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Virginia Commonwealth University

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DEVELOPMENT OF AN EYE MOVEMENT BASED PREDICTIVE MODEL FOR DISCRIMINATION OF PARKINSON'S DISEASE FROM OTHER PARKINSONISMS AND CONTROLS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Biomedical Engineering at Virginia Commonwealth University.

By

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I would like to thank the Michael J. Fox Foundation for the financial support to complete this study. Their ongoing commitment to supporting research to further the understanding of Parkinson's Disease made this, and many other studies, possible.

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This study was orchestrated by Dr. Mark Baron, who helped keep us on track and was always available to answer questions.

And of course, I would like to thank my parents for their unwavering moral support. And my dog for his ability to convince me to get out of the house and go for a walk even when it feels like I am tied to my desk.

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Table of Contents

www.manaraa.com

www.manaraa.com

List of Tables

www.manaraa.com

List of Figures

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List of Acronyms

Acronym	Definition	Acronym	Definition
BG	Basal Ganglia	PEF	Posterior Eye Field
ACC	Anterior Cingulate Cortex	PRE	Predictive
ANOVA	Analysis of Variance	PSP	Progressive Supranuclear Palsy
ANT	Antisaccadic	RBD	REM Sleep Behavior Disorder
CAPSIT	Core Assessment Program for Surgical Intervention	REA	Reading
CBD	Corticobasal Degeneration	REM	Rapid Eye Movement
CEF	Cingulate Eye Field	RMS	Root Mean Squared
CNS	Central Nervous System	ROC	Receiver Operating Characteristic
DLB	Dementia with Lewy Bodies	SC	Superior Colliculus
DLPFC	Dorsolateral Prefrontal Cortex	SEF	Supplementary Eye Field
ET	Essential Tremor	SNpc	Substantia Nigra Pars Compacta
FEF	Frontal Eye Field	STN	Subthalamic Nucleus
HST	Horizontal Step	SWJ	Square Wave Jerk
MoCA	Montreal Cognitive Assessment	UMRBDQ	University of Michigan RBD Questionnaire
MSA	Multiple System Atrophy	UPDRS	Unified Parkinson's Disease Rating Scale
NDSQ	Nocturnal Sleep Disturbance Questionnaire	VCU	Virginia Commonwealth University
NPH	Normal Pressure Hydrocephalus	VP	Vascular Parkinsonism
PD	Parkinson's Disease	VST	Vertical Step

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Abstract

DEVELOPMENT OF AN EYE MOVEMENT BASED PREDICTIVE MODEL FOR DISCRIMINATION OF PARKINSON'S DISEASE FROM OTHER PARKINSONISMS AND CONTROLS

By: MARY ANISA KANNAN, BS, Biomedical Engineering VCU

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Biomedical Engineering at Virginia Commonwealth University.

Virginia Commonwealth University, 08/19/2019

Thesis Advisor: Paul A Wetzel, PhD

Department of Biomedical Engineering

Purpose: Due to the neurological aspects of Parkinson's Disease (PD) and the sensitivity of eye movements to neurological issues, eye tracking has the potential to be an objective biomarker with higher accuracy in diagnosis than current clinical standards. Currently when PD is diagnosed clinically, there is an accuracy of 74% when diagnosed by a general practitioner and 82% when diagnosed by a movement disorder specialist. This study was designed to: 1. Assess eye movements as a potential biomarker for Parkinson's Disease. 2. Determine if eye movements can distinguish between Parkinson's Disease and commonly confounded movement disorders with parkinsonian symptoms. 3. Determine if the eye movements of Rapid Eye Movement Behavior Disorder (RBD) patients who will likely convert to PD are distinguishable from healthy controls and if RBD patients have eye movements with similar features to PD.

Methods: The eye movements of 160 subjects (43 healthy controls, 63 PD, 31 REM Behavior Disorder, and 22 Other Parkinsonisms) were recorded at 500 Hz and analyzed. Each subject performed five eye tracking tasks that included reflexive saccades, inhibition of reflexive saccades, predictive saccades, and reading. Based on an analysis of selected eye movement measurement parameters, a multivariable logistic regression model was developed that compared: PD vs. Control, PD vs. "Other", PD vs RBD, and Control vs RBD. The resulting predictive model was then assessed for accuracy, sensitivity, and specificity.

Results: After screening, the most statistically significant predictors that were included in the final multivariate model were: Site, Sex, Age, Age squared, UPDRS Score, mean absolute fixation velocity (Horizontal Step Task), saccadic duration, average saccadic velocity, and mean fixation velocity (Predictive Task). The model predicted with an accuracy of: 92% for Controls, 88% for PD, 86% for RBD, and 68% for Other Parkinsonisms. The model was best at distinguishing between PD and Other Parkinsomisms with an accuracy of 89% and RBD and Controls with an accuracy of 88%.

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Conclusion: This research found that specific combinations of eye tracking parameters from simple tasks can be used to distinguish between PD and commonly confounded movement disorders with parkinsonism symptoms. The model's ability to distinguish between groups indicates that in a confirmatory study we should have relatively high accuracy in discriminating between groups. This model is able to accurately distinguish Controls from RBDs, however due to an insufficient number of follow-up visits to date, the current study is unable to confirm if the RBDs tested will convert to PD. With such high error rates in diagnosing PD clinically, this model is a potentially beneficial and could serve as an easy screening tool to add to the suite of diagnostic tests and improve clinician's ability to diagnose accurately.

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Introduction

1.1 Summary of Parkinson's and Other Parkinsonisms

Parkinson's Disease is a slow, neurodegenerative disease that often begins years before the symptoms can be recognized and a diagnosis can be made (Kalia & Yang, 2015). Likelihood of diagnosis increases substantially with age, with reported occurrences between 1,400/100,000 in ages 55 to 64 and 4,300/100,000 in ages 85 to 94 (Simuni & Pahwa, 2009). During PD, dopaminergic neurons in the substantia nigra pars compacta (SNpc) die. This leads to reduced dopamine in the basal ganglia (BG) which triggers a wide range of motor symptoms, including tremor and a slow shuffling gait. PD is also associated with a variety of non-motor symptoms such as cognitive impairment, sleep disorders, and fatigue, all of which substantially impact quality of life. During the prodromal period, if PD can be identified before the motor symptoms begin, there is potential for introducing therapy at the most opportune time, to delay or even prevent further neurodegeneration (Kalia & Yang, 2015).

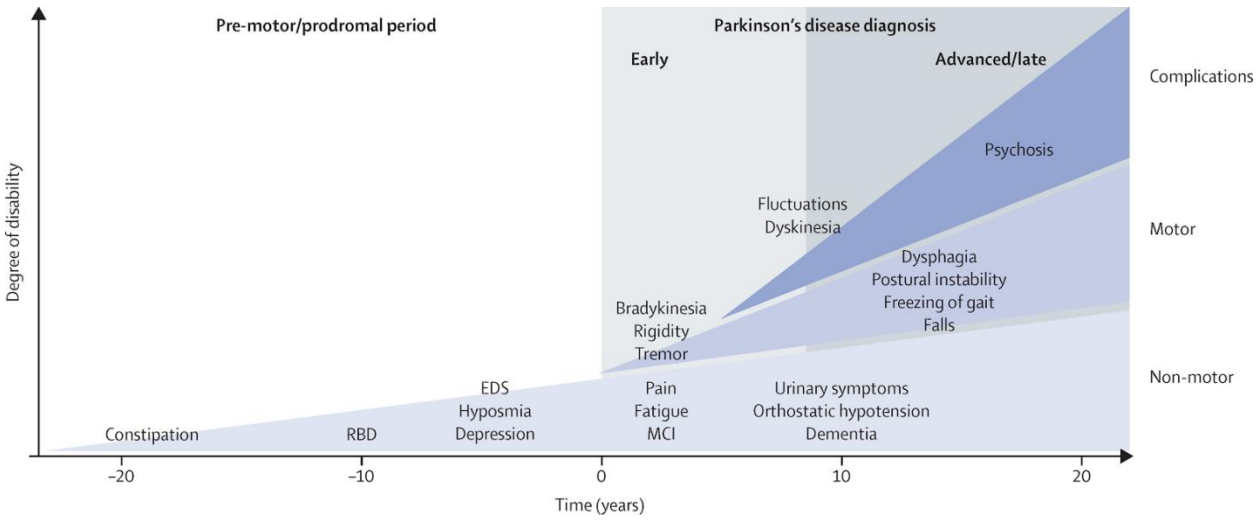

Figure 1: Timeline of PD Diagnosis (Kalia &Yang, 2015)

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by sleep disturbances. It occurs most often in men, Olson et al., 2000 reported seeing it occur in men 87% of the time, with an average onset age of 61. Most commonly reported was a lack of atonia in REM sleep, or the paralysis that usually occurs during REM sleep doesn't occur; leading to motor enactment of dreams that often result in sleep related injuries to both patients and their

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sleeping partners. These can include talking, shouting, grabbing, punching, kicking, and falling out of bed during dream enactment (Tekriwal et al., 2016, Kalia & Yang, 2015). Findings have varied: Postuma, et al., 2015, reported that patients who present with RBD have a 30% chance of developing PD within 3 years of diagnosis and a 66% chance at 7.5 years. Iranzo et al., 2013 found that out of the 44 patients, 36 developed a neurodegenerative disease, including PD, dementia with Lewy Bodies (DLB), multiple system atrophy (MSA), and mild cognitive impairment. In a larger study Iranzo et al., 2014 reported that almost 91% of 174 patients with RBD developed a neurodegenerative syndrome within 14 years. However, the likelihood of development of PD specifically is generally reported to be closer to 40-75% within 10 years of RBD diagnosis (Iranzo et al., 2013, Postuma, et al., 2015, Iranzo et al., 2014, Fereshtehnejad et al., 2017).

1.2 Accuracy and Difficulty of Parkinson's Diagnosis

The only gold standard of diagnosis is a post-mortem pathological examination of the SNpc to look for Lewy body aggregates and de-pigmentation. Multiple studies have been done using post-mortem examinations to confirm diagnosis made in a clinical setting. An overall accuracy of about 74% correct for diagnosis by non-experts (Rizzo et al., 2016) and about 82% for diagnosis by a movement disorder expert (Hughes et al., 1992, Schrag et al., 2002, Rizzo et al., 2016). Overall accuracy of diagnosis has not improved in the past 25 years and no subjective method of diagnosis has proven to be any more accurate.

Parkinson's Disease is commonly misdiagnosed, especially in the early stages, for many other diseases that also have tremor or parkinsonism. These are most often essential tremor (ET), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), normal pressure hydrocephalus (NPH), and vascular parkinsonism (VP) (Rizzo, et al., 2016). Mixed pathologies, overlapping symptoms, lack of a biomarker, and no objective measurements have made it very difficult to diagnose PD accurately and to distinguish it from the other parkinsonisms.

Currently PD is diagnosed using clinical observations. The Unified Parkinson's Disease Rating Scale (UPDRS) is used to track progression of symptoms and allows for some objectivity when looking at symptoms, each motor symptoms is scored, and a final score is tallied. The downside

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is that the scores are still assigned subjectively by clinicians based on a short clinic visit and patient-reported information. Progression of dementia, which is a common neurological effect later in the disease, is tracked and scored commonly with such scales as the Montreal Cognitive Assessment (MoCA). The motor portion of the Core Assessment Program for Surgical Intervention (CAPSIT) is standardly done in order to assess PD patient's suitability for deep brain stimulation implants. This involves a motor task that is commonly used as a more objective rating system for PD patient's motor impairment.

1.3 Eye Movement Basics

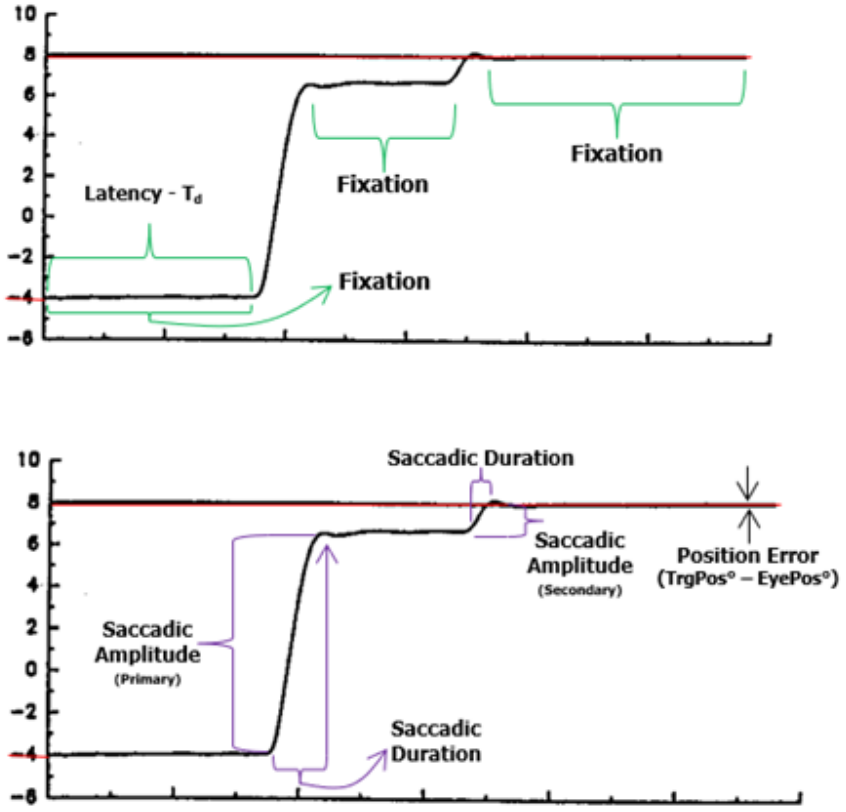

Figure 2: Example of a Saccadic eye movement in response to a step change in target position (with permission from Paul A. Wetzel, PhD)

Eye movements allow us to gather visual information about the world. They also offer deep insights into neurological functioning due to the vast amount of distinct neural pathways needed to perform even simple eye movements. This gateway into brain function can be exploited by recording eye movement responses to different stimuli and analyzing the responses. There are

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two main types of eye movements that can be made in response to a stimuli: saccadic and smooth pursuit.

Saccades are made in response to the position error between the fovea and the target. Humans are limited to about 4 to 5 saccades per second and the reaction time to a change in target position is between 150 to 280 milliseconds. This varies based on amplitude or movement, predictability of the stimulus, attentional awareness, and fatigue. Saccades are involved in everyday tasks such as reading or during visual search (Leigh & Zee, 2015, Cuiffreda & Tannen, 1995). The velocity and acceleration of the saccade are dependent upon the angular distance travelled. They can be made voluntarily without the presence of a stimulus or reflexively in response to a stimulus and have differing cortical control structures (Pierrot et al., 2004).

In the cortex, voluntary or internally triggered saccades, are prepared and triggered by the frontal eye field (FEF) (Figure 2), these types of saccades include predictive saccades and antisaccades. Antisaccades are triggered by first inhibiting the reflexive saccade towards a target, and then triggering a voluntary saccade away from the target. The inhibition of the reflexive saccade uses the dorsolateral prefrontal cortex (DLPFC), where the triggering of the prosaccade uses the frontal eye field (FEF). The response is prepared by the anterior cingulate cortex (ACC) or the cingulate eye field (CEF). The supplementary eye field (SEF) becomes involved in the planning of a sequence saccades (Pierrot et al., 2004). The reflexive saccade, or prosaccade, pathway is distinct from voluntary saccades. It is initiated by the posterior eye field (PEF), assuming a rapid response is required. However, if there is a delayed response, the signal goes through the PEF to the FEF and the DLPFC which is involved in the short-term memory needed to complete the task (Pierrot et al., 2004).

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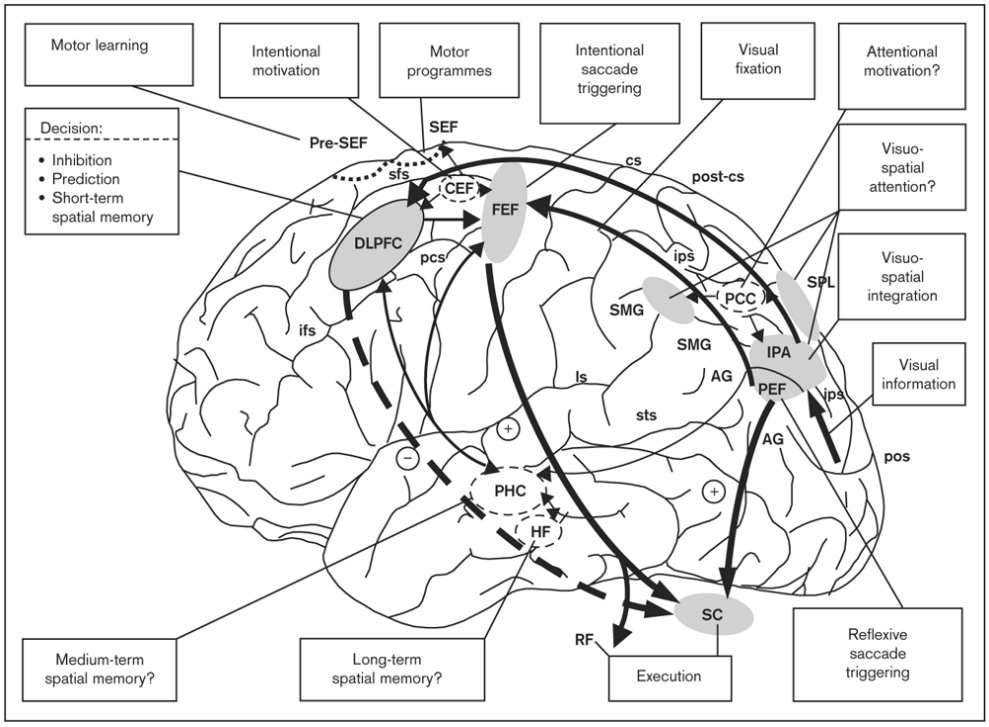

Figure 3: Cortical areas and pathways in saccadic control (Pierrot et al., 2004)

Subcortical structures also have important roles in saccade production. The superior colliculus (SC) acts as the main communication pathways between the retina and the brainstem; both the PEF and FEF pathways use the SC. The basal ganglia (BG) is involved in voluntary saccadic movements and is located on the FEF efferent pathway. Basal ganglia dysfunction is often seen in Parkinson's Disease (PD) because of the lack of dopamine. These effects are varied due to the slow progression of the disease and the brain's ability to develop compensatory methods as the disease state advances (Gaymard, 2012, Gaymard et al., 2016, Chan et al., 2005, Blekher et al., 2009, Matsumoto et al., 2011).

1.4 Eye Movements in Parkinson's

Due to the large amount of cortical and subcortical involvement in eye movements, they can be an indicator of neural functioning in PD and other similar diseases. PD is caused by degeneration of dopaminergic neurons in the substantia nigra leading to a lack of dopamine in the striatum, which is composed of the putamen and the caudate nucleus. This lack of dopamine increases the inhibitory output to the SC and the thalamus. In the substantia nigra this leads to increased

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inhibition and in the subthalamic nucleus (STN) it leads to increased excitation. (Srivastava et al., 2014) All of these affect the saccadic system and therefore can offer insight into PD progression (Turcano, et al., 2018).

Reflexive saccades have been tested in PD subjects with varying results and findings. Some findings show no significant differences in reflexive saccades between PDs and Controls (Briand et al., 1999, Mosimann et al., 2005, Wang et al., 2016, Bhidayasiri et al., 2001 van Koningsbruggen et al., 2009). While others report hypometria, or small saccades that fall short of the intended target, in PD subjects along with changes in the latency of response (Mosimann et al., 2005, Hood et al., 2007, Antoniades et al., 2007, Terao et al., 2011, Van Stockum et al., 2011, Macaskill et al., 2012). Other effects in reflexive saccades due to Parkinson's have been reported as well: disconjugate movements being higher in PD (Versino et al., 2009), differences in reaction time based on the eccentricity of the stimuli (Chambers & Prescott, 2010), and making more express saccades (Chan et al., 2005). Express saccades are a type of reflexive saccade with extremely short latency periods in response to gap stimuli. During an unpredictable smooth pursuit task, Nakamura, et al., 1991, reported seeing slowed latencies and decreased saccadic velocity compared to controls in most of the subjects. There is a consensus that some differences may be present but small sample sizes and varying methodology make it difficult to pinpoint exact changes in reflexive saccades.

The inability to inhibit reflexive saccades is also commonly reported. This task is referred to as anti-saccadic task where subjects are asked to look the opposite direction of the presented stimulus. Most findings report an increase in latency, higher error rates, and lower gain in Parkinson's subjects (Kitagawa et al., 1994, Briand et al., 1999, Chan et al., 2005, Mosimann et al., 2005, Hood et al., 2007, van Koningsbruggen et al., 2009). Notably, some studies showed no differences in error rates or reaction times during anti-saccadic tasks (Lueck et al., 1990, Rivaud-Pechoux et al., 2006, Wang et al., 2016, Ouerfelli-Ethier et al., 2018). Another interesting finding by Cameron et al., 2010, was that when switching between pro and anti-saccade tasks, PD performed better than controls switching from anti to pro, but worse in the opposite direction.

Parkinson's disease subjects have long reported difficulty reading (Archibald et al., 2011) but few studies have been done to record the eye movements of PD subjects during reading

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(Waldthaler et al., 2018, Jehangir et al., 2018, Yu et al., 2016). In the largest of these studies, Jehangir et al. reported that the PD subjects read 20% slower than the controls on all of the reading tests. They found no correlation between reading speed and UPDRS or MoCA but there was a correlation with age and duration of the disease. The other major difficulty with reading as an eye tracking task is that it takes cognition as well as motor skills, so it is difficult to separate the effects of cognitive decline and motor function decline when only looking at a reading task.

There is an ongoing and unresolved debate over the presence of ocular tremor in PD. Our group, Gitchel et al. 2012, reported an ocular tremor present in PD subjects with an average frequency of 5.7 Hz. This led to a debate over whether the tremor was caused by actual eye movement or an artifact due to a combination of body tremor and the type of eye-tracker being used (Kaski et al.. 2013, Duval et al., 2013, Macaskill et al., 2013, Baron et al., 2013, Baron et al., 2014, Kaski & Bronstein, 2017). Though a large-scale study has yet to be implemented in order to specifically identify the source of the apparent ocular tremor, these oscillations are still visible in eye tracking recordings. While we do not investigate the presence of ocular tremor in this study, they are important to investigate due to their potential as an earlier biomarker of PD.

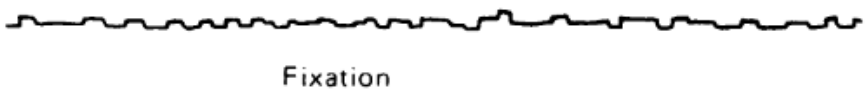

Figure 4: Example of Saccadic Intrusions during Fixation (Rascol et al., 1991)

Saccadic intrusions have also commonly been reported in PD, primarily the presence of square wave jerks (SWJs). SWJs are defined as saccadic intrusions which occur during fixation (Figure 4), they are typically very small amplitude saccades which bring the eyes away from the fixation point briefly. The results have been mixed; some studies report the presence and increased frequency and amplitude of SWJs with PD (Troost & Daroff, 1977, Averbuch-Heller et al., 1999, Shaikh et al., 2010) and our group reported no differences when compared to controls (Gitchel et al., 2012). Neurologically, the process by which the SWJs are occurring have only been hypothesized. Averbuch-Heller et al., reported increased SWJs with a pallidotomy in PD, and proposed that the imbalance of activity in the FEF and supplementary motor eye fields could

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cause an imbalance in the fixation area of the rostral and lead to increased SWJs. Generally, increased frequency of SWJs are attributed to cerebellar dysfunction (Gitchel, et al., 2013).

1.5 Eye Movements in Other Parkinsonisms

Some studies have been done to evaluate eye movements in other parkinsonism diseases with mixed results (Pinkhardt & Kassubek, 2011, Pretegiani & Optican, 2017). Troost & Daroff in 1977 reported seeing low pursuit gain and increased SWJs in PSP. It has also been reported that PSP shows slowed saccades (Rottach et al., 1996, Rivaud-Pechoux et al., 2001, Bhidayasiri et at., 2001, Garbutt et al., 2008). Rivaud-Pechoux et al., 2006 reported increased anti-saccadic rates in PSP. Pinnock et al., 2009 reported that patients with PSP showed larger saccadic intrusions during fixations than controls. However, none of these studies have had more than 10 PSP patients. Such small sample sizes make it difficult to draw definitive conclusions but the relative consistency between the studies shows potential for distinguishing between PSP and other disorders.

Very few studies have looked at eye movements in essential tremors. In our earlier study with 60 ET and 60 Control patients, Gitchel et al., in 2013 reported ET patients to have increased latencies in reflexive saccades and reduced peak velocities. They also reported an increase of SWJs. Another large study by Wójcik-Pędziwiatr et al. in 2016, reported dysmetria in reflexive saccades and increased saccadic latency correlated to the severity of the patient's tremor. Too few studies have been done investigating eye movements in ET to accurately represent the type of dysfunction that may be present.

MSA is sometimes included in larger studies of eye movements of multiple parkinsonisms but typically has small sample sizes and the results have been varied and contradictory. Rottach et al., 1996, reported that MSA showed hypometria and this was more prominent in vertical saccades. However, Bhidayasiri et al., 2001, reported lower velocity vertical saccades in MSA but only had 2 MSA subjects. Pinnock et al., 2009 reported MSA as having increased saccadic intrusion frequency during fixation. All of these studies are significantly limited by their sample size and none had more than 9 MSA subjects.

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Eye movements in CBD have also been studied but almost always as part of a larger study, so subject numbers are low. Many of the findings have been consistent in reporting an increased latency in saccades (Vidailhet et al., 1994, Rottach et al., 1996, Rivaud-Pechoux et al., 2000). Rivaud-Pechoux et al., 2006 showed that CBD and PD patients responded similarly in anti-saccadic tasks where they had higher error rates attempting to switch between pro and anti-saccades. Not enough research has been done in eye movements in other parkinsonism diseases which have the potential to be used as biomarkers for improved detection and sensitivity. While we are interested in NPH and Vascular PD, eye movements in these conditions have not been well studied or documented. A few studies note observing eye movements in these conditions but in such small numbers that nothing is statistically significant.

Objectives

Due to the neurological aspects of Parkinson's Disease and the sensitivity of eye movements to neurological issues, eye tracking has the potential to be an objective biomarker with higher accuracy in diagnosis than current clinical standards. This study was designed to:

i. Assess eye movements as a potential biomarker for Parkinson's Disease
ii. Determine if eye movements can distinguish between Parkinson's Disease and commonly confounded movement disorders with parkinsonism symptoms
iii. Determine whether REM behavior disorder results in eye movements that are distinguishable from healthy controls and if specific eye movements in RBD are predictive of development of Parkinson's Disease

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Methods

2.1 Study Design

Subjects with PD and other movement disorders including: ET, MSA, PSP, CBD, NPH, and VP, were recruited by movement disorder specialists at four sites: Emory University, University of Iowa, Virginia Commonwealth University, and the Hunter Holmes McGuire VA Medical Center. The specialists were instructed to recruit from their patients or other patients confirmed by a movement disorder specialist. to only recruit their own patients, and only patients for which they have a very high certainty of diagnosis. Investigators followed the accepted UK brain bank criteria for diagnosis of PD to include irrefutable and marked benefit from dopaminergic medications. Controls were recruited from spouses, relatives, and friends who came to the clinic with the patient. All patients with significant superimposed ophthalmic or neurological conditions were excluded as well as prisoners, pregnant women, and patients unable to read or speak English.

Subjects with RBD were recruited by sleep specialists. Patients presenting with a history of dream enactment required the following diagnostic criteria: 1) a score ≥ 0.30 on the University of Michigan RBD Questionnaire (UMRBDQ; Consens et al. 2005, Bliwise et al. 2014) and 2) American Academy of Sleep Medicine (AASM) nocturnal polysomnography (NPSG) RBD diagnostic consensus criteria. The Nocturnal Sleep Disturbance Questionnaire (NDSQ) was administered to all RBD subjects but was not used towards inclusion criteria. Subjects with superimposed conditions (including significant PTSD, sleep apnea, other nocturnal parasomnias, nocturnal epilepsy, neurodegenerative conditions or central nervous system (CNS) structural lesions) considered to pose a likely secondary causation for the RBD were excluded.

Subjects were administered the Montreal Cognitive Assessment (MoCA) for dementia screening, subjects with a M0CA score less than or equal to 16 were excluded. Medical history was taken including: age, sex, diagnosis, estimated disease duration, interval since diagnosis, names of current medications. Orthostatic BP was taken as well as a neurological exam to support or refute the diagnosis. The Unified Parkinson's Disease Rating Scale (UPDRS) Part III was completed and videotaped. The Core Assessment Program for Surgical Intervention (CAPSIT) timed tap and walking test, and the Grooved Pegboard Test to test hand dexterity were administered.

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2.2 Eye Tracking

The Eyelink II (SR Research, Ottawa, Ontario, Canada) was used to record eye movements of subjects during five different tasks. This video-based eye tracker was set to record binocularly at 500 Hz during each task using pupil tracking. According to the manufacturer, it has a 0.5º accuracy and a 0.01º resolution. All subjects were calibrated with the built-in 9-point calibration function, with 9 evenly spaced points on a 3x3 grid, followed by a validation sequence which rechecks the position error and confirms accurate calibration. Calibration and validation were re-administered before each new task and a drift correct sequence was employed in order to re-align any drifts in the calculation of the gaze position before recording began. Only calibrations with an acceptable level of error (>0.5º) or higher was accepted, and calibration was redone if there was high error. In order to minimize head movement during recording, an adjustable chin rest was used, and subjects were instructed to rest their head during recording. Stimuli were displayed on a BENQ, 27-inch diagonal, 1920H by 1200V pixel resolution LCD monitor. The monitor was refreshed at 120 Hz and positioned 70 cm from the subject's eyes. The visual target area was no greater than 20º horizontal and 15º vertical. Participants who were unable to calibrate were excluded form results.

2.3 Visual Tasks

The tasks were presented in the order of Horizontal Step (HST), Vertical Step (VST), Predictive (PRE), Antisaccadic (ANT), and Reading (REA).

- Horizontal and Vertical Step: Saccadic task. The target jumped horizontally (or vertically for VST) with a gap of 1 msec. This was randomized and unpredictable both temporally and spatially. Horizontal: mean step size 8.2º, minimum step size 1.0 º, maximum step size 17.8 º, mean duration 2042 msec, minimum duration 490ms, maximum duration 3230 msec, total time 63.3 seconds. Vertical: mean step size 7.8º, minimum step size 1.0 º, maximum step size 17.8 º, mean duration 2042 msec, minimum duration 490 msec, maximum duration 3230 msec, total time 61.3 seconds.
- Predictive: Saccadic Task. The target jumped horizontally in a predictable fashion for the first half of the task (from left to right, right to left, every 1 second with a jump of 20 degrees and a gap of 1 msec). Then the timing was varied slightly with each step for the

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second half, the shortest time was 700 msec and the longest was 1200 msec. The data was analyzed both as a whole and split between first and second halves.

- Antisaccadic: Inhibition of reflexive saccades. Subjects were given instructions to not follow the target when it moved to the right or left and instead to look the opposite direction, but match the distance that was moved. Target positions were: ±2°, ±7°, ±9°, ±12°, and ±17°, duration of each target was 1.7 seconds and 10 trials were given.
- Reading: Saccadic task. 10 texts with 10 lines of text each with roughly the same number of characters were presented. The reading texts presented were randomized from the Miller-Coleman passages (Miller & Coleman, 1967). Reading difficulties ranged from elementary to 12th grade levels. Subjects were asked to read each text and close their eyes when finished. The reading texts were presented at ±10^{o} horizontally from the center.

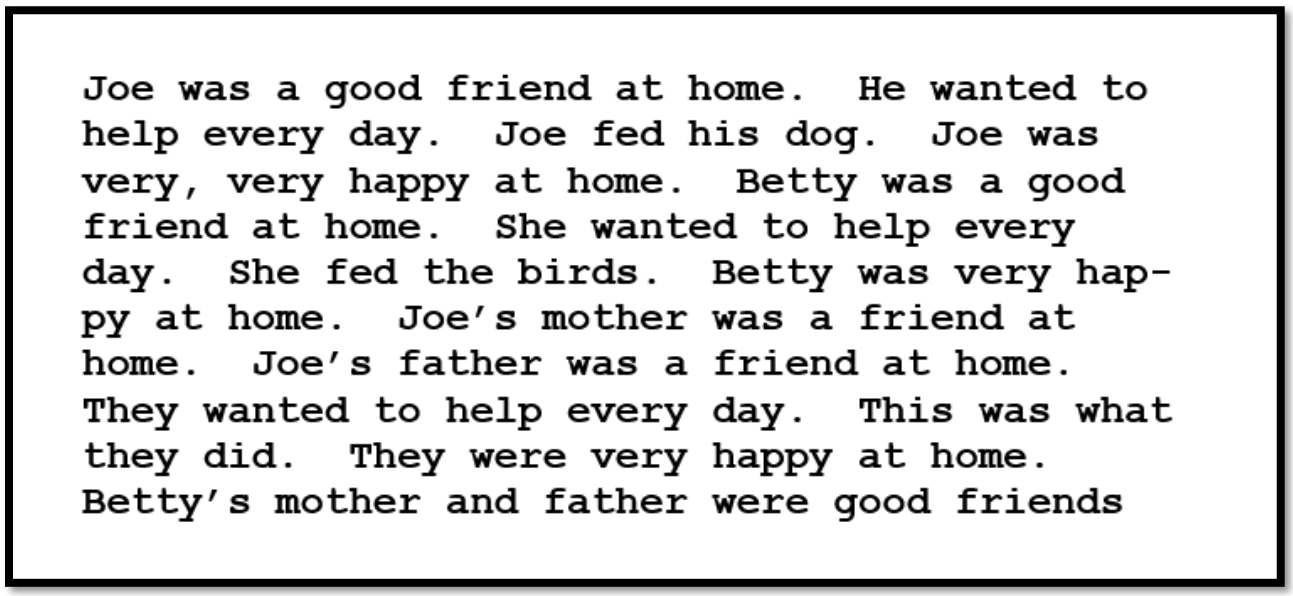

Figure 5: Miller-Coleman Example Text (elementary level) (Miler & Coleman, 1967)

The tasks were always given in the same order and the reading passages given were randomized based on the subject's study number based on a Latin Square Design. This ensured that on any given return visits, subjects would not read the same passages again.

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2.4 Data Processing

All eye movement data collected was extracted by a computer program developed by Dr. Paul Wetzel. The extraction program collected pixel coordinates and converted them to position angles for both the eyes and the stimuli. Blinks and other artifacts are identified by the program and incorporated into the files. All eye tracking files were visually inspected for quality before further automated analysis. In the case of artifacts not identified by the automated extraction, skip files were made manually. Portions of data that included blinks or other artifacts were excluded from the analysis.

The automated analysis program used the two-point central difference method to calculate the magnitude of direction, velocity and acceleration of the eye movements, both horizontally and vertically. Saccades were identified by using threshold values for velocity and acceleration of >15°/s and >400°/s^2. Peak velocities and accelerations were calculated from within the saccadic trajectory. Amplitude of saccades was calculated based on the eye positions during onset and ending of the saccade based on the velocity and acceleration. Saccades identified by the analysis program were visually inspected and confirmed. Stability during fixation was computed using the two-point central difference method for velocity and acceleration. Fixation was defined as times that were not saccades, blinks, or other artifacts. The root mean squared (RMS) during fixation was also computed as a measure of stability. Table 1 provides the full list of all parameters examined, as well as which task they were important for and the directions analyzed.

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Table 1: Eye Movement Parameters Examined

Eye Movement Parameter	ANT	HST	VST	PRE	REA	Horizontal	Vertical
Absolute Saccadic Amplitude							
Saccadic Duration							
Average Saccadic Velocity							
Absolute Peak Saccadic Velocity							
Absolute Peak Saccadic Acceleration							
Absolute Mean Saccadic Acceleration							
Mean Fixation Time							
Overall Root-Mean-Squared Velocity							
Average Root-Mean-Squared Velocity							
Mean Fixation Velocity							
Absolute Time Delay Latency							
Time Delay Lag							
Reading Overall Saccadic Amplitude							
Reading Regression Saccadic Amplitude							
Reading Forward Saccadic Amplitude							
Reading Average Saccadic Amplitude without Return Sweep							
Reading Average Regression Saccadic Amplitude							
Reading Average Forward Saccadic Amplitude							
Reading Primary Return Sweep Amplitude							
Reading Secondary Return Sweep Amplitude							
Reading Overall Fixation Duration							
Reading Regression Duration							
Reading Forward Saccadic Duration							
Reading Lines Read							
Reading Fixations Per Line							
Reading Regressions Per Line							
Left-Right Eye Correlation							
Right-Left Eye Correlation							
Hit latency							

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Hit percent							
Miss latency							
Number of hits							
Number of misses							

2.5 Statistical Methods

Statistical analyses were performed using SAS software (SAS version 9.4, JMP Pro version 14, SAS Institute Inc., Cary NC). Groups demographic and baseline clinical characteristics were compared using Chi-Square or ANOVA tests, as appropriate. The identification of eye movement parameters that discriminate between the four patient groups proceeded in four steps:

1. **Preexisting Differences** – Observing the differences between the four diagnosis groups that exist in the demographic and clinical parameters. Mean values were compared by ANOVA and then, if there was a difference between the groups, the differences were identified using Tukey's HSD (Honestly Significant Difference).
2. **Screening** – For each task group (i.e., ANT, HST, REA, VST, and PRE) and each eye movement parameter within the task, the parameters were screened using univariate ANOVAs. The ANOVA had to pass two criteria for a parameter to be considered for further analysis: An overall significant difference between the four groups ($P < 0.05$), and a significant difference between at least one of the four paired-group comparisons (using a Bonferroni-corrected $P < 0.05/4$ to account for multiple comparisons.).
3. **Multivariable Screening** –A multiple linear regression was performed using the 4-group diagnosis as a multinomial response and the following predictor variables: Sex, Age, and the eye movement parameters that pass the Step 2 screen. Sex and Age were assessed as variables to see if they should remain in the multivariable model. Determined which of the eye movement parameters are statistically significant in the multivariable model. In order to pass this Step 3 screen, the p-value cutoff was $P < 0.05$.
4. **Final Multivariable Model** – The non-significant parameters in the Step 3 were removed to arrive at a final multivariable logistic regression model, where the likelihood of being one or another diagnosis is modelled based on the value of the predictor. A final list of proposed parameters that could be used in a subsequent study for validation was generated. These parameters were used in four separate logistic regression models with

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the following binary responses: PD vs. Control, PD vs. “Other”, PD vs RBD, and Control vs RBD. That is, the first analysis only included the PD and Control participants (and the RBD and “Other” participants would be excluded). In these secondary analyses, it is anticipated that only a subset of parameters may prove useful and, using these, an ROC analysis determined an observed cutoff that will yield estimates of sensitivity and specificity in these datasets.

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Results

Upon a closer inspection, it was discovered that when all the files were converted to be readable by the analysis program, a setting was not changed to use the proper distance between the subject and the screen. Because of this, all the reported amplitudes were slightly smaller (about 1.48 times smaller) than the actual amplitudes. Because it is all a proportional shift, this doesn't affect the statistical significance of the results, in other words what was identified as statistically significantly different remains valid. But it does lead to consistently smaller amplitudes than make sense for the stimuli that was presented, when the problem is resolved we expect larger average values for any value that uses amplitude (i.e., amplitude, velocity, acceleration) and a proportionally larger standard deviation. This problem will be corrected before further analysis is done.

3.1 Demographics

A total of 160 participants were recruited and met all inclusion criteria. VCU recruited 56% of the total, and of those VCU recruited a large proportion of the control subjects. Iowa and Emory recruited more RBD (Table 2). Within the "Other" movement disorders, the diagnoses were: 1 Corticobasal Degeneration, 9 Essential Tremors, 5 Multiple System Atrophy, 3 Progressive Supranuclear Palsy, and 4 Vascular Parkinsonism.

Table 2: Diagnosis by Study Site

	Diagnosis Group					
Site	Control	PD	RBD	Other	Total	%
VCU	33	38	6	12	89	56
Iowa	5	16	9	1	31	19
Emory	5	10	16	9	40	25
Total	43	64	31	22	160	

Abbreviations: PD = Parkinson's disease, RBD = REM sleep behavior disorder, Other = Combined parkinsonism groups

No significant differences were found between the groups based on age ($p = 0.0717$, Table 3). The average participant was 64.9 years old (SD = 10.3, range = 23 to 84). The groups did differ

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by sex ($p < 0.0001$), where control subjects and subjects from the "Other" diagnosis category were more likely to be female. The RBD participates were mostly male (93%).

Table 3: Age and Sex by Diagnosis

	Diagnosis Group			
	Control	PD	RBD	Other
	Age (years)			
Mean	64.7	65.8	60.9	67.9
Std Dev	11.1	8.3	10.1	12.8
Min	31	46	31	23
Max	83	84	83	84
	Sex (n)			
female	29	26	2	12
male	14	38	28	10

Abbreviations: Std Dev = standard deviation, n = count, min = minimum, max = maximum.

3.2 Clinical Measurements

All groups were found to be significantly different in the clinical measurements (Table 4). There were missing values for each of the clinical measurements, where either the value was not recorded, or the participant was unable to complete one of the tasks. The number of non-missing values is reported in the first row of each measurement type. For the MoCA, the "Other" participants had significantly lower scores than the control, PD, and RBD. For the CAPSIT walking test, the Controls had a shorter time than the "Other" participants and PD and RBD were not significantly different from any other group. For the CAPSIT number of steps the "Other" patients took more steps than the rest of the groups. The CAPSIT finger tap test showed the mean time was the same on both the right and left hands. The "Other" participants made significantly less taps than all other groups. For the pegboard on the dominant hand, PD and "Other" participants took 2 minutes longer than the controls to complete the task and for the non-dominant hand the PD participants took longer than controls. Almost all participants finished the pegboard test within the allotted time, therefore the number correct of the pegs placed was

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almost always 25 pegs. For the UPDRS, the PD and “Others” were higher than the controls and the RBD, but there was a large amount of variability within each group.

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Table 4: Clinical Measurements

Clinical Measurement		Diagnosis Group					ANOVA
		Control	PD	RBD	Other	All	P-value
MoCA total	N	42	62	30	22	156	
	Mean	26.83A	27.15A	26.37A	23.82B	26.44	<.0001
	Std Dev	2.49	2.42	2.77	3.61	2.89	
Timed walk (CAPSIT)	N	42	62	29	19	152	
	Mean	10.57B	12.26AB	12.60AB	14.55A	12.14	0.0026
	Std Dev	2.55	4.34	3.06	5.38	4.00	
Number of steps (CAPSIT)	N	33	45	26	18	122	
	Mean	22.03A	23.09A	20.96A	26.61B	22.87	0.0004
	Std Dev	3.34	4.04	2.85	7.52	4.64	
Timed finger tap: left hand (CAPSIT)	N	42	62	27	19	150	
	Mean	55.91A	42.54B	36.34BC	30.95C	43.70	<.0001
	Std Dev	19.87	13.98	18.30	13.23	18.48	
Timed finger tap: right hand (CAPSIT)	N	42	62	27	19	150	
	Mean	54.61A	44.12B	38.34BC	29.92C	44.22	<.0001
	Std Dev	17.37	14.91	19.00	14.45	18.03	
Dominant hand: Time (Pegboard)	N	42	64	29	18	153	
	Mean	01:27B	02:04A	01:48AB	02:07A	01:51	<.0001
	Std Dev	00:19	00:53	00:40	00:45	00:45	

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Dominant hand: Number correct (Pegboard)	N	42	63	29	19	153	
	Mean	25.00	24.79	25.00	24.42	24.84	N/D
	Std Dev	0.00	1.31	0.00	2.52	1.22	
Non-dominant hand: Time (Pegboard)	N	42	63	29	18	152	
	Mean	01:37C	02:17A	01:50BC	02:14AB	02:00	<.0001
	Std Dev	00:27	00:50	00:41	00:41	00:45	
Non-dominant hand: Number correct (Pegboard)	N	42	64	29	19	154	
	Mean	25.00	25.00	25.00	24.37	24.92	N/D
	Std Dev	0.00	0.00	0.00	2.75	0.97	
UPDRS total	N	41	59	29	22	151	
	Mean	0.83B	24.66A	5.00BC	24.05A	14.32	<.0001
	Std Dev	1.73	12.03	5.71	22.54	16.01	

Abbreviations: N = count, Std Dev = Standard Deviation, N/D = No significant difference

Means not connected by the same letter are significantly different by Tukey's HSD ($P < 0.05$).

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3.3 Screening Eye Movement Parameters

The following tables are color-coded based on the significance p value. Green is a significant difference and red no significant difference.

3.3.1 Horizontal Step Task (HST)

The HST parameters were screened (Table 5), four of the parameters passed the screen:

- Absolute Saccadic Amplitude (Horizontal HST)
    - PD made significantly smaller saccades (horizontal) compared to all groups throughout (hypometria)
- Average Saccadic Velocity (H HST)
    - PD had significantly lower average saccadic velocity
- Absolute Mean Saccadic Acceleration (H HST)
    - PD had significantly lower absolute mean saccadic acceleration
- Mean Absolute Fixation Velocity (H HST)
    - Mean absolute fixation velocity was significantly higher in PD compared to controls

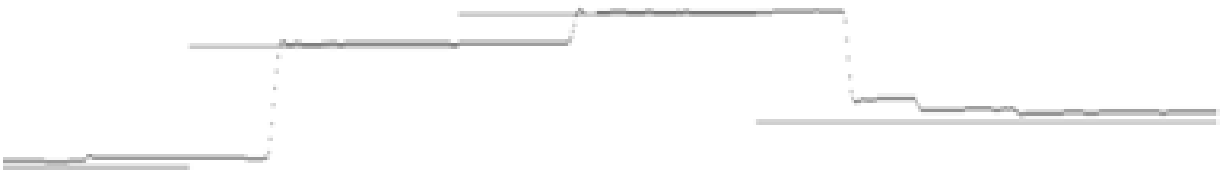

Figure 6: Example of Horizontal Step Stimuli and Response

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Table 5: Parameter Significance for HST

	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Absolute Saccadic Amplitude (H HST)										
N	40	64	30	21	155					
Mean	2.82	2.36	2.85	2.87	2.64	0.0007	0.0067	0.0230	0.0106	0.9991
SD	0.68	0.63	0.85	0.73	0.74					
Absolute Saccadic Amplitude (V HST)										
N	40	64	30	21	155					
Mean	0.65	0.68	0.74	0.53	0.67	0.5780	0.9917	0.6866	0.9583	0.8968
SD	0.73	0.48	0.56	0.19	0.54					
Saccadic Duration (H HST)										
N	40	64	30	21	155					
Mean	27.72	27.06	30.15	30.17	28.25	0.0139	0.9201	0.0787	0.0353	0.2041
SD	3.37	4.80	6.65	6.20	5.25					
Saccadic Duration (V HST)										
N	40	64	30	21	155					
Mean	20.94	22.65	23.09	22.31	22.25	0.2695	0.3333	0.9929	0.9790	0.2912
SD	3.92	5.02	6.34	4.76	5.04					
Average Saccadic Velocity (H HST)										
N	40	64	30	21	155					
Mean	80.69	68.76	78.12	78.71	75.00	0.0002	0.0003	0.0311	0.0182	0.8771
SD	14.69	12.92	16.50	13.86	15.09					
Average Saccadic Velocity (V HST)										
N	40	64	30	21	155					
Mean	30.50	28.90	29.48	33.62	30.07	0.8310	0.9805	0.7976	0.9992	0.9970
SD	22.06	12.37	13.33	38.63	20.38	.	.	.	.	.
Absolute Peak Saccadic Velocity (H HST)										
N	40	64	30	21	155					
Mean	125.19	115.68	121.75	123.62	120.39	0.3677	0.3566	0.6890	0.7737	0.9599
SD	24.04	27.82	34.04	30.97	28.68	.	.	.	.	.

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	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Absolute Peak Saccadic Velocity (V HST)										
N	40	64	30	21	155					
Mean	53.94	47.55	50.99	56.61	51.09	0.8677	0.9184	0.8855	0.9892	0.9947
SD	69.10	23.50	27.58	79.45	49.09	.	.	.	.	.
Absolute Peak Saccadic Acceleration (H HST)										
N	40	64	30	21	155					
Mean	7074.27	6624.69	6851.51	6785.92	6806.45	0.6472	0.5787	0.9830	0.9359	0.9521
SD	1390.39	1707.66	2071.14	1960.43	1738.46	.	.	.	.	.
Absolute Peak Saccadic Acceleration (V HST)										
N	40	64	30	21	155					
Mean	3904.82	2994.16	3381.28	3469.23	3368.46	0.6001	0.5266	0.9413	0.9526	0.9146
SD	5661.28	1524.94	1699.65	3058.59	3310.77	.	.	.	.	.
Absolute Mean Saccadic Acceleration (H HST)										
N	40	64	30	21	155					
Mean	5844.42	4986.03	5543.80	5532.16	5389.50	0.0080	0.0056	0.3237	0.1996	0.7620
SD	1162.50	1105.17	1595.90	1430.28	1309.97	.	.	.	.	.
Absolute Mean Saccadic Acceleration (V HST)										
N	40	64	30	21	155					
Mean	2148.84	1875.53	1970.48	1915.72	1969.89	0.8078	0.7683	0.9995	0.9900	0.9525
SD	1805.92	877.16	1144.97	2039.04	1392.81	.	.	.	.	.
Mean Fixation Time (H HST)										
N	40	64	30	21	155					
Mean	644.02	522.68	664.82	603.79	592.49	0.0096	0.0358	0.4644	0.0216	0.9798
SD	215.25	190.45	293.28	198.04	227.19	.	.	.	.	.
Mean Fixation Time (V HST)										
N	40	64	30	21	155					
Mean	1066.36	926.40	1050.85	1000.85	996.69	0.4498	0.4623	0.9243	0.6371	0.9991
SD	459.72	454.29	611.77	309.05	474.05	.	.	.	.	.

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	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Overall Root-Mean-Squared Velocity *10^4(H HST)										
N	40	64	30	21	155					
Mean	0.99	1.29	1.04	1.12	1.14	0.0627	0.0638	0.6598	0.2367	0.9846
SD	0.29	0.82	0.45	0.37	0.61	.	.	.	.	.
Overall Root-Mean-Squared Velocity *10^4(V HST)										
N	40	64	30	21	155					
Mean	2.90	22.77	27.67	1.89	15.76	0.5537	0.7126	0.8073	0.9952	0.6866
SD	7.81	126.79	98.84	0.83	92.46	.	.	.	.	.
Average Root-Mean-Squared Velocity (H HST)										
N	40	64	30	21	155					
Mean	2.71	3.50	2.96	3.12	3.14	0.0249	0.0177	0.6517	0.2523	0.8613
SD	0.84	1.72	1.08	0.93	1.36	.	.	.	.	.
Average Root-Mean-Squared Velocity (V HST)										
N	40	64	30	21	155					
Mean	3.77	4.47	4.16	4.40	4.22	0.3164	0.2659	0.9990	0.8804	0.8334
SD	1.60	2.12	2.09	1.51	1.92	.	.	.	.	.
Mean Fixation Velocity (H HST)										
N	40	64	30	21	155					
Mean	-0.0008	-0.0004	-0.0004	-0.0008	-0.0005	0.4826	0.5893	0.7054	1.0000	0.7299
SD	0.0010	0.0022	0.0016	0.0015	0.0017	.	.	.	.	.
Mean Fixation Velocity (V HST)										
N	40	64	30	21	155					
Mean	-0.0004	0.0017	0.0008	-0.0004	0.0007	0.2933	0.3204	0.5131	0.9147	0.8389
SD	0.0019	0.0091	0.0038	0.0014	0.0062	.	.	.	.	.
Mean Absolute Fixation Velocity (H HST)										
N	40	64	30	21	155					
Mean	0.01	0.01	0.01	0.01	0.01	0.0127	0.0113	0.2057	0.2769	0.7731
SD	0.00	0.02	0.01	0.00	0.01	.	.	.	.	.

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	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Mean Absolute Fixation Velocity (V HST)										
N	40	64	30	21	155					
Mean	0.00	0.01	0.01	0.01	0.01	0.0142	0.0146	0.1501	0.7590	0.3608
SD	0.00	0.02	0.02	0.00	0.02					
Absolute Time Delay Latency (H HST)										
N	40	64	30	21	155					
Mean	198.10	202.65	211.93	190.72	201.65	0.2972	0.9463	0.6544	0.7358	0.5030
SD	22.09	48.81	40.81	42.34	41.05					
Absolute Time Delay Latency (V HST)										
N	38	58	27	20	143					
Mean	232.74	194.55	197.41	178.00	202.92	0.2989	0.9436	0.6825	0.7186	0.4814
SD	274.07	73.51	74.79	33.94	152.57					
Time Delay Lag (H HST)										
N	40	64	30	21	155					
Mean	198.19	202.89	212.58	191.26	201.98	0.5373	0.6306	0.9755	0.9998	0.7956
SD	22.30	49.32	41.34	44.09	41.68					
Time Delay Lag (V HST)										
N	38	58	27	20	143					
Mean	232.74	194.55	197.41	178.00	202.92	0.5373	0.6306	0.9755	0.9998	0.7956
SD	274.07	73.51	74.79	33.94	152.57					
Left-Right Eye Correlation (H HST)										
N	40	61	30	21	152					
Mean	0.98	0.98	0.99	0.99	0.99	0.8282	0.9995	0.8975	0.9370	0.9214
SD	0.06	0.05	0.02	0.02	0.04					
Right-Left Eye Correlation (V HST)										
N	40	61	30	21	152					
Mean	0.68	0.56	0.47	0.55	0.57	0.1849	0.5253	0.9980	0.6860	0.1368
SD	0.30	0.46	0.45	0.28	0.40					

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Abbreviations: V = vertical, HST = horizontal step task, PD = Parkinson's disease, RBD = REM Behavior Disorder, ANOVA = p-value for 4 group mean comparison, PDvsC = p-value comparing the PD mean and the Control mean, PDvsOther = p-value comparing the PD mean and the Other mean, PDvsRBD = p-value comparing the PD mean and the RBD mean, CvsRBD = p-value comparing the Control mean to the RBD mean.

3.3.2 Vertical Step Task (VST)

The VST parameters were screened (Table 6), two of the parameters passed the screen:

- Absolute Saccadic Amplitude (V VST)
    - Absolute saccadic amplitude was significantly smaller in PD than Controls
- Average Saccadic Velocity (V VST)
    - Average saccadic velocity was significantly slower in PD than Controls
- Absolute Mean Saccadic Acceleration (V VST)
    - Absolute mean saccadic acceleration was significantly slower in PD than Controls

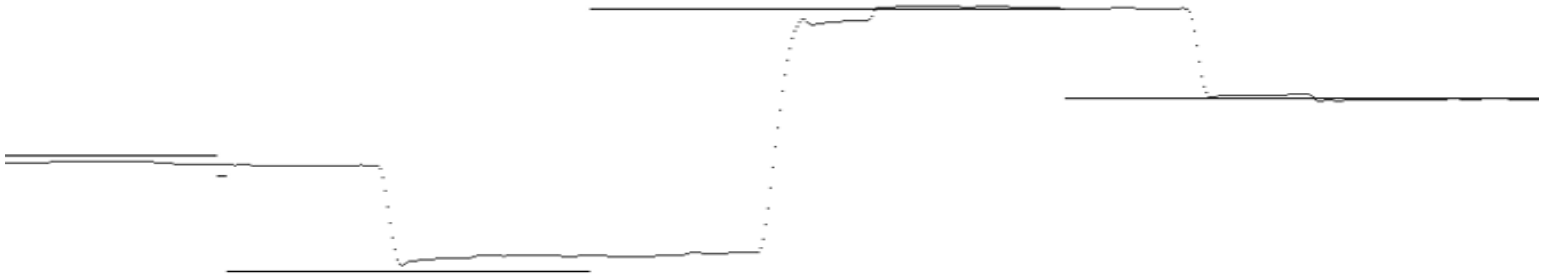

Figure 7: Example of Vertical Step Stimuli and Response

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Table 6: VST Parameter Values

	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Absolute Saccadic Amplitude (H VST)										
N	43	58	30	18	149					
Mean	0.46	0.49	0.50	0.54	0.49	0.4810	0.8891	0.7421	0.9776	0.7548
SD	0.15	0.17	0.22	0.21	0.18					
Absolute Saccadic Amplitude (V VST)										
N	43	58	29	18	148					
Mean	2.55	2.19	2.41	2.49	2.38	0.0223	0.0177	0.2547	0.3933	0.7499
SD	0.54	0.57	0.78	0.55	0.62					
Saccadic Duration (H VST)										
N	43	58	30	18	149					
Mean	20.46	21.34	22.23	20.94	21.22	0.1324	0.5184	0.9673	0.5989	0.0940
SD	2.58	3.20	4.16	2.38	3.20					
Saccadic Duration (V VST)										
N	43	58	29	18	148					
Mean	33.26	33.97	35.88	34.67	34.22	0.1276	0.8741	0.9444	0.2815	0.0963
SD	4.02	4.71	5.82	4.00	4.73					
Average Saccadic Velocity (H VST)										
N	43	58	30	18	149					
Mean	20.79	21.91	20.89	23.02	21.52	0.4449	0.7546	0.8807	0.8509	0.9998
SD	4.42	6.14	5.80	5.85	5.58					
Average Saccadic Velocity (V VST)										
N	43	58	29	18	148					
Mean	61.63	52.39	56.20	58.68	56.58	0.0049	0.0026	0.2682	0.5578	0.2954
SD	12.02	12.33	15.33	11.61	13.25	.	.	.	.	.
Absolute Peak Saccadic Velocity (H VST)										
N	43	58	30	18	149					
Mean	39.40	43.21	38.79	44.26	41.34	0.2477	0.4719	0.9908	0.4375	0.9973
SD	9.99	15.13	12.30	13.57	13.12	.	.	.	.	.

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	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Absolute Peak Saccadic Velocity (V VST)										
N	43	58	29	18	148					
Mean	109.25	93.54	96.55	106.01	100.21	0.0156	0.0149	0.2786	0.9558	0.1724
SD	21.79	24.94	31.03	27.43	26.37	.	.	.	.	.
Absolute Peak Saccadic Acceleration (H VST)										
N	43	58	30	18	149					
Mean	2433.52	2669.89	2384.86	2674.92	2544.89	0.3923	0.5727	1.0000	0.5084	0.9960
SD	783.80	1057.97	816.67	834.01	912.67	.	.	.	.	.
Absolute Peak Saccadic Acceleration (V VST)										
N	43	58	29	18	148					
Mean	6217.88	5322.74	5394.77	5992.15	5678.34	0.0207	0.0233	0.3772	0.9969	0.1226
SD	1301.45	1485.68	1891.54	1637.64	1579.37	.	.	.	.	.
Absolute Mean Saccadic Acceleration (H VST)										
N	43	58	30	18	149					
Mean	1580.40	1679.60	1579.37	1769.00	1641.59	0.5377	0.8046	0.9302	0.8477	1.0000
SD	460.45	638.63	515.58	459.17	545.86	.	.	.	.	.
Absolute Mean Saccadic Acceleration (V VST)										
N	43	58	29	18	148					
Mean	4518.08	3782.70	3954.56	4355.43	4099.69	0.0094	0.0080	0.2400	0.9082	0.1646
SD	1016.87	1015.54	1436.41	1164.89	1161.15	.	.	.	.	.
Mean Fixation Time (H VST)										
N	43	58	30	18	149					
Mean	581.08	521.80	715.60	606.41	588.15	0.0556	0.7797	0.7452	0.0319	0.2695
SD	235.86	251.90	482.51	280.41	316.15	.	.	.	.	.
Mean Fixation Time (V VST)										
N	43	58	29	18	148					
Mean	621.91	585.76	688.68	562.46	613.60	0.1251	0.8286	0.9766	0.1425	0.5517
SD	226.55	198.80	246.06	127.60	212.52	.	.	.	.	.

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	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Overall Root-Mean-Squared Velocity *10^4(H VST)										
N	43	58	30	18	149					
Mean	1.1264	1.3162	1.1286	1.1598	1.2048	0.6701	0.7045	0.9113	0.7767	1.0000
SD	0.4085	1.2281	0.5228	0.7834	0.8720	.	.	.	.	.
Overall Root-Mean-Squared Velocity *10^4(V VST)										
N	43	58	29	18	148					
Mean	1.1156	1.3496	1.1748	1.1978	1.2289	0.3815	0.3439	0.8510	0.6883	0.9848
SD	0.4998	0.8573	0.7348	0.3759	0.6970	.	.	.	.	.
Average Root-Mean-Squared Velocity (H VST)										
N	43	58	30	18	149					
Mean	2.83	2.99	2.88	3.02	2.93	0.8927	0.9087	0.9998	0.9716	0.9988
SD	0.91	1.38	0.86	1.26	1.14	.	.	.	.	.
Average Root-Mean-Squared Velocity (V VST)										
N	43	58	29	18	148					
Mean	3.11	3.56	3.38	3.47	3.38	0.2720	0.2099	0.9911	0.8953	0.7660
SD	1.03	1.18	1.31	0.91	1.14	.	.	.	.	.
Mean Fixation Velocity (H VST)										
N	43	58	30	18	149					
Mean	-0.0021	-0.0027	-0.0012	-0.0018	-0.0021	0.4806	0.8903	0.8853	0.4135	0.8283
SD	0.0020	0.0060	0.0033	0.0013	0.0042	.	.	.	.	.
Mean Fixation Velocity (V VST)										
N	43	58	29	18	148					
Mean	-0.0004	-0.0009	0.0004	0.0001	-0.0004	0.6504	0.9418	0.8849	0.6176	0.9059
SD	0.0044	0.0066	0.0021	0.0018	0.0049	.	.	.	.	.
Mean Absolute Fixation Velocity (H VST)										
N	43	58	30	18	149					
Mean	0.01	0.02	0.01	0.01	0.01	0.4360	0.5237	0.8400	0.5301	0.9993
SD	0.01	0.04	0.01	0.02	0.03	.	.	.	.	.

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	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Mean Absolute Fixation Velocity (V VST)										
N	43	58	29	18	148					
Mean	0.01	0.02	0.01	0.01	0.01	0.6941	0.7062	0.8461	0.9024	0.9945
SD	0.02	0.03	0.02	0.01	0.02	.	.	.	.	.
Absolute Time Delay Latency (V VST)										
N	41	54	29	18	142					
Mean	217.51	233.60	237.43	232.70	229.62	0.1562	0.2302	0.9998	0.9770	0.1877
SD	31.12	43.87	37.38	53.91	41.09	.	.	.	.	.
Time Delay Lag (V VST)										
N	41	54	29	18	142					
Mean	218.29	234.39	238.36	233.94	230.50	0.1673	0.2484	1.0000	0.9761	0.1993
SD	32.65	44.57	38.47	54.60	42.02	.	.	.	.	.
Left-Right Eye Correlation (H VST)										
N	43	55	29	18	145	.	.	.	.	.
Mean	0.38	0.38	0.39	0.48	0.39	0.7691	1.0000	0.7493	0.9977	0.9975
Mean	0.38	0.40	0.34	0.32	0.37	.	.	.	.	.
Right-Left Eye Correlation (V VST)										
N	43	55	29	18	145	.	.	.	.	.
Mean	0.98	0.99	0.98	0.99	0.99	0.6230	0.7417	0.9996	0.7679	0.9999
Mean	0.06	0.02	0.05	0.01	0.04	.	.	.	.	.

Abbreviations: V = vertical, HST = horizontal step task, PD = Parkinson's disease, RBD = REM Behavior Disorder, ANOVA = p-value for 4 group mean comparison, PDvsC = p-value comparing the PD mean and the Control mean, PDvsOther = p-value comparing the PD mean and the Other mean, PDvsRBD = p-value comparing the PD mean and the RBD mean, CvsRBD = p-value comparing the Control mean to the RBD mean.

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3.3.3 Predictive Task (PRE)

The PRE parameters were screened (Table 7), four of the parameters passed the screen:

- Absolute Saccadic Amplitude (H PRE)
    - Absolute saccadic amplitude was significantly smaller in PD compared to controls and RBD
- Saccadic Duration (H PRE)
    - Saccadic duration was significantly longer in RBD compared to controls and PD
- Average Saccadic Velocity (H PRE)
    - Saccadic velocity was significantly smaller in PD compared to controls and RBD
- Mean Fixation Velocity (H PRE)
    - Mean fixation velocity was significantly lower (more negative) than the others

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Table 7: PRE Eye Movement Parameters

	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Absolute Saccadic Amplitude (H PRE)										
N	41	55	31	20	147					
Mean	6.73	5.79	7.16	6.57	6.45	0.0011	0.0262	0.2494	0.0011	0.6651
SD	1.39	1.50	2.01	1.57	1.68					
Absolute Saccadic Amplitude (V PRE)										
N	41	55	31	20	147					
Mean	0.55	0.65	0.75	0.54	0.63	0.3268	0.7737	0.8268	0.8223	0.3556
SD	0.34	0.58	0.69	0.27	0.52					
Saccadic Duration (H PRE)										
N	41	55	31	20	147					
Mean	43.32	44.06	50.65	45.11	45.39	0.0029	0.9776	0.9677	0.0059	0.0035
SD	5.89	8.82	11.95	7.98	9.15					
Saccadic Duration (V PRE)										
N	41	55	31	20	147					
Mean	24.40	25.93	26.38	23.65	25.29	0.2437	0.5893	0.4478	0.9864	0.4928
SD	3.81	6.53	7.00	5.52	5.89					
Average Saccadic Velocity (H PRE)										
N	41	55	31	20	147					
Mean	119.39	99.15	118.26	114.63	110.93	0.0002	0.0006	0.0788	0.0039	0.9974
SD	22.35	22.25	31.43	22.82	26.01					
Average Saccadic Velocity (V PRE)										
N	41	55	31	20	147					
Mean	20.51	21.73	23.72	20.74	21.68	0.5645	0.9332	0.9808	0.8115	0.5304
SD	7.51	10.73	13.11	5.75	9.95	.	.	.	.	.
Absolute Peak Saccadic Velocity (H PRE)										
N	41	55	31	20	147					
Mean	191.29	181.78	192.97	195.50	188.66	0.6491	0.8086	0.7396	0.7697	0.9991
SD	33.03	49.18	72.12	51.90	51.41	.	.	.	.	.

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	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Absolute Peak Saccadic Velocity (V PRE)										
N	41	55	31	20	147					
Mean	37.21	38.97	41.96	36.69	38.80	0.7309	0.9727	0.9710	0.9066	0.7429
SD	17.49	20.47	25.09	10.55	19.65	.	.	.	.	.
Absolute Peak Saccadic Acceleration (H PRE)										
N	41	55	31	20	147					
Mean	10488.4	9969.8	10458.7	10656.4	10311.0	0.7705	0.8478	0.8296	0.8950	1.0000
SD	1970.6	2951.9	4187.3	3339.4	3068.3	.	.	.	.	.
Absolute Peak Saccadic Acceleration (V PRE)										
N	41	55	31	20	147					
Mean	2391.0	2519.5	2655.6	2354.7	2490.0	0.7459	0.9503	0.9484	0.9540	0.7749
SD	1090.7	1197.9	1360.8	828.1	1156.7	.	.	.	.	.
Absolute Mean Saccadic Acceleration (H PRE)										
N	41	55	31	20	147					
Mean	6557.67	5784.54	6549.94	6673.47	6282.53	0.0661	0.1383	0.2056	0.2048	1.0000
SD	1183.05	1431.12	2441.53	2092.58	1756.84	.	.	.	.	.
Absolute Mean Saccadic Acceleration (V PRE)										
N	41	55	31	20	147					
Mean	1425.88	1472.29	1589.45	1509.94	1489.17	0.8607	0.9926	0.9980	0.9190	0.8340
SD	707.90	836.23	966.69	698.91	809.29	.	.	.	.	.
Mean Fixation Time (H PRE)										
N	41	55	31	20	147					
Mean	328.57	290.04	335.64	298.88	311.61	0.0358	0.1056	0.9759	0.0661	0.9834
SD	83.96	76.09	89.22	79.10	83.21	.	.	.	.	.
Mean Fixation Time (V PRE)										
N	41	55	31	20	147					
Mean	439.33	430.84	450.33	456.87	440.86	0.9769	0.9985	0.9802	0.9868	0.9979
SD	191.58	235.42	200.53	448.43	255.11	.	.	.	.	.

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	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Overall Root-Mean-Squared Velocity *10^4(H PRE)										
N	41	55	31	20	147					
Mean	2.15	3.00	2.23	2.91	2.59	0.0948	0.1341	0.9975	0.2703	0.9981
SD	0.86	2.53	1.04	2.39	1.92	.	.	.	.	.
Overall Root-Mean-Squared Velocity *10^4(V PRE)										
N	41	55	31	20	147					
Mean	2.94	3.46	3.12	4.13	3.34	0.1028	0.5259	0.5004	0.8431	0.9779
SD	1.23	1.91	1.60	2.81	1.86	.	.	.	.	.
Average Root-Mean-Squared Velocity (H PRE)										
N	41	55	31	20	147					
Mean	2.73	3.30	2.75	3.24	3.02	0.0790	0.1330	0.9980	0.2101	1.0000
SD	1.03	1.50	1.02	1.30	1.28	.	.	.	.	.
Average Root-Mean-Squared Velocity (V PRE)										
N	41	55	31	20	147					
Mean	3.95	4.27	4.07	4.30	4.14	0.6230	0.6426	0.9998	0.9051	0.9813
SD	1.18	1.51	1.20	1.25	1.32	.	.	.	.	.
Mean Fixation Velocity (H PRE)										
N	41	55	31	20	147					
Mean	-0.0017	-0.0003	0.0006	-0.0052	-0.0012	0.0003	0.4726	0.0009	0.8482	0.1850
SD	0.0040	0.0055	0.0041	0.0057	0.0052	.	.	.	.	.
Mean Fixation Velocity (V PRE)										
N	41	55	31	20	147					
Mean	-0.0006	0.0004	0.0018	0.0001	0.0004	0.5344	0.8821	0.9969	0.8170	0.4608
SD	0.0061	0.0087	0.0050	0.0056	0.0069	.	.	.	.	.
Mean Absolute Fixation Velocity (H PRE)										
N	41	55	31	20	147					
Mean	0.02	0.03	0.02	0.03	0.02	0.1393	0.1969	0.9776	0.2574	1.0000
SD	0.01	0.04	0.01	0.03	0.03	.	.	.	.	.

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	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Mean Absolute Fixation Velocity (V PRE)										
N	41	55	31	20	147					
Mean	0.02	0.03	0.02	0.03	0.03	0.5073	0.7032	0.9999	0.6123	0.9962
SD	0.02	0.03	0.02	0.03	0.03	.	.	.	.	.
Absolute Time Delay Latency (H PRE)										
N	41	55	31	20	147					
Mean	186.04	180.36	201.23	186.13	187.13	0.0921	0.8749	0.9303	0.0575	0.3031
SD	32.32	35.47	37.29	45.46	36.96	.	.	.	.	.
Absolute Time Delay Latency (V PRE)										
N	40	54	30	20	144					
Mean	200.55	214.81	215.13	196.20	208.33	0.9192	0.9571	0.9521	1.0000	0.9698
SD	183.68	89.48	161.20	47.82	133.44	.	.	.	.	.
Time Delay Lag (H PRE)										
N	41	55	31	20	147					
Mean	186.58	180.61	201.91	186.39	187.55	0.0955	0.8674	0.9349	0.0597	0.3182
SD	34.13	36.92	37.33	45.35	37.94	.	.	.	.	.
Time Delay Lag (V PRE)										
N	40	54	30	20	144					
Mean	200.55	214.81	215.13	196.20	208.33	0.9192	0.9571	0.9521	1.0000	0.9698
SD	183.68	89.48	161.20	47.82	133.44	.	.	.	.	.
Left-Right Eye Correlation (H PRE)										
N	40	51	31	20	142	.	.	.	.	.
Mean	0.99	1.00	1.00	1.00	1.00	0.2119	0.1903	0.8540	0.9974	0.3889
SD	0.01	0.00	0.00	0.01	0.01	.	.	.	.	.
Right-Left Eye Correlation (V PRE)										
N	40	51	31	20	142	.	.	.	.	.
Mean	0.72	0.63	0.45	0.49	0.59	0.0372	0.7139	0.6111	0.2651	0.0412
SD	0.28	0.42	0.58	0.41	0.44	.	.	.	.	.

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Abbreviations: V = vertical, HST = horizontal step task, PD = Parkinson's disease, RBD = REM Behavior Disorder, ANOVA = p-value for 4 group mean comparison, PDvsC = p-value comparing the PD mean and the Control mean, PDvsOther = p-value comparing the PD mean and the Other mean, PDvsRBD = p-value comparing the PD mean and the RBD mean, CvsRBD = p-value comparing the Control mean to the RBD mean.

3.3.4 Antisaccadic Tasks (ANT)

The three antisaccadic task parameters were compared (Table 8). None passed the screen.

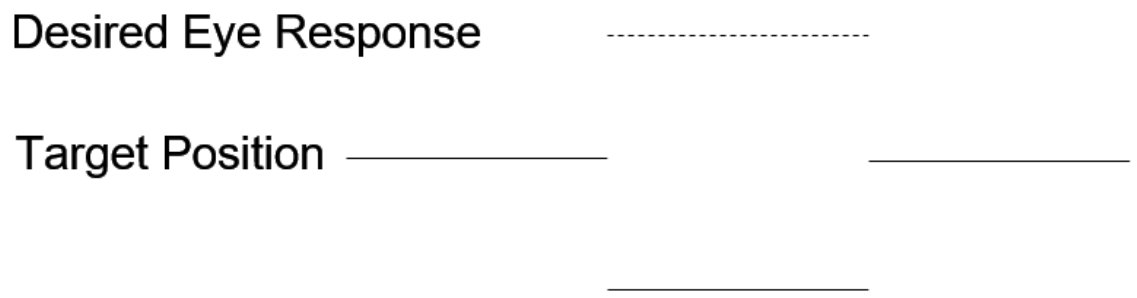

Figure 8: Example of Antisaccadic Stimuli

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Table 8: ANT Eye Movement Parameters

	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Hit percent (ANT)										
N	42	61	28	16	147					
Mean	47.04	37.63	52.35	25.64	41.82	0.0060	0.3103	0.3952	0.0853	0.8526
SD	27.52	25.24	29.61	28.18	27.99					
Hit latency (ANT)										
N	42	61	28	17	148					
Mean	5.78	5.86	5.86	5.93	5.85	0.4993	0.9770	0.4169	0.9650	0.9996
SD	0.30	0.35	0.18	0.37	0.31					
Miss latency (ANT)										
N	42	61	28	16	147					
Mean	5.27	5.25	5.28	5.38	5.28	0.3565	0.5802	0.8486	1.0000	0.7221
SD	0.33	0.23	0.22	0.58	0.31					

3.3.5 Reading Task (REA)

The reading task parameters were compared (Table 9). None passed the screen.

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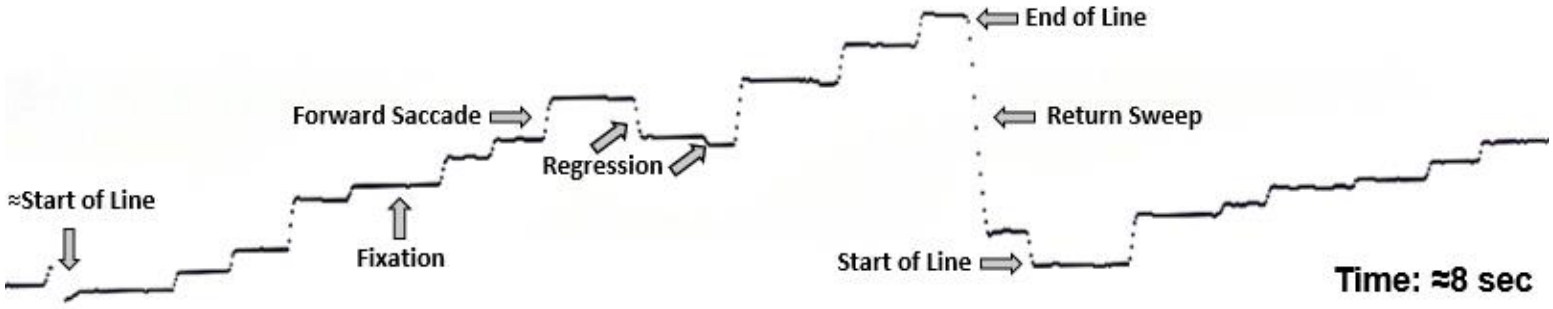

Figure 9: Example of Reading Response and Analysis

Table 9: REA Eye Movement Parameters

	Diagnosis					P-value				
	Control	PD	RBD	Other	All	ANOVA	PDvsC	PDvsOther	PDvsRBD	CvsRBD
Absolute Saccadic Amplitude (H REA)										
N	41	57	26	18	142					
Mean	3.94	3.69	3.87	3.47	3.77	0.1511	0.4139	0.7509	0.7673	0.9856
SD	0.62	0.84	0.97	0.72	0.80					
Overall Root-Mean-Squared Velocity (H REA)										
N	41	57	26	18	142					
Mean	0.0001	0.0001	0.0000	0.0000	0.0000	0.3827	0.9999	0.6813	0.5317	0.5445
SD	0.0001	0.0000	0.0000	0.0000	0.0000					
Overall Root-Mean-Squared Velocity (V REA)										
N	41	57	26	18	142					
Mean	0.0001	0.0001	0.0001	0.0001	0.0001	0.0706	0.1734	0.8656	0.0935	0.9509
SD	0.0001	0.0001	0.0000	0.0000	0.0001					
Average Root-Mean-Squared Velocity (H REA)										
N	41	57	26	18	142					
Mean	3.44	4.08	3.24	3.76	3.70	0.1106	0.3612	0.7218	0.6931	0.9902
SD	1.15	1.95	1.02	1.17	1.53					

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Average Root-Mean-Squared Velocity (V REA)										
N	41	57	26	18	142					
Mean	6.60	6.93	6.48	6.61	6.71	0.6849	0.9653	0.8786	0.9456	0.8012
SD	2.12	2.32	1.68	1.50	2.05					
Reading Overall Saccadic Amplitude (H REA)										
N	41	57	26	18	142					
Mean	4.45	4.12	4.38	3.84	4.23	0.5965	0.8596	0.8477	1.0000	0.9171
SD	0.78	1.02	1.25	0.89	1.00					
Reading Regression Saccadic Amplitude (H REA)										
N	41	57	26	18	142					
Mean	-1.82	-1.78	-1.73	-1.70	-1.77	0.0785	0.2345	0.7258	0.7824	0.9119
SD	0.46	0.40	0.35	0.41	0.41					
Reading Forward Saccadic Amplitude (H REA)										
N	41	57	26	18	142					
Mean	3.04	2.92	2.92	2.76	2.94	0.6531	0.6833	0.9974	0.9978	0.7022
SD	0.60	0.85	0.79	0.64	0.75					
Reading Average Saccadic Amplitude without Return Sweep (H REA)										
N	41	57	26	18	142					
Mean	4.89	4.49	4.72	4.20	4.61	0.6538	0.9032	0.8601	0.9942	0.9888
SD	0.81	1.04	1.31	0.97	1.04					
Reading Average Regression Saccadic Amplitude (H REA)										
N	41	57	26	18	142					
Mean	-1.92	-1.78	-1.76	-1.81	-1.82	0.3794	0.3493	1.0000	0.9060	0.8901
SD	0.68	0.63	0.43	0.48	0.59					
Reading Average Forward Saccadic Amplitude (H REA)										
N	41	57	26	18	142					
Mean	3.02	2.92	2.96	2.75	2.94	0.4593	0.4374	0.7433	0.8638	0.9604
SD	0.55	0.89	0.82	0.63	0.76					
Reading Primary Return Sweep Amplitude (H REA)										
N	41	56	26	18	141					
Mean	-13.53	-13.27	-14.19	-13.70	-13.57	0.0768	0.3440	0.4931	0.9809	0.7482

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SD	1.18	2.30	2.58	1.97	2.06					
Reading Secondary Return Sweep Amplitude (H REA)										
N	41	56	26	18	141					
Mean	-1.18	-1.50	-1.23	-1.39	-1.34	0.6030	0.9506	0.9819	0.7906	0.5575
SD	0.40	0.65	0.35	0.54	0.54					
Reading Overall Fixation Duration (H REA)										
N	41	57	26	18	142					
Mean	252.13	275.91	264.71	276.05	267.01	0.7623	0.8542	0.9367	0.7897	0.9961
SD	31.43	101.72	37.78	35.06	69.99					
Reading Regression Duration (H REA)										
N	41	57	26	18	142					
Mean	265.16	298.54	278.57	268.93	281.49	0.3055	0.9267	0.8699	0.2372	0.5750
SD	46.11	160.18	50.13	45.34	108.18					
Reading Forward Saccadic Duration (H REA)										
N	41	57	26	18	142					
Mean	247.15	262.53	258.46	279.73	259.52	0.0206	0.0201	0.8667	0.1454	0.9812
SD	33.37	56.73	37.31	34.15	45.63					
Reading Lines Read (H REA)										
N	41	56	26	18	141					
Mean	82.44	82.59	87.85	78.17	82.95	0.3472	1.0000	0.7953	0.5989	0.6197
SD	18.42	19.49	10.05	19.30	17.80					
Reading Fixations Per Line (H REA)										
N	41	56	26	18	141					
Mean	6.05	7.52	6.51	7.75	6.94	0.2155	0.2555	0.9966	0.6916	0.9642
SD	1.18	5.69	1.66	3.08	3.91					
Reading Regressions Per Line (H REA)										
N	41	56	26	18	141					
Mean	3.03	3.81	3.16	3.99	3.48	0.0779	0.1444	0.9822	0.4044	0.9923
SD	0.68	2.54	0.98	1.26	1.78					
Left-Right Eye Correlation (H REA)										
N	38	52	25	17	132					
Mean	0.97	0.96	0.97	0.95	0.96	0.7265	0.9495	0.9884	0.8057	0.9778

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SD	0.05	0.10	0.03	0.07	0.07					
Left-Right Eye Correlation (V REA)										
N	38	52	25	17	132					
Mean	0.90	0.89	0.91	0.83	0.89	0.1311	0.9741	0.2396	0.8984	0.9901
SD	0.11	0.13	0.07	0.11	0.12					

Abbreviations: V = vertical, HST = horizontal step task, PD = Parkinson's disease, RBD = REM Behavior Disorder, ANOVA = p-value for 4 group mean comparison, PDvsC = p-value comparing the PD mean and the Control mean, PDvsOther = p-value comparing the PD mean and the Other mean, PDvsRBD = p-value comparing the PD mean and the RBD mean, CvsRBD = p-value comparing the Control mean to the RBD mean

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3.4 Anti-Saccadic Task

The probability of correctly performing the task (a "hit") is summarized in Table 10. In the first two columns are the raw counts of hits and misses by each demographic category. The raw percentage of hits is shown next. A repeated-measures logistic regression model was used to test for the effect of each demographic factor. Adjusting for all other factors, the strongest relationship was with age (P=0.0056) with a 51-52% hit percentage in younger participants declining to 30-35% in older participants. The VCU hit percentage was higher than Iowa or Emory (P=0.0182). Males were more successful than females (P=0.0449). After controlling for demographic factors, there was a significant difference in the hit percentage depending upon diagnosis groups (P=0.0283). The control percentage was significantly higher than the PD (P=0.0135) and the "Other" diagnoses (P=0.0207). There was no significant difference between the PD and the "Other" diagnosis groups (P=0.2740).

Table 10: Hit Percentage by Demographics

	Count		Hit%				
Groups	Hit	Miss	raw	Estimate	95% CI		P-value*
Diagnosis groups							0.0283
control	192	219	47%	53%	44%	61%	
PD	226	373	38%	39%	33%	46%	
Other	180	245	42%	29%	15%	47%	
Sex							0.0449
F	234	394	37%	35%	28%	43%	
M	356	441	45%	45%	35%	55%	
Site							0.0182
VCU	309	535	37%	33%	26%	41%	
Iowa	132	147	47%	42%	30%	55%	
Emory	157	155	50%	44%	34%	55%	
Age range							0.0056
20s	0	10	0%				
30s	15	3	83%	51%	11%	90%	
40s	43	44	49%	52%	32%	71%	
50s	154	123	56%	57%	45%	68%	
60s	209	367	36%	35%	26%	45%	
70s	145	236	38%	38%	28%	49%	
80s	32	54	37%	30%	19%	45%	

* The p-value is calculated in a repeated-measures logistic regression model which included all the factors listed in the table.

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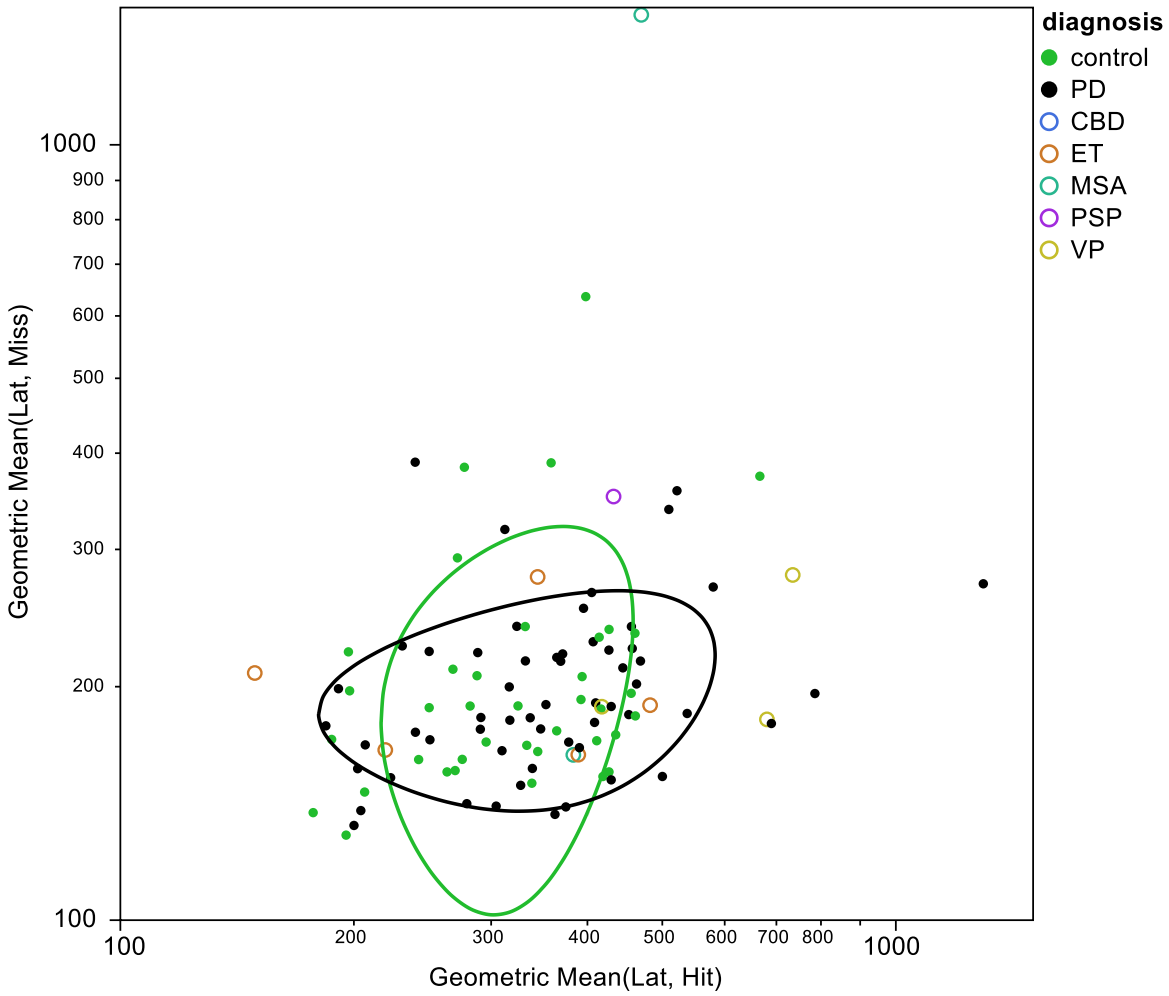
In the average latency for hits and for misses (Figure 10) there does not appear to be a wide separation between controls (green dot and green ellipse) and PD patients (black dot and ellipse). However, this plot only shows the cases where the geometric mean for latency can be calculated for both the hits and misses. By definition, latency for hits is undefined if there were no hits (and the same for misses). Missing values occurred in 15 cases (out of 108 actual values for hit-latency and 121 for miss-latency).

Figure 10. Latency in Hits and Misses



3.5 Predictive Task

The comparison of the first and second halves of the predictive task within each group were observed in order to see the differences between the purely predicable half and the temporally

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changing half (Table 22, see appendix). While there were no significant differences in the averages between the groups, there were significant differences within the groups when comparing the first and second halves. The Control and RBD groups had significantly different amplitudes between the first and second halves of the test where the PD and RBDs had no differences. The absolute peak velocity followed this trend, where the Control and RBD groups had significantly faster movements in the second half and the PD and "Other" groups showed no significant differences. The PD and RBD groups showed significantly higher RMS Velocity in the second half of the task and the Control and "Other" groups showed no differences. Notably, there was also a significant difference ($p < 0.06$) in the latency values between the first and second half in the control group, and no difference between the halves in the rest of the groups.

3.6 Multivariate Screening

Some demographical differences as well as the variables that passed the first screen were combined. The demographics of age and sex discriminate highly between the four groups, so they were included within the multivariate models. The p-value for Sex is <0.0001, and the p-values for linear and quadratic Age are P = 0.0080 and P = 0.0119. Using only those demographics, 43% of the participants can be correctly categorized (Table 11).

Table 11: Prediction Based on Sex and Age

	Predicted					
Actual	Control	RBD	Other	PD	Total	% Correct
Control	15	2	1	25	43	35
RBD	0	11	1	19	31	35
Other	7	0	3	12	22	14
PD	12	12	1	39	64	61
Total	34	25	6	95	160	43

In Figure 11, the relationship between age, sex and probability of each diagnosis is presented. In panel D, females are more likely to be controls than males, so females are above the cutoff value. For panel A, the likelihood of being an RBD is increased for males. It was much harder to

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distinguish the prediction of the "Other" movement disorder diagnosis using only age and sex as seen in panel B. Panel C shows there is a higher likelihood of being PD if the subject is male and the age of 60, but it does not distinguish between groups with high accuracy.

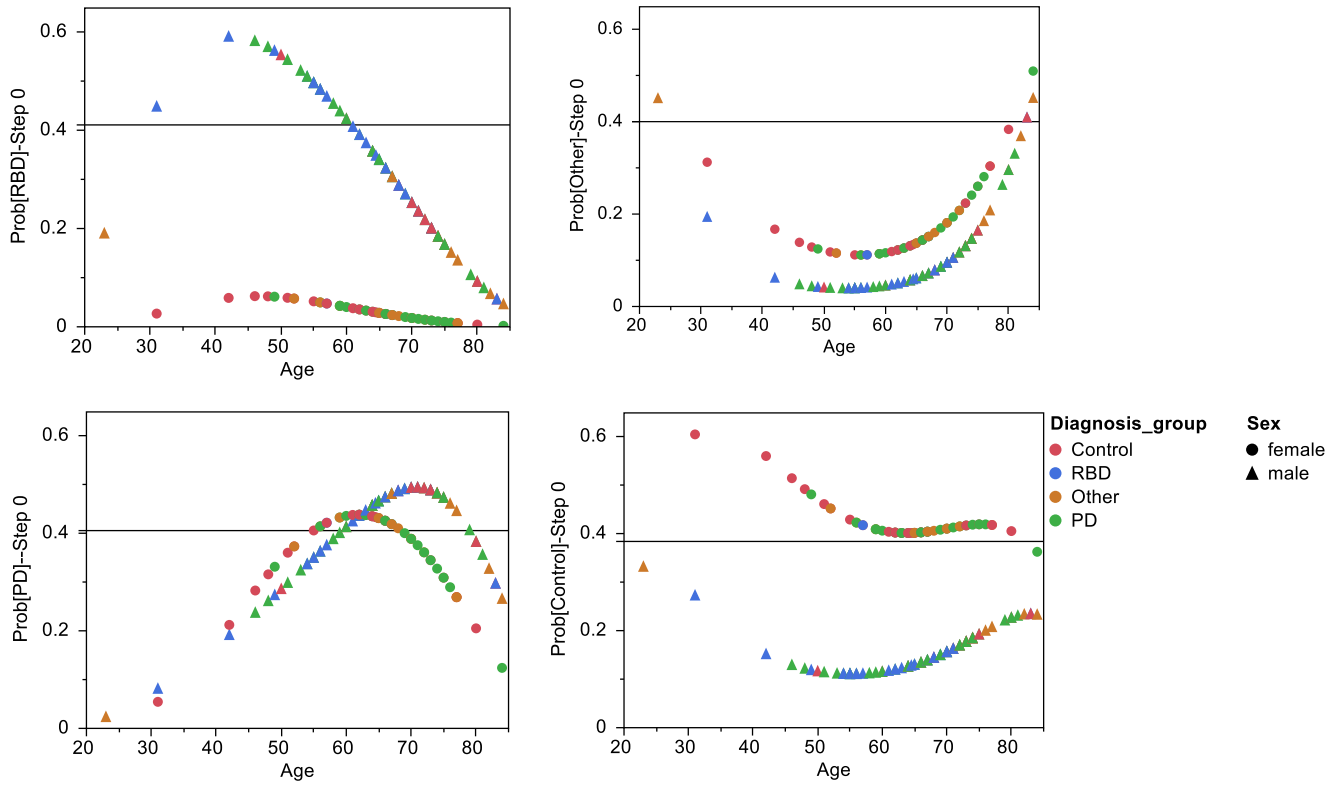

Figure 11: Probability of Diagnosis based on Age and Sex (A,B,C, & D)

Then the overall model was built based on the eye movements parameters that passed the screen. All 10 eye movement parameters that passed the screen were included in the multiple logistic regression model. Many eye movement parameters were no longer significant after adjustment for all predictors (Table 12). If age and sex were removed, the p-values remained very similar.

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Table 12: Predicting Diagnosis Overall Model

Source	Chi-Square	4Dx
Site	18.36	
Sex	33.98	<.0001
Age	14.60	0.0022
Age^2	15.41	0.0015
Absolute Saccadic Amplitude (H HST)	0.83	0.8414
Average Saccadic Velocity (H HST)	2.39	0.4948
Absolute Mean Saccadic Acceleration (H HST)	2.84	0.4168
Mean Absolute Fixation Velocity (H HST)	17.99	0.0004
Average Saccadic Velocity (V VST)	5.69	0.1277
Absolute Mean Saccadic Acceleration (V VST)	4.58	0.2054
Absolute Saccadic Amplitude (H PRE)	3.73	0.2924
Saccadic Duration (H PRE)	18.32	0.0004
Average Saccadic Velocity (H PRE)	7.01	0.0716
Mean Fixation Velocity (H PRE)	5.07	0.1670

All non-significant predictors were removed for the final model (Table 13). Using these parameters alone, the model predicts 60% of all cases correctly (Table 14).

Table 13: Final Predictive Model

Source	Chi-Square	4Dx
Site	18.49	0.0051
Sex	33.87	<.0001
Age	17.28	0.0006
Age^2	10.41	0.0154
Mean Absolute Fixation Velocity (H HST)	18.01	0.0004
Saccadic Duration (H PRE)	15.83	0.0012
Average Saccadic Velocity (H PRE)	13.09	0.0044
Mean Fixation Velocity (H PRE)	23.12	<.0001

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Table 14: Probability of Correct Diagnosis from Final Model

	Predicted					
Actual	Control	PD	RBD	Other	Total	% Correct
Control	21	14	1	2	38	55
PD	9	36	7	3	55	65
RBD	4	9	17	0	30	57
Other	5	3	0	11	19	58
					142	60

In order to illustrate the relationship between all 5 predictors and the 4 outcomes Figure 12 shows the predicted probability for each diagnosis on the vertical axis with the predictor variable on the horizontal axis. The top panel shows a participant with Age=64, Absolute Fixation Velocity (H HST) = 0.01, Saccadic Duration (H PRE) = 45, Average Saccadic Velocity (H PRE) = 111, Mean Fixation Velocity (H PRE) near 0, and female; the bottom panel shows the same for males.

For both a female and a male, a younger participant and an older participant has a higher likelihood of being a Control. The Control line slopes downward as Saccadic Duration (H PRE) increases (and slopes upward as it decreases). For females, as Average Saccadic Velocity (H PRE) increases, the chance of being a Control increases; for males the slope is relatively flat. For Mean Fixation Velocity (H PRE), there is a value where the chance of being a Control peaks and values above and below that result in less chance of Control.

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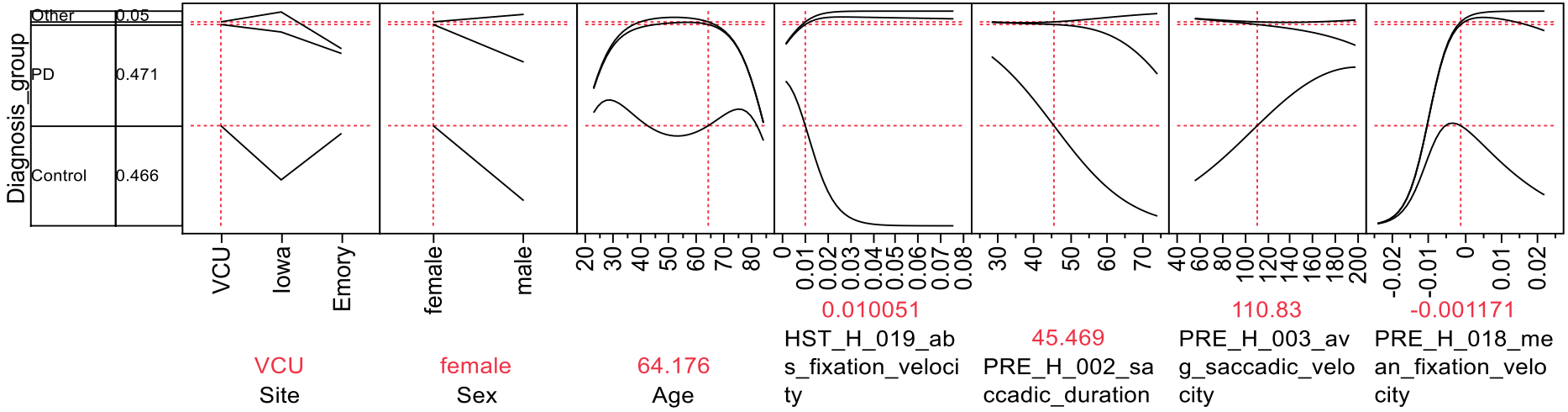
Females



Males

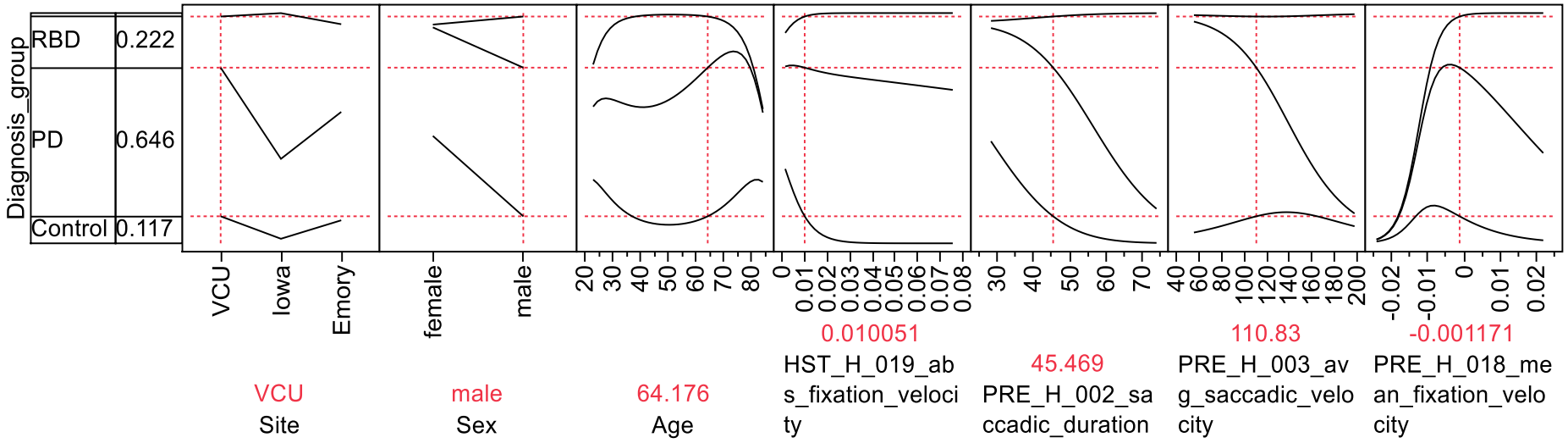


Figure 12: Prediction of Diagnosis from Model

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UPDRS was then added to the model it was also a predictor and contributed significantly to the model, but the eye tracking parameters still added valuable discriminatory power (Table 15). The inclusion of UPDRS also greatly increased the accuracy of diagnosis (Table 16), but the "Other" groups were still difficult to classify correctly.

Table 15: Predictive Model with UPDRS

Source	Chi-Square	P-Value
Site	26.36	0.0002
Sex	33.77	<.0001
Age	13.26	0.0041
Age^2	12.85	0.0050
Mean Absolute Fixation Velocity (H HST)	17.74	0.0005
Saccadic Duration (H PRE)	19.59	0.0002
Average Saccadic Velocity (H PRE)	10.55	0.0144
Mean Fixation Velocity (H PRE)	15.54	0.0014
UPDRS total	125.26	<.0001

Table 16: Predictive Model with UPDRS Accuracy

	Predicted					
Actual	Control	PD	RBD	Other	Total	% Correct
Control	33	0	3	0	36	92
PD	0	44	3	3	50	88
RBD	3	1	24	0	28	86
Other	1	4	1	13	19	68
Total	37	49	31	16	133	86

3.7 Discrimination between Pairs of Diagnostic Groups

The model's ability to discriminate between different pairs of diagnostic groups (PD vs. Control (C), PD vs. "Other", PD vs RBD, and Control vs RBD) was investigated. The results are shown in (Table 17). The color shading shows that a different mix of predictors appear to be useful in discriminating each pair. For comparing PD vs Control, only Mean Absolute Fixation Velocity (H HST) and Saccadic Duration (H PRE) appear important. For comparing PD vs "Other", all the predictors except Saccadic Duration (H PRE) and Average Saccadic Velocity (H PRE) appear important. For PD vs RBD, Sex and Saccadic Duration (H PRE) and Average Saccadic Velocity (H PRE) appear important. For RBD vs Control, Site, Sex, Saccadic Duration (H PRE) and Average Saccadic Velocity (H PRE) appear important.

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Table 17: Logistic Regression for Discrimination between Diagnosis Pairs

Source	Chi-Square	P-Value 4Dx	PDvsC	PDvsOther	PDvsRBD	RBDvsC
Site	18.49	0.0051	0.2685	0.0266	0.0861	0.0038
Sex	33.87	<.0001	0.0010	0.0090	0.0078	<.0001
Age	17.28	0.0006	0.1117	0.0249	0.0567	0.0639
Age^2	10.41	0.0154	0.3095	0.0275	0.5392	0.0845
Mean Absolute Fixation Velocity (H HST)	18.01	0.0004	0.0002	0.0022	0.7077	0.0778
Saccadic Duration (H PRE)	15.83	0.0012	0.0210	0.0720	0.0107	0.0319
Average Saccadic Velocity (H PRE)	13.09	0.0044	0.0687	0.0697	0.0012	0.0220
Mean Fixation Velocity (H PRE)	23.12	<.0001	0.4258	<.0001	0.6415	0.2053

Notes: The results for “4Dx” are the same as that shown in Table 12

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PD vs Control

There were 93 participants in the PD or Control group with non-missing predictor values. The area under the receiver operating characteristic (ROC) curve was a 0.85 (Figure 13). The model accurately diagnosed 76% of the cases (Table 18).

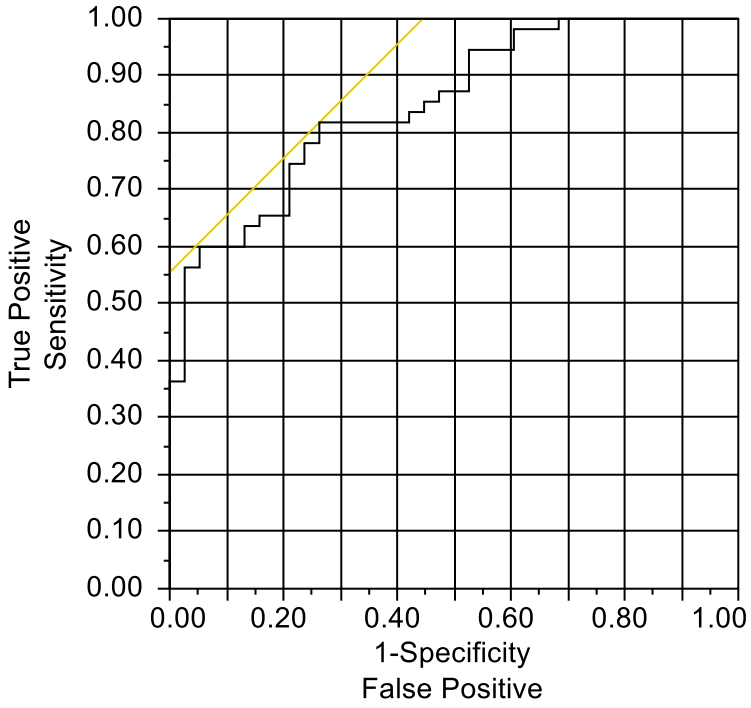

Figure 13: Receiver Operating Characteristic (ROC) Curve for PD vs Control

Table 18. Sensitivity and Specificity for Discriminating PD vs Control

	Diagnosis		
Actual	PD(+)	Control(-)	Total
PD	45	10	55
Control	12	26	38
Total	57	36	93

	Estimate	95% CI	
Sensitivity=	78.9%	68.4%	89.5%
Specificity=	72.2%	57.6%	86.9%
False Positive=	27.8%	13.1%	42.4%
False Negative=	21.1%	10.5%	31.6%
PPV=	81.8%	71.6%	92.0%
NPV=	68.4%	53.6%	83.2%
Accuracy=	76.3%		

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PD vs "Other"

There were 74 participants in the PD or "Other" group with non-missing predictor values. The area under the receiver operating characteristic (ROC) curve was 0.9 (Figure 14). Overall, the model accurately diagnosed 89% of the cases (Table 19).

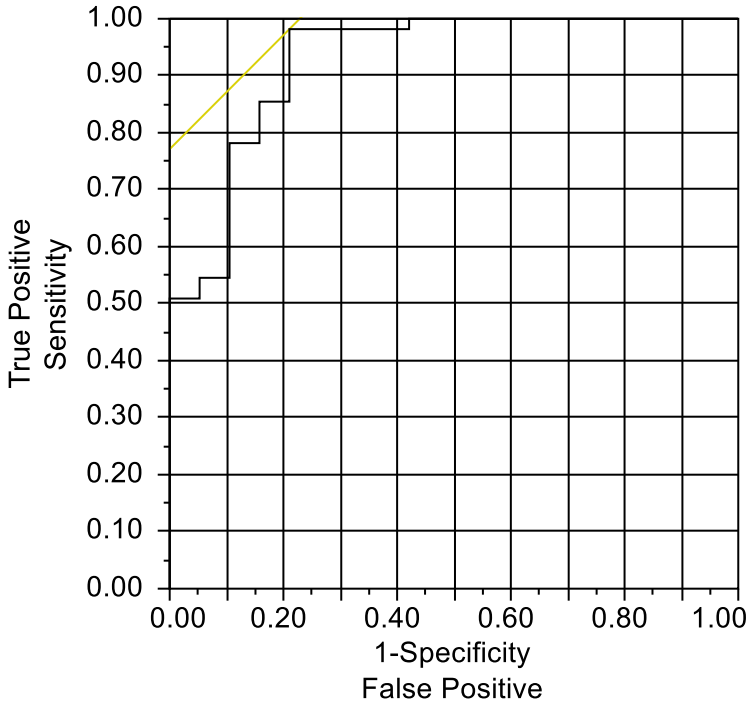

Figure 14: ROC Curve for PD vs "Other"

Table 19. Sensitivity and Specificity for Discriminating PD vs "Other"

	Diagnosis		
Actual	PD(+)	Other(-)	Total
PD	51	4	55
Other	4	15	19
Total	55	19	74

	Estimate	95% CI	
Sensitivity=	92.7%	85.9%	99.6%
Specificity=	78.9%	60.6%	97.3%
False Positive=	21.1%	2.7%	39.4%
False Negative=	7.3%	0.4%	14.1%
PPV=	92.7%	85.9%	99.6%
NPV=	78.9%	60.6%	97.3%
Accuracy=	89.2%		

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PD vs RBD

There were 85 participants in the PD or RBD group with non-missing predictor values. The area under the receiver operating characteristic (ROC) curve was 0.86 (Table 20). Overall, the model accurately diagnosed 78% of the cases (Figure 15).

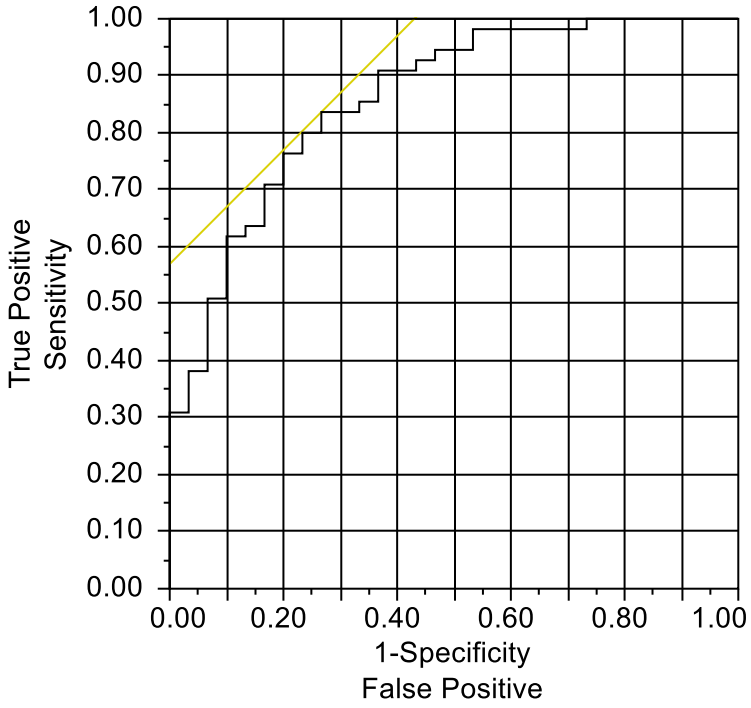

Figure 15: ROC Curve for PD vs RBD

Table 20. Sensitivity and Specificity for Discriminating PD vs RBD

	Diagnosis		
Actual	PD(+)	RBD(-)	Total
PD	47	8	55
RBD	11	19	30
Total	58	27	85

	Estimate	95% CI	
Sensitivity=	81.0%	70.9%	91.1%
Specificity=	70.4%	53.1%	87.6%
False Positive=	29.6%	12.4%	46.9%
False Negative=	19.0%	8.9%	29.1%
PPV=	85.5%	76.1%	94.8%
NPV=	63.3%	46.1%	80.6%
Accuracy=	77.6%		

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RBD vs Control

There were 68 participants in the RBD or Control group with non-missing predictor values. The area under the receiver operating characteristic (ROC) curve was 0.95 (Table 21). Overall, the model accurately diagnosed 88% of the cases (Figure 16).

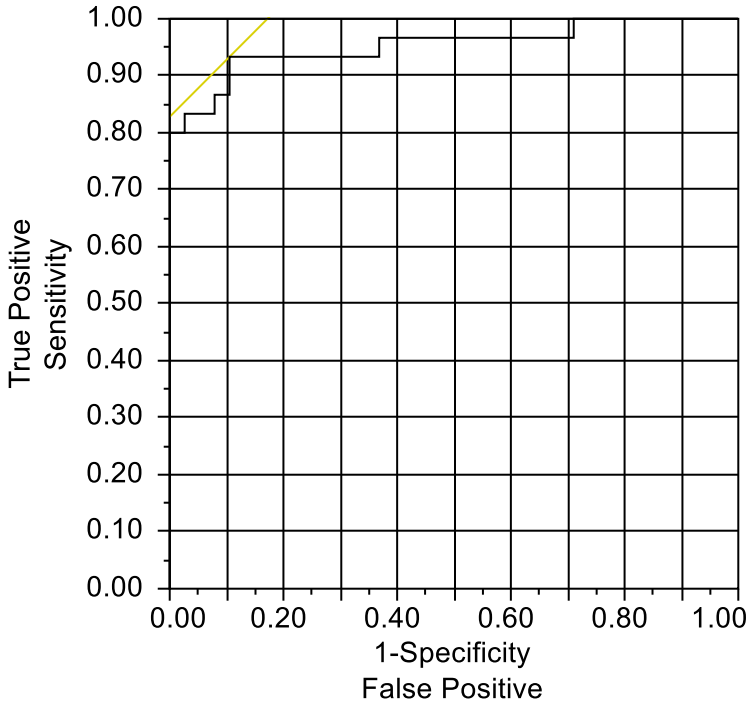

Figure 16: ROC Curve for RBD vs Control

Table 21. Sensitivity and Specificity for Discriminating RBD vs Control

	Diagnosis		
Actual	RBD(+)	Control(-)	Total
RBD	26	4	30
Control	4	34	38
Total	30	38	68

	Estimate	95% CI	
Sensitivity=	86.7%	74.5%	98.8%
Specificity=	89.5%	79.7%	99.2%
False Positive=	10.5%	0.8%	20.3%
False Negative=	13.3%	1.2%	25.5%
PPV=	86.7%	74.5%	98.8%
NPV=	89.5%	79.7%	99.2%
Accuracy=	88.2%		

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Discussion

4.1 Reflexive Saccades (Horizontal and Vertical Step)

Unlike many of the studies, we did see differences within purely reflexive saccades. Most commonly we saw that subjects with Parkinson's made smaller saccades on average during the Horizontal Step Task compared to all the groups. This is confirmed by a lower average saccadic velocity and a lower average saccadic acceleration. This agrees with studies that have shown hypometria in Parkinson's patients (Mosimann et al., 2005, Hood et al., 2007, Antoniades et al., 2007, Terao et al., 2011, Van Stockum et al., 2011, Macaskill et al., 2012). A similar affect was seen in the Vertical Step Task but it was much less obvious. The Parkinson's subjects made significantly smaller saccades than the Control group but there were no other significant differences between groups.

Inconsistent to other studies that found differences in reflexive saccades responses, no significant difference was seen in the latency or time delay response to the stimuli; this indicates no differences in the reaction times between the groups during reflexive saccades. And there were no significant differences between the right and left eye, indicating no major disconjugate movement problems (Versino et al., 2009). The Vertical Step Task revealed slight differences in the Parkinson's group, with the average amplitude being smaller. Few studies have researched in depth the vertical reflexive responses overall but seeing hypometria makes sense due to the presence of hypometria in the horizontal direction.

4.2 Inhibition of Reflexive Saccades

There were no significant differences between error rates and latencies in the antisaccadic task, although it is commonly reported, when looking at only ANOVA t-tests. However, with a repeated-measures logistic regression and controlling for demographic differences (i.e. the age, sex, and site) there was a significant difference in hit rate percentage between the control group and the PD group. This result is consistent with the majority of the research that has examined the anti-saccadic response (Kitagawa et al., 1994, Briand et al., 1999, Chan et al., 2005, Mosimann et al., 2005, Hood et al., 2007, Koningsbruggen et al., 2009). But what is surprising is the lack of a difference in the latency time that is usually reported along with the difference in error rate.

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For the overall predictive model, only the basic ANOVA t-test results were used to find the qualifying features. This was done in order to simplify the overall model and processing. High levels of discrimination between the groups were still achieved without using the logistic model of the antisaccadic data. However, this could be added in the future in order to potentially add more discriminatory power.

4.3 Predictive Stimuli

The predictive stimulus was created as a hybrid in order see if there was a difference in sensitivity to change between PD and Control groups. Differences have been seen in PD patient's ability to follow and react to a purely predictable stimulus (Helmchen, et al., 2012). But this has only been explored deeply with a predictable smooth pursuit target rather than a predictable saccadic target. Still, difficulties have been found in PD patient's ability to anticipate future target movement. The amount of significant differences seen were surprising due to the overall lack of this type of stimuli in other studies. Again, we saw overall hypometria in the PD group when looking at the whole task. There was an interesting effect seen in the PD group compared to the other group; there the PD group had a significantly different type of fixation instability compared to the "Other" movement disorders. It was more negative, which indicates more leftward skewed fixational movements in the PD group. When looking at both halves of the test, this effect does not change due to the stimuli varying. This means it could be an overall neurological effect due to the "sidedness" of PD. This leads to a potential area of further study where the motor scores from each hand, both the tap test in the CAPSIT and the pegboard test, could be correlated to the direction of instability during fixation. It also provides a discriminatory effect between the two groups.

With the two halves of the test compared, the Control and RBD groups had significantly different amplitudes between the first and second halves of the test, where the PD and RBDs had no differences. The control and RBD group made significantly larger saccades in the second half, which indicates a potential learning effect because the stimuli amplitude never changes, only the temporal spacing. The PD and "Other" groups continued to have reactive movements throughout the test rather than predictive movements because the latency remained the same and the amplitude remained small. One large jump and then a second or third smaller corrective saccade is standard in reactive saccades but decreases when it is a predictable stimulus. A "staircase"

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effect has been frequently observed with PD subjects, instead of one large jump they make lots of smaller jumps until reaching the target position. It could be that this type of stimuli elicits the staircase and hypometria effects of PD more consistently than other stimuli.

4.4 Reading

More differences in the reading task were expected, however the analysis for the reading is very preliminary and basic. Because ten texts were presented, all at different, randomized difficulties, further analysis needs to be done on the effect of reading level, dementia, and fatigue effects during the reading. It was expected based on the cognitive aspect of PD that there may be more differences in the eye movements, for instance: longer fixations and increased regression frequency. The absence of these differences indicates that controlling for the cognitive features of neurodegenerative diseases with the MoCA test as a screening tool helped to control for this variable.

4.5 Multivariate Screening

Due to the way PD affects different populations, there was good discrimination between controls and PD's by only looking at age and sex as covariates. PD effects men about 1.5 times more than women in the total population, and on average women do not develop PD until several years after men (Gillies et al., 2014). Because the Control group was recruited from family members who attended the appointment with the patient, we recruited more male PD subjects and more female controls. Due to this, when the model was developed, the effect of sex and age added higher discriminatory power. The larger numbers of males with PD is reminiscent of a general population, but the control group was overly female. Still the effect of age and sex can be very powerful when added to the eye tracking measures in terms of discrimination, so they were included in the model.

Due to differences in recruitment populations based on each site, there was high discriminatory power when looking at the site where the subject was recruited. Because this was a significant discriminator, it was included in the model, though this would not be applicable to the general population. In a more generalized model, site could not be used as a predictor of diagnosis. After the non-significant parameters were removed, the predictive task was the most important. Specifically: the duration and average velocity of horizontal saccades, and mean fixation velocity. The amplitude, duration of the saccade, and velocity of the saccade should all covariate

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together due to the dynamics of the saccade. It was expected that only one would remain significant in the final model. But the saccadic duration does a good job of discriminating between the RBD group and the PD and Control group, where the average saccadic velocity discriminates between the PD group and the Control and RBD.

The probability profiles of these parameters in Figure 4 indicate potential main sequence differences that need to be explored further. Overall it appears that during the predictive task, the PD group is making hypometric movements, this would mean that the saccadic duration, velocity and acceleration should also decrease. But there is no significant difference in saccadic duration between PDs and Controls, despite the differences in amplitude and velocity. Saccadic main sequence differences have not been reported in any studies that could be found by the author. A main sequence difference is expected to be consistent in the population over all tasks. In the HST and VST tasks there is a similar effect seen where the amplitudes of the PD group are significantly smaller, and the saccadic durations are not significantly different. This may indicate slowed saccades in Parkinson's Disease. A main sequence analysis needs to be conducted in order to see if the saccadic durations are significantly slower in PD than controls because this analysis only looked at the averaged values of all the saccades.

Adding UPDRS as a predictor to the model allowed it to be compared with the standard in diagnosis for PD and to see if the eye movement parameters would still add discriminatory power to the overall model. Including the UPDRS resulted in more accuracy for classification of all groups (Table 16) but still falls short when trying to place the "Other" movement disorders together. With only small numbers of the "Other" movement disorders, they were all grouped together in order to see if there was still an ability to distinguish between them and the PD patients. This leads to much higher variance within the other movement disorders group and makes them much more difficult to distinguish between.

Within the predictive model, no PD patients have been mis-classified as controls and no controls have been mis-classified as PD or "Other" movement disorders. Within the RBD group, further exploration must be done to understand how the progression of the disease and how the time since diagnosis can change the severity of symptoms. It is possible that in the early stages of RBD, a subject may present more similarly to a control in their eye movements and towards the later stages may appear closer to a PD patient. There is also a chance that someone with RBD

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may never develop PD, but more follow-ups are needed to assess disease progression in relation to eye movements and the predictive model. An early PD patient may look more like an RBD subject due to the nature of neurodegenerative disease.

4.6 Discrimination between Pairs of Diagnostic Groups

The sensitivity and specificity of the model is certainly over predicted because the model was developed based on the data that was tested on. Confirmatory testing with more data needs to be completed in order to come up with an accurate accuracy value for distinguishing between groups. Because the eye tracking tasks have been narrowed down to what seem to be the most sensitive, Predictive and Horizontal Step, the testing would take up much less time and the test could be combined into one faster screening test.

The PD vs "Other" group was close to 90% accurate when comparing the two groups. PD being misdiagnosed as other diseases, and vice versa, is a large problem because the symptoms are so closely related the in early stages. This shows a lot of potential for differentiating between the disease states quickly and accurately. The other very accurate measure was RBD vs Control. REM Behavior disorder is currently diagnosed with sleep studies and questionnaires (Boeve, 2010). The model offers potential for a screening when someone begins reporting symptoms of REM behavior disorder before committing to a full sleep study. More follow up visits need to be done in order to see if any RBD subjects convert to PD and if that change was visible before the clinical change.

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Conclusion

This research has been successful in understanding that combinations of eye tracking parameters from simple tasks can be used to distinguish between Parkinson's Disease and commonly confounded movement disorders with parkinsonism symptoms. When UPDRS is included as a predictor, it results in an accuracy of 88% for distinguishing PD. This is higher than the 74% accuracy of general practitioners and the 82% accuracy of movement disorder specialists. A confirmatory study needs to be done to prove the model is accurate, but the preliminary results are very promising. When discriminating between PD's and Controls, the model achieved an 89% accuracy. when discriminating between Controls and RBDs, an 88% accuracy was achieved. These accuracy values give good indication that in a confirmatory study should have relatively high accuracy distinguishing between the four groups. The analysis completed, while large, was still very superficial and there are still massive amounts of data available that need to be analyzed further. Adding an analysis of the two-dimensional measures may further improve the discrimination within the model. A main sequence analysis needs to be done on the data from the reflexive saccadic tasks to explore the phenomena of the apparent slowed saccades in PD. The reading data should be analyzed for the effects of text difficulty and fatigue. The use of the site as a predictor included in the model is a major downfall that will need to be updated in order to confirm there is still high accuracy. Without enough follow-up visits, the RBD subjects could not be tracked in order to see which ones develop PD. Once follow-up visits have been completed and some conversions from RBD to PD have been seen the model will need to be updated to see if PD is distinguishable in eye movements before it can be seen clinically. With such high error rates in diagnosing PD clinically, this model is a potentially beneficial and easy screening tool to add to the suite of diagnostic tests and improve clinician's ability to diagnose accurately.

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Appendix

Table 22: Comparison of Halves of Predictive Test

Parameter	Period	Dx	Estimate	95% CI		ProbF	Interaction	Correlation
001_abs_saccadic_amplitude_H	00-15s		6.357	6.091	6.623	0.0000	0.2312	0.81
001_abs_saccadic_amplitude_H	15-30s		6.788	6.475	7.100			
001_abs_saccadic_amplitude_H	00-15s	Control	6.465	5.995	6.936	0.0014		
001_abs_saccadic_amplitude_H	15-30s	Control	7.007	6.455	7.559			
001_abs_saccadic_amplitude_H	00-15s	PD	5.708	5.302	6.114	0.1361		
001_abs_saccadic_amplitude_H	15-30s	PD	5.923	5.446	6.400			
001_abs_saccadic_amplitude_H	00-15s	RBD	6.831	6.290	7.372	0.0008		
001_abs_saccadic_amplitude_H	15-30s	RBD	7.488	6.853	8.123			
001_abs_saccadic_amplitude_H	00-15s	Other	6.423	5.750	7.097	0.1952		
001_abs_saccadic_amplitude_H	15-30s	Other	6.733	5.942	7.523			
001_abs_saccadic_amplitude_V	00-15s		0.643	0.557	0.729	0.0200	0.5174	0.95
001_abs_saccadic_amplitude_V	15-30s		0.607	0.512	0.702			
001_abs_saccadic_amplitude_V	00-15s	Control	0.574	0.422	0.726	0.0692		
001_abs_saccadic_amplitude_V	15-30s	Control	0.525	0.357	0.693			
001_abs_saccadic_amplitude_V	00-15s	PD	0.682	0.551	0.813	0.0234		
001_abs_saccadic_amplitude_V	15-30s	PD	0.629	0.484	0.774			
001_abs_saccadic_amplitude_V	00-15s	RBD	0.754	0.580	0.929	0.9489		
001_abs_saccadic_amplitude_V	15-30s	RBD	0.756	0.564	0.949			
001_abs_saccadic_amplitude_V	00-15s	Other	0.562	0.344	0.779	0.2692		
001_abs_saccadic_amplitude_V	15-30s	Other	0.519	0.279	0.759			
002_saccadic_duration_H	00-15s		44.198	42.704	45.692	0.0000	0.5550	0.86
002_saccadic_duration_H	15-30s		47.351	45.704	48.998			
002_saccadic_duration_H	00-15s	Control	41.577	38.935	44.219	0.0000		
002_saccadic_duration_H	15-30s	Control	45.154	42.242	48.066			
002_saccadic_duration_H	00-15s	PD	42.620	40.339	44.901	0.0000		
002_saccadic_duration_H	15-30s	PD	45.405	42.890	47.919			

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002_saccadic_duration_H	00-15s	RBD	48.599	45.561	51.637	0.0000		
002_saccadic_duration_H	15-30s	RBD	52.564	49.215	55.913			
002_saccadic_duration_H	00-15s	Other	43.997	40.215	47.780	0.0386		
002_saccadic_duration_H	15-30s	Other	46.282	42.112	50.451			
002_saccadic_duration_V	00-15s		25.320	24.322	26.319	0.2059	0.6577	0.84
002_saccadic_duration_V	15-30s		24.925	23.808	26.042			
002_saccadic_duration_V	00-15s	Control	24.653	22.887	26.419	0.4648		
002_saccadic_duration_V	15-30s	Control	24.250	22.275	26.224			
002_saccadic_duration_V	00-15s	PD	26.322	24.797	27.846	0.1503		
002_saccadic_duration_V	15-30s	PD	25.635	23.930	27.340			
002_saccadic_duration_V	00-15s	RBD	26.313	24.282	28.344	0.6917		
002_saccadic_duration_V	15-30s	RBD	26.564	24.293	28.835			
002_saccadic_duration_V	00-15s	Other	23.994	21.465	26.522	0.3473		
002_saccadic_duration_V	15-30s	Other	23.251	20.423	26.079			
003_avg_saccadic_velocity_H	00-15s		112.905	108.889	116.922	0.8880	0.6387	0.84
003_avg_saccadic_velocity_H	15-30s		113.087	108.374	117.800			
003_avg_saccadic_velocity_H	00-15s	Control	119.069	111.968	126.171	0.6803		
003_avg_saccadic_velocity_H	15-30s	Control	120.010	111.676	128.344			
003_avg_saccadic_velocity_H	00-15s	PD	100.417	94.285	106.549	0.3409		
003_avg_saccadic_velocity_H	15-30s	PD	98.538	91.342	105.733			
003_avg_saccadic_velocity_H	00-15s	RBD	117.304	109.137	125.472	0.4389		
003_avg_saccadic_velocity_H	15-30s	RBD	119.338	109.753	128.922			
003_avg_saccadic_velocity_H	00-15s	Other	114.830	104.662	124.999	0.9104		
003_avg_saccadic_velocity_H	15-30s	Other	114.463	102.531	126.395			
003_avg_saccadic_velocity_V	00-15s		21.958	20.236	23.679	0.0382	0.2538	0.90
003_avg_saccadic_velocity_V	15-30s		21.135	19.341	22.928			
003_avg_saccadic_velocity_V	00-15s	Control	20.666	17.622	23.710	0.2856		
003_avg_saccadic_velocity_V	15-30s	Control	19.921	16.750	23.092			
003_avg_saccadic_velocity_V	00-15s	PD	22.668	20.039	25.296	0.0012		
003_avg_saccadic_velocity_V	15-30s	PD	20.680	17.942	23.417			
003_avg_saccadic_velocity_V	00-15s	RBD	23.775	20.274	27.276	0.6630		
003_avg_saccadic_velocity_V	15-30s	RBD	23.426	19.779	27.073			
003_avg_saccadic_velocity_V	00-15s	Other	20.721	16.363	25.080	0.8343		

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003_avg_saccadic_velocity_V	15-30s	Other	20.513	15.973	25.053			
008_abs_peak_velocity_H	00-15s		185.879	177.397	194.361	0.0001	0.1450	0.88
008_abs_peak_velocity_H	15-30s		195.193	185.445	204.942			
008_abs_peak_velocity_H	00-15s	Control	185.456	170.458	200.453	0.0043		
008_abs_peak_velocity_H	15-30s	Control	197.532	180.297	214.768			
008_abs_peak_velocity_H	00-15s	PD	181.252	168.303	194.201	0.6173		
008_abs_peak_velocity_H	15-30s	PD	183.053	168.172	197.934			
008_abs_peak_velocity_H	00-15s	RBD	185.938	168.690	203.185	0.0044		
008_abs_peak_velocity_H	15-30s	RBD	199.808	179.987	219.630			
008_abs_peak_velocity_H	00-15s	Other	190.871	169.398	212.344	0.1131		
008_abs_peak_velocity_H	15-30s	Other	200.380	175.702	225.057			
008_abs_peak_velocity_V	00-15s		39.297	36.082	42.512	0.0691	0.4954	0.93
008_abs_peak_velocity_V	15-30s		38.042	34.342	41.742			
008_abs_peak_velocity_V	00-15s	Control	37.731	32.047	43.415	0.2653		
008_abs_peak_velocity_V	15-30s	Control	36.376	29.834	42.918			
008_abs_peak_velocity_V	00-15s	PD	40.462	35.554	45.369	0.0087		
008_abs_peak_velocity_V	15-30s	PD	37.682	32.034	43.330			
008_abs_peak_velocity_V	00-15s	RBD	42.209	35.672	48.746	0.6584		
008_abs_peak_velocity_V	15-30s	RBD	41.592	34.068	49.116			
008_abs_peak_velocity_V	00-15s	Other	36.786	28.648	44.924	0.8776		
008_abs_peak_velocity_V	15-30s	Other	36.518	27.151	45.885			
009_abs_peak_acceleration_H	00-15s		10124.286	9620.447	10628.125	0.0000	0.0392	0.90
009_abs_peak_acceleration_H	15-30s		10668.828	10089.887	11247.769			
009_abs_peak_acceleration_H	00-15s	Control	10120.064	9229.224	11010.905	0.0009		
009_abs_peak_acceleration_H	15-30s	Control	10866.633	9843.003	11890.262			
009_abs_peak_acceleration_H	00-15s	PD	9964.201	9195.052	10733.350	0.8730		
009_abs_peak_acceleration_H	15-30s	PD	9994.774	9110.976	10878.573			

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009_abs_peak_acceleration_H	00-15s	RBD	10066.133	9041.636	11090.631	0.0026		
009_abs_peak_acceleration_H	15-30s	RBD	10846.166	9668.956	12023.376			
009_abs_peak_acceleration_H	00-15s	Other	10346.745	9071.256	11622.234	0.0518		
009_abs_peak_acceleration_H	15-30s	Other	10967.738	9502.124	12433.352			
009_abs_peak_acceleration_V	00-15s		2478.109	2274.046	2682.171	0.9895	0.2472	0.83
009_abs_peak_acceleration_V	15-30s		2477.283	2261.904	2692.661			
009_abs_peak_acceleration_V	00-15s	Control	2376.276	2015.472	2737.080	0.9792		
009_abs_peak_acceleration_V	15-30s	Control	2373.378	1992.567	2754.190			
009_abs_peak_acceleration_V	00-15s	PD	2612.783	2301.266	2924.300	0.0575		
009_abs_peak_acceleration_V	15-30s	PD	2429.397	2100.606	2758.189			
009_abs_peak_acceleration_V	00-15s	RBD	2607.394	2192.457	3022.331	0.4187		
009_abs_peak_acceleration_V	15-30s	RBD	2710.866	2272.919	3148.813			
009_abs_peak_acceleration_V	00-15s	Other	2315.982	1799.389	2832.574	0.6174		
009_abs_peak_acceleration_V	15-30s	Other	2395.489	1850.250	2940.728			
011_abs_mean_acceleration_H	00-15s		6397.461	6111.199	6683.723	0.8996	0.4120	0.87
011_abs_mean_acceleration_H	15-30s		6407.475	6084.446	6730.505			
011_abs_mean_acceleration_H	00-15s	Control	6551.533	6045.391	7057.675	0.7239		
011_abs_mean_acceleration_H	15-30s	Control	6601.148	6029.997	7172.298			
011_abs_mean_acceleration_H	00-15s	PD	5887.669	5450.668	6324.671	0.1373		
011_abs_mean_acceleration_H	15-30s	PD	5706.820	5213.691	6199.950			
011_abs_mean_acceleration_H	00-15s	RBD	6501.445	5919.364	7083.526	0.4600		
011_abs_mean_acceleration_H	15-30s	RBD	6620.851	5964.008	7277.694			
011_abs_mean_acceleration_H	00-15s	Other	6649.197	5924.512	7373.882	0.7964		
011_abs_mean_acceleration_H	15-30s	Other	6701.082	5883.319	7518.845			
011_abs_mean_acceleration_V	00-15s		1529.531	1392.662	1666.399	0.0187	0.6001	0.88
011_abs_mean_acceleration_V	15-30s		1445.040	1294.626	1595.453			
011_abs_mean_acceleration_V	00-15s	Control	1458.466	1216.468	1700.464	0.1657		
011_abs_mean_acceleration_V	15-30s	Control	1371.001	1105.053	1636.948			
011_abs_mean_acceleration_V	00-15s	PD	1536.147	1327.206	1745.087	0.0050		
011_abs_mean_acceleration_V	15-30s	PD	1381.546	1151.927	1611.164			

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011_abs_mean_acceleration_V	00-15s	RBD	1613.978	1335.672	1892.285	0.3841		
011_abs_mean_acceleration_V	15-30s	RBD	1550.945	1245.096	1856.794			
011_abs_mean_acceleration_V	00-15s	Other	1509.532	1163.044	1856.021	0.7152		
011_abs_mean_acceleration_V	15-30s	Other	1476.667	1095.888	1857.446			
013_mean_fixation_time_H	00-15s		323.803	308.844	338.762	0.0346	0.8407	0.64
013_mean_fixation_time_H	15-30s		308.902	291.681	326.124			
013_mean_fixation_time_H	00-15s	Control	338.463	312.014	364.912	0.4483		
013_mean_fixation_time_H	15-30s	Control	329.071	298.622	359.521			
013_mean_fixation_time_H	00-15s	PD	298.893	276.057	321.730	0.2994		
013_mean_fixation_time_H	15-30s	PD	287.788	261.498	314.079			
013_mean_fixation_time_H	00-15s	RBD	350.283	319.866	380.700	0.0780		
013_mean_fixation_time_H	15-30s	RBD	325.071	290.053	360.089			
013_mean_fixation_time_H	00-15s	Other	307.573	269.704	345.443	0.4333		
013_mean_fixation_time_H	15-30s	Other	293.678	250.080	337.275			
013_mean_fixation_time_V	00-15s		455.227	407.383	503.071	0.3045	0.7402	0.84
013_mean_fixation_time_V	15-30s		441.471	397.617	485.325			
013_mean_fixation_time_V	00-15s	Control	448.389	363.796	532.981	0.9944		
013_mean_fixation_time_V	15-30s	Control	448.222	370.684	525.761			
013_mean_fixation_time_V	00-15s	PD	434.865	361.828	507.902	0.8341		
013_mean_fixation_time_V	15-30s	PD	430.588	363.641	497.535			
013_mean_fixation_time_V	00-15s	RBD	462.159	364.875	559.444	0.8004		
013_mean_fixation_time_V	15-30s	RBD	455.284	366.111	544.456			
013_mean_fixation_time_V	00-15s	Other	475.496	354.377	596.614	0.1980		
013_mean_fixation_time_V	15-30s	Other	431.789	320.771	542.808			
016_overall_rms_velocity_H	00-15s		4.987	4.380	5.593	0.0630	0.9007	0.80
016_overall_rms_velocity_H	15-30s		5.487	4.621	6.354			
016_overall_rms_velocity_H	00-15s	Control	4.181	3.109	5.253	0.5602		
016_overall_rms_velocity_H	15-30s	Control	4.457	2.925	5.989			
016_overall_rms_velocity_H	00-15s	PD	5.952	5.026	6.878	0.1126		
016_overall_rms_velocity_H	15-30s	PD	6.603	5.280	7.926			
016_overall_rms_velocity_H	00-15s	RBD	4.306	3.072	5.539	0.5386		
016_overall_rms_velocity_H	15-30s	RBD	4.640	2.879	6.402			
016_overall_rms_velocity_H	00-15s	Other	5.509	3.973	7.044	0.2753		

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016_overall_rms_velocity_H	15-30s	Other	6.249	4.056	8.442			
016_overall_rms_velocity_V	00-15s		6.729	6.154	7.303	0.0533	0.8086	0.70
016_overall_rms_velocity_V	15-30s		7.348	6.472	8.225			
016_overall_rms_velocity_V	00-15s	Control	5.648	4.633	6.664	0.0975		
016_overall_rms_velocity_V	15-30s	Control	6.586	5.036	8.135			
016_overall_rms_velocity_V	00-15s	PD	7.085	6.208	7.962	0.5085		
016_overall_rms_velocity_V	15-30s	PD	7.407	6.069	8.744			
016_overall_rms_velocity_V	00-15s	RBD	6.109	4.941	7.277	0.6031		
016_overall_rms_velocity_V	15-30s	RBD	6.446	4.664	8.228			
016_overall_rms_velocity_V	00-15s	Other	8.073	6.619	9.527	0.2749		
016_overall_rms_velocity_V	15-30s	Other	8.955	6.736	11.173			
017_avg_rms_velocity_H	00-15s		2.923	2.706	3.140	0.0026	0.8850	0.91
017_avg_rms_velocity_H	15-30s		3.068	2.843	3.293			
017_avg_rms_velocity_H	00-15s	Control	2.682	2.299	3.065	0.2948		
017_avg_rms_velocity_H	15-30s	Control	2.770	2.372	3.167			
017_avg_rms_velocity_H	00-15s	PD	3.219	2.889	3.550	0.0612		
017_avg_rms_velocity_H	15-30s	PD	3.355	3.012	3.699			
017_avg_rms_velocity_H	00-15s	RBD	2.652	2.211	3.093	0.0635		
017_avg_rms_velocity_H	15-30s	RBD	2.831	2.374	3.289			
017_avg_rms_velocity_H	00-15s	Other	3.139	2.590	3.688	0.1439		
017_avg_rms_velocity_H	15-30s	Other	3.314	2.745	3.884			
017_avg_rms_velocity_V	00-15s		3.988	3.758	4.217	0.0000	0.3689	0.84
017_avg_rms_velocity_V	15-30s		4.284	4.039	4.529			
017_avg_rms_velocity_V	00-15s	Control	3.834	3.429	4.239	0.0639		
017_avg_rms_velocity_V	15-30s	Control	4.060	3.626	4.493			
017_avg_rms_velocity_V	00-15s	PD	4.106	3.756	4.456	0.0031		
017_avg_rms_velocity_V	15-30s	PD	4.420	4.045	4.794			
017_avg_rms_velocity_V	00-15s	RBD	3.786	3.320	4.252	0.0005		
017_avg_rms_velocity_V	15-30s	RBD	4.284	3.785	4.782			
017_avg_rms_velocity_V	00-15s	Other	4.224	3.644	4.804	0.3890		
017_avg_rms_velocity_V	15-30s	Other	4.374	3.753	4.994			
018_mean_fixation_velocity_H	00-15s		-0.002	-0.003	-0.001	0.8969	0.7235	0.50
018_mean_fixation_velocity_H	15-30s		-0.002	-0.003	-0.001			

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018_mean_fixation_velocity_H	00-15s	Control	-0.002	-0.003	0.000	0.7053		
018_mean_fixation_velocity_H	15-30s	Control	-0.002	-0.004	0.000			
018_mean_fixation_velocity_H	00-15s	PD	-0.001	-0.002	0.001	0.3313		
018_mean_fixation_velocity_H	15-30s	PD	0.000	-0.002	0.001			
018_mean_fixation_velocity_H	00-15s	RBD	0.000	-0.002	0.002	0.6627		
018_mean_fixation_velocity_H	15-30s	RBD	0.001	-0.001	0.003			
018_mean_fixation_velocity_H	00-15s	Other	-0.005	-0.007	-0.002	0.6397		
018_mean_fixation_velocity_H	15-30s	Other	-0.006	-0.008	-0.003			
018_mean_fixation_velocity_V	00-15s		0.000	-0.001	0.001	0.3143	0.0162	0.59
018_mean_fixation_velocity_V	15-30s		0.001	-0.001	0.002			
018_mean_fixation_velocity_V	00-15s	Control	0.000	-0.002	0.002	0.3711		
018_mean_fixation_velocity_V	15-30s	Control	-0.001	-0.004	0.001			
018_mean_fixation_velocity_V	00-15s	PD	0.001	-0.001	0.003	0.1546		
018_mean_fixation_velocity_V	15-30s	PD	0.000	-0.002	0.002			
018_mean_fixation_velocity_V	00-15s	RBD	0.000	-0.002	0.003	0.0097		
018_mean_fixation_velocity_V	15-30s	RBD	0.003	0.000	0.006			
018_mean_fixation_velocity_V	00-15s	Other	-0.001	-0.004	0.003	0.3296		
018_mean_fixation_velocity_V	15-30s	Other	0.001	-0.003	0.005			
019_abs_fixation_velocity_H	00-15s		0.020	0.015	0.024	0.0186	0.7863	0.88
019_abs_fixation_velocity_H	15-30s		0.024	0.017	0.030			
019_abs_fixation_velocity_H	00-15s	Control	0.015	0.007	0.023	0.5133		
019_abs_fixation_velocity_H	15-30s	Control	0.017	0.005	0.028			
019_abs_fixation_velocity_H	00-15s	PD	0.027	0.020	0.034	0.1048		
019_abs_fixation_velocity_H	15-30s	PD	0.031	0.021	0.041			
019_abs_fixation_velocity_H	00-15s	RBD	0.014	0.005	0.024	0.4091		
019_abs_fixation_velocity_H	15-30s	RBD	0.017	0.004	0.031			
019_abs_fixation_velocity_H	00-15s	Other	0.022	0.010	0.034	0.1006		
019_abs_fixation_velocity_H	15-30s	Other	0.029	0.013	0.046			
019_abs_fixation_velocity_V	00-15s		0.024	0.020	0.028	0.0053	0.9467	0.82
019_abs_fixation_velocity_V	15-30s		0.029	0.023	0.036			
019_abs_fixation_velocity_V	00-15s	Control	0.021	0.013	0.029	0.0478		
019_abs_fixation_velocity_V	15-30s	Control	0.028	0.016	0.039			
019_abs_fixation_velocity_V	00-15s	PD	0.028	0.021	0.034	0.1016		

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019_abs_fixation_velocity_V	15-30s	PD	0.033	0.023	0.042			
019_abs_fixation_velocity_V	00-15s	RBD	0.019	0.010	0.027	0.1048		
019_abs_fixation_velocity_V	15-30s	RBD	0.025	0.012	0.038			
019_abs_fixation_velocity_V	00-15s	Other	0.028	0.018	0.039	0.4377		
019_abs_fixation_velocity_V	15-30s	Other	0.032	0.016	0.048			
023_abs_Latency_Td_H	00-15s		193.095	185.541	200.650	0.0076	0.5075	0.57
023_abs_Latency_Td_H	15-30s		184.081	177.556	190.605			
023_abs_Latency_Td_H	00-15s	Control	191.663	178.306	205.020	0.0576		
023_abs_Latency_Td_H	15-30s	Control	180.392	168.856	191.928			
023_abs_Latency_Td_H	00-15s	PD	181.619	170.087	193.152	0.7561		
023_abs_Latency_Td_H	15-30s	PD	180.037	170.077	189.997			
023_abs_Latency_Td_H	00-15s	RBD	206.656	191.295	222.017	0.1172		
023_abs_Latency_Td_H	15-30s	RBD	195.983	182.716	209.250			
023_abs_Latency_Td_H	00-15s	Other	192.443	173.319	211.568	0.1394		
023_abs_Latency_Td_H	15-30s	Other	179.910	163.393	196.428			
023_abs_Latency_Td_V	00-15s		206.675	183.308	230.041			
023_abs_Latency_Td_V	00-15s	Control	200.550	159.056	242.044			
023_abs_Latency_Td_V	00-15s	PD	214.815	179.103	250.527			
023_abs_Latency_Td_V	00-15s	RBD	215.133	167.220	263.046			
023_abs_Latency_Td_V	00-15s	Other	196.200	137.519	254.881			
025_Td_Lag_H	00-15s		193.208	185.618	200.798	0.0163	0.5263	0.59
025_Td_Lag_H	15-30s		185.164	178.349	191.980			
025_Td_Lag_H	00-15s	Control	191.731	178.311	205.151	0.0994		
025_Td_Lag_H	15-30s	Control	182.031	169.981	194.081			
025_Td_Lag_H	00-15s	PD	181.493	169.906	193.079	0.8783		
025_Td_Lag_H	15-30s	PD	180.718	170.314	191.122			
025_Td_Lag_H	00-15s	RBD	207.167	191.734	222.601	0.1471		
025_Td_Lag_H	15-30s	RBD	197.362	183.504	211.220			
025_Td_Lag_H	00-15s	Other	192.443	173.229	211.658	0.1576		
025_Td_Lag_H	15-30s	Other	180.547	163.294	197.800			

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