Exploring the antisaccade task in relation to motor and cognitive functions in adults with mild to moderate idiopathic Parkinson’s Disease

by

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B.Sc., The University of British Columbia, 2020

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE
in
THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES
(NEUROSCIENCE)
THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

August 2023

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Exploring the antisaccade task in relation to motor and cognitive functions in adults with mild to moderate idiopathic Parkinson’s Disease

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Abstract

Parkinson’s Disease (PD) is a neurodegenerative disease characterized by motor impairments including bradykinesia, rest tremor, and postural instability. In addition, motor dysfunction appears in oculomotor abnormalities, specifically saccadic eye movement deficits. It is now recognized that PD extends beyond motor impairments and affects sensory and cognitive domains. PD alters a range of cognitive functions, but particularly affects response inhibition, even early in the disease course. The antisaccade task is an oculomotor paradigm used to evaluate response inhibition and is a sensitive indicator of PD. Antisaccade task performance has been well characterized in PD patients, but it is unclear what factors contribute to these deficits. Here we investigated whether antisaccade performance in mild to moderate PD is related to motor function, executive function, and or general cognitive ability. We evaluated pro- and antisaccade performance in 17 patients and 20 matched controls. Saccade latencies, amplitudes, and error rates were compared between groups, and were correlated to performance on a series of motor (Timed up and Go test) and cognitive tasks (Trail Making Task, Stroop Task, and matrices sub-test of the Kaufman Brief Intelligence Index). Relative to controls, patients showed smaller amplitude prosaccades, and more than double the frequency of errors when executing antisaccades (patients M=21.7% SD= 18.6%; controls M=10.5%, SD=11.43%; p=0.013; d= 0.72). However, patients performed equal to, or better than controls on the battery of motor and cognitive assessments. Our results cautiously suggest that PD patients show deficits in response inhibition despite an absence of cognitive dysfunction on standard neuropsychological tools. With additional investigation, antisaccade task performance has the potential to be a sensitive indicator of early changes in response inhibition in PD, to be used as a tool in compliment with clinical evaluation.
Lay Summary

Parkinson's Disease (PD) affects the brain and causes problems with motor function, cognition, and can impair eye movements. Here we wanted to understand how PD patients perform on an eye movement test called the "antisaccade task", compared to their motor and cognitive abilities. We tested 17 PD patients and 20 others without PD. In the antisaccade task, participants controlled their eye movements to look at, or avoid looking at, a target. We found PD patients had smaller eye movements and made more mistakes than those without PD. Surprisingly, their cognitive abilities were not affected, as they performed equally well or better than the other group. This suggests that PD may impact eye movements in patients with mild disease, without significantly affecting cognitive functions. The antisaccade task could be a useful tool for detecting early changes in PD. More research is needed to understand the connection between eye movement control and PD to develop effective disease monitoring strategies.
Preface

My supervisor, Dr. Miriam Spering, was responsible for the initial framework of the study design which we adjusted together to align with my research interests. I subsequently narrowed down the study objectives and made changes to the protocol and assessments included. I was responsible for all participant recruitment, testing, data collection, and data analysis. Dr. Spering provided expert knowledge and guidance on the analysis pipeline for the eye tracking data as well as the data analysis plan.

This study was conducted with approval from the UBC Clinical Research Ethics Board (H17-00829).
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List of Abbreviations

BG = basal ganglia
BIS-11 = Barratt Impulsivity Scale version 11
DA = dopamine/dopaminergic
DLPFC = dorsal lateral prefrontal cortex
KBIT-2 = Kaufman Brief Intelligence Index, 2nd edition
MDS-UPDRS = Movement Disorders Society – Unified Parkinson’s Disease Rating Scale
MoCA = Montreal Cognitive Assessment
PD = Parkinson’s Disease
RBD = REM sleep behaviour disorder
Stroop = Stroop Colour and Word Task
TMT = Trail Making Task
TUG = Timed Up and Go Test
Acknowledgements

I offer my most sincere gratitude to my faculty, mentors, and fellow students at UBC, who have inspired and motivated me to pursue neuroscience research at a graduate level. I owe particular thanks to my supervisor and long-term mentor, Dr. Miriam Spering who has shaped me into the scientist I am today and has provided me with professional and personal development over the last seven years.

I thank Dr. Silke Cresswell and Dr. Luke Clark as members of my supervisory committee for challenging me to think critically and providing me with expert guidance during my masters. Thank you to all my lab mates, especially my partner in crime Juana Ayala Castañeda for her cheerleading and MATLAB wizardry, and Philipp Kreyenmeier for helping me with coding, task design, and my endless questions every day.

Thank you to my late dad who motivated my interest in science, and who taught me the fundamentals of scientific and technical writing. Special thanks are owed to my mum and grandparents, whose have supported me throughout my years of education, both emotionally and financially.

Thank you to all the funding and awards support from: CIHR CGS-M, DMCBH endowments, Killam Awards, and the UBC Faculty of Medicine.

And of course, my dog and ultimate companion, Figgy, for supporting everyone in the lab.
Dedication

To the patients living with Parkinson’s who participated in this study, their families, and those in their circles of care.
Chapter 1: Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disease, affecting approximately 100,000 Canadians (Gaskin et al., 2017) and more than 6 million adults worldwide (Feigin et al., 2019). Still the prevalence of PD is projected to double by 2050 as the aging population grows and the life expectancy increases (Rocca, 2018). The hallmark symptoms of PD include slowing of movement (bradykinesia), rigidity, and rest tremor which can interrupt basic activities such as walking, sitting, and speaking (Postuma et al., 2015). However, motor dysfunction extends beyond these classic impairments and includes eye movement abnormalities (Pinkhardt & Kassubek, 2011).

In addition to impaired movement, it is now recognized that PD patients experience a range of non-motor symptoms affecting sensory and cognitive domains (Chaudhuri et al., 2006; Fénelon et al., 2000; Perugini et al., 2016; Weil et al., 2016). Non-motor symptoms interfere with activities of daily living and contribute to increased disability, in turn reducing quality of life (Le roi et al., 2012). PD can impair a range of executive functions (e.g., cognitive flexibility, planning, initiating sequences of behaviour, and decision making) (Dujardin et al., 2013), but response inhibition in particular is impaired early, and is highly prevalent amongst PD patients (Manza et al., 2017). Response inhibition—the ability to suppress or delay habitual behavioural responses to external cues—supports flexible behaviour in everyday life, and when impaired, can result in impulsive actions and choices (Walldhater et al., 2019). Furthermore, deficits in response inhibition can become pronounced in PD patients with increasing disease duration and prolonged use of some antiparkinsonian drugs (Manza et al., 2017).
PD patients show stereotyped eye movement deficits which offer a tool to probe the mechanisms underlying non-motor symptoms affecting cognition. Specifically, the antisaccade task has evolved as a common paradigm to evaluate response inhibition (Munoz & Everling, 2004; van Stockum et al., 2008), and is a sensitive indicator of PD (Lu et al., 2019; Waldthaler, Stock, Student, et al., 2021). Impaired antisaccade performance is well established in PD patients, however it is unclear what factors contribute to this impairment.

Here, we investigated whether antisaccade performance differences in PD are driven by motor function, executive function, general cognitive ability, or a combination of factors. In what follows I will provide a summary of PD starting with the clinical profile, etiology, and neural basis of the disease. Second, I will describe the diagnostic challenges of PD and explain why eye movements offer a valuable tool for probing pathological mechanisms and progression of the disease. Third, I will describe the neurophysiology of saccadic eye movements and will summarize oculomotor impairments in PD. Finally, I review the literature on antisaccade performance in PD and discuss how these oculomotor impairments have been related to other disease features including motor and executive dysfunction, and impulsivity.

The antisaccade task may offer a tool for evaluating non-motor features of PD, but greater investigation is needed to understand its possibilities and limitations before being used as a potential biomarker of the disease.
1.1 PD: clinical presentation, etiology, and neural correlates

PD is a progressive neurodegenerative disease dominated by motor dysfunction. At its core, PD is diagnosed by motor symptoms including bradykinesia and presence of muscular rigidity, rest tremor, and/or postural instability (Postuma et al., 2015). Broadly, PD is associated with two key (post-mortem) neuropathological findings: 1) the presence of alpha-synuclein Lewy neurites and Lewy bodies, and 2) degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta, a nucleus critical for motor control (Borghammer, 2018). DA input from the substantia nigra pars compacta to the basal ganglia (BG) is essential for motor planning and regulation of movement (Graybiel, 2000). Thus, when these neural connections are damaged voluntary motor control becomes dysfunctional (Jankovic & Tan, 2020). It is now accepted that PD extends beyond the motor system as patients experience an array of clinically relevant non-motor symptoms such as gastrointestinal issues, hyposmia, and sleep disturbances among others (Kalia & Lang, 2015). Non-motor symptoms are thought to mark the prodromal phase of PD where disease pathogenesis is beginning but motor symptoms have not yet emerged (Jankovic & Tan, 2020). It has been hypothesized that PD pathology progresses in a stereotyped pattern concurrent with the manifestation of clinical symptoms, defined as Braak Staging (stages 1-6). According to Braak Staging, PD pathology starts in the brainstem, spreads to subcortical structures, then continues to extend rostrally through the brain eventually reaching prefrontal areas, at which point essentially the entire brain is devastated by the disease (Braak et al., 2003).

The cause of PD remains unclear and heterogeneity in disease onset, symptomatology, and progression make it harder to uncover. A combination of factors including aging, genetic susceptibility, and environmental exposures contribute to the etiology of PD, however the exact
contribution of each is debated (Jankovic & Tan, 2020). Interventions including drugs (e.g., levodopa, dopamine agonists, etc.) and deep brain stimulation exist to treat the symptoms of PD, but there is currently no cure, and disease-modifying therapies are still in their infancy (Kalia & Lang, 2015). Objective tools are needed to diagnose and monitor disease progression, aiming to reduce symptomatic burden and maintain overall quality of life for patients.

Broadly, PD is a disorder of the BG, a network of subcortical nuclei composed of four structures: the striatum (made up of the caudate nucleus and putamen), globus pallidus (with internal and external segments), subthalamic nucleus, and substantia nigra (containing the pars compacta, and pars reticulata) (Graybiel, 2000). The BG consists of two main circuits, the direct and indirect pathways, which oppose each other to modulate movement. In the non-diseased brain, the indirect pathway tonically inhibits movement, and the direct pathway releases this inhibition to allow voluntary movement to occur. Both pathways receive excitatory projections from the cortex to the striatum, but the stimulation of different DA receptor subtypes determines which pathway will be triggered. In the direct pathway successive GABAergic projections from the striatum to the internal pallidum and then to the thalamus allow excitatory input to be received by the cortex, releasing inhibition of movement. In parallel, the indirect pathway sends inhibitory projections from the striatum and external pallidum which disinhibit the subthalamic nucleus. Glutamatergic projections from the subthalamic nucleus then excite the internal pallidum, which inhibits the thalamus and the inhibition of movement continues. (Graybiel, 2000; Lanciego et al., 2012). Under normal conditions, the equilibrium of these two pathways results in fluid voluntary movement patterns, however, overactivity of either results in motor dysfunction.
In PD there is overactivity in the indirect pathway, leading to hypokinetic movement. Depletion of DA neurons from the substantia nigra pars compacta to D1 receptors in the striatum reduces activity in the direct pathway, resulting in poverty of purposeful movement (Lanciego et al., 2012). Additionally, connections between the cortex and BG—known as cortico-basal ganglia loops—contribute the higher cognitive control necessary for motor function and action selection, as well as response inhibition (Terao et al., 2013). Specifically, afferent projections from the cortex are sorted and combined in the BG before being relayed to the thalamus, and then projected back to the cortex, forming the ‘loop’ (Lanciego et al., 2012). An imbalance in this prefrontal circuitry can contribute to deficits in executive functions and in downstream processes involving complex motor actions.

The BG has two systems to control voluntary movement of skeletal muscles and eye movements: trunk and limb muscles are controlled by thalamocortical loops, whereas eye movements are controlled via outputs to brainstem motor centres (Hikosaka et al., 2000). Because oculomotor circuits run through the BG, eye movements can also be abnormal in PD, a feature which could have clinical utility for PD and other movement disorders (Lu et al., 2019).

1.2 **Clinical application of eye movement tasks in PD and related disorders**

Diagnosing PD can be challenging; the disease affects a range of somatomotor functions, symptoms vary across patients, and characteristics may be shared between disorders (Kalia & Lang, 2015). For many movement disorders including PD, there is a lack of sensitive tools and objective biomarkers to diagnose, and monitor, disease progression (Abdo et al., 2010). Thus, diagnosis still relies on clinical assessment and subjective rating scales—such as the Movement
Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) (Postuma et al., 2015). While current diagnostic criteria have excellent sensitivity, it does not encompass advancements in our understanding of the prodromal and premotor stages, nor the variable onset of disease and rate of progression (Berg et al., 2013; Stern et al., 2012). Progress has been made in the use of eye movements to delineate between movement disorders (Zhou et al., 2021), classify stages of PD (Brien et al., 2023), and predict and evaluate cognitive state in patients with PD and other neurodegenerative diseases associated with cognitive decline (Stuart et al., 2019; Tao et al., 2020). Eye movements may offer a supplementary tool to detect and monitor changes in somatomotor or cognitive functions in the complex spectrum of symptoms experienced by PD patients.

Eye movement tasks have several advantages in a clinical context. First, it is feasible and non-invasive to measure eye movements in clinical and research settings. Compared to imaging techniques and genetic tests, eye tracking requires minimal equipment and has a low cost and time burden (Politis, 2014). Second, there is a detailed understanding of oculomotor circuitry—which spans the whole brain—thus eye movements can be used to probe the neurobiological mechanisms and behaviours of PD (Brien et al., 2023; Leigh & Kennard, 2004). Third, eye movements offer an objective, time-locked behavioural readout and provide large data sets to explore (Lu et al., 2019). Finally, some eye movement paradigms, specifically the antisaccade task, are sensitive to disease state but are unaffected by the effects of antiparkinsonian medication (Waldthaler, Stock, Student, et al., 2021). The antisaccade task is also thought to be resistant to practice effects with repeat testing, suggesting performance could monitor changes in the disease state in longitudinal studies (Waldthaler, Stock, Student, et al., 2021). Additionally,
the antisaccade includes both pro- and antisaccade trials which allows evaluation of motor and cognitive abilities in a single oculomotor paradigm. Parallel to the development of disease modifying therapies for PD, specific, sensitive, and medication resistant diagnostics are required. Though more research is required, eye tracking may be a contending tool.

1.3 Eye movements in health and PD

1.3.1 The basal ganglia and oculomotor control: the physiology of saccadic eye movements

The BG controls eye movements via multiple outputs to brainstem motor centres, in particular the superior colliculus, which is critical for saccadic eye movements (Hikosaka et al., 2000). A saccade is a quick eye movement adjusting visual fixation between two points (Leigh & Zee, 2015c). Moving the eyes moves the fovea—the area of greatest visual acuity in the retina—to different points of interest in the visual environment, which is essential for visual perception (Hikosaka et al., 2000). Here we focus on two types of saccadic movements: prosaccades, where the eyes orient toward a target, and antisaccades, where the eyes orient in the opposite direction to a target (Leigh & Zee, 2015c). Importantly, prosaccades are a visually guided reflexive movement, whereas antisaccades are considered a volitional movement requiring both motor and executive control (Munoz & Everling, 2004).

The neural pathway for generating a seemingly instantaneous saccade begins with the ‘drive’ for the movement coming from cortical eye fields, containing the frontal eye field and supplementary eye field (Hikosaka et al., 2000). In simplified terms, the BG filters afferent
signals from the cortex and the substantia nigra pars reticulata send axons to the superior
colliculus, a structure of the midbrain with key sensory and motor functions (Sparks, 2002).
During fixation omnipause neurons in the midline of the pons are tonically firing, and when the
superior colliculus receives a saccade command, the tonic firing is inhibited. This disinhibits the
excitatory burst neurons with inputs to the motor nuclei of the extraocular muscles and excites
inhibitory burst cells acting on opposing extraocular muscles. The subsequent saccade involves
two commands: the pulse and the step. First, the motor nuclei of the extraocular muscles increase
firing—the ‘pulse’—which helps overcome the viscous drag of the eye opposing the ocular
movement. The motor neurons decrease firing to modulate tension of the extraocular muscles,
and then return to tonic firing—‘the step’—to maintain the desired tension. The omnipause
neurons then resume their tonic firing to preserve fixation on the new point in visual space
(Sparks, 2002).

While the neural circuitry to execute a prosaccade is isolated primarily to subcortical and
brainstem structures, an antisaccade requires regulation from the cortex. To successfully execute
an antisaccade the reflexive response to orient toward the stimulus must be suppressed.
Specifically, the frontal eye fields in the dorsolateral prefrontal cortex (DLPFC) control
voluntary saccades and the greater prefrontal cortex area is involved in executive control,
including response inhibition (Munoz & Everling, 2004). Additionally, the inferior frontal gyrus,
and the medial and anterior cingulate are involved in delaying or suppressing a motor response
(Waldthaler et al., 2022). It is proposed that connections from these regions to the superior
colliculus allow automatic prosaccades to be suppressed, and voluntary oculomotor movements,
such as an antisaccade, to be generated (Guitton et al., 1985).
1.3.2 Oculomotor impairments in PD

Oculomotor abnormalities are well documented in PD populations, which can be summarized in three key findings (Leigh & Zee, 2015b). First, fixation is disrupted. When the eyes are fixating it is normal to see small adjustments in eye position, less than 0.5 degrees, known as microsaccades (Leigh & Zee, 2015a). Microsaccades allow the visual system to overcome sensory adaptation, however specific patterns of saccadic intrusions occur with greater frequency in brain disorders affecting the BG, brainstem, and cerebellum, including PD (Otero-Millan et al., 2013). PD patients often show stereotyped saccadic intrusions called square-wave jerks. A square-wave jerk involves a pair of small saccades; one away (0.5 - 5.0 degrees) from the fixation target followed by a brief delay (~ 200 ms) before a saccade is made back toward the target to correct the eye position (Leigh & Zee, 2015b). Though square-wave jerks are reported in healthy populations, the frequency and amplitude increase in movement disorders including PD, likely from interruption to inhibitory control on the superior colliculus from the substantia nigra pars reticulata (Otero-Millan et al., 2013).

Second, PD is known to affect smooth pursuit—a type of gaze shift necessary for tracking a moving target (Leigh & Zee, 2015a). Smooth pursuit movements utilize the brainstem circuitry involved in saccade generation but also rely on cortical temporal lobe regions (middle and medial superior) and structures of the cerebellum for motion processing and associated motor responses (Krauzlis, 2005). Relative to controls, PD patients show smooth pursuit deficits, typically seen as decreased eye velocity relative to the target velocity (pursuit gain) which then invokes small saccades to allow the eyes to catch up to the target (Pinkhardt & Kassubek, 2011;
Vidalhret et al., 1994). However, the ability to track a predictably moving target or generate anticipatory eye movement seem to remain intact (Fukushima et al., 2013).

The third, and most well documented, oculomotor deficit in PD patients is observed in saccade performance. PD patients show stereotyped deficits in an array of paradigms testing pro- and antisaccade performance. Prosaccades—whether internally-generated, visually guided, or memory-guided—all show impairment. Overall, prosaccades are decreased in amplitude (hypometric) (Chambers & Prescott, 2010; Leigh & Zee, 2015b). Latency of prosaccades are increased compared to controls, and levodopa has prolonging effects on prosaccade latency (Lu et al., 2019). When a ‘gap’ is applied to the task—a period with no fixation target or cue target presented—patients show more short-latency, ‘express’, saccades (Chan et al., 2005; van Stockum et al., 2008). Interestingly, despite general slowing of voluntary limb movements in PD, peak velocity of saccades is preserved, except in more severe disease states (Leigh & Zee, 2015b). In more severe PD, saccades become markedly smaller in amplitude requiring more small steps to reach a cued target which is represented as a pyramid or staircase pattern on eye movement traces (Kimmig et al., 2002).

1.3.3 Antisaccade impairments and their relationship to other PD features

Saccade abnormalities in PD are consistently reported during antisaccade tasks including immediate, delayed, and remembered paradigms (Waldthaler, Stock, Student, et al., 2021). When comparing patients to controls, PD patients show significantly increased antisaccade latency. In a meta-analysis including more than 700 patients and 600 controls, mean antisaccade latency was 340 ms and 294 ms for patients and controls respectively (Waldthaler, Stock,
PD patients also show significantly decreased amplitude on antisaccade tasks; however the inclusion of a cue landmark improves performance (Briand et al., 1999). Most notable group differences occur in the form of direction errors including ‘changes of mind’, where a saccade is made toward the target and self-corrected to be in the opposite direction. Direction errors are significantly increased in patients with error rates reported to be double that of healthy controls in some studies (Antoniades et al., 2015; Waldthaler, Stock, Student, et al., 2021). These group differences are stable when patients are in an ON or OFF medication state, thus antisaccades are thought to be a better marker of the disease as performance is generally resistant to medication effects. Now, antisaccade parameters have been investigated relative to other clinical disease features, which continues the possibility of using eye movements as a tool in the landscape of PD management.

1.3.3.1 Motor dysfunction

Unsurprisingly, antisaccade performance has been associated with motor dysfunction in PD. Motor impairment is commonly measured by the motor symptom sub-score (Part III) of the MDS-UPDRS (Goetz et al., 2008), or Hoehn & Yahr stage, a scale measuring disease severity and functional impairment (Goetz et al., 2004). Part III of the MDS-UPDRS has been shown to interact with antisaccade performance, where increasing motor symptom burden is associated with prolonged antisaccade latency (Antoniades et al., 2015; Waldthaler, Stock, Student, et al., 2021). Additionally, increased error rate has been correlated with increased Hoehn & Yahr scores (Amador et al., 2006). Though existing studies have reported an association between antisaccade impairments and motor dysfunction, these studies rely on subjective clinical scales for measuring motor deficits but lack objective behavioural measures of physical motor
performance such as the Short Physical Performance Battery or Timed up and Go (TUG) test (Tanzi et al., 2008). Some neuroimaging evidence suggests that motor dysfunction at the level of action preparation—how motor areas are prepared before response initiation—affects the correct execution of an antisaccade (Cameron et al., 2012; Waldthaler et al., 2022). That is, motor impulsivity may in part contribute to antisaccade error rate, opposed to isolated cognitive dysfunction in inhibitory control.

1.3.3.2 Executive function

Cognitive dysfunction contributes to the complexity of PD, where more than 80% of PD patients will suffer mild cognitive impairment, and further progression to dementia is common (Hely et al., 2008). Frontal-executive functions as well as attention, and memory can become compromised in PD, even in the early stages of the disease, and cognitive deficits have been correlated to several eye movement measures (Antoniades et al., 2015; Norie Ito et al., 2016). However, between studies there is variability in the disease stage of participants, the cognitive assessments used, and the antisaccade task design, thus findings do not necessarily reveal the core cognitive deficit or source of eye movement abnormalities (Brien et al., 2023). Impaired response inhibition is evident in PD patients as measured by direction errors in the antisaccade task, indicating an impaired ability to suppress reflexive saccades and select the correct subsequent action (van Stockum et al., 2008; Waldthaler, Stock, Student, et al., 2021). Impaired response inhibition is also observed in PD patients in parallel behavioural measures such as the “Go-NoGo” and “Stroop” tasks (Manza et al., 2017). Direction errors on the antisaccade task are associated with decreased performance on numerous neuropsychological tests measuring response inhibition in addition to other executive functions including the Frontal Assessment
Battery (FAB) and Montreal Cognitive Assessment (Antoniades et al., 2015; Norie Ito et al., 2016). Response inhibition occurs at the intersection between motor, cognitive and motivational control, suggesting impairments may be an indicator of other pathological changes in PD.

1.3.3.3 Impulsivity

Response inhibition deficits in PD fall on a spectrum from mild cognitive impairment to clinical impulsive and compulsive disorders (Manza et al., 2017). Impulse control dysfunction can manifest as motor impulsivity, poor decision making, risk taking, and temporal discounting behaviours, and is thought to be modulated by mesolimbic and prefrontal dopaminergic pathways (Nombela et al., 2014). While dopaminergic medications can reduce core motor symptoms in PD, there is variable effect on response inhibition depending on disease duration and age of disease onset. Dopaminergic medications have been shown to improve response inhibition on some tasks in patients with shorter durations of PD (Manza et al., 2017), but may have different effects on antisaccade error rates based on motor symptom severity (Waldthaler, Stock, Krüger-Zechlin, et al., 2021). It is known that treatment of PD with dopaminergic medications, specifically dopamine agonists, can increase behavioural impulsivity, but recent evidence suggests their impact on oculomotor performance depends on multiple disease characteristics (Waldthaler, Stock, Krüger-Zechlin, et al., 2021). It is clear impulsivity plays a role in antisaccade performance, however trends in antisaccade performance become challenging to interpret in patient populations with more advanced disease. Thus, it is critical that antisaccade performance be evaluated in early PD patients with mild motor deficits to help parse out what factors drive impairments in response inhibition.
1.4 Study goals

Impairments in antisaccade performance are well documented in PD, however it remains unclear how these impairments are related to other disease symptoms. This is an important question because the antisaccade task is increasingly used in research and clinical contexts, but clarity is needed to determine whether or how the task performance relates to disease progression (Brien et al., 2023; Tao et al., 2020). Here we explore whether impaired antisaccade performance in PD is related to motor function, executive function, and or general cognitive ability. This study will provide a comprehensive assessment of reflexive and voluntary eye movements (evaluated by the standardized antisaccade task), motor function, and a range of frontal-executive functions in older adults with mild to moderate idiopathic PD and matched healthy controls.

1.4.1 Hypotheses

1) PD patients will show impairments on the antisaccade task relative to controls, consistent with the literature: hypometric prosaccades (Leigh & Zee, 2015b), increased antisaccade latency and error rate (Waldthaler, Stock, Student, et al., 2021).

2) PD patients will show impairments consistent with disease stage and diagnosis.
   a. Motor function will be slower (bradykinetic) and/or more impaired in patients with longer disease duration and higher motor symptom burden (Kalia & Lang, 2015).
   b. PD patients will show deficits in cognitive function associated with mild disease severity: impaired response inhibition, slower processing speed, relative to global cognitive abilities (Dujardin et al., 2013; Manza et al., 2017).
3) Antisaccade performance relative to motor and cognitive function in PD:

a. On the one hand, if we expect antisaccade latency to be associated with motor function then antisaccade latency in PD patients will be longer. As PD is a hypokinetic disorder, we would expect patients who are slower or more impaired in voluntary motor abilities to also be slower with antisaccades, a volitional eye movement. In turn, slower execution of the antisaccades would increase the time interval for action selection based on the cue position (left vs. right), thus we would expect a reduction in patients’ antisaccade error rate.

b. On the other hand, if we expect antisaccade error rate to be associated with cognitive function, patients will make more antisaccade errors correlated with impaired response inhibition and executive dysfunction. Further, this top-down disinhibition should then also manifest as shorter antisaccade latencies in patients showing worse cognitive deficits.
Chapter 2: Body of thesis

2.1 Methods

2.1.1 Participants

We recruited 44 adults aged 50-80 years old, including 24 patients with mild to moderate idiopathic PD (Hoehn & Yahr 1-2, age of diagnosis >45 years) and 20 age-, sex-, education-matched controls (Table 2.1.1 and Table 2.1.2). Five patients had to be excluded as they were not able to complete the entirety of the eye tracking task. Patients were required to be in a maintenance phase on antiparkinsonian medication (including but not limited to levodopa-carbidopa, dopamine agonists, and or anticholinergic drugs). Eighteen of 19 patients were taking a combination levodopa-carbidopa drug (e.g., Sinemet), and 25% of patients were taking a dopamine agonist. Eligibility criteria for both groups included: no history of ocular diseases (e.g. glaucoma or macular degeneration), ocular motility abnormalities (e.g. amblyopia), or ophthalmic surgeries, were able to provide informed consent (based on a Montreal Cognitive Assessment [MoCA] score of > 22) (Karlawish et al., 2013), no neurological diseases, no untreated depression or change in treatment or symptoms with antidepressant medication within three months, no history of severe traumatic brain injury, surgery, or stroke, and no regular use of benzodiazepines, antipsychotic, or anticonvulsant medications. One healthy control did not complete the MoCA as they frequently administer the cognitive screen to patients and are familiar with the answers. Thus table 2.1.1. reports MoCA scores for 19 controls and 19 patients.

To verify that participants had sufficient visual acuity to see targets presented on a monitor at an arms-length distance, we tested visual acuity and used a cutoff of 20/40 for inclusion. 20/20 is considered normal visual acuity, and we selected a cutoff of 20/40 as this is considered fair visual acuity for adults aged 60 years or older (Gittings & Fozard, 1986). Participants were tested
using the Early Treatment of Diabetic Retinopathy Study Chart at 3 m distance (ETDRS vision chart “R”, Precision Vision Inc., La Salle, IL). Corrective lenses were worn during testing. Fluency in English was required for administration of study procedures, and to control for the effect of native language on cognitive tasks.

Patients were recruited from the Parkinson’s Clinic/ Pacific Parkinson’s Research Centre at UBC Hospital, and healthy controls were recruited from the Metro Vancouver community. All experimental procedures were completed in the Oculomotor Laboratory on the UBC Vancouver Campus. All participants were tested during one session and patient participants were tested in an ON state taking their PD medication(s) as normal. All study procedures were conducted according to the Declaration of Helsinki and approved by the UBC Clinical Research Ethics board. Participants provided written informed consent prior to testing.
Table 2.1.1. Demographic characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>PD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n=20 )</td>
<td>( n=19 )</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>63.6 ± 5.6 (range 53-76)</td>
<td>65.9 ± 5.7 (range 56-78)</td>
</tr>
<tr>
<td>Sex (( n ) female)</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Education level (mean years)</td>
<td>16.7 ± 3.7</td>
<td>17.4 ± 3.6</td>
</tr>
<tr>
<td>Ethnicity (( n )) a</td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Asian (East Asian, South Asian)</td>
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<td>2</td>
</tr>
<tr>
<td>First Nations</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MoCA (mean) b</td>
<td>27.1 ± 2.3</td>
<td>27.8 ± 1.6</td>
</tr>
<tr>
<td>Barratt Impulsivity Scale (BIS) c</td>
<td>59 ± 5.8</td>
<td>56.3 ± 5.2</td>
</tr>
</tbody>
</table>

a Ethnicity totals exceed group totals as some participants reported multiple ethnicities.
b Montreal Cognitive Assessment (scored 0-30) completed at screening. (Nasreddine et al., 2005).
c Range from 30-120
Table 2.1.2. Clinical characteristics of PD group

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Disease duration (yrs.)</th>
<th>Hoehn &amp; Yahr stage (0-5)</th>
<th>MDS-UPDRS score (0-132)</th>
<th>Levodopa Equivalent Daily Dose (mg)</th>
<th>Other PD medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>P04</td>
<td>68</td>
<td>M</td>
<td>5</td>
<td>2</td>
<td>30</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>P05</td>
<td>78</td>
<td>F</td>
<td>3</td>
<td>2</td>
<td>28</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>P06</td>
<td>61</td>
<td>F</td>
<td>7</td>
<td>2</td>
<td>16</td>
<td>100</td>
<td>Amantadine, Dopamine agonist</td>
</tr>
<tr>
<td>P07</td>
<td>64</td>
<td>M</td>
<td>4</td>
<td>2</td>
<td>15</td>
<td>450</td>
<td></td>
</tr>
<tr>
<td>P08</td>
<td>72</td>
<td>M</td>
<td>3</td>
<td>2</td>
<td>33</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>P09</td>
<td>65</td>
<td>F</td>
<td>8</td>
<td>2</td>
<td>20</td>
<td>1100</td>
<td></td>
</tr>
<tr>
<td>P10</td>
<td>60</td>
<td>F</td>
<td>4</td>
<td>2</td>
<td>12</td>
<td>798</td>
<td>COMT inhibitor</td>
</tr>
<tr>
<td>P11</td>
<td>65</td>
<td>F</td>
<td>2</td>
<td>1</td>
<td>21</td>
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<td></td>
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<tr>
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<td>M</td>
<td>7</td>
<td>2</td>
<td>27</td>
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</tr>
<tr>
<td>P13</td>
<td>69</td>
<td>M</td>
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<td>2</td>
<td>11</td>
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<td>Dopamine agonist</td>
</tr>
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<td>P14</td>
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<td>F</td>
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<td>2</td>
<td>11</td>
<td>900</td>
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<td>67</td>
<td>F</td>
<td>8.5</td>
<td>2</td>
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<td>Dopamine agonist</td>
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<td>8</td>
<td>650</td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>P19</td>
<td>72</td>
<td>F</td>
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<td>2</td>
<td>11</td>
<td>300</td>
<td></td>
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<tr>
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<td>M</td>
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<td>2</td>
<td>20</td>
<td>1796</td>
<td>COMT inhibitor</td>
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<tr>
<td>P22</td>
<td>67</td>
<td>M</td>
<td>8</td>
<td>2</td>
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<tr>
<td>P23</td>
<td>57</td>
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<td>8</td>
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<td>1400</td>
<td>Amantadine</td>
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<td>P24</td>
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<td>11</td>
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<tr>
<td>P25</td>
<td>56</td>
<td>M</td>
<td>7.5</td>
<td>2</td>
<td>15</td>
<td>1200</td>
<td>Dopamine agonist</td>
</tr>
</tbody>
</table>

Mean ± SD 65.9 ± 5.7 7.0 ± 3.9 18 ± 8 818.45 ± 472.72

*a* Hoehn & Yahr staging scale for symptom severity: 1=unilateral involvement only, 2=bilateral involvement, 3=postural instability but physically independent, 4=physically dependent, 5=confined to bed or wheelchair.

*b* Movement Disorders Society Unified Parkinson’s Disease Rating Scale, Part III Motor score only. Higher score indicates more symptoms.

*c* Most patients were on combination drugs containing levodopa and carbidopa (e.g., Sinemet). Table reports total equivalent daily dose of levodopa (Tomlinson et al., 2010).

*d* COMT inhibitor=Entacapone, Dopamine agonist=Rotigotine, Pramipexole.
2.1.2 Motor assessments

2.1.2.1 Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)

Motor dysfunction was evaluated using the MDS-UPDRS (Table 2.1.3), the most accepted clinical rating scale for PD (Goetz et al., 2008). The scale is divided into four parts: Part I and Part II are formatted as interview style assessments and evaluate non-motor and motor “experiences of daily living” respectively. Part III includes a “motor examination” and Part IV measures “motor complications”. Completing the MDS-UPDRS in its entirety offers a comprehensive assessment of PD symptoms and impairments, however in this study we are primarily interested in motor symptoms and thus only completed Part III. To complete Part III the examiner uses scripted task instructions and rates the patient on a scale of 0-4 as follows: 0=normal, 1=slight, 2=mild, 3=moderate, and 4=severe. These ratings describe how motor impairment affects the patient’s function in terms of frequency and/or intensity. Part III includes 18 questions, with multiple sections assessing upper and lower limb function independently, for a maximum score of 132 points.
Table 2.1.3 Study assessments

<table>
<thead>
<tr>
<th>Category</th>
<th>Assessment</th>
<th>PD group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population characteristics</td>
<td>Demographics + medical history</td>
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<td>x</td>
</tr>
<tr>
<td></td>
<td>PD history</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Motor function</td>
<td>MDS-UPDRS Part III</td>
<td>x</td>
<td></td>
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<td></td>
<td>Timed Up and Go (TUG) test</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Antisaccade task</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Trail Making Task (Part A&amp;B) (TMT)</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Kaufman Brief Intelligence Test (KBIT-2), matrices</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroop Colour and Word Task</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Barratt Impulsivity Scale (BIS-11)</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

Orange ‘x’ icons indicate assessments only completed by patients.

2.1.2.2 The Timed Up and Go (TUG) test

The Timed Up and Go test (TUG) (Table 2.1.3, Appendix A.2) was used to measure basic functional mobility. The TUG test is a useful assessment of mobility as the combination of movements required are representative of functional tasks involved in Activities of Daily Living such as transferring (from bed or chair), bathing, dressing, and feeding (Katz et al., 1963) and correlates to other clinical scales of patient independence (Podsiadlo & Richardson, 1991). For the TUG participants must rise from a seated chair, walk three metres (10 feet) at a safe and normal pace, turn around, walk back and return to their seated position (Podsiadlo & Richardson, 1991). Individuals are permitted to use a walking aid if needed. The score is measured as the time taken in seconds to complete the task. A time of less than 12 seconds is considered normal for healthy adults aged 60-85 (Bohannon, 2006; Ibrahim et al., 2017).
The TUG was selected as an objective performance measure to complement the MDS-UPDRS. Specifically, the TUG is advantageous over other tests as it is feasible in research settings with a brief administration time and minimal equipment is required. Additionally, the TUG is recommended by the Movement Disorders Society (Bloem et al., 2016), and has strong correlations to the UPDRS Part III, with strong discrimination specifically at lower level of disability and disease severity (Tanji et al., 2008), which is the patient group assessed here.

2.1.3 Eye tracking experiment

2.1.3.1 Visual display and eye tracking apparatus

Participants viewed stimuli on a 33.9 cm x 27 cm CRT monitor at a seated distance of 50 cm. Eye movements of the right eye were recorded using a video-based eye tracker (Eyelink 1000 tower mount; SR Research, Ltd, Ottawa, ON, Canada) at a sampling rate of 1000Hz. Testing occurred in a dimly lit room. Participants had their head supported by a forehead and chin rest attached to the tower mount to reduce head movements. Stimulus display and data collection were run on a PC and the experiment was programmed using MATLAB (R2022b) (MathWorks Inc., Natick, MA) in combination with Psychtoolbox 3.0.8 (Brainard, 1997; Pelli, 1997; Kleiner et al, 2007). All text and stimuli were displayed with a gray background (luminance 100 cd/m2) for maximum contrast.

2.1.3.2 Prosaccade and antisaccade tasks

Participants completed pro- and antisaccades based on the experimental design and principles outlined in the antisaccade consensus guide (Antoniades et al., 2013; Munoz & Everling, 2004) (Table 2.1.3, Figure 2.1.1). In brief, the experiment consisted of five blocks as follows:
prosaccade block with 60 trials, three antisaccade blocks with 40 trials each, and a prosaccade block with 60 trials. A block of practice prosaccades (10 trials) and antisaccades (4 trials) were completed before the first and second blocks respectively. The eye tracker was calibrated and validated using a five-point fixation grid prior to each experiment block. Experiment instructions were presented to the participant before each block and were read aloud by the research assistant. Each trial started by displaying a central fixation target. A combined shape of a black and white bullseye and crosshair (0.3 deg and 0.1 deg radii of the outer and inner circle respectively) was used for fixation as this shape offers the highest fixational stability (Thaler et al., 2013). The fixation foreperiod was randomized between 1-2 seconds followed by a randomized ‘gap’ period with no stimulus displayed for 100-350 milliseconds. Following the gap, a target stimulus (black circle, radius 0.3 deg) was presented in the periphery at 10 deg horizontally to the left or right of fixation. In the prosaccade task participants were instructed to look at the target as fast as possible, whereas in the antisaccade task they were to look in the opposite direction of the cue as fast as possible. No mirror landmark cue was presented on antisaccade trials. The target stimulus remained for 1 second before the trial timed out.
24

2.1.3.3 Eye movement data preprocessing

Eye movements were analyzed offline using MATLAB (R2022b) based on the custom scripts created by our lab. Raw eye movement data was filtered with a low-pass second-order Butterworth filter with cutoff frequencies of 15Hz and 30Hz for position and velocity respectively. Preliminary detection of saccades, microsaccades and blinks was generated using an algorithm developed previously (Engbert & Mergenthaler, 2006). Adjustments were made to the algorithm parameters to be suitable for detecting saccades and microsaccades in older adults.
and patients with PD who are known to have more noise in eye movement recordings. Saccades were detected using velocity (median-based 2D velocity space estimate derived from the raw velocity data), duration (6 ms), and amplitude (>2° for saccades, < 2° for microsaccades) thresholds (Engbert & Mergenthaler, 2006). All trials were then manually inspected. Trials were excluded based on the following: blink during a saccade, incorrectly detected saccades or undetected saccades, loss of eye tracker signal, or noise detected as microsaccades. Practice trials were excluded from analysis. Four patient participants were excluded from analysis as they were not able complete all seven blocks of the task (3 could not keep steady fixation during calibration and validation [P01, P02, P03], and one could not keep their head in the tower mount due to postural instability [P15]) (See Figure 2.1.2). An additional three and six patients were excluded from pro- and antisaccade analyses respectively based on the requirement of having at least 50% of trials included. Thus, seventeen patients were included for analysis of prosaccades, and 14 patients were included for analysis of antisaccades. Twenty controls were included in the analyses unless indicated otherwise.

2.1.3.4 Eye movement performance measures

For all eye movement measures reported we calculated an average across trials per participant. Saccades that were initiated during the gap (premature saccades), or with a latency of 90-120 ms (express saccades) (Fischer & Ramsperger, 1984), were counted but excluded from the primary analysis and were investigated separately (Roll et al., 1996). For the first saccade, latency, velocity, amplitude, and duration were calculated. Latency is defined as the time between cue presentation and the onset of the first saccade (Leigh & Zee, 2015c). For the prosaccade trials, amplitude was calculated as final horizontal eye position minus initial eye position. A mirrored
cue was not presented on antisaccade trials thus accuracy was not calculated. Additionally, the number of direction errors were calculated. Direction errors are operationalized as a trial when a participant looks at the cue instead of in the opposite direction (antisaccade blocks) or looks opposite to the cue (prosaccade blocks). Errors were broken down to include direction errors as described and ‘changes of mind’ where a saccade is made toward the target and quickly corrected to the opposite direction (Figure 2.1.3). A participant was excluded from an analysis if more than 50% of trials were excluded, where pro and antisaccade blocks were considered separately. A total of 756 prosaccades and 499 antisaccade trials from our analysis.

Figure 2.1.2. Flowchart of participant inclusion by participant group
Figure 2.1.3. Example 2D eye traces
Sample 2D eye position traces for all saccade responses from one representative patient observer (P16). Light blue line indicates vertical eye position, black line is horizontal eye position. Grey block represents fixation, orange block indicates duration and position of saccade cue. A) Correct prosaccade, B) Correct antisaccade, C) direction error on antisaccade trial, D) ‘change of mind’ on antisaccade trial.
2.1.4 Cognitive assessments

2.1.4.1 Trail making task (TMT)

The Trail Making Task (TMT) (Table 2.1.3, Appendix A.3) was chosen to evaluate cognitive processing, attention, and task switching (Sanchez-Cubillo et al., 2009; Spreen & Strauss, 1998). The TMT consists of two parts where the participant must draw a continuous line connecting encircled numbers (Part A), or numbers and letters (Part B), in ascending order as quickly as they can (Bowie & Harvey, 2006). Part A is thought to measure processing speed and visual search, and Part B measures working memory and task-switching abilities (Sanchez-Cubillo et al., 2009). The TMT is scored as the time in seconds to completion for Parts A and B with a cutoff time of 300 seconds. Additionally, the ‘switching cost’ can be calculated by subtracting the Part A time from the Part B time (Bowie & Harvey, 2006).

The TMT was selected for this study for two reasons. First, complex attention, visuomotor processing speed, and working memory are known to be cognitive processes affected in the initial milder stages of PD (Muslimović et al., 2005), and thus could affect antisaccade task performance. Second, the TMT measures visuospatial attention that requires the same attention involved in the execution of saccadic eye movements (Amador et al., 2006). The TMT is included here to evaluate whether antisaccade deficits in latency or error rate are related to attention and/or processing speed deficits.

2.1.4.2 Kaufman Brief Intelligence Test, 2nd Edition (KBIT-2)

The Kaufman Brief Intelligence Test, 2nd Edition (KBIT-2) was used to measure general intelligence (Table 2.1.3) (Gray, 2021, p. 202; Kaufman, 1990). The KBIT-2 includes three
subtests, and reports verbal and non-verbal intelligence, which can be interpreted as Crystallized and Fluid Cognition abilities respectively. Fluid Cognition represents dynamic cognitive functions which can be affected by brain pathology, such as PD, or organic aging processes. However, Crystallized Cognition relies on language processes, and is more constant over time (Carlozzi et al., 2017; Craik & Bialystok, 2006). Thus, we opted to only compare performance on the Matrices (Fluid Cognition). The Matrices subtest consists of 46 questions testing abstract reasoning. We report age-corrected standard scores here according to the test manual (Kaufman, 1990).

We chose the KBIT-2 for its brevity, motor-free tests, and applicability to both healthy and diseased adults (Canivez, 1995; Gray, 2021). Other more comprehensive and/or PD-specific batteries would be optimal, however these have not been sufficiently validated for use in healthy populations (Skorvanek et al., 2018).

2.1.4.3 Stroop Colour and Word Task (Stroop Task)

The Stroop Colour and Word Task (Stroop Task) (Table 2.1.3, Appendix A.4) (Stroop, 1935) was used to measure cognitive flexibility, and in parallel, inhibition of cognitive interference (Scarpina & Tagini, 2017). Specifically, the task measures a participant’s ability to inhibit competing actions, a shared requirement in the antisaccade task. The Stroop Task involves three conditions, each 45 seconds. In each condition the participant is presented with a table of 10 rows and 5 columns. The participant is instructed to read the items across the rows from left to right as fast as possible and to correct themself if an error is made. Condition one (W) is word-reading (red, yellow, green, blue), condition two (C) is colour-naming (naming the four colours
from condition 1 presented as rectangles), and condition three is colour-word-naming (CW) (reading the colour of the ink not what the word says) (Scarpina & Tagini, 2017). Conditions one and two are congruent conditions, which are somewhat reflexive. However, condition three is incongruent as the text ink does not match the meaning of the word (for example the word ‘green’ printed in yellow ink), which requires participants to inhibit their reflex to read the word itself while also executing the less automatic task of naming the colour. The number of correctly named items is recorded from each of the conditions (W, C, CW). A predicted colour word score is calculated by: PCW = (W x C)/ (W + C). Following, a Stroop interference score (IG) can be calculated (Golden & Freshwater, 1978): IG = CW - PCW. A lower score suggests greater interference—i.e., it takes longer to name the colour of a word in the CW condition compared to naming the same colour in the colour (C) condition—and a negative score indicates an inability to inhibit interference.

The Stroop Task is a gold standard neuropsychological test measuring inhibitory control which we used to assess the sensitivity of the antisaccade task as a measure of response inhibition. Greater interference scores and lower accuracy on the Stroop Task by PD patients is thought to be a result of dysexecutive function (Hsieh et al., 2008). Thus, similar trends in performance on both tests here would support the hypothesis that impaired performance on the antisaccade task is driven by executive dysfunction rather than motor dysfunction.

2.1.4.4 Barratt Impulsivity Scale (BIS-11)

The Barratt Impulsivity Scale version 11 (BIS-11) (Table 2.1.3, Appendix A.5) is a 30-item self-report questionnaire used to measure trait impulsivity (Patton et al., 1995). Each statement is
scored from 1-4 (Rarely/Never, Occasionally, Often, and Almost always/Always) where 4 represents the most impulsive response option. A subset of questions is worded to indicate a lack of impulsivity and are scored in reverse (e.g., Rarely/Never is scored as a 4). Total scores range from 30-120 where higher scores indicate greater impulsivity. Here we use the BIS-11 to control for group differences in impulsivity as a possible confound to antisaccade task performance.

2.1.5 Statistical analyses

Demographic and clinical characteristics are reported using descriptive statistics: mean and standard deviation for parametric data and median and interquartile range for non-parametric data. All variables of interest were assessed for normality and presence of outliers before subsequent analyses. Given we tested a clinical population where a range of abnormalities are expected, outliers were not removed unless their presence inflated statistical significance between groups, at which point they were removed, and the analysis was re-run. Outliers were defined as values above or below 1.5 times the interquartile range for that variable.

First, eye tracking variables were compared between groups using Welch’s two-sample t-tests and Wilcoxon rank sum tests for parametric and non-parametric variables respectively. To correct for multiple comparisons between saccade parameters we used a post-hoc Bonferroni correction (0.05/3 comparisons = $p<0.0166$ for prosaccade parameters and 0.05/4 comparisons = $p<0.0125$ for antisaccades parameters). Second, Welch’s and Wilcoxon tests were also used to compare differences in performance on motor (TUG test) and cognitive tasks (TMT, Stroop Task, KBIT-2). Third, antisaccade parameters was correlated to clinical, cognitive, and motor variables of interest; Pearson’s correlations (Pearson’s $r$ coefficient reported) were used for
parametric variables and Spearman’s corrections were used for non-parametric variables (Spearman’s rho reported). To calculate effect sizes of group we used Cohen’s \( d \), where \( d = 0.2 \), \( d = 0.5 \), and \( d = 0.8 \) correspond to small, moderate, and large effect sizes respectively. All statistical analyses were performed using R (version 2023.03) (R Core Team, 2022).
2.2 Results

Our statistical analysis started by comparing antisaccade task performance of healthy controls and PD patients. Following, we compared group performance on the motor assessments, and cognitive test battery. Finally, we explored how antisaccade task performance may be correlated to motor and/or cognitive function in PD.

2.2.1 Motor and cognitive performance: PD patients versus healthy controls

To assess whether our patients’ showed dysfunction in physical motor performance or cognitive functions we compared performance in motor and cognitive tasks between groups. We hypothesized that patients would perform worse on assessments of motor function and would show impairment in response inhibition, and in processing speed. For most tests in the assessment battery, patients and healthy controls performed comparably (see Table 2.2.1).

Functional motor ability, evaluated by the TUG test, was slightly decreased in PD patients versus controls, though this result was not significant ($p=0.06$), and both groups performed normally within their age range (Bohannon, 2006; Ibrahim et al., 2017). Group comparisons revealed no significant differences in complex attention or task switching abilities measured by performance on the TMT. In contrast to our expectations, PD patients demonstrated a stronger ability to inhibit competing responses based on their Stroop Task performance (represented by a positive Stroop interference score), although this group difference was not statistically significant. In line with similar or better performance by the PD group, these participants also outperformed healthy controls in the KBIT-2, showing higher fluid intelligence abilities ($p=0.038$). Group comparisons revealed no differences in trait impulsivity measured by the BIS-11 total scores. Taken together
these results show that our sample of patients are high functioning with stable motor and
cognitive abilities in the context of their PD motor symptoms.

Table 2.2.1 Results of motor and cognitive assessments.

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n=20)</th>
<th>PD patients (n=19)</th>
<th>Two-sample unpaired t-tests</th>
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<tbody>
<tr>
<td><strong>Motor function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timed Up and Go (s)</td>
<td>9.5 ± 1.1</td>
<td>10.2 ± 1.2</td>
<td>( t_{(36.6)} = -1.92; p=0.06; d=0.61 )</td>
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<td><strong>Cognitive Function</strong></td>
<td></td>
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<tr>
<td>Trail Making Task (s)</td>
<td>86.4 ± 21.3</td>
<td>92.6 ± 32</td>
<td>( t_{(31.1)} = -0.71; p=0.48; d=0.22 )</td>
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<tr>
<td>Stroop Colour and Word Task Interference Score</td>
<td>-4.5 (16.5)</td>
<td>2 (11)</td>
<td>( W=132.5; p=0.11; d=0.33 )</td>
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<tr>
<td>KBIT-2 matrices age-corrected score</td>
<td>68 (37)</td>
<td>86 (17)</td>
<td>( W=116; p=0.038; d= 0.63 * )</td>
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<td><strong>Impulsivity</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Barratt Impulsivity Scale</td>
<td>59 ± 5.8</td>
<td>56.3 ± 5.2</td>
<td>( t_{(36.8)} = 1.48; p=0.14; d=0.47 )</td>
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</table>

Values are reported as mean ± standard deviation except Stroop and K-BIT scores which are reported as median (IQR)
* Indicates significant difference between groups with \( p < 0.05 \).

2.2.2 Group comparison of prosaccade task performance

In the prosaccade task, participants were shown a cue at a peripheral location and were told to
make a saccade to it as quickly as possible. In this task, we first assessed amplitude where
patients’ saccades were hypometric (i.e., undershot the target) as compared to controls (\( t_{(34.5)} = 3.06; p=0.0043; d=1.01; \) Figure 2.2.1A). Patients’ saccade amplitude results were also overall
more variable as compared to controls (patient mean SD = 1.95 degrees, control mean SD = 1.26
degrees; \( t_{(26.7)} = -4.16; p=0.0003 \)). We did not find differences in mean latency (Figure 2.2.1 B)
between groups (\( t_{(28.5)} = -0.68; p=0.50; d=0.23 \)). However, patients did show a wider range of
prosaccade latencies (Figure 2.2.2). Additionally, in line with variability differences observed for
amplitude, we also found greater variability in saccade latencies in patients as compared to controls (patient mean SD = 66.5 ms, control mean SD = 50.9 ms; $t(30.7) = -2.2; p=0.035$). Next, we evaluated differences in express saccades made during prosaccade trials. These saccades are made within 90 to 120 ms of cue offset and were analyzed to assess any potential speed-accuracy tradeoffs in either the pro- or the antisaccade task. For the prosaccade task, we found no group differences in the frequency of express saccades ($W= 136; p=0.31; d= 0.36$) (Figure 2.2.1 C).
Figure 2.2.1 Group comparisons of prosaccade parameters
Group median and IQR of prosaccades parameters. Blue boxplots represent controls ($n=20$), orange represent PD patients ($n=17$). Dashed horizontal line indicates cue position. A) mean horizontal amplitude, B) mean latency, C) rate of express prosaccades. * Indicates significance of $p<0.0166$ with correction for multiple comparisons.
2.2.3 Group comparison of antisaccade task performance

Next, we compared antisaccade performance between patients and healthy controls. First, we analyzed antisaccade latency. We expected to see increased antisaccade latency in patients in line with a general slowing of motor responses in PD. In contrast to our expectations, we found that patients made antisaccades at a similar mean latency (267.8 ± 57.9 ms) as controls (257.9 ± 37.6 ms) (Figure 2.2.3. A). Congruently, the group difference was not significant ($t_{(26.4)} = -0.6$; $p=0.54; d=0.20$). In terms of antisaccade error rates, we expected patients to make more errors during the antisaccade task, and our findings are in line with this prediction. We evaluated antisaccade task performance using three metrics (see Methods, Figure 2.1.2): total error rate, direction errors (where participants looked at the target cue instead of in the mirrored direction), and ‘changes of mind’ (where they made a saccade toward the cue, but self-corrected with a second saccade in the opposite direction). PD patients showed more than double the rate of total
errors (patients $M = 21.7\%$, $SD = 18.6\%$; controls $M = 10.5\%$, $SD = 11.43\%$; $W=88$; $p=0.013$; $d=0.72$) (Figure 2.2.3 B), direction errors (patients $M = 4.2\%$, $SD = 4.9\%$; controls $M = 0.7\%$, $SD = 1\%$; $W=97$; $p=0.023$; $d=0.96$) (Figure 2.2.3 C), and ‘changes of mind’ (patients $M = 17.4\%$, $SD = 14.7\%$; controls $M = 9.7\%$, $SD = 11\%$; $W=98$; $p=0.02$; $d=0.58$) (Figure 2.2.3 D) relative to controls. Despite the differences in error rates, reflected in moderate to large effects, our group differences were non-significant when corrected for multiple comparisons.
Figure 2.2.3 Group comparisons of antisaccade parameters

Group median and IQR of antisaccade parameters. Blue boxplots represent controls (n=20 except in figure D where n=18), orange represent PD patients (n=17 for latency and n=14 for all other figures). A) mean antisaccade latency, B) antisaccade error rate, C) antisaccade direction errors, D) antisaccade ‘changes of mind’. * Indicates statistical significance for p< 0.0125 with correction for multiple comparisons.
To further explore the increased error rate in PD patients as compared to controls, we analyzed error rates as a function of saccade latency. Figure 2.2.4 shows that the effect of group on antisaccade error rate is largest during saccades of the shortest latency (150-200 ms).

Specifically, we see patients’ antisaccade task performance is only slightly above chance (55%), whereas controls’ saccades at this latency are in the correct direction in 90% of trials ($t_{(28)} = -3.7348; p<0.001$). Importantly, when saccade responses are delayed to 200, we see patients’ task performance improve to almost 95%. At latencies of greater than 200 ms we see both patients and controls make errors less than 5% of the time.

**Figure 2.2.4 Antisaccade task performance as a function of antisaccade latency**

Task performance (percentage of correct antisaccades, lower value indicates worse performance) as a function of saccade latency for healthy controls and PD patients. *** Indicates significance at $p < 0.001$. 

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2.2.4 Antisaccade task performance as an indicator of cognitive and motor function.

We did not find significant group differences for any of the motor or cognitive assessments except the KBIT-2. Thus, we pooled our group data to investigate the relationship between antisaccade task performance and motor function, executive function, and general cognitive ability (third hypothesis). To do this, we generated a preliminary correlogram with all the antisaccade task parameters against all the motor (MDS-UPDRS, TUG), and cognitive scores (TMT, Stroop, KBIT-2, BIS-11) (see Appendix B, Figure 3.2.1). Interestingly, this revealed only one significant correlation. We found a positive correlation between mean antisaccade latency and Stroop interference score (Figure 2.2.6), though the correlation was small (Spearman’s rho = 0.37, \( p=0.024 \)). In isolation, each group showed this correlation, though the control group had a slightly larger association. Our PD group showed no associations between pro- or antisaccade performance parameters and clinical metrics including MDS-UPDRS score, disease duration, or levodopa daily equivalent dose.

![Figure 2.2.5 Relationship between antisaccade latency and Stroop Task performance](image)

Correlation between mean antisaccade latency (ms) and Stroop interference score. Positive Stroop interference score indicates stronger ability to inhibit competing responses.
2.3 Discussion

Systematic impairments in antisaccade task performance are well established in patients living with PD (Waldthaler, Stock, Student, et al., 2021). Here we explored whether these impairments are related to motor function, cognitive function, and or general cognitive ability. We tested high functioning patients with mild to moderate PD on the antisaccade task and compared their performance to a series of motor and cognitive assessments. Our results cautiously suggest that the antisaccade task has greater sensitivity to detect response inhibition deficits in early disease patients, which may not be captured by standard neuropsychological tools. In summary, we report four important findings.

2.3.1 Summary of results

First, patients showed stereotyped prosaccade differences consistent with the literature. One of the oculomotor signatures of PD is hypometric saccades where patients undershoot based on the amplitude of the visual cue (Leigh & Zee, 2015b). Patients in our study demonstrated this deficit, supporting evidence that this saccadic abnormality is seen across the spectrum of PD, and amplitude of visually guided saccades may actually decrease the most in Hoehn & Yahr stages 1-2 and stabilize in later stages (Terao et al., 2013). Second, patients did not show prolonged antisaccade latencies, opposing previous findings, but did make significantly more errors, specifically ‘changes of mind’, during the task. Third, mild PD patients did not show dysfunction in motor or cognitive abilities. And fourth, our patients’ errors on the antisaccade task were not related to motor function, executive function, or general cognitive ability.
2.3.2 Interpretation of results

In contrast to previous research (Waldthaler, Stock, Student, et al., 2021), we did not find prolonged antisaccade latencies in our PD patients. Our results in the context of existing literature may be explained by the mild clinical characteristics of our patient group relative to other study cohorts. In Waldthaler et al.’s (2021) metanalysis on antisaccades in PD the authors report a large group effect \((d = 1.10)\) on antisaccade latency across 13 studies using an antisaccade gap paradigm, like our task used here. However, studies reporting increased antisaccade latency included older patients (Briand et al., 1999) with longer disease duration and greater motor symptoms (measured by the MDS-UPDRS; Hood et al., 2007), or did not report these clinical measures at all (Chan et al., 2005). Thus, previous findings in antisaccade latency may not be extrapolated to predict performance in patients with different disease severity.

Additionally, some studies tested patients exclusively in the OFF-medication state. It is important to highlight this methodical variation and its potential to confound reported trends in patient performance. Antisaccade latency has been reported as a potential biomarker for PD, but these results must be interpreted with caution as the effects may not be applicable to patient populations at early disease stages.

Our findings correspond with multiple studies that have found higher antisaccade error rates in PD patients relative to healthy controls (Antoniades et al., 2015; van Stockum et al., 2008; Waldthaler et al., 2019). Specifically, we found patients’ antisaccade task performance was most impaired during short latency saccades (Figure 2.2.4). Although we did not observe group differences in express saccades, these errors might be driven by the hyper-reflexive response of the oculomotor system to the salient visual cue observed, which is seen in patients’ increased rate
of express pro and antisaccades in some studies (Chan et al., 2005). To successfully execute an antisaccade, the DLPFC must inhibit the reflexive prosaccade via connections to the frontal eye field and midbrain superior colliculus (Munoz & Everling, 2004). It has been proposed that successful inhibition of the reflexive saccade occurs at the level of motor preparation and action selection, before the correct saccade direction is known (Waldthaler et al., 2022). That is, the top-down signals from the DLPFC must be proactive rather than reactive for correct antisaccade behaviour. Frequent ‘changes of mind’ during the antisaccade task may therefore be the result of insufficient preparation of the DLPFC, which in turn leads to reduced inhibition from the frontal eye field, requiring reflexive responses to be corrected. This suggests that motor impulsivity and an inability to inhibit a reflexive response toward the salient cue may be contributing more to poor antisaccade performance opposed to a deficit in cognitive control, as observers were able to identify and rapidly correct their errors.

After conservative corrections for multiple comparisons were applied, our results were not statistically significant, however this could be a function of task difficulty. We followed the antisaccade consensus guide and alternated blocks of pro- and antisaccade trials (Antoniades et al., 2013). However, the task design may need to be adjusted for use in clinical populations. Based on the mild deficits in our patients, an interleaved pro/antisaccade task may have been a more suitable test for our hypotheses as it requires more inhibitory control and task switching abilities. For example, Ouerfelli-Ethier et al. (2018) used an interleaved pro- and antisaccade task with three 40 trial blocks (using equal interleaved pro- and antisaccade trials) and reported the task to be a sensitive indicator of cognitive function in both PD patients and older adults. Additionally, antisaccade performance in patients with different parkinsonian syndromes (PD,
corticobasal degeneration, and supranuclear palsy) has been evaluated using single block task (i.e., blocks of either prosaccades or antisaccades trials) versus mixed block antisaccade tasks (i.e. blocks of randomized and interleaved pro- and antisaccades) (Rivaud-Péchoux et al., 2007).

In their study Rivaud-Péchoux et al. (2007) reported that the PD group showed increased antisaccade error rates on the mixed task and normal performance on the single block task suggesting that oculomotor performance may be mediated by the demands of the task design and associated switching costs.

Our cohort of mildly impaired PD patients showed similar performance in motor and cognitive tasks compared to healthy controls, and outperformed controls on the assessment of fluid cognition (KBIT-2). We selected the TUG test as measure of functional motor ability, however it likely was not the appropriate test to detect mild to moderate motor dysfunction in our patient group. Our patients also performed comparably to controls on the TMT and Stroop Task, with slightly better performance on the KBIT-2. We used performance on the KBIT-2 to control for differences in general intelligence, thus it is possible our patients performed better due to their higher level of education, as years of education is known to be a contributing factor to cognitive test performance (Ceci, 1991). There are two possible explanations for these results. First, the selected battery of cognitive tests may have a floor effect for mild deficits. Second, it is possible that patients do have a degree of executive dysfunction, but that the tests chosen here did not measure that cognitive ability. In future studies, a more cohesive and robust neuropsychological battery validated in healthy and diseased populations, such as the NIH Toolbox Cognition Battery or similar could be used (Gershon et al., 2013; Weintraub et al., 2013).
Our patient group had normal cognitive abilities, and even exceeded the performance of controls, on a collection of standardized neuropsychological tests. However, the frequency of their antisaccade task errors were significantly higher than controls. Despite our expectations, only one correlation was found between antisaccade error rates and motor or cognitive abilities. We found that antisaccade latency had a small positive correlation with the Stroop interference score. This result suggests that those who can suppress reflexive saccades longer before making a voluntary antisaccade may also have better response inhibition with competing demands in other contexts. Together, these results suggest that the antisaccade task may be more sensitive to detect deficits in response inhibition in PD patients with mild disease. Numerous studies have explored the relationship between antisaccade parameters and motor and cognitive abilities. The majority have found positive relationships between antisaccade latency and Hoehn & Yahr, MDS-UPDRS scores, and disease duration, but there is a paucity of results associating these clinical metrics to antisaccade error rates (Waldthaler, Stock, Student, et al., 2021). Many studies evaluating antisaccade performance in relation to other PD features also include patients with significant cognitive impairment, thus the results cannot be extrapolated to our mild, high functioning PD patients included here. Antisaccade error rate has been negatively correlated to MoCA and Frontal Assessment Battery scores, but this finding only became evident in patients with moderate disease (Hoehn & Yahr 3 or more), but not in patients with mild PD (Hoehn & Yahr 1-2) (Waldthaler et al., 2019). In a similar study, antisaccade performance predicted performance on the MoCA, but the PD population included had significantly lower MoCA scores at baseline relative to controls (Ouerfelli-Ether et al., 2018). We intentionally did not include the MoCA beyond its use as a screening tool because it cannot measure subtle cognitive deficits in early PD, and only provides a unidimensional score of cognitive ability (Kletzel et al., 2017).
2.3.3 Limitations

There are limitations to this work that must be considered. First, we cannot dissociate antiparkinsonian medication effects on our findings as we did not complete repeat testing in patients in their ON and OFF states. Requiring patients to withdrawal from medication would likely affect retention over two testing sessions and decrease our final patient sample size. Additionally, growing evidence suggests that antisaccades are resistant to PD medication effects, one of their potential advantages as a biomarker of PD (Lu et al., 2019; Waldthaler, Stock, Student, et al., 2021), indicating background medication likely does not have as great an effect on performance as previously thought. Here, we did not find any correlations between levodopa equivalent daily dose and any eye movement parameter, which provides indirect evidence for this claim. Further, in the context of cognitive testing, the standard 12-hour medication washout period would likely be insufficient to eliminate the residual effects of levodopa (Fera et al., 2007). It is important to note however that we did not control for dosing schedules between patients, which likely resulted in differences in peak medication effects between participants. Thus, it is possible that this affected performance particularly during eye tracking and is an important variable to consider controlling for in future PD patient cohorts.

Second, 25% of our patients were taking a dopamine agonist, which have shown to increase motor impulsivity on measures of response inhibition compared to levodopa (Antonelli et al., 2014). We did not have adequate statistical power to compare this sub-group of patients, but it is possible that these patients may have different antisaccade performance, as has been speculated previously (Hood et al., 2007; Waldthaler, Stock, Krüger-Zechlin, et al., 2021). A previous study investigating the effect of dopamine agonists on antisaccade behaviour reported no effect of the
medication on performance, however this work was conducted in moderate to severe patients with substantial preexisting motor deficits (Crevits et al., 2000). Future studies should consider a sub-analysis of patient performance divided by antiparkinsonian medication type.

Third, our sample size was based largely on feasibility, and was estimated from previous work in our lab (Fooken et al., 2022). With a sample of 16 patients and 18 controls Fooken et al. (2022) reported an effect size of group of 1.12 for ‘change of mind’ errors on the antisaccade task, which is approximately double to our effect size here ($d=0.58$). Though our sample sizes were comparable, the number of trials included in our analysis was smaller than anticipated after excluding those with eye movement artifacts (e.g., blinks, signal loss, incomplete testing etc.), which as a result likely reduced our statistical power. One interesting future direction might be to conduct a longitudinal study with repeat testing of the antisaccade task in PD patients. Such a study could provide predictive claims regarding the relationship between motor or executive functions and antisaccade task performance with the progression of PD or at different disease stages.
Chapter 3: Conclusion

3.1 Summary and significance
In conclusion, our study contributes modest evidence to the growing literature which suggests antisaccade task performance may be a candidate biomarker of PD. Here we demonstrated that mild PD patients show some stereotyped deficits on the antisaccade task, specifically an increased frequency of antisaccade errors relative to controls. Further, patients exhibited these deficits in the absence of other signs of motor or cognitive dysfunction, measured by a battery of standard tests. Together, these results suggest the antisaccade task may be sensitive tool to detect impairments in response inhibition that are not detected with other screening tools, even in patients with a mild form of the disease.

3.2 Clinical applications and future directions
Diagnosis and monitoring of PD can be challenging due the heterogeneity of symptoms affecting sensory, motor, and cognitive systems, and currently there is a lack of sensitive and objective tools available to patients living with PD. PD patients show stereotyped eye movements deficits, which may offer a tool to probe disease mechanisms. Specifically, the antisaccade task has become an accepted paradigm to measure response inhibition in PD (Lu et al., 2019; Manza et al., 2017). However, more research using consistent study methodologies and task designs is needed to fully characterize antisaccade signatures 1) across the PD spectrum and 2) in combination with other carefully chosen variables relevant to the disease. The clinical applications of saccadic eye movements in PD are two-fold. First, antisaccades are thought to be resistant to antiparkinsonian medication effects (Lu et al., 2019; Waldthaler, Stock, Student, et
al., 2021), which could make them (one of many) outcome measures used in clinical trials for future disease modifying drugs. Further, using antisaccades as a behavioural measure promotes the design of pragmatic studies where patients do not need to withdrawal from symptomatic treatment (Lu et al., 2019). Second, preliminary evidence suggests antisaccades differences may be related to disease progression at moderate to severe disease stages. Thus, with continued investigation at these and earlier disease stages of PD, there is promise that the antisaccade task could be developed as a predictive tool of disease progression to be used in collaboration with clinical evaluation.

Specifically, the antisaccade task could be used to monitor changes in motor and cognitive behaviour in those most at risk for developing PD. For example, patients with REM sleep behaviour disorder (RBD) are now known to be at increased risk for developing PD and other synucleinopathies (Iranzo et al., 2014). Briefly, RBD is characterized by violent enactment of dreams during REM stages of sleep with a lack of normal muscle tone (Arnulf, 2012). RBD is thought to represent the prodromal phase of PD, where more than 30% of patients have been reported to develop a Parkinsonian syndrome at five years post-RBD diagnosis, and more than 75% at ten years (Iranzo et al., 2014). Other studies report slightly lower 5- and 10-year risk percentages but the overall trend is consistent (Postuma et al., 2009). Recently, investigation of oculomotor abnormalities in both RBD and PD patients has shown abnormal pupil and blink behaviour (Perkins et al., 2021). Additionally, work has been started to delineate the specific oculomotor biomarkers across various synucleinopathies (e.g., PD, Multiple System Atrophy) versus tauopathies (e.g., progressive supranuclear palsy) as well as for patients with RBD.
(Habibi et al., 2022). This work sets the precedent for continued evaluation of oculomotor abnormalities across neurodegenerative diseases.

Measuring eye movements is non-invasive and inexpensive thus it is suitable to apply these methods outside of research settings in clinical practice. Existing studies have validated a modified antisaccade task to be used at the bedside in patients with varying degrees of neurological impairment (Hellmuth et al., 2012). This research provides a proof of concept for using robust eye movement measurements in the context of clinical care. The antisaccade task offers an objective marker of response inhibition with increasing sensitivity and predictive value in PD patients. Further longitudinal studies at all stages of PD are needed to fully explore the promise and limitations of this oculomotor task.
References


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https://doi.org/10.1002/mds.23429

https://doi.org/10.1016/j.neuropsychologia.2008.07.002


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Appendices

Appendix A - Assessments and questionnaires

A.1 Timed Up and Go test

Timed Up & Go (TUG)

**Purpose:** To assess mobility

**Equipment:** A stopwatch

**Directions:** Patients wear their regular footwear and can use a walking aid, if needed. Begin by having the patient sit back in a standard arm chair and identify a line 3 meters, or 10 feet away, on the floor.

1. **Instruct the patient:**

   When I say “Go,” I want you to:
   1. Stand up from the chair.
   2. Walk to the line on the floor at your normal pace.
   3. Turn.
   4. Walk back to the chair at your normal pace.
   5. Sit down again.

2. **On the word “Go,” begin timing.**
3. **Stop timing after patient sits back down.**
4. **Record time.**

**Time in Seconds:**

An older adult who takes a 12 seconds to complete the TUG is at risk for falling.

**NOTE:** Always stay by the patient for safety.

**Observations**

Observe the patient’s postural stability, gait, stride length, and sway.

Check all that apply:
- Slow tentative pace
- Loss of balance
- Short strides
- Little or no arm swing
- Steadying self on walls
- Shuffling
- En bloc turning
- Not using assistive device properly

These changes may signify neurological problems that require further evaluation.

CDC’s STEADI tools and resources can help you screen, assess, and intervene to reduce your patient’s fall risk. For more information, visit [www.cdc.gov/steadi](http://www.cdc.gov/steadi).
A.2 Trail Making Task (TMT)

Trail Making Test Part A

Patient's Name: ___________________________  Date: ________________
### A.3 Stroop Colour and Word Test

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**Duration:** 45 seconds

**Purpose:** Read aloud the words by following the lines, and this as quickly as possible. When you reach the end of the page, start again from the beginning.
STROOP EFFECT GAME
Part 2 - card C

Duration: 45 seconds
Purpose: Name out loud the color of each rectangle by following the lines, and do this as quickly as possible. When you reach the end of the page, start again from the beginning.
STROOP EFFECT GAME
Part 3 - card B

Duration: 45 seconds
Purpose: By following the lines and as quickly as possible, name out loud the color of each word (not what the word says). When you reach the end of the page, start again from the beginning.

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## A.4  Barratt Impulsivity Scale (BIS-11)

<table>
<thead>
<tr>
<th></th>
<th>Rarely/Never</th>
<th>Occasionally</th>
<th>Often</th>
<th>Almost Always/Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I plan tasks carefully.</td>
<td></td>
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<tr>
<td>2</td>
<td>I do things without thinking.</td>
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<tr>
<td>3</td>
<td>I make-up my mind quickly.</td>
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<tr>
<td>4</td>
<td>I am happy-go-lucky.</td>
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<tr>
<td>5</td>
<td>I don’t “pay attention.”</td>
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<tr>
<td>6</td>
<td>I have “racing” thoughts.</td>
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<tr>
<td>7</td>
<td>I plan trips well ahead of time.</td>
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<tr>
<td>8</td>
<td>I am self controlled.</td>
<td></td>
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<tr>
<td>9</td>
<td>I concentrate easily.</td>
<td></td>
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<tr>
<td>10</td>
<td>I save regularly.</td>
<td></td>
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<tr>
<td>11</td>
<td>I “squirm” at plays or lectures.</td>
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<tr>
<td>12</td>
<td>I am a careful thinker.</td>
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<tr>
<td>13</td>
<td>I plan for job security.</td>
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<tr>
<td>14</td>
<td>I say things without thinking.</td>
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<tr>
<td>15</td>
<td>I like to think about complex problems.</td>
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<tr>
<td>16</td>
<td>I change jobs.</td>
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<td></td>
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<tr>
<td>17</td>
<td>I act “on impulse.”</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>18</td>
<td>I get easily bored when solving thought problems.</td>
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<tr>
<td>19</td>
<td>I act on the spur of the moment.</td>
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<tr>
<td>20</td>
<td>I am a steady thinker.</td>
<td></td>
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<tr>
<td>21</td>
<td>I change residences.</td>
<td></td>
<td></td>
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<tr>
<td>22</td>
<td>I buy things on impulse.</td>
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<tr>
<td>23</td>
<td>I can only think about one thing at a time.</td>
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<tr>
<td>24</td>
<td>I change hobbies.</td>
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<td>25</td>
<td>I spend or charge more than I earn.</td>
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<tr>
<td>26</td>
<td>I often have extraneous thoughts when thinking.</td>
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<tr>
<td>27</td>
<td>I am more interested in the present than the future.</td>
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<tr>
<td>28</td>
<td>I am restless at the theater or lectures.</td>
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<tr>
<td>29</td>
<td>I like puzzles.</td>
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<tr>
<td>30</td>
<td>I am future oriented.</td>
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</table>
Appendix B - Supplementary data

B.1 Preliminary correlograms

Figure 3.2.1 Correlograms of antisaccade task parameters and motor and cognitive scores
A) Values indicate Pearson’s correlation coefficients, B) Coloured squares show correlations with $p < 0.05$, blank squares represent correlations that are not statistically significant.