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Oculomotor Control in Patients with Parkinson's Disease

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

By

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Richmond, Virginia

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Acknowledgement

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Abstract

OCULOMOTOR CONTROL IN PATIENTS WITH PARKINSON'S DISEASE

George T. Gitchel Jr., Bachelor of Science, Biomedical Engineering

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

Virginia Commonwealth University, 2009

Paul Wetzel Ph.D. Biomedical Engineering.

There have been few studies investigating the eye movement behavior of Parkinson's disease patients during fixation. This study objectively measured the eye movements of 36 patients with Parkinson's disease, and 20 age matched controls. Stimuli consisted of ten standardized text passages first organized by Miller and Coleman (9). In addition, subjects followed a randomly displaced step jump target motion. Pendular nystagmus was found in all Parkinson's subjects, with an average frequency of 7.44 Hz. Saccadic peak velocity and duration along the main sequence were not statistically different from controls. A slower rate of reading was also noted in the Parkinson's group in terms of characters per minute, but with no more regressions than normal. Rate of square wave jerks was also found to be normal. This suggests that the hallmark feature of eye movements in Parkinson's disease is a pendular nystagmus during fixation, and all saccadic activity to be normal.

Introduction

Eye movements have been recorded using various techniques for over a century, and finer details

of the mechanics and mechanisms of those movements are discovered every year. When reading

or following a random step displaced target, there are three principle movements that the eye can

make. A fixation is a period of time, typically close to 200 ms, in which the eye remains stable

and gathers visual information about the world around us. These fixations allow us to stabilize

an image of the world on the fovea, which allows us clear, high resolution, color images of our

surroundings. Outside of the narrow fovea that occupies only half a degree of visual angle;

visual acuity drops off very quickly, and vision is less clear in this periphery (1). Thus, the

fixations must remain stable, and have velocities less than five degrees per second in order to

maintain a stable image on the fovea (2). If the fixation is not stable, and moves at more than

about five degrees per second, the image of the world can appear to jump about, and objects are

less well resolved. In a healthy person with good oculomotor control, the fixation is commonly

interrupted by small amounts of drift, and small corrective movements, which can either bring

the fovea back to the intended target, or degrade the image by moving it away from the target. In

between each fixation, a movement called a saccade is generated, and the main purpose is to

focus the fovea on a new point in space, and begin a new fixation and acquisition of visual

information. Saccades are voluntary, high velocity, short duration movements that rotate the

globe of the eye to a new position quickly and accurately. The peak velocity and duration of a saccade are directly related to its amplitude, along the main sequence (1). There is a third state of movement, known as smooth pursuit in which the eyes match the velocity of a target, up to around 8°/second (3). Smooth pursuit is an involuntary movement which requires a moving target to track in order for the type of movement to occur. Thus, humans are incapable of eliciting smooth pursuit type movements without a target to follow. Different types of disease and disorders can affect the parameters of each of these eye movements in many different ways, and are continually being investigated. Dysfunctions of different types of eye movements can be mapped to different locations in the brain, making certain eye movements useful in some bedside examinations. Of interest in the current study is the oculomotor function of the family of movement disorders, more specifically, Parkinson's disease.

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of voluntary motor control, resting tremor, gait disturbances, and other well documented symptoms. These symptoms are due directly to a loss of dopaminergic neurotransmitters in the basal ganglia locus of the brain. Previous studies have shown that the skeletal musculature that controls the movement of the eyes is also affected by the disease (4; 5; 6; 1; 7). Some have argued that Parkinson's disease patients have reduced saccadic velocity, and increased reaction times (8; 6; 9; 10). Others claim that square wave jerks are more prevalent during fixations in patients with PD (11; 12; 13; 14). Some sources claim there is no difference in saccades or square wave jerks, but that the difference only exists during the onset of smooth pursuit of a target moving at constant velocity (8; 15; 16; 6). Clearly, there is a significant disparity between researchers concerning the deficient eye movements of Parkinson's disease patients, and which of the movements are clinically relevant. Recent changes in medicine's understanding of the disorder,

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as well as improvements in the accuracy and ease of use of eye tracking equipment may help elucidate any true differences between Parkinson's disease and other movement disorders. Surprisingly, very little consideration has been paid to the aspects of a fixation in the disease. Stable fixations are required for clear, high resolution vision, and for high acuity. If fixations are not stable, the image of the world can smear on the back of the retina, leading to blurred vision that is not correctable with prescription lenses. This could be a potential problem for patients with Parkinson's disease if their eyes exhibit tremor as their limbs do. In addition, little attention has been paid to the effect of the disease on reading. Since Parkinson's disease is most notably characterized by a tremor at rest, this study was intended to investigate the abnormalities of oculomotor control during rest and fixations. In addition, previously studied parameters such as saccades, latencies, and square wave jerks will all be investigated as well, in order to better understand the movement disorder. Since differential diagnosis is usually difficult with Parkinson's disease and other movement disorders; and since our understanding of PD has improved even over the last 10 years, the confirmed patients in this study may provide more accurate data than those in past studies. Due to previous inadequacies of measure, this study was intent on finding the true oculomotor functions of Parkinson's disease patients in all areas. With our current understanding of disease states and ocular motor function, specific disorders of eye movements related exclusively to Parkinson's disease will be shown with this study. In addition, previously unexplored features of the disorder, such as fixations and reading, will be recorded and reported. The end goal with this study is to discover the root oculomotor behavior of Parkinson's disease, such that it may be used in the future as a diagnostic tool. It is hypothesized that using the following parameters, that it will be possible to detect Parkinson's disease in a pre-

clinical state, and also to reliably differentiate Parkinson's disease from other movement disorders. As such, the following points will be investigated and reported;

- Fixation characteristics of subjects

- Various methods of quantifying fixation instability

- Saccadic functions; Velocity, duration, and main sequence

- Square Wave Jerks

- Latencies or reaction times

- Reading metrics; including rate, perceptual span, and other various parameters

- Examine results and compare to neurological models of Parkinson's disease

Methods

Gaze was recorded from 36 patients with Parkinson's disease (mean age: 68, SD: 7.5), and 20

age matched controls (mean: 62.9, SD: 6.93), all of whom gave written informed consent that

was approved by the McGuire Veteran's Affairs Institutional Review Board. All patients were

pharmacologically confirmed as having idiopathic PD (shown a substantial improvement with a

dopaminergic drug), and were clinically examined in the Parkinson's Disease Research,

Education, and Clinical Center (PADRECC), by a nurse and a neurologist specializing in

movement disorders. If small strokes occur in the basal ganglia, the patient may present as

having symptoms of Parkinson's disease, despite the vascular origin of the symptoms. In

addition, some drugs such as Depakote, Lithium, Abilify, etc, are thought to induce Parkinson's

disease like symptoms (17). Due to the different pathologies of these disorders, any patients

suspected of having an induced Parkinsonism (either drug induced or vascular origin), or any

other additional neurological disorders besides PD were excluded from this study. This ensured

that all patients in the study were confirmed as having Parkinson's disease and nothing else. All

patients were non-demented, and had a Mini-Mental State Exam (MMSE) score of at least 24.

Patients also underwent an exam that rates the Unified Parkinson's Disease Rating Scale

(UPDRS), that is a widely used measure of disease severity (mean: 12.1, SD: 9.69). In addition,

subjects completed the Visual Functioning Questionnaire to screen for any preexisting visual

complaints (18). Data were collected using a video based binocular eye tracker (Eyelink II, SR

Research Ltd, Ontario, Canada), set to record at 500 Hz with 0.01°RMS resolution, while

tracking subject gaze. This eye tracking device illuminates the eye with infrared light, and tracks

the center of the dark pupil, using a small camera placed below each eye, out of the field of

vision. Infrared emitters mounted on the monitor were tracked with the forward facing camera to

compensate for head movement and tremor. The combination of the dark pupil image and the

head tracking camera were combined in the software supplied by SR Research to calculate gaze

angle with a resolution of 0.01° RMS. Stimulus was presented in a darkened room on a LCD

monitor (MultiSync EA 261WM, NEC), placed 75 cm from the patient's eyes.   The height

adjustable display was positioned so that midline on the monitor occupied the same horizontal

plane as the patient's eye. Subjects were seated in a straight backed, non-reclining, non-swivel

chair without wheels. This minimized any extraneous movement of the subject, as persons in a

non-fixed back chair have a tendency to swivel or recline, which could induce error in the

recording. A head restraint was not used due to the unpredictable and uncontrollable nature of

the tremor in the disease, and also to minimize setup time and patient discomfort. Calibration

and validation of the eye tracker was performed on a nine point grid, four times per subject, and

was automated by the SR Research software. This calibration was repeated until the quality of

calibration repeatability was considered "good" by the automated SR research software. This

resulted in a calibration that was accurate to within $0.4°$ over repeated trials of target

displacement. Since the fovea occupies 0.5° of visual angle, this is a reasonable accuracy level

due to the fact that the subject will still be foveating the intended target when positional error is

less than 0.4°. If the calculated error of calibration was above 0.4°, the calibration and validation

procedure was repeated until the error reached an acceptable level of

Patient	Age	UPDRS	Dopa-equivalent	RMS Velocity	SD Velocity	SWJ's / Min	Saccade Latency (ms)	Nystagmus Frequency	Nystagmus Amplitude (°)
1	69	31	1187.5	5.21	5.02	9	292.8	14.5	0.18
2	70	16	2125	7.45	7.27	12	237.8	10.0	0.14
3	68	15	500	6.39	6.18	9	219.4	12.2	0.87
4	65	13	750	7.75	7.09	5	164.2	4.6	0.69
5	82	10	750	5.25	5.14	8	245.6	6.5	0.32
6	58	14	0-500	3.89	3.55	1	225.8	4.6	0.23
7	71	34	2312.5	14.70	13.14	28	231.2	9.5	1.06
8	58	22	1093.75	5.36	4.78	19	193.0	5.7	0.35
9	66	23	375	6.41	6.15	30	241.0	11.9	0.39
10	67	14	0-375	4.63	4.40	6	238.4	5.0	0.32
11	70	11	1000	3.56	3.36	12	239.0	5.0	0.09
12	73	10	1350	2.49	2.33	2	335.0	7.2	0.16
13	57	8	750	3.64	3.46	8	229.8	5.2	0.12
14	65	15	375	4.53	4.35	16	190.0	5.5	0.21
15	57	18	0-750	6.52	5.80	7	204.0	5.6	0.09
16	74	14	1500	5.13	4.88	19	233.2	5.9	0.16
17	66	24	875	4.38	4.12	8	291.4	8.7	0.16
18	77	10	500	5.33	4.17	7	194.8	9.1	0.09
19	58	30	1093.75	5.14	4.80	32	181.4	8.8	0.12
20	56	19	500	3.37	3.24	5	195.6	12.5	0.18
21	73	12	375	6.26	5.99	5	205.8	8.1	0.16
22	73	18	1000	6.10	5.93	31	227.6	9.3	0.09
23	55	26	1100	10.10	9.96	2	226.8	5.3	1.63
24	68	6	375	5.90	5.81	24	216.2	10.1	0.18
25	70	18	1937.5	9.16	8.60	8	304.8	8.6	0.41
26	55	17	375	4.23	3.93	16	289.4	6.1	0.21
27	80	11	500	7.09	6.81	10	281.4	4.8	0.16
28	65	13	1000	7.64	7.16	1	187.0	4.7	0.37
29	88	9	187.5	3.99	3.86	32	200.2	4.7	0.21
30	75	22	1000	4.22	4.09	25	284.6	4.1	0.28
31	68	19	0-330	4.36	4.18	5	220.0	13.3	0.14
32	68	14	1000	5.62	5.50	23	281.6	9.3	0.25
33	69	27	1437.5	5.22	5.06	14	236.6	5.4	0.30
34	75	21	1562.5	4.80	4.70	6	225.4	4.3	0.44
35	80	13	1750	6.92	6.57	6	269.2	7.3	0.12
36	68	20	1000	5.91	5.66	9	236.6	8.2	0.14

Table 1:List of PD Subjects

less than 0.4° on repeated trials. Subjects were presented with ten paragraphs described by Miller and Coleman (19), which were modified by Zuber and Wetzel. The initial prose passages from Miller and Coleman consisted of 36 passages, of varying length. These 36 prose passages are unique in that they are ranked in progressive difficulty by the cloze method. This method was used in such a way that a group of subjects was asked to predict the next word in the paragraph, based on contextual information. The higher the error rate of guessing the correct word, the more difficult the text is considered to be. 35 of the passages were truncated by Zuber and Wetzel to achieve an approximately equal number of character spaces in all passages. They were then grouped into 5 difficulty levels, which were then randomized for difficulty in a Latin Square matrix, so that 2 paragraphs of each of 5 difficulty levels were shown (20). This resulted in a set of ten different random orders of presentation, each with 10 paragraphs shown. They were randomized in such way that the patient would not be able to predict if the next paragraph would be more difficult or less difficult that then previous one presented. The typeface for these text passages was chosen to be Courier Bold. This is a monospaced font, meaning that each character and letter of the font occupies the same horizontal space. Therefore, each letter will subtend the same visual angle horizontally.   This is opposed to a proportional font such as the one used in typing this paper, in which an "i" will occupy a smaller visual angle than a "W". The text was set at a size such that it occupies 20° of visual angle across a sentence, with each letter occupying 0.5°. The average reading task took around 5 minutes for each subject to read all ten paragraphs. In a separate recording, subjects were also asked to follow a random target movement, consisting of step displacements in both the horizontal and vertical directions. Each stimulus in the tracking task lasted for 60 seconds, with a break in between, for a total of just over two minutes. The target for these stimuli was an annulus, sized to occupy 0.5° of visual

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angle, with a high contrast center point of 0.1°. Maximum range of movement was ±20° horizontally, and ±13° vertically. Due to the fact that the tracking target was the same size as the fovea, the minimum displacement for each and every movement was at a minimum 1.5° from the previous position. This requires the subject to make a saccade, and re-fixate on a new position, and not simply drift to the new target location. Both timing and amplitude of step displacements were random and unpredictable. The target remained at a single position for randomly assigned durations, between 0.4 and 2 seconds. Subjects were instructed and encouraged to close their eyes and rest between each recording to prevent fatigue. The automated experiment output data into a proprietary file, which was converted to ascii text using SR research supplied software, and then to binary for use in a previously written plotting program(Wetzel). Data were analyzed off line using a custom written plotting program, which allowed the experimenter to manually extract information from the data, and separate each saccade and each fixation. Saccadic threshold was set at 20°/sec, and was also judged qualitatively due to severe movements in some patients. Any movements of at least 0.25 degrees, and faster than 20°/second were considered to be a saccade. Data was reorganized into a more usable form using Microsoft Excel, while all statistical analysis was conducted using SPSS. For all statistical analysis, α was set to 0.05. Data was tested for normalcy using the Shapiro-Wilk test. Independent sample t-tests were conducted to determine any potential differences between PD and control population data. When conducting statistical analysis, Levene's test for the equality of variances was calculated, and if the significance was found to be less than 0.05, equal variances were not assumed. If equal variances were not assumed, then a Welch's t-test was used to compare the means, which has the ability to compensate for samples with unequal variances (21). These statistical methods were used for each of the parameters reported below. For all box plots shown below, the center line

within the box represents the median of the reported values, while the upper and lower edges of each box represent the first and third quartiles in the data. Upper and lower fences on the stems indicate the maxima and minima in the data that are not considered outliers. Any circle plotted past the outer fence is considered to be an outlier if it is more than one and a half times the interquartile range away from the median. In the case of an asterisk, this indicates an extreme outlier that exists at least three times the interquartile range away from the median. This graphical representation of the data is an excellent method for visually displaying the differences between one parameter of data between two or more different groups.

Finally, the dopa-equivalent (Mean: 925.8, S.D; 545.4) was calculated for each patient, and is shown in Table 1. The dopa-equivalent is a measure of the amount of dopaminergic drug administered per day. It is capable of compensating for various timing throughout the day, as well as the difference between controlled and immediate release. In addition, it accounts for the difference between dopamine replacement therapy, and dopamine receptor agonist drugs (22). This was calculated by taking the total regular dose of levodopa plus carbidopa, plus 0.75 times the dose of controlled release carbidopa plus levodopa, + 10x the dose of any dopamine agonist. This is a measure of what medication level the patients require to maintain control over their symptoms, and could be considered an additional rating of disease severity. Note in Table 1, that subject numbers 6, 10, and 31 have their total dopamine equivalent listed as 0-followed by a number. This indicates that at the time that their eye movements were recorded, they had not yet been prescribed any Parkinson's medication, indicating very short disease progression. The second number indicated the dose they were taking that sufficiently controlled their PD symptoms at a follow up appointment 6 months after the initial recording. No patients with deep brain stimulators were included in this study.

Results

Figure 1 shows pendular nystagmus in a typical PD patient when following the random step

displacement of a target. Pendular nystagmus is when the eyes move in a sinusoidal pattern

around the main intended target, in the horizontal, vertical, or both directions. Historically,

pendular nystagmus has been associated with certain specific brainstem strokes, diseases of

myelin (including multiple sclerosis), and albinism. Acquired pendular nystagmus, as opposed

to one of congenital origin, also usually features a torsional sinusoidal oscillation (1), but the

current equipment is incapable of tracking torsional movements. This pendular nystagmus

feature was seen in all PD patients, in all tasks, with magnitudes ranging from 0.14°-1.63°. To

determine the average frequency, the peak to peak time was estimated along waveforms in each

fixation during both target tracking and reading tasks, used to compute the frequency, and

averaged across all trials. Mean fundamental frequencies were between 4.3 and 14.49Hz for

patients with PD. No statistical difference was found between the tracking and reading tasks.

Mean magnitude of the waveform was 0.265° horizontally and 0.305° vertically, with a mean

frequency of 7.44 Hz. Due to the fact that this feature was seen in the eye movements of all

Parkinson's disease patients, this may lead to 100% sensitivity in detecting PD patients from a

population of controls. Unfortunately the pendular nystagmus will not reach 100% specificity to

PD, due to the documented occurrence of this specific pattern of movement in other disorders.

Only eight of the 34 patients had a larger horizontal component than vertical component; in all the remaining patients the vertical was of larger magnitude by an average of 30%. Twenty four patients had zero phase shift between the vertical and horizontal directions, resulting in oblique gaze trajectory, and 7 patients had 180° phase shift, resulting in an elliptical gaze tremor. Only two patients exhibited a phase shift of 90°, resulting in a circular gaze tremor about the target (23). No phase shift was observed between each eye (convergence/divergence) in any patient. These phase shifts were measured qualitatively, using linked cursors on each of the horizontal and vertical graphs. If both the horizontal and vertical graphs were reaching their apogee, they were considered to have no phase shift. If one was reaching its maxima, as the other reaches its minima, a 180° phase shift was recorded. In the case of one graph reaching a peak, while the other crosses the midline, a 90° phase shift was recorded. This was measured at in at least 10 points in time per subject, in order to determine any differences in behavior over time, of which there were none.
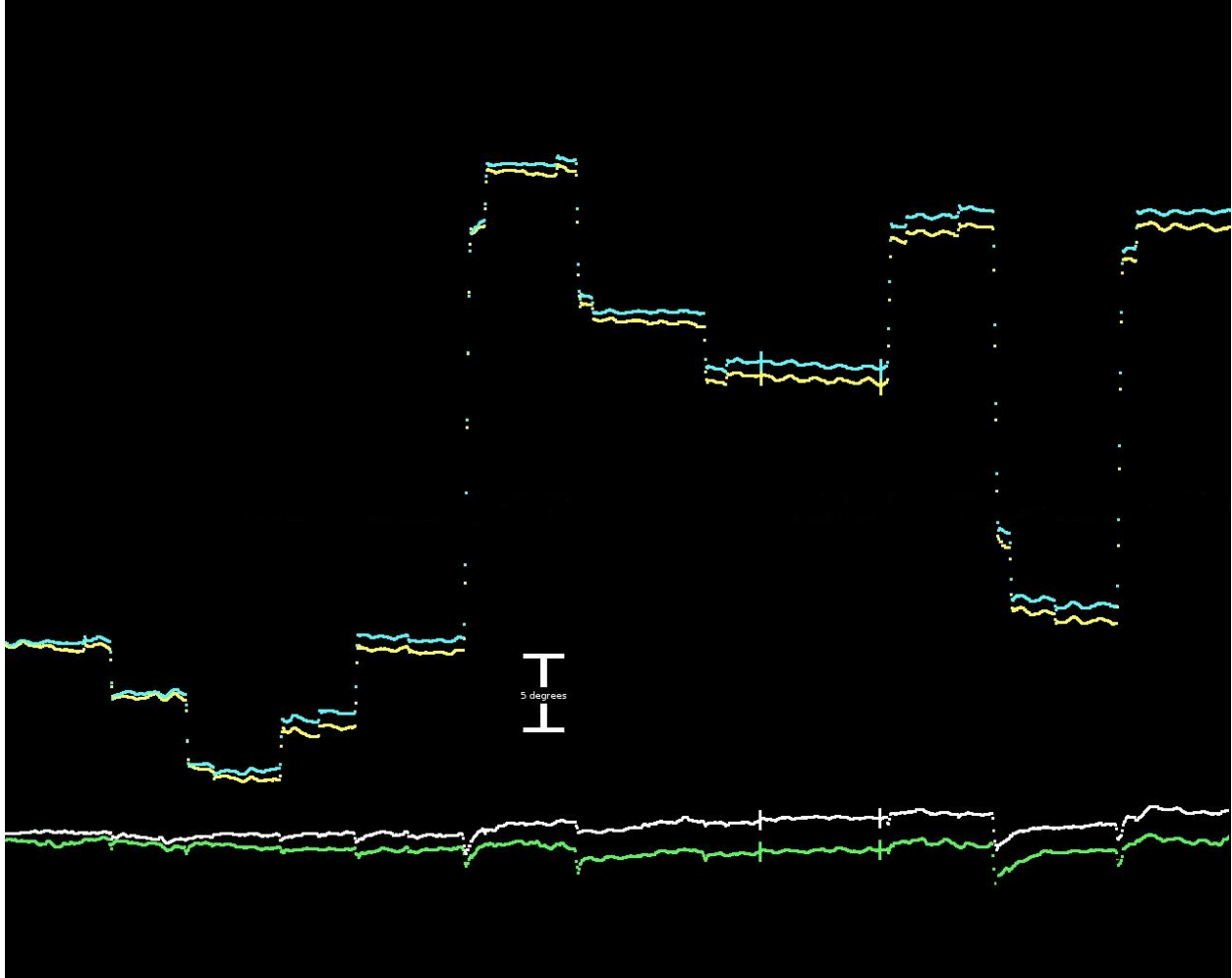
Figure 1: Pendular nystagmus typical of Parkinson's disease. The white scale bar shows a movement of 5°, while the two cursors separate one second of elapsed time. Green and white represent vertical movement, blue and yellow represents horizontal movement. More positive values of the horizontal movement (blue and yellow) equate to rightward movements. Left eye is denoted by the yellow and green points, while the right eye is represented in blue and white.

Quantifying Pendular Nystagmus

Six patients had a sinusoidal tremor, while all others had a complex or irregular sinusoidal motion in their eyes. The magnitude of the tremor varied within each subject's recording. Gaze evoked nystagmus, or jerk nystagmus was not seen in any patient when looking at the edges of the screen, likely due to the fact that the edges of the screen existed at only $\pm 20°$. The magnitude of the pendular nystagmus did not vary with gaze angle, but with time, as if the patient was able to partially control the severity. Many patients are capable of partially controlling the tremor in their periphery when they concentrate on it. It is conceivable that the eye tremor is correlated with the hand tremor, and can be controlled when concentrating. No patient had ever observed or reported tremor in their eyes, but many did have complaints of blurred vision, which could easily be attributed to the pendular nystagmus. While the patient is likely not aware of the ocular tremor, the ocular tremor could be initiated by the same portion of the brain that causes the limb tremor. In this manner, the sinusoidal tremor became larger at times and smaller at others, transiently during the recording. While magnitude was variable with time for each subject, frequency was not; with each patient's complex tremor fundamental frequency varying less than 1 Hz. This again is similar to a patient's peripheral tremor, in that the magnitude may vary greatly, but the main frequency component remains consistent over time. The pendular nystagmus is most clearly quantified by recording the root mean square velocity of each eye during a fixation. This is able to capture motion in both vertical and horizontal directions without cancellation based on movement area or negative values. Standard deviation of velocity provides a measure of the amount of variability of velocity during said fixation. As such, the PD group had significantly higher RMS velocity during fixations than the control group ($p<0.0001$). Average absolute velocity was also significantly higher in PD than controls ($p<0.0001$). The p

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values are the same for RMS velocity and absolute velocity in both the left and right eyes separately (24). When considering movement in the vertical direction, the PD group also exhibits a higher RMS and absolute velocity than the controls ($p<0.0001$). In addition, the standard deviation of velocity of both eyes in each direction was also significantly larger in the PD group than in controls ($p<0.0001$). This shows that the amount of tremor and the variability of said movement were greater in both eyes and each direction in PD than in controls. Box plots of RMS velocity and absolute velocity can be seen in Figures 2 and 3. Standard deviation of velocity during fixation is also shown in Figure 4. In retrospect, it would be beneficial to run the fixation samples through a fast Fourier transform, or power spectral analysis in order to extract more meaningful data from the fixations. This would allow us to find the frequency with the strongest amplitude component, as well as finding harmonics and frequencies contained within the complex sinusoidal tremor. That being said, the RMS velocity is significant in its difference, and clearly captures the increased amount of motion and instability during fixation in Parkinson's disease. Figure 5 shows an example of a PD subject reading a section of one of the truncated texts described by Zuber and Wetzel (20). This figure shows the patient reading two lines of text, as evidenced by the two ascending staircase patterns. Pendular nystagmus is apparent in both the horizontal and vertical directions. This figure clearly shows the nature of the variable magnitude of the nystagmus, in which the magnitude of the pendular nystagmus varies over time, while the main component of frequency remains the same throughout. In addition, this shows the more common form of a complex sinusoid in the output than the previous figure. Figure 1 shows an example of one of the six patients that exhibited pure pendular nystagmus in response to changes in target position. Figure 5 is a more common form of the tremulous instability in PD, in which the patient's eyes exhibit a complex
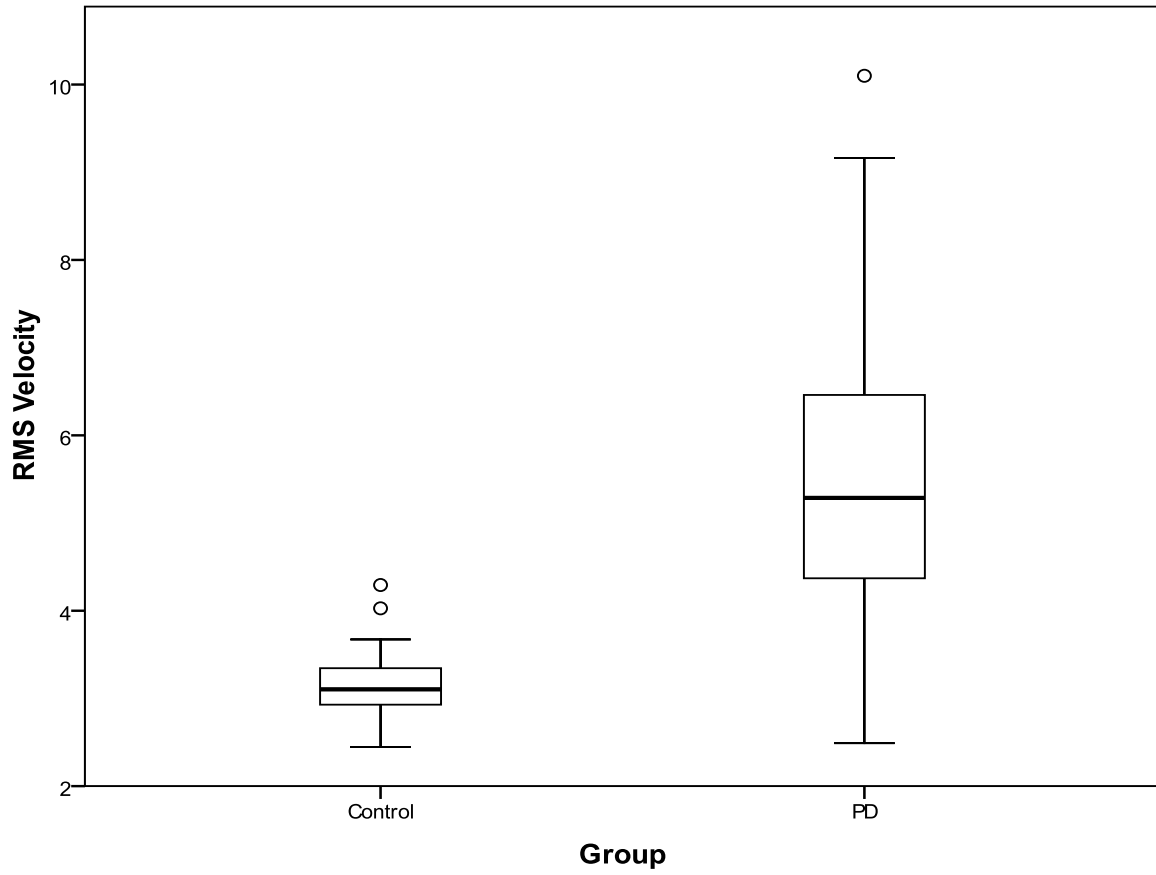
Figure 2: Box plot of RMS velocity between experimental groups

sinusoidal movement pattern, especially in the vertical direction. It is in this case that FFT

analysis would be especially beneficial to extract more data from the waveform. For comparison

sake, an example of a control subject following a step displaced target is shown in Figure 6.

The key difference between the two is the lack of pendular nystagmus in the control, where flat,

tremor free fixations are clearly visible. An occasional square wave jerk or small saccadic

correction is present, but not at an abnormal rate (1). This is the hallmark difference between

control and Parkinson's disease groups; flat, stable, steady fixations, versus tremulous, complex

sinusoidal positions during fixation. Preliminary data shown here suggests that in very early

stages of disease progression, the eye movements exhibit pure pendular nystagmus, and

sinusoidal motion. It appears as if this pendular nystagmus exists before outward features of the

disorder manifest, indicating that this is a potential marker for preclinical diagnosis of

Parkinson's disease. As the disease progresses, the pendular nystagmus transitions to a more

tremulous, complex instability, indicating that this is not typical pendular nystagmus, but instead

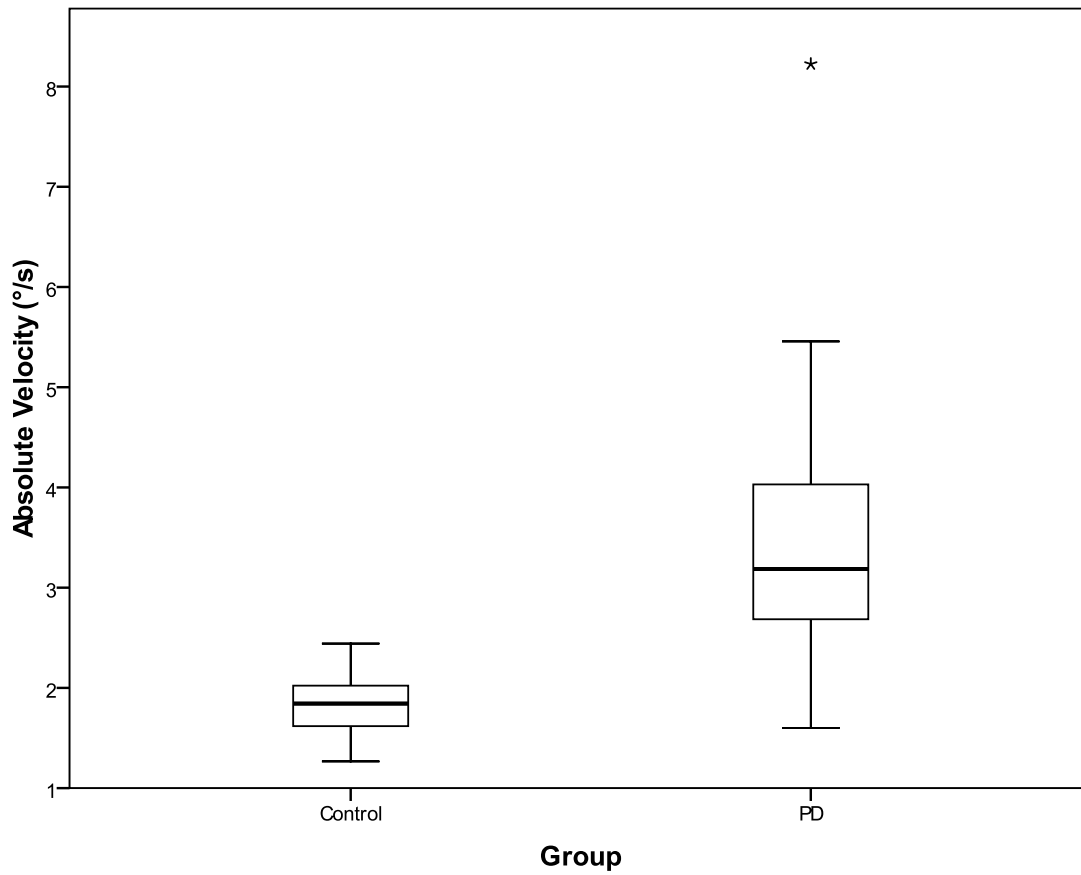is a progressive loss of oculomotor control.

Figure 3: Box plot of absolute velocity between Parkinson's disease and control groups
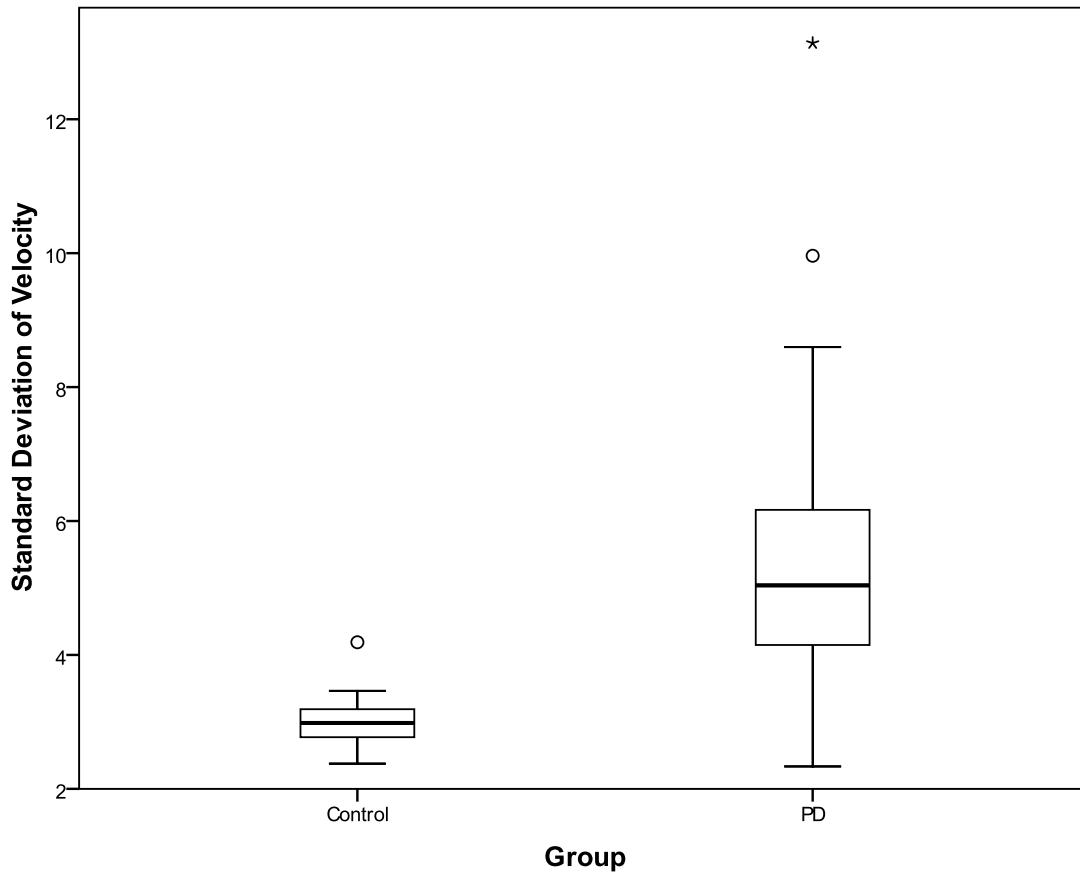
Figure 4: Box plot of the standard deviation of velocity during a fixation between PD and control groups
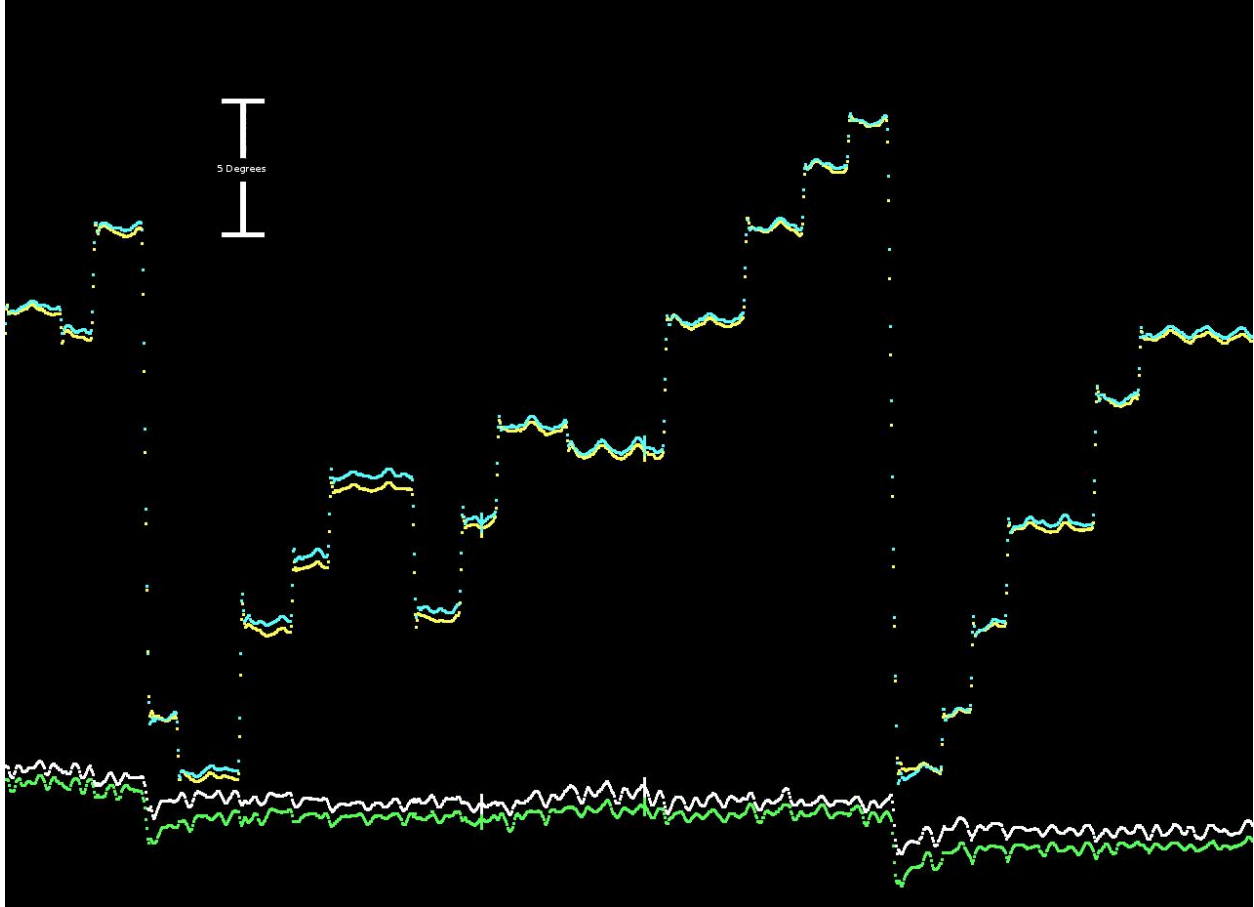
Figure 5: Pendular Nystagmus seen in a Parkinson's disease patient during reading. Note the complex waveform of the tremor, particularly in the vertical direction (Green and white points). Scale bar equates to 5 degrees of movement, and the two cursors are separated by one second of elapsed time.
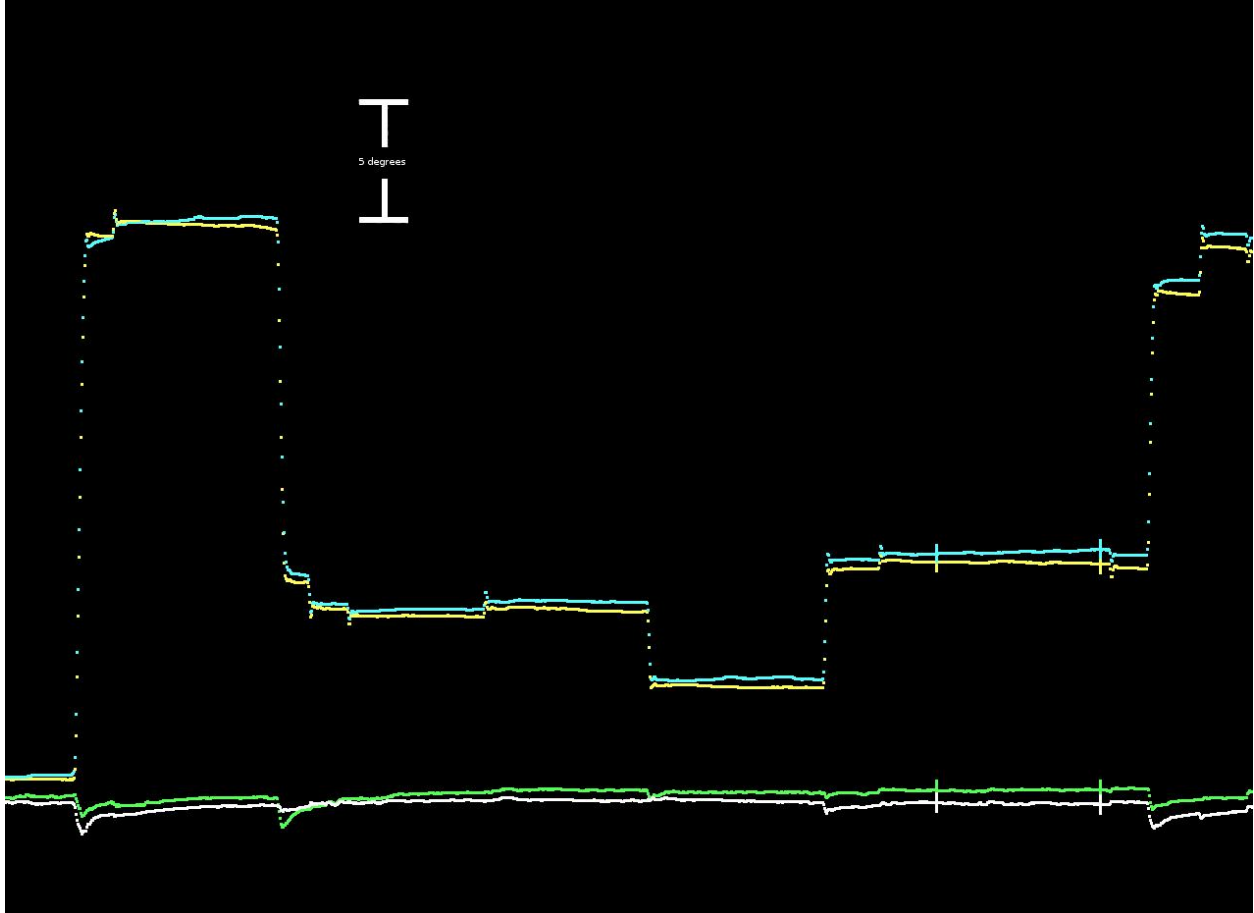
Figure 6: An example of a control when following a step displaced target. Cursors are separated by one second and the scale bar represents 5° displacement. Note the stable fixations and lack of pendular nystagmus

Saccades and the Main Sequence

An excellent method to measure the overall health and integrity of the neural system controlling saccades is to calculate and plot the "main sequence" (2). This main sequence allows the researcher to show a consistent relationship between the amplitude, duration, and peak velocity of each saccade. Saccadic amplitude, velocity, and duration do not significantly differ between patient and control groups. Saccades were compared in terms of peak velocity and duration for given amplitudes, and also compared against the main sequence graphs. Across all amplitudes of saccades, PD patients maintain normal velocity (p=0.560) and duration (p=0.897). Plots of the main sequence can be seen in Figures 7 and 8. The commonly used exponential and power equations used to fit the main sequence relationships are discussed briefly by Leigh and Zee (1). The duration of the main sequence is fit to the equation:

$$Duration = D_1 * Amplitude^n$$

where D_1 is the average duration of a one degree saccade, and n is to be determined. D_1 was found to be 22.85ms for the PD group, and 21.14ms for the control group. For the power equation describing the duration relationship, n for controls is found to be 0.33, while n for PD is 0.31. Similarly, peak velocity is fitted to the equation:

$$Peak\ Velocity = Vmax * (1 - e^{-Amplitude/C})$$

where Vmax is the asymptotic velocity and C is the constant to be determined. Vmax is commonly set to 500°/second, and was done so here as well for all calculations. Similar to

duration, when fitting the exponential equation that describes the peak velocity relationship, c for controls is 12.6, while c =11.2 for PD.

It is clear from Figures 7 and 8, that the amplitude and duration of saccades are very similar in PD and control groups. While these figures show qualitative similarity, there is a small difference in exponential values between the two subject groups. Further studies with more patients will elucidate whether any true differences exist in saccadic behavior between controls and patients with PD.
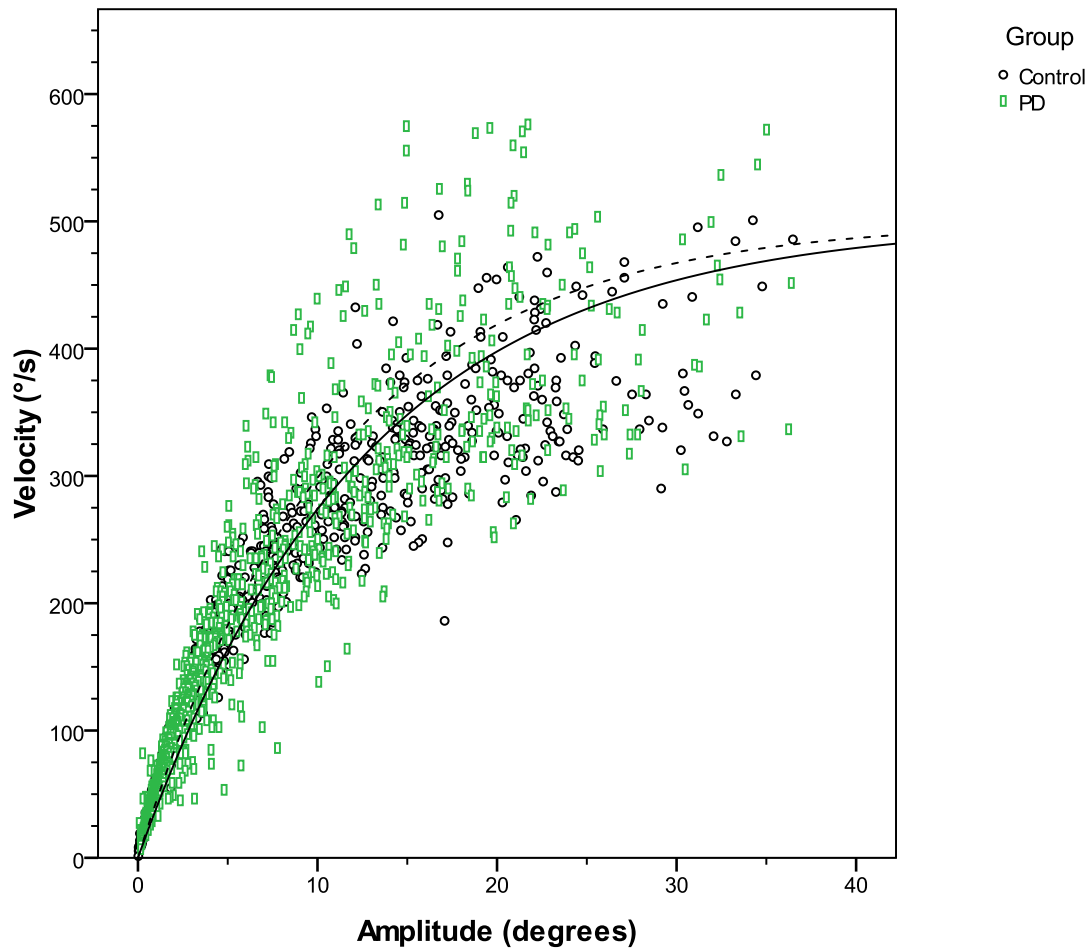
Figure 7: Main Sequence graph of peak velocity per given amplitude. The dashed curve fit line represents the PD group, and the solid line represents the control data.
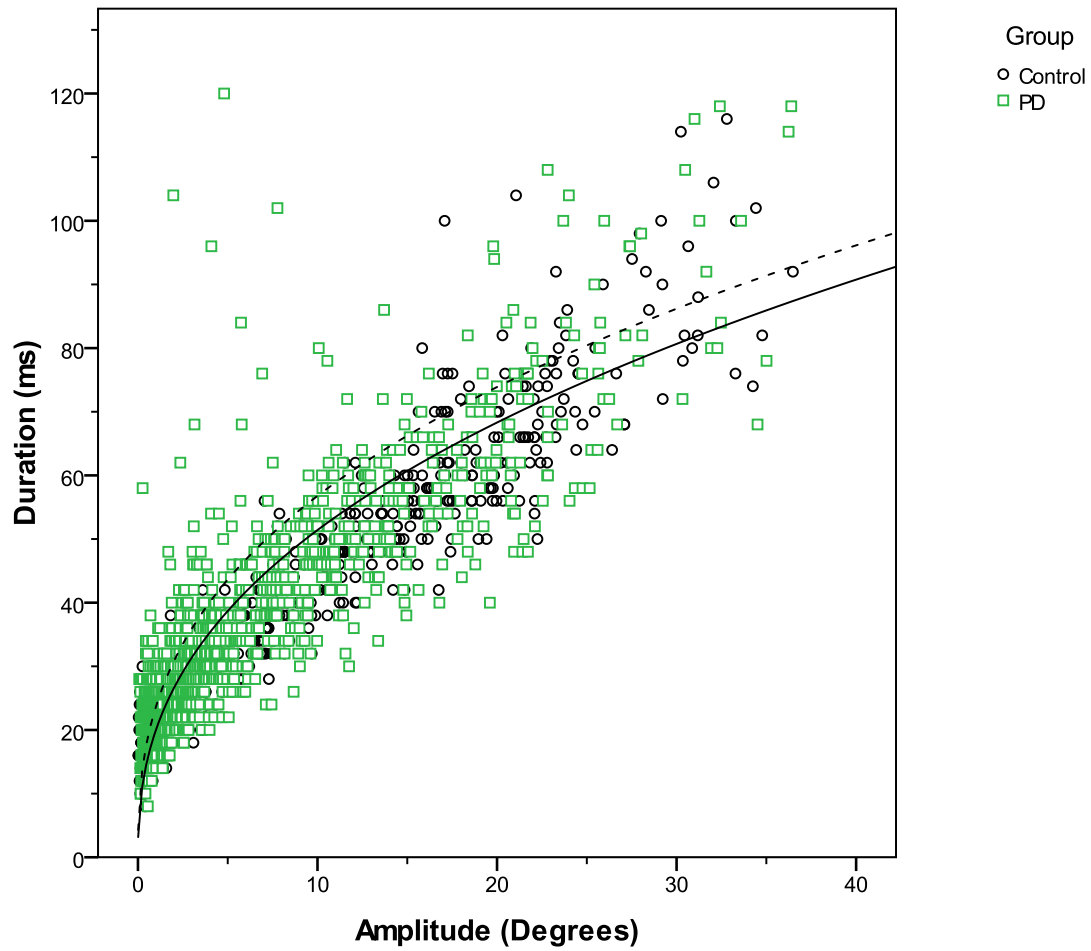
Figure 8: Main Sequence; Duration versus amplitude. Dashed line represents PD data, and solid line is for controls. Note the small group of PD saccades that are of long duration for their given amplitude

Square Wave Jerks

A square wave jerk is an involuntary, disruptive eye movement, in which a small horizontal saccade takes the eyes off of their intended target, and then returns them after a normal saccadic interval. Typically, a square wave jerk is less than half a degree, and lasts for only 200 milliseconds -- the duration of a saccadic interval. They have been reported in normal subjects at a rate up to 20 per minute (2; 1). Examples of square wave jerks can clearly be seen in Figure 9, denoted by white arrows. For this study, any square wave movement less than one degree, and between 75 and 325 ms was considered to be a square wave jerk (1). A previously popular treatment for advanced Parkinson's disease, pallidotomy, has also been reported to significantly increase the frequency of square wave jerks (22). None of the patients in this experiment have had a pallidotomy. The number of square wave jerks was counted from the recording of target motion, and no difference was found between PD and control groups when counting square wave jerks per minute (p=0.587). The mean values were 11.4/min for controls, and 12.7/min for the PD group, and can be seen in Figure 10. This directly contradicts the results found by Rascol et. al. in which they described a higher number frequency of square wave jerks in persons with Parkinson's disease and related disorders. As the medical community learns more about Parkinson's disease and Parkinsonism, more etiologies of the disorder are discovered. Seeing as how the data reported by Rascol is almost twenty years old at this point, it is very possible that those patients would not have been diagnosed with PD today, but would classify as some other type of movement disorder.
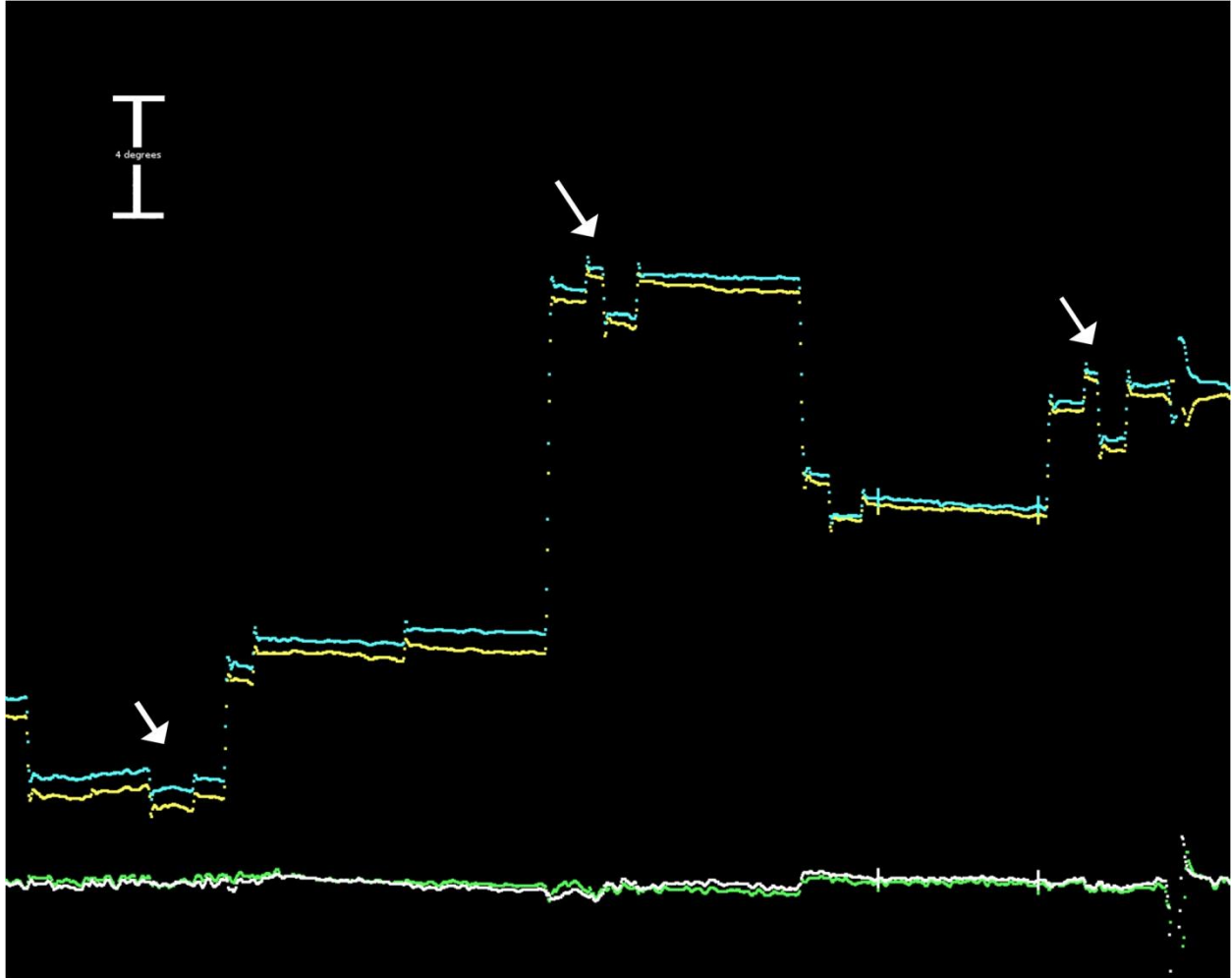
Figure 9: Square wave jerks in a person with Parkinson's disease, noted by white arrows

Latency

Latency of horizontal saccades to a step displaced target was measured during the target motion task, and was tabulated in Excel. Every reaction time for the horizontally step displaced target was calculated and averaged per subject. Normal latencies for saccades are typically 180-200 msec with a standard deviation of 30 msec (2), for a non-predictable movement. If target displacement is regular and periodic, humans are capable of predicting movement, when the eye leads the target motion. This is due to our human ability to predict movements that are periodic and consistent. Since the stimulus here was random in both time and amplitude, the movement is considered to be non-predictable, and should follow the same average latency. Any saccades made prior to target displacement were considered to be anticipatory, and were not recorded in this calculation. No statistical difference was found between the PD and control groups (p=0.776). Average latency among the control group was 232.4ms (SD: 33.2), and in the PD group was 235.4ms (SD: 39.2). It should be noted that our measured latencies were greater for both groups than previously reported by Cuiffreda and Tannen, but the two experimental groups do not differ from each other. This could be due to the fact that saccadic latency will increase approximately 1 ms per year of age (2). Cuiffreda and Tannen do not report the ages of subjects used for thier normal range, but this could easily account for the 30 ms difference. It is possible that our slightly longer latencies were due to target design, subject population age, or some other factor that as of yet is unknown.   A box plot of latency values can be seen in Figure 11.
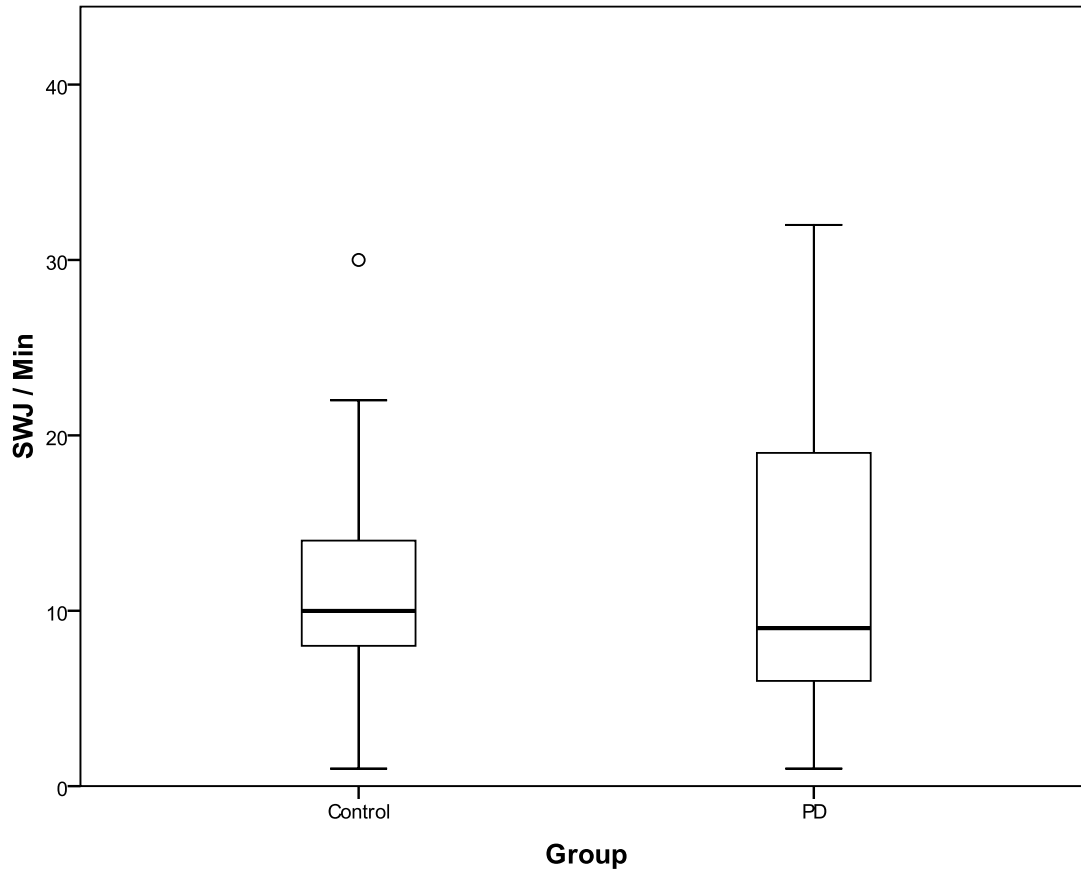
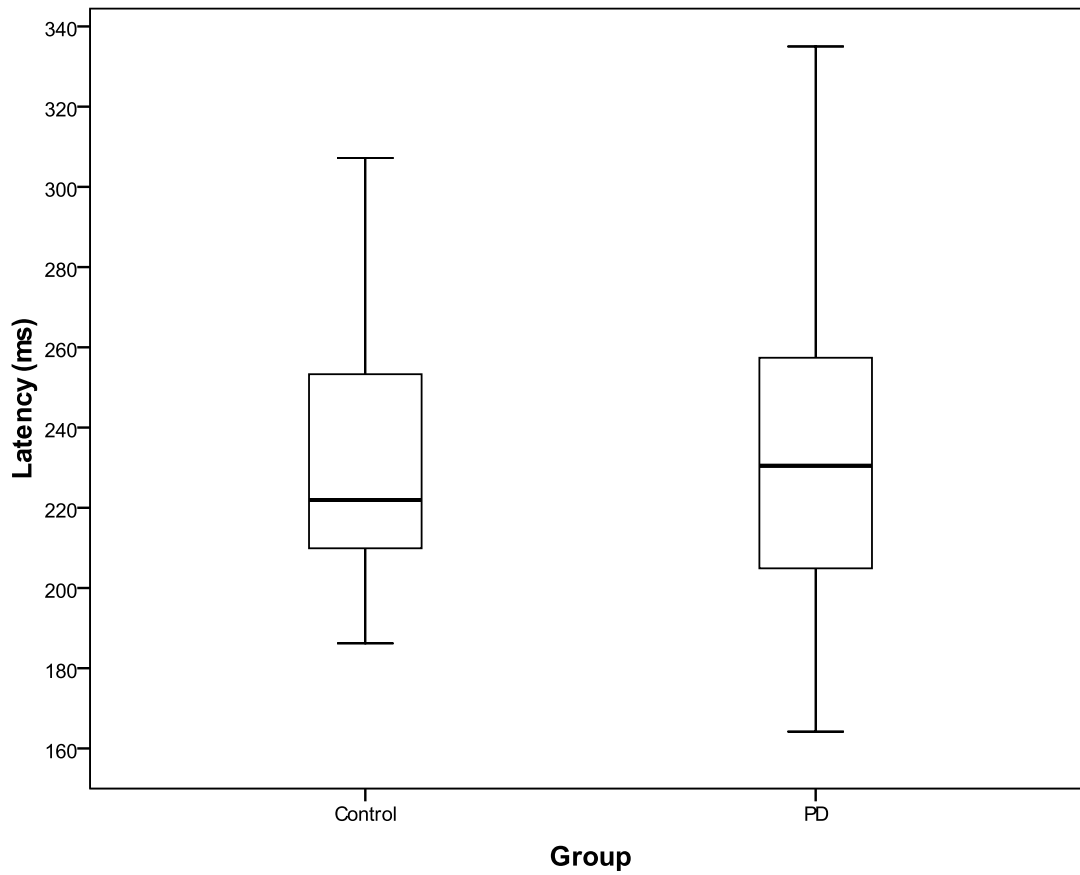**Figure 10: Box plot of the number of square wave jerks per minute when following a random target motion**

Figure 11: Latency measured during step displaced target motions

Regressions

In our culture, normal reading consists of movements left to right, and top to bottom. Occasionally, the eyes move from right to left in order to look back at a previous section of text, and this movement is known as a regression. Typically, these regressions are used to look back at an unfamiliar word or phrase that was not processed properly the first time it was seen. The total number of regressions made during the task of reading ten paragraphs was calculated. During reading tasks, PD and control groups did not differ in the number of regressions ($p=0.189$). A box plot of regressions can be seen in Figure 12.

Reading Speed

Traditionally, reading speed is measured in words per minute, despite previous evidence showing inaccuracies with that metric. Zuber and Wetzel published data that shows that reading speed measured in words per minute declines as difficulty of the text increases (20). This is due to the longer average physical word length for a given text with higher difficulty. They took multiple texts graded for varying difficulty described by Miller and Coleman, and measured reading speed in units smaller than a word across the difficulty levels. They found that when measured in syllables, characters, or letter spaces per minute, that reading speed in college aged students was constant across all difficulties of text. This was confirmed for our control group, and compared to the PD group. As such, reading speed when measured in units smaller than a word, was found to be lower in the PD group ($p=0.02$) than in the control group. Figure 13 shows the box plot of reading speed in characters per minute.
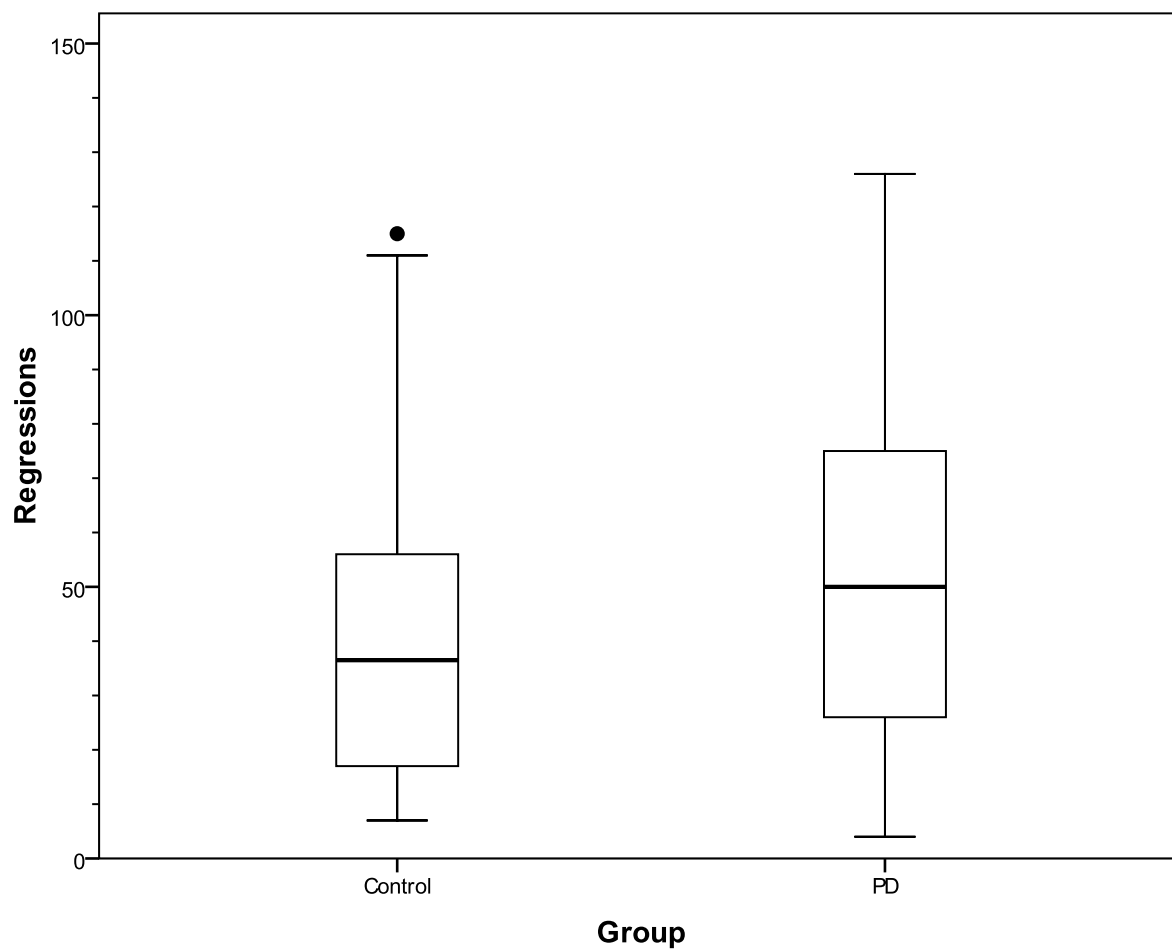
Figure 12: Total number of regressions made when reading ten standardized text passages
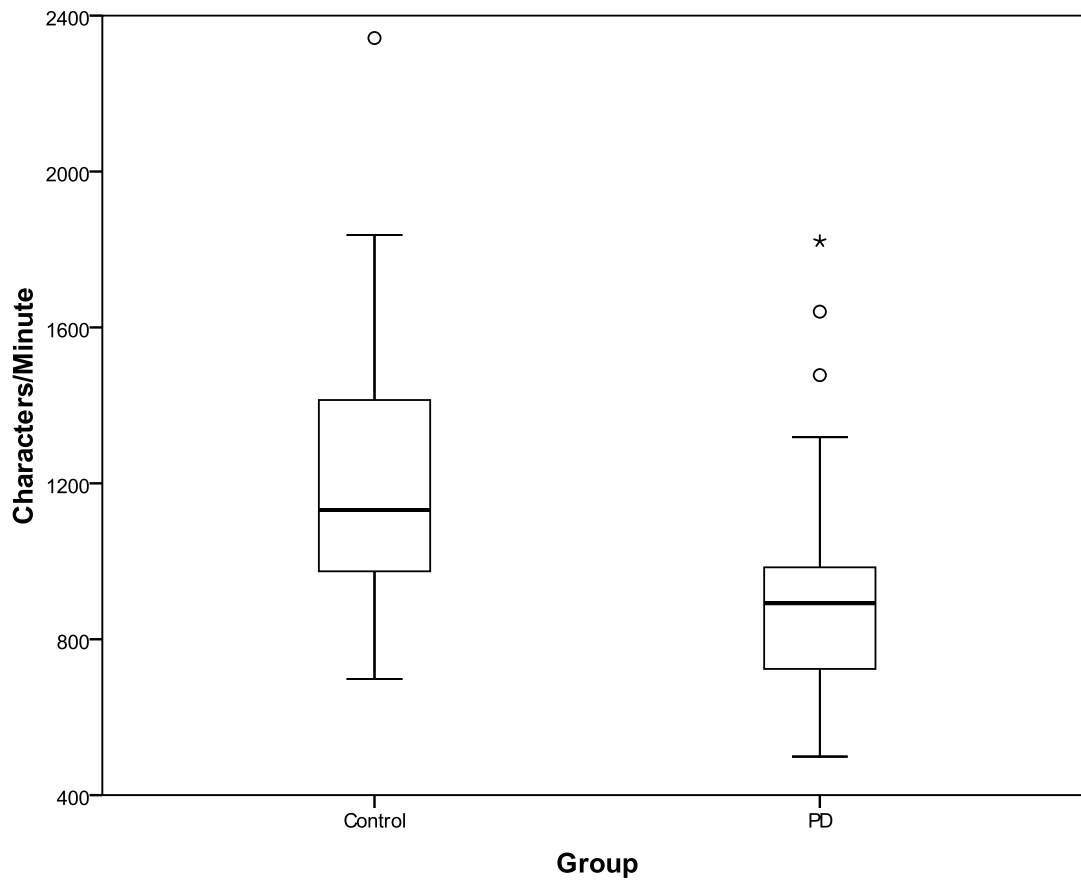
Figure 13: Reading speed measured in characters per minute for both PD and control groups

Figure 14 shows that when recorded in terms of words per minute, that reading rate will decrease as the difficulty of the text increases. This is to be expected as the word length will increase for more difficult technical paragraphs, which results in fewer words in the paragraph. Figures 15, 16, and 17 show reading speed measured in units smaller than words, displaying letter spaces, characters and syllables respectively. The figures show that reading speed in units smaller than a word are constant across all text difficulties. It is also evident that subjects in the control group read faster than PD subjects in all measures of reading speed ($p<0.001$). Another interesting note is that when measured in syllables per minute, it appears that reading rate slightly increases with higher difficulty texts. Similar to the manner in which the number of words decreases with a higher difficulty, more difficult passages also tend to contain more syllables than their easier to read counterparts. In fact the number of syllables per text increases as much as twenty percent from the most simple to the most complex passage. Similarly, the number of words decreases as much as 25% between the easier and more difficult texts. Since the number of letter spaces varies only 7.8%, and characters vary only by 11.7%, these are far more accurate measures of reading rate across varying difficulty levels. As text becomes more difficult to read, subjects require more time to fixate on a position, and collect complex information. Figure 18 shows that as text difficulty level increases, so does average fixation durations, and that PD patients fixate longer than controls ($p<0.0001$). Additional graphs of reading metrics are shown in appendix A. In addition, the elderly controls and PD groups are compared to the college aged normals reported by Zuber and Wetzel.
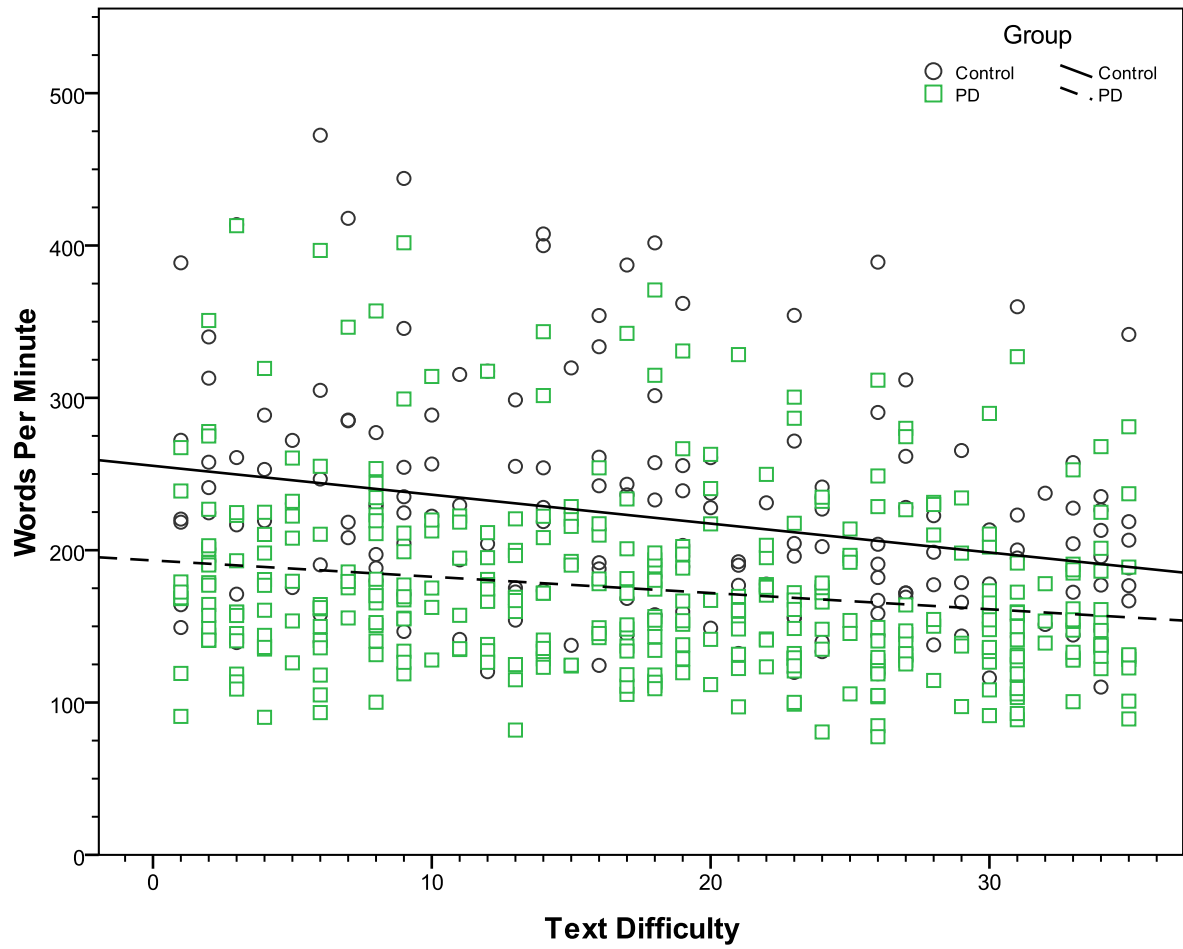
Figure 124: Reading Speed measured in Words per Minute
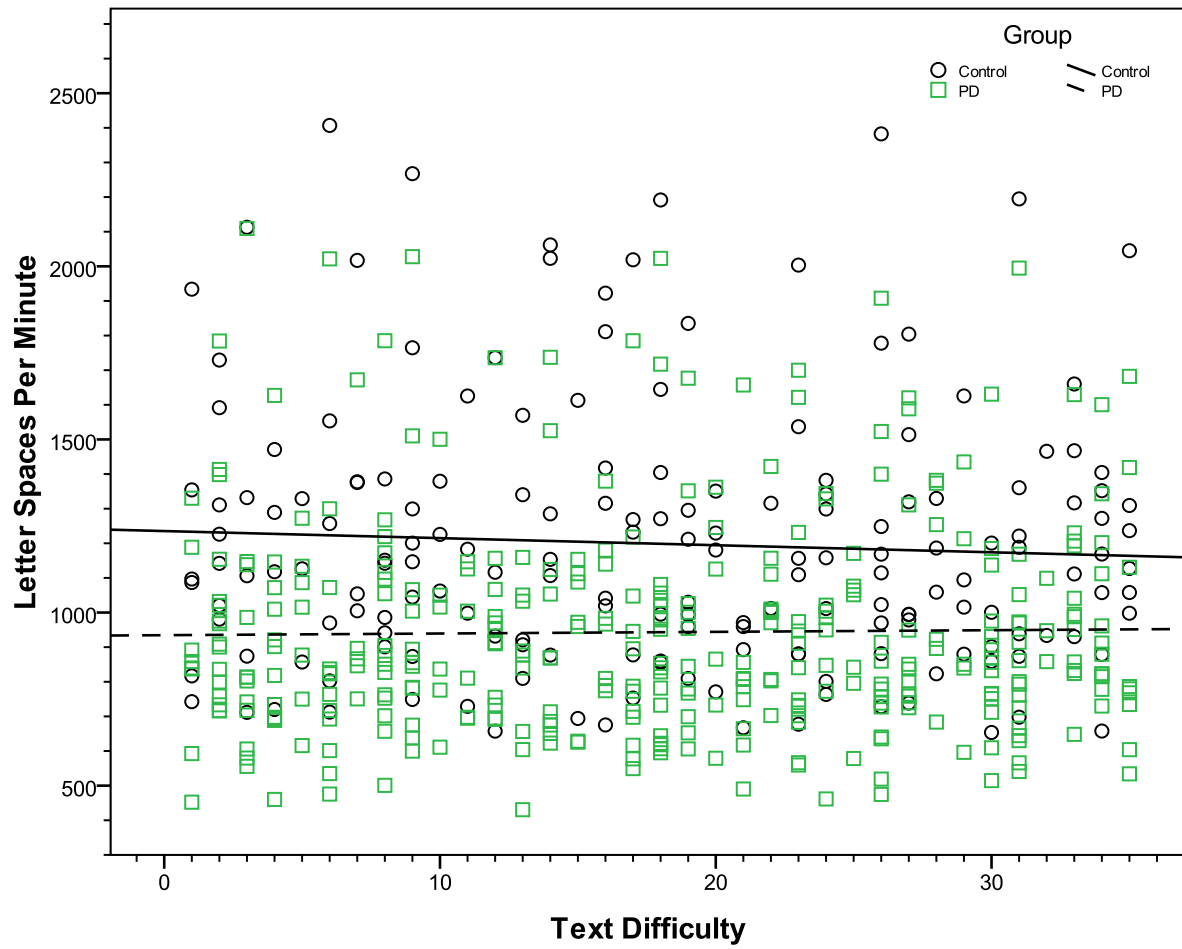
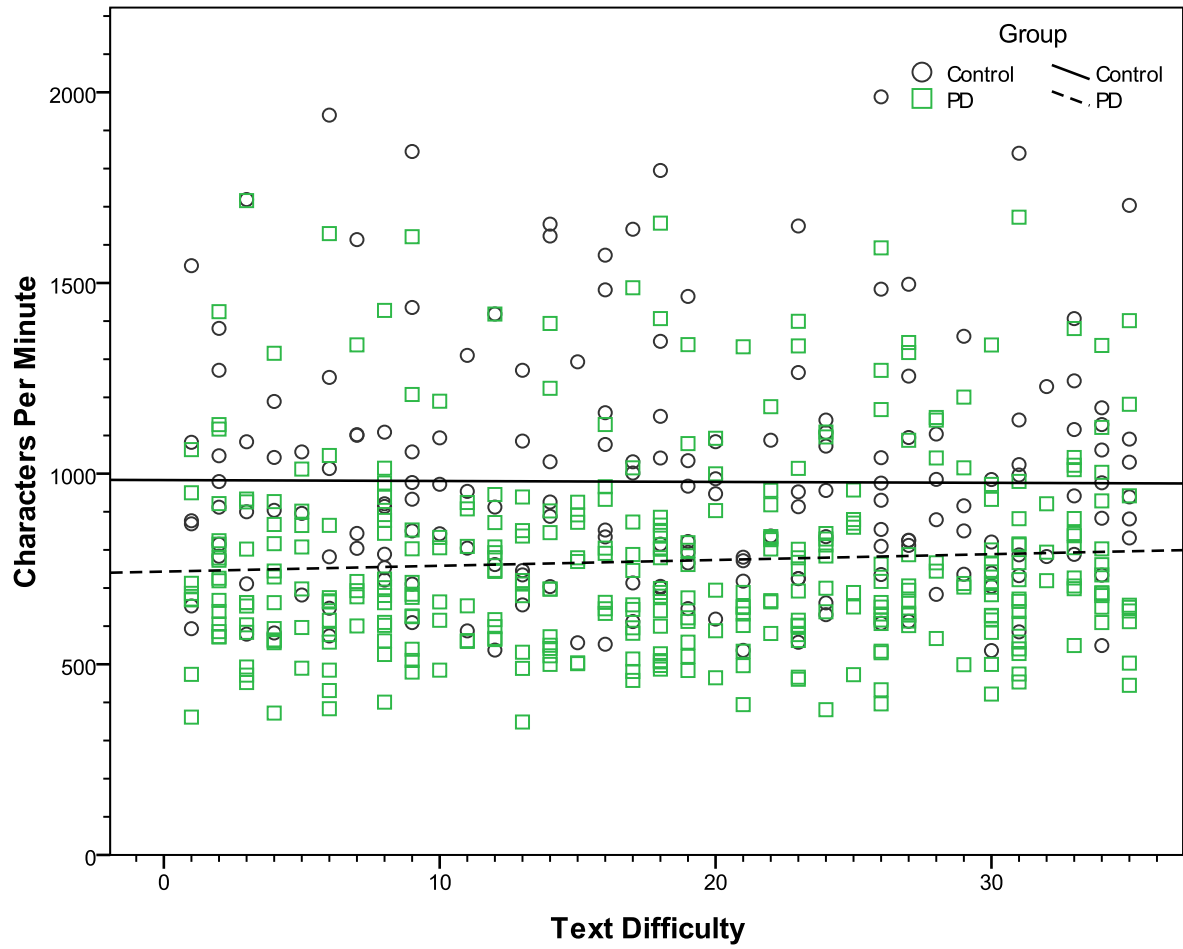**Figure 15: Reading speed measured in letter spaces per minute**

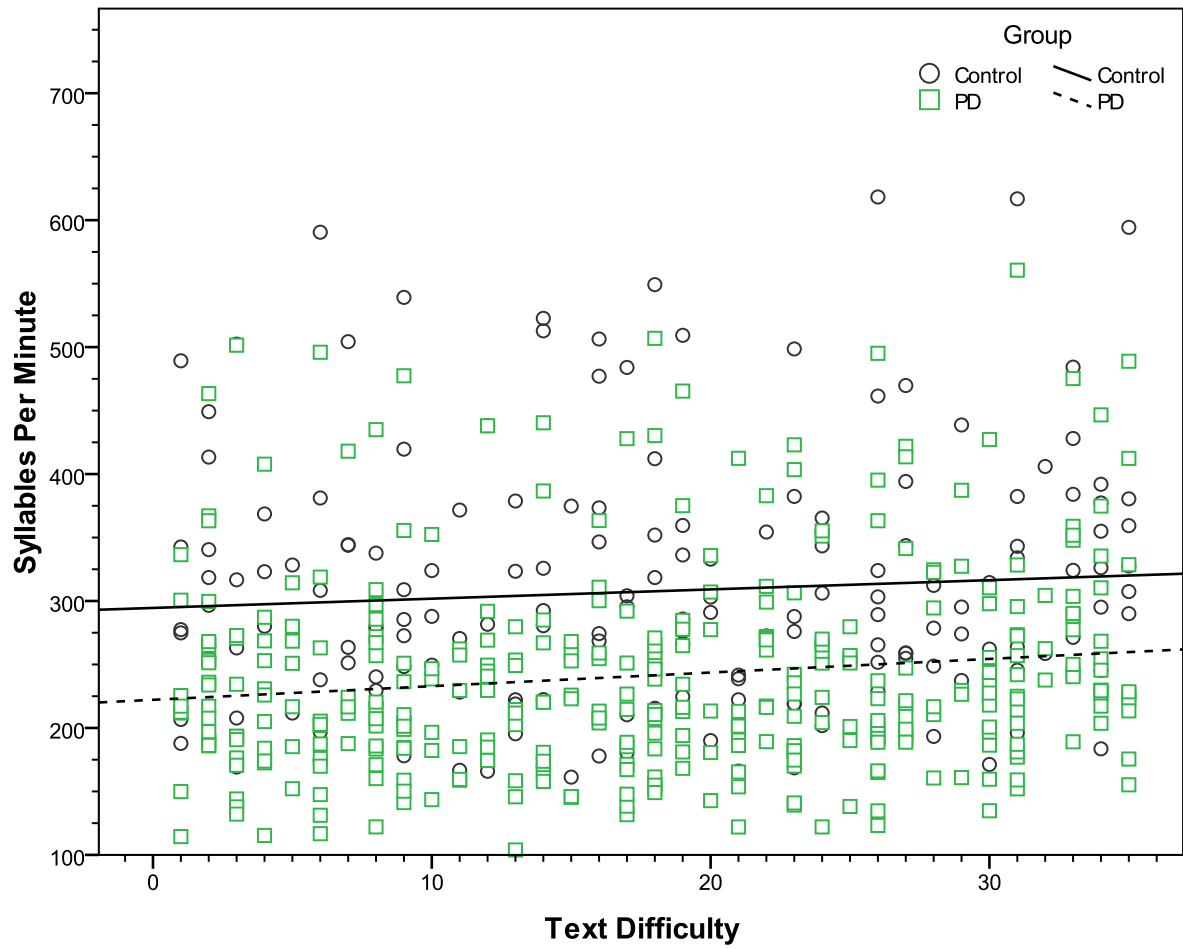**Figure 16: Reading speed measured in characters per minute.**

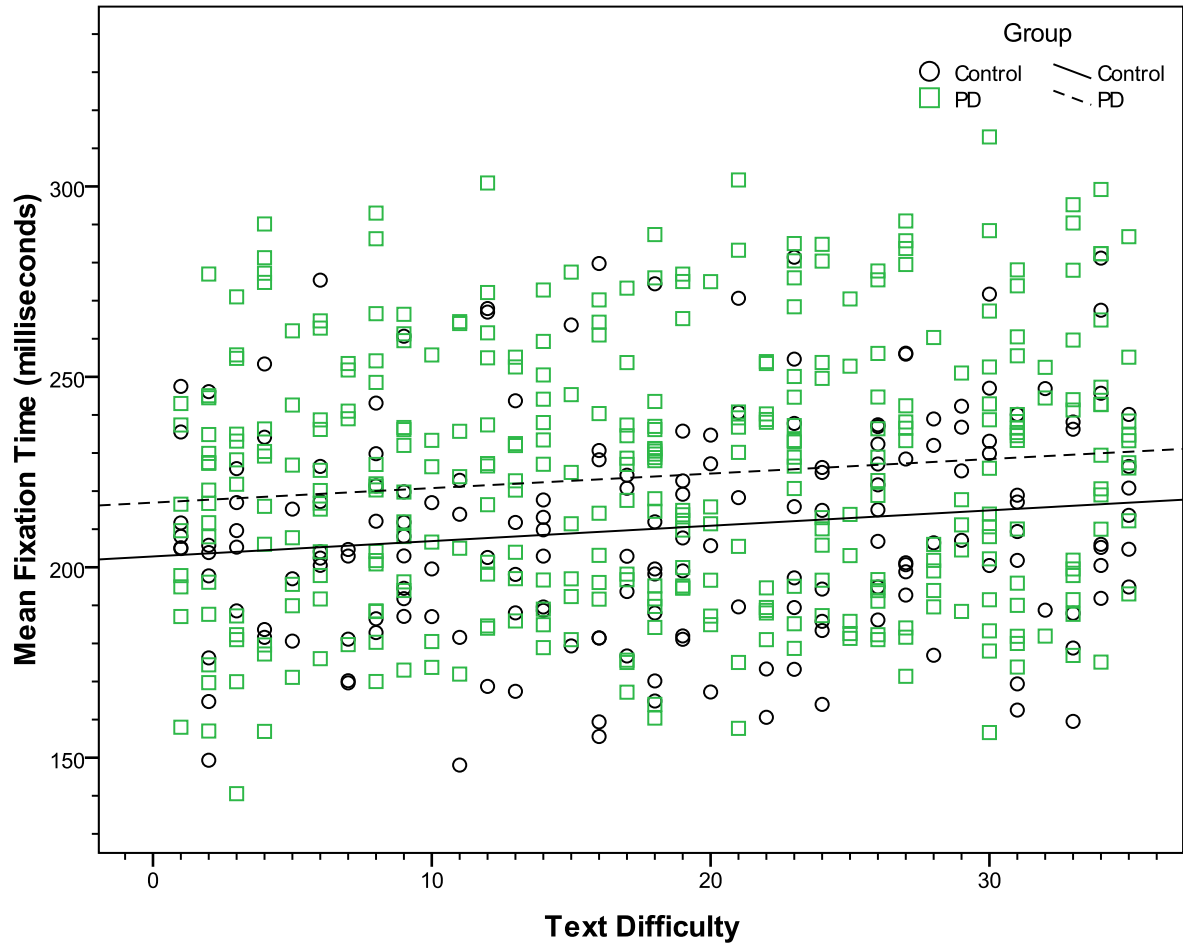**Figure 137: Reading rate measured in syllables per minute**

Figure 148: Fixation durations during reading

Figure 19 shows the average forward saccadic amplitude during reading each of the ten paragraphs. This shows that the control group makes larger saccades (p=0.001) than the PD group during reading. Since the saccadic amplitudes are greater, it also takes fewer fixations to read a line of text, as seen in Figure 20. Again, the control group requires fewer fixations to read each passage (p<0.01) than the PD group does. To further elucidate the differences, the ratio of fixations per letter space is calculated. Figure 21 shows the reading rate compared to the number of fixations per letter space. This graph clearly shows that as a subject reads at a slower pace, it requires more fixations per letter space, regardless of text difficulty. Of note, in the original data published by Zuber and Wetzel, a liner relationship was implied for the college aged normal reader, and a similar relationship is found here as well for the elderly controls. However, when the PD group is considered, there is a hyperbolic curve in the data. This implies that as reading rate slows in Parkinson's disease, that the number of fixations required per letter space increases significantly faster than it would for a control subject. This is partially due to the fact that PD patients tend to make 21% more fixations than controls (p<0.01), and that those fixations are also of a longer duration than controls (p<0.001). This directly accounts for the slower reading speed in patients with Parkinson's disease, and is evidenced by the figures shown here, combined with the fact that saccadic activity is normal. Neither the magnitude nor the frequency of pendular nystagmus was correlated with reading speed decreases. Appendix A also shows this data compared with college aged normal controls.
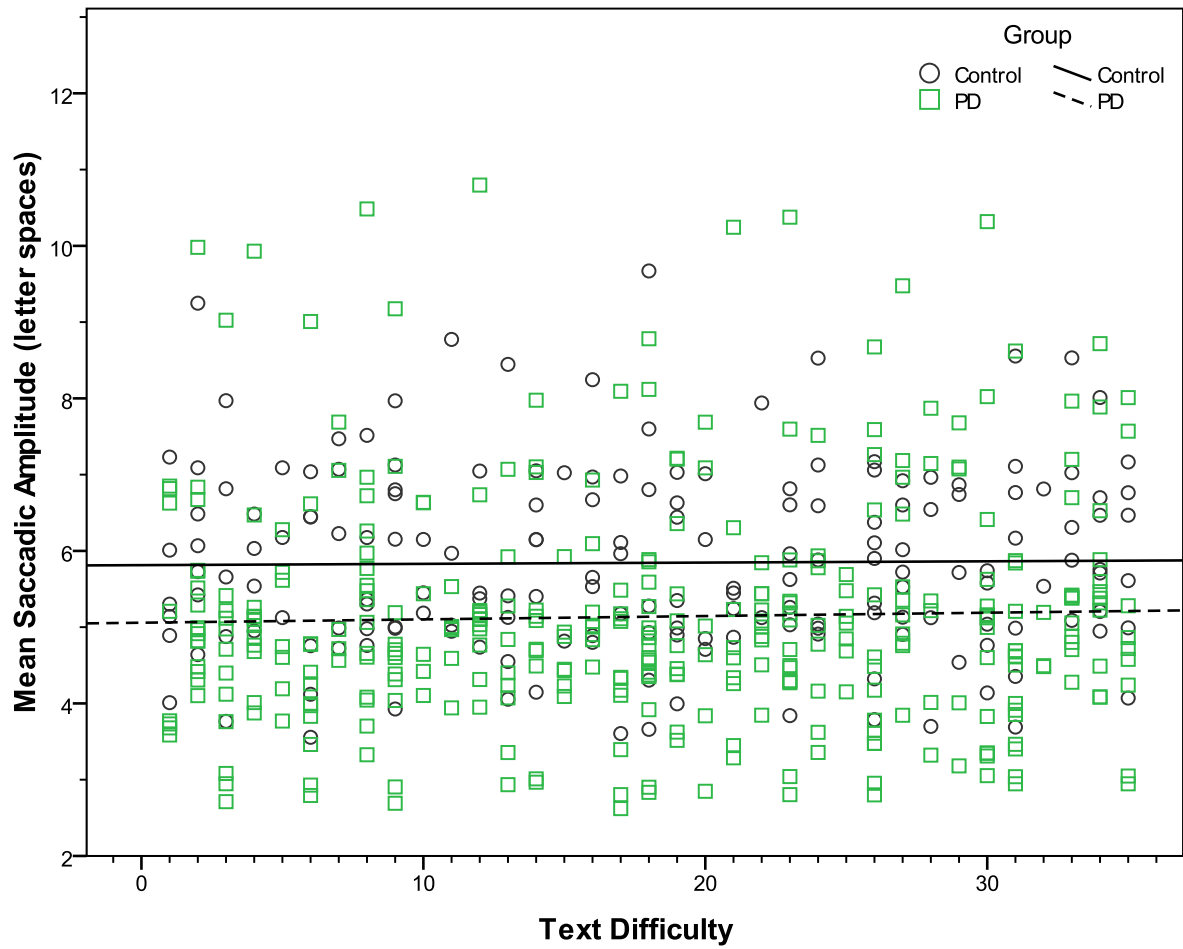
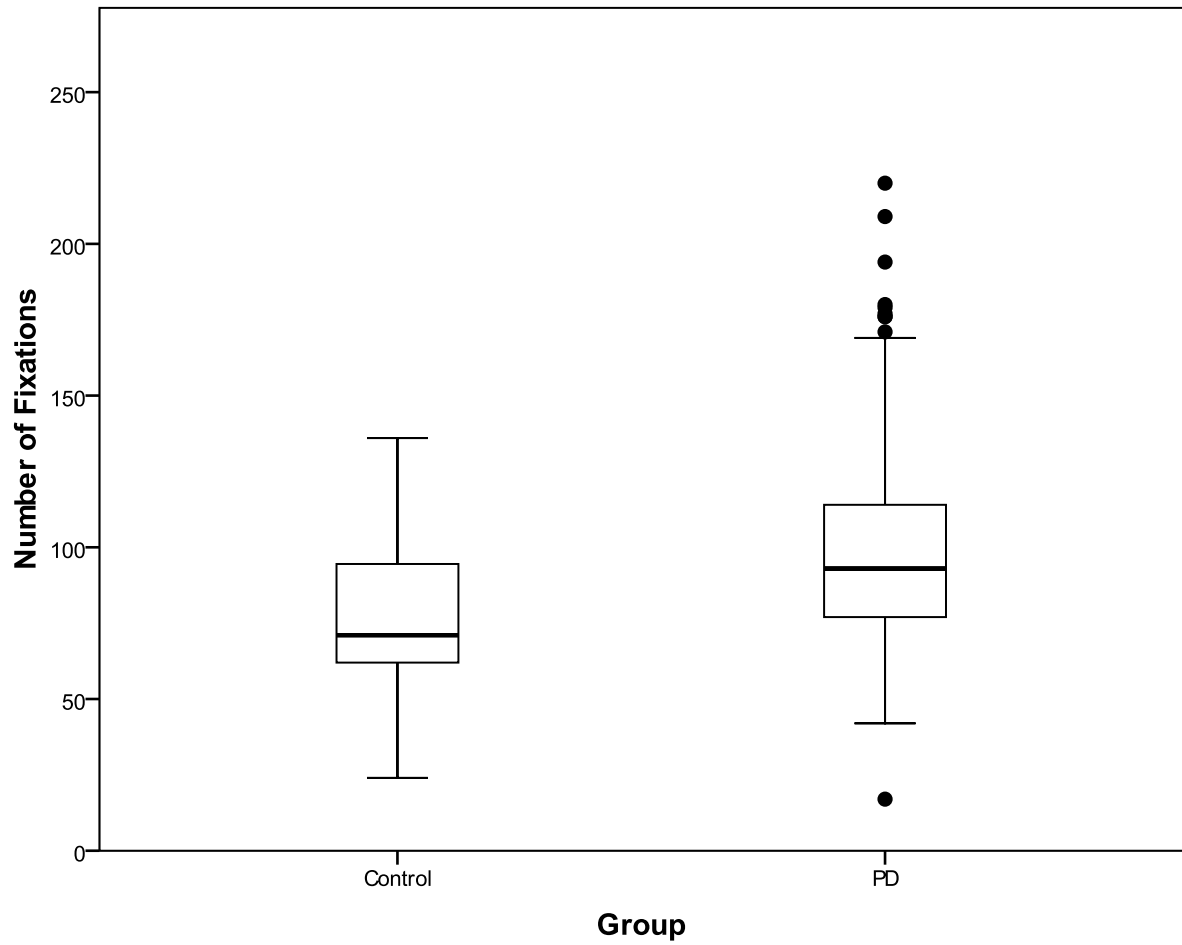**Figure 159: Saccadic amplitude during reading, measured in letter spaces**

Figure 20: Number of fixations required to read average text passage across all difficulty levels

There is a far more interesting and significant feature contained within Figure 21 besides the effect of fixations per letter space on reading rate. The thin vertical line located at 0.1428 fixations per letter space almost equally bisects the number of controls, while PD group is heavily skewed to the right of the line. It is only when the inverse is taken, and we consider the graph in terms of letter spaces observed per fixation that this becomes significant. The inverse of 0.1428 is 7, showing that normal subjects will process 7 letter spaces per fixation on average, but that PD patients are not capable of the same ratio. The bulk of the Parkinson's data is centered around 4.5 to 5 letter spaces per second, indicating that they are not able to resolve as many characters per fixation. It is likely that the PD subjects are not able to group letters together in the same size chunks as controls simply because their visual system is incapable of processing it due to pendular nystagmus. As the eye oscillates, the visual acuity will reduce significantly, and will therefore not be able to process the same amount of data as a stable eye would. If the patient was able to stabilize their eyes, the number of letter spaces per fixation would likely increase to normal levels, thereby increasing their perceptual span. This shorter span of perception is likely the reason that patients make smaller saccades and more numerous fixations to read. This in turn results in slower reading speeds, and impacts a person's quality of life and daily activities.
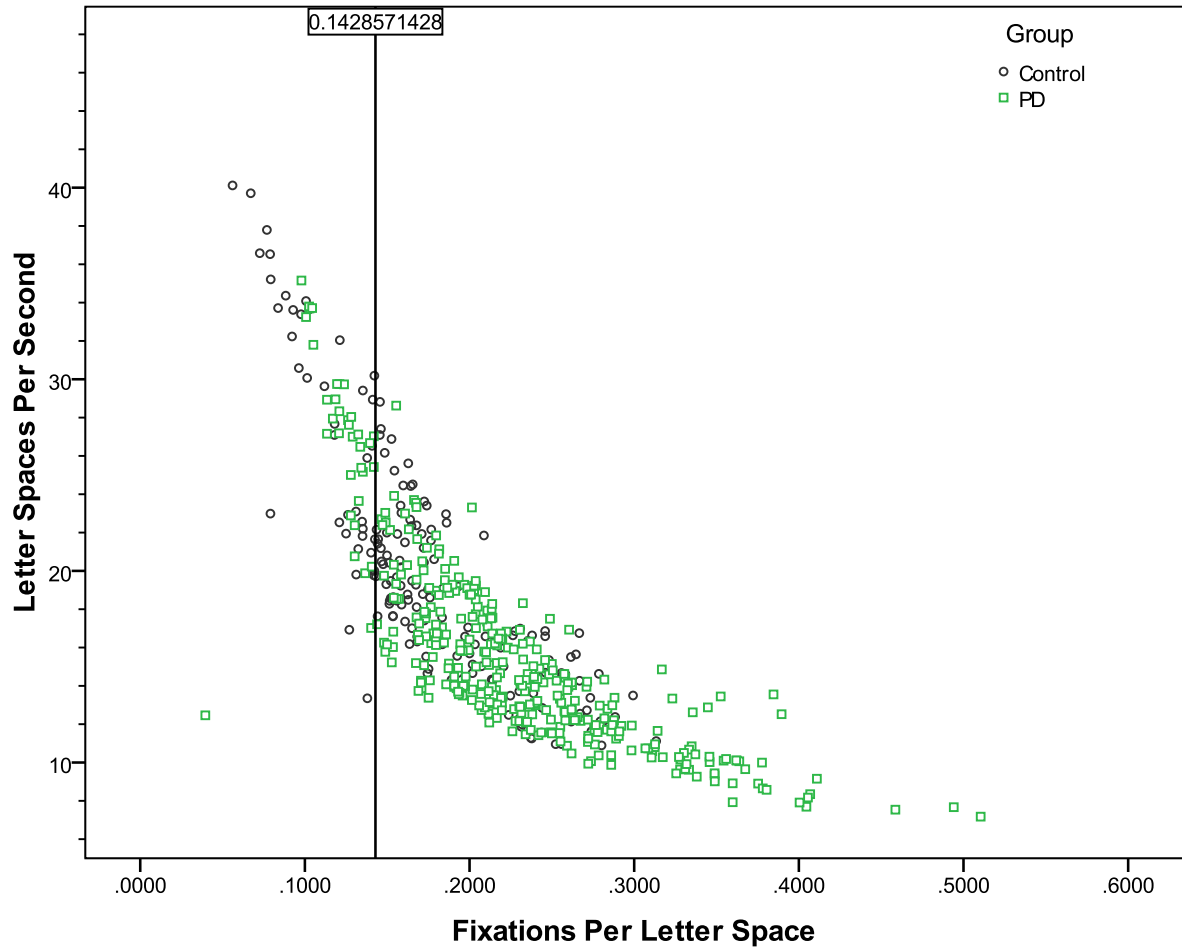
Figure 161: Fixations per letter space versus reading rate

Discussion

These data suggest that the most significant oculomotor dysfunction in patients with Parkinson's disease is a pendular nystagmus, with normal saccadic behavior. This coincides with a common complaint of oscillopsia and blurred vision in Parkinson's disease that cannot be corrected with glasses (25; 4). As pendular nystagmus oscillates the globes of the eyes, the threshold for clear vision of 5°/second is passed (1), leading to reduced visual acuity and smearing of the image on the retina. When qualitatively viewing the data, the pendular nystagmus is most clearly seen when the patient is following a target motion, because of longer fixation times. Due to shorter fixation times during reading, this sinusoidal motion is less obvious, with typically less than one full waveform shown per fixation. Quantitatively, there is no difference between the magnitude of sinusoidal tremor during reading and target motion. With sufficiently large text, as used in the stimulus presented above, this is not significant enough to prevent a patient with PD from reading. However, with normal sized newspaper print, an average of 0.3° of motion at 7.4 Hz would significantly affect the patient's ability to read that text, thereby impacting activities of daily living. The loss of ability to read easily is a common complaint in Parkinson's disease, and can be explained by the complex sinusoidal tremor which is smearing the image on the retina. Currently, the best option for these patients is an assistive device to increase the size and contrast of text. It has yet to be investigated whether or not higher levels of dopamine therapy are able to

significantly reduce this sinusoidal tremor in the eyes as well as the limbs, to further improve quality of life. Differences in oculomotor control using a deep brain stimulator however have been shown to improve fixation stability (26). Future study could show that best medical therapy has an effect on the eyes as well as the extremities. If this is shown to be a reliable method of quantifying tremor changes with different medication levels, eye movements could conceivably be used to more accurately prescribe medication, or adjust a deep brain stimulator to a more precise level of symptom relief.

The neural anatomy of the basal ganglia is a complex system built upon tonic inhibition, and negative feedback loops. A general schematic of the neural wiring of the basal ganglia and its efferent connections can be seen below in Figure 22. The characteristic loss of dopamine occurs mainly in the Substantia Nigra pars Compacta (SNpc), and this leads to myriad cascading effects on the other areas of the basal ganglia. Firstly, the dopaminergic output of the SNpc serves functionally to regulate the output of the Striatum, as well as the globus pallidus external – subthalmic nucleus circuit. The striatum can be thought of as the functional input of the basal ganglia. The end result of the feedback loops is an inhibition of the Thalamus, which for these purposes will be one of the main outputs. As another feedback mechanism, the Thalamus stimulates the striatum through the cortex of the brain, in order to balance the system. Most pertinent to this discussion, is that the Substantia Nigra pars Reticulata (SNr) projects inhibitory neurons to the Superior Colliculus (SC), where eye movements are programmed (27; 28).

The Superior Colliculus (SC) is a brain area that is topographically mapped to the retina, and is tonically inhibited by the basal ganglia. In this manner, each point on the retina is mapped to a specific location on the SC, and this retinotopic map is used to program eye movements. If a fixation is intended, there is a tonic low frequency activity within the foveal area of the rostral

SC. If smooth pursuit is planned, the area just outside of the foveal mapping zone is active to

program for velocity and error, and the tonic activity increases in frequency (29; 30). According

to Basso et al, the firing rate of SC neurons is directly correlated with positional errors on the

retina (31; 32), with higher firing rates correlated with larger positional errors. Finally, if a

saccade is the intended movement to a visual stimulus, the area of the SC that is mapped to the

intended position begins to fire rapidly in a burst. In this manner the SC helps to program the

direction and magnitude of the movement of the eyes, without sending the actual motor signal.

These programmed movements then travel over the third cranial nerve (oculomotor nerve) to

innervate the extraocular muscles. Some research suggests that the rostral pole of the SC

contains so called "fixation neurons" that fire continuously during fixation, and cease firing

during an eye movement (1). These fixation neurons project to omnipause neurons in the

brainstem reticular formation to suppress saccadic initiation. The omnipause neurons inhibit

burst neurons, which use a temporal coding to determine saccadic amplitude. This reticular

formation converts the spatial or retinotopic map into temporal code to program timing of eye

movements and amplitudes of those movements (33).   The frontal pole of the SC is not

innervated by the basal ganglia, but relies on signals from the middle and rear portions of the SC

where the smooth pursuit and saccadic centers are, and which are innervated by the basal ganglia

and frontal eye fields. In this way, the frontal eye fields are strongly excitatory to the middle and

rear SC and constantly stimulate it to produce an eye movement (34). This movement is only

made possible when the inhibitory signals from the basal ganglia (the SNr and thalamus

specifically) are removed. Similarly, Leigh and Zee report that stimulation of this rostral pole of

fixation neurons suppresses reflexive saccades, indicating it is essential for stable fixations.

These previous studies have clearly shown that the superior colliculus is critical in programming saccadic eye movements, but what of the afferent connections to the SC, and the implications of activity in those areas when the eyes should be fixating? When considering eye movements, the SC receives its major inputs from the SNr, thalamus, and frontal eye fields. The SC is capable of determining retinal position error, and programming an eye movement based on that error, but is only allowed to execute that movement if allowed to do so by its afferent connections. Kazmierczak et. al. used 14 patients to show that complete removal of the Thalamus via stereotactic thalamotomy, resulted in no changes in oculomotor reflexes in reflexive eye movements (25). This suggests that while the thalamus may innervate and regulate some functions of the SC, it does not affect the oculomotor control system. This leaves the frontal eye fields, along with the SNr and its afferent connections to impact the function of the SC.

Neurons within the Substantia Nigra pars Reticulata (SNr) typically have a very high firing rate, which tonically inhibit the thalamus, and more importantly the SC. This functionally serves to prevent eye movements, and allow fixations for stable gaze (35). When the firing rate of the SNr is very high, the SC is prevented from programming an eye movement. When smooth pursuit is required, the SNr reduces its firing rate, thereby lowering the inhibition to the SC and allowing some movement. When a saccade is required, the SNr completely pauses the tonic inhibition for a short time, allowing for a fast, ballistic eye movement, which is quickly stopped when the tonic inhibition returns (36). Due to this behavior, the SNr is able to modulate smooth pursuit and saccades, allowing or not allowing the eyes to make a movement. In other words, the SNr must be inhibited to allow the eyes to move. This disinhibition of the SC by inhibiting the SNr is determined by other areas of the Basal Ganglia.
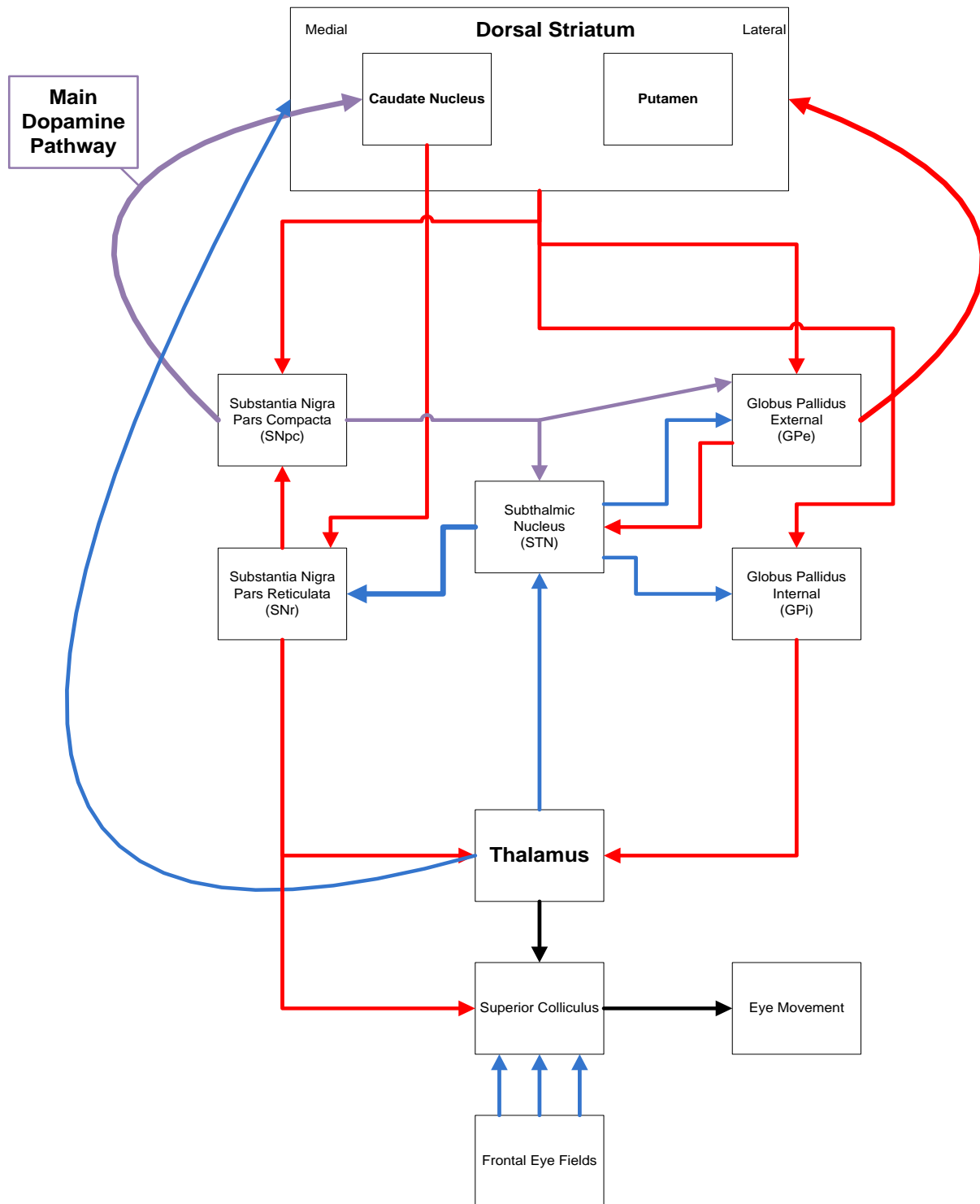
Figure 172: Neural organization of the Basal Ganglia. Red Pathways are considered to be inhibitory, while blue pathways are excitatory. The main dopamine pathway that is reduced in Parkinson's disease is shown in purple.

As mentioned previously, the SNr has a high tonic firing rate that inhibits the SC, and prevents movement. As the tonic discharge decreases, faster and faster eye movements are allowed; with a total pause in discharge occurring for a saccade. The SNr is inhibited by the caudate nucleus (CN) in the striatum, and excited by the subthalmic nucleus (STN). Due to this, stimulation of the CN results in limited inhibition of the SC, and will tend to allow an eye movement **(37)**. Conversely, excitation of the STN will further inhibit the SC, preventing an eye movement. Since the CN receives dopaminergic regulation from the SNpc, the ability of the CN to regulate the SNr will be compromised in Parkinson's disease. Similarly, the globus pallidus, both external and internal (GPe and GPi respectively), are affected in Parkinson's disease. A lack of dopamine from the SNpc will functionally decrease GPi activity, and increase GPe activity **(38)**. The pathway that decreases the GPi activity is known as the direct pathway and is stimulated by dopamine. Conversely, the Indirect pathway increases activity in the GPe, and is inhibited by dopamine. Therefore, in PD, the indirect pathway is overactive, and the direct pathway is inhibited, which leads to an imbalance of the two pathways. Furthermore, Obeso reports that in a normal subject the firing rate of GPe and GPi neurons should be roughly the same, but in PD patients, the GPe firing frequency may be twice that of the GPi **(39)**. He claims that this results in an oscillation in the firing frequency of the STN neurons that averages between 4 and 8 Hz. Bevan et al confirm these findings, suggesting that in Parkinson's disease, the STN and GPe specifically become synchronous and oscillate their firing rate at around 6 Hz **(40)**. Additionally, Bevan notes that the pathway between the STN and GPe is the only reciprocally innervated pathway that is both excitatory and inhibitory and regulated by dopamine. In their study from 2000, Ray et. al. use an animal model of Parkinson's disease to show that tremor frequency in

the periphery is bimodally distributed around 5 and 11 Hz. They also find that GPe and STN oscillations were also bimodally distributed, but at 7 and 13 Hz, with much stronger power spectra at 7 Hz. They found no oscillatory burst behavior in normals, but found that GPe neurons in a PD model would release a burst of impulses at the rate of 7 Hz **(41)**. Any oscillatory behavior in the GPe and STN reciprocal pathways will yield an oscillation in the stimulation of the SNr, and therefore oscillatory behavior of the SC inhibition. This behavior reported by the three papers above also correlates very closely with the majority of the patients in this study, in which the fundamental frequency component of the pendular nystagmus was typically 4-8 Hz.

Summing the previous concepts, we see that in Parkinson's disease, the loss of dopamine from the SNpc will in effect encourage the cyclical disinhibition of the superior colliculus through the SNr. There is currently no data to determine if increased inhibitory signals from the CN, or reduced excitatory signals from the STN have a more significant effect on the genesis of pendular nystagmus. The 2003 study by O'Sullivan et. al. tested 5 patients off medication before and after a pallidotomy, in which the globus pallidus was ablated (14). They reported an increased number of square wave jerks (SWJ's) in their subjects after the surgery, but missed the key finding that was reported here. One of their figures showed the eye movement position trace of a patient fixating on a non-moving target for 30 seconds. There are clearly more SWJ's after the surgery than before, but more interestingly, pendular nystagmus is clearly present in both the before and after surgery graphs, and was not reported in the paper. Since the sinusoidal tremor was not reported, it cannot be quantified, but a qualitative assessment of the graph anecdotally shows a larger magnitude of pendular nystagmus post-pallidotomy of the GPi. This may suggest that removing the GPi will further disrupt the fine balance between the GPi, GPe-STN circuit

(42). This shows that oscillatory inhibition signals are being sent to the SC and reticular formation in PD patients, and this potentially explains the genesis of pendular nystagmus. This oscillatory inhibition could be allowing the oculomotor control system to constantly encode a small amount of error in different directions, leading to the sinusoidal motion. The pathway proposed in this paper for the source of pendular nystagmus is as follows; As the SNpc stops releasing dopamine, the delicate balance between GPe and GPi activity is disrupted through the loss of dopaminergic innervations of the STN and GPe. As a result, the GPe and STN firing rates are greatly affected, eventually becoming oscillatory and synchronous due to improper negative feedback from the rest of the basal ganglia complex. This oscillatory synchronized signal affects the stimulation of the SNr, and therefore leads to an oscillatory disinhibition of the SC. This likely takes some time to occur, as the cyclical oscillation may need to progress until the disinhibition reaches past a minimum threshold in order to encode a small retinal error outside of the rostral pole fixation neurons of the SC and induce pendular nystagmus.

It should be noted that five patients did not read every sentence of every paragraph. These five patients made a habit of skipping one or more lines per paragraph. It is unknown why the patient skipped them, or if they even noticed. This could be partially due to the depression that is heavily co-morbid with Parkinson's disease and lack of enthusiasm during the task, strictly motor control related, or it could be partially cognitive. The effect on the data is negligible since it does not affect the velocity parameters during a fixation, however it should be mentioned that they were clearly not concerned with comprehension. We cannot be certain whether reading speed was affected by ocular tremor, slow cognitive decline, general apathy towards the task, or a combination of the above.

Despite the fact that a few subjects skipped lines of text, it is clear that patients with Parkinson's disease have a slower rate of reading than controls. These data show that PD subjects read on average 21% slower than controls, when measured in the more accurate metric of letter spaces or characters per minute. Reading rates for control subjects were slightly slower than those reported by Zuber and Wetzel, on all accounts. In terms of characters per minute, these aged controls took 11% longer to read than the college students previously reported are, and are 27.6% slower when measured in letter spaces per minute. The PD group however, was at least 43% slower in all metrics than the college students reported by Zuber and Wetzel. These data show that age will slightly decrease reading speeds, and patients with PD will take almost twice as long to read a passage as a college aged student.

When reading rate is compared to the number of fixations per letter space, the change in behavior becomes clearer. As the eye oscillates due to pendular nystagmus, the image of the world will degrade, and not be as clear on the retina. Due to this, less visual information is collected per fixation, and peripheral vision is also decreased due to lowered contrast sensitivity. This directly affects the ability to process textual information, and will result in a greater number of fixations during reading due to a smaller perceptual span that is reduced in PD. More fixations will allow the patient to group the information into smaller "packets", and will therefore increase the ratio of fixations per letter space. This functionally allows the patient to collect and analyze visual information about fewer letters at one time. Since fixations during reading are both of longer duration, and more numerous in PD than controls, the reading rate decreases. This implies that reading speed is directly affected by eye movement parameters, and not a cognitive decline. Oscillation of the globe of the eye results in a degraded image, requiring more fixations per letter to allow the patient to read.

Saccades are high velocity, voluntary movements of the eyes that direct the fovea to a new point of interest. Since the clinical characteristic tremor in PD disappears during voluntary movement, or action, it would stand to reason that the saccadic movements would be spared in PD. It should be expected that much like the outward clinical tremor that the oculomotor system would also oscillate at rest, but not during an action movement. The data presented above confirms that saccades in Parkinson's disease differ little from controls. The main sequence graphs show few deviations from the normal group, and very similar curve fitting lines with similar exponential values. Peak velocities were found to be the same as aged matched controls, albeit with more variability in the Parkinson's group. We do note a group of saccades in the duration versus amplitude graph that appear to be of a much longer duration for their amplitude, and it should be noted that all of them came from the same subject in the PD group. Every attempt was made to include patients that have only Parkinson's disease, but without a full record of MRI and PET data for each subject, it is not 100% certain that there was not a patient with an underlying disorder. It is possible that this patient with long saccades had a second underlying disease that was not yet visible clinically, but had already begun to affect the saccadic duration. There is mounting recent evidence that patients with Parkinson's disease are more likely to also develop Essential Tremor and vice versa, and that the secondary disease most often goes undiagnosed (43; 44; 45). Consider the scenario in which a patient is diagnosed with Parkinson's disease, and then later develops essential tremor; one of two scenarios most commonly happen. One is that the patient is then re-categorized as an atypical form of Parkinsonism. The other possibility is that the symptoms of essential tremor are never noticed because they are being masked by the symptoms of PD. In either case, often the secondary disorder is not recognized, nor is it treated. It is conceivable that one or more of the patients in this study has begun to develop a secondary

disorder that is not yet visible clinically, but may already be affecting eye movements. Despite the fact that this study may include one patient with an as of yet undiagnosed disorder, it is still likely more accurate than 20 year old studies, due to the major advances in properly diagnosing movement disorders in the past 10 years.

Kimming et al described the behavior of saccades in Parkinson's disease as being severely hypometric and multiple stepped if the target is remembered, but normal if the target is currently present in the visual field. In the case of a constantly present visual stimulus (such as this experiment), saccades are just as hypometric as those in normal subjects. These data show that saccades are hypometric to the same degree as controls, similar to the behavior described by Kimming et al (12).

None of the reported parameters of ocular motion correlated with the patient's UPDRS score. It may be possible that the parameters of RMS velocity during fixation, and the magnitude and frequency of pendular nystagmus are more reliable indicators of disease severity than the UPDRS score is. Since the UPDRS score is purely subjective, it can vary based on which clinician administered the test. The oculomotor behavior during fixation is a purely quantitative measure that cannot be influenced by bias or user error. Further study may elucidate whether or not the eye movements of a patient can lead to a better classification of disease status.

Summary

The results of this study have shown significant new oculomotor features of Parkinson's disease, and contradict previous studies regarding saccades and square wave jerks. Patients with Parkinson's disease make normal saccades, but have significant difficulty maintaining stable fixations. Pendular nystagmus oscillates the globes at an average of 7.44 Hz, leading to loss of clear foveal vision given a large enough magnitude. RMS velocity of the eyes during a fixation is currently the best method of quantifying the pendular nystagmus, although future studies will implement an FFT or power spectra analysis. Patients tend to read more slowly than healthy controls, but they do not make a higher number of regressions than controls. In addition, we find that reading rate measured properly does not vary with text difficulty, implying that the difference in reading rate is not cognitive, but directly due to the eye movement parameters. Saccadic latencies when following a target displacement are the same as control subjects. Oscillation of the GPe-STN pathway leads to cyclical disinhibition of the SC, which may be the neural genesis for pendular nystagmus. Pendular nystagmus in the eyes is the ocular analogue to a rest tremor in the hands, and as such, should be considered a classic feature of Parkinson's disease.

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Appendix A: Supplementary Figures of Reading Metrics

These supplementary figures show different metrics of reading rate between PD subjects and controls. In addition, previously shown graphs of reading rate and eye movement parameters are shown here with the inclusion of data from college aged normal subjects initially reported by Zuber and Wetzel. The first two supplementary figures show fixations per letter space versus the mean fixation time. Both figures show relatively tight clustering for each subject, with clusters seemingly less dense in the PD group. Note the difference in scale on the ordinate axis. The two groups are graphed separately simply for clarity. It is clear that the control subjects are typically closer to the origin of the graph, indicating their faster overall reading speed. Supplementary Figure 3 shows reading rate in letter spaces per second versus the mean fixation duration. This data implies that as the duration of a fixation decreases, reading time increases. The trend also implies that there is a greater speed increase for controls as they decrease their fixation times than there is for PD subjects.
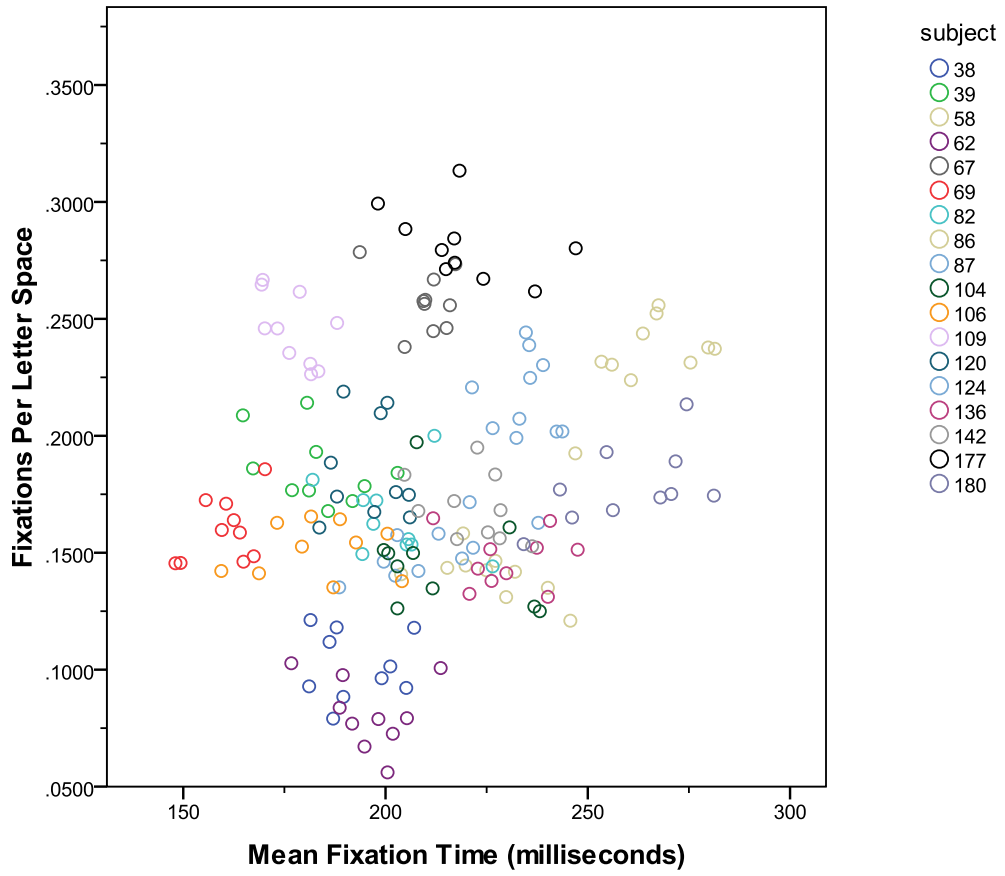
Supplementary Figure 1: Fixations per letter space versus mean fixation time in control subjects
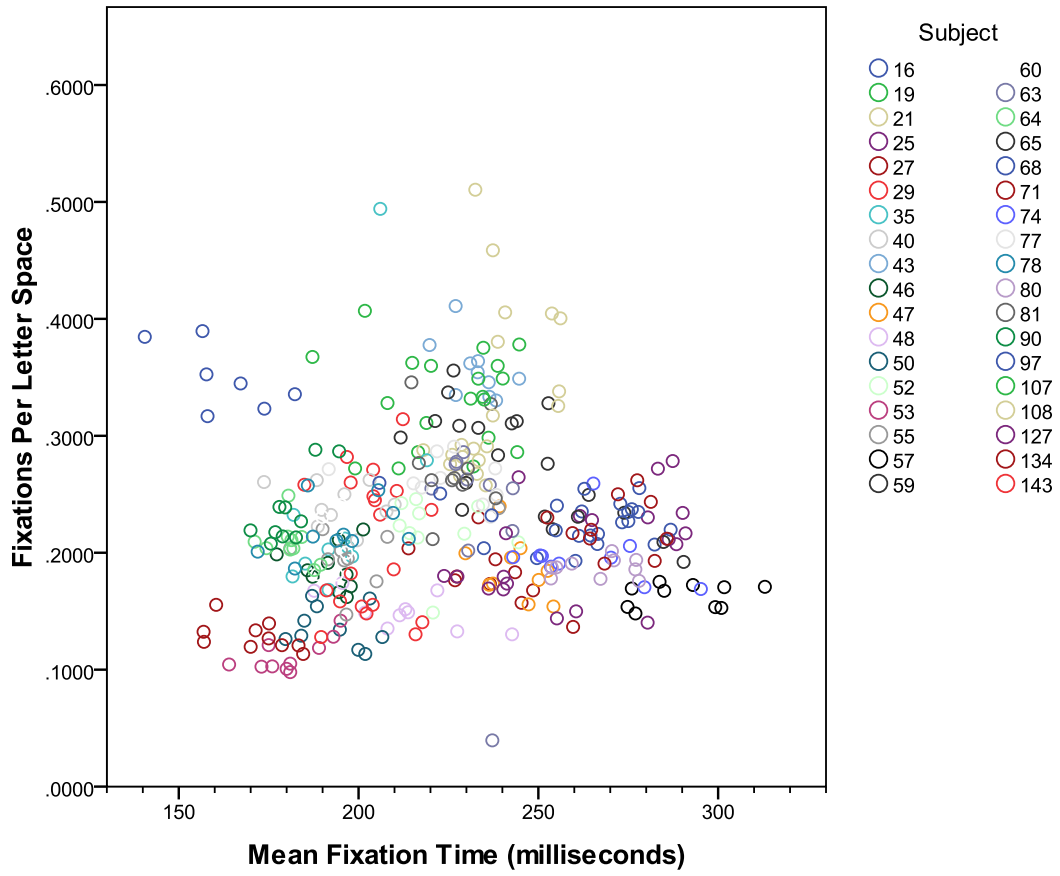
Supplementary Figure 2: PD subjects
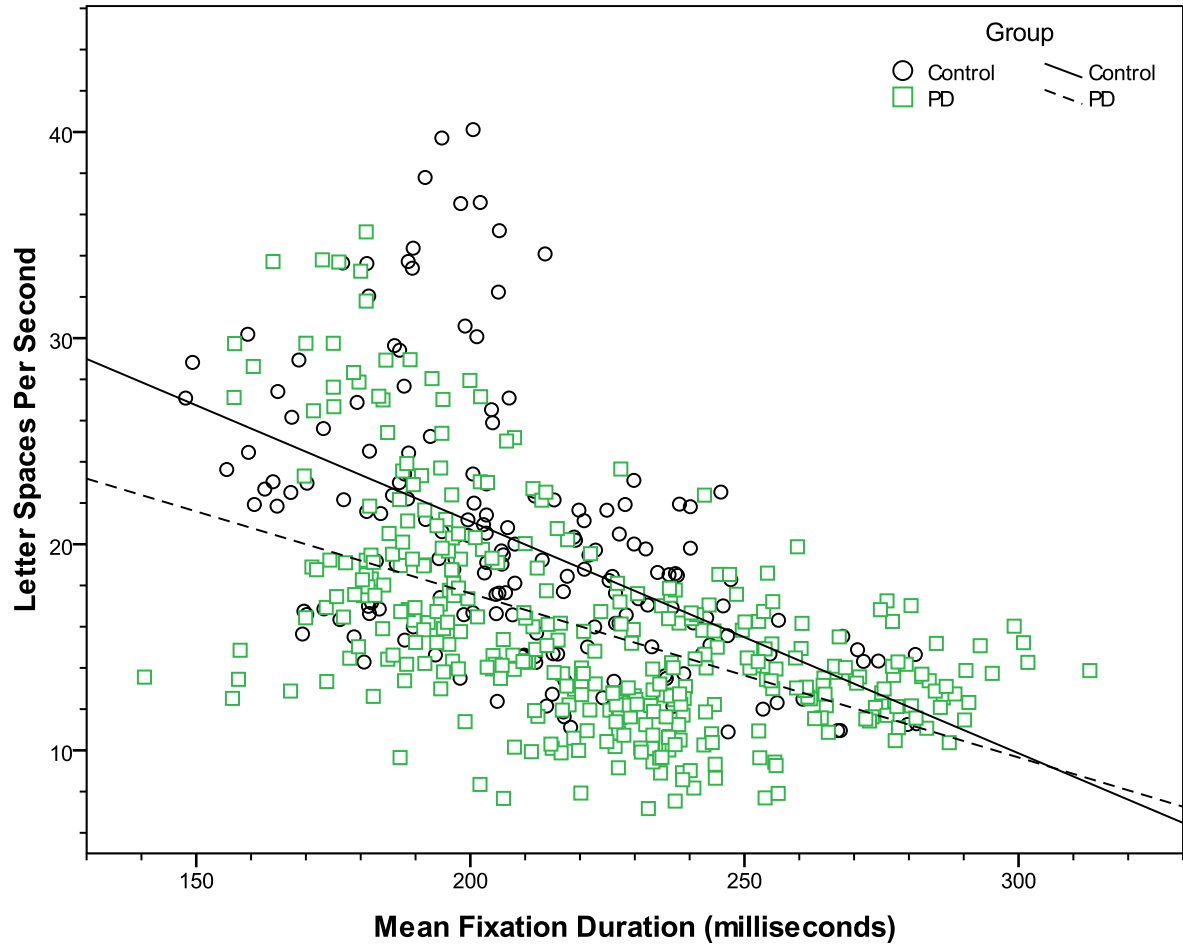
**Supplementary Figure 3: letter spaces per second versus Mean fixation duration**

Supplementary Figure 4 shows the same data as supplementary Figure 3, but includes data from Zuber and Wetzel. This shows the faster reading speed for college aged students and longer fixation times in that population, result in a greater percentage decrease in reading speed. Supplementary Figure 5 also shows that college aged controls have larger saccadic amplitudes when reading that either PD patients or elderly controls.

Supplementary Figure 6 shows the relationship between reading speed and fixations per letter space. It is shows that both groups of normal subjects maintain a linear relationship, where fixations per letter space directly affects reading rate. In the PD group however, the relationship is hyperbolic, in which a greater number of fixations per letter space will slow reading only to a point, after which the penalty on speed is less. We can also interpret this by considering the inverse of the abscissa, or the number of letter spaces being processed per fixation. From supplementary Figure 6, it shows that the majority of healthy subjects are capable of processing somewhere between 5 and 10 letter spaces in each fixation. Conversely, some PD patients are capable of reading at those speeds, while the bulk of them process 3 to 7 letter spaces per fixation. The college aged group is equally bisected at 7 letter spaces per fixation, which also bisects the elderly control group that has a different slope. The PD group however is heavily skewed to the right of that, indicating that textual information is not grouped and acquired in similar chunks. As described earlier, the PD patients are not capable of maintaining 7 ± 2 letter spaces per fixation. Interestingly, both college age and elderly controls are approximately evenly split at 7 letter spaces per fixation, but have different slopes in how that affects their reading speed.
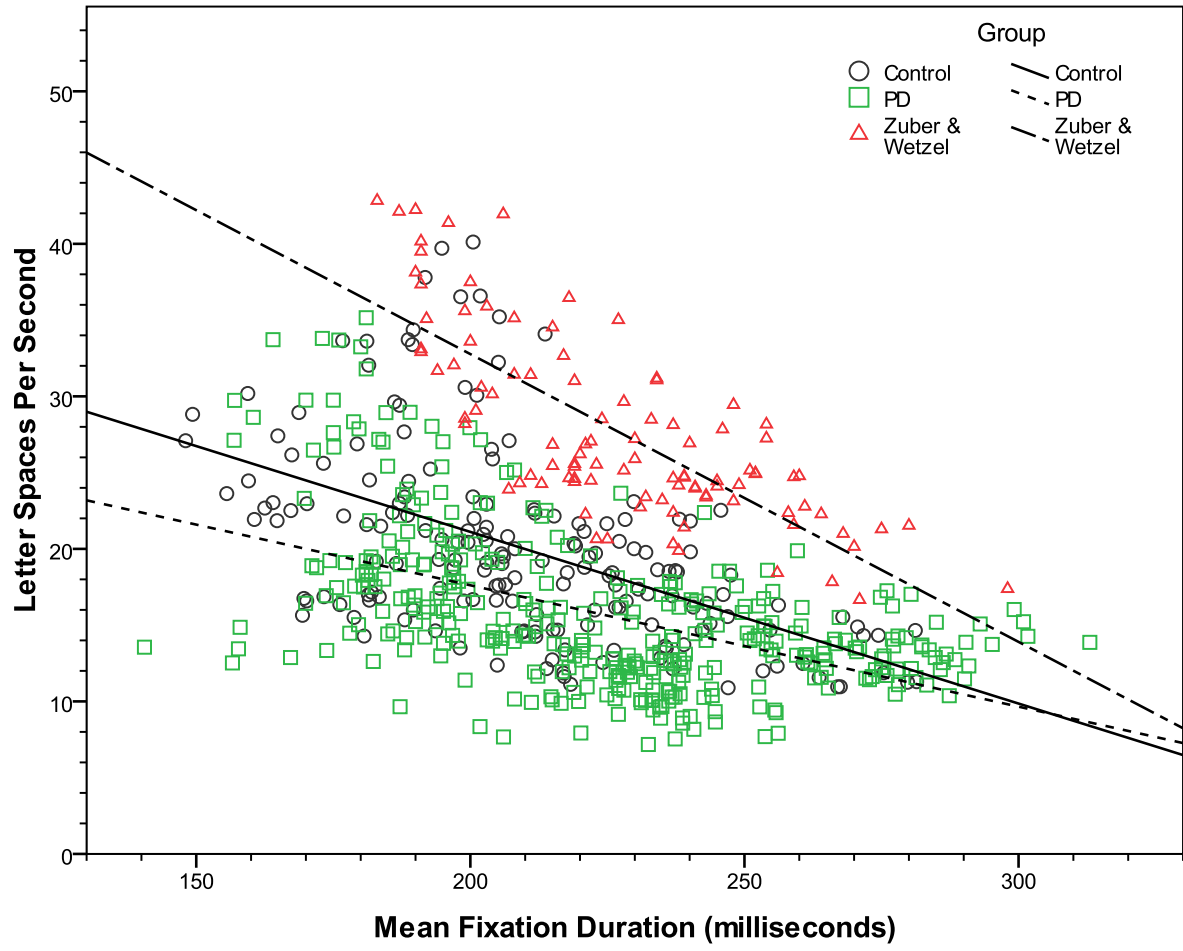
Supplementary Figure 4: Reading Rate vs mean fixation duration, across young controls, elderly controls, and PD patients
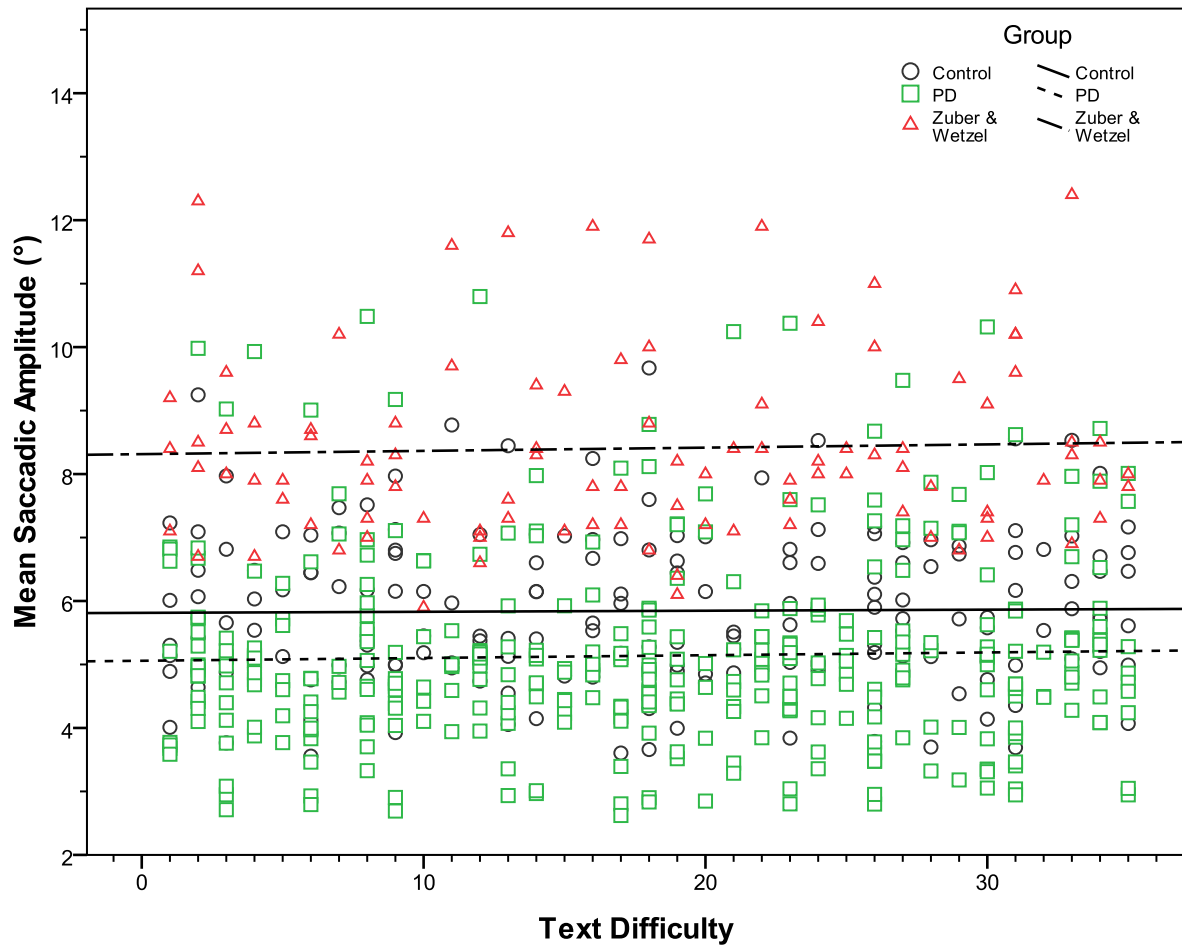
Supplementary Figure 5: Average saccadic amplitude across all three populations
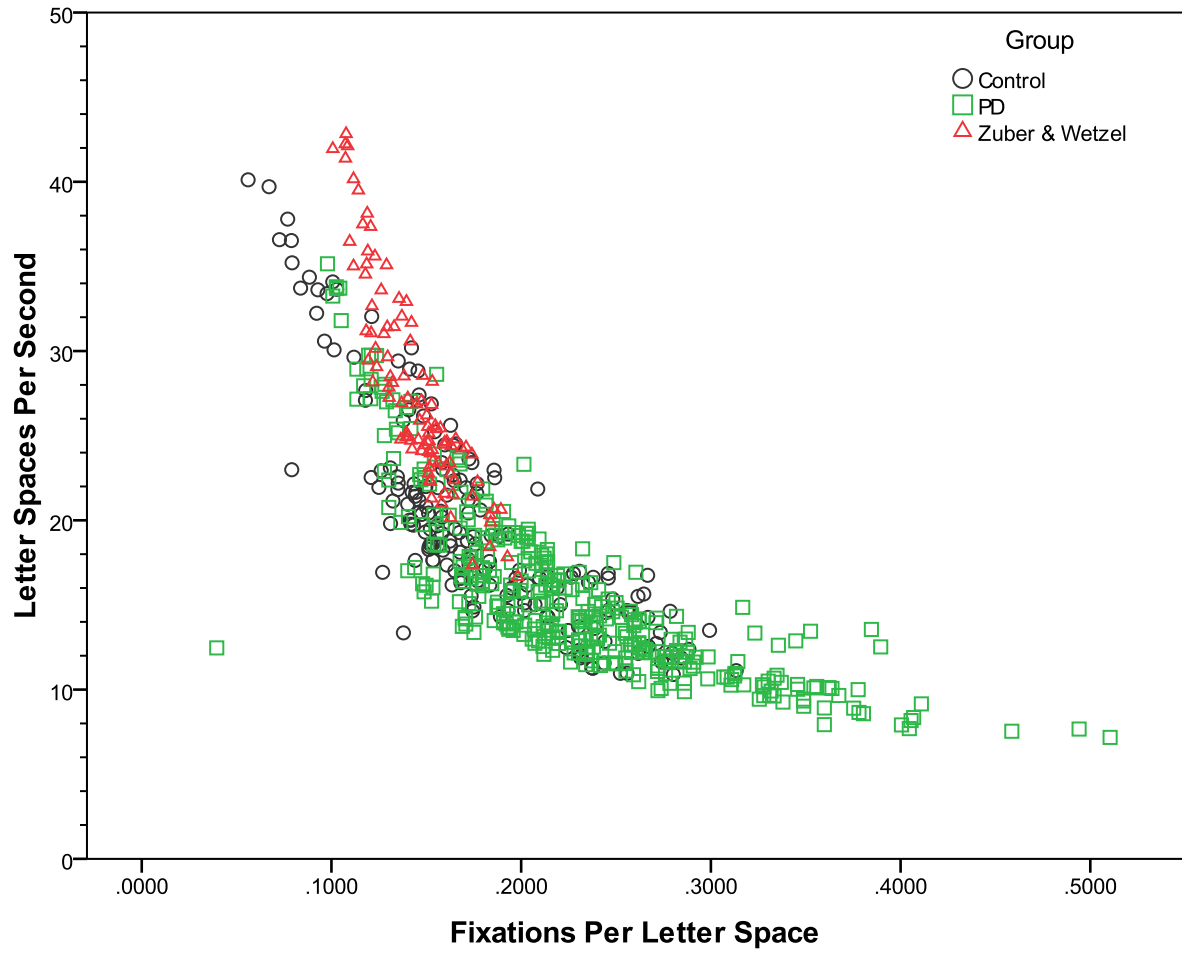
Supplementary Figure 6: Reading rate versus F/LS in all three subject populations.

Vita

George Thomas Gitchel Jr. was born on the Fourteenth of May, 1983 in Fairfax Virginia and is a citizen of the United States of America. He graduated Bishop Ireton high school in Alexandria Virginia in 2001. He went on to receive his bachelor's degree in biomedical engineering at Virginia Commonwealth University in Richmond, Virginia in 2006. During his senior year, he received a grant from Verizon for his work on creating a set of cryogenically cooled clamps for material testing of soft biological tissues in the orthopaedics lab. He began working on a master's degree in Biomedical Engineering at Virginia Commonwealth University in the fall of 2007. Concurrently, he began his research at the Parkinson's Disease Research, Education, and Clinical Center (PADRECC), at the Hunter Holmes McGuire Veteran's Affairs Medical Center in Richmond, Virginia. His research continues at the time of this publication, and involves other neurological and movement disorders besides Parkinson's disease.