Original Research Article

Analysis of temporal saccade prediction in Parkinson's Disease using video-based eye tracking

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Abstract

In Parkinson's Disease, key brain regions involved in generating saccades and producing adaptive anticipatory behaviour are impacted, however the intersection of these deficits is not well characterized. Effective Parkinson's Disease biomarkers are lacking, and video-based eye tracking provides a low-cost, non-invasive means to quantify eye-movement behaviour and address this knowledge gap. In a preliminary study, we analyzed predictive saccade behaviour in eight Parkinson's patients (ON and OFF medication) and twenty controls aged 51-80 years. Participants performed a visual metronome task, moving their eyes in synchrony with a visual target jumping at a fixed rate on a computer screen. This was contrasted with a random task where the timing of target jumps was not predictable. Saccades made in anticipation of target appearance were classified as predictive, while those made significantly after were classified as reactive. There were no significant differences in saccadic metrics (i.e., reaction time, peak velocity, and amplitude) between groups. Parkinson's Disease's impact on saccade reaction time and predictive saccade generation was subtle, however these patients generated multi-stepping, hypometric saccades with reduced velocity compared to controls. The effects of dopaminergic medication on saccade metrics were inconsistent, with some improvement of saccade amplitude. Weak to moderate correlations were obtained between saccade metrics and disease severity and duration. This pilot study contributes to the understanding of saccade performance in evaluating the neural underpinnings of motor impairments in Parkinson's Disease. Further investigation with more participant recruitment will be necessary to identify which saccade features are sensitive and specific to Parkinson's Disease.

Keywords: Predictive saccades, Parkinson's Disease, Eye movements, Eye tracking, Carbidopa levodopa, Biomarker

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Introduction

To interact with a rapidly changing world, we must gather information on relevant stimuli and integrate this information with other environmental and timing cues, or previous experience to anticipate events and execute motor commands accordingly (1). Identification of rhythmic environmental stimuli allows for a shift from reactive to predictive motor responses when a stimulus is expected, which is crucial for adaptive sensorimotor behaviour (2-4).

Saccades are rapid eye movements that shift the point of fixation from one location to another. The saccadic eye movement system provides a highly precise, non-invasive means of exploring the cognitive control of behaviour and quantifying neurological function, as saccades are quick, non-fatiguing, and can be measured easily and objectively (5). Several areas in the frontal cortex, parietal cortex, thalamus, basal ganglia (BG) and brainstem exert control over the premotor saccade circuit (6). Furthermore, processing of timing-related cues necessary for prediction utilizes the frontal cortex, BG, cerebellum, and thalamus (7-12).

In Parkinson's Disease (PD), key brain regions involved in generating saccades and predictive behaviour are impacted. PD is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta of the BG, and progressive loss of voluntary motor control resulting in bradykinesia, rigidity, and tremor (13). The BG and cerebral cortical regions are particularly important in saccade control due to their converging projections to the superior colliculus (SC) in the midbrain. The SC sends projections to both the vertical and horizontal gaze centers in the reticular formation and provides the motor command to initiate a saccade. To make voluntary saccades, the BG sustains inhibitory input to the SC allowing relevant signals to be selected from the cerebral cortex, and generation of an appropriate saccade. However, this is impaired in PD (14-17).

Research indicates that quantitative assessment of eye movement patterns can contribute to differential diagnosis in neurodegenerative diseases (18,19). The predictive-saccade paradigm used here is particularly useful for probing areas relevant to temporal prediction and saccade initiation given that they overlap with regions impacted by PD (i.e., brainstem, cerebellum, SC, thalamus, BG, and frontal cortex) (20-23). Here we use the predictive-saccade task and a random pro-saccade control task to investigate prediction and saccade control in PD patients and healthy age-matched controls.

Certain studies investigating predictive-saccade behaviour have demonstrated PD-related deficits, while others found insignificant differences from controls (24-30). A handful of studies using the predictive-saccade task in PD [7-14 PD patients/study (50–75 years)], show that they had delayed initiation of predictive-saccades and on average, decreased saccade amplitude compared to controls (24,27,31). However, given the studies' small sample sizes and limitations or variations in measurement instruments (i.e. using electro-oculography vs videonystagmography vs infrared-sensitive eye tracking camera), predictive-saccade performance in PD has yet to be comprehensively characterized. When recruitment is complete, this study will have a larger cohort size, with variation in patient age and disease severity, that should provide stronger, more reliable results compared to previous studies.

We aim to record saccade performance using video-based eye tracking to analyze prediction performance in PD patients versus controls, PD medication effects, and how performance relates to motor symptoms. We hypothesize that PD patients will make more hypometric (reduced amplitude) saccades and more timing and direction errors. These errors arise from an inability to predict the rhythmicity of the stimuli; however, these errors should be reduced when PD patients take dopamine replacement medication.

Methods

Study participants

This study was approved by the Human Research Ethics Committees of Queen's University (protocol ID: PHYS-007-97). Adults between the ages of 50-85 years old diagnosed with PD, as well as age-matched healthy controls were recruited. All participants had normal or corrected vision. Study visits occurred at the Centre for Neuroscience Studies laboratories located in Kingston General Hospital and Hotel Dieu Hospital, Kingston, Ontario. Criteria for inclusion/exclusion were established prior to any study visits or data analysis. Participant demographics are summarized in Table 1. Eight PD Patients were asked to participate in two study visits lasting 1.5-2 hours each. It was verified that all PD patients took Carbidopa-levodopa (Sinemet) medication for the disease and those with a Deep Brain Stimulator were excluded. To evaluate whether there was any medication effect, patients were randomized to participate either with (PD-ON) or without (PD-OFF) their medication for the first study visit and conducted the opposite for the second visit. This was achieved by asking patients to postpone their dose prior to the appointment to ensure a 4-hour wash-out period. Sinemet has a short half-life of one to two hours, therefore this was sufficient to ensure that there would be no medication effect. Twenty healthy volunteers were recruited to the control group (CTRL). Nine controls completed two study visits to establish learning effects when making comparisons to PD patients' repeated visits, but the remaining eleven controls completed only one visit. Those with neurologic, psychiatric, or ocular diagnoses and/or those taking psychotropic medications were excluded. Prior to the eye-tracking tasks, all participants completed a brief demographic questionnaire and the Montreal Cognitive Assessment (MoCA) to assess cognitive functioning (excluded from data analysis if MoCA < 20). A neurologist from the Kingston Health Sciences Centre helped recruit patients and administer the Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor assessment (UPDRS-III) to determine PD patients' motor disease progression in the OFF state (32). The assessment included a Hoehn and Yahr Stage (H&Y) rating to describe the functional disability of their PD.

Recording of eye movements

During each session, participants were asked to complete two computer-based eye-tracking tasks, during which a high-speed camera measured pupil size and position, providing output of eye positions and movements. Participants were seated in a dark room, 60 cm away from a computer screen with their head position stabilized by a fixed head mount and chin rest. A 9-point grid-based calibration was used to calibrate the camera lens before each block of trials (and repeated when needed) and eye position accuracy within 1° of the visual targets was considered acceptable. Experimental stimuli were presented on the screen as circular red targets (with a diameter of 0.5° from centre) on a 17-inch LCD iiYama Prolite monitor at a screen resolution of 1280×1024 pixels with a 60-Hz refresh rate, subtended at a view angle of 32×26°. Screen luminance was measured to be 44 cd/m^2 with an optometer for LCD monitors. Monocular (right) eye tracking was conducted using the video-based eye tracker EyeLink 1000 Plus consisting of a camera with a 500 Hz sampling rate and a mean eye position accuracy of 0.5°.

Procedure and experimental paradigm

In the metronome task, participants were instructed to look at a visual target that jumped from side-to-side on the screen, such that the stimulus location and timing was predictable after the first presentation. The random task appeared the same, but the timing of each target jump was unpredictable. During each trial, participants were cued with a red central fixation point (FP) on a blank screen that was illuminated for a randomized duration between 1-1.5 s. As the FP disappeared, a peripheral target appeared simultaneously either 10° right or left of the central FP, on the horizontal axis and alternated back and forth for a total of 12 target steps (Figure 1A). Each step following the initial target was 20° apart, as gaze shifts of under 20 degrees do not require additional head movement (33).

In the metronome task, the target oscillated consistently in a square-wave manner at each rate of 0.66, 0.8, 1, 1.33, or 2 Hz, in a randomized order. These five target rates corresponded to inter-stimulus intervals (ISI) of 1500, 1250, 1000, 750, and 500 ms, respectively. The metronomic temporal pattern of the stimuli allowed the participant to anticipate the stimulus appearance. In the random task, one of the five ISIs was randomly selected for each target step, such that the timing of the next target jump was unpredictable. The order of the predictive and random tasks was counterbalanced across participants within each group.

Eye-tracking data analysis

Computer software was used to preprocess eye-tracking data and this “marking” was verified by an experimenter to ensure accuracy. Data was analyzed using custom scripts written in MATLAB version R2021b (MathWorks). The following metrics were calculated for saccades within the Predictive and Random tasks: eye movement amplitude as distance from start to final end point (°), peak eye velocity (°/s), saccade reaction time (SRT) (ms), defined as the time

between target appearance and initial saccade onset. Saccades were defined as eye movements with peak velocity >30°/s, acceleration >9500°/s^2, and distance >0.15°. If eye position data were lost in a target step (i.e., due to blink) this step was excluded. Mean SRTs were calculated for saccades within the predictive and random tasks and were classified as predictive (<100 ms), express (100-140 ms) and regular (>140 ms), divisions and nomenclature that are consistent with existing literature examining a senior population (Figure 1B, C) (34-37). Express and regular saccades are triggered by the appearance of a visual stimulus and are reactive. Express saccades are produced when the visual response to target appearance that is sent to the SC is directly transformed into a motor command, producing the fastest visually evoked saccade (38-40). The percentage of predictive, express, and regular saccades per participant were computed for comparison across all trial conditions, as well as analyzed across participant groups (PD-ON, PD-OFF, CTRL).

Statistical analysis and model selection

The following comparisons were calculated between groups: differences in SRT, saccade amplitude, and peak velocity in terms of the Predictive and Random tasks. To explore any relationship between clinical progression and saccade behaviour, correlations between disease duration, motor deterioration (UPDRS-III), SRTs, percentage of PS (%PS), velocity, and amplitudes for predictive and reactive saccades were computed for each task variation. Before any statistical analysis, the Shapiro-Wilk normality test (appropriate for small sample sizes) was applied to all variables (41). Four Mixed-design ANOVAs (PD-OFF vs CTRL) were conducted for the dependent variables saccade amplitude, velocity, %PS saccades and SRT across the within-subject factor ISI (6 levels, 5 metronome task variations and random task) and the between-subjects factor Group. Next, a PD-ON vs PD-OFF repeated-measures ANOVA with two within-subjects factors (ISI and Medication State) was computed since this was more sensitive to the effect of medication.

The order of medication state was counterbalanced with all PD patients to attempt to control for any learning effects. However, at this stage in recruitment, only two PD patients came in OFF medication for their first visit. Therefore, we had a subset of the CTRL group come in for two visits to explore whether a learning effect existed. They conducted the predictive and random task during both visits, the order of which was randomly interleaved between sessions. Then, a CTRL V1 vs CTRL V2 repeated-measures ANOVA with two within-subjects factors (ISI and Visit) was computed. Finally, the within-subjects factors were correlated with measures of disease duration and motor deterioration (UPDRS-III) (two-tailed Pearson's correlation).

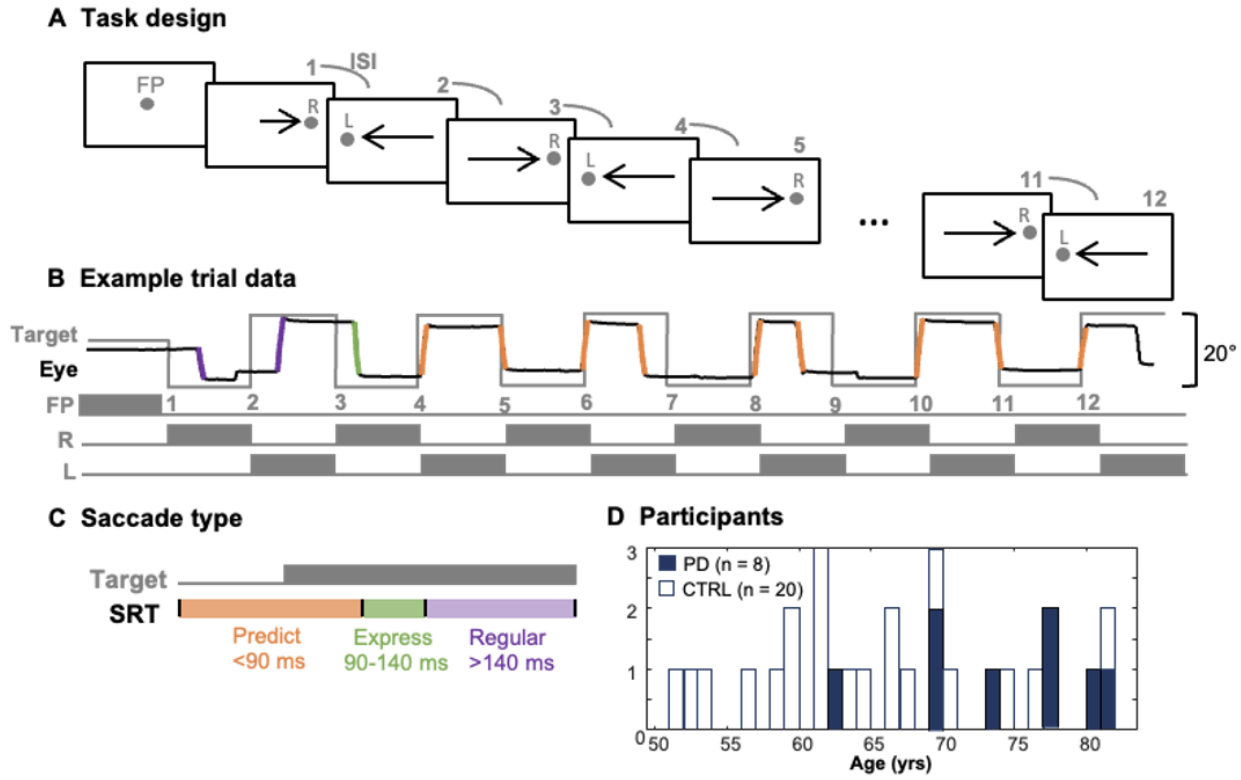

Figure 1. Predictive saccade task design, sample data, and participant distribution. **(A)** In the metronome task (first developed by Stark et al.), participants were cued with a central FP followed by 12 targets that alternated 10° right (R) and left (L) from the center (20). There were five blocks of trials (in a pseudorandom order), with 12 target steps each, delivered at a fixed target rate of 0.66, 0.8, 1.0, 1.33, 2.0 Hz per trial, with the corresponding ISIs of these target rates being 1500, 1250, 1000, 750, and 500 ms, respectively. Participants were instructed to move their eyes as quickly as possible to follow the target. In the random task, one of the five target rates was randomly selected for each target step, making the timing of the next target appearance unpredictable, while all other aspects of the task were held constant. **(B)** Definition of saccade type by SRT: predictive (SRT < 100 ms) in orange, express (SRT: 100–140 ms) in green, and regular (SRT > 140 ms) in purple. **(C)** Sample eye position data collected during one trial from a single control participant. The colour scheme of each step corresponds to the type of saccade generated depending on its SRT. **(D)** Histogram of participants' ages that were included in experimental analysis. Navy blue represents PD patients and white represents CTRL. Reproduced from Calancie et al. (4).

Table 1. Demographic and Clinical Characteristics of PD Patients and Controls

Characteristic	**Control (*n* = 20)**	**PD (*n* = 8)**
Females, *n* (%)	14 (70.0)	4 (50.0)
Age (years)	63.4 ± 7.9	73.5 ± 6.0
MoCA	26.2 ± 2.0	24.9 ± 3.3
UPDRS-III		25.6 ± 13.8
Hoehn-Yahr		
0–2		6 (75.0%)
3–5		2 (25.0%)

Mean results + SD categorized by group.
Hoehn-Yahr: Hoehn and Yahr staging of Parkinson disease; MoCA: Montreal Cognitive Assessment; PD: Parkinson's disease group; UPDRS-III: Unified Parkinson's disease Rating Scale motor assessment

Results

Data were excluded from two control participants due to MoCA scores below threshold and one participant in the visual metronome task because of poor quality eye-tracking. Statistical analyses were conducted on 7 PD patients and 20 control participants. Four variables (SRT, %PS, amplitude, and velocity) were analyzed across 6 ISIs (500 ms, 750 ms, 1000 ms, 1250 ms, 1500 ms, random), creating a total of 24 dependent variables. The Shapiro-Wilks test for normality was passed by 22/24 dependent variables in PD-OFF, 24/24 dependent variables in PD-ON, 20/24 in CTRL Visit 1 (V1) and 20/24 in CTRL Visit 2 (V2). Mixed design ANOVAs were conducted to compare PD-OFF vs CTRL (between-subjects factor: Group, within-subject factor: ISI). Two-way repeated measures ANOVAs were conducted to compare PD-OFF vs PD-ON (within subjects factors: ISI and medication state). Where the test of sphericity was violated, the corrected Greenhouse-Geisser F-value was reported.

Task metrics

SRT

Figure 2A demonstrates the cumulative distribution frequencies for SRTs during the 750 ms and 1500 ms trials of the metronome task and the random task (the extremes of ISI, the 500 ms condition was too difficult for all groups).

For PD-OFF vs CTRL, group did not have a significant impact on SRT ($F[1, 24] = 1.129$, $p = 0.299$) and there was no significant interaction effect between ISI and group on SRT ($F[2.750, 66.002] = 1.230$, $p = 0.305$, Greenhouse-Geisser). For PD-OFF vs PD-ON, SRT did not significantly vary for different medication states ($F[1, 5] = 0.168$, $p = 0.699$), nor was there a significant interaction effect between ISI and medication state on SRT ($F[5, 2]) = 1.137$, $p = 0.367$).

In summary, presence of disease does not significantly impact SRT, nor does medication state within the PD group.

Percentage of Predictive Saccades

Figure 2B demonstrates the percentage of each saccade type (predictive, express, or reactive) generated across the same trials. For all groups, as ISI increased, the %PS decreased while the percentage of reactive saccades increased, with the random task having the lowest %PS, providing a significant main effect of %PS across the different ISI when comparing PD-OFF vs CTRL ($F[2.831, 67.936] = 17.092$, $p < 0.001$, Greenhouse-Geiser) and PD-OFF vs PD-ON ($F[5, 25] = 4.219$, $p = 0.006$).

When comparing PD OFF vs CTRL, there was no significant main effect of group on %PS ($F[1, 24] = 0.049$, $p = 0.828$). PD medication state did not have a significant main effect on %PS ($F[1, 5] = 0.037$, $p = 0.855$). Although the trend of ISI was consistent across group comparisons, the %PS generated in the metronome and random task does not significantly vary with group or medication state of PD patients.

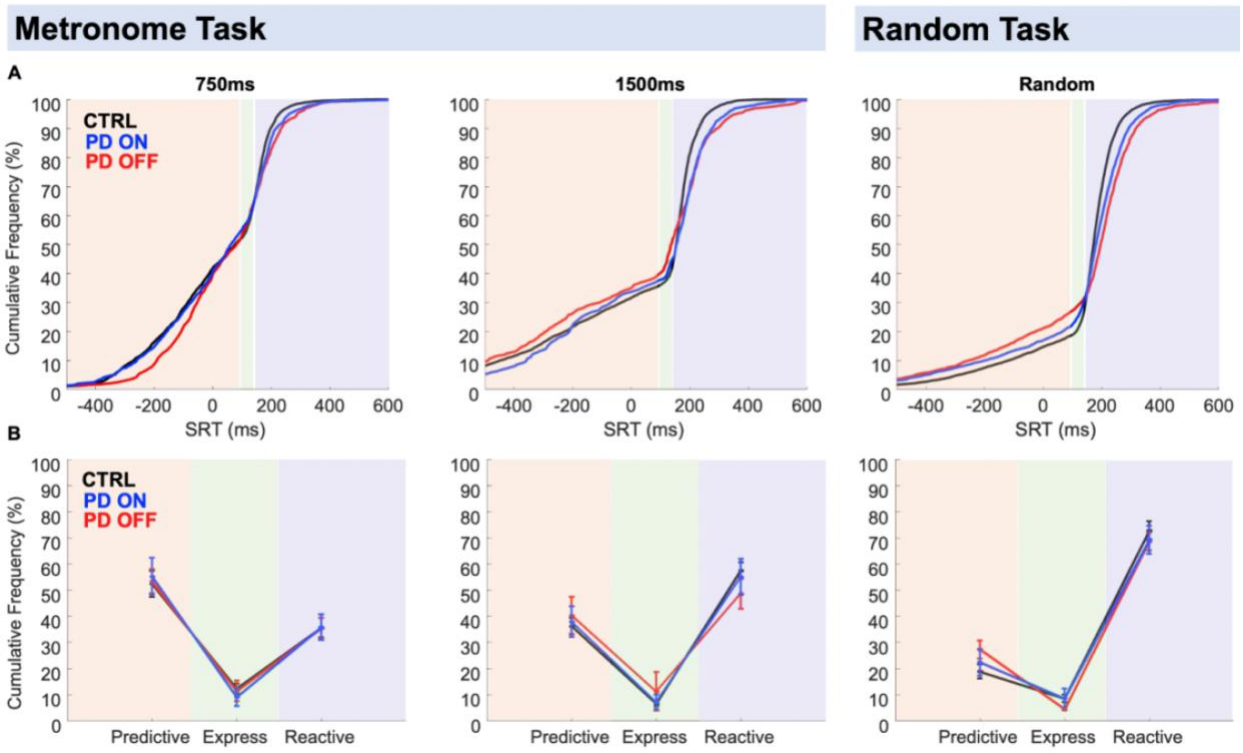

Figure 2. Cumulative distribution frequency of saccade reaction times for controls and PD patients ON/OFF medication. **(A)** Cumulative distribution for SRTs for CTRL group, PD patients on medication (PD ON), and PD patients off medication (PD OFF), during the Metronome task at 750 ms and 1500 ms and the Random task. **(B)** Cumulative frequency by saccade type (predictive, express, or reactive) during the three task variations for CTRL, PD ON, and PD OFF.

Amplitude

There was no significant ISI x group interaction for amplitude ($F[3.307, 79.362] = 1.783$, $p = 0.152$) when comparing PD OFF vs CTRL. Similarly, there was no significant ISI x medication state interaction for amplitude ($F[5, 25] = 0.523$, $p = 0.757$) when comparing PD OFF vs PD ON. Interestingly, the median saccade amplitude of CTRL was greater than that of PD-OFF across all task variations (Figure 3), however this was not statistically significant ($F[1, 24] = 3.107$, $p = 0.091$). Considering that the p-value for this test is approaching .05, perhaps with a larger sample of PD-OFF, this difference would be significant. Finally, amplitude did not significantly vary for different PD medication states ($F[1, 5] = 0.329$, $p = 0.591$). However, by examining Figure 3, it can be seen that medication may improve PD patients' saccade amplitude when generating predictive saccades with a reduced ISI (750 ms trial) or reactive saccades (in the random task).

Additionally, PD patients generated many "multi-stepping" saccades (MSS) (Figure 4), compared to CTRL that generated very few. Overall PD patients had greater variability in saccade amplitude which can be reflected in the higher standard deviations (SD) (± 1.09-1.52°)

compared to controls (± 0.34-0.51°) observed across ISIs. However, it is important to note that SD could also be impacted by the different sample sizes of PD and CTRL.

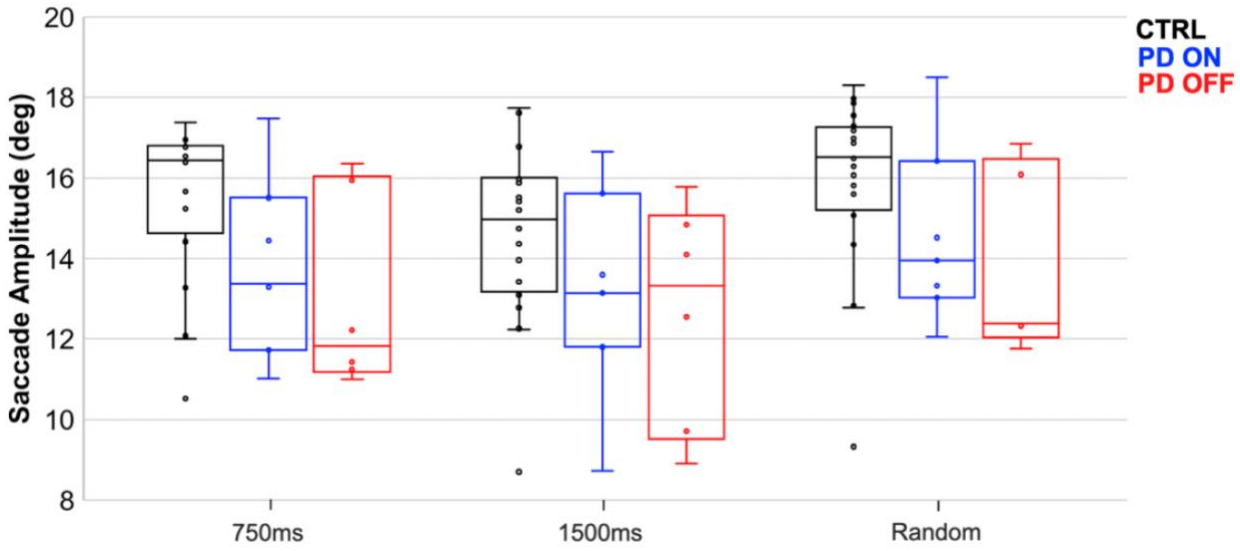

Figure 3. Saccade amplitude for controls and PD patients ON/OFF medication. Box plot comparing saccade amplitude between CTRL, PD ON, and PD OFF groups for the Metronome task at 750 ms and 1500 ms and the Random task.

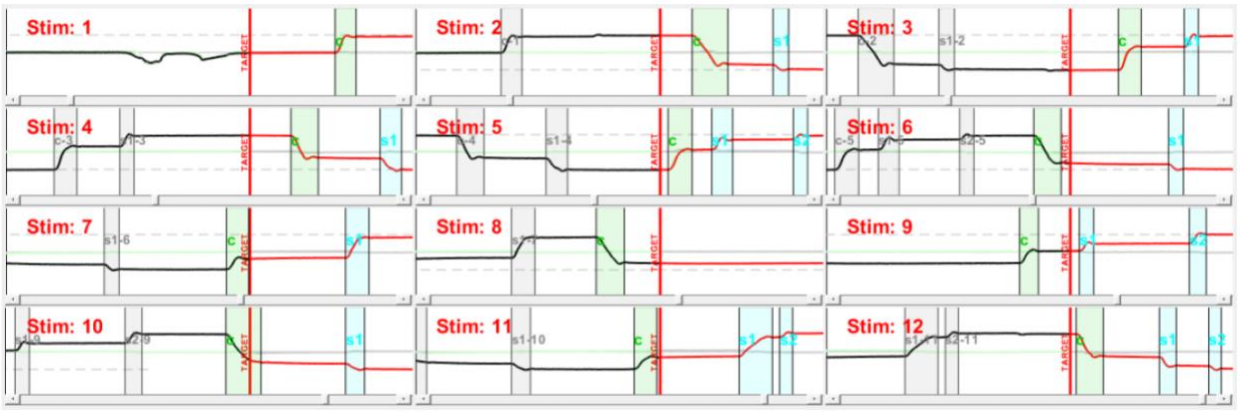

Figure 4. Multi-stepping saccades in PD patients. Sample data trace from a PD patient OFF medication completing the 750 ms variation of the metronome task. The red line indicates stimulus appearance for each target step of the trial. C (green) marks "correct" initial saccades, while S (blue) indicates additional "step" saccades. Grey blocks are used to mark the saccade(s) from the previous stimulus.

Peak Velocity

Statistical analysis comparing groups revealed similar results for saccade peak velocity as other saccade metrics. When comparing PD-OFF vs CTRL, there was no significant main effect of group ($F[1, 24] = 2.531$, $p = 0.125$), nor any interaction effects of group x ISI ($F[2.227, 53.449] = 0.786$, $p = 0.473$, Greenhouse-Geiser) on peak velocity. PD medication state also did not have a significant main effect on peak velocity ($F[1, 5] = 0.029$, $p = 0.871$), nor was there any interaction effect of medication state x ISI on peak velocity ($F[5, 25] = 0.899$, $p = 0.497$).

Although saccade amplitude and peak velocity did not significantly differ between PD-OFF and CTRL, Figure 5 demonstrates descriptively how the saccade amplitude-velocity relationship is altered in PD. For both predictive and reactive saccades, PD-OFF demonstrated a greater spread of saccade amplitudes, and PD-OFF typically generated predictive and reactive saccades with a reduced velocity compared to CTRL for a given amplitude. Furthermore, within both groups, saccade amplitude was lower for PS than reactive saccades.

Square root model fits were derived using these raw data points to estimate the main sequence of each group's predictive, express, and regular saccades across the five target rates in the metronome task (Figure 6). Although there is no clear medication effect for the PD group model fits, both PD groups consistently generated saccades with a reduced amplitude for a given velocity compared to CTRL for predictive, express, and reactive saccades.

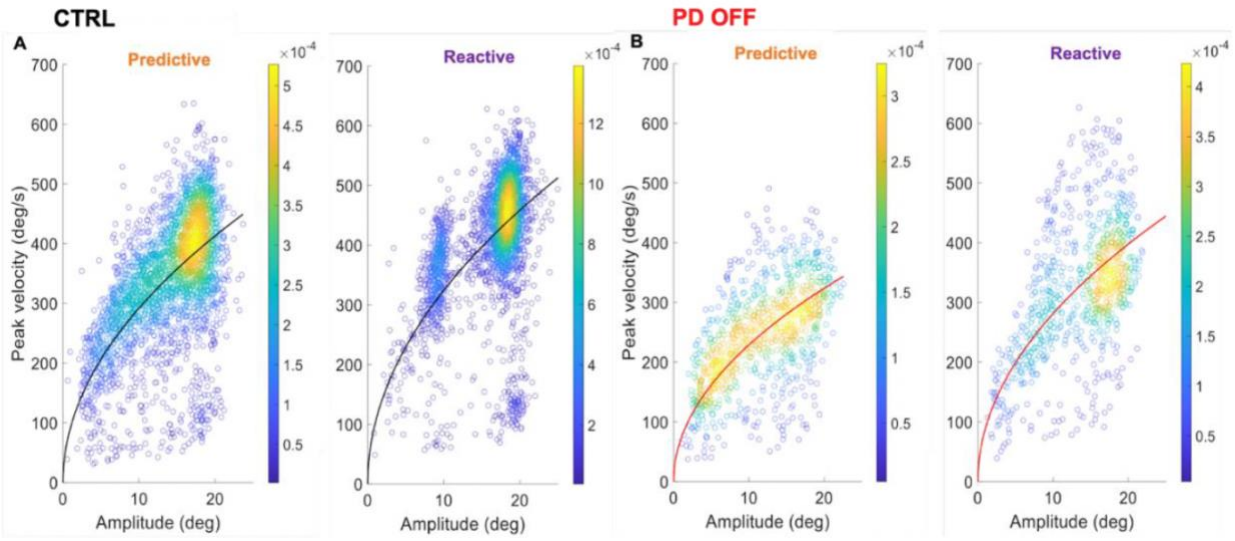

Figure 5. Saccade peak velocity vs. amplitude for predictive and reactive saccades in controls and PD Patients OFF medication. Raw data points of saccadic peak velocity and amplitude are shown for predictive and reactive saccades made by **(A)** CTRL and **(B)** PD-OFF across the five target rates in the metronome task. These were used to calculate the main sequence model fits for each plot. A kernel density estimate was applied to the scatterplot data to visualize the density of the data points, with warmer colours indicating increased density.

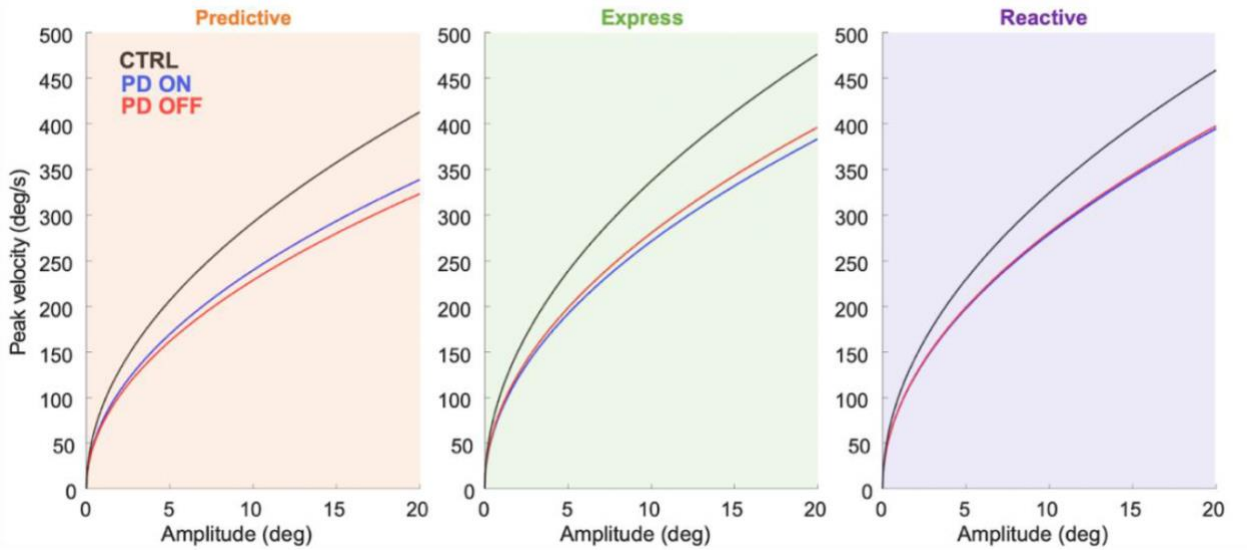

Figure 6. Main sequence of predictive, express, and reactive saccades made by PD patients ON/OFF medication and controls. Square root model was fit to estimate the main sequence of predictive, express, and reactive saccades made by CTRL, PD ON, and PD OFF subjects across the five target rates in the Metronome task.

Motor impairment and disease duration

Correlations were computed between the PD-OFF saccade parameters (SRT, %PS, amplitude and velocity) and UPDRS-III score across the 6 ISI variations. Correlations were replicated for saccade parameters and disease duration.

No significant correlations were observed among the four saccade parameters across target frequencies and UPDRS-III (range of ρ values: 0.03–0.62). Similarly, no relationship was observed between the four saccade parameters across target frequencies and disease duration (range of ρ values: 0.002–0.50). This could be due to limited sample size of PD patients that came in OFF medication (n = 7). Although not significant, there was a moderate, negative correlation observed between saccade amplitude and UPDRS-III, especially in the 750 ms trial and random task (Figure 7).

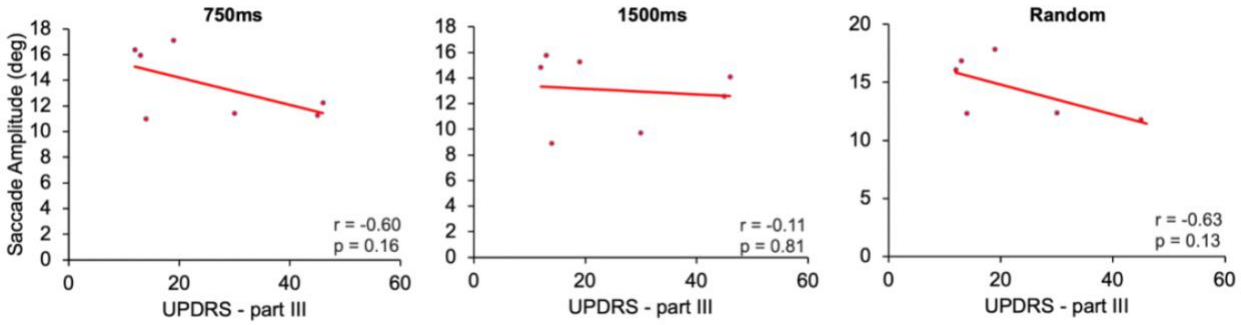

Figure 7. Correlations of PD OFF Saccade Amplitude with UPDRS-III for Each Task Condition

Learning effects

Two-way repeated measures ANOVAs were conducted to compare CTRL V1 vs CTRL V2 (within subjects factors: ISI and visit). There was no statistically significant difference between visits 1 and 2 for SRT ($F[1, 8] = 4.672$, $p = 0.063$), %PS ($F[1, 8] = 4.638$, $p = 0.063$), and peak velocity ($F[1, 8] = 1.330$, $p = 0.282$). Saccade amplitude significantly varied between the two visits ($F[1, 8] = 9.045$, $p = 0.017$), indicating a potential learning effect of visit number on amplitude that could impact PD OFF vs CTRL comparisons.

Discussion

The present study investigated temporal saccade prediction in PD patients with the objective of contrasting their task performance with controls. Furthermore, it aimed to determine the impact of PD medication on prediction and associations between performance and motor symptoms. SRT and %PS did not vary between groups, however PD patients generated hypometric MSS with reduced velocity compared to CTRL. Hypometria (but not other saccade metrics) was moderately correlated with greater disease severity. The implications of these findings will be analyzed in relation to their potential use in future eye tracking approaches, which could have diagnostic significance for PD. This paper summarizes the preliminary findings of this study. As recruitment continues, trends discussed here will become further elucidated.

SRT and predictive saccade performance

PD patients had similar SRTs and ability to generate PS compared to healthy controls, which was consistent across medication states. This is supported by studies investigating PS in PD that have not found group differences in saccade latency or in the ability to implement a predictive eye movement strategy (30,31,42). However, it has been reported that PD patients produce fewer PS in response to a predictable stimulus sequence, and instead make more visually triggered, reactive saccades following target appearance (24). Another study indicated that PD patients did

eventually begin launching PS to align their focus with target appearance, but compared to controls, they were slower to begin using this strategy (27).

Increased latency of visually-triggered saccades in PD is most commonly attributed to increased inhibition of the SC by the substantia nigra pars reticulata producing oculomotor bradykinesia/akinesia (14,19,43). Those that have found comparable or reduced SRT in PD have proposed other theories for neurological deficits that may lead to reduced inhibitory control or a potential adaptive mechanism that patients develop to cope with their disability (15,43).

Chan et al. found that in a pro- and anti-saccade task, PD patients were less able to inhibit reflexive saccades to the target, even when instructed to (15). The voluntary saccade system inhibits the generation of reflexive saccades, therefore a defective system in PD could induce more hyper-reflexiveness (44). Saccadic eye movements that occur before target appearance could be caused by either a similar lack of inhibitory control, evoking a 'premature' saccade, or by a genuine attempt to predict the target appearance, evoking a true PS (43). Multiple studies have suggested that dysfunctional BG and cortical inputs in PD may lead to increased excitability of SC neurons that trigger saccades or that general attention deficits may contribute to these premature responses (45-48).

In this study, the potential impulsivity of PD patients' saccades may mask their inability to generate adaptive PS, giving the appearance that their SRT and %PS is no different from controls. Future research examining PS tasks should incorporate an element of design that differentiates oculomotor impulsivity from prediction (43).

Saccade amplitude and multi-step saccades

PD patients tended to make hypometric MSS across each task variation compared to controls. This hypometria, which was exacerbated in predictive conditions, is consistent with previous studies examining a PS task (24,27,31). Hypometric saccades have been widely reported in PD (15,17). It is suggested that hypometric voluntary saccades occur in PD due to increased inhibition of the SC and reduced preoculomotor drive due to dysfunction of frontal cortex-BG-SC circuits (49,50). Alternatively, hypometria may result due to hyperactivation of the cerebellum in PD (23).

Due to PD patients' saccade hypometria, they frequently generated corrective MSS to reach the final target position. These MSS were also seen in CTRL, but were more prominent in the PD group, regardless of medication state. MSS in PD and primate models have been reported in other studies as well (51-53). Fragmentation of gaze shifts may reflect inappropriate inhibition of the saccade generator, the SC, and improper reactivation of omnipause neurons between steps (54,55). Alternatively, they may be a consequence of saccade hypometria (49). Although trends in SRT and predictive ability are less clear in PD, amplitude and abnormal fragmentation of saccades may be a more robust saccade metric to consider in future saccadic eye-tracking paradigms.

Saccadic peak velocity and amplitude relationship

The main sequence describes the relationship between saccade amplitude and peak velocity (56). This relationship is typically logarithmic: peak saccade velocity increases with increasing saccade amplitude but then saturates with larger saccades. The prevailing belief is that the main sequence optimizes the trade-off between speed and accuracy of saccades for a particular amplitude (56-58).

This study's results indicated that for a given amplitude PD patients generated saccades with a reduced velocity, however they generated saccades with a much greater spread of amplitudes compared to controls. These findings are contrary to those of recent studies investigating saccadic eye movements in PD that demonstrated an insignificant difference between PD patients and controls main sequence linear fit (59,60). However, Fooken et al. does support the observed variability in PD patient's saccade amplitudes and velocities across trials (60). These studies used different tasks to measure reactive saccade performance (Fooken et al. using a pro- and anti-saccade task and Habibi et al. using a "Free Viewing" video clip task), which could explain the present study's contradictory findings, as the predictive saccade task would require additional cognitive function for timing and planning (which may be impaired in PD). If differences in main sequence between PD patients and CTRL are indeed true, they may provide an added dimension of biomarker potential for predictive saccade-based eye tracking tasks.

Medication effects and disease progression

Overall, no significant differences between PD patients ON and OFF dopaminergic medication were identified. Mild improvement in saccadic amplitude was seen with medication (not to a significant level), a result supported by Rascol et al. (61). Several studies have found that dopaminergic treatment does not improve saccadic parameters such as latency, amplitude, and accuracy (16,62,63). This finding may carry significant implications, as it suggests that individuals with PD may not need to forego doses of their medication when completing eye-tracking assessments. Such an outcome would augment the viability of eye-tracking as a diagnostic tool, while also ensuring that PD patients do not suffer from any unwanted side effects resulting from medication withdrawal.

There were no significant correlations between saccade metrics and motor impairment (UPDRS-III) or disease duration. This is contradictory to previous studies that have shown SRT to be positively associated with UPDRS-III (64). Importantly, there was a moderate negative correlation observed between saccade amplitude and UPDRS-III. Therefore, as gross motor impairment increased, PD patients generated more hypometric saccades. Habibi et al. found that, in a sample of 27 PD patients, saccade frequency and average amplitude were significantly negatively correlated with UPDRS-III (59). Therefore, with more participants, this potential trend in amplitude could be verified.

Limitations and future directions

The primary limitation of this study was that it was not sufficiently powered, which may limit the validity of these observations. CTRL had a mean age that was 10 years lower than PD and was 70% female. As recruitment continues for PD and CTRL, age and gender will be properly balanced.

Additionally, PD patients were limited to relatively early stages of PD (see Table 1 for H&Y scores), where differences in saccade performance and disease status may not be as apparent. PD patients that were recruited had little to no cognitive impairment, therefore it is uncertain how those with more severe impairment or dementia may be able to perform eye tracking tasks. By recruiting more PD participants with a greater range of disease severity, trends in abnormal PS performance may be more prominent.

Conclusion

In summary, our findings support the use of saccade tasks to assess the neural basis of motor control deficits in PD. Nonetheless, more research is needed to distinguish particular saccade characteristics that are sufficiently sensitive and specific to predict PD and their relation to current clinical scores.

Author Biographies

MKB: Currently in medical school at McMaster University, Hamilton, Canada and completed an undergraduate degree (BScH) at Queen's University, Kingston, Canada. Helped conceive the study, conducted study visits, analyzed data, and wrote the manuscript.
SS: Currently in neurology residency at Queen's University, Kingston, Canada. Helped conceive the study, recruit and assess study patients.
OC: Currently in medical school at Queen's University, Kingston, Canada and completed a PhD in 2023 focused on eye tracking in psychiatric disease. Helped conceive the predictive task and developed the data analysis algorithms.
DCB: Data analyst with 20 years of experience in programming eye trackers, data analysis algorithms, and developing behavioural eye tracking tasks. Programmed the predictive task on the EyeLink 1000 eye tracker.
BCC: Research scientist with 30 years of experience in eye tracking. Developed the pre-processing pipeline for analysis of saccade metrics in the predictive task.
DPM: Senior professor with over 40 years of experience in eye tracking. Helped conceive the study, interpret the data analysis and draft the manuscript.

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