Visual Functions in Parkinson's Disease

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Background: Freezing of gait (FOG) is considered to be a motor disorder symptom that affects some Parkinson Disease (PD) patients; however, it is hypothesized that sensory systems may also be involved in FOG.

Purpose: The purpose of this thesis is to measure different 2-dimensional (2-D) and 3-dimensional (3-D) clinical visual functions in FOG and non-FOG PD patients. The ability to maintain adequate alignment of the two eyes was assessed by measuring fixation disparity curve. The other objective of this thesis was to look at integrity of autonomic nervous system (ANS) and two non-motor functions mediated by the cholinergic system in FOG and non-FOG PD patients. FOG PD patients may have greater impairment of one, or more, of these functions.

Methods: The 2-D visual function measurements included high and low contrast visual acuities using Early Treatment Diabetic Retinopathy Study charts, low spatial frequency contrast sensitivity using Pelli-Robson chart, horizontal and vertical Vernier acuity using The Freiburg Visual Acuity Test. These tests were conducted under photopic, and then under mesopic conditions.

The 3-D visual function measurements included local (contour) and global (random dot) stereopsis at near. Local stereoacuity was measured using Circles and MKH-

Haase Line tests. Global stereoacuity was measured using the MKH-Haase Steps, TNO, Randot 3, and Butterfly tests. Fixation disparity curves were measured using the Saladin Near Point Card.

Constriction and dilation pupil light reflexes (PLRs) were measured by using a handheld monocular pupillometer to evaluate the integrity of ANS. The inspection time (IT) was determined by a simple length discrimination task to evaluate the integrity of the cholinergic system.

Twenty-two FOG PD patients, 25 non-FOG PD patients, and 25 aged matched healthy controls (HC) completed all of the measurements in this project.

Results: FOG group had worse 2-D visual resolution results than other two groups especially under the mesopic condition. FOG group also had worse stereopsis than the other two groups. An impairment in global stereopsis was more common than local stereopsis in both PD patient groups. The reduction in stereopsis among PD patients was not associated with the fixation disparity.

Both PD patient groups showed significant differences from healthy controls in most of PLR constriction parameters. FOG PD patients showed larger deficits than non-FOG PD patients in some of the constriction parameters. Both groups of PD patients had longer dilation latencies than healthy controls.

FOG PD patients had slower IT scores than healthy controls. IT scores for the non-FOG PD patients fell in between the FOG and HC results.

Conclusions: FOG patients have a greater impairment in both 2-D and 3-D visual functions. Whether these impairments are contributing to the FOG or just associated with FOG is uncertain. FOG patients also had larger impairments in non-dopaminergic mediated functions such as PLRs and IT, which suggests that FOG patients have greater impairment in two functions that involve cholinergic neurotransmitters.

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Dedication

A special feeling of gratitude to my loving parents Mubarak and Humidah.

To my beloved wife Sarah.

To my brothers Areif, Hisham, Hussam, and Khalid

To my sisters, Ghadah, Hind, and Asma

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Chapter 1
GENERAL INTRODUCTION

1.1 BACKGROUND

Parkinson's disease (PD) is a neurodegenerative disorder that affects the central and peripheral nervous systems and leads to disturbance of body motor functions such as bradykinesia (slow movement), muscle rigidity, resting tremor (shaking), and postural instability (Bernheimer et al., 1973).

Parkinson's disease is the second most widespread neurodegenerative disorder after Alzheimer's disease, and the most common neurodegenerative disease among older adults in developed countries. The estimated prevalence of PD in industrial countries is 0.3% and the incidence rate is about 8-18 per 100,000 person years (de Lau & Breteler, 2006). With increasing age, the prevalence increases to about 1% among those who are above 60 years old, and about 4% among those who are above 80 years old (de Rijk et al., 1995; Guttmacher et al., 2003).

Reduction of the dopamine neurotransmitter through cell death is considered as the primary cause of motor disturbances in PD patients (Scatton, et al., 1983). The majority of cell death occurs within the basal ganglia complex, specifically in the frontal part of substantia nigra (or the black substance) which is called the pars compacta (Davie, 2008; Rabey & Hefti, 1990).

Before any movement occurs, the basil ganglion complex inhibits various motor systems. Once a movement is coded, signals are sent to the basal ganglion to release inhibition (i.e. disinhibit) of the specific motor pathway. Dopamine release is one of the neurotransmitters responsible for the disinhibition. If the dopamine levels are low, such as in PD situation, then there is less disinhibition and patients will exhibit hypokinesia (i.e., slow body movement) or, akinesia (i.e., no body movement). PD is managed usually by prescribing Levodopa in order to compensate for the intrinsic reduction of dopamine. The additional dopamine may produce excessive dopamine levels, which results in hyperkinesia (i.e. increased body movement) (Obeso et al., 2008).

The basal ganglia is connected to many different parts of brain such as superior colliculus, cerebral cortex, thalamus, and the brain stem through different channels i.e. motor, oculo-motor, associative, limbic and orbitofrontal circuits. These circuits are responsible for different functions including body movement, eye movement, perception, learning, attention, emotions, behaviors, cognitive abilities…, etc. For this reason, basal ganglia are not only involved in motor function, but they are also involved in sensory and cognitive functions. In addition, dopamine is found throughout different sites of the nervous system. These two findings have led investigators to look at other sensory and cognitive functions in PD. Non-motor disorders include anxiety, depression, cognitive dysfunction, sleeping disorders, pain, olfactory disturbances, visual hallucinations and impaired visual function have been

reported in PD patients (Chaudhuri, Healy, & Schapira, 2006; Chaudhuri & Schapira, 2009; Hou & Lai, 2007; Park & Stacy, 2009; Poewe, 2008).

PD patients are also characterized by non-motor symptoms and signs that are probably not solely due to a reduction in dopamine. These deficits are believed to be due to primarily the cholinergic system dysfunctions. Different cholinergic system dysfunctions in PD patients have been reported. Within the autonomic nervous system, these include cardiovascular functions, sexual and urinary problems, gastrointestinal problems, respiratory difficulties and thermoregulation problems. In the visual system, the pupil light reflex (PLR) is mediated by the autonomic nervous system. Different parameters of pupil light reflex are affected in PD patients (Chaudhuri et al., 2006; Chaudhuri & Schapira, 2009; Micieli, Tosi, Marcheselli, & Cavallini, 2003).

Deficits in the cortical cholinergic systems are also linked to learning and executive function. Calabresi, et al (2006) hypothesize that some of the cognitive deficits in PD patients are due to a combination of dopamine and acetylcholine depletion because an increase in dopamine is not sufficient to affect certain cognitive performance and acetylcholinesterase inhibitors are useful in the treatment of dementia associated with PD. They further hypothesized that at the cellular level, dopamine and acetylcholine interact to produce the synaptic changes associated with learning and memory (Calabresi et al., 2006). This interaction is altered in PD and so these patients

experience problems with working memory and learning tasks. Given these findings, it is not surprising that different sensory and cognitive functions are impaired along with motor functions in PD (Obeso, et al., 2008), despite James Parkinson's statement in his opening chapter that "the senses and intellect being uninjured " in his detailed description of the disease bearing his name (Parkinson, 2014).

Postural instability is one of the motor disturbances associated with PD disease. Two features of postural instability are falls and freezing of gait (FOG). Freezing of gait is defined as discontinuous or interrupted episodes, which lasts for few seconds, of inability to produce or maintain a forward movement or to make a turn (Gordin, Kaakkola, & Teräväinen, 2003). The underlying pathophysiological mechanisms for falls and FOG are not completely understood, but these mechanisms may be linked. First, these two symptoms are more common in the advance stages. Second, freezing of gait often leads to falls. Third, both of these two problems often have poor responses to dopaminergic treatment (Bloem et al., 2004; N. Giladi, Hausdorff, & Balash, 2013; Giladi et al., 1992; Nutt et al., 2011).

Although FOG is considered classically as motor dysfunction in PD patients, it is now hypothesized that impairment of different non-motor systems may contribute to FOG (Giladi et al., 2007). Balance is a function that depends on intact processes from the visual, vestibular and somatosensory systems and from the motor outputs of muscles. The sensory and motor systems are integrated through different pathways in the brain

and work together to produce normal response of posture and locomotion (Gordin et al., 2003). Deficits in the sensory portion of balance may contribute to FOG. Almeida and Lebold (2010) hypothesized that the visual perception of the surrounding space is impaired in FOG patients more than non-FOG patients and that might contribute to their freezing symptoms. FOG patients have more visuospatial judgement and motion perception errors compared to non-freezers and normal individuals. The visuospatial deficits were correlated with their walking performances (Almeida & Lebold, 2010). FOG patients underestimated the actual distances to a target during both static and dynamic conditions more than non-freezers patients and normal individuals (Martens, Ellard, & Almeida, 2014). They also have more difficulty in moving through a narrow doorway compared with non-FOG ones (Silveira et al., 2015). This latter finding is consistent with their underestimation of distances. That is, objects appear closer to them compared to non-FOG. Nevertheless, removing visual cues will increase the number of FOG occurrences. The number of FOG occurrences/episodes increase when patients were asked to walk toward a door in a dark room compared to a well-lit room where they have full vision of their bodies and door. This finding suggests other sensory inputs involved in movement are impaired, there is problem with integration of the balance systems or both problems occur. The association of FOG with various visuospatial deficits and the non-responsiveness of FOG to dopamine also suggest that the FOG could be a result of an acetylcholine deficit/imbalance.

Impaired function of higher cortical centres is believed to be responsible for the visuospatial problems associated with FOG. The question we are addressing is whether basic clinical visual functions are affected differently in FOG patients. A number of basic visual problems have been reported in PD, but the studies did not separate the PD patients into freezers and non-freezers. Before reviewing these functions, however, I will review the pathophysiological changes in the visual system associated with PD.

1.2 RETINA IN PARKINSON'S DISEASE

Dopaminergic neurons are located in different layers of the retina with an A18 subtype of amacrine cells of the inner plexiform layer being one of the more studied cells. The highest concentration is located in the perifoveal area of the primate retina (Archibald et al., 2009; Bodis-Wollner, 2013; Frederick et al., 1982; Nguyen-Legros, et al., 1993; Nowacka, et al., 2015). The inputs to these dopaminergic amacrine cells in the retina are not clearly defined, but A18 amacrine cells receive their input mainly from rod bipolar and, to lesser extent cone bipolar cells. The output of the amacrine cells is primarily to the retinal ganglion cells (Archibald, et al., 2009). Autopsy studies on PD patients showed severe loss in concentration of dopaminergic neurons in the perifoveal area of the retina (Tsironi, et al., 2012).

In general, dopaminergic neurons are involved in mediating the visual signals from cone and rod bipolar pathways to ganglion cells (Djamgoz & Wagner, 1992; Mangel & Dowling, 1985; Mangel & Dowling, 1987; Witkovsky, 2004). In many species, stimulating the retina with increasing light results in an increase of dopamine released especially from the amacrine cells (Da Prada, 1977; Godley, Flaherty, & Wurtman, 1985; Iuvone et al., 1978; Kramer, 1971; Lamb & Pugh, 2004). The current theory is that dopamine plays a role in controlling the size of ganglion cell receptive fields (center-surround mechanism). An increase in dopamine reduces the size of the receptive field and may increase the strength of the antagonistic surround (Wink & Harris, 2000a). In contrast, a reduction in dopamine increases the size of the receptive field centre and reduces the strength of the antagonistic surround. The larger receptive field combined with the weaker surround would reduce the resolving power of the visual system (Bodis-Wollner, 2013; Brandies & Yehuda, 2008).

Systemic injection of the protoxin MPTP (1-methyl, 4-phenyl, 1-2-5-6 tetrahydropyridine) into primates destroys dopaminergic neurons. The effects of the protoxin MPTP on the retina were to reduce the amplitude and increase the latency of both pattern evoked electroretinogram (PERG) and pattern visual evoked potential (PVEP) signals. Both of these functions improved temporarily after administering levodopa (Ghilardi et al., 1988). The PERG studies indicate that the dopamine deficit was affecting the function of the inner retinal layers. Injection of neurotoxin 6-hydroxydopamine into the retina produced similar results. Both the amplitude and

phase of pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP) were abnormal especially for the higher spatial frequency stimuli (Ghilardi, et al., 1989).

Electroretinogram (ERG) studies in PD patients have reported that PERG amplitudes were reduced, which is consistent with the animal models. The flash ERG was also affected. The ERG b-wave amplitude was reduced in PD patients, which suggests that the dopamine deficit primarily affects the inner retinal layers. Visual evoked potential (VEP) results in PD were also consistent with the animal models. The VEP amplitudes were lower and the latencies of P100 and N15 signals where longer in PD patients. Moreover, there was an inverse correlation between the latency of P100 waves of VEP and the amplitude of PERG which suggests that the abnormalities of VEP signals in PD patients was mainly retinal in origin (Gottlob, et al., 1987; Nightingale, Mitchell, & Howe, 1986). Dopaminergic treatment can reduce the latencies of both the ERGs and VEPs (Bodis-Wollner, 2013; Bodis-Wollner et al., 1987; Bodis-Wollner et al., 1982; Ellis et al., 1987; Nowacka et al., 2015; Popova, 2014).

Optical coherence tomography (OCT) is a retinal imaging technique that can examine different retinal nerve fiber layers. OCT studies showed that the macular region is thinner in PD patients relative to healthy control subjects (Simao, 2013). More specifically, the inner nuclear, inner plexiform, and outer nuclear layers are all thinner in PD patients compared to healthy subjects. This thinning in the more proximal

layers of the retina is consistent with loss of dopaminergic amacrine cells in retina (Chorostecki et al., 2015). The anatomical and electrophysiological studies of primates and individuals with PD patients support the concept that some central visual functions, as previously reported, deterioration may due to dopaminergic deficiency in the retina.

1.3 HIGHER VISUAL AREAS IN PARKINSON'S DISEASE

Dopaminergic neurons were found in lateral geniculate nucleus (LGN) and occipital cortex in rats (Herrera, Machado, & Cano, 1993), in the occipital, parietal, frontal cortex in nonhuman primates (Berger, Gaspar, & Verney, 1991; Scatton et al., 1983), and in visual cortex of cats and humans (Parkinson, 1989; Phillipson, Kilpatrick, & Jones, 1987). There are two main dopaminergic pathways in the midbrain that may also influence visual processing. The first one originates in the substantia nigra and projects into the visual cortex. The second one starts from the tegmentum and projects into the frontal cortex (Nguyen-Legros et al., 1993).

Visual processing begins at the retina and these signals are transmitted to the LGN by the optic nerve. The majority of fibers from the LGN project to the primary visual cortex, or "V1 area" in the occipital lobe. A smaller number of fibers project to the superior colliculus. From V1 area, the visual signal projects to the secondary visual cortex, or (V2) area. Two major pathways carry information from V2 to higher centers. The first pathway is called the ventral, or "What" visual pathway. This

pathway is also referred to as the parvo system because its inputs start from the parvo cells at retina and LGN. From V1 and V2, the ventral pathway projects to V4 area, lateral occipital cortex, and inferior temporal cortex (IT) areas. The input to the ventral pathway is mainly from the fovea and it is concerned with analysing central vision properties like fine details, contrast and colours under daylight conditions (photopic vision). The second pathway is called the dorsal, or "Where" visual pathway. This pathway is also referred to as the magno pathway because the ganglion cells feed into the magno cell layers at the LGN which then project to the visual cortex. The projections from V1 and V2 go to areas V3A, middle temporal cortex (MT/V5), middle superior temporal cortex (MST) and posterior parietal cortex. Input to the magno system is mainly from the perifoveal area and peripheral retina. The dorsal system involved primarily in analysing peripheral vision properties like perception under dim light conditions (mesopic and scotopic vision), localization of target, movement of objects, and depth perception (Daw, 2011).

1.4 VISUAL FUNCTIONS IN PARKINSON'S DISEASE

There have been many reports of visual deficits in moderate to severe PD patients. Harris (1998) and Armstrong (2011) have reviewed visual functions in PD patients. The list of deficits includes decreased high and low contrast visual acuity, reduced spatial and temporal contrast sensitivity, abnormal colour vision, peripheral visual field constrictions, abnormal ocular alignment, abnormal saccadic and smooth pursuit

eye movements, dry eye, reduced blink rate, abnormal pupil light reaction, visual hallucinations, abnormal dark adaptation, abnormal depth perception (Armstrong, 2011; J. Harris, 1998).

In the next sections focus on the deterioration of several visual functions in PD patients in order to determine whether one of the main visual pathways (parvo or magno) is preferentially affected in the disease. I will also focus on other ocular functions that are controlled by prefrontal cortex pathway and the cholinergic system pathway as well.

1.4.1 Visual Functions Mediated by Ventral Pathway in Parkinson's disease

Spatial vision is defined as the ability of our visual system to detect or resolve spatially defined detail. The two common clinical spatial vision measurements are visual acuity and contrast sensitivity. Visual acuity is measured by varying the size of objects with a fixed contrast to determine the smallest detail that can be resolved. Contrast sensitivity is measured by maintaining the object at a fixed size but varying the contrast until the object can just be resolved (Schwartz & Meese, 2010).

1.4.1.1 Visual Acuity

Several studies have shown a reduction in visual acuity in PD patients. Nowacka et al. (2014) showed that visual acuity at distance using ETDRS log MAR charts was reduced by 0.08 log units in PD patients (VA = 0.15 ±0.23) relative to control subjects. This reduction is approximately equivalent to a reduction in acuity of one

line. Repka et al. (1996) showed that the mean visual acuity using Snellen acuity chart was poorer in the Parkinson's patients (20/39) compared with controls (20/28). This reduction was larger than reported by Nowacka, et al by 0.06 log units (15%). A reduction in high contrast acuity in PD does not always occur. Two studies reported that visual acuity for high contrast letters was unaffected by PD (Regan & Neima, 1984; Tzoukeva, et al. 2008). However, both studies reported that the PD patients' low contrast acuities were significantly reduced. The reduction tended to be larger in more severe cases (Tzoukeva, et al. 2008). Treatment of PD may only produce a marginal, if any, improvement in visual acuity. Jones et al (1992) reported that the PD patient tended to have an improvement in acuity with treatment, although the improvement was not statistically significant, and Tzoukeva et al (2008) reported no improvement in acuity with treatment.

The reduction in visual acuity is consistent with the hypothesis that the receptive fields of the ganglion cells are larger in PD. Nevertheless, it is still possible that the decrease in visual acuity is due to cortical dopaminergic reduction. The association of visual acuity reduction with the severity of the disease suggests that there could be both retinal and cortical involvement and it is impossible to distinguish between them from measuring visual acuity alone (Jones et al., 1992; Repka, et al., 1996). Other confounding factors could be responsible for any reduction in acuity.

These factors include dry eye, poor blinking or abnormal fixational eye movements (Armstrong, 2011). Another confounding factor is that the prevalence of ocular diseases is higher in PD patients. Nowacka, et al. (2014) found that nuclear and posterior subscapular cataract, age-related macular degeneration (ARMD), blepharitis and glaucoma rates were higher in PD patients compared with age-matched healthy control subjects.

Visuospatial perception is affected in patients with PD, particularly in PD with FOG (Johnson, et al., 2004a; Lord, et al., 2012; Martens et al., 2014; Silveira et al., 2015). It is possible that these visuospatial problems include a reduction in visual acuity, which suggests that FOG patients would have a larger reduction in visual acuity compared with non-FOG patients.

1.4.1.2 Spatial and Temporal Contrast Sensitivity:

Spatial contrast sensitivity is usually measured by varying the contrast of sinusoidal grating until the grating pattern is just visible. This is repeated for a wide range of spatial frequencies (i.e. different widths of the grating bars). The majority of these studies on PD patients agree that there is loss in contrast sensitivity at medium and high spatial frequencies (the narrower grating bars), especially for the cases with more advanced PD (Hutton et al., 1991). The loss in contrast sensitivity was marked mostly at 4.8 cycles per degree (cpd), which was the peak region of the contrast sensitivity function in controls.

The losses in contrast sensitivity of medium and high spatial frequencies were consistent with losses reported in the visual evoked potential (VEP) studies (Bodis-Wollner et al., 1987; Harris, Calvert, & Phillipson, 1992).

The loss of contrast sensitivity in PD is consistent with a decrease in retinal dopamine and corresponding increase in receptive field size. However, the loss in contrast sensitivity in some PD patients appears to be greater for horizontally oriented stimuli than vertically oriented stimuli. This finding suggests the cortical origin of contrast sensitivity loss rather than retinal origin (Bulens et al., 1986; Bulens, Meerwaldt, & Van der Wildt, 1988; Regan & Maxner, 1987). Interestingly, contrast sensitivity improves in PD patients after administrating L-DOPA (Bulens et al., 1986; Hutton, Morris, & Elias, 1993).

Bulens and his coauthors described 'notch losses' in the contrast sensitivity function of PD patients. These losses occur only in the medium spatial and not anywhere else in the spatial frequency domain (Bulens et al., 1986; Bulens et al., 1988). Their interpretation is that this deficit represents selective loss visual neurons tuned to this range of frequencies. However, one should interpret their results with caution because uncorrected astigmatic refractive errors can create notch defects and differences in contrast sensitivity at different orientations (Apkarian et al., 1987; Regan & Maxner, 1987).

The severity of FOG correlated with losses of contrast sensitivity especially at lower spatial frequencies. Losses in low frequency contrast sensitivity was considered to be a stronger predictor for the freezing of gait severity more than motor impairments

(Davidsdottir et al., 2005; Lord et al., 2012). The loss of sensitivity at the lower spatial frequency is suggestive, but not definitive, of magno pathway loss rather than a parvo pathway loss. It is possible that freezer patients would have greater losses in magno pathway.

Temporal contrast sensitivity measured using a 4 degree circle with range of flickering rates (1, 2, 4, 6, 8, and 16 Hz.) showed that PD patients had lower temporal contrast sensitivity especially at the higher flicker rates (8, and 16 Hz). These results suggest that there could be either a deficit in the magno pathway or a general reduction in the retinal gain such that the dopamine deficiency was equivalent to lowering the retinal illuminance (Bodis-Wollner et al., 1987).

There is an interaction between the spatial and temporal contrast sensitivity functions in normals. If the flicker rate of the grating pattern increases from 1 Hz to 10Hz in normals, sensitivity at low spatial frequencies increases and sensitivity at the medium and high spatial frequencies decreases. The changes in sensitivities are thought to be due to a decrease in the strength of antagonistic surround of the receptive fields. In some PD subjects, increasing the flicker rate to 8 Hz decreased their sensitivity at all spatial frequencies without any sensitivity enhancement at the low spatial frequencies. This suggests that dopamine is involved in controlling the ganglion cell receptive field and if it is absent or in a low concentration, the receptive field surround is not very strong for the 1 Hz stimulus so that increasing the flicker rate decreases the contrast sensitivity at all spatial frequencies (Bodis-Wollner et al., 1987).

1.4.2 Visual Functions Mediated by Dorsal Pathway in Parkinson's disease

1.4.2.1 Perception under Dim Light Condition (after Dark Adaptation):

The human visual system is capable of operating under a wide range of lighting conditions. The two general processes involved in this large operating range are light and dark adaptation. Light adaptation is the ability of our visual system to adjust to increasing levels of light and maintain a high relative sensitivity to changes in the stimuli relative to the background. The initial phase of light adaptation occurs within a few seconds. On the other hand, dark adaptation occurs when we go from a bright environment to a dark environment. In this situation, the visual system is optimized for detecting a small amount of light on the absolute scale. As with light adaptation, the time course depends on the change in magnitude that occurs in the background environment. If the change in the background is about a factor of 100, then dark adaptation takes only a few seconds (Howard, Tregear, & Werner, 2000). However, if the change in light levels goes from operating based on cone input to operating based on the more sensitive rods, then the time course is 10 to 20 min. (Lamb & Pugh, 2004).

The light levels in an urban environment at night fall within the s mesopic range where both rods and cones are providing input. Since PD is characterised by a dopaminergic level reduction, it possible that their mesopic vision is compromised, particularly their spatial resolution in dim lighting (Beaumont et al. 1987). Two studies found that there were similarities in peripherally viewing contrast sensitivity functions between dark-adapted normal individuals (by wearing neutral density

filters) and light-adapted PD patients. This finding supports the view that dopaminergic neurons are involved in the light-dark adaptation processes and a decrease of dopamine release in the dark adapted retina weakens the strength of the antagonistic surround of the receptive fields (Harris et al., 1992; Wink & Harris, 2000b). This would suggest that visual resolution of PD patients might decrease more as background light levels decreased. Whether dopamine depletion will affect the visual resolution of a totally dark adapted eye is uncertain. The possible role of visual impairment on the freezing of gait disorders in PD patients was discussed earlier in this literature review. If it is true that FOG is associated with visual dysfunction, then it is possible that freezers will suffer more than non-freezers at low light level vision such as walking or driving a car during night. A questionnaire study showed that PD patients had difficulties with driving cars especially during night. Half of PD patients of that study were freezers but the study did not compare between freezers and non-freezers patients (Davidsdottir et al., 2005) How visual function at low light levels is affected by PD has not been fully described.

1.4.2.2 Vernier Acuity:

Another type of visual assessment is measuring the ability of subjects to tell when two targets are misaligned. This kind of acuity measurement is called hyperacuity. Traditional visual acuity is limited by the cone spacing in the fovea and the optical quality of the eye. The average spacing between the cones in the fovea is 0.6 minutes of arc (approximately 40 seconds of arc) and so this would be the minimum separation between two points or lines that could be resolved if the optics of the eye

were perfect. The term hyperacuity arises from the fact that one's ability to judge whether two objects are in alignment l ranges from between 3 to 8 second of arc. These values are about 10 times better than the resolution threshold of human eyes; hence the term hyperacuity. In addition, optical image degradation has only a small or little effect on hyperacuity. This suggests that the hyperacuity task depends more on neural processing in higher visual centers beyond the retinal level to detect the small differences in the spatial locations of the two lines (Elliott, Whitaker, & Thompson, 1989; Westheimer, 1979).

Vernier acuity is a form of hyperacuity. It is the ability to detect the slight horizontal misalignment of two vertical lines (or bars). Vernier acuity can be as low as 3 second of arc (arc sec) in individuals who have had extensive practice and approximately 20 arc sec for naïve subjects (Fahle & Edelman, 1993; Levi, Klein, & Aitsebaomo, 1985; Schwartz & Meese, 2010; Westheimer, 1979).

Previous studies on the effect of age on Vernier acuity are mixed. Some showed there are no significant differences between age groups. Others showed there are no changes in Vernier acuity threshold until age of 60 years or above. However, these studies agree that Vernier acuity is minimally affected by the optical degradation due to normal aging changes. The studies that showed a decrease in in Vernier acuity in older people, assumed that the decrements were due to aging neural processes (Elliott et al., 1989; Enoch et al. 1999; Li, Edwards, & Brown, 2000; Odom et al., 1989).

Measuring Vernier acuity may be useful for evaluating the magno pathway neural functions of the PD visual system. The task has the advantage that optical problems such as mild cataracts have minimal affect. Vernier acuity as a function of light level may also allow one to tease out dopamine deficiencies at the higher centers versus at the retinal level. If the Vernier acuity decreases at a greater rate at lower luminance in PD subjects relative to normals, then the larger decrement increase could be due to less precise positional information leaving the retina because the ganglion cell receptive fields are larger.

To my knowledge, Vernier acuity has not been investigated in patients with PD. One study that could be misinterpreted as a hyperacuity task was by Jones, et al (1992). They actually measured visual resolution in PD patients by asking subjects to discriminate when a circle was separated from the reference line. A Vernier task would be to ask when the line no longer bisected the circle. A task that could be related to Vernier acuity is orientation discrimination. Orientation discrimination could be a type of hyperacuity because one is measuring the relative angular position. Trick, et al. (1994) reported that PD patients had a loss in orientation discrimination for horizontal bars, but normal orientation discrimination for vertical bars in PD patients compared with healthy controls. This result suggests that vertical Vernier acuity should be worse (bars are horizontal) (Trick, et al., 1994).

It may be important to look at the Vernier acuity in PD patients for both horizontal oriented lines (i.e. detect a misalignment in the vertical direction) and vertical oriented lines (i.e. detect a misalignment in the horizontal direction). PD patients have difficulties with judgments of horizontal orientations relative to vertical judgments (Danta & Hilton, 1975; Fahle & Harris, 1998; Trick et al., 1994).

1.4.2.3 Motion Perception:

Flicker and temporal spatial contrast sensitivity are impaired for some PD patients; therefore, motion perception may also be affected since it involves processing changes in position over time. However, it is also possible that contrast sensitivity could be normal and motion perception could be impaired because of deficiencies in the higher motion processing centers of the magno pathway.

Different studies showed motion detection deficits at high level among PD patients comparing to age-matched controls. One of the studies measured the motion perception by using the Useful Field of View test. This study showed that PD patients had more motion perception errors comparing to healthy controls; however, this study could not discriminate whether the motion detection deficit was originally retinal or cortical in PD patients (Uc et al., 2005).

Coherent motion thresholds were measured for cognitively intact PD patients and for age-matched controls. This paradigm starts with over a hundred dots moving in random directions. The percentage of dots that are moving in the same direction increase until the subject can identify the direction of nonrandom motion. This is

considered a global motion task since the subject must integrate the information of a relatively large area of their visual field. PD patients required a significant higher percentage of dots moving in the same direction relative to age-matched controls (Trick et al., 1994).

Castelo-Branco and his coworkers used a hierarchical approach to study temporal and motion perception in PD subjects (Castelo-Branco et al., 2009). They categorized the visual stimuli based on where in the visual system the processing likely occurred. Contrast sensitivity to a high temporal frequency target was their low level stimulus. Detection of this stimulus is believed to be mediated by the magno pathway. The intermediate-to- high level stimulus was global motion integration stimuli using random dot kinetogram (RDKs). This type of motion integration is believed to be mediated by the cortical dorsal pathway. They also looked at the relationship between the two stimuli. For all levels of stimuli, PD patients showed more deficits than healthy controls. However, the temporal contrast sensitivity impairment from the retinal level could not explain the motion integration deficits at the cortical level in PD patients, as there was no relationship between the two motion perception tests. From this study, it appears that motion perception in PD patients due to impairment in the cortical areas and not necessarily due to dopaminergic reduction in the retinal level.

Lee and Harris (1999) used a questionnaire to assess motion and space perception in everyday life of PD patients. The patients reported that they had difficulties when they tried to move through narrow spaces at their home, and they had difficulties determining the movement of pedestrians and vehicles in the street. They also reported difficulties in judging distances in space (i.e. distances between objects, or when they try to reach an object).

1.4.2.4 Stereopsis (Depth Perception):

The reports of difficulties in judging distances could result from an impairment in stereopsis (Lee & Harris, 1999). Stereopsis is a relative depth perception that arises from the integration of slightly different information from each eye in the visual cortex (I. P. Howard, 1995). Stereopsis is the highest level of binocular vision function possible to assess in the clinic (Rowe, 2012; Rutstein & Daum, 1998; Steinman & Steinman, 2000). Stereopsis is assessed with either simple shapes, such as circles (i.e. contour stereopsis), or random dot patterns (i.e. global stereopsis). The contour stereopsis perception arises from the integration of nearly identical images viewed by each eye. On the other hand, global stereopsis is the perception of form in depth that arises when viewing random pattern stereograms. That is, the form is perceived only when seen in depth.

One of the main differences between the two types of stereopsis is integration of the information from each eye into a single percept. In contour stereopsis, the nearly identical contour information present in the images from each eye. Global stereopsis,

however, requires complex algorithms to extract the depth and form information. As a result, individuals often have more difficulty in perceiving depth information present in random pattern stereograms.

Flowers & Robertson (1995) showed that global stereopsis for suprathreshold complex patterns in depth was impaired in the advanced stages of PD, but perception of simple global stereopsis suprathreshold patterns in depth was not impaired in mild and moderate PD subjects. Because interpretation of complex 2-D images was also impaired in the advanced stages, they believed that the inability to interpret complex 3-D images reflected a general visual-spatial processing deficit in higher visual and cortical levels rather than a deficit just in depth perception. Thus, their results support the hypothesis that visual deficits in PD patients could either be of retinal origin or result from deficits in the higher visual centers. Kim et al (2011) reported that contour stereopsis was impaired in PD patients. This study also found that the contour stereopsis dysfunction was associated with other visual cognitive dysfunctions (e.g. visual memory and visual perception constructive function) which suggest that the deficit in contour stereopsis is associated with dopaminergic depletion in the cortical level. However, they did not investigate the possible role of retinal dopaminergic depletion as a potential factor of depth perception deficit. Sun et al (2004) found the number of individuals who had abnormal contour stereopsis was higher in PD patients than healthy controls and there was no improvement on stereopsis after taking medications for PD group. The impairment of stereopsis correlated with the

motor dysfunction, which suggests that the stereopsis deficits may be related to the severity of the disease. The interesting finding in this study is that they performed color perception tests and they found patients had more error scores than the controls. PD patients who had abnormal stereopsis had significantly worse color perception scores than PD patients with normal stereopsis. The latter finding suggests that the retinal dysfunctions in PD patients may contribute to higher visual deficits in PD patients such as contour stereopsis (Sun et al., 2014).

Imaging studies of the human brain have shown activity related to binocular disparities or stereopsis in the occipital cortex, parietal cortex (V3A in particular), frontal cortex and cerebellum. Data from nonhuman primates' cellular recording has identified cells that are stimulated by contour and random dot stereo stimuli in visual areas V1 and V2 and throughout the parietal lobe visual areas. Based on these and similar findings, stereopsis was thought to be mediated by the dorsal visual pathways (i.e., the "where visual system"). Supporting this hypothesis was the report that extensive lesions in the parietal lobe resulted in partially loss of any depth perception. Nevertheless, cells in the ventral visual areas (i.e. the "what visual system") have also been to shown to respond to both contour and random dot stereo patterns in more recent experiments. Some of these cells in the inferotemporal cortex respond best to certain shapes whether the shape is formed by contours or seen in depth within a random dot pattern. These cells tend to be located in the posterior inferotemporal cortex (Daw, 2011).

Cowey & Porter (1979), have shown that lesions in a monkey's inferotemporal cortical area will impair detection of forms in depth generated by random dot stereo patterns, whereas lesions earlier in cortical visual centers do not impair global stereopsis. Given that processing binocular disparities involves perception of objects in depth, form in random dot stereograms and control of vergence eye movements, it is not surprising that multiple areas of the brain are involved in processing this information.

Given the multiple areas in the brain where stereopsis is processed, it is difficult to conclude that any impairment in stereopsis could be due to a dopamine deficiency in the parietal cortex. Nevertheless, the association of impaired stereopsis with other visual spatial problems in more severe cases may reflect changes in the inferior temporal cortex or ventral pathway.

Stereopsis is only one factor that contributes to depth perception. There are several monocular clues that also contribute to depth, but stereopsis is one of the more salient clues. Some monocular clues are static such as perspective and others are dynamic such as optic flow (Daw, 2011). Impairment of any of the depth perception clues, as well as, impairment in the integration between the visual and motor systems in PD patients could lead to further movement disorders. Distance estimation of a remembered target is more inaccurate in PD patients than healthy controls during static (when they are not walking), active dynamic (when they walked toward it), or passive dynamic (moving on a wheel chair) conditions (Martens et al., 2013). Results from this study confirmed that there are more errors in distance estimation during

active movement condition than other two conditions. They attributed distance estimation deficit during active moving to two potential factors; a deficit in the proprioceptive perception, which is controlled by somatosensory system; or problems in the integration between proprioceptive and visual perception systems. In a subsequent study, they found that FOG-PD patients had more errors in distance estimation during both static and dynamic conditions than non-freezers DP patients and healthy controls (Martens et al., 2014). The results of this study suggest that the motor disturbances that cause freezing of gait disorders could be due to two different perceptual impairments: the visuospatial (vision only) or visuomotor (vision and proprioception) deficits.

The previous studies showed deficits in both contour and global stereopsis in PD, but no one has compared the stereo thresholds for both global and contour stereopsis for the same group of patients. Determining the threshold for global and contour stereopsis could be useful in monitoring the progression of the disease and may be a predictor of mobility in more complex environments. It is possible that global and contour stereopsis could be affected differentially in freezers and non-freezers PD because of how the two types of depth perception information are processed. It is also possible that the two types of stereopsis are equally affected which could be a result of either a sensory-integration deficit in visual areas or problems in controlling vergence eye movements.

1.5 EYE MOVEMENTS IN PARKINSON'S DISEASE

Eye movements can be classified as either conjugate or disconjugate movements. Conjugate eye movements are defined as both eyes moving in the same direction such as saccade or smooth pursuit eye movement. These eye movements provide bifoveal fixation for a target moving across our visual field or bifoveal fixation as one scans objects in the visual field. Disconjugate eye movements are defined as the eyes moving in opposite directions. Disconjugate eye movements are synonymous with vergence eye movements. Vergence eye movement can be convergent, when the two eyes move toward each other, or divergent, when the two eyes move away from each other. Vergence eye movements provide bifoveal fixation for objects at different distance from one's body. Vergence eye movements allow one to maintain single binocular vision over a wide range of retinal image disparities (Hung, et al., 1994; Leigh & Zee, 2015).

The generation of eye movements is thought to begin in the visual motor areas (i.e. frontal eye field) in the frontal cortex. Signals are then sent to the superior colliculus and from there to extra ocular nuclei and then to the extraocular muscles. The basal ganglia and substantia nigra are located within the eye movement pathway between the frontal cortical areas and superior colliculus. Thus, it is possible that the dopaminergic pathway (basal ganglia and substantia nigra) mediate the neural activities of the eye movement pathway. Numerous studies have reported impairments in eye movements in PD patients (Fukushima et al., 2015; Hanuška et

al., 2015; Pinkhardt et al., 2012; Tereshchenko, et al., 2015). In the next subsections, I will review two types of eye movements in PD patients.

1.5.1 Vergence Eye Movement

Previous studies showed PD patients have difficulty with many near visual tasks and report reading difficulties and diplopia. The clinical findings are consistent with a diagnosis of convergence insufficiency. These findings include remote near point of convergence and reduction in fusional vergence amplitude at near compared to age matched normal individuals. Most of these functions improved after patients were treated with dopamine (Almer, et al., 2012; Biousse et al., 2004; Racette, et al., 1999). These findings suggest that the dopaminergic pathway regulates or influences convergence eye movements.

A video oculography study of vergence eye movements in PD patients showed there was a significant delay of both convergence and divergence eye movements among PD patients compared to age matched normal individuals. These delays were not correlated with the severity, duration, or the treatments of the disease, which suggests that the dopaminergic system does not affect the vergence system in PD patients. (Hanuška et al., 2015).

The conflicting conclusions could be a result of multiple areas involved in the control of the vergence eye movements. Alvarez et al. (2014) compared the neural activity and convergent peak velocity in non-PD convergence insufficiency patients and

control subjects using functional MRI (fMRI). The participants looked at 3 different targets representing 3 different vergence demands; far, middle, and near. The results showed that the convergence peak velocity in the patient group was lower than controls. Functional activities from frontal eye field, posterior parietal cortex and cerebellar vermis correlated with reduction of convergence peak velocity in the patient group (Alvarez et al., 2014). It is possible that latency deficits are due to defects in the non-dopaminergic pathways regulating vergence eye movements and other vergence problems are due to defects in the dopaminergic pathways. Neural activities of vergence system adaptation were studied on two monkeys while their vergence system adapted to both cross and uncrossed disparities. Extracellular recordings indicated that prism adaptation was not complete in the vergence-related neurons located dorsal lateral to the ocular motor nucleus (Morley, Judge, & Lindsey, 1992). The authors concluded that other sites were responsible for prism adaptation and these sites were distal the ocular motor nucleus. However, Takagi, et al. (2003) showed that lesions to the cerebellum vermis impaired vergence adaptation in monkeys, suggesting that central sites also play a role in prism adaptation. Although neither of these studies rules out a possible role of the basal ganglion dopaminergic system in vergence adaptation, the electrophysiological studies suggest that vergence adaptation may be mediated by primarily a cholinergic system.

Fixation disparity is the small ocular misalignment of one eye or both eyes when the two eyes are fixating on an object during normal binocular vision. The two images in the case of fixation disparity do not stimulate corresponding retinal points, but they

do fall within Panum's fusional area and so a single image is perceived (Ogle, Mussey, & De, 1949; Ogle, 1951; Ogle & Prangen, 1951). If nonius lines are presented dichoptically (i.e. each line presented separately to each eye), while the person fixates on an object with both eyes, the nonius lines will be perceived in slightly different visual directions when a fixation disparity is present. The angular separation between the two lines (in minutes of arc) is the amount of fixation disparity. Schor (1980) described fixation disparity as a small error in the vergence system that is required to maintain fusion when the fast component of the vergence system changes.

Fixation disparity can be measured as a function of the vergence or accommodation demands; that is, by placing prisms or lenses of varying powers in front of the eyes while the observer looked at two nonius dichoptic lines. The fixation disparity plotted as a function of different powers of prisms, or lenses, is known as *the forced vergence fixation disparity curve (FDC)*. There are 4 different parameters can be obtained from Fixation disparity curve which are: i) Y intercept (the fixation disparity value in minutes of arc), ii) X intercept (the associated phoria in prism diopter), iii) slope at the center of the curve, and iv) the curve type (Ogle et al., 1949; Ogle, 1951; Ogle & Prangen, 1951). Figure 1-1 shows an example of the FDC when prism is placed before each eye.

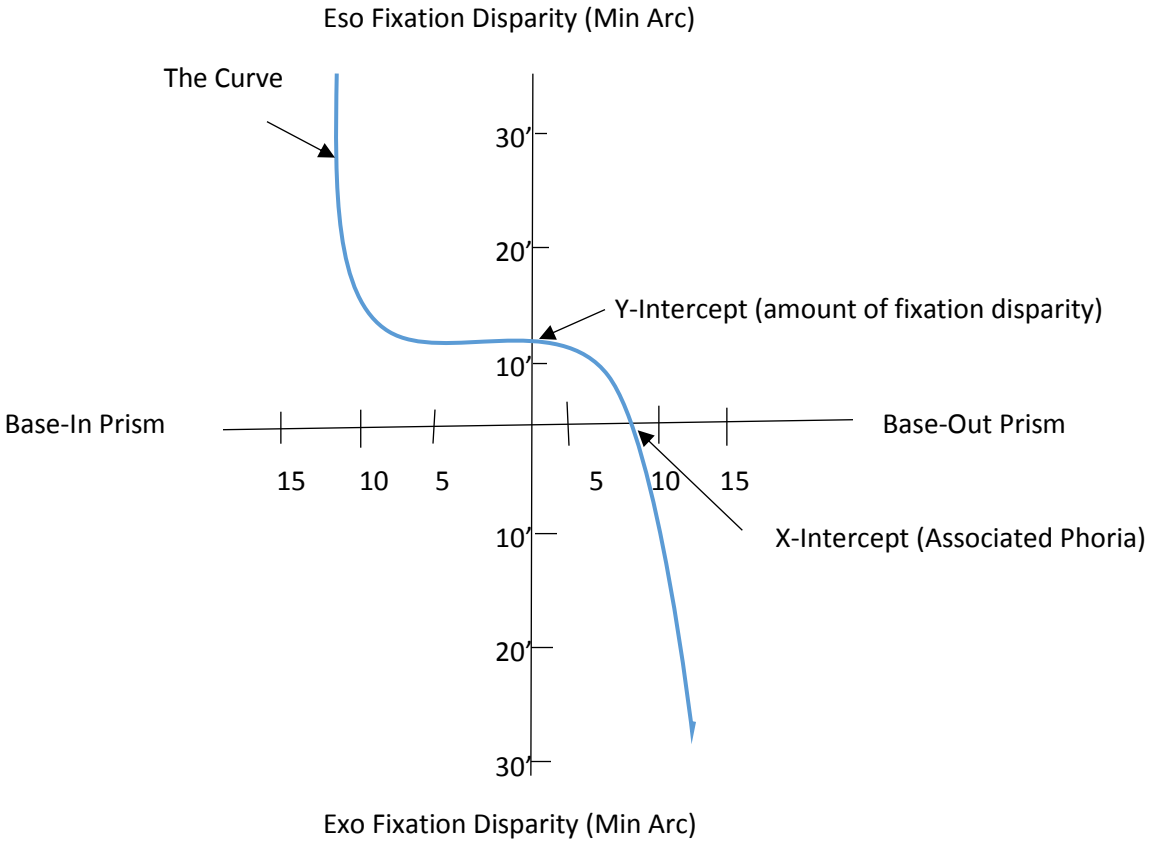


Figure 1-1: Forced Vergence Fixation Disparity Curve

There are four different types of fixation disparity curves (Figs. 1-2-1-5) (Ogle et al., 1949). These curves describe how the vergence system adapts to stress introduced by prims. Individuals who have good vergence system adaptation to both base-in and base-out prism are usually show a Type I curve, and these individuals are usually asymptomatic. However, other curve types may indicate binocular vision abnormalities. Individuals who adapted very well to base-out prism and poor adaptation to base-in prism are more likely to have eso (inward) deviation, and so they are more likely to have Type II curve. In the contrast, Type III curve individuals adapt to base-in prism better than base-out prism and they usually have an exo (outward) deviation. Type IV curve indicates unstable binocular vision and bad vergence adaptation to both base-in and base-out prisms (Schor, 1979a; Schor, 1979b). Another important parameters of FDC is the slope. Flat slope usually indicates good vergence adaptation. On the other hand, a steep slope is an indicator for a bad vergence adaptation (Sheedy & Saladin, 1978).

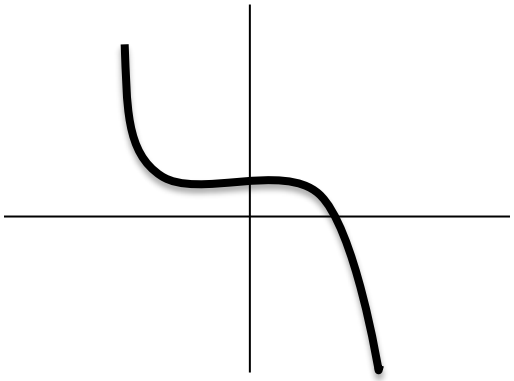


Figure 1-2: Forced Fixation Disparity Curve Type 1

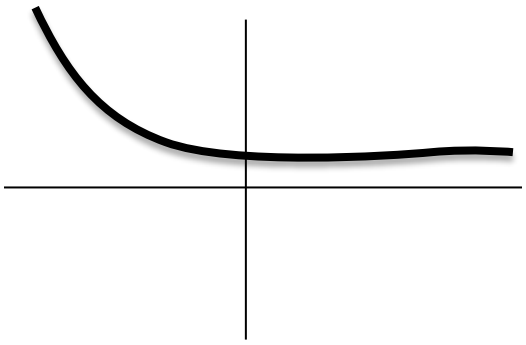


Figure 1-3: Forced Fixation Disparity Curve Type 2

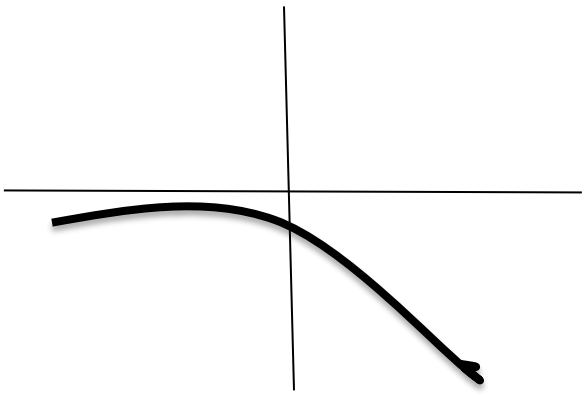


Figure 1-4: Forced Fixation Disparity Curve Type 3

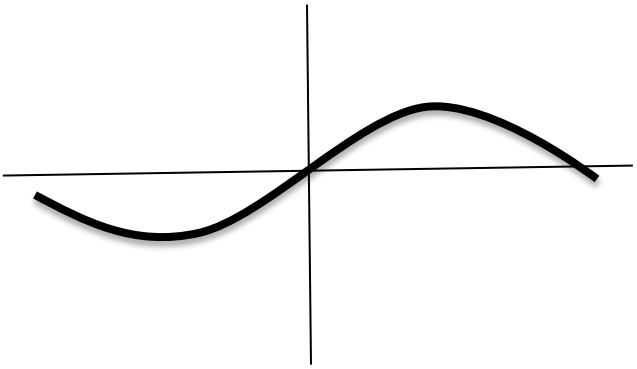


Figure 1-5: Forced Fixation Disparity Curve Type 4

Patients who have binocular vision disorders, such as convergence insufficiency, are characterized by abnormalities in their vergence system adaptation and do not have good vergence adaptation for near targets. Thus, it is expected these patients would not show Type I curve of FDC (Scheiman & Wick, 2008).

Since the fixation disparity curve can be used to evaluate the vergence system, and the vergence system is impaired in some PD patients, it is worthwhile to investigate vergence adaptation by generating fixation disparity curves in PD patients. If PD patients have poor vergence system adaptation, then it is expected to have less PD patients with Type 1 curves, and more non-Type 1 curves compared to healthy controls. Moreover, it is important to look at the magnitude of the fixation disparity (without prisms or lenses in front of eyes) and how it could be related to stereopsis dysfunction in PD patients. To my knowledge, fixation disparity and fixation disparity curves have not been investigated in PD patients.

1.5.2 Voluntary Saccadic Eye Movements

Voluntary saccadic eye movements (predictive and anti-saccadic tasks) are affected in PD patients (Antoniades et al., 2015; Chan et al., 2005). In predictive, or anticipatory, saccadic eye movements, saccades are made toward a predictive location. Anti-saccades are more complicated. In anti-saccadic tasks, the eye movement is in the opposite direction of a target, but with same amplitude (Hung et al., 1994; Leigh & Zee, 2015). There are two mechanisms involved in anti-saccadic eye movements. The

first one is to inhibit the saccadic eye movement toward a target. The second is to generate an eye movement toward the opposite direction, but with an amount equal to the presented target. Therefore, anti-saccadic tasks require more attentional and cognitive abilities than other saccadic eye movements (Wong, 2008).

Mild to moderate PD patients did not show a significant difference in anti-saccadic tasks relative to normal individuals; however, patients with severe PD, had more anti-saccadic errors and increased in latencies. PD patients who were treated with anticholinergic drugs had more anti-saccadic errors than those who did not receive these drugs (Kitagawa, Fukushima, & Tashiro, 1994). This suggests that acetylcholine depletion contributes to the anti-saccadic errors in PD patients. It is thought that the frontal cortex, especially the frontal eye field, controls the suppression of the movement toward a target in anti-saccadic task. Anti-saccadic errors correlated with poor performance on executive function tests in PD patients. Executive function is also mediated by areas in frontal cortex. This suggests that there is a general deficit in the frontal lobe functions in some PD patients.

This study suggests that there is an evidence of early cognitive impairment in PD patients occurring at approximately the same time as when the motor symptoms start to develop. Moreover, the anti-saccadic errors are probably due to cognitive dysfunction regulated mainly by the prefrontal cortex pathway rather than dopaminergic pathway (Antoniades et al., 2015). Previous studies showed anti-saccadic errors are associated with frontal cortex lesions. In animals, anti-saccadic

errors were associated with neural responses in the frontal eye field, supplementary eye field, and in the prefrontal cortex (Kitagawa et al., 1994).

The severity of freezing of gait is associated with cognitive dysfunction mediated by the frontal lobe (Amboni et al., 2008). If frontal cortex is involved in gait freezing, then these subjects may show more deficits in pro and anti-saccadic tasks than non-freezer patients.

1.6 PUPIL LIGHT REFLEX IN PARKINSON'S DISEASE

Pupil constriction begins with stimulation of the photoreceptors and intrinsically photoreceptive retinal ganglion cells. Ganglion cell axons enter the pretectal area of the midbrain through brachium of the superior colliculus and terminate in the pretectal olivary nucleus. Axons from these nuclei project bilaterally through the posterior commissure of Edinger-Westephal (EW) nuclei. Neurons from EW nucleus innervate the parasympathetic ciliary ganglion neurons, which send postsynaptic projections to the constrictor muscle in the iris.

The sympathetic autonomic system controls pupil dilation (Micieli, Tosi, Marcheselli, & Cavallini, 2003). The first order efferent nerves originate in the posterior hypothalamus and terminate at the ciliospinal center of Budge and Waller in the spinal cord. From here, the second order leave through the ventral horn of the spinal cord and ascend to the superior cervical ganglion. The third order neurons leave the ganglion and innervate the dilator muscle.

Neural losses occur in several autonomic centers in PD patients including EW nucleus, ciliospinal center, locus coeruleus and other higher autonomic centers (Chan-Palay & Asan, 1989; Gelpi et al., 2014). ANS dysfunctions in PD patients are believed to be due to mainly acetylcholine (ACh) and norepinephrine (NE) neurotransmitters depletion rather than the dopaminergic reduction (Chaudhuri et al., 2006; Chaudhuri & Schapira, 2009; Micieli et al., 2003).

Previous studies showed that the latency of constriction onset, amplitude of constriction (pupil radius after 2 minutes of dark adaptation - minimum pupil radius after reaction to light), maximum constriction velocity and maximum constriction acceleration are affected in PD patients. These studies suggest that a dopamine deficiency in the retina or cortex is not responsible for the changes in the different pupillometric parameters because there was no correlation with any other motor symptoms of the disease (Giza, et al., 2011; Goetz, Lutge, & Tanner, 1986). In addition, there are more PLR parameters affected in cognitive impaired PD patients than those patients who have normal cognitive function (Stergiou et al., 2009). PLR parameters of cognitive impaired PD patients were similar to the pupil dysfunction reported in Alzheimer's disease patients. This suggests that both groups of patients have the same central cholinergic (parasympathetic) deficit (Fotiou et al., 2009).

Amboni et al. (2008) reported that freezing of gait and its severity are associated with frontal cognitive dysfunction and the severity of the frontal cognitive dysfunction respectively. Patients who experience gait freezing may show a greater impairment of

parasympathetic function (e.g. PLR) than those who do not experience gait freezing. This would support the hypothesis that cholinergic systems may be impaired in gait-freezing individuals.

1.7 VISUAL PROCESSING SPEED IN PARKINSON'S DISEASE

Visual information processing speed is the ability to detect a characteristic of a stimulus that is presented for a specified time interval. The minimum presentation time required for an individual to visually identify the physical characteristics of a stimulus is called the inspection time (IT) (Deary & Stough, 1996; Johnson, Almeida, Stough, Thompson, Singarayer, & Jog, 2004b; Nettelbeck, 1982; Thompson, Stough, Ames, Ritchie, & Nathan, 2000; Vernon, 1986). An IT task can predict humans' general intelligence, the performance abilities and the cognitive abilities (Petrill, Luo, Thompson, & Detterman, 2001).

PD patients have significant deficits on reaction time (RT) tasks because RT tasks require motor responses (Gauntlett-Gilbert & Brown, 1998). However, from those studies someone cannot conclude whether such deficits are due to the motor system disorders of PD or it is more likely due to delay in the processing speed of the visible information. Because IT does not require motor responses from subjects, it can measure the perceptual processing speed. Thus, IT measurement, unlike RT measurement, can be used to dissociate between the deficits (slowness) in motor response and the delay in the information processing speed within impaired movement population such as PD (Johnson et al., 2004b).

Different studies have shown that PD patients have significantly slower visual processing speed compared to aged match controls. However, these studies used different visual stimuli than traditional IT task. For example, one PD patient needed significantly longer presentation times to recognize motion-defined letters than age-matched controls and this delay in the perceptual speed did not improve after taking dopaminergic medication (Giaschi, Lang, & Regan, 1997). The limitation of this study is that the task required eye movements to track the letters so it is possible that the eye movement disorders in PD patients contributed to the delay in the processing speed. Even if eye movements are controlled, PD patients still showed significant slower processing speed than healthy controls using visual recognition tasks (Bachmann et al., 1998). Moreover, the performances of those patients did not improve after receiving medications, which is consistent with Giaschi et al. (1997) results.

Other studies that examined IT in PD reported mixed results. In one study, subjects were required to recall the sequence of 4 random letters presented for varying durations. The results from this study showed that the medicated PD patients needed longer presentation times compared with the healthy controls (Shipley et al., 2002). In another study, two lights were presented to the subjects at slightly different times, and the subjects' responses were to identify which light was presented first. The ITs for this task were not significantly different between PD who were on-medication and age-matched healthy controls (Phillips et al., 1999). Sawamoto et al. (2002) developed visual stimuli that required mental-operations tasks to evaluate visual

processing speed. The result from this study showed that PD patient group needed longer presentation times than healthy controls. However, this study also involved higher-order of intelligent processing so that it was not a simple IT task (Sawamoto et al., 2002). Johnson et al. (2004) examined the IT task by presenting a simple figure, which consists of two vertical lines. The lines differed in length and the subjects identified the longer line. Results showed that on-medicated patients required significantly longer presentation times in order to identify the longer line compared with healthy controls. Moreover, the IT score for the PD patients group was not significantly different between 'ON' and 'OFF' medication status (Johnson et al., 2004b).

Stough, et al., (2004) proposed that the dopaminergic pathway and dopamine levels in healthy subjects did not regulate visual information processing speed. Results from Johnson et al. (2004) supported this hypothesis as the IT deficits was not improved significantly when patients were on their 'ON' medication time vs. 'OFF' medication time. It is possible that IT deficits in PD patients are distinct from the motor impairments (Johnson et al., 2004b).

There is reasonable evidence that the cholinergic system mediates IT (Nathan & Stough, 2001). IT was significantly slower in patients with Alzheimer's disease compared with healthy controls (Deary et al., 1991) and nicotine acetylcholine receptors (nAChRs) are involved in IT processing. Thus, manipulating nicotine acetylcholine pharmacologically may affect the IT score in healthy subjects

(Thompson et al., 2000). There is evidence that nicotine acetylcholine receptors (nAChRs) are reduced in PD patients especially in the nigrostriatal pathways (Court et al., 2000). It is possible that these receptors are also reduced in the areas, which are responsible for visual processing, which could explain the slower IT times for PD patients.

FOG symptoms among some PD patients may be independent from the dopaminergic reduction and it is now hypothesized that the cholinergic system dysfunction may be involved. If this hypothesis were correct, then one would expect that FOG patients could have slower IT score compared with the non-FOG patients and the increase time to process visual information may contribute to the FOG symptoms.

Chapter 2
RESEARCH OBJECTIVES

2.1 PURPOSE:

The purpose of this project is to conduct cross-sectional studies focusing on the characteristics of 2-dimensional and 3-dimensional clinical visual functions in PD patients. The study is essentially examining the visual resolution and localization capabilities of PD patients for 2-D stimuli and 3-D visual stimuli. The 2-D visual functions will be visual acuity for high and low contrast letters and contrast sensitivity for low spatial frequencies in both daylight (photopic) and dim light (mesopic) conditions. Individuals who experience gait freezing may have impaired acuity and/or contrast sensitivity, especially under low light levels. The 2-D localization capabilities will be assessed by Vernier acuity for both vertical and horizontal offsets in both daylight (photopic) and dim light (mesopic) conditions. This ability could be differentially affected in patients who experience gait freezing and contribute to their inability to judge their lateral position relative to any edges in the scene. Local (contour) and global (random dot) stereopsis will be the 3-D functions measured in the study. Impaired stereopsis could lead to reduced mobility because PD individuals have difficulty judging relative distances of objects. Furthermore, our pilot data suggests that global stereopsis, measured with random dot tests, may be affected sooner, or to a greater extent, than local stereopsis in PD patients. The ability to control eye alignment when viewing near objects (Fixation Disparity) will be measured. This is important to determine because reduced depth perception could be

due to an inability to maintain adequate alignment of the two eyes. PD patients' ability to control their eyes may help determine whether any reduction in depth perception is a cognitive problem or related to problems with eye movement control. The fixation disparity curve may also provide further insight into any impairment of their vergence system.

Measuring visual functions by using those clinical tests in this project will allow us to analyze visual performance within different visual channels or pathways. Also, measuring these visual functions in same group of patients can help us to determine whether the patterns of damage is due to dorsal pathway (magno) or ventral pathway (parvo) in PD patients, and whether these damages contribute to freezing of gait disorders. Deficits to both magno and parvo visual pathways have been reported in the same group of PD patients. However, there was no correlation between deterioration in visual functions that mediated by magno vs. parvo pathways (Silva et al., 2005). Another study showed that there was a preferential impairment in visual function mediated by the dorsal visual pathway in FOG-PD patients (Lord et al., 2012). These two studies suggest that the dorsal (magno) and ventral (parvo) pathways are affected in PD patients by using non-clinical visual tests and the degree of loss in the dorsal pathway may be larger in FOG. A greater impairment of the "where" visual pathways could be contributing to the FOG symptoms. One of the problems in determining whether there is selective damage to one pathway is that any changes in the retina associated with PD may be nonselective. For example, the changes could be similar to decreasing the retinal illuminance. A decrease in retinal

illumination will affect parvo-mediated functions such as colour vision and visual acuity along with magno mediated functions such as sensitivity to flicker and stereoacuity. The other complicated factor is that the ventral and dorsal pathways interact with each other. There are extensive interconnections between the two streams (Felleman & Van Essen, 1991).

Another purpose of this project is to look at other ocular and perceptual functions in PD patients that represent different pathways. We will measure the pupil light reflex (PLR) and the visual information processing speed, which represent primarily the cholinergic pathway among PD patients who experience FOG freezing of gait vs. those who are not to determine whether these measurements can discriminate between different PD groups. This would support the hypothesis that more than just the dopaminergic pathways are affected in PD.

This work could also help in improving our understanding of the progression of PD, the contribution of basic visual function to gait freezing, and potentially provide simpler tests to evaluate the progression and severity of the disease.

2.2 HYPOTHESES:

The general hypothesis of this thesis project is that freezing of gait (FOG) PD patients have more visual perceptual difficulties than non-FOG PD patients and healthy controls, and this may contribute to their freezing symptoms. Specific hypotheses of this thesis project are:

1. Freezing of gait (FOG) PD patients have larger deficits in using 2D clinical visual stimuli especially under low light levels (Study 1).
2. Freezing of gait (FOG) PD patients have larger deficits in using 3D clinical visual stimuli and ocular misalignments (Study 2).
3. Freezing of gait (FOG) PD patients have larger impairments of pupil light reflex (PLRs). This could be due to a combination of sensory or motor deficits (Study 3).
4. Freezing of gait (FOG) PD patients have slower visual information processing speed (IT) due to cholinergic system dysfunction (Study 4).

Chapter 3
GENERAL METHODS

3.1 PARTICIPANTS:

The study took place at the Sun Life Financial Movement Disorders Research and Rehabilitation Center (MDRC), Wilfrid Laurier University, Waterloo, ON. Although many subjects have participated in other experiments at the Centre, none had participated in a vision experiment. Many were familiar with some of the tests through their interactions with their eye care practitioner. The subjects were classified into three groups as follows:

1. Two on-medication Parkinson's disease patient groups (Freezing and Non-Freezing): all of patients met the criteria of Parkinson's disease according to MDS-UPDRS scaling system (Giladi et al., 2000; Goetz et al., 2008). Patients with other neurological disorders, brain lesions or concussions were excluded. Freezing vs. non-freezing patients were determined based on the freezing of gait questionnaire for PD patients (Giladi et al., 2000; Goetz et al., 2008).
2. Age matched healthy control group: subjects free from of any neurological disorders, brain damage history, positive history of Parkinson's disease, or concussions.

The exclusion criteria for all participants were a history of diabetes, nystagmus, strabismus, and/or corrected visual acuity worse than 20/30 at distance or near in either eye. All patients and healthy controls were recruited from the MDRC database.

The subjects gave informed written consent before participating. The study was approved by University of Waterloo's and Wilfrid Laurier University's Offices of Research Ethics.

3.2 Neurological & Cognitive Assessments:

The first step was to determine the severity and cognitive ability of the PD patients or the cognitive abilities of the healthy controls. Dr. Quincy Almeida classified the severity of the disease and the freezing vs. non-freezing patients according to MDS-UPDRS scaling system (Giladi et al., 2000; Goetz et al., 2008). The Montreal Cognitive Assessment Test (MoCA) was used to assess cognitive status (Nasreddine et al., 2005).

3.3 Visual Screening (Eligibility):

This assessment followed the neurological and cognitive assessments. Visual acuity and ocular alignment (i.e. cover test and near point of convergence) were measured to determine whether the participants met the eligibility criteria. If they did not meet the acuity requirement, then acuity was reassessed with a pinhole. If the acuity improved, then a refraction was performed.

Twenty-two FOG PD patients, 25 non-FOG PD patients and 25 healthy controls participated in this thesis project. All of patients and healthy controls completed the 4 studies in this thesis. Tables A1 and A2 (Appendix A) list the demographic characteristics for every FOG and non-FOG PD patients including age, sex, severity

(MDS-UPDRS score), duration of the disease, cognitive status (MoCA score), and list of medications that patients were taking during testing.

Table 3-1 shows the mean values (mean ± SD) of different demographic characteristics of the participants and whether the differences were significant between groups.

Table 3-1: Means and SDs of the demographic characteristics of the participants

Groups	FOG	non-FOG	Healthy Controls	The differences (P value)
Sample Size (N) (Male/Female)	22 (14/8)	25 (19/6)	25 (8/17)	NA
Age	72.31 (6.9)	67.52 (9.4)	70.43 (7.67)	0.059
Cognitive (MoCA) Score	24.95 (4.27)	25.76 (2.18)	26.48 (2.16)	0.221
Severity (UPDRS) Score	22.41 (7.94)	19.96 (9.58)	NA	0.349
Duration of the Disease	10.52 (6.6)	8.08 (6.35)	NA	0.203

3.4 Study 1: Visual Resolution and Localization using 2D Visual Stimuli under Photopic and Mesopic Conditions

In the next sections, I will describe the visual tests and procedures used in the first study.

3.4.1 Distance Visual Acuity:

High and low contrast visual acuities were measured binocularly at 4 meter distance using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Fig 3-1) (Ferris et al., 1982). Participants started reading from the largest letter size with their habitual distance glasses or with modified refractive power using trail lenses and frame. The participants continue to read the smaller letters row. Testing ended when participants read 2 out of 5 letters correctly. Visual acuity was recorded using the logMAR system in which each letter equals 0.02 logMAR (Hazel & Elliott, 2002). The chart was placed in a self-illuminated cabinet. The luminance of the high contrast charts was 122 cd/m^2 and 116.2 cd/m^2 for the low contrast chart.

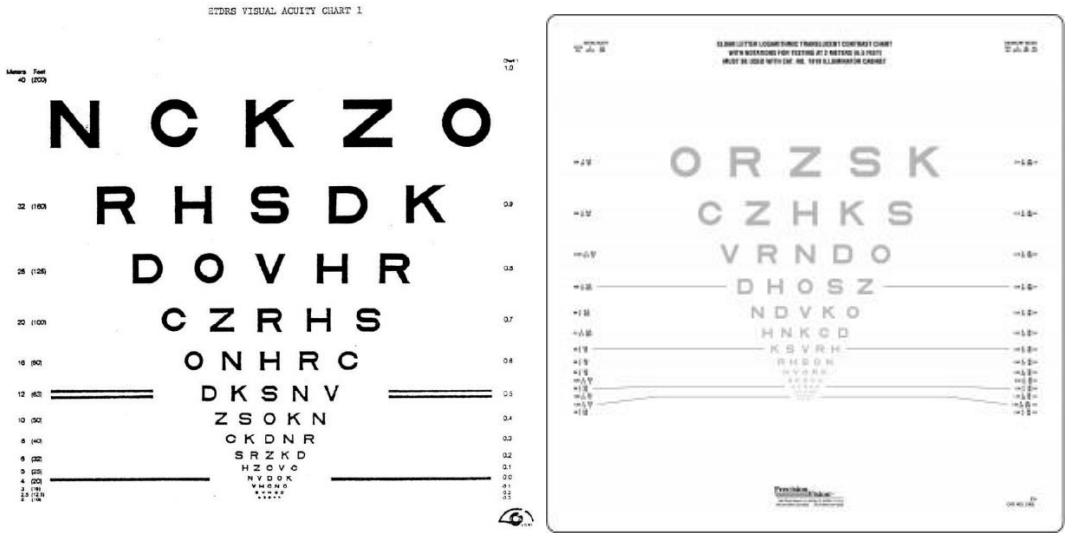


Figure 3-1: High and Low Contrast ETDRS Visual Acuity Charts at distance

(Images courtesy of Precision Vision)

3.4.2 Contrast Sensitivity:

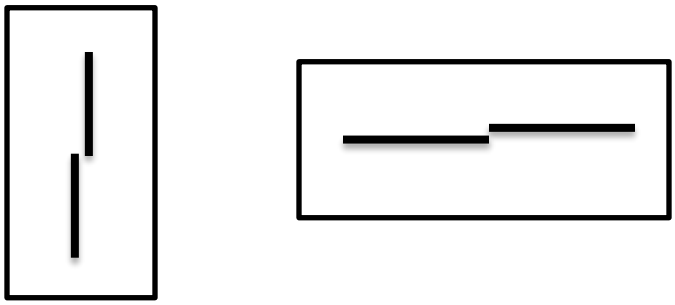
Contrast sensitivity at low spatial frequencies was measured with the Pelli Robson chart (Fig 3-2) (Elliott, Sanderson, & Conkey, 1990; Pelli & Robson, 1988). This chart consists of 8 lines of fixed size random letters that decrease in contrast from top to bottom. Each line consists of two groups of three letter of slightly different contrasts. Subjects viewed the chart from 1 m using habitual distance or intermediate glasses on, whichever made the chart clearer. Following the procedure of Elliott, et al, (1990), subjects started reading at the highest contrast letters (100%) and continued until they could read only one letter in a group of three letters. Contrast sensitivity was determined by subtracting 3 from the number of letters read correctly and then multiplying by 0.05 log unit. The chart luminance was 117.6 cd/m^2.

Figure 3-2: Pelli-Robson Contrast Sensitivity Chart

(Images courtesy of Precision Vision)

3.4.3 Vernier Acuity:

The Freiburg Visual Acuity Test (FrACT) (Bach, 1996) measured horizontal and vertical Vernier acuity. The Vernier acuity task consisted of two nonius lines display on a 27-inch wide computer screen at distance of 6 meter from participants. The luminance of the screen was 161.4 cd/m^2. The computer program was calibrated so that each pixel of the computer screen subtends 0.19 min arc at distance of 6 meter away from the screen. This allows one to measure Vernier acuity up to 4.67 in decimal scale, which is equal to 12 sec arc. The participants performed the test with their habitual distance glasses or with the modified refractive correction. Figure 3-3 shows an illustration for the horizontal and vertical Vernier acuity targets.



A **B**

Figure 3-3: An illustration shows the Vernier Acuity Test

A: Horizontal Verner Acuity Test, B: Vertical Vernier Acuity Test

The FrACT uses a two alternative forced choice method to measure Vernier acuity. For the vertical orientation (measuring lateral separation), participants had to respond whether the top line was to the left or the right of the stationary bottom line to measure the horizontal Vernier acuity, and whether the right line was below or above the left line to measure vertical Vernier acuity. The Vernier acuity was calculated in a seconds of arc by the computer program using the best PEST psychometric method. This method considers 56.25% of the correct responses to calculate the threshold level (Lieberman & Pentland, 1982; Treutwein, 1995).

The experiment began with a practice session. Horizontal Vernier acuity was measured before vertical. At each trail, participants needed to give a response verbally and the examiner entered their responses using a keyboard. There was audio

feedback after each response as to whether the response was ‘correct’ or ‘wrong’. The test consists of 42 trials. The presentation time for the stimulus was up to 1 second. The lines were then replaced by a random dot mask that remained on the screen for 200 milliseconds. This pattern prevented the subjects from making judgments based on an afterimage. Participants were given 30 seconds to make a decision. If they could not make a decision within a 30 second period, then the response was counted as ‘wrong’.

3.4.4 Visual resolution and localization under Mesopic Condition:

High contrast visual acuity, low contrast visual acuity, contrast sensitivity and horizontal & vertical Vernier acuity were measured as described above but this time at a lower light level (mesopic condition). Visual acuity and contrast sensitivity were measured by using different version of letters to avoid the memorizing effect.

Participants wore a welding helmet with a 1.0 ND plate filter in front of eyes for the low light conditions. A black cloth was attached from the back and on both sides of the helmet in order to block any possible source of light that might reach the participants’ eyes as shown in Fig 3-4. Participants wore the helmet with their habitual distance glasses or the modified refractive correction. The room lights were turned off. Participants adapted to the lower dim light for 5 min. The 5 min interval for dark adaptation was selected so that both cone and rod photoreceptors were providing inputs (mesopic condition) (Schwartz & Meese, 2010). Table 3-2 shows the luminance of different visual resolution tests under low light level.

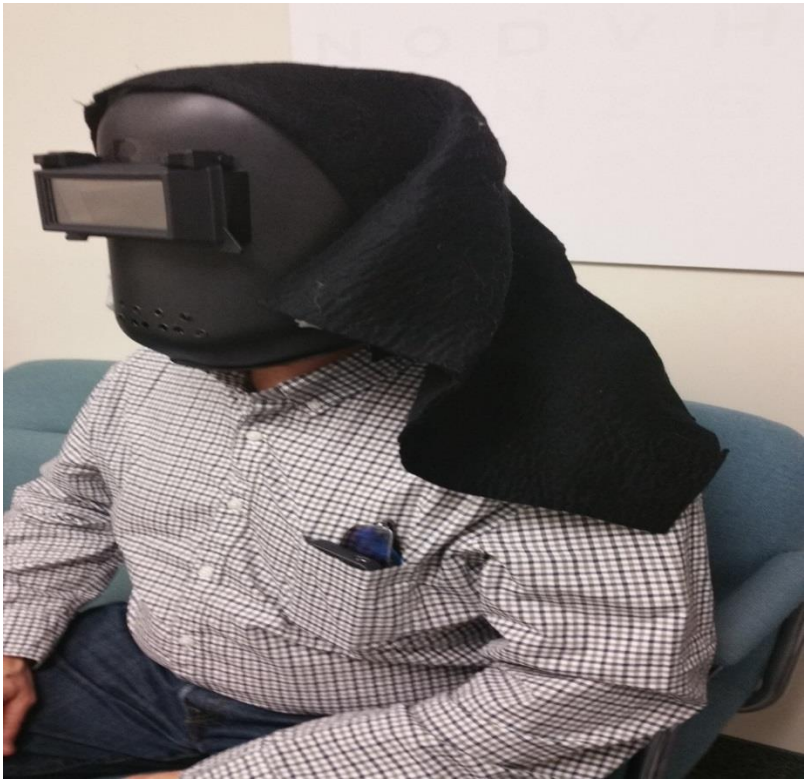


Figure 3-4: A participant wearing welding helmet with filter in front of eyes in order to reduce the light level.

Table 3-2: The luminance of different visual resolution tests under low light level.

Test	Luminance
Visual Acuity High Contrast	1.4 cd/m^2
Visual Acuity Low Contrast	1.11 cd/m^2
Pelli-Robson Contrast Sensitivity	0.23 cd/m^2
Vernier Acuity	1.8 cd/m^2

3.5 Study 2: Binocular Vision Characteristics (Stereopsis and Fixation Disparity)

In the next sections, I will describe the visual tests and procedures used in the second study.

3.5.1 Stereopsis (3-D Visual Tests):

Local (contour) and global (random dot) stereopsis were measured using six clinical stereo tests at 40 cm distance (Fig 3-5). Table 3-3 lists the stereoacuity tests and their clinical features. The design, methods and the clinical procedures of these tests described elsewhere (Eskridge & Eskridge, 1991; Rutstein & Daum, 1998; Scheiman & Wick, 2008; Scorth, 2012). Stereoacuity was measured for both crossed and uncrossed disparities.

Figure 3-5: The clinical stereoacuity tests

A: MKH-Haase Test, B: TNO Test, C: Circles Test and Butterfly Tests, D: Random Dot 3 Test

Table 3-3: Features of Clinical Stereoacuity Tests

Test	Type	Type of Disparity	Disparity Rage (sec arc	Type of Filters	Light level	Comments
Circles Test ***(Stereo Optical Co., Inc. Chicago, IL, USA).***	Local	Crossed and Uncrossed	800 – 40	Polaroid	280 lx	Measures stereopsis to near-threshold values, Monocular Clues
MKH-Haase Line Test ***(Carl Zeiss Vision GmbH, Aalen Germany)***	Local	Crossed and Uncrossed	180 – 10	Polaroid	150 cd/m^2	Measures stereopsis to near-threshold values, Monocular Clues
MKH-Haase Steps Test ***(Carl Zeiss Vision GmbH, Aalen Germany)***	Global	Crossed and Uncrossed	360 – 30	Polaroid	150 cd/m^2	Measures stereopsis to near-threshold values, Complex Shape
Random Dot 3 Test ***(Vison Assessment Corp. , IL, USA)***	Global	Crossed and Uncrossed	160 – 12.5	Polaroid	280 lx	Measures stereopsis to near-threshold values
TNO Test ***(Alfred P. Poll Inc., NY, USA)***	Global	Crossed and Uncrossed	480 – 15	Red-Green	280 lx	Measures stereopsis to near-threshold values
Butterfly Test ***(Stereo Optical Co., Inc. Chicago, IL, USA).***	Global	Crossed	2000 – 700	Polaroid	280 lx	Uses complex shape

A test started by explaining the procedure. Crossed disparities were always measured before uncrossed disparities for all tests. Crossed disparities were measured by holding the test booklet on the upright position with the Polaroid or red-green filters in front of participants' eyes, whereas uncrossed disparities were tested by holding the test booklet upside down. Participants started by identifying the maximum disparity stimulus. If they were correct, then they proceeded through the rest of the test until they either identified all the disparities correctly or made an error. The lowest disparity level that was correctly perceived by participants was recorded. If a participant could not resolve the maximum disparity after 90 sec, then the testing was stopped. The 90-second was based on pilot work, which found that the majority of participants could identify the disparity within 90 sec. Time to complete each test was also recorded using manual stopwatch. Testing stereopsis was performed while participants were wearing their habitual reading glasses or the modified refractive correction using trial lenses and frame.

3.5.2 Fixation Disparity:

Horizontal fixation disparity and horizontal fixation disparity curves were measured at 40 cm. using Saladin Near Point Card (Michigan College of Optometry, Ferris State University) (Fig 3-6) (Corbett & Maples, 2004). The Saladin Near Point Card is a repeatable test to measure fixation disparity and fixation disparity curve (Corbett & Mapoples, 2004).

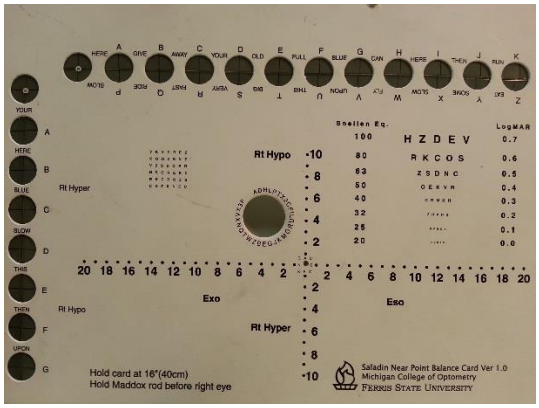


Figure 3-6: Saladin Near Point Card

Participants were seated behind the phoropter and using their habitual reading glasses or the modified refractive correction power was inserted into the phoropter along with the Polaroid lenses to dissociate the nonius lines. The Saladin Card was mounted on the phoropter using a rod. An incandescent lamp was placed just behind the Saladin Card to illuminate the nonius lines. The illuminance was 185 lx on the front of the card, and 360 lx on the back of the card. The test started by asking the participants to look at the horizontal row of circular openings at the top of the card. There were two nonius vertical lines inside each circular opening. The right eye saw the top lines and the left eye saw the bottom lines. Participants were also asked to look at the words and letters around those circles and to make them clear during the testing. In order to familiarize the participants with the test, they were asked to look with both eyes

opened at one circular opening that the fixation disparity is high (i.e. vertical lines are horizontally misaligned). The participants were directed to look at each individual opening until they found the one with the best horizontal alignment of the vertical lines. This value was the fixation disparity.

To generate the horizontal fixation disparity curve, participants were asked to look at the circular opening again but this time with a range of prismatic power introduced in front of their eyes. Risley prisms were used to add 3^{Δ}, $6^{\Delta,}$ $9^{\Delta,}$ and 12^{Δ} prism demands in front of their eyes. Except for the 3^{Δ} trial, the prism power was divided equally between the eyes and the direction alternated between base in and base out. Participants were asked to pick the one circle with the best horizontal alignment of the vertical lines every time the prismatic power changed. The amount of fixation disparity was plotted against the prismatic power in order to generate the fixation disparity curve (Fig 1). Four different parameters can be obtained from the fixation disparity curve: i), the amount of fixation disparity (Y-intercept), ii) the amount of associated phoria (X-intercept), iii) the slope, which is the amount of fixation disparity at 3^{Δ} BI minus the amount of fixation disparity at 3^{Δ} BO divided by 6 (Slope = $Y_1 - Y_2 / X_1 - X_2$) and iv) the curve type.

3.6 Study 3: Pupil Light Reflex

The pupil light reflex (PLRs) parameters were measured using a NeurOptics™ PLR™ -3000 Pupillometer (NeurOptics, Inc. Irvine, CA, USA). PLR-300 is a handheld monocular pupillometer that can measure both pupil constriction and pupil dilation parameters (Fig 3-7). PLR-3000 records the pupil size using an infrared camera (32 frames/sec) and can measure the pupil size to within +/- 0.03 mm.

Figure 3-7: PLR-3000 Pupillometer

(Images courtesy of NeurOptics)

PLR-3000 pupillometer measures both pupil constriction and pupil dilation parameters. To measure the pupil constriction parameters, bright stimuli flash against dark background. To measure pupil dilation parameters, the subjects adapt to a steady light and then it is extinguished for a brief period. Table 3-4 list all of the stimuli characteristics used in this study for both constriction and dilation conditions.

Table 3-4: Stimuli characteristics used to measure PLRs

Protocol	Constriction Condition	Dilation Condition
Definition	Stimuli brighter than Background	Stimuli Dimmer than the Background
Stimulus Intensity	50 uW	0 uW
Background Intensity	0 uW	50 uW
Measurement Duration	5 seconds	5 seconds
Stimulus Duration	0.07 second	1.07 second

- uW: micro Watts

The procedure was explained and demonstrated. Next, participants adapted to a darkened room for 5 min. This time allows pupils to expand to the maximum amount. The illuminance on the participants' chair during the dark condition was less than 0.1 lx. Pupil constriction was measured next for the right eye followed by the left eye. Measurements were repeated three times with 30 sec intervals between trials on each eye alternatively.

After that, the light of the room was turned on in order to measure the pupil dilation parameters. The procedures were similar to the constriction condition measurements except that the measurements were collected in a bright room. If a participant blinked during the measurement, then the data was deleted and another measurement was made. The pupillometer software calculates the various parameters automatically. The raw data and calculated parameters were downloaded to a computer for analysis.

Tables 3-5 and 3-6 list all of PLR parameters that were calculated by the PLR-3000 for constriction and dilation conditions respectively.

Table 3-5: PLR parameters for the constriction condition

Function	Definition	Unit
Initial Diameter (Init)	Initial dark adapted pupil size before constriction	mm
End Diameter (End)	Pupil diameter at maximum of constriction	mm
Constriction Percentage (Con %)	(Init – End) / Init	%
Latency of Constriction (LAT-C)	Time to onset of constriction	Millisecond (msec)
Average Constriction Velocity (ACV)	The average speed of the pupil constriction	mm/sec
Maximum Constriction Velocity (MCV)	The maximum speed of the pupil constriction	mm/sec
Re-Dilation Velocity (re-ADV)	The average speed of the pupillary re-dilation after the pupil has reached the peak of constriction	mm/sec
75 % Recovery Time (T75%)	The time to reach 75 % of the original baseline pupil diameter after the peak of the constriction	sec

Table 3-6: PLR parameters for the dilation condition

Function	Definition	Unit
Initial Diameter (Init)	Initial light adapted pupil size before dilation	mm
End of Diameter (End)	Pupil diameter at peak of dilation	mm
Dilation Percentage (Dia %)	(Init – End) / Init	%
Latency of Dilation (LAT-D)	Time to onset of dilation	Millisecond (msec)
Average Dilation Velocity (ADV)	The average speed of the pupil dilation	mm/sec

3.7 Study 4: Visual Information Processing Speed (Inspection Time)

The fourth study was an inspection time (IT) task developed by using Psychocinematics. The stimulus was calibrated for a 13-inch screen wide Mac Book computer placed 50 cm away from participants. The luminance of the screen was 360 cd/m^2.

The IT stimulus consisted of two vertical lines connected from the top by a horizontal line. The vertical lines differed in length and the participant's task was to identify which line was longer. The length of the long line was 29 mm, and the length of the short line was 21 mm. The visual angle of the long line was 199.32 min of arc and the visual angle of the short line was 144.36 min of arc. The difference in the angular length of the two lines was 55 min arc, which was much larger than the subjects' minimum angle of resolution for high contrast targets. A trial started with fixation cross appearing in the middle of the screen for 500 msec. Next, the IT stimulus

appeared and remained visible for a variable amount of time. A mask that consisted of random length vertical lines was presented next and remained on the screen for 360 msec. The duration of the stimulus was varied using a staircase procedure. The IT threshold was the duration at which 50% of the responses were correct (Stough et al., 2001; Stough et al., 2001). Figure 3-8 depicts the IT procedure.

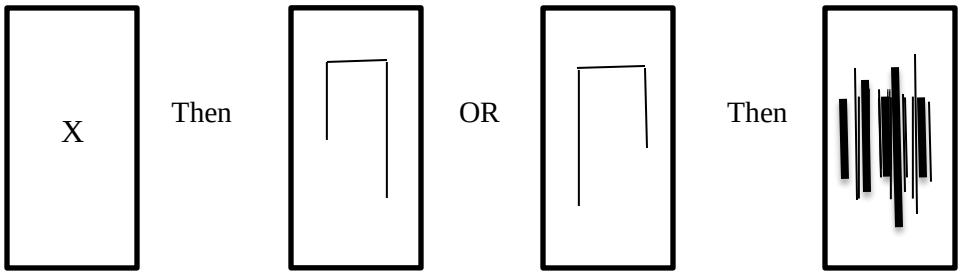


Figure 3-8: Inspection Time (IT) Procedure

Participants practiced until they could complete one full run of the test. They viewed the display with their habitual reading glasses. Participants responded verbally and examiner entered the responses into the computer program so that no motor action was required. Participants were instructed to give their responses after the stimulus (the two vertical lines) disappeared. They were encouraged to be as accurate as they could regardless how much time they spent before they made a response.

Chapter 4

VISUAL RESOLUTION AND LOCALIZATION USING 2-D VISUAL STIMULI UNDER PHOTOPIC AND MESOPIC CONDITIONS IN FREEZING AND NON-FREEZING PARKINSON'S DISEASE PATIENTS

4.1 SUMMARY

This study focused on different 2-D visual resolution tasks under photopic and mesopic conditions in FOG PD, non-FOG PD patients, and age matched healthy controls. Results from this study showed that FOG PD patients have a greater impairment for most of 2-D visual resolution tasks. The reduction was larger under the mesopic condition.

4.2 INTRODUCTION

Freezing of gait (FOG) is a main movement disorder symptom that presents in certain PD patients especially those in the advance stages. It may lead to further complications such as falls, reduction in quality of life, and lack of independence (Bloem, et al, 2001; Bloem et al., 2004; Moore, Peretz, & Giladi, 2007). FOG-PD patients experience intermittent episodes; that could last for a few seconds; of inability to produce or maintain a forward movement or to make a turn. FOG is more likely to occur when the person is walking in narrow spaces such as passing through corridors or doorways (Cowie et al., 2010; Giladi, Hausdorff, & Balash, 2013). The

pathophysiological mechanism of the FOG symptom is unclear. Even though freezing of gait is classically considered as one of the motor disturbances, recent evidence suggests that the pathophysiological underlying FOG involves both motor and non-motor systems (Almeida & Lebold, 2010; Giladi, et al., 2007; Grabli et al., 2012).

The concept that the FOG disorder has a distinct pathophysiological mechanism from other motor disorders in PD arises from the fact that FOG does not respond positively to dopaminergic treatment, whereas other motor disorder symptoms do respond (Giladi et al., 2007). In addition, FOG is strongly associated with non-motor symptoms such as depression, stress, anxiety, and cognitive dysfunctions (Bodis-Wollner, 2003; Giladi & Hausdorff, 2006; Lieberman, 2006).

The underlying pathophysiology of FOG has not been established. Among the recent theories is the cross-talk model suggested by Lewis and Barker (2009). In normal individuals, the basal ganglion is involved in the coordination of a number of neural activities. These neural activities include motor, cognitive and limbic processes and these processes both complement and compete with other in terms of the basal ganglion resources. In PD-FOG patients, the loss of dopamine alters the balance from competing inputs so that there is now cross talk between these inputs. In certain situations, this cross-talk put an excessive load on the processing capacity of the striatum, and combined with reduced responses from the output nuclei, this results in increased inhibition of the thalamus (i.e. a failure of disinhibition) which in turn inhibits movement (Lewis & Barker, 2009).

Based on the cross-talk model, a PD patient walking in a crowded environment or narrow corridors has an increase in the amount of sensorimotor input. This increase in input overloads the system and produces the FOG. Simply overloading the system with sensory input may not be the only mechanism responsible for FOG. PD patients have more visuospatial perception errors than healthy controls (Johnson et al., 2004), and FOG patients have more visuospatial judgement and motion perceptual errors compared to non-freezers and healthy controls. Furthermore, the performance on these tasks correlated with the severity of the gait disorder (Almeida & Lebold, 2010; Cowie et al., 2010; Martens et al., 2014; Silveira et al., 2015). Thus, the degraded quality of visuospatial information could be contributing to FOG symptoms. PD patients have a higher dependence on visual cues to help them to control their posture (Suarez et al., 2011) and so it is possible that FOG is due to degraded visual information involved in balance and posture. Because of the degraded visual information, the FOG patients are less sure of their balance in making the next movement and so they stop.

The reduction in visual acuity and contrast sensitivity reported for PD could be partially responsible for the visuospatial perception deficits (Jones & Donaldson, 1995, Archibald et al., 2011; Jones, Donaldson, & Timmings, 1992; Nowacka, et al., 2014). However, the visual acuity differences between groups were small and so it is unlikely that the visual acuity reduction was solely responsible for the visual perception errors. However, the impairment in visual acuity is larger when using low contrast letters (Tzoukeva, et al, 2008, Regan & Neima, 1984). Contrast sensitivity at

medium and high spatial frequencies was affected as well in PD patients (Bodis-Wollner et al., 1987). The losses were more severe in advanced stages of PD patients (Hutton et al., 1991). Importantly, the loss in contrast sensitivity is correlated with the severity of FOG disorders (Davidsdottir, Cronin-Golomb, & Lee, 2005; Uc et al., 2005).

PD is characterised by a reduction in retinal dopamine. Dopamine is an important retinal neurotransmitter that may mediate visual resolution by increasing the strength of the antagonistic surround in the retinal receptive fields. Lower dopamine levels would result in a decrease in visual acuity and contrast sensitivity at medium to high spatial frequencies. As the light levels decrease, the dopamine levels decrease, the strength of the antagonistic surround weakens and so spatial resolution decreases. Because the PD patients already have a lower level of dopamine, the antagonistic surround is weakened to a greater extent and so they would be expected to have greater reduction in visual resolution in dim lighting conditions (Beaumont et al., 1987). Supporting this hypothesis is data showing that peripheral contrast sensitivity functions were similar between dark-adapted healthy individuals and light-adapted PD patients (Harris et al., 1992; Wink & Harris, 2000b).

In questionnaires, PD patients report more difficulties driving especially during night. Half the PD patients in that study were freezers but the study did not compare between freezers and non-freezers patients (Davidsdottir et al. 2005). If FOG is associated with visual dysfunction, then it is possible that freezer patients would have

a larger visual acuity and contrast sensitivity impairment than non-freezer patients especially under dim lighting conditions. However, any deficit in visual resolution would suggest that it was caused by a decrease in dopamine at the retinal level.

4.3 AIM OF THE STUDY

The purpose of this study is to run cross-sectional studies focusing on the characteristics of 2-dimensional clinical visual functions in FOG and non-FOG PD patients. The study is examining the visual resolution and localization capabilities of PD patients for 2-D visual stimuli. The 2-D visual functions will be visual acuity for high and low contrast letters and contrast sensitivity for low spatial frequencies in both daylight (photopic) and dim light (mesopic) conditions. The 2-D localization capabilities will be assessed by Vernier acuity for both vertical and horizontal offsets in daylight (photopic) and dim light (mesopic) conditions. This ability could be differentially affected in patients who experience gait freezing and contribute to their inability to judge their lateral position relative to any edges in the scene.

Measuring these visual functions in the same group of patients may help us to determine whether the patterns of damage are due to dorsal pathway (i.e. visual acuity and contrast sensitivity under photopic condition) or ventral pathway (i.e. Vernier acuity and visual resolution under mesopic vision) in PD patients, and whether these deficits could contribute to freezing of gait disorders.

4.4 METHODS

4.4.1 Procedures:

The testing procedures and protocols of the study were fully explained in details in Chapter 3. Briefly, high contrast visual acuity, low contrast visual acuity, contrast sensitivity and horizontal & vertical Vernier acuities were measured in random order. These visual tests were measured twice, first under a photopic condition and then under a mesopic condition (after 5 min of dark adaptation). All of these measurements were measured binocularly while participants wearing their habitual glasses or the modified optical refractive correction for the appropriate testing distance. Twenty-two FOG PD patients, 25 non-FOG PD patients and 25 healthy controls participated on this study. Table 3-1 (Chapter 3) list the subject demographics.

4.4.2 Data Analysis:

Comparison of different visual function tests under different lighting conditions were analyzed between groups using repeated measures analysis of variance (RMANOVA) model with the various tests and lighting conditions as the within subject factors and the three groups as the between-subjects factor. All pairwise between-group comparisons were evaluated with the Tukey's post hoc test. The second analysis was examining the relationships between different visual functions and the severity, duration, and MoCA scores in PD patients by calculating the Pearson correlation

coefficients. IBM SPSS ver. 24 was used for this data analyses. The criterion of $p \leq 0.05$ was used to determine a significant effect.

4.5 RESULTS

4.5.1 High and low contrasts visual acuities under photopic and mesopic conditions:

Table B1 (Appendix B) lists the means and standard error of the means (SEMs) for all groups. Figure 4-1 shows the means for the high and low contrast visual acuity for the two light levels. As expected, visual acuities were lower for low contrast letters ($F= 1061.66$, $DF =1$, $p<0.0001$), and lower light levels ($F= 881.226$, $DF=1$, $p<0.0001$). There was also a significant interaction in contrast by light levels ($F= 59.650$, $DF =1$, $p<0.001$) confirming that the low contrast acuity was affected more than high contrast acuity by the decrease in the light level.

The differences between groups was significant ($F= 15.632$, $DF =2, 69$, $p<0.001$). Pairwise multiple comparisons showed that the differences between healthy controls and both FOG and non-FOG PD groups reached to statistically significant levels ($p < 05$). However, the differences between FOG and non-FOG groups approached, but did not reach the significant level ($p=0.091$). Two interactions that included groups were significant. First, there was significant interaction between groups and contrast levels ($F=4.034$, $DF =2, 69$, $p=0.022$), and significant interaction between groups and light levels ($F=8.334$, $DF =2, 69$, $p=0.001$); however, the interaction between

different contrasts, light levels, and groups was not significant ($F=1.219$, $DF = 2, 69$, $p = 0.302$). Taken together, the data showed that both non-FOG and FOG had lower high and low contrast visual acuity than HC. Lowering the light level reduces low contrast visual acuity in FOG PD group more than other two groups, and non-FOG PD was lower than HC. However, reduction in high contrast visual acuity after lowering light level was almost equal across groups.

High and Low Contrast Visual Acuity under Photopic and Mesopic Conditions

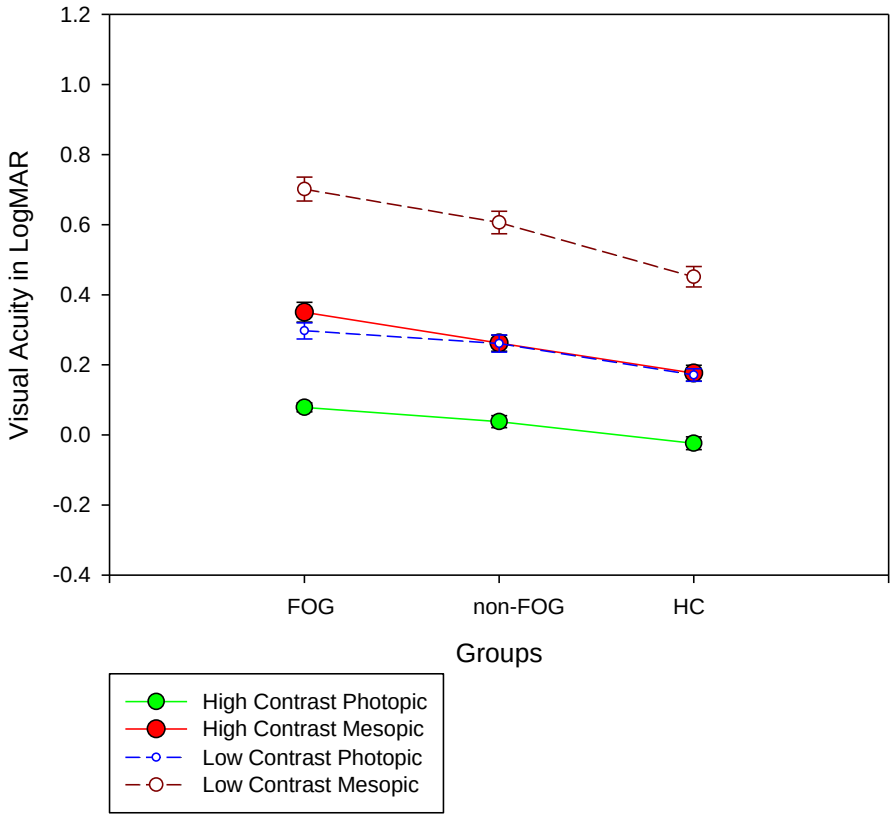


Figure 4-1: Means plot of visual acuity for each group

Error bars represent the standard error of the means

4.5.2 Pelli-Robson contrast sensitivity under photopic and mesopic conditions:

Table B2 (Appendix B) lists the means and standard error of the means (SEMs) for all groups. Figure 4-2 shows the Pelli-Robson contrast sensitivity results. As expected, the contrast sensitivity was significantly lower under low light levels ($F= 552.521$, $DF =1$, $p<0.0001$). The interaction between groups and light levels was significant ($F=10.533$, $DF =2, 69$, $p<0.0001$). Differences between groups were significant as well ($F= 34.982$, $DF =2, 69$, $p<0.001$). Pairwise multiple comparisons showed that differences was significant between healthy controls and both FOG ($p<0.001$) and non-FOG PD ($p=0.007$) groups respectively. The differences between FOG and non-FOG groups is significant as well ($p<0.001$). These results suggest that contrast sensitivity affected to greater extent in FOG PD patients than the other two groups, and non-FOG PD patients were affected more than HC after reducing the light level.

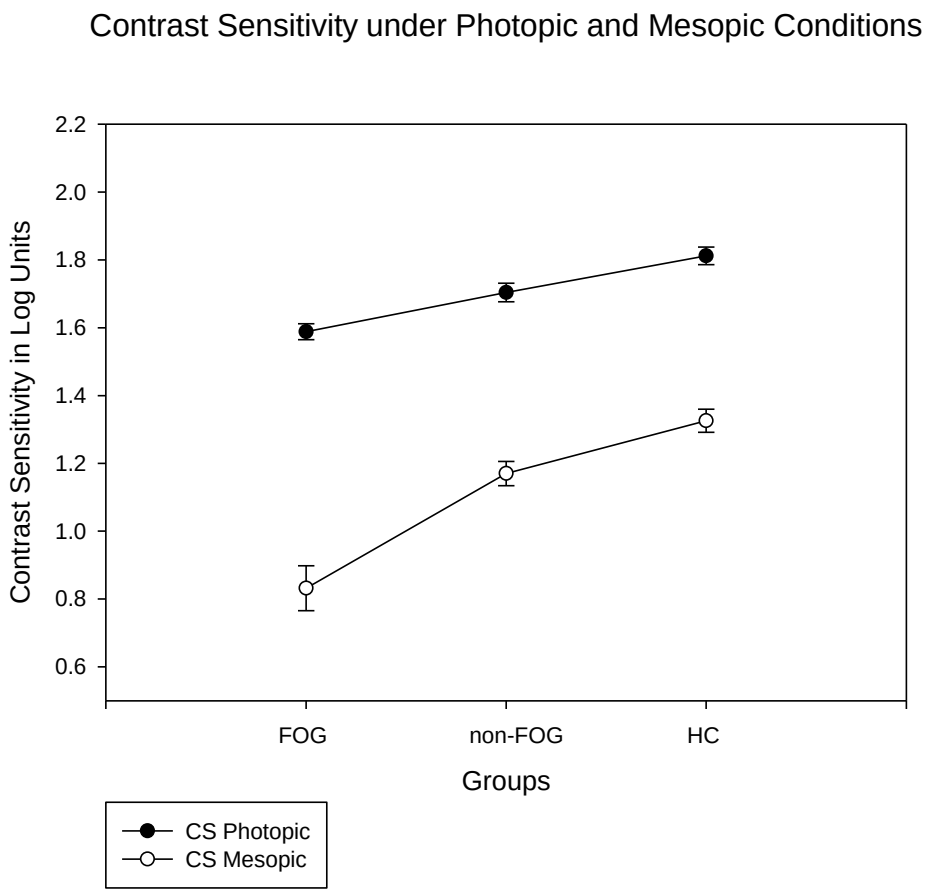


Figure 4-2: Means plot of Pelli-Robson contrast sensitivity for each group
Error bars represent the standard error of the means

4.5.3 Horizontal and vertical Vernier acuity under photopic and mesopic conditions:

Table B3 (Appendix B) lists the means and standard error of the means (SEMs) for all groups. Figure 4-3 shows the results for the horizontal and vertical Vernier acuity under different light levels for all groups. Although the difference was small, the vertical Vernier acuity was significantly larger (worse) than horizontal Vernier acuity ($F= 5.094$, $DF =1$, $p= 0.027$). In addition, Vernier acuities were larger (worse) in low light levels ($F= 257.172$, $DF=1$, $p<0.0001$). The interaction between different light levels and orientations within subjects was not significant ($F= 3.039$, $DF =1$, $p = 0.086$). This indicates that both horizontal and vertical Vernier acuities were affected similarly by low light levels.

The differences between groups were significant ($F= 20.472$, $DF =2, 69$, $p<0.001$). Pairwise multiple comparisons showed that differences were significant between healthy controls and both FOG ($p<0.001$) and non-FOG PD ($p=0.002$) groups respectively. The difference between FOG and non-FOG groups was significant as well ($p=0.013$).

The analysis revealed a significant interaction between groups and different light levels ($F=14.328$, $DF =2, 69$, $p<0.0001$), but not between groups and orientation ($F=1.34$, $DF =2, 69$, $p=0.268$) and the 3-way interaction between light level, orientation, and group ($F=2.961$, $DF = 2, 69$, $p = 0.061$), although the latter result was approaching significance. Taken together, the data showed that the non-FOG and

FOG had lower Vernier acuity with FOG having the lowest. Lowering the light level reduces Vernier acuity, especially for the PD groups, and there was the suggestion that HC and non-FOG had better horizontal Vernier acuity, especially at the lower light level, whereas the FOG subjects did not show this difference.

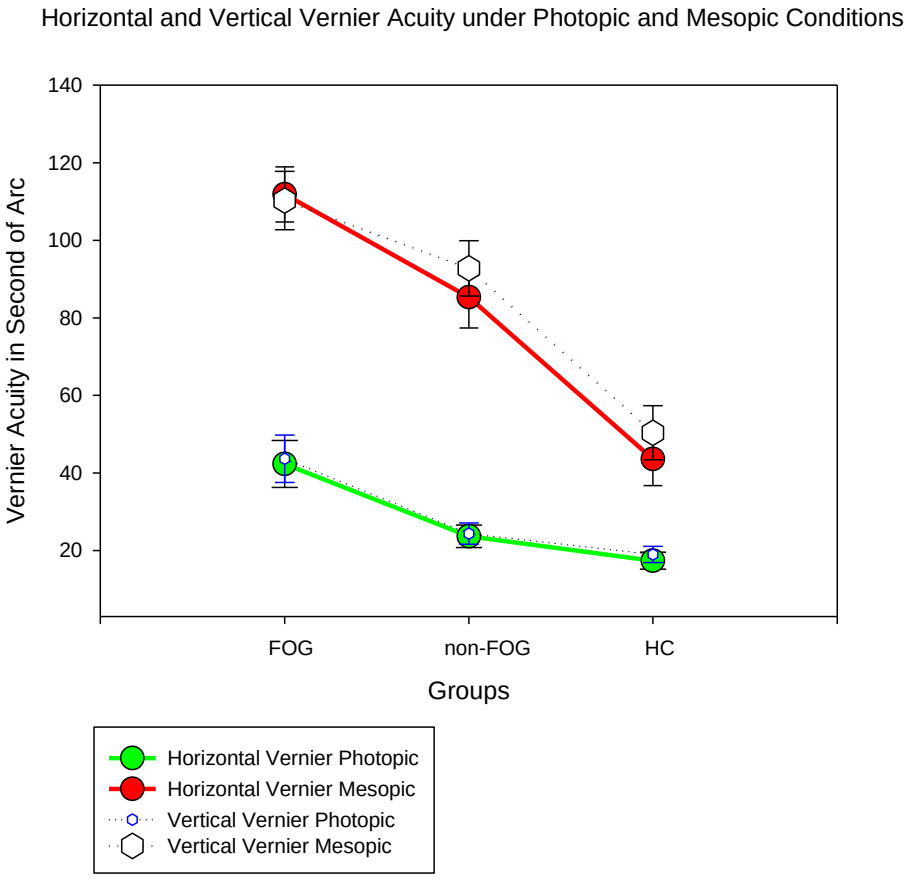


Figure 4-3: Means plot of horizontal and vertical Vernier acuity for each group Error bars represent the standard error of the means

4.5.4 Relationships between different visual functions and severity, duration, and cognitive abilities of PD Patients:

Relationships between different visual function tests under different conditions with severity (UPDRS score) of the disease, duration of the disease and the cognitive status (MoCA) score were tested by performing Pearson correlation coefficients for FOG and non-FOG PD patient groups separately. None of the visual function tests correlated significantly with severity, duration, or the cognitive status of the FOG PD group. The results for the non-FOG PD patient group were similar for most of the tests. There were two exceptions to this general trend. First, there was a weak positive, but significant correlation ($\rho = 0.397$, $p=0.049$) between MoCA score and contrast sensitivity score under dim lighting condition. Second, there was a negative correlation between MoCA score and horizontal Vernier acuity under bright light condition ($\rho = - 0.444$, $p=0.028$).

These results suggest that the deficits in different visual function tests under different conditions are independent of the severity, duration, and the cognitive status of the disease if they have FOG symptoms. This trend generally held for the non-FOG although contrast sensitivity in low light levels and Vernier acuity for horizontal displacement decreased as their cognitive scores decreased.

4.6 DISCUSSION

To my knowledge, this is the first study to examine different visual functions on the same individuals of PD patients using 2-D clinical tests under different light levels with respect to freezing of gait symptom. Both PD groups showed a greater reduction in all visual functions relative the health controls with the FOG usually having the larger reduction.

Multinomial logistic regression was conducted using all of visual resolution tests and light levels in order to determine the best discriminant parameters between groups. The results showed that the final logits regression model adequately fits our data (Chi-square test = 78.584, DF=20, $p<0.0001$). Table 4-1 shows the rank order of the different visual resolution tests that could best discriminate different subject groups. Contrast sensitivity under low light level was the best discriminant among other parameters between groups and the top five predictors were either a low contrast visual resolution task or a relative spatial judgment. Although the photopic high contrast acuities were reduced in the PD patients, the test was poor in discriminating between the two PD groups.

Table 4-1: The rank order of different visual resolution tests that can discriminate groups

Test	Chi-Square	DF	P value
Intercept	7.448	2	0.024*
Contrast Sensitivity Mesopic	16.704	2	0.000*
Vertical Vernier Acuity Mesopic	8.424	2	0.015*
Low Contrast VA Photopic	6.975	2	0.031*
Horizontal Vernier Acuity Mesopic	6.638	2	0.036*
Horizontal Vernier Acuity Photopic	5.790	2	0.055
Vertical Vernier Acuity Photopic	4.519	2	0.104
High Contrast VA Mesopic	2.115	2	0.347
Contrast Sensitivity Photopic	1.535	2	0.464
High Contrast VA Photopic	0.475	2	0.788
Low Contrast VA Mesopic	0.170	2	0.918

* The parameter shows significant effect between groups

Table 4-2 shows the parameter estimates for the two PD patient groups when they are compared separately with the healthy controls using the different parameters on Table 4-1. We can clearly predict that healthy controls can significantly perform better than FOG PD patient group on Pelli-Robson contrast sensitivity test under mesopic condition and this parameter was the best discriminant between these two groups. However, this parameter is not as good discriminator between non-FOG PD group and HC. This clearly suggests that contrast sensitivity under low light level affected to greater extend among FOG PD patients.

Table 4-2: The visual resolution parameter estimates of two PD patient groups to healthy controls

Group	Test	B	DF	P value
FOG	**Intercept**	32.694	1	0.041*
	Contrast Sensitivity Mesopic	-15.591	1	0.016*
	Vertical Vernier Acuity Mesopic	-0.146	1	0.037*
	Low Contrast VA Photopic	-19.879	1	0.198
	Horizontal Vernier Acuity Mesopic	0.162	1	0.035*
	Horizontal Vernier Acuity Photopic	-0.245	1	0.032*
	Vertical Vernier Acuity Photopic	0.19	1	0.091
	High Contrast VA Mesopic	11.73	1	0.252
	Contrast Sensitivity Photopic	-8.854	1	0.288
	High Contrast VA Photopic	6.3	1	0.59
	Low Contrast VA Mesopic	1.399	1	0.883
Non-FOG	**Intercept**	4.112	1	0.589
	Contrast Sensitivity Mesopic	-0.943	1	0.745
	Vertical Vernier Acuity Mesopic	0.009	1	0.735
	Low Contrast VA Photopic	6.8	1	0.318
	Horizontal Vernier Acuity Mesopic	0.026	1	0.305
	Horizontal Vernier Acuity Photopic	-0.112	1	0.125
	Vertical Vernier Acuity Photopic	0.007	1	0.89
	High Contrast VA Mesopic	-0.92	1	0.882
	Contrast Sensitivity Photopic	-3.133	1	0.425
	High Contrast VA Photopic	-0.446	1	0.955
	Low Contrast VA Mesopic	2.346	1	0.685

* The parameter shows significant effect between groups

Another way to examine the ability of the tests to discriminate between the 3 groups is to examine the association between high contrasts VA under photopic condition with other visual resolution tests. Table 4-3 shows the Pearson correlation values for all groups. The majority of the correlations were significant except the shaded cells on table 4-3. The relatively good correlations between clinical visual acuity and most of the other tests indicates that high contrast acuity may be the only test necessary to predict resolution capabilities for a variety of different stimuli. The exceptions are the mesopic contrast sensitivity and mesopic Vernier (horizontal) acuity. The lack of a significant correlation between these results and clinical visual acuity combined with the multinomial logistic regression suggests that PD should have their contrast sensitivity and/or Vernier acuity assessed under mesopic conditions in order to get a more complete picture of their basic visual function.

Table 4-3: Correlation between high contrast VA under photopic condition with other visual resolution tests.

Test	High Contrast VA under Photopic Condition		
	FOG	**Non-FOG**	**HC**
Low Contrast VA Photopic	0.801**	0.657**	0.799**
High Contrast VA Mesopic	0.643**	0.529**	0.842**
Low Contrast VA Mesopic	0.703**	0.558**	0.606**
Contrast Sensitivity Photopic	-0.298	-0.594**	-0.408*
Contrast Sensitivity Mesopic	-0.578**	-0.273	-0.365
Horizontal Vernier Acuity Photopic	0.550**	0.596**	0.616**
Vertical Vernier Acuity Photopic	0.493*	0.641**	0.442*
Horizontal Vernier Acuity Mesopic	0.545**	0.370	0.481*
Vertical Vernier Acuity Mesopic	0.496*	0.446*	0.507**

* Correlation is significant at 0.05 level
** Correlation is significant at 0.01 level

This study found that best corrected high contrast visual acuity in PD patient was relatively worse than healthy controls, which was consistent with some studies (Nowacka et al. 2014, Repka et al. 1996, Jones et al. 1992), but not others who did not find a difference (Regan and Neima, 1984; Tzoukeva, et al. 2008). Although our results were significantly different, the difference in the mean high contrast acuities between the healthy controls and non-FOG subjects was only 0.062 LogMAR, which was only 3 letters different. One of the reasons for the small difference was that the inclusion criterion restricted individuals to an acuity of 0.2 LogMAR (6/9) or better and so are range of acuities within sample was small.

The reduction in contrast sensitivity shown in our PD subjects agreed with all of the previous studies regardless that different studies used different contrast sensitivity

tests (Hutton et al., 1991, Bodis-Wollner et al., 1987; Harris, Calvert, & Phillipson, 1992; Tzoukeva et al, 2008). This decrease was even larger in low light levels and in FOG group. Although none the previous studies compared contrast sensitivity in FOG with non-FOG or health controls. Davidsdottir et al, (2005) found that the severity of FOG correlated with losses in contrast sensitivity especially at lower spatial frequencies. Interestingly, they reported that the loss in contrast sensitivity was a better predictor of the freezing of gait severity than motor impairments (Davidsdottir, Cronin-Golomb, & Lee, 2005). We did not find a relationship between the severity of FOG symptoms and visual function because our sample had generally mild-to-moderate FOG. Nevertheless, the result that contrast sensitivity was the best discriminator between the groups was consistent with their findings that contrast sensitivity could be a very good predictor of FOG symptoms.

Previous studies showed that reductions in visual acuity and contrast sensitivity were associated with the severity PD, but only in the moderate-to-severe cases (Jones et al., 1992; Repka, Claro, Loupe, & Reich, 1996; Hutton et al., 1991; Bodis-Wollner et al., 1987; Harris, Calvert, & Phillipson, 1992). Although we found reductions in visual resolution tasks in the PD groups, there was no correlation between the reduction and severity of the disease. The lack of association in our study could be due to that all of our PD patients were either mild or moderate cases, and there were no severe cases.

Vernier acuity is believed to be mediated by the magno pathway (Kéri et al., 2004; Kéri & Benedek, 2009; Livingstone & Hubel, 1994), although there is not general

agreement (Skottun & Skoyles, 2010). Our results for the healthy controls showing a significant decrease in acuity under low light level was consistent with a previous study (Livingstone & Hubel, 1994). Vernier acuity in PD has not been reported before. Orientation discrimination in PD patients showed a loss in both horizontal and vertical oriented bars compared to healthy controls, but the difference was bigger and significant for horizontal bars only (Trick et al., 1994). This suggests that vertical Vernier acuity should be worse. Our results showed PD patients showed significant loss in both horizontal and vertical oriented Vernier acuity compared to healthy controls, but there was not a clear difference between the horizontal and vertical acuities. The vertical Vernier acuity tended to be worse than the horizontal acuity for healthy controls and non-FOG at the low light level, but the relative difference was similar for both groups, and the difference only approached statistical significance. Trick et al. did not specify the luminance of their monitor and so it is difficult to determine whether the lack of difference in our study was due to a lack of statistical power or whether any orientation specific loss of Vernier acuity in non-FOG PD subjects is luminance dependent. If it is the latter case, then the selective positional discrimination losses suggested for non-FOG subjects may occur at a higher light level than healthy controls.

The reduction in resolution is consistent with the hypothesis that the receptive fields of the ganglion cells are larger in PD due to retinal dopaminergic reduction (Bodis-Wollner, 2013; Brandies & Yehuda, 2008). Retinal imaging technique showed that different retinal layers are thinner in PD patients relative to control subjects (Simao,

2013). The thinning was more in the proximal layers of the retina, which is consistent with loss of dopaminergic amacrine cells in retina (Chorostecki et al., 2015). Polo et al (2016) reported that the reductions in visual acuity and contrast sensitivity correlated with the structural changes of the retinal layer in PD patients, especially the retinal ganglion cells layer. Contrast sensitivity was the most affected visual function that was correlated with the structural changes in the retina of PD patients (Polo et al., 2016).

Assuming that the ganglion receptive field follows the difference of Gaussian model, reducing the strength of the antagonistic surround would reduce visual resolution, but it would also increase the sensitivity of the center of the receptive field and result in an increase in contrast sensitivity at lower spatial frequencies, or certainly no change in contrast sensitivity. Our results suggest that there is an overall reduction in the receptive field sensitivity in addition to a potentially greater loss of the antagonistic surround.

Our results, combined with the evidence of retinal thinning suggest that PD results in a general reduction in contrast sensitivity that is equivalent to placing a neutral density filter in front of the eye. Our photopic data suggest that the density of the filter is no greater than 1.0 for the FOG-PD because their mean photopic resolution acuity and contrast sensitivity were reduced relative to HC, but not as much as was found for HC when they viewed through the 1.0 ND filter. However, the reduction in FOG Vernier acuity is approximately equal to the corresponding value for the HC when viewing through a 1.0 ND filter. The non-FOG PD did not show as large of a

loss so that their equivalent filter would be less dense. Reducing the light levels to the mesopic region would then have a larger effect on the PD subjects because their sensitivity is already lower. The reduction in Vernier acuity could be due to less precise positional information leaving the retina because the ganglion cell receptive fields are larger.

It is well established that PD is characterized by oculomotor dysfunction which could affect their ability to fixate on a target of regard (Antoniades et al., 2015; Chan et al., 2005). Another theory for reduction in visual acuity in PD patients is that the decreased acuity is due to abnormal fixational eye movements (Armstrong, 2011). We cannot rule this possibility out, but our results suggest that if there are abnormal fixational eye movements, the problem worsens in low light.

PD patients are usually treated with dopaminergic medications such as dopamine agonists to enhance the release of dopamine in basal ganglia, or by the anticholinergic medications to reduce the acetylcholine levels, or by combination of both kinds of treatment (Naylor, 2005). There are several ocular and visual adverse reactions to these treatments that has been already reported in PD patients. The most common adverse reactions are loss of visual acuity, blurry vision, dry eye, photophobia, visual hallucinations, reduced accommodation, nystagmus, and reduced saccadic eye movements (Friedman & Neumann, 1972; Michell et al., 2006; Pearlman, Kadish, & Ramseyer, 1977; Peters et al., 2000; Spiers, Calne, & Fayers, 1970). Thus, it is

possible that the reduction in different visual resolution tasks among our PD patients is secondary to their treatment effects on the visual system.

Measuring different visual resolution tests under two different light levels in the same group of patients can help us to determine whether the pattern of damage is due to dorsal pathway (magno) or ventral pathway (parvo) in PD patients, and whether this damage contribute to freezing of gait disorders. The general losses found in our study suggest that both the magno and parvo pathways are affected. However, the result that the Pelli Robson contrast sensitivity at low light levels and the Vernier acuity were the best at distinguishing between the 3 groups suggests that the FOG subjects had a larger deficit in the magno pathway. This conclusion is consistent with a previous study (Lord et al., 2012).

Regardless of our interpretation of the results, the result that FOG had larger reduction in visual function at low light levels suggests that they should have an increase in their FOG episodes under dim lighting conditions (i.e. street light level).

Chapter 5
BINOCULAR VISION CHARACTERISTICS (STEREOPSIS AND FIXATION DISPARITY) IN FREEZING AND NON-FREEZING PARKINSON'S DISEASE PATIENTS

5.1 SUMMARY

This study is measuring some of the binocular vision characteristics in FOG PD, non-FOG PD patients, and age matched healthy controls. Binocular vision measurements include local and global stereopsis using different clinical stereo tests, along with fixation disparity and fixation disparity curves. The fixation disparity measures are primarily an assessment of the vergence motor system and the clinical stereo tests assess the combined effects of motor and sensory aspects of binocular vision. Results from this study showed that FOG group had worse stereopsis than non-FOG group, and non-FOG group had worse stereopsis than healthy controls. The impairment of global stereopsis was more common than local stereopsis in PD patient groups. The reduction in stereopsis among PD patients was not associated with fixation disparity. The results suggest that measuring stereopsis could be used to monitor progression of non-motor symptoms in PD patients.

5.2 INTRODUCTION

Normal binocular single vision is defined by the Dictionary of Visual Science, as "*the use of both eyes simultaneously in such a manner that each retinal image contributes to the final precept"* (Hofstetter, 2000). Binocular vision was classified by Worth into

three degrees or levels, which is referred to as Worth's classification of binocular vision. The first degree is *Simultaneous Perception*, which is the perception of the two images of an object of regard from both eyes at the same time. The second degree is *Fusion*, which is the formation of a single image by combining the two images. Fusion is sub-categorized into sensory fusion and motor fusion. Sensory fusion is the ability of blending the two images into one. Motor fusion is the ability to align the eyes so that the image in each eye falls within a specified area of each retina. The third degree is *Stereoscopic Vision*, which is the ability to perceive fine relative depth from the two retinal images (cited by Rutstein, 1998; Steinman, 2000; and Rowe, 2012).

Stereopsis arises from the integration of slightly different information from each eye in the visual cortex (Howard, 1995). Stereopsis is considered the highest level of binocular visual function that can be assessed clinically (Rutstein, 1998; Steinman, 2000; and Rowe, 2012). Stereopsis can be measured using simple shapes, which is called local or "*contour*" stereopsis, or using random dot or "*global*" stereopsis. Chapter 1 describes these two types of stereoscopic vision in more detail.

Suprathreshold global stereopsis using complex patterns is impaired in advance stages of PD patients (Flowers & Robertson, 1995). This study suggests that the deficit in global stereopsis is not due to the dopaminergic retinal reductions in PD patients; instead, it is mainly due to cortical dysfunction (Flowers & Robertson, 1995). Contour stereopsis is impaired as well in PD patients and the deficit in stereopsis is

associated with visual cognitive abilities and motor disturbances of patients, which suggests there is relationship between the dopaminergic reduction and stereopsis dysfunction in PD patients (Kim et al., 2011). The reduction in contour stereopsis is also associated with failure on color vision tests which suggests that the deficit in stereopsis may due to degradation of the one, or both, monocular images at the retinal level in PD patients (Sun et al., 2014).

Although the previous studies showed that both contour and global stereopsis could be affected in PD, no one has compared both global and contour stereopsis for the same group of patients. It is possible that global and contour stereopsis could be differentially affected in freezer and non-freezer PD patients because of how the two types of depth perception information are processed. If they are equally affected, then there may be either a sensory-integration deficit in visual areas or problems in controlling vergence eye movements. Regardless, of the underlying cause, determining the threshold for global and contour stereopsis may be useful in monitoring the progression of the disease and may be a predictor of mobility in more complex environments.

Impairment of any of the depth perception cues, as well as, impairment in the integration between the visual and motor systems in PD patients could lead to further movement disorders. It was found that FOG-PD patients had more errors in distance estimation of a remembered target during both static and dynamic conditions than non-FOG PD patients and healthy controls (Martens et al., 2014). These results suggested that the motor disturbances that cause freezing of gait disorders could be

due to two different perceptual impairments; the visuospatial (vision only) and visuomotor (vision and proprioception) deficits.

Vergence eye movements are affected in PD patients (Hanuška et al., 2015). One way to evaluate the vergence system is to measure the fixation disparity curve. The fixation disparity curve measures vergence adaptation. Moreover, it is important to look at how the fixation disparity data relates to stereopsis dysfunction in PD patients because a vergence eye movement deficit could contribute to reduced stereopsis. To my knowledge, fixation disparity and fixation disparity curves have not been investigated in PD patients.

5.3 AIM OF THE STUDY

The purpose of this study is to assess the 3-dimensional clinical visual functions in FOG and non-FOG PD patients by measuring local (contour) and global (random dot) stereopsis. Impaired stereopsis could lead to reduced mobility because PD individuals, especially FOG patients, have difficulty judging relative distances of objects; therefore, it is possible that FOG patients have larger depth perception deficits than non-FOG patients and healthy controls.

Fixation disparity assesses the ability to control eye alignment when viewing an object with both eyes. Reduced depth perception could be due to an inability to maintain adequate alignment of the two eyes rather than a sensory or cognitive problem. Thus, fixation disparity is important to determine in PD patients. Moreover,

the fixation disparity curve may also provide further insight into any impairment of their vergence system in PD patients.

5.4 METHODS

5.4.1 Procedures:

Local and global stereopsis were measured with different clinical tests in random order. The stereo tests were, Circles Test, Random dot Butterfly Test, MKH-Haase Line Test, MKH-Haase Steps Test, TNO Test and Random dot Randot 3 Test. For each test, stereoacuity for crossed disparities was measured before uncrossed disparities. Chapter 3 describes the tests in more detail. After completing the stereopsis tests, the horizontal fixation disparities and fixation disparity curves were measured using the using the Saladin Near Point Card. Participants viewed all tests binocularly while wearing their habitual glasses or the modified optical refractive correction for the given test. Chapter 3 describes the testing procedures. Participants of this study were the same of those who participated on the previous study.

5.4.2 Data analysis:

There were a number of participants who could not resolve the maximum stereo disparity on a given global stereo test. For these participants, a value twice the maximum disparity for that given test was assigned. All participants could perceive at least the maximum disparity on the local tests.

Because the range of disparities on the various stereoacuity tests was limited, the stereoacuity values were not normally distributed. As a result, statistical significance between groups was determined using non-parametric statistical tests.

Results of stereoacuity tests between groups were analyzed according to the following methods. First, comparisons between groups for each stereo test were analyzed by using non-parametric ANOVA on the Ranks test. All pairwise, comparisons were measured by Dunn's method. Second, because the minimum disparity and step size varies across tests, the number of participants who attained the minimum stereo threshold, the number of participants who attained 60 sec arc or better, and number of participants who failed to resolve the maximum stereo threshold of a given test were determined. Statistical analysis across groups was carried out by using the Chi-square test based on the number of subjects who attained 60 sec arc, or better, for all local and global stereo tests. The 60 sec arc criterion was used because it is usually considered to define the upper limit of normal stereopsis in clinical settings (Kim et al., 2014).

The time to complete each test was also recorded. A value of 90 seconds was assigned to all subjects who could not see the maximum disparity on a given test. These data were analyzed using a One Way ANOVA test. Tukey's post-hoc test was used to perform the pairwise multiple comparisons. The relationships between different

stereoacuity tests and the severity, duration and MoCA scores in PD patients were examined by running Pearson correlation coefficients.

For each stereoacuity test, except the Random dot Butterfly Test, both crossed and uncrossed stereopsis were measured. Direct comparisons between the two disparities, after pooling all of the three subjects groups together, were performed by running the Signed Ranks test for each test separately. Results showed that the crossed disparity results were significantly lower than the uncrossed disparities on the Circles Test, Line Test and Steps Test. Although the median values for the crossed disparities were smaller on Random dot Randot 3 Test, and TNO Test, they did not reach statistical significance. Because there were statistical differences between crossed and uncrossed disparities for some tests and a similar trend was present on other tests, the crossed and uncrossed stereoacuity for each test were analyzed separately.

The parameters of the fixation disparity curve that were analyzed included the amount horizontal fixation disparity (Y-intercept), the amount of horizontal associated phoria (X-intercept), and the slope of the curve. Because these parameters were not normally distributed, ANOVA on Ranks test was performed to compare the differences between groups. The curve type was also considered between groups by counting the number of participants who have different types of curves. Differences between groups in terms of curve types' frequencies were tested by applying Chi-square test. Finally, correlation between the amount of fixation disparity and different

stereoacuity scores were performed using non-parametric Spearman correlation coefficients. The criterion of $p \leq 0.05$ was used to determine a significant effect. IBM SPSS ver. 24 was used for this data analyses.

5.5 RESULTS

5.5.1 Comparison of local stereoacuity tests between groups:

Table C1 (Appendix C) lists the median, the minimum, the maximum, and the range of the two local stereoacuity tests for all groups. Non-parametric ANOVA on Ranks test showed the differences between groups were statistically significant for both Circles and Line tests. Table 5-1 shows the Ranks test results and all of the pairwise comparisons. Figures 5-1 and 5-2 show the box-plot graphs of Circles test-crossed and uncrossed disparities respectively where the all of the pairwise comparisons between groups were significantly different. Figure 5-3 shows the box-plot graph of Line test -crossed disparity where only significant pairwise comparisons were between the health controls and the two PD groups.

Table 5-1: ANOVA on Ranks tests of local stereoacuity tests between groups

Test	ANOVA	DF	P value	Pairwise Multiple Comparisons		
				Groups	Non-FOG	HC
Circles Crossed	32.35	2	<0.001	FOG	Yes	Yes
				Non-FOG		Yes
Circles Uncrossed	29.96	2	<0.001	FOG	Yes	Yes
				Non-FOG		Yes
Line Crossed	28.2	2	<0.001	FOG	No	Yes
				Non-FOG		Yes
Line Uncrossed	27.84	2	<0.001	FOG	No	Yes
				Non-FOG		Yes

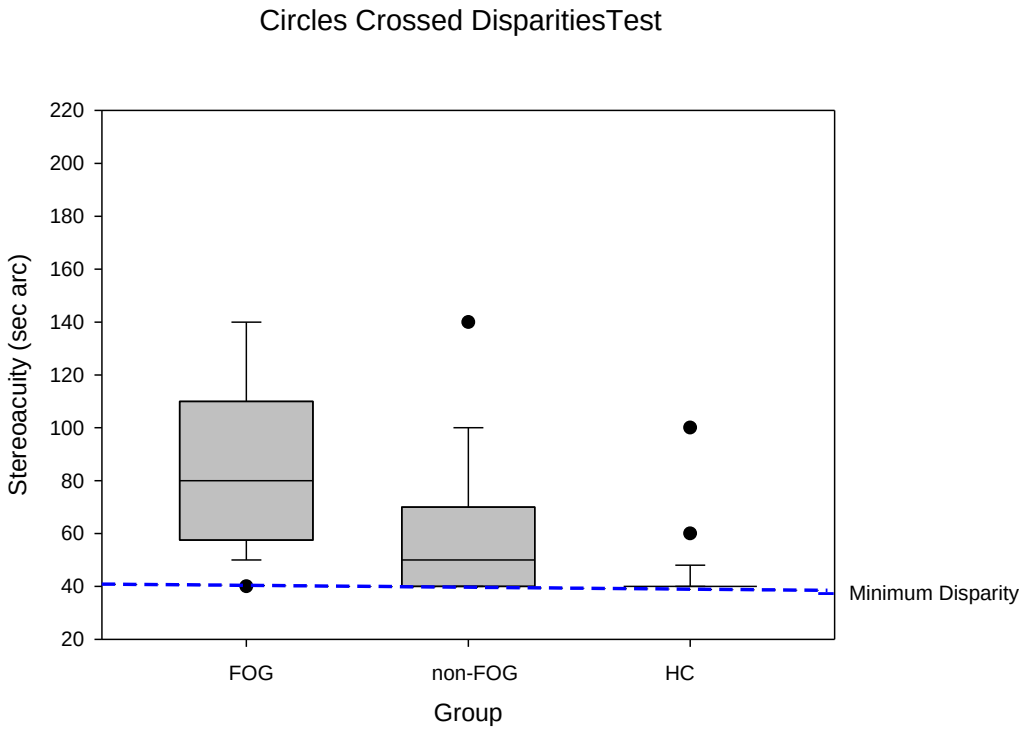


Figure 5-1: Box plot of the Circles Crossed Disparity test.The vertical bars represent 10% to 90% percentile, the box represents 25 % to 75% quartiles, the solid horizontal lines represent the medians, and the ● are the outliers, the blue dashed line represent the minimum stereoacuity level

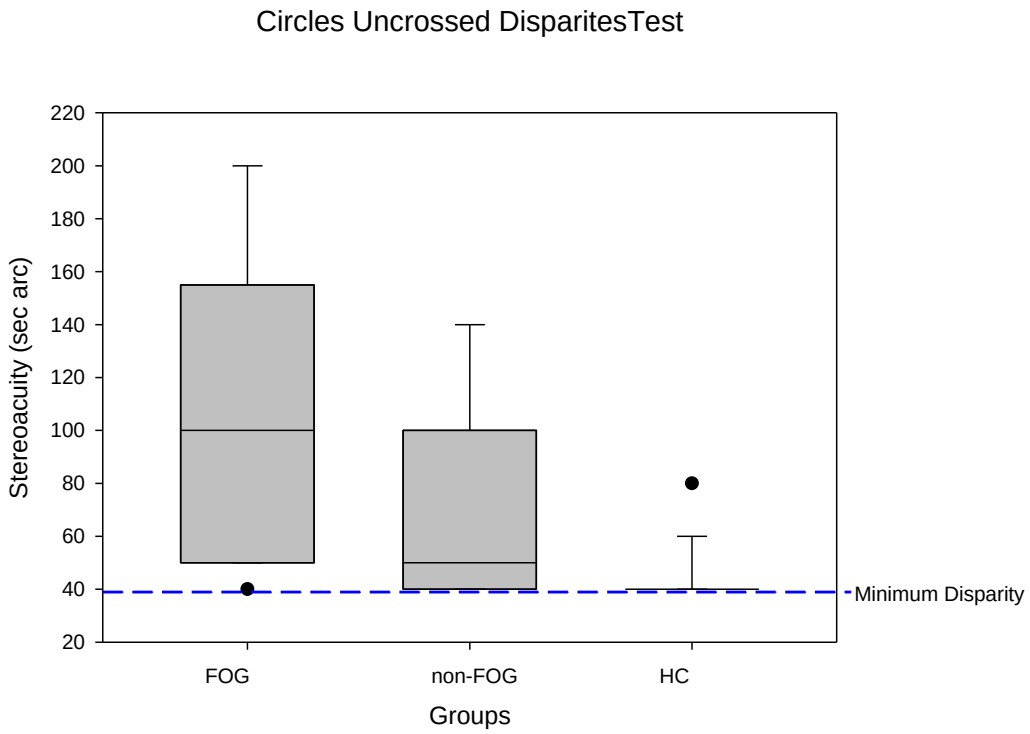


Figure 5-2: Box plot of the Circles Uncrossed Disparity test. The vertical bars represent 10% to 90% percentile, the box represents 25 % to 75% quartiles, the solid horizontal lines represent the medians, and the ● are the outliers, the blue dashed line represent the minimum stereoacuity level

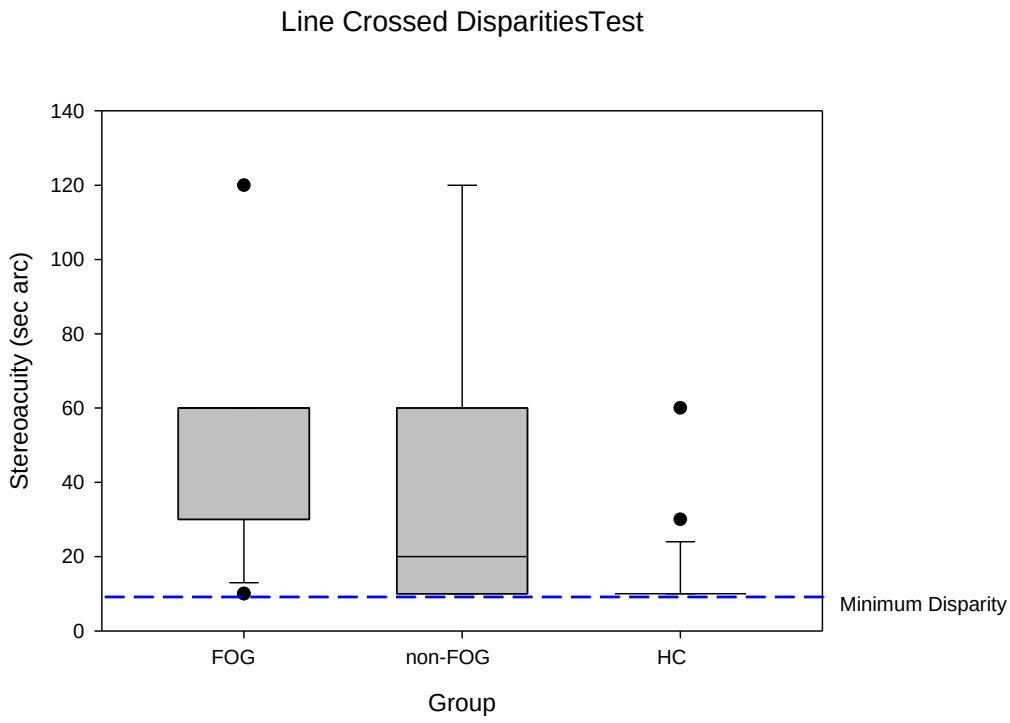


Figure 5-3: Box plot of the Line Crossed Disparity test. The vertical bars represent 10% to 90% percentile, the box represents 25 % to 75% quartiles, the solid horizontal lines represent the medians, and the ● are the outliers, the blue dashed line represent the minimum stereoacuity level

Table C2 (Appendix C) summarizes the results of number of participants who attained different stereoacuity levels on local stereo tests. Figure 5-4 shows the percentages of participants from each group who obtained 60 sec arc, or better, on both Circles and Line tests-crossed disparity respectively. The results of uncrossed disparity tests showed the same trends, that most of the subjects in each group could obtain at least 60 sec arc on the line test, whereas the percentage of PD subjects, especially the FOG, who could obtain that level on the Circles test was lower. Chi-square test showed that frequencies in each group were significantly different for the Circles test-crossed disparity (X^2 =17.96, DF= 2, and p=<0.001). However, Chi-square test did not show significant differences between the groups frequencies for the Line test-crossed disparity (X^2 =3.49, DF= 2, and p=0.174).

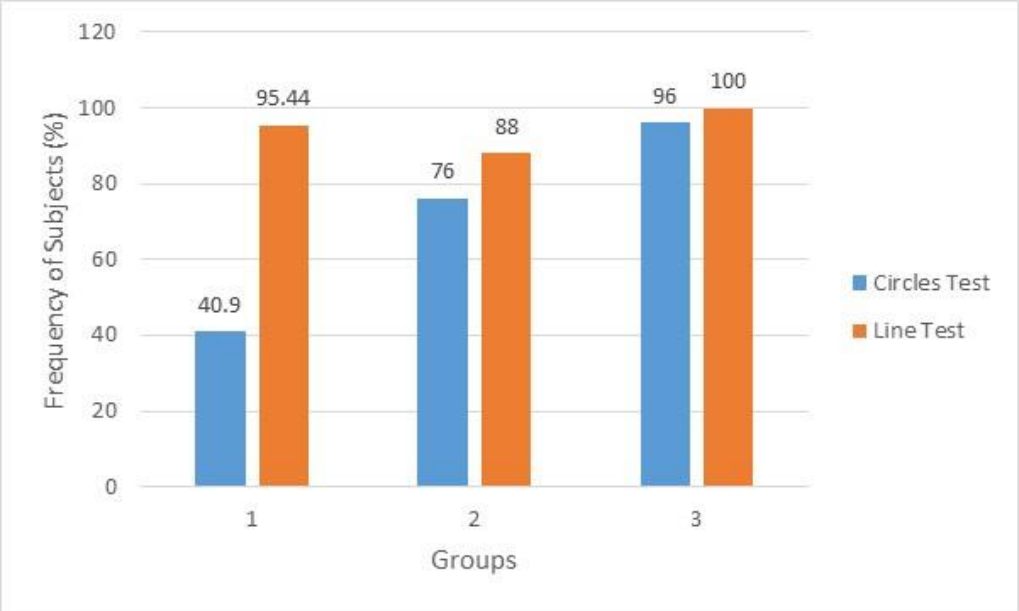


Figure 5-4: Vertical bars showed the percentages of subjects who resolved 60 sec arc or better on two contour stereoacuity tests for all groups

1: FOG PD, 2: non-FOG PD, 3: HC

Table C3 (Appendix C) shows the mean and standard error of the mean of the time that the participants needed to complete each local stereoacuity test. Figure 5-5 shows the mean times needed to complete each of crossed-disparity local stereoacuity tests for all groups. The one-way ANOVA test showed that the differences between groups were significant for both Circles and Line test for both crossed and uncrossed disparities. Pairwise multiple comparisons showed the healthy controls had significantly lower (i.e. faster) completion times than both FOG and non-FOG PD patient groups. Even though, the non-FOG PD patient group were, on average, faster than the FOG PD patient group with local stereo tests, the differences between the two PD patient groups were not statistically significant (Table 5-2).

Table 5-2: One-way ANOVA tests of times needed to perceive local stereoacuity tests between groups

Test	**ANOVA**	**DF**	**P value**	**Pairwise Multiple Comparisons**		
				Groups	Non-FOG	HC
Circles Crossed	4.67	2,69	0.013	FOG	No	Yes
				Non-FOG		Yes
Circles Uncrossed	7.17	2,69	0.001	FOG	No	Yes
				Non-FOG		Yes
Line Crossed	15.84	2,69	0.001	FOG	No	Yes
				Non-FOG		Yes
Line Uncrossed	16.37	2,69	0.001	FOG	No	Yes
				Non-FOG		Yes

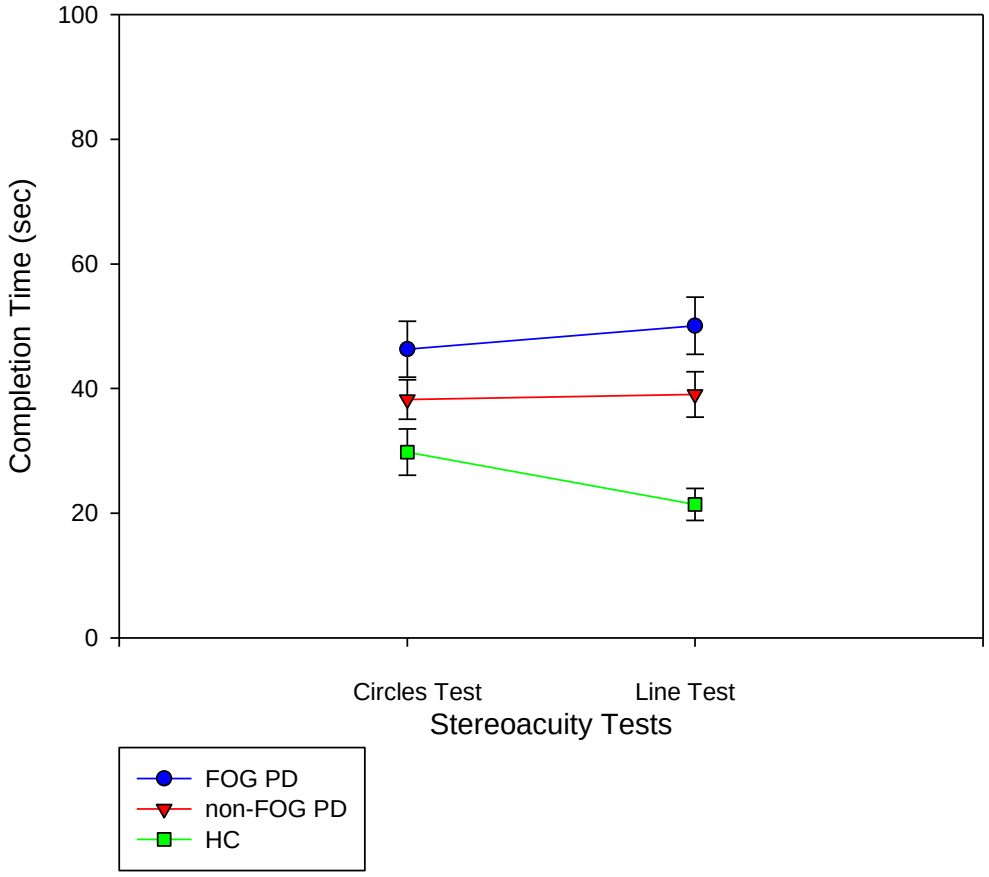


Figure 5-5: Means plot of completion time of crossed-disparity local stereoacuity tests for each group

Error bars represent the standard error of the means

5.5.1 Comparison of global stereoacuity tests between groups:

Because the random dot Butterfly test used very large stereo disparities, most of the participants from all groups could see the minimum disparity on that test. Only 4 FOG participants and 1 non-FOG participant could not see the minimum disparity (i.e. 700 sec arc) on Butterfly test. All participants from all groups could see the maximum disparity. Because all of the HC saw the minimum disparity, only the FOG and non-FOG were included in the Chi-square analysis. The frequencies of two patient groups who could see the minimum disparity were not significantly different (X^2= 2.4757; p=0 .115). Table C4 (Appendix C) lists the median, the minimum, the maximum, and the range of the global stereoacuity tests for all groups. Non-parametric ANOVA on Ranks test showed the differences between groups were statistically significant for Steps, Randot 3 and TNO global tests. Table 5-3 lists the differences between groups based on the median values and all of the pairwise comparisons. Figure 5-6 shows the box-plot graph of TNO test-crossed disparity where the all of the pairwise comparisons between groups were significantly different. Figures 5-7, and 5-8 show the box-plot graph of Steps test-crossed disparity and Randot 3 test-crossed disparity respectively where the pairwise comparisons showed significant differences only between the control group and the two PD groups. In addition to having lower stereoacuity, the figures show that very few of the FOG subjects could perceive the maximum disparity on any of the tests.

Table 5-3: ANOVA on Ranks tests of global stereoacuity tests between groups

Test	ANOVA	DF	P value	Pairwise Multiple Comparisons		
				Groups	Non-FOG	HC
Steps Crossed	35.72	2	<0.001	FOG	No	Yes
				Non-FOG		Yes
Steps Uncrossed	34.98	2	<0.001	FOG	No	Yes
				Non-FOG		Yes
Randot 3 Crossed	30.56	2	<0.001	FOG	No	Yes
				Non-FOG		Yes
Randot 3 Uncrossed	29.32	2	<0.001	FOG	No	Yes
				Non-FOG		Yes
TNO Crossed	29.24	2	<0.001	FOG	Yes	Yes
				Non-FOG		Yes
TNO Uncrossed	27.26	2	<0.001	FOG	Yes	Yes
				Non-FOG		Yes

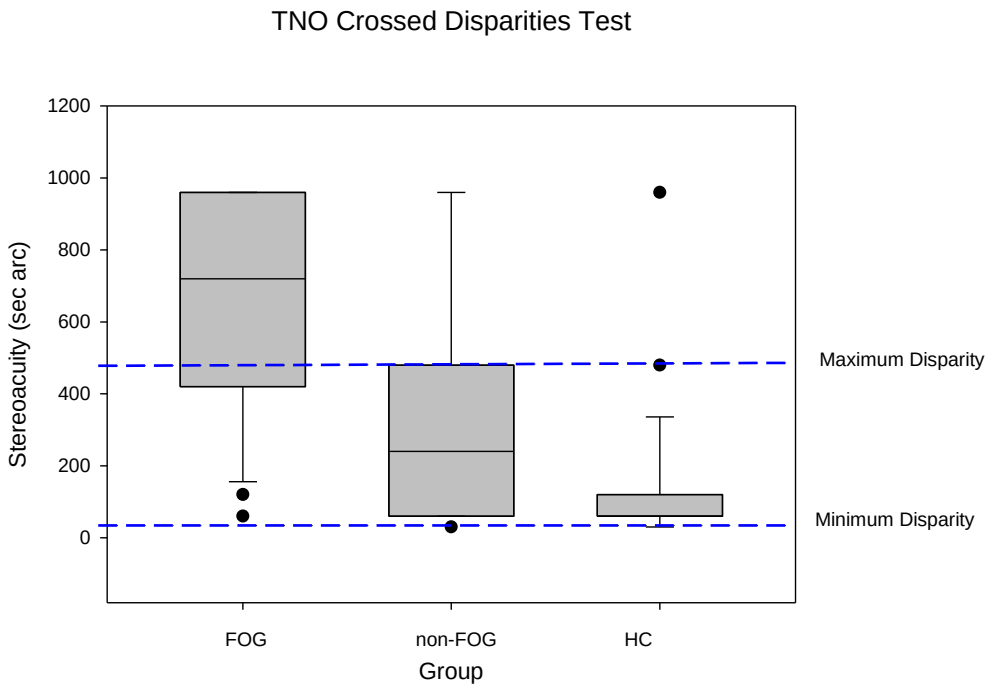


Figure 5-6: Box plot of the TNO Crossed Disparity test. The vertical bars represent 10% to 90% percentile, the box represents 25 % to 75% quartiles, the solid horizontal lines represent the medians, and the ● are the outliers, the blue dashed lines represent the minimum and maximum stereoacuity levels

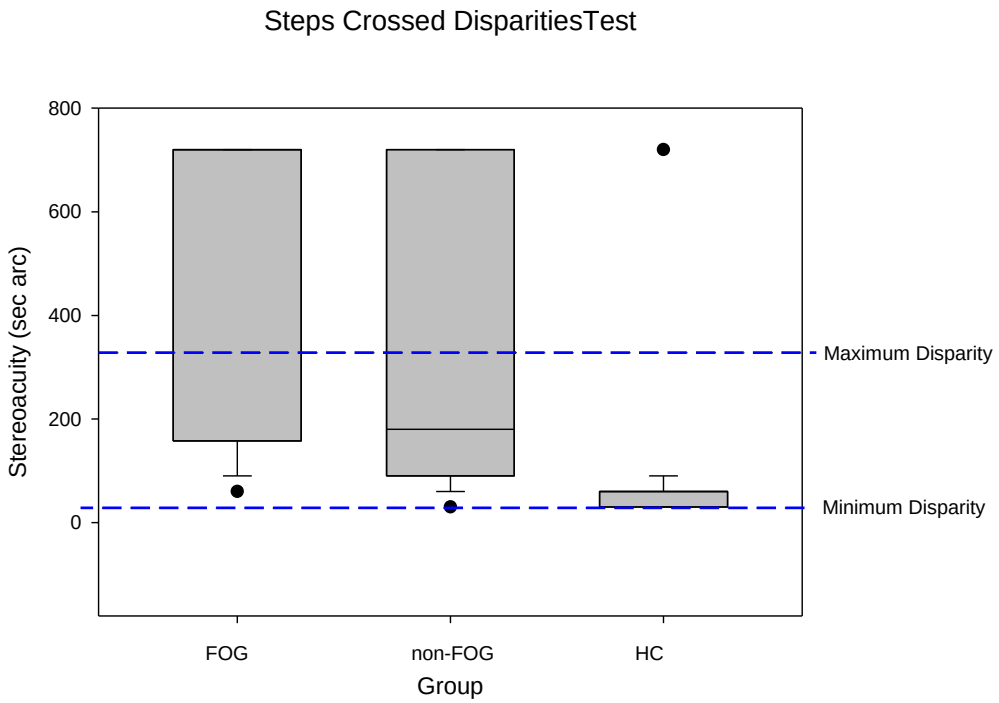


Figure 5-7: Box plot of the Steps Crossed Disparity test. The vertical bars represent 10% to 90% percentile, the box represents 25 % to 75% quartiles, the solid horizontal lines represent the medians, and the ● outliers, the blue dashed lines represent the minimum and maximum stereoacuity levels

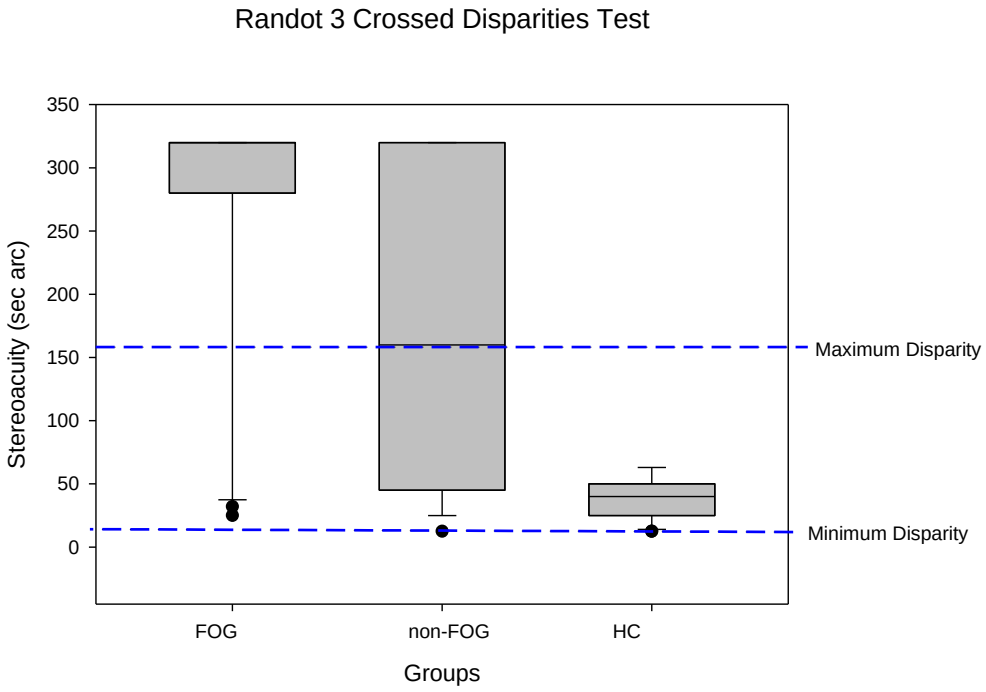


Figure 5-8: Box plot of the Randot 3 Crossed Disparity test. The vertical bars represent 10% to 90% percentile, the box represents 25 % to 75% quartiles, the solid horizontal lines represent the medians, and the ● are the outliers, the blue dashed lines represent the minimum and maximum stereoacuity levels

Table C5 (Appendix C) summarizes the results of the percentage of subjects who attained different stereoacuity levels on global tests for each group. Figure 5-9 shows the percentages of participants from each group who attained 60 sec arc or better on different random dot stereoacuity tests. The results of uncrossed disparity tests showed the same trends that only a minority of the PD could obtain at least 60 sec arc on the global tests and this was particularly challenging for the FOG on the TNO and Steps test. Chi-square test showed that the frequencies between groups were significantly different for all three tests for both disparities; Step test-crossed disparity (X^2 =35.317, DF= 2, and p=<0.001); Randot 3 test test-crossed disparity (X^2 =21.230, DF= 2, and p=<0.001); and TNO test-crossed disparity (X^2 =18.375, DF= 2, and p=<0.001).

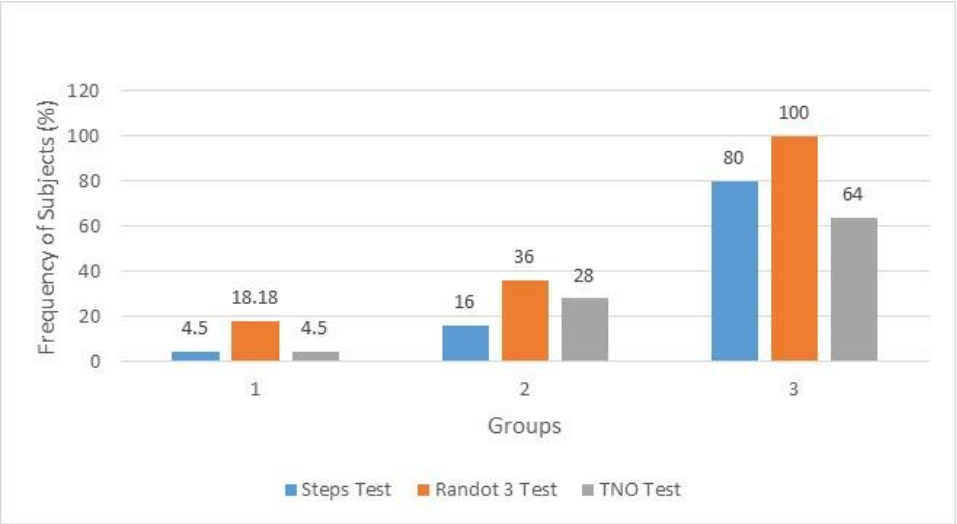


Figure 5-9: Vertical bars showed the percentages of subjects who resolved 60 sec arc or better on three random dot stereoacuity tests for all groups

1: FOG PD, 2: non-FOG PD, 3: HC

Table C6 (Appendix C) shows the mean and standard error of the mean of the time that the participants needed to complete each global stereoacuity test. Figure 5-10 shows the mean plots of the time needed to complete each of crossed-disparity global stereoacuity tests for all groups. The ANOVA analyses showed that, with the exception of the TNO, there was significant group effect for the global tests (ANOVA). Most pairwise comparisons showed that both PD groups were significantly slower in completing the test than the HC, but not significantly different from each other even though the non-FOG PD patient group were, on average, faster than the FOG PD. This result was for both crossed and uncrossed disparities. Although the results from the TNO did not reach statistical significance (but approached significance for the crossed disparity), the trend between groups was similar to other tests. That is HC were faster than both FOG PD and non-FOG PD groups, and the non-FOG PD group was faster than FOG PD ones. The one test where the two PD group did differ significantly was the random dot Butterfly test, where the non-FOG PD group was significantly faster than the FOG PD group, but slower than the HC (Table 5-4). The latter finding is probably due to the complexity of the pattern of Butterfly test in depth that required more time for the FOG group to resolve.

Table 5-4: One-way ANOVA tests of times needed to perceive global stereoacuity tests between groups

Test	ANOVA	DF	P value	Pairwise Multiple Comparisons		
				Groups	Non-FOG	HC
Steps Crossed	13.23	2,69	<0.001	FOG	No	Yes
				Non-FOG		Yes
Steps Uncrossed	12.65	2,69	<0.001	FOG	No	Yes
				Non-FOG		Yes
Randot 3 Crossed	10.29	2,69	<0.001	FOG	No	Yes
				Non-FOG		Yes
Randot 3 Uncrossed	10.53	2,69	<0.001	FOG	No	Yes
				Non-FOG		Yes
TNO Crossed	3.02	2,69	0.055	FOG	No	No
				Non-FOG		No
TNO Uncrossed	1.36	2,69	0.263	FOG	No	No
				Non-FOG		No
Butterfly	25.328	2,69	<0.001	FOG	Yes	Yes
				Non-FOG		Yes

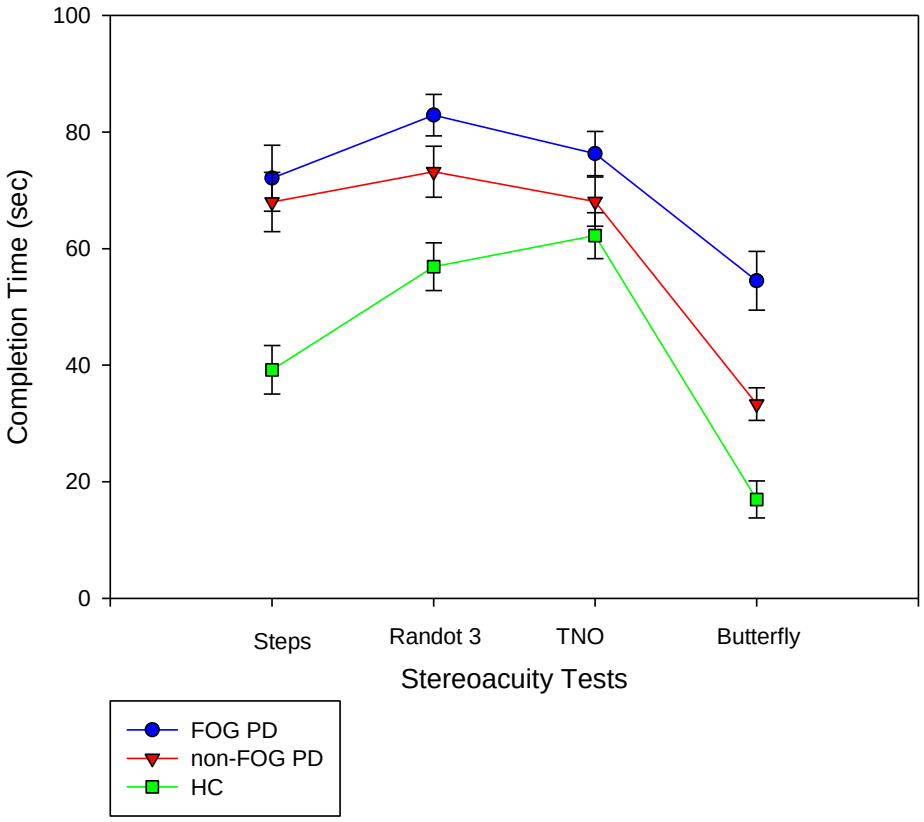


Figure 5-10: Means plot of completion time of crossed-disparity global stereoacuity tests for each group

Error bars represent the standard error of the means

5.5.3 Relationships between different stereoacuity tests and severity, duration, and cognitive abilities of PD Patients:

None of stereoacuity tests had a significant correlation with severity, duration, or the cognitive status in the FOG PD patient group. In contrast to the FOG PD results, several tests were correlated with the severity and duration of the non-FOG PD or cognitive status. First, there was a significant correlation between the severity of the disease and Circles test-uncrossed disparity ($\rho = 0.48$, $p=0.014$). Second, there was a significant correlation between the duration of the disease and Steps test for both crossed ($\rho = 0.417$, $p<0.001$) and uncrossed ($\rho = 0.421$, $p=0.036$) disparities. Finally, there was a negative correlation between the cognitive status and the Circles test-uncrossed disparity ($\rho = - 0.497$, $p=0.012$), and TNO test-uncrossed disparity ($\rho = - 0.405$, $p=0.044$). The correlations between the cognitive status and all stereoacuity tests were not significant for the healthy controls.

5.5.4 Comparison of fixation disparity and fixation disparity curve parameter between groups:

Table C7 (Appendix C) shows the means, standard deviations, medians, and standard error of the means for the horizontal fixation disparity, horizontal associated phoria, and slopes for all groups. Positive values indicate an eso-deviation, and negative values indicate exo-deviation. Comparisons between groups for different fixation disparity parameters were performed based on the median values by applying non-parametric ANOVA on Ranks test because the results were not normally distributed. None of the comparisons between groups showed any significant differences for any

of the fixation disparity parameters ($p>0.61$ for all parameters). Table C8 (Appendix C) lists the percentages of participants in each group who had the different fixation disparity curve types. Figure 5-11 shows the frequencies of the various curve types for each group. From the graph, the FOG PD patient group had more type 4 curve than the other two groups, whereas healthy controls had more type 1 curves more than the two patient groups. Nevertheless, the differences in frequencies were not significant based on Chi-square test ($X^2 = 7.091$, DF=6, $p=0.312$). These results suggests that, even though the amount of fixation disparity, associated phoria, slopes, and curve type were not significantly different across groups, it is still possible that some PD patients have less stable vergence system compared with healthy controls.

There was no significant correlation between the different fixation disparity parameters and the severity of the disease, duration, or the cognitive status of patients.

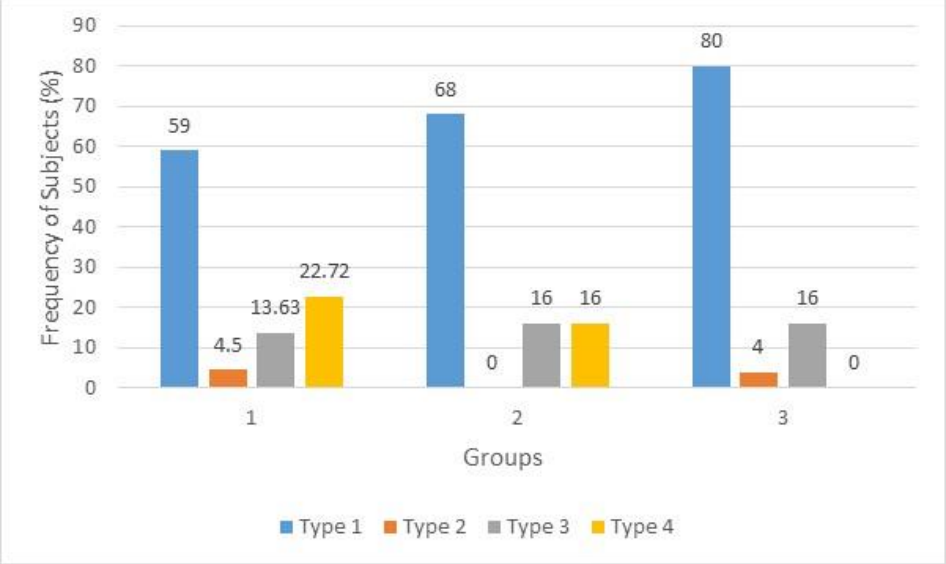


Figure 5-11: Percentages of subjects who had the various types of fixation disparity curve for all groups.

1: FOG PD, 2: non-FOG PD, 3: HC

5.5.5 Relationships between stereoacuity and fixation disparity:

Relationships between the amount of fixation disparity and the stereoacuity tests were tested for each group by using the non-parametric Spearman regression test. Results showed that none of the local or global stereoacuity tests were significantly correlated with the amount of fixation disparity for FOG and non-FOG PD patient groups. Relationships between different stereoacuity tests and fixation disparity for healthy controls were not significant in most cases. There were 3 cases where the correlations were significant. First, there was a positive correlation between the fixation disparity and Circles test- uncrossed disparity ($\rho = 0.58$, $p=0.0025$). Second, there was also a positive correlation between fixation disparity and Line test- uncrossed disparity ($\rho = 0.46$, $p=0.019$). Third, the correlation between fixation disparity and TNO test- uncrossed disparity ($\rho= 0.42$, $p=0.0382$). These results suggest that the larger stereoacuity deficits in the two PD groups were not influenced by their vergence system instability as measured by the fixation disparity parameters. Rather, it probably reflects more sensory-cognitive dysfunctions.

5.6 DISCUSSION

The main objectives of this study project were to evaluate the binocular depth perception of PD subjects by measuring local (contour) and global (random dot) stereoacuity using different clinical stereo tests. This was the first study to evaluate stereoacuity in FOG PD patients. The findings from this study clearly show that both global and local stereopsis were significantly worse in both FOG and non-FOG PD

patients compared with healthy controls. PD subjects, especially the FOG showed reductions in global stereopsis tests more frequently than local stereopsis tests. Although the difference did not always reach statistical significance, the FOG group had worse stereoacuity based on the median values, or the frequencies of subjects who could not obtain at least 60 sec arc or better relative to the non-FOG. The tests where the two PD showed similar losses were the Line test, Steps test, and Randot 3 test. The reasons for the variability across tests were probably due to differences in the disparity range and step size along with the spatial characteristics of the tests.

In terms of which test is best at separating the groups, multinomial logistic regression was conducted with all of local and global stereoacuity tests. The results showed that the final logits regression model adequately fits our data (Chi-square test = 87.428, DF=22, $p<0.0001$). Table 5-5 shows the rank order of different stereoacuity tests that could best discriminate between the different subject groups. The Randot3 and TNO global stereo tests were the best discriminators between groups. The standard cross disparity presentation appeared to be sufficient. In contrast, groups were not discriminated by any of local stereo tests.

Table 5-5: The rank order of different stereoacuity tests that can discriminate groups

Test	Chi-Square	DF	P value
Intercept	1.110	2	0.574
Global Randot3 Crossed Disparity	11.433	2	0.003*
Global TNO Uncrossed Disparity	7.582	2	0.023*
Global TNO Crossed Disparity	6.082	2	0.048*
Global Randot3 Uncrossed Disparity	5.386	2	0.068
Local Circles Crossed Disparity	3.048	2	0.218
Local Line Crossed Disparity	2.180	2	0.336
Global Steps Crossed Disparity	2.130	2	0.345
Global Steps Uncrossed Disparity	1.930	2	0.381
Local Circles Uncrossed Disparity	0.771	2	0.680
Global Butterfly Crossed Disparity	0.201	2	0.905
Local Line Uncrossed Disparity	0.020	2	0.990

* The parameter shows significant effect between groups

Table 5-6 shows parameter estimates for the two PD patient groups when they are compared separately with the healthy controls using the different parameters on table 5-5. Again, Randot 3 and TNO global stereo tests were the best discriminant between either of the two patient groups comparing to HC and the local tests were not sufficient to discriminate each group from the HC.

Table 5-6: The stereoacuity parameter estimates of two PD patient groups to healthy controls

Group	Test	B	DF	P value
FOG	**Intercept**	-25.177	1	0.000*
	Global Randot3 Crossed Disparity	0.102	1	0.020*
	Global TNO Uncrossed Disparity	-0.013	1	0.113
	Global TNO Crossed Disparity	0.015	1	0.059
	Global Randot3 Uncrossed Disparity	-0.071	1	0.038*
	Local Circles Crossed Disparity	-0.100	1	0.229
	Local Line Crossed Disparity	0.088	1	0.291
	Global Steps Crossed Disparity	-0.026	1	0.170
	Global Steps Uncrossed Disparity	0.025	1	0.190
	Local Circles Uncrossed Disparity	-0.011	1	0.889
	Global Butterfly Crossed Disparity	0.031	1	0.256
	Local Line Uncrossed Disparity	0.081	1	0.425
Non-FOG	**Intercept**	-23.054	1	0.000*
	Global Randot3 Crossed Disparity	0.089	1	0.037*
	Global TNO Uncrossed Disparity	0.016	1	0.040*
	Global TNO Crossed Disparity	-0.018	1	0.031*
	Global Randot3 Uncrossed Disparity	-0.055	1	0.090
	Local Circles Crossed Disparity	-0.127	1	0.121
	Local Line Crossed Disparity	0.110	1	0.183
	Global Steps Crossed Disparity	-0.019	1	0.256
	Global Steps Uncrossed Disparity	0.019	1	0.284
	Local Circles Uncrossed Disparity	0.079	1	0.436
	Global Butterfly Crossed Disparity	0.031	1	0.465
	Local Line Uncrossed Disparity	-0.010	1	0.898

* The parameter shows significant effect between groups

Although PD subjects had lower global stereoacuity on all tests, the TNO and Randot 3 emerged as the best tests for discriminating between the 3 groups. It is not clear as to why these two tests were the best discriminators. Both presented disparities that were less than 20 sec arc, but the maximum disparity of the Randot 3 was only 180 sec arc and the TNO was 480 sec arc. The result that the TNO was a good discriminator between groups could be that fact that TNO used red-green filters to isolate the image for each eye and these filters reduce the retinal illuminance more than the Polaroid filters. Based on the mesopic visual resolution results, one might expect that the performance of the PD groups, especially the FOG subjects would be worse.

The reason why the Randot 3 was a good discriminator may be related to the pattern formed by the disparities. The stimulus for each disparity is a diamond-shaped background of random dots. The objects that are seen in depth are circles located near the vertices. In the normal test presentation, one of the circles has a crossed disparity and other three have an uncrossed disparity so that the patient should see 3 circles behind the background and one in front. Near, the stereoacuity limit, the individual circles may not be apparent, but diamond background could appear slanted in depth with the closest part corresponding to the crossed disparity circle. Although the circle-form is not obvious, its location can be identified using this information. It is possible that PD patients, especially the FOG, could not interpret this artifact correctly or they had difficult processing a global stereopsis stimulus that had both crossed and uncrossed disparities present.

Our results showing that that PD patients had more difficulties of resolving simple global stereopsis patterns appears to contradict the Flowers and Robertson (1995) study that found no difference between HC and PD for simple random dot patterns. However, their simple patterns were likely well above threshold for the PD group. The result that all the subjects could perceive the Butterfly correctly, which was composed of large disparities was consistent with their findings; however, our PD subjects did require more time to perceive the pattern.

Flowers and Robertson (1995) attributed the PD group's inability to perceive complex global stereopsis patterns to general visuospatial processing deficits. The correlations between the TNO and Circle stereo acuities and cognitive status in the non-FOG were consistent with their conclusion. The result that both the TNO (i.e. global stereopsis) and the Circles (contour stereopsis) deficits were correlated with cognitive function suggests that the general visuospatial deficits could include difficulty matching corresponding features from each eye to give rise to a single percept, especially for the non-FOG subjects. This could be why the Line test results in terms of perceiving at least 60 sec arc were better than the Circles contour test. Matching points along thin line contours was likely easier and more precise than matching points on thick annuli images (Howard, 1995). The other factor that may have made Line test easier was the luminance of the self-illuminated background of the Line test was brighter than the Circle test.

Associations between different stereoacuity tests and photopic high contrast visual acuity, photopic horizontal and photopic vertical Vernier acuity were tested by running Spearman correlation coefficient (Table 5-7). Only three significant correlations were found and two of these were only within the healthy controls. These results suggest that the impairments seen in the PD were not related to decrements found in their 2-D visual resolution. This lack of association suggests that the stereopsis deficits seen in the PD groups were due to impairments in higher visual centers rather than degraded input from each eye. Stereopsis is a complex process that is mainly controlled by the extra striatal cortex (Cao & Grossberg, 2012; Westheimer, 2009). Interestingly, contour stereopsis was associated with horizontal Vernier acuity in healthy controls, which suggests that both functions are mediated by higher visual centers (Stevenson, Cormack, & Schor, 1989).

Table 5-7: Correlations between different visual resolution tests and stereoacuity tests

Groups	2-D Resolution Tests	Circles (Local)	Lines (Local)	Steps (Global)	Randot 3 (Global)	TNO (Global)
FOG	VA	0.11	0.399	0.388	0.141	0.378
	H. Vernier	-0.310	-0.254	-0.083	0.021	-0.039
	V. Vernier	-0.318	-0.245	-0.181	-0.028	-0.179
Non-FOG	VA	0.127	0.074	0.403*	0.22	0.10
	H. Vernier	0.132	-0.105	0.119	0.097	0.038
	V. Vernier	0.206	0.065	0.121	0.011	-0.008
HC	VA	0.347	0.337	-0.107	0.306	0.021
	H. Vernier	0.583*	0.558*	-0.074	0.201	-0.075
	V. Vernier	0.219	0.260	-0.095	0.225	-0.033

* Correlation is significant at 0.05 level

Our results showing deficits in contour stereopsis agreed with the previous studies (Sun et al., 2004; Kim et al., 2011). One of the conclusions from our study is that an abnormal finding on a contour test will be dependent on the test and the definition of abnormal stereopsis. If abnormal stereopsis is defined as less than 60 sec arc and a contour test similar to the Line test is used then about 10% of each PD group would have abnormal stereoacuity. However, for the Circle test, nearly 60% of the FOG PD subjects have abnormal stereopsis.

The previous studies reported that reduced contour stereopsis was more likely in PD patients with more severe motor dysfunction (Kim et al., 2011, Sun et al., 2014). Our results were mixed in that the only significant correlation between stereoacuity and disease severity was with uncrossed disparity Circles test. The lack of association between different stereo tests and the severity of the disease in this study could be because all of PD patients on this study were either in their mild or moderate severity level.

Fixation disparity and associated phoria provide an assessment of the vergence eye movement since the two eyes are not totally dissociated during the testing. Although different studies reported that PD patients had different oculomotor deficits including vergence eye movements (Hanuška et al., 2015, Almer et al., 2012; Biousse et al., 2004; Racette et al., 1999), none of these studies looked at the fixation disparity or the associated phoria. These two parameters are often used to assess the slow component of the vergence system. Our results did not reveal any significant differences between groups nor correlations with stereoacuity. Generating fixation disparity curves can give us information about the integrity of the slow component of vergence system. The FOG PD group had more type 4 curve than other two groups; however, the frequency of subjects who had type 4 curve were not significantly different than other two groups. Assuming that a type 4 curve is more common in PD patients, the finding suggests that PD patients, especially the FOG group, could have less vergence system adaptation when adding prismatic stress. This would be consistent with PD subjects reporting more frequent eyestrain and tiredness when reading. It is possible that the

instability of their vergence system is due to cortical mechanisms, rather than a dopaminergic reduction. Hanuška et al (2015) reported that activity in frontal cortical areas, such as frontal eye filed (FEF), influence the latency of vergence eye movements in PD patients; however, we are not certain whether the FEF also affect the vergence system adaptation.

Nevertheless, the fixation disparity and associated phoria may not be the best test to measure vergence system abnormalities in PD. The fixation disparity, associated phoria and slope are not necessarily optimum clinical parameters to identify non-PD subjects with oculomotor problems (Sheedy & Saladin, 1977).

Stereopsis impairments were not associated with the fixation disparity in both PD patient groups although some of the parameters were associated with the stereoacuity in the HC. Interestingly, these associations were found for uncrossed disparities, which normally are not measured clinically. One possible reason for the lack of association in the PD group was that PD variability was large. The higher variability was reflected in the higher frequency of the Type 4 curves in the PD groups.

Regardless of the underlying cause, our results indicate that FOG PD group has a greater loss in stereopsis than the non-FOG group as the complexity level of the target increases. This finding suggests that FOG PD patients need more time to analyze a crowded environment during walking, and this may lead to or increase the FOG episodes during their movements.

Chapter 6

PUPIL LIGHT REFLEX IN FREEZING AND NON-FREEZING PARKINSON'S DISEASE PATIENTS

6.1 SUMMARY

Non-motor autonomic nervous system (ANS) dysfunctions have been reported in PD patients. The pupil light reflex (PLR) is a reliable measure of the sympathetic and parasympathetic ANS. Different dilation and constriction PLR parameters may be used to investigate whether FOG PD patients have more impairment than non-FOG PD patients or healthy controls of the sympathetic or parasympathetic ANS system. Results of this study showed that most of constriction parameters and dilation latency of both patient groups differed significantly from healthy controls. FOG PD patients showed larger pupil size under light condition and larger deficits in constriction latency than non-FOG PD patients. These results suggest that the cholinergic ANS systems is affected in PD more than the adrenergic system.

6.2 INTRODUCTION

Different autonomic nervous system (ANS) dysfunctions including abnormal pupil light reflexes (PLR) have been reported in PD (Giza et al., 2011; Goetz, Lutge, & Tanner, 1986). Moreover, cognitively impaired PD patients had more PLR parameters abnormalities than those patients who had normal cognitive function which supports the thinking that PD is not just a dopaminergic function problem function since cognitive abilities are controlled by the frontal lobe where the pathways are mediated

by acetylcholine (ACh) and other non-dopaminergic neurotransmitters (Stergiou et al., 2009).

Freezing of gait (FOG) PD patients are characterized by having different pathophysiological mechanism than non-freezers. Frontal cognitive dysfunctions were found to be associated with FOG PD patients (Amboni et al., 2008); however, to my knowledge, there are no comparisons between FOG-PD and non-FOG PD patients using PLR parameters. It is possible that FOG-PD patients could have a larger impairment of this ANS function than non-FOG patients. This would support the hypothesis that cholinergic (parasympathetic), or perhaps adrenergic (sympathetic), ANS system may be impaired in FOG individuals.

6.3 AIM OF THE STUDY

The purpose of this study is to compare different pupil constriction and dilation parameters in FOG-PD and non-FOG PD with each other and age-matched health controls. Measuring both the constriction and dilation parameters will allow us to assess both the cholinergic and adrenergic pathways of the pupil reflexes.

6.4 METHODS

6.4.1 Procedures:

The pupil light reflex (PLRs) parameters were measured using a NeurOptics™ PLR™ -3000 Pupillometer (NeurOptics, Inc. Irvine, CA, USA).The testing procedures and protocols of this study were fully explained in details in Chapter 3. Participants of this study were the same of those who participated in the previous studies.

6.4.2 Data Analysis:

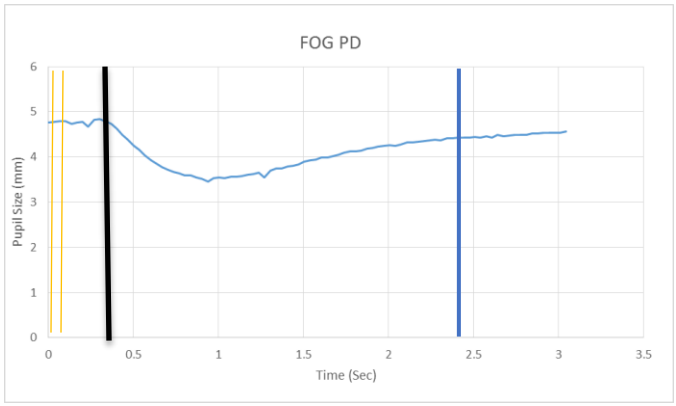
Constriction and dilation PLRs parameters were measured three times on each eye. The average from the three measurements was calculated for each eye separately. The right and left eye parameters were compared by a paired t-test for each group separately. Results showed that none of the PLRs comparisons were statistically significant between eyes for any group. For this reason, the average values of the two eyes were used for further comparisons.

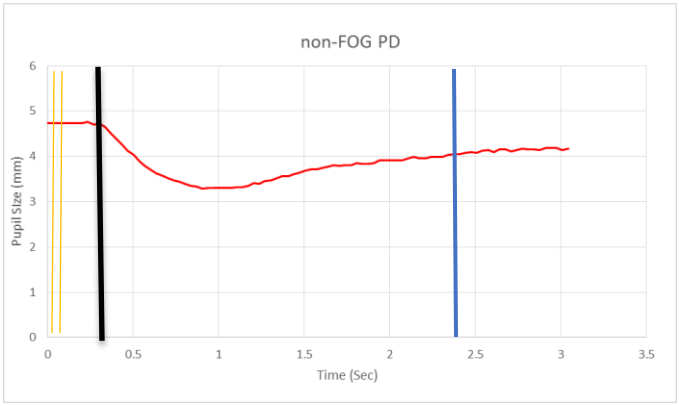
Differences between groups were examined using one-way ANOVA with Tukey's post hoc tests to examine all pairwise comparisons between groups. The second analysis examined the associations between different PLRs and the severity, duration, and MoCA scores in PD patients by calculating the Pearson correlation coefficients. IBM SPSS ver. 24 was used for this data analyses. The criterion of $p \leq 0.05$ was used to determine statistical significance.

6.5 RESULTS

6.5.1 Constriction pupil light reflex:

Figure 6-1 shows representative data of the pupil diameter as a function of time after the eye was stimulated with the white light pulse. Table 6-1 shows means and standard error of the means of different constriction parameters. Table 6-2 shows the ANOVA results and the pairwise multiple comparisons between groups for those parameters that showed a significant group effect. There was a significant group effect for all the constriction parameters, except the minimum diameter (End) ($F=2.193$, $DF= 2, 69$, $p=0.119$), and the re-dilation velocity (re-ADV) ($F=2.112$, $DF = 2, 69$, $p=0.129$). Pairwise comparisons showed, however, that the group effect was primarily due to the differences between the one, or both, of the PD groups and the HC for most parameters. The only significant difference between the FOG and non-FOG PD was the constriction latency (LAT-C), and T 75%.





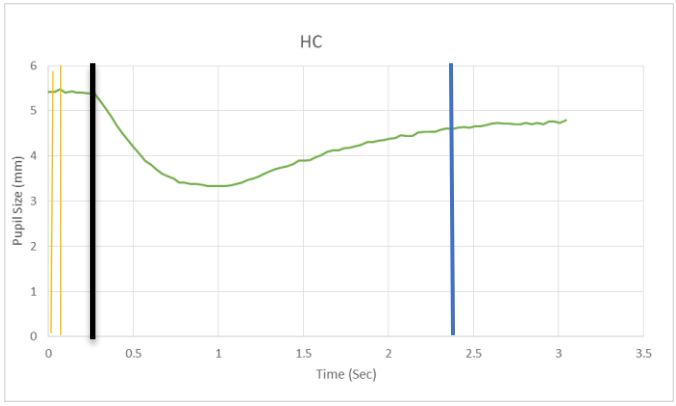


Figure 6-1: Pupil size response to light stimulus as a function of time in 3 representative participants from each group. The two yellow vertical lines shows where the stimulus started and ended, the black vertical line shows the constriction latency, the blue vertical line shows T75%

Table 6-1: Means and SEMs for different constriction PLRs for all groups

Group		Initial (mm)	End (mm)	Amount –Con (mm)	Con (%)	LAT-C (msec)	ACV (mm/sec)	MCV (mm/sec)	re-ADV (mm/sec)	T75 % (sec)
FOG (N=22)	Mean	5.22	3.80	1.42	27.81	0.26	2.92	4.15	1.05	1.25
	Std. Error of Mean	0.15	0.14	0.07	1.18	0.005	0.10	0.12	0.037	0.09
non-FOG (N=25)	Mean	4.64	3.29	1.32	29.15	0.24	2.95	4.06	1.03	1.50
	Std. Error of Mean	0.22	0.18	0.072	1.14	0.01	0.13	0.17	0.07	0.08
HC (N=25)	Mean	5.28	3.59	1.69	32.43	0.21	3.41	4.63	0.90	1.76
	Std. Error of Mean	0.20	0.17	0.06	0.96	0.01	0.11	0.14	0.04	0.03

Table 6-2: One way ANOVA tests of constriction PLRs between groups

Test	ANOVA	DF	P value	Pairwise Multiple Comparisons (P values)		
				Groups	Non-FOG	HC
Initial	3.299	2,69	0.034	FOG	0.1	0.974
				Non-FOG		0.056
Amount - Con	7.8	2,69	0.001	FOG	0.63	0.021*
				Non-FOG		0.001*
Con%	4.68	2,69	0.012	FOG	0.672	0.012*
				Non-FOG		0.086
LAT-C	27.128	2,69	<0.001	FOG	0.006*	<0.001*
				Non-FOG		<0.001*
ACV	5.45	2,69	0.006	FOG	0.977	0.014*
				Non-FOG		0.019*
MCV	4.09	2,69	0.021	FOG	0.904	0.084
				Non-FOG		0.024*
T75%	13.652	2,69	<0.001	FOG	0.041*	<0.001*
				Non-FOG		0.022*

(*): Differences between groups is significant at 0.05 significant level

6.5.2 Dilation pupil light reflex:

Figure 6-2 shows representative data of the pupil diameter as a function of time after the light was extinguished for 1.03 second. Table 6-3 lists the means and standard error of the means different pupil dilation parameters for all groups. One way ANOVA showed the differences between groups were statistically significant for all of the dilation PLR parameters except the dilation percentage of change (Dia %) ($F=1.757$, $DF= 2, 69$, $p=0.180$) and the dilation velocity (ADV) ($F=1.82$, $DF = 2, 69$, $p=0.169$). Table 6-4 shows the results and the pairwise multiple comparisons between groups for those parameters who showed significant differences between groups.

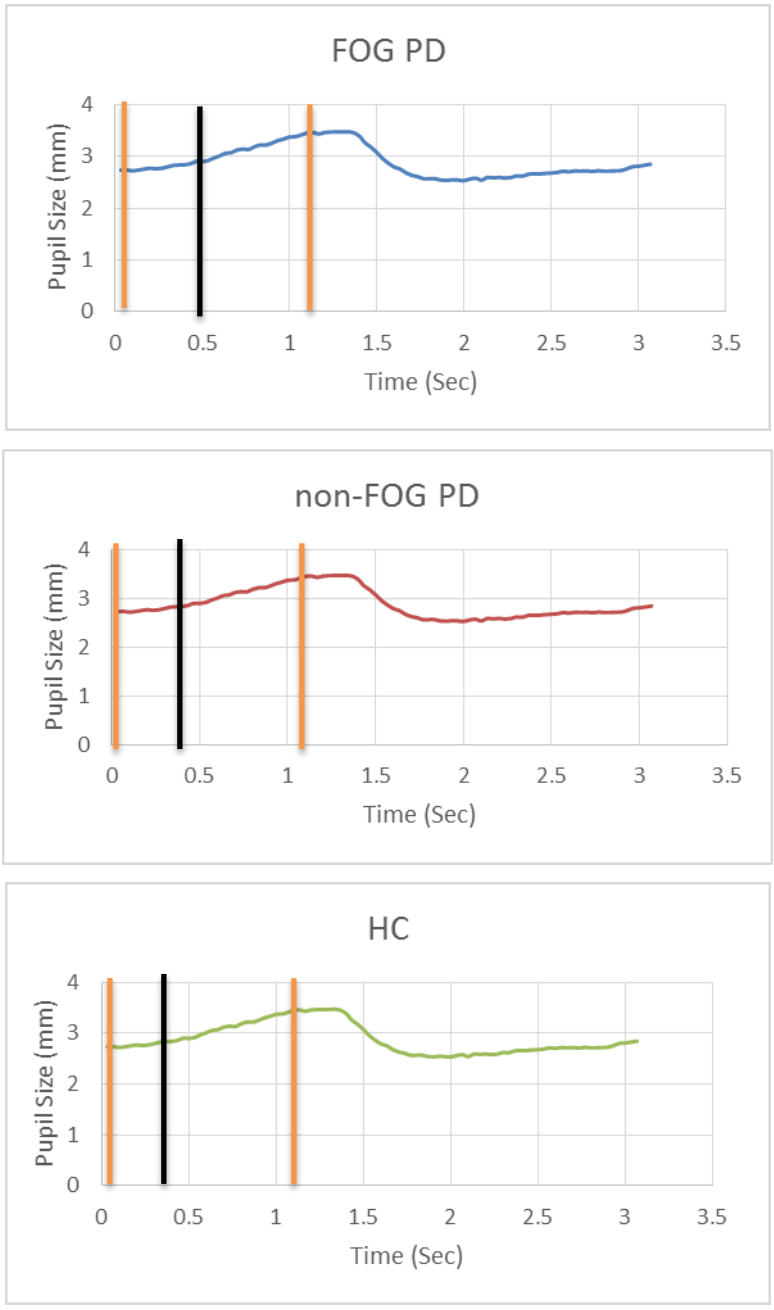


Figure 6-2: Pupil size response to light stimulus as a function of time in 3 different participants representing the 3 subject groups. The two orange lines shows where the stimulus started and ended, the black vertical line shows the dilation latency

Table 6-3: Means, SDs, and SEMs for different dilation PLRs for all groups

Group		Initial (mm)	End (mm)	Amount-Dia (mm)	Dia (%)	LAT-D (msec)	ADV (mm/sec)
FOG (N=22)	Mean	2.90	3.43	0.53	19.25	0.40	0.87
	Std. Error of Mean	0.09	0.11	0.028	0.92	0.016	0.036
non-FOG (N=25)	Mean	2.54	2.96	0.41	16.81	0.39	0.74
	Std. Error of Mean	0.093	0.10	0.03	1.15	0.010	0.054
HC (N=25)	Mean	2.53	3.02	0.48	19.43	0.34	0.80
	Std. Error of Mean	0.06	0.09	0.03	1.20	0.013	0.05

Table 6-4: One way ANOVA tests of dilation PLRs between groups

Test	ANOVA	DF	P value	Pairwise Multiple Comparisons (P values)		
				Groups	Non-FOG	HC
Initial	5.517	2,69	0.006	FOG	0.014*	0.013*
				Non-FOG		0.99
End	6.049	2,69	0.004	FOG	0.05*	0.018*
				Non-FOG		0.89
Amount - Dia	3.83	2,69	0.027	FOG	0.021*	0.56
				Non-FOG		0.233
LAT-D	5.24	2,69	0.008	FOG	0.75	0.009*
				Non-FOG		0.048*

(*): Differences between groups is significant at 0.05 significant level

6.5.3 Relationships between different PLR parameters and severity, duration, and cognitive abilities of PD Patients:

Relationships between different PLR parameters with severity (UPDRS score) of the disease, duration of the disease and the cognitive status (MoCA score) were examined by calculating the Pearson correlation coefficients for FOG and non-FOG PD patient groups separately. Results showed that none of the constriction or dilation PLR parameters correlated significantly with severity, duration or the cognitive status of the FOG PD patient group. The results for the non-FOG PD patient group were similar for most of the PLR parameters; however, there were two exceptions to this general trend. First, there was a negative and significant correlation ($\rho = -0.428$, $p=0.033$) between UPDRS score and constriction percent change. That is, the more severe the disease, the smaller the relative change in pupil size for the non-FOG subjects. Second, there was a negative correlation between MoCA score and T 75% recovery ($\rho = - 0.539$, $p=0.012$). That is, the more cognitive impairment, the longer it takes to re-dilate after the light was extinguished.

6.6 DISCUSSION

Non-motor symptoms due to ANS dysfunctions have been reported in PD patients (Stern, Lang, & Poewe, 2012, Parkinson, 2014). Both sympathetic and parasympathetic branches of ANS are known to be affected (Ziemssen & Reichmann, 2010). Measuring the pupil size under light and dark conditions and measuring different pupil light reflex (PLR) parameters is a relatively easy and non-invasive

technique to evaluate the integrity of the ANS sympathetic and parasympathetic pathways (Wilhelm & Wilhelm, 2003).

The main objectives of this study were to examine both constriction and dilation parameters of the pupil light reflex (PLR) to determine whether the cholinergic mediated (parasympathetic) and adrenergic mediated (sympathetic) ANS were differentially affected in FOG PD and non-FOG patients. In addition, the previous clinical results might help disentangle the afferent (sensory) PLR vs. efferent (motor) PLR pathways. This information would help us to determine whether the problem originates in the retina or in the central nervous system.

Most of constriction parameters and dilation latency among dilation parameters were significantly different for one or both of PD patient groups compared with healthy controls. Our results were in agreement with previous findings for those common constriction parameters (Giza et al., 2011; Goetz, et al., 1986). Similar to previous studies (Giza et al., 2011; Goetz, et al., 1986), our results suggest that pupil changes could be independent from the dopaminergic deficiency because there was no correlation with any other motor symptoms of the disease except for one case, which could be a spurious correlation. In addition, others have reported that dopaminergic treatment has no effect on different PLR parameters (Harris, 1991; Hori et al., 2008).

Multinomial logistic regressions were conducted for all of constriction and dilation PLR parameters separately in order to determine the best discriminant parameters between groups. The results showed that the final logits regression models adequately

fit our data for the constriction parameters (Chi-square test = 96.961, DF=18, $p<0.0001$), and for the dilation parameters (Chi-square test = 27.684, DF=12, $p=0.006$). Table 6-5 shows the rank order of different PLR parameters that can best discriminate different subject groups. Except the constriction percentages, the average constriction velocity and maximum constriction velocity, the other constriction parameters were good discriminators between groups. Dilation latency was the only parameter that could discriminate between groups among dilation parameters. These findings suggest that both parasympathetic and sympathetic ANS pathways were affected in PD patients compared with healthy controls, and the parasympathetic ANS pathway is more affected than sympathetic ANS pathway in PD patients.

Table 6-6 shows parameter estimates of the two PD patient groups separately to the healthy controls using the different constriction and dilation PLR parameters in Table 6-5. If we look at the constriction latency (LAT-C) B coefficient for the FOG, it is 175.773. This indicates that LAT-C is very good at discriminating between HC and FOG. The value for the non-FOG is 125.8, which was still high, but it was not significant. Thus, the constriction latency (LAT-C) is a good discriminator between HC and FOG PD patient group, but not as good between HC and non-FOG PD patient group. Even though re-dilation velocity (re-ADV) did not show significant differences on average between groups, the logistic regression model suggests that this parameter is a good discriminator for both of PD patient groups compared with healthy individuals.

Table 6-5: The rank order of different PLR parameters that can discriminate groups

	Test	Chi-Square	DF	P value
Constriction Parameters	**Intercept**	0.276	2	0.871
	re-ADV	20.332	2	0.000*
	LAT-C	15.413	2	0.000*
	Amount of Constriction	13.754	2	0.001*
	End	12.088	2	0.002*
	Init	11.732	2	0.003*
	T 75% Recovery	10.349	2	0.006*
	Con %	3.912	2	0.141
	MCV	3.658	2	0.161
	ACV	2.182	2	0.336
Dilation Parameters	**Intercept**	5.289	2	0.071
	LAT-D	7.648	2	0.022*
	Amount of Dilation	3.803	2	0.149
	Init	3.225	2	0.199
	End	3.181	2	0.204
	ADV	0.904	2	0.636
	Dia %	0.040	2	0.980

* The parameter shows significant effect between groups

Table 6-6: The parameter estimates of PLR of two PD patient groups to healthy controls

	Group	Test	B	DF	P value
Constriction Parameters	**FOG**	**Intercept**	-0.076	1	0.998
		re-ADV	26.551	1	0.020*
		LAT-C	175.773	1	0.022*
		Amount of Constriction	-427.556	1	0.652
		End	-458.675	1	0.629
		Init	450.402	1	0.635
		T 75% Recovery	-10.677	1	0.051
		Con %	-1.506	1	0.065
		MCV	-6.446	1	0.112
		ACV	5.111	1	0.106
	Non-FOG	**Intercept**	-6.369	1	0.819
		re-ADV	29.195	1	0.012*
		LAT-C	125.774	1	0.079
		Amount of Constriction	-456.701	1	0.630
		End	462.050	1	0.626
		Init	-469.458	1	0.621
		T 75% Recovery	-2.093	1	0.667
		Con %	-0.967	1	0.140
		MCV	-3.545	1	0.341
		ACV	4.301	1	0.140
Dilation Parameters	**FOG**	**Intercept**	-9.961	1	0.036*
		LAT-D	11.390	1	0.030*
		Amount of Dilation	-13.882	1	0.869
		Init	-9.037	1	0.913
		End	11.173	1	0.893
		ADV	0.483	1	0.856
	Non-FOG	**Intercept**	-3.880	1	0.404
		LAT-D	11.308	1	0.023*
		Amount of Dilation	-84.252	1	0.243
		Init	-74.388	1	0.288
		End	75.091	1	0.285
		ADV	2.439	1	0.368

* The parameter shows significant effect between groups.

Previous studies showed that maximum constriction velocity and maximum constriction acceleration were the best discriminants among PLR constriction parameters between PD patients and healthy controls (Yamaji, Hirata, & Usui, 2000, Giza et al., 2011; Stergiou et al., 2009; Fotiou et al., 2009). Several reasons could explain different findings of our study compared with the previous studies. First, the temporal resolution of the pupillometric systems were different. The pupillometer in this study had a frame rate of 32 frames per second, whereas the other the pupillometric systems were much faster with a frame rate of 263 frames per second.

Second, different studies used different experimental conditions and different stimulus light intensities. We used 50 mW as the stimulus intensity in this study. It could be that this light level was not sufficient to show PLR dysfunctions among some PD patients. Different stimulus intensities can change different PLR responses (Bremner, 2012a; Ellis, 1981; Sharma et al., 2016). In addition, the previous studies included PD patients with more severe cases, which could contribute to the difference in results. Another factor is that the previous studies based their conclusions on comparing the ROC curves of the individual parameters. This approach may produce different results from the multinomial logistic regression.

PLR parameters are not solely controlled by the motor responses of ANS. Deficits in the retina or optic nerve could affect PLR as well. Reduction in retinal illuminance levels can reduce light adapted baseline pupil sizes and produce similar decrements in

PLR parameters as found in our study (Bremner, 2012a; Ellis, 1981; Sharma et al., 2016; Bergamin, Zimmerman, & Kardon, 2003; Ellis, 1981). This means that some of pupil deficits seen in our results could be a result of retinal dysfunction, given the visual acuity and contrast sensitivity losses found in PD subjects.

One PRL parameter deficit that could be either a sensory deficit or parasympathetic motor deficit is the minimum pupil size after constriction (i.e. End) (Thiagarajan & Ciuffreda, 2015). A deficit in either branch of the pathway could produce a larger minimum pupil diameter. Our minimum pupil diameter results do not allow for any further analysis on this parameter because there was no significant difference+ between groups. This result suggests that the minimum pupil diameter is not a very sensitive parameter for measuring pupil deficits in PD patients.

Another difference that could be due to sensory deficit is a larger initial pupil size under light adaptation (Initial). The larger mean FOG PD initial pupil size under light conditions suggests that FOG PD group had a larger sensory deficit due to lower retinal inputs. This pupil deficit would be consistent with the greater losses found in the visual resolution results for FOG subjects. Although a larger pupil size under light suggests sensory deficits, it is has been suggested that larger pupil size under light conditions reflects dysfunctions in parasympathetic (cholinergic) nervous system due to an acetylcholinergic (ACh) reduction (Bremner, 2009; Loewenfeld & Lowenstein,

1993). However, this parameter is not considered as a strong indicator of the cholinergic system dysfunction (Yamaji, Hirata, & Usui, 2000).

A third parameter that is known to reflect the retinal contribution to PLR is the amount of constriction (Bergamin & Kardon, 2003; Fotiou et al., 2007; Lowenstein, Kawabata, & Loewenfeld, 1964). Both PD patient groups had lower amount of constriction compared with healthy controls, which suggests that either their retinal function or optic nerve function was impaired. Constriction latency (LAT-C) is fourth indicator of the sensory inputs to the pupil responses (Bitsios, et al., 1996; Bos, et al., 1990; Capó-Aponte, et al., 2013). This parameter was shown to be one of the strongest discriminator between groups among the r constriction parameters. The longer latency for FOG-PD subjects due to a retinal deficit was consistent with our finding that FOG PD group had larger deficits in visual acuity and contrast sensitivity especially under low light levels (Chapter 4).

Additional supporting evidence that the PLR deficits were sensory based comes from a study by Salter et al (2009). They measured constriction PLR parameters using the same device in multiple sclerosis (MS) patients with optical neuritis. Their MS patients had reduced high contrast visual acuity, low contrast visual acuity and contrast sensitivity. In addition, all of constriction parameters were found to be significantly affected in MS patients compared with the healthy controls. Moreover, the reduction in constriction percentage, average constriction velocity and maximum constriction velocity along with the increase in constriction latency found in the MS

group were comparable to the changes found in our PD patients results. They also reported that thinning in different retinal layers including total macular volume due to optic neuritis could predict the deficits in different constriction PLR parameters. Lagreze and Kardon (1998) also found a correlation between the estimated ganglion cell loss and the relative afferent pupillary defect (RAPD) in optic neuritis. In his review, Simao (2013) summarized a number of studies reporting a thinning of the retinal nerve fiber in similar regions of the eye in PD patients. It is possible that this retinal deficit underlies the deficits in pupil function. Nevertheless, he pointed out that the amount of thinning was not correlated with visual function or duration of the disease and so more study about the proposed linkage is required.

Retinal inputs to PLR response is a combination the signals originating at the rods and cones and the intrinsic response of the Intrinsically-photosensitive Retinal Ganglion Cells (ipRGCs), which project to the pretectum. Although the role of the ipRGCs in the PLR response is still being studied, it appears that these cells play a major role in maintaining the steady-state size of the pupil (McDougal & Gamlin, 2010). There is evidence that ipRGCs may be damaged in open angle glaucoma (ONG). The differences between red and blue post-illumination pupil responses were reduced in patients with ONG relative to controls. A smaller difference between the post-illumination responses is believed to indicate damage to ipRGCs (Kankipati, Girkin, & Gamlin, 2011). The input into the ipRGCs includes dopaminergic amacrine cells and so it is possible that the larger mean pupil size under light adaptation found

in the FOG-PD arises from reduced dopaminergic inputs into these cells in addition to reduced input from the photoreceptor pathways.

Because it is possible that many of the PLR deficits could be due to a sensory deficit, the associations between different PLRs and different 2D visual resolution tests were tested by calculating the Pearson correlation coefficients. We used those 2D visual resolution tests that showed good discrimination between groups based on the logistic regression model. These included contrast sensitivity under low light levels, low contrast visual acuity under high light levels and horizontal & vertical Vernier acuities under low light levels (Table 4-1). The high contrast visual acuity under high light levels was included as well because it would be included any assessment of visual function in PD. Table 6-7 shows correlations between PLR parameters and high contrast visual acuity under high light levels, and contrast sensitivity under low light levels. The correlations with the other 2-D resolution tests are shown on Table D1 (Appendix D). None of the correlations in the appendix were significant. The majority of correlations in Table 6-7 were also not significant within each group. However, there were few exceptions, which are shown on the highlighted cells. The lack of consistent correlations across the various visual parameters with PLR parameters do not exclude the possibility that some PRL deficits found in this study are mainly sensory related, especially if there are separate pathways mediating the pupil reflexes and the visual resolution tasks.

Table 6-7: Associations between different PLR and visual resolution tests.

PLR Parameters	FOG		non-FOG		HC	
	High Contrast VA Photopic	Contrast Sensitivity Mesopic	High Contrast VA Photopic	Contrast Sensitivity Mesopic	High Contrast VA Photopic	Contrast Sensitivity Mesopic
Init-Con	-0.438*	-0.025	0.287	0.0079	0.053	0.10
End-Con	-0.450*	0.109	0.136	-0.02	0.11	0.08
Amount of Constriction	0.003	-0.277	0.525**	0.109	-0.14	0.12
Con %	0.258	-0.220	0.26	0.047	-0.29	0.03
LAT-C	0.030	0.055	-0.37	-0.01	0.24	-0.399*
ACV	0.072	-0.404	0.661**	-0.02	-0.22	0.06
MCV	0.081	-0.419	0.642**	-0.069	-0.16	0.11
re-ADV	0.004	-0.403	0.26	-0.03	-0.17	0.22
T75 %	0.086	-0.021	0.106	0.067	-0.076	0.11
Init-Dia	-0.278	-0.109	0.25	0.20	0.23	0.038
End-Dia	-0.234	-0.117	0.32	0.140	0.13	0.047
Amount of Dilation	0.010	-0.099	0.30	-0.113	-0.10	0.058
Dia %	0.210	-0.168	0.146	-0.25	-0.30	0.194
LAT-D	0.215	-0.149	-0.07	0.23	0.09	-0.048
ADV	0.015	-0.314	0.408*	-0.078	-0.11	0.065

(**): Correlation is significant at the 0.01 level
(*): Correlation is significant at the 0.05 level

Nevertheless, we cannot completely rule out a motor pathway dysfunction. First, our result that very few of the visual resolution losses correlated with PLR deficits suggests that deficits may not be just sensory. A lack of correlation between the PRL and VEP latencies was also reported in MS patients when the disease was inactive (Jakobsen, 1990; Pozzessere et al., 1997). A study was done on rats found that the number of retinal photoreceptors do not predict the PLRs, which suggests the PLR is not a good indicator of the integrity of retinal photoreceptor cells (Kovalevsky et al., 1995). Although none of these findings excludes the possibility that the ganglion cells to the pretectum are affected differentially relative to the cells projecting to the LGN, it does raise the question as to whether there is also a motor dysfunction.

Second, the result that the initial pupil size under dark adaptation was smaller in the non-FOG PD group suggests a motor deficit in this group of PD patients. A smaller pupil size in darkness is a sign of either increase in parasympathetic influence or reduction in sympathetic input (Bremner, 2009; Loewenfeld & Lowenstein, 1993, Pettigrew, Sanderson, & Levick, 1986). Nevertheless, this imbalance was not evident in the minimum pupil size during constriction or the during the light adapted state before the dilation was measured, which suggests that the result could be due to other factors such as attention or general arousal level (Bradley et al., 2008; Stanners et al., 1979). As to why these levels would be different in the non-FOG subjects is uncertain.

Third, the maximum constriction velocity was slower in the two PD groups, which suggests a parasympathetic deficit (Bitsios et al., 1996; Bos et al., 1990; Capó-Aponte et al., 2013). However, previous studies have shown that there is a positive and significant relationship between pupil response velocities with the amplitude size change. This means that, if constriction amplitude is lower for a certain disease patient, then it is expected that their constriction velocity is slower and there is no new information gained by looking at each parameter (Bitsios et al., 1996; Kaufman et al., 2011; F. D. Bremner, 2012b; Ciuffreda, Joshi, & Truong, 2017). There was a positive and significant relationship between pupil constriction velocities and the amplitude size change and both PD groups also had significantly smaller constriction amplitudes. Linear regression results of maximum constriction velocity (MCV) vs. amplitude of constriction were significant ($r \geq 0.818$, $p>0.001$) for all subject groups.

Scatterplots of these relationships are shown on Figure 6-3 for all subject groups. All of groups showed the expected strong and significant relationships between MCV and constriction amplitude. The FOG group has a flatter slope for pupil constriction than the other two groups. The results should be interpreted cautiously because these data are across subjects and not within, but it suggests that the subjects in the FOG group who had a relatively large amplitude of constriction had the slower pupil velocity response. This could indicate a deficit in the parasympathetic motor pathway. The difference in slopes between the groups suggests that measuring the PRL reflexes as a function of light level may help determine separate the sensory deficit from any motor deficit.

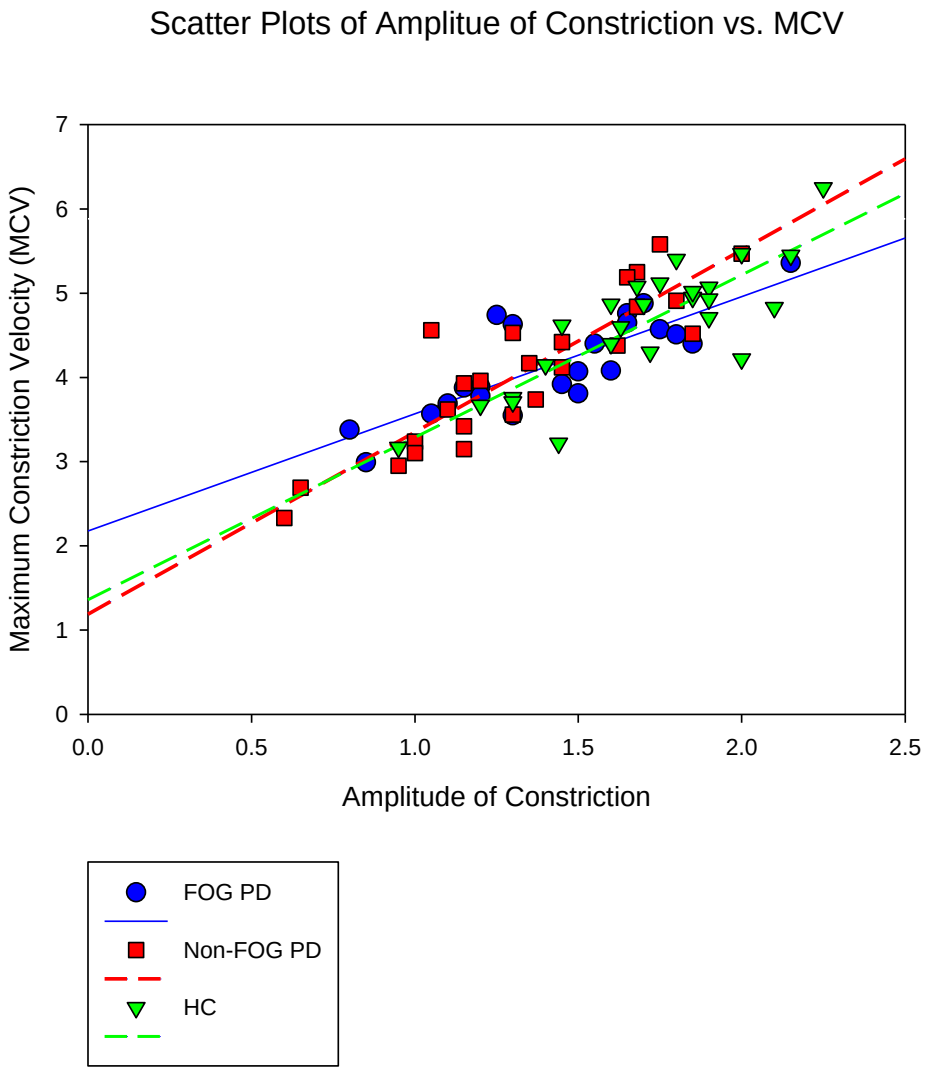


Figure 6-3: Scatter plots of pupil maximum constriction velocity (MCV) as a function amplitude of pupil constriction for the subject groups

Fourth, it may not possible to exclude the motor contribution to the results of constriction latency (LAT-C). Comparisons between FOG and non-FOG PD patient groups regarding this parameter showed FOG group had significant longer constriction latency compared to non-FOG group. The longer constriction latency could suggest deficits in either afferent (sensory) or efferent (motor) parasympathetic pathway of ANS. However, constriction latency is not considered as a good as maximum constriction velocity to represent the cholinergic (motor) mediated pathway of ANS (Capó-Aponte et al., 2013, Yamaji, Hirata, & Usui, 2000).

Delay in T75% recovery time and slower re-dilation velocity were considered to be strong indicators of motor impairment in the sympathetic pathway of ANS due to adrenergic reduction (Capó-Aponte et al., 2013, Bremner, 2009). Unexpectedly, both PD patient groups showed faster recovery time (T75%) and faster re-dilation velocity after pupil constriction (re-ADV) compared to healthy controls with FOG being faster than non-FOG group on these two parameters. Faster T75% and re-ADV that were shown in PD patients could be secondary to less constriction percentages (Con %) that were shown among PD patients compared to healthy controls. That means because both PD patient groups constricted less than healthy controls, then it expected that their re-dilation recovery time and velocity would be faster. This finding suggests two things. First, both PD patient groups have no obvious motor impairment in the sympathetic pathway of ANS compared to healthy controls. Second, faster T75% and re-ADV in PD patient groups is a secondary effect to motor

impairment in the parasympathetic pathway of ANS. However, the results of dilation latency (LAT-D) showed both PD patient groups had significant delay compared to healthy controls. Also, the amount of dilation of non-FOG PD patient were less than the other two groups which still it may not possible to exclude the potential impairment of sympathetic pathway of ANS among PD patients. Similar to our results, it has been found PD patients had faster but not significant 50% re-dilation recovery time than healthy controls (Micieli et al., 1991).

Cognitively impaired PD patients have been shown to have more constriction PLR deficits than those patients who have normal cognitive function (Stergiou et al., 2009). The deficits in the cognitive impaired PD patients were similar to the pupil dysfunction reported in Alzheimer's disease patients. This suggests that both groups of patients have the same central cholinergic deficit (Fotiou et al., 2009). It has been shown that freezing of gait and freezing of gait severity are associated with frontal cognitive dysfunction and frontal cognitive dysfunction severity respectively (Amboni et al., 2008). Cognitive impairment could be due to degeneration of subcortical regions such as locus coeruleus (LC) in brain stem. This area is known to be affected in PD and Alzheimer disease patients (Zarow et al., 2003).

It is possible that the PLR deficits are due to alterations in the brain stem rather than more centrally or in the peripheral pathways. The locus coeruleus (LC) in the brain stem is one possible site. Pupil size is a good indicator of activity in the LC (Joshi et al., 2016; McDougal & Gamlin, 2015). Rapid changes in the release of acetylcholine

(ACh) and adrenaline (NE) occur due to variation activity in LC. The LC activity changes the pupil responses (Reimer et al., 2016). Because FOG PD patients showed larger impairments on some of sympathetic and parasympathetic PLR parameters, it is possible that adrenergic and cholinergic systems are impaired in FOG PD patients to a greater extent than non-FOG PD patients due to abnormal activities in LC or other autonomic cortical centers.

Although the results confirmed that the PLR were affected in PD, we could not rule out that many of these deficits were due to degraded sensory input from the retina. The general trend in the results was that the deficits reflect a deficit in the parasympathetic pathway, but there is also data suggesting a sympathetic deficit. It is possible that measuring the PRL for different light levels may provide a better understanding of the pupil deficits in PD.

Chapter 7
VISUAL PROCESSING SPEED IN FREEZING AND NON-FREEZING PARKINSON'S DISEASE PATIENTS

7.1 SUMMARY

Visual information processing speed, or the inspection time (IT), which is independent from the motor response, is a reliable measure of the cholinergic system integrity. Thus, IT can be used to investigate whether FOG PD patients have a larger impairment in cholinergic mediated functions than non-FOG PD patients and healthy controls. Results of this study showed that FOG PD patients had slower IT score than healthy controls. IT scores for the non-FOG PD patients fell in between the two other groups. These results support the hypothesis that the cholinergic system is integrity is affected more in FOG PD patients.

7.2 INTRODUCTION

Inspection time (IT); unlike reaction time (RT); is a reliable measure of visual processing speed that does not require any motor responses (Deary & Stough, 1996; Johnson et al, 2004b; Nettelbeck, 1982; Thompson, et al, 2000; Vernon, 1986). IT can be used to investigate the integrity of the cholinergic mediated functions and can predict the intelligence and the cognitive abilities of individuals (Petrill et al., 2001; Nathan & Stough, 2001). PD patients have slower ITs relative to healthy controls

(Johnson et al. 2004). IT is unaffected by dopaminergic treatment and is independent of motor impairments (Giaschi, Lang, & Regan, 1997; Bachmann et al., 1998, Shipley et al., 2002, Sawamoto et al. 2002, Johnson et al. 2004).

As it is already mentioned in previous chapters that freezing of gait (FOG) symptom among some PD patients may be independent of the dopaminergic reduction and it is now hypothesized that cholinergic system dysfunction may be involved; therefore, FOG patients may have slower IT scores compared to non-FOG patients. If this true, then slower visual information processing may contribute to the FOG symptoms.

7.3 AIM OF THE STUDY

The purpose of this study is compare visual information processing speed; or inspection time (IT), of PD patients who experience FOG vs. non-FOG to determine whether these measurements can discriminate between different PD groups.

7.4 METHODS

7.4.1 Procedures:

The inspection time (IT) stimulus was developed using Psychocinematics. The testing procedures and protocols of this study were fully explained in Chapter 3. Participants of this study were the same of those who participated in the previous studies.

7.4.2 Data Analysis:

Comparisons of IT scores were performed by ANOVA on Ranks test based on the median values due to the non-normal distribution of the data. Associations between the severity of the disease, duration, and the cognitive status of patients with IT scores were evaluated by Pearson correlation coefficient for FOG and non-FOG PD patient groups separately. IBM SPSS ver. 24 was used for this data analyses. The criterion of $p \leq 0.05$ was used to determine a significant effect.

7.5 RESULTS

Figure 7-1 shows the box plot of IT scores for all groups. Table 7-1 lists the mean, standard deviation (SDs), and the median of IT scores in milliseconds for all groups. The FOG PD group has the highest (more time needed to process the target) and most variable IT scores. ANOVA on Ranks test showed that the differences between groups were significant. (ANOVA on Ranks =14.512, DF=2, $p<0.001$). Pairwise multiple comparisons between groups revealed that the difference was only significant between healthy control and FOG PD patients. The differences between non-FOG PD patient group and other two groups were not significant.

Table 7-1: Means, SDs, and Medians of IT in milliseconds for all groups

Group	Mean	Std. Deviation	Median
FOG (N=22)	76.8	58.2	58
non-FOG (N=25)	49.36	21.8	54
HC (N=25)	36.44	16.48	33

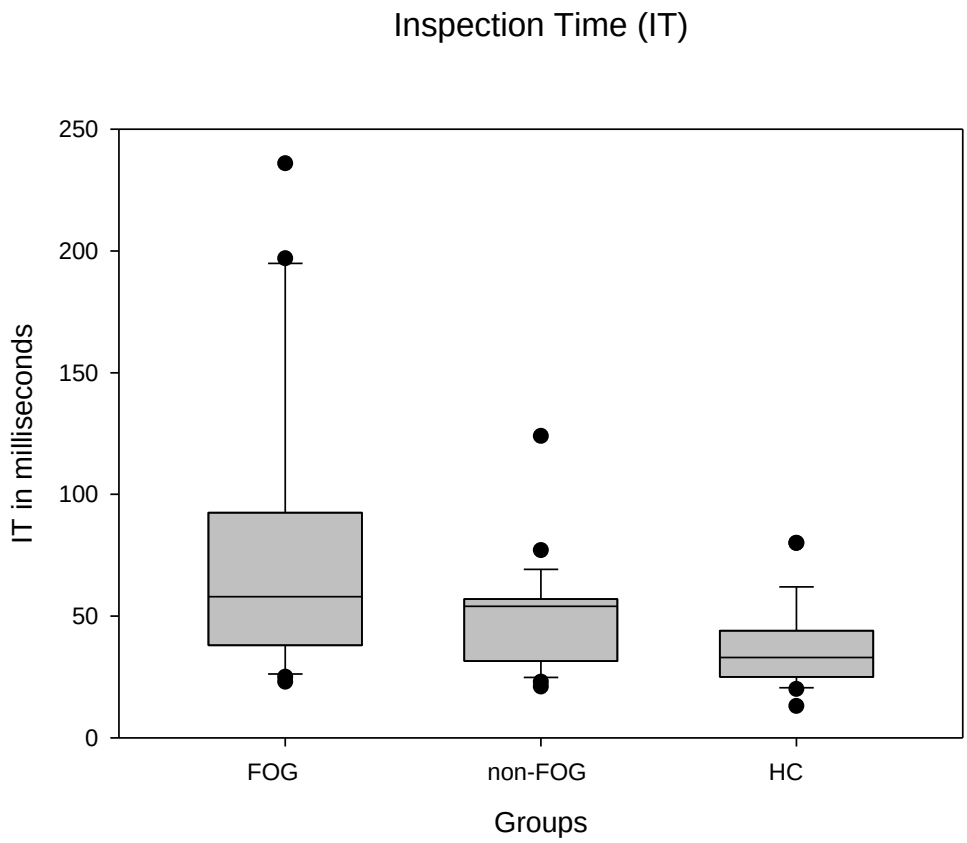


Figure 7-1: Box plot shows the differences between groups based on the IT score. The vertical bars represents 10% to 90% percentile, the box represents 25 % to 75% quartiles, the solid horizontal line represents median differences, and ● outliers

Correlations between the UPDRS score and the IT score for the non-FOG-PD group was significant ($\rho = 0.446$, $p=0.025$), and the correlation approached significance in the FOG-PD subjects ($\rho = 0.417$, $p=0.054$) indicating that longer IT were associated with more severe PD, especially in the non-FOG. There was no significant correlation between the duration of the disease with the IT score in FOG PD group ($\rho = -0.34$, $p=0.121$), and the non-FOG PD group ($\rho = -0.021$, $p=0.922$).

There was significant negative correlation between the MoCA score and IT score for the FOG PD ($\rho = -0.432$, $p= 0.045$), non-FOG PD ($\rho = -0.476$, $p=0.016$), and HC ($\rho = -0.411$, $p=0.0415$), confirming that longer IT is associated with lower cognitive ability. Figure 7-2 shows the scatterplots of IT and MoCA scores for all subject groups. Scatterplots showed that FOG PD patient groups has higher regression y-intercept and steeper slope than other two groups which means that FOG PD patients who had slow IT score are likely to have more cognitive impairments.

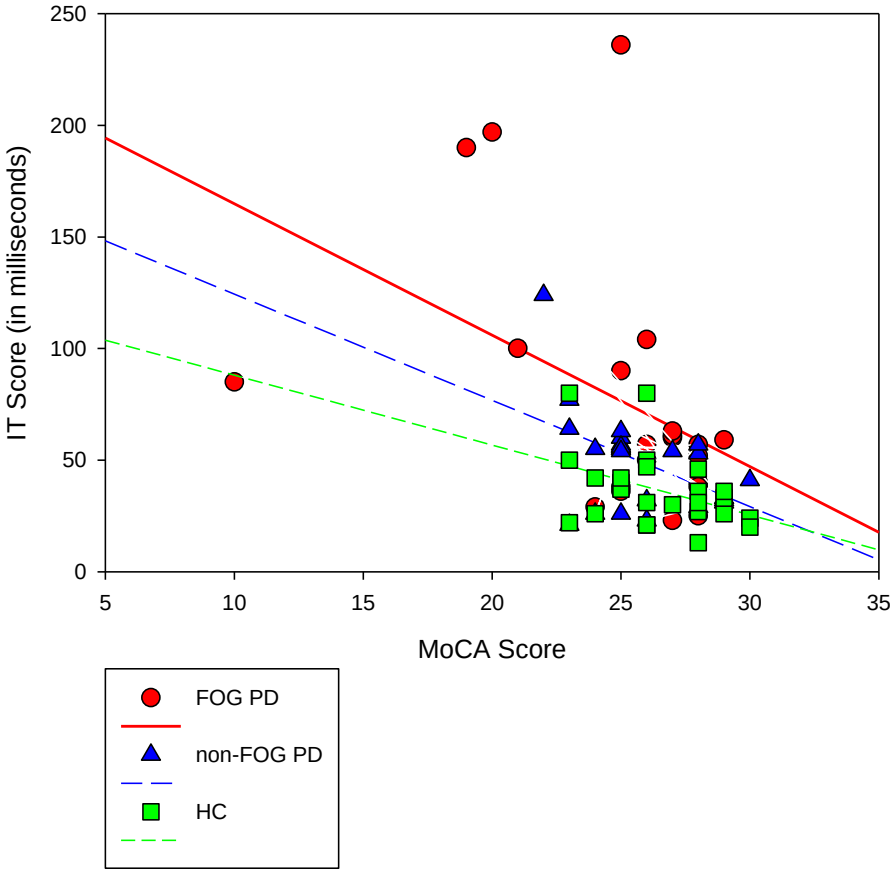


Figure 7-2: Scatter plots of IT score as a function MoCA score for the subject groups

7.6 DISCUSSION

IT can be used to evaluate the cholinergic system integrity (Nathan & Stough, 2001). The longer IT values for the FOG group were consistent with the hypothesis that they have a general cholinergic system dysfunction. However, the differences were only significant between FOG PD group and healthy controls. Non-FOG PD group fell in between with slower and more variable IT score on average than healthy controls; but faster than the FOG group. These results suggest that both PD groups had a cholinergic deficit, with FOG PD having a more severe impairment. Although not unique to the FOG PD patients, the longer processing time could contribute to the FOG symptoms. Nevertheless, it is unlikely that the slower visual processing speeds are solely responsible for the symptoms given that several FOG subjects had IT within the normal range.

Visual processing speed could be related to one's ability to resolve the difference in the line length. However, the difference in the line length was 55 min arc, which was 36 times longer than the high contrast acuity limit for inclusion in the study. Additional evidence that the difference in lines was easily resolved are the correlations between the IT scores and high contrast VA, horizontal Vernier, vertical Vernier acuities, and stereo tests. Table 7-2 lists the Pearson correlation coefficients. Except for the correlation between IT and vertical Vernier acuity in HC, none of the correlations were statistically significant for both patient groups. These findings further indicate that the delay in IT in PD patients was not due to the reduction in their visual resolution capabilities.

Table 7-2: Correlation coefficients (R) between IT and visual resolution tests for all groups

Visual Resolution Tests	IT		
	FOG	Non-FOG	HC
High Contrast VA Photopic	0.031	0.223	0.297
Horizontal Vernier Acuity Photopic	-0.065	-0.220	0.251
Vertical Vernier Acuity Photopic	-0.006	-0.025	0.50*
Local Circles Stereo Test	-0.014	0.089	-0.092
Local Line Stereo Test	0.168	0.162	-0.087
Global Steps Stereo Test	-0.306	0.211	0.414
Global Randot3 Stereo Test	-0.121	0.103	0.029
Global TNO Stereo Test	0.050	-0.010	0.423

(*): Correlation is significant at the 0.05 level

Previous studies that examined IT in PD reported mixed results. Phillips et al., (1999) reported that the ITs were not significantly different between PD patients and age-matched healthy controls, whereas other showed significant differences between the two groups (Shipley et al., 2002; Sawamoto et al., 2002). One reason for the mixed results was that some of these studies used higher-order of intelligent processing so that it was not a simple IT task. However, Johnson et al. (2004) used a similar target to the one used in this study. Their results showed that on-medication patients required significantly longer IT compared with healthy controls (Johnson, et al, 2004b).

Our results may provide additional reasons for the conflicting results between studies. First, if FOG subjects are included in the PD group, then the ITs are more likely to be longer than controls. None of the previous studies reported whether there were FOG PD patients among their study sample. Second, the correlations of IT with the MoCA and UPDRS showed if the cognitive ability was impaired or PD was more severe,

then the IT of the PD group was more likely to be longer than controls. Our finding that IT was longer with lower MoCA scores support the concept that the IT test is a reliable measure of the intelligence and the cognitive functions (Petrill et al., 2001).

As to why some FOG participants' ITs increased either before or to a greater extent compared to non-FOG participants is not clear. It is believed that the dopaminergic reduction in PD does not affect the visual information processing speed (Stough et al 2001). Moreover, the IT score on the PD patients group was not significantly different between 'ON' and 'OFF' medication status (Johnson et al, 2004b). IT processing was found to be influenced by nicotine acetylcholine receptors (nAChRs). Pharmacologically blocking the nicotine acetylcholine receptors increased the IT score in healthy subjects (Thompson et al., 2000). There is evidence that nicotine acetylcholine receptors (nAChRs) are reduced in different locations of the striatum that includes the basal ganglia and nigrostriatal pathways. These receptors are involved in stimulating the release of dopamine and so the reduction of these receptors can cause an attenuation in dopamine release such as the case in PD patients (Court et al., 2000). A reduction in nicotine acetylcholine receptors (nAChRs) is also associated with reduced cognitive ability (Court et al., 2000). It is possible that the FOG patients have the initial loss of the nAChRs in the striatum region and visual processing areas that affects both motor and processing speed, whereas non-FOG have the initial loss in the cognitive areas that eventually includes visual processing speed.

The slower IT among FOG PD patients was consistent with the results of Study 2 (Chapter 4) that FOG PD patients needed more time to perceive the depth in different stereoacuity tests. Association between IT and the time to complete the Butterfly stereoacuity test was examined by applying Pearson correlation coefficient for the 3 subject groups separately. The result showed that the two variables are moderately and significant correlated to each other for the FOG PD group only (ρ= 0.444, p=0.0386). The two variables were not significantly correlated for both non-FOG PD (ρ= 0.103, p=0.625) and HC (ρ= 0.114, p=0.588). Figure 7-3 shows the linear regression between IT and the time to complete Butterfly stereoacuity test for the FOG PD patient group. This result suggest that FOG PD patients needed more time to analyze the visual space around them and that may contribute to the occurrence or to increase the freezing episodes (Martens, Ellard, & Almeida, 2014).

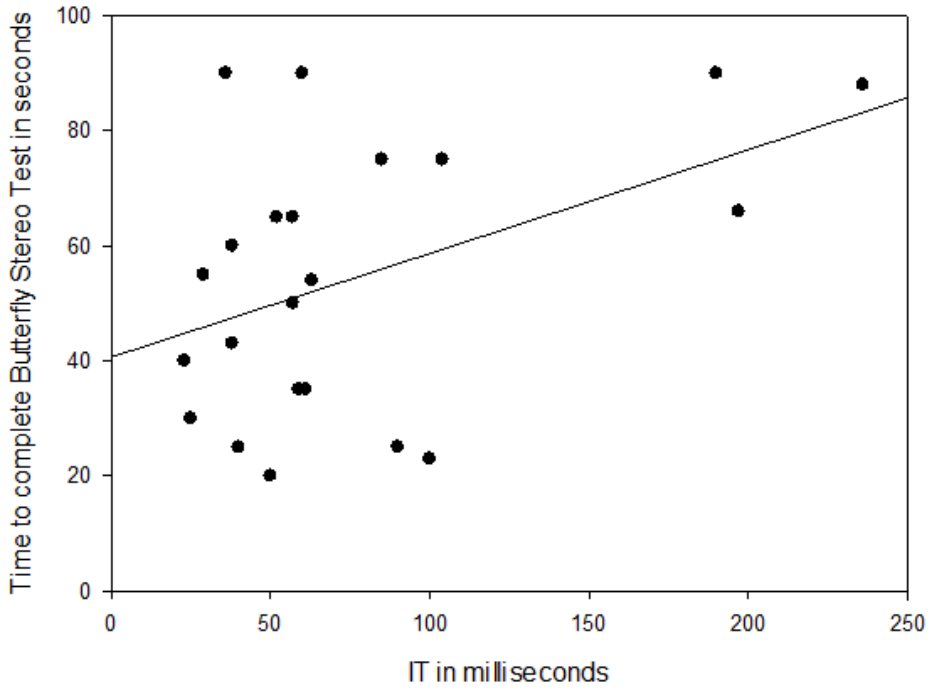


Figure 7-3: Linear regression plot between IT score and the time to complete Butterfly stereoacuity test for the FOG PD group.

Chapter 8
GENERAL DISCUSSION AND CONCLUSIONS

The main objective of this thesis was to evaluate different visual functions using 2-D and 3-D clinical tests in persons with PD with a special interest in determining whether the functions were affected differentially in persons who experiencing FOG symptoms. Measuring the different visual functions could help in determining whether any sensory deficits could be contributing to the FOG symptoms.

Results from Study 1 (Chapter 4) showed that both PD groups had a greater impairment in most of 2-D visual resolution tests compared with healthy controls. The FOG PD tended to have the larger deficits. The reduction was larger under mesopic conditions especially with FOG group. This last finding suggests that the deficit was due to decreased dopamine level at the retina affecting the dark adaption processes. The results do not show a selective loss of functions mediated by either the magno or parvo pathways; however, magno pathway mediated visual functions (i.e. the Pelli Robson contrast sensitivity at low light levels, and the Vernier acuity) were the best tests at distinguishing between the 3 groups. This suggests that the FOG subjects had a larger deficit in the magno (dorsal) pathway.

Results from Study 2 (Chapter 5) showed that both PD groups had lower stereopsis than the HC with the FOG having the worse stereopsis. Impairment of global stereopsis was shown to be more frequent than the local stereopsis loss in PD groups. The reduction in stereopsis among PD participants was not associated with fixation

disparity or other 2-D visual resolution tests. These results suggest that stereopsis deficits in PD were due to impairments in higher visual centers rather than degraded input from each eye or inadequate vergence eye movements. Similar to the finding of Study 1, this study suggests that FOG PD participants had greater impairment in visual functions that were mediated by the magno (dorsal) pathway (i.e. global stereopsis) than non-FOG patients or healthy controls.

Our findings confirm other studies showing that both magno and parvo visual pathways deficits may be present in the same group of PD patients. Silva et al. (2005) found the deficits in visual functions that were mediated by magno vs. parvo pathways were not correlated which is consistent to the results of this study. FOG-PD patients did have a preferential impairment in visual function mediated by the dorsal (magno) visual pathway, which is consistent with other findings (Lord et al., 2012). Our findings in FOG group could reflect a more general impairment of visual processing that is mediated by dorsal visual pathway (Davidsdottir et al., 2008). It is believed that the visuospatial information that is processed by the dorsal stream is used in taking motor actions; thus, the term *"vision for action"* used to describe the dorsal pathway processes (Goodale, 2014). However, that does not exclude the contribution of visual information that is processed by ventral visual system. Inputs from both systems have been shown to contribute to the motor responses as both systems are connected extensively (Goodale, 2014).

FOG PD patients have more deficits in visuospatial judgement, motion perception, and visual perception of the surrounding space than non-FOG patients and that might contribute to their freezing symptoms and walking performance (Almeida and Lebold 2010). Another study showed that FOG patients underestimated the actual distances to a target during both static and dynamic conditions more than non-freezers patients and normal individuals (Martens, Ellard, & Almeida, 2014). It is unclear as to how much of this deficit was due to the loss of stereopsis since individuals can also use monocular depth clues and whether deficits in visual resolution hindered their ability to judge distances.

It is not clear as to how much the reduction in the basic visual functions of visual resolution, contrast sensitivity and depth perception contribute to visuospatial and motion perception problems during walking among FOG PD patients. Impaired visual acuity was found to be associated with reduction of different gait parameters such as step length and gait velocity in older adults (Hallemans, et al., 2010; Shin, An, & Yoo, 2015; Spaulding et al., 1994). Impaired contrast sensitivity was also found to be associated with reduction of different gait parameters such as step width, step length, gait velocity and fear of falling (Moes & Lombardi, 2009; Swigler et al., 2012; Wang et al., 2012; Wood et al., 2009). Impairment in depth perception was found to be associated with difficulties in avoiding obstacles during gait in older adults (Menant, St George, Fitzpatrick, & Lord, 2010). It would be important to measure different visual functions among PD patients along with walking through gate assessments.

This would give more information as to whether the reduction in basic visual functions in PD patients can contribute to walking through gates difficulties.

Several studies have shown that visual cues may facilitate or improve the movement and walking through gates in PD patients (Vitório et al., 2012). Visual cues such as stripes on the floor is one clue. The stripes enhanced the optic flow and the perception of these stripes was improved ability of persons with PD to walk through gates (Azulay et al., 1999). Because FOG PD patients had greater impairment of contrast sensitivity test particularly in low light levels, using high contrast visual cues in a well-lit environment may help them overcome their FOG symptoms (Davidsdottir, Cronin-Golomb, & Lee, 2005; Mestre, Blin, & Serratrice, 1992).

The other objective of this thesis was to look at other ocular and perceptual functions in FOG and non-FOG PD patients. These include constriction and dilation pupil light reflex (PLR) and the visual information processing speed or the inspection time (IT). These measurements represent primarily the cholinergic and adrenergic pathways. Measuring PLR and IT can help us to determine whether PD patients also have a cholinergic deficit in the ANS or higher cortical centers and whether the FOG-PD are affected to a greater extent.

Results from Study 3 (Chapter 6) showed that most of constriction parameters and some dilation parameters were affected in both patient groups compared with healthy controls. The deficits in constriction parameters in PD patients were believed mainly

due to deficits in sensory inputs from the retina or the optic nerve rather than motor responses. FOG PD patients had more constriction parameter deficits that are known to be mediated by the afferent (sensory) visual pathway such as constriction latency (LAT-C). This finding was consistent with the results found in Study 1, which showed a greater impairment of different visual functions in FOG PD patients. However, it is not that easy to separate the sensory causes from motor responses in some of constriction PLR deficits found in this study. The deficits in dilation latency and the amount of dilation that were present in both PD groups were likely due to an adrenergic system dysfunction. The larger pupils of the FOG PD group in the light could be due to a greater imbalance between parasympathetic/sympathetic autonomic nervous systems or a sensory deficit.

Results from study 4 (Chapter 7) showed that FOG PD patients had a slower mean IT score than healthy controls. IT score on non-FOG PD patients fell in between the other two groups. These results support the Study 3 results that the cholinergic system affected in FOG patients more than non-FOG PD patients.

Different visual parameters that were measured in this thesis were shown to be associated with the severity of the disease (UPDRS score), the duration of the disease, or with the cognitive status (MoCA score) among the non-FOG PD group but not with the FOG PD group. We are not certain why these associations were shown to be significant with some cases among non-FOG PD group but not with the FOG PD group. Probably FOG PD group was more variable in terms of the severity of the disease and cognitive status than non-FOG PD group even though the differences

between groups were not statistically significant. The lack of associations between the cognitive status (MoCA score) and different visual parameters among FOG PD group could also be due to the fact that MoCA test is not considered as a comprehensive test for the cognitive impairments. Rather, it is considered as a quick screening test of mild cognitive impairments (Nasreddine et al., 2005).

The results of different studies showed that the FOG PD patient group had larger deficits compared to the other two groups in tests that are believed to reflect the cholinergic system activities. This may suggest that FOG patients had a larger deficits in the central cholinergic system which could contribute to the FOG symptom and other motor disturbances. The contribution of cholinergic system to motor functions has been studied in PD rat models. It was found that the fall rates was more frequent in rats, that were injected with dual 192 IgG-saporin /6-hydroxydopamine (6-OHDA) than rats with either isolated cholinergic or isolated dopaminergic lesions(Kucinski et al., 2013). This drug partially destroys both cortical cholinergic and dopaminergic systems respectively. Kucinski et al. (2013) hypothesized that after dual cholinergic-dopaminergic lesions, the attentional resources mediated by the cholinergic pathways can no longer compensate for the impairment of striatal control of movement in complex environment, as a result, falls occurs.

CONCLUSIONS:

Results from Study 1 and Study 2 can be summarized as follows:

1. Both PD patient groups have greater impairment in basic visual functions that are mediated by magno (dorsal) and parvo (ventral) visual functions compared with healthy controls.
2. The impairment was greater in FOG PD patients than non-FOG PD patients especially with magno (dorsal) mediated visual functions.
3. It was not possible to determine whether the reduction in 2-D visual resolution tests was due to dopamine deficits at the retinal or cortical level. However, the reduction in 3-D visual resolution tests in PD was likely caused by deficits at the cortical level.

Results of study 3 and study 4 can be summarized as follows:

1. Both PD patient groups had pupillary light reflex parameter abnormalities. It was difficult to determine whether the abnormalities were due to impaired sensory input or deficits in the parasympathetic motor input. Nevertheless, the FOG-PD group had larger differences for the parameters that were likely due to a sensory impairment, whereas parameters that were likely due to motor deficits were equally affected in both PD groups. There was also evidence that the pupillary sympathetic pathway was affected in PD.

2. The slower IT in FOG PD patients support the hypothesis that they may have a cholinergic system dysfunction in the higher cortical centers that process visual information.

Finally, the results of this thesis show that FOG PD patients had more deficits in different visual and other perceptual functions than other two groups, and the non-FOG PD patients had more visual deficits than healthy controls. These findings may suggest that the non-motor functions (i.e. sensory visual functions) can predict the occurrence of FOG symptoms better than the motor dysfunctions. This conclusion agrees with previous finding that the loss in contrast sensitivity can predict the FOG symptom better than the motor dysfunctions (Davidsdottir et al., 2005). Given these findings, PD patients are encouraged to check their eyes in routine basis and make sure their vision is fully corrected in order to avoid any movement difficulties especially in crowded and/or dim lighted environment.

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Appendix A

Table A1: Demographic Characteristics of FOG PD Patients

ID	Age	Sex	UPDRS-Score	Duration	MoCA Score	Treatment List
F001	63	M	25	20	28	Sinemet, Amantadine
F002	81	M	29	4	21	Sinemet
F003	81	M	21	2.5	24	Sinemet
F004	69	M	16.5	20	25	Stalevo, Mirapex
F005	76	M	39.5	4	19	Sinemet
F006	72	M	18	12	29	Sinemet, Comtan, Mirapex
F007	60	M	13.5	18	28	Amantadine
F008	76	M	31.5	1	25	No Meds
F009	73	M	14	3	28	Apo-levocarb, Azilect
F010	74	F	21.5	8	26	Sinemet
F011	59	F	32.5	1	28	No Meds
F012	66	F	20	12	20	Sinemet, **Seroquel**
F013	72	F	24	7	27	Sinemet/Apo-levocarb
F014	77	M	18.5	14	25	Sinemet, Requip
F015	78	M	28	6	26	Sinemet
F016	75	M	10	13	25	Sinemet, Stalevo, Requip, Azilect
F017	87	M	31.5	12	10	Sinemet
F018	76	M	29	18	27	Sinemet, Amantadine
F019	73	M	22	17	26	Sinemet
F020	68	M	7	14	28	Sinemet, SinemetCR, Azilect
F021	69	F	23	5	27	Sinemet, Requip
F022	66	M	18	20	27	Sinemet

Table A2: Demographic Characteristics of non-FOG PD Patients

ID	Age	Sex	UPDRS-Score	Duration	MoCA Score	Treatment List
N001	59	F	22	14	28	Sinemet
N002	84	M	22	2	25	Sinemet
N003	58	M	13.5	14	24	Sinemet, Amantadine, Apo-trihexphenidyl
N004	90	M	7.5	15	25	Sinemet
N005	67	F	29	6	23	Sinemet, Mirapex
N006	60	M	9	13	30	Sinemet, Stalevo, Requip, Mirtazipine
N007	59	M	9	10	26	Sinemet, Stalevo
N008	71	M	17.5	12	28	Sinemet, Mirtazipine
N009	67	M	19.5	4	25	Apo-levocarb
N010	77	M	13	2.5	23	Sinemet
N011	71	M	18.5	1.5	25	Apo-levocarb
N012	65	F	29.5	1	25	Sinemet
N013	58	F	9.5	5	29	Sinemet, Azilect, Entacapone
N014	65	M	19	3	25	Apo-levocarb
N015	63	M	25.5	7	26	Sinemet
N016	56	M	24	1	28	Apo-levocarb
N017	54	M	53.5	10	22	Apo-levocarb, Trihexphenidyl
N018	69	M	16	24	29	Sinemet, Amantadine
N019	80	M	28	13	25	Prolopa
N020	76	M	20.5	5	29	Sinemet
N021	76	M	22.5	8	25	Apo-levocarb
N022	71	F	26	6	24	Trihexphenidyl
N023	74	M	20	3	25	Sinemet
N024	58	M	11	1	27	Sinemet
N025	60	F	13.5	21	23	Sinemet, Amantadine

Appendix B

STUDY 1 RESULT TABLES

Table B1: Means, Standard deviations, and standard error of the means for different visual acuity conditions for all groups

Group		Bright (Photopic) Condition		Dim (Mesopic) Condition	
		High Contrast	**Low Contrast**	**High Contrast**	**Low Contrast**
FOG (N=22)	Mean	0.078	0.29	0.35	0.70
	Std. Deviation	0.059	0.108	0.13	0.159
	Std. Error of Mean	0.012	0.023	0.028	0.034
non-FOG (N=25)	Mean	0.038	0.26	0.26	0.60
	Std. Deviation	0.085	0.12	0.11	0.159
	Std. Error of Mean	0.017	0.024	0.022	0.031
HC (N=25)	Mean	-0.024	0.17	0.176	0.45
	Std. Deviation	0.091	0.089	0.112	0.145
	Std. Error of Mean	0.018	0.017	0.022	0.029

Table B2: Means, Standard deviations, and standard error of the means for different contrast sensitivity conditions for all groups

Group		Contrast Sensitivity	
		Bright (Photopic) Condition	**Dim (Mesopic) Condition**
FOG (N=22)	Mean	1.588	0.831
	Std. Deviation	0.110	0.309
	Std. Error of Mean	0.023	0.066
non-FOG (N=25)	Mean	1.704	1.170
	Std. Deviation	0.136	0.178
	Std. Error of Mean	0.027	0.035
HC (N=25)	Mean	1.812	1.326
	Std. Deviation	0.129	.0172
	Std. Error of Mean	0.025	0.034

Table B3: Means, Standard deviations, and standard error of the means for different Vernier acuity conditions for all groups

Group		Bright (Photopic) Condition		Dim (Mesopic) Condition	
		Horizontal	**Vertical**	**Horizontal**	**Vertical**
FOG (N=22)	Mean	42.32	43.65	111.85	110.26
	Std. Deviation	28.30	28.67	33.28	35.32
	Std. Error of Mean	6.03	6.11	7.09	7.53
non-FOG (N=25)	Mean	23.66	24.36	85.32	92.79
	Std. Deviation	14.49	13.68	39.53	35.71
	Std. Error of Mean	2.89	2.73	7.90	7.14
HC (N=25)	Mean	17.37	18.99	43.56	50.36
	Std. Deviation	10.95	10.38	34.09	34.93
	Std. Error of Mean	2.191	2.076	6.81	6.98

Appendix C

STUDY 2 RESULT TABLES

Table C1: Medians, the minimums, the maximums, and the ranges of the local stereoacuity tests for all groups

Group		Circles Test		Line Test	
		Crossed	**Uncrossed**	**Crossed**	**Uncrossed**
FOG (N=22)	Median	80	100	60	60
	Minimum	40	40	10	10
	Maximum	140	200	120	180
	Range	100	160	110	170
non-FOG (N=25)	Median	50	50	20	20
	Minimum	40	40	10	10
	Maximum	140	140	120	120
	Range	100	100	110	110
HC (N=25)	Median	40	40	10	10
	Minimum	40	40	10	10
	Maximum	100	80	60	60
	Range	60	40	50	50

Table C2: Frequencies of participants who attained different stereothreshold criteria on local tests

Groups	Criteria	Circles Test		Line Test	
		Crossed	**Uncrossed**	**Crossed**	**Uncrossed**
FOG (N=22)	**Minimum**	1 (4.5 %)	1 (4.5 %)	2 (9 %)	2 (9 %)
	≤ 60”	9 (40.9 %)	9 (40.9 %)	21 (95.45 %)	19 (86.36 %)
	No Maximum	0	0	0	0
non-FOG (N=25)	**Minimum**	10 (40 %)	10 (40 %)	9 (36 %)	8 (32 %)
	≤ 60”	19 (76 %)	15 (60 %)	22 (88 %)	20 (80 %)
	No Maximum	0	0	0	0
HC (N=25)	**Minimum**	23 (92 %)	21 (84 %)	22 (88 %)	21 (84 %)
	≤ 60”	24 (96 %)	24 (96 %)	25 (100 %)	25 (100 %)
	No Maximum	0	0	0	0

Table C3: Means and standard error of the means of the times needed to perceive local stereoacuity tests for all groups

Group		Circles Test		Line Test	
		Crossed	**Uncrossed**	**Crossed**	**Uncrossed**
FOG (N=22)	Mean	46.3	42.2	50.1	48.3
	SEM	4.5	3.3	4.5	4.4
non-FOG (N=25)	Mean	38.2	37.2	39.1	40.1
	SEM	3.1	2.9	3.6	3.6
HC (N=25)	Mean	29.8	26.92	21.4	20.4
	SEM	3.7	2.4	2.5	2.3

Table C4: Medians, the minimums, the maximums, and the ranges of the global stereoacuity tests for all groups

Group		Steps Test		Randot 3 Test		TNO Test	
		Crossed	**Uncrossed**	**Crossed**	**Uncrossed**	**Crossed**	**Uncrossed**
FOG (N=22)	Median	720	720	320	320	720	960
	Minimum	60	60	25	25	60	120
	Maximum	720	720	320	320	960	960
	Range	660	660	295	295	900	840
non-FOG (N=25)	Median	180	180	160	160	240	240
	Minimum	30	30	12.50	12.50	30	30
	Maximum	720	720	320	320	960	960
	Range	690	690	307.50	307.50	930	930
HC (N=25)	Median	60	60	40	40	60	120
	Minimum	30	30	12.50	12.50	30	30
	Maximum	720	720	63	100	960	960
	Range	690	690	50.50	87.50	930	930

Table C5: Frequencies of participants who attained different stereothreshold criteria on global tests

Groups	Criteria	Steps Test		Randot 3 Test		TNO Test	
		Crossed	Uncrossed	Crossed	Crossed	Crossed	Uncrossed
FOG (N=22)	**Minimum**	0	0	0	0	0	0
	≤ 60"	1 (4.5 %)	1 (4.5 %)	4 (18.18 %)	4 (18.18 %)	1 (4.5 %)	0
	No Maximum	14 (63.63 %)	14 (63.63 %)	17 (77.27 %)	17 (77.27 %)	11 (50 %)	12 (54.5 %)
non-FOG (N=25)	**Minimum**	1 (4 %)	1 (4%)	1 (4 %)	1 (4 %)	0	0
	≤ 60"	4 (16 %)	3 (12 %)	9 (36 %)	7 (28 %)	7 (28 %)	7 (28 %)
	No Maximum	8 (32 %)	8 (32 %)	10 (40 %)	10 (40 %)	3 (12 %)	2 (8 %)
HC (N=25)	**Minimum**	9 (36 %)	7 (28 %)	2 (8 %)	2 (8 %)	0	0
	≤ 60"	20 (80 %)	19 (76 %)	25 (100 %)	22 (88 %)	16 (64 %)	12 (48 %)
	No Maximum	1 (4 %)	1 (4 %)	0	0	1 (4 %)	1 (4 %)

Table C6: Means and standard error of the means of the times needed to perceive global stereoacuity tests for all groups

Group		Steps Test		Randot 3 Test		TNO Test		Butterfly Test
		Crossed	**Uncrossed**	**Crossed**	**Uncrossed**	**Crossed**	**Uncrossed**	
FOG (N=22)	Mean	72.1	72.3	82.9	80.7	76.3	73.7	54.5
	SEM	5.6	5.6	3.5	4.	3.7	4.6	5.1
non-FOG (N=25)	Mean	68	68	73	73	68	68.6	33.3
	SEM	5.1	4.9	4.3	4.4	4.2	4.8	2.7
HC (N=25)	Mean	39.2	39.8	56.9	52.9	62.2	63.1	16.9
	SEM	4.1	4.3	4.1	4.6	3.9	3.9	3.1

Table C7: Means, SDs, Medians, and SEMs for different fixation disparity parameters for all groups

Group		Horizontal Fixation Disparity Parameters		
		Fixation Disparity (Y-Intercept)	**Associated Phoria (X-Intercept)**	**Slope**
FOG (N=22)	Mean	-0.4091	-1.0455	-0.1068
	Std. Deviation	1.333	2.645	0.420
	Median	0	0	0
	Std. Error of Mean	0.284	0.563	0.089
non-FOG (N=25)	Mean	-0.60	-0.84	-0.083
	Std. Deviation	1	1.99	0.353
	Median	0	0	-0.1600
	Std. Error of Mean	0.20	0.398	0.070
HC (N=25)	Mean	-0.68	-1.20	-0.030
	Std. Deviation	0.90	1.870	0.229
	Median	0	0	0
	Std. Error of Mean	0.180	0.374	0.045

Table C8: Frequencies of participants who had different fixation disparity curve type

Groups	Type 1	Type 2	Type 3	Type 4
FOG (N=22)	13 (59 %)	1 (4.5 %)	3 (13.63 %)	5 (22.72 %)
non-FOG (N=25)	17 (68 %)	0	4 (16 %)	4 (16 %)
HC (N=25)	20 (80 %)	1 (4 %)	4 (16 %)	0

Appendix D

STUDY 3 RESULT TABLE

Table D1: Associations between different PLR and visual resolution tests.

PLR Parameters	FOG			non-FOG			HC		
	Low Contrast VA Photopic	H. Vernier Mesopic	V. Vernier Mesopic	Low Contrast VA Photopic	H. Vernier Mesopic	V. Vernier Mesopic	Low Contrast VA Photopic	H. Vernier Mesopic	V. Vernier Mesopic
Init-Con	-.290	-.003	-.026	.112	-.111	-.141	-.042	.150	.089
End-Con	-.404	.079	.085	.027	-.057	-.119	.012	.199	.127
Amount of Constriction	.220	-.169	-.230	.252	-.173	-.105	-.171	-.038	-.049
Con %	.331	-.181	-.218	.149	-.177	-.058	-.209	-.245	-.175
LAT-C	-.033	-.248	-.218	-.109	.210	.034	.378	.231	.226
ACV	.083	.174	.204	.268	-.235	-.119	-.304	-.124	-.104
MCV	.177	.087	.019	.234	-.265	-.136	-.237	-.129	-.104
re-ADV	-.026	.272	.251	.051	.087	.152	-.263	-.127	-.046
T75 %	.303	.158	.328	.258	.071	.087	-.097	.095	-.072
Init-Dia	-.200	-.053	-.035	.047	.034	-.005	.284	.073	-.008
End-Dia	-.187	-.023	.005	.049	-.007	.002	.126	.090	.007
Amount of Dilation	-.068	.092	.143	-.037	-.083	.054	-.243	.098	.036
Dia %	.072	.116	.155	-.073	-.070	.087	-.525	.016	-.018
LAT-D	.298	.041	.146	-.175	.020	-.078	.249	-.031	.027
ADV	.110	.227	.195	-.042	-.179	.057	-.216	.066	.017

- None of correlations were significant at 0.05 level