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The Effects of Parkinson's on Fixational Stability

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THE EFFECTS OF PARKINSON'S DISEASE ON FIXATIONAL STABILITY

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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Abstract

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By Erin L. Mallahan, M.S.

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

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Major Director: Dr. Paul A. Wetzel
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Parkinson's disease (PD) is a progressive, neurological movement disorder. The stability of eye movements in PD is not well understood but many patients report difficulty doing tasks that require stabilized fixation and gaze. The ability to stabilize an image on the retina is critical is acquiring visual information. The purpose of this study was to compare the stability of fixational eye movements of PD patients to those of age-matched controls. Eye movements during simple fixation tasks were recorded from 66 subjects (ages 52 to 84), and 36 age-matched controls (ages 58-85). The absolute velocity of the fixational eye movements were recorded and correlated to a clinical measure of disease

progression as measured by the Unified Parkinson's Disease Rating Scale (UPDRS). Unstable, non-rhythmic eye movements were seen in the PD patients. There were significant differences in the absolute velocity and standard deviation between the control group and the PD group in both the horizontal and vertical directions. The correlation of the absolute velocity to the UPDRS was not significant. Parkinson's disease does appear to affect the stability of eye movements. The instabilities in the eye movements appear to precede body tremor. This could lead to an early method for diagnosis and analysis of the disease.

CHAPTER 1 Introduction

Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder, first described in 1817 by James Parkinson, that involves a decreased level of dopamine. Dopamine is a neurotransmitter that is produced in the brain and controls movement and coordination. With PD, a person's dopamine production levels begin to decrease. This is followed by the death of the cells in the brain that produce dopamine.[1] While the cause of PD is not known, some of the physiological changes that occur are known. One relationship affected by a decrease in dopamine is the one between dopamine and acetylcholine. This is normally an antagonistic relationship in which neurons are inhibiting and exciting to regulate movement. The decrease in dopamine results in uncontrolled excitatory impulses, which causes an imbalance of the motor systems.[2]

There are several areas of the brain that PD is thought to affect, but the most common is the substantia nigra. The substantia nigra is a nucleus located in the midbrain, and is divided into two parts; the pars reticulate (SNr) and the pars compacta (SNc). Nerve cells in the SNr send dopamine to both sides of the brain.[3] There is also pathological evidence of degeneration of melanin-containing cells in the SNc. This is caused by the decrease in dopamine, as melanin is a by-product of dopamine synthesis [1].

The substantia nigra is functionally related to the basal ganglia [4], which are cell groups within the cerebral hemisphere[5]. The basal ganglia modulate signals that originate in the cerebral cortex to direct individual muscles during voluntary movement. Damage to the basal ganglia can result in a disruption of these movements. Common symptoms of basal ganglia-related disorders, akinesia and bradykinesia, are also common symptoms of PD. The primary symptoms of PD are resting tremor, rigidity, akinesia, bradykinesia, and postural instability.

Akinesia describes a problem initiating movement. Studies in nonhuman primates showed that basal ganglia are most active in the planning phase of movement [5]. Therefore, akinesia is an outward sign of the disruption in the basal ganlia's role in the planning and generation of programmed movement. Bradykinesia describes the slowing of movement [6], and is seen as a reduction in velocity and amplitude of movement [5]. Although the resting tremor is a commonly recognizable symptom, other symptoms of the disease can be more debilitating for the patients. PD symptoms usually begin unilaterally, and can progress to affecting both sides. Parkinson's is diagnosed by identifying some of these characteristic symptoms.

There are several clinical measures used to quantify these symptoms. These measures are generally subjective, thereby showing limitations of the currently used scales. A more objective way of measuring the progression of the disease could be a major asset to the study of this disease. The Unified

Parkinson's Disease Rating Scale (UPDRS) is one of the most widely used clinical measures. This scale was developed by incorporating parts from the multiple scales that were previously being used. The goal of the UPDRS was to provide a comprehensive way for clinicians to monitor disabilities and impairments caused by PD. It is broken into four sections: Behavior and Mood, Activities of Daily Living, Motor, and Complications. The UPDRS is currently the most commonly used PD assessment scale, and is also widely used throughout the world. It is commonly used as a reference in studies rating specific aspects of PD.[7] UPDRS scores for the Motor section (III) can range from 0 to 108. The scores are determined by a clinician by answering a series of questions and assigning a value of 0-4 for each question, with 0 being no disability and 4 being severe disability. The motor section of the UPDRS covers questions on speech, facial expression, resting tremor, postural tremor, rigidity, finger taps, hand movements, rapidly alternating pronation and supination of hands, leg agility, ability to arise from chair, posture, gait, postural stability, and body bradykinesia[8]. It can then be seen, that this clinical scale does not address visual problems.

The next most widely used rating scale for Parkinson's disease is the Hoehn and Yahr (HY) staging scale. The scale uses stages (1-5) to evaluate disease severity. It is over 30 years old, but was modified in the 1990s to include 0.5 increments. The stages range from unilateral impairment (Stage 1) to bilateral impairment, postural instabilities, loss of physical independence, and

being wheelchair or bed-bound (Stage 5). Although the HY scale accounts for some of the major aspects of the progression of PD, it has several limitations. The stages are limited in number and are non-linear. The scale, which weighs postural instability as a major gauge of PD progression, does not give much weight to other motor factors and does not give any consideration to non-motor aspects of PD. [9]

Although the cause of PD is not yet known, there are factors that have been determined that play a role. The role of genetics does not appear to be significant, although there have been reports of people within a family suffering from PD. Some genes have been found defective in some of these people, but the majority of PD cases are still random.[10] Besides genetic factors, environmental factors such as place of residence, source of drinking water, and occupational or residential exposure to industrial chemicals and processes are also thought to play a role in PD[11]. Research has yet to determine what is causing the cell death leading to PD, but some theories that have arisen are free radicals, prompted by oxidation, cause cell death. Others suggest that there is some dysfunction of mitochondria while others think that excitotoxicity, when neurotransmitters become unbalanced, may be the cause. Most researchers believe the cause is a combined effect of genetic, environmental, and biological factors. [10]

Parkinson's disease affects both men and women and can be found in all ethnic, economic, and geographical groups. While as many as half of the cases

in the US may be undiagnosed, it is estimated that 1.5 million people in the US suffer from PD, with 60,000 new cases being diagnosed each year. Although some patients are diagnosed earlier, onset is usually after age 60. [12] A study by Van Den Eeden, et al. studied 588 newly diagnosed cases of PD in a northern California clinic to determine incidence rates for age, race, and gender. The study showed the male to female ratio of incidence to be 1.9:1. The incidence rates for both males and females rose rapidly after the age of 60. The study found only 4% of the patients were under the age of 50. The male to female ratio was approximately 2.0:1 in all racial groups (non-Hispanic white, Hispanic, Black, and Asian) except Asians, where the incidence of PD was slightly higher in females. [13] The reason for this irregularity is not known, however it is suggested that perhaps it is due to environmental factors.

There are now several treatments available for patients with PD. It is important to know that these treatments help lessen symptoms, but there is currently no cure for this disease. Treatment can include the use of pharmacological treatment, surgery, or a combination of both. The most commonly used pharmacological treatment is levodopa (L-dopa). It first became available is the 1960's-1970's. It is initially very effective in reducing symptoms, but the effectiveness diminishes and the side effects can be debilitating [14].

There are also several kinds of surgeries that patients may receive. Ablative surgeries were the common way of treating Parkinson's beginning in the 1950s. When drugs like L-dopa were discovered, surgeries became less often

used. When the effects of the drug became more prevalent, surgeries became popular again. Ablative surgeries, like thalamotomies and pallidotomies use electrodes to destroy cells in the brain that are overactive in PD patients. In the mid-1990s a non-ablative surgery was discovered.

Deep brain stimulation (DBS) involves implanting a small lead into the thalamus and connecting it to a small pacemaker-like device. On the end of the lead is a multi-site stimulating electrode. This technique does not destroy cells; it temporarily disables them by firing rapid pulses of current [15]. This technique has become very popular in the last few years because it has several advantages over ablative surgeries and because it has had very promising results. DBS is reversible, and can be adjusted to obtain maximal benefits. It can also be performed on both sides of the brain, while the risks of cognitive or neurological deficits are too high to have bilateral ablative surgery [16]. There are current studies to determine the best place to implant the lead. There are several areas in the brain that are currently used, including the globus pallidus internus (GPi), the subthalamic nucleus (STN), and the ventral intermediate nucleus (VIM) of the thalamus. VIM stimulation treats tremor well but not the other symptoms of the disease. GPi stimulation and STN stimulation are thought to treat all of the major symptoms [14].

Oculomotor System

Parkinson's disease is often thought of as a neurological disease that affects the motor system, and the visual effects are often overlooked. However,

about 40% of the fibers in the brain carry "information related to visual function"[5], so some type of visual dysfunction often occurs with damage to the brain. The oculomotor system is very complex and involves coordination from various aspects of the system. The saccadic system controls foveation, and the pursuit system tries to match the eye's velocity to that of the moving target's. [17]

The fovea is the part of the retina with the greatest visual acuity. While the region of the fovea covers a visual angle of about 2°, the greatest acuity is found in a 0.8° area of the fovea[18]. The eyes move allowing the target to fall on the fovea for maximum acuity [19]. The stabilization of this stationary target on the fovea is described as fixation. If the movement of the image on the retina exceeds 4°/sec[20,21] , vision is degraded. The length of a fixation varies with task. A typical fixation during silent reading lasts at least 200ms, while a typical fixation during typing lasts about 400ms [20]. During fixation the eye is relatively stable while information is being extracted, however, there are very small eye movements occurring during fixation.

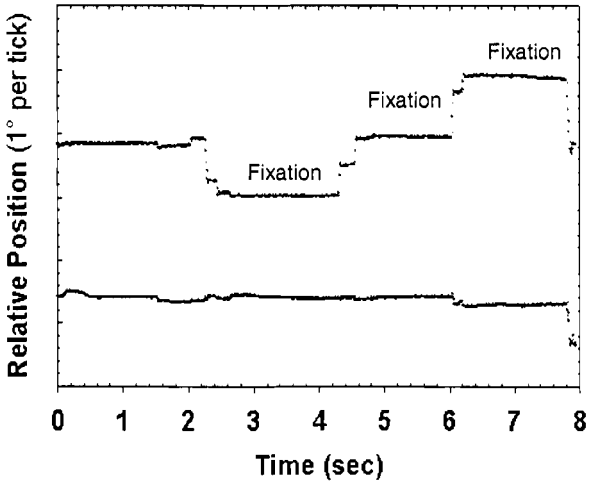


Figure 1: Example of a Typical Fixation

Tremor is a high frequency movement, typically from 30-100Hz with an amplitude of 5 to 30-sec arc, and is not correlated between the two eyes. Drift, which is also not correlated between the two eyes, is a low-velocity movement with an amplitude of 1 to 5-min arc, with irregular movement and frequency. Microsaccades occur once or twice each second, with an amplitude of 5-min arc. Microsaccades are highly correlated between the two eyes. [17,19,20,22] Sometimes abnormal fixations occur resulting from slow drift, saccadic intrusion, or nystagmus, an involuntary rhythmic oscillation of the eye [19].

Saccadic eye movements are voluntary movements used to move the eye from one position to another without following an object between the two points. They consist of high-velocity, accurate eye movements that foveate on the intended object. They are generated by a high frequency neural pulse that move the eye to a new position quickly, and a tonic step that maintains the eyes in the new position. The reaction time of the saccadic system, which refers to the time between the target's movement onset and the onset of the saccade, is about 200 ms. Sometimes, abnormalities can be found in the saccadic system. Slowed dynamics is when the peak velocity is slower than normal. The duration of the saccade can also be longer during slowed dynamics. There can also be inaccurate amplitude, when the number of dysmetric saccades increases. This creates the need for more corrective saccades. This abnormality is sometimes seen in PD patients. The third abnormality is delayed initiation, in which there is an abnormally long reaction time.[17] The occurance of this abnormality increases

with age.

The pursuit system, a continuous system that is not under voluntary control, is in control of the smooth movement tracking of objects. The pursuit system does this by matching the eye velocity to the velocity of the moving target. Because the eyes are foveated on the object for sustained times, there is better resolution and more gathering of information. If there is an error in positioning of the pursuit system, it is corrected with a saccade. The pursuit system has a latency of 100ms. [17]

Normal activities in which the head moves could potentially cause smearing of images on the retina. Two systems prevent this from happening. The vestibular system compensates for brief head movements, and the optokinetic system compensates for prolonged head movements. These two systems work together to allow head and body movements without affecting the visual system. The vestibular system is important for maintaining overall body posture, equilibrium, and muscle tone, but it is also important in maintaining the stability of images on the retina during brief head movements. It does this by producing eye movements that compensate for the head movements. [17] The compensatory system is critical in maintaining a stable gaze during normal movements.

One of the most complex tasks involving eye movements is reading. Reading involves many systems of the body working together because there is a large cognitive element as well as an oculomotor element. The typical reading

pattern resembles a staircase, as seen in Figure 2[33] below. The reading pattern of a PD patient can vary greatly from this predictable pattern. The pattern is less stable and tremor can be seen (Figure 3[35]). If PD is shown to affect the eye's ability to stabilize an image or if it affects the ability to have a stable gaze, the ability to acquire the visual image can be lessened.

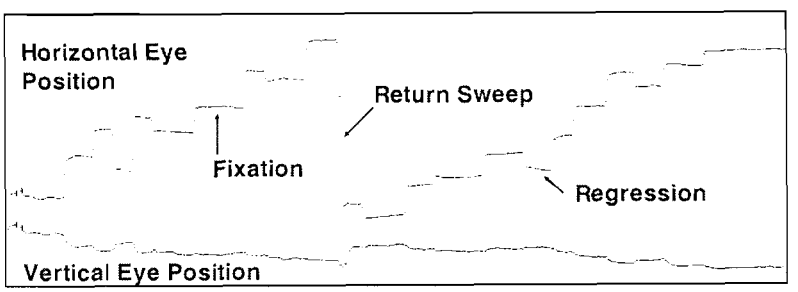


Figure 2: Normal eye movement recording while reading

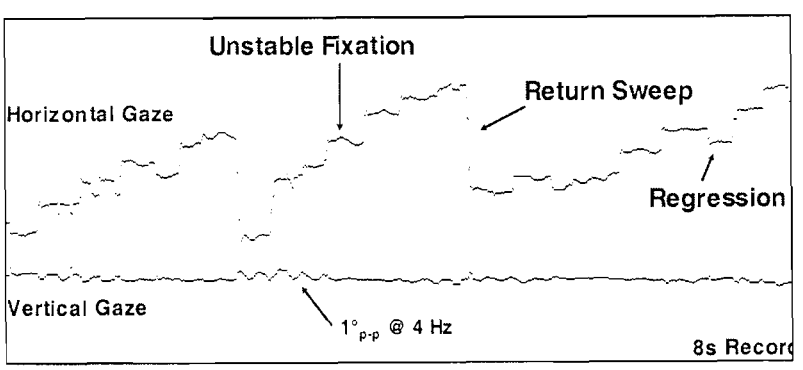


Figure 3: Eye movement recording while reading for a PD patient

Aging and the Visual System

Aging has been found to affect the visual system in several ways. While the fixational eye movement system does not show significant changes in stability due to aging, the range of fixation does decrease with age. For example, the maximal limits of the field of fixation during adduction decrease from 57 degrees for 20-29 year olds to 54 degrees for ages 50 and older[17]. Beginning around age 40, the lens begins to lose its elasticity and becomes more flattened in its relaxed state. Because the lens focuses light on the retina, this change in shape affects a person's ability to accommodate. [5] Aging has also been shown to affect the saccadic system. The reaction time increases with age at a rate of 1 to 2 ms per year. The peak velocity of the saccades decrease with age, but the accuracy of the saccades has not been found to decrease with age [17]. Affects of aging can also be seen in the pursuit system. There is a decrease in the gain, and increase in saccades, and a decreased initial acceleration, which can decrease by 30% [17]. The increase in saccadic activity is caused by an increase in positioning errors, which are corrected by saccades. There can also be an increase in the velocity latency, but no change has been seen in the acceleration latency [17].

Parkinson's Disease and the Visual System

Parkinson's disease has been shown to have an effect on the visual system. Many PD patients complain of visual problems, but these complaints may be overlooked as age-related complications or less important than the other

symptoms of PD. However, more research is being done on the effects of PD on the visual system. These effects however, can lead to drastic declines in patients' quality of life, including problems with reading, driving, watching television, and other daily activities. One explanation for the effect of PD on the visual system is that the basal ganglia are affected in PD. This area of the brain is related to eye movements, including saccadic activity. Lesions to the basal ganglia can result in impaired stimulus-response reactions [23].

There are known effects of Parkinson's disease on the visual system. Common abnormalities include hypometric saccades and impaired smooth pursuit [24, 25,18]. Steady fixation has been found to be interrupted by saccadic intrusion[26], where the eyes make saccades instead of maintaining fixation[18]. Upward gaze has also been found to be restricted in PD patients[27], but this is also observed in normal elderly patients[28]. Corin et al. [27] reported oculomotor abnormalities in three quarters of their PD patients. In visually guided tasks, advanced PD patients showed prolonged mean latencies [29]. Manual tracking in PD patients have shown slowed movements and poor sinusoidal tracking as well as a significant reduction in saccadic accuracy [24]. Along with reduced saccadic accuracy, slowed saccadic initiation can be seen [30,24,29,25]. It appears that the akinesia that is a major symptom of PD can also be seen it the oculomotor system of patients with mild, untreated PD [24].

Chan et al. [31] studied 18 PD patients and 18 controls to determine effects of PD on the saccadic system. They found that there were characteristics

of saccadic eye movements that were affected by PD. The subjects were instructed, among other tasks, to look toward a peripheral stimulus as soon as it appeared. The PD patients were found to make more express saccades in this task than the control group, showing that they have deficits in their ability to inhibit automatic saccades. The author suggests that these results are consistent with a disorder of the prefrontal basal ganglia circuit. [31] Another study found that the amplitude of saccades increased ninety minutes following a dose of L-dopa, showing that there may be a correlation between dopamine and control of some ocular movements. There have also been studies to examine the effects of dopamine loss in the retina. The levels of dopamine in the retinas of patients with PD were less than the controls. This may show that the loss of dopamine in the retina and some areas of the brain associated with the visual system may be the cause of visual problems in PD patients. [2]

These studies are beginning to show the effects of PD on everyday visually related tasks. Balance, which is also affected by PD, can play a role in visual problems[2]. As stated above, reading is a very complex task that involves several systems within the body. Fundamental to reading is the ability to stabilize fixation and gaze. These studies may help to explain the difficulty for PD patients to read.

Objective

The ability to fixate and control eye moments is fundamental for the extraction of visual information. The objective of this study is to determine the

effects of PD on the stability of fixational eye movements. The goals of this study are to determine the effects of PD and treatments on eye movements, to compare data with those of age-matched controls, and to correlate the data with currently used clinical measures of PD. While there have been numerous studies on the effects of PD on the saccadic system and on the pursuit system, the effects of the disease on fixation has been overlooked. Studying fixation is important because the ability to stabilize fixation is critical in obtaining visual information. It is important for the general health community to understand these effects of the disease and how they affect patients' quality of life.

CHAPTER 2 Methods

Subjects

The subjects who participated in this study were recruited from Virginia's Commonwealth University's Ambulatory Care Center (ACC) clinic as well as the Parkinson's Disease Research, Education, and Clinical Center (PADRECC) at the Hunter Holmes McGuire Veterans Affairs Medical Center (VA). The 66 subjects ranged in age from 52 to 84 years, with the average age 71.5 years, and are comprised of 50 males and 16 females. Nineteen males and 14 females comprised the 33 PD patients from the ACC, and 31 males and 2 females comprised the 33 PD patients from the PADRECC. Spouses or friends accompanying patients to the clinics were used as age-matched controls. The importance of the age-matched controls is to have a basis of comparison for age-related affects on the visual system. There were 36 controls, 6 males and 30 females, ranging in age from 58 to 85 years, with the average age 71.7 years. Three males and 8 females comprised the 11 controls from the ACC, and 3 males and 22 females comprised the 25 controls from the PADRECC.

The recruitment and testing of all subjects and controls were conducted under protocol approved by both VCU's and the VA's IRB. Subjects were informed of the procedures before beginning and all subjects, patients and controls, gave informed consent about participating in the study. Patients were

tested immediately before or following their scheduled clinical appointment in which they where evaluated and given a clinical measure of disease severity based on the motor section of the Unified Parkinson's Disease Rating Score (UPDRS). Clinicians had the option of excluding patients who, due to cognitive abilities could not give informed consent.

Apparatus and Setup

Horizontal and vertical eye movements of the right eye were recorded using a pupil cornea, head-mounted eye tracking system (Vision 2000, El Mar, Inc., Toronto, Canada). The non-collimated infrared beams, pulsed at 120 Hz, illuminate the subject's eyes while sensors detect the two corneal reflections (Figure 4). Because the infrared beams are non-collimated, the pupil remains dark. A beam-splitter redirects the reflected infrared light from the eye to a two-dimensional charge coupled device (CCD) array located above the eye.[32] The image of the eye as well as the corneal reflection are viewed on a small video monitor, allowing adjustment of infrared intensity for maximum contrast. The 2D CCD array measures the intensity of the infrared light reflected from the eye along the rows and columns, and maps it to a three-dimensional topographical map, where the corneal reflections appear as peaks and the pupil appears as a sink hole. The image of the eye is then fitted to an ellipsoid and an algorithm is used to estimate the pupillary center using the corneal reflections (Figure 5). The algorithm estimates the center of the pupil using the known optical center and the

estimated visual center. This information produces a signal that is sent to a computer for processing and viewing.

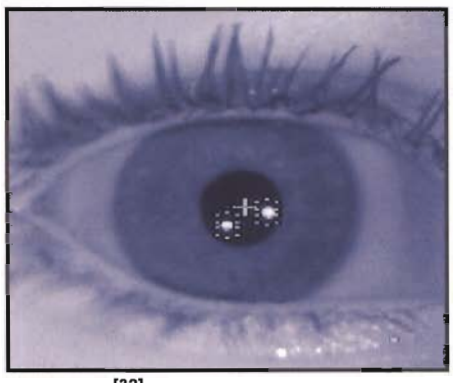


Figure 4[32]: Estimate of pupil center and corneal reflections

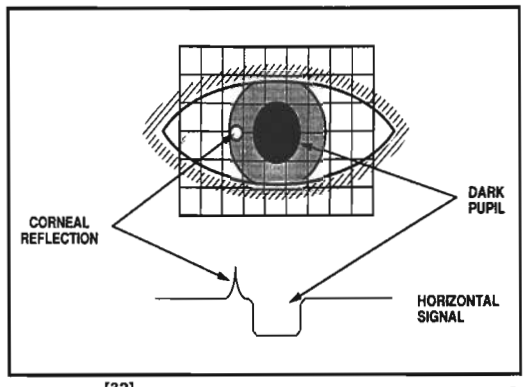


Figure 5[32]: Mapping of image onto 2D CCD array

The head-mounted portion of the eye tracker weighs less than 300 grams and has a measurement range is ±45° horizontally and ±35° vertically. The vertical range can be less due to occlusions such as the lids or lashes. The resolution is better than 0.2°.[32] A six-degree-of-freedom, magnetic, head-tracking device (Flock of Birds, Ascension Technologies, Burlington, VT) was attached to the top of the eye tracker, and the transmitter was located close to the back of the head to minimize non-linearities and distortions. The head tracker provides x, y, and z positions as well of yaw, pitch, and roll angles.

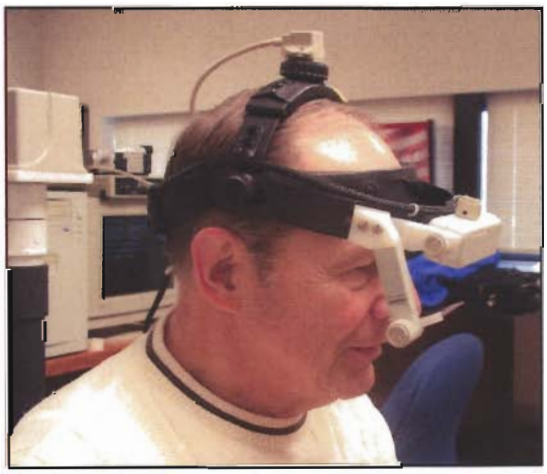


Figure 6[35]: Eye and Head tracking system

The eye and head tracking systems both sample and output data at a rate of 120 Hz. The serial outputs of each system were linked to a Toshiba™ notebook computer through two USB-to-serial port converters (IOGEAR Model GUC232A). The serial interface port and experimental control program that was used to communicate with both trackers was developed by Dr. Paul A. Wetzel. The serial port on the eye tracker ran at 38k baud, and the head tracker at 115k baud. The head tracker runs at a higher rate to accommodate the large amount of data it is sampling because of the six degrees-of-freedom.

Experimental Procedures

The fixation target board is a flat black board with yellow target dots located at 0, ± 5°, and ± 10° in both the horizontal and vertical directions (see Figure 7). The target board is located on a laboratory jack, enabling it to be adjusted for each subject so the horizontal axis was lined up with their eyes. Each subject was seated at a table in a lighted room. The eye-head tracking system was put on each subject's head, and they were told that they should move their head and eyes normally. The system allows the subjects to move freely, with limited restrictions. The band is adjustable so the system fits snuggly on the subject's head. The eye can be viewed on a small video monitor, allowing for adjustments for position and focus. The intensity of the infrared beams is also adjusted to obtain ideal contrast.

The device is calibrated for each subject before the testing begins. This process takes less than one minute and is done by having the subject look at the

target dots on the fixation target board in an order preprogrammed within the system. After calibration, the subjects, seated one meter from the center of the fixation target board, were verbally instructed to fixate on the target dots located on the fixation target board. The test lasted about 2 minutes for a quick assessment so as not to fatigue the subjects. Subjects were also given smooth pursuit and compensatory tasks. This data was observed to verify the behavior of the compensatory system was working, but was not analyzed.

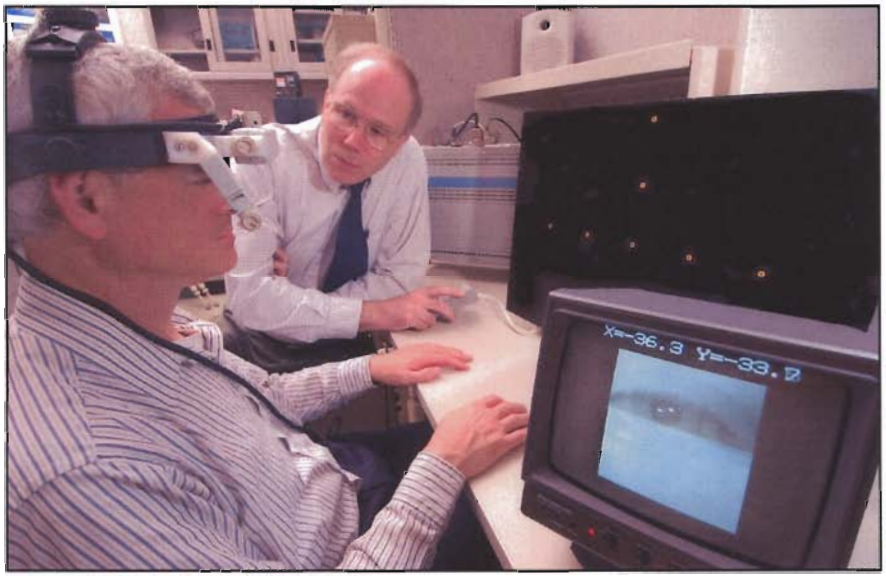


Figure 7[33]: Experimental Setup

A difficulty sometimes arises in collecting data because many of the patients wear glasses and/or have ptosis. While the system can be used with glasses, the data obtained is not always usable. Interference from the eyelids occluding the majority of the pupil can make it impossible for the eye tracker to be calibrated because it is dependent on the view of the pupil. If a subject wore

glasses, the system was adjusted so that they could complete the experiment with the glasses on. This is accomplished by reducing the glare of the infrared light onto the lenses of the glasses by angling away from the beam-splitter so that they do not interfere with the corneal reflections. Four of the subjects (2 PD patients and 2 controls) did not have usable data due to either problems during calibration or the data was too chaotic to be usable.

Data Analysis

The data is complied, and the recordings are converted to binary VfPlot files and saved in a sequential format. These files are then parsed into individual horizontal, vertical, pupillary, x, y, z, yaw, pitch, and roll files. These recordings can then be viewed in the VfPlot program (written by Dr. Paul A. Wetzel) as head and eye movements. Cursors are used to obtain information from the plots such as position, velocity, and absolute velocity measurements, as well as their standard deviations. The cursors are manually placed at the beginning and end of each fixation. All possible fixations had to meet certain criteria to be counted as a fixation. They had to be greater than 125 ms to be considered and measured as a fixation. This value was constant for all data analyzed, and was decided based on standard fixation lengths while also considering standard deviations of fixation lengths and effects of age or disease. Corrective saccades less than 125 ms were not counted as fixations. The program saves the data between each set of cursors and stores it in a file for each patient. The information obtained from the head and eye data includes velocity, acceleration,

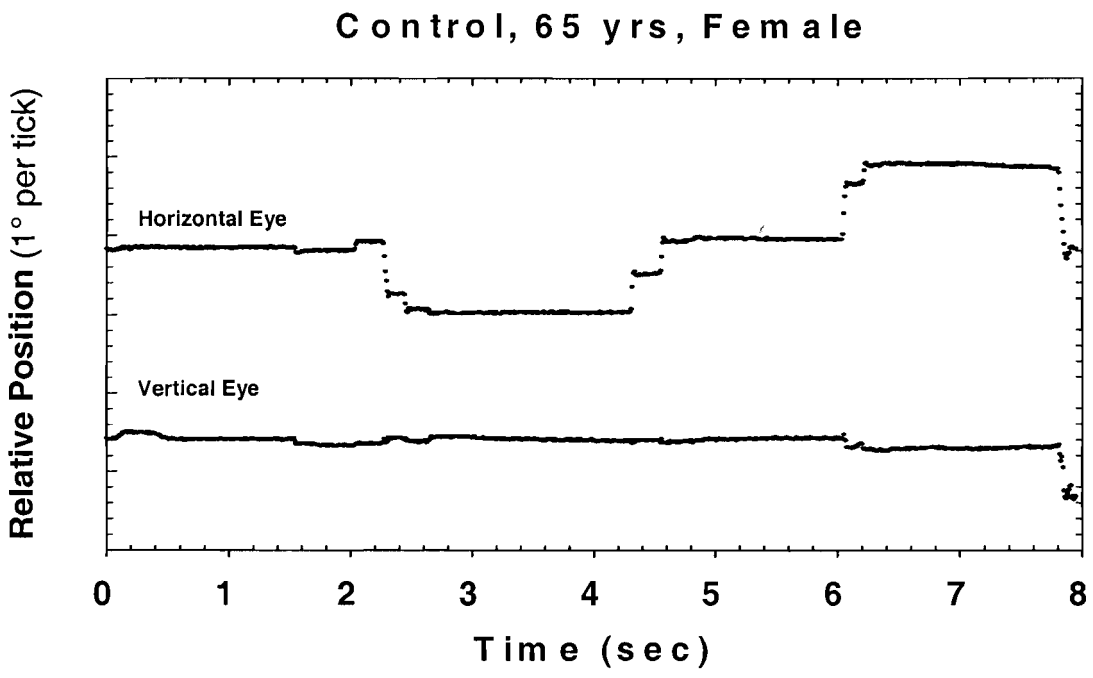
position, and time. The program calculates average velocity, sum of squares, and duration of fixation and number of points within each fixation. VfPlot calculates the velocity at each point using a 2-point central difference method. This method uses information from the surrounding points to calculate the value for each point, and is unique because it provides an accurate measure of velocity and suppresses noise through a low pass filter [36].

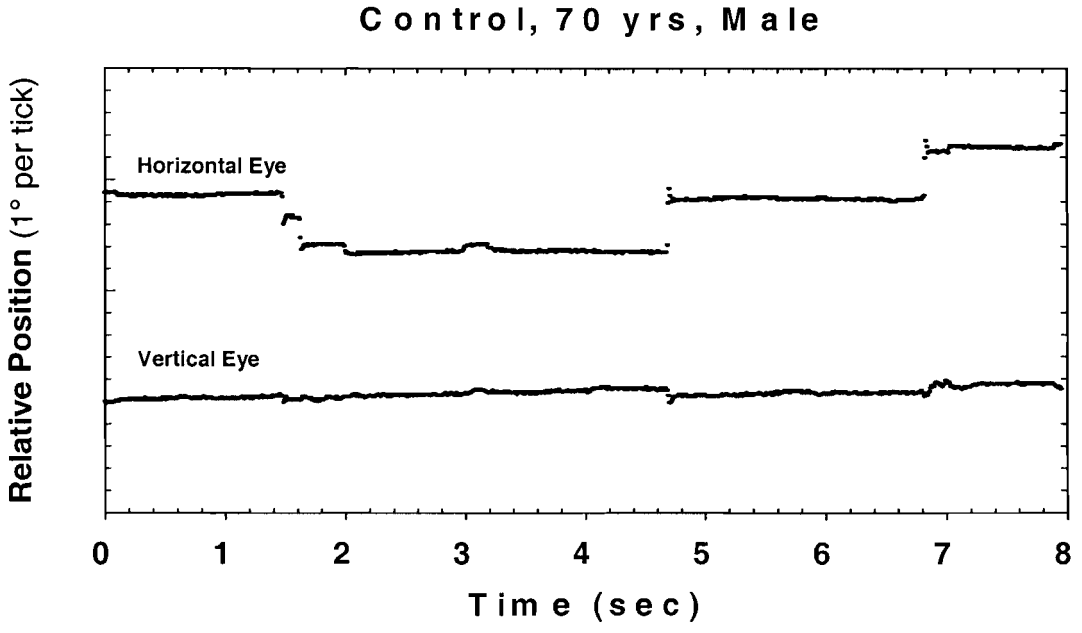
The VfPlot program saves the data obtained between the cursors in an ANSII file which is opened in Microsoft Excel™ for editing and extraction of data. The data obtained were analyzed for eye and head position and for the number and duration of fixations, saccadic amplitude and duration, and velocity. These data values were compared to the data of the controls. They were statistically analyzed for differences in average absolute velocity of movement during fixations between the patients and controls. The absolute velocity of the eye movement was chosen as a measurement to show instabilities in the eyes. Because some movements were positive and some negative, the velocities of these movements would cancel each other if the average of them was taken. To account for this, the absolute velocity was used to show the true movement of the eye. The data was analyzed to determine any correlation between groups and/or UPDRS ratings. The data were analyzed using the JMP™ statistical software.

CHAPTER 3 Results

Observational differences between the eye movements of the PD patients and the controls were seen during initial inspection of the eye movement data (Figures 8 and 9). The head data was inspected and showed no signs of movement and/or tremor, so the gaze was not affected by head movement and is due to eye position. The control group data followed very predictable patterns and movements, while the PD data did not. The eye movements in the PD data appeared to be unstable because the recordings were not as straight and predictable as the control group data. As described in the literature, an increased number of fixations in the PD group were observed. The PD patients required more saccades to get to the desired target position.

The three recordings below show recordings of eye movements during the simple fixation tasks. These are a representative sample of the typical, stable fixations seen in the control group. The third recording is from an 85 year old man. While saccadic intrusion can be seen, the fixations are stable, providing further evidence of the age effects of the visual system.


Control, 65 yrs, Female
Relative Position (1° per tick)
Horizontal Eye
Vertical Eye
0
1
2
3
4
5
6
7
8
Time (sec)


Control, 70 yrs, Male
Relative Position (1° per tick)
Horizontal Eye
Vertical Eye
0
1
2
3
4
5
6
7
8
Time (sec)

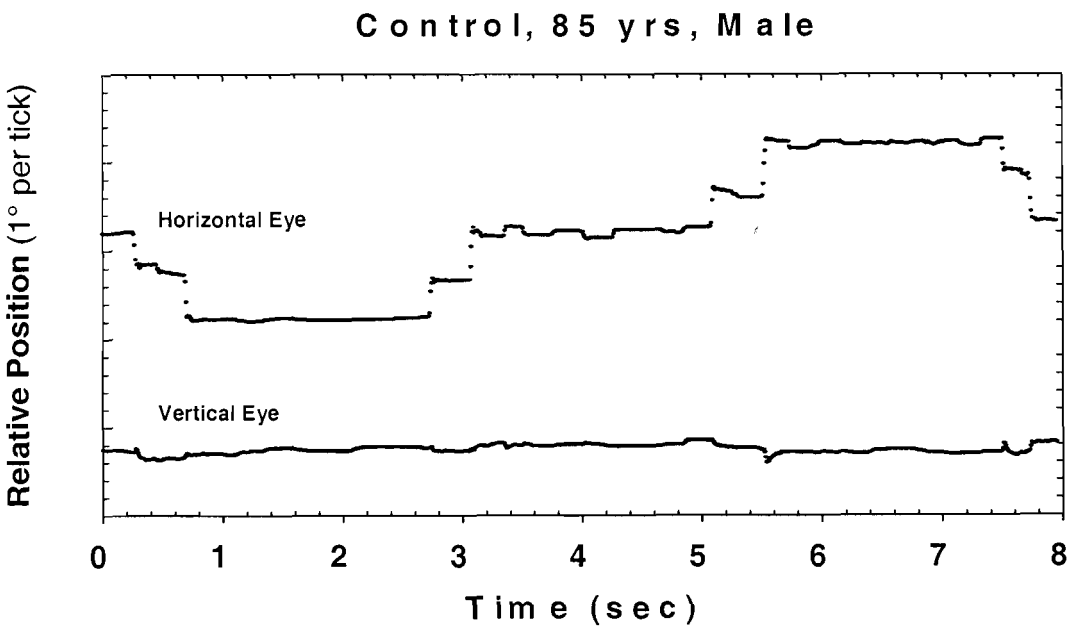
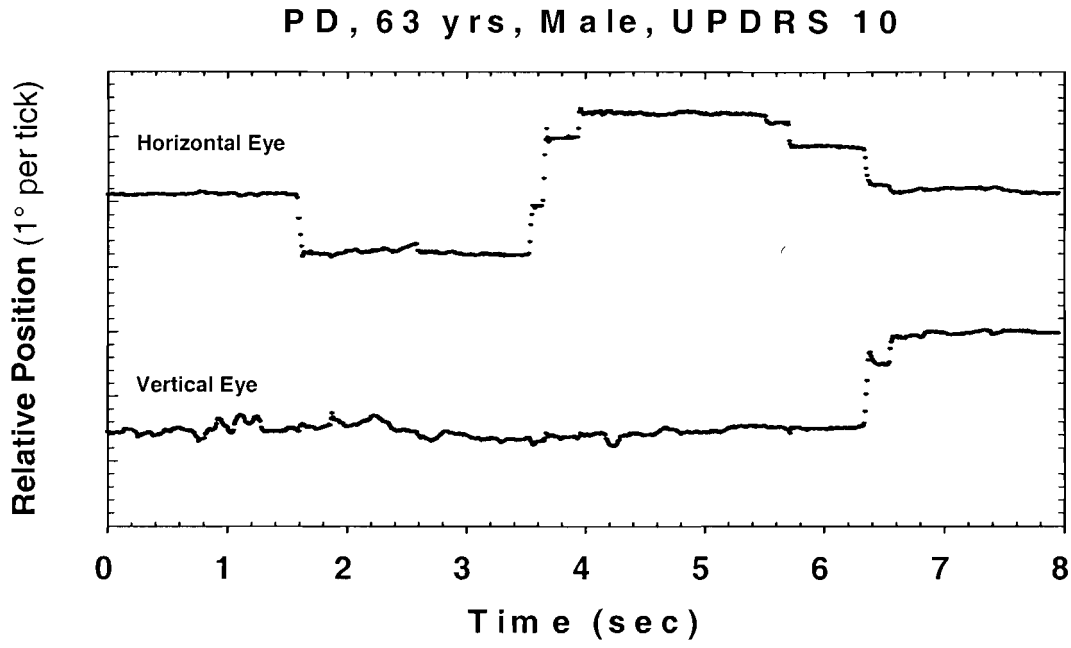
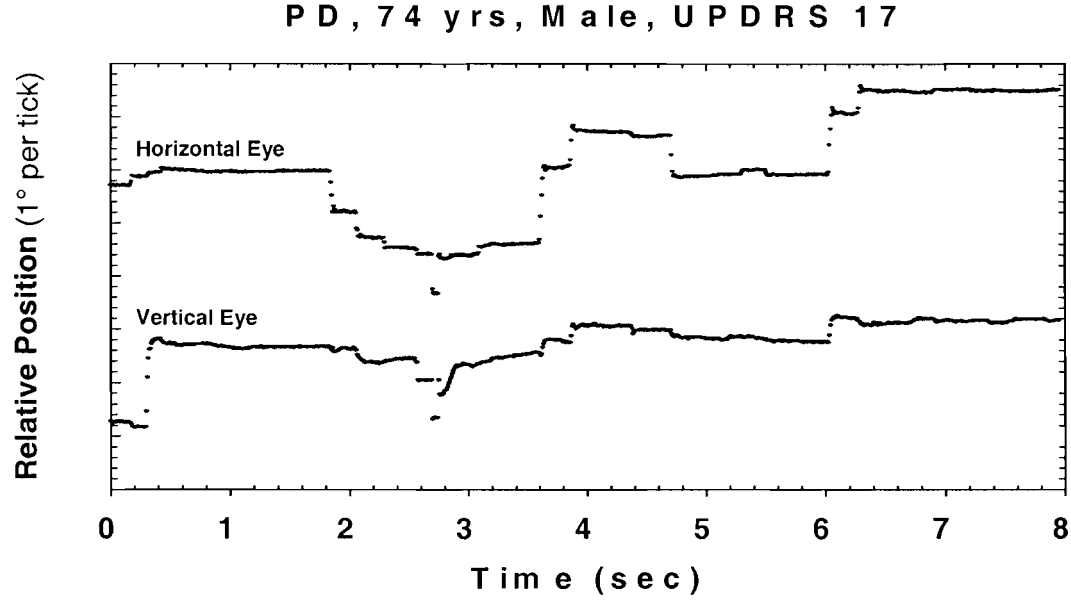
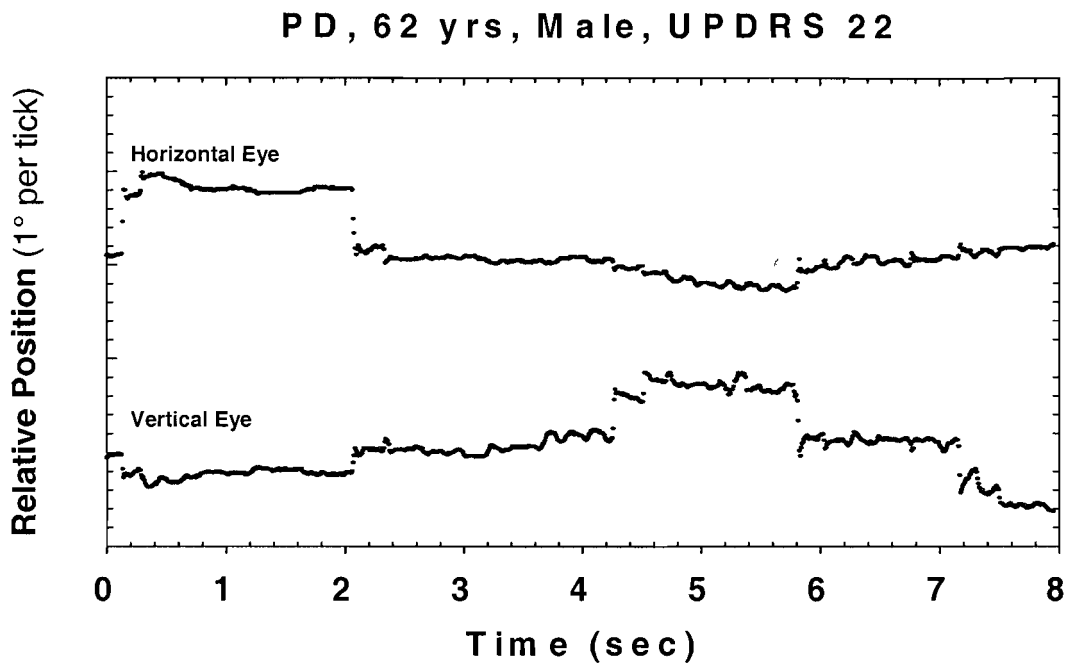


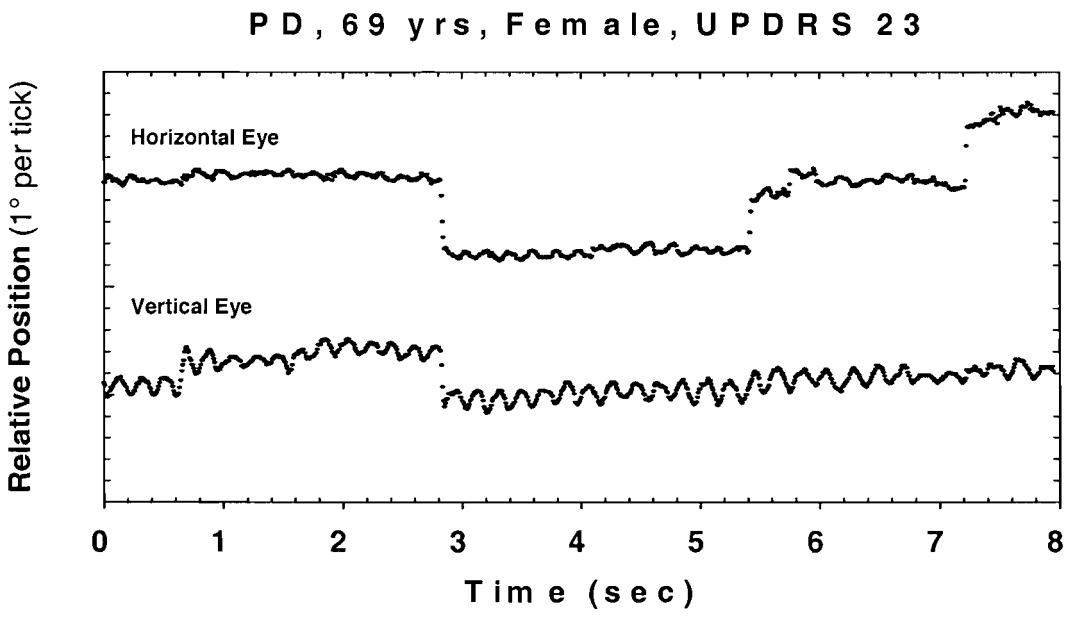
Figure 8: Sample recordings of eye positions for Control group

The following five recordings are a representative sample of those recorded from the PD group. They are showing individuals with increasing UPDRS scores and show mildly unstable fixations to more severe unstable fixations, to continual nystagmus that may or may not affect eye movements in both eyes.


PD, 63 yrs, Male, UPDRS 10
Horizontal Eye
Vertical Eye
Relative Position (1° per tick)
0
1
2
3
4
5
6
7
8
Time (sec)


PD, 74 yrs, Male, UPDRS 17
Horizontal Eye
Vertical Eye
Relative Position (1° per tick)
0
1
2
3
4
5
6
7
8
Time (sec)


PD, 62 yrs, Male, UPDRS 22
Horizontal Eye
Vertical Eye
Relative Position (1° per tick)
0
1
2
3
4
5
6
7
8
Time (sec)


PD, 69 yrs, Female, UPDRS 23
Horizontal Eye
Vertical Eye
Relative Position (1° per tick)
0
1
2
3
4
5
6
7
8
Time (sec)

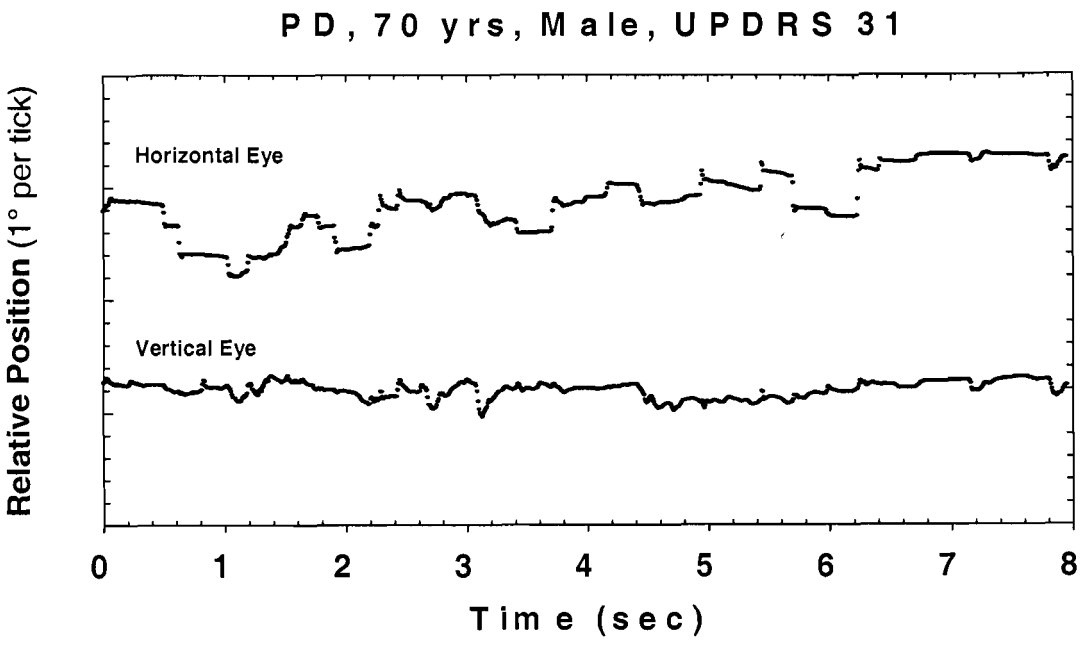


Figure 9: Sample recordings of eye positions for PD patients

Positional data was briefly analyzed to determine how useful it would be in determining instabilities of eye movements. The largest range of eye movements instructed in the fixation task was ±20°. Figure 10 shows the positional data for both the control group and the PD group. The data was predicted to be clumped around the axis at 0, ±5°, ±10°, ±15°, and ±20°. The actual positional data did not behave in this way. While there are concentrated values along the horizontal and vertical axis, there are many positional data well outside the instructed range. The figure also shows the saturation of the device. Figure 11 shows the same data restricted to those positions less than 30°.

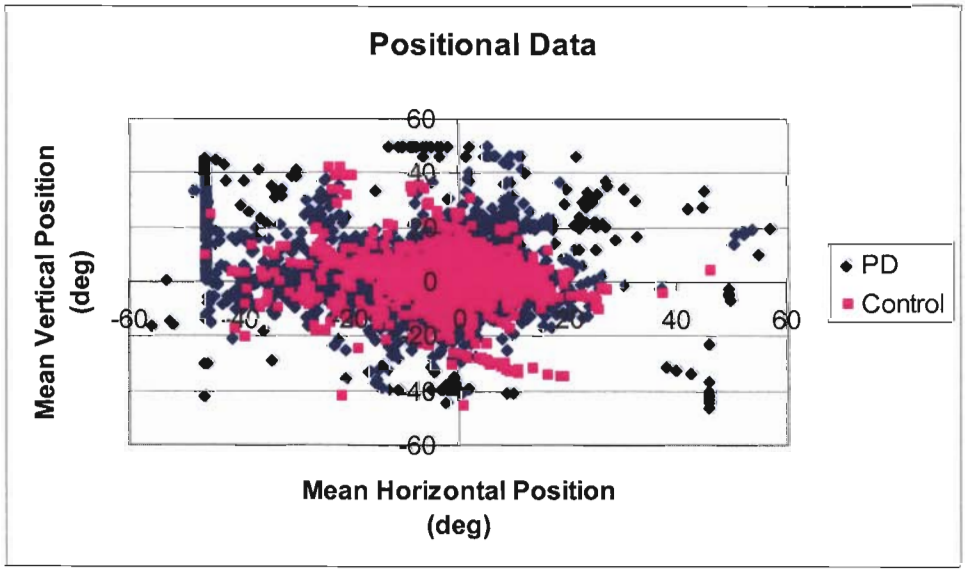


Figure 10: Positional data for control group and PD group.

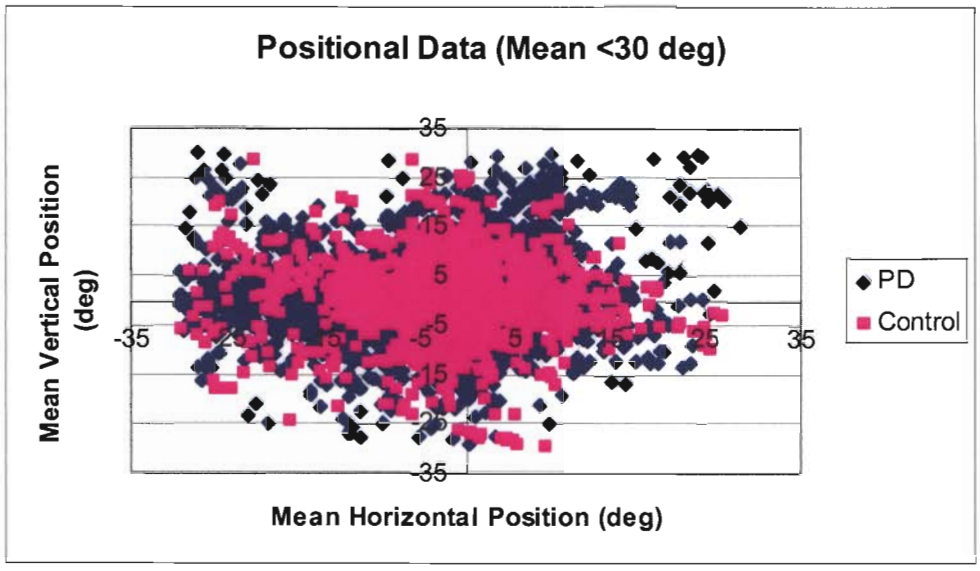


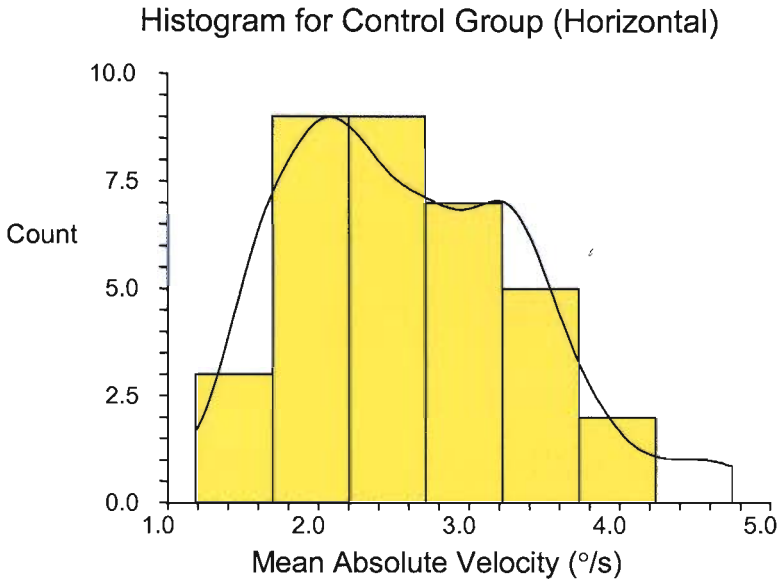
Figure 11: Positional data restricted to positions less than 30°.

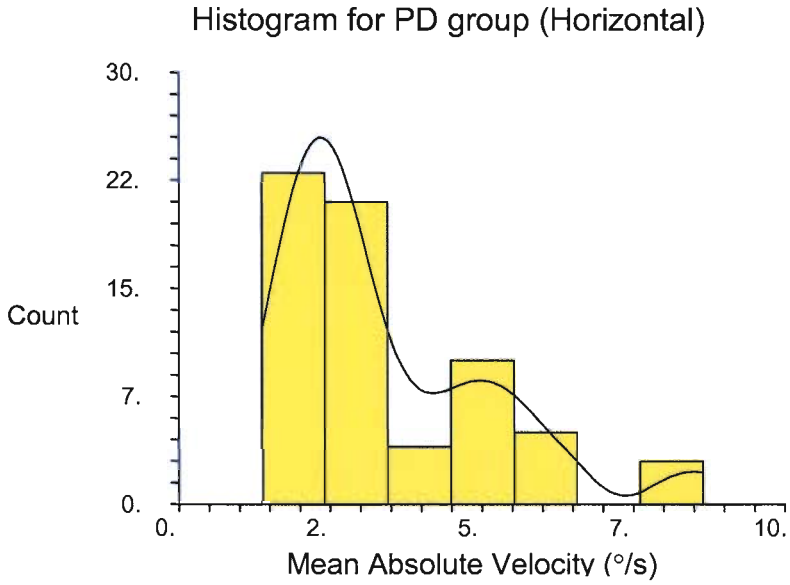
The average number of points per fixation was higher in the control group than the PD group (Table 1) in both the horizontal and vertical directions. This may support the observation that PD patients require more saccades to accomplish the same visual task. Given a time frame, if they are making more saccades to get to a target, there is less time to spend fixating on the actual target. Because the subjects are instructed verbally when to fixate on each target dot, there may be some small differences in how long they were given to fixate before the investigator called out the next target. While the average absolute velocities are higher in the vertical direction in both the CTL and PD groups, the average number of points per fixation does not vary with direction of eye movement.

	Direction	Total # of Fixations	Total # of Points	Avg # of points per fixation
CTL	Horizontal	2763	221786	80
CTL	Vertical	2841	228782	81
PD	Horizontal	7754	557759	72
PD	Vertical	7772	559786	72

Table 1: The average number or points per fixation is greater in the CTL group in both the horizontal and vertical directions.

Preliminary analysis of the PD data showed a high degree of skewness as compared to the control group (Figures 12 and 13). Because of this, parametric methods of statistical analysis could not be used to analyze the data. The data also did not meet the assumptions of non-parametric tests, so to correct for this, both the PD and control group data were normalized using a logarithmic transformation. A repeated-measures-mixed-model ANOVA test was then used to determine any significant differences between the average absolute velocity during fixations between the patient and control groups.





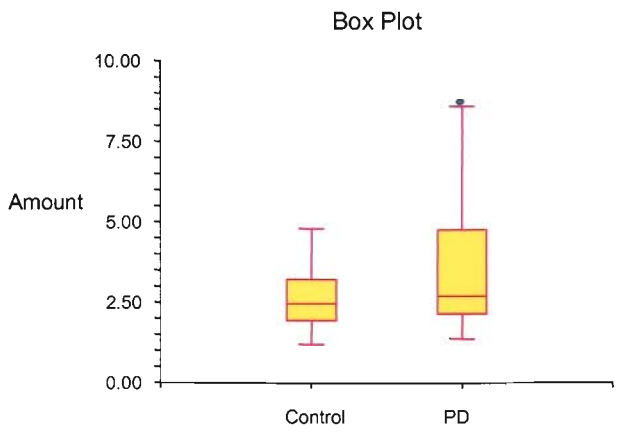
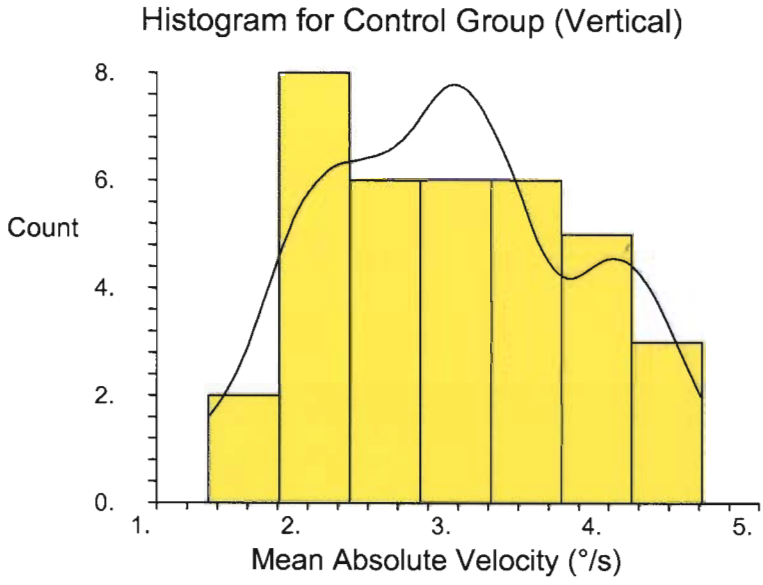
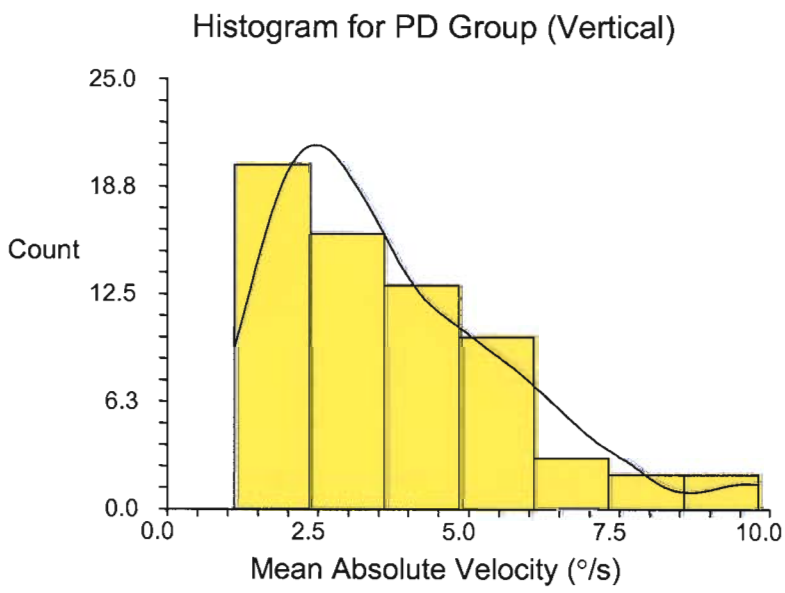


Figure 12: Distributions of Mean Absolute Velocity of eye movements in the horizontal direction during fixation for Controls and PD patients.





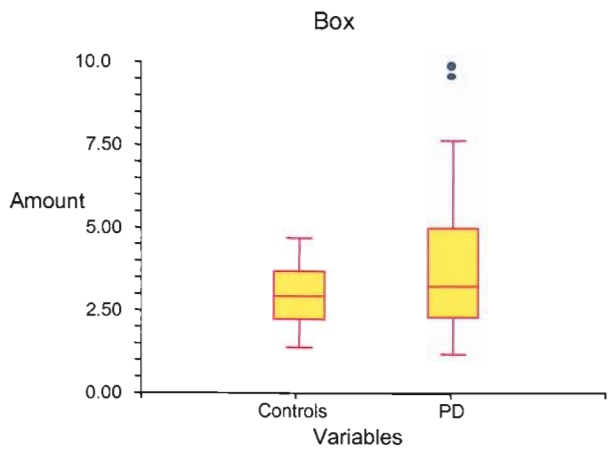


Figure 13: Distributions of Mean Absolute Velocity of eye movements in the vertical direction during fixation for Controls and PD patients.

The absolute velocities of the fixational eye movements were greater in the vertical direction in both the PD and control groups, and the standard deviations of the movements were also greater in the vertical direction in both groups (Figure 14 and Table 2). Instabilities within fixations were observed for a majority of the PD patients, while only few were seen in controls. These differences were measured using the repeated-measures-mixed-model ANOVA test. This test showed statistically significant (0.05 level) differences of the average absolute velocity of eye movement during fixations and the standard deviations between the PD patients and the controls in both the horizontal and vertical directions (Table 2).

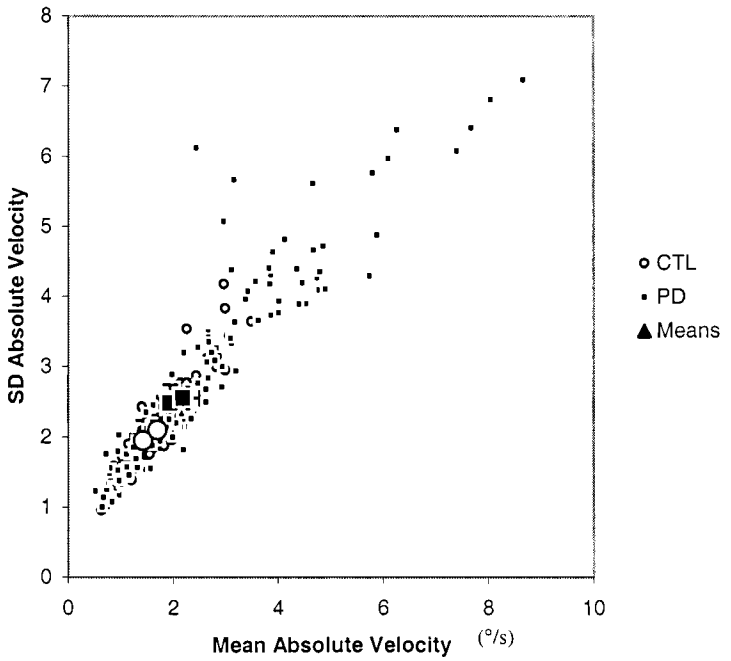


Figure 14: Scatter plot showing standard deviation of absolute velocity vs mean absolute velocity. This figure shows the overlap between CTL and PD velocities, but also shows that the PD group means are higher.

		Velocity		
Group	orientation	gMean	95% CI	
CTL	horizontal	1.425	1.186	1.712
	vertical	1.702	1.417	2.045
PD	horizontal	1.940	1.697	2.217
	vertical	2.186	1.912	2.498
		SD Velocity		
		gMean	95% CI	
CTL	horizontal	1.952	1.702	2.238
	vertical	2.099	1.831	2.406
PD	horizontal	2.485	2.249	2.745
	vertical	2.556	2.314	2.823

Table 2: The geometric means (gMean, °/s) are the result of transforming back from the logarithmic values of the absolute velocities and standard deviations during fixation used during the statistical analysis. The gMean differences between the PD and Control (CTL) groups are significant at the 95% CI.

Before recording, notes about certain characteristics were taken on the subject. Table 3 shows those patients who are DBS patients, as well as those who are not on any PD medication. Those that complained of visual problems are also listed. The average absolute velocity of eye movement was calculated for each subgroup; patients not on any PD medication, patients with DBS, and patients who complained of visual problems or problems reading. While the average velocities were higher than the PD group in all but one subgroup (visual problems-vertical), there were only two that were found to be significantly different. Patients with DBS had a average velocity significantly lower than those of the whole PD group (in the vertical direction), and patients

who complained of visual problems had a significantly higher average velocity than those of the whole PD group (in the horizontal direction).

Subject #	Notes
PD 4	without meds
PD 5	recent DBS, just adjusted
PD 7	bilateral DBS, visual problems during reading
PD 19	bilateral DBS, complaints of visual problems
PD 29	no longer reading (former attorney)
PD 36	DBS just adjusted
PD 39	problem with reading
PD 41	no meds, PD for ~1yr
PD 42	occasional bluriness
PD 44	complaints of vision problems
PD 47	no complaints of vision, but no longer reads
PD 49	difficulty reading
PD 50	difficulty with reading, bluriness
PD 51	No PD meds, hasn't started the meds yet
PD 52	no PD meds, diagnosed ~1 yr ago
PD 53	DBS patient, recorded after adjustment
PD 61	complained of visual difficulty
PD 64	no PD meds
PD 66	bilateral DBS

Table 3: Notes about some of the PD patients that were taken before recording.

Group	Orientation	gMean (°/s)	No PD meds	DBS	Visual Problems
CTL	horizontal	1.425	-	-	-
	vertical	1.702	-	-	-
PD	horizontal	1.940	2.159	1.801	2.390*
	vertical	2.186	2.043	1.787*	2.140

Table 4: Comparison of gMeans between individual groups.
*** indicates significant difference**

A linear regression model was used to determine if there was a correlation between the absolute velocity during fixation and disease severity, as measured by the UPDRS rating. The tests did not show significance in the correlation for either direction, however there was a higher degree of correlation in the horizontal direction than in the vertical (Figures 15 and 16). The critical correlation coefficient is 0.2787, $p = 0.05$ level with 48 *dof*. The regression coefficient in the horizontal direction is equal to 0.2077, and the critical correlation coefficient in the vertical direction is equal to 0.005.

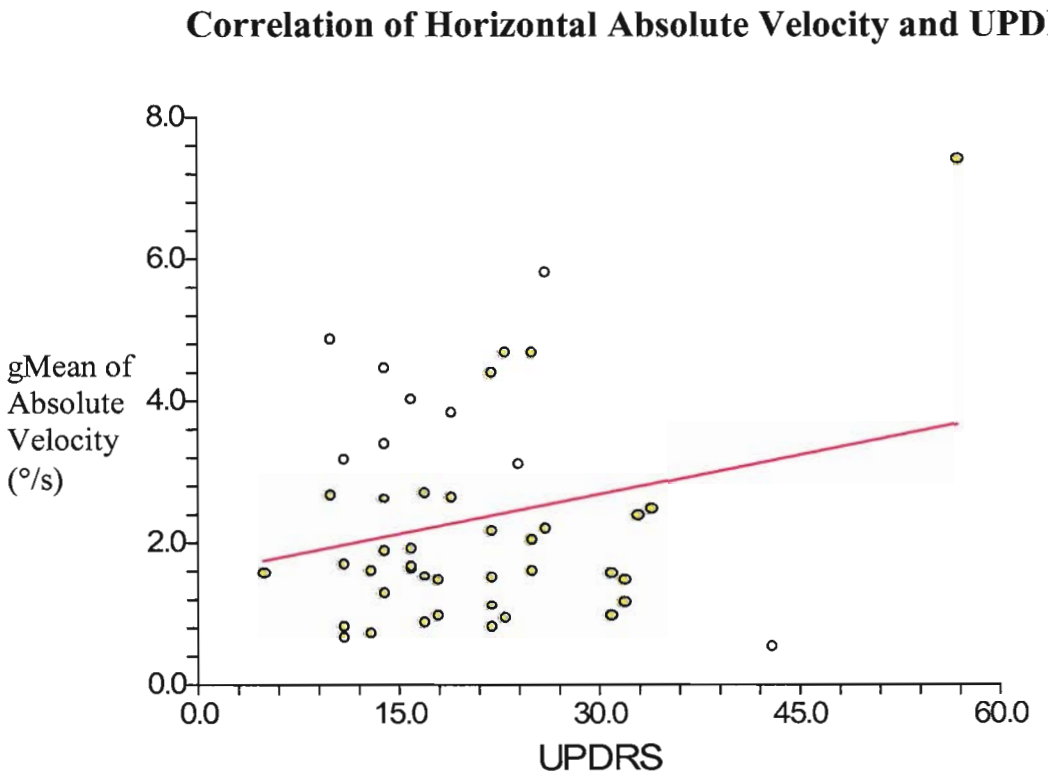


Figure 15: Correlation of Horizontal Absolute Velocity during Fixation and Clinical Measure (UPDRS).

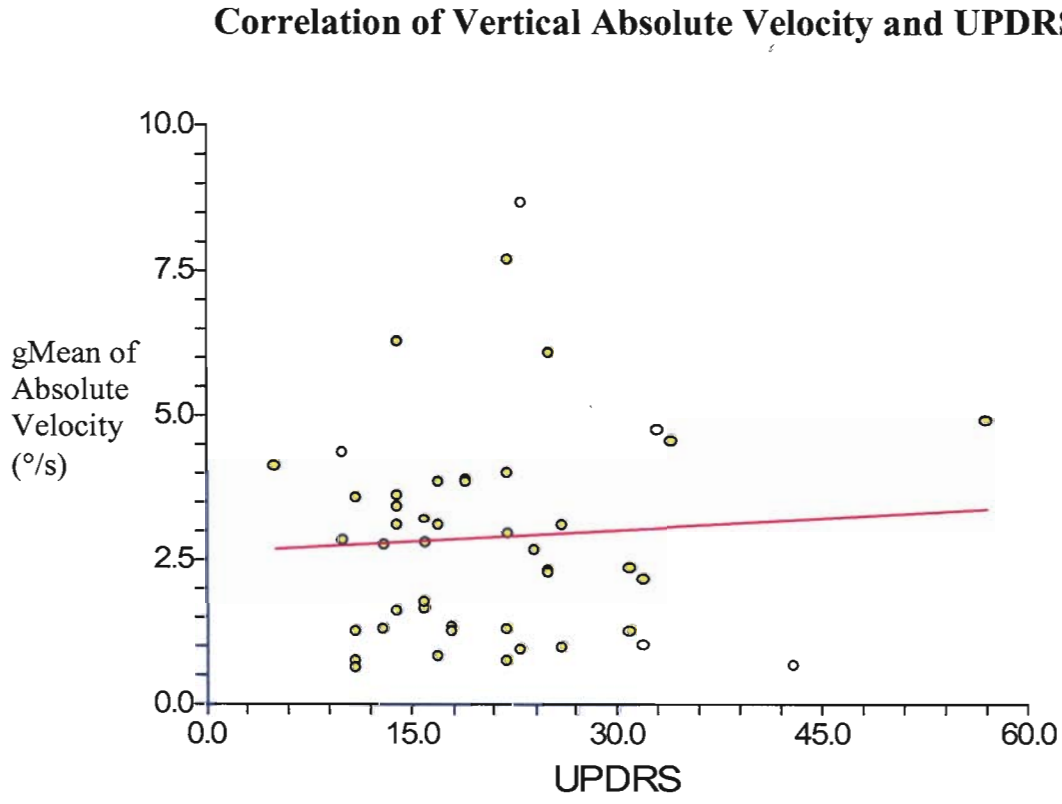


Figure 16: Correlation of Vertical Absolute Velocity during Fixation and Clinical Measure (UPDRS).

CHAPTER 4 Discussion

Parkinson's patients were found to have unstable eye movements during fixation. Because the ability to stabilize fixations is necessary in acquiring visual information, this can lead to a decrease in quality of life, as it impacts their ability to see clearly, including reading and watching television. This study supports results from other studies that there are effects on the visual system from PD.

Eye movements can be analyzed in different ways, but a popular method is using algorithms to determine where saccades, fixations, or compensatory movements are located in the data. This is not possible with the eye movement data for the PD patients. Even in the simple fixation tasks, their eye movements are very unpredictable and do not follow any set pattern. Some of the analysis becomes subjective as one tries to determine where the patient is looking and when are they fixating. While it is important to have criteria in identifying fixations, it may be more difficult in the PD data to identify fixations using only those criteria.

Initial observation of the eye movement recordings showed dramatic differences between the controls and the PD patients. The control group recordings tended to appear very stable, with "clean" lines and easily identifiable fixations. The PD data was less stable, with some data appearing difficult to identify fixations. The recordings had many small, non-rhythmic instabilities,

sometimes appearing as a very noisy signal. There were several PD recodings in which rhythmic oscillations (nystagmus) was identified. These patients tended to be further along in the progression of the disease. Other observations showed that PD patients made more fixations than the control groups to accomplish the same task, and the average length of fixations were longer in the CTL group as compared to the PD.

Methods for comparing instability in the fixational eye movements can include using eye position, velocity, and standard deviations of these. Positional data can be affected by individual differences between subjects, but the standard deviation of position can give insight into instability of the eye movements. One study showed that there was an increased standard deviation of position in patients with PD when compared to age-matched controls [34]. This supports the findings in this study that there is an increase of instability in eye movements of PD patients. Because of the limitations of positional data, velocity of the eye movements, as well as the standard deviation of the velocity, was used in this study. This allows for detection of additional movements in the eyes of PD patients that can give insight into the instabilities seen in these patients.

The distributions of the absolute velocity in both the horizontal and vertical directions were highly skewed for the PD data, but it was normal for the control group, demonstrating the irregularity of the PD data. The standard deviations of the PD data were also highly skewed. The logarithmic transformation values of the original data were used in the statistical analysis to normalize the data. The

repeated-measures-mixed-model ANOVA accounts for the repeated number of fixations within each subject. The lengths of fixation were weighted in the analysis, but when not weighted, the same trends occurred. The results of the ANOVA test showed that there were significant differences in the geometric means between the patients and controls in both the horizontal and vertical directions. The results show (Figure 12) that there is some overlap in mean values between the control group and the PD group; however the PD group means are significantly higher. These results are significant because they show that Parkinson's disease does have an effect on fixational stability.

A linear regression was performed to determine the correlation between the absolute velocity of eye movements and the clinical measure, UPDRS. A significant correlation would demonstrate the opportunity to use eye movements as an objective measure of disease progression. The correlation was not significant in either direction; however, there was a disparity between the levels of correlation between the two directions. The correlation in the horizontal direction was very close to the significant level, while in the vertical direction, the two measures were found to be independent with almost not correlation.

The reasons for this difference are unknown, but it may be affected by the limited vertical movements seen in normal older patients as well as those with Parkinson's disease. Research shows vertical eye movements become restricted with age[28], but horizontal eye movements do not. Age effects may be

affecting the correlation between the velocity of the eye movements and the UPDRS scores.

Medication may have had a large impact on the result of this study. The subjects were not required to stop their medications for this study, nor were they required to be tested during only "on" or "off" times during their medication cycle. This may affect the study in several ways. While there were significant differences between the absolute velocities of eye movements during fixation of controls and patients, more significant differences may be found if the patients were off of their medications. Medication may have also effected the correlation of the velocity to the UPDRS. The correlation of the UPDRS rating and the absolute velocity of eye movements during fixation were not found to be significant, although a relationship can be seen. An accurate assessment of this correlation would require the patients to be not only clinically evaluated, but also tested without medications. Assuming that the medications are helping the symptoms, the UPDRS ratings may be lower on the medication than without. Another way to test for this correlation would be to run the study on a large number of patients with deep brain stimulators (DBS). These patients can easily turn on and off the device and can be assessed clinically and participate in the study with the device on and off. As seen in Table 3, the mean absolute velocity of the known DBS patients was significantly lower (in the vertical direction) than the mean of the whole PD group.

This study could be improved in several ways. The sequence in which the subjects are instructed to fixate on the target dots should be standardized. This would allow for easier graphical comparisons, as well as statistical analysis of comparative positional data. The subjects, as well as controls, can be tested multiple times over time, to record their results as the disease progresses. As stated above, using DBS patients can be beneficial because eye movement data can be recorded without the influence of PD medication. Testing the DBS patients while "on" and "off" could also show what affect the DBS, and possibly medications, may have on the stability of eye movements in the patients.

Another method for improving this study would be to measure the eye movements or both eyes. Measuring the eye movements monocularly may be customary in eye movement studies due to the normal behavior of eye acting in synchronization with each other; however, because of the unusual eye movements seen in these PD patients, it may not be a valid assumption that the left eye is doing the same things as the right. This is particularly true with PD patients because PD begins unilaterally and progresses to become bilateral. It would follow that if a patient is only showing symptoms of the left side and we are measuring the right eye, that there should be no effects of PD in their eye movements. This however, is not what was seen in the results. This may strengthen the hypothesis that the instabilities in the eye movements precede outward tremor in the limbs.

Another aspect not addressed in this study is the effect of position angle on the stability of the eyes. The stability of eye movements at 0 compared to ±5°, ±10°, ±15°, ±20°, etc., was not examined in this study, but it is known that the eyes become less stable at large angles in either direction. Further research can compare the stability of the eyes at different distances in PD patients and compare that controls.

Future research can include the use of accelerometers to measure body tremor during the study so that the data can be correlated with the eye data obtained. The sub-sections of the UPDRS Motor section (III) can also be correlated to the data individually to determine if certain sub-sections are highly correlated to the fixation data. Another way to compare the data would be to include a standard questionnaire as part of the study to evaluate patient's complaints, such as problems reading, watching television, and problems with blurriness. This qualitative analysis of their complaints can be grouped and compared to their eye movement data to determine any correlation.

The future of this research lies in several areas. If these unstable eye movements preceded visual signs of tremor in other parts of the body, as seen in this study, this simple visual test can be used for early detection of Parkinson's disease. It may also be used as a more objective clinical measure of the progression of the disease. These results can also lead to further research into medications including treatment for these fixation instabilities. This can also lead to improvements in DBS technology that can allow for treatment of these visual

instabilities as well. These improvements can lead to a better quality of life for PD patients.

CHAPTER 5 Conclusions

In order to extract visual information, it is critical to have the ability to stabilize fixation and gaze. If the fixation is unstable, the images can be smeared on the retina causing a loss of acuity and contrast sensitivity. Studies are beginning to show that fixational stability is compromised in patients with Parkinson's disease. This can lower the quality of life for these patients. Further research into this area may lead to medication that can help stabilize fixation for these patients. It is first crucial to understand what affect the disease is having on the patients and the magnitude of what losing fixational stability means to them.

A large amount of information acquired is through the visual system. A deficit in this system can have profound effects on the patients' lives. Patients can lose the ability to read, drive, watch television, or even see other people clearly. Because the ability to stabilize fixation and gaze is so important in acquiring information, more research needs to be done to better understand the how Parkinson's disease affects the visual system.

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Literature Cited

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Appendices

APPENDIX A

				Avg ABSVelocity (°/s)		Std Dev.	
Subject #	Age	Sex	Location	Horizontal	Vertical	Horizontal	Vertical
CTL 1	75	F	VA	2.829	2.653	7.679	4.799
CTL 2	78	F	VA	3.053	3.081	4.581	3.787
CTL 3	65	F	ACC	2.898	4.106	3.287	5.672
CTL 4	81	F	VA	3.408	3.281	6.385	6.064
CTL 5		F	VA	1.992	2.685	2.354	3.721
CTL 6		F	ACC	4.751	1.99	11.033	17.467
CTL 7	67	F	VA	2.297	3.143	4.055	3.896
CTL 8		F	VA	2.517	2.902	3.578	2.897
CTL 9	65	F	VA	2.455	2.571	3.248	2.548
CTL 10	76	F	VA	1.912	2.819	8.991	4.948
CTL 11	75	F	VA	2.377	2.077	2.832	2.736
CTL 12	79	F	ACC	3.086	3.661	4.142	7.962
CTL 13	61	F	VA	1.750	2.702	2.403	2.816
CTL 14	77	F	VA	2.28	4.158	2.862	4.864
CTL 15	58	F	VA	1.937	2.171	2.168	3.546
CTL 16	62	F	VA	1.803	3.314	3.431	9.448
CTL 17	68	F	VA	1.187	1.977	1.973	2.408
CTL 18	75	F	VA	1.784	2.246	2.077	2.434
CTL 19	77	F	VA	3.489	3.170	7.416	8.069
CTL 20		F	VA	3.198	3.279	4.715	3.435
CTL 21	70	F	VA	3.132	2.639	4.554	3.049
CTL 22	73	F	VA	2.372	3.825	3.835	4.317
CTL 23	66	F	VA	1.703	1.906	2.652	2.573
CTL 24	75	F	ACC	2.525	3.234	3.285	3.039
CTL 25	69	F	VA	1.905	1.462	2.635	2.074
CTL 26		F	ACC	3.026	4.153	3.288	3.96
CTL 27	76	F	VA	1.621	1.833	2.501	2.551
CTL 28	66	F	ACC	2.472	2.392	4.520	3.153
CTL 29	72	F	ACC	3.348	3.982	2.959	4.063
CTL 30		F	ACC	4.218	4.596	5.711	5.444
CTL 31		M	ACC	3.756	4.624	4.659	4.579
CTL 32		M	ACC	3.637	4.102	6.192	7.586
CTL 33	70	M	ACC	2.413	2.899	2.994	4.962
CTL 34	85	M	VA	1.944	2.155	3.258	2.332
CTL 35	77	M	VA	3.261	3.470	4.240	5.985
CTL 36		M	VA	1.533	1.343	1.955	2.136

MAX 85
MIN 58
AVG 71.8

Control data divided by subject

APPENDIX B

					Avg ABSVelocity (°/s)		Std Dev.	
Subject #	Age	Sex	UPDRS	Location	Horizontal	Vertical	Horizontal	Vertical
PD 1	53	F	19	ACC	4.701	6.745	5.722	8.723
PD 2	73	F	11	ACC	4.497	4.894	9.652	9.531
PD 3	80	F	18	ACC	5.478	4.669	5.215	6.511
PD 4	59	F	57	ACC	8.545	5.415	7.730	5.477
PD 5		F	25	ACC	5.710	7.125	8.691	8.715
PD 6	70	F	8	ACC	2.544	2.885	3.166	3.232
PD 7	56	F	9	ACC	5.000	2.841	5.572	4.392
PD 8	71	F	11	VA	2.272	2.003	2.393	2.217
PD 9	73	F	26	ACC	8.663	4.026	7.572	4.848
PD 10	79	F	19	VA	4.863	4.056	7.693	9.21
PD 11	55	F	14	ACC	3.065	7.576	4.54	11.388
PD 12	68	F	14	ACC	6.042	5.754	5.776	5.355
PD 13	79	F	23	ACC	2.651	2.317	6.071	4.228
PD 14	61	F		ACC	3.761	6.680	3.600	6.488
PD 15	81	F	6	ACC	5.954	2.331	5.122	2.161
PD 16	69	F	23	ACC	6.273	9.475	6.123	9.922
PD 17		M		VA	2.047	1.514	3.334	1.487
PD 18	75	M		VA	2.077	2.232	2.723	1.856
PD 19	84	M		VA	2.118	1.622	2.830	2.840
PD 20	74	M	17	ACC	6.335	9.814	5.429	5.996
PD 21		M		VA	2.102	2.598	1.915	3.137
PD 22	78	M	33	ACC	2.866	5.819	2.912	4.801
PD 23	52	M	17	ACC	1.419	1.112	2.746	2.547
PD 24	60	M	15	ACC	4.132	2.704	4.150	1.746
PD 25		M	32	ACC	3.218	3.753		
PD 26		M		VA	2.189	3.698	3.686	4.551
PD 27	72	M		VA	2.424	1.908	2.397	2.104
PD 28	68	M	10	VA	4.837	3.878	7.474	4.237
PD 29		M		VA	1.454	2.486	2.084	2.720
PD 30	80	M	23	ACC	4.793	5.550	5.967	5.618
PD 31	81	M		VA	3.301	3.132	6.866	5.917
PD 32		M		VA	3.031	1.393	4.818	0.294
PD 33		M		VA	3.311	1.503	6.247	2.185
PD 34	79	M		VA	3.331	5.014	4.835	4.619
PD 35	81	M	25	ACC	2.460	2.792	7.577	7.16
PD 36	71	M	22	ACC	8.295	5.440	9.128	6.717
PD 37	60	M		VA	1.86	1.529	2.103	1.514
PD 38	74	M		VA	2.893	4.433	4.656	5.45

PD 39	80	M		VA	1.671	1.415	2.571	1.444
PD 40	56	M		ACC	2.693	2.463	3.139	3.983
PD 41	84	M		VA	1.888	1.794	3.912	3.11
PD 42	66	M		VA	3.048	4.513	3.595	3.725
PD 43	70	M	18	ACC	2.142	2.585	3.319	2.745
PD 44	79	M		VA	2.419	2.171	3.628	3.59
PD 45	77	M	18	VA	1.747	3.422	4.239	11.514
PD 46		M		VA	2.692	3.886	3.397	4.418
PD 47	73	M		VA	2.543	3.709	5.219	5.379
PD 48	70	M		VA	2.571	3.149	3.964	3.026
PD 49	77	M		ACC	5.526	4.569	10.148	10.974
PD 50		M		VA	1.832	2.314	1.828	2.314
PD 51	71	M		VA	2.614	3.227	2.456	2.988
PD 52	72	M	12	VA	2.875	2.749	2.922	2.214
PD 53	69	M		VA	2.136	2.216	3.892	2.465
PD 54	63	M	10	ACC	3.710	5.588	4.065	5.944
PD 55	79	M		VA	5.158	3.736	6.037	3.922
PD 56		M		VA	1.367	2.180	1.957	3.994
PD 57	62	M	22	ACC	4.405	7.337	5.492	9.03
PD 58		M		VA	2.328	2.655	2.823	3.258
PD 59	83	M	11	ACC	2.166	1.688	17.125	17.214
PD 60	80	M		VA	2.712	3.021	3.721	2.198
PD 61	83	M	24	ACC	4.816	4.041	9.502	7.029
PD 62	74	M	21	ACC	2.231	2.058	5.487	3.225
PD 63	81	M	18	VA	1.758	1.687	4.330	2.855
PD 64	56	M	11	ACC	1.709	3.247	3.171	6.168
PD 65	65	M	5	ACC	1.869	5.845	2.417	7.192
PD 66	74	M	21	ACC	2.001	5.766	1.343	5.39

MAX 84
MIN 52
AVG 71.5

PD data divided by subject

VITA

Erin Lorain Mallahan was born May 18, 1981 in Long Beach, New York, to Peter M. Mallahan and Deborah S. Mallahan. She has three siblings, Betsy, Sean, and Cailee. She graduated from Virginia Commonwealth University in May 2003 with a B.S. in Biomedical Engineering and a minor in Mathematical Sciences. She graduated from VCU in August 2005 with a M.S. in Biomedical Engineering.