MULTISENSORY INTEGRATION RELEVANT FOR BALANCE AND GAIT IN PATIENTS WITH GLAUCOMA

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Falls are a concern in glaucoma. Visual field (VF) loss in glaucoma is traditionally thought to be the main cause of falls. However, glaucoma is not only an eye disease but also a brain syndrome. Thus, impairments of central sensory integration processes important for balance/gait may also be a contributing factor. These processes require higher cognitive resources related to attention. Research has shown that patients with glaucoma have worse balance when standing on foam, which alters proprioceptive information, and cognitive impairments related to executive function.

The overarching goal of this study was two-fold: (1) to examine how glaucoma impacts the interference between balance/gait and attention, and (2) to determine if this interference could be linked to brain alterations. To achieve this goal, balance/gait assessments with and without an information-processing (IP) task were conducted and a brain MRI scan was collected in a sample of patients with glaucoma. The findings suggest that glaucoma severity negatively impacts balance but only when proprioception is minimized and attentional resources are diverted from postural control. In addition, brain connectivity measures were correlated with the IP task performance, but only in conditions where proprioception is minimized. Gait assessments also suggest that challenging proprioceptive conditions are associated with worse gait performance in glaucoma.

Additionally, this project examined the impact of acute VF loss in adults with healthy vision in an attempt to identify the impact of sudden VF loss without the longer-term adaptation effects of glaucoma. Sudden VF loss had the greatest impact when proprioception is minimized, suggesting that sudden VF loss may affect central sensory integration processes. Further, peripheral vision may be more sensitive to movement in the visual environment than central vision. Lastly, falls incidence and fear of falling (FoF) were assessed in patients with glaucoma. The incidence of recurrent falls and FoF increased with more advanced glaucoma. In summary, this study may have identified underlying central mechanisms that contribute to falls in glaucoma. This information is important to future efforts focused on the development of effective management, rehabilitation and treatment protocols of patients with glaucoma.

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PREFACE

I would like to sincerely thank my advisor, Dr. Cham for her support throughout my PhD journey. Under her guidance, I have transformed from a novice researcher to a true biomechanist. I would like to acknowledge and thank my committee members: Dr. Kevin Chan, Dr. Ian Conner, Dr. Mark Redfern and Dr. Gadi Wollstein. I was so fortunate to have a committee comprised of experts so willing to contribute their unique skills and knowledge to my project. Thank you also to everyone at the Human Movement and Balance Lab for providing a sounding board and help whenever it was needed. There are also so many others at the University of Pittsburgh who contributed to this research in some way or another and I extend my gratitude to them for always helping in any way possible.

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LIST OF ACRONYMS

The following acronyms are used frequently throughout the manuscript:

AD = Axial diffusivity

AMD = Age-related macular degeneration

BNAVE = Balance near automatic virtual environment

COP = Center of pressure

CRT = Choice reaction time

DTI = Diffusion tensor imaging

DTI-MD = DTI mean diffusivity

FA = Fractional anisotropy

FoF = Fear of falling

IP = Information processing

NPL = Time-normalized path length

POAG = Primary open angle glaucoma

RD = Radial diffusivity

RNFL = Retinal nerve fiber layer

SOT = Sensory organization test

VF = Visual field

VF MD = Visual field mean deviation

1.0 INTRODUCTION

1.1 GLAUCOMA

Glaucoma is a leading cause of blindness, second only to cataracts (Kingman 2004). It is estimated that approximately 3 million Americans were diagnosed with glaucoma in the year 2010, however because glaucoma preferentially affects older adults, this number is expected to rise as the population ages (Quigley and Broman 2006). Studies have predicted that 64.3 million people will have glaucoma globally in 2020, with this number increasing to 118 million by 2040 (Tham, Li et al. 2014). Glaucoma is and will continue be a global health concern, making proper screening, treatments and training protocols a high priority.

Glaucoma causes damage to the retinal ganglion cells in the optic nerve, leading to irreversible peripheral visual field loss and blindness. There are several types of glaucoma that are characterized by cupping of the optic disc and thinning of the retinal nerve fiber layer (RNFL). The most prevalent type of glaucoma is primary open angle glaucoma (POAG), which is defined by an internal blockage of aqueous humor flow pathway that causes increased intraocular pressure, which then can lead to damage to the optic disc (Weinreb, Leung et al. 2016).

A complicating factor in glaucoma is that many patients are asymptomatic with regards to functional vision loss until the disease has reached an advanced stage (Leite, Sakata et al. 2011). Therefore, early screening and diagnosis of glaucoma is important to slow the progression of the disease. Diagnosis typically involves an assessment of structural damage to the optic nerve head and RNFL using imaging (Weinreb, Leung et al. 2016). The imaging modality used to assess degeneration of the RNFL in this project was optical coherence tomography, which is non-invasive and allows for measurements of RNFL thickness to be taken around the entire circumference of the retinal nerve (Bourne, Medeiros et al. 2005). The RNFL progressively becomes thinner as glaucoma progresses, so RNFL thickness can also be used to assess disease severity. For simplicity, RNFL thickness in this dissertation referred to the mean thickness of the RNFL from each eye. Structural damage, specifically RNFL thinning, has been shown to precede functional vision loss (Sihota, Sony et al. 2006, Wollstein, Kagemann et al. 2012). Functional visual field loss is assessed using perimetry that provides a psychophysical measurement of what a patient is able to see (Jonas, Aung et al. 2017); in the present study, the mean deviation from normal visual field in each eye was used. Throughout this dissertation, both structural (RNFL thickness) and functional (visual field mean deviation) were used to quantitatively assess glaucoma.

1.2 FALLS AND GLAUCOMA

Although the etiology of falls is complex and multidimensional in nature, it is well known that vision impairments are among the top risk factors for geriatric falls and falls-related injuries. Specifically, significant associations between falls and poor visual acuity (Tinetti, Speechley et al. 1988, Ivers, Cumming et al. 1998, Lord and Dayhew 2001, Klein, Moss et al. 2003), diminished contrast sensitivity (Lord, Clark et al. 1991, Lord, Ward et al. 1993, Lord, Ward et al. 1994, Ivers, Cumming et al. 1998, Lord and Dayhew 2001), depth perception (Lord and Dayhew 2001) and visual field (VF) losses (Ivers, Cumming et al. 1998, Coleman, Cummings et al. 2007, Freeman, Munoz et al. 2007) have been reported in the literature. In the Salisbury Eye Evaluation study, Freeman and colleagues examined associations between falls and a number of visual impairments including visual acuity, contrast sensitivity and VF losses (Freeman, Munoz et al. 2007). After controlling for demographic and health status, this study reported that only VF losses, particularly peripheral VF losses, remained significantly associated with falls (Freeman, Munoz et al. 2007). Other studies have reported similar findings (Kuyk, Elliott et al. 1996, Kuyk, Elliott et al. 1998, Kuyk and Elliott 1999, Hassan, Lovie-Kitchin et al. 2002, Turano, Broman et al. 2004, Coleman, Cummings et al. 2007). Glaucoma specifically has been shown to increase risk of falling fourfold (Lamoureux, Chong et al. 2008). Further, the risk of falling increases as the disease progresses (Lamoureux, Chong et al. 2008, Black, Wood et al. 2011).

In addition to an increased risk of falling, patients with glaucoma are more likely to have fear of falling (Ramulu, van Landingham et al. 2012, Yuki, Tanabe et al. 2013, Nguyen, Arora et al. 2015). Fear of falling is associated with decreased quality of life (Garatachea, Molinero et al. 2009, Cinarli and Koc 2017), activity avoidance (Nilsson, Drake et al. 2010, Kader, Iwarsson et al. 2016), and increased mortality (Chang, Chen et al. 2017). Additionally, glaucoma severity has been shown to be associated with less physical activity (Ramulu, Maul et al. 2012, Nguyen, Arora et al. 2015) and less travel from home (Ramulu, Hochberg et al. 2014). Thus, understanding the underlying reasons why patients with glaucoma fall and experience fear of falling are important clinically.

1.3 BALANCE CONTROL

Decreased balance performance during standing has been linked to increased prevalence of falling in older adults (Overstall, Exton-Smith et al. 1977, Melzer, Benjuya et al. 2004). Therefore, understanding the underlying mechanisms that contribute to decreased balance are important in understanding why patients with glaucoma fall and how to prevent falls. Balance requires accurate postural control to (1) maintain equilibrium in a specified posture (i.e. standing) and (2) to produce an appropriate reaction to an external disturbance (Pollock, Durward et al. 2000).

1.3.1 Multisensory integration

To produce appropriate reactions in order to maintain balance and prevent falling, the postural control system must accurately interpret and integrate sensory information from multiple inputs, a process known as multisensory integration. There are three main sensory inputs important for balance: vision, proprioception and vestibular. Effective integration of these sensory channels involves (1) resolving conflicting sensory inputs if two or more channels provide contradictory body state-related information and (2) relying on accurate sensory channels to generate postural adjustments if one or more afferent inputs are inaccurate/noisy or absent (Peterka 2002, Asslander and Peterka 2014). For example, if visual inputs necessary for postural control are absent, vestibular and proprioceptive inputs will be upregulated to compensate for visual deficits (Asslander and Peterka 2014).

1.3.2 Attention and balance control

Daily activities of living require multitasking where individuals are exposed to multiple sensory inputs that imply multiple actions. However, information-processing (IP) capabilities in the brain are limited and accurate responses to all inputs are not always possible. Postural control studies have shown that attentional resources are involved in sensory challenging conditions, particularly in older adults (Redfern, Jennings et al. 2001, Redfern, Mûller et al. 2002, Verghese, Buschke et al. 2002, Furman, Muller et al. 2003, Redfern, Talkowski et al. 2004, Yogev, Giladi et al. 2005, Hausdorff, Doniger et al. 2006, Holtzer, Friedman et al. 2007, Scherder, Eggermont et al. 2007, Yogev-Seligmann, Hausdorff et al. 2008, Redfern, Jennings et al. 2009, Mendelson, Redfern et al. 2010, Holtzer, Wang et al. 2012, Montero-Odasso, Verghese et al. 2012, Sparto, Fuhrman et al. 2013). This is empirically evident in experimental postural control studies using dual task paradigm protocols that combine an IP task with a postural challenge, creating interference between the two tasks in older adults (Redfern, Jennings et al. 2001, Redfern, Mûller et al. 2002, Redfern, Talkowski et al. 2004, Redfern, Jennings et al. 2009, Mendelson, Redfern et al. 2010, Sparto, Fuhrman et al. 2013). Typically, the IP task is more affected than the postural task as balance adjustments are given priority (i.e. “posture first” principle) (Redfern, Jennings et al. 2001, Muller, Jennings et al. 2004).

Glaucoma is associated with cognitive impairments in a number of domains, including executive function (Yochim, Mueller et al. 2012, Bulut, Yaman et al. 2016), that are associated with sensory processing for postural control. In particular, the impact of changes in executive function, particularly attentional processes, may have a detrimental effect on postural control in glaucoma patients. This hypothesis is consistent with previously published pilot studies suggesting that (1) balance in patients with glaucoma worsens when performing a secondary task to a greater extent than in healthy controls (Kotecha, Chopra et al. 2013) and (2) gait requires greater “mental effort” in patient with glaucoma compared to healthy controls (Geruschat and Turano 2007).

1.4 ROLE OF VISION IN BALANCE CONTROL

As previously stated, vision is one of the three main sensory inputs required for postural control. The importance of vision for balance is evident when comparing postural sway during conditions when vision is available to when vision is absent (i.e. eyes are closed). Healthy young adults sway more when both eyes are closed compared to when one or both eyes are open (Wu and Lee 2015). Further, postural sway response to a driving visual stimuli is has been reported to be greater during binocular (both eyes open) vision compared to monocular (one eye open) vision, suggesting that the amount of sensory input from vision is important for balance (Moraes, Lopes et al. 2009, Moraes, de Freitas et al. 2016).

Because glaucoma leads to peripheral vision loss and patients must rely more heavily on central vision, it is necessary to understand the role of both central and peripheral vision in postural control. There is some disagreement in the literature as to the roles that central and peripheral vision play in maintaining balance. Three general hypotheses of VF influences on postural control have been put forth in the literature: (1) the peripheral dominance theory that peripheral vision is more important than central vision in postural control (Amblard and Carblanc 1980); (2) the retinal invariance hypothesis suggests that central vision is just as important as peripheral vision in the control of posture (Straube, Krafczyk et al. 1994); and (3) the functional sensitivity hypothesis suggests that the periphery of the retina is most susceptible to lamellar optic flow and the central part is most sensitive to radial optic flow, and thus both central and peripheral have important, but functionally different, roles in maintaining posture (Stoffregen 1985, Warren and Kurtz 1992, Bardy, Warren Jr et al. 1999).

1.5 ROLE OF VISION IN GAIT

Vision provides important feedback necessary for motor control of gait. Previous studies have established that vision impairments negatively affect gait performance. Decreased visual acuity, contrast sensitivity and VF deficits have been linked to a higher rate of inability to complete walking tests (e.g. 8 meter walking test, Buck Center walking test) compared to healthy vision (Salive, Guralnik et al. 1994, West, Gildengorin et al. 2002). Poor contrast sensitivity is associated with decreased gait speed, increased step width, increased double support time (Wood, Lacherez et al. 2009) and decreased stride length (Wood, Lacherez et al. 2009, Duggan, Donoghue et al. 2017). Induced central VF loss in healthy adults resulted in decreased gait speed and increased double support time compared to normal vision (Timmis, Scarfe et al. 2016). Similarly, induced altered (e.g. limited vision, tunnel vision, double vision) or absent (i.e. eyes closed) vision in healthy adults has been correlated to altered gait compared to normal vision (Hallemans, Beccu et al. 2009, Helbostad, Vereijken et al. 2009, Pilgram, Earhart et al. 2016). There is also evidence that the motor control system is able to adapt to altered or absent vision by upregulating other sensory inputs such as vestibular and proprioception. For example, Reynard et. al. reported that gait speed in healthy adults was reduced when blindfolded compared to eyes open. However, when speed was controlled for between blindfolded and eyes open conditions, there was no difference in gait variability or stability (Reynard and Terrier 2015). Thus, healthy adults may adopt a more cautious gait strategy in response to vision loss, but they are able to use other senses to maintain stability. There is also evidence for long-term sensory adaptations to chronic vision loss; gait was less perturbed in participants who were blind compared to blindfolded healthy adults (Hallemans, Ortibus et al. 2010).

1.6 GLAUCOMA AS A NEURODEGENERATIVE DISEASE

Glaucoma has been thought of primarily as an eye disease that induces peripheral VF defects. However, the pioneering work of Gupta, Yücel and colleagues provided evidence that primary open angle glaucoma (POAG) is not only an eye disease, but is also a neurodegenerative condition that impacts the visual pathway in the brain of patients diagnosed with this condition in various ways (Gupta and Yucel 2001, Gupta and Yucel 2003, Gupta and Yucel 2006, Gupta and Yucel 2007, Gupta and Yucel 2007, Gupta and Yucel 2007, Gupta and Yücel 2007, Yucel and Gupta 2008, Yucel and Gupta 2008, Gupta, Greenberg et al. 2009). POAG alters brain structure (Li, Cai et al. 2012, Zikou, Kitsos et al. 2012, Williams, Lackey et al. 2013) and function (Dai, Morelli et al. 2013). More specifically, significant changes in grey matter density and grey and white matter volumes have been reported in patients with POAG in vision-related brain regions in the occipital lobe (Li, Cai et al. 2012, Williams, Lackey et al. 2013), and these changes are modulated by the disease severity. Research has shown that brain alterations may not be limited to vision related regions of the brain; Boucard et al. found preliminary evidence of white matter deterioration in the corpus callosum and parietal lobe (Boucard, Hanekamp et al. 2016). Zikou and colleagues reported voxel-based microstructural changes in parts of the basal ganglia, including the putamen and the caudate nucleus (Zikou, Kitsos et al. 2012). Resting-state functional MRI also suggested reduced intrinsic functional connectivity between visual cortex and balance-related brain regions in patients with POAG (Dai, Morelli et al.

2013). Further, brain alteration in the visual pathway of patients with glaucoma may precede functional deficits in the VF (Murphy, Conner et al. 2016).

Previous studies of brain connectivity in glaucoma have reported decreased fractional anisotropy (FA), as well as increased mean diffusivity (MD) and radial diffusivity (RD) in the optic radiation of patients with glaucoma versus healthy controls (Garaci, Bolacchi et al. 2009, Engelhorn, Michelson et al. 2012, Zhang, Li et al. 2012, Murai, Suzuki et al. 2013, Kaushik, Graham et al. 2014, Schmidt, Mennecke et al. 2014, Boucard, Hanekamp et al. 2016, Tellouck, Durieux et al. 2016, Li, Miao et al. 2017). Zhang et al. reported increased optic radiation axial diffusivity (AD) in patients with glaucoma (2012), while others have shown that there is decreased optic radiation AD (Li, Miao et al. 2017) or no difference in optic radiation AD between glaucoma and control groups (Kaushik, Graham et al. 2014, Tellouck, Durieux et al. 2016). Fewer studies have examined the relationship between glaucoma and DTI measures outside of the optic radiation, but there is evidence of structural degeneration of white matter in the brain beyond the primary visual pathway (Schmidt, Mennecke et al. 2014, Boucard, Hanekamp et al. 2016).

1.7 GOALS

This project focused on the ability of patients with glaucoma to centrally integrate multisensory inputs important for balance and gait, with the hope that it would provide insights into the etiology of balance and gait impairments in this population. This knowledge is important to develop and implement effective intervention programs targeted on the treatment of specific postural control impairments, e.g. central integration of multisensory inputs relevant for balance/mobility, that contribute to falls in patients with glaucoma. For example, established balance rehabilitation fundamentals, used in vestibular patients (Whitney and Rossi 2000, Sparto, Furman et al. 2004, Brown, Whitney et al. 2006, Alsalaheen, Mucha et al. 2010, Alrwaily and Whitney 2011, Whitney and Sparto 2011, Alghadir, Iqbal et al. 2013, Alahmari, Sparto et al. 2014), may be effective in patients with glaucoma. Moreover, this project aimed to unravel potential neuro-mechanisms explaining balance impairments in patients with glaucoma that could be used to monitor the effectiveness of balance rehabilitation therapies.

The goals of this doctoral research were as follows:

- **Goal 1:** Assess falls incidence and fear of falling during daily activities of living in patients with glaucoma [Chapter 2].
- **Goal 2:** Examine the impact of acute visual field loss in adults with healthy vision to identify the impact of sudden visual field loss without the longer-term adaptation effects of glaucoma [Chapter 3].
- **Goal 3:** Determine the association between glaucoma and the ability to integrate sensory information and attention relevant for balance [Chapter 4].
- **Goal 4:** Determine the association between glaucoma and the ability to integrate sensory information and attention during gait [Chapter 5].
- **Goal 5:** Examine brain connectivity in glaucoma and its relationship to attention and balance control in glaucoma [Chapter 6].

2.0 GLAUCOMA AND FEAR OF FALLING, A SURVEY STUDY

I would like to acknowledge Dr. Susan Whitney for her assistance in the development of the falls survey.

2.1 INTRODUCTION

Falls and falls-related injuries are a significant clinical concern in patients with glaucoma. Glaucoma increases risk of falling by three to four times (Haymes, Leblanc et al. 2007, Lamoureux, Chong et al. 2008), and this risk increases as glaucoma progresses (Black, Wood et al. 2011). Further, patients with glaucoma have a higher incidence of falls-related injuries including femur fractures (Colon-Emeric, Biggs et al. 2003, Lamoureux, Chong et al. 2008, Patino, McKean-Cowdin et al. 2010, Loriaut, Loriaut et al. 2014). The high rate of falls and falls-related injuries in glaucoma increase the cost of medical care in patients with glaucoma (Bramley, Peeples et al. 2008).

In addition to falls-related physical injuries, patients with glaucoma have greater fear of falling (FoF) symptoms compared to healthy individuals, and FoF symptoms are modulated by glaucoma severity (Turano, Rubin et al. 1999, Ramulu, van Landingham et al. 2012, Yuki, Tanabe et al. 2013). FoF is defined as a concern about falling that causes avoidance of activities of daily living (Tinetti and Powell 1993). FoF is often linked to depression (Moreira Bde, Dos Anjos et al. 2016), activity avoidance (Lachman, Howland et al. 1998, Yardley and Smith 2002, Fletcher and Hirdes 2004), as well as decreased quality of life (Lachman, Howland et al. 1998, Cinarli and Koc

2017) in a number of populations. FoF has also been associated with worse balance performance (Maki, Holliday et al. 1991, Vellas, Wayne et al. 1997, Rosen, Sunnerhagen et al. 2005, Atmaca, Tander et al. 2013, Althomali and Leat 2017). As in other clinical populations with FoF symptoms, in glaucoma, patients with significant FoF are less active than patients who have no or minimal FoF (Wang, Rousseau et al. 2012, Nguyen, Arora et al. 2015). It is worth noting that on the positive side, there is evidence that training programs designed to improve balance can actually reduce FoF, irrespective of fall history (Hagedorn and Holm 2010, Gusi, Carmelo Adsuar et al. 2012).

The aims of this study were threefold:

- Aim 1: This study aimed to correlate both functional (visual field mean deviation – VF MD) and structural (retinal nerve fiber –RNFL thickness) with history of falls and FoF in glaucoma. Previous studies have examined the prevalence of falls and FoF in glaucoma by assessing functional visual field (VF) loss only and not measures of structural loss to the optic nerve associated with glaucoma. Because RNFL thinning is known to precede functional VF deficits (Sihota, Sony et al. 2006, Wollstein, Kagemann et al. 2012), RNFL thickness, in addition to VF MD, was expected to be linked to falls and FoF in glaucoma.
- Aim 2: Determine if there are specific activities of daily living that cause increased concern of falling in patients with glaucoma. Previous studies have used one overall measure to assess FoF in glaucoma, either by a single FoF question (“Are you afraid of falling?”) (Turano, Rubin et al. 1999, Yuki, Tanabe et al. 2013), or by assessing FoF during multiple activities with one weighted measure of FoF (Ramulu, van Landingham et al. 2012, Nguyen, Arora et al. 2015). Understanding which activities

are associated with FoF in glaucoma may help in designing training protocols to reduce FoF and fall risk. Complex tasks that challenge the postural system (e.g. stairs, walking on slippery surface) were expected to be the most sensitive to FoF in glaucoma.

- Aim 3 (exploratory): Because there is evidence that balance training protocols may reduce FoF, a pilot aim of this study was to observe whether balance performance and FoF are related in patients with glaucoma. Glaucoma patients concerned about falling were anticipated to have worse balance (i.e. higher sway magnitude and time-normalized path length of center of pressure (COP)) than patients who were not concerned.

2.2 METHODS

2.2.1 Participants

Individuals diagnosed with glaucoma were recruited from an NIH funded study entitled “Novel Glaucoma Diagnostics for Structure and Function” (NIH R01-EY013178 / Clinical Trials #NCT00286637). A survey about falls and FoF was mailed to 2,653 individuals with directions on how to complete the survey and return to the study team. Ninety-nine (N=99) participants with glaucoma responded by completing the survey. The complete survey can be found in Appendix A. Demographic information including age and glaucoma assessment measures (RNFL thickness and VF MD) was collected for survey participants. Written informed consent approved by the University of Pittsburgh Institutional Review Board was obtained with the survey.

For exploratory Aim 3 of the study comparing FoF with balance performance, a subset (N= 8) of participants who completed the mailed survey was recruited to complete a balance assessment. Balance subset participants were able to stand for at least 2 hours. Exclusionary criteria for the balance subset were self-reported orthopedic, neurological, pulmonary or cardiovascular conditions that may negatively impact balance and ocular pathologies other than glaucoma. Potential balance subset participants were also excluded if they were taking any central nervous system anti-depressant drugs, including benzodiazepines or barbiturates, or taking more than five prescription drugs, as both may increase fall risk (Caramel, Remarque et al. 1998, Weiner, Hanlon et al. 1998). Written informed consent approved by the University of Pittsburgh Institutional Review Board was obtained prior to balance testing.

2.2.2 Protocol

The survey included two components; the first consisted of questions about falling prevalence in the last year (Studenski, Duncan et al. 1994, Tinetti 2003). A fall was defined as an event that results in coming to rest inadvertently on the ground or floor or other lower level. A summary of the questions and possible answers are summarized in Table 1.

Table 1. Survey questions related to prevalence of falls in the last year.

Fall prevalence questions
Have you fallen in the last year?
Never
Once
Twice
3 times or more
How often have you broken a bone from a fall after the age of 50?
Never
Once
Twice
3 times or more
Did any of the falls result in a visit to the doctor/emergency room or hospitalization?
Yes
No

The second component of the survey was the Falls Efficacy Scale International (FES-I), a well-validated means of assessing FoF (Yardley, Beyer et al. 2005). The FES-I contains 16 questions, each asking for the level of concern when completing daily activities of living. Level of concern is assessed on a four-point scale (not at all concerned, fairly concerned, somewhat concerned and very concerned). Activities included range from simple in-home tasks (e.g. cleaning the house, preparing simple meals) to difficult activities in the community (e.g. walking on slippery surface, walking in a crowd).

The balance assessment completed by a subset (N=8) of survey participants consisted of an adapted version of the Sensory Organization Test (SOT) on an Equitest posture platform (Neurocom, Inc) located in the Jordan Balance Disorders Laboratory within the Eye & Ear Institute of Pittsburgh. Participants wore a safety harness that would prevent hitting the floor in the event that they lost their balance. During balance testing, participants were instructed to stand as still as possible without locking their knees. The SOT has been shown to be effective at evaluating sensory integration capabilities relevant to balance (Nashner, Black et al. 1982, Bronte-Stewart, Minn et al. 2002). The Equitest platform is capable of sway-referencing, which provides rotations of the floor and/or the visual scene in direct proportion to an individual's sway of vision and/or proprioception, respectively. For example, sway-referencing the floor causes movements of the support surface in an attempt to keep the ankle angle constant. The purpose of using sway-referencing of the floor is to reduce the reliability of proprioceptive information from the ankle for balance. The same principle is used for sway-referencing of the visual scene, resulting in erroneously stable vision even though the person is swaying (Nashner, Black et al. 1982). The platform records ground reaction forces under the feet during standing. Sway referencing was provided through the method of low-pass filtering of the center of pressure (COP) data collected by the Equitest platform. There are six conditions in the SOT test, including combinations of fixed / sway-referenced visual scene and floor conditions and eyes closed / open conditions. For brevity purposes, only SOT condition 1 (eyes open, fixed visual scene, fixed floor) and SOT condition 4 (eyes open, fixed visual scene, sway-referenced floor) were included in exploratory Aim 3. These conditions were selected to compare quiet standing (SOT condition 1) to a condition where balance control was challenged via reduced proprioception (SOT condition 4). Reduced proprioception has been shown to negatively impact balance in patients with glaucoma compared to healthy adults (Black, Wood et al. 2008, Kotecha, Richardson et al. 2012).

Balance trials lasted 3 minutes and postural sway was assessed using the anterior-posterior COP data collected at a sampling frequency of 100 Hz. COP data was filtered using a low-pass Butterworth filter with a cutoff frequency of 2.5 Hz. Sway magnitude was defined as the root-mean-square (RMS) of the filtered COP displacement [Equation 1]. Time-normalized path length (NPL) of the COP was calculated by averaging the absolute value of the derivative over time [Equation 2].

Equation 1. Center of pressure root mean square

$$COP\ RMS = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(COP_i - COP_{avg}\right)^2}$$

Equation 2. Center of pressure time-normalized path length

$$COP\ NPL = \frac{1}{T}\sum_{i=1}^{N}\left|COP_i - COP_{i-1}\right|$$

T = duration of trial

2.2.3 Analysis

Statistical analysis was performed in JMP Version 10 (SAS Institute, Inc). Preliminary analyses were performed to unravel potential sample bias between (1) the patient group who were asked to participate in the survey study and did not respond, (2) the participants who completed the survey study and (3) the subset of participants who completed balance assessments as part of exploratory Aim 3. Two-way t-tests were performed to determine differences in mean age, RNFL thickness and VF MD between all groups.

Aim 1 analyses: The first analyses aimed to determine if there were differences in age and glaucoma assessments between individuals who experienced falls or recurrent falls and those who did not. Falls in the last year were categorized into 0 or ≥1 falls, and two-way t-tests were performed to test if the mean age and glaucoma assessments were statistically different between 0 and ≥1 falls. Similar t-tests were run to determine differences in age and glaucoma assessments in recurrent fallers (≥2 falls) versus non-recurrent fallers (0-1 falls). Also of interest was the seriousness of the sustained falls-related injuries evaluated based on the incidence of medical care sought as a result of falling, so the mean age and glaucoma assessments of those who visited a doctor or emergency room after a fall. This information was compared to those who fell but did not seek medical attention. Glaucoma was assessed using RNFL thickness and VF MD of better and worse eyes for all analyses. Statistical significance was set at 0.05 for all analyses.

Aim 2 analyses: The second set of analysis aimed to determine if age and glaucoma assessments (RNFL thickness and VF MD) were correlated with FoF during activities of daily living. The four-point scale used in the FES-I was converted into two categories: not concerned if participants answered "not at all concerned" and concerned for all other answers ("somewhat concerned," "fairly concerned," and "very concerned"). A two-point scale was used because there were not enough participants to detect statistically meaningful differences between the four levels of concern. Two-way t-tests were performed for each of the 16 FES-I activities to assess whether mean age, RNFL thickness or VF MD differed between participants concerned about falling and those who were not concerned. Statistical significance was set at 0.05 for all analyses.

Exploratory Aim 3 analyses: Due to the small sample of participants (N=8) who completed both the survey and balance assessment, COP RMS and NPL during SOT conditions 1 and 4 were only qualitatively compared to FoF in an effort to determine if worse balance performance is associated with increased FoF. To focus comparisons on the most meaningful activities of daily living, only the FES-I activities where over half (N>50) of survey participants expressed concern about falling were included. The 50% threshold was used to identify and concentrate on activities that would be beneficial to include in training interventions to improve balance and prevent falls in patients with glaucoma. Therefore, only the following activities were compared to balance measures: walking up/down stairs, walking on a slippery surface, walking on an uneven surface and walking up or down a slope.

2.3 RESULTS

The mean VF MD of the more glaucomatous eye of the 99 participants was similar to that of the population who were mailed the survey ($p>0.05$). However, the survey participants group had greater mean age, lower mean VF MD of the better eye, and thinner RNFL in both eyes than the larger population ($p<0.05$) [Table 2]. The subset of survey participants who also completed balance assessments had similar in age and glaucoma assessments (RNFL thickness and VF MD) to the survey participant group ($p<0.05$) [Table 2].

Table 2. Mean and standard deviation of demographic information of the population who received mailed surveys, the participants who completed the survey and the subset of participants who completed both survey and balance assessment. RNFL thickness is reduced and VF MD becomes more negative as glaucoma advances. *Denotes statistically significant differences between the population who received surveys and the group of participants who completed the survey.

	N	Age (years)	VF MD worse eye (dB)	VF MD better eye (dB)	RNFL thickness worse eye (mm)	RNFL thickness better eye (mm)
Mailed survey	2653	65.9 ± 14.1*	-8.5 ± 8.2	-1.9 ± 3.9*	70.3 ± 13.2*	86.3 ± 12.9*
Survey participants	99	71.1 ± 10.7*	-8.8 ± 7.6	-3.3 ± 4.8*	64.0 ± 12.5*	75.7 ± 11.2*
Balance subset	8	68.0 ± 7.3	-9.5 ± 7.8	-1.8 ± 3.3	64.1 ± 6.4	77.6 ± 13.2

VF MD of the better and worse eyes was significantly lower ($p_{\text{worse eye}}=0.03$, $p_{\text{better eye}}=0.04$) in recurrent fallers (2 or more falls in past year) compared to non-recurrent fallers (0 or 1 falls in the past year) [Table 3]. There were no significant differences in RNFL thickness or age between recurrent and non-recurrent fallers. There were no statistical differences in age, VF MD or RNFL thickness, between fallers (1 or more fall in past year) and non-fallers (0 falls in past year) ($p>0.05$).

Those who sought medical care as a result of falling were older than those who did not visit a doctor or emergency room after falling (p=0.009). The VF MD of the worse eye among those who needed medical care after falling was greater (i.e. less VF loss) than those who did not (p=0.04) [Table 3].

Table 3. Mean and standard deviation age, VF MD and RNFL thickness for better and worse eyes among participants who experienced a fall in the last year, recurrent falls in the last year, and those who sought medical care after falling. RNFL thickness is reduced and VF MD becomes more negative as glaucoma advances. *Denotes statistically significant differences in mean between two groups (p<0.05).

	N	Age (years)	VF MD worse eye (dB)	VF MD better eye (dB)	RNFL thickness worse eye (mm)	RNFL thickness better eye (mm)
Fall in last year						
0	54	72.9 ± 8.7	-8.1 ± 8.0	-2.7 ± 4.3	63.9 ± 12.7	77.1 ± 9.8
≥1 falls	44	68.9 ± 12.5	-9.7 ± 7.1	-4.0 ± 5.3	64.0 ± 12.4	73.8 ± 12.7
Recurrent falls in last year						
0-1 falls	81	70.8 ± 12.6	-8.0 ± 7.2*	-2.8 ± 4.3*	63.7 ± 12.8	76.0 ± 11.2
≥2 falls	17	68.4 ± 14.1	-12.4 ± 8.6*	-5.6 ± 6.1*	65.1 ± 11.4	74.2 ± 11.6
Medical care as a result of fall						
Yes	25	71.2 ± 11.3*	-7.9 ± 11.3*	-3.3 ± 5.7	62.1 ± 12.4	74.3 ± 12.2
No	21	63.2 ± 10.8*	-12.0 ± 9.0*	-5.5 ± 5.7	66.5 ± 11.2	74.8 ± 13.0

The results of the FES-I show that those with concern about falling during activities of daily living had more advanced glaucoma than those who had no FoF. VF MD of concerned participants was significantly lower (i.e. worse VF loss) than those who were not concerned for 8 of the 16 activities in the worse eye and 9 activities in the better eye. RNFL of the worse and better eyes were significantly thinner among participants with a FoF in 4 and 3 activities, respectively, than those who were not concerned about falling. Age had an impact on 4 of the activities, with older participants having greater concern about falling than younger participants (p<0.05) [Table 4]. The activities in which over half of participants were concerned about falling were those that involved walking in difficult environments (i.e. walking up/down stairs, walking on a slippery surface, walking on uneven surface, and walking up or down a slope). In these conditions, VF MD of one or both eyes was significantly less among concerned participants than those who had no FoF ($p<0.05$) [Table 4].

Table 4. Mean and standard deviation age, VF MD and RNFL thickness for better and worse eyes among participants who were concerned and not concerned about falling during activities included in the FES-I. RNFL thickness is reduced and VF MD becomes more negative as glaucoma advances. *Denotes statistically significant differences in mean between participants who were concerned about falling compared to those who were not concerned ($p<0.05$).

	N	Age (years)	VF MD worse eye (dB)	VF MD better eye (dB)	RNFL thickness worse eye (mm)	RNFL thickness better eye (mm)
Cleaning house						
Concerned	18	73.5 ± 10.3	-11.4 ± 8.2	-5.8 ± 6.2*	59.9 ± 12.2	73.6 ± 13.1
Not concerned	80	70.5 ± 10.8	-8.2 ± 7.4	-2.8 ± 4.3*	64.9 ± 12.4	76.2 ± 10.8
Dressing/undressing						
Concerned	16	75.2 ± 9.8*	-10.5 ± 7.6	-3.7 ± 4.9	58.6 ± 11.5*	74.3 ± 11.1
Not concerned	82	70.3 ± 10.8*	-8.5 ± 7.6	-3.2 ± 4.8	65.0 ± 12.5*	76.0 ± 11.3
Preparing meal						
Concerned	12	75.2 ± 10.7	-13.8 ± 8.5*	-7.7 ± 6.8*	55.0 ± 8.0*	67.3 ± 10.6*
Not concerned	86	70.5 ± 10.7	-8.1 ± 7.3*	-2.8 ± 4.3*	65.2 ± 10.8*	76.9 ± 10.8*
Bath/Shower						
Concerned	43	72.1 ± 12.1	-9.4 ± 8.2	-4.1 ± 5.8	62.4 ± 14.7	75.3 ± 10.2
Not concerned	55	70.3 ± 9.5	-8.4 ± 7.1	-2.7 ± 3.8	65.3 ± 10.3	76.0 ± 12.0
Shopping						
Concerned	22	73.1 ± 10.2	-12.4 ± 8.6	-6.8 ± 6.3	61.5 ± 11.3	73.2 ± 12.2
Not concerned	76	70.5 ± 10.9	-7.7 ± 7.0	-2.4 ± 4.0	64.7 ± 12.8	76.4 ± 10.9
Get in/out of chair						
Concerned	12	72.4 ± 11.2	-11.1 ± 9.0	-6.6 ± 7.3	61.7 ± 12.1	73.7 ± 13.5
Not concerned	86	70.9 ± 10.7	-8.5 ± 7.4	-3.0 ± 4.3	64.3 ± 12.6	76.0 ± 11.0
Up/down stairs						
Concerned	53	71.3 ± 11.5	-10.3 ± 8.0*	-4.7 ± 5.7*	63.3 ± 14.9	75.4 ± 11.9
Not concerned	45	70.9 ± 9.8	-7.0 ± 6.8*	-1.8 ± 3.0*	64.7 ± 9.1	76.0 ± 10.4
Walk around neighborhood						
Concerned	35	71.9 ± 10.8	-11.1 ± 8.3*	-5.1 ± 6.1*	61.5 ± 11.1	73.2 ± 11.7
Not concerned	63	70.6 ± 10.8	-7.5 ± 7.0*	-2.4 ± 3.6*	65.4 ± 13.1	77.1 ± 10.8

Table 4 (continued).

	N	Age (years)	VF MD worse eye (dB)	VF MD better eye (dB)	RNFL thickness worse eye (mm)	RNFL thickness better eye (mm)
Reaching for object						
Concerned						
Not concerned	29	71.9 ± 13.7	-8.4 ± 7.8	-3.9 ± 5.3	64.3 ± 14.4	74.9 ± 12.2
	69	70.8 ± 9.3	-9.0 ± 7.6	-3.1 ± 4.6	63.8 ± 11.6	76.0 ± 10.8
Answer telephone						
Concerned	20	74.7 ± 11.9*	-11.2 ± 8.9*	-5.5 ± 5.9*	61.5 ± 11.1	74.7 ± 11.6
Not concerned	78	70.2 ± 10.3*	-8.2 ± 7.2*	-2.8 ± 4.4*	64.6 ± 12.8	75.9 ± 11.2
Walking on slippery surface						
Concerned	85	71.7 ± 11.0	-9.2 ± 7.8*	-3.4 ± 4.9	63.4 ± 12.9	75.2 ± 11.1
Not concerned	13	67.1 ± 7.4	-6.2 ± 5.6*	-3.0 ± 4.0	67.5 ± 8.9	78.6 ± 12.1
Visiting friend/relative						
Concerned	18	74.7 ± 9.9*	-11.6 ± 8.8	-5.9 ± 7.3	58.3 ± 11.0*	71.1 ± 11.1*
Not concerned	80	70.3 ± 10.8*	-8.2 ± 7.2	-2.9 ± 4.1	65.2 ± 12.5*	76.7 ± 11.0*
Walking in crowd						
Concerned	32	73.4 ± 12.1	-11.4 ± 8.3*	-5.5 ± 6.6*	62.1 ± 12.5	73.8 ± 12.4
Not concerned	66	70.0 ± 10.0	-7.5 ± 6.98*	-2.4 ± 3.4*	64.8 ± 12.5	76.5 ± 10.6
Walking on uneven surface						
Concerned	75	71.5 ± 11.3	-9.4 ± 7.8*	-3.8 ± 5.1*	63.6 ± 13.5	75.0 ± 10.6
Not concerned	23	69.6 ± 8.5	-6.7 ± 6.6*	-2.0 ± 3.3*	65.0 ± 8.9	78.0 ± 12.9
Walking up/down slope						
Concerned	56	73.3 ± 10.5*	-9.4 ± 7.8	-4.2 ± 5.6*	62.9 ± 14.8	74.2 ± 11.6
Not concerned	42	68.2 ± 10.5*	-8.1 ± 7.4	-2.3 ± 3.4*	65.3 ± 8.6	77.6 ± 10.5
Social event						
Concerned	24	72.3 ± 11.0	-12.8 ± 8.7*	-6.8 ± 7.2*	58.4 ± 10.4*	69.3 ± 11.2*
Not concerned	74	70.5 ± 10.7	-7.5 ± 6.8*	-2.4 ± 3.4*	65.7 ± 12.6*	77.7 ± 10.5*

Comparing FoF and balance performance, participants who expressed concern for falling during challenging walking activities had greater COP NPL during SOT conditions 1 and 4 than those who were not concerned about falling. FoF participants had greater COP RMS than participants who were not afraid of falling, however, the differences in COP RMS were not as great as those observed in COP NPL [Table 5].

Table 5. Mean and standard deviation of center of pressure root mean square (COP RMS) and time-normalized path length (COP NPL) during standing compared to concern of falling during challenging walking activities. Overall, RMS and NPL of concerned participants were greater than participants who were not concerned about falling.

	N	SOT 1 COP RMS (cm)	SOT 1 COP NPL (cm/s)	SOT 4 COP RMS (cm)	SOT 4 COP NPL (cm/s)
Up/down stairs					
Concerned	1	0.83	0.86	1.74	2.65
Not concerned	7	0.51 ± 0.22	0.70 ± 0.22	1.54 ± 0.62	1.91 ± 0.33
Walking on slippery surface					
Concerned	5	0.55 ± 0.20	0.79 ± 0.22	2.03 ± 0.75	2.14 ± 0.46
Not concerned	3	0.55 ± 0.33	0.62 ± 0.20	1.29 ± 0.28	1.77 ± 0.13
Walking on uneven surface					
Concerned	4	0.58 ± 0.21	0.85 ± 0.18	1.83 ± 0.72	2.29 ± 0.35
Not concerned	4	0.52 ± 0.27	0.59 ± 0.17	1.29 ± 0.33	1.71 ± 0.16
Walking up/down slope					
Concerned	2	0.56 ± 0.37	0.76 ± 0.14	1.63 ± 0.64	2.47 ± 0.25
Not concerned	6	0.54 ± 0.21	0.71 ± 0.25	1.35 ± 0.55	1.85 ± 0.31

2.4 DISCUSSION

This study shows that prevalence of recurrent falls and FoF are related to assessments of glaucoma. Specifically, participants who were recurrent fallers (≥2 falls in the past year) had greater VF loss in better and worse eyes than those who did not experience multiple falls. VF loss in both eyes was generally greater in participants with FoF than those not concerned about falling, particularly during challenging walking conditions. RNFL thickness was related to FoF for some activities surveyed, but not as many activities as VF MD. Lastly, during challenging walking conditions where over half of the surveyed population expressed FoF, there is preliminary evidence that decreased balance performance (i.e. increased COP NPL and to a lesser extent increased COP RMS during SOT conditions 1 and 4) is associated with FoF.

The finding that recurrent fallers having more severe glaucoma than non-recurrent fallers is consistent with a previous study that showed glaucoma was a factor differentiating recurrent fallers from those who experienced a single fall over a yearlong period (Yoo 2011). However, patients who sought medical care as a result of falling had less severe VF loss in the worse eye than those who fell, but did not seek medical care. There are two possible explanations for this result; the first is that patients with early/moderate glaucoma were less concerned about falling and therefore exhibited more risk taking behavior than those with severe glaucoma, which may have led to more serious falls and fall-related injuries in mild/moderate glaucoma patients. Alternatively, the results show that participants who required medical care as a result of a fall were older than those who did not seek care. In this case, age may be a stronger predictor of need for medical care after a fall.

The present results are consistent with previous reports of FoF in patients with glaucoma using VF loss as the assessment of glaucoma. Ramulu et al. studied FoF in glaucoma using the University of Illinois at Chicago Fear of Falling Measure, a questionnaire that asks about concern about falling during sixteen activities similar to those in the FES-I (Velozo and Peterson 2001). The findings show that patients with glaucoma have an overall greater FoF than healthy controls, and greater FoF is associated with more severe VF loss (Ramulu, van Landingham et al. 2012). When FoF is assessed with a single question (i.e. “Are you afraid of falling?”), the findings are mixed in the literature. One study found greater FoF in glaucoma than healthy controls (Yuki, Tanabe et al. 2013), whereas another study found no difference in FoF between the two groups (Turano, Rubin et al. 1999). It is unclear why there are discrepancies between Turano's study and more recent studies, as the participants are overall similar in age and glaucoma severity. Only one study has related FoF in glaucoma to functional measures, specifically the amount of time spent doing moderate or vigorous activity each day. A moderate or severe FoF in patients with glaucoma was associated with a fourfold decrease in time spent in moderate/vigorous activity compared to those with little or no FoF (Nguyen, Arora et al. 2015).

RNFL thickness, a structural assessment of glaucoma, was not related to prevalence of recurring falls and was not as sensitive to FoF as VF MD, a functional assessment of glaucoma. RNFL thickness was anticipated to be lower in recurrent fallers than non-fallers and in those with FoF compared to unconcerned participants. This hypothesis was based on research showing that RNFL structural damage precedes functional loss in the visual field and can also be used to detect glaucoma before functional measures of the VF (Sihota, Sony et al. 2006, Wollstein, Kagemann et al. 2012). Based on the results of this study, it appears that risk of falling and FoF may be governed by functional measures of VF loss. Vision is an important sensory input for balance and mobility (Balasubramaniam and Wing 2002, Peterka 2002, Peterka and Loughlin 2004, Maurer, Mergner et al. 2006) so the results of this study reflect that recurrent falls and FoF are associated with loss of the visual inputs necessary for stability.

The activities that glaucoma patients expressed the greatest concerns about falling were: walking up/down stairs, walking on a slippery surface, walking on an uneven surface and walking up or down a slope. Similar reports have shown that these activities (with the exception of walking up/down stairs) are linked to a greater FoF compared to other FES-I activities in active, healthy older adults (Liu 2015). These specific activities require gait adaptations and well-coordinated responses to prevent falling, which may explain why they are associated with increased FoF (Livingston, Stevenson et al. 1991, Redfern, Cham et al. 2001, Cham and Redfern 2002, Thies, Richardson et al. 2005, Marigold and Patla 2008, Lawrence, Domone et al. 2015).

Preliminary trends show that FoF in glaucoma patients was associated with worse balance performance, specifically higher sway velocity and to a lesser extent sway magnitude. Sway velocity (COP NPL) appeared to be a more sensitive balance measure than sway magnitude (COP RMS) in detecting changes in balance between FoF participants and those who are not afraid of falling. The greatest difference in COP NPL was observed when comparing balance during SOT condition 4 to FoF during uneven walking. This is particularly interesting because proprioceptive cues are reduced by sway-referencing floor in SOT condition and proprioceptive cues are noisy when walking on an uneven floor. Thus, training patients with glaucoma to adapt to altered proprioceptive cues relevant for balance may help to improve balance control and reduce FoF. FoF has been shown to be correlated to balance deficits in healthy older adults (Maki, Holliday et al. 1991, Vellas, Wayne et al. 1997) and stroke patients (Rosen, Sunnerhagen et al. 2005). However, it remains unclear whether FoF causes increased postural sway on balance tests or whether FoF is a reflection of impairments in the postural control system (Maki, Holliday et al. 1991). Because the present results are from a small pilot sample, future work should further explore the interaction between FoF and balance control in patients with glaucoma to determine if balance intervention training may help reduce FoF and activity avoidance.

A limitation to this study was the method by which the survey was conducted. Surveys were mailed to 2,653 individuals and only ninety-nine (3.7%) completed and returned the survey. An improved response rate would have provided a larger sample size and statistical power to detect differences in falling and FoF in patients with glaucoma. Future studies should consider alternative methods of surveying glaucoma patients, such as conducting in-person questionnaires during regularly scheduled clinic visits. Additionally, the relationship between RNFL and VF MD is not linear; there is a threshold of ~17% of structural loss (RNFL thinning) before detectable VF loss (Wollstein, Kagemann et al. 2012). Because of this, RNFL thickness may be a more important predictor than VF MD of falls and FoF in the early stages of glaucoma before there is noticeable VF loss. Therefore, although VF MD was more sensitive to changes in FoF in the current population, future work should assess the relationship between fall risk and FoF to RNFL and VF MD in different groups (i.e. early, moderate, advanced glaucoma) as opposed to the current approach that did not stratify disease stages.

2.5 CONCLUSION

Functional measures of visual field loss in glaucoma are associated with recurrent falls and FoF. Further, there is preliminary evidence that increased postural sway velocity, and to a lesser extent sway magnitude, is associated with FoF in patients with glaucoma. This is important to developing balance-training interventions to decrease fall risk and FoF.

3.0 EFFECTS OF ACUTE PERIPHERAL/CENTRAL VISUAL FIELD LOSS ON STANDING BALANCE

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3.1 INTRODUCTION

Vision impairments are among the leading risk factors for falls and falls-related injuries. Lamoureux and colleagues reported a twofold increase in the risk of falling with severe vision impairment in one eye and mild/moderate visual disability in the other eye (2008). Hip fractures are also associated with poor vision (Felson, Anderson et al. 1989). Specific aspects of visual function implicated in falls include poor visual acuity (Lord and Dayhew 2001), diminished contrast sensitivity (Lord, Clark et al. 1991, Lord, Ward et al. 1993, Lord, Ward et al. 1994, Lord and Dayhew 2001), depth perception (Lord and Dayhew 2001) and visual field (VF) losses (Coleman, Cummings et al. 2007, Freeman, Munoz et al. 2007). In the Salisbury Eye Evaluation study, Freeman and colleagues examined associations between falls and visual impairments including visual acuity, contrast sensitivity and VF losses. After controlling for demographic and health status, only VF losses, particularly peripheral VF losses, remained significantly associated with falls (Freeman, Munoz et al. 2007). Further, the impact on gait and stability is related to the amount of VF loss. Timmis et al. used a contact lens model similar to that used in the present study to occlude the central VF to varying degrees in healthy young adults. The results show that individuals exhibited gait adaptations and different obstacle avoidance techniques when 20˚ central VF was occluded, but not when 10˚ central VF was occluded (Timmis, Scarfe et al. 2016). This suggests that there may be a functional threshold whereby visual field losses lead to balance and gait deficits. Consequently, in the present study, the focus is on the role of severe peripheral and central VF losses on balance.

Two of the most prominent ocular pathologies affecting visual fields in older adults are age-related macular degeneration (AMD) and primary open-angle glaucoma (Thylefors and Negrel 1994, Cruickshanks, Hamman et al. 1997, Augood, Vingerling et al. 2006). AMD and glaucoma lead to progressive and chronic loss of the central and peripheral visual fields, respectively. Both AMD and glaucoma populations have been associated with an increased prevalence of falls; there is approximately a 2.6-fold in the risk of falling in patients with AMD compared to their age-matched controls (Szabo, Janssen et al. 2008). One study conducted in Singapore in adults over 40 years old reported a fourfold increase in the risk of falls with glaucoma (Lamoureux, Chong et al. 2008). Similar trends were confirmed in other countries including Canada and USA (Guse and Porinsky 2003, Haymes, Leblanc et al. 2007, Bramley, Peeples et al. 2008).

What remains unclear is the underlying reason as to why patients with glaucoma (i.e. with peripheral VF deficits) and with AMD (i.e. central VF deficits) experience a higher rate of falls than those with normal vision. There are two main types of mechanisms that could potentially explain the contribution of VF deficits to the risk of falling in AMD and glaucoma. The first mechanism is the inability to detect environmental hazards (Friedman, Freeman et al. 2007).

Patients with glaucoma have been shown to perform as well as healthy controls when crossing an obstacle course (Turano, Rubin et al. 1999, Friedman, Freeman et al. 2007); however, mobility performance measures in obstacle avoidance tasks have been positively linked with the size of the binocular central scotoma in AMD (Hassan, Lovie-Kitchin et al. 2002). These findings suggest that while patients with AMD may be at an increased risk of falls due to their inability to detect environmental hazards, another mechanism is responsible for the increased risk of falls in patients with glaucoma. The second potential mechanism linking VF with falls in the impact on balance; specifically, the impact of VF on sensory integration important for postural control. Effective integration of multisensory information (i.e. vision, proprioception and vestibular inputs) is a process often termed "sensory re-weighting" (Peterka 2002, Mahboobin, Loughlin et al. 2005, Jeka, Allison et al. 2006, Mahboobin, Loughlin et al. 2009, Asslander and Peterka 2014, Logan, Kiemel et al. 2014, Asslander and Peterka 2016). This process involves resolving conflicting sensory inputs if two or more channels provide contradictory body state-related information and relies on accurate sensory channels to generate postural adjustments if one or more afferent inputs are inaccurate/noisy or absent (Peterka 2002, Asslander and Peterka 2014, Asslander and Peterka 2016).

There is some dispute in literature as to the roles that central and peripheral vision play in maintaining balance. Three general hypotheses of VF influences on postural control have been put forth in the literature: (1) the peripheral dominance theory that peripheral vision is more important than central vision in postural control (Amblard and Carblanc 1980); (2) the retinal invariance hypothesis suggests that central vision is just as important as peripheral vision in the control of posture (Straube, Krafczyk et al. 1994); and (3) the functional sensitivity hypothesis suggests that the periphery of the retina is most susceptible to lamellar optic flow and the central part is most sensitive to radial optic flow, and thus both central and peripheral have important, but functionally different, roles in maintaining posture (Stoffregen 1985, Warren and Kurtz 1992, Bardy, Warren Jr et al. 1999). A reason why there are varying conclusions in previous studies may be due to different experimental methods of testing the VF. Some studies do not remove part of the VF, but rather provide stimulus to only part of the field; others have used goggles to block part of the VF. These methods may not be consistently and accurately removing input to the central/peripheral visual fields; thus this study aimed to employ a novel way to induce acute VF losses by using painted contact lenses in otherwise completely normal subjects to isolate the effect of VF loss alone (Nau 2012). Further, studies on the influence of central and peripheral vision on balance control are difficult in patients due to the presence of systemic or ocular co-morbidities. Additionally, previous research has shown that patients with chronic central VF loss exhibit adaptations in gait kinematics and adopt more cautious strategies when obstacles are presented (Timmis and Pardhan 2012, Timmis, Scarfe et al. 2014). The contact lens model used in this study eliminated potential confounders of co-morbid conditions or long-term adaptations by offering a novel within-subject approach to improve understanding of the etiology of balance impairments in individuals with VF losses at an increased risk of falls.

This study aimed to determine the effect of acute peripheral and central VF losses on postural control in healthy young and older adults. The overarching hypothesis was that both central and peripheral vision are important in the maintenance of balance; however, peripheral vision would be critical in detecting motion, particularly when proprioception is inaccurate. Furthermore, these hypothesized effects of the loss of central-peripheral vision on balance were expected to be greater in older adults than young adults. To test this hypothesis, two dynamic posturography tests were used to assess differences in balance between (1) acute central and peripheral VF losses compared to baseline vision and (2) young and older adults wearing VF occluding contact lenses. Displacement (center of pressure RMS) and time-normalized path length (NPL) of postural sway were measured, with a greater RMS and NPL representing a decrease in balance control. It was anticipated that both RMS and NPL would be greatest during acute peripheral VF occlusion, followed by acute central VF occlusion, with the baseline (no occlusion) producing the minimum sway measures. These differences were expected to be amplified when sensory cues from the proprioceptive system were unreliable and when the postural system was driven by an external stimulus. Additionally, it was expected that there would be a greater difference in sway during VF occlusion compared to baseline in older adults than young adults.

3.2 METHODS

3.2.1 Participants

Nine young (aged 27.8 ± 2.1 years, 4 female) and eleven older adults (aged 72.2 ± 5.1 years, 7 female) were recruited. Eligible individuals were healthy and able to stand for at least 2 hours. Exclusionary criteria included self-reported orthopedic, neurological, pulmonary or cardiovascular abnormalities hindering normal balance and gait. Additionally, individuals were excluded if they were taking any central nervous system anti-depressant drugs, including benzodiazepines or barbiturates, or taking more than five prescription drugs, as both have been associated with increased fall risk (Caramel, Remarque et al. 1998, Weiner, Hanlon et al. 1998). Written informed consent approved by the University of Pittsburgh Institutional Review Board was obtained prior to participation.

3.2.2 Protocol

Two visits were required to complete the study; the first visit consisted of screening procedures and the second included the experimental dynamic posturography session. Screenings excluded some potential participants from continuing to the experimental session. Subjects with cognitive impairment, defined as a score of less than 24 on the Mini-Mental Status Exam, were excluded (Folstein, Folstein et al. 1975, Tombaugh and McIntyre 1992). Participants with vestibular abnormalities were excluded by rotational chair tests (ROTO) (Arriaga, Chen et al. 2005) performed by a neurologist with expertise in balance disorders. Lower extremity sensation was tested bilaterally using Semmes-Weinstein monofilaments to measure cutaneous pressure thresholds. Subjects were excluded if they could not sense the Semmes-Weinstein 5.07/10 g monofilament, which is considered to be the threshold for protective sensation (Kumar, Fernando et al. 1991, Kuyk, Elliott et al. 1996, Armstrong, Lavery et al. 1998). Lastly, participants underwent a complete ocular and vision examination by an optometrist to ensure normal vision.

At the end of their first visit, participants who met all eligibility criteria were fitted by an optometrist with custom contact lenses to be worn during the experimental session. Lenses were made with appropriate prescription for full distance correction for each participant. Two sets of lenses were custom painted for each subject: central VF occluding lenses and peripheral VF occluding lenses (Adventures in Colors, Golden, CO) [Figure 1]. Central VF occluding lenses were painted with central opacities measuring 8 mm and peripheral VF occluding lenses were painted with peripheral opacities leaving a 1 mm clear center, according to previously established parameters that have been shown to produce moderate to severe visual deficits (Nau 2012).

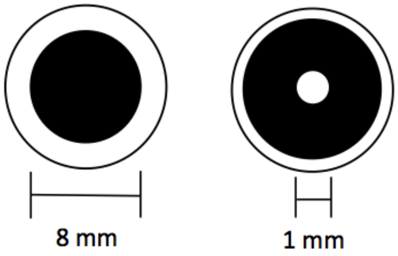


Figure 1. Central (left) and peripheral (right) VF occluding lens model.

The experimental session consisted of two dynamic posturography assessments. Prior to both tests, participant's eyes were dilated to eliminate variability from iris movement and to ensure a constant VF during data collection. The first assessment was a dynamic posturography test adapted from the Sensory Organization Test (SOT) using an Equitest posture platform (Neurocom, Inc) located in the Jordan Balance Disorders Laboratory within the Eye & Ear Institute of Pittsburgh. The SOT is a well-established test used to evaluate sensory integration abilities relevant to postural control (Nashner 1982, Bronte-Stewart, Minn et al. 2002). The platform provides sway-referenced rotations of the floor and/or the visual scene. Sway referencing is accomplished by rotation in direct proportion to an individual's sway, thus reducing correct sensory information from the modality being sway-referenced (vision if the visual scene is sway-referenced or proprioception if the floor is sway-referenced) (Nashner 1982). Sway referencing was provided through the method of low-pass filtering of the COP data collected by the Equitest platform. There are six conditions in the SOT test, including combinations of fixed / sway-referenced visual scene and floor conditions and eyes closed / open conditions [Table 6]. Prior to beginning the test, all participants donned a safety harness that would catch them in the event of a loss of balance. Participants were instructed to cross their arms across the chest and to stand as still as possible without locking their knees. The six conditions were presented in order and repeated three times, once for each lens condition: central VF occluding lenses, peripheral VF occluding lenses, and no occlusion. The presentation order of the peripheral VF occluding lenses and central VF occluding lenses were randomized, and the no occlusion condition was always presented last. One trial of each condition, including the eyes-closed conditions (SOT conditions 2 and 5), was collected per lens condition and trial length was set at 60 s. Eyes-closed conditions were repeated to act as a control as there should not be any VF occlusion effects on these conditions. Postural sway was assessed using the center of pressure (COP) data collected at a sampling frequency of 100 Hz.

Table 6. SOT trial descriptions including eye, vision and proprioception conditions.

Trial	**Visual scene (Vision)**	**Floor (Proprioception)**
1	Fixed (reliable)	Fixed (reliable)
2	Eyes closed (absent)	Fixed (reliable)
3	Sway-referenced (minimized)	Fixed (reliable)
4	Fixed (reliable)	Sway-referenced (minimized)
5	Eyes closed (absent)	Sway-referenced (minimized)
6	Sway-referenced (minimized)	Sway-referenced (minimized)

The second dynamic posturography test, which examined postural response to a moving visual environment, took place in the Medical Virtual Reality Center in the Eye and Ear Institute of Pittsburgh. The Medical Virtual Reality Center contains a custom built virtual environment, termed the BNAVE (Balance Near Automatic Virtual Environment), that creates an immersive visual surround by projecting computer generated images onto three adjoining screens positioned to the left, front and right of the participant (Jacobson, Redfern et al. 2001, Musolino, Loughlin et al. 2006). A contiguous image is projected onto the screens and provides a full (180°) horizontal field of view. The image presented to participants consisted of a “bulls-eye” pattern of six alternating black-and-white concentric rings surrounded by a checkerboard of black-and-white squares [Figure 2]. The visual scene (central bulls-eye + peripheral checkerboard) moved radially in an anterior-posterior sinusoidal pattern with an amplitude of 20 cm and a frequency of 0.25 Hz (Jasko, Loughlin et al. 2003). Each trial lasted 100 s, with 20 s of fixed visual stimuli at the beginning and the end and 60 s of sinusoidal perturbed stimuli in the middle. Four trials were collected for each of the three lens conditions, two with fixed floor and two with sway-referenced floor. The presentation of lens conditions was the same as in the first posturography test. Again, a harness system was used to prevent injury if participants fell. COP data was collected at 100 Hz from a NeuroTest^{TM} platform (Neurocom, Inc). Technical difficulties were experienced when collecting two older participants and thus they were excluded from further analysis in the BNAVE test only.

Figure 2. Experimental setup for second balance test with participant standing in the BNAVE and visual stimulus projected onto screens.

3.2.3 Analysis

Sway data, as measured by the COP, from both the adapted SOT test and the BNAVE test was first down-sampled to 20 Hz and then filtered using a low-pass Butterworth filter with a cutoff frequency of 2.5 Hz. For the adapted SOT test, the first and last five seconds of each condition were removed to eliminate any transient effects. For each trial of the BNAVE test, only the 60-s portion with the sinusoidal visual perturbation were analyzed, and the first and last 5 s of this portion were removed. Due to technical difficulties, the second trial of the sway-referenced flooring condition was missing for 3 participants. Therefore, only the first trial of each flooring condition in the BNAVE test was used in analysis, which is also consistent with the single trial collected in the adapted SOT test.

For both the adapted SOT test and BNAVE test, two sway variables were calculated: (1) anterior-posterior displacement was quantified by the root mean square (RMS) of anterior-posterior COP [Equation 1, page 17] and (2) the time-normalized path length (NPL) of the anterior-posterior COP [Equation 2, page 17]. NPL was calculated by taking the absolute value of the derivative of the COP and then averaging over time (Maurer and Peterka 2005). Only outcome measures in the anterior-posterior direction were considered in the analyses, as all perturbations were in the anterior-posterior direction in both posturography tests.

A series of mixed linear models was fitted for each condition of the adapted SOT test with either RMS or NPL as the dependent variable; age group, lens condition and their interaction as fixed effects of interest; and a participant-within-age group as a random effect to account for multiple measurements from the same participant. Upon observing distributional deviations of residuals from normality in probability-probability plots, the dependent variables were natural log transformed and the models were re-fitted. Appropriately constructed means contrasts were used to make various comparisons of interest between lens conditions and age groups. Specifically, the overall VF occlusion effect was tested within each age group and the overall age effect was tested within each VF occlusion condition. A similar analytic strategy was employed in the BNAVE test, with floor condition instead of the SOT condition in the adapted SOT test. To mitigate effects of multiple comparisons on type I errors, between-lens post hoc pairwise comparisons were made only if the overall VF occlusion effect was significant within age group. SAS® version 9.3 (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses with α=0.05.

3.3 RESULTS

In the adapted SOT test, as expected, VF occlusion did not impact balance measures in either age group during the eyes-closed conditions (SOT conditions 2 and 5). Therefore, data under these conditions will not be further discussed. VF occlusion had a significant effect on NPL, but only in older adults and during SOT condition 4 (p= 0.02, F=4.59) [Figure 3] and SOT condition 6 (p=0.01, F=4.59) [Figure 3], i.e. when the floor is sway-referenced. Thus, further post-hoc tests comparing VF occlusion conditions were conducted in older adults for these SOT conditions. These tests showed that under SOT condition 4, older adults exhibited on average 23% greater NPL in both central and peripheral VF occlusion conditions compared than no occlusion (p=0.02 and p=0.01, respectively). Central and peripheral VF occlusion yielded similar NPL values in older adults under SOT condition 4 (p>0.1). When both vision and floor were sway-referenced in SOT condition 6, older adults exhibited on average a 23% increase in NPL when central vision was available (both in the no VF occlusion and peripheral VF occlusion conditions) compared to central VF occlusion condition (p=0.01 and p=0.02, respectively). Additionally, older adults displayed overall significantly greater NPLs than young adults across VF occlusion and SOT conditions ($p<0.05$) [Figure 3]. A final result in the adapted SOT test is that VF occlusion did not have an impact on COP displacement, i.e. RMS ($p>0.05$) Table 7]. This finding was true in young and older adults. In addition, COP displacement was similar between young and older adults under all three VF occlusion and SOT conditions ($p>0.05$) [Table 7].

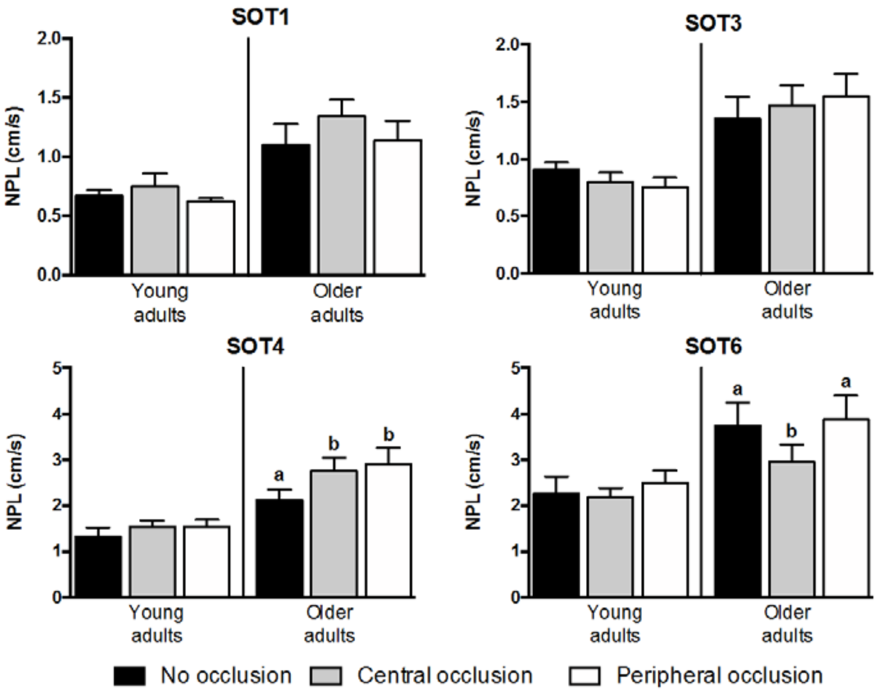


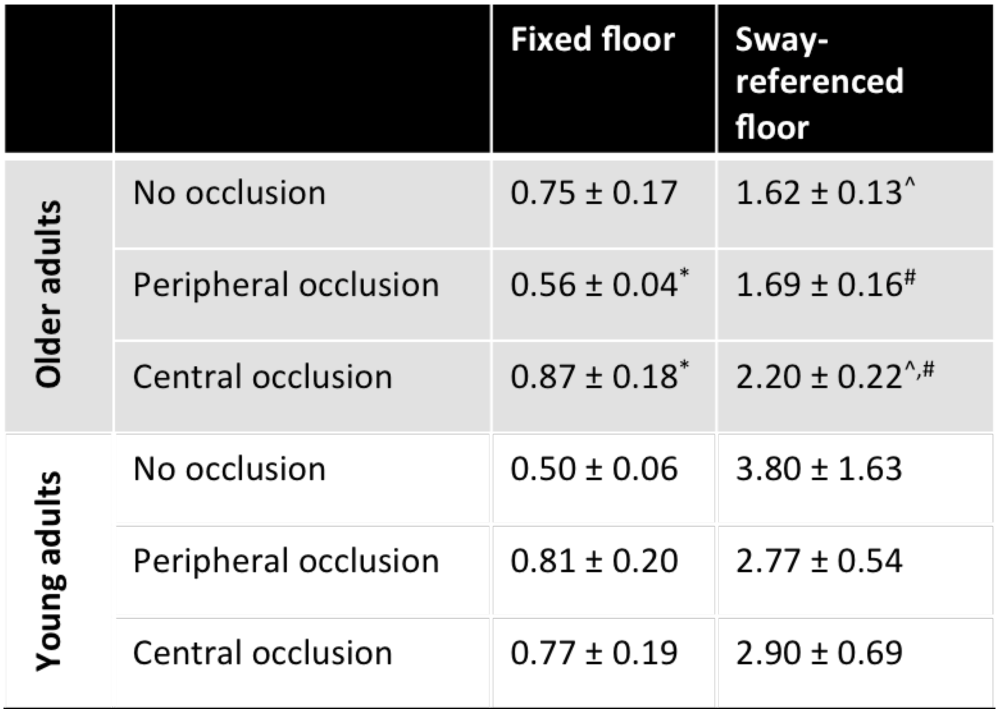
Figure 3. Mean and standard error of NPL (cm/s) values from the adapted SOT test. VF occlusion conditions labeled with different letters are statistically different ($p<0.05$); for conditions not labeled there were no effects of VF occlusion on NPL. Significant results are: (SOT4) NPL during central occlusion was 21% greater than no occlusion ($p=0.02$) and was 25% greater during peripheral occlusion than no occlusion ($p=0.01$) in older adults only; (SOT6) NPL during no occlusion was 24% greater than central occlusion ($p=0.02$) and was 23% greater during peripheral occlusion than central occlusion ($p=0.01$) in older adults only. In general NPL was greater in older adults than in their young counterparts for all VF occlusion and SOT conditions ($p<0.05$).

Table 7. Mean and standard error of RMS (cm) values from adapted SOT test. VF occlusion and age group did not have a significant effect on COP RMS during the adapted SOT test.

		SOT 1	SOT3	SOT4	SOT6
Older adults	No occlusion	0.51 ± 0.05	0.66 ± 0.07	1.09 ± 0.08	1.95 ± 0.15
	Peripheral occlusion	0.46 ± 0.06	0.66 ± 0.07	1.33 ± 0.07	1.96 ± 0.18
	Central occlusion	0.59 ± 0.06	0.63 ± 0.05	1.19 ± 0.09	1.69 ± 0.18
Young adults	No occlusion	0.42 ± 0.05	0.57 ± 0.08	1.66 ± 0.42	2.12 ± 0.46
	Peripheral occlusion	0.38 ± 0.03	0.53 ± 0.06	1.32 ± 0.26	2.51 ± 0.41
	Central occlusion	0.44 ± 0.03	0.55 ± 0.05	1.64 ± 0.25	2.23 ± 0.33

In contrast to findings in the adapted SOT test, in the BNAVE test, VF occlusion had a significant effect on COP displacement, but only in older adults. This finding holds true both when the floor is fixed (p=0.03, F=3.89) and sway-referenced (p=0.05, F=3.39) [Table 8]. Thus, further post-hoc tests comparing VF occlusion conditions were conducted in older adults. These tests demonstrated that in older adults, RMS increased during central VF occlusion compared to peripheral VF occlusion when the floor was fixed (45% difference, p=0.01). Similarly, when the floor was sway-referenced, RMS of older adults was greatest when the central VF was occluded (30% greater than peripheral VF occlusion, p=0.04; 25% greater than no occlusion, p=0.02) [Table 8]. Peripheral VF occlusion yielded similar COP displacement behavior to no occlusion conditions in older adults, both under fixed and sway-referenced floor conditions.

Table 8. Mean and standard error of RMS (cm) values from the BNAVE test. Significant results are: (*) sway magnitude in older adults was 45% greater during central occlusion than peripheral occlusion when the floor was fixed (p=0.01); (^) sway magnitude in older adults was 25% greater during central occlusion than no occlusion when the floor was sway-referenced (p=0.02); (#) sway magnitude in older adults was 30% greater during central occlusion than peripheral occlusion when floor was sway-referenced (p=0.04).



		Fixed floor	**Sway-referenced floor**
Older adults	No occlusion	0.75 ± 0.17	1.62 ± 0.13^
	Peripheral occlusion	0.56 ± 0.04*	1.69 ± 0.16#
	Central occlusion	0.87 ± 0.18*	2.20 ± 0.22^,#
Young adults	No occlusion	0.50 ± 0.06	3.80 ± 1.63
	Peripheral occlusion	0.81 ± 0.20	2.77 ± 0.54
	Central occlusion	0.77 ± 0.19	2.90 ± 0.69

VF occlusion impacted NPL of older adults when the floor was fixed (p=0.01, F=5.98) [Figure 4]. Further post-hoc pairwise comparison tests in older adults when the floor was fixed revealed that NPL was significantly greater during central VF occlusion than both peripheral VF occlusion (27% difference, p=0.01) and no occlusion (46% difference, p=0.003). However, when the floor was sway-referenced, only young adults exhibited significant changes in NPL during different occlusion conditions (p=0.03, F=3.79). More specifically, NPL of young adults under sway-referenced floor conditions was 27% greater during central VF occlusion (p=0.01) and 22% greater during peripheral VF occlusion (p=0.04) than no occlusion. In general, NPL differences between young and older adults were minimal across VF occlusion and floor conditions [Figure 4].

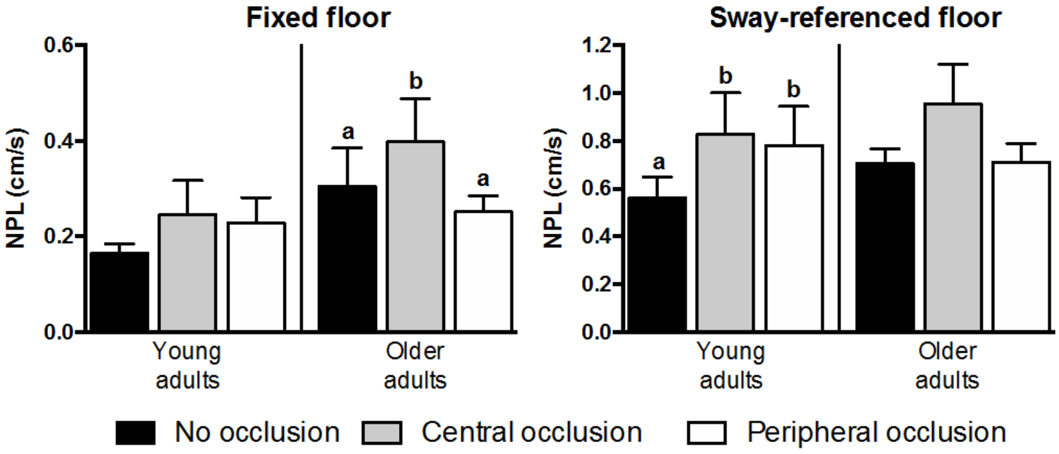


Figure 4. Mean and standard error of NPL (cm/s) values from the BNAVE test. VF occlusion conditions labeled with different letters are statistically different (p<0.05); for conditions not labeled there were no effects of VF occlusion on NPL. Significant results are: (Fixed floor) NPL during central occlusion was 27% greater than no occlusion (p=0.01) and 46% greater than peripheral occlusion (p=0.01) in older adults only; (Sway-referenced floor) NPL was 27% greater during central occlusion than no occlusion (p=0.01) and 22% greater during peripheral occlusion than no occlusion (p=0.04) in young adults only. Older adults NPL was significantly greater than young adults only during central occlusion when the floor was fixed (p<0.05).

3.4 DISCUSSION

In this study, young and older healthy participants with normal vision completed balance assessments under three VF occlusion conditions: (1) acute occlusion of central vision, (2) acute occlusion of peripheral vision and (3) no occlusion. Thus, this study was able to determine the effect of acute VF loss on balance, a first step toward understanding the underlying mechanisms of falls in patients with VF defects. Comparing patient populations to understand the impact of VF deficits alone on balance is challenging due to multiple confounding factors associated with clinical conditions. Thus, prior clinical studies have not been able to fully elucidate underlying mechanisms explaining how specific VF defects result in postural instability and ultimately falls. The contact lens model was used to create either central or peripheral VF losses in healthy populations and thus allowed the use of a within-subject approach to improve understanding of the etiology of VF loss-related balance/gait impairments. Further, the results of this study show how older adults respond differently to VF loss affects than young adults.

The two balance tests used in this experiment allowed us to investigate the impact of acute central/peripheral VF loss on balance when visual cues are reliable (adapted SOT test, Conditions 1 and 4), reduced (adapted SOT test, Conditions 3 and 6) and moving (sinusoidal visual scene movement at 0.25 Hz in the BNAVE test) as well as when balance-related proprioceptive cues are altered. When balance-related visual cues were reliable, acute VF occlusion had little effect unless proprioceptive cues were altered via sway referencing (SOT condition 4). Sway NPL increased in both central and peripheral VF occlusion compared to baseline in older adults, but not young adults. This suggests that older adults are more sensitive to any occlusion of the VF when they cannot rely more heavily on proprioceptive inputs.

There were no VF occlusion differences seen in standing balance when visual cues were unreliable and vestibular and proprioceptive inputs were normal (SOT condition 3). However, when both visual and proprioceptive cues were altered via sway-referencing (SOT condition 6), in older adults only, having central vision as in the no occlusion and peripheral occlusion produced a greater balance control challenge (greater NPL values) compared to occluding the central VF (i.e. having peripheral VF only). This finding suggests that having peripheral vision alone increase the sensitivity of the postural control system to motion, which is important when proprioceptive information is unreliable. Thus, peripheral vision may be influential for maintaining balance in ways that are different than central vision, particularly in older adults.

When the postural control system was externally driven by the sinusoidal movement of the visual scene in the BNAVE, older adults showed an overall increase in displacement and velocity when central VF was occluded, i.e. only peripheral vision is available. These findings confirm previous findings from the adapted SOT6 condition that the postural control system is most sensitive to motion-related visual cues from the peripheral VF. Thus, in the BNAVE test, sensitivity of the postural control system to these cues from the peripheral VF was the greatest when they were erroneous. Young adults showed an overall effect of VF occlusion (both central and peripheral) compared to baseline, but only when the floor was sway-referenced. This suggests that the postural control system in young adults is only impacted by VF loss during the most challenging balance conditions when both visual and proprioceptive sensory inputs are altered.

This study found that only NPL was sensitive to differences in age groups within occlusion condition, specifically in the adapted SOT test. NPL, similar to mean velocity, in particular has been shown to be a sensitive measure of balance control in elucidating postural instabilities in populations including Parkinson’s disease (Rocchi, Chiari et al. 2002, Maurer, Mergner et al. 2003, Maurer and Peterka 2005) and older adults (Maki, Holliday et al. 1990, Prieto, Myklebust et al. 1996, Maurer and Peterka 2005). Similarly, NPL was more sensitive to differences in age groups, as well as VF occlusion, than RMS in this study. There was no consistent age difference within occlusion condition in NPL for the BNAVE test, suggesting that older adults were generally able to adapt to the externally driven visual input to the same extent as young adults. It should be noted that the older participants in this study were overall healthy and exclusionary criteria for this study were very rigorous and individuals with vestibular, proprioceptive, neurological, or musculoskeletal conditions prevalent in older populations were not considered for this study. Thus, greater age effects would be expected if older participants were representative of the general population; however, for the purpose of teasing out the effects of VF occlusion alone, strict exclusionary criteria were necessary for this study.

A potential limitation to this study was the use of sway-referencing to minimize proprioceptive inputs, as it may have impacted the visual input. It is well-established that sway-referencing the floor produces decreased balance stability (Nashner 1982, Peterka 2002); the results of this study, as expected, showed an increase in both displacement and velocity during sway-referenced floor conditions compared to baseline. Because sway-referencing increases sway and head motion, sway-referencing the floor also increased the amplitude of visual motion experienced by participants. Therefore, visual input may have had a greater impact on balance and the differences seen between VF occlusion conditions may not have been due to sensory re-weighting but to a change in visual information available to the central versus peripheral sensory systems. However, this effect is minimized in SOT condition 6, when both the floor and vision are sway-referenced and visual motion is synched with body sway.

As discussed previously, the data from both tests used in the present study suggest that both central and peripheral vision are important to maintaining balance, but peripheral vision in particular may be more sensitive to motion. The results of the present study lend support to the functional sensitivity hypothesis that postulates central and peripheral play different but necessary roles in postural control. Previous literature is mixed regarding which theory is most accurate, with some supporting the peripheral dominance theory (Lestienne, Soechting et al. 1977, Amblard and Carblanc 1980) and others refuting it in support of the functional sensitivity hypothesis (Stoffregen 1985, Warren and Kurtz 1992, Bardy, Warren Jr et al. 1999).

The central neural processing of visual information is consistent with the specific influences of peripheral vision on balance seen in this study. More specifically, neuroimaging studies have demonstrated that the representation of the far periphery of the retina sends inputs to area MT/MST (middle temporal area/medial superior temporal area) (Palmer and Rosa 2006). MST in particular has been linked to hierarchical vestibular processing (Chen, DeAngelis et al. 2011). Therefore, interruption of this pathway through elimination of peripheral visual input should have a negative effect on postural control, as seen by the increased postural NPL when peripheral vision was occluded and proprioception was minimized. The tracing studies above provide the structural and mechanistic evidence for the clinical findings that interruption of peripheral vision (for example in glaucoma) more negatively impacts a patient’s ability to maintain postural control than patients with central vision loss caused by macular degeneration (Ramulu 2009, Popescu, Boisjoly et al. 2011). Additionally, visual information is divided into two streams in the brain: parvocellular ganglion cells in the fovea of the retina send information to the ventral stream, while magnocellular ganglion cells in the periphery send information to the dorsal stream (Livingstone and Hubel 1987). The dorsal stream contains a fast cortical pathway and has a more direct connection to and from V1/V2 than the ventral stream (Stephen, Aine et al. 2002). Therefore, because visual cues from the peripheral field have a more direct and faster pathway through the brain, when the peripheral VF is blocked these fast-moving signals are no longer available to the postural control system.

A potential confounding factor that was not included in statistical analysis was intersubject variations in the VF. Participants were assumed to have normal VF and did not undergo VF tests to screen for any potential abnormalities. Additionally, the deficits induced by the central and peripheral occluding contacts were assumed to be constant for all participants based upon previously established parameters (Nau 2012). Including VF measures from tests taken under the three VF occlusion conditions (i.e. central occlusion, peripheral occlusion, no occlusion) in statistical models would have accounted for intersubject VF variability.

While this study allowed us to examine the impact of acute short-term peripheral vision and central vision loss on balance in healthy subjects using a within-subject experimental design, future studies should compare the results from this study of healthy adults to those with chronic visual impairments such as glaucoma and AMD. One reason for the need of such comparison is that this study did not account for the long-term adaptation effects associated with these conditions. For example, recent literature suggests that structural and functional brain changes occur with glaucoma (Li, Cai et al. 2012, Zikou, Kitsos et al. 2012, Dai, Morelli et al. 2013, Williams, Lackey et al. 2013) and perhaps to a lesser extent, macular degeneration (Dilks, Julian et al. 2014, Hernowo, Prins et al. 2014, Burge, Griffis et al. 2016, Prins, Plank et al. 2016). Thus, comparing results of acute VF occlusion to chronic impairments due to glaucoma and AMD will help tease out the effects of these brain changes versus peripheral vision loss alone on balance.

3.5 CONCLUSION

This study examined within-subject effects of acute peripheral and central VF occlusion on standing balance. The results suggest that while both peripheral and central vision play important but different roles in maintaining balance; peripheral vision may be more sensitive to movement in the visual environment. VF occlusion had the greatest impact when balance-related sensory inputs from proprioception were unreliable, suggesting that VF loss may affect sensory integration of the postural control system. Further, older adults were more sensitive to VF occlusion than young adults. Future work should compare acute VF occlusion examined in this study to chronic VF loss diseases such as glaucoma and macular degeneration.

4.0 RELATIONSHIP BETWEEN GLAUCOMA AND CENTRAL MULTISENSORY INTEGRATION RELEVANT FOR BALANCE

4.1 INTRODUCTION

Glaucoma is a leading cause of low vision and is the second primary cause of blindness worldwide, affecting over 60 million individuals (Quigley and Broman 2006). Glaucoma is characterized by degeneration of the retinal ganglion cells and induces visual field defects (Weinreb and Khaw 2004). Individuals with glaucoma have been reported to exhibit diminished mobility (Turano, Rubin et al. 1999, Nelson, Aspinall et al. 2003, Ramulu 2009, Fenwick, Ong et al. 2016) and an increased risk of falling (Lamoureux, Chong et al. 2008, Black, Wood et al. 2011). The visual impairment found in glaucoma, particularly visual field loss, is among the top risk factors for geriatric falls and falls-related injuries (Ivers, Cumming et al. 1998, Coleman, Cummings et al. 2007, Freeman, Munoz et al. 2007). Therefore, understanding the mechanisms that contribute to balance performance in this population is clinically important to prevent falls and fall-related injuries.

One mechanism that may contribute to falls in glaucoma is an impaired central ability to effectively integrate sensory information relevant for balance. The ability to maintain balance relies on the central integration of sensory information relevant for postural control, i.e. vision, proprioception and vestibular (Balasubramaniam and Wing 2002, Peterka 2002, Peterka and Loughlin 2004, Maurer, Mergner et al. 2006). Findings of postural control studies in glaucoma suggest that balance control is indeed worse in patients with glaucoma compared to controls, particularly when proprioceptive information is altered, e.g. standing on foam (Shabana, Cornilleau-Peres et al. 2005, Black, Wood et al. 2008, Kotecha, Richardson et al. 2012). Further, neuroimaging studies have also provided in-vivo evidence that central processing in the brain may be altered in the brain of glaucoma. These studies suggest that glaucoma is not only an eye disease, but also a neurodegenerative syndrome (Gupta and Yucel 2001, Gupta and Yucel 2003, Gupta and Yucel 2006, Gupta and Yucel 2007, Yucel and Gupta 2008). In particular, primary open angle glaucoma (POAG) is associated with changes in brain structure (Li, Cai et al. 2012, Zikou, Kitsos et al. 2012, Williams, Lackey et al. 2013) and function (Dai, Morelli et al. 2013). Of particular relevance to sensory integration abilities important for balance are the findings of (1) Zikou and colleagues, who reported voxel-based microstructural changes in parts of the basal ganglia in patients with glaucoma (Zikou, Kitsos et al. 2012), and those of (2) Dai and colleagues, who reported reduced intrinsic functional connectivity between the primary visual cortex and the precentral gyrus and the anterior lobe of the cerebellum, both of which are important for motor control, as well as the postcentral gyrus that is responsible for sensory processing important for balance (Dai, Morelli et al. 2013). There is also evidence of alterations in parts of the brain that are involved in attention; reduced cortical thickness has been observed in the anterior prefrontal cortex in patients with glaucoma compared to healthy adults (Wang, Li et al. 2016). Frezzotti et al. reported reduced grey matter volume in the frontal lobe as well as reduced functional connectivity in the working memory network and dorsal attention network in advanced glaucoma compared to normal (Frezzotti, Giorgio et al. 2014).

An effective integration of sensory information relevant for balance requires higher cognitive resources, specifically attention-related resources, particularly when controlling upright stance in sensory challenging conditions, e.g. when altering or minimizing proprioception (Redfern, Jennings et al. 2001, Redfern, Mûller et al. 2002, Verghese, Buschke et al. 2002, Furman, Muller et al. 2003, Redfern, Talkowski et al. 2004, Yogev, Giladi et al. 2005, Hausdorff, Doniger et al. 2006, Holtzer, Friedman et al. 2007, Scherder, Eggermont et al. 2007, Yogev-Seligmann, Hausdorff et al. 2008, Redfern, Jennings et al. 2009, Mendelson, Redfern et al. 2010, Holtzer, Wang et al. 2012, Montero-Odasso, Verghese et al. 2012, Sparto, Fuhrman et al. 2013). This is empirically evident in experimental postural control studies using dual task paradigm protocols that combine an information-processing task with a postural challenge, creating interference between the two tasks in older adults (Redfern, Jennings et al. 2001, Redfern, Mûller et al. 2002, Redfern, Talkowski et al. 2004, Redfern, Jennings et al. 2009, Mendelson, Redfern et al. 2010, Sparto, Fuhrman et al. 2013). In healthy adults, the information-processing task is typically more affected than the postural task as balance adjustments are given priority (i.e. “posture first” principle) (Redfern, Jennings et al. 2001, Muller, Jennings et al. 2004). Glaucoma is associated with cognitive impairments in a number of domains, including executive function and attention (Yochim, Mueller et al. 2012, Bulut, Yaman et al. 2016). Previously published pilot studies reinforce the hypothesis that attentional processes are involved in balance impairments in glaucoma: (1) balance in patients with glaucoma worsens when performing a secondary task to a greater extent than in controls (Kotecha, Chopra et al. 2013) and (2) gait requires greater “mental effort” in patients with glaucoma than in controls (Geruschat and Turano 2007).

There is convergent preliminary evidence in the literature that a mechanism for decreased balance in glaucoma could involve impaired executive functioning and its impact on central sensory integration processes. Thus, the goal of this study was two-fold:

1. To determine the association of glaucoma severity with the ability to integrate sensory information relevant for balance. The hypothesis was that advanced stages of glaucoma

would be associated with worse standing balance measures, particularly during sensory challenging conditions.

2. To determine the influence of attention on sensory integration abilities relevant for balance during standing in patients with glaucoma, with the hypothesis that advanced stages of glaucoma would be associated with a greater interference between an information-processing (IP) task and sensory processing abilities important for balance.

4.2 METHODS

To achieve the goal of this study, an established standing dual task paradigm (Furman, Muller et al. 2003, Redfern, Talkowski et al. 2004, Mendelson, Redfern et al. 2010) was used determine if and how glaucoma alters the interaction between attention and sensory processing necessary for balance. The standing dual task paradigm included an information-processing task, specifically an auditory choice reaction time (IP-CRT) task, presented concurrently while standing in challenging sensory conditions. Thus, balance abilities were assessed with and without the IP-CRT task.

4.2.1 Participants

A total of seventeen (N=17) individuals diagnosed with glaucoma were recruited for this study. Baseline balance assessments (without performing the IP-CRT task) were conducted in all subjects. Balance data with and without the IP-CRT task were collected in a subset of this sample (N=12). Reaction time data for 2 out 12 subjects had to be excluded due to technical difficulties. Written informed consent approved by the University of Pittsburgh Institutional Review Board was obtained prior to participation. All recruited participants were clinically diagnosed with glaucoma and had previously had a comprehensive ophthalmic evaluations at the UPMC Eye Center that included a clinical exam, VF testing (Humphrey Field Analyzer; Zeiss, Dublin, CA) and a spectral-domain optical coherence tomography (Cirrus HD-OCT, Zeiss, Dublin, CA). Participants were able to stand for at least 2 hours. Exclusionary criteria were self-reported orthopedic, neurological, pulmonary or cardiovascular conditions that may negatively impact balance and ocular pathologies other than glaucoma. Potential participants were also excluded if they were taking any central nervous system anti-depressant drugs, including benzodiazepines or barbiturates, or taking more than five prescription drugs, as both may increase fall risk (Caramel, Remarque et al. 1998, Weiner, Hanlon et al. 1998). Glaucoma was assessed two ways: (1) using a structural measure, specifically retinal nerve fiber layer (RNFL) thickness as measured by spectral-domain optical coherence tomography and (2) using a functional measure, specifically visual field mean deviation (VF MD) assessed by automated Humphrey perimetry.

4.2.2 Protocol

Prior to data collection, participants in the subset group (N=12) who completed the dual task paradigm were trained to allow them to become familiar with the task and to establish stable performance. The auditory IP-CRT task was a frequency-discrimination auditory choice reaction time task. Participants wore headphones and held a button in each hand and were instructed to push the button in their dominant hand if the stimulus was a high tone (980 Hz) or push the button in their non-dominant hand if the stimulus was a low tone (560 Hz). The auditory stimuli were generated by a custom Labview (National Instruments) program that randomized high/low tones such that approximately half of each tone was presented and stimuli were spaced every 4 seconds with an added random time of +/- 2.0s to reduce the stimulus predictability. Participants continued training for a total of 8-10 trials, until mean reaction time (RT) stabilized (mean RT of trials within 50ms of each other) and RT standard deviation was below 100ms.

Standing balance was assessed using dynamic posturography adapted from the Sensory Organization Test (SOT) on an Equitest posture platform (Neurocom, Inc) located in the Jordan Balance Disorders Laboratory within the Eye & Ear Institute of Pittsburgh. The SOT has been shown to be effective at evaluating sensory integration capabilities relevant to balance (Nashner, Black et al. 1982, Bronte-Stewart, Minn et al. 2002). The Equitest platform is capable of sway-referencing, which provides rotations of the floor and/or the visual scene in direct proportion to an individual's sway of vision and/or proprioception, respectively. For example, sway-referencing the floor causes movements of the support surface in an attempt to keep the ankle angle constant. The purpose of using sway-referencing of the floor is to reduce the reliability of proprioceptive information from the ankle for balance. The same principle is used for sway-referencing of the visual scene, resulting in erroneously stable vision even though the person is swaying (Nashner, Black et al. 1982). The platform records ground reaction forces under the feet during standing. Sway referencing is provided through the method of low-pass filtering of the center of pressure (COP) data collected by the Equitest platform. There are six conditions in the SOT test, including combinations of fixed / sway-referenced visual scene and floor conditions and eyes closed / open conditions [Table 6, page 36]. Participants wore a safety harness that would prevent hitting the floor in the event that they lost their balance. During balance testing, participants were instructed to stand as still as possible without locking their knees. The dual task subset of participants completed the SOT conditions in order from 1-6, repeating each condition twice: first for baseline (no IP-CRT task) and second with the IP-CRT task. The number of auditory stimuli per trial was

45. For participants not included in the dual task subset, the six adapted SOT conditions were only presented once and in order from 1-6. All trials lasted 3 minutes and postural sway was assessed using the COP data collected at a sampling frequency of 100 Hz. Participants were given 2 minute breaks every 2 trials (6 minutes of standing) to minimize effects of fatigue.

4.2.3 Analysis

COP data were first down-sampled to 20 Hz and low-pass filtered using a fourth-order Butterworth filter with a cutoff frequency of 2.5 Hz. Additionally, the first thirty and last five seconds of each condition were removed to eliminate any transient effects. Because visual and proprioceptive sway referencing occur only in the anterior-posterior direction, only the anterior-posterior COP data was used to quantify postural sway. Sway magnitude was defined as the root-mean-square (RMS) of the filtered COP displacement [Equation 1, page 17]. The time-normalized path length (NPL) of COP was calculated by summing the absolute value of the differences over time [Equation 2, page 17]. The COP RMS and COP NPL were log-transformed for statistical analysis to ensure normality of residuals. Performance on the IP-CRT task was assessed using the median RT during each trial. The RTs were normalized within subject by calculating the difference between SOT conditions 2-6 and SOT condition 1 (e.g. $\Delta RT_{SOT4} = medianRT_{SOT4} - medianRT_{SOT1}$).

Mixed-linear regression analyses were conducted using JMP Version 10 (SAS Institute Inc). Before examining the relationship between glaucoma and balance, a regression analysis was run within SOT condition to confirm that there were no effects of age on the outcome measures (i.e. COP RMS, COP NPL and ΔRT). The first set of regression analyses examined the association of glaucoma severity and standing balance within each SOT condition while no IP-CRT task was performed. All 17 subjects were used in this analysis. Two measures of glaucoma severity were considered: (1) structural measure of glaucoma severity (RNFL thickness) and (2) functional measure of glaucoma severity (VF MD) of the worse eye. RNFL and VF MD were considered individually, each in a separate regression model. The dependent variables of interest were the balance measures, specifically the log-transforms of COP RMS and COP NPL.

The second set of regression analyses aimed to determine the impact of glaucoma severity on the attentional control of balance. More specifically, for the balance assessments, the log-transform of COP RMS and COP NPL were the dependent variables and the fixed effects were glaucoma severity (VF MD and RNFL thickness), IP condition (IP-None or IP-CRT) and their first order interaction. Participant was included as a random effect and the analysis was performed within each SOT condition. The final analysis examined the association between glaucoma severity and RT by performing a linear regression analysis with ΔRT as the dependent variable and glaucoma severity (VF MD or RNFL thickness) as the independent variable. The analysis was performed within each SOT condition. Statistical significance was set at $\alpha=0.05$ for all analyses.

4.3 RESULTS

Participant characteristics are summarized in Table 9. There were no significant effects of age on COP RMS, COP NPL or ΔRT during any of the SOT conditions ($p>0.05$). There was no impact of glaucoma severity on sway or RT during SOT conditions where the eyes were closed (SOT condition 2 & 5) in any of the statistical analyses performed. These conditions acted as a control and will not be discussed further.

Table 9. Characteristics of participants with glaucoma. (*) Denotes participants who did not complete IP-CRT during adapted SOT test. (^) Denotes participants without reaction time data.

Participant ID	Gender	Age (years)	VF MD worse eye (dB)	VF MD better eye (dB)	RNFL thickness worse eye (μm)	RNFL thickness better eye (μm)
1*	M	62	-30.32	-11.36	51	58
2	F	80	-21.04	-4.89	57	75
3*	M	56	-17.57	0.99	76	104
4^	M	72	-14.94	-0.20	61	77
5	M	65	-12.00	-8.57	65	74
6	F	53	-7.25	-3.63	45	71
7	M	80	-5.05	-2.73	71	73
8*	M	70	-4.84	-0.40	93	113
9	F	56	-3.94	-2.07	73	74
10*	M	67	-3.87	-1.90	57	69
11	M	66	-3.47	-1.84	60	66
12	F	60	-3.30	0.69	71	89
13^	F	69	-2.01	0.46	60	63
14	M	70	-1.96	-1.36	63	73
15	F	54	-1.73	-1.10	75	85
16	F	54	-0.30	-0.27	95	98
17*	F	71	-0.44	-0.05	85	88
All	**9 male**	**65.7±8.9**	**-8.97±9.49**	**-2.37±3.28**	**67.1±14.1**	**80.2±14.8**

Baseline Analysis: In the baseline (IP-None) condition, there was no association between glaucoma severity and either measure of standing balance (COP RMS or NPL) for any SOT conditions. This was true whether glaucoma was assessed by a structural (RNFL thickness) or a functional (VF MD) measure. Baseline sway measures are presented in Table 10.

Table 10. Mean (Standard Deviation) [Range] center of pressure displacement (RMS) and time-normalized path length (NPL) during SOT baseline (no IP-CRT task) conditions (N = 17).

Adapted SOT Condition	Baseline COP RMS (cm)	Baseline COP NPL (cm/s)
1	0.61 (0.20) [0.29-0.97]	0.95 (0.60) [0.50-3.14]
3	0.70 (0.20) [0.37-1.08]	1.06 (0.37) [0.49-1.83]
4	1.54 (0.58) [0.95-2.92]	2.17 (0.80) [0.90-4.26]
6	2.12 (0.44) [1.17-2.89]	3.41 (1.30) [1.60-6.01]

Balance measures during dual task conditions: The analysis of the sway measures during the dual task condition revealed a significant effect of the interaction between glaucoma severity and IP condition on NPL, but only during SOT condition 4 (fixed vision, sway-referenced floor). Furthermore, this relationship was significant for RNFL thickness (p=0.05, F=4.77) but not VF MD of the worse eye (p> 0.05) [Figure 5]. Specifically, thinner RNFL values were associated with increases in NPL when performing the IP-CRT task relative to baseline (no IP-CRT task) conditions. IP condition or the interaction between glaucoma severity and IP condition did not have a significant effect on sway magnitude assessed using COP RMS (p>0.05). Finally, the main effects of glaucoma severity and IP condition did not have any significant effects on balance in any of the SOT conditions.

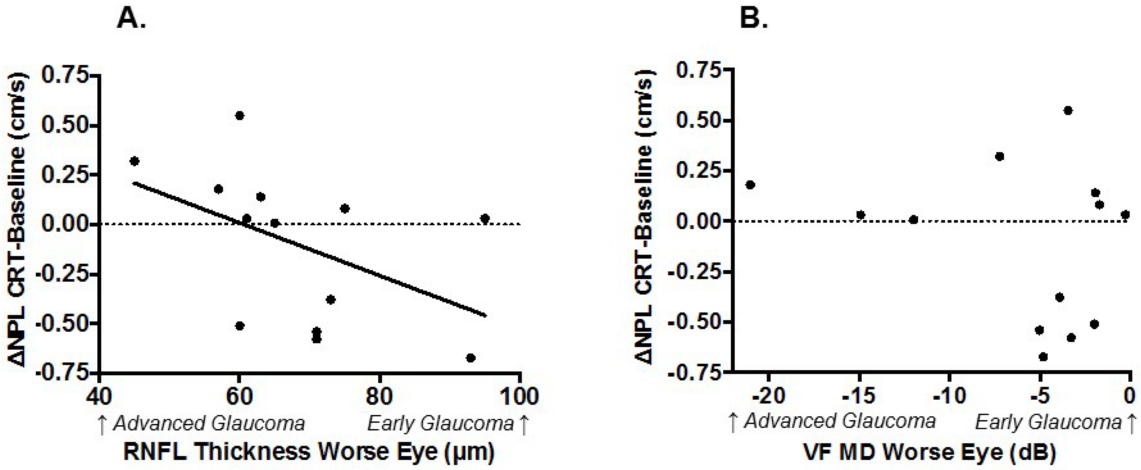


Figure 5. Difference in time-normalized path length during the CRT task from the baseline during no CRT task (ΔNPL) for SOT condition 4 (N=12). ΔNPL is plotted against (A.) RNFL thickness of the worse eye and (B.) VF MD of the worse eye. The association between RNFL thickness and ΔNPL was statistically significant (p=0.05, F=4.77) with ΔNPL increasing with thinner RNFL. The relationship between ΔNPL and VF MD did not reach statistical significance (p=0.24, F=1.5).

Reaction time measures during dual task: The RTs during the IP-CRT conditions are presented in [Table 11]. Reaction time changes from baseline ($\Delta RT_{SOT4-SOT1}$) were associated with glaucoma severity assessed using RNFL thickness, but only during SOT condition 4. Specifically, $\Delta RT_{SOT4-SOT1}$ decreased with smaller RNFL values in advanced glaucoma stages (p=0.004, F=15.33). This relationship was not statistically significant when VF MD was used to measure glaucoma severity (p>0.05) [Figure 6].

Table 11. Mean (Standard Deviation) [Range] median RT during IP-CRT conditions (N = 10).

Adapted SOT Condition	CRT task Median RT (ms)
1	433 (119) [294-819]
3	443 (108) [346-801]
4	448 (100) [312-760]
6	472 (98) [356-780]

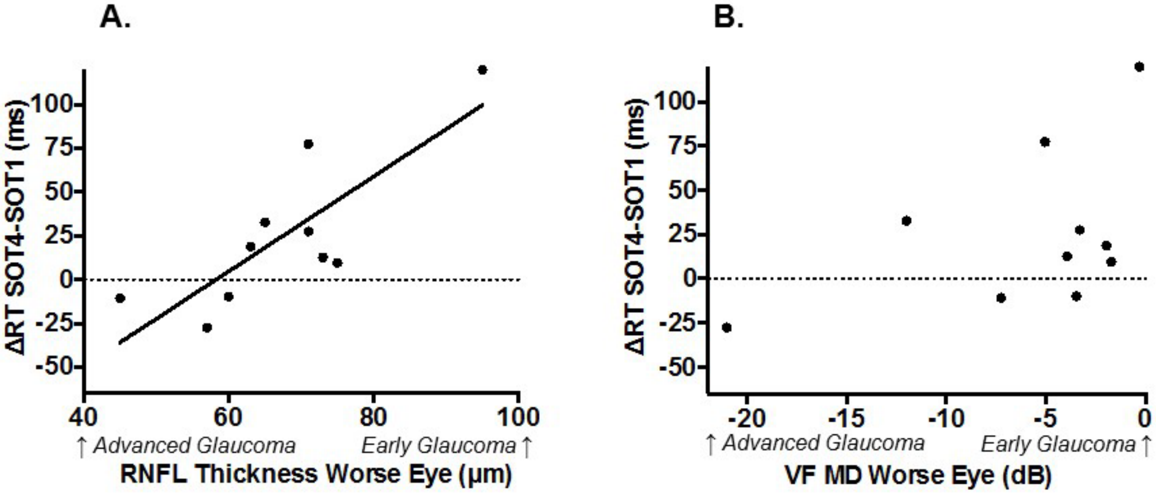


Figure 6. Difference in reaction time (ΔRT) between SOT condition 4 and SOT condition 1 versus (A.) RNFL thickness of the worse eye, and (B.) VF MD of the worse eye. As RNFL thickness decreases (i.e. POAG stage is more advanced), ΔRT decreases (p=0.004, F=15.33). The relationship between ΔRT and VF MD did not reach statistical significance (p=0.16, F=2.4).

4.4 DISCUSSION

The findings of this study suggest that there is interference between balance and attention when standing on sway-referenced floors (SOT condition 4) in patients with more advanced POAG as assessed by RNFL thickness. Performing an information-processing task, in this case an auditory choice reaction time task, while standing on a sway-referenced floor (i.e. reduced proprioception) was associated with greater sway NPL relative to a baseline (no IP-CRT task) condition. This effect was dependent on glaucoma severity as assessed by RNFL thickness; specifically thinner RNFL values were associated with greater NPL changes when performing an IP task relative to no task. During the same condition (SOT condition 4), thinner RNFLs (more advanced glaucoma) were also associated with *faster* response times to the IP-CRT task when compared to quiet standing (SOT condition 1). In the baseline (no IP-CRT task) conditions, glaucoma severity did not impact NPL in any of the SOT conditions. Finally, sway displacement (RMS) was associated with glaucoma severity in any of the SOT and dual task conditions.

The increase in postural sway velocity (NPL) with advancing glaucoma when the floor was sway-referenced (SOT condition 4) suggests that patients with glaucoma may be more dependent on proprioception to maintain balance. When proprioceptive cues are minimized, the postural control system must increase reliance on available inputs (e.g. vision and vestibular inputs), a process that requires attention resources (Peterka 2002). Participants were able to accurately reweight sensory integration to maintain balance when not performing a dual task, as there was no overall effect of glaucoma severity on balance in SOT condition 4. However, when a dual task (IP-CRT task) is added, attentional resources may be taken away from sensory integration, resulting in a reduced ability to resolve conflicting sensory information. During the IP-CRT condition, there can be interference between the information processing task and maintaining balance, resulting in a performance detriment on one or both tasks (Redfern, Jennings et al. 2001, Muller, Jennings et al. 2004). This was seen in SOT condition 4, where balance worsened (postural sway velocity increased) in patients with advanced glaucoma when attention is required for both postural control and the IP-CRT task.

Interestingly, while balance of patients with more advanced glaucoma was challenged in SOT condition 4 when performing an IP-CRT task, they responded faster to the IP-CRT task. This is in contrast to findings of previous dual task postural control studies in healthy older adults showing that information processing is slowed as balance adjustments are given priority, known as the "posture first" strategy (Redfern, Jennings et al. 2001, Muller, Jennings et al. 2004). Perhaps the current findings suggest that patients with advanced glaucoma are less able to prioritize balance. Conversely, early glaucoma participants exhibited the "posture first" response where their balance stability was improved but response to CRT task worsened when proprioceptive cues were inaccurate. This was only seen when the postural control system was challenged by minimizing proprioceptive cues, implying that there may be a central processing impairment in glaucoma that reduces the ability to accurately integrate sensory inputs.

The main result that balance deteriorates in advanced glaucoma stages when performing a dual task on sway-referenced floors is in agreement with findings of Kotecha and colleagues, who also observed a trend of increased sway in glaucoma patients compared to controls when completing a dual task when standing on a foam surface (Kotecha, Chopra et al. 2013). The main difference between the two studies is the dual task used; Kotecha et al. used the Serial Sevens Test (participants count down from 100 by sevens) and did not measure information processing performance. The Serial Sevens Test lacks specificity and performance may be tied more to arithmetic skill rather than attentional processing capabilities (Young, Jacobs et al. 1997, Karzmark 2000). The present study used an established auditory IP-CRT task that allows for quantification of performance on the information processing task as well as the postural control task.

The findings of this study were not always consistent with findings from previously studies on the impact of glaucoma on standing balance [Table 12]. For example, in this study the relationship between glaucoma and balance was not statistically significant in the baseline (no dual task) conditions. In contrast, when comparing glaucoma patients to healthy controls, prior studies have shown decreased reliance on vision for balance, but an increased proprioceptive contribution to postural control in glaucoma (Shabana, Cornilleau-Peres et al. 2005, Kotecha, Richardson et al. 2012). In addition, prior studies that investigated glaucoma severity, as assessed by VF MD, found that advanced disease stage is associated with increased postural sway, especially when standing on foam surfaces (Black, Wood et al. 2008, Kotecha, Richardson et al. 2012, de Luna, Mihailovic et al. 2017). It is important to address apparent disagreements with previously published findings in light of the following differences in the methods and patients' characteristics used across studies [Table 12]:

- The method of balance assessment varied across studies. To my knowledge, this is the only study that used dynamic posturography (adapted SOT test) to assess balance in glaucoma. There are fundamental differences between using foam versus sway referencing the flooring surface (Forth, Taylor et al. 2006): (1) the SOT test uses a non-compliant surface that is computer-controlled to move in phase with an individual's sway in the anterior-posterior direction, keeping the ankle angle at 90^o. Thus, sway-referencing the floor, the method used in this study, is an effective way to minimize proprioceptive balance cues at the ankles and to induce instability mainly in the AP direction; (2) in contrast, a foam surface is compliant in all directions, and thus induces instability in multiple directions by altering (i.e. introducing noisy) sensory information at the receptors located on the bottom of the feet. Postural control studies have indeed shown that balance assessments using the SOT test and a foam surfaces are not always correlated (Wrisley and Whitney 2004, Forth, Taylor et al. 2006, Mulavara, Cohen et al. 2013).

- Another factor that complicates the comparison across studies are the different outcome balance variables; there is inconsistencies between using displacement, velocity and/or acceleration to quantify postural sway [Table 12].
- Finally, patients' characteristics, including age and glaucoma disease severity, may be different [Table 12]. In particular, the mean VF loss in this study was less severe than that of other studies. This may account for the lack of trends or statistical significance seen in current results that have been previously reported. Also, it is important to note that this study investigated the impact of disease severity on balance, and a patient versus control comparison was not conducted. However, the mean sway magnitude of glaucoma participants during the SOT test are similar to those previously reported in healthy older adults (Redfern, Jennings et al. 2001) and the average median reaction time during quiet standing (433 ms) to the auditory CRT task is faster in the present glaucoma patients compared to observed reaction times (534 ms) while seated in healthy older adults (Redfern, Chambers et al. 2017).

Table 12. Summary of studies that assessed balance in patients with glaucoma.

Study	Participants	Methods	Results
Shabana et al. 2005	35 glaucoma (21 controls) Age: 40-66 years (mean =52) Median VF MD ~ -4 dB	Balance assessed on foam/firm floor, eyes open/closed Glaucoma severity assessed using VF MD and Advanced Glaucoma Intervention Study (AGIS) score of better eye, worse eye and mean of both eyes Outcome variables: 1. Sway velocity 2. Stabilization ratio (ratio of velocity during eyes open / eyes closed conditions)	Sway velocity higher in glaucoma patients than controls, but only during eyes open conditions No interaction between glaucoma and floor condition on sway velocity Visual contribution to posture (stabilization ratio) decreases as VF MD decreases
Black et al. 2008	54 glaucoma (no controls) Age: 65 years and older (median 74) Median binocular VF MD: -2.50 RNFL better eye: 84.7 µm	Balance assessed on foam/firm floor, eyes open/closed Glaucoma severity assessed using binocular VF MD and better eye RFNFL Outcome variables: 1. Postural sway area; 2. Visual stability ratio (1 – sway area$_{\text{eyes open, foam}}$/sway area$_{\text{eyes closed,foam}}$)	Advanced glaucoma severity (VF MD & RNFL) associated with increased postural sway area on firm and foam surfaces RNFL greatest predictor of visual stability ratio, but VF MD also significant
Kotecha et al. 2012	24 glaucoma (24 controls) Age: 65 ± 5 years Median better eye VF MD: -7.3 dB Median worse eye VF MD: -15.2 dB	Balance assessed on foam/firm floor, eyes open/closed Glaucoma severity assessed using binocular VF MD Outcome variables: 1. COP displacement (RMS), 2. Sway velocity, 3. Visual contribution to sway (velocity$_{\text{eyes closed, foam}}$/velocity$_{\text{eyes open, foam}}$), 4. Somatosensory contribution to sway (velocity$_{\text{foam}}$-velocity$_{\text{firm}}$)	Glaucoma patients had lower visual contribution but greater somatosensory contribution to sway than controls VF MD was predictor of visual contribution and somatosensory contribution to sway No difference in COP RMS between glaucoma patients and controls, but there was an interaction between floor and participant group
Kotecha et al. 2013	12 glaucoma (12 controls) Age: 69±4 years Median better eye VF MD: -10.8 dB	Balance assessed on foam/firm floor, eyes open only, with/without dual task (serial sevens) Glaucoma severity assessed using VF MD of better eye Outcome variables: COP displacement (RMS)	The only difference in COP RMS between control and glaucoma patients was during dual task /foam floor condition No differences in sway between glaucoma patients and controls during firm floor (with/without dual task)
de Luna et al. 2017	236 glaucoma Age: mean 71 years Mean better eye VF MD: -4.5 dB	Balance assessed on firm/foam floor, eyes open/closed Glaucoma severity assessed using integrated VF sensitivity Outcome balance variables: 1. Sway acceleration (RMS), 2. Jerk (time derivative of acceleration), 3. Visual dependence (sway$_{\text{eyes closed}}$/sway$_{\text{eyes open}}$)	Glaucoma severity associated with greater acceleration during foam floor/eyes open condition only Visual dependence decreases as glaucoma becomes more severe

In this study, RNFL (a structural measure of glaucoma severity) was associated with changes in dual task performance while VF MD (a functional measure glaucoma severity) was not. This may be due to two factors:

- Functional changes in the primary visual cortex of the brain may occur prior to visual functional deficits (Murphy, Conner et al. 2016) and there is a threshold of structural loss in the retinal nerve before measurable deficits in the visual field (Sihota, Sony et al. 2006, Wollstein, Kagemann et al. 2012), and thus RNFL may indeed be a better marker of balance disability than VF MD in early disease stages. The only study to examine both functional (VF MD) and structural (RNFL thickness) measures of glaucoma and their relationship with balance found RNFL thickness to be a better predictor of visual contribution to balance (Black, Wood et al. 2008).
- The reported RNFL - VF MD difference may be an artifact of the limited VF MD range available in this study.

A limitation to the present study was the relatively small sample size (N=17) and the limited spread of glaucoma severity, specifically as quantified by VF MD. The current sample population had a large concentration of patients with early glaucoma compared to advanced glaucoma. Therefore, to better understand how glaucoma impacts balance and attention over the continuum of disease stages, future studies should include patients with a greater range of glaucoma severity. The present study did not include age-matched healthy controls, so it cannot be confirmed that the reported results are observed only in patients with glaucoma. The RNFL becomes thinner with age (Alamouti and Funk 2003), so comparing balance performance of the glaucoma patients in this study to healthy controls is necessary to discern whether the correlation between RNFL and balance/attention measures are due to glaucoma alone and not another factor such as age.

Another potential limitation was that the impact of location of glaucomatous damage in the visual field was not examined. Studies have shown that inferior visual field loss negatively impacts balance and mobility to a greater extent than loss in the superior visual field (Wood, Lacherez et al. 2009, Black, Wood et al. 2011, Subhi, Latham et al. 2017). However, there are some inconsistencies in literature as de Luna et al. did not find any significant difference in sway measures between glaucoma patients with superior versus inferior visual field loss in a large participant group (N= 236) (de Luna, Mihailovic et al. 2017). Future work should consider the impact of location of visual field loss, as that may be more sensitive in detecting balance impairments than MD of the entire VF. Related to this point, it is unclear why the findings in SOT condition 4 (sway-referenced floor) were not paralleled in SOT condition 6 (sway-referenced floor and visual scene). Again, it is worth noting that severity and patterns of visual field loss (i.e. superior vs. inferior hemifield and right vs. left VF), were not accounted for in this study. It is likely that the visual stimulation in SOT condition 6 varied across participants. Therefore, sway-referencing the visual scene may not have provided a well-controlled condition contributing to high variability among sway data.

4.5 CONCLUSION

In this study, RNFL thickness was associated with increase sway velocity when proprioceptive sensory inputs are inaccurate and a concurrent information processing task is presented. This implies that glaucoma may impact the central multisensory integration processes for balance. Future studies should include patients with greater progression of the disease as well as healthy age-matched controls to fully understand the central versus peripheral mechanisms of glaucoma’s impact on postural control.

5.0 IMPACT OF GLAUCOMA ON GAIT, WITH A FOCUS ON MULTISENSORY INTEGRATION

5.1 INTRODUCTION

The risk of falling is three times greater in individuals with glaucoma compared to healthy controls (Haymes, Leblanc et al. 2007). Further, as visual impairment due to glaucoma increases, so does the risk of falls and falls-related injuries (Black, Wood et al. 2011). Impaired gait may be a contributing factor to falls (Hausdorff, Edelberg et al. 1997, Newstead, Walden et al. 2007). Previous gait research in glaucoma is limited. Patients with glaucoma walk slower than individuals with healthy vision, and advanced disease stage is associated with slower gait and wider strides (Turano, Rubin et al. 1999, Mihailovic, Swenor et al. 2017). Further, patients with glaucoma are more prone to bumping into obstacles when completing an obstacle course than healthy controls (Friedman, Freeman et al. 2007, Mihailovic, Swenor et al. 2017).

The ability to maintain balance relies on the central integration of sensory information relevant for postural control, i.e. vision, proprioception and vestibular (Balasubramaniam and Wing 2002, Peterka 2002, Peterka and Loughlin 2004, Maurer, Mergner et al. 2006). In a similar way, vision, proprioception and vestibular sensory inputs are required for normal gait (Patla 1997, Campos, Butler et al. 2012). In healthy adults, vision provides important information about the environment both near and far during gait, whereas proprioception and vestibular cues are both body-based. For example, vision provides information about environmental obstacles so that they can be proactively avoided (i.e. step around or over an obstacle), while proprioception and vestibular senses are used retroactively to respond to obstacles (i.e. reactive response to the foot contacting an object) (Patla 1997). Previous studies have established that vision impairments negatively affect gait performance. Induced central visual field loss in healthy adults resulted in decreased gait speed and increased double support time compared to normal vision (Timmis, Scarfe et al. 2016). Similarly, induced altered (e.g. limited vision, tunnel vision, double vision) or absent (i.e. eyes closed) vision in healthy adults was correlated to altered gait compared to normal vision (Hallemans, Beccu et al. 2009, Helbostad, Vereijken et al. 2009, Pilgram, Earhart et al. 2016). There is also evidence that the motor control system is able to adapt to altered or absent vision by upregulating other sensory inputs such as vestibular and proprioception. For example, Reynard et. al. reported that gait speed in healthy adults was reduced when blindfolded compared to eyes open. However, when speed was controlled for between blindfolded and eyes open conditions, there was no difference in gait variability or stability (Reynard and Terrier 2015). This suggests that healthy adults adopt a more cautious gait strategy in response to vision loss, but they are able to use other senses to maintain stability. Sensory integration during gait in patients with glaucoma has not been studied.

There is also limited evidence suggesting that performing a dual task during walking impairs gait in patients with glaucoma. More specifically, glaucoma patients' response time to a dual task (e.g. pressing a trigger in response to vibration of handheld joystick) is slower when exposed to complex walking activities (i.e. stair climbing, walking in crowded environment) than during baseline walking (Geruschat and Turano 2007). Additionally, a dual task (e.g. carrying cup or tray) impacts the temporal and spatial characteristics of gait (i.e. slower gait, shorter steps, wider strides), particularly in patients with advanced disease stage (Mihailovic, Swenor et al. 2017).

In light of previously published findings and current research gaps, this pilot study was conducted to examine the attentional control of gait in patients with glaucoma, focusing specifically on stability when walking in sensory challenging conditions. Sensitive and established dual-task protocols (Furman, Muller et al. 2003, Redfern, Talkowski et al. 2004, Mendelson, Redfern et al. 2010) were used to examine interference between an information processing (IP) task, specifically an auditory choice reaction time (IP-CRT) task, and walking stability in sensory challenging conditions. The aims of the study were:

- **Aim 1:** Determine the interaction between attention and baseline gait performance in patients with glaucoma, and how this relationship changes with glaucoma severity. Performing the IP-CRT task was expected to negatively impact gait variables (i.e. slower gait speed, increased gait variability, reduced gait smoothness), with a greater effect in patients with advanced glaucoma.
- **Aim 2:** Examine the impact of challenging sensory conditions (i.e. soft flooring, dimmed lighting) on gait performance and response to the IP-CRT task in patients with glaucoma, and whether the effect of challenging sensory conditions changes with glaucoma severity. Gait variables were expected to be altered in challenging sensory challenging conditions (i.e. slower gait speed, increased gait variability, reduced gait smoothness), with a greater effect in patients with advanced glaucoma. Additionally, walking in sensory challenging conditions was anticipated to require greater attention (resulting in slower reaction time to the IP-CRT task) in patients with glaucoma. For both aims, glaucoma was assessed by both structural (retinal nerve fiber layer (RNFL) thickness) and functional (visual field mean deviation (VF MD)) measures.

5.2 METHODS

5.2.1 Participants

Seventeen adults diagnosed with glaucoma were recruited to complete a gait assessment [Table 13]. Participants were able to stand for at least 2 hours. Exclusionary criteria were self-reported orthopedic, neurological, pulmonary or cardiovascular conditions that may negatively impact balance and ocular pathologies other than glaucoma. Potential participants were also excluded if they were taking any central nervous system anti-depressant drugs, including benzodiazepines or barbiturates, or taking more than five prescription drugs, as both may increase fall risk (Caramel, Remarque et al. 1998, Weiner, Hanlon et al. 1998). Glaucoma was assessed two ways: (1) using a structural measure, specifically retinal nerve fiber layer (RNFL) thickness as measured by spectral-domain optical coherence tomography and (2) using a functional measure, specifically visual field mean deviation (VF MD) assessed by automated Humphrey perimetry.

Table 13. Characteristics of participants with glaucoma. RNFL thickness is reduced and VF MD becomes more negative as glaucoma advances. (*) Denotes participants who only completed hard floor, well-lit condition. (^) Denotes participants without reaction time data.

Participant ID	Gender	Age (years)	VF MD worse eye (dB)	VF MD better eye (dB)	RNFL thickness worse eye (µm)	RNFL thickness better eye (µm)
1*	M	62	-30.32	-11.36	51	58
2	F	80	-21.04	-4.89	57	75
3^	M	56	-17.57	0.99	76	104
4^	M	72	-14.94	-0.20	61	77
5	M	65	-12.00	-8.57	65	74
6*	F	53	-7.25	-3.63	45	71
7*	M	80	-5.05	-2.73	71	73
8*	M	70	-4.84	-0.40	93	113
9	F	56	-3.94	-2.07	73	74
10*,^	M	67	-3.87	-1.90	57	69
11	M	66	-3.47	-1.84	60	66
12	F	60	-3.30	0.69	71	89
13^	F	69	-2.01	0.46	60	63
14	M	70	-1.96	-1.36	63	73
15	F	54	-1.73	-1.10	75	85
16	F	54	-0.30	-0.27	95	98
17*,^	F	71	-0.44	-0.05	85	88
All	**9 male**	**65.7±8.9**	**-8.97±9.49**	**-2.37±3.28**	**67.1±14.1**	**80.2±14.8**

5.2.2 Protocol

Prior to data collection, participants were trained on the IP-CRT task to become familiar with the task and to establish stable performance. The IP-CRT task was a frequency-discrimination auditory choice reaction time task. Participants wore headphones and held a button in each hand and were instructed to push the button in their dominant hand if the stimulus was a high tone (980 Hz) or push the button in their non-dominant hand if the stimulus was a low tone (560 Hz). The auditory stimuli were generated by a custom Labview (National Instruments) program that randomized high/low tones such that approximately half of each tone was presented and stimuli were spaced every 4 seconds with an added random time of +/- 2.0s to reduce the stimulus predictability. Participants continued training for a total of 8-10 trials, until mean reaction time (RT) stabilized (mean RT of trials within 50ms of each other) and RT standard deviation was below 100ms.

All participants completed baseline gait assessment (hard floor, well-lit environment) with and without the IP-CRT and a subset of participants (N=11) completed gait assessments under challenging sensory conditions (i.e. soft floor, dimmed lighting). Reaction time data for 4 participants had to be excluded because of technical difficulties.

Motion capture (Vicon Motion Systems, Oxford, UK) was used to collect kinematics of the feet and sternum during walking at a frequency 120 Hz. Additionally, 3D body acceleration was collected at a frequency of 1080 Hz from an accelerometer (Delsys Inc., Boston, MA) attached posteriorly to the lumbar spine. Prior to walking trials, a static standing trial (~5 seconds) was collected.

Participants were asked to walk along a 7 m x 2 m oval track [Figure 7] at a comfortable pace on two different floors: (1) the hard floor condition consisted of a firm vinyl tile covered floor to record baseline gait, and (2) the soft floor condition consisting of a walkway covered with a soft carpet meant to alter somatosensory cues. Additionally, there were two different visual (lighting) conditions: (1) well-lit which served as baseline, and (2) dimmed lighting to create challenging visual inputs. Participants completed gait conditions with the CRT task (IP-CRT) and without the CRT task (IP-None). During the IP-CRT condition, the number of auditory stimuli was 45. A full factorial experimental design was used to expose participants to all possible combinations of floor, lighting and IP conditions for a total of 8 walking trials. Trials were blocked by floor (soft floor first, hard floor second) and participants completed well-lit trials first (IP-None then IP-CRT) then dimmed trials (IP-None then IP-CRT) within each floor condition. Trials lasted 3 minutes and seated breaks were given every 2 trials (6 minutes of walking) to prevent fatigue.

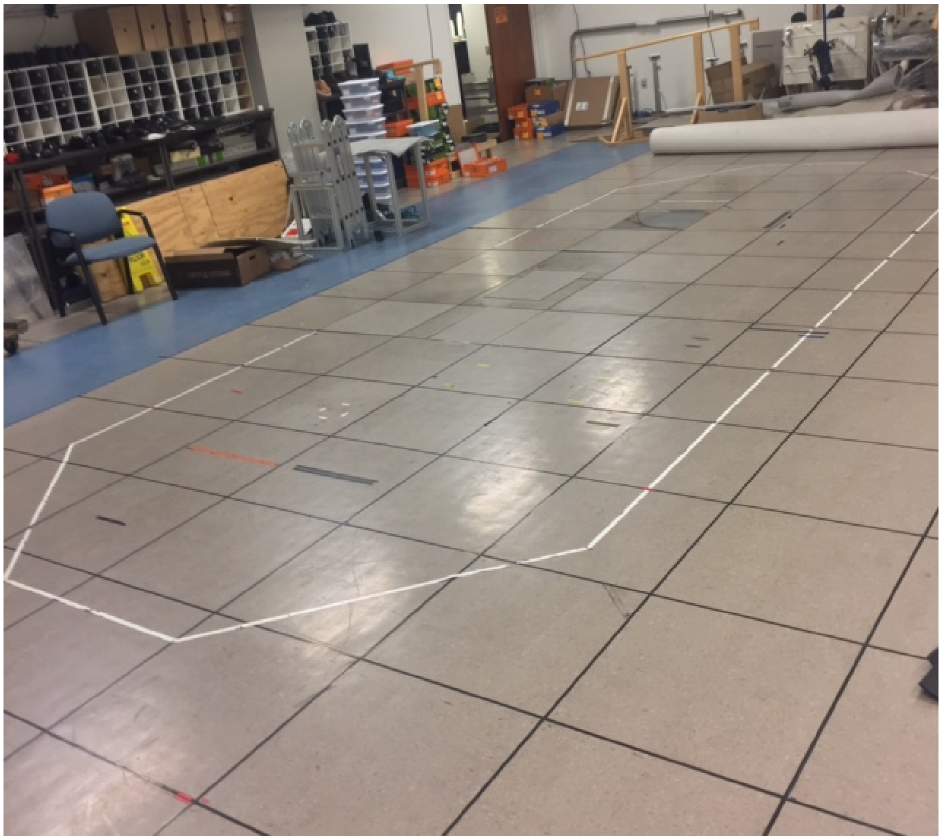


Figure 7. Experimental walkway setup during hard floor, well-lit condition. The walking track is denoted by white tape on the floor. During soft floor conditions, a carpet was placed over the walkway and lights were turned down for dimmed lighting condition.

5.2.3 Analysis

Gait trials were first parsed to eliminate the 2m short sides of the track as well as the turns around the oval, so that only the central 5m of the long 7m “straightaways” were analyzed. Marker data was filtered with a low-pass Butterworth filter with a cutoff frequency of 6 Hz to remove high-frequency noise. Heel strike and toe off of each gait cycle within the straightaways were defined from toe markers on the heel. The following variables were calculated for each 3-minute trial:

1. Gait speed: Distance traveled over time of sternum marker.
2. Stance and swing time variability: Standard deviation of stance (heel contact to toe off) and swing (toe off to heel contact) phases of gait from the right leg, respectively.
3. Gait smoothness: Harmonic ratio of in-phase components of the acceleration signal (even harmonics) to out-of-phase components (odd harmonics) as described by Menz et. al. (2003). A large harmonic ratio translates to more smooth, or rhythmic, gait. Gait smoothness was calculated in the vertical (V), anterior-posterior (AP) and medial-lateral (ML) directions and was normalized within subject to the harmonic ratio of the static standing trial (~5 seconds) collected before walking trials.
4. Reaction time (for IP-CRT trials only): median RT to the 45 stimuli presented during walking trials.

Aim 1 analysis: Mixed-linear analysis was performed using JMP Version 10 (SAS Institute Inc). The first set of regression analyses examined the effect of glaucoma severity and IP condition (IP-None or IP-CRT) on baseline gait variables (hard floor, well-lit environment). All 17 subjects were used in this analysis. Two measures of glaucoma were considered: (1) RNFL thickness and (2) VF MD of the worse eye. Thus, the effect of RNFL and VF MD were considered individually, each in a separate regression model. The dependent variables of interest were the gait measures: gait speed, stance and swing time variability, and gait smoothness. Log transforms of gait variables were used to normalize residuals, with the exception of gait speed because raw data as well as the residuals from a linear fit against glaucoma severity (VF MD and RNFL thickness) were normally distributed. Fixed effect of interest was glaucoma severity (VF MD or RNFL thickness), IP condition (IP-None or IP-CRT), and the first order interaction between glaucoma severity and IP condition. Participant was included as a random effect.

Aim 2 analyses: The second set of regression analyses aimed to determine the impact of glaucoma severity and challenging sensory and attentional conditions on gait performance. Only the subset (N=11) of participants, who completed the challenging flooring and lighting conditions, were included in these analyses. Gait speed, the log transforms of stance and swing time variability, and the log transform of gait smoothness were the dependent variables. The fixed effects included a full factorial model of glaucoma severity (VF MD or RNFL thickness), IP condition (IP-None or IP-CRT), flooring condition (hard or soft floor) and lighting condition (well-lit or dimmed lighting). Participant was included as a random effect. The results of these regression analyses revealed non-statistically significant lighting effects (main effect or interaction with other fixed variables) on gait. Thus, the analysis was repeated and lighting condition was omitted as an independent effect in the regression model and dependent gait variables were averaged across lighting conditions. Therefore, the final Aim 2 analysis model included glaucoma severity, IP condition, flooring condition and their first order interactions as fixed effects. Participant was included as a random effect. A separate analysis was run to examine the impact of glaucoma severity and flooring condition on RT by conducting a linear regression analysis with median RT as the dependent variable. Independent variables included were and glaucoma severity (VF MD or RNFL thickness), flooring condition, and their first order interaction. Participant was included as a random effect. Statistical significance was set at $\alpha=0.05$ for all analyses.

5.3 RESULTS

Aim 1 results: Baseline gait data with and without the IP-CRT task were collected and measures obtained are presented in Table 14. There was no overall effect of glaucoma severity, whether quantified by RNFL thickness or VF MD, on the measures of gait during baseline walking (hard floor, well-lit environment). Similarly, neither IP condition nor the interaction of glaucoma severity and IP condition was associated with baseline gait measures (p>0.05) [Table 15].

Table 14. Mean (STD) gait characteristics and IP-CRT reaction time of glaucoma patients recruited in this pilot study during walking under different flooring and dual task conditions. (*)There were main effects of IP condition (p=0.04) and flooring condition (p=0.0001) on gait speed. (^) There was a main effect of IP condition on vertical (V) and anterior-posterior (AP) gait smoothness (p=0.04).

Gait variable	IP-None Hard floor	IP-CRT Hard floor	IP-None Soft floor	IP-CRT Soft floor
Gait speed (m/s)*	1.22 (0.15)	1.25 (0.15)	1.10 (0.15)	1.14 (0.15)
Stance time variability (ms)	19.72 (7.52)	20.99 (12.24)	24.74 (11.26)	19.72 (6.90)
Swing time variability (ms)	20.45 (7.00)	19.06 (11.86)	23.94 (14.14)	19.91 (7.41)
V gait smoothness^	2.71 (1.09)	2.72 (1.15)	3.25 (1.05)	2.98 (1.08)
AP gait smoothness^	2.80 (0.65)	2.78 (0.61)	3.17 (0.49)	2.99 (0.70)
ML gait smoothness	1.93 (0.94)	1.99 (1.00)	1.96 (0.84)	1.91 (0.83)
IP-CRT task median RT (ms)	–	427 (52)	–	433 (75)

Table 15. Statistical p-values from linear regression model examining effect of glaucoma severity, as defined by 1) VF MD and 2) RNFL thickness, information processing (IP) condition and their first-order interaction on gait measures. Statistical significance was set at 0.05.

	Gait speed (m/s)	Stance time variability (ms)	Swing time variability (ms)	V gait smoothness	AP gait smoothness	ML gait smoothness	IP-CRT task median RT (ms)
1. VF MD							
VF MD	0.99	0.52	0.98	0.61	0.67	0.47	0.16
IP condition	0.07	0.20	0.26	0.27	0.34	0.98	--
VF MD*IP	0.14	0.82	0.36	0.18	0.30	0.14	--
2. RNFL thickness							
RNFL thickness	0.60	0.25	0.20	0.92	0.19	0.22	0.27
IP condition	0.10	0.15	0.24	0.31	0.35	0.98	--
RNFL*IP	0.61	0.15	0.25	0.64	0.42	0.73	--

Aim 2 results: There was an interaction effect between glaucoma severity and floor condition on gait speed, but only when glaucoma severity was assessed using RNFL thickness. More specifically, glaucoma severity did not have an impact on gait speed during the baseline (hard floor) condition [Figure 8]. However, gait speed was reduced while walking on the soft-floor compared to walking on the hard floor (baseline), and this effect was greater with RNFL thinning (p=0.04, F=4.70) [Figure 9]. There were main effects of IP condition (p=0.04) and flooring condition (p=0.0001) on gait speed [Table 14, Table 16]. IP condition also had a significant effect on gait smoothness in the vertical and anterior-posterior directions (p=0.04). There was no main effect of glaucoma severity, whether quantified by RNFL thickness or VF MD, on measures of gait [Table 16]. Lastly, swing phase variability, stance phase variability, and gait smoothness were not impacted by glaucoma severity (RNFL thickness or VF MD), IP condition, floor condition, or their first order interactions.

Median RT to the IP-CRT task was not modulated by glaucoma severity [Table 14-15]. There was also no effect of flooring condition on RT.

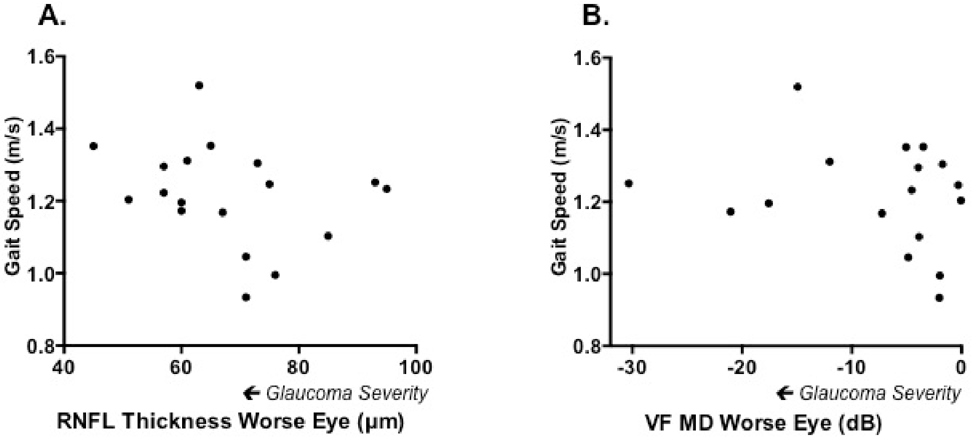


Figure 8. Gait speed during hard floor condition versus (A.) RNFL thickness and (B.) VF MD of the worse eye. Glaucoma severity did not have a main effect on gait speed during the hard floor condition (p>0.05).

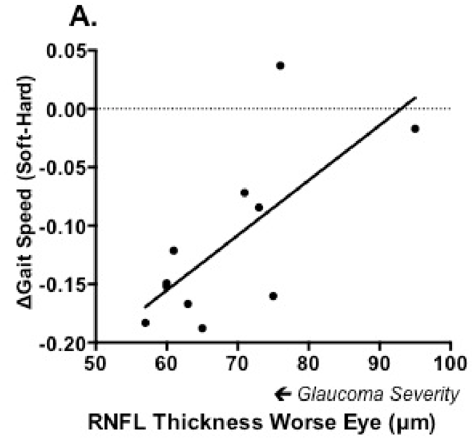


Figure 9. Difference in gait speed between soft and hard floor condition versus glaucoma assessments (A.) RNFL thickness and (B.) VF MD of the worse eye. Patients with more advanced glaucoma walked slower on the soft floor than hard floor but only when glaucoma was assessed using RNFL thickness (p=0.04, F=4.70).

Table 16. Statistical p-values from linear regression model examining effect of glaucoma severity, information processing (IP) condition, flooring condition, and the first-order interaction of main effects on gait measures. Glaucoma severity was assessed by (1.) VF MD and (2.) RNFL thickness. *Denotes statistically significant effects (p<0.05).

	Gait speed (m/s)	Stance time variability (ms)	Swing time variability (ms)	V gait smoothness	AP gait smoothness	ML gait smoothness	IP-CRT task median RT (ms)
1. VF MD							
VF MD	0.96	0.93	0.40	0.72	0.78	0.37	0.23
IP condition	0.04*	0.23	0.11	0.04*	0.04*	0.81	--
Floor condition	<0.0001*	0.29	0.22	0.70	0.27	0.86	0.68
VF MD*IP	0.12	0.37	0.96	0.20	0.12	0.45	--
VF MD*Floor	0.56	0.38	0.87	0.91	0.93	0.64	0.72
IP*Floor	0.42	0.09	0.89	0.63	0.47	0.58	--
2. RNFL thickness							
RNFL thickness	0.81	0.63	0.33	0.76	0.89	0.32	0.28
IP condition	0.04*	0.23	0.10	0.04*	0.04*	0.83	--
Floor condition	<0.0001*	0.29	0.20	0.67	0.25	0.86	0.54
RNFL*IP	0.84	0.15	0.28	0.35	0.94	0.91	--
RNFL*Floor	0.001*	0.95	0.23	0.79	0.08	0.07	0.34
IP*Floor	0.35	0.09	0.86	0.62	0.43	0.54	--

5.4 DISCUSSION

The results of this pilot study show that glaucoma severity may impact gait performance when somatosensory cues are altered, as in the soft floor condition. The difference in gait speed between soft and hard floor conditions was modulated by RNFL thickness; participants with advanced glaucoma (thinner RNFL) walked more slowly during the soft floor condition. Conversely, participants with early glaucoma (thicker RNFL) had similar gait speed during both floor conditions. Therefore, because the interaction between glaucoma severity and proprioception condition was seen in such a small sample size, it is feasible that glaucoma may impact the central integration of the sensory information necessary for mobility.

The results also indicate that there was an overall effect of IP condition on gait speed, which is consistent with previously reported findings in healthy adults (Yogev-Seligmann, Rotem-Galili et al. 2010). Similarly, consistent with previous studies in healthy older adults (Doi, Makizako et al. 2012), IP condition had a main effect on gait smoothness. Because these findings have been observed in healthy populations, the impact of the dual task on gait speed is not unique to patients with glaucoma.

RNFL thickness, and not VF MD, was related to gait speed. These results may be reflective of the study population that had a concentration of participants with mild visual field deficits (VF MD worse eye >-6 dB). Therefore, this study did not accurately capture gait patterns on the moderate and advanced ends of the glaucoma continuum. Structural loss is known to precede functional loss of the visual field (Sihota, Sony et al. 2006, Wollstein, Kagemann et al. 2012), thus the results of this study are reflective of gait performance in early stages of glaucoma before there is substantial VF loss has occurred. Additionally, this pilot study did not include healthy age-matched controls to confirm that observed results are due to glaucoma alone and not another factor, such as age, that may impact gait parameters.

Previous studies of the impact of glaucoma on gait speed have led to mixed results. One such study found that gait speed is modulated by glaucoma severity (Turano, Rubin et al. 1999), which is different from the present pilot study where this relationship is only seen when comparing floor conditions. This difference may be due to the walking environment: Turano et al. use a straight 29-m walkway with no turns while this study analyzed 5-m straight-aways on an oval track. Friedman et al. found association between gait speed and glaucoma severity during an obstacle course that challenged sensory inputs (2007). Similar to this pilot study, Mihailovic et al. showed gait speed decreased with glaucoma severity, but only during challenging walking conditions (carrying a tray) and not during baseline walking (2017).

Gait measures were not sensitive to changes in visual (lighting) condition (main effects and first order interaction with glaucoma severity), a finding that was somewhat unexpected. Similarly, an increase in CRT reaction time during challenging sensory conditions compared to baseline were anticipated, but there was not statistical significance. Reduced lighting conditions has been linked to decreased gait performance (e.g. decreased stride length, decreased stride time, increased gait variability) in healthy adults (Huang, Chien et al. 2017). Additionally, gait characteristics are altered when peripheral vision is blurred to induce tunnel vision in healthy older adults (Helbostad, Vereijken et al. 2009). However, glaucoma may reduce reliance on vision (Shabana, Cornilleau-Peres et al. 2005, Black, Wood et al. 2008, Kotecha, Richardson et al. 2012, de Luna, Mihailovic et al. 2017) and an increase dependence on proprioception for balance (Kotecha, Richardson et al. 2012). This may why the altered gait parameters observed in healthy adults were not seen in patients with glaucoma and why altered proprioception, and not altered lighting, had an effect on gait speed in this study.

As mentioned previously, a major limitation of this study was the testing environment. The size of the oval track was only 7 x 2 m, which is not ideal for collecting consistent walking data. To turn around the track, participants slowed down and decelerated as they approached the curve and then sped up and accelerated when they reached the next straight-away. Gait smoothness is lower when walking in a circular path compared to normal straight walking (Brach, McGurl et al. 2011). Thus, even though only the central 5 m of the 7-m straight-aways were analyzed, it is likely that turns still impacted gait within that window. To get a more accurate representation of how glaucoma impacts gait and attention, a more appropriate testing environment should be used with a longer track to ensure consistent gait is achieved in the capture volume.

5.5 CONCLUSION

This pilot study was limited by the sample size and testing environment, but the interaction between glaucoma severity and floor condition suggest that there may be changes in sensory integration necessary for gait in individuals with glaucoma. Future work should continue exploring this trend by investigating more challenging somatosensory conditions in a larger sample of glaucoma patients.

6.0 RELATIONSHIP BETWEEN BRAIN CONNECTIVITY AND BALANCE IN GLAUCOMA

6.1 INTRODUCTION

Glaucoma has been primarily thought of as an eye disease that leads to irreversible visual field (VF) loss and blindness (Weinreb, Leung et al. 2016). However, the pioneering work of Gupta, Yücel and colleagues provided evidence that glaucoma is not only an eye disease, but is also a neurodegenerative condition that impacts the brain’s visual pathway in patients diagnosed with this condition in various ways (Gupta and Yucel 2001, Gupta and Yucel 2003, Gupta and Yucel 2006, Gupta and Yucel 2007, Gupta and Yucel 2007, Gupta and Yücel 2007, Yucel and Gupta 2008, Yucel and Gupta 2008, Gupta, Greenberg et al. 2009). Both brain structure (Li, Cai et al. 2012, Zikou, Kitsos et al. 2012, Williams, Lackey et al. 2013) and function (Dai, Morelli et al. 2013) may be altered in glaucoma patients. More specifically, significant changes in grey matter density and grey and white matter volumes have been reported in patients with glaucoma in vision-related brain regions in the occipital lobe, and these changes are modulated by disease severity (Li, Cai et al. 2012, Williams, Lackey et al. 2013). Further, functional brain alterations in the primary visual cortex may precede detectable deficits in the VF (Murphy, Conner et al. 2016). Research has also shown that brain alterations in glaucoma may be more widespread and are not limited to the visual pathway; Boucard et al. found preliminary evidence of white matter deterioration in the corpus callosum and parietal lobe (Boucard, Hanekamp et al. 2016). Zikou and colleagues reported voxel-based microstructural changes in parts of the basal ganglia, including the putamen and the caudate nucleus (Zikou, Kitsos et al. 2012). Differences in volume (Chen, Wang et al.

2013, Williams, Lackey et al. 2013, Jiang, Zhou et al. 2017) and blood flow (Jiang, Zhou et al. 2017) have been seen in the frontal gyrus, which plays a role in cognition and executive functioning, in glaucoma patients compared to healthy controls (Chen, Wang et al. 2013). Resting-state functional MRI also suggested reduced intrinsic functional connectivity between visual cortex and brain regions important for balance and attention, specifically the precentral gyrus (i.e. primary motor cortex responsible for voluntary muscle movements), postcentral gyrus (i.e. primary somatosensory cortex), the frontal gyrus that plays a role in attention and executive function, and the anterior lobe of the cerebellum that is involved in proprioception, in patients with glaucoma (Hendelman 2000, Dai, Morelli et al. 2013).

Patients with glaucoma fall at a greater rate than healthy adults (Guse and Porinsky 2003, Haymes, Leblanc et al. 2007, Bramley, Peeples et al. 2008, Lamoureux, Chong et al. 2008, Patino, McKean-Cowdin et al. 2010). Postural control studies have suggested that glaucoma is associated with an impaired ability to effectively and reliably integrate sensory information important for balance, i.e. vision, proprioception and vestibular (Shabana, Cornilleau-Peres et al. 2005, Black, Wood et al. 2008, Kotecha, Richardson et al. 2012, Kotecha, Chopra et al. 2013, de Luna, Mihailovic et al. 2017). For example, standing balance worsens (increased sway magnitude and sway velocity) in glaucoma to a greater extent than in controls when balance-related proprioceptive cues are altered, e.g. standing on foam (Black, Wood et al. 2008, Kotecha, Richardson et al. 2012, Kotecha, Chopra et al. 2013, de Luna, Mihailovic et al. 2017). It has been well established that the ability to maintain upright stance relies on the central integration of vision, proprioception and vestibular information relevant for balance control (Balasubramaniam and Wing 2002, Peterka 2002, Peterka and Loughlin 2004, Maurer, Mergner et al. 2006, Asslander and Peterka 2014). Specifically, this feedback balance control process is dependent on the ability to regulate the degree of reliance of the postural control system on each of these sensory channels (Balasubramaniam and Wing 2002, Peterka 2002, Peterka and Loughlin 2004, Maurer, Mergner et al. 2006, Asslander and Peterka 2014). For example, if vision is unreliable, e.g. loss of vision or walking in dark or moving environment, the postural control system in healthy adults increases its reliance on proprioception and vestibular information (Peterka 2002, Peterka and Loughlin 2004). Effective sensory integration plays a significant role in balance control, particularly in older adults (Amblard and Carblanc 1980, van Asten, Gielen et al. 1988, Jasko, Loughlin et al. 2003, Berencsi, Ishihara et al. 2005).

Attentional resources are involved in resolving sensory conflict related to balance control (Redfern, Jennings et al. 2001, Redfern, Mûller et al. 2002, Verghese, Buschke et al. 2002, Furman, Muller et al. 2003, Redfern, Talkowski et al. 2004, Yogev, Giladi et al. 2005, Hausdorff, Doniger et al. 2006, Holtzer, Friedman et al. 2007, Scherder, Eggermont et al. 2007, Yogev-Seligmann, Hausdorff et al. 2008, Redfern, Jennings et al. 2009, Mendelson, Redfern et al. 2010, Holtzer, Wang et al. 2012, Montero-Odasso, Verghese et al. 2012, Sparto, Fuhrman et al. 2013). For example, people are often exposed to multiple sources of sensory information that imply multiple actions. Responses to all of this information are not possible, as conflicting cognitive and motor responses would occur. Information is selected/inhibited because our capability of processing information is limited. This is empirically evident when two tasks are presented concurrently (e.g. the dual-task paradigm); the performance on one or both tasks suffers relative to the performance of each individually. Typically, response to one of the tasks is delayed as ‘attention’ processes one task transiently prohibiting interference from the other. An information-processing (IP) task, e.g. push a button when hearing an auditory stimulus, combined with a postural challenge, e.g. standing on moving platforms, can create interference between the two, especially in older adults (Redfern, Jennings et al. 2001, Redfern, Mûller et al. 2002, Redfern, Talkowski et al. 2004, Redfern, Jennings et al. 2009, Mendelson, Redfern et al. 2010, Sparto, Fuhrman et al. 2013). Typically, information processing is slowed (longer response times to the IP task) as balance adjustments are given priority (i.e. "posture first" principle) (Redfern, Jennings et al. 2001, Muller, Jennings et al. 2004). Evidence of greater interference between attention and balance control has been reported in glaucoma in limited studies suggesting that (1) balance in patients with glaucoma worsens when performing a secondary IP task to a greater extent than in controls (Kotecha, Chopra et al. 2013) and (2) gait requires greater "mental effort" in patient with glaucoma than in controls (Geruschat and Turano 2007).

In summary, there is preliminary but convergent evidence that a potential mechanism for worsening balance in glaucoma is the greater interference between attention and balance-related sensory integration processes. It remains unclear whether this increased interference is linked to the brain connectivity alterations reported in glaucoma. Thus, the goal of this pilot study was two-fold:

- **Aim 1:** Examine the association between brain connectivity, assessed using diffusion tensor imaging (DTI), and clinical glaucoma assessment measures including retinal nerve fiber layer (RNFL) thickness and visual field (VF) loss. Glaucoma assessment measures, specifically smaller RNFL and greater VF loss, were expected to be associated with altered brain connectivity not only in the primary visual pathway but also in brain regions associated with balance control and attention.
- **Aim 2:** Systematically probe the potential link between alterations in brain connectivity and attentional influences on balance control in glaucoma (assessed using standing dual task paradigms).

6.2 METHODS

Subjects diagnosed with glaucoma underwent two tests (two visits): an MRI scan and an established dual task paradigm balance test (Furman, Muller et al. 2003, Redfern, Talkowski et al. 2004, Mendelson, Redfern et al. 2010). DTI data were extracted from the MRI scan to quantify brain connectivity in white matter tracts of interest. The dual task paradigm balance test included an information processing (IP) task, specifically an auditory choice reaction time (IP-CRT) task, presented concurrently while standing in challenging sensory conditions (e.g. moving floors and visual environments). Thus, balance abilities were assessed with and without the IP-CRT task. Aim 1 analyses consisted of examining associations between the DTI measures and clinical measures of glaucoma (RNFL thickness and VF-MD), while analyses in Aim 2 were focused on linking DTI measures with the dual task paradigm outcome measures, specifically balance (sway magnitude and sway velocity) and reaction time to the IP-CRT task.

6.2.1 Participants

Eight (N=8) adults diagnosed with glaucoma were recruited. Exclusionary criteria were self-reported orthopedic, neurological, pulmonary or cardiovascular conditions that may negatively impact balance and ocular pathologies other than glaucoma. Potential participants were also excluded if they were taking any central nervous system anti-depressant drugs, including benzodiazepines or barbiturates, or taking more than five prescription drugs, as both may increase fall risk (Caramel, Remarque et al. 1998, Weiner, Hanlon et al. 1998). Prior to enrollment, participants were screened for any metallic implants or foreign bodies that could affect safety or image quality of the MRI scan. Two measures commonly used in assessing glaucoma severity were included in analyses: (1) structural measure of retinal nerve fiber layer (RNFL) thickness and (2) functional visual field mean deviation (VF-MD) of the worse eye. A summary of participant demographic information including gender, age, VF-MD and RNFL thickness is provided in Table 17. Written informed consent approved by the University of Pittsburgh Institutional Review Board was obtained prior to participation.

Table 17. Characteristics of participants who completed MRI scan. Participant IDs are consistent with those for the balance protocol in Chapter 4. (^) Denotes participant without reaction time data.

Participant ID	Gender	Age (years)	VF-MD worse eye (dB)	VF-MD better eye (dB)	RNFL thickness worse eye (µm)	RNFL thickness better eye (µm)
2	F	80	-21.04	-4.89	57	75
5	M	65	-12.00	-8.57	65	74
11	M	66	-3.47	-1.84	60	66
12	F	60	-3.30	0.69	71	89
13^	F	69	-2.01	0.46	60	63
14	M	70	-1.96	-1.36	63	73
15	F	54	-1.73	-1.10	75	85
16	F	54	-0.30	-0.27	95	98
All (mean±SD)	**3 male**	**64.8±8.7**	**-5.73±7.15**	**-2.11±3.14**	**68.3±12.4**	**77.9±11.9**

6.2.2 Protocol

MRI scan collection: One visit was dedicated to the MRI scan. DTI data was collected on a 3 T Siemens Allegra scanner (Siemans, Erlangen, Germany) using a single-channel transmit/receive head volume coil. A 3D magnetized prepared rapid acquisition gradient echo (MPRAGE) image was collected to use as localizer to confirm consistent positioning before DTI scans. A single-shot spin-echo echo-planar imaging pulse sequence was used to acquire DTI data with the following parameters: repetition time = 5200 ms, echo time = 80 ms, field of view = 20.5x20.5 cm^2, 104x104 imaging matrix, and 38 contiguous 3 mm thick axial slices. One non-diffusion-weighted image

(b_0) and 12 diffusion gradient directions at diffusion weighting factor (b)=850 s/mm^2 were acquired.

Dual paradigm balance test: Balance testing and DTI scans occurred on different days with no more than 2 months passing between visits. The dual task paradigm was used participants completed an adapted version of the six conditions of the sensory organization test (SOT) with and without a secondary IP-CRT task.

IP-CRT task: Participants were first trained on the IP-CRT task to establish stable performance. The auditory IP-CRT task was a frequency-discrimination auditory choice reaction time task. Participants wore headphones and held a button in each hand and were instructed to push the button in their dominant hand if the stimulus was a high tone (980 Hz) or push the button in their non-dominant hand if the stimulus was a low tone (560 Hz). The auditory stimuli were generated by a custom Labview (National Instruments) program that randomized high/low tones such that approximately half of each tone was presented and stimuli were spaced every 4 seconds with an added random time of +/- 2.0s to reduce the stimulus predictability. Participants continued training for a total of 8-10 trials, until mean RT stabilized (mean RT of trials within 50ms of each other) and RT standard deviation was below 100ms.

Balance test: Standing balance was assessed using dynamic posturography adapted from the Sensory Organization Test (SOT) on an Equitest posture platform (Neurocom, Inc) located in the Jordan Balance Disorders Laboratory within the Eye & Ear Institute of Pittsburgh. The SOT has been shown to be effective at evaluating sensory integration capabilities relevant to balance (Nashner, Black et al. 1982, Bronte-Stewart, Minn et al. 2002). The Equitest platform is capable of sway-referencing, which provides rotations of the floor and/or the visual scene in direct proportion to an individual's sway of vision and/or proprioception, respectively. For example, sway-referencing the floor causes movements of the support surface in an attempt to keep the ankle angle constant. The purpose of using sway-referencing of the floor is to reduce the reliability of proprioceptive information from the ankle for balance. The same principle is used for sway-referencing of the visual scene, resulting in erroneously stable vision even though the person is swaying (Nashner, Black et al. 1982). The platform records ground reaction forces under the feet during standing. Sway referencing was provided through the method of low-pass filtering of the center of pressure (COP) data collected by the Equitest platform. There are six conditions in the SOT test, including combinations of fixed / sway-referenced visual scene and floor conditions and eyes closed / open conditions [Table 6, page 36]. Participants wore a safety harness that would prevent hitting the floor in the event that they lost their balance. During balance testing, participants were instructed to stand as still as possible without locking their knees. The dual task subset of participants completed the SOT conditions in order from 1-6, repeating each condition twice: first for baseline (no IP-CRT task) and second with the IP-CRT task. The number of auditory stimuli per trial was 45. For participants not included in the dual task subset, the six adapted SOT conditions were only presented once and in order from 1-6. All trials lasted 3 minutes and postural sway was assessed using the COP data collected at a sampling frequency of 100 Hz. Participants were given 2 minute breaks every 2 trials (6 minutes of standing) to minimize effects of fatigue.

6.2.3 Analysis

MRI scan processing: DTI was used to quantify structural integrity of white mater tracts that are responsible for communicating information between different regions of the brain. DTI utilizes noninvasive magnetic resonance imaging (MRI) to measure the magnitude and direction of diffusion anisotropy of water molecules in the brain. In white matter tracts, water diffusion is in general unconstrained in the direction parallel to tract fibers but is restricted in directions parallel to fibers; in other words, diffusion is anisotropic (Conturo, Lori et al. 1999, Alexander, Lee et al. 2007). Fractional anisotropy (FA) is a DTI measure used to quantify overall white matter structural integrity by measuring the magnitude of anisotropic diffusion. FA is unitless and ranges from 0 to 1, with a value of 0 representing unrestricted diffusion and 1 representing diffusion that is completely anisotropic and restricted to one direction (Pierpaoli and Basser 1996). This study also used the following measures to examine white matter structure:

(1) mean diffusivity (DTI-MD): measure of total diffusion in a voxel

(2) axial diffusivity (AD): rate of diffusion in principal diffusion direction

(3) radial diffusivity (RD): rate of diffusion perpendicular to principal diffusion direction

As mentioned previously, this study aimed to investigate white matter structural integrity in brain areas that play roles in vision, balance and attention. Thus, the focus was on the following five tracts:

1. optic radiation: bundle of axons connecting the lateral geniculate nucleus of the thalamus to the primary visual cortex. The optic radiation is necessary for transmitting visual information (Kier, Staib et al. 2004).
2. superior occipito-frontal fascicle: long fiber bundle that connects frontal and occipital lobes and transmits visual information to the anterior frontal lobe (Forkel, Thiebaut de Schotten et al. 2014). There is evidence that the superior occipito-frontal fascicle plays a role in spatial awareness, which is important for vision, balance and attention (Karnath, Rorden et al. 2009, Thiebaut de Schotten, Dell'Acqua et al. 2011).

(3) inferior occipito-frontal fascicle: long fiber bundle that connects the occipital cortex and parietal lobe to the frontal lobe (Martino, Brogna et al. 2010). There is evidence that the inferior occipito-frontal fascicle plays a role in attention and visual processing (Catani and Thiebaut de Schotten 2008)

(4) corpus callosum: largest bundle of white matter in the brain and connects the right and left hemispheres. The corpus callosum plays functional roles in motor control, perception and cognition which are all critical processes for balance (Doron and Gazzaniga 2008).

(5) cingulum: bundle of fibers that connects parts of the frontal and temporal lobes and may be involved in emotion cognition, attention and memory (Jones, Christiansen et al. 2013, Gunbey, Ercan et al. 2014).

DTI data was first pre-processed to correct for eddy currents and then FA maps were co-registered and transformed to align with the 1x1x1 mm^3 MNI152 standard space using FMRIB Software Library (FSL). FA data was computed across subjects using tract-based spatial statistics (TBSS) in FSL (Smith, Jenkinson et al. 2006) and a custom-written MATLAB (MathWorks, Inc) program. The same process was repeated to calculate DTI-MD, RD and AD. Average DTI measures were obtained in white matter tracts of interest including the optic radiation, superior occipito-frontal fascicle, inferior-frontal fascicle, corpus callosum and cingulum. Regions of interest were defined using the Juelich atlas (Burgel, Schormann et al. 1999, Burgel, Amunts et al. 2006).

Dual paradigm balance test processing: Only balance measures from SOT conditions 1 and 4 were included in the analyses to compare a challenging postural condition (SOT condition 4) with quiet standing (SOT condition 1). SOT condition 4, in which proprioceptive cues are altered by sway-referencing the floor, was selected because reduced proprioception has been shown to negatively impact balance in patients with glaucoma compared to healthy adults (Black, Wood et al. 2008, Kotecha, Richardson et al. 2012). COP data were first down-sampled to 20 Hz and low-pass filtered using a fourth-order Butterworth filter with a cutoff frequency of 2.5 Hz. Additionally, the first thirty and last five seconds of each condition were removed to eliminate any transient effects. Because sway referencing occurs only in the anterior-posterior direction, only the anterior-posterior COP data were used to quantify postural sway. Sway magnitude was defined as the root-mean-square (RMS) of the filtered COP displacement [Equation 1, page 17]. The time-normalized path length (NPL) of COP was calculated by summing the absolute value of the differences over time [Equation 2, page 17]. The COP RMS and COP NPL were log-transformed for statistical analysis to ensure normality of residuals. Performance on the IP-CRT task was assessed using the median RT for each subject during each trial. Both the median RT in SOT conditions 1 and 4 as well as the difference in RT between the challenging sensory condition and quiet standing (e.g. $\Delta RT_{SOT4} = medianRT_{SOT4} - medianRT_{SOT1}$) were assessed.

Statistical Analyses: Linear regression analyses were conducted using JMP Version 10 (SAS Institute Inc). Aim 1 focused on the relationship between glaucoma assessment measures (RNFL thickness and VF-MD loss) and DTI measures (FA, DTI-MD, RD and AD) in the white matter tracts of interest (optic radiation, superior occipito-frontal fascicle, inferior-frontal fascicle, corpus callosum and cingulum). Simple linear analyses were used, regressing individually each DTI measure on RNFL and VF. In Aim 2 analyses, the association between DTI measures and performance on the dual task paradigm (balance measures including RMS and NPL and response time to the auditory IP task) was examined. More specifically, COP RMS, COP NPL, median RT and ΔRT_{SOT4} were each individually regressed on the DTI measures. Statistical significance was set at $\alpha=0.05$ for all analyses.

6.3 RESULTS

Aim 1: Figure 11 shows representative diffusion-based MRI parametric maps from glaucoma participants with different disease severities. RNFL thickness was related to DTI measures. FA of the optic radiation decreased with RNFL thinning (p=0.02, F=9.4) [Figure 11]. DTI-MD of the optic radiation (p=0.049, F=5.9), superior occipito-frontal fascicle (p=0.04, F=6.5) and corpus callosum (p=0.03, F=8.5) increased as RNFL thickness decreased [Figure 12]. Only the superior occipito-frontal fascicle (p=0.02, F=8.9) and corpus callosum (p=0.01, F=14.9) showed significant relationship between AD and RNFL thickness with AD increasing as RNFL thickness decreased [Figure 13]. Similarly, RD increased with RNFL thinning in the optic radiation (p=0.03, F=7.7) and the corpus callosum (p=0.049, F=6.2) [Figure 14]. DTI measures of the cingulum were not associated with RNFL thickness (p>0.05). Additionally, there was no significant relationship between DTI measures and VF-MD (p>0.05).

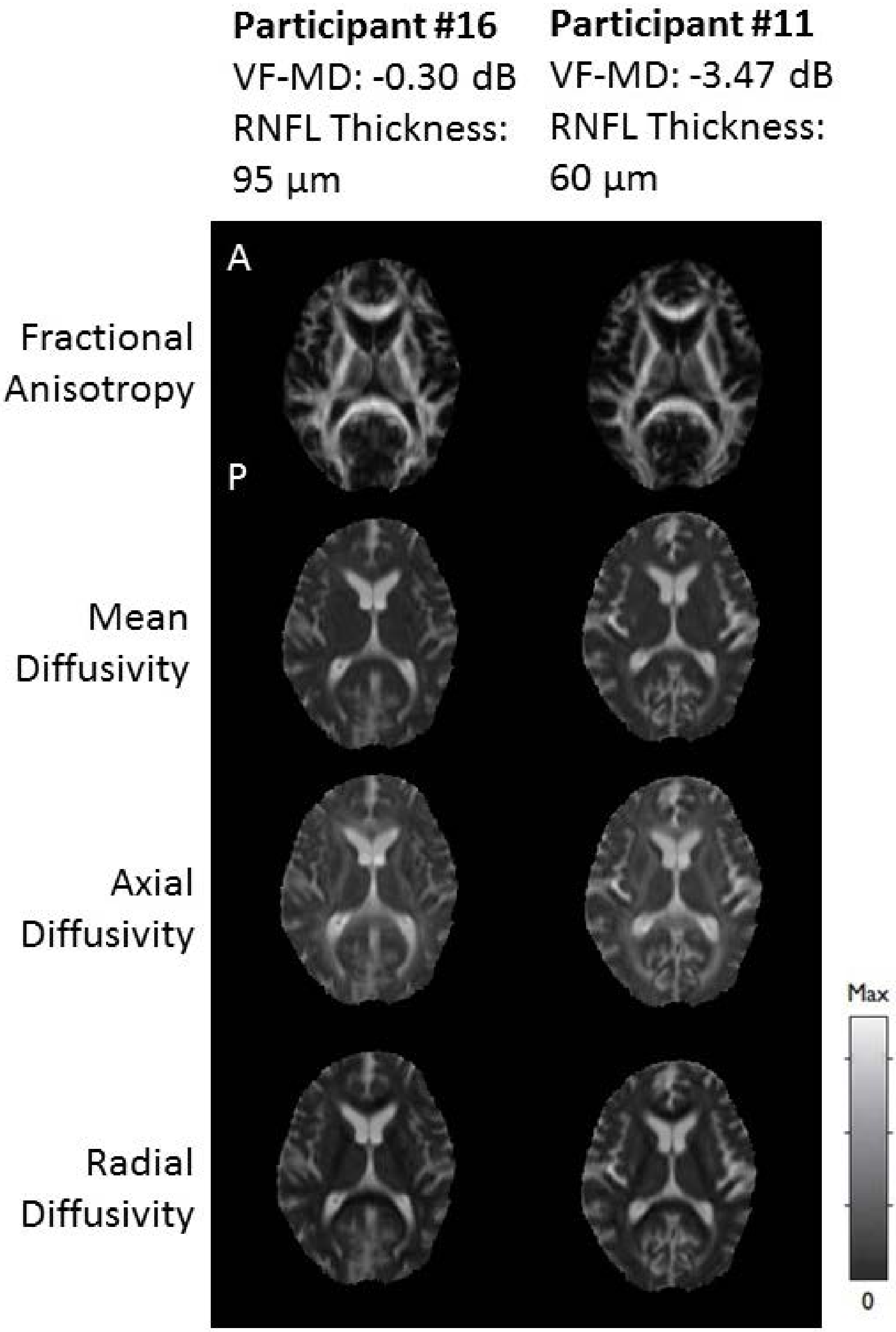


Figure 10. Sample DTI parametric maps of representative glaucoma participants of different disease stages, with participant #11 having more advanced glaucoma than participant #16 [maximum = 1 (fractional anisotropy), 5.0 $\mu m^2/ms$ (mean diffusivity, axial diffusivity, radial diffusivity)].

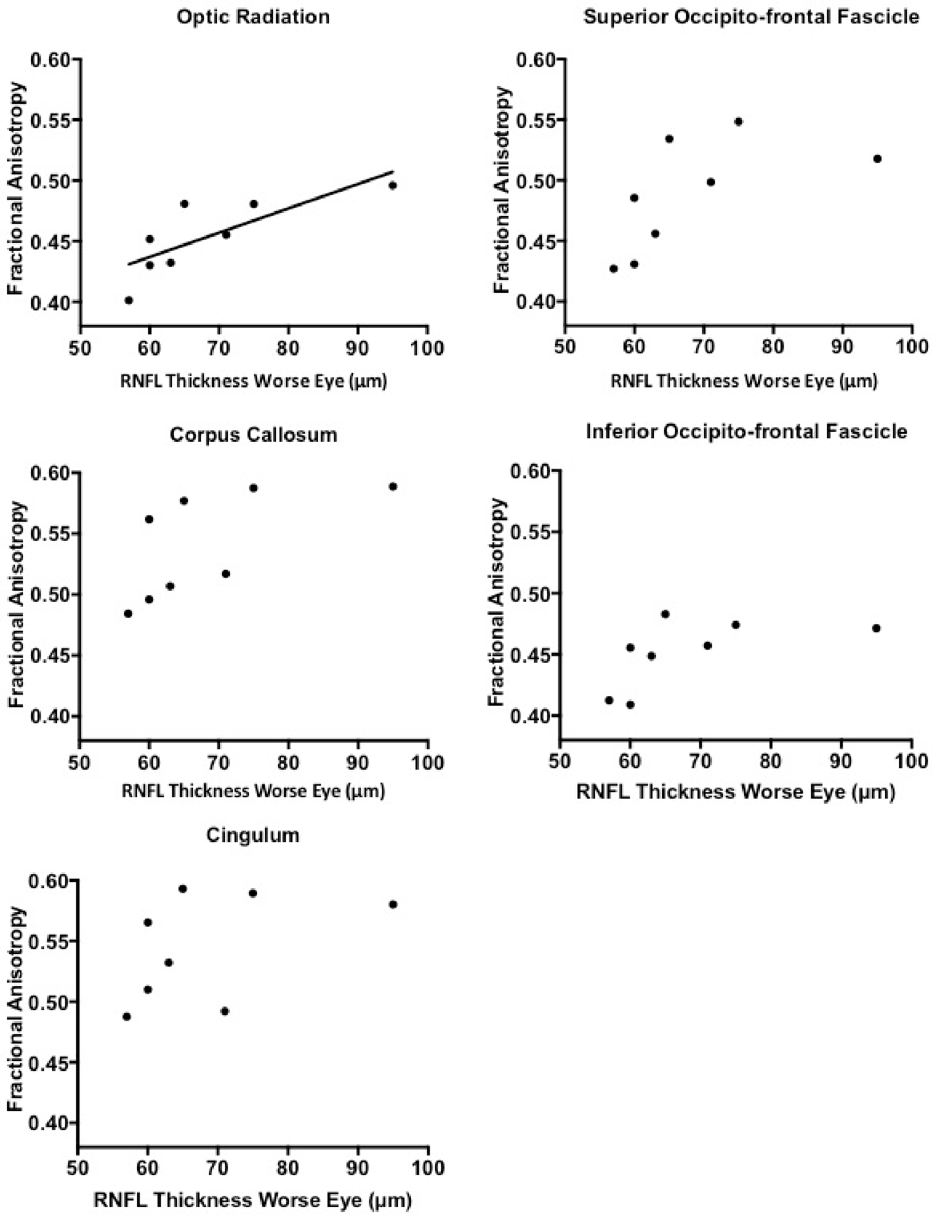


Figure 11. Relationship between retinal nerve fiber layer (RNFL) thickness and fractional anisotropy of the brain in glaucoma. Fractional anisotropy of the optic radiation decreased with RNFL thinning (p=0.02, F=9.4). The relationship between fractional anisotropy and RNFL thickness was not significant in the superior occipito-frontal fascicle (p=0.11, F=3.6), inferior occipito-frontal fascicle (p=0.13, F=3.0), corpus callosum (p=0.08, F=4.3) and cingulum (p=0.25, F=1.7).

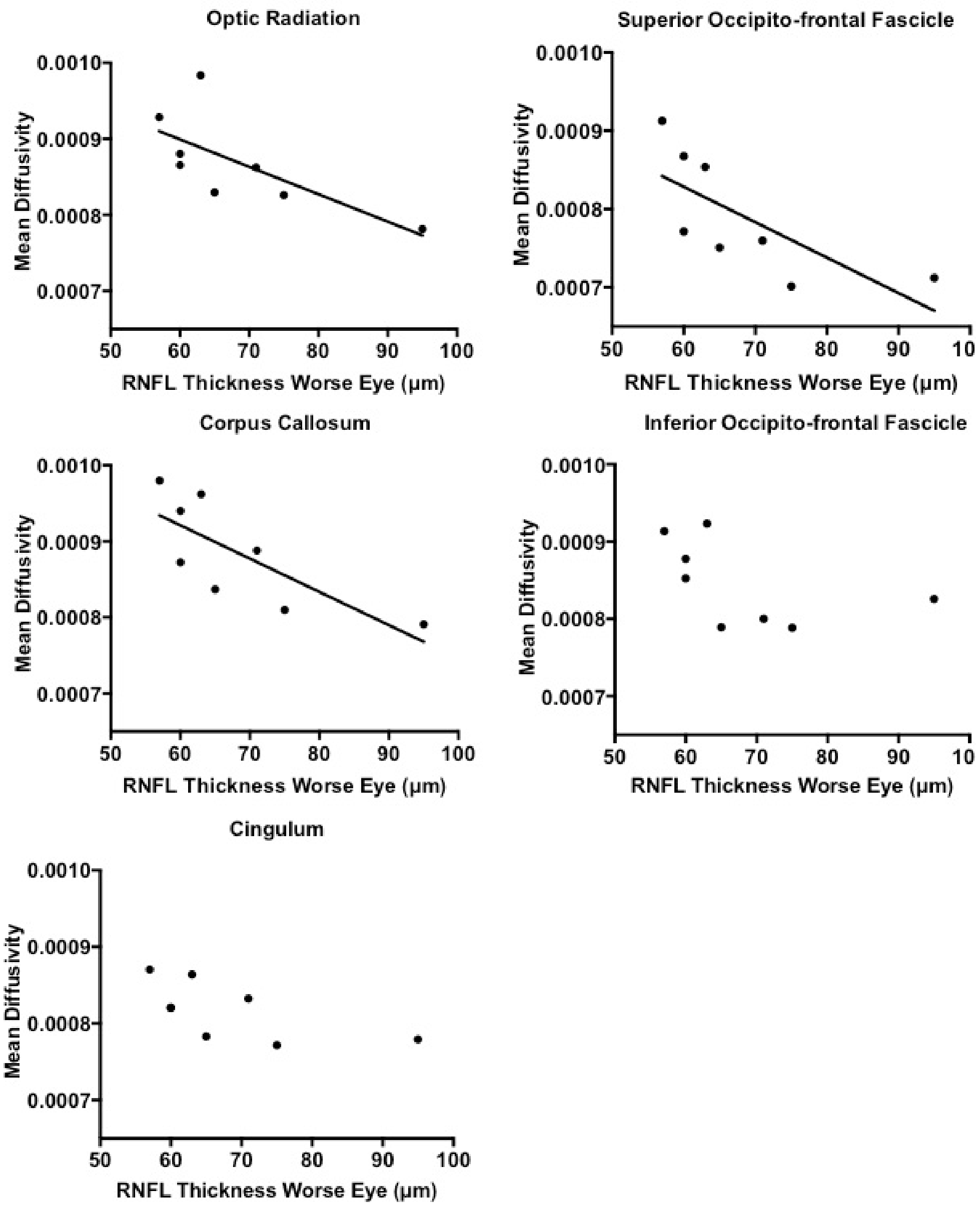


Figure 12. Relationship between retinal nerve fiber layer (RNFL) thickness and mean diffusivity of the brain in glaucoma. Mean diffusivity of the optic radiation (p=0.049, F=5.9), superior occipito-frontal fascicle (p=0.04, F=6.5) and corpus callosum (p=0.03, F=8.5) decreased as glaucoma severity increased (i.e. RNFL thickness decreased). There was no significant relationship between mean diffusivity and RNFL thickness in the inferior occipito-frontal fascicle (p=0.20, F=2.0) and cingulum (p=0.09, F=4.0).

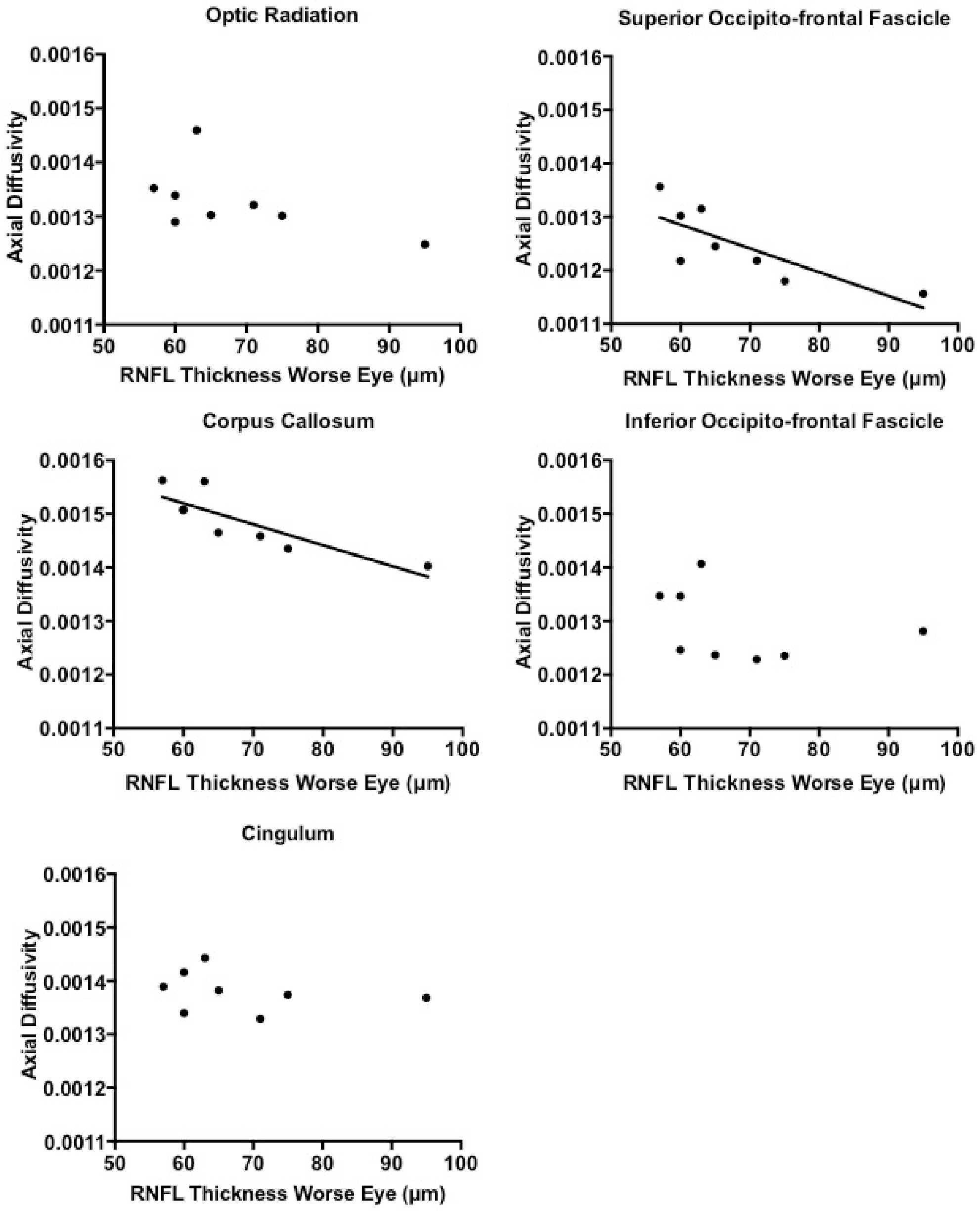


Figure 13. Relationship between retinal nerve fiber layer (RNFL) thickness and axial diffusivity of the brain in glaucoma. Axial diffusivity of the superior occipito-frontal fascicle (p=0.02, F=8.9) and corpus callosum (p=0.01, F=14.9) increasing as RNFL thickness decreased. There was no significant relationship between axial diffusivity and RNFL thickness in the optic radiation (p=0.15, F=2.7), inferior occipito-frontal fascicle (p=0.4, F=0.8) and the cingulum (p=0.5, F=0.5).

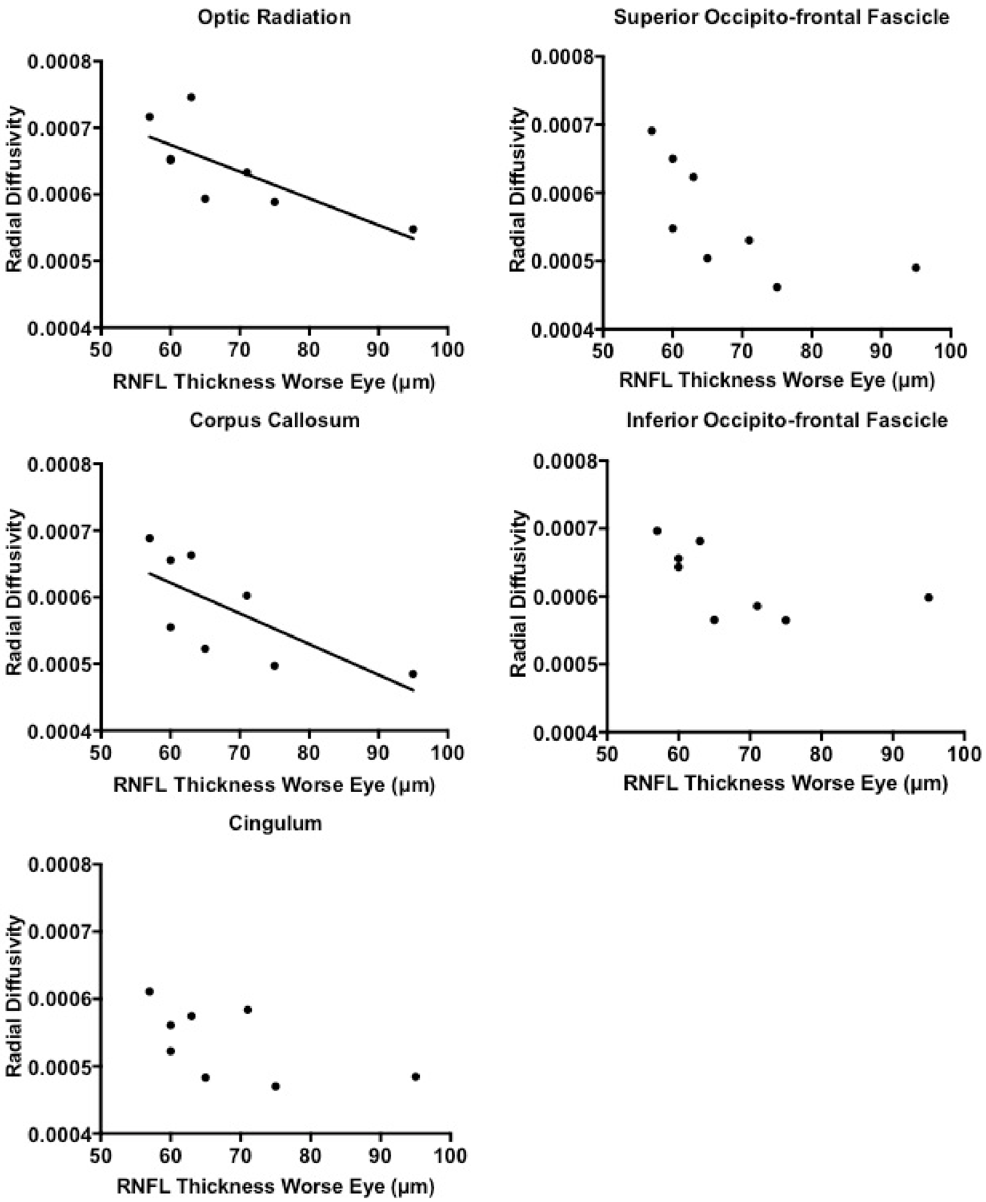


Figure 14. Relationship between retinal nerve fiber layer (RNFL) thickness and radial diffusivity of the brain in glaucoma. Radial diffusivity increased with RNFL thinning in the optic radiation (p=0.03, F=7.7) and the corpus callosum (p=0.049, F=6.2). There was no significant relationship between radial diffusivity and RNFL thickness in the superior occipito-frontal fascicle (p=0.06, F=5.2), inferior occipito-frontal fascicle (p=0.15, F=2.8) and cingulum (p=0.14, F=3.0).

Aim 2: Median RT during SOT condition 4 was correlated with DTI structural measures. Specifically, median RT during SOT condition 4 decreased as FA decreased in the optic radiation (p=0.04, F=7.3), superior occipito-frontal fascicle (p=0.01, F=19.0), and inferior occipito-frontal fascicle (p=0.02, F=12.7) [Figure 15]. Decreased median RT during SOT condition 4 was observed as DTI-MD increased in the superior occipito-frontal fascicle (0.01, F=17.3), inferior occipito-frontal fascicle (p=0.01, F=14.5) and corpus callosum (p=0.03, F=7.2) [Figure 16]. A similar negative relationship was seen between median RT during SOT condition 4 and AD of the superior occipito-frontal fascicle (p=0.04, F=8.0), inferior occipito-frontal fascicle (p=0.01, F=6.7) and corpus callosum (p=0.04, F=6.0) [Figure 17]. Lastly, median RT during SOT condition 4 decreased as RD increased in the optic radiation (p=0.04, F=6.0) superior occipito-frontal fascicle (p=0.01, F=22.9), inferior occipito-frontal fascicle (p=0.01, F=22.2) and corpus callosum (p=0.04, F=6.2) [Figure 18]. DTI measures of the cingulum were not associated with median RT during SOT condition 4 (p>0.05). There was no significant relationship between DTI measures and ΔRT_{SOT4} (p>0.05). There was no correlation between DTI measures and median RT during SOT condition 1 (baseline standing) (p>0.05). Lastly, no significant associations were observed between DTI measures and COP RMS or COP NPL in either SOT conditions 1 or 4 (p>0.05).

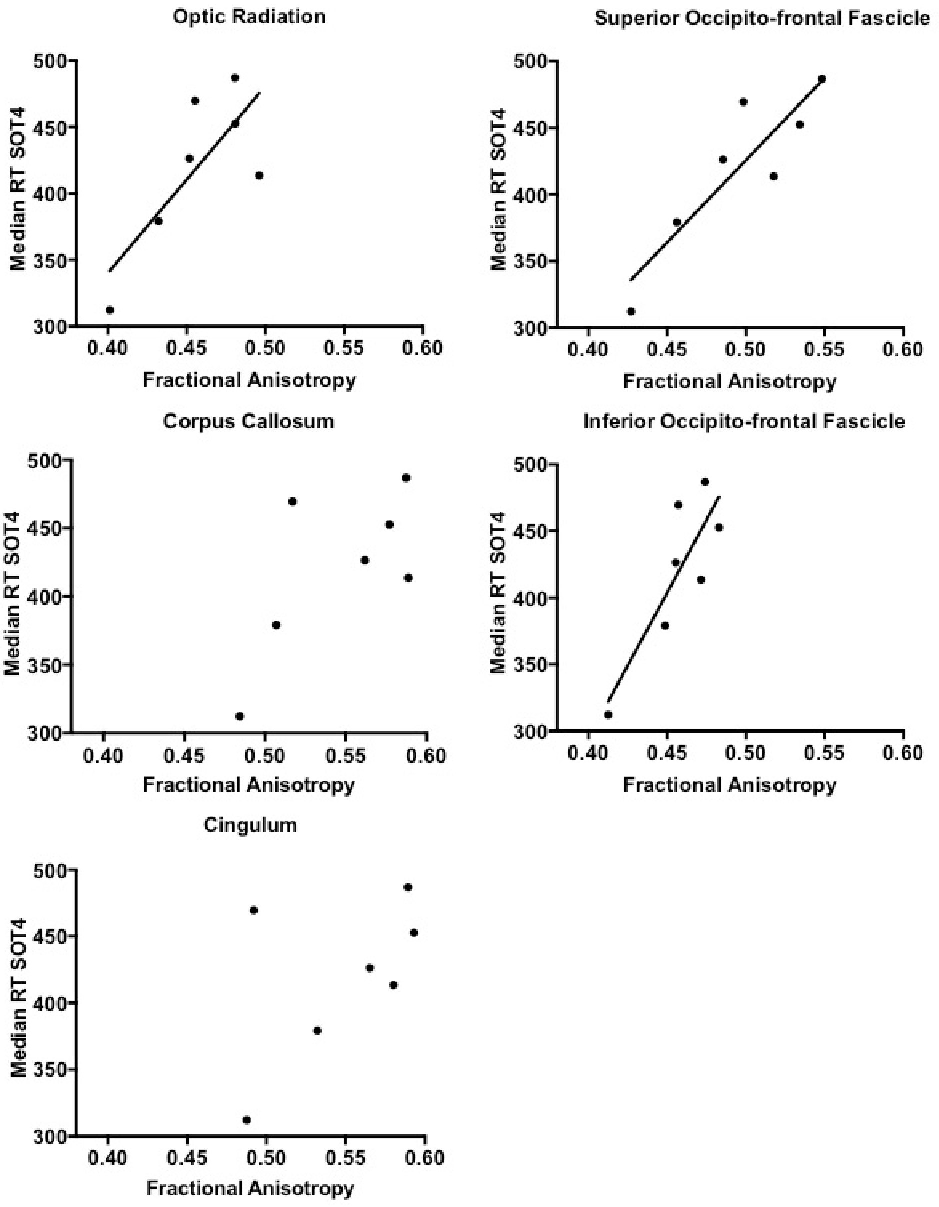
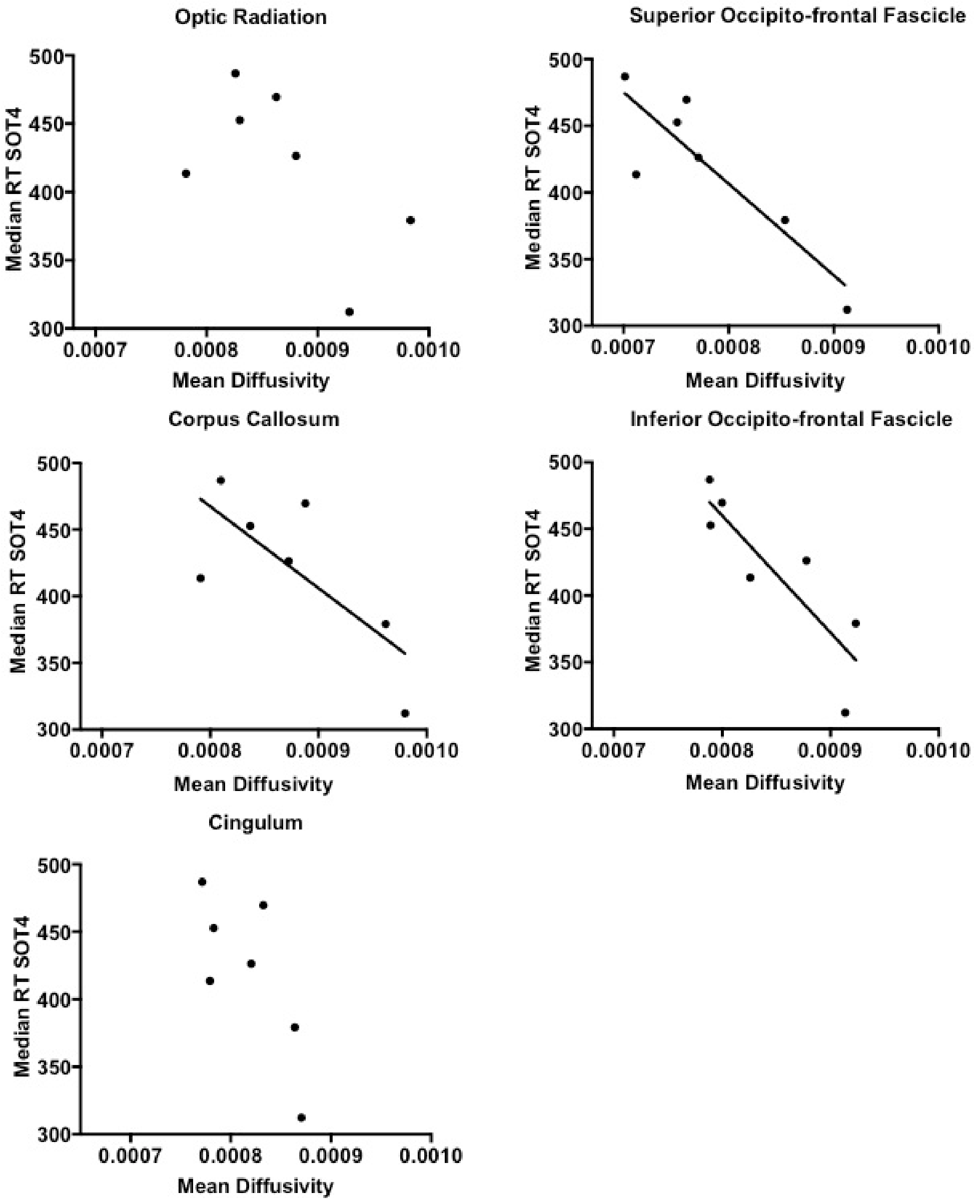


Figure 15. Relationship between RT performance during the challenging postural condition (SOT4) and fractional anisotropy (FA) measures. Median reaction time (RT) is plotted as a function of FA in white-matter tracts. Median RT increased as FA increased in the optic radiation (p=0.04, F=7.3), superior occipito-frontal fascicle (p=0.01, F=19.0), and inferior occipito-frontal fascicle (p=0.02, F=12.7). There was no significant relationship between median RT and FA in the corpus callosum (p=0.08, F=4.2) and cingulum (p=0.22, F=2.0).



Optic Radiation

Superior Occipito-frontal Fascicle

Corpus Callosum

Inferior Occipito-frontal Fascicle

Cingulum

Figure 16. Relationship between RTs recorded during the challenging postural condition (SOT4) and mean diffusivity (MD) in white matter tracts. Decreased median RT was observed as MD increased in the superior occipito-frontal fascicle (0.01, F=17.3), inferior occipito-frontal fascicle (p=0.01, F=14.5) and corpus callosum (p=0.03, F=7.2). There was no significant relationship between median RT and MD in the optic radiation (p=0.07, F=4.6) and cingulum (p=0.06, F=6.1).

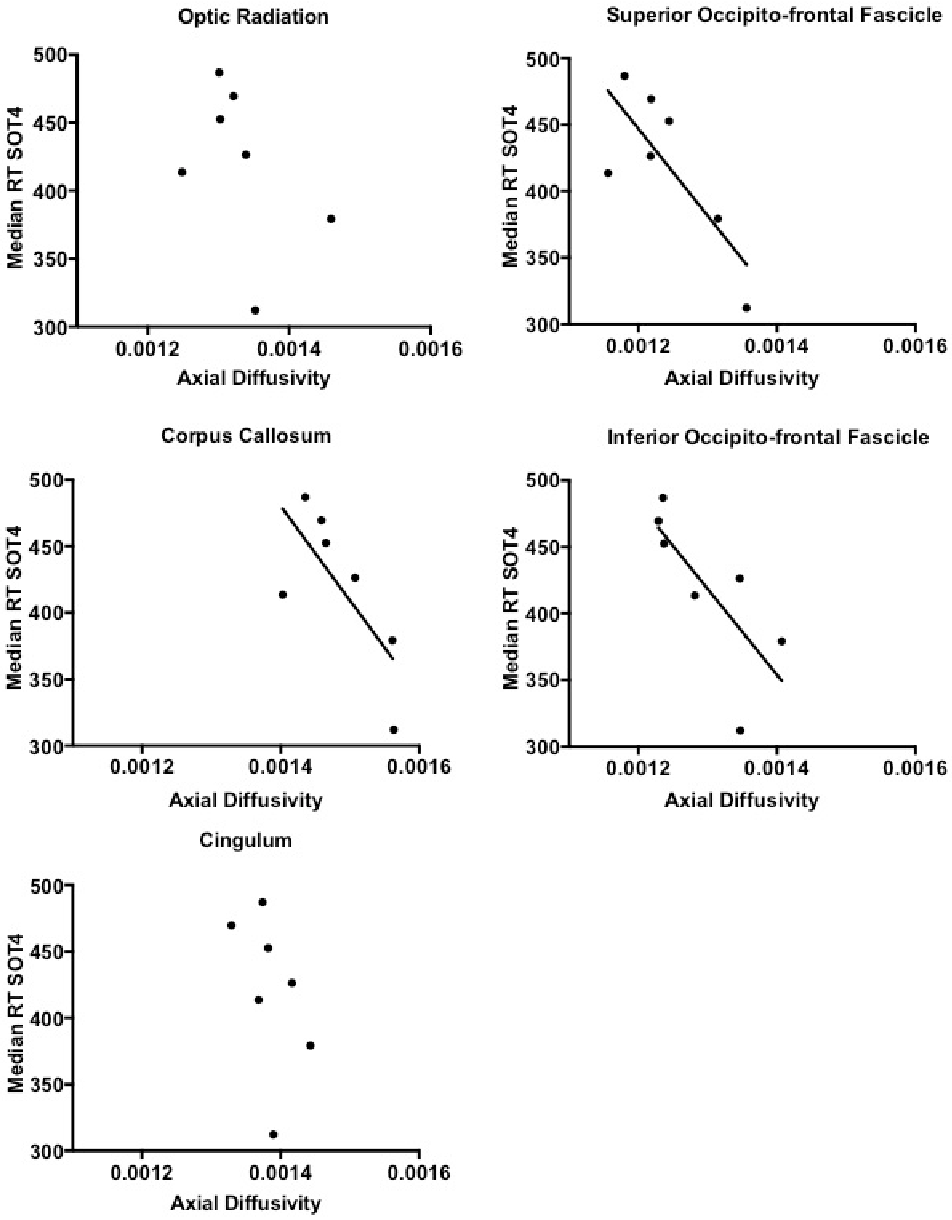


Figure 17. Relationship between RTs during a challenging postural condition (SOT4) and axial diffusivity (AD) in glaucoma. Median reaction time (RT) to the IP-CRT task is plotted as a function of AD in white-matter tracts. Decreased median RT was observed as AD increased in the superior occipito-frontal fascicle (p=0.04, F=8.0), inferior occipito-frontal fascicle (p=0.01, F=6.7) and corpus callosum (p=0.04, F=6.0). There was no significant relationship between median RT and AD in the optic radiation (p=0.18, F=2.2) and cingulum (p=0.28, F=1.4).

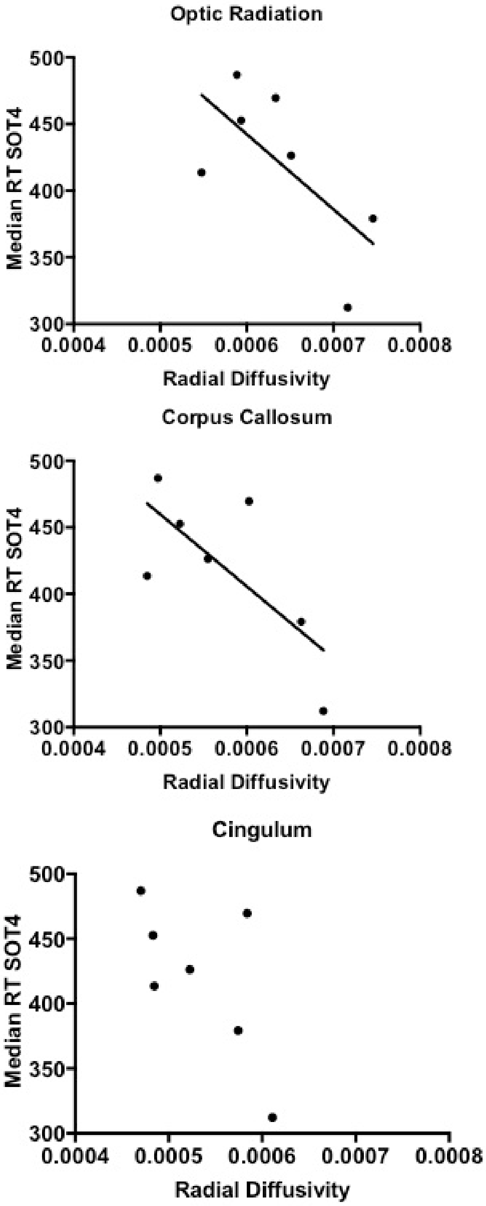


Figure 18. Relationship between performance on a dual information processing (IP-CRT) task during a challenging postural condition (SOT4) to radial diffusivity (RD) in glaucoma. Median reaction time (RT) to the IP-CRT task is plotted as a function of RD in white-matter tracts. Median RT during SOT condition 4 decreased as RD increased in the optic radiation (p=0.04, F=6.0) superior occipito-frontal fascicle (p=0.01, F=22.9), inferior occipito-frontal fascicle (p=0.01, F=22.2), corpus callosum (p=0.04, F=6.2). There was no significant relationship between median RT and RD in the cingulum (0.12, F=3.6).

6.4 DISCUSSION

The results provide additional evidence consistent with previous studies (Garaci, Bolacchi et al. 2009, Engelhorn, Michelson et al. 2012, Zhang, Li et al. 2012, Murai, Suzuki et al. 2013, Kaushik, Graham et al. 2014, Schmidt, Mennecke et al. 2014, Boucard, Hanekamp et al. 2016, Tellouck, Durieux et al. 2016, Li, Miao et al. 2017) that alterations in white matter structure within and beyond the primary visual pathway of glaucoma patients are related to RNFL thickness. DTI measures were associated with RTs while standing during the challenging postural condition (SOT condition 4), a relationship that was not present in RTs during quiet standing (SOT condition 1). These results provide preliminary evidence that increased attentional demands for postural control during challenging sensory conditions may be related to white matter structural changes seen in glaucoma patients.

Previous studies have shown that patients with glaucoma have lower FA (Garaci, Bolacchi et al. 2009, Engelhorn, Michelson et al. 2012, Zhang, Li et al. 2012, Murai, Suzuki et al. 2013, Kaushik, Graham et al. 2014, Schmidt, Mennecke et al. 2014, Boucard, Hanekamp et al. 2016, Tellouck, Durieux et al. 2016, Li, Miao et al. 2017) in the optic radiation than healthy age-matched controls. What drives these decreases in FA remains unclear, so studying the patterns of diffusional changes (DTI-MD, RD, AD) may provide a more complete picture of how brain connectivity is altered in glaucoma. Higher DTI-MD (Garaci, Bolacchi et al. 2009, Zhang, Li et al. 2012, Kaushik, Graham et al. 2014, Tellouck, Durieux et al. 2016), and higher RD (Zhang, Li et al. 2012, Kaushik, Graham et al. 2014, Tellouck, Durieux et al. 2016, Li, Miao et al. 2017) have been observed in the optic radiation of patients with glaucoma compared to healthy age-matched controls. Findings comparing AD in glaucoma patients to controls are mixed: Li et al. found that AD was lower in glaucoma than controls (Li, Miao et al. 2017), while other studies found increased

AD in glaucoma than controls (Zhang, Li et al. 2012) or no difference between AD among groups (Kaushik, Graham et al. 2014, Tellouck, Durieux et al. 2016). In this study, AD did not appear to change significantly with RNFL thickness decrease in the optic radiation. The inconsistencies in AD observations in glaucoma are likely due to differences in patient populations and study methodology. A major issue in comparing results from one study to another is in the way glaucoma is assessed. While RNFL thickness and VF loss are commonly reported, there is no standard as to whether one or both eyes should be assessed, and if both eyes are assessed, whether eyes should be classified by severity (i.e. worse and better as in this study) or as right/left eye. Additionally, differences in MRI collection parameters (i.e. b-value, slice thickness, field strength, echo and repetition times) may lead to divergent results when comparing studies. A standard MRI collection protocol may help to reduce inconsistencies in future studies.

Correlations between DTI measures in the optic radiation and glaucoma assessments have been reported, with decreased FA (Boucard, Hanekamp et al. 2016, Tellouck, Durieux et al. 2016, Li, Miao et al. 2017) and increased DTI-MD (Tellouck, Durieux et al. 2016, Li, Miao et al. 2017) and RD (Tellouck, Durieux et al. 2016, Li, Miao et al. 2017) as glaucoma advances. More specifically, Boucard et al. found correlation between RNFL thickness but not VF-MD and FA in the optic radiation (2016), Tellouck et al. reported links between both RNFL thickness and VF-MD and DTI measures (FA, DTI-MD and RD) in the optic radiation (2016), while Li et al. observed a relationship between disease stage, as assessed by the Hodapp-Parrish-Anderson scale which is based on VF-MD (Hodapp 1993), in DTI measures (FA, DTI-MD and RD) in the optic radiation but did not examine RNFL thickness (2017). Similar trends were observed in the present pilot study, with a negative correlation between FA in the optic radiation and RNFL thickness and positive correlations between DTI-MD and RD in the optic radiation and RNFL thickness.

However, there was no relationship between VF-MD and DTI measures, which is consistent with the findings of Boucard et al. but different than those of Tellouk et al. As mentioned previously, comparing results of brain connectivity studies in glaucoma is difficult as discrepancies may be caused by inconsistent glaucoma assessments and MRI protocols.

Fewer studies have examined the relationship between glaucoma and widespread brain changes beyond of the primary visual pathway. Boucard et al. reported decreased FA in the callosal body of glaucoma patients compared to controls and that FA values in the brain with glaucoma were correlated to optic nerve damage. No differences in DTI-MD were reported in the brain of patients with glaucoma (Boucard, Hanekamp et al. 2016). Schmidt et al. found decreased FA in the major white matter tracts examined in this pilot study, specifically in the corpus callosum, occipito-frontal fascicle and the left but not right cingulum (Schmidt, Mennecke et al. 2014). Thus the findings of the present pilot study corroborate the hypothesis that changes of white matter in the brain of glaucoma extends beyond the primary visual pathway.

This study provides preliminary evidence that that measures of white matter integrity are correlated to behavioral measures related to attention and balance control in glaucoma. Specifically, faster response times to a secondary IP task during a challenging postural condition were related to lower FA values, and higher DTI-MD, RD and AD values in the several white matter tracts including the superior and inferior occipito-frontal fascicles. Further, faster response times were correlated with lower FA values and higher RD values in the optic radiation as well as higher DTI-MD, RD and AD in the corpus callosum. Participants with the fastest RT and lower values of FA (higher MD/RD/AD) were those with the greatest RNFL thinning. These patients appear to have prioritized their performance on the IP task. Conversely, patients with high RNFL thickness had slower RT during SOT condition 4, higher FA (lower MD/RD/AD) and were previously shown to prioritize balance over response to the IP task (Chapter 4). Interestingly, there were no significant relationships between response time and DTI measures in the cingulum despite the cingulum's potential role in attention (Gunbey, Ercan et al. 2014). However, this may be explained by the reported lack of differences in DTI measures of the right cingulum between patients with glaucoma and healthy controls (Schmidt, Mennecke et al. 2014), suggesting that glaucoma may not impact the cingulum in the way it does other white matter tracts of the brain. Prior studies suggest that white matter structural integrity, particularly in the corpus callosum, may be linked to motor control in healthy adults (Zahr, Rohlfing et al. 2009, Sullivan, Rohlfing et al. 2010), further supporting the hypothesis that alterations in brain connectivity in glaucoma are linked to balance control.

The relationship between IP task response time and DTI measures was only observed in SOT condition 4, where proprioceptive cues related to balance are altered and therefore increasing the challenge to the postural control system. These results may possibly be a reflection of participants with greater RNFL structural loss and brain connectivity alterations prioritizing the IP task despite the challenge to the postural control system, suggesting that these patients have a greater challenge in efficiently allocating attentional resources. Compared to participants with greater RNFL structural loss, participants with less structural loss (high RNFL thickness) had slower responses to the IP task, suggesting that these participants were prioritizing balance control over the IP task (i.e. posture first strategy), which has also been observed in healthy adults (Redfern, Jennings et al. 2001, Muller, Jennings et al. 2004). The link between secondary IP-CRT task performance and white matter structural measures was not present during quiet standing (SOT condition 1) when balance-related proprioceptive cues are accurate. Surprisingly, there was no relationship between DTI measures and postural sway magnitude and velocity (COP RMS and NPL) in SOT conditions

1 or 4. If balance control and brain connectivity were examined in patients with greater structural RNFL loss than those included in the present study, a greater impact on the interference between attention and balance control would be expected such that there may be an effect on balance measures during dual task standing.

Due to the exploratory nature of this pilot study, there are several limitations that should be addressed in future studies. A major limitation is that DTI measures and behavioral balance and attention measures in glaucoma patients were not compared to healthy age-matched controls. Therefore, it is difficult to discern whether the correlation between DTI measures and RNFL thickness are due to glaucoma alone and not another factor such as age, as DTI measures and RNFL thickness are known to decrease with age (Alamouti and Funk 2003, Burzynska, Preuschhof et al. 2010). Similarly, it is unclear if the link between DTI measures and response to the secondary IP-CRT task during standing are a result of degeneration of white matter due to glaucoma, or if it is also a reflection of central processing capabilities related to attention and balance which can be influenced by a number of factors including aging. Further, age was not included as a covariant in the linear regression models in order to maximize the degrees of freedom given the small sample size (N=8). Lastly, results were not corrected for multiple comparisons to reduce false negatives, however this means that it is possible that some of the significant trends reported may be false positives. Future studies should also consider examining correlation between brain alterations beyond white matter structure and behavioral measures, for example, grey and white matter volume and density as well as functional connectivity.

6.5 CONCLUSION

This pilot study provides preliminary evidence that alterations white matter structure in select tracts of the brain including the superior and inferior occipito-frontal fascicles, the optic radiation and the corpus callosum are associated with retinal nerve fiber layer thickness in glaucoma patients. Additionally, brain connectivity in patients with glaucoma may be related to central processing of attentional and sensory information during standing, as brain connectivity measures were related to response time to a secondary information-processing task during a sensory challenging balance condition. Further work is necessary to address the limitations of this exploratory pilot study to better understand how brain alterations associated with glaucoma impact balance, which is important in developing effective interventions to prevent falls in patients with glaucoma.

7.0 CONCLUSION

Falls are a concerning problem in patients with glaucoma. The overall purpose of this doctoral research was to examine how sensory integration necessary for balance and gait is impacted by glaucoma, as I hypothesized that altered sensory integration capabilities may be a contributing factor to the high risk of fall in patients with glaucoma.

The first part of this doctoral research (Chapter 2) examined the association between glaucoma, fall prevalence and fear of falling (FoF). Whereas previous studies had only examined falls and FoF in relation to functional visual field (VF) loss (Turano, Rubin et al. 1999, Ramulu, van Landingham et al. 2012, Yuki, Tanabe et al. 2013), this study also examined the relationship between falls, FoF and structural loss to the RNFL. The results showed that functional VF loss was more closely related to recurrent falls and FoF than RNFL thickness in patients with glaucoma. I believe that this finding suggests that there is likely a threshold of functional VF loss before glaucoma becomes a fall risk and increases FoF. Further, this part of my research contributes to advancements in understanding FoF in glaucoma because FoF was assessed during different activities of daily living, which allowed me to identify those activities (i.e. stairs, walking on uneven or slippery surfaces, and ascending/descending slopes) that incited the greatest FoF in patients with glaucoma. Because FoF is associated with activity avoidance (Lachman, Howland et al. 1998) and decreased quality of life (Cinarli and Koc 2017), this knowledge is influential in designing training protocols to maintain mobility and independence in patients with glaucoma. Further, in an exploratory analysis, I provided preliminary evidence that FoF may be linked to impaired balance in patients with glaucoma. This is particularly significant because previous studies have shown that training protocols designed to improve balance can also reduce FoF

(Hagedorn and Holm 2010, Gusi, Carmelo Adsuar et al. 2012), and thus it may be possible to introduce balance training programs as a clinical treatment to prevent falls and reduce FoF in patients with glaucoma.

The next section of my research (Chapter 3) focused on the effects of acute peripheral and central VF loss on standing balance by inducing peripheral and central VF loss in healthy adults with normal vision and performing within participant analyses. Acute VF occlusion had the greatest impact when proprioceptive cues were minimized. Older adults were more sensitive to acute VF loss than young adults suggesting that older adults may be more reliant on vision for balance. Further, peripheral vision appeared to be more sensitive to movement in the visual environment than central vision. It is difficult to tease out the effects of vision loss alone on balance in patients with chronic vision loss because of comorbidities, long-term adaptations to vision loss, and possible alterations in the brain. Therefore, this study was significant because it lead to a better understanding of the effects of VF loss alone on balance control.

This research examined the impact of glaucoma on sensory integration and attentional processes important for balance (Chapter 4). This study delved deeper into the cause of balance impairments in glaucoma than previous studies because the protocol utilized an established sensitive dual task paradigm (Furman, Muller et al. 2003, Redfern, Talkowski et al. 2004, Mendelson, Redfern et al. 2010) that allowed for the assessment of attentional performance during standing in sensory challenging conditions. The dual task paradigm was coupled with the Sensory Organization Test to assess sensory integration capabilities, thereby allowing for the interaction between attention and sensory processing in patients with glaucoma to be evaluated. The interference between balance control and attention was linked to RNFL thickness but only when proprioception is unreliable. Participants with early glaucoma exhibited behavior observed in healthy adults by prioritizing balance control over a dual attention task (i.e. posture first strategy) (Redfern, Jennings et al. 2001, Muller, Jennings et al. 2004), whereas participants with advanced glaucoma had difficulty prioritizing balance. In this sample population, balance and attention measures were significantly correlated with RNFL thickness, which is a structural assessment of glaucoma, but not functional VF loss. This is significant because RNFL thinning has been shown to precede VF loss (Sihota, Sony et al. 2006, Wollstein, Kagemann et al. 2012). Thus, I believe that it is important to develop balance-training protocols that address the interference between attention and balance control in glaucoma. Training protocols should also be employed when structural loss is observed and *before* functional VF loss begins, as I have previously shown that VF loss is more closely related than RNFL thickness to recurrent falls. These balance-training protocols should focus on challenging proprioceptive conditions because balance impairments were most evident when proprioceptive cues were altered.

Similar to the previous section, my research also examined the impact of glaucoma on gait with a focus on sensory integration relevant to postural control (Chapter 5). A dual task paradigm was used during gait assessments in which participants were presented with challenging proprioceptive (soft carpeted floor) and visual (dimmed light) conditions. Despite limitations to the testing environment, this study provided preliminary evidence that RNFL thickness is linked to gait speed when proprioceptive cues are altered. There was no significant relationship between glaucoma and lighting condition during gait assessments. These results agree with those of the balance tests and suggest that balance and gait performance of patients with glaucoma worsen when proprioceptive cues are altered. I postulate that patients with glaucoma adapt to the loss of vision by increasing their reliance on proprioception for balance and gait and that is why balance/gait was impaired when proprioceptive cues were altered in this study. I believe that balance-training protocols focused on optimizing responses to altered proprioception may improve multisensory integration during balance and gait in patients with glaucoma.

The final piece of my doctoral research aimed to determine if there is a relationship between glaucoma and alterations in brain connectivity as well as a relationship between brain connectivity and balance control in patients with glaucoma (Chapter 6). Balance and attention measures were compared to brain connectivity in white matter of the brain. This study was exploratory in nature but the results provided additional evidence that alterations to white matter in the brain of glaucoma extend beyond the primary visual pathway, specifically to the superior and inferior occipito-frontal fascicles and the corpus callosum. More significantly, the results of this study provided initial evidence that white matter integrity in the brain of glaucoma may be linked to behavioral measures related to balance control. Brain connectivity measures in the optic radiation, superior and inferior occipito-frontal fascicles and the corpus callosum were correlated to response to a dual information-processing task during a balance assessment that altered proprioceptive cues. The relationship between brain changes and balance control in glaucoma should be studied further by examining modalities beyond diffusion tensor imaging used in this project such as structural magnetic resonance imaging (MRI) to assess brain volume and density as well as functional MRI to study brain activity. Because there appears to be a link between alterations in the brain and balance control, clinical measures to prevent falls in patients with glaucoma should not only focus on vision loss but at potential neurological issues that may contribute to impaired balance.

The greatest limitation to this research was the subject population. A majority of participants had early glaucoma and only mild VF defects, thus the results may not have accurately reflected the impact of advanced glaucoma on balance, gait and brain connectivity. If I were to repeat this study, I would make a greater effort to recruit an equal amount of participants with early, moderate and advanced glaucoma. Additionally, I would include age-matched controls. Comparing results in patients with glaucoma to healthy controls would confirm whether observed relationships are due to glaucoma alone or if another factor such as age is involved. A second major limitation to this research was the testing environment for the gait assessments. The gait assessments were performed on a 5x7 m oval track which (1) did not allow for long enough straight walking to accurately capture consistent gait and (2) contained curves that influence gait patterns. Future studies should correct for this limitation by collecting gait measures on a long and straight path.

APPENDIX A

FEAR OF FALLING SURVEY

A **fall** is defined as an event which results in you coming to rest inadvertently on the ground or floor or other lower level.

1. Have you fallen in the last year?

☐ Never → skip to question #6 ☐ Once ☐ Twice ☐ 3 times or more

2. How often have you had a broken bone from a fall after the age of 50?

☐ Never ☐ Once ☐ Twice ☐ 3 times or more

3. Have you sustained a broken bone at any of the following locations?

☐ Vertebrae? How often? ____________ ☐ Rib, breast bone? How often? ____________

☐ Collarbone? How often? ____________ ☐ Upper arm? How often? ____________

☐ Wrist? How often? ____________ ☐ Hand? How often? ____________

☐ Pelvis? How often? ____________ ☐ Hip bone? How often? ____________

☐ Ankle, foot? How often? ____________

4. What was the cause of broken bones?

☐ Slipped in icy conditions ☐ Slipped in wet conditions ☐ I tripped

☐ I fainted ☐ I fell from a staircase, chair, from a ladder ☐ Sports activity

☐ Other (please describe: _________________________) ☐ Do not know

5. Did any of the falls result in a visit to the doctor/emergency room or hospitalization?	☐ Yes ☐ No
6. Do you have osteoporosis (brittle bones)?	☐ Yes ☐ No ☐ Do not know
7. Do you have osteopenia (thinning of your bones)?	☐ Yes ☐ No ☐ Do not know
8. Do you have diabetes?	☐ Yes ☐ No ☐ Do not know

9. Have you had a heart arrhythmia (irregular heart beat diagnosed by a doctor)? ☐ Yes ☐ No ☐ Do not know

10. Have you ever been diagnosed with cancer? ☐ Yes ☐ No → go to question #13

11. Where? ____

12. Did you receive any of the following? ☐ Drug therapy ☐ Radiation

13. Has a doctor or other health professional ever told you that you had symptoms from an inner ear problem such as:

☐ Vestibular Neuritis? ☐ Meniére’s disease? ☐ Benign Paroxysmal Positional Vertigo?

☐ Other? ☐ No ☐ Do not know

14. How often over the last 12 months did you do a moderate or vigorous workout?

Examples of moderate or vigorous workout: badminton, golf, cycling, swimming, difficult gardening, lifting, long walking/hiking tours, brisk walking, fast dance, a difficult chore, wash and polish the car, aerobics, skiing, jogging or running.

☐ Never ☐ Seldom ☐ Less than 1 hour per week ☐ 1-3 hours per week

☐ 4-7 hours per week ☐ More than 7 hours per week

15. Do you have constant tingling/numbness of your feet? ☐ Yes ☐ No

16. Do you take any medications? ☐ Yes ☐ No → stop

17. How many medications? __________

Please list them: ____

____

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