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Investigation of Visual Perceptions in Parkinson's Disease and the Development of Disease Monitoring Software

Matthew Bernardinis, *The University of Western Ontario*

Supervisor: Patel, Rajni V., *The University of Western Ontario*
Co-Supervisor: Jog, Mandar S., *The University of Western Ontario*
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Abstract

Non-motor Parkinson's Disease (PD) symptoms are substantial factors of PD arising throughout disease stages, yet their diagnosis and monitoring remain a challenge. Sensory abnormalities in PD occur across sensory systems and disease stages, contributing to disease-related impairments. However, the extent of symptoms is unknown, with inadequate monitoring and treatment options furthering disease management difficulties. The current work studies movement-independent visual perceptions of time, displacement and velocity in PD patients across disease stages using levodopa, deep brain stimulation (DBS), or no PD therapy. Perceptual tasks were conducted using a computer-generated graphical device designed with a focus on simplicity and flexibility. Perception of all tested visual modalities was impaired in PD (often extending to early PD stages), with negligible levodopa and DBS induced improvement. The observations help explain visuospatial, visual recognition and timing deficits occurring in PD while providing potential disease markers, and validates the graphical tool's usefulness for disease diagnosis and monitoring.

Keywords

Parkinson’s disease, non-motor Parkinson’s symptoms, visual perception, temporal perception, velocity perception, displacement perception, computer-generated graphical tool, levodopa, deep brain stimulation, difference threshold, Weber’s Law

Lay Summary

Parkinson's disease (PD) is one of the most common movement disorders in Canada, affecting over 100, 000 Canadian residents, leading to an economic burden of over $120 million a year. Although the movement-related symptoms are the most commonly known, non-motor symptoms are also widely present in the disease throughout all stages, and are commonly reported to be the more significant contributors to deficits in patient quality of life. The primary focus of treatment however is still directed at the motor symptoms, with available therapies and diagnostic procedures primarily targeting these motor symptoms. Furthermore, the extent of non-motor symptoms has yet to be discovered. Due to the disease symptoms presenting themselves differently on an individual basis, and numerous non-motor symptoms arising early in the disease (sometimes before motor symptoms) optimized patient treatment does not occur in many cases. Based on the above, this thesis aims to study select visual non-motor phenomena, to examine their potential dysfunction in PD, as well as their potential use for disease monitoring and diagnostic procedures. This thesis analyzes the visual perception of time, displacement and velocity in individuals with PD, the effect of common pharmaceutical (levodopa) and non-pharmaceutical (deep brain stimulation) therapies on these perceptions, and the use of a computer-generated graphical tool to analyze the said perceptions. It was found that all of the studied perceptions were abnormal in PD, even at the early stages of the disease. Furthermore, the tested therapies did not appear to improve these perceptions, with levodopa potentially having a detrimental effect on temporal and velocity perceptions. The use of the graphical software was validated throughout the studies and was shown to be a potential disease monitoring and diagnostic tool that can be easily implemented in clinical and non-clinical settings to aid disease management. Furthermore, the findings regarding the studied perceptual dysfunction occurring independently of movement provides further insight into non-motor PD abnormalities, while helping to explain the phenomena of timing, spatial, and object recognition deficits occurring in PD.

Co-Authorship Statement (where applicable)

Chapters 2, 3, and 4 in the thesis contain the text, figures, and tables from manuscripts that have been published, are under review for publication or are intended to be published. Apart from the author of the current thesis, Seyed Farokh Ataszar (S.F.A.), Mandar S, Jog (M.S.J.) and Rajni V. Patel (R.V.P.) were the other authors on these papers. S.F.A. (postdoctoral fellow supervised by R.V.P.) was a mentor and advisor and contributed to the development of the idea, design of the research, preparation of the setup, and analysis of the data and results. R.V.P. proposed the research problem, contributed to the development of the research plan, and the preparation of the papers. M.S.J. was the clinical lead of this project. All research activities of this paper were supervised by R.V.P. and M.S.J who are joint supervisors of the current thesis research. All funding for this work was provided from grants awarded to R.V.P. All authors reviewed the manuscripts of the papers that are included in this thesis.

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List of Abbreviations

BG— Basal Ganglia

CSTC—Cortico-Striatal-Thalamo-Cortical

DBS—Deep Brain Stimulation

DL—Difference Threshold

fMRI—Functional Magnetic Resonance Imaging

FOG—Freezing of Gait

GABA—Gamma-aminobutyric acid

GPe—Globus Pallidus pars Externa

GPi—Globus Pallidus pars Interna

IQR—Interquartile Range

levodopa—L-dihydroxyphhenylalanine

LT—Lower Threshold

MoCA—Montreal Cognitive Assessment

MRI—Magnetic Resonance Imaging

PD—Parkinson's Disease

PD-D—Parkinson's Disease Dementia

PD-VH—Parkinson's Disease related Visual Hallucinations

PSE—Point of Subjective Equality

SNc—Substantia Nigra pars Compacta

SNr—Substantia Nigra pars Reticulata

STN—Subthalamic Nucleus

UPDRS—Unified Parkinson's Disease Rating Scale

UT—Upper Threshold

WF—Weber's Fraction

Preface

Tell me and I forget. Teach me and I remember. Involve me and I learn.

- Benjamin Franklin (Traditional Chinese proverb)

Chapter 1

1 Introduction

This chapter will provide an overview of the Parkinson's Disease (PD) symptoms, with a focus on non-motor abnormalities occurring in PD. A specific focus will be on visual perceptions of time, displacement and velocity, reviewing what is currently known regarding the effect of PD on these symptoms. Furthermore, this section will provide a brief outline of levodopa (L-dihydroxyphenylalanine) and deep brain stimulation (DBS) therapies, and their effect on non-motor symptoms of PD.

1.1 Background

PD is the second most common neurodegenerative disorder in Canada, affecting over 100,000 residents and leading to an annual economic burden over $120 million [1]. The incidence of PD in Canada is growing (projected to affect 164,000 individuals by 2031) [1], the lack of prevention methods and long-term management treatments emphasize the significance of this neurological puzzle for Canadians and the country as a whole [2]. PD has been considered a movement abnormality since its 19th century description by James Parkinson, in which he specified motor symptoms such as bradykinesia, resting tremor, muscular rigidity and impairments of posture and gait [3]. However, Dr. Parkinson also noted that non-motor abnormalities including sensory, mood, autonomic and sleep disorders commonly affect those with PD [4]. It was later determined that many major PD symptoms are rooted in the death of dopaminergic neurons in the substantia nigra pars compacta (SNc), leading to abnormal basal ganglia (BG) functioning [5]. Although a greater focus has been given to motor symptoms of the disease in the past, non-motor symptoms substantially contribute to decreased quality of life (often to a greater extent than motor symptoms) [6–8], increased economic burden [9, 10] and increasing the rate of patient institutionalization [11].

Current approaches to PD treatment focus on alleviating motor symptoms, appearing to be inadequate for treating many non-motor disease symptoms [12]. Levodopa, a first line pharmaceutical PD therapy, appears to have a variable effect on non-motor

symptoms, though beneficial effects are often seen with regard to motor impairments [4]. Subthalamic DBS, a promising late-stage PD treatment involving electrical stimulation of the BG generally elicits similar therapeutic effects as levodopa; however, its effect on non-motor symptoms are still relatively unknown [13]. Although the burden of the non-motor symptoms of PD are substantial there is a current lack of adequate treatment methods. However, there is growing evidence that many non-motor symptoms arise before the development of motor symptoms—sometimes by years [14]—making them promising targets for early diagnosis of PD or helping to identify at risk populations. We have conducted perceptual analysis of three visual modalities (time, displacement, and velocity), and designed a computer-generated graphical tool to assess individual ability for these perceptions. It is our hope that the work in this thesis will lead to the development of software capable of assessing some non-motor aspects of PD to help provide better treatment to those suffering, while also assessing certain perceptions and how they are affected by PD as well as levodopa/DBS.

1.2 Parkinson's Disease Epidemiology and Pathophysiology

This subsection will provide an outline of the scope of PD and how great of an influence it has on humanity, as well as a summary of the neural basis for PD to improve understanding of the neurophysiological concepts discussed in later chapters.

1.2.1 Prevalence and Incidence

PD is the most common movement disorder involving progressive neurodegeneration of the central nervous system [15]. There is currently no method to cure or stop the disease progression [2]. General estimations regarding PD's prevalence is 1–2 cases per 1000 people in unselected populations [16], with approximately 1% of people over the age of 60 suffering from the disease [17]. There prevalence of PD in North America is between 111–329 cases per 100 000 [18]. There is large variance seen in the reported PD incidence, which may be due to methodological differences in the diagnostic criteria and means of attaining PD status; most reports however show around 10–20 individuals per 100,000 to develop PD [15]. Early-onset development of PD (before the age of 50) is rare, only occurring in 4% of cases [19]. Studies focusing on the incidence of "at risk" populations

(individuals above 55 or 65) showed PD incidence rates to be 410–529 persons per 100,000 [24]. Age is the greatest risk factor for PD development, as the diseases incidence increases in an exponential fashion, peaking at 80 years of age [20].

1.2.2 General Pathology

The primary pathological symptom of PD is the progressive loss of dopaminergic neurons in the SNc, which project to the putamen through the dopaminergic nigrostriatal pathway [21], with past work showing an approximate 75–95% post-mortem reduction in SNc neurons in PD patients compared to age-matched controls [22]. However, degeneration of SNc neurons occurs in substantial volumes early in the disease as well [23]. The moderate to severe loss of dopaminergic neurons in the SNc likely leads to the motor symptoms typical in PD, especially those involved with reduced movement [24]. Neural degeneration occurring in PD is not contained to the SNc, with cellular degeneration occurring in regions such as the hypothalamus, amygdala, raphe nucleus, locus coeruleus, and the dorsal motor nucleus of the vagus [21].

Another hallmark of PD is Lewy pathology, where mutations to the SNCA gene lead to misfolded α-synuclein proteins [2]. The misfolded α-synuclein proteins are insoluble, causing aggregation and the formation of inclusions in the neuronal cell body or cell processes (Lewy bodies and Lewy neurites respectively) [21]. Lewy body pathology is not limited to the neurons of the brain, with protein aggregations occurring in the spinal cord and peripheral nerves as well [2, 25, 26]. It has been suggested via the Braak model that PD occurs in 6 stages involving Lewy pathology, with the peripheral nervous system being affected first (pre-motor stages 1–2), followed by caudal (brain stem, olfactory bulb) brain regions (stage 3: motor features caused by nigrostriatal dopamine deficiency), and lastly the rostral (frontal) portions of the brain being affected (stage 4 - 6: advanced disease with increased non-motor symptoms arising) [27]. Although the Braak model provides a good explanation for the development of non-motor symptoms related to cognitive impairment occurring in late stage PD [28, 29] and other non-motor abnormalities occurring at early PD stages such as olfaction and constipation [30], further studies are still needed to confirm the Braak model for other non-motor symptoms [2]. Furthermore, not all PD patients display Lewy pathology, suggesting PD neurodegeneration to be more

complex than simple Lewy pathology involving protein mutations beyond those affecting α-synuclein [31, 32].

1.2.3 Classical Model of Basal Ganglia Function in Parkinson's Disease

The BG is a group of interconnected neuronal nuclei primarily consisting of the striatum, globus pallidus pars interna (GPi), globus pallidus pars externa (GPe), substantia nigra pars reticulata (SNr), the subthalamic nucleus (STN) and the SNc [33]. The neurotransmitter released from the projections of the GPi, GPe, striatal and SNr neurons is the inhibitory gamma-aminobutyric acid (GABA), whereas the STN projections release the excitatory neurotransmitter glutamate [34]. The motor cortical areas involved in BG circuits also release excitatory neurotransmitter (glutamate) which acts on other regions of the BG [35]. Lastly, the SNc neurons release the neurotransmitter dopamine, which can have either excitatory or inhibitory effects based on the nuclei it acts on [33]. There are other neurotransmitters released in the BG, however they are of little importance to the study of BG function in PD. The BG projects to the thalamus, where further projections to the higher neural areas of the cortex occur [36]. Although the BG has great importance with motor behaviour, it is involved in many other processes ranging from timing to learning and memory [37, 38].

The classical model used to describe BG neuronal pathway loops generally refers to the BG's motor function and involves both a direct and an indirect pathway. This motor circuit best describes the BG's function and dysfunction in relation to movement disorders [35]. As can be seen in Figure 1.1, motor areas of the cortex project to dorsal parts of the striatum (i.e. the putamen) via excitatory connections using glutamate. The neurons of the striatum enact an inhibitory response on the output nuclei of the BG (primarily the GPi and SNr) via a direct and indirect pathway. Striatal neurons involved in the direct pathway project GABA directly to the GPi and SNr, inhibiting their projections (which are also inhibitory) to the thalamus (which has connections with the cortex), thus closing the loop [35]. The striatal neurons involved in the indirect pathway elicit an inhibitory response on the GPe, which in turn has inhibitory projections to the STN. The connections from the STN however are excitatory, and project to the GPi and SNr which project to the thalamus

and finally back to the cortex. Thus, the direct pathway leads to an inhibition of GPi and SNr activity, while the indirect pathway is excitatory for these nuclei [35]. The balance of activity from the direct and indirect pathways are modulated by dopamine, released by SNc neurons projecting onto the thalamus. Striatal neurons involved in the direct pathway contain dopamine D1 receptors, where-as those involved in the indirect pathway have dopamine D2 receptors, leading to striatum neuronal excitation and inhibition respectively [35]. Direct glutaminergic connections from the cortex to the striatum also exist, causing excitation of the striatum and providing further central influence on the BG loop (Fig**.** 1.1).

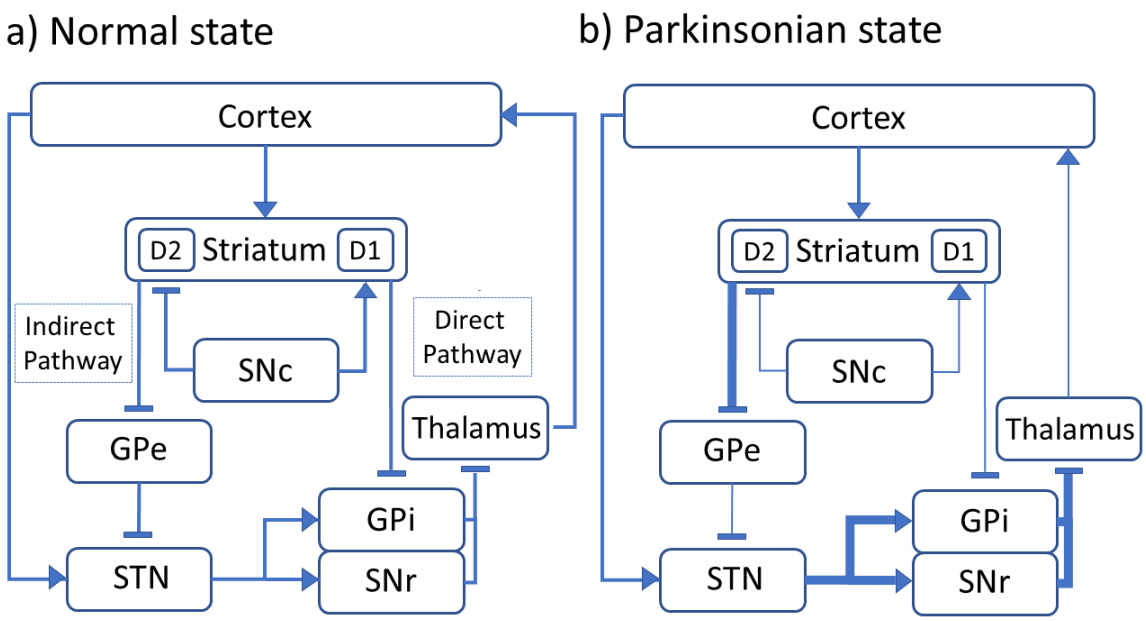

Figure 1.1: BG circuitry in normal and PD states
Summary of the current motor circuitry model of the cortico-BG-thalamus loop. Pointed arrows signify excitatory projections and blunted arrows inhibitory, with the thickness of the line being proportional to the projection's strength. **a)** represents the circuits functionality in normal states, with **b)** showing alterations that occur during PD. For both **a)** & **b)**, the direct pathway involves dopaminergic modulation (from SNc projections) of the D1 receptor to the output nuclei, with the indirect pathway involving dopaminergic modulation (from SNc projections) of the D2 receptors to the GPe. In the Parkinsonian state reduced SNc neurons lead to reduced dopaminergic attenuation of both indirect and direct pathway, causing hyperactivity of the STN and the output nuclei.

PD causes large quantities of neuronal death to occur in the SNc, leading to depleted amounts of dopamine modulating the striatum over time. This in turn leads to increased activity of the GPi and SNr, causing increased inhibition of the thalamo-cortical and brainstem motor systems (Fig. 1.1) [35]. This BG model accounts for the occurrence of bradykinesia (slow movements), akinesia (lack of movement), and difficulties in movement that occurs in PD. The use of levodopa or dopamine agonist pharmaceuticals (which act to restore neural dopamine levels) help to restore normal BG function to effectively reduce movement abnormalities occurring in PD patients. An undesirable side effect of levodopa medication however is sporadic movements known as dyskinesia. The classical BG model explains that this phenomenon is caused by excessive inhibition of striatal neurons projecting to the GPe, causing less inhibition of the GPe, then over-inhibition of the STN (reducing its activity), in turn decreasing the activity of the GPi and SNr output neurons. This leads to excessive activity in the cortical motor areas, and sporadic dyskinetic movements [35]. The outcome of DBS to the STN is also accurately described by the classical BG model. As DBS causes an ablation effect on the neural region it acts on, using it on the STN reduces this nuclei's activity which is overexcited in PD, thus helping to restore proper activity levels of the GPi and SNr and improving the movement symptoms of PD [35, 39]. DBS of the GPi works in a similar fashion as STN stimulation [36]. Though the classical model of the BG is not perfect, it does a good job of simply and elegantly providing a basis for BG function in healthy and disease states, as well as the effect of different therapies [36].

1.3 Current Parkinson's Disease Treatment

A major complication of PD treatment is that there are currently no therapy options available that significantly slow or stop the progression of PD. Due to the heterogeneous nature of the disease it appears that no given singular treatment will be capable of "curing" PD; however, it is likely that future treatments will offer individualized therapies based on the symptoms and needs of a given patient [2]. Although there are yet to be preventative treatments or cures for PD, there are still methods for treating the symptoms of PD, with the aim of improving the lives of the patients suffering from the disease.

1.3.1 Pharmacological PD Treatment

The first-line treatment for PD has classically been, and continues to be drugs which enhance intracerebral dopamine concentrations or activate dopaminergic receptors, such as levodopa (which is capable of crossing the blood-brain barrier (unlike dopamine) before being converted to dopamine), dopamine agonists, monoamine oxidase type B inhibitors and amantadine [40, 42]. Due to the current inability of PD therapies to cure or slow the progression of the disease not all patients begin treatment right away. Therapeutic intervention typically begins as soon as symptoms become problematic for the patient to attempt to improve quality of life [2]. Many movement related abnormalities arising early in the disease progression like bradykinesia and muscular rigidity are treated well with dopaminergic treatments, while monoamine oxidase type B inhibitors only cause marginal improvements, making dopaminergic drugs the primary pharmaceutical intervention when symptoms are more severe. The effect of dopaminergic treatments is more variable for disease related tremors; however anti-cholinergic drugs can be effective for this symptom [2].

Use of dopaminergic drugs (especially dopamine agonists) is however not without cost, with adverse reactions such as nausea, daytime sleepiness and excessive fluid retention in parts of the body. Furthermore, dopaminergic medications can lead to impulse control issues, seen through excessive gambling, eating, spending, and hypersexuality. The occurrence of visual hallucinations is also a common side effect of dopaminergic treatment [2]. As dopaminergic therapies generally are the most successful at alleviating motor complications in PD, and levodopa has a lower risk of side effect development, it is generally used as a first-line PD treatment [2, 41]. Levodopa use is not without fault however, as prolonged use can lead to motor complications involving motor fluctuations while using the medication (ON periods: levodopa is functioning as intended; OFF periods, levodopa is not functioning as intended, leading to severe motor symptoms) as well as sporadic "dyskinetic" movements [2]. Due to these complications, levodopa use is often refrained until necessary, or used sparingly while coupled with monoamine oxidase type B inhibitors or dopamine agonists (though the believed benefits are not yet validated) [42, 43]. Some non-dopaminergic pharmaceuticals are used to treat specific non-motor

symptoms of PD. Clozapine is commonly used to treat psychosis. However, there is a minute risk of a deadly adverse drug reaction (affecting 0.38% of patients) necessitating regular monitoring or the use of the much less effective Quetiapine [44]. Interestingly, the use of cholinesterase inhibitors by PD patients with dementia can lead to reductions in visual hallucinations and delusions, with specific selective serotonin agonists appearing to reduce psychotic symptoms without altering motor function [45, 46].

Motor fluctuations, dyskinesia and psychosis associated with long term use of dopaminergic medication signifies the progression of PD to advanced stages, further reducing patient quality of life. It is believed that motor fluctuations and dyskinesia might be caused by the late stage occurrence of pulsatile stimulation of striatal dopamine receptors, brought on by decreased striatal dopamine levels [2]. Combining previously mentioned pharmaceutical compounds with levodopa are common means to reduce the side effects of such treatments, with slow releasing dopaminergic medication currently being developed with hopes to reduce OFF motor fluctuations [40, 47]. An alternative method of achieving consistent blood-levodopa levels is to inject a concentrated levodopa-carbidopa gel into the small intestine via a portable pump, which shortened OFF duration (lengthening ON durations) in late stage PD patients without dyskinesia [47]. Treatments that elicit effects on multiple neurotransmitter systems such as amantadine and clozapine often effectively treat dyskinesia, with pharmaceuticals containing nicotinic or serotonergic properties potentially acting as treatments for drug induced motor complications as well [40, 48]. The efficacy levodopa has towards late-stage PD symptoms (motor and non-motor) is generally poor, suggesting these symptoms are caused by abnormalities in other neurotransmitter systems [48]. Accordingly, some cholinesterase inhibitors have been shown to be effective in the treatment of dementia and reductions in falls [49, 50]. As can be gathered from the above, the optimal treatment of PD using pharmacological agents is a difficult task requiring personalized therapeutic approaches.

1.3.2 Deep Brain Stimulation

The discovery of lesion-like effects occurring from high-frequency DBS led to its clinical use in treating neurological disorders through selective neural targeting (Fig. 1.2). High-frequency DBS of the STN (and less frequently the GPi) significantly improves

bradykinesia, rigidity, and tremor, decreasing the patient's average levodopa dose use by 60% [39, 51]. This reduction in levodopa use in turn reduces its undesirable side-effects, further improving patient quality of life [52]. Surgical teams use magnetic resonance

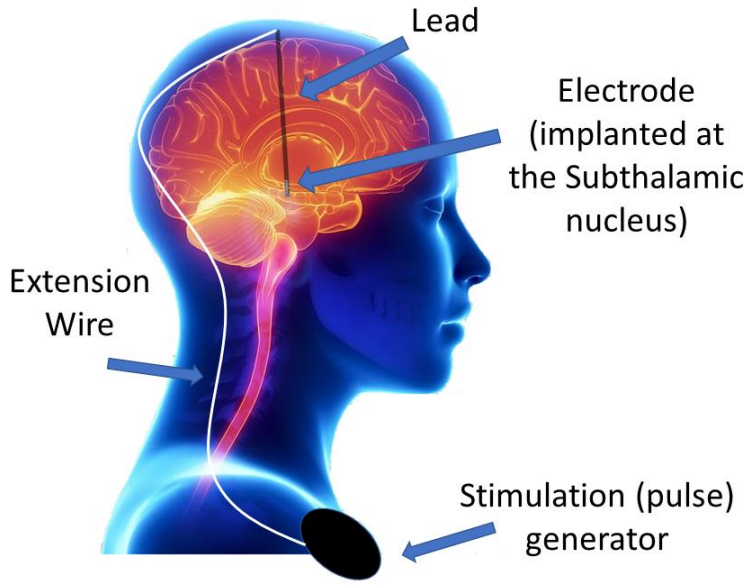

Figure 1.2: DBS of the Subthalamic Nucleus

Pictorial representation of DBS to the STN. A generator located sub-dermally at the chest generates electrical pulses which are transferred to the electrode which is in contact with the STN. The electrode is at the tip of a lead that was surgically implanted into the brain. The electrical pulses alter neuronal activity, and when controlled properly (based on location that the pulses are received, and the electrical current being used) provides therapeutic effects to the receiving individual.

imaging (MRI) localization to choose the implantation target, although errors can occur due to MRI distortion and brain expansion (due to reduced intracranial pressure from the drill hole). DBS can be administered unilaterally (to one side of the brain only) or bilaterally, depending on the patient's affected neural areas. Although it is not fully understood, it is believed DBS functions as an ablation by jamming neural messaging, inhibiting neural firing, and through inhibition of some neurotransmitters and hormones [53–55]. Patients are considered for surgery based on what stage of the disease they are at (with late stage patients being prioritized in Canada) and if the symptoms DBS successfully improves are present. DBS is not an effective treatment for cognitive deficits and dementia,

and in fact often worsens it due to the trauma occurring during surgery. Furthermore, DBS typically functions in a similar fashion to Levodopa when considering the efficacy of the therapy on an individual [56].

When comparing PD symptom severity with the DBS turned ON vs. OFF there was substantial improvements seen ON DBS, analyzed using the Unified PD Rating Scale (UPDRS) [39]. The UPDRS is made up of 4 examinations; section I– mental and cognitive changes (including mood); section II– changes in daily living activities; section III– motor symptoms; section IV– therapeutic complications, sensory systems, fluctuations and dyskinesia [39]. The UPDRS is the current gold standard diagnostic examination for the assessment of PD symptom severity and quality of life and has been validated through countless studies [39, 57]. Patients in a DBS ON, Drug OFF state had 50% and 52% increases in section II and section III UPDRS scores respectively compared to their pre-operation scores, with DBS additionally providing a 23% improvement in PD symptoms compared to ON medication patients [58, 59]. The efficacy of STN DBS experiences modest reductions over time, in contrast to levodopa's significant efficacy deterioration [60–62]. Tremor improvements were seen with up to 70% reductions, along with a 50% improvement in akinesia [63]. Reductions in dystonia, improved postural stability and gait are other positive outcomes of DBS use [39]. DBS induced neural plasticity and reduced levodopa use leads to major dyskinesia reductions (with reported reductions as great as 70%), substantially improving patient quality of life [39, 63, 64]. Motor symptoms are however only mildly improved (or not at all improved) when using DBS compared to ON medication states, however reductions in medication use leads to the previously discussed benefits, compounded by stable therapy [39]. Long-term DBS use sees PD symptoms progressing in a "natural" way, suggesting that extended use does not have side effects [65].

The use of DBS is not without risk and side effects, many of which arise from surgical complications. Although reported data differs considerably between reports, one study analyzing 526 patients saw that 3.4% of DBS implantation surgery resulted in asymptomatic hemorrhages, 4.4% in transient symptoms, and 0.6% caused permanent symptoms in patients. As 2–4% of cases have severe adverse effects from surgery (mainly

due to intracranial hemorrhage) pre-operative MRI's are critical for operation success through planning the implantation around blood vessels and non-targeted neural regions [59]. Non-permanent complications such as post-operative confusion (in around 10% of patients) can arise due to small intracranial contusion (bruising), minimal bleeding, or uncontrollable factors like prolonged open brain surgery and dopaminergic drug withdrawal [63, 66]. Although surgery related infections and complications sometimes occurring, as well as complications with the receiving of DBS, these are generally non-severe and treatable [39]. Cognitive impairments such as sadness, (hypo)mania, hilarity, impulse aggressive behaviour disorder can develop in the post-operative stage, however they tend not to persist [39]. Although apathy and depression might be associated with receiving DBS surgery, the most common chronic cognitive change is declines in word fluency [67–68]. It should be noted that these cognitive alterations were not seen in younger and non-demented patients [39]. Cognitive decline does generally occur over time (or is accelerated) with DBS-STN use, which can lead to impulsive decisions and dementia [96, 71]. There are many advantages to DBS over medication alone, and both appear to have the same occurrence of adverse events. However, it seems there is a greater occurrence of serious adverse events in those receiving DBS (though most are related to incorrect implantation or hardware failure) [58, 72]. Although there are risks involved with DBS use, they are typically not severe, and stimulation generally provides large improvements over medications for appropriate patients.

1.4 Symptoms of Parkinson's Disease

Although some symptoms are commonly attributed to PD, such as tremor, bradykinesia, and freezing of gait (FOG), the extent of abnormalities that could arise in patients with PD is vast, with no patient displaying every phenotypic trait of the disease. However, regardless of the symptoms occurring in a given PD patient, overtime these symptoms usually worsen, with many posing substantial detriment to patient health and quality of life.

1.4.1 Parkinson's Disease Motor Symptoms

Although PD was not truly defined until work conducted by James Parkinson's in the 19th century, the classic motor symptoms were described much earlier in Indian and Chinese

texts dating back to approximately 1000 BC [3]. These classical symptoms include rest tremor, muscular rigidity, bradykinesia, akinesia and postural and gait impairments [2]. Further motor symptoms such as softness of speech, impairments in handwriting and difficulties with swallowing are examples of other symptoms that could arise in the disease [3, 73]. These motor symptoms present in an asymmetrical or heterogeneous manner, leading to two major PD subtypes: tremor-dominant PD (generally with other motor symptoms being mild) and non-tremor-dominant PD (generally involving akinetic or rigid movements and impairments of gait and posture) [2]. Additionally, a hybrid or indeterminate subgroup exists where patients display several motor disease phenotypes of similar severity [2]. Interestingly, the disease subgroups might have different pathogenesis and causes, as well as the tremor-dominant subtype of the disease often progressing slower and causing less functional disability compared to non-tremor subtypes [74, 75].

As PD motor features are typically linked to dopaminergic disorder, typical first line treatment of PD involves the use of dopamine replacement agents such as levodopa. When initially used in proper doses, levodopa elicits large improvements over the classical motor symptoms of PD. However, after 5 years of levodopa use 75% of PD patients no longer receive stable and effective treatment from the medication [76]. Although from a clinical standpoint levodopa appears to slow the progression of PD motor symptoms, neuro-imaging studies show its use led to accelerated decay of nigrostriatal nerve terminals, further questioning the drugs long term use [77]. DBS of the STN has become the gold standard for advanced-stage PD surgical procedures. However, as previously discussed, DBS use is not without flaws as post-surgery complications as well as stimulation of non-targeted neural regions can have negative side effects for the patient receiving the therapy [39].

1.4.2 Parkinson' Disease Non-Motor Symptoms

Though motor abnormalities and reduced dopamine levels are typical clinical markers of PD disease, non-motor PD symptoms arise at all disease stages with some frequently arising prior to motor symptoms [78]. Unlike motor symptoms, many non-motor disease symptoms are not caused by dopamine deficiency, and instead are related to deficiencies of different neurotransmitters [78]. Accordingly, most non-motor symptoms do not

respond well to current PD treatment methods, making the management of these symptoms a major challenge in the treatment of PD. The non-motor features of PD are widespread, and (like motor features) asymmetrical, ranging over multiple classes of impairment. Here we will describe some of the non-motor features of PD, however it should be noted that this is not a comprehensive review, with notable abnormalities such as sleep disorders and autonomic dysfunction not being reported.

1.4.2.1 Neuropsychiatric Features

The neuropsychiatric features of PD can be present early in the disease's progression (at the pre-motor phase), persisting into late stages, fluctuating with the ON-OFF motor states [4]. A common neuropsychiatric feature of PD is anxiety, affecting up to 60% of patients [79]. These anxieties include general anxiety, social phobias, panic attacks, and are frequently (but not always) accompanied by depression [80, 82]. Anxiety is associated with low dopamine levels, accordingly, pharmaceutical dopamine replacement and DBS both reduce depressive symptoms, however this is not necessarily entirely due to reduced anxieties as improvements in motor functions may also play a role [82, 83]. As anxiety (and the associated depression) often arise before motor symptoms, these symptoms may encompass pathologies beyond SNc degeneration [84].

As previously mentioned, depression commonly affects individuals with PD, being clinically significant in 35% of patients. Although PD related depression is generally a milder form than depression in non-PD individuals, it is more commonly accompanied by apathy and anhedonia [85]. Although depression can arise at all stages of PD, it displays correlations with duration of disease, motor severity, motor fluctuations and dosage of dopaminergic replacement medication [86]. Depression in those with PD may be a symptom of PD pathology, reactionary to PD related disabilities, an individual phenomenon or a combination of the three, making it a complex problem and explaining why only some benefit from dopaminergic therapy [87]. Both individuals with and without PD suffering from depression show alterations to the dopaminergic, serotonergic and noradrenergic systems [88]. Although there is considerable evidence for alterations to the dopaminergic and noradrenergic systems in those with PD depression compared to PD non-depressed patients, there are confounding results regarding serotonergic function being a

factor in depression development in PD [88–101]. Anti-depressive medication targeting the noradrenergic system appears to be the most effective medication for the treatment of PD related depression [92].

Dementia and cognitive dysfunction commonly affect individuals with late stage PD; though this may be caused by natural aging processes, up to 83% of late stage PD patients suffer from some form of cognitive decline [93]. Individuals with tremor-dominant PD are less susceptible to the development dementia than individuals with non-tremor-dominant PD [94]. Late-stage PD dementia does not have a BG origin, but is related to Lewy body pathology of the cortical regions, with increased Lewy body/neurite mass correlating to increased severity of dementia [95]. Dopaminergic treatment poses little benefit and often worsens psychosis and hallucinations associated with PD dementia, however early cognitive impairments (such as impaired executive function) arising in early-stage PD appears to be dopamine dependent and may be improved by dopaminergic drugs [96–98]. Other symptoms of cognitive decline such as recognition and memory do not respond to these drugs, suggesting multiple neural pathways using different neurotransmitters are affected in PD [97]. Furthermore, too much or too little dopamine can lead to cognitive impairments, explaining why cognitive function varies throughout the stages of the disease and when using dopaminergic therapy [99].

Similarly to dementia, psychosis (generally presented through visual hallucinations and delusions) often arises in late stage PD, affecting 40% of patients [100]. MRI studies have revealed little difference in cortical structure between PD patients with and without psychosis. There are however alterations seen in the processing of visual stimuli, which may be further affected by reduced retinal dopamine levels caused by PD [101]. The use of dopamine therapies can lead to the development of psychosis in PD, and dopamine antagonists are in fact sometimes used to reduce the symptoms of psychosis [98]. Processes utilizing acetylcholine are also implicated in the development of psychosis, with anticholinergic drug use aiding in the development of psychosis due to further impairments to cortical cholinergic transmission [102].

1.4.2.2 Sensory Features

Pain and somatosensory dysfunction are common sensory abnormalities of PD, affecting up to 80% of the patient population [103, 104]. Pain in PD can present as either nociceptive (occurring at peripheral pain receptors), or neuropathic (neurologically rooted) pain, and often fluctuates based on motor fluctuations (with it being worse in the OFF state) [103, 105–107]. Nociceptive pain occurs in PD due to musculoskeletal dysfunction (for example, dysfunctions that lead to stiffness), with neurological pain having central origin and developing due to neurodegeneration [4]. Reduced levels of dopamine at the BG alter pain thresholds in PD patients, with dopaminergic medication increasing pain thresholds during ON periods [108]. However, since dopamine replacement therapy does not eliminate pain in PD there are likely other non-dopaminergic mechanisms involved in PD induced pain. As both the serotonergic raphe nuclei and the noradrenergic locus coeruleus brain regions are involved in the tuning of pain sensations and are pathologically altered in PD, they likely contribute to abnormal pain perception in PD [88]. Treatment primarily focuses on alleviating pain in the OFF periods with dopaminergic medications and other pain modulating drugs if needed. If painful dystonia is present and not aided by dopamine use then botulinum toxin injections may be used where the dystonia is present [4, 109].

One of the classical non-motor symptoms of PD is olfactory disturbances (presenting as hyposmia and anosmia), which develops in over 90% of PD patients and often arising before motor symptoms of the disease [88]. Hyposmia has often been considered a promising early biomarker of PD and is sometimes paired with other disease markers to assist in diagnosis [88]. As previously mentioned, early dysfunction of smell could be due to the spread pattern of Lewy bodies/neurites in PD starting at the medulla. However, olfactory dysfunction in late stage PD may be linked to cholinergic denervation and the onset of dementia and other cognitive deficits as well [88, 110]. Due olfactory cells being unchanged and reductions in the volume of the olfactory bulb neural region in PD, it appears that the abnormality has a central origin [111, 112]. There appears to be little to no disturbance of the dopaminergic and serotonergic neurons in the olfactory bulb and its associated nuclei, which corresponds to the lack of effect caused by dopaminergic medications [88, 113]. Although olfactory function appears to have promise in assisting in

clinical diagnosis of PD, our lack of understanding its pathological model impairs the understanding of olfaction's relationship to PD progression [88].

1.4.2.3 Visual features

Although a perceptual abnormality, visual disturbances occurring in PD are of particular importance to the work described in this thesis. Disturbances to visual processes are a common phenomenon in PD, affecting up to 78% of individuals with the disease [114]. Poor vision in PD often stems from poor visual acuity (especially low contrast acuity) as well as impairments in colour discrimination [115, 116]. Death of dopaminergic neurons in the retina may be the cause of poor visual acuity, however dopaminergic therapy has only moderate effects, suggesting other factors such as abnormal eye movements or blinking [117]. 24% of patients also suffered from reduced visual fields (in the same fashion as glaucoma patients), suggesting PD causes reduced visual field size or increased risk of glaucoma development [118]. Deficits in oculomotor function (namely saccadic and smooth pursuit eye movement) are common visual symptoms of PD, affecting 75% of patients [119]. The maximum saccadic speed (rapid eye movement used to shift visual attention) in the horizontal plane and reaction times are slowed in PD, and patients often under-reaching their target. Furthermore, smooth pursuits sometimes involving choppy mini saccades as opposed to smooth movements [119, 120]. Smooth pursuit movements have been shown to be impaired at early stages of the diseases with evidence supporting the same trend for saccades. The dopamine reductions occurring at the BG are believed to be the cause of oculomotor deficiency [121, 122]. Patients sometimes suffer from nystagmus (repetitive uncontrolled eye movements) and difficulties with convergence for changing depth, which can result in blurriness and double vision [119, 123, 124]. Furthermore, reductions in the frequency of blinking occurs during PD, leading to a staring, "mask face" appearance [125].

Visual impairments in PD extend to complex visual processes involving brain regions extending beyond the retina. Individuals with PD show deficits in visuospatial orientation, extending to difficulties determining what is vertical, proper positioning of body parts in space (proprioception), and conducting route-based walking tasks [126, 127]. Deficits have also been seen in visuospatial working memory (which is selectively

impaired early in PD), possibly indicating the degeneration of the BG, dorsal visual stream and/or the frontal/prefrontal cortex [128]. The conduction of memory tasks involving specific spatial orientations, as well as orientation and motion discrimination is impaired in PD [128]. These task deficits in PD suggest that abnormalities in visual processing lie beyond retinal abnormalities due to involvement of higher visual centres [140]. The perception of face discrimination, as well as the ability to imagine a certain face is also abnormal in some PD cases [129]. Furthermore, perceiving certain emotions through facial recognition (especially negative emotions like anger) is disrupted in PD [130]. Patients with PD also can display difficulties staying focused on relevant goals for problem solving tasks involving visual stimuli [114]. Visual hallucinations can also arise chronically in PD, especially among individuals using levodopa or dopamine agonists [140]. One study saw 40% of PD patients suffer from hallucinations within the last 3 months, with chronic visual hallucinations occurring in 22% of patients [131]. Severe cognitive dysfunction, disease duration and excessive daytime sleepiness are all predictors for the development of visual hallucinations, with even minor hallucinations increasing the risk of depression [114].

Numerous pathological changes affect the visual system of PD patients [114]. There are a few alterations when considering direct changes to the eye, with the most notable being the loss of neurons and dopamine in the retina, leading to reductions in retinal dopamine levels [132]. Dopamine is an important neurotransmitter in the retina, as it assists in the organization of cell receptor fields and modulates the activity of photoreceptors (which are responsible for converting light information to electrical information) [133, 134]. Cell loss of the retina is the most severe in the peripheral regions; however, thinning of the optic nerve also occurs at the retinal fibre layer [132, 135]. In addition to retinal alterations, it has been shown in vitro that the iris is not able to contract to the same degree as the iris' of healthy individuals [136]. Central visual abnormalities include abnormal energy availability of the primary visual cortex, as individuals with PD see glucose metabolism rates reduced by up to 23% [132, 137]. This compounded with reduced dopamine levels at the visual cortex, BG, and possibly superior colliculus could be the root of abnormal saccade production [138]. Furthermore, the BG is directly involved in saccadic eye movements which in turn have anatomical overlapping with smooth pursuits, possibly explaining why both are abnormal in PD [114]. Functional changes also occur at the fronto-

striatal neural network and the temporal-occipital cortex which, can present early in PD, leading to impairment in memory tasks and problems [139, 140].

1.5 Perception of Displacement, Time, and Velocity

A primary focus of this thesis is to analyze temporal, displacement and velocity visual perceptions in PD patients. The following section will look into the processing of these perceptions in healthy individuals, and what is known about their alterations in PD.

1.5.1 The Perception of Time and Parkinson's Disease

The perception of time is a vital component of human life, necessary for navigation through space in today's fast paced world. Be it engaging in everyday activities from kicking a soccer ball to playing the piano or remembering to pick up a friend from the airport, accurate timing is necessary for many aspects of life. However, unlike other biological sensory systems, there are numerous neural mechanisms that function together and interact with other physiological systems. Here we will discuss neural timing mechanisms, as well as the known timing deficits present in PD.

1.5.1.1 Functional and Neural Timing Mechanisms

The perception of time does not occur uniformly across all magnitudes of time, with multiple systems being used to perceive various timing magnitudes and achieve different timing goals [141]. Circadian rhythms are timing mechanisms functioning over the range of 24 hours and are largely influenced by the daily light/dark cycles and the control of sleep and metabolic cycles [142]. Interval timing of the seconds-to-minutes range is involved in decision making, foraging and arithmetic involving multiple steps [141]. Millisecond timing is necessary for the accurate control of movements, as well as speech generation/recognition, and playing or dancing along to music [141]. These timing mechanisms of different magnitudes involve different neural mechanisms to achieve their separate goals. The suprachiasmatic nucleus of the hypothalamus being used for the circadian clock, coordinating the tissue-specific rhythms through mechanisms such as light input and social information (often used for mating periods) [143, 144]. Work investigating the neural mechanisms of timing appear to indicate two individual timing circuits. The first

being an automatic, discontinuous timing system working in the range of milliseconds that is processed by the cerebellum. The second timing system is continuous, controlled by conscious thought (requiring the individual's attention), and is controlled by the BG and other interconnected neural regions [141]. Millisecond timing operations at the cerebellum are believed to be controlled through long term potentiation/depression and possibly intrinsic neural firing properties [141]. However, changes in the cellular activity during timing activities of monkeys were also found in the BG, thalamus, prefrontal cortex, and the premotor cortex [145]. Although this appears to indicate millisecond timing involves the use of many neural systems beyond the cerebellum, the involvement of the oculomotor and skeleton-motor effector systems are likely the cause for much of the observed involvement from other neural centres [145]. Interval timing uses a wider range of neural components, with it necessitating an intact striatum, but not cerebellum or suprachiasmatic nucleus; however, both the striatum and cerebellum may be activated simultaneously to control different performance aspects [141, 146, 147]. It should be noted that interval timing displays a scalar property in that time estimation errors are proportional to the magnitude of the estimated time (via a linear relationship) [146].

When considering the neuronal method for interval timing (which is the most focused physiological timing process), the most common classic internal clock model comes from the pacemaker-accumulator model (Fig. 1.3) [141, 149]. In this model, pulses are emitted at regular intervals by a pacemaker to be temporarily stored in the working memory via an accumulator [150, 151]. During the feedback (reward) stage, the number of pulses received from the accumulator for a given time duration is moved from the working memory to the reference memory [141, 152]. The number of pulses accumulated for the current subjective time are compared to the pulses stored from a past, remembered event to estimate the amount of time that has passed in a given situation. The pacemaker-accumulator model has several advantages to its use: its simplicity encourages its use across many species and tasks; it separates clock, memory and decision stages (allowing for the mapping of each stage to a neural region and transmitter system); and its success in predicting testable timing hypotheses [152–154]. Pharmacological testing was the first to demonstrate that the clock stage (which is modulated by dopaminergic agents) and the memory stage (which is modulated by cholinergic agents) are separate neural entities [141,

152]. Although the pacemaker-accumulator model succeeds in many ways as an internal clock model, it is still unclear if it holds much relevance to the brain structures and neural mechanisms involved in interval timing. This is exemplified by the model's implications of direct/exclusive connections between the speed of the internal clock and the dopamine system, which has been questioned by PD studies and inconsistencies seen in the effect of dopaminergic drugs, and dopamine's involvement in processes beyond internal clock speed that affect temporal perception (such as attention) [141, 155–158].

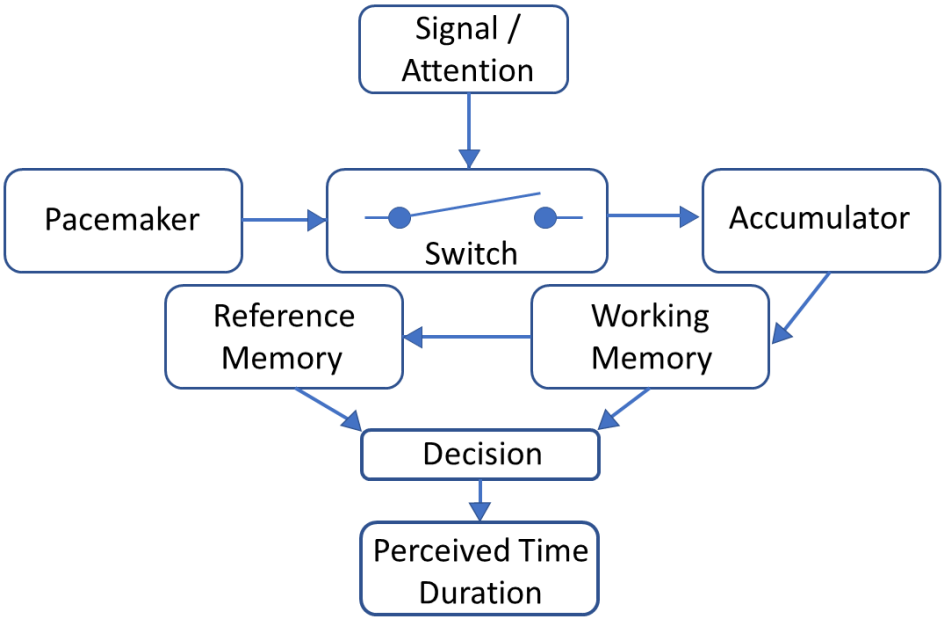

Figure 1.3: Pacemaker-Accumulator Timing Model

Summary of the pacemaker-accumulator timing model, in which a pacemaker is constantly emitting pulses at a constant rate. When a signal is given or attention is focused on timing tasks the switch is turned ON, after which the pulses for the time duration of interest are counted by the accumulator and stored in the short-term working memory. This information is compared to known time durations that have been stored in the reference memory, after which a decision is made regarding the length of the timing duration, allowing for its perception.

Although the pacemaker-accumulator timing model has been very useful towards understanding the neural mechanisms underlying timing, it currently appears to have inaccuracies, namely the fact that the BG does not have an exclusive temporal processing

role. More current work shows the BG's role in temporal processing is to monitor the thalamo-cortico-striatal circuit's activity, and to detect certain working memory patterns [159–161]. To account for this, the striatal beat-frequency (SBF) model was designed to describe timing through the activity of thalamo-cortico-striatal loops, where timing depends on the coincidental activation of neurons of the dorsal striatum (which are believed to contribute to executive function and decision making) and cortical neural oscillators [145, 161, 162]. In this model cortical oscillators are synchronized to a particular timing task, changing cortico-striatal transmissions (through long-term potentiation/depression) and increasing striatal neuron sensitivity towards the detection of cortical oscillators of the specific pattern [163–166]. In the SBF model the dopaminergic neurons of the SNc and ventral tegmental area are responsible for the cortical oscillation synchronization and task-dependent cortico-striatal transmission changes [141, 167]. It was shown that when a reward is expected at a certain time, the dopaminergic neurons display characteristic signal burst patterns at the time of the expected award, along with sustained activity throughout the timing interval [168]. Thus, the SBF model postulates that cortical oscillator synchronization is initiated through a dopaminergic burst at the beginning of the timing trial, with the sustained activity being caused by an attentional activation of the cortico-striatal circuits. In this model, updates to the cortico-striatal transmission causes the dopaminergic activity burst which occurs at the time of expected reward (i.e. when the desired timing is completed) [169]. The SBF model of timing currently appears to an adequate model due to its mechanisms being consistent with the postulated neural regions involved with timing (frontal cortex and striatum), along with it importantly reproducing the scalar property of timing (necessary for accurately predicting human interval timing) [145]. Though there are still properties of the model that need to be addressed (namely similarities seen between counting and timing [141, 170]), it (alongside the imperfect striatal beat-frequency model) still shows great value in interval timing predictions for certain timing tasks and pharmacological (namely dopaminergic and cholinergic) intervention.

1.5.1.2 Basal ganglia and Dopaminergic Involvement in Timing, and the Effect of Parkinson's Disease

Although the exact neurological mechanisms of time perception are yet to be fully understood, it is clear that both the BG and dopamine play a substantial role in interval timing [145]. Past pharmacological and animal studies have shown dopamine agonists and antagonists to respectively speed up and slow down judgments of time [171]. Furthermore, animal studies indicate lesions to the SNc lead to improper timing that can be corrected to some degrees through levodopa use, implying the dopaminergic pathway's importance in subjective timing [171, 172]. Animal studies also point to the BG as being a primary contributor to interval timing [172]. As PD leads to decreased neural dopamine levels and abnormal BG functioning studies regarding PD's effect on timing have been used to increase knowledge on dopamine and the BG's role in temporal perception. In 50% of time estimation studies and 67% of time production studies there were reported deficits in PD patients compared to control participants [172]. Levodopa appeared to improve temporal perception in some work; although this implies a role of dopamine in timing [172], there have been notable discrepancies in which PD patients perform the time perception tasks better when OFF levodopa [171, 173]. This might be caused by "dopamine overdose" in the frontal-striatal circuits involved in temporal processing as they may not be severely affected in early stages of PD. Thus, while the levodopa doses are optimal for correcting movement abnormalities, they are detrimental towards timing operations [174, 275]. Again, with time reproduction studies, there was not a uniform disruption seen in temporal reproduction for PD patients, with 67% of the studies showing PD related abnormalities (with the 71% of the studies that show timing differences in the PD also showing improvements from levodopa use) [172]. An interesting phenomenon that has been observed in PD patients during time reproduction tasks is the "migration effect", in which smalltime intervals are overestimated, and smaller intervals are underestimated [173]. With regards to temporal discrimination studies (the ability to differentiate stimuli from one another), 60% of the studies showed abnormalities in PD patients, with no studies showing improvements from levodopa, and one in fact showing medication-based impairments [38, 172]. Based on past work PD appears to affect timing processes, however these temporal dysfunctions are not present in all timing tasks or for certain patient groups. Furthermore,

the majority of past work studying temporal perception in PD patients involves the use of the motor system, leading to confounding results regarding the observed dysfunction being potentially caused by motor or timing deficits. It is very likely that the BG and dopamine are involved in timing, as they are key components of the previously described models which best describe and predict timing currently, and due to the observed timing deficits in PD patients. The positive effect subthalamic DBS has towards improvements in timing tasks for PD patients further provides evidence for the BG's role in temporal processing [172]. However, due to the deficits in attention, working memory and motor function occurring in PD [2, 176, 177], it is not fully understood what the root cause of timing impairment affecting PD patients is.

1.5.2 The Perception of Displacement and Parkinson's Disease

Unlike temporal perception, there have been few studies focusing on visual displacement and velocity perception in relation to PD. The neural and visual processes involved in the perception of these modalities will be discussed in the following subsections, along with the few observations made for velocity and displacement perception in PD.

1.5.2.1 The Visual System

Humans have the ability to recognize a specific object in milliseconds, a mechanism that is neurally processed via the ventral visual stream [178]. However, the specific mechanisms regarding human object recognition is still largely unknown. Before discussing the ventral visual processing stream (which is responsible for processing visual representations of objects and object features [179]) a brief outline of the visual system and how light information is processed will be presented. When light enters the eye, it is focused by the cornea and lenses of the eye onto the retina where the light-sensitive cells are located [179, 180]. These retinal cells convert light information to electrical information, which is then sent to central neural regions and eventually higher visual centres [179, 181]. The information is first transferred through the lateral geniculate nucleus (LGN), and from thereto the primary visual cortex (V1) where processing occurs [179]. It should be noted that atrophy of the LGN was observed in non-demented PD patients suffering from visual hallucinations, indicating potential alterations occurring in

the early stages of visual processing for some PD patients [182]. Furthermore, some cells of the retina are dopaminergic, with decreased dopamine levels being observed in the fovea (most neuronally dense portion of the retina) [183].

The receptive fields of the V1 neurons organize input from groups of retinal cells correlating to a patch of the retina (i.e. retinotopic representation). Each of the V1 cells is tuned to a specific, simple visual stimulus (such as a line) from a particular portion of the retina. Neuron groups representing a patch of retina compose a hypercolumn, which are organized in a grid structure [179]. These hypercolumns are responsible for extracting stereopsis (depth using visual information from both eyes), colour, and line orientation information for the specific retinal patch it encodes [179]. Although there are no visible pathological changes to the V1 of PD patients, there were observed abnormalities in lipid metabolism at the V1 of PD patients [184]. Further primary visual dysfunctions in PD include impairments in colour discrimination and contrast sensitivity.

After information is processed by the V1, it will be sent to the higher visual areas where it is continued to be processed. The information is initially sent to the V2 and V3, which also display a retinotopic representation. It is in these higher visual areas that the simple visual features extracted by the V1 are grouped together into objects. Beyond visual feature extraction, an individual's interpretation of the object plays an important role in visual perception (via top-down interpretations), with the higher visual areas being responsible for relating images to memories of familiar objects [179]. Beyond the V2 and V3, there are many more visual processing centres responsible for the interpretation of certain attributes of the image that is being perceived. These higher visual centres are mainly part of two streams, the dorsal "where" stream along the intra parietal sulcus (involved with perceiving where an object is in space and producing movement to a particular location in space), and the ventral "what" stream projecting to the inferior temporal lobe (which is responsible for the accurate identification of objects) (Fig. 1.4) [179]. The complex processing of visual stimuli allows for simple image features to be grouped together and accurately perceived by the individual to achieve detailed vision.

1.5.2.2 The Ventral Visual Stream, Object Recognition and Parkinson's Disease

Current evidence points to the ventral visual stream projecting to the inferior temporal lobe as the primary neural component involved in object identification [185]. The neurons of this stream encoding certain objects use a sparse strategy, in which there are very few neurons coding (and firing upon recognition) very particular objects (such as a known face) [185]. The inferotemporal (IT) cortex (comprised of V2 and V3 neurons) is composed of neurons which recognize patterns of complex visual features, causing a strong, precise neuronal response to specific groups of objects (e.g. neurons that excite to images of a specific body part). This information is then sent to the lateral occipital complex (LOC), which has specific neuron groups that respond to particular object classes (i.e. horses), or specific objects of an object class (e.g. neuron(s) of the fusiform face area which respond to a particular individuals face) (Fig. 1.4) [179]. Perceptual learning leads to a "filling in" of object features by the LOC, so that familiar objects can be viewed in different orientations, or with portions visually occluded and still be accurately perceived [186].

Through the collecting and compiling of simple visual features of an object, the ventral visual stream displays selective neuronal firing (with as few as one neuron) to accurately identify an object [185]. In this regard, visual displacement information between multiple object features is one of the simple visual features that is neurally extracted and utilized in perceiving a certain object. The independent features of the object are patched together using cues based on displacements between notable object features measured an *allocentric* manner (using external objects as reference points) as well as feature orientation [179]. It should be noted that abnormalities in object recognition as well as specific object feature recognition (such as facial emotions) have been observed in PD, although attentional deficits and working memory deficits question if these findings signify abnormalities in the ventral visual stream [187–191]. In this regard, testing simple perceptions that are neurally computed earlier in the ventral visual pathway might aid in resolving the confounding observations. The IT cortex is implicated in the perception of length and orientation through lesion and fMRI studies [292–294]. To accurately perceive displacement, one must perceive both the length and the orientation of the displacement.

This provides motivation for the current work which looks to analyze simple linear displacements in PD, to observe potential deficits, which might indicate abnormalities in the IT cortex of PD patients.

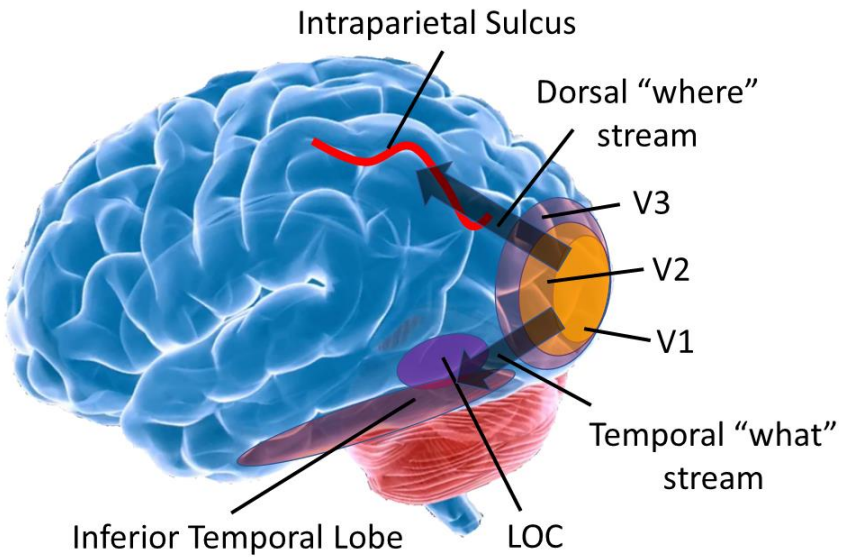

Figure 1.4: Visual Processing Pathways of the Brain

Simple visualization of the dorsal "where" and temporal "what" visual processing streams responsible for the processing of visual spatial and visual recognition of objects respectively. The primary visual cortex (V1) initially receives information from the retina and begins to extract visual features from this light information. This information is moved to the V2 and V3 where image processing continues, before continuing on one of the two predominant visual processing streams for detailed representation of visual stimuli.

1.5.3 Visual Spatial perception, Velocity perception and Parkinson's Disease

In order for an individual to move their body or a limb to a certain location in space, they must utilize visual information to accurately perceive their surroundings. The visual processing pathway involved visually perceiving space and positioning the body

accordingly is the dorsal stream, which follows the intraparietal sulcus (Fig. 1.4) [179]. There are several neural regions that are involved in the perception of motion, the primary contributor being the area MT+ (containing the MT and MSTl/d areas) situated around the ascending limb of the inferior temporal sulcus (ITS). Without the MT+ area moving objects would appear as still images transporting through space, making accurate perception of velocity very difficult [179, 195]. Unlike the ventral visual stream, the dorsal stream neurons have large receptor fields, and visual information is distributed across large populations of neurons [185]. Although this means the MT+ has poor visual acuity, it has great ability to determine object direction and speed and produces efferent motor signals capable of eliciting accurate limb movements [179, 185]. Furthermore, the dorsal and ventral visual streams share information, allowing for rapid identification and localization of objects [196]. However, the reference point used for measuring the spatial location of an object differs from that used in object perception, with spatial processing using one's self as the *egocentric* reference [197]. These egocentric representations allow us to visually map space around ourselves for navigation of the body, which has been shown to be abnormal in PD [198, 199]. The LGN cells involved in the dorsal visual stream are sensitive to low acuity visual motion in a particular direction, sending this information for further processing directly to the MT and indirectly through the V2/3 [179].

Similar to the lower visual processing centres, the MT is organized in a grid of columns that receive input from a patch of retina. The current model of this neural region shows the columns further dividing into mini-columns tuned to a particular direction and depth of motion, with each cell of the mini column being tuned to a particular velocity [179]. Although this neuronal layout has been proven in monkeys, fMRI work on humans has not yet proven that the columnar organization further subdivides to specify motion direction [200, 201]. From the MT the visual information is sent to the lateral MSTl or dorsal MSTd where it is sued to perceive when an object moves (allowing for object pursuit) or when the visual background moves (to sense when the perceiving individual moves) respectively [201, 202]. The MSTl utilizes smooth pursuits to persistently remain focused on the object being tracked. Oculomotor impairments in PD cause smooth pursuit and saccadic dysfunction, which is improved by dopaminergic medication [119, 203]. This could however be due to motor dysfunction as opposed to improper saccade efferent

firings. Individuals with PD also display abnormalities in the visual tracking of objects [204], which again further provides evidence for impairments in the dorsal visual processing stream or instead be caused by motor dysfunction. Thus, past clinical work has shown that processes involving the dorsal visual stream are abnormal in PD, however due to movement abnormalities confounding results it is not yet resolved if perceptual dysfunction does occur. Evidence for perceptual impairment has been observed in motion and orientation perception of moving gradients in PD [128, 205]. These perceptions however utilize MSTd information by mimicking the sensation of environmental shift as opposed to perceptions involving the movement parameters of an object (processed by the MSTl). The accurate perception of object speed is not only important for recreational activities, but also for ensuring safety in circumstances using heavy machinery such as driving. Findings of driving impairments occurring in PD are potential indicators of dorsal stream abnormalities [199, 206, 207], however as this is a complex process involving many neural components beyond accurate speed perception of an object further analysis should be done to reduce confounding findings.

1.6 Diagnosis and Monitoring of Parkinson's Disease

Though *An essay on the shaking palsy* by James Parkinson was released in 1817 it was not until 1960 that clinical trials began for the use of levodopa in treating PD [208]. Further advancements in treating PD symptoms have been made which greatly improve motor function, but the outcomes are unreliable for PD non-motor symptoms. Though increased knowledge regarding non-motor PD symptoms reveals its significance towards detriments in patient quality of life, there are still no therapies aimed at directly alleviating these symptoms, and very few clinical evaluations for non-motor symptoms exist. Still, the four PD features that are key clinical markers for the diagnosis of PD are resting tremor, rigidity, akinesia/bradykinesia and postural instability, even though certain non-motor symptoms are recognized as early disease markers [208]. There are numerous PD rating scales that provide an evaluation of the motor severity of an individual's PD. The Hoehn and Yahr scale for example provides non-specific assessments of PD progression ranging from a score of 0 (non-Parkinsonian) to 5 (immobile unless assisted) [209]. However, the most common rating scale used to monitor PD and assess patient impairment is the UPDRS,

which is commonly used by clinicians to track disease progression [210]. The UPDRS consists of numerous sections; I – Mentation, Behaviour and Mood (assess the presence of intellectual and thought impairments, as well as depression); II – Activities of Daily Living (analyzes the ability to perform daily activities such as speech, hygiene, walking and tremor); III – Motor Examination (examines patient movement ability); IV – complications in Therapy (such as dyskinesias and fluctuations), as well as sections relating disease severity to modified Hoehn and Yahr staging, and the Schwab and England Activities of Daily Living scale (rating out of 100% the patients ability to perform daily activities) [235].

Although non-motor symptoms are understood to be significant disease factors arising across disease stages, clinical diagnosis primarily uses the cardinal motor symptoms of the disease, their response to levodopa, and the exclusion of non-PD motor abnormalities [208, 211]. Although the clinical diagnosis of PD is rather straightforward when the classical symptoms present early in the disease, many cases arise where current diagnostic practices have difficulty (and often fail) with accurate diagnosis [209]. Although neuroimaging techniques to assess PD are being explored, there is yet to be enough evidence regarding their results to warrant use in clinical applications for the foreseeable future [208, 212]. PD diagnosis is currently hindered due to there being vast disease phenotypes, while still predominantly focuses on the core motor symptoms, with the insufficiencies greatly affecting diagnosis and monitoring of non-motor symptoms. Although the UPDRS (the current PD monitoring gold standard) does analyze some non-motor features of the disease it does not encompass the wide range of symptoms. A non-motor symptom questionnaire was created to help address these concerns, allowing for patients to report their non-motor symptoms which can allow for their monitoring [4]. Other questionnaires and scales such as the PDQ-39 scale display effectiveness in monitoring non-motor symptoms but have little efficacy regarding disease diagnosis [4]. Scales such as the Hamilton Depression Score and Epworth Sleepiness Scale are able to assess non-motor dysfunction that occur in PD, but are not specific to PD, again limiting their effectiveness with disease diagnosis. As the sensory symptoms of PD have been shown to appear across disease stages (sometime arising before motor symptoms), it seems that they would be rational targets for the diagnosis and monitoring of PD. Unfortunately, there are yet to be reliable clinical evaluations of PD sensory symptoms that aid in disease

diagnosis and monitoring [213]. As optimized patient treatment occurs when accurate symptom diagnosis and management takes place as early as possible, there are clear needs for improved clinical diagnostic techniques to account for the heterogeneous nature of PD.

1.7 Rationale

PD presents itself in different manners for different individuals, leading to different pathologies and difficulties that the patients must manage. Although the non-motor symptoms of PD are not as visible as the motor symptoms, they have been shown to have at least as substantial an impact on patient quality of life. However, the breadth of non-motor symptoms is not fully known, elevating difficulties with diagnosis, monitoring and treatment of the disease. This is observed through use of dopaminergic medications and DBS therapy to treat PD symptoms, as the marked improvements seen on motor functionality are not carried over to the non-motor symptoms that display a much more varied therapy response. Perceptual deficits, including those involving visual systems have been observed in PD across all stages, often predating motor symptoms. Accurate processing of visual information is a fundamental component of countless day to day activities and is necessary for the accurate perception of the world around us. Accordingly, visual time, speed, and displacement perceptions are used to safely operate machinery, navigate space, carry out daily tasks such as driving, and accurately identify objects. Abnormalities in processes utilizing these visual modalities suggests perceptual impairment, however these deficits could be due to the known sensorimotor integration or motor impairments occurring in PD, warranting further analysis.

Although past decades have seen great increases in known information of non-motor PD symptoms, there are still no adequate methods of diagnosing and monitoring many of the symptoms. However, this should be a priority of disease management as it will not only lead to improved treatment, but also could assist in the early diagnosis and monitoring of PD as a whole. Since some perceptual symptoms such as olfactory disturbances are known often arise before motor symptoms, diagnostic procedures based on these perceptual modalities show promise in assisting with PD diagnosis and monitoring. As access to technology becomes more wide-spread and cost effective, the development of disease monitoring software would come at a time allowing for it to be

accessible to vast amounts of individuals, allowing for more convenient, cost effective neurological assessment. Considering visual stimuli, designing computer-based diagnostic software for these perceptual modalities (should they be affected in PD) would prove a much simpler task than diagnostic tools for perceptions such as olfaction, further increasing usage potential and accessibility for those in need. Furthermore, due to the heterogeneous nature of PD, assessment of the disease from multiple perspectives would lead to improvements with its clinical analysis, and thus the patient group as a whole. Based on the literature review given above for PD and PD related therapies and clinical assessments, as well as the neural basis of visual time, displacement and velocity perception, this thesis explores the following hypothesis.

1.8 Hypothesis

It is hypothesized that the visual perception of velocity, time, and displacement is abnormal in PD patients compared to non-PD individuals, and that the use of levodopa medication or DBS therapy for treating PD alters the patients' perceptual abilities for these tested modalities.

1.9 Objectives

1.9.1 Objective 1: Are movement-independent visual perceptions abnormal in Parkinson's Disease?

As discussed throughout this chapter, perceptual abnormalities commonly occur in PD across disease stages, however the extent of impairment is not known. We have conducted various studies which analyze visual temporal, displacement, and velocity perceptual abilities of PD patients. These visual modalities are important contributors to the accurate perception of the world visually, and impairments in any would substantially degrade patient quality of life and help explain certain phenomena occurring in PD. This work aimed to analyze base visual perception abilities independent from any movements that could confound results, allowing for the study of visual perceptual ability as opposed to motor functioning. Two-alternative forced choice experiments were conducted for visual temporal, displacement, and velocity perception. The methodology and outcomes of these studies are presented in Chapters 2, 3, and 4 respectively.

1.9.2 Objective 2: What is the effect of common PD treatments on visual perception ability?

Previous discussions in this chapter have noted the inconsistent effect of levodopa and DBS therapies in the treatment of non-motor PD symptoms, with the current therapies often having no beneficial or detrimental effects on these symptoms. To study how popular current PD treatments affect the studied perceptions, both levodopa pharmaceuticals and DBS were examined in terms of efficacy towards improving visual temporal, displacement, and velocity perception. PD patients using these therapies conducted the experiment twice, both ON and OFF of their respective treatments. Furthermore, early stage *de novo* PD patients who were not using any PD therapy at the time of testing also conducted the experiments, providing insight on how these visual perceptions are affected early in the disease progression.

1.9.3 Objective 3: Development of a computer-generated graphical tool for analysis of visual perceptions

As previously noted, there is a lack of diagnostic methods that address the non-motor symptoms of PD disease. Due to the heterogeneous nature of PD and some non-motor (including sensory) symptoms presenting before motor symptoms, diagnostic tools assessing non-motor PD symptoms would provide valuable clinical tools to assist in the accurate diagnosis and monitoring of the disease. In the current work, a computer-generated graphical tool was designed using the Matlab/Simulink environment to analyze and quantify visual perceptions. In this platform, the toolbox was designed to recreate specified times visually, as well as use information on the amount of pixels on the testing monitor that correlate to certain distances in cm, allowing accurate displacement distances and velocities (in terms of the quantity of pixels being displaced and pixels per second respectively) to be achieved. Through this, it was possible to display on the computer monitor accurate measurements for the specific perceptual, allowing for the design of perceptual tests and clinical applications (described in subsequent chapters). Furthermore, the ability to present successive stimuli based on experimenter input (for example by clicking the left mouse button) was a necessary feature of the tool as it allowed the experiments to progress with customized rates, based on the patient's response rate and

desired frequency and duration of break periods. Our goal was to validate the use of the graphical tool (or a similar tool) for the assessment of visual perceptions, so that it can be successfully used in the assessment of perceptual ability and be further developed into a clinical tool for use in assessing visual perceptions.

1.10 Thesis Outline

The chapters are as follows:

- ***Chapter 2*** assesses the visual temporal perception abilities of PD patients using time magnitudes in the range of seconds and milliseconds
- ***Chapter 3*** assesses the visual allocentric displacement perception abilities of PD patients
- ***Chapter 4*** assesses the visual object velocity perception abilities of PD patients
- ***Chapter 5*** provides conclusive statements for the thesis, as well as an insight into the continuation of the work in the future.

Each of chapters 2, 3, and 4 analyzes the therapeutic effect of levodopa and DBS on the respective perceptual modality and use the computer-generated graphical tool to assess perception.

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Chapter 2

2 Differential Temporal Perception Abilities in Parkinson's Disease Patients Based on Timing Magnitude

This chapter contains the text of a paper (with the same title) that is currently being considered for journal publication. This work has been published in its preliminary form in the *9th International IEEE EMBS Conference on Neural Engineering, San Francisco, USA, 2019* conference proceedings, titled "Visual Temporal Perception in Parkinson's Disease Analyzed Using a Computer-Generated Graphical Tool".

2.1 Introduction

Parkinson's Disease is a progressive neuro-degenerative disease generally characterized by neuronal death in the BG, leading to heterogeneous motor abnormalities [1, 2]. Non-motor symptoms are also present in the vast majority of PD patients throughout all disease stages [3, 4]. Although these non-motor symptoms were classically not considered substantial factors of PD, they are increasingly being shown to contribute to decreased patient quality of life, in many cases to a greater degree than motor-symptoms [3–7]. Numerous common PD non-motor symptoms such as olfaction disturbances and rapid eye movement sleep behaviour disorder frequently predate the appearance of motor symptoms [8, 9]. Accordingly, extensive work has studied the use of non-motor symptoms as early disease markers; however, this has not yet lead to reliable methods for the early detection of PD [10, 11]. Although non-motor symptoms are known to be both important factors of PD and in some cases potential disease markers, accurate diagnosis and treatment of these symptoms remains a challenge [12]. Further shortcomings in effective treatment and monitoring of non-motor features arise from gaps in knowledge regarding the extent of these symptoms.

Of the studied non-motor deficits occurring in PD, abnormalities in some perceptual processes have been observed [4]. One of the perceptual abnormalities that has been noted in PD is the disruption of temporal perception and temporal processing [13–17]. However, like many studies analyzing perceptions in PD, past assessments of timing have often required patient movement. As movements are impaired in PD, the timing

aspects of these studies are confounded and the main source of the observed deficits is unknown [14, 18–20]. It is not clear whether the reported deficits in perceiving the fabric of time affecting PD patients arise due to impaired temporal processing, impairments in motor timing, or both. The current study sought to address these issues by isolating temporal perception from related motor actions allowing for its independent analysis. To do this, a novel computer-generated graphical tool was developed and utilized to quantitatively assess visual temporal discrimination independent of participation movement in patients with PD. As sensory symptoms like olfaction deficits (which arise in up to 90% of PD patients) are noted as potential biomarkers for PD [4], there is the possibility of other perceptual PD biomarkers. Furthermore, past work has shown abnormal neural connectivity occurring during attention-demanding temporal perception tasks is a distinguishing factor between PD patients with no clinically significant cognitive impairments and control participants [21]. Thus, temporal perception can potentially be used in the assessment and tracking of PD. Accordingly, a visual computer-based graphical tool was designed to help track and diagnose PD, providing a simple assessment that can be used in any setting.

Further shortcomings of work studying temporal perception in PD are seen in few perceptual discrimination (ability to discern between two stimuli differing in magnitude) studies in favour of detection (ability to detect stimuli apart from a baseline) tasks, with many past discrimination work involving goal-directed movements and one neural timing mechanism (i.e. interval timing in the range of seconds) [21, 22]. This is exemplified in research conducted by Artieda et al. that concluded those with PD display deficits in both motor timing tasks and time estimation tasks across multiple sensory modalities [14, 19]. Temporal discrimination is used daily in everyday activities as it is involved in processing subjective timing (an individual's perception of the amount of time that has passed since a certain event) [23, 24]. Based on current subjective timing models, different neural regions are responsible for timing operations depending on the timing scale [24, 25]. The BG for example is believed to be an important component in the perception of time in the range of seconds to minutes, while little evidence points to its involvement at the millisecond timing range [24]. As PD does not cause dysfunction at all neural regions—but substantial abnormalities in some regions such as the BG—it is possible that timing processes of scales

utilizing neural regions heavily affected by PD will be affected, whereas other timing scales will not be heavily affected in PD. For the reasons discussed above, the computer-generated graphical tool was designed to test visual temporal discrimination abilities of PD patients in the range of milliseconds and seconds to address these knowledge gaps.

The primary patient group for the study consisted of mid-stage PD patients using levodopa oral medication (half-life: 0.5 - 1.5 hours) to restore neural dopamine levels. Levodopa's reported effect on temporal perception of PD patients has confounding results, with some work suggesting levodopa improves internal clock function of PD patients [19], and others suggesting its use leads to temporal impairments [26, 27]. Levodopa generally produces positive outcomes for the movement abnormalities of PD (such as tremor and bradykinesia), however recent MRI work suggests that it also enhances the weakened connectivity between the cortico-striatal-thalamo-cortical (CSTC) motor circuit that is involved in the control of timing and movement [28, 29]. Dopamine's influence on timing events extends to internal time keeping allowing for accurate and precise time estimations, reproductions, and perceptions, as well as direct modulation of CSTC connections involved in motor timing [18, 30–32]. Furthermore, the ideal dosage of dopamine for treating PD motor symptoms contributes to the "migration effect" occurring in PD, in which small time frames are overestimated and large time frames are underestimated [33]. Levodopa in general has a variable effect for non-motor PD symptoms, often eliciting no effect or detrimental effects [5, 34]. Due to levodopa's confounding outcomes in past work and the inclusion of movements in past PD temporal studies, the effect of levodopa on visual temporal perception is still not known. An additional two PD patient groups consisting of fewer patients were also tested as case study groups. One of these groups consisted of early-stage de novo patients (patients who are not yet using any PD therapies [35]). The third patient group that was studied had mid- to late-stage PD and exclusively utilized DBS of the subthalamic nucleus. The outcome of DBS use is similar to that achieved from levodopa use, leading to substantial motor improvement [36]. Also, like levodopa, the non-motor effects of DBS therapy are variable and, in many cases, unknown (such is the case with temporal perception). Considering the above, the effect of levodopa and DBS therapy on visual temporal perception is still not fully understood, even though this perception is critical for interacting in dynamic environments. Patients who were using a PD therapy

were studied ON and OFF their respective treatments to analyze their efficacy regarding temporal perception.

The main unit used to quantify an individual's perceptual abilities was the difference threshold (DL; minimum magnitude change needed to differentiate a stimulus from a standard stimulus). Two standard stimuli (0.5 seconds and 1 second) were used to test temporal perception for timing magnitudes in the range of milliseconds and seconds (via interval timing) respectively. These standards were chosen as millisecond and interval timing utilize different neural regions and mechanisms [24], we wanted to analyze perception of PD patients at both of these timing magnitudes. Furthermore, attentional and memory deficits that often affect PD patients would be exacerbated by the testing of greater time magnitudes [37–39]). Longer durations would also substantially increase testing times, further risking invalid data due to patients experiencing increased fatigue leading to attentional slips.

In addition to perceptual sensitivity (via DL), this study sought to analyze visual temporal perception coherency in PD patients according to Weber's Law. Work done by Weber and Fechner [40, 41] led to Weber's Law, stating that a person's difference threshold (DL) is directly related to the magnitude of the standard stimulus for a given sensory modality. The ratio of DL to a standard stimulus is constant across different magnitudes of stimuli, displayed through the Weber's Fraction (WF; defined as $WF = DL/S$, where S represents the standard stimulus magnitude). The majority of perceptions analyzed using WF have validated Weber's Law, with exceptions seen at extremely low stimuli magnitudes [40, 41]. The effect of PD on temporal perception coherency has not yet been observed, motivating this study component. Many past works have shown timing abnormalities to occur in PD, although several involve motor timing or perceptions linked to movements. Furthermore, the BG appears to have a central role in timekeeping (in the seconds to minutes range) that is directly modulated by dopamine [24, 42–44]. The BG is theorized to increase the frequency of pulsator pulses that are collected and measured to determine time durations [30, 32]. Increased dopamine levels in the CSTC circuit also reduces uncertainties in time estimations [32]. Alterations in BG activity (due in part to dopamine deficiency) appear to cause disruptions in the internal clock's 'core timer', motor

timing, and decision making involved in time perception [13, 22, 45, 46]. The above mentioned notes lead to our primary chapter hypotheses that (A) *Visual temporal perception (including perceptual coherency) of PD patients is impaired compared to control participants*, and (B) *levodopa will reduce the visual timing disturbances in PD patients by restoring BG function, thus tightening the boundaries of temporal function*. Case studies involving small patient groups were also conducted to see the effect that DBS has on temporal perception, as well as to analyze if visual temporal perception is abnormal in early-stage de novo PD patients. As DBS improves BG function (acting similarly to levodopa), it is also hypothesized that it will provide benefits to a PD patient's visual temporal perception. Due to the BG still being impaired to some extent in de novo patients, it is hypothesized that they will display impairments in visual temporal perception. This chapter systematically analyzes visual temporal discrimination at different timescales in PD patients independent of goal directed movements that could influence participant timing ability, while evaluating the effect of the two common PD therapies and analyzing the coherency of the perceptual capability being studied.

2.2 Results

2.2.1 Demographic Data and PD-Related Clinical Characteristics

A total of 37 PD patients were tested: 25 (22 male, 3 female) who use Levodopa, 6 (4 male, 2 female) who use DBS, and 6 (4 male, 2 female) de novo patients not currently using any medication for their PD; as well as 17 control participants (14 female,3 male). All participants were residing in the Southern Ontario region at the time of testing. Clinical and demographic data related to the PD patients are shown in Table 2.1. Oculomotor examination was conducted on all patients by an experienced clinician, and only those without deficits were recruited.

2.2.2 Temporal Perception: Healthy vs. PD

DL was used to quantify perceptual abilities, with smaller DLs signifying better perceptual acuity (and thus ability) (Fig. 2.1). Each participant had two cumulative Gaussian distribution functions produced, one for each of the standard stimuli. The slope of the function is inversely proportional to DL, with steeper slopes indicating smaller DLs, and

thus increased perceptual abilities (Fig. 2.2). The unpaired (independent samples) t-test was used to compare DLs of control and PD participants both ON and OFF of levodopa.

Table 2.1: Demographic and clinical data for PD patients.

Abbreviations: MoCA - Montreal Cognitive Assessment; UPDRS -Unified Parkinson's Disease Rating Scale

Demographic Data	**Levodopa**	**DBS**	**De Novo**	**Control**
Number	25	6	6	17
Age (years)	70.04 ± 6.80	55.16 ± 8.99	74.17 ± 3.97	67.71 ± 8.82
Sex (m/f)	22/3	4/2	4/2	3/14
Years Since Diagnosis	6.88 ± 4.36	11.5 ± 4.04	3.12 ± 2.0	N/A
Clinical Data				
MoCA (out of 30)	26.68 ± 2.17	26.67 ± 3.08	27.83 ± 2.14	27.23 ± 1.59
UPDRS motor sub-scale OFF Therapy	23.92 ± 6.69	34 ± 10.51	22.33 ± 7.91	N/A
UPDRS motor sub-scale ON Therapy	14.72 ± 6.07	22.33 ± 7.91	N/A	N/A
UPDRS motor sub-scale OFF vs. ON Difference	9.20 ± 5.09	21 ± 5.62	N/A	N/A

Statistical significance was achieved with values of $p \leq 0.005$. A datum point was considered an outlier and not considered for statistical evaluation if it was greater than $1.5 * Inter{-}Quartile\ Range$ (IQR) above the third quartile, or less than $1.5 * IQR$ below the first quartile.

When comparing the DLs for the standard stimulus of 0.5 seconds for all individuals with PD (n = 37) to the control subjects, there were no significant differences in temporal perception between control subjects (average DL: 0.1867 ± 0.11) and both PD patients OFF their respective therapies (average DL: 0.2150 ± 0.076; p-value = 0.280) and ON their therapies (average DL: 0.2181 ± 0.086; p-value = 0.259) (Fig. 2.3). However,

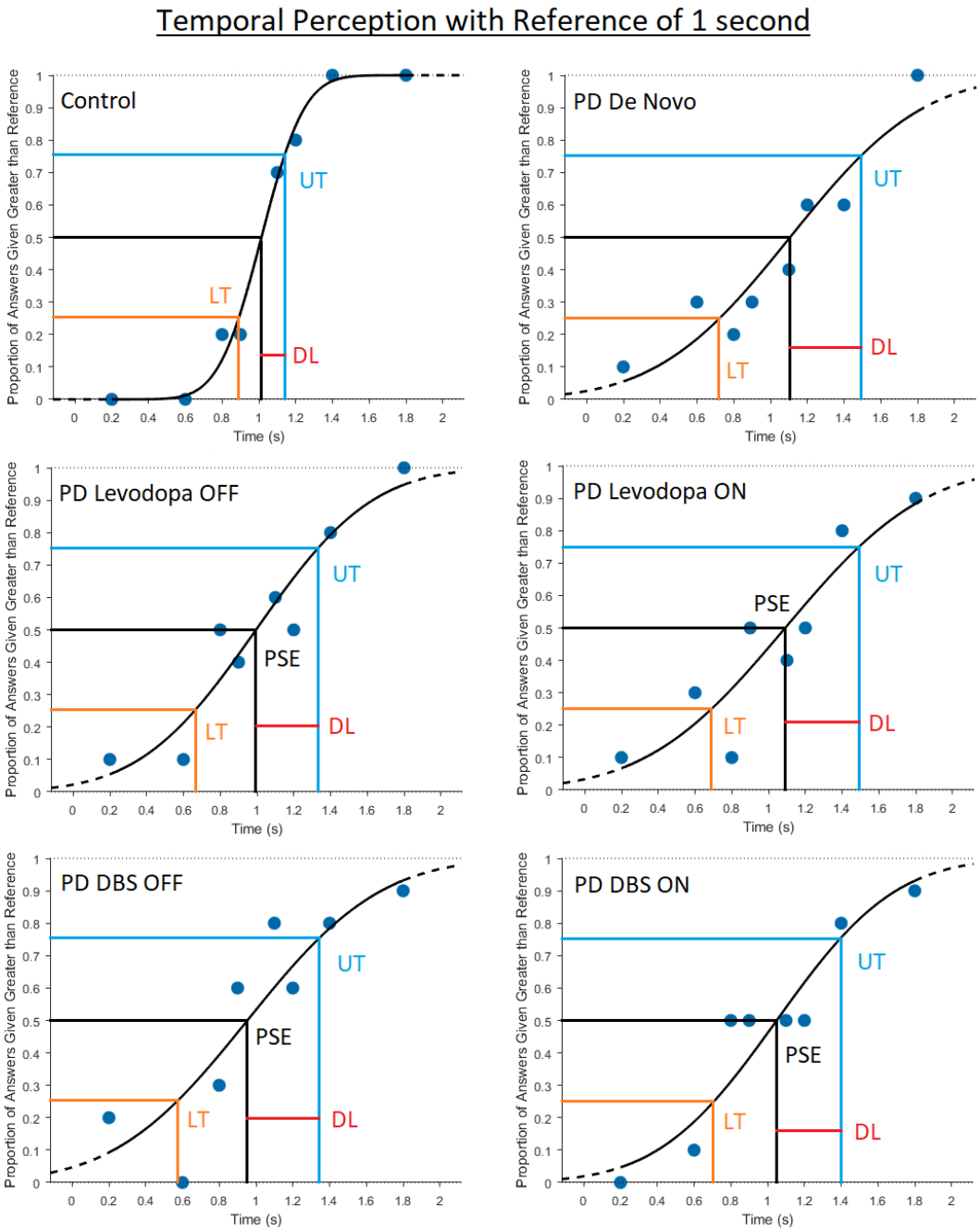

Figure 2.1: Example Cumulative Gaussian Distribution functions regarding temporal perception used for subject analysis. Subject DL was analyzed by subtracting the Point of Subjective Equality (PSE) from the Upper Threshold (UT; or subtracting the Lower Threshold [LT] from the PSE). UT and LT are the points of the function which the subject answered correctly 75% of the time for a given standard stimulus. Larger DLs signify decreased perceptual sensitivity.

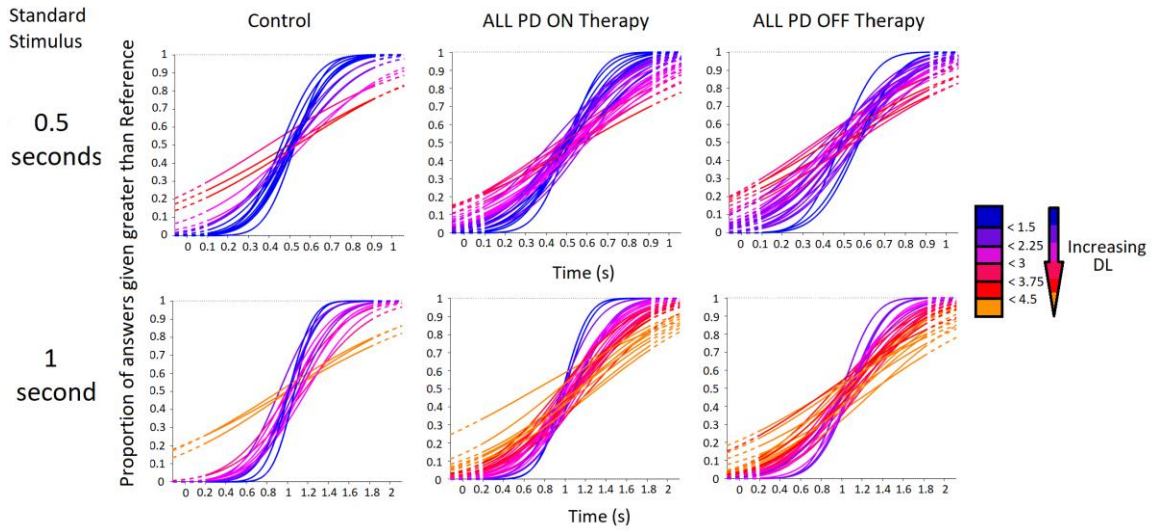

Figure 2.2: Gaussian distributions of temporal perception showing perceptual performance of individual participants. Categorized via disease state and standard stimulus. Curves are colour coded based on the participants DL (which is inversely proportional to function slope) for a certain condition. Curves that are more blue belong to participants displaying lower DL's (greater slopes) and thus having better perceptual abilities, with red/orange curves signifying the opposite

when comparing the DLs of control participants for the standard stimulus of 1 second (average DL: 0.2233 ± 0.068) to all PD patients, the PD patients OFF their respective therapies (average DL: 0.3678 ± 0.130 had significantly greater DLs (p-value < 0.001). When PD patients were ON their therapies (average DL: 0.3789 ± 0.14) they also displayed significant increases (p-value < 0.001) in DLs for the standard stimulus of 1 second compared to control participants (Fig. 2.3). A note on figure 2.3 and subsequent figures presented in this thesis, in some cases the y-axis of sub-figures differ from one another. The sub-figures with differing y-axis do not have data that is compared to one another, instead they contain data from a specific participant group with a certain therapeutic condition while providing focus on values of interest.

As can be seen in Fig. 2.4A), PD participants using levodopa as their PD therapy showed insignificant (p-value = 0.434) differences of DLs (average DL: 0.2101 ± 0.083) compared to control participants (average DL: 0.1867) when OFF levodopa at the standard stimulus of 0.5 seconds. When ON levodopa, PD participants again showed insignificantly

(p-value = 0.345) differing DLs (average DL: 0.2176 ± 0.098) compared to control participants at the standard stimulus of 0.5 seconds (Fig. 2.4A). For the standard stimulus of 1 second, PD participants OFF levodopa displayed significantly greater (p-value = 0.003)

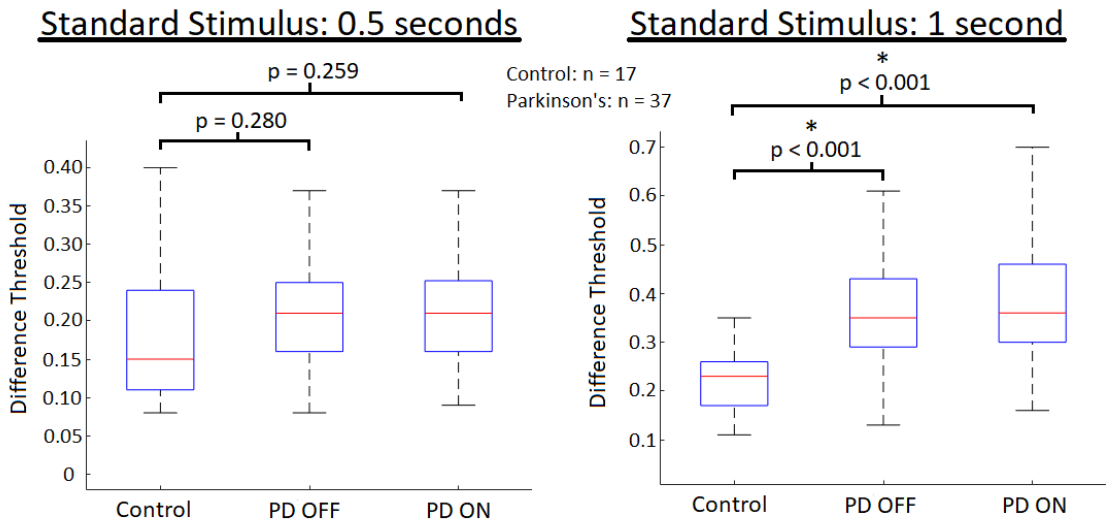

Figure 2.3: Temporal perception difference thresholds of all PD patients (n = 37) regardless of treatment state compared to control participants. The standard stimulus of 0.5 seconds is displayed on the left, and 1 second on the right; with boxplots related to PD patients OFF and ON their respective therapies. The red lines are the median DL for each group. The bars represent the data spectrum. PD patients did not show any impairments in temporal perception at the standard stimulus of 0.5 seconds ON or OFF of PD therapies. However, there were significant impairments seen at the standard stimulus of 1 second OFF PD therapies (p-value <0.001) and ON PD therapies (p-value < 0.001).

DL's (average DL: 0.3351 ± 0.024) compared to the control participants (average DL: 0.2233). Again, when using levodopa, similar results were seen, with PD participants ON levodopa displaying significantly greater (p-value < 0.001) DL's (average DL: 0.3806 ± 0.14) compared to the control participants (Fig. 2.4B).

It should be noted that both the DBS and de novo PD groups have relatively small n-values (n = 6 each). Thus, the statistical evaluation that was conducted on these groups should serve as observations of interest for these particular groups. The statistics do not necessarily represent these patient populations, however the trends seen do provide insight

to the temporal perception abilities of these groups, providing interesting case studies and rationale to further expand testing to support larger patient groups. Participants with PD who were utilizing DBS therapy in general displayed similar results to PD participants using levodopa. At the standard stimulus of 0.5 second PD participants OFF DBS

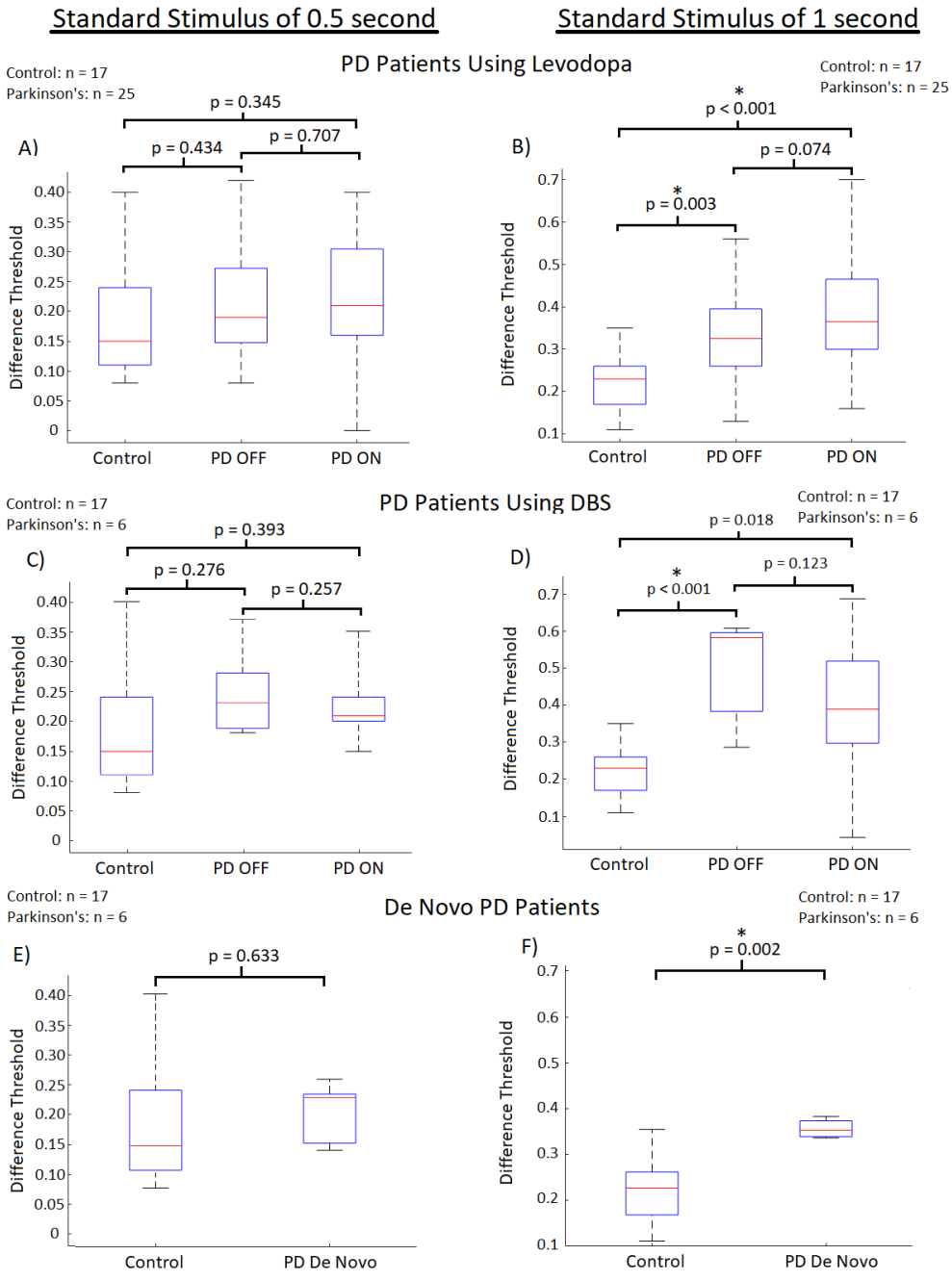

Figure 2.4: The difference thresholds separated by individual therapies obtained through temporal perception examination The standard stimulus of 0.5 seconds is

displayed on the left, and that of 1 second on the right. The redlines are the median DL for each group. The bars represent the data spectrum. Regarding the standard stimulus of 0.5 seconds, there were no significant differences in DLs observed between PD patients OFF and ON levodopa and DBS compared to controls. De Novo PD patients did not display significant differences in DL compared to controls as well. Use of levodopa and DBS therapies did not lead to significant changes in the DLs of PD patients. For the standard stimulus of 1 second, significant differences in DL were observed between PD patients OFF and controls (p-value = 0.003), as well when ON levodopa and controls (p-value < 0.001) were also seen. PD patients using DBS displayed significant increases in DL when OFF DBS (p-value < 0.001), however when ON DBS no significant DL increases were seen when compared to controls. De Novo PD patients also displayed significantly greater DLs than controls (p-value = 0.002) at the standard stimulus of 1 second. No significant differences were seen when PD patients were administered their respective therapies at the larger standard stimulus of 1 second.

displayed insignificant (p-value = 0.276) DL differences (average DL: 0.2460 ± 0.076) compared to control participants (average DL: 0.1867). When ON DBS, the PD participants also displayed insignificant (p-value = 0.393) DL differences (average DL: 0.2290 ± 0.071) at the 0.5 second standard stimulus compared to controls (average DL: 0.1867) (Fig. 2.4C). Like participants using levodopa, at the larger tested standard stimulus magnitude (of 1 second) PD participants OFF DBS displayed significantly greater (p-value < 0.001) DLs (average DL: 0.5062 ± 0.14) compared to the control participants (average DL: 0.2233). However, when ON DBS, no significant differences (p-value = 0.018) were seen between the means of PD participants ON DBS (average DL: 0.3873 ± 0.22) compared to controls (average DL: 0.2233) at the larger temporal magnitudes of 1 second (Fig. 2.4D).

The third PD group that was tested consisted of de novo PD patients who were not undergoing any treatment for their PD at the time of testing. At the smaller tested standard stimulus of 0.5 seconds, the de novo PD patients showed did not significantly differ (p-value = 0.633) in mean DL (average DL: 0.2093 ± 0.043) compared to control participants (average DL = 0.1867) (Fig. 2.4E). However, as with all other PD patient groups there was significant increases (p-value = 0.002) seen in the DLs of de novo PD patients (average DL = 0.35565 ± 0.021) compared to control participants (average DL: 0.2233) (Fig. 2.4F).

2.2.3 Effect of Levodopa and Deep Brain Stimulation on Temporal Perception

To analyze the effect that levodopa and DBS has on the temporal perception of PD participants, the paired two-tailed T-test was used, with statistical significance being achieved with p-values ≤ 0.05. The use of levodopa did not elicit any significant effects on temporal perception for the PD participants using the therapy. At the smaller tested magnitudes of time using the standard stimulus of 0.5 seconds the use of levodopa did not significantly alter patient DL compared to when the participants were OFF levodopa (p-value = 0.707) (Fig. 2.4A). At the greater tested magnitudes (using a standard stimulus of 1 second) there were no significant differences (p-value = 0.074) seen when levodopa was used, however a potential trend may be present regarding the increase of participant DL when ON levodopa compared to when OFF (Fig. 8B). Similar to levodopa, the use of DBS therapy did not elicit significant changes in patient temporal perception. With regard to the smaller standard stimulus (0.5seconds), the use of DBS did not lead to significant alterations between participants DLs (p-value = 0.257) (Fig. 2.4C). At the standard stimulus of 1 second there were no significant differences (p-value = 0.123) in DL when DBS was turned ON vs. OFF, however again a potential trend regarding the effect of DBS may be present regarding DL improvement when the patients DBS device was turned ON (Fig. 2.4D). A note of interest, when comparing a participants DL (considering all participants with PD) OFF their respective therapies to the UPDRS subsection III scores there were significant correlations at both the standard of 0.5 seconds ($R = 0.570$; p-value < 0.001) and the 1 second standard ($R = 0.339$; p-value = 0.050). When PD patients were using their respective therapy however, there were no significant correlations between an individual's DL and UPDRS section III score for both the 0.5 second standard ($R = -0.131$; $p = 0.483$) and the 1 second standard ($R = 0.085$; p-value = 0.655).

2.2.4 Temporal Perception Coherency

To analyze the perceptual coherency of participants, the WF was calculated at both standard stimuli magnitudes. In normal, healthy conditions, it is expected that there will be strong correlations between the WFs for the different standard stimuli (as an individual's WF is constant across standard stimuli magnitudes). To analyze this in study participants,

Pearson correlation coefficients were applied to compare the similarity between WFs at the two tested standard stimuli. Note that in perfectly idealized conditions the slope of the line of best fit used in calculating the Pearson correlation coefficient (R) will be 1 (as the WF of both the y- and x-axis' are the same), will have an axis intercept at (0,0), and R will equal 1. Deviations in the slope and the y-intercept of the line of best fit will lead to decreases in R, signifying abnormal relationships between WF of different standard stimuli and thus abnormal perceptual abilities across participant groups. Statistical significance was achieved with values of $p \leq 0.05$. For the control group there were very strong WF correlations between the two tested standard stimuli (R: 0.932, p-value < 0.001). Although not as

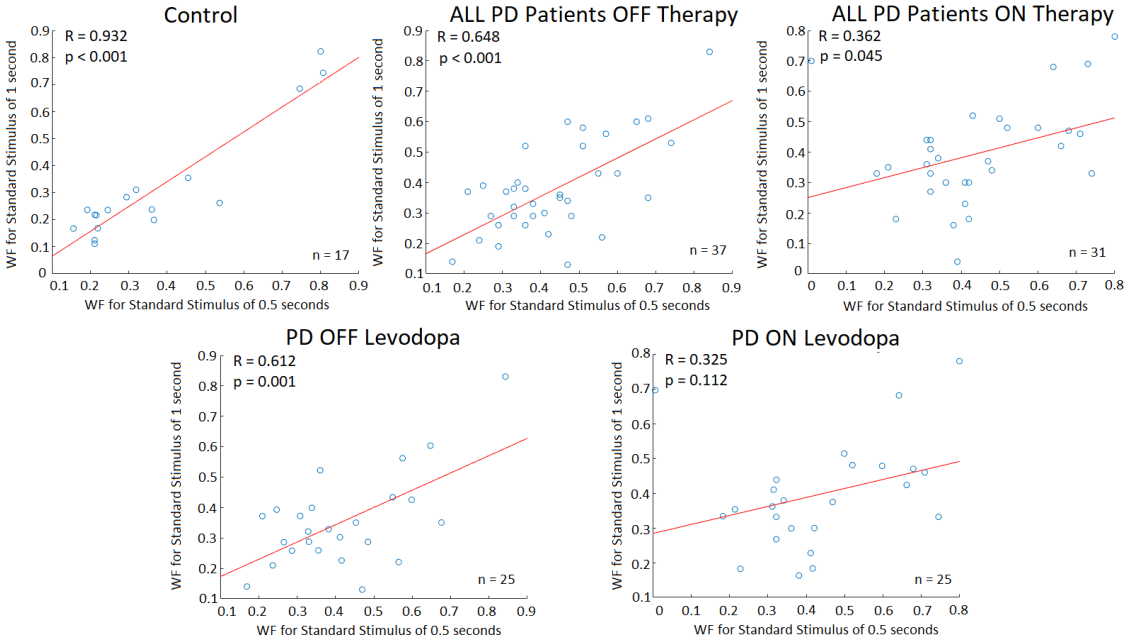

Figure 2.5: Correlations between participant WF at the standard stimuli of 0.5 and 1 seconds. Points displaying high similarity between their x and y values signify that the participant displayed little to no difference in the WF values at different stimulus magnitudes, and thus are in accordance with Weber's Law. Correlation plots of DBS and de novo patients are not shown due to small sample sizes (n = 6 for each group).

strong of a correlation was seen in all PD patients OFF their respective therapies, they still displayed significant, strong correlations between the WF at different standard stimuli

magnitudes (R: 0.648, p-value < 0.001). When all PD patients ON their respective therapies were analyzed, significant correlations were also seen between WFs (R: 0.362, p-value = 0.045), however the correlation was not as strong as when OFF PD therapy. When looking at PD patient groups separated by PD therapy usage, PD participants OFF levodopa also showed strong WF correlations between the two tested standard stimuli (R: 0.612, p-value = 0.001). However, when these PD patients were ON levodopa they did not display significant correlations between their WFs at the two tested standard stimuli (R: 0.325; p-value = 0.112). For PD participants using DBS, no significant correlations for the WFs between standard stimuli were observed in OFF (R: 0.635, p-value = 0.176) and ON (R: 0.608, p-value = 0.200) DBS states. De novo PD patients did not show any significant correlations between the WFs of the two standard stimuli (R: 0.691, p-value = 0.129) as well (Fig. 2.5).

2.3 Discussion

The current work showed overall that individuals with PD displayed impairments in the tested visual temporal discrimination task (regardless of disease duration) compared to healthy controls. In addition, levodopa and DBS therapies were shown to elicit minimal effect on the temporal discrimination, and, perceptual coherency was generally disrupted in PD patients. It should be noted that the average age of DBS patients was significantly lower than that of the levodopa, de novo and control participant groups. The effect of age did not appear to affect a participants DL as no correlations were seen between a participants age and DL. Furthermore, the duration of PD for DBS patients on average was significantly greater than the Levodopa and control participant groups, which is assumed due to them being at late stages of the disease. Interestingly, both OFF and ON therapy for both the 0.5 and 1 second standard stimuli significant correlations between a patient's years since PD diagnosis and DL were seen. It should be noted, the statistical findings for the DBS and de novo groups should not be considered conclusive evidence for the temporal perception findings in these groups due to their small sample sizes. Instead, these case studies provide an interesting view on how patients at different disease stages and utilizing different treatments are affected with regards to temporal perception ability. The main findings of this study are in-line with past work showing impairments in time perception

and processing for PD patients, as well as work signifying the BG's importance in temporal perception at specific time magnitudes [14–17, 19, 20, 48]. The current study however has observed these impairments independent of task-related patient movement, as well as differential perceptual ability based on the scale of time that was used during testing. It should be noted that these impairments are not attributed to abnormalities in oculomotor control, deficits in visual acuity, or clinically diagnosed cognitive deficits common in PD (such as Parkinson's Disease Dementia [PD-D] or Parkinson's Disease related Visual Hallucinations [PD-VH]) as participants were tested diagnostically for these symptoms. Furthermore, it is unlikely that the observed deficiencies seen in PD subjects were due to deficits of attention or working memory which commonly affect persons suffering from PD [49], as there was no deficit seen in the perception of time at the smaller tested magnitudes. Thus, the observed temporal perception impairments are likely due to abnormal timing processes occurring in PD.

Subjective timing processes for different time scales achieve different goals and are controlled by different neural regions [23, 24]. In this regard, timing in the range of milliseconds is responsible for proper motor control, speech recognition and production, and playing music [50–52]. The cerebellum has been shown to be the primary neural structure involved in millisecond timing through cerebellar lesion studies of motor timing and rapid, discontinuous timing tasks, with neuroimaging studies providing further evidence [53–56]. Furthermore, based on current research, there is no conclusive evidence that the BG are involved in neural timing in the range of milliseconds [57]. The current work observed no vision-based temporal perception impairments at the smaller tested standard stimulus (utilizing time scales only in the millisecond range) in PD participants, coinciding with current knowledge regarding subjective timing in the range of milliseconds. Although connections between the cerebellum and BG exist [58], there has been no evidence suggesting the BG's involvement in millisecond timing, which is further confirmed by the results in the current study. Timing in the range of milliseconds is however important for the control of motor functions and motor timing, which are known to be impaired in PD [20, 23, 24, 59]. These motor timing impairments seen in previous studies can be attributed to abnormal motor function occurring in PD, as suggested by the current study and past work comparing motor timing in PD patients and people with

cerebellar lesions [60]. Interestingly, it was previously shown that millisecond timing was heterogeneously impaired in some (but not all) PD patients [61], however as all tasks involved motor timing these observed abnormalities likely indicate heterogeneous motor timing in the millisecond range for PD patients. The PD patients tested in the current study did show correlations between perceptual impairment and disease duration for both the 0.5 and 1 second standards. This could indicate that at earlier stages of the disease when the BG is the predominantly affected neural region that timing processes utilizing the BG are impaired. As the disease progresses and spreads to other neural regions impairments in timing processes that don't involve the BG might occur (such as millisecond timing). However, this could also be caused by a general increase in impairment (perceptual or otherwise) occurring as PD progresses. The core findings of the current study appear to confirm that timing processes in the scale of milliseconds independent of motor functions are not impaired in PD, providing further evidence that the timing control elicited by the cerebellum at this scale functions independently of the BG.

Timing processes in the range of seconds to minutes utilize the interval timing method, which is believed to involve attention of current events and memories of past events to estimate time duration [24]. Interval timing utilizes multiple neural regions including the BG, with the SNc (dopamine producing cells of BG that experience mass neuronal loss during PD) modulating timing processes of the Striatum [24, 48, 62]. With this considered, past findings of abnormal temporal production, reproduction, and estimation in PD patients aligns with the postulated interval timing models largely involving the BG [14, 19, 20, 59, 63]. At the larger tested magnitudes (standard stimulus of 1s), patients utilizing levodopa (when both ON and OFF), as well as de novo patients, and DBS patients OFF stimulation displayed significant impairments in temporal perception compared to control participants, with potential trends regarding impaired temporal perception for DBS patients ON therapy also being observed. These findings demonstrate that visual temporal discrimination independent of movement is indeed abnormal in PD, yet there are limitations on these abnormalities based on the BG's role as an internal clock. Interestingly, observations demonstrating a discrepancy in temporal perception occurring in PD based on the scale of time was seen. This work strengthens postulated subjective timing models in the range of milliseconds–controlled by the

cerebellum with no (or negligible) BG influence–and interval timing models which are largely influenced by the BG. Interestingly, past work investigating weakened CSTC circuit activity in PD that is at least partially responsible for timing deficits suggest increased cerebellar activity occurs to attempt to compensate, potentially indicating entirely different timing processes occur during PD [29]. The current study has also demonstrated that these perceptual abnormalities are occurring early in disease development. As previously studied perceptual deficits occurring in PD such as olfaction often predate disease motor symptoms [4], it is possible that visual temporal abnormalities also predate motor symptoms, providing an easy to test disease marker.

The use of the two tested therapies did not elicit any significant effects on the visual perception of time. At the lower temporal magnitudes (standard stimulus of 0.5 second) this is expected as the postulated timing mechanism is controlled by the cerebellum, which is not dopamine dependent [23, 24, 27]. The lack of effect caused by levodopa at the larger tested magnitudes (standard stimulus of 1 second) is more peculiar due to the postulated role of BG in time perception at this scale and the occurrence of reduced striatal dopamine levels in PD [23, 24]. Although studies have attributed levodopa to improved internal clock function [64], this could be attributed to improvements in working memory (an important component of interval timing) caused by levodopa. As the time scales were rather small in magnitude for the current study, this may have reduced error's that occur from abnormal working memory and memory systems rooted in improper striatal activation, which are aided by dopaminergic therapy [22]. Furthermore, the detrimental effect of dopamine antagonists on internal timing seems to be more pronounced than beneficial effects of dopamine agonists [65–67]. Interestingly, if any trend is occurring from levodopa use it is negative, which has also been observed in previous work [27]. However, based on the statistical analysis, levodopa did not lead to significant alteration in PD patient's capabilities in the tested visual perception task. The use of DBS did not lead to significant alterations in a subject's ability to perform the perceptual task either. However, there was a potential trend towards DBS-based improvements in the perceptual task. Due to the small sample size, it is possible that the statistical analysis is not representative of the effect of DBS on temporal perception, yet, previous work showed neural timing improvements after DBS of the subthalamic nucleus [25]. Based on the finding of the current work, it appears

that DBS may be more effective at restoring temporal perceptions in the absence of motor actions, however both PD therapies have minimal if any effect on the tested visual temporal perception. The finding that correlations exist between and individuals UPDRS part III subsection score and DL OFF the patient's respective therapy suggest that like motor abnormalities of PD, sensory abnormalities (or in the least the tested visual temporal perception) also further deteriorate as the disease progresses. However, the lack of correlations when patients were ON their therapies between a subject's UPDRS part III score and DL further suggests that while the tested PD therapies do improve movement abnormalities of PD, they do not have the same positive outcome with visual temporal perception. Although Weber's Law is maintained for the majority of tested sensory modalities, past work has questioned its merit in temporal perception [68]. Linear relationships between perceptual accuracy and stimulus magnitude (via Weber's Law) intemporal perception were shown to occur in healthy subjects between 0.2 – 2 seconds; however, other work involving visual timing showed consistency in the WF of standard stimuli at 0.6 and 0.9 seconds, but not at 1.2 seconds [68]. In the current work, strong correlations between WFs from the two tested standard stimuli were seen for control participants and PD participants OFF therapy (as well as PD patients using levodopa when OFF medication). Interestingly, no significant correlations between WF calculations at different standard stimuli were seen when these patients were ON levodopa. Although perception coherency via Weber's Law did occur in the tested healthy patients, it is still not certain whether Weber's Law is maintained in visual temporal perception across a wide range of stimuli magnitudes. However, this finding further promotes the possibility of levodopa acting negatively in terms of visual temporal perception, prompting further research into both levodopa's effect on temporal perception and Weber's Law in relation to this perception. No correlations in WFs between the 0.5 and 1 second standards were seen in patients using DBS therapy (both ON and OFF) and de-novo patients. This is likely partially due to the small sample sizes of each group (n= 6 for both groups).

The small sample sizes of both the DBS and de novo groups were a limitation of the current work. Due to restricted patient recruitment/testing time frames, as well as a small candidate pool for the DBS group (with only 10% of potential candidates utilizing the treatment) and de novo group (due to the recruitment centre [University Hospital] being

a tertiary care hospital) the recruitment of large numbers of PD patients in these groups was a challenge. However, the results from these groups provide interesting insight into how these populations might function with regards to temporal perception, prompting further research of the groups. Further study limitations were the constant order of patients conducting experiments first OFF PD therapies, followed by ON therapies. This was due to the testing occurring in one day, and the approximate 12 hours needed for an individual to be considered clinically OFF levodopa (which all non-de novo PD patients were utilizing for treatment). Although this is common practice for PD experiments involved ON/OFF analysis, and extended breaks were provided for participants, fatigue could have occurred for some participants.

The current study demonstrated abnormalities in visual temporal discrimination independent of goal-directed movement occur in PD in timing scales utilizing interval timing. However, these deficits were not seen with millisecond timing. This supports commonly postulated subjective timing models outlining the BG's lack of function in neural timing in the millisecond range, and involvement in neural timing in second to minute range. This was also seen in early stage de novo PD patients, suggesting that visual temporal discrimination is disrupted early in the disease. Thus, visual temporal discrimination shows potential as an early disease marker that could be used in diagnostic scenarios, due to the simplicity of testing this perception. A non-invasive, easy-to-use computer graphics-generated tool was implemented to test this perception. The toolbox can be easily modified, allowing for the analysis of different sensory modalities in research or clinical settings. Furthermore, the toolbox is not taxing from a computer processing standpoint, allowing it to be used in a wide variety of clinical and non-clinical settings. Testing of early stage PD patients (specifically those who do not yet display significant motor impairments) should be carried out to further analyze a potential diagnostic use of the toolbox for neurological disorders such as PD. As non-motor PD symptoms often arise before motor symptoms [4], this tool or similar software could be a valuable asset to assist physicians with early diagnosis of the disease. Furthermore, potential clinical importance of the computer-generated graphical tool is exemplified through its design, as no goal directed movements which could confound perceptual analysis occur, contrasting current diagnostic timing tests (such as the Purdue peg board) which utilize extensive movements

[69]. Although movements (via talking) were necessary for the analysis, these actions had zero impact on the analyzed perception as response time was not a considered factor, ensuring motor capabilities had no role in the observations. Due to the simple to use, flexible nature of the graphical tool, its use could assist in the widespread monitoring of neurological disorders, potentially in the comfort of the user's home or local community centres should it be further validated. This could allow for more regular disease monitoring that benefits from the tool's accessibility, further assisting disease prognosis by providing more complete disease analytics for clinicians to utilize. Further studies should also investigate a potential use of the toolbox for predicting the onset of PD-D (which may have visual markers such as abnormal colour perception [70]) to further assist physicians with the monitoring of the disease. Many current PD monitoring tools focus on motor symptoms of the disease [71, 72]; however, disease phenotype varies from patient to patient, meaning many do not receive optimum treatment for their conditions or realize the extent of their disease symptoms. The graphics-tool used in this study provides a simple means for analysis of non-motor perceptual modalities affected in neurological disorders such as PD. Future work will continue testing visual perceptual modalities in PD, as well as assess perceptual abilities at different disease stages and for different sensory systems (such as auditory perceptions) to further validate the use of perceptual testing toolboxes in clinical and research use. We hope that the computer-generated graphical tool will one day be used in conjunction with other state of the art clinical diagnostic/disease monitoring tools to provide improved clinical outcomes for the treatment of neurological disorder, allowing those suffering to have the greatest quality of life that is possible.

2.4 Methods

2.4.1 Demographics and Clinical Assessment

The study protocol for this work was approved by the Research Ethics Board of the University of Western Ontario. All experiments were conducted in accordance with the Declaration of Helsinki, as well as the Tri-Councel Policy Statement of Ethical Conduct for Research Involving Humans in Canada. All participants provided informed consent regarding their participation in the study. Furthermore, the participant displayed in Fig. 2.6 provided consent allowing for their image to be used in publications of the research. All

participants in the study were recruited from the Movement Disorders Program at University Hospital, London Health Sciences Centre, Ontario, Canada, where they were diagnosed and have been regularly treated for their PD. Study protocol details and consent forms were provided to patients prior to participation. For this study, 25 participants were recruited who had mid-stage PD (22 male, 3 female) and were on levodopa therapy. Six patients with mid-late stage PD were recruited who have been receiving DBS therapy (4 male, 2 female), as well as 6 early-stage PD de novo patients who were not currently receiving any treatment for their PD. Table 2.1 provides the clinical details and demographic data about the recruited participants. In addition, 17 healthy, age-matched control participants (14 female, 3 male) with no known neurological or psychiatric disorders were recruited for the study. The patients and participants were from the Southern Ontario region of Canada. For this study, all PD patients fulfilled the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria. Participants utilizing levodopa therapy refrained from taking the medication 12 hours prior to experimentation, ensuring that they were in the OFF levodopa state. Similarly, participants receiving DBS had their device turned OFF upon arrival at the testing centre. These participants had to wait at least 45 minutes, ensuring that they were not experiencing any effects from the DBS therapy. After the participants completed the experiment in the OFF state, they were administered 300 mg of levodopa if this was their primary therapy (unless their regular levodopa dose was 100 mg or less, in which case they were administered 200 mg); or their DBS device was turned ON to the patients regular stimulation levels if their primary PD treatment was DBS. After an hour's break the participants went through the experiments again in their ON state. All participants conducted the experiment ON and OFF PD therapy in a one-day testing session. It should be noted that although participants utilizing DBS typically would take it alongside levodopa, for the duration of the experiment they did not take any levodopa medication. This was to ensure that the effect of DBS was not confounded by the effect of levodopa. The severity of motor symptoms affecting the PD participants was assessed using the motor subsection (section 3) of the UPDRS both ON and OFF PD therapy. All PD subjects also conducted a cognitive assessment using the Montreal Cognitive Assessment (MoCA) [73]. Assessments of visual acuity (reading tasks and tests using the Snellen eye chart), smooth pursuit and saccades were carried out for all participants

(including control participants). Furthermore, the control group was questioned to detect symptoms of neurological disorder (including PD) as part of the control participant screening. Exclusion criteria (for both control and PD groups) include the presence of considerable cognitive impairments (MoCA < 25), impairments in visual diagnostic tasks, and the presence of visual hallucination (VH). Furthermore, PD patients utilizing pharmacological therapies other than Levodopa were excluded from the study.

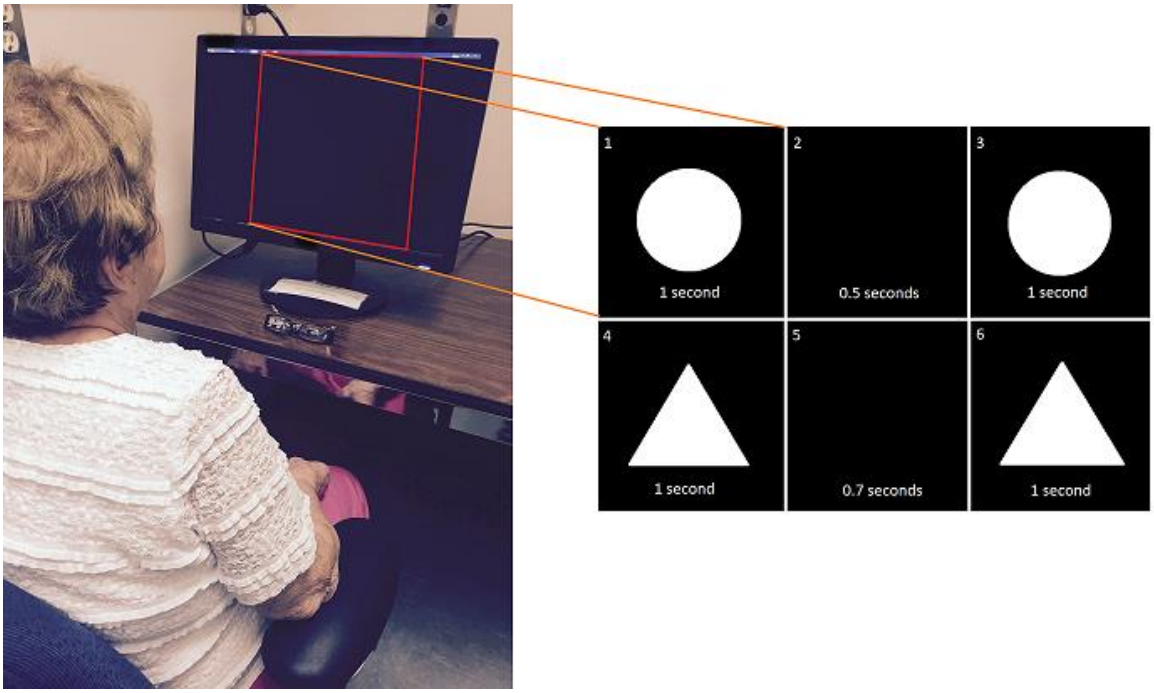

Figure 2.6: Experimental Setup and Visual Temporal Perception Task

For testing the LG Flatron W2242PM 22-inch (resolution 1680 x 1050) computer monitor was used, with participants sitting at a comfortable viewing position approximately 2 feet away from the monitor. The testing room has only the participant and experimenter, with excess stimuli (such as sounds, distracting visual) minimized. Illustrative examples of the visual temporal discrimination task shown on right, with each quadrant section representing a specific time window in a single trial on the computer monitor viewed by the participant. In each trial, the participant compares the time period between the appearance of circles to the time period between the appearance of circles. The participant verbally answers which time period they perceived to be smaller. The example trial begins with Image 1 being shown for 1 second, followed by Image 2 being shown for 0.5 seconds, followed by Image 3 being shown for 1 second. After a 1 second period where the screen is blank, Image 4 is shown for 1 second, followed by Image 5 being shown for 0.7 seconds, followed by Image 6 being shown for 1 second

2.4.2 Testing Apparatus

A graphics-enabled tool running in Matlab/Simulink was designed at Canadian Surgical Technologies and Advanced Robotics (CSTAR) to examine vision-based temporal perception. The graphical environment of this toolbox can be easily modified, allowing for the examination of various visual sensory modalities. The tool was utilized to study visual temporal discrimination in the current study, with all visual inputs being displayed on an LG Flatron W2242PM 22-inch monitor (resolution: 1680 x1050). The participants sat approximately 2 feet away from the monitor (Fig. 2.6). The height of the chair and the monitor were adjusted for optimum comfort. In order to reduce possible visual and auditory distractions, the subjects were located in an isolated room with the experimenter. Fig. 2.1 shows the station utilized for the experiment.

2.4.3 Experiment

A two-forced alternative choice experiment consisting of 160 trials based on the method of constant stimuli for difference thresholds described by Gescheider [40] was carried out to examine temporal perception. Each trial in the experiment began with a large, central white circle appearing in the middle of the computer monitor for 1 second before disappearing, leaving a blank screen. After a variable amount of time, the white circle reappears for 1 second, before again disappearing. This is followed by the appearance of a large, central white triangle on the monitor for 1 second, disappearing for a variable amount of time, and reappearing for 1 second before disappearing. At the end of each trial the subject compares the period of time between the appearance of the circles to the period of time between the appearance of the triangles, verbally answering which time period they perceive to be the shortest (can alternatively be thought of as "which shape was blinking the fastest"). The participant had no time constraints regarding their response, thus although movement was necessary to produce a response, it had no effect on the analysis of patient perception. At the 80th trial, a mandatory break was given to the participants, with as many additional breaks as desired by the participants given throughout the experiment. Two standard stimuli of 0.5 and 1 seconds were tested, with one of these two standard stimuli

being present in every trial. The presentation of stimuli comparisons was completely random, with both standard stimuli being blended together for testing. For each standard stimulus there were 8 comparison values: 0.1, 0.3, 0.4, 0.45, 0.55, 0.6, 0.7 and 0.9 seconds for the standard stimulus of 0.5 seconds; and 0.2, 0.6, 0.8, 0.9, 1.1,1.2, 1.4 and 1.8 seconds for the standard stimulus of 1 second. The comparison values were chosen so that those differing in magnitude the least from the standard stimulus was answered correctly approximately 50% of the time, and those differing the most in magnitude from the standard stimulus were almost always answered correctly (Fig. 2.6). It should be noted that control and de novo PD patients conducted the experimental task once, whereas the PD patients using levodopa and DBS conducted the task twice (in both their ON and OFF states). It is unlikely that the repetition of the experiment lead to improvements based on experiment familiarity however as the PD participants only conducted the task once in a given therapeutic state (with task familiarity not transferring over through therapeutic states). Furthermore, although the enhancement of neural networks related to visual perceptual tasks can occur in adults (i.e. visual perceptual learning), this is a long-term change that would not occur in a single experimental session (such as our work) [74, 75].

2.4.4 Analysis

The number of correct and incorrect responses were computed for each comparison value of a particular standard stimulus. These values were input into the Psignifit 4.0 third party Matlab toolbox, creating a cumulative Gaussian distribution psychometricfunction76. From the psychometric function the Point of Subjective Equality (PSE), Upper Threshold (UT) and Lower Threshold (LT) (points on cumulative Gaussian distribution function correlating to 0.5, 0.75 and 0.25 points on the x-axis respectively [Fig. 2.1]) were obtained and utilized to calculate the participants difference threshold (DL), calculated as $DL = PSE - LT$ or $DL = UT - DL$ (Fig. 2.1). As described by Gescheider [40], the DL is a value that signifies the difference in the stimulus magnitude necessary for a participant to discern a stimulus as being different from the standard stimulus that it is compared to. Thus, the smaller one's DL is the more sensitive they are towards the tested perceptual modality at the given standard stimulus [40]. Apart from perceptual sensitivity, the perceptual coherency of a participant was also analyzed using WF. According to Weber's Law, the

ratio of DL to standard stimulus is constant across the magnitudes of stimuli [40]. This is displayed through the WF, defined as WF=DL/S, where S represents the standard stimulus magnitude.

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Chapter 3

3 Abnormal Vision-Based Displacement Perception and Perceptual Linearity in Parkinson's Disease

This chapter contains the paper (with the same title) that is being considered for journal publication. This work has been published in its preliminary form in the *40th International Conference of the IEEE Engineering in Medicine and Biology Society, Honolulu, USA, 2018* conference proceedings, titled "Visual Displacement Perception in Parkinson's Disease Analyzed Using a Computer-Generated Graphical Tool".

3.1 Introduction

Parkinson's disease is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the brain stem [1]. The disease phenotype is typically classified by the heterogeneous presence of motor symptoms such as resting tremors and muscle stiffness [2]. However, non-motor symptoms can arise at all disease stages, often posing greater detriments in patient quality of life, and eliciting greater influence on institutionalization and economical health burdens compared to motor symptoms [3–5]. The current PD monitoring practice lacks accurate diagnosis of non-motor impairments, thereby leading to a lack of recognition and treatment for many of these symptoms [3, 6]. Furthermore, the severity and extent of non-motor impairments has not been fully described in PD [7]. The breadth of knowledge regarding non-motor PD symptoms is however growing, with an increasing amount of research on sensory, neuropsychiatric, autonomic, and sleep dysfunction [8].

In this regard, visual and oculomotor dysfunctions have frequently been observed in patients suffering from PD [3, 9, 10]. Impairments in colour contrast perception, hallucinations, and oculomotor control were some of the first documented visual impairments in PD, arising across many disease stages [11–14]. Visuospatial abnormalities also commonly affect individuals who have PD, with 78% of patients in a self-reporting study displaying either visual, visuospatial or both visual and visuospatial deficits [15]. Although these spatial deficits can hinder performance in memory, representation and perceptual tasks in three-dimensional space, they can also pose risks to the patients' health

and quality of life [15]. Visuospatial impairments contribute to balance deficits, increasing the chance of falling, thus, increasing the risk of injury; which can be exceedingly problematic as PD patients display greater reliance on vision for movement than their non-PD counterparts [15–17]. Abnormal visuospatial perception of objects in the environment also contributes to movement abnormalities in PD such as freezing of gait (FOG; difficulty with the initiation of walking) [18, 19]. Furthermore, impairments in attentional tasks and tasks involving accurate limb movement in response to perceived visual stimuli occur in PD [20, 21]. However, most of the studies that have explored visual perceptions caused by PD have involved associated movement responses, raising the question: what is causing the observe dysfunctions? Sensorimotor integration impairments are well documented in PD, and likely contribute to many of the studied visual perception deficits [22–24]. In addition, the BG - a brain region drastically affected by PD - is known to be an important group of subcortical nuclei involved in the production and fine tuning of accurate movements [25]. *Thus, it is not clear in many studies if there are abnormalities in isolated visual perceptions of space, or if the deficits are caused by sensorimotor integration and/or motor deficits arising from movements produced in response to the tested visual stimuli.*

Although those with PD show deficits in proprioceptive displacement and egocentric (visual perception using one's own body as a reference point) displacement perceptions [23, 26–29], allocentric (visual perceptions using an object as a reference point) displacement perception independent of motor outputs has not been investigated yet. Neural regions associated with allocentric visual space representations are used in the recognition and memory of objects, with visual information largely being processed down the ventral occipitotemporal stream [30, 31]. Since the ventral stream processes visual information to identify objects as opposed to direct movements in response to visual stimuli (which is processed down the dorsal stream), studying the effect of PD on perceptions processed by the ventral stream may provide evidence that visual processing independent of motor activity is abnormal in PD, helping to explain phenomena occurring in PD that utilize this processing stream [30]. Movement abnormalities like FOG and environmental navigation deficits in PD may be caused in part by inaccurate representations of visually perceived objects [15, 17–19]. Individuals with PD also show impairments in object recognition and accurate recognition of some facial emotions [32–35]. The above-

mentioned deficiencies occurring in PD all utilize allocentric visual displacement information, using distances between objects and object features to create the full representations necessary for accurate recognition. This provides evidence that there may be disturbances in the ventral occipitotemporal visual processing pathway in PD.

The current study has sought to answer three research questions. The main objective of this study (the **first research question**) was to explore potential visual allocentric displacement perception abnormalities occurring in PD independent of motor-responses and specific object-related memories. The results provide insight into the potential ventral visual processing abnormalities occurring in PD. This is building on preliminary work which showed a small sample of PD patients had impairments in this perception, prompting further, more in-depth investigation. In addition, in this work (as the **second research question**) we examine the effect that levodopa (half-life: 0.5-1.5 hours) medication and DBS of the subthalamic nucleus have on allocentric visual displacement perception. Early-stage PD patients not currently utilizing PD therapies known as “de novo” PD patients were also examined, allowing for analysis over a range of PD disease stages. Levodopa is a common first-line treatment that generally improves motor dysfunction occurring in PD. However, it has variable effect on the non-motor features [3]. This is exemplified in the visual system through improvements in colour contrast perception after levodopa administration and detriments in the proprioceptive perception of arm displacements [26, 36]. DBS has proven to be an effective late-stage PD treatment, specifically when levodopa side effects such as dyskinesia and motor fluctuations are severe [37]. DBS in general elicits effects similar to levodopa (when it is optimally functioning), with it also displaying varying therapeutic effects depending on the non-motor symptom [38]. As levodopa and DBS can improve, impair or have no effect on a given non-motor symptom, its effect on visual allocentric displacement perception was unknown. This provided further motivation for the study to investigate the positive or negative effects of these PD therapies on allocentric visuospatial perception. The third research question that was investigated deals with linearity between perceptual accuracy and stimulus magnitude, an important perceptual trend consistently occurring in healthy individuals. This trend was first observed in the nineteenth century when E.H. Weber sought a method to quantify perceptions independent of the perceptual modality. Based on

his studies, the DL of weight perception was found to be related to stimulus intensity as a linear function [39].This work, continued by G. Fechner, has led to Weber's Law, which states that the ratio of an individual's DL (amount of magnitude change necessary to discern a stimulus from a different stimulus of fixed magnitude [standard stimulus]) to the standard stimulus is constant [40]. The quantifiable value of Weber's Law, WF, is defined as $WF = DL/S$, where S represents the standard stimulus magnitude. Weber's Law has been validated in a large number of tested modalities [39, 40]. It is widely accepted that perceptions of healthy humans measured by WF have a linear relationship, following Weber's Law. Motivated by this, the current study measured participant WF to analyze the linearity of visual displacement perception, evaluating if individuals with PD display linear relationships in allocentric displacement perception of different stimuli magnitudes. To our knowledge this is the first time WF is used to evaluate perceptual capabilities of PD patients. Its use was motivated by the observation of potential underlying phenomena regarding the effects of PD therapies which cannot be observed through the direct measurement of absolute changes in perceptual capability. If validated in this study this could be used as a strong tool to investigate the effect of PD and dopaminergic medications deeper with regards to its potential benefit for not only perceptual ability, but also on the underlying perceptual patterns seen through perceptual linearity.

3.2 Methods

3.2.1 Participants

Thirty-seven patients with middle- to late-stage PD (30 male, 7 female) and 15 healthy, age-matched controls (12 female, 3 male) with no known neurological or psychiatric disorders participated in the study. The PD patients were recruited from the Movement Disorders Program at London Health Sciences Centre, University Hospital in London, Ontario, Canada, where they were diagnosed and regularly treated. All patients fulfilled the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria. Of the 37 PD patients, 25 were treated using levodopa medication daily. At the beginning of the experiment the PD patients refrained from taking Levodopa for at least 12 hours, ensuring they were completely OFF Levodopa. After the patients performed the experiment in OFF Levodopa conditions, they were administered 300 mg of levodopa (unless their regular dose was 100

mg or lower, in which case they were administered 200 mg). None of the patients had dyskinesia with this acute dose. The patients conducted the experiments ON and OFF levodopa on the same day, with a break of an hour between drug administration. Motor symptoms were assessed ON and OFF levodopa using section 3 (motor sub-scale) of the UPDRS. Six of the PD patients were using DBS therapy. If these individuals were also using levodopa they were asked to refrain from using the medication the day of testing. When the patients using DBS entered the lab their DBS device was turned OFF. After a 45-minute waiting period they carried out the examinations in the same fashion that patients using levodopa did. After completing the first round of experiments their DBS device was turned back ON to the exact same parameters it was set to when the patient arrived for testing. De novo PD patients (n = 6) only had to carry out the experiments once as they were not using any PD therapies. Neurological assessment of PD patients was conducted using the MoCA [41]. Visual assessments for visual acuity (using reading tasks and the Snellen eyechart), smooth pursuit and saccades were performed on all patients by an experienced clinician. Patients were excluded from the study if they displayed visual, visuomotor or substantial cognitive impairments (MoCA < 25). Furthermore, PD patients experiencing PD-VH were excluded from the study. Parkinson's Disease patients using pharmacological medication other than levodopa were also omitted from the study. The study protocol for this work was approved by the Research Ethics Board of the University of Western Ontario (REB# 107253). All experiments were conducted in accordance with the Declaration of Helsinki, as well as the Tri-Councel Policy Statement of Ethical Conduct for Research Involving Humans in Canada. All participants provided informed consent regarding their participation in the study. Furthermore, the participant displayed in Fig. 3.1 provided consent allowing for their image to be used in publications of the research.

3.2.2 Testing Apparatus

Participant visual input for the tests was solely displayed on a LG Flatron W2242PM 22-inch visual monitor (resolution: 1680x 1050). Participants sat in a comfortable, upright position 2 feet in front of the computer monitor (Fig. 3.1). Both the height of the chair and monitor were adjusted for optimum viewing. Each participant and the examiner were in an isolated room, minimizing auditory and visual distractions. The visual perception test

was run in a graphics environment designed at CSTAR and connected to a Matlab-Simulink program controlled by the experimenter.

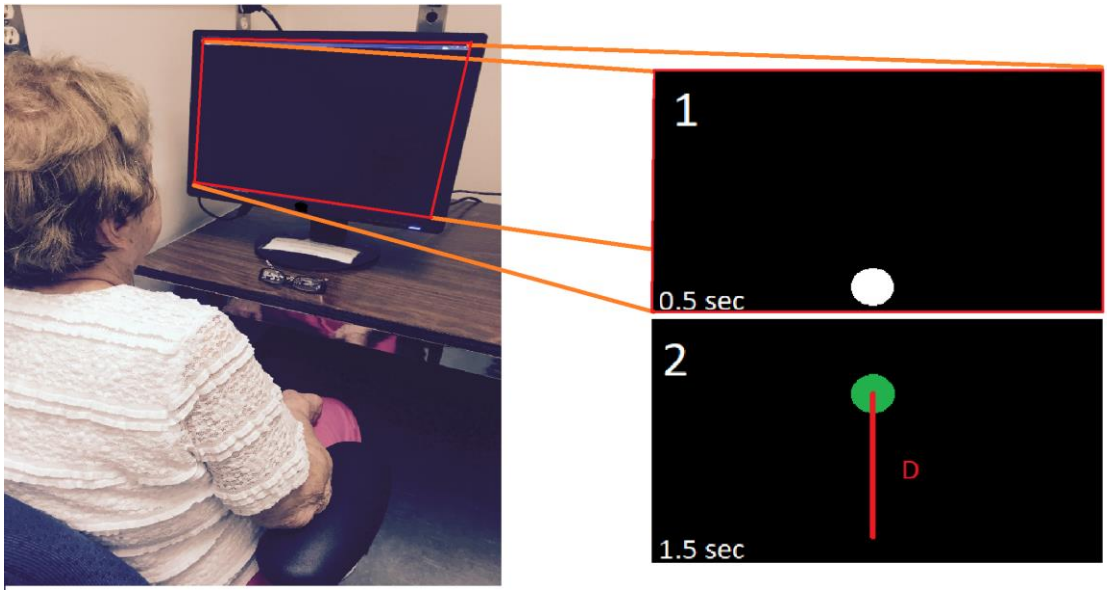

Figure 5: Testing apparatus and displacement perception experiment. The perceptual task was conducted on the LG Flatron W2242PM 22-inch (resolution 1680 x 1050) computer monitor at a comfortable viewing position for the participant, who is sitting approximately 2 feet away from the monitor. The testing room has only the participant and experimenter, with excess stimuli (such as sounds, distracting visual) minimized. To the right an illustrative example of the allocentric visual displacement perception task with each image-pane showing a specific time window in a single trial on the computer monitor viewed by the participant. In each trial the participant compares a pair of white to green circle displacements (only one displacement shown here). The participant verbally answers which displacement distance they perceived to be greater. The example trial begins with Image 1 being shown for 1 second, followed by Image 2 being shown for one second. After a 1 second period where the screen is blank, a similar process is repeated, however the displacement distance (D) is different. It should be noted that the red line is not shown in the experiment. Displacement (D) is used in this figure to show the displacement distances that are estimated by the participant (and compared to another circle displacement.

3.2.3 Analysis

Initially the correct and incorrect patient responses from the experiment were computed for each comparison value of a given standard stimulus. This data was input to the Psignifit

4.0 third quality party Matlab toolbox, which produced a cumulative Gaussian distribution psychometric function [42]. The participants' PSE for both standard stimuli were calculated by this toolbox. The UT and LT signify the magnitude of displacement that was discerned from the standard stimulus 75% of the time [39], and was obtained through analysis of the psychometric function, described in Fig. 3.2. As seen in Fig. 3.2, the DL was calculated by subtracting the LT from the PSE, of the PSE from the UT (both yielding the same result due to function symmetry). The DL signifies the difference in stimulus magnitude necessary to differentiate it from the standard stimulus. Thus, smaller DLs signify better perceptual ability. Datum points were considered outliers and omitted from analysis if they were $1.5 * IQR$ above the third quartile, or $1.5 * IQR$ below the first quartile.

3.3 Results

3.3.1 Demographic Data, PD Related Clinical Characteristics

In this study, 37 PD patients in total were tested; 25 (22 male, 3 female) using levodopa, 6 (4 male, 2 female) using DBS, 6 (4 male, 2 female) de-novo patients, and 15 control participants (12 female, 3 male) were included. All participants were recruited from the Southern Ontario region. Demographic and clinical data for the PD patients are shown in Table 3.1. All patients were examined for oculomotor deficits by an experienced clinician and only those without deficits were recruited.

3.3.2 PD vs. Control Displacement Perception Findings

The DL was the main descriptor used to quantify the perception of participants. The DL signifies the change in magnitude necessary to perceptually differentiate a stimulus from the standard stimulus. Smaller DLs signify increased perceptual sensitivity (Fig. 3.2). The task to measure displacement perception is displayed in Figure 3.1. The results of PD and control participants were fit to a cumulative Gaussian distribution, produced using the Psignifit 4.0 third party Matlab toolbox (as seen on Fig. 3.2). The individual cumulative Gaussian distribution curves produced by a certain participant in a certain condition display an inverse relationship between subject DL and curve slope, with greater slopes and function shifts implying impaired perception (Fig. 3.3). The paired two -tailed t-test was utilized for statistical analysis of PD patients, comparing their perception ON and OFF

levodopa. The unpaired (independent samples) two-tailed t-test was used for comparisons between PD and control groups.

Table 3.1: Demographic and clinical data for PD patients. Abbreviations: MoCA – Montreal Cognitive Assessment; UPDRS – Unified Parkinson's Disease Rating Scale

Demographic Data	Levodopa	DBS	De Novo	Control
Number	25	6	6	15
Age (years)	70.04 ± 6.80	55.16 ± 8.99	74.17 ± 3.97	67.26 ± 9.04
Sex (m/f)	22/3	4/2	4/2	3/12
Total Years of Education	13.4 ± 2.14	13.33 ± 2.50	13.00 ± 1.67	14 ± 1.79
Clinical Data				
MoCA (out of 30)	26.68 ± 2.17	26.67 ± 3.08	27.83 ± 2.14	27.13 ± 1.50
UPDRS motor sub-scale OFF Therapy	23.92 ± 6.69	34 ± 10.51	22.33 ± 7.91	N/A
UPDRS motor sub-scale ON Therapy	14.72 ± 6.07	22.33 ± 7.91	N/A	N/A
UPDRS motor sub-scale OFF vs. ON Difference	9.20 ± 5.09	21 ± 5.62	N/A	N/A

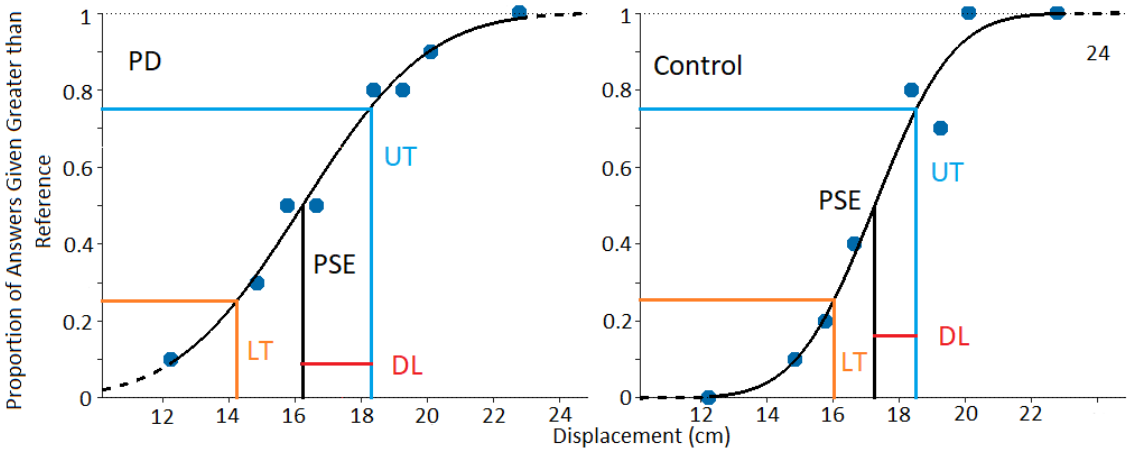

Figure 6: Individual Cumulative Gaussian Distribution examples used for subject analysis regarding displacement perception abilities. Subject DL was analyzed by subtracting the PSE from the Upper Threshold (UT; or subtracting the Lower Threshold [LT] from the PSE). The UT and LT are the points of the function which the subject answered correctly 75% of the time for a given standard stimulus. Larger DLs signify decreased perceptual sensitivity**.**

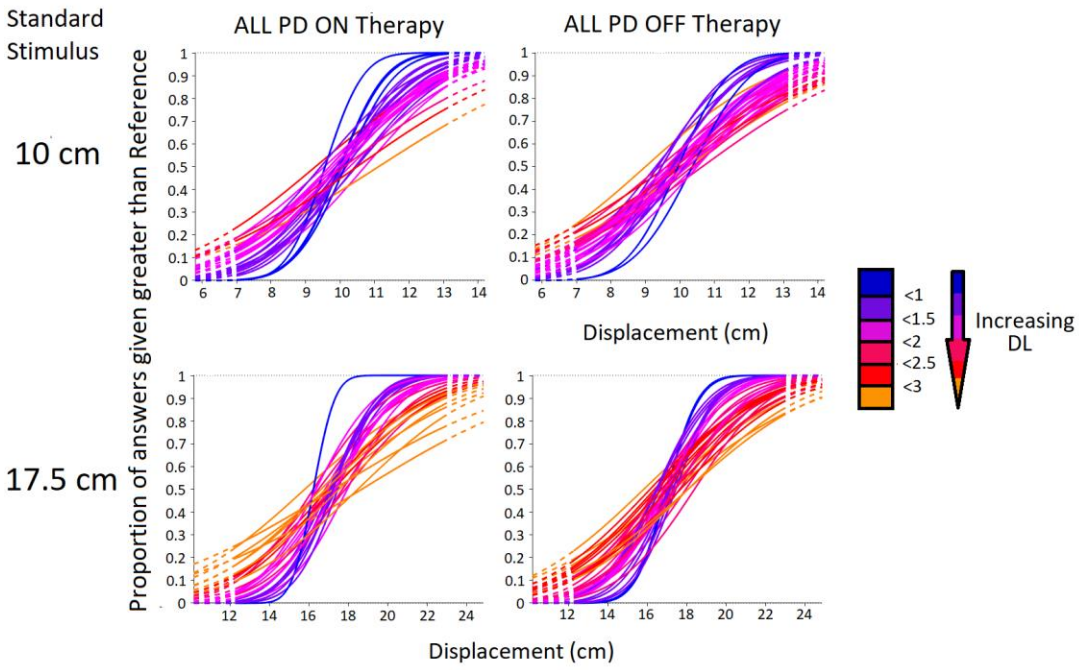

Figure 7: Displacement Perception Gaussian distributions showing perceptual performance of individual PD participants using Levodopa. Sub-figures categorized by therapeutic state and standard stimulus. Curves are colour coded based on participant DL (which is inversely proportional to function slope) for a certain condition. Curves that are more blue belong to participants displaying lower DL's (greater slopes) and thus having better perceptual abilities, with red/orange curves signifying the opposite.

For the displacement perception experiment, two different displacement magnitudes were used, with the standard stimulus for smaller magnitudes being 10 cm, and the standard stimulus of larger magnitudes being 17.5 cm. When comparing all PD patients to control participants, there were no abnormalities in displacement seen at the smaller standard stimulus between individuals with Parkinson's disease and control individuals OFF their respective therapies (the average DL for PD patients OFF their therapy was 1.6944 ± 0.48; the average DL for control participants was 1.6026 ± 0.58; p-value = 0.595) and ON their respective therapies (the average DL for PD patients ON their therapy was 1.5037 ± 0.47; p-value = 0.566) (Fig. 3.4). However, for the larger tested standard stimulus of 17.5 cm, PD patients displayed significant impairments in visual displacement perception OFF of their respective therapies (the average DL for PD patients OFF their therapy was 2.2207 ± 0.75; the average DL for control participants was 1.6956 ± 0.44; p-

value = 0.006), as well as significant impairments while ON their PD therapies (the average DL for PD patients ON their therapy was 2.1043 ± 0.78; p-value = 0.033) (Fig. 3.4).

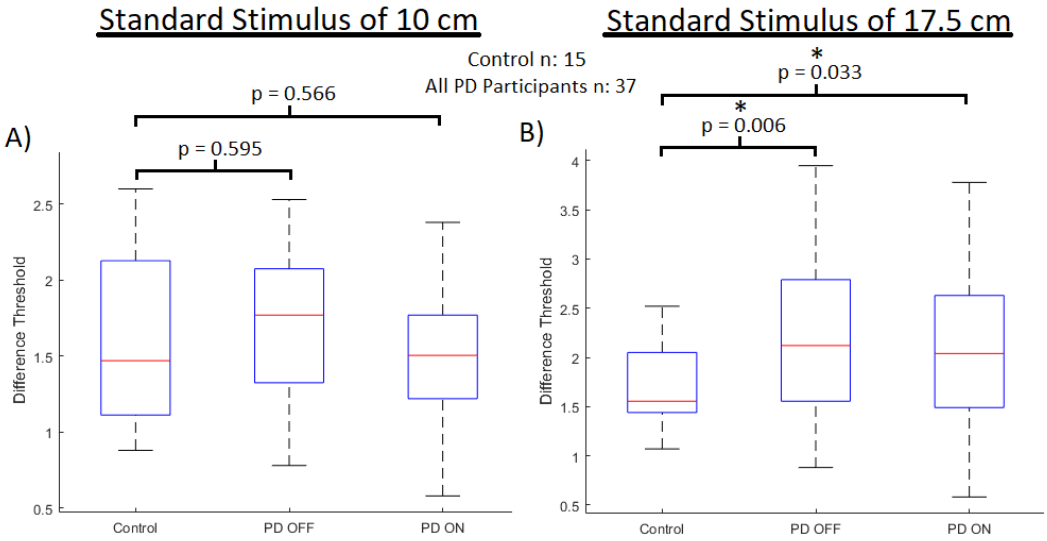

Figure 8: Displacement Difference thresholds of all PD patients compared to control participants. The standard stimulus of 10 cm is displayed on the left, and 17.5 cm on the right; with boxplots related to PD patients OFF and ON their respective PD therapies compared to control participants. The red lines are the median DL for each group. The bars represent the data spectrum. PD patients did not show any impairments in displacement perception at the standard stimulus of 10 cm ON or OFF of PD therapies. However, there were significant impairments seen at the standard stimulus of 17.5 cm OFF PD therapies (p-value =0.006) and ON PD therapies (p-value = 0.033).

Considering only the PD patients utilizing levodopa medication for the standard stimulus of 10 cm, the average DL for PD patients OFF levodopa was slightly and insignificantly greater (p-value = 0.954) than that for control participants (the average DL for patients OFF levodopa was 1.6132 ± 0.49; the average DL for control participants was 1.6026 ± 0.58). PD patients also showed slightly, however insignificantly increased DLs (p-value = 0.372) when they were ON levodopa compared to the tested controls (the average DL for patients ON levodopa was 1.4115 ± 0.36) (Fig. 3.5). Thus, at the smaller magnitudes of displacement there was no observed perceptual impairments of displacement in PD patients both ON and OFF levodopa. For the larger tested standard stimulus (i.e., 17.5 cm), the DL of PD patients OFF levodopa was significantly greater (p-value = 0.041) than control participant DLs (the average DL for patients OFF levodopa

was 2.0892 ± 0.68; the average DL for control participants was 1.6956 ± 0.44). In addition, there was a relatively strong trend (p-value = 0.120) regarding greater DLs for PD patients ON levodopa compared to control participants (the average DL for patients ON levodopa was 2.0318 ± 0.79) (Fig. 3.5). Thus, at the greater tested magnitudes individuals with PD showed significant perceptual impairments in displacement ON and OFF levodopa compared to the tested controls.

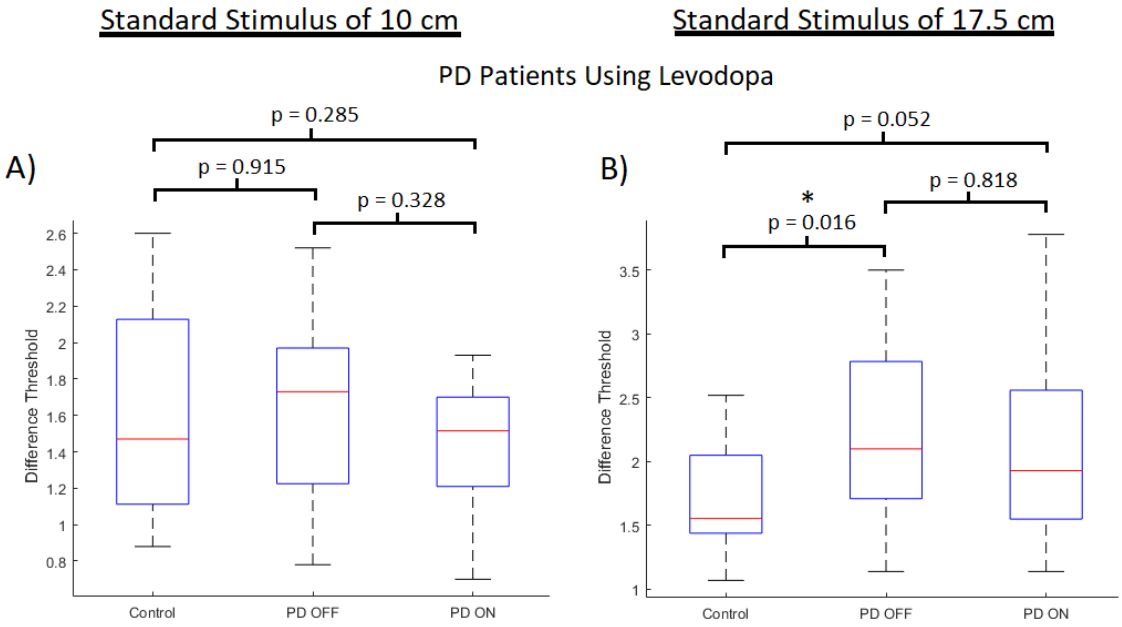

Figure 9: Displacement difference thresholds comparing control subjects to PD patients using Levodopa. DL's obtained through displacement perception examination with the standard stimulus of 10cm being shown on the left and of 17.5 cm on the right. The red lines are the median DL for each group. The bars represent the data spectrum. Regarding the standard stimulus of 10 cm, there were no significant differences in DLs observed between PD patients OFF Levodopa and controls, PD patients ON levodopa and controls, and PD patients ON and OFF levodopa. For the standard stimulus of 17.5 cm, significant differences in DL were observed between PD patients OFF Levodopa and controls (p-value = 0.041), and a relatively strong trend regarding increased DLs between PD patients ON levodopa and controls (p-value = 0.120) were also seen.

Levodopa medication did not elicit any significant effects on the perception of displacement. Regarding the standard stimulus of 10 cm, an insignificant trend towards

reduced DLs was observed after the patient received levodopa (the average DL of patients OFF levodopa was 1.6088 ± 0.51; the average DL of patients ON levodopa was 1.4357 ± 0.56). In addition, for the standard stimulus of 17.5 cm there was a slight, but insignificant increase in DL (p-value = 0.655) after the participants received levodopa (the average DL of patients OFF levodopa was 1.9539 ± 0.59; the average DL of patients ON levodopa was 2.0318 ± 0.79) (Fig. 3.5).

3.3.3 Displacement Perception Linearity

To assess correlations in the WF of the two tested stimuli magnitudes the Pearson correlation coefficient was used. Typically, it is expected that there will be a linear relationship between the WF of different standard stimulus magnitudes (based on Weber's Law), which is signified by substantial correlations between WFs of different standard stimuli. This study shows that for the control group, there was very strong correlation between the WF of the standard stimuli (Pearson correlation (R): 0.928, p-value < 0.001). When comparing all PD patients OFF their respective therapies together, they did not show a significant correlation between WFs of the tested standard stimuli (R = 0.250, p-value = 0.135). However, when all PD patients were using their respective therapies, there was a significant correlation seen between the WFs (R = 0.762, p-value < 0.001). When specifically looking at the PD patient group that was using levodopa, significant correlations were not observed for the WF of different standard stimuli when OFF levodopa (Pearson correlation: 0.235, p-value = 0.258). When these PD participants were administered levodopa, strong correlations were observed between the WFs of different stimuli (Pearson Correlation: 0.821, p-value < 0.001) (Fig. 3.6). The above is summarized in Table 3.2.

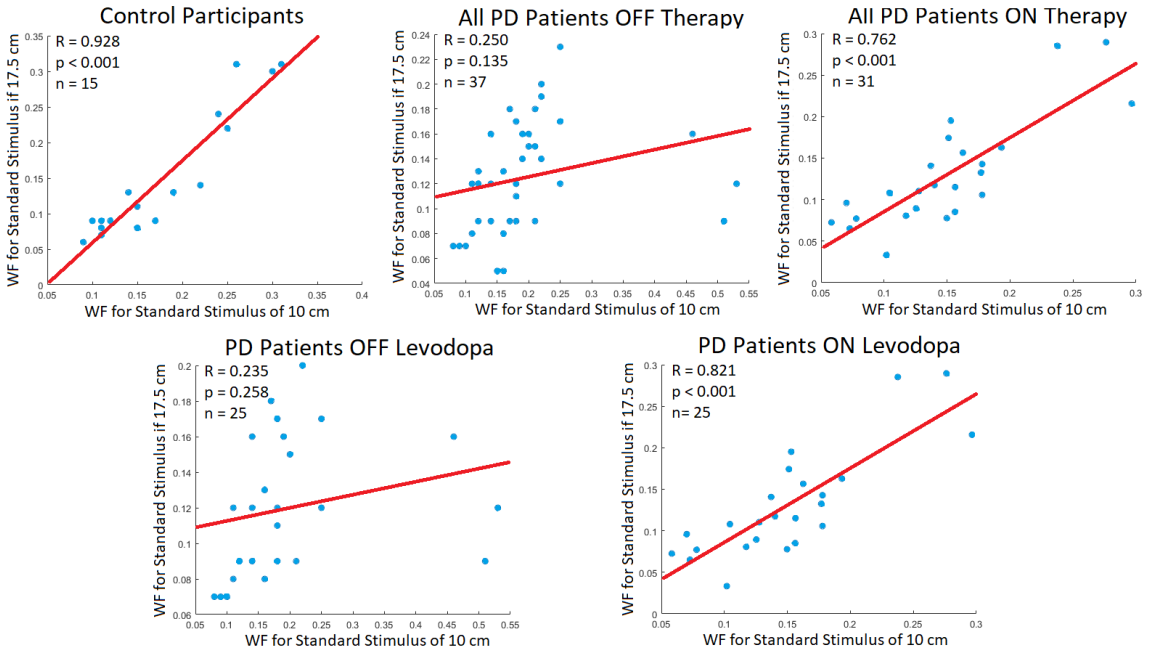

Figure 10: Correlations between participant WF at the standard stimuli of 10 and 17.5 cm. The red line signifies the line of best fit for the correlation data points. Points that have a high similarity between their x and y axis values signifies that the participant followed Weber's Law, displaying little to no difference in the WF calculated at the standard stimuli of 10 cm and17.5 cm. Correlation plots for DBS and de-novo PD patients are not shown due to small sample sizes (n = 6 for each group)

Table 2.2: Results of correlations in WFs calculated at the standard stimuli of 10 cm and 17.5cm

Participant Group	**Correlations in WFs of Different Standard Stimuli Magnitudes (Pearson Correlation [R]; p-value)**
Control (n = 15)	R = 0.928; p < 0.001
All PD Patients OFF respective therapies (n = 37)	R = 0.250; p = 0.135
ALL PD Patients ON respective therapies (n = 37)	R = 0.762; p < 0.001
PD Patients OFF Levodopa (n = 25)	R = 0.235; p = 0.258
PD Patients ON Levodopa (n = 25)	R = 0.821; p < 0.001

3.4 Case Study A: Deep Brain Stimulation

Besides the results given in previous sections, in this work, a pair of small sample sized groups of patients using either DBS therapy or not using any PD therapies (early stage de-novo patients) were also analyzed as case studies. The intention of these case studies were to observe potential trends regarding the visual displacement perception abilities of early stage and late stage PD patients (de novo and DBS patients respectively), as well to see if any perceptual effect arose from the use of DBS. Due to the small sample sizes for these two groups the statistical tests act more so as indicators of trends rather than confirmation that certain differences are occurring between certain populations. The Gaussian distributions representing participant perceptual abilities are displayed on Fig. 3.7.

When looking at DLs between control participants and PD patients using DBS at the standard stimulus of 10 cm, PD participants displayed on average greater DLs (p-value = 0.032) than controls when OFF of DBS (the average DL for patients OFF DBS was 2.0702 ± 0.29). However, when ON DBS, there was only a slight, non-significant increase in DLs (p-value = 0.976) for PD patients compared to controls (the average DL for patients ON DBS was 1.60792 ± 0.20). With regards to the standard stimulus of 17.5 cm, patients OFF DBS displayed significantly greater DLs (p-value = 0.025) compared to control participants (the average DL for patients OFF DBS was 2.9901 ± 0.86). At the larger standard stimulus, small, insignificant increases in DLs (p-value = 0.158) were seen for PD patients on DBS compared to controls (the average DL for patients ON DBS was 2.347 ± 0.94) (Fig. 3.8). DBS patients displayed overall impairments in displacement perception, specifically when they were not using their treatment. PD patients using DBS in their OFF state displayed a strong correlation between the WFs of different standard stimuli (Pearson's Correlation: 0.972, p-value = 0.001). However, when these patients were ON DBS, they did not display any significant correlations in the WFs of the different standard stimuli (Pearson Correlation: 0.384, p-value = 0.452).

For these PD patients using DBS, no significant differences in DLs were seen between ON and OFF DBS states. At the smaller standard stimulus there was an

insignificant decrease in DLs (p-value = 0.167) when patients were ON DBS (the average DL of patients OFF DBS was 2.0609 ± 0.17; the average DL for patients ON DBS was 1.5749 ± 0.21). At the larger tested magnitudes (standard stimulus 17.5 cm) there was again an insignificant decrease in DLs (p-value = 0.560) when the patients were using DBS (the average DL for patients OFF DBS was 2.9907 ± 0.86; the average DL for patients ON DBS was 2.5819 ± 0.37) (Fig. 3.8). Although there were decreases seen when PD patients were using their respective therapies (especially for those on DBS), these improvements in DL were not significant. It should be noted that a strong trend towards reduced DLs was observed when participants were ON DBS. However, due to the small sample size of the DBS PD group (n = 6) it is possible that the statistical analysis is not representative of the therapy's perceptual improvements. In all but one of the patients using DBS, reduced DLs were observed when ON DBS at both standard stimuli magnitudes, further promoting the possibility of unrepresentative statistical outcomes.

3.5 Case Study B: de Novo Patients

The final patient group that was tested was the early stage de novo PD patients, who were not using any PD therapies at the time of testing. The Gaussian distributions representing participant perceptual abilities can be seen on Fig. 3.7. For the smaller standard stimulus of 10 cm, there was a slight, insignificant increase in the DLs (p-value = 0.749) of de novo PD patients compared to the control group (the average DL for de-novo patients was 1.6787 ± 0.44). At the larger tested standard stimulus of 17.5 cm, de novo patients displayed a strong (but insignificant) trend towards greater DLs (p-value = 0.158) compared to the control group (the average DL for de-novo patients was 2.3474 ± 0.94) (Fig. 3.8). Thus, early stage PD patients did not display significant differences in PD compared to the controls. The de novo PD participants did not show any significant correlations between the WFs of the tested standard stimuli (Pearson Correlation: 0.412, p-value = 0.416). All PD groups displayed discrepancies in Weber's Law in some therapeutic state, contrasting the control group which had a strong correlation between the WFs (Fig. 3.6). To reiterate again, the statistical analysis of the case studies are not necessarily representative of the patient subgroup populations due to their small sample size, however the trends that were found present interesting information on how the patients of different disease stages,

utilizing different treatments are affected by the disease. The above findings regarding perceptual linearity is summarized in Table 3.2, with the observations regarding perceptual ability being summarized in Table 3.3.

Table 3.3: Results for DL % increases and comparison of means via two-tailed t-tests for the Levodopa, DBS and De Novo PD groups

Compared Participant Groups (x vs. y)	**Increase in DL (%x > y); t test (x vs. y) p-value**		
	Levodopa (n = 25)	DBS (n = 6)	De Novo (n = 6)
PD OFF vs. Control (Standard Stimulus: 10 cm)	0.6614%; p = 0.954	29.19%; p = 0.032	4.755%; p = 0.749
PD OFF vs. Control (Standard Stimulus: 17.5 cm)	23.21%; p = 0.004	76.34%; p = 0.025	1.384%; p = 0.158
PD ON vs. Control (Standard Stimulus: 10 cm)	-11.64%; p = 0.372	0.3351%; p = 0.976	N/A
PD ON vs. Control (Standard Stimulus: 17.5 cm)	19.83%; p = 0.120	38.44%; p = 0.158	N/A
PD OFF vs. PD ON (Standard Stimulus: 10 cm)	12.06%; p = 0.164	28.75%; p = 0.167	N/A
PD OFF vs. PD ON (Standard Stimulus: 17.5 cm)	3.987%; p = 0.655	27.40%; p = 0.56	N/A

3.6 Discussion

This study investigated allocentric visual displacement perception while excluding goal-directed motor responses for those with PD. In addition, the effect of levodopa and DBS medication and perceptual linearity was investigated. The PD patient group showed overall impairments in displacement perception compared to controls. The observed deficiency cannot be due to oculomotor deficiencies since all participants were examined for these malfunctions before conducting the tests. Furthermore, PD patients with PD-D and PD-VH

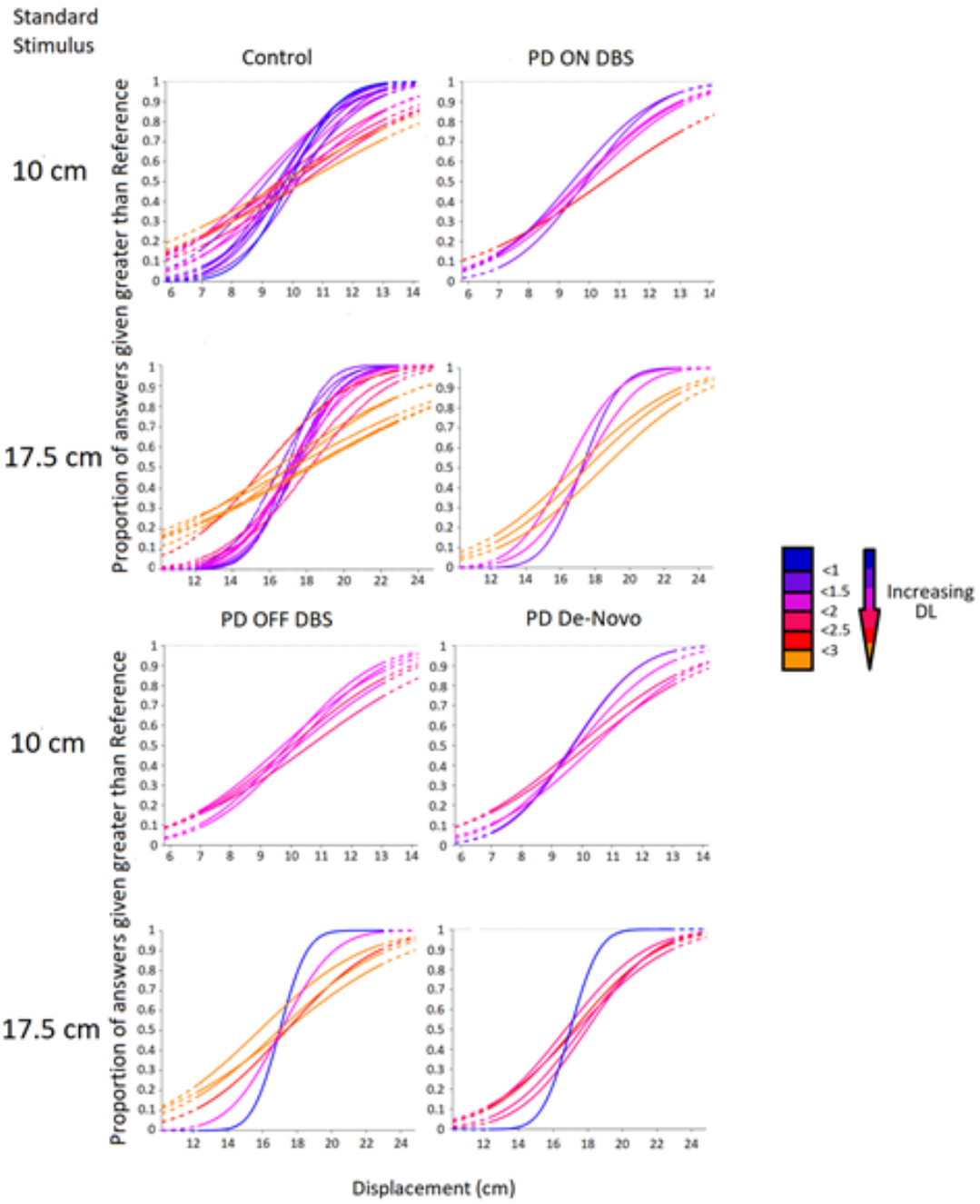

Figure 11: Displacement Gaussian distributions of individual participants categorized by disease state, therapeutic state and standard stimulus. Curves are colour coded based on the participants DL (which is inversely proportional to function slope) for a certain condition. Curves that are more blue belong to participants displaying lower DL's (greater slopes) and thus having better perceptual abilities, with red/orange curves signifying the opposite.

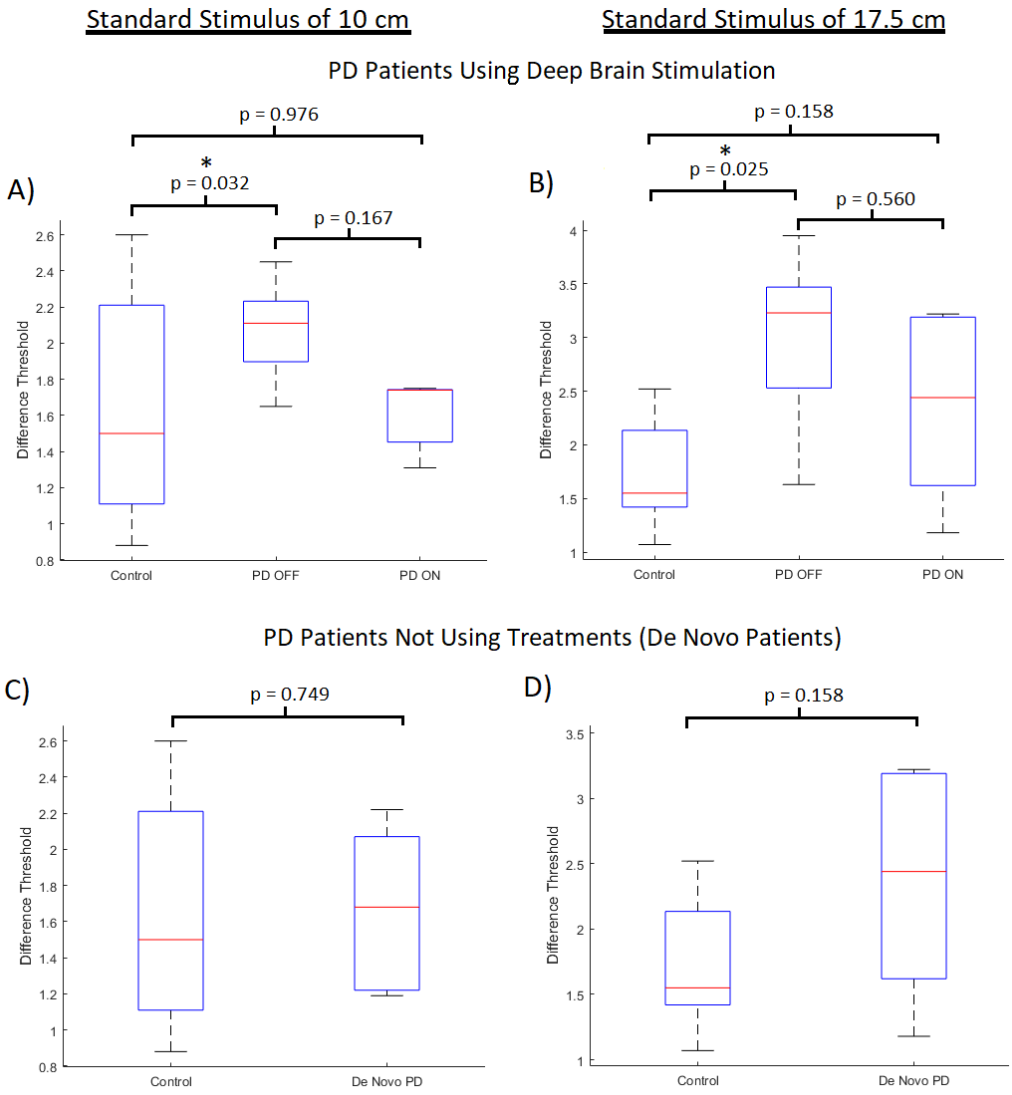

Figure 12: Difference thresholds obtained through displacement perception examination of DBS and de novo patients. The standard stimulus of 10cm is shown on the left and 17.5 cm on the right. The red lines are the median DL for each group. The bars represent the data spectrum. Regarding the standard stimulus of 10 cm, patients using DBS had significantly greater (p-value = 0.032) DL's than controls while OFF DBS; however, when ON there were no significant differences. There was also no significant difference between patients ON and OFF DBS. De novo patients did not display patients using DBS had significantly greater DLs than controls when OFF DBS (p-value = 0.025) as well, however no significant differences were seen in DLs between patients ON DBS and controls. There were no significant differences between de-novo patients and control patients at this standard stimulus. Levodopa and DBS did not elicit significant changes in DL for PD patients.

were omitted from the study. Therefore, the observed perceptual abnormalities are not likely due to cognitive deficit. Thus, the current study showed that allocentric visual displacement perception is abnormal in mid-stage PD patients (using levodopa), and late stage PD patients (using DBS), and that observed deficiencies are not likely arising from the motor or sensorimotor integration complications of the disease due to the task isolating perception from motor activity. The early stage PD patients did not however show significant impairments in the visual displacement perception task.

In general, PD patients showed increased DLs – signifying decreased perceptual sensitivity – in visual displacement perception compared to the control group for the larger tested displacement magnitudes. Previous research has shown that patients with PD-D and/or PD-VH (both common in late stage PD) displayed impaired visual memory and object perception [43, 44]. Both vision-based memories and perception of specific objects are neurally processed through the ventral occipitotemporal processing stream [30]. However, it cannot be determined if executive, visuospatial and memory impairments occurring in PD-D, and visual abnormalities due to PD-VH were responsible for the observed visual memory and object perception deficits, or if the findings were caused by deficits in the ventral processing stream [30, 31, 45, 46]. The current study however provides evidence that impairments in the occipitotemporal visual processing stream occur in mid-stage PD before PD-D and PD-VH symptoms arise. It is important to note that although working memory and attentional deficits are well noted symptoms of PD [47, 48], it is unlikely that these contributed to the observed perceptual abnormalities for the levodopa and de novo PD groups as no deficits were seen at the smaller displacement magnitudes that were tested. This further provides new evidence that the observed allocentric displacement perception dysfunctions may be arising due to disruptions in the ventral occipitotemporal pathway. Our findings along with past work showing impairments of object identification and recognition of facial features and emotions [32–35] might indicate dysfunction in neural regions along the ventral visual processing stream that respond to certain classes of objects (and specific objects/faces) such as the inferior temporal cortex and fusiform face area [49, 50]. It should be noted patients that were utilizing DBS therapy did however show deficits in the perception task at both testing magnitudes. As individuals in this study that were using DBS were at a later stage of the

disease, it is possible that the increased disease severity contributed to memory and/or attentional deficits which lead to decreased performance at all testing magnitudes. However, increasingly severe PD symptoms may lead to an increasingly impaired processing of visual displacements via the occipitotemporal pathway, leading to a broader range of perceptual deficits. This note is further motivated due to all PD patients conducting memory tasks, with those showing substantial deficits being excluded from the study.

Levodopa and DBS were shown to have no significant effect on the tested visual displacement at both of the tested standard stimuli, aligning with past studies suggesting these therapies predominantly benefit PD motor symptoms, having a minimal effect on non-motor symptoms [3]. Both levodopa and DBS modulate dopaminergic neural pathways of the BG, however, neural dysfunction in PD is not limited to dopaminergic dysfunction in the BG [37]. Non-dopaminergic neural abnormalities (such as cholinergic, noradrenergic and glutamatergic dysfunction) also contribute to PD symptoms [51]. In this regard, FOG, which is heavily influenced by improper visuospatial perception, responds poorly to dopaminergic treatment [18]. Also, recent work suggests the occurrence of FOG is based on improper noradrenergic neural function as opposed to dopaminergic dysfunction [52]. As visuospatial processing involves both allocentric and egocentric visual perceptions [31], the perceptual abnormalities observed in the current study may contribute to the visuospatial deficits seen in PD. This suggestion is further supported by the lack of a significant response from levodopa in the current study, which is consistent with levodopa's lack of effect on PD symptoms utilizing visuospatial information (such as FOG). Furthermore, past research concluded levodopa did not lead to improvements in the object recognition capabilities of PD individuals [53]. Thus, the lack of effect caused by levodopa for previously researched visual perceptions utilizing displacement information and in our current study suggests the postulated ventral visual processing stream impairments in PD are not caused by dopamine related dysfunction. Interestingly, past work has suggested that DBS of the subthalamic nucleus lead to impairments in the recognition of certain facial emotions [54]. Although accurate facial emotion recognition requires much more than just visual displacement perception, this further contributes to the idea that the observed perceptual abnormalities are not caused by a dysfunction of dopamine dependent BG processes. However, it should be noted that a relatively strong

trend regarding reductions in patient DL when ON DBS (compared to when OFF DBS) was observed. Furthermore, statistical abnormalities were seen in the DL of DBS patients OFF stimulation compared to controls, with no statistical observations seen when these patients were ON stimulation (Fig. 3.8). Thus, it appears DBS might cause improvements of visual displacement perception abnormalities seen in PD patients; however, due to the small sample size of PD patients using DBS, future work should further investigate this therapies effect on the tested perception.

In the current study, patients with PD in general did not show linear perceptual capability in visual displacement perception. To the best of our knowledge this is the first time that linearity of a perceptual ability and the effect of dopaminergic medication has been investigated in patients with PD. Although displacement perception of control participants was consistent with Weber's Law, PD patients deviated from this in some cases, suggesting the possibility of nonlinearity in perceptual capabilities of PD patients. According to the analog coding hypothesis mental processes occur in a continuum, meaning higher-level mental processes function similarly to related lower-level processes, follow the same laws, and display similar attributes [55]. It was further shown that some cognitive processes exhibit attributes similar to those found in related sensory and perceptual processes [55]. Regarding visual perception of displacement, both accurate visual perception and accurate processing of visual information in higher visual areas is needed to accurately perceive visual displacements. As the visual stimuli of both the smaller and larger displacement magnitudes per trial are identical (two white and two green circles on a black background), it is likely that discrepancies in the linearity of Weber's Law occur in higher visual processing areas. This further suggests that the displacement perception abnormalities may be rooted in dysfunctional ventral visual processing in PD, causing deviations from perceptual linearity seen in healthy individuals. The results also imply that the observed perception abnormalities were not caused by memory and attention problems, as this should lead to deficits at both tested standard stimuli. Interestingly, when patients were utilizing levodopa they showed very strong perceptual coherency, while OFF Levodopa no correlations between the WF of the tested standard stimuli were seen. This appears to indicate a role of levodopa in visual displacement perception, possibly regarding a "tightening" of an individual's perceptual boundaries, causing more consistent perception

across stimulus magnitudes. To further explore the observed perceptual non-linearity occurring in PD an increased range of stimuli magnitudes should be tested.

For this work a graphical tool that can be used to test visual perceptions was designed and validated. The tool is easily modified, allowing for the testing of various perceptual modalities, stimulus magnitudes and stimulus orientations. The current study can be extended to encompass more orientations and stimuli magnitudes, as well as different perceptual modalities to further examine how perceptions are abnormal in PD, with future work aiming to assess the use of the graphical tool for diagnostic and disease monitoring purposes. Based on the study's results, perceptions of the larger tested magnitudes were abnormal to some extent across disease stages. Although no significant impairments were observed in the early-stage de novo PD patients at the larger tested standard stimulus, there was a relatively strong trend towards impaired visual displacement perception for the standard stimulus of 17.5 cm. Future work should seek to analyze this perception over a large time scale, to see if visual displacement perception abilities does indeed deteriorate as PD becomes more severe. A study limitation is that similar to most ON/OFF levodopa studies, PD patients always conducted the experiment first OFF levodopa/DBS, followed by ON levodopa/DBS. As each subject participated in only one experimental session, it was necessary that they begin the experiment OFF levodopa, as one must refrain from levodopa for 12 hours to be considered in an OFF state. Thus, it is possible that participants experienced increased fatigue in their ON state compared to their OFF state. However, the hour break between sessions and breaks during testing should have provided sufficient mental relief to the participants.

In summary, allocentric visual displacement perception independent of associated movements was assessed in PD ON and OFF levodopa/DBS therapies, as well as in early-stage patients. Mid- to late-stage PD patients using either levodopa or DBS therapies displayed significant impairments in displacement perception of the larger tested magnitudes, however these impairments were only seen at the smaller magnitudes in the late-stage patients utilizing DBS. The work has revealed visual perceptual impairments in PD that are not due to abnormal motor or sensorimotor integration function, suggesting that impairments in the ventral occipitotemporal visual processing pathway occur in PD.

Future work should further investigate the neurological basis for these abnormalities, as well as different perceptual modalities that may be affected in PD.

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Chapter 4

4 Vision-based Velocity Perception in Parkinson's Disease: Skewed Perception of the Fabric of Time and Space

This chapter contains the paper (with the same title) to be submitted for journal publication.

4.1 Introduction

Non-motor symptoms of Parkinson's Disease (PD) are as common and important as their motor counterparts when considering disease related implications on the quality of life of those affected, institutionalization costs, and economic burden on the healthcare system [1–5]. Although the importance of non-motor symptoms has been noted in the literature, the characteristics of these symptoms are yet to be fully discovered. This challenge is compounded by difficulties in diagnosis and treatment of PD; thus, the non-motor symptoms are often neglected during the process of PD management [1, 6, 7]. Of these non-motor disease symptoms, perceptual abnormalities have been noted to occur across various sensory systems—sometimes appearing before the onset of motor symptoms—raising concerns regarding the affected individual's performance in daily activities such as navigation and the operating of vehicles [8–13]. One of the sensory systems primarily affected is the visual system, with abnormalities ranging from colour and contrast perceptual deficits to visual recognition, spatial, and vision-based motion perception impairments [12–15]. The accurate visual perception of velocity is fundamental for navigation, mobility, and motor control, with deficits substantially impacting an individual's quality of life. Although direct measurements of velocity perception can be made when there is an interaction between a human limb and the moving object (for example measuring muscle spindle activity), similar direct measurements are not currently available for the visual perception of velocity. A factor for this may be that perceiving the speed of visual stimuli may involve the processing of multiple sensory modalities, requiring proper timing, judgement of position, information integration, and optimal sensory functioning (via the eye). In this work, for the first time, the capability of PD

patients is examined regarding the perception of velocity visually, while observing the effect of dopaminergic medication and DBS therapy. For this we conducted a visual velocity perception task independent of movement for PD patients at different stages of the disease who utilized either levodopa, DBS or no therapy, as well as control participants. For the first time it is shown that accurate visual perception of an object's speed is abnormal in PD, with impairments extending to early stages of the disease. Furthermore, levodopa medication appears to be detrimental to this perception. The linearity in perception is also examined and reported. This work not only sheds light on perceptual deficits occurring in PD that have everyday implications, but also suggests visual velocity perception as a promising modality to be used for disease diagnosis and monitoring in the future.

4.1.1 Background

Parkinson's Disease (PD) is the second most common chronic progressive neurodegenerative disease that has been extensively researched, uncovering many motor and non-motor symptoms that both significantly impact patient quality of life. However, the symptoms targeted for therapeutic intervention, as well as clinical diagnosis and monitoring markers have almost exclusively been the motor symptoms, often causing treatment outcomes that do not address all disease symptoms [16, 17]. The root cause of PD is believed to be major degeneration of dopaminergic neurons at the SNc, leading to reduced dopamine levels at the BG, in turn causing heterogeneous motor symptoms [17–19]. Accordingly, pharmaceutical and surgical interventions seek to restore BG function and alleviate disease motor symptoms, often with excellent efficacy [20, 21]. However, the non-motor symptoms do not universally respond well to these treatments like motor symptoms do. Non-motor symptoms instead display a much more variable response to dopaminergic and DBS therapies that can be beneficial, detrimental, or neutral depending on the symptom, suggesting neurotransmitters other than dopamine are also involved (and functioning abnormally) for some non-motor symptoms [1, 4, 8, 22]. Although there has been increased attention given to the importance and extent of non-motor PD symptoms in recent years, there is still a substantial lag in the management of non-motor symptoms compared to PD motor symptoms. This in many cases leads to non-optimized clinical outcomes as non-motor symptoms can be left unnoticed and untreated by practitioners [7].

It is clear that improvements in the understanding of non-motor PD symptoms are necessary for improved patient care. This would also help enhance patient quality of life as adverse events related to navigation and environmental interactions that contribute to everyday living (from crossing a street to driving a car) would be directly clinically monitored and addressed. By understanding the characteristics and variability of non-motor symptoms clinicians will be better equipped to diagnose, assess, and treat patients. It can also provide new information for developing new treatments and improve upon the early diagnosis and comprehensive monitoring practices of PD.

4.1.2 Current Study Rationale and Procedure

To address the current uncertainty regarding the perceptual abilities of PD patients for vision-based velocity, as well as uncertainties regarding the neural processing of velocity in general, a perceptual task was carried out on a computer-generated graphical tool capable of quantifying perceptual abilities independent of movements. It should be noted that there is a lack of studies that focus specifically on visual perceptions of motion that function independently from goal-directed movements and motor-control, causing results that are influenced by degraded motor functioning occurring in PD [23]. Although accurate perception of object velocity is imperative for conduction of several activities of daily living such as the accurate navigation through our dynamic world, obstacle avoidance, and the operating of automobiles, vision-based velocity perception has yet to be analyzed in PD. In this work, vision-based velocity perception is examined for 25 patients with PD utilizing levodopa therapy, 6 PD patients using subthalamic DBS therapy, 6 de novo patients in early stages of PD, as well as 17 age-matched control participants. All participants conducted occulomotor and cognitive diagnostic testing, ensuring those included in the study did not display substantial visual or cognitive deficits that could affect the main experiments results. The primary visual velocity perception examination was designed to solely test perceptual ability (without any goal-directed motor inputs) through a two-forced alternative choice discrimination test composed of 200 trials according to the method of constant stimuli described by Gescheider et al. [24].

In each trial of this study, two circles (each moving at a constant but different vertical velocity) were presented in series, with the subject verbally answering (without

any time constraint) which circle they perceived to be moving the fastest. One of two standard stimuli (10 cm/s or 25 cm/s) were present in each trial at random, with 5 greater and 5 lesser comparison speed magnitudes compared 10 times to each standard. Upon completion of the velocity discrimination task subject responses were broken up based on standard stimulus and input to the psignifit 4 psychometric measurement toolbox, i.e., psignifit 4 [25], which is a third party Matlab toolbox used to produce a cumulative Gaussian distribution used for perceptual quantification of each standard stimulus. Patients using either levodopa or DBS conducted the velocity discrimination task both ON and OFF their respective therapy, allowing for the analysis of therapy's efficacy on the studied perception. The subject's DL for each standard stimulus and therapeutic state was obtained through analysis of Gaussian distributions (Fig. 4.1), indicating the stimulus magnitude needed by an individual to discern said comparison stimulus as different from the tested standard stimuli [24]. An individual with a smaller DL for a given perceptual modality will have increased perceptual sensitivity, thus displaying better perceptual abilities. This allowed for the quantification and comparison of visual velocity perceptual abilities between participants and participant states.

4.2 Results

4.2.1 Velocity Perception in PD

Firstly, the mean DLs of all PD patients OFF and ON their respective therapies to control participants. PD patients showed statistical impairments in visual velocity perception of speeds compared to the standard stimulus magnitude of 10 cm/s. The DLs of control participants (mean DL: 1.24 ± 0.39) were significantly smaller than those of all tested PD patients OFF of their therapies (mean DL: 1.62 ± 0.47; control vs. PD OFF p-value: 0.008). PD patients ON their therapies (mean DL: 1.81 ± 0.56) again displayed perceptual impairments compared to healthy individuals (control vs. PD ON p-value: 0.001) (Fig. 4.2). When refining the patient groups based on their therapy usage these smaller PD participant groups still displayed impaired velocity perception for the smaller magnitude speeds. Considering the PD patients using levodopa, strong (yet insignificant) trends showed impairments in visual velocity perception when OFF therapy compared to ON

therapy (mean DL: 1.55 ± 0.52; control vs. PD OFF levodopa p-value: 0.061). When participants were administered (ON) levodopa, they displayed significant perceptual

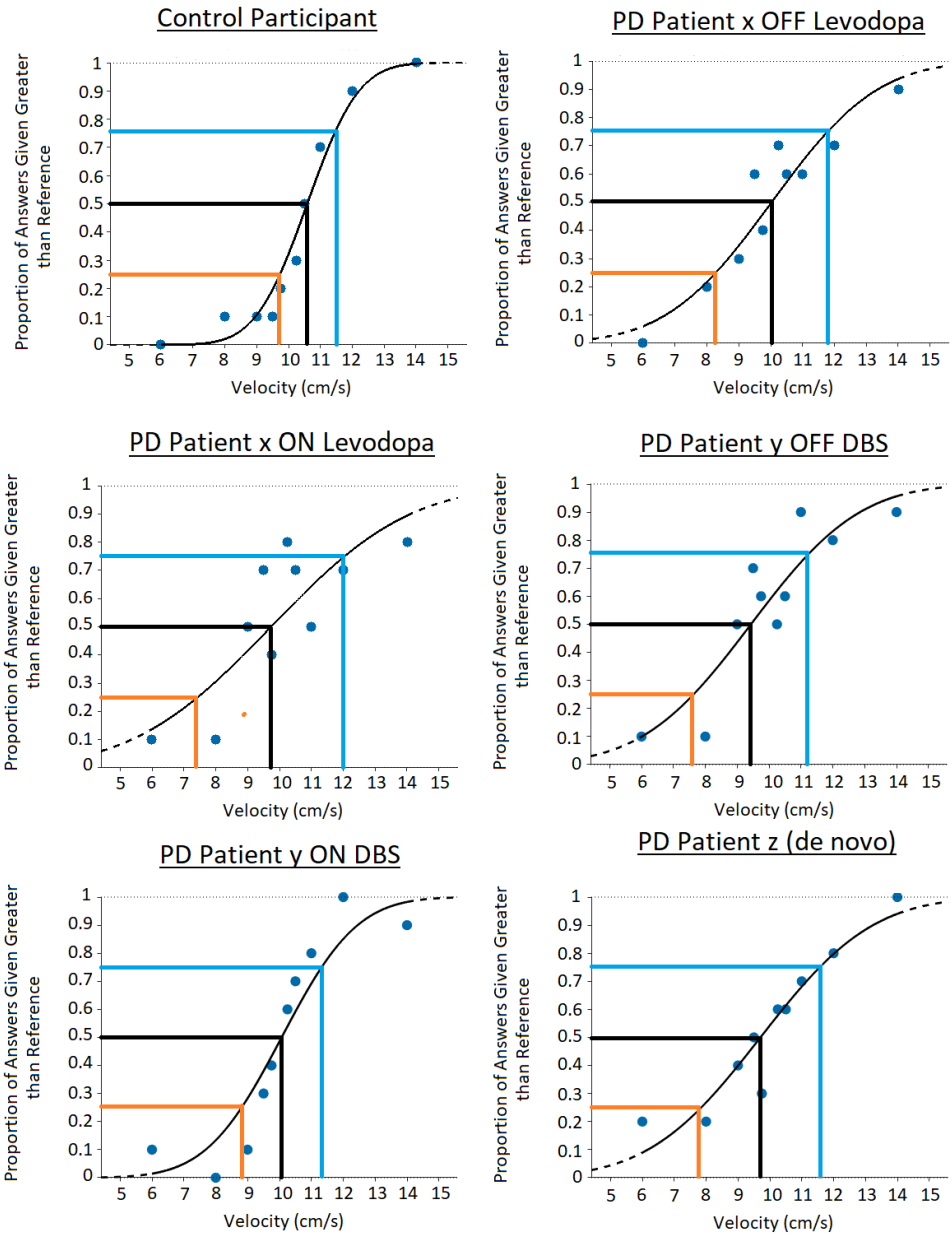

Figure 4.1: Cumulative Gaussian Distribution examples used for subject analysis of velocity perception. Subject DL was analyzed by subtracting the Point of Subjective Equality (PSE) from the Upper Threshold (UT; or subtracting the Lower Threshold [LT] from the PSE). UT and LT are the points of the function which the subject answered correctly 75% of the time for a given standard stimulus. Larger DLs signify decreased perceptual sensitivity.

impairments (mean DL: 1.81 ± 0.62; control vs. PD ON levodopa p-value: 0.003). The late stage PD patients using DBS to treat their PD displayed significant impairments both ON DBS (mean DL: 1.82 ± 0.58; control vs. PD ON DBS p-value: 0.016) and OFF DBS (mean DL: 1.81 ± 0.28; control vs. PD OFF DBS p-value: 0.005). Impairments in velocity perception using the smaller standard stimulus extended to the early stages of the disease, with significant perceptual impairments seen in de novo patients (mean: 1.75 ± 0.27; control vs PD de novo p-value: 0.015) (Fig. 4.3).

In contrast to the smaller reference stimulus, at higher tested velocities (using the standard stimulus of 25 cm/s) there were no statistical differences observed in perceptual ability between control and PD participants. The DLs of control participants (mean DL: 3.85 ± 1.67) did not substantially differ from the DLs of PD patients OFF their respective therapy (mean DL: 3.59 ± 1.40; control vs. PD OFF p-value: 0.557) and ON therapy (mean DL: 4.06 ± 1.40; control vs. PD ON p-value: 0.661) (Fig. 4.2). Considering only patients utilizing levodopa medication, no significant differences in perceptual abilities for the visual velocity task ON levodopa (mean DL: 4.30 ± 1,74; control vs. PD ON levodopa p-value:0.407) and OFF levodopa (mean DL: 3.57 ± 1.14; control vs. PD ON levodopa p-value: 0.551) were observed. Similarly, perceptual abilities of patients using DBS did not differ from control participants ON DBS (mean DL: 4.15 ± 1.87; control vs. PD ON DBS p-value: 0.710) and OFF DBS (mean: 4.27 ± 2.43; control vs. PD OFF DBS p-value: 0.639) for the standard stimulus of 25cm/s. Again, this trend persists in the early stages of PD, as the DL of de novo patients (mean DL: 3.00 ± 1.00) did not differ significantly from control participants (control vs. PD de novo p-value: 0.260) (Fig. 4.3).

4.2.2 Velocity Perception Linearity

In this work, to further analyze participants' perceptual ability perceptual linearity was also examined using Weber's Law. Weber's Law states that an individual's DL is directly proportional to the magnitude of the standard stimulus, in that the greater the stimulus magnitude the greater the magnitude change necessary to differentiate stimuli. This is exemplified through consistent correlations in the WF (defined as $WF = DL/S$,

where S is standard stimulus magnitude) for standards differing in magnitude [24]. Weber's Law has been validated for healthy individuals over a wide range of sensory modalities [26, 27]. The effect that PD and levodopa have on perceptual linearity is largely unknown, although linearity provides a different means of measurement to assess perceptual abilities. In the current work, Pearson correlation analysis of the participants' WF for the 10 cm/s and 25 cm/s standards for a certain therapeutic condition were analyzed, with high correlation between WFs signifying perceptual linearity and satisfaction of Weber's Law. The results showed that for the control group there were moderate correlations seen between the two WFs (Pearson Correlation [R] = 0.534, p-value: 0.027), signifying their accordance with Weber's Law. Interestingly, when all PD patients were analyzed as a group, moderate correlations were also seen in the OFF medication state (R = 0.432, p-value: 0.008). However, this perceptual coherency was not observed with patients were ON their respective therapies, for which a very small, insignificant correlation is observed (R = 0.168, p-value: 0.367). A similar trend was observed when specifically examining the performance of patients using levodopa, with Weber's Law being satisfied in the OFF state (R = 0.496, p-value: 0.012), but not the ON state (R = 0.142, p-value: 0.497) (Fig 4.4).

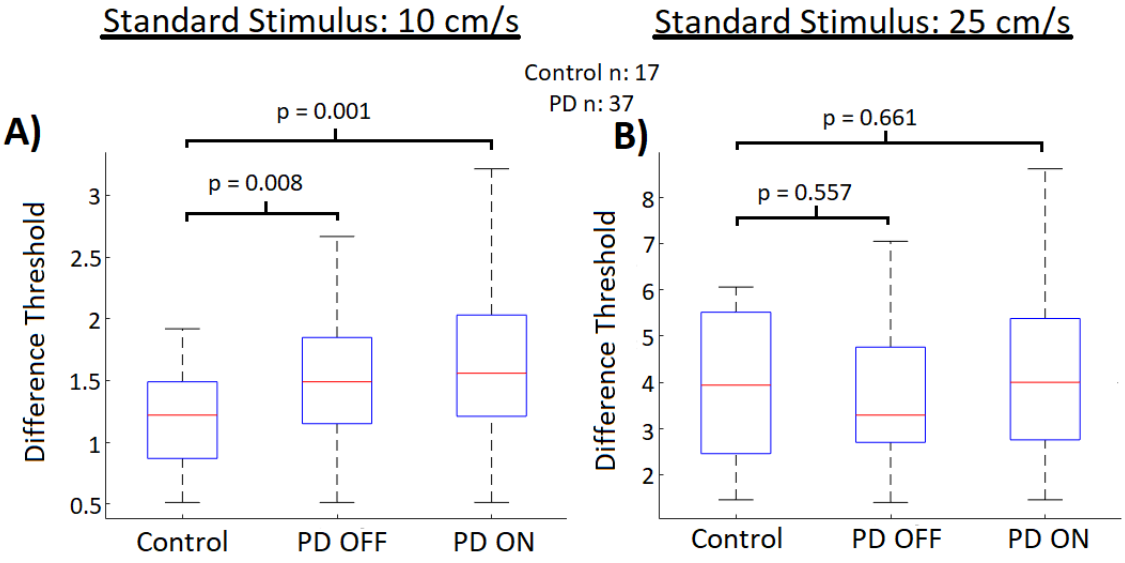

Figure 4.13: Velocity perception difference thresholds of all PD patients (n = 37) regardless of treatment state compared to control participants. The standard stimulus of 10 cm/s is displayed on the left, and 25 cm/s second on the right; with boxplots related

to PD patients OFF and ON their respective therapies. The red lines are the median DL for each group. The bars represent the data spectrum. PD patients did not show any impairments in temporal perception at the standard stimulus of 0.5 seconds ON or OFF PD therapy. However, there were significant impairments seen at the standard stimulus of 10 cm/s OFF PD therapy (p-value = 0.008) and ON PD therapy (p-value = 0.001).

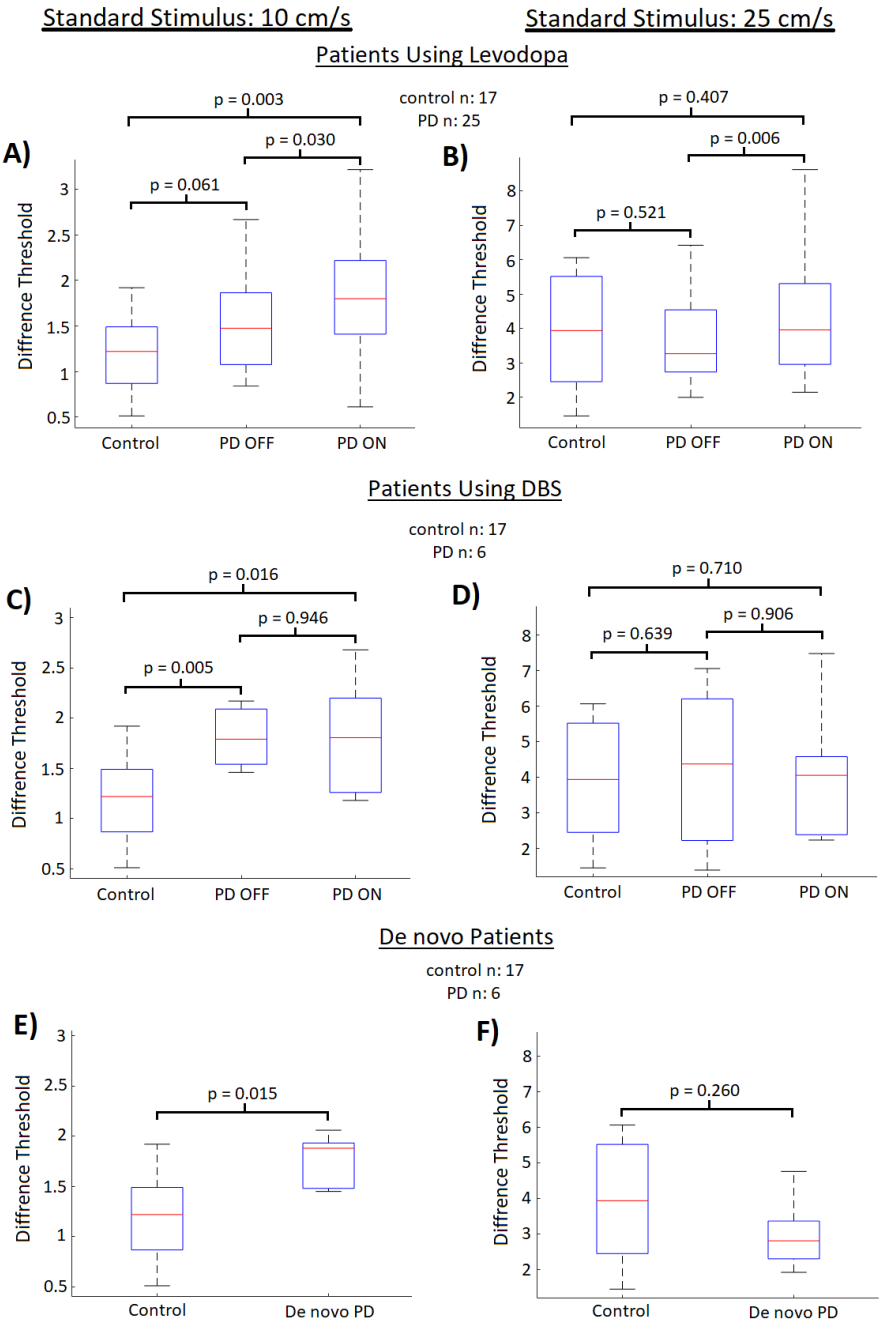

Figure 14: Velocity difference thresholds separated by individual therapies/de novo obtained through velocity perception examination. The standard stimulus of 10 cm/s

displayed on the left, and that of 25 cm/s on the right. The red lines are the median DL for each group. The bars represent the data spectrum. Regarding the standard stimulus of 25 cm/s, there were no significant differences in DLs observed between PD patients OFF and ON levodopa and DBS compared to controls. De novo PD patients did not display significant differences in DL compared to controls as well. Although use of DBS did not lead to significant changes in the DLs of PD patients, there were significant differences (p-value = 0.006) elicited by levodopa use. For the standard stimulus of 10 cm/s, substantial differences in DL were observed between PD patients OFF levodopa and controls (p-value = 0.061), as well as significant differences when ON levodopa compared to controls (p-value = 0.003) were also seen. PD patients also significantly differed in perceptual abilities when administered levodopa compared to their OFF state (p-value = 0.030). PD patients using DBS displayed significant increases in DL when OFF DBS (p-value =0.005), and ON DBS (p-value = 0.016). De novo PD patients also displayed significantly greater DLs than controls (p-value = 0.015) at the standard stimulus of 10 cm/s. DBS use did not lead to significant differences at both tested standard stimuli magnitudes.

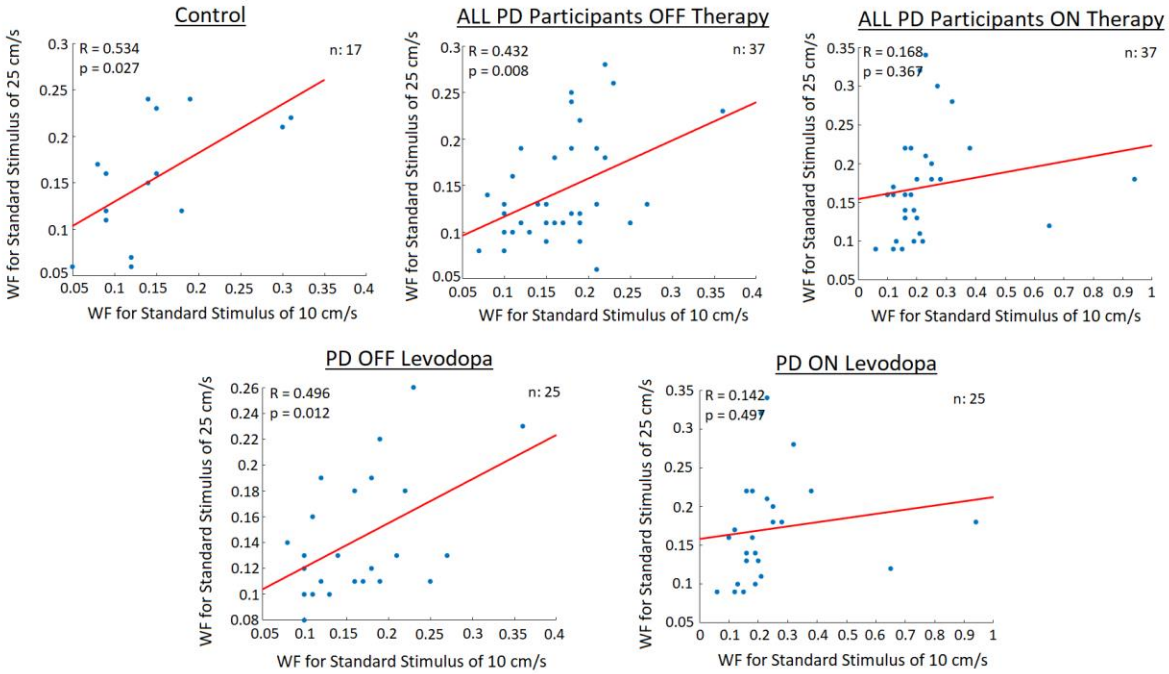

Figure 15: Correlations between participant WF at the standard stimuli of 10 and 25 cm/s. Points displaying high similarity between their x and y values signify that the participant displayed little to no difference in the WF values at different stimulus magnitudes, and thus are in accordance with Weber's Law. Correlation plots of DBS and de novo patients are not shown due to small sample sizes (n = 6 for each group).

4.3 Discussion

The current work has observed deficits in visual velocity perception (independent of related movements) occurring in individuals with PD, and the degrading effect of dopaminergic therapy on the perception sensitivity and linearity according to Weber's Law. Interestingly, the significant perceptual impairment was statistically validated for the slower tested velocities, while comparison with the faster standard stimulus of 25 cm/s did not show statistically different perceptual capability compared with the healthy group. A potential explanation for this observation could involve the manner that the neural system processes vision-based velocity inputs. Considering the mathematical formula for velocity (V), in which $V = \Delta D/T$ (where D and T signify displacement and time respectively), time perception deficits, displacement perception deficits or deficits in multimodal sensory fusion could affect the perception of velocity if neural calculations of visual velocity are indeed processed in this manner. When considering velocity perception as a problem of multimodal information fusion that is neurally complied, impairment of either time or displacement would contribute to abnormalities in perceiving velocity. As discussed in Chapters 2 and 3, the visual perception of both displacement and time functions abnormally in individuals with PD. Thus, abnormalities in the processing of visual velocity may be rooted in one, or both of these sensory modalities. Evidence for this phenomenon can be seen with temporal deficits as abnormalities were observed in the second, but not millisecond range; correlating to deficits occurring at slower velocities with movement durations in the second range, but not the greater velocities with movement durations in the millisecond range. Also of interest, the administration of levodopa led to detriments in velocity perception at both standard stimuli, persisting at the greater standard stimulus (25 cm/s). Furthermore, perceptual coherency was shown to be disrupted significantly after the administration of levodopa for the patients using the therapy. In the past, levodopa medication has been shown to have variable efficacy with regard to non-motor symptoms. However, it has been suggested that levodopa induced impairments of temporal perception are a repercussion of dopamine overdose, in which levodopa concentrations that are ideal for treating motor symptoms are detrimental for certain timing procedures [31]. The detrimental effects of levodopa on velocity perception further suggests the use of temporal information during the neural processing of visual velocity information.

The analysis of speed perception in PD has been explored in a few past studies, however these works aimed to mimic environmental movement as opposed to object movement [32, 33]. Although both environmental movement and object movement are controlled by similar neural complexes (the dorsal MST and lateral MST respectively) that interact with one another, the information processed by the dorsal MST is used for gauging movement of the perceiving individual, while the lateral MST provides details about object movement and velocity [34, 35]. As the lateral MST processes object motion information to allow the perceiving individual to visually track and interact with the said object, it can be assumed that individuals with PD will display abnormalities in MST-related processes if the results from the current study are rooted in MST dysfunction. This is indeed the case, as PD patients have displayed impairment with the visual tracking and grasping of objects in space [36–38]. It should be noted that smooth pursuit functioning is impaired in PD [39], possibly signifying oculomotor impairments as the root cause of visual velocity perception as opposed to perceptual abnormalities. However, all patients had diagnostic assessment of oculomotor functioning by a trained clinician to ensure no severe abnormalities were present. As only one of the standard stimuli had observed abnormalities this further suggests a perceptual, and not an oculomotor deficit was responsible for the observations.

The current work provides evidence that visual perception of objects velocity is impaired in PD. This implies an inaccurate representation of an object in space, which could be caused by inaccurate estimations of dynamic changes in object position (i.e. speed), inaccurate perception of time, or inaccurate fusion. In summary, PD and dopaminergic medications can potentially affect perceptions of the fabric of space and time, which can directly affect task conduction in this 4^{th}-dimentional coordinate. The observed deficit, which may appear early in the disease progression (as shown in the current work's results for de novo patients) presents a concern for those who have developed PD but are not yet diagnosed. The greatest concern regarding abnormal velocity perception involves the operation of heavy machinery such as vehicles. Past studies validate the presence of these concerns as individuals suffering from PD exhibit impairments in driving abilities [40–42]. Driving is a complex task that involves attention and motor control (both known to be impaired later in PD progression), as well as accurate perception of object's velocities. The latter is a critical aspect which should be

systematically investigated early in the disease's progression to assess the risks brought on by the improper perception. The protocol proposed and presented in this work used a simple virtual reality environment (which can be easily implemented on any computer and other devices such as smart phones) can be considered an in-clinic diagnostic and monitoring tool that would be able to provide quantitative measures regarding one's vision-based perceptual ability of speed and linearity of this perceptual ability. As mentioned, visual perception of velocity appears to be sensitive to deficits in other sensory modalities and/or the fusion of sensory information. Considering this, velocity perception abnormalities in PD may be magnified compared to temporal, displacement, and sensory integration deficits on their own, increasing graphical tool's sensitivity to neurological based perceptual disorders. This motivates further investigation of this modality for early diagnosis, monitoring of disease progression, and for better assessment of one's disease induced perceptual risks. It should be noted that the presented velocity perception assessment tool is simple to use, flexible with regards to the perceptual modality that is to be tested, and does not require much computational power, allowing it to be utilized in many clinical and non-clinical settings. As the graphical tool shows promise for use with diagnosis and monitoring of neurological disorders, future work will aim to further validate its use through continued perceptual studies to further validate efficacy (specifically with early stage patients to analyze its diagnostic potentials), as well as study the effectiveness of pairing the tool with other potential disease monitoring and diagnostic tools (such as haptic enabled robotic systems). The current work uncovered a vision-based velocity perception deficit in PD that potentially has substantial implications and presents a tool to systematically assess perceptual deficits occurring during neurological disease.

4.4 Methods

4.4.1 Participants

The study protocol for this work was approved by the Research Ethics Board of the University of Western Ontario. All experiments were conducted in accordance with the Declaration of Helsinki, as well as the Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans in Canada. All participants provided informed consent regarding their participation in the study. Furthermore, the participant displayed in Fig.

4.5 provided consent allowing for their image to be used in publications of the research. All of the PD participants were recruited through the Movement Disorder Program, at the University Hospital, London, Ontario, Canada. This is the care centre at which they were diagnosed with PD, receive treatment and regularly monitor the disease. A total of 25 participants using levodopa (22 male, 3 female), 6 using DBS (4 male, 2 female), 6 de novo (4 male, 2 female), as well as 17 age-matched control participants with no known neurological disorder were tested. A summary of the demographic and clinical data for the patients can be seen in Table 2.1. All patients were from Southern Ontario, and recruited at the University Hospital in London, Ontario, Canada. All of the PD patients for this study fulfilled the UK Parkinson's Disease Brain Bank criteria. Patients using levodopa (half-life: 1.5 hours) were instructed to refrain from medication for at least 12 hours prior to assessment, ensuring complete metabolism necessary for OFF testing. Similarly, patients using DBS were instructed to refrain from Levodopa use 12 hours prior to assessment, with their DBS device being turned OFF upon arrival to the testing centre. After patients completed the visual velocity perception task in the clinically defined OFF state they either were given 300 mg of levodopa (unless their typical dosage was 100 mg or less, in which case they were given 200 mg of levodopa) or had their DBS device turned on to their usual stimulation levels depending on the patients primary PD therapy, then conducting the experiment in their ON medication state. It should be noted that a 1-hour break was given between the OFF and ON portion of the experiment. Furthermore, those using DBS did not take any Levodopa for their ON testing, preventing confounding results from therapeutic-related task improvement. Diagnostic assessment of Parkinson's Disease motor severity (via the UPDRS part III [motor subsection]) was conducted in both ON and OFF states, with cognitive assessment (via the MoCA) being carried out before beginning the perceptual task. Also prior to testing (in the OFF state) visual diagnostic tests for smooth pursuit, saccades, and visual acuity (via reading tasks and the Snellen eye examination) were also conducted. Those that showed visual impairments (including visual hallucinations) and/or cognitive impairments (defined as MoCA score < 25) were omitted from the study. Furthermore, participants using PD medication other than Levodopa were excluded from study participation. It should be noted that a participant conducted all testing in a single session.

4.4.2 Testing Apparatus

The computer-generated graphical tool used for the testing of visual velocity perception runs in the Matlab/Simulink platform, and was designed at the Canadian Surgical Techniques and Advanced Robotics lab. Although the tool was used to test visual velocity perception, its design is flexible by nature, allowing it to be easily modified to test other visual perceptions. The visual velocity perception experiment was displayed on the LG Flatron W2242PM 22-inch monitor (resolution: 1680 x 1050). The participant conducting the experiment was seated upright in the chair (that was adjusted in its height for maximum comfort) approximately 2 feet away from the monitor (Fig. 4.5). The participant was tested in a room alone with the experimenter with minimal auditory and visual stimuli (apart from the task) in order to reduce attentional slips.

4.4.3 Experiment

A two-forced alternative choice perceptual experiment composed of 200 trials was carried out according to the method of constant stimuli for different thresholds as described by Gescheider [24]. Each trial began with a horizontally central white circle with a black, centred hole starting at the top of the computer monitor and moving at a constant velocity to the bottom of the monitor. Once reaching the bottom, the same circle again appeared at the top of the monitor, moving at the same constant velocity to the bottom. After this there was a gap of 2 seconds, followed by a solid white, horizontally centralized circle moving from the top to the bottom of the screen at a constant velocity in two successions. Thus, in each trial there were two circles each moving at a constant (but different) velocity, and the exposure the participant had to each circle was twice the duration of the circle moving from the top to bottom of the screen. For each trial the participant must answer verbally which circle they perceived to be moving the fastest (Fig. 4.5). There was no time constraint for the verbalization of their answer, thus movement impairments would not affect participant

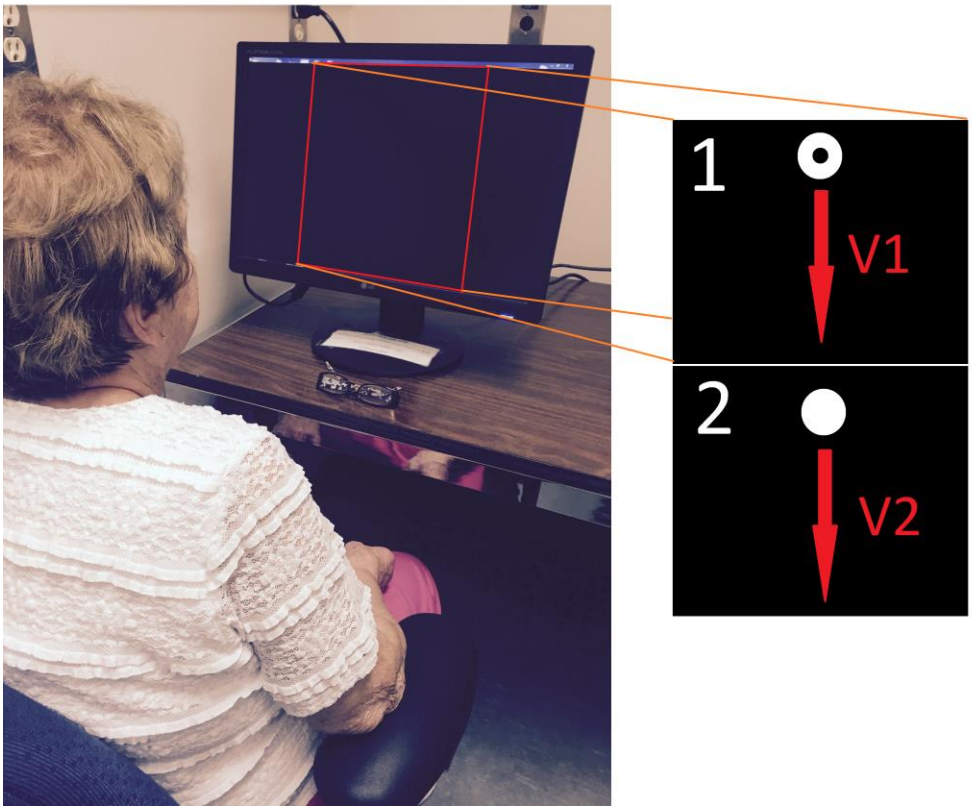

Figure 16: Testing apparatus and velocity perception experiment. The LG Flatron W2242PM 22 inch (resolution 1680 x1050) computer monitor was used for testing, set up at a comfortable viewing position for the participant, who is sitting approximately 2 feet away from the monitor. The testing room has only the participant and experimenter, with excess stimuli (such as sounds, distracting visual) minimized. Illustrative examples of the velocity discrimination task shown on right, with the two squares representing the two objects which are compared. In each trial, the participant compares the constant vertical velocity of a circle with a hole to the constant vertical velocity of a solid circle. The participant verbally answers which circle they perceived to be moving faster. The exposure of each circle is moving from the top to the bottom of the screen twice, and the circles are separated by a 2 second waiting period. Note the arrows are not present in experimental settings.

success. In each trial one of two standard stimuli (10 cm/s or 25 cm/s) would be present and compared to one of 10 comparison velocities. The comparison values were chosen so that healthy individuals would always be able to differentiate the standard from the comparison differing the most in magnitude, and would answer correctly 50% of the time for the comparison value with the smallest magnitude difference from the standard (i.e. the

participant was guessing). Each comparison velocity was examined in 10 trials, with its order in relation to both the standard and other comparison values being randomized. At the midway point of analysis (100th trial) a mandatory break was given to the participants; however, they were able to take as many breaks for as long as they desired throughout testing. It should be noted that control and de novo patients conducted the task once, however patients using DBS and levodopa conducted the experiment twice in both ON and OFF states. It is however unlikely that perceptual learning occurred, as the patients conducted the experiment only once for a given therapeutic state. Furthermore, neural learning for visual tasks is a process that occurs over long periods of time, with the one-day testing session being too short for any meaningful learning [43, 44]. The psignifit 4.0 third party Matlab psychometric assessment toolbox was used to calculate and create a cumulative Gaussian distribution foreach standard stimulus, allowing for perceptual quantification of each participant (Fig. 4.1).

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Chapter 5

5 Conclusions and Future Work

5.1 Conclusions

The purpose of this thesis was to explore certain visual perceptions in PD and develop disease diagnostic software. The perceptual modalities examined were not influenced by the motor system (which is impaired in PD), with PD disease patients ranging from early to late stages of the disease, and using levodopa, DBS, or no therapy for their PD, and compared to healthy controls. Following the objectives described in Chapter 1, the thesis was divided into three chapters, focusing on the temporal, displacement, and velocity perceptual modalities respectively, with the computer-generated graphical tool being used and validated for each perceptual modality. The goal of the work presented in this thesis was to develop a simple virtual reality tool that is able to use visual non-motor PD symptoms in the clinical assessment of PD, of potential perceptual modalities that would function well with this tool, and to expand the knowledge of perceptual deficits occurring in PD. This work is the first step of the research goal to produce a tool capable of diagnosing and monitoring non-motor symptoms in PD. This takes into account the heterogeneous presentation of PD symptoms and considers the presence of non-motor symptoms before many motor symptoms. The work presented in this thesis provides a foundation for future work that will create a fully realized computational tool to accurately quantify and assess non-motor perceptions for use in neurological assessment. The overall conclusions from these chapters will be discussed in this section.

Chapter 2 studied visual temporal perception in the range of milliseconds and seconds. Our aim was to investigate temporal discrimination in PD without any motor influence (due to motor timing impairments), while further exploring the influence of the BG on timing and how therapies targeting the BG affect timing. For all patient groups, there were no impairments seen at the smaller tested magnitudes (using millisecond timing). However, all PD groups displayed significant impairments at the larger tested magnitudes (using interval timing). Neither levodopa nor DBS therapy led to significant improvements in timing abilities. Levodopa resulted in a strong trend towards impairing

timing processes and caused a deterioration in perceptual coherency according to Weber's Law. It was shown that timing abnormalities in PD occur in the seconds range but does not extend to the millisecond range. Furthermore, observed timing deficits were shown to not be solely caused by motor deficiency. This provides evidence to support internal clock models involving the BG (among other neural regions) in interval timing, and cerebellar control of millisecond timing.

The investigation described in Chapter 3 studied allocentric visual displacement perception. Individuals with PD displayed significant perceptual impairments, with mid– to late–stage PD patients being particularly affected. The use of levodopa and DBS did not lead to statistically significant differences in the tested perceptual abilities of patients. However, DBS use showed a promising trend towards improvement in visual displacement perception. Regarding perceptual linearity analyzed via Weber's Law, control group subjects closely followed a linear relationship, however, all tested PD groups displayed a significantly degraded linear relationship for perception of vision-based displacement in the OFF-therapy state. Although Levodopa and DBS therapies did not cause improvements in the tested perception, their use did strengthen perceptual linearity relationships, suggesting a potential benefit to treatment use. Overall, these findings might suggest abnormal ventral occipitotemporal visual processing occurs in PD, which could contribute to freezing of gait, visuospatial deficits and abnormal object recognition.

Chapter 4 focused on the visual velocity perception of objects and investigated potential abnormalities that arise during PD and with the use of certain PD therapies. As with earlier chapters, PD patients displayed impairments with the accurate perception of visual velocity, affecting patients at early, mid, and late disease stages. These dysfunctions were only observed at the smaller tested standard stimulus (10 cm/s) however, with no differences in perceptual ability occurring between PD and control participants at the larger standard (25 cm/s). Interestingly, levodopa appeared to have a detrimental effect on perceptual abilities of visual velocity, as significant impairments in perceptual sensitivity for patients ON levodopa (compared to being OFF levodopa) were observed. Furthermore, perceptual linearity (which was maintained in control and OFF therapy PD groups). The use of DBS did not however lead to alterations in velocity perception. These observations

highlight perceptual dysfunction in PD that has implications in navigational deficits and also highlights risks involving accurate speed perception such as the operation of automobiles that affects those with PD.

Throughout the work described in this thesis, a computer-generated graphical tool was used to analyze the perceptual ability for certain sensory modalities. The graphical tool proved to be capable of this task, with its flexible nature allowing for simple modifications to enable the analysis of various modalities. A primary goal of the toolbox development was for it to be simple to use, as well as easy to run on current computational devices. The clinical analysis of non-motor symptoms in PD is currently lacking, a substantial problem based on the disease's heterogeneous nature. We hope the computer toolbox developed and used for the work in this thesis will be able to assist with the monitoring and management of PD, with it being used in both clinical and non-clinical settings (such as community or patients' homes). In addition, we hope that the use of a similar device will assist with disease diagnosis and monitoring, allowing for more optimized treatment to improve the quality of lives of those suffering from PD.

5.2 Future Work

As previously noted, the computer-generated graphical tool can be easily operated, and its use has been demonstrated with the visual time, displacement, and velocity perceptual modalities. One direction of future work will be to explore different perceptual modalities in PD, including those using different sensory systems, such as the auditory system. This work will aim to provide insight into particular sensory modalities that prove to be ideal targets for the monitoring and diagnosis of PD. The analysis of sensory modalities studied in this thesis may also be performed with different parameters. For example, displacement perception (which was studied in a 2-dimensional allocentric fashion in this thesis) can be studied using a virtual reality headset (such as the oculus rift) to enable consideration of the perception of 3-dimensional depth displacement. Although this analysis also involves visual displacement perception, depth displacement relies on egocentric coordination, involving different neural processing, potentially providing increased sensitivity to disease-related sensory abnormalities. Furthermore, future work will increase focus on patients in the early stages of PD. As discussed throughout the thesis, several sensory

abnormalities arise in the early stages of PD, with some predating motor dysfunctions. In order to maximize the potential of a computer tool similar to the one used in the work described in this thesis, it should analyze some perceptions arising at the early disease stages, allowing for the tool to assist with disease diagnosis. Similarly, future work will seek sensory modalities that progress in severity with PD disease progression, to assist in monitoring of PD. A method of analysis that was outside of the scope of the current thesis is to assess an individual's perceptual abilities across modalities (comparing their perceptual abilities collectively involving time, displacement and velocity tasks), and relating these abilities to motor functionality. Future work should assess the potential relationships between perceptual, motor, and integrative impairments that occur in PD. This can provide further insight in neural abnormalities occurring during the disease, and potentially lead to clinical assessment modalities or tests that are of increased sensitivity with regard to disease-based differences in ability. To further improve the clinical assessment viability of the work in this thesis, the graphical tool is planned for use in tandem with haptics-enabled robotic devices. These devices would further increase the diagnostic range of the computer-generated tool, as perceptions involving the motor system (such as proprioception and kinesthetics) could be incorporated in assessments. A future focus of great importance is the refining of the disease monitoring tool's interface to allow for its use in a variety of settings. Though the implementation of the tool in clinical (and other) settings is not currently the primary focus, it is the ultimate focus of the research. By creating a user-friendly interface allowing for simple analysis and modification of the diagnostic test parameters, it will be possible to use the device to its maximal potential, and hopefully lead to improvement in PD management. Further work to increase accessibility, such as the development of a smartphone/tablet app will also be pursued in the future.

Appendices

Appendix A: Ethics Approval (Levodopa and Control Participants)

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

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

Review Type: Full Board
HSREB File Number: 107253
Study Title: Normative whole-body kinematic data of responsivity to Levodopa in Parkinson disease

HSREB Amendment Approval Date: September 07, 2017
HSREB Expiry Date: November 27, 2017

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Received August 23, 2017	
Revised Letter of Information & Consent	Control Group	2017/08/18
Revised Letter of Information & Consent	PD Group	2017/08/18

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

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

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

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

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

Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

EO: Erika Basile ___ Grace Kelly ___ Katelyn Harris___ Nicola Morphet ___ Karen Gopaul ✓ Patricia Sargeant ___

Appendix B: Ethics Approval (DBS Participants)

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

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

Review Type: Full Board
HSREB File Number: 108453
Study Title: The Use of Whole-Body Kinematic Technology for Optimizing Current Steering Deep Brain Stimulation in Parkinson's disease Patients

HSREB Amendment Approval Date: September 25, 2017
HSREB Expiry Date: October 20, 2017

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Received September 15, 2017	
Revised Letter of Information & Consent	Received August 23, 2017	

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

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

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

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

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

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

EO: Erika Basile ___ Grace Kelly ___ Katelyn Harris___ Nicola Morphet ___ Karen Gopaul ✓ Patricia Sargeant ___

Appendix C: Ethics Approval (de Novo Participants)

Western Research

Date: 23 August 2018

To: Mandar Jog

Project ID: 107433

Study Title: Kinematic biomechanical characterization of upper limb Parkinson's disease tremor for optimization of botulinum toxin type A injection parameters

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: 04Sept2018

Date Approval Issued: 23/Aug/2018 09:37

REB Approval Expiry Date: 01/Mar/2019

Dear Mandar Jog ,

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

Documents Approved:

Document Name	Document Type	Document Date	Document Version
107433 MPD LOI [main] (8-17-2018) clean	Consent Form	17/Aug/2018	2.1
107433 MPD LOI perception (8-21-2018) clean	Consent Form	21/Aug/2018	1.31
107433 MPD Western Protocol Version 3.1 (8-17-2018) - clean	Protocol	17/Aug/2018	3.1
Velocity Perception Examination Sheet Data Set 1	Other data collection forms	16/May/2018	1

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

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

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

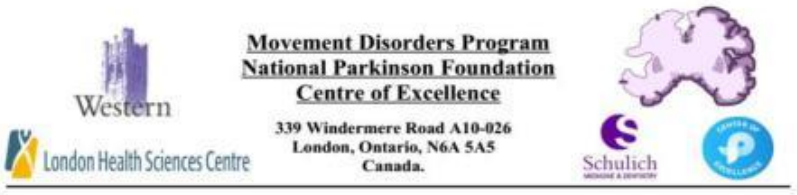
Sincerely,

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

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

Appendix D: Letter of Informed Consent (LOI&C) for Levodopa Participants.

Same LOI&C for Controls, except ON/OFF medication information is omitted.



Letter of Information and Consent- PD Patient group

Study Title

Normative whole-body kinematic data of responsivity to levodopa in a Parkinson disease cohort.

Principal Investigator

Dr. Mandar Jog, MD Neurology, London Health Science Movement Disorders Clinic
University Hospital ext.

This consent form explains the research study you are invited to join as part of the Parkinson disease (PD) patient group. Please ask the study doctors or the study personnel to explain any words or facts that you do not understand. You should keep a signed copy of this consent form. You may wish to discuss this study with your family and friends before making your decision. If you decide to take part in the research study, you must sign this form before you have anything done for this research study.

Study Doctors and Personnel

- Dr. Mandar Jog
- Dr. Rajni V. Patel
- Dr. Philippe Rizek
- Dr. Niraj Kumar
- Dr. Farokh Atashzar
- Mr. Marcus Pieterman
- Mr. Greydon Gilmore
- Mr. Navid Baktash
- Ms. Sogand Kashefi
- Mr. Jai Patel
- Ms. Adrianna Tsang
- Dr. Shahbazi Mahya
- Mr. Amit Srivastava
- Mr. Matthew Bernardinis
- Mr. Christopher Ward
- Ms. Lauren Tindale
- Mr. Mitchell Adamson
- Ms. Carly Jackson

Background and Purpose of Study

The gold standard of care for Parkinson disease (PD) is the use of levodopa to manage common motor symptoms associated with the disorder. Common motor symptoms include tremor, slowness of movement, rigidity and postural instability. However, in advanced stages of PD, the efficacy of levodopa can decline and motor symptoms fluctuate throughout the day. As these motor fluctuations occur, significant impact to the individual's quality of life makes

treatment difficult. After 5 years of oral levodopa treatment, more than half of all individuals with PD develop levodopa-related complications, such as motor fluctuation and dyskinesia's (involuntary muscle movements).

Our observational project will study 120 participants with PD and 120 control participants. It is considered an observational study because no therapeutic intervention is involved. PD participants will be further divided into disease duration cohorts to examine motor fluctuations at various stages in PD. A combination of clinical rating scales and full-body kinematic measurements will be used to assess motor symptoms in participants. By using motion sensors that are miniaturized and non-intrusive, these wearable devices will accurately measure motor symptoms. PD participants will be assessed OFF (where therapy is not providing benefit in terms of stiffness and mobility) and ON (where therapy is providing benefit in terms of stiffness and mobility) levodopa. In this study, a participant is to be considered OFF levodopa when it has been 12 or more hours since their last dose of levodopa medication has been taken. A participant is to be considered ON levodopa at approximately 45 minutes after taking their normal dose of levodopa. By assessing PD participants in the ON and OFF state, responsivity to the drug can be defined at different points in the disease duration. This will assist in characterizing which motor symptoms become more or less responsive to levodopa as PD progresses. Furthermore, insight into the evolution of motor symptoms in response to levodopa in PD participants will assist physicians in optimizing levodopa treatment at each point in disease duration.

Study Procedures

Based on your screening information, the study doctor will determine if you are eligible to join this study.

If you decide to join, you will be asked to sign this consent form and you must agree to follow the instructions given by the research staff during the study.

This study requires you to attend 1 visit (approximately 3 hours) at the research facility. The visit will require you to come to Dr. Jog's research facilities located in Thomson Hall Engineering Building at Western University in London, Ontario. Please note that the participant must be **OFF** all levodopa medication for 12 hours prior to the visit. The last dose taken by the participant should be the evening before the visit at no later than 8:00 PM.

You will undergo the following procedures and tests during your visit:

• You will be asked about your medical history, any ongoing medical conditions you may have and specific information about the history of your Parkinson's disease. You will be asked to provide your current medications with specific information about the length of time you have been on your PD medications.

• You will be asked to use a haptic device to perform a task in a virtual environment displayed on a monitor.

• You will be asked to perform a walking task with sensors placed on your leg and shoes.

• You will be asked to use an assistive writing device while writing.

• You will be asked for your height and weight, and specific limb measurements will be taken (i.e. Foot length).

• You will be videotaped from the neck down. Videotape recordings help to corroborate and validate the kinematic recordings to actual participant state during analysis. Videotape recordings will be kept for 5 years.

• A UPDRS test will be performed in both ON and OFF state. This UPDRS test is commonly used to assess Parkinson's motor symptoms and includes assessments of your speech, facial expressions, balance, and arm and leg movements.

• You will be asked to place a motion capture suit over your regular clothes in order to conduct various motor tasks.

• You will be asked to perform sitting tasks such as arms at rest, arms held up in front of your body and turning each hand over in a pronation-supination motion. Following this, you will be asked to walk around a 25 meter walkway at your normal pace, four times. You will then be asked to walk at your fast-as-possible pace around the track, four times. Finally, you will be asked to walk backwards for 10 meters, twice.

• You will be asked to perform speech tasks into a microphone which will involve the repetition of certain lingual sounds and the reading of passages aloud.

• You will be asked to complete all motor and speech tasks during both your OFF and ON medication state.

• You will be asked to take your normal dosage of medication mid-way through the visit.

• You will complete several clinical scales including: geriatric depression scale, Montreal cognitive assessment, unified dyskinesia rating scale, activity balance confidence scale, speech assessment scale, Parkinson's disease questionnaire and freezing of gait questionnaire.

• You will be asked to perform sitting perceptual tasks in the ON/OFF state in a virtual environment displayed on a monitor such as temporal perception, displacement perception and velocity perception. You will be asked to provide verbal responses to questions asked during the task.

• You will be asked to perform proprioceptive perceptual tasks in the ON/OFF state using a haptics-enabled device (such as the KINARM Exoskeleton), such as temporal perception, displacement perception, or velocity perception. The device may passively move the participants limb, require the subject to move the device, or involve the subject to explore shapes of different geometry, size, texture or stiffness. You will be asked to provide verbal responses to questions

asked during the task.

At the end of your visit you will resume your usual PD medication schedule.

Potential Benefits

There may be no direct benefit from taking part in the study, but the information gained from this study may help to better treat patients with Parkinson's disease in the future.

Risks and Discomforts

The full body suit is a light weight and fully portable technology for collecting information about your mobility. There is a minimal risk associated with wearing such a suit as the system only uses simple sensors that are attached to the suit. Some study participants may experience discomfort such as itching and sweating while wearing the suit.
Some study participants may experience minor emotional distress with completing the scales and questionnaires. Scales will be administered by an experienced researcher trained in administering items in a sensitive manner. You will be allowed rest periods as necessary during the scales and questionnaires to facilitate comfort.

Some study participants may 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 wirelessly, so there are no intrusive wires in the walking path.

Voluntary Participation

Participation in this study is voluntary. At any point during the study, you may refuse to participate, refuse to answer any questions or withdraw from the study with no effect on your future care.

Any new information learned during your participation in the study that may affect your decision to partake in the study will be relayed to you.

You are free to withdraw from the study at any time.
If you withdraw from the study, we will need to use the data collected up to your withdrawal (data will not identify you).

Physical Injury Resulting from Participation

You should report any discomforts, problems, or research related injuries immediately to Dr. Mandar Jog at Ext. . If you are injured and that injury was caused by direct participation in the study, your doctor will provide usual medical care. If this occurs, you will not be financially responsible for medical expenses.

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.

Compensation

You will not receive any monetary compensation for your participation in this study.

Study-related Communications

In order to participate in the program we will ask for you to provide your phone number to the study team and to advise the study team if your phone number changes during the study.

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 location for 15 years. A list linking your study number with your name will be kept by the study doctor in a secure place, separate from your study file.

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. Only research study staff will be able to access this number and link it with your personal information. .

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.

Conflict of Interest

All of the doctors treating you have an interest in completing this study. Their interests should not influence your decision to participate in this study.

Questions about the Study

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 at . If you have questions about the conduct of the study or your rights as a research participant, you may call Dr. David Hill, Scientific Director, Lawson Health Research Institute at

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.

Consent to Participate- PD Patient Group

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

Signature of Research Participant	Printed Name	Date
Signature of Investigator	Printed Name	Date
Signature of Person Obtaining Consent	Printed Name	Date

Appendix E: LOI&C for DBS Participants

London Movement Disorders Center
339 Windermere Rd, BLL-250
London, Ontario, Canada N6A 5A5
(519) 685-8500 ext.76708

Letter of Information and Consent

Study Title: The use of whole-body kinematic technology for optimizing current steering deep brain stimulation in Parkinson's disease patients

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

Protocol Version: 8.0

Protocol Date: 1/June/2018

Participant Number: BSC - __ __

In this Consent document, "you" always refers to the study participant. Participants of this study must be able to give informed consent and cannot have a substitute decision maker (SDM) (i.e. someone who makes the decision of participation on behalf of a participant).

This consent form explains the research study you are invited to join. Please ask the study doctor or the study staff to explain any words or facts that you do not understand. You should keep a signed copy of this consent form. You may wish to discuss this study with your family and friends before making your decision. If you decide to take part in the research study, you must sign this form before you have anything done for this research study.

Introduction

We are inviting you to voluntarily participate in a research project designed to assess the use of a new method in the practice of a surgical procedure known as deep brain stimulation (DBS). This procedure allows electrical signals to be sent to brain areas related to control of body movement – one area being the subthalamic nucleus (STN). The device being implanted in the STN is part of the routine DBS therapy; therefore, the surgery and clinical management of your DBS device will not be changed. However, during the research visits of this study, we will be exploring a new method of delivering current to the appropriate brain region.

During DBS, electrodes are placed deep in the brain and are connected to a programmable stimulator device. Similar to a heart pacemaker, the stimulator uses electric pulses to help regulate the amount of stimulation delivered to the electrodes. The doctor controls the stimulator settings with a wireless device and stimulation settings can be adjusted as a patient's condition changes over time. The surgical procedure to implant the electrodes will have been clearly explained to you by your surgeon and neurologist, and you will have already signed a separate consent form for this operation as part of the treatment of your Parkinson's disease (PD).

Currently, the delivery of current is directed toward the same brain region for all patients. A new DBS technique has broadened our ability to control and thus, investigate different programming settings of the stimulator device. Through stimulating different regions in the brain, this investigation can help us to determine the best location to deliver current, for each patient. The ability to change where and how much current is being delivered is called current-steering. This study seeks to investigate current-steering with the use of your DBS device to determine the effectiveness of this new programming technique.

Background

DBS of the STN is a therapy for individuals who are no longer responding to Levodopa (the current drug used to treat PD) as well as they were at the start of their treatment. The purpose of the method of DBS is to stimulate target brain structures while minimizing the stimulation of surrounding regions. The success of DBS therapy is reliant on 3 main aspects: 1) proper patient selection, 2) accurate placement of the electrode lead within the brain, 3) effective selection of stimulator settings of the DBS device. The precise location of the electrode lead and the stimulator settings contribute equally to the therapeutic effect for the patient. However, if the electrode is misplaced within the brain tissue, corrective surgery possesses an added risk for the patient.

The DBS device being used for this study will allow the current to enter the patient's brain through multiple contact points. The device used in this study is not new; however, current steering or the ability to control the amount of current delivered at each contact point is a new technique. The technique of current steering will be investigated in this study. The current steering feature of DBS devices has not been extensively researched. Current steering allows for a more personalized treatment of PD. The ability to direct the current to the optimal location for each patient is a very promising approach to improve the therapeutic success of DBS.

In this study, we attempt to use our lab expertise to investigate the current steering technique. The STN is composed of many different types of brain cells that respond differently to electrical stimulation. It is hypothesized that PD symptom relief is highly dependent on the location of DBS electrical stimulation. Therefore, it is predicted that current steering can change the area of brain tissue being stimulated, and a notable change in PD motor and perceptual features will result as different types of STN brain cells can be targeted. The objectives of the study are:

1. Investigate whether using current steering settings during DBS to direct the current to an optimal location within the brain tissue has any direct effect on PD motor and perceptual symptoms.
2. Determine if there are common settings of the programmable DBS device that are best for treating symptom improvement among all patients.

We are looking to investigate current steering in 16 persons that have undergone STN-DBS recruited from the Movement Disorders Clinic at London Health Sciences Centre (LHSC). This study will require you to come to the research lab 4 days a week for a month post-operation.

Study Funding

The study is funded in part by Boston Scientific who manufacture the DBS device being used in the current study. Other funding is coming from a research grant from Movement Disorders Center at London Health Sciences Centre (LHSC).

Inclusion and Exclusion criteria

If you decide to join, you will be asked to sign this consent form and you must agree to follow the instructions given by the research staff during the study. You may not participate in this study if you participated in another clinical research project less than 4 weeks ago. Based on your screening information, the study doctor will determine if you are eligible to join this study.

Inclusion criteria:

1. Diagnosed Idiopathic Parkinson Disease with excellent response to levodopa medication
2. A score of between II-IV on the Hoehn-Yahr scale
3. Severe motor fluctuations with disabling off periods and dyskinesia during on phases
4. Assessed for eligibility for the DBS procedure
5. Able to give informed consent
6. Able to visit the clinic for assessment
7. No dementia or psychiatric abnormalities.

Exclusion criteria:

1. Any previous brain surgery or a cardiac pacemaker
2. If your medication routine is unstable and/or you take levodopa containing medications less than 3 times a day.
3. Any diagnosis of dementia, severe cognitive disturbances or severe psychiatric symptoms (in particular hallucinations and depression) as assessed by DSM criteria
4. Any hip or joint replacements (unless well treated as assessed by the study team)
5. Lack of compliance at follow-up.
6. *Additional exclusion criteria for perceptual test:* Severe visual impairment determined from visual testing (i.e., convergence insufficiency)

Study Tools

The study will make use of several technological devices to objectively measure all motor symptoms associated with Parkinson's disease. The whole-body mobility is assessed using a motion capture suit which houses several motion sensors that track all body movements. You will be dressed in a lightweight, stretchable, and breathable 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. Walking will be assessed using a pressure sensor carpet walkway. You will be required to walk across the carpet so that the system can capture your walking patterns in various ways. Your speech will also be recorded using a head mounted microphone and a digital recording device. To assess the perceptual capabilities of the PD subjects, a computational virtual reality environment and haptics-enabled robots (such as the KINARM Exoskeleton) may be used.

You will also complete standard clinical scales at each visit that are used to monitor motor and non-motor features of Parkinson's disease (Table 1.)

Table 1. Clinical scales used at every visit.

Clinical Scale	Description
The Unified Parkinson's Disease Rating Scale (UPDRS)	A widely used clinical scale used to measure the impairment and disability associated with Parkinson Disease
The Montreal Cognitive Assessment (MoCA)	A brief 30-question test which assesses different types of cognitive abilities such as short-term memory and concentration.
Freezing of Gait Questionnaire (FOG-Q)	A 6 item questionnaire used to monitor freezing of gait in Parkinson's disease
Activities-specific Balance Confidence (ABC) Scale	A 16 item scale that measures one's confidence in maintaining their balance when completing specific activities
Beck's Depression Inventory	A 21 item questionnaire used to measure affect related to depression

All visits will be recorded with a video camera for data analysis purposes only. The recorded videos will be coded and not linked to your personal information. You may opt-out from these recordings by selecting an option on page 10 of this letter.

Study Procedure and Design

This is a trial seeking to optimize a patients' DBS device programming using objective and quantitative data that will be obtained from kinematic technology such as the motion capture suit and the carpet walkway.

Participants will then undergo DBS implantation into the STN on both sides of the brain with the Boston Scientific DBS device. Patients will be given at least 4 weeks to recover from the operation; for instance, from week 0 to week 4. At least 6 weeks post-operation, each participant will undergo a 4-week titration regime to determine the effect that current steering has on their primary motor symptoms. Classic hallmark PD symptoms will be assessed using the kinematic technology.

Visit 1: 1 week before surgery

Study participants will be seen one week prior to the DBS surgery to assess their response to the levodopa medication. You will arrive at the research laboratory after being OFF levodopa medications for 12 hours. Full body mobility assessments will be conducted in your OFF state using the motion capture suit, carpet walkway and the speech recorder. Following these assessments, you will be asked to take 135% of your usual levodopa medication. For example, if the patient usually takes 100mg of levodopa for the treatment of their PD, 135% of that would be 135mg. During the wait time for the medication to take into effect, clinical rating scales for movement difficulties and other difficulties

(depression, memory etc.) will be completed (outlined in Table 1.). Once the levodopa medication has taken effect a full body mobility assessment will be conducted in your ON state using the motion capture suit, carpet walkway and the speech recorder.

Visit 2: at least 4 weeks post-surgery

At least 4 weeks post-operation a Movement Disorder Neurologist will turn on the patients' device.

*****Note: The next visit sessions will occur over 1 consecutive month, with 4 visits each week*****

Visit 3-6: at least 6 weeks post-surgery

During these visits 16 current steering paradigms will be explored, 4 each day. These setting paradigms will be randomized for each participant so the same settings are not presented in the same order for each person. Your device will also be set to 20% more of the therapeutic amplitude (current) you will be at clinically. After each current steering setting is implemented, a 30-minute wait period will be allowed for the setting to take effect. Full body assessments will be performed for each setting change as well as the UPDRS. At the end of each day, following the 4 setting changes, your DBS device will be returned to the original setting you came in with. At the end of the week you will be turned to a setting that was found to be most beneficial. You will then be asked to return the following week.

Visit 7-10: at least 7 weeks post-surgery

This visit will be the exact same as visits 3-6 except the amplitude (current) of the device will be increased by 40% of the baseline setting.

Visit 12-15: at least 8 weeks post-surgery

This visit will be the exact same as visits 3-6 except the amplitude (current) of the device will be increased by 60%.

Visit 16-19: at least 9 weeks post-surgery

This visit will be the exact same as visits 3-6 except the amplitude (current) of the device will be increased by 80%.

Visit 20(optional): at least 12th week post-surgery

During this visit, the subject's various perceptual capabilities will be measured. The subject will be asked to perform two-forced alternative choice perceptual tasks while sitting down. These tasks will be displayed on a computer monitor and the patient will be asked to provide verbal responses to questions asked during the tasks. The perceptual tasks will involve tasks to test for temporal perception, displacement perception and velocity perception (an example is when two objects are shown on a monitor and the participant is asked to tell which object is moving faster or further). Alternatively, the subjects may carry out proprioceptive perceptive tests (such as temporal, displacement and velocity perception) using a hapticsenabled device (such as the KINARM exoskeleton). An example of a task involves the subject comparing two speeds of passive movement (powered by the haptics device), and verbally answering which of the compared speeds they perceive to be faster.

Study Tasks

Patients will perform various tasks during the programming sessions including:

1. **Relaxed position (20 Seconds)**: The participants are asked to rest their arms in neutral position while: back hunched forward, both forearms on legs, and hands hanging loose between legs. The participants hold this position for 20 seconds.
2. **Supported Posture (20 seconds)**: The participants are asked to rest their arms in neutral position on the arm rests of a chair. The participants hold this position for 20 seconds.
3. **Pronated Posture (20 seconds)**: While sitting, participants fully extend their arms forward with hands in pronation at shoulder height level. The participants hold this position for 20 seconds.
4. **Supinated Posture (20 seconds)**: While sitting, participants fully extend their arms forward with hands in supination at shoulder height level. The participants hold this position for 20 seconds.
5. **Pronation-supination (20 seconds)**: Same position as posture, participants are asked to turn hands one at a time and as fast as possible so that their palms face up and down alternatively. The participants keep this motion for 20 seconds.
6. **Normal walking (90 seconds)**: consists of rising from a chair and walking around a 25 meter track 5 times at a preferred normal pace.
7. **Fast walking (90 seconds)**: consists of rising from a chair and walking around a 25 meter track 5 times at a fast as possible pace.
8. **Backwards walking (90 seconds)**: consists of rising from a chair, turning around and walking down the 7 meter long gait carpet. Once off the carpet the patient turns around and walks backwards across the carpet back into the starting chair.
9. **180 Degrees Turn (60 seconds)**: while standing, the participant is asked to turn left/right 180 degrees on the spot to face the back. After a few seconds, they are asked to return to the original position. This task is performed for 8 turns.
10. **Speech recording (120 seconds)**: a microphone will be taped to the patients' cheekbone and speech tasks will be carried out.
11. **UPDRS (5 minutes)**: this clinical rating scale will be carried out to assess motor symptom severity after each setting change.
12. **Visual Temporal Perception (about 30 minutes)**: Patients will perform a 2-Alternative-Forced-Choice task composed of approximately 160 trials. In each trial, comparisons between the time of shapes flashing on the screen (i.e., the first shape appears, disappears for varying amount of time [this time changes between trials and shapes compared in trials] then reappears again briefly before disappearing permanently. This is followed by another shape flashing on the screen. The subject will be asked which time duration between the shape disappearing and reappearing was faster (or if they were the same) between the two compared shapes in each trial.
13. **Visual Displacement Perception (about 30 minutes)**: Patients will Perform a 2 Alternative Forced Choice task composed of approximately 160 trials. In each trial a shape at a certain point displayed on a computer monitor will displace to twice, the subject must answer which displacement was greater, or if their displaced was of the same magnitude.

14. **Visual Velocity Perception (about 40 minutes):** Patients will perform a 2-Alternative-Forced-Choice task composed of approximately 200 trials. In each trial two shapes will be moving in opposite directions on a computer monitor for 10 seconds, the subject must answer which velocity was greater, or that the velocities are the same speed.
15. **Proprioceptive Temporal Perception (about 30 minutes):** Patients will perform a 2-Alternative-Forced-Choice task composed of approximately 160 trials. In each trial, subjects should compare the difference in time between the release of force applied from the haptics device (i.e., in each trial, the device will apply force, remove force for a set time, apply force again, remove force a second time, reapply force, end of trial). The subject will be asked which time duration between the removal of the force applied to the patient and the force being reapplied was longer (or if they were the same) between the two compared pauses in force for each trial.
16. **Proprioceptive Displacement Perception (about 30 minutes):** Patients will perform a 2-Alternative-Forced-Choice task composed of approximately 160 trials. In each trial the subject's limb will begin at a starting point and be passively displaced twice from this starting point. The subject should compare the proprioceptive displacements and verbally answer which displacement they felt was greater, or that the displacements were the same.
17. **Proprioceptive Velocity Perception (about 40 minutes):** Patients will perform a 2-Alternative-Forced-Choice task composed of approximately 200 trials. In each trial the haptic device will passively move the patient's limb at a certain velocity for around 7 seconds, and then move their limb again for around 7 seconds. The subject will then compare the speeds of the limb movements, and verbally respond which speed they perceived to be greater, or that they perceived the speed to be the same.

Each task will be performed twice with the exception of tasks 6, 7, 9-11. The total amount of time for the motor testing sessions is approximately 20 minutes with appropriate rest periods. Perceptual tests will be done when the DBS system is turned off, and again when it is turned on during one day of experimenting.

Possible Risks and Harms

This study has some risks that we know about. There is also a possibility of risks that we do not know about and have not been seen in study participants to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study.

Risks are grouped according to two categories; a brief overview is provided for ***standard of care risks*** which your doctor will have discussed with you in greater detail. The second group is risks related to ***participation in this research study***:

Study Related Risks

Withholding of medication: You may have transient worsening of parkinsonian symptoms following overnight withdrawal of antiparkinsonian medications. However, this should be no different from the procedure performed as part of the routine clinical assessment before and after surgery. You may get tired during the procedure. You will be OFF medications about 12 times total throughout the study.

Risks of Current Steering: You may experience worsening of motor symptoms during the setting changes at the research visits. Some common side effects patients report during settings changes are:

1. Worsening of motor features associated with Parkinson's disease
2. Tingling and numbness in limbs
3. Dizziness and lightheadedness
4. Upset stomach
5. Blurred vision
6. Slurred speech

While these symptoms do not usually occur it is important to monitor for them. The study team understands the common side effects and will monitor them throughout the study. Should you be experiencing any of these symptoms, or others, please let the study team know.

Risks associated with study tools: The full body suit is a light weight and fully portable technology for collecting information about your mobility. There is a minimal risk associated with wearing such a suit as the system only uses simple sensors that are attached to the suit. Some study participants may experience discomfort such as itching and sweating in their body while wearing the suit. Some study participants may experience minor emotional distress with completing the scales and questionnaires. Scales will be administered by an experienced researcher trained in administering items in a sensitive manner. You will be allowed rest periods as necessary during the scales and questionnaires to facilitate comfort.

Possible Benefits

You may not directly benefit from the study, but the information obtained may lead to new knowledge on movement disorders and may lead to new treatment for movement disorders.

Compensation

You will not be compensated for participating in this research study, however you will be reimbursed for parking expenses and potential travel costs.

Confidentiality

Personal Health Information

If you agree to join this study, the study doctor and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you and includes your:

1. Name
2. Address
3. Partial Date of birth
4. New or existing medical records that includes types, dates and results of medical tests or procedures
5. Telephone Number

Research Information in Clinical Records

If you participate in this study, information about you from this research project may be stored in your hospital file and in the LHSC computer system. The study team can tell you what information about you will be stored electronically and if you have any concerns about this, or have any questions, please contact the laboratory at

The following people may come to the hospital to 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 is following proper laws and guidelines:

1. Representatives of Lawson Health Research Institute (LHRI) including the LHRI Research Ethics Board
2. Representatives of the University of Western Ontario Health Sciences Research Ethics Board.
3. The study sponsor or its representatives'/partner companies (Canadian Institutes of Health Research and Boston Scientific)
4. Representatives of Health Canada or other regulatory bodies (groups of people who oversee research studies) outside of Canada, such as the United States Food and Drug Administration.

The information that is collected for the study will be kept in a locked and secure area by the study doctor for 25 years. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital.

Following completion of the study, identifiable videos and photographs will be stored using a code number only and will never leave University Hospital. The videos and photographs will remain stored in a secure location and will not be viewed by anyone outside the study team without your permission. If these videos are used for scientific presentations or education purposes, you will not be identified as all personal identifiers (such as your face) will be blurred or blackened out. All videos and photographs will be destroyed after the study is complete.

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.

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. No new information will be collected without your permission.

Alternatives to study participation

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

Withdrawal from the study by the investigator

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

Rights as a Participant

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost. By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

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 at . If you have questions about the conduct of the study or your rights as a research participant, you may call Dr. David Hill, Scientific Director, Lawson Health Research Institute at

Publication

If the results of the study are published, your name will not be used. If you would like to receive a copy of any potential study results, please contact Dr. Mandar Jog at

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: The use of whole-body kinematic technology for optimizing current steering deep brain stimulation in Parkinson's disease patients

Principal Investigator: Dr. Mandar Jog, MD

Medical Personnel:

Dr. Mandar Jog, MD – Neurologist

Ms. Heather Russell – Clinic 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.

- ☐ I give permission for my visits to be recorded on camera for data analysis purposes only
- ☐ I do not give permission for my visits to be recorded on camera

_____	_____	_____
Signature of Study Participant	**Printed Name**	**Date**
_____	_____	_____
Signature of Investigator	**Printed Name**	**Date**
_____	_____	_____
Signature of Person Obtaining Consent	**Printed Name**	**Date**

Appendix F: LOI&C for De Novo Participants

London Health Sciences Centre

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

Letter of Information and Consent

Study Title: Kinematic biomechanical characterization of upper limb Parkinson's disease tremor for optimization of botulinum toxin type A injection parameters

Optional Study: Visual perceptions independent of motor output

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

Introduction

We are inviting you to voluntarily participate in an optional portion of our research project which evaluates and treats upper limb tremor in Parkinson's disease (PD) patients using botulinum toxin type A (BoNT-A). The objective of this optional study component is to analyze visual perceptions in PD, and examine how they differ from those without PD, as well as how these perceptions are affected at different disease stages. The study aims to examine visual temporal, velocity, and displacement perceptions without correlated motor-outputs in "de-novo" (recently diagnosed patients not currently using pharmaceutical or deep brain stimulation [DBS] therapy) PD patients. Due to your inclusion in the BoNT-A study you have eligibility to participate in the perceptual sub-study. The aim of the study is to learn more about alteration in neural activity during PD, with the hope of using this information to develop disease diagnostic computer models.

Nature of the research project and tasks involved

We are looking to investigate visual perceptions without an associated motor-response in **25 "de-novo" Parkinson's disease (PD) patients** who are not currently using PD pharmaceutical or DBS therapy, who will be recruited from the Movement Disorders Clinic at Lawson Health Sciences Centre (LHSC).

We are inviting you to participate in this study as we believe that you fit the criteria for study eligibility. The visual temporal, velocity, and displacement perception tasks will provide insight to how PD affects different neural regions that are not involved with movement production. Furthermore, it will provide insight on how the disease affects the brain at different PD stages. You will not have to change your medications in any way for this study. Furthermore, participation will not affect scheduling of your routine clinic visits.

The experimenter might ask you to be photographed or videoed while conducting the experiment. Your eligibility to participate will not be affected by your decision to be photographed/videoed or not.

This is a completely optional part of the study, you are not required to be photographed or videoed if you choose not to be. If you allow photographs/videos to be taken of yourself the photographs/videos would consist of yourself conducting the experiment, with all photographs/videos being taken behind you. Thus, your face will not be displayed in the photograph/video, instead the back-side of yourself and the testing apparatus (computer monitor displaying perceptual tests) will be photographed/videoed. The photographs/videos will be stored on a password encrypted USB drive kept in Dr. Jog's research lab for a maximum of 15 years, and accessible by only the primary experimenter. The videos/photographs may be used for demonstrative purposes in publications and project presentations, to help viewers visualize the experimental set up and how the experiments were conducted.

Study Eligibility:

You are eligible for the optional perceptual portion of the study based on the following: 1) having been diagnosed with PD and not using PD pharmaceutical treatment (such as Levodopa) or PD DBS therapy.

Exclusion Criteria

Visual Deficit: If you display oculomotor deficiencies (such as smooth pursuit or saccadic eye movement problems) then you are not eligible for participation in the study. Furthermore, although perfect visual acuity is not necessary, you will not be permitted to participate in the study if you display sever visual acuity deficits. Note that visual acuity can be tested with glasses on, thus if impairments are aided by glasses this will not be considered an exclusion criterion.

Study Outline

The research visit will require you to come to Dr. Mandar Jog's research facilities located at University Hospital, London, Ontario. The perceptual portion of the study will take place in one session.

At this study visit you will be asked to complete the following tasks, which are described below:

1) Complete Unified Parkinson's Disease Rating Scale (UPDRS) diagnostic motor function test
2) Complete Montreal Cognitive Assessment (MoCA) diagnostic test
3) Complete visual diagnostic tests
4) Complete visual velocity, temporal, ad displacement perceptual tests

UPDRS Diagnostic Test
The UPDRS test is a standard method for assessing the severity of common movement disorders in PD. This test requires assessment of limb stiffness, arm and hand movements, gait and balance analysis, among other assessments. This diagnostic procedutre will likely have been performed at every neurology appointment you have had with Dr. Jog regarding your PD.

MoCA Diagnostic Test
The MoCA is a short, simple cognitive assessment designed to indicate severe cognitive deficiencies that may be present in the tester. The tasks involve brain teasers, memory, and fluency tasks, among others.

Eye Examinations
Saccadic and smooth pursuit eye examinations will be carried out to examine any potential oculomotor deficits present in the participant. These are simple, non-invasive tests which require the participant to

make certain eye movements for analysis. Visual acuity tests will also be carried out. These will require that you accurately read (with or without glasses) text on a computer monitor, and/or use the Snellen eye chart for visual acuity examinations.

Visual Perception Testing:
Temporal, velocity, and displacement perceptual tasks will be carried out. All the tasks are visually based. The tasks will be displayed on a computer monitor while you are sitting comfortably approximately 2 feet back from the screen. The experimenter will control the pace of the experiment. Subjects will not be required to perform any motor-outputs in response to tasks (such as arm movements). However, after each trial the subject will provide a verbal answer. The task will be performed while the participant is sitting down. The experimenter will provide mandatory breaks. The participant can request additional breaks at any time during the experiment. These breaks will last as long as necessary/desired by the participant. Temporal and displacement perceptual tasks will generally take between 15-25 minutes, with the velocity perception task taking generally 40-50 mins. The entire experiment (including diagnostics) will take approximately 2 – 2.5 hours.

Study Timeline

The perceptual testing will take place in one day that lasts approximately 2 – 2.5 hours at Dr. Jog's research facility in the University Hospital. The study session can take place at any date and time that is the best for the you. This includes research days for the main portion of this study (BoNT-A injection days), as well as non-injection days.

Potential Benefits

There will be no direct benefits received by you by participating in the perceptual portion of the research study. The information gained from this study may help to better treat patients with PD in the future.

Risks and Discomforts

Due to the nature of the experiments (sitting down) there are minimal risks and discomforts involved with the perceptual experiments. Discomforts may arise from sitting for prolonged periods of time. Breaks can be provided at any time in the experiment where you will be able to walk or stretch.

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 location for 15 years. A list linking your study number with your name will be kept by the study doctor in a secure place, separate from your study file.

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. Only research study staff will be able to access this number and link it with your personal information.

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.

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. Parking will however be compensated at $20.00 for the study visit.

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 tremor management 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 at If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Patient Experience Office at LHSC at ext. or access the online form at: 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

Kinematic biomechanical characterization of upper limb Parkinson's disease tremor for optimization of botulinum toxin type A injection parameters
Optional Study: Visual perceptions independent of motor-output

STUDY DOCTOR

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

Permission to Record Video and/or Photographs (OPTIONAL)

I give permission to the experimenter to record a video and/or photograph myself while I am conducting the visual perception experiments: _____ (Initialize if giving consent)

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

Signature of Research Participant	Printed Name	Date
Signature of Investigator *not present during consent	Printed Name	Date
Signature of Person Obtaining Consent	Printed Name	Date
Signature of Witness	Printed Name	Date

Appendix G: UPDRS Part III: Motor-Subsection

INITIAL VISIT PACKET NACC UNIFORM DATA SET (UDS) **LBD MODULE**

Form B3L: UPDRS Part III — Motor Examination[1]

ADC name: _____ Subject ID: _____ Form date: ___/___/_____

Visit #: ___ Examiner's initials: ___

INSTRUCTIONS: This form is to be completed by the clinician or other trained health professional. For additional clarification and examples, see LBD Module Coding Guidebook for Initial Visit Packet, Form B3L. Check only one box per question.

1. Speech

- ☐ 0 Normal.
- ☐ 1 Slight loss of expression, diction, and/or volume.
- ☐ 2 Monotone, slurred but understandable; moderately impaired.
- ☐ 3 Marked impairment, difficult to understand.
- ☐ 4 Unintelligible.
- ☐ 8 Untestable. (SPECIFY REASON): _____

2. Facial expression

- ☐ 0 Normal.
- ☐ 1 Minimal hypomimia, could be normal "poker face."
- ☐ 2 Slight but definitely abnormal diminution of facial expression.
- ☐ 3 Moderate hypomimia; lips parted some of the time.
- ☐ 4 Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.
- ☐ 8 Untestable. (SPECIFY REASON): _____

3. Tremor at rest

3a. Face, lips, chin

- ☐ 0 Absent.
- ☐ 1 Slight and infrequently present.
- ☐ 2 Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
- ☐ 3 Moderate in amplitude and present most of the time.
- ☐ 4 Marked in amplitude and present most of the time.
- ☐ 8 Untestable. (SPECIFY REASON): _____

[1]Fahn S, Elton RL, UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent developments in Parkinson's disease, Vol. 2. Florham Park, NJ: Macmillan Healthcare Information, 1987:153-163, 293-304. Reproduced by permission of the author.

Tremor at rest (CONTINUED)

3b. Right hand

☐0 Absent.
☐1 Slight and infrequently present.
☐2 Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
☐3 Moderate in amplitude and present most of the time.
☐4 Marked in amplitude and present most of the time.
☐8 Untestable. (SPECIFY REASON): _____

3c. Left hand

☐0 Absent.
☐1 Slight and infrequently present.
☐2 Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
☐3 Moderate in amplitude and present most of the time.
☐4 Marked in amplitude and present most of the time.
☐8 Untestable. (SPECIFY REASON): _____

3d. Right foot

☐0 Absent.
☐1 Slight and infrequently present.
☐2 Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
☐3 Moderate in amplitude and present most of the time.
☐4 Marked in amplitude and present most of the time.
☐8 Untestable. (SPECIFY REASON): _____

3e. Left foot

☐0 Absent.
☐1 Slight and infrequently present.
☐2 Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
☐3 Moderate in amplitude and present most of the time.
☐4 Marked in amplitude and present most of the time.
☐8 Untestable. (SPECIFY REASON): _____

4. Action or postural tremor of hands

4a. Right hand

☐0 Absent.
☐1 Slight; present with action.
☐2 Moderate in amplitude, present with action.
☐3 Moderate in amplitude with posture holding as well as action.
☐4 Marked in amplitude; interferes with feeding.
☐8 Untestable. (SPECIFY REASON): _____

4b. Left hand

☐0 Absent.
☐1 Slight; present with action.
☐2 Moderate in amplitude, present with action.
☐3 Moderate in amplitude with posture holding as well as action.
☐4 Marked in amplitude; interferes with feeding.
☐8 Untestable. (SPECIFY REASON): _____

5. Rigidity

(Judged on passive movement of major joints with participant relaxed in sitting position. Cogwheeling to be ignored.)

5a. Neck

☐0 Absent.
☐1 Slight or detectable only when activated by mirror or other movements.
☐2 Mild to moderate.
☐3 Marked, but full range of motion easily achieved.
☐4 Severe, range of motion achieved with difficulty.
☐8 Untestable. (SPECIFY REASON): _____

5b. Right upper extremity

☐0 Absent.
☐1 Slight or detectable only when activated by mirror or other movements.
☐2 Mild to moderate.
☐3 Marked, but full range of motion easily achieved.
☐4 Severe, range of motion achieved with difficulty.
☐8 Untestable. (SPECIFY REASON): _____

Rigidity (CONTINUED)

5c. Left upper extremity

☐0 Absent.
☐1 Slight or detectable only when activated by mirror or other movements.
☐2 Mild to moderate.
☐3 Marked, but full range of motion easily achieved.
☐4 Severe, range of motion achieved with difficulty.
☐8 Untestable. (SPECIFY REASON): _____

5d. Right lower extremity

☐0 Absent.
☐1 Slight or detectable only when activated by mirror or other movements.
☐2 Mild to moderate.
☐3 Marked, but full range of motion easily achieved.
☐4 Severe, range of motion achieved with difficulty.
☐8 Untestable. (SPECIFY REASON): _____

5e. Left lower extremity

☐0 Absent.
☐1 Slight or detectable only when activated by mirror or other movements.
☐2 Mild to moderate.
☐3 Marked, but full range of motion easily achieved.
☐4 Severe, range of motion achieved with difficulty.
☐8 Untestable. (SPECIFY REASON): _____

6. Finger taps

(Participant taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.)

6a. Right hand

☐0 Normal.
☐1 Mild slowing and/or reduction in amplitude.
☐2 Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐3 Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐4 Can barely perform the task.
☐8 Untestable. (SPECIFY REASON): _____

Finger taps (CONTINUED)

6b. Left hand

☐0 Normal.
☐1 Mild slowing and/or reduction in amplitude.
☐2 Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐3 Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐4 Can barely perform the task.
☐8 Untestable. (SPECIFY REASON): _____

7. Hand movements

(Participant opens and closes hands in rapid succession with widest amplitude possible, each hand separately.)

7a. Right hand

☐0 Normal.
☐1 Mild slowing and/or reduction in amplitude.
☐2 Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐3 Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐4 Can barely perform the task.
☐8 Untestable. (SPECIFY REASON): _____

7b. Left hand

☐0 Normal.
☐1 Mild slowing and/or reduction in amplitude.
☐2 Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐3 Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐4 Can barely perform the task.
☐8 Untestable. (SPECIFY REASON): _____

8. Rapid alternating movements of hands

(Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.)

8a. Right hand

☐0 Normal.
☐1 Mild slowing and/or reduction in amplitude.
☐2 Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐3 Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐4 Can barely perform the task.
☐8 Untestable. (SPECIFY REASON): _____

Rapid alternating movements of hands (CONTINUED)

8b. Left hand

☐0 Normal.
☐1 Mild slowing and/or reduction in amplitude.
☐2 Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐3 Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐4 Can barely perform the task.
☐8 Untestable. (SPECIFY REASON): _____

9. Leg agility

(Participant taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches.)

9a. Right leg

☐0 Normal.
☐1 Mild slowing and/or reduction in amplitude.
☐2 Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐3 Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐4 Can barely perform the task.
☐8 Untestable. (SPECIFY REASON): _____

9b. Left leg

☐0 Normal.
☐1 Mild slowing and/or reduction in amplitude.
☐2 Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐3 Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐4 Can barely perform the task.
☐8 Untestable. (SPECIFY REASON): _____

10. Arising from chair

(Participant attempts to arise from a straight-back wood or metal chair with arms folded across chest.)

☐0 Normal.
☐1 Slow; or may need more than one attempt.
☐2 Pushes self up from arms of seat.
☐3 Tends to fall back and may have to try more than one time, but can get up without help.
☐4 Unable to arise without help.
☐8 Untestable. (SPECIFY REASON): _____

11. Posture

☐0 Normal erect.

☐1 Not quite erect, slightly stooped posture; could be normal for older person.

☐2 Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

☐3 Severely stooped posture with kyphosis; can be moderately leaning to one side.

☐4 Marked flexion with extreme abnormality of posture.

☐8 Untestable. (SPECIFY REASON): _____

12. Gait

☐0 Normal.

☐1 Walks slowly, may shuffle with short steps, but no festination or propulsion.

☐2 Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

☐3 Severe disturbance of gait, requiring assistance.

☐4 Cannot walk at all, even with assistance.

☐8 Untestable. (SPECIFY REASON): _____

13. Postural stability

(Response to sudden posterior displacement produced by pull on shoulders while participant erect with eyes open and feet slightly apart. Participant is prepared.)

☐0 Normal.

☐1 Retropulsion, but recovers unaided.

☐2 Absence of postural response; would fall if not caught by examiner.

☐3 Very unstable, tends to lose balance spontaneously.

☐4 Unable to stand without assistance.

☐8 Untestable. (SPECIFY REASON): _____

14. Body bradykinesia and hypokinesia

(Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)

☐0 None.

☐1 Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

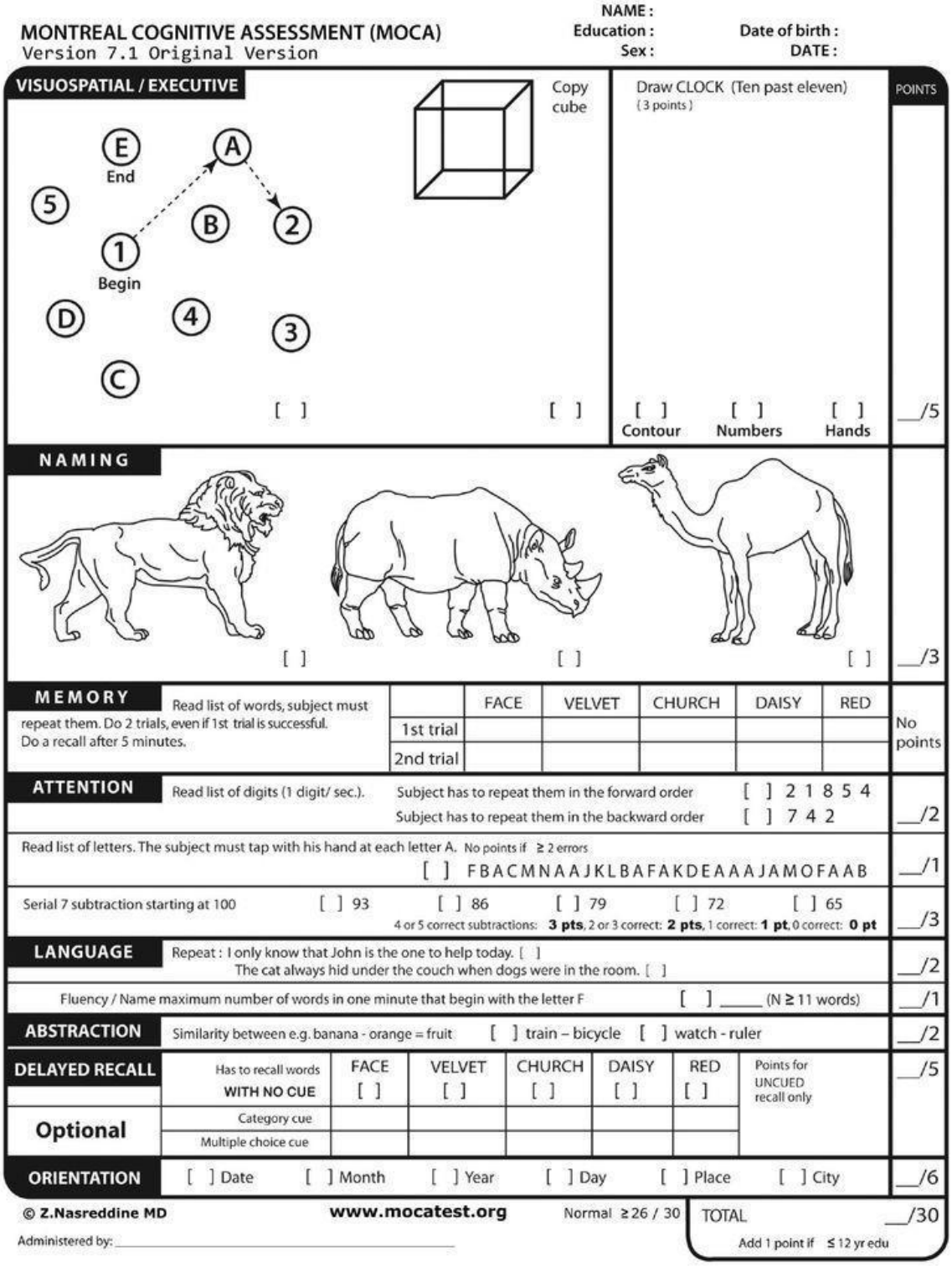
☐2 Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

☐3 Moderate slowness, poverty, or small amplitude of movement.

☐4 Marked slowness, poverty, or small amplitude of movement.

☐8 Untestable. (SPECIFY REASON): _____

Appendix H: MoCA



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube [ ]

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

NAMING [ ] [ ] [ ] /3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

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

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

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

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

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

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

DELAYED RECALL

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

/5

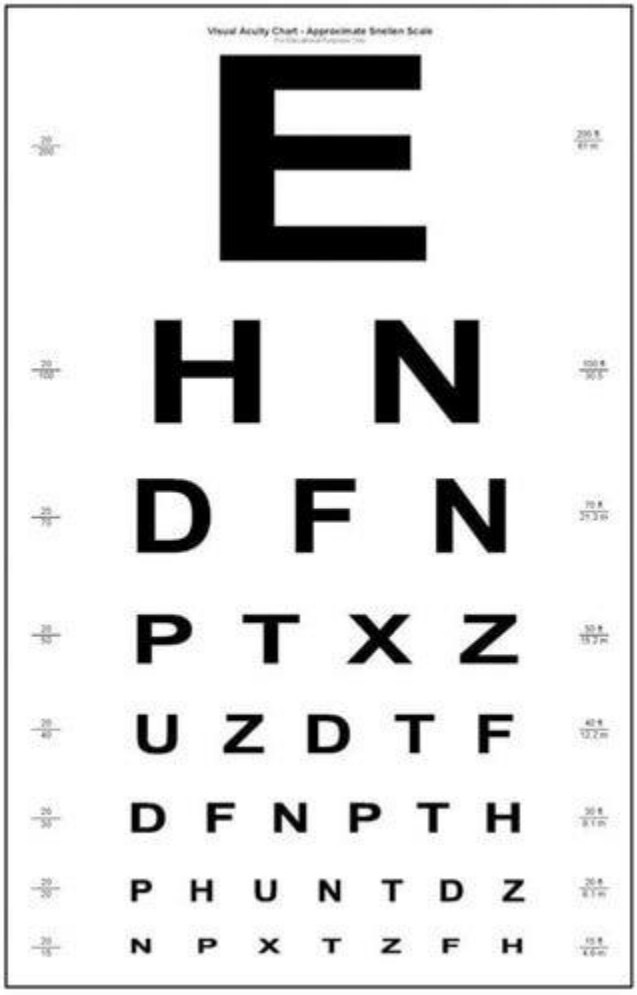
ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City /6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30 TOTAL /30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Use Body Text or Normal style for text in this section.

Appendix I: Snellen Eye Chart



Curriculum Vitae

Name: Matthew Bernardinis

Post-secondary Education and Degrees:
The University of Western Ontario
London, Ontario, Canada
2012-2016 BMSc

Related Work Experience
Teaching Assistant
The University of Western Ontario
2016-2018

Conference Proceedings:

Bernardinis, M., Atashzar, S., F., Jog, M., S., & Patel, R., V., Visual Displacement Perception in Parkinson's Disease |Analyzed using a Computer-Generated Graphical Tool. *IEEE Engineering in Medicine and Biology Conference,* HI, USA, 2018. (Platform presentation)

Bernardinis, M., Atashzar, S., F., Jog, M., S., & Patel, R., V., Visual Temporal perception in Parkinson's Disease Analyzed Using a Computer-Generated Graphical Tool. *IEEE EMBS Conference on Neural Engineering*, CA, USA, 2019. (Poster presentation)

Journal Proceedings:

Bernardinis, M., Atashzar, S., F., Jog, M., S., & Patel, R., V., Differential Temporal Perception Abilities in Parkinson's Disease Patients Based on Timing Magnitude. Submitted to *Nature Scientific Reports*

Bernardinis, M., Atashzar, S., F., Jog, M., S., & Patel, R., V., Abnormal Vision-Based Displacement Perception and Perceptual Linearity in Parkinson's Disease. Submitted to *Movement Disorders*

Bernardinis, M., Atashzar, S., F., Jog, M., S., & Patel, R., V., Vision-based Velocity Perception in Parkinson's Disease: Skewed Perception of the Fabric of Time and Space. To be submitted soon