOG.

1.5 Changes in Force Control in People With FOG

People with PD who present with FOG typically have more impaired gait than people without, since it is such a debilitating phenomenon. Considering the usefulness of external cues in aiding in the restoration of gait during freezing episodes, it is thought that the automaticity of movement (or “the internal drivers of movement”) are impaired, which is likely the result of degradation of the BG [87]. This could therefore result in the need for people who experience FOG to rely more heavily on voluntary mechanisms to control gait, which is known to be impaired [87].

1.5.1 Force Control

It is possible that part of the deficits of FOG originate from a deficiency or inability to generate enough internal force to initiate or continue movement [11], [87], [88]. A study by Burleigh-Jacobs et al. [88] measured ground reaction forces in people with PD with levodopa-responsive FOG who all presented with freezing episodes while off their dopaminergic medication and healthy controls and found significantly reduced ground reaction forces during gait initiation in the PD cohort. The study also found that APAs were affected in the PD cohort while off dopaminergic medication. The study found that, in recorded episodes of FOG, there was a lack of any APAs, “suggesting that freezing is related to lack of initiation of postural adjustments” [88]. Levodopa was found to improve
APA time [88]. Deficits in postural control were similarly found in another study between people with PD with FOG compared to people with PD without FOG [27].

In a study of isometric force control in the lower limbs by Tan et al. [24], they measured the ability of subjects from 3 different cohorts (controls, people with PD, and people with PD with FOG) to scale their forces to 10% and 30% of their MVC. They found that there was no discrepancy between the ability to scale forces between the 3 cohorts under normal conditions [24]. This demonstrates that those with FOG, like other people with PD, still retain an ability to scale their force.

### 1.5.2 Visuomotor Control

In addition to changes during gait initiation in people with FOG, they were found to have slower velocity than healthy controls [88]. Other studies found that stride length was shorter in people with FOG [26], [61] and that the variability of stride length was larger in people with FOG [61], [89] than people with PD without FOG. Similarly, another study found that reduced step length and smaller APAs have been related to changes in pathophysiology in FOG in the SMA [90]. Therefore, other measures of force reduction, in addition to a potential inconsistency in control, may be seen in people with FOG and at a greater effect than deficits seen in PD. Administration of levodopa medication in people with levodopa-responsive FOG, like in APAs, was found to decrease variability of stride length, a gait variable associated with freezing events [89].

A study that measured visuomotor control in a tracing task in the upper limb in people with PD found that while Unified Parkinson’s Disease Rating Scale (UPDRS) scores – a standard clinical measure of motor impairment in PD - of motor issues in the upper limbs did not correlate with observed deficits of visuomotor control, they found that UDPRS scores of gait and posture did correlate with these deficits [20]. While it seems that the correlation could be spurious, there is growing evidence that difficulties in postural and gait control may be related to deficits of visuospatial processing. For example, a different study had participants with PD with FOG perform a stepping-in-place task to measure freezing events while also completing standardized tests of executive and visuospatial cognitive impairment [25]. They found that the visuospatial cognitive test was able to
differentiate between people who experience freezing from those who do not. In addition to this, all metrics of freezing in the stepping-in-place task correlated with the visuospatial cognitive test [25].

These results imply that deficits in visuospatial processing may contribute to measures of gait change present in people with FOG [25]. It is important to mention, however, that deficits of executive control also likely contribute to deficits in gait. A study by Naismith et al. [91] found that the difficulty in set-shifting seen in people with FOG (such as experiencing freezing events during turning) were correlated with executive tasks of attentional set-shifting. As mentioned in section 1.3.1, pathophysiology and contributions to FOG are complex and still not well understood.

A very interesting study [89] endeavoured to examine the influence of spatial changes of external stimuli known to provoke freezing events, i.e., a doorway, changing the width of a doorway relative to each participant's shoulder width and observing how gait changes in response to the environment. It was found that people with FOG slowed their gait just prior to the doorway at a rate that was inversely proportional to the width of the doorway. In other words, the speed of gait in people with FOG was significantly worse when the doorway was very close to the width of their shoulders. It was suggested in [89] that this deficit indicated a dysfunction of the interpretation of external visual information, further implicating sensorimotor processing issues in people with FOG.

1.5.3 Timing

Section 1.5.1 discussed a study that demonstrated deficits of axial force generation (the APAs). Delays of APAs in people with PD with FOG have been observed by other studies as well [23], [26], [27]. In addition to the variability in step length found in people with FOG, there was also a variability in step timing, characterized as an arrhythmicity of steps in PD freezers [25]. In this study, arrhythmicity was correlated with both cognitive measures of executive and visuospatial processing [25].

Overall, it appears that in people with PD with FOG there is a reduction in force control - including in magnitude or motor motivation of output - compared to people with PD.
without FOG, and higher variability in visuospatial control. While there has been continuing focus on research to investigate aspects of force control in gait, there is limited work relating to these deficits in standard reaching tasks. In addition to this, no studies were found that measure force control aspects in similar tasks in both the upper and lower limbs. While there is no reason to suspect that underlying principles of motor control would be different for different parts of the body [87], there were no studies found investigating this information using a standardized task. Due to the implicated pathophysiology and observed changes in gait and therefore axial and lower limb control, it would also be interesting to observe differences in motor control in people with FOG in both upper and lower limbs. Finally, due to the complex integration of control systems required for gait to occur, it would be beneficial to test force, visuomotor, and timing control in both the upper and lower limbs to understand how these are affected in people with FOG outside of the demanding attentional nature of gait.

1.6 Kinesthesia in PD with and without FOG

Observed changes in force, visuomotor, and timing characteristics in motion seen in PD has implicated the BG as a centre for sensorimotor integration [24], [33], [57], [92], and dopamine depletion has been associated with observed changes of gain in output motion [29]–[32]. However, it is still not clear how or where in the motion control system these motor commands become altered. More specifically, are the changes in motion control in PD a defect of the computed motor signals, or could they originate earlier in the processing stream as an inability to correctly integrate and evaluate the sensory information itself?

1.6.1 Normal Sensory Control

1.6.1.1 Kinesthetic Sensors

In humans, internal motion is generated by muscles. However, the interpretation of internal and external motion is far more complex than a single type of sensory organ. This thesis will focus on sensory organs used in kinesthetic perception (also known as kinesthesia), or the “sense of position and movement in our limbs” [93].
Sensory organs implicated in kinesthesia include those in the skin, joints, tendons, and muscles [28], [93], [94]. Within the skin, there are mechanoreceptors capable of detecting changes in stretch of the skin that are used in kinesthesia [93]. Joint capsule receptors detect angular position changes at extremes of flexion and extension [93], [94], while Golgi tendon organs (sending signals along type Ib afferent fibres [95]) detect changes in position in addition to force [94].

There are two other afferent neurons that have been mentioned in reviews that send kinesthetic information to the brain known as type Ia and type II afferent fibres [94]. Type Ia afferent fibres carry information regarding nerve endings in the muscle spindles that are sensitive to velocity and length changes, while type II afferent fibres carry information from these fibres specific to length change [94]. Since type Ia and type II afferent information is obtained from the muscles themselves, there are implications of interactions between motor and sensory information transmitted back to the brain which is difficult to explore [93]. Ultimately, this sensory information must be processed by the brain to form a sense of position and effect of motion.

1.6.1.2 Integration of Sensory Information

The way that body position and motion is perceived is likely not only obtained from these sensors, but also compared to an internal model of expected movement, sometimes referred to as the efferent copy [94], [96]. This concept is similar to modelling of robotic control systems, in which the sensory input from the sensors described in section 1.6.1.1 act as feedback in a closed-loop control system and compared to the predicted copy of movement in an estimator [96], [97], as seen in Figure 1.2, which was obtained with permission from [96]. It is thought that the estimated state is also our sense of kinesthesia [93].
Figure 1.2: Figure obtained with permission from “Optimality Principles in Sensorimotor Control” [96]. In this model, the controller (presumably containing the basal ganglia) selects a motor command. The motor commands are distributed as few-to-many through the synergies of agonistic and antagonistic muscle groups (the biomechanical plant) [93]. Executed motion, in addition to effects of external sources of force and motion, is perceived by the various sensory organs (sensory apparatus). The sensory data is returned as many-to-few, as this large amount of information must be integrated to estimate the next movement required to complete the task [93]. Sensory data, along with the efference (or efferent) copy (an internal copy of expected sensory signals based on the motor command), are integrated within the estimator to produce an estimated state, which is then used to update the controller.

1.6.2 Kinesthesia in PD

1.6.2.1 Physical Changes to Kinesthetic Sensors in PD?

One of the theories of the progression in PD, called Braak’s hypothesis, suggests that some cases of PD may originate from the introduction of a foreign body into a person either through the olfactory system or through the vagal nerve (i.e., through the stomach) that slowly traverses through these peripheral structures and progress inwards [40]. An example of sensory changes that support this are changes in olfactory perception in PD, which has
been found to precede motor symptoms in many cases [94]. Other sensory changes identified include those to tactile, thermal, and pain receptors located in the skin [98].

To explore potential changes in sensors involved in kinesthesia in PD, one study studied the tonic vibration reflex in people with PD and healthy controls but found that the spinal reflex mechanisms are unaltered in PD [99]. In contrast, there may be evidence of changes to type II fibres that contribute to PD rigidity, however it is thought that this is not the sole contributor to the symptom [47], [95]. Inhibition of tendon jerk also appears to be reduced in PD (related to the type Ib fibres) and contributes to increased muscle tone characteristic of rigidity in PD [47]. Therefore, there may be some evidence of reflex changes in certain aspects of PD, though it is far more complex than simply a change in the sensory organs, known due to its association with changes in the BG and alleviation of symptoms through the administration of dopaminergic medication. Also, in relationship to Braak’s hypothesis, there is no evidence that the peripheral nervous system involved in motion would be affected in the proposed process of peripheral progression of PD [100]. Overall, most evidence still directs attention to defective integration of sensory information in PD, especially the motor symptom of bradykinesia [57].

1.6.2.2 Deficits in Kinesthesia in PD

Some studies indicate that kinesthesia may be impaired in PD by observing what happens to motion in the absence of visual feedback. A review of these studies [94] summarize that patients are “less accurate, more variable, slower, less smooth, and hypometric as compared to controls”, especially under conditions of removed visual feedback. Interestingly, at least one of the studies included in this analysis and one other tested a condition where visual feedback was present in a target reaching task, but vision of the target itself was obscured, and found that movement was still less affected in PD than in the condition of no visual feedback [80], [101].

Other studies have focussed on detecting thresholds and kinesthesia in joints in the upper and lower limbs. For example, one study focussing on the knee joint in a passive movement condition rotated the lower leg about the knee joint at a constant rate, and asked participants to respond as soon as they observed a noticeable change in knee joint angle [102]. They
found that, controlling for reaction time using a separate test, participants with PD still required larger angular displacements to detect angular changes in the knee [102]. Another study in the elbows measured both passive and active perception of angular change to measure joint position sense, and found that in both conditions, participants with PD were less accurate and had less precision than healthy age-matched controls [103].

Further, researchers have investigated how potential changes in kinesthesia affect the interpretation of external objects. For example, studies that investigated changes in perception of weight [104] and object curvature [105], [106] all found that people with PD had higher sensory thresholds of perception and lower accuracy in detection of concavity, respectively.

A theory related to altered kinesthesia is related to potential for an altered sense of motor effort in PD, similar to the idea of reduced gain described in section 1.6. One study investigated this in a force matching task [107]. Each participant was required to match a provided force using one limb with visual feedback, and then output the same amount of force in the other limb without visual feedback. They found that while PD participants were capable of visually matching the required force in one limb, they failed to reproduce the required force in the opposite limb [107].

In contrast to the previously mentioned studies, Tan et al. [24] measured the effects of visual occlusion of movement and effects of vibration on the patellar tendon in a target force matching task. They found that there was no difference between people with PD and healthy age-matched controls in all four conditions of the trials: (i) vision, no vibration; (ii) vision, vibration; (iii) no vision, no vibration; (iv) no vision, vibration. As described in a review by Proske [93], although much of the research indicates perturbed kinesthesia in PD, there is still sufficient evidence to the contrary that the sense needs to be explored, especially in relationship to the internal and external perception of force.

1.6.2.3 The Effect of Levodopa on Kinesthesia

Interestingly, there is some indication that the administration of levodopa medication could have a negative impact on kinesthesia in PD. Most studies demonstrating this relate to
impairment of axial kinesthesia [108]–[110]. For example, one of these studies [108] observed detection thresholds in people with PD and age-matched controls by asking participant to state in which direction (left or right) their body was being twisted. They measured this perception at both the trunk and the hips and found that thresholds for perception in PD increased while participants were taking their dopaminergic medication, although these changes were not correlated with their dose of levodopa [108]. Another study [110] found that levodopa negatively impacted “fine adjustment of postural control”, and that potentially this could indicate overdose of the ventral striatum with dopamine after administration of levodopa.

One study of appendicular effects of levodopa [111] did find that dopaminergic medication “depressed” kinesthesia in people with PD. This study evaluated PD patients both off and on levodopa medication in estimation of elbow angle and in a matching test of contralateral elbow angle [111]. Both tests resulted in statistically worse performance while PD participants were on levodopa medication as opposed to off medication. Therefore, while much of the evidence points to deficits in kinesthesia caused by PD, it is important to understand the role that dopaminergic medication plays in kinesthesia in addition to known motor improvements.

1.6.3 Kinesthesia in FOG

1.6.3.1 Changes of kinesthetic and visuomotor perception in FOG

In section 1.5.1 deficits of force control, especially in the context of gait, were explored, which given the exploration of kinesthetic deficits in PD, could indicate further deficits in people with PD with FOG. In section 1.6.3, an experiment performed by Tan et al. [24] found there were no significant changes in people with PD compared to healthy controls under four different conditions of force matching, manipulating conditions of vision and vibration of the patellar tendon. Their study also had a PD with FOG cohort were similarly able to produce and maintain the correct output force under the condition of vision and no vibration. However, the PD with FOG cohort significantly undershot the target force under both conditions of loss of vision and vibration [24], indicating defective kinesthesia and visuomotor deficits may be present in people with FOG.
Given the implication of visuomotor impairments in FOG, other research has explored visual deficits in PD and found them to be more significantly correlated with axial impairments in PD [112], though these results were not specific to PD with FOG. Specifically implicated visual senses impaired in relation to movement include deficits in object and motion processing and deficits of spatial neglect [112].

Evidence of the effects of cueing presented earlier [9], [10], [70], [113], however, could plausibly implicate that ability to direct attention to salient information could also be responsible for kinesthetic and visuomotor changes in people with PD with FOG. To explore this idea, one study [114] used two conditions of normal walking and one of dual-tasking (or a requirement to complete a task while walking) while under additional conditions in the presence and absence of visual cues. They found that in their PD with FOG cohort, their gait improved from the no visual cue state to the visual cue state irrespective of whether the participants were in the dual-task condition. This suggests that despite visuomotor deficits in FOG and known difficulties in focusing attention in FOG, there is likely a role of kinesthesia as well [114]. In addition to this, their PD with FOG cohort had significantly worse gait under all conditions compared to their PD- cohort, suggesting that kinesthesia may be worse in people with FOG compared to those without [114]. Another study [115] investigating potential cognitive impacts in FOG explored the effects of cognitive and sensorimotor therapies on gait, and similarly explored the effects of a dual-task condition and lack of vision had on metrics of gait in people with FOG in a randomized controlled trial. Similar to the previous study, even with training they found that people with FOG performed worse in the kinesthetic challenge (the condition without vision). However, this study found that under cognitive training, participants only had improved gait in the dual-task condition compared to before training, while under kinesthetic training, participants performed better in both the dual-task and kinesthetic challenge [115]. Overall, while cognition and visuomotor control clearly play a role in FOG, there are indications of impacted kinesthesia in FOG that need to be explored.

1.7 Rationale

PD is an increasingly prevalent disease with prominent motor features that can be described as deficits in force, visuomotor, and timing control and implicates the BG as the structure
that plays a primary role in these measurable motor changes. PD also frequently presents with FOG as a poorly understood but disabling symptom that is not always alleviated by levodopa. Additionally, while most evidence during investigation of kinesthesia in PD indicates that as a centre for sensorimotor control, the BG may incorrectly integrate kinesthetic information, there is some existing literature that indicates kinesthesia may be preserved in PD. The role of the standard treatment of PD, levodopa, is not clear as it has been found to both increase and decrease acuity of kinesthesia. Further, there is some indication that kinesthesia may be impaired more drastically in people with PD with FOG than in people with PD but without FOG. While this is important to note, this thesis does not explore changes in kinesthesia in FOG but instead suggests it for future investigation. Ultimately, this thesis serves to adapt and use haptic robotic tools to further understand force control changes caused by PD and the influence of levodopa therapy.

1.8 Hypotheses

a. It is hypothesized that force output in people with PD is reduced, and more severely reduced in people with PD with FOG. Rather than being restricted to the lower limbs and in gait, this is a broader feature present in people with FOG.
b. It is hypothesized that timing and visuomotor deficits are present in similar tasks in the upper and lower limbs.
c. It is hypothesized that force perception in active movement in the upper limbs is worse in people with PD than healthy age-matched controls.
d. It is hypothesized that levodopa medication may worsen force perception in people with PD.
1.9 Objectives

a. Objective 1: Determine if there are motor changes in people with PD with FOG relative to other PD patients that relate to force and visuomotor control for similar tasks in both the upper and lower limbs.

b. Objective 2: Development of a haptic tool and experiment to detect changes of perception in upper limbs.

c. Objective 3: Determine if force perception in active movement is impaired in PD.

d. Objective 4: Assess the effect of levodopa on perception of force in PD.

1.10 Thesis Outline

Chapter 2 presents results from an experiment to explore changes in force, visuomotor, and timing control in people with PD with and without FOG using a haptics-based upper and lower limb robot. The chapter addresses hypotheses (a) and (b). Chapter 3 describes the modification of a commercial haptic device called a Novint Falcon (Falcon) using a neural network to produce accurate force output for the purpose of testing upper limb force perception in people with PD, which is described in Chapter 4, which addresses hypotheses (c) and (d). Chapter 5 summarizes the main results of the work presented in the thesis and suggests possible continuing work.

1.11 References


Chapter 2

2 Force Control Issues in Upper and Lower Limbs in People with Parkinson’s Disease and Freezing of Gait

2.1 Introduction

Parkinson’s Disease (PD) is a progressive neurological movement disorder characterized by four cardinal motor symptoms - tremor, rigidity, bradykinesia (slowness of movement), and posture and gait difficulties. In the upper limbs these symptoms can manifest as difficulties in performing visuomotor tasks (such as reaching for an object) [1], while in the lower limbs these symptoms may manifest as stooped posture or shuffling of gait [2]. Despite the differences in presentation of symptoms in the upper and lower limbs, both are caused by the loss of dopaminergic neurons of the nigrostriatal neuronal pathway [3] located in a structure of the brain called the substantia nigra. The dopamine precursor, levodopa, is the gold standard symptomatic therapy that can restore the striatal dopamine levels. In most cases of PD, this restoration of dopamine alleviates motor symptoms in both the upper and lower limbs, thereby improving quality of life.

More than half the people in the advanced stages of PD experience a debilitating symptom in the lower limbs called freezing of gait (FOG) [4], which is a distinctly different phenomenon from shuffling of gait (short and quick steps). FOG is the sudden inability to initiate or continue gait and may be triggered by cognitive, affective, or environmental factors (e.g., through narrow doorways or in crowded settings) [5]. For most who experience FOG, the symptom is relieved by dopaminergic medication [6]. However, for many FOG is resistant to levodopa [7] and presents while they are “on” levodopa medication, even while other motor symptoms in the upper and lower limbs are well controlled. This may be because higher dosages of levodopa are needed to alleviate FOG but increase the risk of levodopa-induced dyskinesias [8] (involuntary writhing movements), and therefore lower levodopa dosages are selected to medically optimize their treatment. FOG may also be a result of structural changes in non-dopaminergic regions of the brain network, including those “involved in visuospatial functions of the right
hemisphere” [9], [10], and has been shown to be associated with reduced expression in cholinergic pathways such as in the temporal region [11].

Due to the development of sensors and interactive robotic tools, people have been able to quantify motor changes in PD. In the upper and lower limbs, reductions in force output in isokinetic tasks of muscle strength have been measured in people with PD compared to healthy, age-matched controls [12]–[15]. Studies have also noted reductions in velocity in PD in the upper limb in reaching tasks [16], [17], and reduced walking speed in the lower limbs [2]. Some have hypothesized that changes in velocity are a result of improper scaling of the motor command signal sent from the basal ganglia [18]–[20]. In measurements of visuomotor control, poorer performance in measures of movement path efficiency and direction error [17], [21], and increases in reaction time [1], [22] have been found in the upper limb. No studies were identified that examine if visuomotor changes that occur in the upper limb are similarly expressed in the lower limb. However, experiments in PD demonstrate increases in reaction time in reaching tasks in the upper limbs [1], [22] and time taken to initiate gait in the lower limb [23].

No studies of isometric force production performed were found about people with PD and upper-limb freezing (the equivalent of FOG in the upper limb). In the lower limb, people with PD with FOG were found to be able to match target forces in isometric tasks as well as people with PD without FOG [24]. Deficits in upper limb motor performance, such as identification of freezing in finger tapping [25] or bimanual pen-tapping tasks have also been demonstrated [26]. Both studies demonstrated a correlation of these freezing events with clinical FOG scores in the lower limb, though upper limb freezing is typically not seen clinically. However, they were performed while participants were off their medication and did not investigate freezing while on medication, and neither investigated visuomotor performance measures such as velocity, path efficiency or reaction time. Though deficits in visuospatial reasoning were implicated in FOG while participants were stepping in place [27], studies directly studying visuomotor changes in the lower limbs have not been conducted. Timing deficits when shifting weight during step initiation were found in people with FOG compared to people with PD without FOG [28], [29]. Based on the predominant presentation of symptoms in the lower limb in people with FOG, it is logical to assume that
force output, visuomotor control, and timing would all be worse in this group of people in the lower limb than the upper limb, but there is not sufficient evidence available to either confirm or deny this assumption.

In this pilot study, a mobile haptic device capable of delivering seated visuomotor tasks was used to observe force, visuomotor control, and timing in both upper and lower limbs [30]. It is proposed that due to the common implicated structure and effective treatment of levodopa to alleviate upper and lower limb symptoms in people with PD, similar deficits in visuomotor control found in the upper limbs also exist in the lower limbs. It is also suspected that, while on their medication, PD patients with levodopa-unresponsive FOG have similar force, visuomotor, and timing deficits in the upper limbs as people with PD without FOG, but due to implicated brain structures in FOG and deficits in visuospatial reasoning, these deficits are more pronounced in the lower limbs. Finally, people with PD may have more difficulties adjusting force and visuomotor control to match increased or decreased force requirements of the task than people without PD, and this issue may be more pronounced in the lower limbs in people with FOG.

2.2 Methods

2.2.1 Cohort Demographics

To distinguish between force and visuomotor control deficits caused by PD with and without FOG, data was collected from three age-matched cohorts: 8 healthy controls, 5 people with PD without FOG (PD-), and 5 people with PD with levodopa-unresponsive FOG (PD+). Subjects were identified as having Levodopa-resistant FOG by clinical assessment and the Freezing of Gait Questionnaire (FOG-Q). The PD- cohort did not present with any FOG symptoms in either the ON or OFF levodopa states. Subjects in both PD cohorts had been diagnosed with PD for at least 3 years, medically optimized on oral medications for at least 3 months prior to enrolment and did not undergo advanced device aided interventions (such as deep brain stimulation or spinal cord stimulation) at the time of the study.
2.2.2 Task Description

A 3-degree-of-freedom (DOF) multi-functional upper- and lower limb mobile haptics-enabled robot described in [30] and [31] was used in two visuomotor reaching tasks (Western University Research Ethics Board REB#107451 and 108252). The control of the device and the tasks was developed at CSTAR in Simulink® for MATLAB® R2015b and QUARC™ 2.5 (from Quanser Inc, Markham, ON, Canada) using a visual virtual environment also developed at CSTAR. The mobile robot can move on a plane (such as a desk or the ground) and rotate about its centre for a total of 3 DOF. The output of the robot was controlled by scaling the interactive force and torque between subject and robot measured by the mounted six-axis HEX-70-CE-2000N OptoForce sensor to a desired output velocity according to a selected control mode. Each task involved 12 outer targets on a screen that appeared in a fixed, randomized order, and the participants were asked to move the robot that controlled an on-screen cursor to each target (Figure 2.), thus completing one subtask. After moving the cursor to the centre of a target, participants then moved the cursor towards the central home target before moving to the next outer target to complete the next subtask. When each outer target appeared on the screen, the robot either exerted more force, intermediate force, or less force, in the direction of the applied force of the user in the resistive, neutral, and assistive control modes, respectively. More specifically, the neutral mode used the measured interaction forces between the participant and the device to control the velocity of the robot such that the participants did not feel like they were experiencing any forces from the robot and could move freely. The resistive mode required a higher amount of force compared to the neutral mode to generate the same amount of velocity in the direction of measured force such that the participants felt like they were opposing a force applied by the robot. Finally, the assistive mode required a lower amount of force compared to the neutral mode to generate the same amount of velocity such that the participants felt like it was very easy to move, but not that they were getting pulled by the robot in the direction of applied force. The control mode selected for each subtask occurred in a fixed, randomized order. This was to observe if force, visuomotor, or timing deficits changed under varied force conditions in both PD cohorts relative to controls. There was a 10 second time limit, and each participant was asked to complete each task only once for each limb. Participants were seated for all tasks. All
members of both PD cohorts were in their ON state at the time of the test and were able to complete the entire experiment.

Figure 2.1: When completing the tasks in the upper limb (a), a participant held onto the joystick and moved their arm in the desired direction to move the white square on the screen. The user's objective was always to move the white square as quickly and efficiently as possible to the green square, the desired target location. (b) The foot attachment on the robot. A subject’s foot rested on the orange piece, and the white strap was tightened to a comfortable level while not allowing the foot to slip out.

A joystick was attached to the device when completing the tasks in the upper limb as in Figure 2. (a), and a special foot attachment replaced the joystick when completing the tasks in the lower limb as in Figure 2. (b). When used in the upper limbs, the robot was placed on a desk at a comfortable distance and position from the participant. The foot attachment allowed the participants to complete the task in the lower limb from a comfortable and seated position.

2.2.3 Data Collection and Metrics

Two ADNS 9800 optical sensors collected position data and a 6-axis HEX-70-CE-2000N OptoForce force/torque sensor provided force measurements at 100 Hz. Force and velocity signals were filtered with 2nd order Butterworth filters with a cut-off frequency of 5 Hz.

Force and velocity profiles were manually inspected for every set of collected data. That containing non-linearities due to sensor drift were removed prior to analysis, which was
less than 1% of collected files. Each recording was divided into subtasks according to when
a new target appeared on the screen and when the next target was achieved.

Average force and \((F_{\text{mean}})\) maximum force \((F_{\text{max}})\) were measures of exerted force
magnitude by each participant during the tasks. Measures of visuomotor control included
average velocity \((v_{\text{mean}})\), and maximum velocity \((v_{\text{max}})\). During data collection, it was
visually observed that participants with PD experienced stopping events while very close
to achieving the desired target. A stop was defined as a velocity magnitude below 0.0025
m/s lasting longer than 0.2 seconds. An example of a stopping event is plotted in Figure
2.2 (a). The total time stopped \((t_{\text{stopped}})\) was calculated as the sum of stops in each control
mode over the entire task.

Other measures of visuomotor control included the accuracy of the spatial approach
between cohorts, which was determined by calculating the efficiency of the path to achieve
the target, and the error in the angle of the directed force relative to the direction of the
target from the current robot position. The path efficiency \((\varepsilon)\) was calculated as the ratio
between the shortest path from the starting point to the target, and the length of the actual
path taken by the user to reach the target. The force direction error \(\theta_{\text{error}}\) was calculated as:

\[
\theta_{\text{error}} = \frac{1}{N} \sum_{i=0}^{N} \cos^{-1} \left( \frac{\hat{F}_i \cdot (\hat{x}_f - \hat{x}_i)}{\|\hat{F}_i\| \|\hat{x}_f - \hat{x}_i\|} \right)
\]

(1.1)

where \(\hat{F}_i\) and \(\hat{x}_i\) are the force and position vectors at time \(i\), \(\hat{x}_f\) is the location of the target,
and \(N\) is the number of data samples collected while the user completed the subtask.

Timing in the reaching tasks was also recorded for each of the cohorts. Reaction time \((t_{\text{react}})\)
was calculated as the time taken from the appearance of the new target to when the user
begins to direct the cursor to the new target, and total time \((t_{\text{total}})\) was calculated as the time
taken from the appearance of the new target to when the target is acquired.

To test whether an increase in \(t_{\text{react}}\) and \(t_{\text{total}}\) translated into a scaled proportion of the
temporal force profile in the PD- and PD+ cohorts relative to the healthy controls, the time
of the peak force and the time when half the area under the force-time curve occurred in
each subtask was calculated. These times were scaled relative to $t_{total}$ to find the relative peak force time ($r_{peak}$) and relative median force time ($r_{med}$). An example of a typical force profile is plotted in Figure 2.2 (b).

The Movement Disorder Society (MDS) Unified Parkinson’s Disease Rating Scale (UPDRS) part III (motor) scores were collected from all PD participants while in the ON levodopa state (seen in Appendix E).

Figure 2.2: Typical temporal profiles for a single subtask. (a) An example of a patient with PD with FOG stopping as they approach the target, where the grey blocked region shows the duration of $t_{stopped}$ during a subtask. (b) An example of a typical force-time curve for a Control participant, showing the $r_{peak}$ and $r_{med}$. 
2.2.4 Statistical Analysis

Statistical analysis was performed using GraphPad Prism 9.5.0. The data for each metric was separated according to cohort, control mode, and limb type. To examine if there were differences across cohorts and under varied control modes in the upper and lower limbs, two-way mixed analysis of variance (ANOVA) statistical tests were performed with Bonferroni-corrected post-hoc tests for inter-mean differences between cohorts in each mode. Data for each two-way mixed ANOVA was examined for outliers, normality across cohorts using the Shapiro-Wilk test [31], and equality of variances using the Brown-Forsythe Test. Post-hoc tests examined for normality of residuals using Q-Q plots. Sphericity was never assumed, and a Geisser-Greenhouse correction was applied where required. If distributions were approximately normal but variances across cohorts were not equal, Dunnett’s (Dt) post-hoc tests were used. If normality and equality of variances could not be assumed, a transform was applied. If assumptions were still violated, inter-mean differences were calculated using Dunn’s (Dn) tests.

2.3 Results

Summarized in Table 2.1 are the gender, age, years with PD, and the UPDRS part III motor scores of the cohorts. All demographic data listed in Table 2.1 did not have statistically significant differences between the cohorts.
Table 2.1: Baseline demographic data of the three cohorts. Presents proportion of males to females (M/F), and the mean and standard deviation (std. dev.) of their age, years with PD, UPDRS Part III Motor Scores, and UPDRS Part III Motor Scores Segmented into upper (UL) and lower (LL) limbs. Statistical significance (p-value) was determined using $\alpha = 0.05$.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PD-</th>
<th>PD+</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>4/3</td>
<td>5/0</td>
<td>4/1</td>
<td>N/A</td>
</tr>
<tr>
<td>Age</td>
<td>69.13 (4.88)</td>
<td>69.80 (5.59)</td>
<td>75.80 (2.59)</td>
<td>0.055</td>
</tr>
<tr>
<td>Years with PD</td>
<td>N/A</td>
<td>6.20 (1.79)</td>
<td>10.60 (5.94)</td>
<td>0.206</td>
</tr>
<tr>
<td>UPDRS</td>
<td>N/A</td>
<td>25.8 (7.22)</td>
<td>31.30 (6.87)</td>
<td>0.252</td>
</tr>
<tr>
<td>UL UPDRS</td>
<td>N/A</td>
<td>11.10 (3.53)</td>
<td>14.30 (3.56)</td>
<td>0.333</td>
</tr>
<tr>
<td>LL UPDRS</td>
<td>N/A</td>
<td>6.90 (2.54)</td>
<td>9.90 (4.07)</td>
<td>0.199</td>
</tr>
</tbody>
</table>

2.3.1 Two-Way Mixed ANOVA

The two-way mixed ANOVA results in Table 2.2 and Table 2.3 show statistically significant cohort and control mode interactions in the upper limb for $F_{mean}$, $v_{mean}$, $v_{max}$, $\varepsilon$, and $\theta_{error}$ (p<0.001) in the upper and lower limbs, respectively. In the lower limb, cohort and control mode interactions were statistically significant for $F_{mean}$ (p < 0.001), $F_{max}$ (p < 0.045), $v_{mean}$ (p < 0.001), $v_{max}$ (p < 0.001), $t_{stopped}$ (p < 0.026), $\varepsilon$ (p < 0.002), and $t_{total}$ (p < 0.010). For all metrics in both the upper and lower limbs, control modes affected the results (p < 0.001). Due to the consistency of the influence of control mode across cohorts as determined by examining box plots, post-hoc inter-means tests were performed for select metrics. However, they were performed between cohorts in each control mode. The results also show that matching by subject under each control mode was very highly statistically significant for all metrics (p < 0.001) except for relative $r_{med}$ (p = 0.013).
Table 2.2: Two-Way mixed ANOVA interactions and control mode and cohort main effects in the upper limbs. *p < 0.05. **p < 0.01. *** p < 0.001.

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Mode x Cohort</th>
<th>Mode</th>
<th>Cohort</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_{\text{mean}}$</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$F_{\text{max}}$</td>
<td>0.0516</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$v_{\text{mean}}$</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$v_{\text{max}}$</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$t_{\text{stopped}}$</td>
<td>0.08</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>0.004**</td>
<td>&lt;0.001***</td>
<td>0.013*</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$\theta_{\text{error}}$</td>
<td>0.02**</td>
<td>&lt;0.001***</td>
<td>0.0778</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$t_{\text{react}}$</td>
<td>0.5763</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$t_{\text{total}}$</td>
<td>0.7848</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$r_{\text{peak}}$</td>
<td>0.4172</td>
<td>&lt;0.001***</td>
<td>0.0706</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$r_{\text{med}}$</td>
<td>0.1511</td>
<td>&lt;0.001***</td>
<td>0.0971</td>
<td>&lt;0.001***</td>
</tr>
</tbody>
</table>

2.3.2 Inter-Means Comparisons

All inter-means comparisons are reported with 95% confidence interval (CI). The ratios between the means of the cohorts are presented for the $F_{\text{mean}}, F_{\text{max}}, v_{\text{mean}},$ and $v_{\text{max}}$ metrics to allow for the comparison in performance between the upper and lower limbs due to its relevance in the discussion. The difference in means is presented for all other parametric tests, and the mean rank difference is presented for non-parametric Dunn’s tests. For a summary of means (medians), please see Table 2.4 and Table 2.5 for the upper and lower limbs, respectively. For a summary of the p-values for all inter-means tests, please see Table 2.6 and Table 2.7 for the upper and lower limbs, respectively.
Table 2.3: Two-Way mixed ANOVA interactions and control mode and cohort main effects in the lower limbs. *p < 0.05. **p < 0.01. *** p < 0.001.

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Mode x Cohort</th>
<th>Mode</th>
<th>Cohort</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_{\text{mean}}$</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$F_{\text{max}}$</td>
<td>0.045*</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$v_{\text{mean}}$</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$v_{\text{max}}$</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$t_{\text{stopped}}$</td>
<td>0.026*</td>
<td>&lt;0.001***</td>
<td>0.010*</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>0.002**</td>
<td>&lt;0.001***</td>
<td>0.0727</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$\theta_{\text{error}}$</td>
<td>0.1904</td>
<td>&lt;0.001***</td>
<td>0.3525</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$t_{\text{react}}$</td>
<td>0.1653</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$t_{\text{total}}$</td>
<td>0.010**</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>$r_{\text{peak}}$</td>
<td>0.489</td>
<td>&lt;0.001***</td>
<td>0.8605</td>
<td>0.013*</td>
</tr>
<tr>
<td>$r_{\text{med}}$</td>
<td>0.5834</td>
<td>&lt;0.001***</td>
<td>0.9849</td>
<td>&lt;0.001***</td>
</tr>
</tbody>
</table>
Table 2.4: Means and standard deviations of cohorts under all modes for each of the metrics in the upper limbs. In cases where non-parametric tests were used, medians and quartiles are shown.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Metrics</th>
<th>Control</th>
<th>PD-</th>
<th>PD+</th>
<th>Control</th>
<th>PD-</th>
<th>PD+</th>
<th>Control</th>
<th>PD-</th>
<th>PD+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F_{mean} (N)</td>
<td>4.63 (0.66)</td>
<td>4.26 (0.92)</td>
<td>3.07 (0.39)</td>
<td>2.62 (0.69)</td>
<td>2.36 (0.52)</td>
<td>1.63 (0.36)</td>
<td>2.07 (0.35)</td>
<td>1.89 (0.48)</td>
<td>1.20 (0.27)</td>
</tr>
<tr>
<td></td>
<td>F_{max} (N)</td>
<td>8.15 (1.43)</td>
<td>7.45 (2.02)</td>
<td>5.06 (1.10)</td>
<td>5.35 (1.66)</td>
<td>5.02 (1.95)</td>
<td>3.13 (0.74)</td>
<td>4.85 (0.89)</td>
<td>4.10 (1.20)</td>
<td>2.64 (0.77)</td>
</tr>
<tr>
<td></td>
<td>v_{mean} (cm/s)</td>
<td>2.13 (0.34)</td>
<td>1.71 (0.44)</td>
<td>1.18 (0.26)</td>
<td>2.99 (0.70)</td>
<td>2.44 (0.60)</td>
<td>1.76 (0.51)</td>
<td>3.65 (0.59)</td>
<td>2.89 (0.72)</td>
<td>1.95 (0.51)</td>
</tr>
<tr>
<td></td>
<td>v_{max} (cm/s)</td>
<td>5.01 (1.02)</td>
<td>4.13 (1.37)</td>
<td>2.89 (0.60)</td>
<td>7.83 (2.23)</td>
<td>6.65 (2.65)</td>
<td>4.47 (1.01)</td>
<td>10.87 (2.00)</td>
<td>7.99 (2.49)</td>
<td>5.39 (1.79)</td>
</tr>
<tr>
<td></td>
<td>t_{stopped} (s)</td>
<td>0.1 (0.11)</td>
<td>0.84 (0.39, 2.09)</td>
<td>1.76 (0.58, 4.64)</td>
<td>0 (0, 1.26)</td>
<td>0.78 (0.26, 3.78)</td>
<td>3.52 (1.96, 9.70)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0.33)</td>
<td>0.20 (0, 1.24)</td>
</tr>
<tr>
<td></td>
<td>ε (%)</td>
<td>85.76 (6.92)</td>
<td>87.38 (5.75)</td>
<td>72.84 (14.65)</td>
<td>77.81 (5.82)</td>
<td>78.35 (7.09)</td>
<td>72.88 (11.07)</td>
<td>68.15 (8.11)</td>
<td>75.19 (7.29)</td>
<td>64.23 (14.16)</td>
</tr>
<tr>
<td></td>
<td>θ_{error} (°)</td>
<td>35.91 (6.74)</td>
<td>34.14 (6.40)</td>
<td>46.83 (14.17)</td>
<td>41.43 (5.25)</td>
<td>42.17 (6.18)</td>
<td>43.21 (8.41)</td>
<td>47.84 (4.29)</td>
<td>43.04 (6.63)</td>
<td>49.82 (11.66)</td>
</tr>
<tr>
<td></td>
<td>t_{react} (s)</td>
<td>0.44 (0.11)</td>
<td>0.56 (0.16)</td>
<td>0.87 (0.33)</td>
<td>0.42 (0.11)</td>
<td>0.52 (0.13)</td>
<td>0.64 (0.15)</td>
<td>0.37 (0.08)</td>
<td>0.44 (0.13)</td>
<td>0.54 (0.22)</td>
</tr>
<tr>
<td></td>
<td>t_{total} (s)</td>
<td>2.65 (0.84)</td>
<td>3.21 (0.79)</td>
<td>6.13 (2.05)</td>
<td>2.13 (0.53)</td>
<td>2.63 (0.68)</td>
<td>4.51 (1.39)</td>
<td>2.04 (0.43)</td>
<td>2.36 (0.59)</td>
<td>4.53 (1.45)</td>
</tr>
</tbody>
</table>
Table 2.5: Means and standard deviations of cohorts under all modes for each of the metrics in the lower limbs. In cases where non-parametric tests were used, medians and quartiles are shown.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Metrics</th>
<th>Control</th>
<th>PD-</th>
<th>PD+</th>
<th>Control</th>
<th>PD-</th>
<th>PD+</th>
<th>Control</th>
<th>PD-</th>
<th>PD+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistive</td>
<td>$F_{\text{mean}}$ (N)</td>
<td>4.85 (0.44)</td>
<td>4.33 (0.76)</td>
<td>3.08 (0.28)</td>
<td>2.68 (0.20)</td>
<td>2.44 (0.35)</td>
<td>1.70 (0.23)</td>
<td>2.21 (0.20)</td>
<td>1.90 (0.44)</td>
<td>1.22 (0.18)</td>
</tr>
<tr>
<td>Neutral</td>
<td>$F_{\text{max}}$ (N)</td>
<td>8.92 (0.82)</td>
<td>8.47 (1.48)</td>
<td>5.83 (1.20)</td>
<td>6.37 (0.74)</td>
<td>5.64 (1.05)</td>
<td>3.86 (0.53)</td>
<td>5.54 (0.64)</td>
<td>4.31 (0.84)</td>
<td>2.82 (0.38)</td>
</tr>
<tr>
<td>Assistive</td>
<td>$v_{\text{mean}}$ (cm/s)</td>
<td>2.19 (0.25)</td>
<td>1.64 (0.38)</td>
<td>1.08 (0.14)</td>
<td>3.01 (0.34)</td>
<td>2.32 (0.44)</td>
<td>1.64 (0.38)</td>
<td>3.76 (0.39)</td>
<td>2.79 (0.73)</td>
<td>1.66 (0.23)</td>
</tr>
<tr>
<td>Control</td>
<td>$v_{\text{max}}$ (cm/s)</td>
<td>5.53 (0.64)</td>
<td>4.50 (0.78)</td>
<td>3.34 (0.62)</td>
<td>9.57 (1.06)</td>
<td>7.31 (1.52)</td>
<td>5.49 (0.87)</td>
<td>12.61 (1.51)</td>
<td>8.57 (2.01)</td>
<td>5.58 (0.78)</td>
</tr>
<tr>
<td>Resistive</td>
<td>$t_{\text{stopped}}$ (s)</td>
<td>0 (0, 0.60)</td>
<td>1.04 (0.37, 2.36)</td>
<td>1.85 (0.20, 2.58)</td>
<td>0 (0, 0.37)</td>
<td>0.35 (0, 1.34)</td>
<td>0.53 (0, 4.39)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0.05)</td>
<td>0.2 (0, 0.56)</td>
</tr>
<tr>
<td>Neutral</td>
<td>$\varepsilon$ (%)</td>
<td>85.85 (5.84)</td>
<td>83.18 (5.30)</td>
<td>73.64 (11.62)</td>
<td>73.16 (7.53)</td>
<td>73.20 (5.46)</td>
<td>65.60 (12.14)</td>
<td>58.87 (53.92, 64.18)</td>
<td>64.31 (58.84, 70.89)</td>
<td>63.95 (53.06, 68.54)</td>
</tr>
<tr>
<td>Assistive</td>
<td>$\theta_{\text{error}}$ (%)</td>
<td>36.54 (6.13)</td>
<td>41.00 (4.76)</td>
<td>42.06 (8.90)</td>
<td>45.83 (4.62)</td>
<td>47.25 (4.76)</td>
<td>48.97 (10.15)</td>
<td>53.41 (51.40, 56.31)</td>
<td>51.41 (48.60, 53.63)</td>
<td>51.58 (46.76, 58.30)</td>
</tr>
<tr>
<td>Control</td>
<td>$t_{\text{react}}$ (s)</td>
<td>0.43 (0.34, 0.49)</td>
<td>0.61 (0.47, 0.74)</td>
<td>0.83 (0.57, 1.01)</td>
<td>0.35 (0.31, 0.41)</td>
<td>0.52 (0.39, 0.58)</td>
<td>0.57 (0.45, 0.72)</td>
<td>0.35 (0.32, 0.39)</td>
<td>0.45 (0.39, 0.51)</td>
<td>0.55 (0.50, 0.61)</td>
</tr>
<tr>
<td>Resistive</td>
<td>$t_{\text{total}}$ (s)</td>
<td>2.46 (0.45)</td>
<td>3.57 (0.96)</td>
<td>5.77 (0.77)</td>
<td>2.23 (0.41)</td>
<td>2.94 (0.69)</td>
<td>4.71 (1.44)</td>
<td>2.29 (0.38)</td>
<td>2.94 (0.90)</td>
<td>4.82 (1.09)</td>
</tr>
</tbody>
</table>
Table 2: Table of \( p \)-values in the upper limbs. * \( p < 0.05 \), ** \( p < 0.01 \), *** \( p < 0.001 \).

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Control vs. PD-</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.622</td>
<td>&gt;0.999</td>
<td>0.066</td>
<td>0.261</td>
<td>0.452</td>
<td>&gt;0.999</td>
<td>&gt;0.999</td>
<td>0.097</td>
<td>0.217</td>
</tr>
<tr>
<td>Resistive</td>
<td></td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.030*</td>
<td>0.026*</td>
<td>0.085</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td>0.008**</td>
<td>0.017*</td>
<td>0.016*</td>
<td>0.062</td>
<td>0.909</td>
<td>0.014*</td>
<td>0.041*</td>
<td>0.033*</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>0.830</td>
<td>&gt;0.999</td>
<td>0.132</td>
<td>0.519</td>
<td>0.355</td>
<td>&gt;0.999</td>
<td>&gt;0.999</td>
<td>0.015*</td>
<td>0.187</td>
</tr>
<tr>
<td>Control vs. PD-</td>
<td></td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.001**</td>
<td>0.006**</td>
<td>0.632</td>
<td>&gt;0.999</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.006**</td>
<td>0.632</td>
<td>&gt;0.999</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td>0.020*</td>
<td>0.044*</td>
<td>0.044*</td>
<td>0.083</td>
<td>0.492</td>
<td>0.563</td>
<td>&gt;0.999</td>
<td>0.064</td>
<td>0.003**</td>
</tr>
<tr>
<td>PD- vs. PD+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assistive</td>
<td>0.760</td>
<td>0.317</td>
<td>0.037*</td>
<td>0.005**</td>
<td>0.350</td>
<td>0.107</td>
<td>0.217</td>
<td>0.023*</td>
<td>0.495</td>
</tr>
<tr>
<td>Control vs. PD-</td>
<td></td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.006**</td>
<td>&gt;0.999</td>
<td>&gt;0.999</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.006**</td>
<td>&gt;0.999</td>
<td>&gt;0.999</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001***</td>
<td>0.016*</td>
<td>0.012*</td>
<td>0.027*</td>
<td>0.512</td>
<td>0.165</td>
<td>0.487</td>
<td>0.012*</td>
<td>&lt;0.001***</td>
</tr>
</tbody>
</table>
Table 2.7: Table of p-values in the upper limbs. *p < 0.05. **p < 0.01. ***p < 0.001.

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Control vs. PD-</th>
<th>Control vs. PD+</th>
<th>PD- vs. PD+</th>
<th>Control vs. PD- FOG</th>
<th>Control vs. PD+</th>
<th>PD- vs. PD+</th>
</tr>
</thead>
<tbody>
<tr>
<td>t_total</td>
<td>0.002**</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.431</td>
<td>&lt;0.001***</td>
<td>0.31*</td>
</tr>
<tr>
<td>t_react</td>
<td>0.001**</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.838</td>
<td>&lt;0.001***</td>
<td>0.766</td>
</tr>
<tr>
<td>θ_error</td>
<td>0.311</td>
<td>0.161</td>
<td>&gt;0.999</td>
<td>0.030*</td>
<td>&gt;0.999</td>
<td>0.120</td>
</tr>
<tr>
<td>t_react</td>
<td>&gt;0.999</td>
<td>&gt;0.999</td>
<td>0.389</td>
<td>&gt;0.999</td>
<td>0.184</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>V_max</td>
<td>0.008**</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.003**</td>
<td>&lt;0.001***</td>
<td>0.009**</td>
</tr>
<tr>
<td>V_mean</td>
<td>0.001*</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.002**</td>
<td>&lt;0.001***</td>
<td>0.001**</td>
</tr>
<tr>
<td>F_max</td>
<td>&gt;0.999</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.223</td>
<td>&lt;0.001***</td>
<td>0.004**</td>
</tr>
<tr>
<td>F_mean</td>
<td>0.223</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
<td>0.213</td>
<td>&lt;0.001***</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

Resistive
Neutral
Assistive
In the upper limbs, the Control cohort had significantly higher $F_{\text{mean}}$ than the PD+ cohort ($p < 0.001$) in the resistive (1.5, CI(1.31 to 1.74)), neutral (1.6, CI(1.21 to 2.18)), and assistive (1.7, CI(1.35 to 2.22)) modes, and the PD- cohort also had higher $F_{\text{mean}}$ than the PD+ cohort in the resistive (1.4, CI(1.09 to 1.78), $p = 0.008$), neutral (1.4, CI(1.05 to 2.06), $p = 0.020$), and assistive (1.6, CI(1.19 to 2.12), $p < 0.001$) modes. Similar results were found in the lower limb; the Control cohort had significantly higher $F_{\text{mean}}$ compared to the PD+ cohort ($p < 0.001$) in the resistive (1.6, CI(1.42 to 1.74)), neutral (1.6, CI(1.39 to 1.79)), and assistive (1.8, CI(1.59 to 2.10)) modes, and the PD- cohort had significantly higher $F_{\text{mean}}$ compared to the PD+ cohort ($p \leq 0.002$) in the resistive (1.4, CI(1.15 to 1.73)), neutral (1.4, CI(1.20 to 1.73)), and assistive (1.6, CI(1.19 to 2.10)) modes. There were no statistically significant differences in both the upper and lower limbs between the Control and PD- cohorts in $F_{\text{mean}}$ during the reaching tasks. Very similar patterns of differences between cohorts were found in $F_{\text{max}}$, the results of which can be seen in Table 2.4 and Table 2.5 for the upper and lower limbs, respectively. $F_{\text{max}}$ results can be seen in Figure 2.3 (a) and (b). Similar results were also found in $v_{\text{mean}}$ and $v_{\text{max}}$ as in $F_{\text{mean}}$ and $F_{\text{max}}$. However, $v_{\text{mean}}$ in the lower limbs was significantly higher in the Control cohort than the PD- cohort ($p \leq 0.007$) in the resistive (1.3, CI(1.10 to 1.63)), neutral (1.3, CI(1.10 to 1.54)), and assistive (1.3, CI(1.09 to 1.68)) modes, with very similar results in $v_{\text{max}}$ (Figure 2.3 (c) and (d)). P-values of statistical tests can be seen in Table 2.6 and Table 2.7.

To summarize these results, the PD+ cohort had similar reductions in force and velocity compared to the Control and PD- cohorts in both the upper and lower limbs. Typically, the PD- cohort did not differ significantly from the Control cohort in the four metrics. In the lower limb, the Control cohort had significantly higher $v_{\text{mean}}$ and $v_{\text{max}}$ than the PD- cohort, though the differences between the cohorts was proportionally similar in the lower limb as they were in the upper limb.
Figure 2.3: Cohort means and standard deviations for select metrics in both the upper (UL) and lower (LL) limbs for (a) UL $F_{\text{max}}$, (b) LL $F_{\text{max}}$, (c) UL $v_{\text{max}}$, (d) LL $v_{\text{max}}$, except for (e) UL $t_{\text{stopped}}$, and (f) LL $t_{\text{stopped}}$, which show medians and interquartile ranges.
Cohorts were found to similarly scale their force to adjust to the changes of resistance according to the control mode. In the upper limbs, the PD+ cohort $F_{\text{mean}}$ in the resistive mode was 1.9 times that in the neutral mode (CI(1.19 to 1.70), $p < 0.001$). $F_{\text{mean}}$ was 1.8 times greater ($p \leq 0.001$) in the resistive mode than the neutral mode in the PD- (CI(1.47 to 2.32)) and Control (CI(1.77 to 2.24)) cohorts in the upper limb, and this same proportion was found in the lower limb in the PD+(CI(1.10 to 1.67)), PD- (CI(1.47 to 2.32)), and Control (CI(1.85 to 2.49)) cohorts. $F_{\text{mean}}$ was between 1.2 and 1.4 times greater ($p \leq 0.002$) in the neutral state compared to the assistive state in the upper limbs for the PD+ (CI(1.19 to 1.55)), PD- (CI(1.11 to 1.40)), and Control (CI(1.13 to 1.42)) cohorts, and in the lower limbs for the PD+ (CI(1.17 to 1.67)), PD- (CI(1.13 to 1.45)), and Control (CI(1.13 to 1.31)) cohorts.

Overall, the PD+ cohort had longer $t_{\text{stopped}}$ than the Control cohort in the upper and lower limbs, where these differences were mostly statistically significant. Though the PD- cohort tended to have longer $t_{\text{stopped}}$ than the Control cohort and shorter $t_{\text{stopped}}$ than the PD- cohort, these results were not found to be statistically significant. In the upper limb, the PD+ cohort had significantly longer $t_{\text{stopped}}$ during the reaching tasks than the Control cohort in the resistive (Dn: 10.84, $Z = 2.58$, $p = 0.030$), neutral (Dn: 12.88, $Z = 3.10$, $p = 0.006$), and assistive (Dn: 9.55, $Z = 3.09$, $p = 0.006$) modes. Though the PD+ cohort also had longer $t_{\text{stopped}}$ than the PD- cohort in all three modes, these results were not statistically significant. There were no statistically significant differences in $t_{\text{stopped}}$ between the PD- and Control cohorts in any mode in the upper limbs. In the lower limbs, the PD+ cohort had statistically significantly longer $t_{\text{stopped}}$ than the Control cohort ($p \leq 0.009$) in the resistive (Dn: 13.13, $Z = 3.10$) and assistive (Dn: 9.32, $Z = 2.97$) modes. The PD- cohort had longer $t_{\text{stopped}}$ than the Control cohort in the resistive mode (Dn: 12.36, $Z = 3.02$, $p = 0.008$). Though the PD+ cohort had longer $t_{\text{stopped}}$ than the PD- cohort in the lower limbs in all three modes, these results were not statistically significant. These results can be seen in Figure 2.3 (e) and (f).

Metrics of visuospatial control show the PD+ cohort tends to perform slightly worse in the resistive mode than the Control and PD- cohorts, and the PD- cohorts performed as well as the Control cohort. In the upper limbs, $\varepsilon$ was significantly lower in the PD+ cohort than both the Control (-1.81%, CI(-3.42 to -0.19), $p = 0.026$) and PD- (-2.01%, CI(-3.65 to -
cohorts in the resistive mode. Similarly, \( \varepsilon \) was significantly lower in the lower limbs of the PD+ cohort and Control cohort (12.21\%, CI(4.22 to 20.20), \( p = 0.002 \), and lower in the PD+ cohort than in the PD- cohort (9.55\%, CI(0.74 to 18.36), \( p = 0.030 \)) in the resistive mode. In the upper limb, the PD+ cohort had significantly larger logarithmic transform of \( \theta_{\text{error}} \) than the PD- cohort in the resistive mode (-0.11, CI(-0.25 to 0), \( p = 0.041 \)), but not in the other modes. There were no other statistically significant differences between any of the cohorts.

Some improvements were seen in visuomotor control in the PD+ cohort as resistance increased. The PD+ cohort did not perform statistically differently between either the resistive and neutral mode or the neutral mode and assistive mode but did have lower \( \varepsilon \) in the resistive mode than the assistive mode in both the upper (0.96\%, CI(-1.65\% to -0.27\%), \( p = 0.08 \)) and lower (Dn: 16.00, \( Z = 3.77, p < 0.001 \)) limbs. As in \( \varepsilon \), the PD+ cohort did have significantly lower \( \theta_{\text{error}} \) in the upper (0.96, CI(0.27 to 1.65), \( p = 0.008 \)) and lower (10.71, CI(2.50 to 18.92), \( p = 0.01 \)) limbs in the resistive mode from the assistive mode.

Increases in visuomotor control performance were seen in the PD- and Control cohorts as resistance increased, and these differences were more pronounced than in the PD+ cohort. In the upper limbs, the inverted square root of \( \varepsilon \) was 1.7 and 1.6 times greater in the neutral than the resistive mode (\( p < 0.001 \)) in the PD- (CI(1.35 to 1.92)) and Control (CI(1.22 to 1.83)) cohorts, respectively. In the lower limbs, the raw metric was 1.1 and 1.2 times (\( p \leq 0.001 \)) for the PD- (CI(1.07 to 1.21)) and Control (CI(1.11 to 1.24)) cohorts, respectively. The PD- cohort did not have a significantly higher \( \varepsilon \) in the assistive from neutral mode (\( p > 0.05 \)) in the upper limbs, while the Control cohort was 1.3 times higher (CI(1.32 to 1.92)). However, both cohorts were significantly higher between the two modes, by 1.1 times (CI(1.05 to 1.23), \( p = 0.004 \)) and 1.2 times (CI(1.14 to 1.29), \( p < 0.001 \)) in the PD- and Control cohorts, respectively. Both the PD- and Control cohorts decreased their \( \theta_{\text{error}} \) in the resistive mode from the neutral mode (\( p \leq 0.009 \)), shown by the logarithmic transform in the upper limbs in the PD- (1.53, CI(0.06 to 0.13)) and Controls (1.42, CI(0.02 to 0.11)), and in the lower limbs in the PD- (6.25, CI(1.84 to 10.66)) and Control (17, \( Z = 3.00 \)) cohorts. Only the Control cohort had statistically significant lower \( \theta_{\text{error}} \) in the neutral mode.
from the assistive mode in the upper (1.07, CI(0.65 to 1.48), p < 0.001) and lower (14, Z = 2.4) limbs.

$t_{react}$ and $t_{total}$ were significantly delayed in both the PD+ and PD- cohorts in the upper and lower limbs compared to the Control cohorts. In the upper limbs, the logarithmic transform of the PD+ cohort $t_{react}$ was significantly slower than both the Control cohort (p < 0.001) in the resistive (-0.23 s, CI(-0.34 to -0.12)), neutral (-0.18 s, CI(-0.26 to -0.10)), and assistive (-0.22 s, CI(-0.33 to -0.11)) modes, and the PD- cohort in the resistive (-0.14 s, CI(-0.27 to -0.01), p = 0.033) and assistive (-0.14 s, CI(-0.26 to -0.03), p = 0.012) modes. The PD- cohort $t_{react}$ was significantly slower than the Control cohort in the neutral (-0.09 s, CI(-0.18 to -0.01), p = 0.015) and assistive (-0.07 s, CI(-0.26 to -0.03), p = 0.023) modes.

In the lower limbs, the PD+ cohort $t_{react}$ was significantly slower than the Control cohort (p < 0.001) in the resistive (Dn: 30.42, Z = 5.07), neutral (Dn: 33.42, Z = 5.58), and assistive (Dn: 34.55, Z = 5.76) modes. However, the PD+ cohort only had significantly slower $t_{react}$ than the PD- cohort in the assistive mode (Dn: 16.86, Z = 2.55, p = 0.032). The PD- cohort had significantly slower $t_{react}$ than the Control cohort (p ≤ 0.007) in the resistive (Dn: 20.75, Z = 3.58), neutral (Dn: 25.26, Z = 4.36), and assistive (Dn: 17.69, Z = 3.05) modes. In the upper limbs, the logarithmic transform of the PD+ cohort had significantly longer $t_{total}$ than both the Control cohort (p < 0.001) in the resistive (-0.36 s, CI(-0.50 to -0.23)), neutral (-0.32 s, CI(-0.46 to -0.18)), and assistive (-0.34 s, CI(-0.46 to -0.21)) modes, and the PD-cohort (p ≤ 0.003) in the resistive (-0.27 s, CI(-0.42 to -0.13)), neutral (-0.23 s, CI(-0.38 to -0.07)), and assistive (-0.28 s, CI(-0.42 to -0.14)) modes. The $t_{total}$ by the PD- cohort were not significantly different than those of the Control cohort. In the lower limbs, the PD+ cohort had longer $t_{total}$ than both the Control cohort (p ≤ 0.002) in the resistive (-3.31 s, CI(-4.06 to -2.56)), neutral (Dt: -2.49 s, CI(-3.90 to -1.07)), and assistive (-2.53 s, CI(-3.34 to -1.72)) modes, and the PD- cohort in the resistive (-2.20 s, CI(-3.02 to -1.37), p < 0.001), neutral (Dt: -1.77 s, CI(-3.24 to -0.30), p = 0.018), and assistive (-1.88 s, CI(-2.78 to -0.99), p < 0.001) modes. In contrast to the upper limbs, the PD- had longer $t_{total}$ than the Control cohort in the lower limbs in the resistive (-1.11 s, CI(-1.83 to -0.39), p = 0.002) and neutral (Dt: -2.49 s, CI(-1.37 to -0.06), p = 0.031) modes.
There were no statistically significant differences in $r_{\text{peak}}$ or $r_{\text{med}}$ between any of the cohorts in any of the modes.

2.4 Discussion

This is the first known study to report the force and visuomotor performance of PD participants without FOG (PD-), and 5 PD participants with levodopa-unresponsive FOG (PD+) while in the ON levodopa state using a reaching task under three control modes (resistive, neutral, and assistive) in both the upper and lower limbs and comparison with age-matched Controls. The 3 cohorts were statistically similar in age, clinical motor scores, and other baseline characteristics. While the number of participants in each cohort was small, the trends of performance across the control modes were visually similar for all cohorts. The performance of the PD+ cohort in $F_{\text{mean}}$, $F_{\text{max}}$, $v_{\text{mean}}$, and $v_{\text{max}}$, $t_{\text{stopped}}$, $t_{\text{react}}$, $t_{\text{total}}$, and was generally significantly worse in the upper and lower limbs than both the Control and PD- cohort. The PD- cohort performed markedly worse than the Control cohort in metrics of $v_{\text{mean}}$, $v_{\text{max}}$, $t_{\text{react}}$, and $t_{\text{total}}$ in the lower limbs. The PD+ cohort had longer $t_{\text{stopped}}$ during the reaching tasks than the Control cohort in all three modes in the upper limb, and in the resistive and assistive modes in the lower limb. The PD- cohort had longer $t_{\text{stopped}}$ than the Control cohort in the lower limbs in the resistive mode. Similar performance was found across all cohorts in $r_{\text{peak}}$, $r_{\text{med}}$, and $\theta_{\text{error}}$ in both the upper and lower limbs in all modes. The PD+ cohort demonstrated reduced efficiency compared to the Control and PD- cohorts in the upper limb resistive mode and the Control cohort in the lower limb resistive mode.

2.4.1 A Global Reduction in Force Output in People with Levodopa-Unresponsive FOG

Recent works in animal models and humans have considered the pedunculopontine nucleus (PPN) to be a centre for gait pattern generation [32] and is part of the motor network of control for the lower limbs that receives input from the basal ganglia. Since freezing of gait is related to a difficulty in initiation or continuation of gait, it has been thought (especially in those with levodopa-unresponsive FOG [33]) that freezing episodes may be caused by reduced output from the PPN [34] resulting in episodes of an inability to correctly time
step movements. However, Nieuwboer et al. [36] noted that “the basal ganglia may have a role during the co-regulation of force and timing of movement” in FOG and showed that force amplitude in gait experiences sudden decreases immediately before freezing episodes. By performing reaching motions, potentially separating the needs for force production from rhythmic movement required in gait, the results demonstrate that not only do people with levodopa-unresponsive FOG have reduced force production (and consequently slower velocities) in the lower limbs relative to other people with PD while in the ON state, but they also experience significantly reduced force production in similar proportional deficits in the upper limbs. This suggests that people with levodopa-unresponsive FOG also experience a global deficit of force amplitude generation that is not restricted to gait (Figure 2.4), and this may not be caused by a decrease in physical capacity to produce force [24] but is rather an issue of control.

This study did not demonstrate statistically significant differences between the PD- and Control cohorts in measures of force in either upper or lower limbs. Two studies by Inkster and Allen [14], [15] for the lower limb did show muscle strength deficits in PD, but it is possible that deficits were not seen in the PD-cohort because the experiment did not require high enough forces to reveal this deficit. Differences between the PD- and control cohorts in the lower limb, while statistically significant, were not proportionally different from differences found in the upper limb. The results are consistent with Robichaud [12] and Stelmach [13], which suggest that issues in force production are primarily a decrease in the slope of force-time curve of force generation and the smoothness of this force-time curve, respectively.
Figure 2.4: Models of communication between the basal ganglia as a central controller for motion in (a) people with PD without FOG and (b) people with PD and with FOG. In (a), people with PD in the ON-state of their levodopa medication have most retained motor control to the upper and lower limbs with deficits in velocity and increased time to complete tasks, represented by the dotted outline of the basal ganglia. In (b), the black outline represents what is hypothesized the motor control pathways looked like, where control from the basal ganglia to the lower limb is altered while control to the upper limbs remains the same. The red represents a control model that matches the results of this paper, where motor control to the upper limbs is also altered. The dotted outline of the basal ganglia represents altered focus and attention in this group that does not seem to be as intact as those without FOG on levodopa, and how visuomotor control is not increased as well in the resistive mode as it was in the PD- and Control cohorts.

2.4.2 Retained Control of Force Amplitude Generation in PD

Figure 2.3 (a) and (b) with Figure 2.3 (c) and (d) show that the PD+ cohort, like the PD- and Control cohorts, could increase the amplitude of their force output in response to an increase in the resistance of the robot, and these changes were proportionally similar between cohorts across resistances in both the upper and lower limbs. Also of note is that $F_{mean}$ in the resistive mode by the PD+ cohort exceeds $F_{mean}$ in the Control and PD- cohorts in the assistive mode. This suggests a remaining capacity of people with PD with and without FOG to adjust the magnitude of their output force according to changes in the
environment in a goal-oriented task. However, PD patients with FOG may select for an inappropriately low gain in their output force even while on their levodopa medication. This inappropriate selection of gain has been observed and modelled in people with PD without FOG [18], [19], [35], where the gain can be described as “motor motivation” and is set by the amount of dopamine in the striatum [19]. This suggests that despite the selection of a clinically optimal dose for patients with levodopa-unresponsive FOG, typical doses are still not only unable to alleviate FOG but may also be unable to increase the motor motivation to a “normal” level.

2.4.3 A Minimum Force Threshold and its Impact on Movement

Though there was no significant difference between the PD- and PD+ cohorts in the $t_{\text{stopped}}$ metric, in general, $t_{\text{stopped}}$ in the PD+ cohort was greater than that of the PD- cohort and statistically different from the Control cohort in most modes in both the upper and lower limbs. It is also important to note that during stopping events, although there was no movement, there was still force applied by the PD+ cohort that did not exceed a required threshold to start movement, which is also demonstrated by the significant increase in time spent in stopping episodes in the resistive mode. This minimum threshold was eventually overcome by the PD+ cohort to complete the reaching motion or begin a new reaching motion.

This could suggest that difficulties in shifting weight between gait stances in people with FOG [28], [29] may be related to a global and distinct reduction in ability to generate force during visuomotor reaching tasks. This would be similar to anecdotal evidence from the clinic in which verbally cueing oneself to “make a big step” may allow someone to think about making a much larger step, and therefore generate a large enough gain to overcome a minimum threshold of force and begin walking again. Potentially, to overcome a minimum threshold required to make a step, a person with PD may need to select for a much larger gain or “energizing” command is required from the basal ganglia than what they may usually select [20].
2.4.4  External Cueing of Amplitude Changes?

This study showed that while there were few differences between the PD- and Control cohorts in metrics of $\varepsilon$ and $\theta_{\text{error}}$, increasing resistance in control mode typically improved both metrics of visuomotor control (i.e., increased $\varepsilon$ and decreased $\theta_{\text{error}}$). Therefore, it is likely that basic visuomotor control remains mostly intact in people with PD without FOG. Though many studies have shown visuomotor control deficits, these seem to be restricted to those of amplitude gain rather than of any kind of directional error [36]. The results are not considered to be counter to those found by Gaprielian et al. [17], which found smaller movement areas in upper limb reaching tasks in people with PD compared to healthy Controls, likely related to a reduction in ability to adapt to a higher cognitive load found in people with PD and their tendency to undershoot targets in reaching tasks [36], [37]. The results also may have not shown changes in $\varepsilon$ and $\theta_{\text{error}}$ in the PD- cohort from Controls since the cognitive loads were not as high as they were in the studies by Gaprielian [17] and Inzelberg [21].

However, these same metrics of visuomotor control did not scale proportionally relative to the other cohorts as was made apparent by the significant differences found between the Control and PD+ cohorts in the resistive mode. The results of this study do not contradict those reported in other studies [9], [10] on changes in visuomotor control in FOG but suggest that the effects of basal ganglia dysfunction may be more significant with regard to the effects of FOG than may have been previously theorized.

Due to known timing deficits in FOG, several studies have investigated and shown the benefit of using visual, auditory [38] and vibrotactile cues [39] as either preventative or rescue measures in the alleviation of FOG [40]. It is thought that these external cues capture the attention of people with FOG, directing them to focus on salient information to the task at hand and “filter out” irrelevant information. The study presented in this paper caused the cohorts to increase their force output to adapt to the change in resistance of the task, there was also a trend amongst all 3 cohorts that $\varepsilon$ increases and $\theta_{\text{error}}$ decreases as resistive input from the robotic device increases. It is suggested that similar to timing cues, cues of increased amplitude could assist in increasing the attention of someone with FOG on relevant task information of amplitude. However, while these attentional cues may benefit
people with PD without FOG, there may only be minimal benefit on these cues to visuospatial control [27] in people with levodopa-unresponsive FOG.

2.4.5 An Opportunity for Rehabilitation?

In this study, $t_{\text{react}}$ and $t_{\text{total}}$ were affected in the ON-state in both PD cohorts, as has been found in other studies in reaching tasks [22], [23], and gait initiation in people with FOG [28]. However, it was found that the relative timing of peak and median forces in the force-time curve were not altered in PD with and without FOG, similar to the conclusions of Pope et al. [41]. Therefore, despite abnormal scaling of the force output required to perform reaching tasks, there remains underlying patterning of movements in PD with and without FOG,

Though it does not change the progression of the disease, there is significant evidence that regular attendance of physical therapy improves the ability to perform daily activities in PD [42]. It should be noted that within this review by Keus et al., there is mention of investigating physical therapy in PD for reaching and grasping, but studies that include this are not mentioned, nor are any suggestions made. Reaching for objects with the upper limbs is crucial for the completion of most self-care tasks, and the ability of a person with PD to perform those tasks often reduces as age increases.

Furthermore, there is evidence of the benefit of robotic rehabilitation in FOG [43]. These methods typically require a person to be strapped into a weight-bearing harness over a treadmill, and a single system may cost hundreds of thousands of dollars. Without a machine such as this, therapy methods may provide an environment in which falls due to FOG may still occur. Therefore, it is possible that mobile robotic haptic tools such as that used within this paper present an opportunity for safe physical therapy as an alternative to larger, more expensive methods. By applying higher forces in a safe and seated environment, this device may provide an opportunity for upper and lower limb strength training in a seated (and therefore safe) environment to allow people with debilitating axial PD symptoms to maintain strength and mobility that they may lose if they avoid walking [44].
2.5 Conclusions and Future Work

The results of this pilot study suggest that people with levodopa-unresponsive FOG may not have a deficit of force and timing control restricted to the lower limb in gait, but instead have a global deficit of force output. The reductions in force and velocity were very significant and may be related to freezing episodes and difficulties in gait initiation in people with levodopa-unresponsive FOG. It is postulated that there is a retained ability in people with levodopa-unresponsive FOG to increase and decrease force amplitude, but that the forces selected are not appropriately scaled to tasks.

People with levodopa-unresponsive FOG experienced more periods of stopping during the tasks of this study, especially when the device was in the resistive mode. Difficulties in shifting weight during freezing episodes in gait could be related to a difficulty in generating sufficient force in a sufficient time period to begin or continue gait even as postural changes have already been made. As external timing cues can assist in preventing or alleviating freezing episodes, it is suggested that external cues of force amplitude, such as those provided in the resistive mode in this study, could also serve as a cue to focus attention on increasing force amplitude in stepping to complete a step.

This study showed increases in reaction time that are reduced in people with PD with and without FOG but were typically significantly more pronounced in people with FOG in both the upper and lower limbs. Similar experiments could be conducted with larger cohorts to determine whether stopping episodes can be attributed to the capture of upper limb freezing events [25], which were found by Nieuwboer et al. [26] in repetitive upper limb tasks and correlated with freezing scores, and whether there is a relationship between upper and lower limb freezing events in similar tasks. Other works could also investigate if reductions in muscle power may occur in people with FOG due to an avoidance of physical movement and exercise and, if present, what role this may play in continued difficulties with FOG.

To further separate the impacts of levodopa medication on force and visuomotor control in FOG, future studies will look to increase the sizes of the cohorts, as well as investigate if there are differences between people with FOG alleviated by levodopa and those that have FOG that is not improved with dopaminergic drugs while they are in the OFF- and ON-
state. Future studies may also look to compare the performance of people with FOG in lower limb reaching tasks to measurements of freezing episodes and gait initiation.

2.6 Limitations

The main limitation of this pilot study is the small sizes of the cohorts. This work also did not explore the impact that reduction in cognition associated with FOG (including visuospatial processing deficits) may have had on the results.

2.7 References


Chapter 3

3 Neural Network-Based Calibration of a Conventional Haptic Device to Improve Accuracy and Repeatability

3.1 Introduction

Parkinson’s disease (PD) is typically defined as a movement disorder [1]. However, there is a significant amount of research dedicated to understanding if it is not simply the output of motion that is affected in PD, but the ability to accurately perceive motion [2]–[4]. However, it is unclear within this body of evidence if there is actually a deficit of sensory perception, or kinesthesia, in PD [2].

Recent research has begun to investigate whether there is a deficit of perception of external objects [5], [6]. There is a significant history of testing haptic and kinesthetic perception to allow for optimal design of haptic devices to generate environments that can be perceived as realistic [7]. Much of this research is based on the use of a measure called Weber Fraction [8], which states that a limit or threshold of the smallest difference a person can reliably detect between two different stimuli is proportional to the magnitude of the reference stimuli. If this holds true for haptic and kinesthetic perception, a haptic device can be designed to output reasonably accurate forces below this perceptual threshold for most people and be used to generate forces that can be perceived as accurate. Haptic technologies also allow for greater flexibility in the design of mechanical components of psychophysical experiments. For example, it would be very easy to change a psychophysical experiment from one that tests for the discriminatory ability of two different objects to one that tests for the ability to detect discontinuities in force in a constant motion, or changes in direction of a haptic field. Using a robotic haptic device also allows for direct measurement of user responses in software, allowing for a more integrated experiment.

In the work described in Chapter 4 of this thesis, it was desired to use a commercial haptic device called a Novint Falcon (Falcon), model number: NF1-L01-004, to create a pair of constant forces that could be felt by users to investigate possible changes of kinesthesia in PD. Upon initial testing of the device, it was found that, without modification of its control,
the force output of the device was not accurate or consistent throughout the workspace. This chapter describes the adaptation of this commercial haptic device to produce acceptably accurate forces throughout the workspace for use in the designed experiment in Chapter 4.

3.2 Methods

3.2.1 Tools

The Falcon haptic device was originally designed for haptic feedback in gaming. It was therefore designed with a controller that made it safe for use in a range of gaming applications. The Falcon employs a 3-limb parallel manipulator configuration and is restricted to 3 translational degrees of freedom (DOF). This was convenient for the application considered for this device, as it may provide more stability for the wrist for users. Initial testing of the device was done to observe its geometric workspace, which is shown in Figure 3.1. For more detailed descriptions and images of the physical workspace, or information such as the dimensions of the legs of the device, the reader is directed to the work of Martin and Hiller [9] and Stamper [10].

![Figure 3.1: Position datapoints collected from the Falcon workspace.](image)
The original handle that comes with the Falcon is quite small, and therefore would make it significantly more challenging for people with PD to interact comfortably using it. Since the goal was to increase the accuracy of the force output while it is being used by a person, a force sensor was mounted on the device and integrated in the handle. Therefore, a larger handle – about the size of a typical door handle – was designed such that the hardware that connects the handle to the moving platform of the device could be used (Figure 3.2 (a)). The handle also had to be lightweight to not overburden the existing motors on the device. A lightweight PLA 3D-printed handle was designed and fabricated in the lab (see Figure 3.2 (b)).

![Figure 3.2: a) Handle and sensor mounted on the Falcon; (b) redesigned handle with integrated ATI force sensor.](image)

A 6 DOF ATI Nano43 force/torque sensor (calibration SI-18-0.25) was used that had a maximum sensing range of 18 N within each translational direction, as well as 250 N·mm of torque about each axis. These values, along with the resolution of the device, are shown in Table 1, and the position of the frame of reference of the ATI sensor relative to the Falcon can be seen in Figure 3.3. Since the device was only to be used in the z-direction of the force sensor, minimal torque from the user was expected, and the maximum of 18 N in the z-direction was not expected to be exceeded by any user since the maximum output of the Falcon was anticipated to be no greater than 10 N from initial testing. If more than 10
N were applied during testing within the viable workspace, the sensor would still be sufficient. Only if the user is actively pressing against the physical bounds of the device’s workspace would one expect the sensor’s force and torque to reach saturation.

Table 3.1: Sensing range and resolution along indicated axes of the ATI Force sensor.

<table>
<thead>
<tr>
<th></th>
<th>$F_x, F_y, F_z$</th>
<th>$T_x, T_y, T_z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensing Range</td>
<td>18 N</td>
<td>250 N-mm</td>
</tr>
<tr>
<td>Resolution</td>
<td>1/256 N</td>
<td>1/20 N-mm</td>
</tr>
</tbody>
</table>

Figure 3.3: Rotation matrices of the Falcon workspace (blue) and the ATI F/T sensor, when the origin of the frame of the ATI sensor (red) is superimposed on the origin of the workspace of the Falcon.

3.2.2 Design Selection

To improve the accuracy of the Falcon, several strategies were considered. One option was closed-loop control using the signal from the force sensor, in which the required force could be updated according to the value measured on a mounted force sensor. However, this would require very careful calibration of control and had potential for several issues.

One issue was that there are several regions for which using the force sensor to update the output force of the Falcon would be inappropriate, such as when the device handle gets
very close to the limits of the workspace of the device. Another issue was when the velocity and acceleration of the device are in the $+x$ direction, the measured force cannot be attributed to the force output of the Falcon alone. For example, in the $x$ direction, the user applies a force opposing the force produced by the Falcon; therefore, as long as the handle was moving in the $x$-direction, any compressive force measured by a force sensor mounted on the device could be attributed to the Falcon, whereas any additional force applied by the user that is greater than that applied by the Falcon would cause movement of the handle. It was also desirable to use existing encoders available on the device, and on-board velocity estimation to allow for as little modification of the Falcon as possible. However, this meant that motor currents (and therefore torques) and acceleration of the platform were not measured directly, weakening the accuracy of control methods available for closed-loop control.

Finally, and most importantly, not only was the haptic device to be used by healthy subjects, a system in which it is very difficult to predict response to the controller, but the device was to be used by people with PD. This results in a wide range of outputs including from arms with rigidity - which would likely result in slower force-time curves [11] - or with tremor, which could be considered as a sinusoidal signal in which the force magnitude could be unpredictable and could change with time.

Due to the challenges of a closed-loop control approach that has the measured force in the loop, the design of a map over the existing Falcon closed-loop controller to make the force output of the device more accurate was selected. This project considered two approaches to solve the problem using a mapping, which were the method of least mean squares (LMS) and machine learning. LMS, while a useful tool in minimizing the error of the device, does not allow for the same ease in flexibility of the number of parameters available in machine learning. Machine learning also allows for convenient alteration of inputs and parameters of a neural network (NN).

It was decided to use a force sensor mounted on the device to measure the actual force output relative to the position and velocity of the device. The position and velocity data collected from the device, the data obtained from the force sensor, along with the desired
input command can be used to train a NN to increase the accuracy and repeatability of the haptic output of the Falcon.

### 3.2.3 Data Collection

To train the NN, data was collected from 5 healthy subjects, who were all found to be able to exert good control over their movement and follow precise instructions.

The experiment in Chapter 4 was designed to have a constant force from the Falcon in the direction of the positive $x$-axis of the device. Users would experience this as a force pushing towards them. Each participant was asked to move as close to a constant velocity, and every time they interacted with the device, they were to complete one full motion from the front of the workspace to the back of the workspace. This was done to avoid large fluctuations in the collected force data. Participants were asked to complete these reaching motions at different velocities to further diversify the dataset.

To train the NN mapping, the input of the NN was the measured Cartesian endpoint position ($p_x, p_y, p_z$) and velocity ($v_x, v_y, v_z$) as determined from the Falcon, and the measured force ($F_a$) from the ATI sensor. These were used to predict the output, which was the force command ($F_c$) given to the Falcon, as in Figure 3.4 (a). In this way, when the trained NN is implemented as a map between the desired force ($F_d$) and $F_c$ of the device (as in Figure 3.4), the NN can predict the required $F_c$ to allow $F_a$ to approach $F_d$. 
During data collection, $F_c$ was selected to be a continuous function to avoid plateaus during training, since this NN should be one of regression. To achieve this, a sinusoidal function was selected such that it fluctuates by $\pm 4$ N about 3 forces (4, 6, and 8 N), each which were presented to each subject during data collection. The frequency of the sinusoidal function was selected to be 0.0005 Hz (Figure 3.5); slow enough that as each subject moves, $F_c$ does not change faster than the person's movement. In addition to this, similar to a training technique used in [13], random noise was injected in the command, which varied between $\pm 0.25$ N to increase the variability of the training values. This random noise was selected to be small enough that even at forces at or close to 3 N, the variation was not felt by the subjects.
3.2.4 Pre-Processing

Due to the nature of the device and the design of the experiment described in Chapter 4, data was excluded if it was too close to the outer bounds of the workspace, or the direction of the velocity was in the +x direction. Initial tests of the device found that frictional components of movement were too high at levels from around 0 N to 3 N, and therefore data collected at these forces was excluded from the experiment. It was also excluded since discriminatory force thresholds seem to steadily increase from about 3 N [14], getting larger as the forces approach zero. Additionally, $F_a$ values that exceeded two standard deviations (considered outliers in measured force caused by human variability) were excluded from the dataset.

During training, processing of data such as adding filters to position, velocity, and force was tried; however, it was found that adding filters decreased the accuracy of the training of the NN, and therefore no filters were applied beyond those directly from the Falcon and the ATI Force Sensor.
3.2.5 Training

After the data was collected and processed from all 5 participants, there was a total of 220,000 samples, which were split randomly according to a 70/15/15 train/testing/validation rule. During initial NN training, structural changes, such as the number of layers, were changed to find the number of layers that produced the best results. Once this was determined, a focus was placed on tuning parameters such as number of neurons in hidden layers and learning rates, as these were found to be the most important hyperparameters for tuning the NN. It was also found that batch normalization allowed for faster learning in the NN. Rectified Linear Units (relu) were used in all hidden layers, and linear output was used for the output layer.

Since the goal of the NN training was to minimize the error \( e \) of \( F_a \) between \( F_d \), a mean squared error loss function was selected. However, during testing, it was found that this did not distribute \( e \) proportionally across the desired range of \( F_d \) (i.e., \( e \) was higher at lower forces). Therefore, the loss function was normalized with respect to \( F_d \) (similar to a normalized least-mean squares approach) as seen in equation (1):

\[
L = \frac{1}{N} \sum_{i=1}^{N} \left( \frac{y_i - \hat{y}_i}{y_i} \right)^2
\]

(1)

where \( y_i \) is the true commanded force value, and \( \hat{y}_i \) is the NN-estimated force value command. Not taking the square root of this function allowed for higher penalties for forces further away from \( F_c \), thereby increasing the accuracy of the NN.

Once the NN was trained, it was desired to calculate by how much \( e \) was reduced, and if this reduction in \( e \) produced sufficiently accurate forces for the experiment in Chapter 4. To do this, the collected data was divided into plane regions, segmented by 1 cm boundaries along the \( x \)-axis of the Falcon, across a range of constant \( F_c \) values (3 N to 8 N). For example, one segment of data was collected within the range \( 0.00 \text{ m} \leq p_x < 0.01 \text{ m} \), where \( F_c \) was 5 N. To evaluate accuracy, two metrics were selected: scaled mean absolute error (\( e_{sma} \)) of \( F_a \) as in equation (2) and scaled root mean squared error (\( e_{srms} \)) as in equation (1), to evaluate how much the outliers of \( F_a \) deviated from \( F_d \).
\[ \varepsilon_{\text{ma}} = \frac{1}{N} \sum_{t=1}^{N} \frac{y_t - \hat{y}_t}{y_t} \]  

(2)

3.3 Results and Discussion

3.3.1 Machine Learning

During initial testing of the NN, it was found that 4 hidden layers produce the best results without adding unnecessary complexity to the NN (similar results were found when the NN had 5 or 6 layers). The number of parameters that resulted in the best NN is shown in Figure 3.6. This model achieved a loss of 4.3% on the test dataset, and 4.2% on the validation dataset, demonstrating that the NN achieved good results without overfitting the data.

![Figure 3.6: Hidden layers of trained NN.](image)

Before implementing the trained NN, it was desired to observe how it changed the value of \( F_c \) throughout the workspace. The changes the NN makes to \( F_c \) to achieve \( F_d \) during training indicates that the unchanged Falcon controller was significantly underestimating the required motor torques. Results in Figure 3.7 (a) through (e) plot the data of predicted values of \( F_c \) under constant conditions of \( p_y, p_z, v_x, v_y, v_z \), where \( p_y \) and \( p_z \) were modified between the graphs to represent data the handle moving along different axes the Falcon workspace. Random \( p_x \) values were generated for each selected \( F_d \). The results of this (Figure 3.7 (a) through (e)) show there were not always unique \( F_c \) values at lower forces (typically when \( F_c \) was at 4 N or lower), or within the tested range close to the front of the workspace \( (p_x \geq 0.02 \text{ m}) \). It was therefore anticipated that the device may have larger error at \( F_d \leq 4 \text{ N} \) and \( p_x \geq 0.02 \text{ m} \). Testing of the NN proceeded while considering these bounds. Similar graphs were generated in Figure 3.8 (a) through (c), which plotted predicted values of \( F_c \) under constant conditions of \( p_y, p_z, v_x, v_y, v_z \), where \( v_x \) was modified to observe how \( F_c \) changes at interquartile ranges of velocities obtained during data collection. These plots
show at typical velocity values collected during the experiment in this range that velocity has minimal impact on the output of the NN.

Figure 3.7: Examples of how the trained NN modifies $F_c$ given $F_d$ for the median velocity obtained during data collection of 0.05 m/s in the negative direction of the $x$-axis. All data was along an axis parallel to the $x$-axis at coordinates (a) $p_y = 0.0$ m, $p_z = 0.0$ m, (b) $p_y = -0.025$ m, $p_z = 0.01$ m, (c) $p_y = 0.025$ m, $p_z = 0.01$ m, (d) $p_y = 0.0$ m, $p_z = -0.03$, (e) $p_y = 0.0$, $p_z = 0.03$. 
Figure 3.8: Examples of how the trained NN modifies $F_e$ given $F_d$ for (a) the lower quartile (0.035 m/s), (b) the median, and (c) the upper quartile (0.075 m/s) of velocity obtained during data collection in the negative direction of the x-axis, where $p_y = p_z = 0.0$ m, (a) $p_y = 0.0$ m, $p_z = 0.0$ m, (b) $p_y = -0.025$ m, $p_z = 0.01$ m, (c) $p_y = 0.025$ m, $p_z = 0.01$ m, (d) $y = 0.0$ m, $p_z = -0.03$, (e) $p_y = 0.0$, $p_z = 0.03$.

3.3.2 Implementation

The results for $e$ using equations (1) and (2) for the regions specified in section 3.2.5 can be seen in Table 3.2, Table 3.3, Table 3.4, and Table 3.5. The $e$ across the entire workspace without the NN was found to be 16% (Table 3.2) and 15% (Table 3.3) for $e_{s|m|s}$ and $e_{sma}$, respectively. With the NN, the error across the workspace was reduced to 9.2% (Table 3.4) and 2% (Table 3.5) for $e_{s|m|s}$ and $e_{sma}$, respectively. Further, if the data where $F_d$ was 3 N and the device position was at the front of the workspace ($p_x \geq 0.02$ m) is also excluded, the $e_{s|m|s}$ was found to be 4.3%, and the $e_{sma}$ at 0.6%. Overall, when the NN was tested with the controller of the Falcon, it was found to have significantly improved the accuracy of the output force of the device.
Table 3.2: $e_{srms}$ calculated for regions along the $x$-axis, specified by the start and end columns, for $-0.03 \, m \leq p_y, p_z \leq +0.03 \, m$ without the NN. Errors that exceed 0.06 (6%) are highlighted in pink.

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Table 3.3: $e_{sma}$ calculated for regions along the $x$-axis, specified by the start and end columns, for $-0.03 \, m \leq p_y, p_z \leq +0.03 \, m$ without the NN. Errors that exceed 0.06 (6%) are highlighted in pink.

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Table 3.4: $e_{srms}$ calculated for regions along the x-axis, specified by the start and end columns, for $-0.03 \text{ m} \leq p_y, p_z \leq +0.03 \text{ m}$ with the NN. Errors that exceed 0.06 (6%) are highlighted in pink.

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Table 3.5: $e_{sma}$ calculated for regions along the x-axis, specified by the start and end columns, for $-0.03 \text{ m} \leq p_y, p_z \leq +0.03 \text{ m}$ with the NN. Errors that exceed 0.06 (6%) are highlighted in pink.

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3.4 Conclusions and Limitations

Overall, it was determined that the NN produced sufficiently accurate force output between 4 N and 8 N within a large enough workspace to proceed with the experiments in Chapter 4, though with specific limits on $F_d$. As described earlier, implementation of the NN map is restricted in two ways. The first is the range of forces for which future experiments would be viable. Below 4 N, the force output is not accurate or reliable enough to be used in an experiment that requires accurate force output. Also, above 8 N, for some regions of the workspace this may require the motors outputting a torque higher than what the device is rated for and therefore may wear out the Falcon more quickly. The second way it is restricted is that the very front of the workspace appears to not output reliable forces, especially for forces at or below 5 N. Finally, the design of the NN map is restricted to one direction of force output, and therefore cannot be used if $F_d$ were to be in any other direction besides that of the $x$-axis.

The experiment done in Chapter 4, was designed and selected very carefully to avoid commanding forces at the front of the device. Conveniently, during testing and design of the experiment this was found to be desirable, as subjects tended to want some distance between when they first start moving and when they begin interacting with each virtual object.

3.5 References


Chapter 4

4 Perception of Force in the Upper Limbs May Not be Affected by Parkinson’s Disease or Levodopa Therapy

4.1 Introduction

Parkinson’s Disease (PD) is a progressive neurological disorder that presents with an array of psychological, sleep, and movement symptoms. PD is most notably characterized by its motor symptoms, which can include tremor, bradykinesia (slowness of movement) and rigidity. These motor symptoms are thought to originate from the deterioration of dopaminergic neurons in a region of the midbrain called the substantia nigra [1], and are typically well managed by a dopaminergic precursor, levodopa.

There is some speculation as to whether these motor symptoms only originate from issues of motor control. Some research has proposed that difficulties begin prior to selection of motor commands and may be a defect of faulty sensory information itself [2]. This research is related to Braak’s hypothesis published in 2003, which demonstrates that some patients with PD experience disease progression starting peripherally, and through the course of the disease progresses to the substantia nigra and other motor regions of the brain [3]. For example, some with idiopathic PD first experience issues of olfactory perception many years prior to the appearance of motor symptoms [4]. However, this peripheral nervous system deterioration does not necessarily occur for all patients with PD and does not seem to be associated with sensory (afferent) neurons employed in motion [5]. Therefore, others have proposed that motor symptoms may be a result of improper integration of sensory information in PD and implicate the basal ganglia as a prominent sensorimotor integration centre in the brain [6].

Excluding vision, this integration of sensory information can produce a “sense of position and movement in our limbs” [7], which can be referred to as proprioception, or *kinesthesia*. In the upper limbs, there is evidence that joint and limb position sense is impaired in passive movements in PD [8]–[10]. In active movements, an internal sense of motor effort may also be impaired [11]. Other works have focussed specifically on perception of external forces and objects and have also found a deficit in PD in haptic touch and their sense of
curvature of objects [12], [13] using haptic robotic tools, which rely on the integration of proprioceptive information with “tactile and pressure cues” [14]. However, a review by Proske [7] states that there is still conflicting evidence regarding whether there is actually disturbed kinesthesia in PD, as some studies find there is no significant difference between people with PD and healthy, age-matched controls. For example, a study by Tan et al. [15] demonstrated no significant differences between people with PD and healthy age-matched controls in a muscle vibration study in the perception of force.

It is unclear what role the administration of levodopa medication has in kinesthesia. Some studies have investigated whether axial kinesthetic sense- or the sense of balance and trunk position - is altered by levodopa medication, and found that axial kinesthesia is not improved, but may actually be hindered by the administration of levodopa medication, even as clinical motor scores improve [16]–[18]. Similarly, O’Suilleabhain et al. [19] noted in their study that kinesthesia may be acutely depressed by dopaminergic medication. Overall, it should be noted that information regarding the effects of levodopa in upper limb movement is minimal, especially regarding kinesthesia when it really matters - during motion. Therefore, this experiment aimed to determine whether active force perception in the upper limbs is altered in PD, and whether it is worsened by levodopa medication.

4.2 Methods

4.2.1 Experimental Design

To measure active force perception in the upper limbs, an experiment was designed to calculate each individual's Weber fraction (WF) [20] which denotes the percentage difference of just noticeable stimulus strength. A commercial haptic device (Falcon model number NF1-L01-004) was adapted (Figure 4.1) to produce an output force with mean error of 1.4% and average root mean squared error below 6% across the range of force outputs and device workspace used in the experiment. The workspace (a haptic field) contained two haptic cubes, each assigned with either a reference force or a comparative force that was always larger (stronger) than the reference force. It was the task of each participant to correctly identify the stronger comparative force.
Figure 4.1: The Falcon with the modified handle and integrated force sensor that was used in the experiment. The handle was designed to be about the size of a door handle to allow for comfortable and easy gripping.

To better navigate between the two cubes presented in the haptic field, the experiment was set up to have minimal visual feedback on a screen (Figure 4.2). The haptic cubes were represented on the screen by two blue squares, and a white ball represented the cursor to enable each participant to interact with each square. Each participant was asked to interact first with the square on the right by aiming for the middle of the square and "pushing" into it, during which time they could feel a force being reflected back to them. They were then asked to push into the second square on the screen in the same manner, and report which square they felt was "harder" to push (which would correspond to the square assigned the comparative force). Each participant was allowed to attempt a trial without blinding them to their hand when the difference between the reference and comparative forces were very large. After this, a box was placed over the device and hand to reduce the visual feedback a participant could receive from their own arm movement, and therefore separate kinesthesia from visual perception. To keep the
attention of the participant, if they correctly selected the square with the stronger comparative force, the selected square would turn green; if the participant selected the square corresponding to the weaker reference force, the selected square would turn red. The colour change of the squares only remained for 1 second, at which point the next trial would begin.

Figure 4.2: Image of the active force perception experiment. The user pushes into each square, and then tells the experimenter which cube had the higher force. The experimenter inputs this information in the program by hitting the correct key, and then the selected key either turns green or red depending on whether the user selected the correct square or not (in this image, the correct square was selected and turned green). The screen in the video shows what the experimenter sees; they observe the forces from the force sensor.
The reference force and comparative force were assigned randomly to each square for each trial, so the square with the comparative force could not be predicted by the participant. The reference force was selected such that its magnitude was larger than forces in discriminatory perception tasks known to have reduced WF resolution (typically below 3 N) [21], and such that the comparative force could be selected low enough to reduce fatigue during the repetitive motions of the experiment, which could influence the results [22]. For each trial, the reference force was selected according to a psychophysics method, i.e., based on how people perceive external stimuli. This was done to identify each individual's force discrimination threshold using a three-interval forced-choice adaptive staircase method [23]. In this method, the difference between the reference and comparative forces varied according to the answers provided by the participant in the previous trial(s), in a 3-to-1 ratio; that is, if a participant correctly selected the stronger force 3 times in a row, the difference in forces assigned to each square decreased logarithmically (the difference between the forces reduced by 1.4 times every time this was achieved). However, if the participant incorrectly selected the stronger force once, the difference in forces increased by a factor of 1.7. The ratio of 1.7 to 1.4 was experimentally selected so the steps up and down in force are not too large or too small to the user, respectively. This method aims to achieve a perceptual threshold at about 79.4% correct, or in other words, estimate the perceptual threshold for each user at the point where they can correctly select the stronger force 79.4% of the time. The comparative force always began at 7.5 N and was adjusted according to the rules described for the selected staircase method. To ensure that the comparative force was always measurably distinguishable from the reference force by a force sensor during testing, a minimum limit of the comparative threshold was selected at 4.8 N. This threshold corresponds to a WF of \( (4.8 - 4.5 \text{ N})/4.5 \text{ N} = 0.067 \), which is well below the average threshold of 0.15 WF for force perception in similar experiments in healthy subjects [15], [21]. In case a participant was capable of distinguishing between reference and comparative forces at this threshold 6 times in a row, it was hypothesized that their actual threshold of perception may be at or below a WF of 0.067, in which case the program would perform an early exit resulting in an early end of the experiment. Otherwise, the experiment would end when the number of “reversals” of direction of changing forces reached 10 (typically between 40 and 50 trials). The WF for each
individual was then calculated by taking the average of the differences between reference and comparative forces at each point of reversal and dividing by the reference force. An example graph of one experiment completed by a control subject can be seen in Figure 4.3.

![Force vs. Trial Responses](image-url)

**Figure 4.3**: Example of a full experiment for one control participant for one of the hands tested. On the first descent, the experiment only requires one correct answer to descend to prevent fatigue and more quickly approach the perceptual threshold of the individual. Once an incorrect answer is given for a trial, the difference between the reference force and comparative force increases, or there is a “reversal” in direction of the experiment. Then, it takes 3 correct answers in a row for the experiment to reverse direction again, reducing the difference between the reference and comparative forces. Once 10 reversals occur, the experiment ends. The WF is calculated as the average of the reference forces at each reversal point.

4.2.2 Collection of Demographic Information

Data was collected from two cohorts, a control cohort (N = 8) and a PD cohort (N = 14), which were tested while both off their medication for over 12 hours (OFF-state) and between 1 and 1.75 hours after receiving their levodopa medication (ON-state).
All work was done with the consent of the participants under Western University Research Ethics Board REB#108252. Each participant with PD were tested twice; the first time when off their levodopa medication (OFF-state) in which all participants had been off their levodopa medication for at least 12 hours [24], and then assessed a second time between 1 and 2 hours after administration of dopaminergic medication (ON-state). For all participants, the data recorded included age, dominant hand, sex, and date of birth. For participants with PD, additional assessments were performed including MDS-UPDRS Part III assessments when they were in both the OFF- and ON-state, and a Montreal Cognitive Assessment (MoCA) to test for cognitive ability while in the ON-state (which can be seen in Appendix F).

Participants were excluded from the study if they had diabetic neuropathy or other known neurological disorders, including head injuries that resulted in unconsciousness, or if they received a score of 17 or lower on the MoCA. They were also excluded if they experienced physical disability in the upper limbs that prevented them from performing repetitive upper limb movements.

4.2.3 Statistical Analysis

All analyses were completed in SPSS v29.0. Normality and equality of variance of the measured variables were determined using the Shapiro-Wilk test and Levene’s test, respectively. If data was determined to be normal, comparisons between the PD cohort while in the OFF and ON states were determined using two-tailed paired sample t-tests, and comparisons between the control cohort and the PD cohort in either the ON or OFF state were calculated using two-tailed independent samples t-tests. If data was not normally distributed, specified non-parametric tests were used.

4.3 Results

Results of the statistical analysis of dimensionless WFs are presented with group size, means and standard deviations of data corresponding to each cohort, and with t scores and p-values using an alpha level of 0.05 and 95% confidence intervals (CIs). In the case of non-parametric tests, data is presented with medians instead of means. In comparisons involving the PD cohort in the OFF state, one participant could not complete the analysis.
in one arm due to severe tremor that made it difficult to complete the experiment, and their data was excluded from the PD cohort in that state. A different participant experienced dyskinesias in the ON state that also made it difficult to complete the experiment, and their data was excluded from analyses involving the PD cohort in the ON state.

The control (N = 8, Mean Rank = 11.00) and PD (N = 15, Mean Rank = 12.53) cohorts were confirmed to be age-matched using a Mann-Whitney U Test, and the medians between them were not statistically different (p = 0.636), as seen in Figure 4.4.

![Boxplot of distributions of age for the control and PD cohorts.](image)

**Figure 4.4: Boxplot of distributions of age for the control and PD cohorts.**

To determine if active force perception was affected by PD, the average performance of both hands for the control cohort (0.154 ± 0.069) and the PD cohort (0.158 ± 0.047) in the OFF state - as seen in Figure 4.5 (a) - were compared and were not statistically different (0.003, t = 0.125, CI(-0.048 to 0.054), p > 0.05). Variability of performance was measured as the absolute difference - as seen in Figure 4.5 (b) - between hands for each participant in the Control (0.036 ± 0.028) and PD cohort in the OFF state (0.081 ± 0.072) were also compared. There was no statistical significance (0.045, t = 1.684, CI(-0.011 to 0.101), p > 0.05).
Similar comparisons were completed within the PD cohort between the OFF and ON state to determine if administration of levodopa affected active force perception. The average performance of the PD cohort between the OFF (0.016 ± 0.046) and ON (0.189 ± 0.069) state was not found to be statistically different (-0.027, t = -1.880, CI(-0.058 to 0.004), p > 0.05), as seen in Figure 4.5 (c). There was also no significant difference between the OFF (0.081 ± 0.075) and ON (0.069 ± 0.063) state when comparing the absolute difference between hands for each participant (0.012, t = 0.454, CI(-0.046 to 0.070), p > 0.05), as seen in Figure 4.5 (d).

Since the difference between the PD cohort in the OFF and ON state was not statistically different, but the average WF in the ON state was higher than the WF in the OFF state, the average WF between the control cohort (0.154 ± 0.069) and PD cohort (0.190 ± 0.066) in the ON state was compared. This result was also found not to be statistically significant (0.035, t = 1.170, CI(-0.027 to 0.098), p > 0.05), as seen in Figure 4.5 (e).

To examine if the performance within the PD cohort in and between the ON and OFF state was related to which arm was more severely affected by PD, the WFs were separated into two groups within each state according to most affected hand and least affected hand, as calculated by taking the higher corresponding UPDRS Score (items 3.3 to 3.6 and 3.15 to 3.17 for upper limbs only, as seen in Appendix E). These comparisons were also done between dominant and non-dominant hands to observe if handedness played any role in the results.
Figure 4.5: Means and 95% CIs for comparisons for a) average WF for PD in the OFF-state compared to Controls, b) difference between WF of hands for PD in the OFF-state compared to Controls, c) average WF for PD in the OFF-state compared to PD in the ON-state, d) difference between WF of hands for PD in the OFF-state compared to PD in the ON-state, and e) average WF for PD in the ON-state compared to Controls.
Within the OFF state, the difference between the most affected (0.154 ± 0.078) and least affected (0.161 ± 0.065) hands was not significantly different (-0.007, t = -0.230, CI (-0.070 to 0.057), p > 0.05), as in Figure 4.6 (a). There was also no difference between the dominant (0.153 ± 0.066) and non-dominant (0.117 ± 0.008) hands (-0.009, t = -0.292, CI(-0.072 to 0.055), p > 0.05), as in Figure 4.6 (b).

Within the ON state, the difference between the most affected (0.180 ± 0.089) and least affected (0.199 ± 0.071) hands was not significantly different using a Wilcoxon Signed Rank Test (-0.028, W = 73 p > 0.05) as seen in Figure 4.6 (c). There was also no difference between the dominant (0.190 ± 0.084) and non-dominant (0.189 ± 0.077) hands (0.001, t = 0.050, CI(-0.052 to 0.055), p > 0.05), as seen in Figure 4.6 (d). It was confirmed that there was no statistical difference between dominant (0.156 ± 0.075) and non-dominant (0.153 ± 0.071) hands in performance of this test within the Control cohort as well (0.003, t = 0.161, CI(-0.037 to 0.042), p > 0.05), as seen in Figure 4.6 (e).
Figure 4.6: Means and 95% CIs for a) WF in the most-affected hand compared to the least affected hand in PD in the OFF-state; b) WF in the dominant hand compared to the non-dominant hand in PD in the OFF state; c) WF in the most-affected hand compared to the least affected hand in PD in the ON state; d) WF in the dominant hand compared to the non-dominant hand in PD in the ON-state; and e) WF in the dominant hand compared to the non-dominant hand in Controls.
There was no statistical difference (-0.019, t = -0.613, CI(-0.086 to 0.048), p > 0.05) for the most affected hand between the OFF (0.161 ± 0.077) and ON (0.180 ± 0.093) state (Figure 4.7 (a)), or for the least affected hand (-0.038, t = -1.690, CI(-0.086 to 0.010), p > 0.05) between the OFF (0.161 ± 0.065) and ON (0.199 ± 0.071) state (Figure 4.7 (b)).

![Figure 4.7: Means and 95% CIs for a) WF in the most affected hand in PD compared in the OFF-state and the ON-state, and b) WF in the least affected hand in PD compared in the OFF-state and the ON-state.](image)

Finally, average WF results within the Control and PD cohorts in the OFF and ON states, and WFs in most and least affected hands in the PD cohort in both the OFF and ON states, were not found to be correlated to age, years taking dopaminergic medication, MoCA score, UPDRS Part III Score (separated by limb as previously listed for most and least affected arms), or number of years diagnosed with PD.

## 4.4 Discussion

### 4.4.1 Discriminatory Force Perception Not Impaired in PD

When considering how and why motor control is affected in PD, one can think about the human body in a similar manner to a robotic system – a closed loop system that has inputs (sensory organs), outputs, or a mechanical plant (muscles), and a controller (the brain). Figure 4.8 shows an example of how this motor control system could be modelled as a closed-loop control system and was adapted from [4] and [25]. In this system, the controller
tells the biomechanical plant how to move based on a pre-selected movement, producing motor output. This output, combined with external perturbations that may not have been predicted by the controller, is then perceived by the sensory organs of the body and converted into a set of signals sent to an estimator. This estimator then compares an internal representation of the motor output, or efferent copy, with the sensory input, to produce an estimated state, or the sense of perception [4]. This perception of movement could then be compared to the desired movement by the controller to alter the motor commands sent to the biomechanical plant. If perception of external forces in active movement were affected in PD, it would have to originate from one of these components.

Figure 4.8: Conceptualization of motor control in humans based on the work reported in [4] and [25]. In Parkinson’s Disease, it is theorized that symptoms of bradykinesia present as a reduction in gain motor control output. This could affect the efferent copy, or the internal representation of expected motor control, thereby impacting perception, the comparison of the efferent copy and afferent information. It is also possible that if the peripheral nervous system were affected in PD, that the afferent input would be inaccurate, and therefore falsely alter perception.

Given a major symptom set in PD is the set of motor symptoms, some research has investigated whether the motor system itself is affected in PD. Within the system in Figure 4.8, there is some influence of the biomechanical plant on the measured sensory inputs. This is because muscle spindles contain a sensor called an Ia afferent sensor, whose
perception is influenced by the lengths of the muscle fibres [7]. This means that it is possible that motor output may directly affect sensory input, and that faulty motor output in PD could affect perception. However, at least one study has found that this part of the peripheral nervous system is not affected in PD [5], [26].

Other research has investigated whether the sensory inputs themselves are impaired in PD. Some of these sensory inputs have been found to be affected, such as tactile, thermal, and pain receptors in the skin [2]. Research by Braak et al. [3], though finding that some cases of PD may progress peripherally, did not find that the spinal cord was affected in PD, therefore reducing the possibility that the disease could progress from the sensory and motor nerves that would be involved in the motor controller system [5].

Overall, this leaves the controller and estimator components of the system modelled in Fig. 8 as likely culprits of causes for deficits in sensorimotor integration [6]. In terms of an effect of the controller, it has long been hypothesized that in PD, deterioration of the basal ganglia in PD results in a reduction of gain of the output of the controller, which in turn results in symptoms such as bradykinesia [27]. In this way, it is possible that the reduction in gain of the motor output of the system could alter perception in active movement. However, the results of this study did not find, at least in the upper limbs in PD, that active force perception appears to be impaired while people with PD are in the OFF-state. These results were not dependent on hand dominance and were not related to one hand being more affected by PD than the other. Therefore, it appears that it may only be the motor output of the controller that is affected by PD.

A study by Klockgether et al. [28] found that, without visual feedback, people with PD routinely underestimate how far they have moved, suggesting an impairment in kinesthesia. Impaired kinesthesia is expected to result from some defect of the estimator in the model described in Figure 4.8. However, a fundamental part of this experiment was that a user must perceive two different forces in this experiment and compare them. This requires pressing into and feeling one of the forces and forming a mental copy of the sensations associated with that force. Then, a person must actively compare this copy of external force to the second force that they are actively perceiving. Perhaps, in a discriminatory task, the
perception of force is similarly affected between the memory of a force and the active perception of another force. This may explain why an underestimation of motion can be observed in people with PD, but a deficit of comparative force perception was not seen in the results of this chapter.

4.4.2 Active Force Perception Not Altered by Levodopa

Based on the results of the experiments, active force perception in the upper limbs does not seem to be impaired in PD in the ON-state either. It would be expected that if kinesthesia were impaired by PD, that it would be similarly improved by the administration of levodopa like the motor symptoms are. Since the results of this experiment did not find perception of force was impaired in PD, it makes sense that levodopa did not seem to affect the perception of force as well. However, there is a growing body of evidence that other aspects of perception – such as visual perception of position and movement [29], [30], axial kinesthesia [16]–[18] is impaired by levodopa medication. Perhaps for some perception modalities such as those in axial kinesthesia, if there is no change to perception in the OFF-state, then altering motor movement in the ON-state may affect expected motor output due to a “saturation of the ventral striatum” [18], thereby changing active force perception.

4.5 Conclusions

It appears that an ability to discriminate between external forces actively in the upper limb remains intact in people with Parkinson’s Disease. There is also no relationship, at least in this discriminatory task, between active force perception and the severity of the clinical motor symptoms. Though the range of forces tested in this experiment were selected carefully, this study did not test the cohorts under different force conditions. Future experiments could test the same cohorts at different force thresholds, with comparative forces both above and below the reference force. By adding these conditions, a better description of if and how force perception may be altered in PD could be developed.

Further experiments should include larger cohorts and compare discriminatory active force tasks to other active force tasks, such as detection of changes in a force field as one moves through it to observe if the results of the discriminatory task are related to similarly affected efferent copies.
Due to the results of global reduced force output in people with PD with freezing of gait (FOG) presented in Chapter 2, it would also be interesting to explore how perception of external forces is affected in people with FOG, and how this compares to people without FOG. Evidence of this as a possibility is supported by the results of a muscle vibration study that did not find deficits in people with PD compared to healthy age-matched controls but did find deficits in people with PD with FOG [31].

Finally, only 3 participants in this study experienced dyskinesias that were not severe enough to interfere with the experiment to observe how this side effect of levodopa medication may impact active force perception. With a larger cohort, it may be interesting to explore how different levels of dyskinesia may impact force perception as well.

4.6 Limitations

One possible limitation of the device used in the experiment could be the range of output forces. All participants in this study could perceive the differences between the reference and comparative forces when the comparative force was at the higher range of forces used in the experiment (i.e., near or at 7.5 N). Therefore, increasing the upper threshold of the range of the haptic device would not have altered the results of this experiment. However, we must also consider the lower range of values that the comparative force could take (i.e., at or near 4.8 N). Due to the limitations of accuracy of the device, a lower limit of 4.8 N for the comparative force was selected such that the smallest difference of force between the reference and comparative forces was 0.3 N. Three participants in the Control cohort and 6 participants in the PD cohort (6 in the OFF state and 2 in the ON state) could obtain this lower threshold 6 times in a row in either 1 or both of their arms, and therefore ending the experiment early. This lower threshold corresponds to a WF of 0.067 (the difference between reference and comparative forces of 0.3 N, divided by the reference force of 4.5 N). Similar experiments – allowing for free interaction with a force – found the average WF in healthy people to be about 0.15 at the point where participants, on average, can correctly select between two stimuli 50% of the time. Given that sensory perception decreases with age, one would expect the average WF of an older cohort to perform as well or worse than a younger cohort in a similar experiment. However, the performance of the control and PD-off cohorts was similar to that of the
healthy controls in the experiments. It must be noted that the average WFs of the cohorts all followed normal distributions as well. Though the lower threshold capability of the device was not low enough for some, this did not result in a positive skew in either cohort. Therefore, it was not expected that even if the accuracy of the device was improved – and therefore allowed for a smaller difference than 0.3 N between the reference and comparative forces – that this would result in a noticeable change in the results of the experiment.

Secondly, typical fixed-choice staircases often repeat the experiment several times, and then take the average of each of the calculated WF to estimate the actual WF of each participant [32]. However, this was not considered viable due to the constraints of testing people with PD in the ON-state. The current testing of two hands and performing the UPDRS Part III motor test usually took on average 0.5 hours in total. Even testing once more in each hand would remove each PD participant from the ideal window of levodopa testing. The nature of repetitively testing active perception of higher forces also had potential to induce fatigue, which is known to affect kinesthesia even in healthy individuals [33]. Since people with PD may move slower or take more time to perform each movement in the OFF-state in addition to a central sense of fatigue [34], this could have artificially inflated the WF of the PD cohort while in the OFF-state.

The cohorts selected for this study were at most in a Hoehn and Yahr stage of 2, and therefore more severe states of the disease were not tested. It is possible that individuals with a more severe state of the disease may have altered kinesthetic sense as discussed by Torres et al. in [35]. Considering these challenges, the potential impacts of repetitive testing and fatigue offer an interesting avenue for future exploration of this work.

4.7 References


Chapter 5

5 Concluding Remarks and Future Work

5.1 Concluding Remarks

This thesis explored changes in force control in people with Parkinson's Disease (PD) using interactive haptic tools. Chapter 1 served to break down and summarize relevant studies related to the concept of force control in appendicular motion and focussed on two components: motor output of the system, and interpretation of kinesthetic information. The output of force control was further divided into 3 subcomponents: control of force magnitude, visuomotor control, and motion timing. Understanding of force control was observed in people with PD and those who experience the phenomenon of FOG. Analysis of kinesthesia studied the influence of PD and levodopa therapy, and observations of kinesthesia were restricted to the upper limb. The goal of this thesis was to adapt and implement haptics-enabled robotic tools in the exploration of force control changes caused by PD and the influence of levodopa therapy. The work presented in this thesis highlights the usefulness and possibilities of haptics-enabled tools in understanding how force control is altered in PD and sets the basis for future work and need to explore motor changes in people with PD with FOG.

Chapter 2 explored changes in force control experienced by people with PD and levodopa-unresponsive FOG while participants were on levodopa therapy using a dual upper- and lower-limb mobile haptics-based robot. The results of the pilot study found that people with levodopa-unresponsive FOG may have deficits of force and timing control present in both the upper and lower limbs rather than one restricted to the lower limbs or in gait. These deficits may be related to freezing episodes and difficulties in gait initiation in people with levodopa-unresponsive FOG. However, there may remain an ability to increase and decrease force output according to the resistive conditions of the task. It is possible that in addition to neuronal loss in pathophysiology found in people with freezing of gait, dysfunction of the basal ganglia may play a larger role in FOG symptoms than previously thought.
Chapter 3 described an artificial neural network (NN) based modification of a commercial haptic device to output accurate and repeatable forces. The modified device was implemented in Chapter 4 to study the influence of PD and levodopa therapy on perception of force in a discriminatory task in the upper limbs. This small cohort study did not find differences between PD and control cohorts in force discrimination within the selected force range, nor improvements or deficits in kinesthesia due to levodopa therapy. While some studies support this finding, most point to a deficit in kinesthesia in PD; therefore, similar experiments should be performed with adjustments, suggested in the next section.

5.2 Future Work

Some potential improvements for the modification of the Novint Falcon (Falcon) haptic device described in Chapter 3 include more subjects from which to collect data to further increase the variety of data on which to train the NN. It is possible that increasing the size of the workspace for which the data was collected could also improve the accuracy and applicability of the device based on NN training. Finally, more adaptations could be made to the Falcon to allow for more accurate measurements of positions and velocities.

Both cohort studies in this work were completed with small sample sizes. Future work should include a larger number of individuals in each cohort. In the experiment presented in Chapter 2, there were 3 cohorts: controls, people with PD, and people with PD with levodopa-unresponsive FOG. Future work should consider introducing a fourth cohort consisting of people with levodopa-responsive FOG. In addition to this, the tests were performed while PD participants were on their levodopa medication. Work testing the 4 cohorts in addition to levodopa testing could help in understanding changes in FOG and the influence of levodopa medication and possibly on the unresponsiveness of FOG to levodopa therapy. More effective tools to test kinesthesia in the lower limbs are needed. Set-up of these experiments should include standardized subjective and objective testing metrics in gait (such as the FOG-Q to assess how each individual feels FOG episodes affect their quality of life, and measurement of gait parameters using cameras and gait carpets) to enable comparison of trends between changes in gait and force control in the upper and lower limbs. Experiments similar to those presented in Chapter 4 could be developed to explore potential changes in kinesthesia in people with FOG, as suggested for Chapter 2 to
study cohorts with both levodopa-responsive and unresponsive FOG. Tests of cognitive and executive capacity, in addition to tests of strength in the upper and lower limbs to control for potential muscle weakness, could be performed as part of a battery of tests. Ideally, both types of experiments should be performed on the same individuals within each cohort so that reliable and meaningful relationships between force control and kinesthesia may be drawn, providing further insight into the phenomena of FOG, its responsiveness to levodopa therapy, and the nature of force control. This would help to enhance our understanding of the nature of PD and how it impacts perception and movement, and ultimately allow for better informed treatment options and directions of future rehabilitative care.

Haptic tools provide researchers with the ability to generate well-controlled, interactive environments that can accurately measure and compare control system changes in people, and need not be restricted to PD. They present an opportunity to compare small changes in performance across people of different age ranges, abilities, and neurological conditions. Software virtual environments and their interactive nature also lend to the development of engaging experiments, potentially leading to a better overall experience for participants. In addition to cohort studies, the robotic haptic device used in Chapter 2 (based on the results of the experiment) presents an interesting opportunity to study the potential effects of rehabilitation of force in severe cases of PD, such as those with levodopa-unresponsive FOG. Future studies could also investigate its in-home use (given its mobile nature) for longitudinal studies and examination of its short- and long-term impacts on force control and gait.
Appendices

Appendix A: Ethics Approval (Participants with PD with FOG)

Date: 11 August 2022
To: Mandar Jog
Project ID: 107451
Review Reference: 2022-107451-69723
Study Title: Thoricoc dorsal spinal cord stimulation for the treatment of gait and balance impairments in Parkinson disease

Application Type: HSREB Amendment Form
Review Type: Delegated
Meeting Report Date: 23/Aug/2022
Date Approval Issued: 11/Aug/2022 11:32
REB Approval Expiry Date: 22/Jan/2023

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:

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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 Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on HarmonisationGood 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 IRB00000940.

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

Electronically signed by:

Ms. Nicola Geoghegan-Morphet, Ethics Officer on behalf of Dr. Philip Jones, HSREB Chair, 11/Aug/2022 11:32

Reason: I am approving this document.

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Appendix B: Ethics Approval (Participants with PD and Controls)

Western Research

Date: 6 May 2022
To: Mandar Jog
Project ID: 108252

Study Title: Observation of Movement Disorders using Kinematics and Electrophysiology
Application Type: HSREB Amendment Form
Review Type: Delegated
Full Board Reporting Date: 24/May/2022
Date Approval Issued: 06/May/2022 14:28
REB Approval Expiry Date: 27/Sep/2022

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.

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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 000000940.

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

Sincerely,
Ms. Nicola Goghegan-Morphet, Ethics Officer on behalf of Dr. Philip Jones, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Appendix C: Letter of Information and Consent (LOI&C) for Participants with PD with FOG

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.

SCS LOI version 5.0 (October 18, 2019)
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 administered and will take 30 minutes to complete:
  o 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.
  o 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”
  o 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.
  o Parkinson’s disease Questionnaire (PDQ)-8
    ▪ Self-administered questionnaire rating aspects of functionality and well-being consisting of 8 items.
  o MATTIS Dementia rating scale
    ▪ Assesses overall level of cognitive functioning.

Visit 2: One-four weeks pre-operation:

  o 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.

  o 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.

  o 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 allotted 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.
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 at 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 behavioral 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:

SCS-LOI version 5.0 (October 18, 2019)
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 rare, 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 be 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 [phone number]. 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 [phone number] or access the online form at: [https://apps.lhsc.on.ca/?q=forms/patient-experience-contact-form](https://apps.lhsc.on.ca/?q=forms/patient-experience-contact-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.

<table>
<thead>
<tr>
<th>Signature of Research Participant</th>
<th>Printed Name</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Signature of Investigator</td>
<td>Printed Name</td>
<td>Date</td>
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<tr>
<td>*not present during consent</td>
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<tr>
<td>Signature of Person Obtaining Consent</td>
<td>Printed Name</td>
<td>Date</td>
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</table>

SCS-LOI version 5.0 (October 18, 2019)
Appendix D: LOI&C for Participants with PD and Controls

Letter of Information and Consent

Study Title: Observation of Movement Disorders Using Kinematics and Electrophysiology
Subtitle: Participants from Movement Disorders Clinic LOI

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

Daytime Phone Number: [Redacted]

Introduction

We are inviting you to voluntarily participate in our research project designed to characterize the differences between movement disorders (MD) using biomechanics/kinematics/body motions and unique brain activity hallmarks of MDs using electrophysiological assessments. Multiple movement disorders have overlapping symptoms, which may have unique motor characteristics and electrophysiological hallmarks that we can measure using kinematic motion sensors or by electrophysiological recordings of brain activity, respectively.

The study objectives include the use of motion sensors and/or electrophysiological recordings: 1) the study the composition of, and characterize, different motor symptoms across several movement disorders using motion sensors, 2) study the effect of a standard of care intervention you are already or going to begin taking as prescribed by your physician by kinematics and electrophysiology recordings, 3) if symptoms change over a 6-month or 12-month period, a repeat of assessments may be required, which will be recommended during your clinical follow-ups by your physician.

Nature of the research project and tasks involved

We are looking to recruit 500 persons with bothersome motor symptoms from the London Health Sciences Centre (LHSC).

We are inviting you to participate in this study as we believe that the use of a kinematic device (multiple motion sensors paired with analysis software developed by our laboratory) to characterize your biomechanics or the use of an electrophysiological assessment to better understand any electrophysiological hallmarks will help us better understand the differences between movement disorders with overlapping motor symptoms. The use of kinematics was based from our previous studies involving motor assessments of Parkinson disease, Essential Tremor, and Cervical Dystonia patients. The use of electrophysiological assessments is well established in the assessment or monitoring of movement disorders, you may not need to complete every assessment outlined in this LOI and identification of which type of assessment will be explained to you prior to your study consent. If the characterization of your motor symptoms is required, then the use of kinematic
assessments will be conducted at a one-time visit. Kinematics and electrophysiological assessments allow us to better understand how your symptoms are affected by your current medications and may take up to two study visits to complete. If your symptoms change over a 6-month or 12-month time-period as noted by your physician, we would like to repeat the study assessments; thus a maximum total 4 visits would take place. You will not have to change your medications in any way for this study. Participation in this study will not affect the routine management of your movement disorder. Scheduling of your routine clinic visits will not change.

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.

**Study Eligibility**

You are eligible for the study based on the following: 1) a diagnosis of some movement disorder by your neurologist, and 2) you have bothersome motor symptoms resulting from your movement disorder.

**Study Outline**

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

At your study visit you may be asked to complete the following tasks, which are described in detail below:

1. Complete a kinematic assessment of your motor symptoms
2. Complete an assessment of the severity of your motor symptoms
3. Complete an electrophysiological assessment that may include: electroencephalogram (EEG), transcranial magnetic stimulation (TMS), or electromyography (EMG) protocols
4. Complete questionnaires regarding your quality of life
5. Complete a cognitive assessment
6. Complete proprioception tasks. Proprioception means how you perceive or how aware you are to the position and movement of your body.
7. Eye tracking assessment

**Kinematic Assessments**

“Kinematics” is the use of motion sensors to capture body movements.

During upper limb assessments, for ease of access and placement of motion sensors, you will be asked to wear a loose fitting shirt or may need to change into a hospital gown (top only you will not have to take off your pants/skirt). You will have sensors placed (using tape that is safe for your skin) onto your arms and hands in order to measure your upper limb movements. For full-body assessments you may be asked to wear motion-capture suit (jacket and pants) over your clothes, which contains a number of sensors throughout. You will then be asked to perform several tasks such as resting your arms in your lap, extending your arms out in front of you, holding a cup, etc. so that your movements can be captured across a variety of postures and activities. You may also be asked to walk around a 25-meter oval walkway at different paces for assessment of your gait biomechanics. During head and neck
assessments, you will be fitted with a headband containing sensors and will have sensors placed on your shoulders and the back of the neck. Only the kinematic tasks relevant to your movement disorder will be used in the assessment.

Clinical Scales and Questionnaires:

During each visit a researcher may ask you to complete clinical scales or questionnaires to assess your disease severity, quality of life, and cognitive ability. Only the scales and questionnaires relevant to your movement disorder will be used in the assessment.

Medical History Review

If your referring physician deems it appropriate for the objectives of the study, researchers may review your medical for information relevant to the motor symptoms being studied (for example: family history, prescription or recreational drug use history, MRI scans etc.).

Electrophysiological assessment:
An electroencephalogram (EEG) assessment while you are seated, resting with eyes closed for 5 minutes will be conducted when you are either before and/or following a treatment. This will approximately take 30 minutes. 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.

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 and can be viewed using an electromyogram (EMG). EMG can be used to study muscular activity, such as tremor, during different positions (e.g. seated versus standing). This can be used to better understand your motor symptoms.

The proprioception, target choice reaching task, will be conducted using either the pictured device (figure below, left) or the KINARM device (figure below, center). Using the toggle on the device, you can move the cursor towards different targets that will be presented on the screen. You will be asked to put your hand on a device called the “Falcon” (pictured below, right) where different pressures will be applied, and you will be asked to determine which is stronger. 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.
**Eye tracking** assessment will be conducted using the pictured set-up below. You are seated and dots or lines move across the screen, and you must follow these targets using your eyes. The assessment takes approximately 10 minutes and breaks can be taken if you feel fatigued.

![Eye tracking setup](image)

**Study Timeline**

This study may require you to attend one assessment visit. Your referring physician may want to assess you before and after a treatment, and thus two visits may be appropriate. If your referring physician believes that your motor symptoms will change drastically in the next 6 months, you may be asked to attend a follow-up visit to characterize these changes.

**Potential Benefits**

You will likely not experience any direct benefit to participating in this study. However, the information we gain by assessing your motor symptoms could improve the understanding of your movement disorder.

**Risks and Discomforts**

If you choose to participate you will need to take approximately 1-2 hours out of your day to attend the assessment at University Hospital. Some participants may experience minor emotional distress while completing the scales and questionnaires. Scales will be conducted by an experienced researcher trained in administering items in a sensitive manner. Participants will be allowed rest periods as necessary during the scales and questionnaires, as well as throughout the kinematic assessments, in order to facilitate comfort.

Some study participants may be uncomfortable with being videotaped. However, video recording will be optional and the research team is only recording from neck down whenever possible in an attempt to preserve participant anonymity.

Some study participants may experience fatigue with the laboratory walking 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 and uploaded wirelessly (via wifi),
so there are no intrusive wires in the walking path. Participants may be fatigued from doing the Breaks will be provided between tasks as necessary.

*Risks associated with TMS:*
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.

**Data Collection, Use of information, and Confidentiality**

The data collected from you for the study will be kept electronically and securely using the LHSC computer network. No information identifying you will be sent outside of the hospital. The study doctor and staff will keep all study data in a secure and confidential for 15 years.

Information and data obtained in the study will not be labeled with any of your personal information that will be collected (name, initials, partial date of birth, medical record number, etc.). To help ensure that your information is kept confidential, you will be assigned a unique participant number, a number special to you for this study. 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. Only research study staff will be able to access this number and link it with your personal information. This list will be destroyed 15 years following completion of the study.

Representatives from University of Western Ontario Health Sciences Research Ethics Board and Lawson’s Quality Assurance and Education Program may have access to study related information in order to ensure the study is following the proper laws and regulations. De-identified information (all identity will be blacked out & not revealed) from your health records may be copied and used to confirm the study procedures. Your records will be kept as private as possible under the law. Total privacy cannot be promised. By signing this consent form, you are allowing someone to review your records.

De-identified electrophysiology data will be shared with the Department for Experimental Medicine Science, Faculty of Medicine, Lund University in Lund, Sweden. This center are experts in the analysis of EEG data.

**Participation Discontinuation**

You may be asked to leave the study if you do not follow directions or if the study shows signs of causing medical harm to you. If you are asked to leave the study, the reasons will be discussed with you.
Monetary compensation
You will not be paid for participation in this study.

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

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

Alternatives to study participation
The alternative to study participation is to continue on your current course of medication and/or motor symptom management with your current neurologist.

Persons to Contact with Questions
For more information about this research study you can contact the research lab at [Contact Information]. 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 at [Contact Information]. If you have questions about the conduct of the study or your rights as a research participant, you may call the LHSC Patient Relations Office at [Contact Information].

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

Observation of Movement Disorders Using Kinematics and Electrophysiology

STUDY DOCTOR

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

I consent to having my kinematic assessments videotaped for the sole purpose of ensuring data collection accuracy (optional): □ Yes □ No

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.

<table>
<thead>
<tr>
<th>Signature of Research Participant</th>
<th>Printed Name</th>
<th>Date</th>
</tr>
</thead>
</table>

| Signature of Investigator *not present during consent | Printed Name | Date |

| Signature of Person Obtaining Consent | Printed Name | Date |

108252 - LOI version 9.0 (06-May-2022)
Appendix E: UPDRS Part III: Motor Examination

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

- **ON** is the typical functional state when patients are receiving medication and have a good response.
- **OFF** is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see." Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "UR" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs it in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter.

For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

---

3a Is the patient on medication for treating the symptoms of Parkinson's disease? □ No □ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

- □ ON: On is the typical functional state when patients are receiving medication and have a good response.
- □ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on levodopa? □ No □ Yes

3.C1 If yes, minutes since last levodopa dose: ___________
3.1 SPEECH

Instructions to examiner: Listen to the patient’s free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient’s work, hobbies, exercise, or how he got to the doctor’s office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables), and tachypnea (rapid speech, running syllables together).

0: Normal: No speech problems.
1: Slight: Loss of modulation, diction, or volume, but still all words easy to understand.
2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow.
3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood.
4: Severe: Most speech is difficult to understand or unintelligible.

3.2 FACIAL EXPRESSION

Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling, and parting of lips.

0: Normal: Normal facial expression.
1: Slight: Minimal masked facies manifested only by decreased frequency of blinking.
2: Mild: In addition to decreased eye-blink frequency, masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted.
3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest.
4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.
### 3.3 RIGIDITY

**Instructions to examiner:** Rrigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Normal: No rigidity.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Rigidity only detected with activation maneuver.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.</td>
</tr>
</tbody>
</table>

### 3.4 FINGER TAPPING

**Instructions to examiner:** Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Normal: No problems.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.</td>
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3.5 HAND MOVEMENTS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.

3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down, and then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st supination-pronation sequence.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.
3.7 TOE TAPPING

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

0: Normal: No problems.
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.
2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.
3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the 1st tap.
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

3.8 LEG AGILITY

Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.
2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.
3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the 1st tap.
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.
### 3.9 ARISING FROM CHAIR

**Instructions to examiner:** Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt up to a maximum of two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:</td>
<td>Normal: No problems. Able to arise quickly without hesitation.</td>
</tr>
<tr>
<td>1:</td>
<td>Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair.</td>
</tr>
<tr>
<td>2:</td>
<td>Mild: Pushes self up from the arms of the chair without difficulty.</td>
</tr>
<tr>
<td>3:</td>
<td>Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using the arms of the chair, but can get up without help.</td>
</tr>
<tr>
<td>4:</td>
<td>Severe: Unable to arise without help.</td>
</tr>
</tbody>
</table>

### 3.10 GAIT

**Instructions to examiner:** Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for “freezing of gait” (next item 3.11) while patient is walking. Observe posture for item 3.13.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:</td>
<td>Normal: No problems.</td>
</tr>
<tr>
<td>1:</td>
<td>Slight: Independent walking with minor gait impairment.</td>
</tr>
<tr>
<td>2:</td>
<td>Mild: Independent walking but with substantial gait impairment.</td>
</tr>
<tr>
<td>3:</td>
<td>Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person.</td>
</tr>
<tr>
<td>4:</td>
<td>Severe: Cannot walk at all or only with another person's assistance.</td>
</tr>
</tbody>
</table>
3.11 FREEZING OF GAIT

Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment.

0: Normal: No freezing.
1: Slight: Freezes on starting, turning, or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking.
2: Mild: Freezes on starting, turning, or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking.
3: Moderate: Freezes once during straight walking.
4: Severe: Freezes multiple times during straight walking.

3.12 POSTURAL STABILITY

Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient’s limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13.

0: Normal: No problems. Recovers with one or two steps.
1: Slight: 3-5 steps, but subject recovers unaided.
2: Mild: More than 5 steps, but subject recovers unaided.
3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner.
4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.
### 3.13 POSTURE

**Instructions to examiner:** Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No problems.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Not quite erect, but posture could be normal for older person.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Stooped posture, scoliosis or leaning to one side that cannot be corrected voluntarily to a normal posture by the patient.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Flexion, scoliosis or leaning with extreme abnormality of posture.</td>
</tr>
</tbody>
</table>

### 3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA)

**Instructions to examiner:** This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No problems.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Slight global slowness and poverty of spontaneous movements.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Mild global slowness and poverty of spontaneous movements.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Moderate global slowness and poverty of spontaneous movements.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Severe global slowness and poverty of spontaneous movements.</td>
</tr>
</tbody>
</table>

### 3.15 POSTURAL TREMOR OF THE HANDS

**Instructions to examiner:** All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No tremor.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Tremor is present but less than 1 cm in amplitude.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Tremor is at least 1 but less than 3 cm in amplitude.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Tremor is at least 3 but less than 10 cm in amplitude.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Tremor is at least 10 cm in amplitude.</td>
</tr>
</tbody>
</table>
### 3.16 KINETIC TREMOR OF THE HANDS

**Instructions to examiner:** This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner’s finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No tremor.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Tremor is present but less than 1 cm in amplitude.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Tremor is at least 1 but less than 3 cm in amplitude.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Tremor is at least 3 but less than 10 cm in amplitude.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Tremor is at least 10 cm in amplitude.</td>
</tr>
</tbody>
</table>

### 3.17 REST TREMOR AMPLITUDE

**Instructions to examiner:** This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking, and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor.

As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating.

**Extremity ratings**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No tremor.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>&lt; 1 cm in maximal amplitude.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>≥ 1 cm but &lt; 3 cm in maximal amplitude.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>≥ 3 cm but &lt; 10 cm in maximal amplitude.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>≥ 10 cm in maximal amplitude.</td>
</tr>
</tbody>
</table>

**Lip/Jaw ratings**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No tremor.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>&lt; 1 cm in maximal amplitude.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>≥ 1 cm but &lt; 2 cm in maximal amplitude.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>≥ 2 cm but &lt; 3 cm in maximal amplitude.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>≥ 3 cm in maximal amplitude.</td>
</tr>
</tbody>
</table>
### 3.18 Constancy of Rest Tremor

**Instructions to examiner:** This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variably at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

- **0:** Normal: No tremor.
- **1:** Slight: Tremor at rest is present ≤ 25% of the entire examination period.
- **2:** Mild: Tremor at rest is present 26-50% of the entire examination period.
- **3:** Moderate: Tremor at rest is present 51-75% of the entire examination period.
- **4:** Severe: Tremor at rest is present > 75% of the entire examination period.

**Score**

### Dystonia Impact on Part III Ratings

A. Were dystonias (chorea or dystonia) present during examination?  
   - [ ] No  
   - [ ] Yes

B. If yes, did these movements interfere with your ratings?  
   - [ ] No  
   - [ ] Yes

### Hoehn and Yahr Stage

- **0:** Asymptomatic.
- **1:** Unilateral involvement only.
- **2:** Bilateral involvement without impairment of balance.
- **3:** Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.
- **4:** Severe disability; still able to walk or stand unassisted.
- **5:** Wheelchair bound or bedridden unless aided.
Appendix F: Montreal Cognitive Assessment
# Curriculum Vitae

<table>
<thead>
<tr>
<th>Name:</th>
<th>Caroline Aitken</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-secondary Education and Degrees:</strong></td>
<td>The University of Western Ontario London, Ontario, Canada 2015-2020 B.E.Sc.</td>
</tr>
<tr>
<td><strong>Honours and Awards:</strong></td>
<td>Dean’s Honour List The University of Western Ontario 2015-2016, 2017-2020 The Western Scholarship of Excellence The University of Western Ontario 2015</td>
</tr>
<tr>
<td><strong>Conference Presentations:</strong></td>
<td>44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society Glasgow, Scotland 2023</td>
</tr>
<tr>
<td><strong>Related Work Experience:</strong></td>
<td>Teaching Assistant The University of Western Ontario 2021-2022</td>
</tr>
</tbody>
</table>