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Temporal processing in auditory and visual systems: Evidence of wider central nervous system involvement in glaucoma.

Ms Fleur O’Hare

A thesis submitted in fulfillment of the requirements for the degree of Master of Philosophy in Ophthalmology.

Department of Ophthalmology
University of Melbourne
October 2011
Abstract

**Background:** Open Angle Glaucoma (OAG) is a condition that is characterised by a loss of retinal ganglion cells; which in turn inhibits visual signals, through a reduction in the levels of information being sent to the brain for processing. The degree and rate at which this inhibition occurs can vary greatly between individuals and therefore may be a consequence of innate differences in sensory nerve susceptibility to injury. In the event of an underlying neuronal susceptibility, signs of auditory processing dysfunction may be observed in individuals with OAG.

**Aims:** The purpose of this study was to examine whether individuals with OAG display signs of central auditory processing dysfunction. Concurrent investigation of specific visual processing functions was conducted to assess if any similarities in neural processing dysfunction were evident across both visual and auditory systems within the same individuals.

**Methods:** *Experiment 1:* A comprehensive range of peripheral and central auditory processing tests were conducted in 42 OAG individuals and matched controls. Central auditory function tests included evoked potential measures, tests for auditory temporal processing and speech perception.

*Experiment 2:* Based on the findings of Experiment 1, specific auditory temporal processing tasks were performed in conjunction with hierarchical visual temporal processing tasks.

**Results:** *Experiment 1:* Compared to age equivalent controls, OAG participants displayed significantly poorer amplitude modulation detection and speech perception under high levels of background noise. Amplitude modulation detection moderately correlated with speech perception and ABR performance within both groups. Collectively, signs indicated evidence of impaired auditory neural temporal processing in a significant proportion of the OAG cohort.

*Experiment 2:* OAG Individuals showed a tendency toward poorer performance on both auditory and visual discriminatory tasks that require a high degree of temporal resolution. Specifically, poorer speech perception under competing noise as well as impaired visual speed discrimination for slow velocities were identified in a significant proportion of OAG
individuals (39.13% and 47.82% respectively, were below the 90\textsuperscript{th} percentile of control performance). Overall, performance on auditory processing tasks did not correlate with performance on visual processing tasks for either group.

**Conclusions:** A subgroup of OAG individuals display evidence of central auditory neural processing dysfunction which implies that glaucoma may be associated with other non-visual sensory neural deficits. As such, the results indicate increased neuronal susceptibility in these individuals.

**Clinical Significance:** This is the first study to explore auditory function in OAG individuals beyond assessing sound detection or the integrity of the middle and inner ear. A proportion of OAG individuals have shown signs of central auditory processing dysfunction with subsequent difficulty in perceiving speech in noisy environments. It is therefore suggested that individuals with OAG, who report hearing difficultly, be subsequently assessed to explore the impact and extent of this difficulty in relation to challenging auditory environments. This process will ensure a more comprehensive assessment is undertaken which will lead to more direct and appropriate treatment options offered. In regard to the visual findings, OAG individuals with impaired speed and motion discrimination may require interventional strategies to improve driving/pedestrian safety and navigation, an area for future research. Overall, further research to explore other specialised auditory functions in glaucoma patients would be warranted along with an investigation into how having both auditory and visual impairment impacts upon communication and quality of life.
Declaration

This is to certify that:

i) The thesis comprises only my original work towards the Masters degree except where indicated in the Preface.

ii) Due acknowledgement has been made in the text to all other material used.

iii) The thesis is less than 40,000 words in length, exclusive of tables, figures, bibliography and appendices.

____________________

Fleur O’Hare
Preface

i) This research work has been carried out in collaboration with the Centre for Eye Research Australia and several departments of the University of Melbourne, namely the Ophthalmology, Optometry and Vision Sciences and Otolaryngology departments.

ii) This research study is completely my own original work.

iii) My supervisors have contributed in conception and design, critical appraisal, statistical input, logistical support and final approval of the thesis.

iv) This work has not been submitted for other qualifications.

v) This work has been carried out for the purposes of my MPhil candidature.

vi) This research received joint funding from the Ophthalmic Research Institute of Australia and the Glaucoma Australia foundation.

vii) There was no third party involvement in any component or at any stage of this research.
Acknowledgements

This thesis would not have been completed without the valued interest and help of many people who were involved in the project. Among them were the willing participants, supporting staff at the collaborative University departments and my colleagues at the Centre for Eye Research Australia. My deepest gratitude extends to them all with a special mention of appreciation going to my auditory specialist colleagues Kelley Graydon, Danielle Tomlin, Peter Carew and Donella Chisari. In addition a special mark of appreciation is extended to the “visual lab team” at the department of Optometry and Vision Sciences for their continued guidance and support.

My initial inspiration for conducting this research project was derived from Professor Jonathan Crowston. His enthusiasm and passion for research is infectious and his confidence in my abilities ensured my sustained motivation and pleasure in executing sound research under his valued guidance. My enjoyment throughout this research project was also enhanced by having the opportunity to work with Dr Allison McKendrick and Associate Professor Gary Rance. Both of who were instrumental throughout this project by providing continued support, direction and a prescription for calm optimism.

My gratitude is also extended to Beverley Lindsell, Catia Sicari and Michael Braham of the Glaucoma Australia Foundation who generously supported this project and who provided a keen interest throughout my research journey. My final thanks go to exceptional family and friends for their continuous encouragement and reassurance.
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Chapter 1: Introduction

1.1 Glaucoma

Glaucoma is an optic neuropathy characterised by changes to the optic nerve head morphology, accompanied by thinning and specific loss of retinal ganglion cells (RGCs). These changes produce visual function deficits and visual field damage which, if left without treatment, can progress to complete and permanent vision loss (Vrabec & Levin, 2007). Open angle glaucoma (OAG) is the most common type of glaucoma in Europeans and is characterized by the presence of optic neuropathy in the absence of an identifiable secondary cause such as trauma or anterior segment malformation (Weinreb & Khaw, 2004). In diagnosing OAG a comprehensive ocular examination is recommended with special evaluation of medical and ocular history, an open anterior chamber on gonioscopy, sequential evaluation of the optic nerve head (size, neuroretinal rim, nerve fibre layer, presence of peripapillary atrophy and presence of disc haemorrhage) and visual field assessment. In addition, consideration of key risk factors for developing the condition is important in gauging not only the level of individual susceptibility but also the predicted rate of progression.

In Australia, the prevalence of OAG is around 3% in people over 40 years which currently equates to around 300,000 affected individuals with the majority aged over 70 years (Mitchell et al., 1996; Roachtchina & Mitchell, 2000; Wensor et al., 1998). After macula degeneration, glaucoma is collectively the second most common cause of irreversible blindness in Western society (Attebo et al., 1996). To avoid blindness, public health campaigns encourage regular eye tests especially after the age of 50 years.

Despite our understanding that glaucoma is a multifactorial disease there are gaps in our knowledge with regards to why some individuals develop the condition and others may not, even though they may share the same risk factors. A body of research has explored this conundrum by firstly examining the structural changes occurring at the optic nerve head, the primary site targeted in the disease process. Secondly, consideration of how changes at this level impact upon the structure and function of the visual pathway has also been widely researched in an attempt to identify the most sensitive test to detect the condition early. Thirdly, consideration of the impact of glaucoma outside the visual pathways has begun to broaden the understanding about other heterogeneous causes and consequences of the
disease. This review will summarize what is currently known about the physiological and functional impacts of glaucoma to arrive at where further research is needed.

1.1.1 Physiological and functional changes in the visual pathway in glaucoma

It is widely believed that the primary region of injury in glaucoma is near and within the optic nerve head and that cell loss is confined to the inner retinal ganglion cells (Quigley, 1999; Weinreb & Khaw, 2004). There are around 1.5 million retinal ganglion cell (RGC) axons that comprise each optic nerve. These axons originate at the RGC bodies within the neural retina, travel within the nerve fibre layer toward the optic disc where they exit the eye through the lamina cribrosa to form the optic nerve. The optic nerves are part of the Central Nervous System (CNS) that transmit visual information from the retina to the brain along the visual pathway. In mammals, including humans, the visual pathway consists of the eye, optic nerve, optic chiasm, optic tract, lateral geniculate nucleus (LGN), optic radiations, visual cortex and visual association cortex (Salin & Bullier, 1995; Shatz, 1997).

The glaucomatous process is marked by structural degenerative changes to components of the visual pathway. Primary degenerative changes occur to RGCs leading to apoptosis (cell death). Early morphological changes include shrinkage of RGC cell body, dendrites and axons (Morgan et al., 2000; Shou et al., 2003; Weber et al., 1998). The sequence of degeneration to RGC components is not entirely clear however initial changes in dendritic structure have been shown to have critical consequences on synaptic efficacy (Rosen & Stevens, 2010; Weber & Harman, 2005). Aberrant synaptic activity and loss is increasingly viewed as a key to the glaucomatous process producing functional signs of visual dysfunction (Bowd et al., 2006; Caprioli, 1989; Harwerth et al., 2002; Weber & Harman, 2005).
The visual pathway from the retina to the visual cortices. Forming the nerve pathway from the eyes to the brain, retinal ganglion cell (RGC) axons terminate at four subcortical regions in the brain: the lateral geniculate nucleus (LGN) of the thalamus, the superior colliculus (SC), the pretectum and the hypothalamus. The axons of cells in the LGN then form magnocellular and parvocellular processing pathways to the visual cortex (VC). Figure used with permission from (Liu et al., 2011).

The structural and functional consequences of RGC damage include early impairment in visual processing involving the coding of spatial and temporal features of visual stimuli (Sample et al., 2000b; Sample et al., 2006). Broadly, alterations in spatial processing impact upon the way RGC code information such as stimulus colour, intensity and shape (i.e. via retinal receptive field characteristics and on-off centre surround characteristics) whilst disturbances to temporal processing would impair signal transmission regarding stimulus movement and the change of these features with time (i.e. via direction sensitive and transient versus sustained neural firing patterns) (see reviews (Bongard et al., 2009; Kaplan & Benardete, 2001; Nassi & Callaway, 2009). Given these features of RGCs, a body of research has focused on the most effective psychometric method to detect early glaucomatous RGC damage with past trends favouring measuring elements of contrast sensitivity, for example through short-wavelength or frequency doubling perimetry (Johnson & Samuels, 1997; Johnson et al., 2000b; Sample, 2000; Sample et al., 2000a). However within the last decade, advancement in the understanding of the physiological nature of the differing types of RGCs, along with improvements in testing selective cell functions, have led
to a variety of methods used to detect early glaucoma (Anderson, 2006; Ansari et al., 2002; Tafreshi et al., 2009) (discussed in more detail below). Additional functional and vision-specific techniques that are currently used also reflect improved understanding of the impact of glaucoma throughout the visual system. Experimental and post-mortem research has highlighted that progressive damage of RGC axons can cause subsequent degenerative changes further along the visual pathway impacting upon the LGN, optic radiations and visual cortex (Malpelgi et al., 1996; Yucel et al., 2000; Yucel et al., 2003) (or for review see Liu et al., 2011).

1.1.2 LGN and visual processing in glaucoma

The LGN is a major visual processing region between the retina and the visual cortex. In recent years, evidence has been accumulating that supports the theory that glaucomatous changes at the LGN and striate cortex are more likely to be secondary in nature to RGC axonal injury rather than occur due to primary damage (Yucel et al., 2003). This follows research investigating how other neurodegenerative diseases, such as Alzheimer’s disease (AD), spread throughout the CNS. The mechanism thought to be responsible is transsynaptic or transneural degeneration which signifies the spread of disease from an affected neuron to a healthy neuron via aberrant synaptic activity, causing retrograde neuronal dysfunction and death (Saper et al., 1987; Su et al., 1997).

In glaucoma this has been exemplified in experimental primate research models exploring the function and synaptic connections at the LGN from diseased RGCs (Yucel & Gupta, 2008). In primate models, an acute rise in intraocular eye pressure (IOP) has been shown to lead to transsynaptic degeneration, characterized by neuron shrinkage and atrophy (Bowd et al., 2006; Caprioli, 1989; Harwerth et al., 2002; Quigley, 1999; Weber & Harman, 2005; Yucel et al., 2001; Yucel et al., 2003) (add Quigley 1999; Yucel 2001, 2003). Compatible with transsynaptic degeneration at the LGN is a loss of connectivity secondary to synaptic deterioration, the functional consequences of which affect the three major processing channels of vision, namely the magnocellular (M), parvocellular (P) and koniocellular (K) (Conforti et al., 2007; Fu et al., 2009; Ly et al., 2010; Weber et al., 2000; Whitmore et al., 2005; Yucel et al., 2000; Yucel et al., 2001; Yucel et al., 2003). Psychophysical research supports degenerative changes of these key neural channels with functional deficits observed in glaucoma patients on visual perceptual tasks involving the processing of spatial and temporal components of vision from RGC cells (Ansari et al., 2002; Battista et al., 2009;
McKendrick et al., 2004; McKendrick et al., 2009; McKendrick et al., 2007; Shabana et al., 2003; Vogt et al., 1998).

The M pathway is thought to have a major temporal processing role (Merigan et al., 1991; Schiller & Malpeli, 1978) thus evidence suggestive of M pathway damage is reflected on tasks adopting low spatial frequency but high temporal frequency test stimuli (see review (McKendrick & Johnson, 2011)). Consistent with this, early or suspect glaucoma eyes reportedly reveal impaired flicker-sensitivity (Tyler, 1981) and elevated temporal contrast discrimination thresholds (Breton et al., 1991; Horn et al., 1995; McKendrick et al., 2004), both of which can be measured on specific types of perimetry testing (for example temporal modulation perimetry, frequency doubling perimetry and flicker defined form perimetry) (Quaid & Flanagan, 2005; Rota-Bartelink, 1999). Given its role in coding temporal cues, the M pathway from the inner retina, through the LGN, to the primary visual cortex performs intermediate levels of motion analysis which subsequently contributes to more complex integrated motion discrimination at later stages of processing (Snowden & Freeman, 2004; Snowden & Hess, 1992).

Historically it was thought that larger type (‘parasol’) RGCs connecting with the M pathway were most vulnerable to damage in developing glaucoma (Glovinsky et al., 1991; Quigley et al., 1987). However, more recent research suggests that the glaucomatous process is not RGC class selective and that in some individuals all cell types are affected (Ansari et al., 2002; McKendrick et al., 2004; McKendrick et al., 2007). This means impairment may also occur to functions mediated between smaller type (‘midget’) RGCs and the P pathway as well as functions supported by the bistratified RGCs and the K pathway. Functional changes suggestive of damage to these pathways include disrupted spatial processing and colour discrimination (P pathway: red-green, K pathway: blue-yellow) (Perry & Cowey, 1984; Schiller & Malpeli, 1978). Evidence is also growing that supports the P pathway in facilitating temporal processing especially at the cortical level where the M and P signals overlap in integrating motion direction cues (see review (DeYoe & Van Essen, 1988)). Degeneration of M, K and P neurons at the LGN mirror the degree of optic nerve fibre loss which is linearly linked with increases in IOP (Yucel et al., 2001) and eventual visual field loss in experimental glaucoma models (Sasaoka et al., 2008). Furthermore, glaucomatous degeneration of LGN neurons may drive some of the neural processing disturbances and structural degenerative abnormalities observed in the visual cortex (Yucel et al., 2003).
1.1.3 Visual cortex in glaucoma

In the primary visual cortex, V1, trajectories from the LGN terminate in specific and highly organized ocular dominance columns (Hubel, 1963). It is here that spatial and temporal visual information is more firmly analyzed and interpreted (Foster et al., 1985; Tolhurst & Movshon, 1975). Irrespective of mechanism, glaucoma triggers secondary structural and functional decay of LGN neurons (Yucel et al., 2001) which in effect threatens the quality of M and P neural input to areas of V1 (Yucel et al., 2003). For example psychophysical research suggests that glaucoma patients have impaired ‘first order’ processing of depth perception cues and make impaired direction and speed discrimination judgments in accordance with predominantly impaired input from the M pathway to V1 (Bullimore et al., 1993; Chen et al., 2003; Duncan et al., 2007; Essock et al., 1996; McKendrick et al., 2005).

Electrophysiological methods, such as multifocal visual evoked potential measures, have also suggested functional cortical changes which correlate to visual field loss in some individuals with OAG (Bach, 2001; Bach, 2006; Grippo et al., 2006). At the cellular level, experimental glaucoma models have shown reduced metabolic and neurochemical activity in regions of V1 (Crawford et al., 2000; Yucel et al., 2003). Studies involving functional magnetic resolution imaging (fMRI) in OAG patients with visual field loss also highlight reduced activation of cortical neurons along with reduced grey matter density in areas that share connections with impaired or lost RGCs (Boucard et al., 2009; Duncan et al., 2007; Gupta et al., 2006a). Recently, fMRI techniques are being used to explore the connections of V1 to other cortical areas, particularly with reference to temporal processing mechanisms (Dumoulin et al., 2003).

1.1.4 Extrastriate regions in glaucoma

Little is known about higher order cortical damage in glaucoma. That which is reported mainly focuses on the disruption of second order perception of motion. Previous lesion and brain imaging studies have shown that the cortical regions of V5 (the medial temporal visual area) and of the parietal lobe, make key contributions to the perception of motion (Barton et al., 1995; Maunsell & Newsome, 1987; Maunsell & van Essen, 1983; Newsome & Pare, 1988). Evidence to suggest that higher order changes in visual processing may occur in patients with glaucoma is derived from a small number of studies showing that glaucoma patients display impaired global motion (or motion coherence) perception which requires more complex and integrated neural processing of both spatial and temporal signals.
(Karwatsky et al., 2006; McKendrick et al., 2005). Indeed further research to explore the impact of glaucoma upon central processing mechanisms would be beneficial in confirming the relevance of CNS changes occurring in the disease continuum. This would build upon the well established evidence of ascending neural processing dysfunction and may provide insight into the physiological mechanisms that underlie the spread of glaucomatous disease from the optic nerve through the visual system.

1.2 Mechanism of injury within the visual pathways in Glaucoma

There have been a number of proposed mechanisms for initiating optic nerve injury in glaucoma. Damage to RGC axons is the primary pathology with potential injury to axons occurring within the peripapillary inner retina, disc or anterior optic nerve head (Weinreb & Khaw, 2004). Heightened vulnerability of RGC axons to injury is thought to exist at the optic nerve head as this is where axons converge and turn posterior to form the optic nerve (Vrabec & Levin, 2007). Previous research has focused on the passage of RGC axons through the optic nerve head which has generated two major theories for initiating axonal injury. Specifically impaired retrograde nutrient transport and RGC neural dysfunction can be result from either mechanical stress and/or vascular impairment (Quigley, 1999; Vrabec & Levin, 2007; Yucel & Gupta, 2008). These two key mechanisms can be a consequence of raised intraocular eye pressure (IOP) which triggers a physical deformation of the optic nerve head as well as interrupted blood flow and oxygen delivery to this area.

On a ‘mechanical’ level, raised IOP damages the structure of the lamina cribrosa, a perforated collagen plate at the optic nerve head through which RGC axons transverse to form the myelinated optic nerve (Quigley et al., 1981). Elevated IOP leads to stretching and posterior plate displacement of the lamina cribrosa which causes a shearing of the RGC axons. This process disrupts the function of the RGC axons with the degree to which this occurs varying between optic nerves (Levy & Crapps, 1984; Miller & Quigley, 1988; Quigley et al., 1994a; Quigley & Addicks, 1981; Quigley et al., 1981; Quigley et al., 1983; Zeimer & Ogura, 1989). This theory supports the clinical findings in glaucoma patients of peripheral visual field defects occurring before more central field loss considering this area is supplied by retinal nerve fibre axons traversing the lamina cribrosa more laterally where the shear stresses are thought to be maximal (Burgoyne et al., 1995; Yan et al., 1994).
Mechanisms involved in RGC degeneration may also occur independent of local mechanical stressors involving raised IOP. Disturbed blood flow to the optic nerve head has been reported in individuals with an underlying impairment in their cardiovascular system or widespread ischemic disorders (Brown et al., 2002; Hayreh et al., 1999; Omoti & Edema, 2007; Tielsch et al., 1995). Indeed support for a ‘vascular theory’ of glaucoma has grown from population based studies highlighting an association between glaucoma progression and cardiovascular risk factors such low perfusion pressure (Leske et al., 2008; Tielsch et al., 1995). Some evidence supports an association between glaucoma and systemic vascular dysregulation, a condition characterized by inadequate cardiovascular circulation throughout the body (Flammer et al., 2002; Flammer et al., 2001; Grieshaber et al., 2007; Mozaffarieh et al.). During times when the optic nerve is under impaired metabolic supply, neurons may be at increased risk of injury (Flammer et al., 2002; Mozaffarieh et al., 2008).

In addition to vascular dysregulation, additional systemic factors have also been implicated in threatening RGC survival and they include other vascular risk factors such as diabetes (Newman-Casey et al., 2011), alterations in the endocrine system, autonomic nervous system and immune system (Pache & Flammer, 2006; Tezel et al., 2007). It can be speculated that the impact of these factors on optic nerve head structure and function must not be homogenous as evidenced firstly from epidemiological findings that not all people with raised intraocular eye pressure develop glaucoma and secondly from the observation that in those that do develop optic neuropathy, differences exist in the rate and degree of visual dysfunction (see reviews (Coleman & Miglior, 2008; Rossetti et al., 2010)) or (Boland & Quigley, 2007; Gordon et al., 2002; Johnson et al., 2000a; Leske et al., 2008; Nemesure et al., 2007; Quigley, 1998; Quigley et al., 1994b; Sample et al., 2000a; Sample et al., 2000b; Varma et al., 2004; Zangwill et al., 2005). This underpins the hypothesis that optic nerves vary in their resistance to injury with some optic nerves succumbing to injury more readily than others. This may be a consequence of individual genetic disposition (Wiggs, 2007) or may be more closely related to differences in the aging process. The role of aging in potentially influencing why some optic nerves are more or less tolerant to potential injurious factors is gaining wider research interest (Kawai et al., 2001; Kong et al., 2009).

### 1.3 Aging and neuronal vulnerability to injury

Open angle glaucoma prevalence increases exponentially with age and this might be due to exacerbated metabolic decline in some susceptible individuals (Vickers, 1997). Whilst the
aging process is known to be dynamic, a leading theory suggests that aging may be associated with a disruption to cell metabolism. This aging theory suggests that the aging process is linked with the production of free radicals and the accumulation of other oxidants produced by aerobic respiration which promote biomolecular cell damage (Van Voorhies, 2001). A major line of evidence suggests that the aging process produces changes to mitochondrial function, the result of which either precedes or follows the production of these biomolecular toxins (Beckman & Ames, 1998a; Beckman & Ames, 1998b; Boveris & Chance, 1973). Mitochondria play a critical role in maintaining cellular homeostasis and are involved in a number of cellular metabolic functions that include oxidative energy production, maintaining intercellular calcium levels and control of neuronal excitability and synaptic transmission (Osborne, 2010). Of note is that mitochondrial impairment, whether inherited or acquired, has been reported as causally linked to age-related neurodegenerative conditions such as Parkinson’s disease, Huntington’s disease, Alzheimer’s disease and Friedreich’s Ataxia (Gibson et al., 2010; Goldblum et al., 2007; McKinnon et al., 2002; Ning et al., 2008; Voncken et al., 2004).

Support for the link between aging and neuronal injury has been further derived from studies examining functional decline in cognitive and sensory functions. These studies have generally shown age related increases in sensory perceptual thresholds and decreases in evoked sensory cortical activity in older versus younger individuals (D’Esposito et al., 1999; Humes et al., 2009; Johnson et al., 2000c; Peiffer et al., 2009). Studies in the visual and auditory modalities, the most widely researched sensory systems, indicate that aging changes occur not only at the level of the sensory organ, such as cataract changes in the lens of the eye and loss of hair cells in the cochlea of the ear, but also within the neural substrate of the sensory pathways (Navarro-Mora et al., 2011; Spear, 1993). Specific sensory pathway changes can be detected on an anatomical level, such as reduced cortical grey matter, as well as on a functional level, such as decreased amplitudes measured on visual and auditory electrophysiological tests (Fjell et al., 2006; Gates et al., 2008; Good et al., 2001; Jackson & Owsley, 2003; Justino et al., 2001a; Sowell et al., 2003; Tisserand et al., 2004). A substantial body of research exploring central cortical changes occurring through aging has also shown decrements in neural integration centres responsible for vision and hearing (for example (Barsz et al., 2002; Jackson & Owsley, 2003; Peiffer et al., 2009; Schmolesky et al., 2000; Stephen et al., 2010)). The central nervous system is also affected by physiological and
hormonal changes associated with aging which subsequently impact upon neural metabolic homeostasis (Barbieri et al 2009).

In summary several theories have been proposed that attempt to shed light on what are the key mechanisms that trigger optic nerve damage in OAG. The exact pathophysiology behind glaucomatous optic neuropathy is not known however there is accumulating evidence that there are multiple factors, such as mechanical stress and alterations in ocular blood flow, that impinge upon RGC survival with some RGCs being more susceptible to injury than others. It is likely that innate differences in optic nerve resistance to injury exist and this theory may help to explain the IOP independent increase in OAG prevalence with age. Indeed aging is not a homogenous process which is why in some individuals it may lead to a more rapid decline in metabolic and physiologic function. Research investigating the impact of metabolic decline in aging suggests that mitochondrial dysfunction may play a critical role in neurodegeneration. In line with this link, impairment in mitochondrial function could potentially render RGC energetically compromised and susceptible to secondary insults that they may have ordinarily tolerated. Overall these theories have inspired the growing opinion that an underlying neuronal susceptibility influences the risk of developing OAG.

In keeping with this theory of neuronal susceptibility it can be speculated that a combination of these factors, or indeed others not yet identified, place some optic nerves more at risk of damage than others in the broader age equivalent population. Further, if a proportion of aging individuals possess more vulnerable nerves within the CNS, including their optic nerves, they may also be more likely to reveal functional deficits outside the visual system. At present, it is unclear whether CNS involvement in patients with OAG is restricted to the visual pathways through chronic damage or whether other non-visual sensory deficits are part of the disease profile. Parallel sensory system impairment may arise in individuals who have populations of neurons innately susceptible to injury from central systemic pathogenic mechanisms (Pache & Flammer, 2006).

1.4 Changes outside the visual pathways in glaucoma.

The plausibility of functional changes occurring outside the visual pathways in glaucoma may be supported from studies looking at the incidence of glaucoma in other neurodegenerative conditions. A small number of studies involving either functional in vivo techniques or postmortem analysis in humans with Alzheimer’s disease (AD) have shown a trend for a
higher degree of axonal loss in the optic nerves of the majority of patients with advanced AD compared with unaffected AD patients of a similar age (Hedges et al., 1996; Justino et al., 2001b; Kergoat et al., 2001a; Kergoat et al., 2001b). These findings need to be interpreted with caution as there are conflicting results pertaining to early AD cases (Kergoat et al., 2001b) however they do provide support for the plausibility of widespread systemic vulnerability to CNS nerve damage with increasing age and therefore suggest the potential for observing other sensory neural changes outside the visual pathways in older individuals with glaucoma.

1.4.1 Multi-sensory deficits in glaucoma

To date, data on non-visual sensory deficits associated with OAG patients are sparse. Two recent studies have explored olfactory function in individuals with OAG and both suggest impairment in one aspect of olfactory function1, namely detection ability, but only in selective OAG sub groups (Gugleta et al., 2010; Mozaffarieh et al.). It was reported by Gugleta et al (2010) that compared to age and gender matched controls, OAG individuals have poorer odour detection thresholds yet better odour discrimination ability, most marked in those “without a history of cold hands and feet”. Concurrently Mozaffarieh et al. (2010) also reported these findings in OAG cases and further described the pattern in those participants without symptoms of primary vascular dysregulation (PVD).

Results from both studies imply that the risk of impaired olfactory function in OAG may depend upon the presence (or absence) of other co-morbidities such as systemic vascular dysfunction which appears to reduce the risk of olfactory impairment and therefore may be less common in OAG individuals with concurrent vasospasm. Alternatively, the development of olfactory impairment in OAG may a consequence of a central neurodegenerative process given that a loss of olfactory detection ability has been shown to also be a precursor for mild cognitive impairment and in more extreme cases the onset of idiopathic Parkinson’s disease or Alzheimer type dementia independent of age and other confounders (Hawkes, 2003; Mesholam et al., 1998; Nores et al., 2000). Further research examining the overlap between olfaction, cognition and OAG given its neurodegenerative roots, is warranted to confirm if these associations exist and indeed offer evidence to support or disprove a common central neuronal vulnerability theory.

1 Olfactory ability has three measurable components: threshold, identification and discrimination.
Most of the research exploring non-visual sensory deficits in OAG has centred on the incidence of hearing loss in association with glaucoma. These studies have not been unanimous in reporting a link between hearing impairment in primary cases of OAG with dispute arising across OAG subtypes, namely variable incidence in high and low tension groups (Kremmer et al., 2004; Kremmer et al., 2000; Shapiro et al., 1997). Specifically, the dispute may be based on differences in the classification of OAG individuals based on diagnostic criteria. The evidence supporting a systemic link with peripheral hearing loss² in secondary causes of OAG is more cohesive, specifically in patients with pseudoexfoliation where the hearing loss is attributed to the accumulation of extracellular matrix within the inner ear (Aydogan Ozkan et al., 2006; Cahill et al., 2002; Detorakis et al., 2008; Shaban & Asfour, 2004; Turacli et al., 2007; Yazdani et al., 2008). Extracellular material builds up within both the cochlear and vestibular organs of the inner ear which degrades neuro-electrical stimulation of the vestibulocochlear nerve producing both hearing and postural disturbances (Turacli et al., 2007; Turgut et al., 2010).

No study to date has explored auditory function in individuals with glaucoma beyond assessing sound detection. Measuring sound detection signifies the function of the peripheral auditory system, the ear, but does not reflect the more central processing mechanisms of the auditory pathway. This is paramount given that is now known that hearing deficits can arise from problems occurring through the auditory pathway even in the presence of adequate cochlear outer hair cell function (Rance, 2005; Starr et al., 1996; Starr et al., 2000). Therefore if we were to anticipate neuronal susceptibility in the auditory system of glaucoma patients what changes are we likely to see? To approach this question one might consider the parallels between the two sensory systems particularly with reference to specialized central processing abilities.

1.5 Key functional aspects of both auditory and visual systems

As mentioned, glaucoma is associated with neural processing deficits within the visual pathways that are believed to result from direct insult to retinal ganglion cells. Although the pathophysiologial mechanisms mediating visual processing deficits in glaucoma are not yet clear, studies involving OAG individuals suggest that early RGC dysfunction disrupts temporal properties of visual perception (Stamper, 1989; Trick, 1985; Tyler, 1981). This implies that

² Peripheral hearing loss is that attributed to a deficit at the cochlear level, also referred to as sensorineural hearing loss. Middle ear function is normal.
pathways mediating visual temporal processing may be particularly vulnerable to glaucomatous damage or that tests that uncover any temporal processing impairment are highly sensitive and specific in indicating early signs of optic nerve injury.

1.5.1 Temporal processing

Temporal processing is a specialized percept that is performed across all sensory and motor control centres within the brain and involves the computation of the time course of stimuli (Eagleman et al., 2005; Mauk & Buonomano, 2004). Specifically, temporal processing assists with interpretation of the dynamic changes in the timing of visual and auditory stimulation that typify everyday sensory experiences. Within the visual system, adequate temporal processing allows for the detection of a change in luminance or contrast over time which assists in the central ability to process motion (see review (McKendrick & Johnson, 2011)). Within the auditory system, temporal resolution permits recognition of a change in sound over time which paves the way for central processing abilities such as speech comprehension (for review (Bailey, 2010; Moore, 2008)). As such, if disrupted auditory function involving temporal processing was suspected in OAG individuals then exploration beyond sound detection has merit given that peripheral hearing loss typically doesn’t affect temporal processing (Moore, 1985; Moore, 1995) whereas neural hearing loss (auditory neuropathy) does (Rance et al., 2010a; Rance et al., 2004; Sek & Moore, 1995; Starr et al., 1991; Zeng et al., 2005; Zeng et al., 1999).

1.5.2 Methods to uncover auditory pathway disruption

In contrast to peripheral hearing loss, which is typically associated with impaired cochlear function (pre-synaptic dysfunction), neural hearing loss or signs of auditory pathway disruption may be caused by damage to the cochlear nerve (post-synaptic dysfunction). Damage to the cochlear nerve can compromise neural processing ability involving the coding of temporal input (Zeng et al., 1999). Specifically, auditory neurons have the capacity to encode fine temporal structure of sound by synchronizing (termed ‘phase-locking’) their neural firing pattern up to frequencies of 4 kHz (Malone et al., 2010; Sachs & Young, 1979). Indeed if interest is in uncovering signs of auditory processing disruption in individuals with glaucoma, then deficits may be observed on tasks that rely on the precise representation of timing cues in their auditory pathway. Individuals that reveal disrupted periodicity in auditory neural firing in the presence of normal outer hair cell function are classified as having ‘auditory neuropathy/dyschrony’ (AN/AD) (Starr et al., 1996; Starr et al., 2000).
Disrupted auditory neural activity may also arise from decreased neural populations (Berlin et al., 2003).

Electrophysiological testing is essential in the diagnosis of auditory neuropathy with tests measuring electrical neural response potentials throughout the auditory pathway. One commonly adopted method to assess early neural activity is auditory brainstem response (ABR) testing which measures the neural conduction efficiency of the auditory nerve, VIII cranial nerve, to the brainstem (Jewett et al., 1970). In the presence of optimal sound detection, disrupted auditory neural activity within the auditory pathway is thought to signify the presence of underlying central nervous system pathology (Starr, 1978; Starr & Achor, 1975). The causes of AN/AD are numerous and include neural demyelinating and degenerative diseases, compressive lesions, ischaemia and metabolic insults (see review (Starr et al., 2008)). Despite this causal range, evidence of a delay between the main peaks of the waveform response (interpeak latency wave I-V) and/or abnormal wave V latency-amplitude characteristics, are thought to be particularly suggestive of a central more widespread neurological disturbance (Starr et al., 2000). In its severest form, AN/AD patients typically show absent electrophysiological recordings and impaired sound detection ability (Berlin et al., 2010).

1.6 Neurological causes for visual and auditory impairment

One neurological condition that reveals widespread disturbances within the CNS with key deficits in auditory and visual function is Friedreich’s Ataxia (FRDA), a condition caused by a genetic mitochondrial mutation (in the FXN gene) (for review see (Delatycki et al., 2000)). These patients display a range of peripheral and central system disturbances with significant impairment in neural temporal processing therefore producing perceptual deficits in discriminating changes in the timing of both visual and auditory stimuli (Amantini et al., 1984; Carroll et al., 1980; Livingstone et al., 1981). Subsequently, a significant percentage of individuals with FRDA show severely abnormal visual evoked potential measures, auditory brainstem recordings and speech perception deficits (Rance et al., 2010a; Rance et al., 2010b; Rance et al., 2008). Given FRDA involves both auditory and visual functional deficits; it may be useful as a model for considering concurrent auditory and visual processing impairment occurring in optic neuropathies.
1.6.1 Auditory neuropathy in conjunction with optic neuropathy

Recent research has emerged that has explored auditory processing in forms of optic neuropathy other than glaucoma that are linked with a mitochondrial abnormality for example in individuals with Leber’s hereditary optic neuropathy (LHON) (Ceranic & Luxon, 2004; Mondelli et al., 1990; Yu-Wai-Man et al., 2008). LHON, a maternally inherited optic neuropathy, resembles OAG in that the disease targets retinal ganglion cells (Sadun et al., 2000). A small number of studies have provided some insight into the characteristics that may typify auditory processing dysfunction in optic neuropathies driven by an underlying impairment in mitochondrial production (Yu-Wai-Man et al., 2010; Yu-Wai-Man et al., 2009). Unpublished data from our laboratory involving 32 individuals with LHON found that a significant proportion have abnormal ABR recordings, either prolonged main wave peak latencies or entirely absent responses. In addition, participants revealed various combinations of neural temporal processing disruption such as impaired auditory temporal modulation detection ability with abnormal speech perception capabilities, particularly in noise, compared to age-matched controls. The possibility of similar auditory processing deficits in individuals with glaucoma, a condition that shares some pathological and phenotypic similarities to LHON (O’Neill et al., 2009) has not been investigated to date.

1.7 Summary of background

The challenge of understanding glaucoma pathogenesis has been boosted from examining other age-related neurodegenerative conditions such as Alzheimer’s disease and Parkinson’s disease. With respect to these conditions, a considerable body of research has been conducted that highlights their association with multiple changes within the CNS including multi-sensory impairment. Given that glaucoma shares a similar aetiologic profile to these neurodegenerative diseases, it seems justifiable to discern whether glaucoma is also associated with CNS involvement. Specifically by examining the functional behavior of other sensory neural pathways, such as auditory, in OAG individuals, our understanding about why certain individuals are more susceptible to developing glaucomatous optic nerve injury will be enhanced.

The current study aims to explore auditory processing function in individuals with OAG to explore the underlying theory that glaucomatous optic nerve damage results from a global CNS vulnerability to neural injury from any number of systemic abnormalities. The auditory system was selected from among the other sensory systems for several reasons including its
dominant neural interconnection with the visual system (Peiffer et al., 2009; Taylor & Campbell, 1976) as well as its functional connection with communication and quality of life (Crandell & Smaldino, 2000). In addition there are well established and validated methods for measuring auditory processing function. These considerations, along with the fact that no study to date has explored auditory processing in individuals with glaucomatous optic neuropathy, have provided the motivation for the current study. The current study aims to assess whether auditory processing dysfunction occurs in glaucoma and in doing so provide further clarity on whether changes outside the visual pathways are recognizable as part of the disease profile. Overall the current study intends to shed some light on the growing speculation that glaucoma is part of a more widespread neuronal vulnerability.
1.8 Experiment 1: Hypothesis and Aim

**Hypothesis 1:** Individuals with open angle glaucoma have auditory processing dysfunction.

**Aim 1:** To investigate auditory processing abilities function in individuals with open angle glaucoma and determine whether poorer functions exist compared to age-matched controls.

**Rationale 1:** Glaucoma pathogenesis is believed to be multi-factorial and the risk of developing the condition varies between individual suspects. Consequently it is hypothesized that in certain individuals their optic nerves are more vulnerable to damage than others in the broader population and this may be due to innate differences in the global response of their neurons to injurious factors. If global neuronal susceptibility does exist then functional changes, other than those observed in visual neurons, may be identified in other sensory neurons such as within the auditory system.

Like the visual system, the auditory system performs highly specialized processing functions so functional deficits may be identified through testing high level perceptual ability. No study to date has explored auditory processing function in OAG thus this study will provide novel findings on whether glaucoma is associated with signs of auditory neuropathy.

Results will be described for this experiment then the aims and hypotheses for Experiment 2 will follow with subsequent results.
Chapter 2 : Research Design for Experiment 1

2.1 Selection of Methods

The research design including the materials and methods selected to test hypothesis 1 were chosen based on a thorough review of the literature for leading practices in conjunction with consideration of the feasibility of adopting methods at the available sites. The auditory protocol for Experiment 1 was refined following consultation with one of my supervisors, Associate Professor Gary Rance, who has expertise in the area of auditory neuropathy and its perceptual assessment. The auditory protocol was performed by one of two trained, masked, audiologists. I enrolled participants into the study, performed the visual pre-screening evaluation, collected and analysed the data. All diagnoses were verified by my supervisor Professor Jonathan Crowston, a specialist trained Ophthalmologist.

A prospective, cross sectional, case comparison study was chosen where a sample of individuals with open angle glaucoma was compared to an age matched (within ± 2 years) control sample without glaucoma on measures of auditory function.

2.1.1 Sample size calculation

Given that this is the first reported study to examine auditory processing function in glaucoma patients, the effect size was estimated from studies examining auditory function in adults. Based on previous research exploring temporal amplitude modulation (Eddins, 1999; Rance et al., 2010a), a 10% difference in performance between groups with a standard deviation of 2 decibels is an estimate of effect size for the intended sample. A sample size of 35 in each group has >90% power to detect a difference in means of 1.47 (decibels) with a significance level of 0.05 (two-tailed). Given that previous literature featured young adults aged less than 40 years, a minimum of 35 participants in each sample was sought to allow for a wider standard deviation, or greater variability, expected on auditory function responses in older individuals.

2.2 Participants

2.2.1 Ethics approval

Ethics approval for Experiment 1 was obtained from the Human Ethics and Research Ethics Committee of the Royal Victorian Eye and Ear Hospital, Melbourne, Victoria, on the 21st
February 2009 (Approval number: 08/814H). The study protocol adhered to the tenets of the Declaration of Helsinki and written informed consent was obtained from all study participants following explanation of the nature and purpose of the study.

2.2.2 Inclusion Criteria

Individuals were invited to participate if they could satisfy the following criteria:

- Confirmed diagnosis of open angle glaucoma (OAG) involving evidence of optic neuropathy in the presence of an open aqueous drainage angle, not attributed to a secondary cause (Shaarawy et al., 2009).
- English as their first or equal first language spoken in view of both prescreening visual and auditory assessment tasks featuring English letters.
- Aged between 50 and 70 years with the lower limit reflecting a common age when OAG is first diagnosed and the upper limit reflecting the age beyond which significant age-related loss in sound detection and auditory processing ability occurs (Cruickshanks et al., 2003; Mitchell, 2002; Wilson et al., 1999).

2.2.3 Exclusion Criteria

Potential participants were asked about any history of self perceived hearing difficulty, including its severity, onset and duration, whether a hearing test had been performed in the past and if hearing aids were recommended or provided. A detailed medical history was also taken including past history, treatment or risk factors for ear disease. This included being asked about exposure to loud noise and systemic factors affecting general health. Participants were also questioned regarding medical history known to affect visual function. As a result participants were excluded if they reported any of the following:

- Moderate hearing loss.
- Ear trauma, ear surgery, acute or chronic history of upper respiratory infection.
- Use of ototoxic medications (such as gentamicin or streptomycin).
- Employment in a noisy environment.
- Use of medications known to affect sensory processing ability and cognition such as anticholinergics, antipsychotic and psychiatric therapies (exclusion considered on a person by person basis).

There were no specific visual exclusion criteria for this experiment.
2.2.4 Cases

Individuals with OAG were identified from patients attending either private or public eye clinics in which I was employed as an Orthoptist. Additional referrals into the study were also obtained from colleagues who practiced at other private eye clinics. All sources of participants came from practices or clinics within Metropolitan Melbourne, Victoria.

Power calculations indicated a sample size of 35 was ideal however a total of 50 cases were invited to participate allowing for those with incomplete data and those that may have been later excluded based on results to hearing threshold assessment. From the sample of 50 who underwent examination, 42 cases were included in final statistical analysis. Seven cases were excluded from statistical analysis owing to their primary diagnoses of either pseudoexfoliation syndrome (4 cases) or pigment dispersion syndrome (3 cases). These are secondary types of OAG and represent separate aetiologies with differing phenotypic features from primary OAG cases (Shaarawy et al., 2009). One case was also excluded as it was suspected that they may have had juvenile onset OAG. The current study only included primary cases of OAG in statistical analysis to ensure the sample contained individuals likely to share the same pathomechanisms for their disease (Shaarawy et al., 2009).

2.2.5 Controls

Individuals who were confirmed to not have any clinical signs of glaucoma and in whom could be matched to a glaucoma participant, based on their age, were invited to participate in the study. Controls were identified from lists of patients managed through the general eye clinics at the Royal Victorian Eye and Ear Hospital. Additional referrals into the study were also obtained from cases, namely family members or friends, and staff colleagues. All cases were comprehensively assessed and if eligible, invited to participate in the study.

A total of 50 controls were assessed and completed this experiment. No control participant was found to have any serious vision-threatening eye disease with most having a normal ocular exam. Ten controls (20%) were found to have early signs of cataract formation but optimal central acuity. One control participant was found to have a minor, unilateral macula disturbance with visual acuity at 6/9 (0.2 LogMAR) but this subject was not precluded from participating\textsuperscript{3}. From this sample, 42 individuals were selected to proportionately age

\textsuperscript{3} This individual was referred for specialist opinion and diagnosed with non-active central serous retinopathy.
match the case sample for statistical analysis. The final control sample was selected in a masked fashion with only the age information available for comparison to the glaucoma group.

2.3 Materials and Methods

Unless otherwise specified, all equipment was supplied by departments of the University of Melbourne. Visual equipment was supplied by the Department of Ophthalmology, Centre for Eye Research Australia, and auditory equipment was supplied by the Department of Otolaryngology.

2.3.1 Visual Clinical Evaluation (screening protocol)

Participants who consented to participate in the study had detailed medical and ocular histories recorded and then were examined on a range of ocular diagnostic tests. This involved assessment of best corrected visual acuity (BCVA), automated perimetry and a dilated examination of the anterior and posterior segments of the eye. Fundus examination was coupled by monoscopic disc photography and where available, disc imaging (methods described in more detail below). Visual clinical evaluation was performed prior to auditory assessment and in most cases on a separate occasion. The average time between visual screening procedures and study assessment (auditory function) measures was 1 week.

2.3.2 Best corrected visual acuity (BCVA)

BCVA was assessed using the 3 metre Early Treatment Diabetic Retinopathy Study (EDTRS) vision chart that featured English Standard optotypes (Patz & Smith, 1991). This chart is constructed on a logarithmic scale (logarithm of the minimum angle of resolution: logMAR) and has five optotypes per line from +1.0 to -0.3 logMAR (Snellen equivalent 6/60 to 6/3 respectively). Each letter represents a score of 0.02 log units and each line has a 0.1 log unit difference in letter height between them. Each eye was assessed separately and the eye suspected of having poorer acuity was assessed first with alternate patching of the non-tested eye. Participants were assessed with current distance glasses (if appropriate) followed by a pin hole (1.2 millimetres) assessment if vision was equal to or less than 0.1 (Snellen equivalent 6/9). Participants who improved with pin hole assessment were subsequently refracted using subjective refraction techniques. BCVA was recorded in logarithmic units and represented the total numbers of letters read correctly.
2.3.3 Visual Field Assessment

Automated perimetry was performed monocularly using the Humphrey Visual Field Analyzer using the 24-2 SITA standard program with a white size 111 stimulus under standard conditions (HVF; Carl Zeiss Meditec, Dublin, CA, USA). Visual fields were performed if an assessment had not been undertaken within 3 months of testing.

In the test strategy the ‘24’ refers to the area of the field tested, measured from the degrees from central fixation. The ‘2’ indicates the pattern of points tested and in this strategy the algorithm tests in a grid with points placed 6 degrees apart taken from above and below the horizontal and vertical meridian. At the commencement of the examination, a point in each quadrant is tested to determine the patients’ threshold levels, which are then used to estimate the neighboring areas. Information from surrounding test locations is used to estimate staircase starting values which alter during the test based on the pattern of responses (Bengtsson et al., 1998; Wild et al., 1999).

On the print out of the visual field test result, two global indices are calculated and recorded. The mean deviation (MD – either elevation with positive notation or depression with negative notation) is representative of the overall age-matched field loss (Flammer, 1986). The threshold sensitivity varies across the visual field but the MD is useful as a general parameter indicating the extent of field abnormality. The pattern sensitivity deviation (PSD) represents focal loss within the visual field and also accounts for generalized threshold depression (Flammer, 1986). An increased PSD is therefore a more specific marker for visual field abnormalities than MD alone (Kanski, 2003).

Both eyes were tested sequentially using the calculated near correction, with the eye tested first randomized between participants. The field was deemed reliable if there were less than 20% fixation losses (Glaser, 1999; Hardage & Stamper, 1989) and the result was classified into one of six categories based on a modified visual field classification system by Mills et al. (Mills et al., 2006). This system takes into account the MD, PSD and the location and depth of field loss. Field test results were classified as either normal, mild, moderate, advanced, severe and end stage loss. Grading visual function was part of phenotyping each participant and confirming the correct diagnosis (further details are presented in Table 3.1 in results section, pg 32).
2.3.4 Anterior and posterior segment examination

Clinical evaluation of the anterior and posterior segment of the eye was performed using the Haag Streit slit lamp (BD 900; Haag Streit Inc, Koeniz, Switzerland). Measurement of intraocular pressure was performed using the Goldman tonometer (AT 900; Haag Streit Inc, Koeniz, Switzerland) and when available central corneal thickness was determined using an ultrasound pachymeter (SP-2000; Tomey, Erlangen, Germany). These measurements were taken to assist in confirming the diagnosis. Open angle glaucoma was defined as optic neuropathy in the presence of no identifiable secondary cause with or without visual field loss characteristic of glaucoma (Shaarawy et al., 2009). Attention was paid to the pattern of intraocular eye pressure prior to treatment as well as identified risk factors for developing the condition to assist with confirmation of the correct diagnosis. For example risk factors such as a family history of glaucoma, a medical history of hypertension and vasospasm were noted (Shaarawy et al., 2009).

Monoscopic fundus and disc images were taken using the Canon non-mydriatic retinal camera (CR6; Canon Inc, Japan). Disc imaging was taken using the Ocular Coherence Tomograph (OCT; Model 3000, Carl Zeiss Meditec, Dublin, CA, USA). Disc Imaging was used to verify ophthalmoscopy findings and also provided the participant with a ‘take home’ copy of select results as a source of feedback regarding the health of their optic nerves.

Clinical evaluation results obtained from all participants were reviewed by a masked Ophthalmologist (JC) to confirm correct diagnosis. No participants included in Experiment 1 were deemed to be incorrectly diagnosed. As mentioned, one control participant was identified with macula pathology and was referred for specialist Ophthalmological assessment.

2.4 Auditory experimental protocol

The auditory experimental protocol consisted of 4 key measurement tasks described below. Tasks were administered by one of two trained audiology students in examination rooms at the Royal Victorian Eye and Ear Hospital or within participant’s homes. Background noise was checked prior to testing and if it exceeded 40 decibels another test environment was sought. Similar instructions were administered to participants with sound detection being conducted first followed with the remaining tests randomized between participants. Total test time was around one hour.
2.4.1 Sound Detection

Detection of air conducted pure tones was assessed for each ear separately using a portable audiometer (Grason-Stradler 61 77) and a pair of TD-49 headphones as the transducer. The audiometer was calibrated prior to commencing the experiment, following manufacturer’s guidelines, and checked thereafter at the start of each testing session. Hearing thresholds at frequencies 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 kilohertz (kHz) were measured. The sound detection threshold at each frequency was recorded in decibel hearing level (dB HL). Testing began approximately 20-30dB above the expected threshold and continued in descending 10dB steps below threshold. Subsequently 5dB ascending steps were taken until two out of three sounds were heard as determined by the participant’s verbal ‘yes’ confirmation. The threshold for each frequency was recorded with the pattern of sound detection thresholds across the frequency range plotted on a data collection form (see Appendix 1). In this study normal hearing ability was defined as the pure-tone average of hearing thresholds 0.5, 1.0, 2.0 and 4.0 kHz ≤25 dB HL in each ear (non-sound proof condition). This criterion is in line with epidemiology based normative data (Cruickshanks et al., 2003; Mitchell, 2002).

2.4.2 Auditory Brainstem Response

Auditory brainstem response (ABR) testing was undertaken to ascertain the function and integrity of the auditory nerve, eighth cranial nerve, and the auditory brainstem. It was performed using the AUDERA evoked potential system and stimuli were presented using a single ER-4 insert earphone into the tested ear. To conduct this test, participants were seated in a comfortable position and electrodes (ground and reference) were positioned on the forehead and mastoid following preparation of the skin area.

ABR waveforms represent early evoked neural activity occurring within 15 milliseconds following the presentation of an audible stimulus or acoustic click delivered at 90 dBnHL. Acoustic clicks (100 microsecond’s duration) were presented at a rate of 33.1Hz. Each individual ABR waveform consists of 7 positive peaks each representing neural activity at different regions of the auditory pathway (see Figure 2.2) (Buchwald & Huang, 1975; Jewett et al., 1970). ABR waveforms are averaged from 2000 stimulus presentations with the averaged latencies and amplitudes of the main positive peaks recorded for analysis. Specifically the absolute peak latencies (in milliseconds) and peak to peak amplitudes (in microvolts) are recorded for waves I and V. In addition their inter-wave peak latencies and ratio of the amplitude difference between wave I and V is also used for statistical analysis.
The examination of features of these 3 main waves are conventional for clinical interpretation of the ABR with normative reference data and diagnostic criteria are available (Chiappa et al., 1979; Jacobson et al., 1980; Jiang et al., 1993; Jiang et al., 1991). Testing time took around 10 minutes for both ears.

2.4.3 Amplitude Modulation Detection

Auditory amplitude modulation detection measures temporal resolution or the sensitivity for detecting sinusoidal amplitude modulation changes in a broadband noise carrier modulated at a rate of 150 Hz (Eddins, 1999; Rance, 2005; Zeng et al., 1999). It was measured using an amplitude modulation test based on a psychophysical test procedure reported by Dawson et al 1998 and refined by Rance et al 2004 (Dawson et al., 1998; Rance et al., 2004). Specifically, in the current study, amplitude modulation was produced using the Same Different (SD) test software (version 1.0, designed by David Grayden, Bionic Ear Institute, copyright 2004) and recorded directly onto a host laptop as digital wave files in a 16-bit format with a 44,100 hertz (Hz) sampling rate.

This task presents auditory stimuli through ER-4 insert ear phones to the tested ear. The participant was firstly presented with background stimuli which consisted of broadband noise bursts presented in a 500 millisecond on/off sequence. The participant was then
required to identify the target stimuli which consisted of a randomly presented string of modulated shifts of the background stimuli, akin to detecting a change in the overall amplitude of the sound envelope. The participant was required to depress a button each time he/she heard a variation in the signal or ‘when the background noise sounds different’.

The target stimuli were automatically generated by multiplying the bursts of background noise by a dc-shifted sine wave. Depth of modulation was determined by the amplitude of the modulating sine wave with amplitude modulation levels varying from 0 to -30 decibels (dB) in 3 dB increments (see test Figure 2.1). The rate of modulation was fixed at 150 Hz and the presentation level for both the target and background stimuli was randomly varied between 82 dB sound pressure level (dBSPL) and 88 dBSPL to reduce the likelihood that loudness level differences provided cues to target identification.

![Diagram](image)

**Figure 2.2** Diagram highlighting the sinusoidal nature of the amplitude detection task which modulates a continuous white noise stimulus at 150Hz. The mean depth required for amplitude modulation detection in normal healthy young adults (aged 20-40 years) is represented by the dashed line at -17.5 dB. Note dB = decibels. *Reproduced with permission from Rance et al., 2009.*

A temporal modulation detection threshold for each ear was established representing the minimal detectable modulation depth perceived on 70% of occasions at that modulation depth. The final result was recorded in negative decibels with the larger the decibel value representing the smaller the perceivable difference perceived between background noise.
and target stimuli. Based on previous data a normal amplitude modulation threshold for an adult aged between 20 and 30 years is -17.5 dB with a standard deviation 1.1 dB (Rance et al., 2009). See Figure 2.1 to illustrate task. Currently, no data is available for normal amplitude modulation thresholds in older healthy adults.

2.4.4 Speech Perception

This task sought to determine the number of phonemes or speech sounds, each containing 3 phonemes, a participant could perceive from a list of 50 monosyllable words each characterized by consonant-nucleus-consonant (CNC) components (see Appendix 3). These CNC words are phonemically balanced to Australian English. Both speech and background noise stimuli were presented concurrently to the same ear with both delivered using Windows Media player through an ER-4 insert earphone. The words were presented at 85dBSPL whilst the background noise, 4 talker babble, was presented at four different levels representing four listening conditions; quiet (no competing background noise) and speech in noise +10dB, +5dB and 0dB (CNC word at same level as background) signal to noise ratios (SNR). For statistical analysis the quiet listening condition was assigned a SNR value of +20dB.

Participants were instructed to repeat the word they heard and each correctly identified phoneme was allocated a score of 1 with a maximum score of 3 for each CNC word. The total number of correct phonemes out of a maximum of 150 was converted to a percent correct score.

2.5 Statistical Analyses

All analyses were performed using the statistical software package Minitab (version 16; Dell Inc., United States). An analysis of the normality of the data using the Anderson-Darling test revealed that the majority of outcome variables were not normally distributed. Therefore for single outcome group comparisons the Kruskal-Wallis statistical test was selected with the median and interquartile range values reported. In examining the impact of more than one factor, including controlling for covariate/s, on an outcome variable the results using

---

4 Negative annotation is the conventional way to record amplitude detection thresholds with the larger the negative value representing the greater the departure from 0db which signifies the maximum (100%) possible difference between the background and target stimuli. This scale can be approximately converted into a percentage of the maximum amplitude (See Appendix 2).

5 The Kruskal-Wallis test is the non-parametric version of analysis of variance.
analysis of variance (ANOVA) \(^6\) will be reported. This model was deemed appropriate given the data satisfied the test assumptions including a small, albeit modest departure from normality for each numerical outcome variable measured on a continuous scale (Armitage et al., 2001).

For examining performance across levels of the same task a repeated measures analysis of variance model (RM ANOVA) was conducted with the between-participant main factor being ‘group’ (glaucoma versus control) and the within-participant factor being outcome levels, controlling for the covariates of average hearing level and age. Age was included as a covariate even though participants were age matched given that the control participant could be ± 2 years from the glaucoma participant. If either a significant main effect of one variable or interaction effect between two variables were identified in RM ANOVA, an analysis using a separate series of adjusted ANOVA models were conducted to determine which factor contributed to the statistical level. In a separate series of analyses, the main effect of ‘stage’ of disease within the glaucoma group was explored, controlled for average hearing level and age. Spearman’s correlations were performed, where appropriate, to identify the strength of relationships between auditory tasks.

### 2.6 Summary of outcome measures

The primary aim of this experiment was to investigate auditory function ability in participants with OAG compared to participants without OAG. Evidence to support the hypothesis would be reflected by a statistically significant (alpha < 0.05) difference in the groups’ central performance tendency on one or more of the auditory function tasks described. Specifically poorer temporal amplitude modulation thresholds, delayed ABR waveform peaks and overall conduction times as well as poorer speech perception scores may be identified in the glaucoma group. Consideration of any trends in the data along with evaluating any clinical significance was also conducted.

\(^6\) Adjusted analysis of co-variance (ANCOVA) and repeated measure analysis of variance (RM_ANOVA) are performed under a General Linear Model in the chosen statistical software package. This model concurrently performs regression analysis which allows for the reporting of the strength of associations via regression coefficients. It also allows an examination of the standardized residuals therefore a check of the appropriateness of the model to each data set could be assessed.
Chapter 3 : Results for Experiment 1

3.1 Hypothesis Rationale

The primary aim of this experiment was to investigate auditory function ability in participants with OAG compared to participants without OAG. Examination of the central tendency in the data between groups was made with emphasis on any overall group performance differences on auditory function tasks, namely amplitude modulation detection, speech perception scores across listening conditions and ABR waveform latency-amplitude characteristics.

Hypothesis 1: Individuals with open angle glaucoma have auditory processing dysfunction.

Aim 1: To investigate auditory processing abilities in individuals with open angle glaucoma and determine whether poorer function exists compared to age matched controls.

3.1.1 Data description

Data were collected from both ears. Results for a single ear, left ears, will be reported with results for the right ears presented in Appendix 6. Of note, similar results were obtained if analysis was performed for randomized ears – performed for background checking and not reported herein. Reporting unilateral data reflects the trend in ophthalmic research to report data for one eye only which may be based on confounding issues such as statistical handling of repeated measures or dependant data (Grimes & Schulz, 2002; Varner, 2008). Reference to both ears will be made toward the end of this chapter with respect to examining the ratio of performance between ‘best’ and ‘worst’ ears for each group.
Table 3.1 Baseline and visual function characteristics for each group (left ears).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glaucoma N=42</th>
<th>Control N=42</th>
<th>P Value#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (interquartile range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>59 (54, 66)</td>
<td>60 (54, 64)</td>
<td>0.842</td>
</tr>
<tr>
<td>Central VA</td>
<td>0.00 (-0.10, 0.00)</td>
<td>-0.10 (-0.20, 0.00)</td>
<td>0.003*</td>
</tr>
<tr>
<td>MD</td>
<td>-3.47 (-9.20, -0.50)</td>
<td>-0.71 (-1.15, 0.32)</td>
<td>0.000*</td>
</tr>
<tr>
<td>PSD</td>
<td>2.98 (1.70, 9.65)</td>
<td>1.42 (1.22, 1.63)</td>
<td>0.000*</td>
</tr>
<tr>
<td>RNFL</td>
<td>66.50 (52.00, 78.26)</td>
<td>94.76 (88.64, 100.86)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Stage of disease† – number (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disease</td>
<td>14 (33.33)</td>
<td>39 (92.86)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>10 (23.81)</td>
<td>3 (7.14)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>7 (16.67)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>6 (14.29)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (9.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End Stage</td>
<td>1 (2.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>42 (100)</strong></td>
<td><strong>42 (100)</strong></td>
<td></td>
</tr>
</tbody>
</table>

†Reference: Modified glaucoma staging system proposed by Mills et al (2006)
#Kruskal-Wallis test; *Significant at p <0.05. Key: VA = visual acuity, MD = mean defect, PSD = pattern sensitivity deviation, RNFL = mean retinal nerve fibre layer, VF = visual field. Measurement scales: Central VA in log units, MD and PSD in decibels, RNFL in microns.

3.1.2 Baseline Characteristics

Data were collected on the demographic and phenotypic characteristics of participants and is summarised in Table 3.1. No statistically significant difference was found between the median ages in each group (H = 0.06, df = 1, p=0.842). The proportion of females was 66.7% and 64.3% in the glaucoma and control groups respectively (χ² (1, 42) = 0.053, p=0.820). The majority of control participants, 92.86%, had no visual field loss (grade 0). The remaining 7.14% displayed minimal visual field changes that were not characteristic of glaucomatous loss rather were likely cataract induced (Guthauser & Flammer, 1988). Glaucoma participants had a range of disease severity with the majority having minimal to mild grades of visual field loss (57.14%: stage 0 and 1) (see Table 3.1). Both groups had
optimal and normal standard central visual acuity with the control group having a slightly better median value (logMAR -0.1, Snellen equivalent 6/5) compared to the glaucoma group (logMAR 0.00, Snellen equivalent 6/6). Median mean defect, pattern sensitivity and retinal nerve fibre layer were found to be significantly poorer in the glaucoma group compared to controls (p<0.001, see Table 3.1). These median values in optic nerve structure and function are as expected for both older, healthy eyes and eyes with mild staged glaucomatous optic neuropathy (Blumenthal et al., 2000).

3.2 Sound Detection

No significant group differences were found between the median sound detection thresholds in decibels (dB) for the majority of frequencies assessed (0.50, 1.0, 4.0 and 8.0 kilohertz (kHz), see Table 3.2). For median threshold detection levels at 0.25 and 2.0 kHz the glaucoma group had significantly better scores which may reflect quieter test room environments (greater impact at 0.25 kHz) or the inclusion of smaller sample sizes of glaucoma participants tested at these frequencies (a reflection of slightly different ranges tested between examiners). Figure 3.1 illustrates the median hearing threshold levels were within the normal range for frequencies up to 2.0 kHz however were abnormal at 4.0 and 8.0 kHz for both groups with a larger range of responses in the glaucoma group. This finding is consistent with what is expected for older adults, namely a reduction in high frequency sound detection with increasing age (Cruickshanks et al., 2003; Mitchell, 2002).

The overall sound detection threshold for each group is shown in Table 3.2. The average sound detection threshold was calculated as the conventional average hearing threshold across the four frequencies 0.5, 1.0, 2.0 and 4.0 kHz. The four frequency average (4FA) hearing threshold estimate for each group was used when hearing level was considered a covariate factor in further statistical analysis. No significant difference was identified between the average 4FA between the glaucoma and control groups at baseline (F (1, 83) = 0.34, p = 0.562).
Table 3.2 Overall sound detection levels for each group

<table>
<thead>
<tr>
<th>Frequency (KHz)</th>
<th>Glaucoma N=42</th>
<th>Control N=42</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Interquartile range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25∞</td>
<td>7.50 (5.00, 12.50)</td>
<td>20.00 (10.00, 20.00)</td>
<td>0.018*</td>
</tr>
<tr>
<td>0.50</td>
<td>10.00 (10.00, 18.75)</td>
<td>15.00 (10.00, 20.00)</td>
<td>0.304</td>
</tr>
<tr>
<td>1.00</td>
<td>10.00 (10.00, 20.00)</td>
<td>15.00 (10.00, 20.00)</td>
<td>0.383</td>
</tr>
<tr>
<td>2.00</td>
<td>15.00 (10.00, 23.75)</td>
<td>20.00 (15.00, 25.00)</td>
<td>0.033*</td>
</tr>
<tr>
<td>4.00</td>
<td>27.50 (10.00, 40.00)</td>
<td>25.00 (15.00, 36.25)</td>
<td>0.929</td>
</tr>
<tr>
<td>8.00</td>
<td>40.00 (17.50, 63.75)</td>
<td>35.00 (17.50, 45.00)</td>
<td>0.384</td>
</tr>
<tr>
<td>4FA</td>
<td>16.25 (10, 23.75)</td>
<td>18.13 (13.44, 24.06)</td>
<td>0.305</td>
</tr>
<tr>
<td>Mean ± Standard Deviation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4FA</td>
<td>18.15 ± 8.95</td>
<td>19.17 ± 13.44</td>
<td>0.562†</td>
</tr>
</tbody>
</table>

Key: 4FA = average of 0.5, 1.0, 2.0 and 4.0 Kilohertz (kHz), #Kruskil- Wallis Test; †ANOVA; * Significant p < 0.05, ∞ note that at this frequency sample sizes were vastly different (glaucoma = 10, control = 41) which could lead to erroneous t statistic.
3.3 Auditory Brainstem Response (ABR)

Interpretation of the ABR is based on consideration of latency and amplitude of waveform components. The mean latency in milliseconds for each group for the main ABR waves I, III and V are shown in Figure 3.2. Results for the control group are within what is expected for older adults (Rosenhamer & Holmkvist, 1982; Rowe, 1978).

Using a 3 x 2 repeated measures ANOVA model with wave peak latency as the within participant factor and group as the between participant factor (covariates: age and average hearing level) there was no statistically significant difference between groups across the 3 main wave peak latencies (F (1, 80) = 0.911, P = 0.343). Minimal differences in the latencies of waves I and III between groups can be observed in Figure 3.2 however, there was a small trend toward a delay in the glaucoma group for the main peak latency of wave V compared to controls. No significant interactions were identified between ABR latency, average hearing level or group however a main effect of increasing age was apparent (F (1,80) = 6.350, p = 0.014).

Consideration of the interpeak latency intervals between groups was also examined. As shown in Figure 3.3 and 3.4, a proportion of glaucoma participants displayed more prolonged interpeak latencies between waves I-V, namely 11/42 ears (26.2%), but this was
not found statistically significant for univariate or multivariate analysis (F (1, 83) = 3.88, p = 0.073).

Figure 3.2: Average ABR recording highlighting main peak latencies in milliseconds for each group; waves I, III and V are indicated approximately by stars.

Figure 3.3: Individual raw scores with overlying plotted mean (middle bar) and standard deviations (upper and lower bars) for ABR interpeak latencies (waves I-V) for each group; glaucoma 4.16 ± 0.31 and control 4.07 ± 0.17; n = 42 ears.
Figure 3.4: ABR interpeak latencies (wave’s I-V) for glaucoma participants. A proportion of left ear responses, 11/42 (26.2%), fall outside (represented by pink circles) the upper limit of the mean control performance (90th percentile) equating to >4.30 milliseconds.

A similar 2 x 2 model was applied to examine any difference across peak to peak ABR amplitudes for waves I and V between groups. ABR amplitudes were found to be comparable between groups (F (1, 80) = 0.698, p = 0.198). Age and average hearing levels did not have any main effects within or between groups.

Collectively findings for ABR testing suggest that the majority of glaucoma participants have similar ABR waveform patterns to age equivalent controls.

3.4 Amplitude Modulation Detection

A threshold estimate on this task is interpreted by the average depth required for a 150Hz modulated noise stimulus to be perceived. The median amplitude modulation detection threshold was identical in each group (-12.00 dB) but with differing interquartile ranges (glaucoma: -12.63 to -9.00 dB and control: -15.00 to -12.00 dB). Given this distribution, glaucoma participants overall displayed significantly poorer amplitude modulation detection ability compared to controls (Kruskal-Wallis test: H = 5.54, DF = 1, p = 0.019).

Comparing mean group threshold estimates, for the purpose of examining impact of covariates, also highlighted poorer overall glaucoma performance compared to control, -13.92 ± 5.08 and -11.50 ± 3.00 dB respectively (see Figure 3.5). Despite the majority of glaucoma participants performing within the normal range, a greater number of glaucoma participants fell below the lower limit value (90th percentile) of the control performance range (13/42 glaucoma ears (30.95%) versus 8/42 (19.04%) control ears) (see Figure 3.6).
As can be observed from Figure 3.5, 2 control participants had exceptionally good amplitude modulation detection ability. Removing these two performers from the analysis, which were 3.5 standard deviations away from the average control performance, did not impact upon the between group significance level. Furthermore, glaucoma group performance still remained inferior to that of controls following the adjustment for covariates (F(1, 81) = 5.04, p = 0.028). Within this model, average hearing level was not significant but age was found to influence group performance (F(1, 82) = 22.95, P < 0.001). No statistically significant main effect was found for stage of disease within glaucoma participants (F(1, 83) = 1.07, p = 0.386).

Figure 3.5: Individual raw scores with overlying plotted mean (middle bar) with standard deviations (lower and upper bars) for temporal amplitude detection thresholds for each group; glaucoma -11.50 ± 3.00 dB versus control -13.92 ± 5.08 dB.

Figure 3.6: Individual raw scores for amplitude modulation detection for the glaucoma group highlighting 13/42 left ears (30.95%) (represented by pink circles) that fall below the lower 90\textsuperscript{th} percentile value of control performance (i.e. less than -12.0 dB).
3.5 Speech Perception

Speech perception ability was evaluated under four listening conditions or signal in noise (SNR) ratios. As shown in Figure 3.7, participants displayed progressive difficulty in speech perception ability with increasing background noise (main effect of listening condition: $F(3, 240) = 9.70$, $p < 0.000$). Using a $4 \times 2$ repeated measures ANOVA model with listening condition (SNR level) as the within participant factor and group as the between participant factor (covariates: age, average hearing level) a significant interaction was identified between listening condition and group indicating the effect of noise on perceptual ability was not identical across groups ($F(3, 240) = 3.43$, $p = 0.018$). A significant effect of average hearing level was also identified between groups ($F(1, 80) = 9.96$, $p = 0.002$).

Firstly to address these findings, a series of adjusted ANCOVA models were performed to elucidate which listening condition had the largest effect on group performance. Inspection of Figure 3.7 shows a trend toward a greater difference in group performance with increasing SNR levels. However, individual analyses indicated no significant difference between mean group performances at each level (all $p > 0.05$), adjusted for average hearing threshold and age. On the other hand, average hearing level again had a significant impact upon results under each model (for example at SNR 0: $F(1, 83) = 9.31$, $p = 0.003$). These results suggest commensurate speech perception ability in glaucoma participants compared to controls however the influence of hearing detection threshold upon performance warrants further investigation given that the range of hearing thresholds at higher frequencies was larger within the glaucoma sample (as was shown in Figure 3.3).
Figure 3.7: Speech perception interval plots of the mean and ± standard deviation (% correct) for each group across listening condition. Key: SNR = Signal in noise ratio in decibels.

Individual scatter plots for each SNR level shown below – displayed separately for clarity with mean (middle interval bar) and ± standard deviations (upper and lower bars) indicated.

A) Speech perception at SNR +20 dB
B) Speech perception at SNR +10 dB

C) Speech perception at SNR +5 dB

D) Speech perception at SNR +0 dB
3.5.1 Speech perception scores in normal hearing participants

Previous analyses showed a main effect of hearing level on speech perception scores. To minimise this effect, participants with normal to near normal hearing sensitivity above 4 kHz were selected and analyses repeated. As a result, 17 glaucoma and 17 controls were excluded as they revealed hearing threshold detection levels above 35 decibels at 4.0 kHz in their left ears. Between the remaining groups (n=25) no differences were identified for age and gender disposition (p<0.05) and median overall hearing frequency threshold (Kruskil-Wallis test: H = 3.43, df = 1, p = 0.064). Within these normal hearing participants, speech perception ability was again found to interact with listening condition under a similar repeated measures ANOVA model described above (F (3, 141) = 3.35, p = 0.021).

Speech performance between these smaller sub-samples of participants was not found to be statistically significant, adjusted for age (see Table 3.3). As shown in Table 3.3, glaucoma participants displayed a trend toward poorer speech perception ability compared to controls under the most challenging listening condition, accounting for an average a 5% reduction at SNR 0 dB. As expected, age and average hearing level did not have significant main effects within or between groups. These results suggest that glaucoma participants generally display commensurate speech perception ability with age equivalent controls under quiet to low level background noise but show a trend toward increased difficulty with speech understanding when background noise becomes more marked.

Table 3.3 Percentage speech perception scores across listening conditions for normal to near normal hearing participants; n=25.

<table>
<thead>
<tr>
<th>Signal in Noise ratio</th>
<th>Glaucoma</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Mean ± Standard Deviation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+20dB</td>
<td>93.96 ± 8.27</td>
<td>94.88 ± 5.54</td>
<td>0.544</td>
</tr>
<tr>
<td>+10dB</td>
<td>85.06 ± 8.99</td>
<td>85.52 ± 10.36</td>
<td>0.672</td>
</tr>
<tr>
<td>+5dB</td>
<td>72.93 ± 12.29</td>
<td>69.68 ± 10.11</td>
<td>0.383</td>
</tr>
<tr>
<td>+0dB</td>
<td>41.51 ± 11.47</td>
<td>46.56 ± 10.86</td>
<td>0.061</td>
</tr>
</tbody>
</table>

SNR values represent the difference in stimulus to background level in decibels (dB). SNR +20 signifies background noise at a minimum (quiet) whereas SNR +0 signifies background noise at the same level as the stimulus (highly competitive)
3.6 Additional auditory findings

3.6.1 Correlations between auditory tasks

Table 3.4 highlights the significant correlations between auditory tasks for each group. It can be observed that amplitude modulation detection performance correlated moderately with both speech perception and features of the ABR waveform. For example, a linear relationship was identified between amplitude modulation detection ability and the interpeak latency for wave’s I-V in both groups (controls = 0.59, p <0.001; glaucoma = 0.34, p = 0.025). This correlation suggests the handling of temporal cues is critical throughout the auditory pathway. In addition, auditory processing measures correlated with peripheral sound detection thresholds. For example, speech perception ability strongly correlated with average hearing detection thresholds for both groups (p < 0.05). (See Appendix 6 - correlations similar in right ears).

3.6.2 Disease Severity in Glaucoma Participants

A series of analyses to those described were performed to explore the impact of stage of disease or visual dysfunction on auditory outcome variables in the glaucoma sample, adjusted for average hearing level and age. No significant differences were found between disease stages or individual visual function indices (MD and PSD) for any auditory outcome variable. This may be due to a small and uneven spread of glaucoma participants in moderate to advanced disease stages. Furthermore, no correlations were identified between retinal nerve fibre layer thickness and any auditory outcome variable.

3.6.3 Inter-ear performance between groups

A total of 15/25 (60%) of glaucoma participants had asymmetrical stages of disease with a general trend toward more advanced disease in left eyes (Appendix 5 and 6). Given this preponderance for asymmetrical staging, the glaucoma group as a whole was examined compared to the control group in terms of the magnitude of any difference in right and left ear performance between groups. A ratio (best ear ÷ worst ear) of performance was conducted to explore the degree to which right and left ear performance compared for each subject with a ratio of 1.0 representing no difference in performance and < or > 1.0 indicating a difference. The mean group ratio was then compared to determine whether the degree of asymmetry varied between groups on select tasks. There was no statistically significant difference between the magnitude of asymmetry between ears for the majority
of tasks (one-way ANOVA tests, p > 0.05; see Appendix Table 5) except for ABR interpeak latency where the glaucoma group displayed a greater degree of asymmetry compared to controls (F (1, 82) = 4.94, p = 0.029).

Table 3.4: Spearman’s correlation coefficients and significance levels between auditory tasks for each group.

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Glaucoma</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman’s rho</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Age + AM</td>
<td>0.487</td>
<td>0.001</td>
</tr>
<tr>
<td>HFA + Speech SNR 5 dB</td>
<td>-0.361</td>
<td>0.017</td>
</tr>
<tr>
<td>HFA + Speech SNR 0 dB</td>
<td>-0.406</td>
<td>0.007</td>
</tr>
<tr>
<td>AM + Speech SNR 5 dB</td>
<td>-0.389</td>
<td>0.011</td>
</tr>
<tr>
<td>AM + Speech SNR 0 dB</td>
<td>-0.286</td>
<td>0.067 (trend)</td>
</tr>
<tr>
<td>AM + ABR I-V latency</td>
<td>0.342</td>
<td>0.025</td>
</tr>
<tr>
<td>AM + ABR V latency</td>
<td>0.348</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Key: AM = amplitude modulation detection, ABR = Auditory brainstem response, SNR = signal in noise, HFA = hearing 4-frequency average threshold.

### 3.7 Summary of findings

Based on the results to Experiment 1, investigation into auditory neural function through ABR testing showed a trend toward a longer average interpeak latency (wave’s I-V) in the glaucoma group compared to age equivalent controls. From within the glaucoma group, a proportion (26.2%) revealed an interpeak latency outside the 90th percentile of control mean
performance. Measures to assess basic auditory pathway processing function revealed clearer evidence of auditory processing dysfunction in the glaucoma cohort as reflected by an overall impairment in amplitude modulation detection ability compared to the control group. In addition to these findings, glaucoma participants with normal to near normal high frequency hearing capacity displayed a trend toward increased difficulty perceiving speech under the most challenging listening condition (SNR +0 dB), accounting for a 5% lower speech score compared to hearing matched controls. Responses between auditory function tests were found to correlate for each group and suggest an underlying relationship in auditory neural temporal processing mechanisms.

Based on the distribution of results for ABR interpeak latency (wave’s I-V), amplitude modulation detection and speech perception under challenging listening conditions, there is evidence that a subgroup of participants have increased difficulty on specific tasks in both groups with the proportion being significantly higher in the glaucoma group. Along with confirming these findings, data provide the impetus to explore auditory temporal processing in more detail and consider whether other measures of auditory function may be more sensitive in uncovering any neural impairment.

Further characterisation of the perceptual consequences of any central auditory pathway dysfunction in certain OAG individuals may allow comparison with psychophysical performance on visual processing measures. The question arises as to whether performance on auditory neural processing tests mirror visual processing changes (or vice versa) in the same individuals with OAG. Characterising glaucoma status by examining both auditory and visual perceptual processing may be more justifiable than exploring auditory function alone given that for the current experiment visual function was ascertained only from clinical tests that staged glaucoma disease based on visual field analysis. Given that typically glaucoma produces early visual processing changes before that detected on conventional perimetry (Aref & Schmitt, 2005; Drance, 1985; Motolko et al., 1982), examination of specialized visual processing elements involving temporal discrimination would allow a more direct comparison to similar tasks explored in the auditory domain.
3.8 Experiment 2: Hypotheses and Aims

**Hypothesis 2:** Individuals with glaucoma have temporal processing impairment in both the auditory and visual systems.

**Aim 2a:** To determine whether glaucoma patients with auditory temporal processing difficulty also have abnormalities in visual temporal processing ability.

**Aim 2b:** To determine whether functional loss is generalized across temporal tasks or is specific for subsets of temporal information.

**Rationale 2:** A deficit in auditory temporal processing ability was found in individuals with glaucoma in Experiment 1. The second part of the study aimed to confirm this finding and to explore the extent and precise nature of the deficit through more in depth perceptual investigations which allowed an examination of responses on a range of temporal processing tasks. This experiment was designed to explore hierarchical levels of temporal processing in both the auditory and visual systems. In doing so, Experiment 2 aimed to further highlight any specific characteristics of auditory and visual temporal processing dysfunction in individuals with glaucoma. Overall this experiment aimed to support the primary hypothesis that glaucoma is associated with changes outside the visual pathways owing to the potential that some individuals with OAG have an increased global vulnerability to CNS insults.
Chapter 4 : Research Design for Experiment 2

4.1 Development of Hypothesis 2

The primary aim of Experiment 2 was to investigate auditory function tasks that utilize temporal resolution and discrimination ability in more detail. A secondary aim of this experiment was to concurrently assess auditory and visual temporal processing abilities in the same individuals and investigate whether any deficits observed are occurring across sensory systems for specific temporal sensitivities.

Individuals with glaucoma are known to develop disturbances to visual processing ability as a result of changes to the structure and function of retinal ganglion cells (RGC) (Drance, 1985; Drasdo et al., 2008). Research in the neurofunctional and psychophysical domains have shown that these morphological changes can manifest into functional alterations along the visual pathway such as impaired temporal contrast ability at the level of the RGC through to impaired global motion discrimination ability at the cortical level (Battista et al., 2009; Duncan et al., 2007; Essock et al., 1996; Gupta et al., 2006b; Gupta & Yucel, 2003; He, 2007; McKendrick et al., 2004; McKendrick et al., 2005; McKendrick et al., 2009; Sahraie et al., 1996; Tyler, 1981; Vickers et al., 1997; Vogt et al., 1998; Willis & Anderson, 2000). Experiment 2 aimed to identify whether any temporal processing abnormalities identified in the auditory system mirror those expected in the visual system of the same individuals. Thus conclusions on whether dual sensory temporal processing deficits exist in individuals with open angle glaucoma compared to age and gender-matched controls can be drawn.

4.2 Selection of Methods

The research design, including choosing the materials and methods selected to test hypothesis 2, was based on a thorough review of current practices and trends reported in the literature as well as consideration of the resources available. The auditory protocol for Experiment 2 was adopted from Experiment 1 yet was modified to explore temporal processing ability in more detail. This protocol was designed with consultation with my supervisor Associate Professor Gary Rance and the assessments were performed by a single, masked, specialist trained audiologist. The visual protocol for Experiment 2 was confirmed following consultation with by my supervisor Dr Allison McKendrick who has expertise in visual psychophysical assessment and has a special interest in glaucoma. Visual function tests were designed to reflect the hierarchical auditory temporal processing functions
explored. Visual clinical evaluation of all participants and the conductance of the visual psychometric protocol were performed by me following detailed training.

4.3 Sample size calculation

Based on auditory results from Experiment 1, a sample size of 25 in each group is required to detect a true difference in mean amplitude modulation depth of 2 decibels (13.5% difference; standard deviation <5dB) between groups with a power of 0.80 and an alpha level of 5%.

This sample size is adequate when also considering reported literature on visual function specific to temporal flicker processing. Namely a sample size of 25 pairs of observations has above 80% power to detect a mean difference of at least 1.8 decilogs when the population standard deviation is assumed to be 2.3 decilogs based on previous research by Tyler (1981).

Hypothesis 2: Individuals with open angle glaucoma have temporal processing impairment in both auditory and visual systems.

Aim 2a: To determine whether glaucoma patients with auditory temporal processing difficulty also have abnormalities in visual temporal processing ability.

Aim 2b: To determine whether functional loss is generalized across temporal tasks or is specific for subsets of temporal information in each sensory system.

4.4 Participants

4.4.1 Ethics approval

Ethics approval for Experiment 2 was obtained from the Human Ethics and Research Ethics Committee of the University of Melbourne, Victoria, on the 21st Dec 2009 for 12 months (Approval number: 0932963). Study protocol adhered to the tenets of the Declaration of Helsinki and written informed consent was obtained from all study participants following explanation of the nature and purpose of the study.

4.4.2 Inclusion Criteria

Identical inclusion criteria were adopted from Experiment 1 with the addition of a visual acuity clause to ensure visual competency for visual psychometric testing:
• Central best corrected visual acuity in each eye of at least 0.2 (Snellen equivalent 6/12).

4.4.3 Exclusion Criteria

Identical exclusion criteria were adopted as for Experiment 1.

4.4.4 Cases

All participants with a diagnosis of OAG from Experiment 1 were invited to participate in Experiment 2. Of the 42 OAG cases, 11 agreed to participate in Experiment 2. The remaining 16 case subjects were recruited using the same methods that were described for Experiment 1 (refer to page 22).

Power analysis indicated a sample size of 25 was optimal but a total of 27 cases were invited to participate. All cases had a confirmed diagnosis of open angle glaucoma, either with a history of high or low untreated intraocular eye pressure. Two cases failed to attend assessment appointments due to personal reasons therefore a total of 25 cases completed Experiment 2.

4.4.5 Controls

All control participants from Experiment 1 were invited to participate in Experiment 2. Of the 42 controls, 12 agreed to participate in experiment 2. The remaining 16 control subjects were recruited from the same sources as previously described in Experiment 1 (see page 22). Controls were selected if they met the inclusion and exclusion criteria and could be age and gender matched to a glaucoma participant.

A total of 28 controls were assessed and completed Experiment 2. From this sample, 25 were selected to proportionately match the case sample for statistical analysis. The final control sample was selected in a masked fashion with only the age and gender information available for comparison to the glaucoma group.

Gender matching was introduced in Experiment 2 as there is a reported difference in performance between males and females on visual temporal processing tasks (Blough & Slavin, 1987; Kaufmann et al., 2001; Snowden & Kavanagh, 2006).
4.5 Materials and Methods

All equipment was supplied by departments of the University of Melbourne. Visual equipment and the use two assessment laboratories were supplied by the Department of Optometry and Vision Sciences. Auditory equipment was supplied by the Department of Otolaryngology and Auditory Services.

4.5.1 Visual Clinical Evaluation

All participants had written informed consent procedures and underwent a complete or modified ocular examination. New participants to the study had a complete and comprehensive ocular assessment as described in Experiment 1. Participants who had previously participated in the study had a modified screening evaluation that included updating medical and ocular history, an assessment of monocular BCVA and an undilated examination of the anterior and posterior segments of each eye. Fundus examination was coupled by disc imaging using the Heidelberg Retinal Tomograph (HRT; software version 2.0, Heidelberg Engineering, Dossenheim, Germany) which was performed after visual psychophysical measures. Visual field assessment was not repeated if the last reliable field test was performed within 3 months of the clinical evaluation appointment. Generally new subject assessments were conducted one week prior to experimental testing whereas repeat evaluations were conducted on the same day as testing procedures. Akin to Experiment 1, diagnoses were verified by a masked, specialist trained Ophthalmologist. No participants included in Experiment 2 were deemed to be incorrectly diagnosed.

4.5.2 Randomisation procedures

Several aspects of the entire experimental protocol described below were randomized and this included the test order for eye and ear (alternate), order of testing (visual versus auditory) and order of both individual visual and auditory psychophysical procedures. Randomisation of the outcome tasks was conducted using an online, computer generated randomization sequence with 5 levels.

4.6 Visual experimental protocol

4.6.1 Visual materials and methods

Visual tasks were created using custom software (Cambridge Vision Research System VSG version 2/5) and hosted through the Matlab 7 program (Mathworks, Natick, MA). High resolution stimuli were displayed on a 21 inch monitor (resolution 1264 x 947 pixels, 120 Hertz frame rate, GS20 Trinitron, Sony, Tokyo, Japan). Participants used a button box to indicate responses (model CB3, Cambridge Research Systems). Visual processing tasks were designed to examine levels of temporal processing that mirrored functions assessed in the auditory domain. Pilot testing of the visual psychometric protocol was conducted to refine experimental procedures before the commencement of study assessments (see Appendix 4 for pilot data results).

Stimuli were presented at eye level in mesopic background conditions (approximately 70 cd/m²) to reduce the impact of glare and reflections on the monitor. Participants were required to adapt to the room illumination for one minute before testing. Participants viewed the monitor from a distance of one metre wearing their refractive correction if appropriate. Their head was positioned using a chin and forehead rest and the non-tested eye was covered. Tests were performed foveally (centrally).

The test protocol assessed a temporal contrast detection threshold at two rates, 10 hertz (Hz) and 30 Hz, speed discrimination ability at two references speeds, 2 degrees per second (deg/s) and 8 deg/s, and global coherent motion detection ability. Two trials were obtained for each task and the average of the two values was used for statistical analysis. Regular rest breaks were adopted throughout the visual test protocol. The visual protocol was conducted in one single session and total assessment time for both eyes was around 50 minutes. The specifics of each task are detailed below.

4.6.2 Temporal contrast sensitivity (temporal amplitude thresholds).

This task measured contrast sensitivity for a small flickering patch (circle 1.5 degrees radius) as illustrated in stimulus Figure 4.1. The stimulus patch was automatically presented for 500 milliseconds to either the left or right of a central fixation marker and the participant was required to indicate left or right by pressing the appropriate button on the CB3 box. This equates to a two alternate forced choice (2AFC) response pattern.
Two temporal frequencies, or flicker rates, were assessed, one at an intermediate frequency level of 10 Hz and the other at a high frequency level of 30 Hz. The patch stimulus was initially presented at 40% suprathreshold contrast and altered using a staircase method - 0.2% steps with six reversal stages in the sequence of presentations. A reversal occurred when either 2 correct responses were obtained, contrast decreased, or following one incorrect response, contrast increased, at that step size - two up and one down staircase. This procedure produced estimates based on 71% correct performance level (Wetherill & Levitt, 1965) with the overall contrast detection threshold determined from the average of the last four reversals.

![Figure 4.1 Stimulus targets for central visual psychometric tasks. Top: contrast detection of a small flickering patch (1.5 degree radius). Middle: speed discrimination between two grating panels (spatial frequency: 2 cycles per degree). Bottom: global motion detection of coherent movement within 100 mobile dots; shown on left 100% coherence and on right 50% coherence.](image)

4.6.3 Speed Discrimination

This task measured speed discrimination ability using a pair of first order drifting luminance gratings and was based on experimental procedures from Raghuram et al. (Raghuram et al., 2005). Each pair of gratings was vertically orientated at 90 degrees and displayed in a square frame measuring 1.5 degrees in dimension (see stimulus Figure 4.1).
The grating squares were separated by 1.5 degrees and the gratings themselves had a spatial frequency of 2 cycles per degree. The gratings drifted in opposite directions horizontally and no fixation target was present between the two stimuli. Gratings were 75% contrast and the background luminance was 50 cd/m2. Two reference speeds were tested; 2 deg/s (or 4 Hz) and 8 deg/s (or 16Hz). Pairs of gratings were presented for 500 milliseconds and the participant was asked to choose whether the grating on the left or right was moving the fastest. This was therefore a 2AFC response procedure.

One of the pair of drifting gratings moved at the ‘reference’ speed whilst the other ‘test’ grating moved at a speed controlled by an interleaved staircase procedure – two staircase patterns running concurrently, each with 4 reversals. A two up and one down staircase procedure was adopted where two consecutive correct responses were required to decrease the relative speed difference between the two gratings and conversely an incorrect response increased the relative speed difference. The test grating speed was initially presented 50% faster than the reference speed with a 20% change in the relative speed difference on each reversal. The last two reversals of each interleaved staircase were averaged as the final speed detection threshold. This value represented the minimum threshold speed increment required to tell that the test grating was drifting faster than the reference grating. For statistical analysis the minimum percentage speed discrimination threshold was converted to a Weber Fraction (reference grating speed – test grating speed ÷ reference grating speed). Converting thresholds to a Weber Fraction also allowed comparison of values between the two reference speeds assessed.

### 4.6.4 Global Motion Coherence Thresholds

This task measured the minimum number of stimuli required to detect coherent motion and was based on the methods of McKendrick et al. (McKendrick et al., 2005) Each stimulus frame consisted of 100 small, high contrast circular dots (luminance 170 cd/m^2, diameter 8.6 minutes of arc) shown within 10 degrees of central fixation against a black background (0.5 cd/m^2) (see stimulus Figure 4.1 and Appendix 4). A percentage of dots moved either to the right or left with the remaining dots moving in random directions. The dots were randomly and automatically selected to either move in the signal or random direction. Random assignment of dots to move in the signal direction for each frame assists in reducing the impact of local motion cues (McKendrick et al., 2005). Each stimulus frame was
presented for 400 milliseconds and the participant had to make a decision as to whether the majority of the dots were moving left or right. Responses were made using the CB3 box.

Frames were presented using an interleaved staircase procedure with 4 reversals. Initially 80% of dots moved in the signal direction with a step size of 8% for the first two reversals. At least two correct responses were required for the coherence level to reduce with one incorrect response increasing the coherence level and beginning the next reversal sequence. Step size varied during the run and dropped to 4% for the third reversal and 2% for the final reversal for both interleaved staircases. The average of the last 2 reversals from both staircase procedures was recorded as the global coherent motion detection threshold. This value represented the average percentage threshold estimate.

4.7 Auditory experimental protocol

4.7.1 Sound Detection

Sound detection for air conduction pure tones was performed for each ear adopting the same methods as described for Experiment 1 (refer to page 26). One masked, trained audiologist performed the auditory assessments for this experiment in a quiet laboratory located within the Department of Optometry and Visual Sciences. The same definition of normal versus abnormal hearing level was kept constant across both experiments.

4.7.2 Amplitude Modulation Detection

This task was repeated to confirm findings from Experiment 1 as well as providing a consistent measure across experiments to check for test reliability in those subjects who participated in both experiments. In addition results from Experiment 1 indicated a correlation between performance on this task and other auditory function tasks investigated supporting previous reports of a relationship between levels of auditory temporal processing (Rance et al., 2009; Rance et al., 2010a; Rance et al., 2008). Task apparatus and procedures were identical as described in Experiment 1 (refer to page 27).

4.7.3 Frequency Discrimination

The task sought the minimum detectable frequency difference perceived for both low and high frequency signals and is based on the techniques described by Rance et al. in 2004 (Rance et al., 2004). The low frequency range featured a background stimulus at 500 Hz and
targets were presented above and across a range from 502 to 700 Hz. In comparison the high frequency range featured a background stimulus at 4000 Hz (4 kHz) and the targets were presented above and across a range from 4010 to 4700 Hz.

These two levels were chosen to explore the hypothesis that ears with auditory temporal processing disruption will have abnormal frequency discrimination at 500 Hz but normal at 4 kHz. This is in line with temporal sensitivity of auditory neurons and their respective firing patterns. Specifically auditory signals for low frequencies involve a temporal component due to ‘phase locking’ where neurons are able to reflect the stimulus waveform in their firing patterns (Moore et al., 2006a; Rance et al., 2004). In comparison, neurons responding to high frequencies are less able to reflect the stimulus waveform as the stimulus waveform is occurring at a rapid rate preventing the capacity to ‘phase lock’ or fire at the same pace (Moore et al., 2006a; Rance et al., 2004).

The presentation of auditory stimuli for either signal band was initially presented at a suprathreshold frequency determined and selected by the examiner. For each measure the target auditory frequencies were presented using a 4 up and 3 down staircase method – initial 10 Hz steps then progressive 50% decrements. Each stimulus, either background or target, was presented for 500 milliseconds (ms) with a 500ms interval between stimuli. Target stimuli were presented at random intervals and consisted of a short string of 3 tones at the frequency step level. This procedure produced estimates of a 70% correct performance level and the frequency discrimination threshold estimate was determined following the smallest perceivable frequency difference identified correctly on 4 out of 6 times at that frequency level (with no false positives). The result was expressed in Hz and will be referred to as frequency discrimination limens in reference to this task. To date, no frequency discrimination data has been collected on individuals with glaucoma. However studies investigating frequency discrimination in middle to late aged healthy adults with near-normal hearing sensitivity reveal threshold differences between 6-10 Hz for 500 Hz and 38-50 Hz for 4 kHz (Moore, 1985; Moore & Peters, 1992; Rance et al., 2010a; Tyler et al., 1983).
4.7.4 Speech Perception

Procedures and apparatus were similar to that adopted for Experiment 1 (refer to page 29) with two modifications;

1) The number of CNC words was reduced from 50 to 25 to reduce testing time and reduce the likelihood of patient fatigue or loss of concentration. This modification was performed without threatening the reliability of the test owing to the reported validation of the chosen list (Peterson & Lehiste, 1962).

2) The CNC list of 25 words was presented at one listening condition only, namely at speech to noise ratio (SNR) of 0 dB. At this level the speech stimulus is presented in the tested ear at the same amplitude level as the background (4 talker babble) noise. The selection of a single task level was made on the basis of the results shown in Experiment 1. In addition, testing at SNR 0 dB is the most challenging listening condition hence most likely to reveal a difference in performance between groups. In support of the hypothesis, ears with auditory temporal processing disruption may show evidence of impaired speech perception under conditions requiring higher degrees of temporal precision.

4.8 Selection of statistical procedures

4.8.1 Normality testing and choice of statistical methods

To assess whether the data collected were normally distributed a series of normality tests, using the Anderson-Darling (AD) test and Ryan-Joiner (RJ) correlation statistic, were performed on grouped data along with plotting and analyzing the differences in raw scores between groups. Normality tests were performed on both auditory sound detection thresholds and visual acuity logMAR results. The results to the AD test suggested the data were close to but not normally distributed for both auditory and visual tests (P<0.05). However the RJ test indicated a closer approximation to normal with a correlation coefficient of 0.93 (p = 0.010) for visual acuity and 0.99 (p = 0.100) for sound detection.

Based on relatively small sample sizes, single outcomes will be explored using the Kruskal-Wallis test with group median and interquartile ranges reported. Examining the influence of multiple variables on an outcome of interest was deemed to be best explored using an Analysis of Variance (ANOVA) model adjusting for covariates (as described in Experiment 1) given fairly modest departures from normality for these data. Under ANOVA, repeated
measure analyses were performed to examine differences between and across groups across similar tasks. Correlations between auditory and visual parameters, where appropriate, were performed using Spearman’s rho.
Chapter 5: Results for Experiment 2

5.1 Hypothesis Rationale

The primary aims of this experiment were to explore neural temporal processing efficiency in more detail between groups with the intention of investigating temporal processing levels in both the auditory and visual systems of participants. Examination of the central tendency in the data between groups was made and in line with the hypothesis the results were evaluated for any evidence of poorer temporal processing in the glaucoma group compared to the controls (or vice versa), for example on low level processing tasks such as auditory amplitude modulation detection and visual temporal contrast detection.

Hypothesis 2: Individuals with open angle glaucoma have temporal processing impairment in both auditory and visual systems.

Aim 2a: To determine whether glaucoma patients with auditory temporal processing difficulty also have abnormalities in visual temporal processing ability.

Aim 2b: To determine whether functional loss is generalized across temporal tasks or is specific for subsets of temporal information in each sensory system.

5.2 Data description

Data was collected from 25 cases and 25 age and gender-matched controls producing a sample size of 25 single ear observations and 23 single eye observations for comparison. Two subjects from both groups did not participate in vision experiments. Data from left ears and left eyes for each group will be reported with results for right ears and eyes shown in Appendix 8. Separate analyses examining the degree of asymmetry versus symmetry between right and left ears and eyes is represented in Appendix 7 and will be referred to at the end of this chapter.

5.3 Baseline Characteristics

Data were collected on the demographic and phenotypic characteristics of participants and is summarized in Table 5.1. No statistically significant difference was found between the median ages in each group (Kruskal Wallis test: $H = 0.10$, $DF = 1$, $p = 0.748$). The study samples comprised 7/25 (28%) males in each sample group. The majority of control
participants, 84%, had no or minimal visual field loss (grade 0). Four control participants displayed a few depressed points in their visual fields likely induced by cataract lens changes (Guthauser & Flammer, 1988). Glaucoma participants had a range of disease severity with the majority having minimal or moderate grades of visual field loss (48%: stage 0, 20%: stage 2) (see Table 5.1). Central visual acuity was comparable between groups but median mean defect, pattern sensitivity and retinal nerve fibre layer were found to be significantly poorer in the glaucoma group compared to controls (p<0.05, see Table 5.1). These median values in optic nerve structure and function are as expected for both older, healthy eyes and eyes with early staged glaucomatous optic neuropathy (Blumenthal et al., 2000).

### Table 5.1: Baseline and visual function characteristics for each group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glaucoma N=25</th>
<th>Control N=25</th>
<th>P Value#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (interquartile range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>61 (57.50, 65.50)</td>
<td>61 (58.00, 64.50)</td>
<td>0.748</td>
</tr>
<tr>
<td>Central VA</td>
<td>0.04 (-0.05, 0.19)</td>
<td>0.00 (-0.06, 0.10)</td>
<td>0.003*</td>
</tr>
<tr>
<td>MD</td>
<td>-1.71 (-4.84, -0.50)</td>
<td>-0.43 (-1.85, 0.44)</td>
<td>0.010*</td>
</tr>
<tr>
<td>PSD</td>
<td>1.98 (1.56, 7.86)</td>
<td>1.42 (1.31, 1.71)</td>
<td>0.000*</td>
</tr>
<tr>
<td>RNFL</td>
<td>78.26 (68.73, 85.18)</td>
<td>92.23 (87.02, 95.36)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Stage of disease† – number (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disease</td>
<td>12 (48.00)</td>
<td>21 (84.00)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>4 (16.00)</td>
<td>4 (16.00)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (20.00)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>3 (12.00)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End Stage</td>
<td>1 (4.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25 (100)</strong></td>
<td><strong>25 (100)</strong></td>
<td></td>
</tr>
</tbody>
</table>

†Reference: Modified glaucoma staging system proposed by Mills et al (2006)
#Kruskal-Wallis test; *Significant <0.05, VA = visual acuity, MD = mean defect, PSD = pattern sensitivity deviation, RNFL = mean retinal nerve fibre layer. Measurement scales: Central VA in log units, MD and PSD in decibels, RNFL in microns.
5.4 Auditory assessment results

5.4.1 Sound Detection

Hearing detection ability was deemed to be normal (≤25dB HL) in both groups for frequencies up to 4.0 kilohertz (kHz) (Figure 5.1). Table 5.2 illustrates no significant difference between the median hearing detection thresholds at each frequency assessed between groups. The mean ± standard deviation for the four frequency average (4FA; average 0.25, 0.50, 2.0 and 4.0 kHz) hearing threshold was 18.65 ± 6.33 dB HL in the glaucoma group and 16.40 ± 5.94 dB HL in the control group. Similarly the overall median threshold for the glaucoma group was higher than controls (17.50 dB HL versus 16.25 dB HL) with a slightly larger interquartile range (IQR) for the glaucoma group however this was not statistically different (Table 5.2).

Table 5.2: Overall sound detection levels for each group

<table>
<thead>
<tr>
<th>Frequency (KHz)</th>
<th>Glaucoma N=25</th>
<th>Control N=25</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (Interquartile range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td>17.50 (14.38, 24.38)</td>
<td>16.25 (13.75, 18.75)</td>
<td>0.670</td>
</tr>
<tr>
<td>0.50</td>
<td>15.00 (10.00, 22.50)</td>
<td>15.00 (10.00, 22.50)</td>
<td>0.304</td>
</tr>
<tr>
<td>1.00</td>
<td>15.00 (7.50, 20.00)</td>
<td>15.00 (10.00, 17.50)</td>
<td>0.698</td>
</tr>
<tr>
<td>2.00</td>
<td>10.00 (5.00, 20.00)</td>
<td>10.00 (5.00, 15.00)</td>
<td>0.614</td>
</tr>
<tr>
<td>3.00</td>
<td>20.00 (12.50, 27.50)</td>
<td>15.00 (10.00, 25.00)</td>
<td>0.468</td>
</tr>
<tr>
<td>4.00</td>
<td>20.00 (15.00, 35.00)</td>
<td>20.00 (10.00, 30.00)</td>
<td>0.333</td>
</tr>
<tr>
<td>6.00</td>
<td>30.00 (25.00, 47.50)</td>
<td>30.00 (20.00, 42.50)</td>
<td>0.329</td>
</tr>
<tr>
<td>8.00</td>
<td>30.00 (15.00, 57.50)</td>
<td>30.00 (15.00, 50.00)</td>
<td>0.689</td>
</tr>
<tr>
<td>4FA</td>
<td>17.50 (14.38, 24.38)</td>
<td>16.25 (13.75, 18.75)</td>
<td>0.161*</td>
</tr>
<tr>
<td><strong>Mean ± Standard Deviation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4FA</td>
<td>18.65 ± 6.33</td>
<td>16.40 ± 5.94</td>
<td>0.201†</td>
</tr>
</tbody>
</table>

Key: 4FA = average 0.5, 1.0, 2.0 and 4.0 kHz. * Kruskil-Wallis test. † ANOVA.
5.4.2 Amplitude Modulation Detection

A threshold estimate on this task is interpreted by the mean depth required for a 150 Hz modulated noise stimulus to be perceived. In contrast to Experiment 1, no distinction in temporal resolution ability on this task was found between glaucoma participants and controls (Kruskal-Wallis test: $H = 0.05$, df =1, $p = 0.937$). However as shown in Figure 5.2, a trend for poorer performance is evident in the glaucoma group with the median response being lower in the glaucoma group compared to controls (glaucoma: -12.00 dB / IQR -15.25 to -9.00 dB and control: -14.50 dB / IQR -15.00 to -10.50 dB). In an adjusted ANOVA model to account for covariates, age and average hearing level did not impact upon group performance. No statistically significant main effect was found for stage of disease within glaucoma participants ($F (1, 24) = 0.72$, $p = 0.587$).

See summary box below for results of test-retest variability between Experiment 1 and 2.
Additional analysis: Test-retest variability on amplitude modulation detection

In those subjects that participated in both experiments, a test to assess whether responses varied across temporal amplitude modulation assessments was carried out. For these 25 subjects (48 ears), the distribution of the difference in test 1 and test 2 scores was normal (p=0.100). An ANOVA analysis using the Bartlett’s statistic, showed that the variance between the tests and within the tests were similar (Test statistic = 0.97, p = 0.922). The results for this task were moderate to highly correlated (Pearson’s coefficient = 0.612, p = 0.004). With respect to the distribution of variances, these results imply good test-retest reliability of the task.

However, an observation of the absolute threshold values from test 1 to test 2 showed that 45% of subject ears had identical scores, 48% revealed a decrement in performance (mean -3.59 dB ± 1.30) and 7% showed an improvement in performance (mean -2.17 dB ± 1.44). An adjusted ANOVA model showed no main effect of ear or group (p > 0.05). Given similar performance trends for both glaucoma and control subjects, results suggest a generally negative practice effect.
5.4.3 Frequency Discrimination

Frequency discrimination is a measure of the smallest detectable difference in two frequencies. This ability was measured at low frequencies, reference target at 500 Hz, and at high frequencies, reference target at 4 kHz. The mean group performance for frequency difference limens at 500 Hz was 12.04 ± 8.38 Hz for the glaucoma group and 11.64 ± 5.07 Hz control group (Figure 5.3). The frequency difference limens at 4 kHz were correspondingly 73.48 ± 16.13 and 78.00 ± 25.82 Hz (Figure 5.4). Comparing mean group responses at both reference stimuli was performed using a 2 x 2 repeated measures adjusted ANOVA with reference frequency level as the within subject factor and group as the between subject factor. No significant difference was found between groups across frequencies (F (1, 43) = 0.952, p = 0.355). Average hearing level did not have a significant impact upon group performance however age did interact with frequency discrimination level (F (1, 43) = 5.412, p = 0.025).

As shown in Figures 5.3 and 5.4 (shown separately as different scales), the distribution of scores around the mean group performance was similar between samples. The magnitude of the difference in mean values was similar at both reference limens, namely 5% at 4 kHz (in favour of better glaucoma performance) and 3% at 500 Hz (in favour of better control performance (group difference ÷ control mean). Data for right ears is shown in Appendix 8 and is in contrast to the findings for left ears (trend for poorer discrimination in glaucoma group for 500 Hz).

![Figure 5.3](image_url)

**Figure 5.3:** Individual raw scores with overlying mean (middle interval bar) and standard deviations (upper and lower bars) for frequency discrimination at 500 Hz; glaucoma 12.04 ± 8.38 Hz versus control 11.64 ± 5.07.
Figure 5.4: Individual raw scores with overlying mean (middle interval bar) and standard deviations (upper and lower bars) for frequency discrimination at 4 kHz; glaucoma 73.48 ± 16.13 Hz versus control 78.00 ± 25.82 Hz.

5.4.4 Speech Perception

The median speech perception score was 40% for each group but with a lower interquartile range in glaucoma participants compared to controls; 27-47% versus 37-48% respectively. Despite a broader range of scores in the glaucoma group, no statistically significant difference was found between groups (Krusk-Wallis test: H = 3.21, df = 1, p = 0.073).

However, when considering data in an adjusted model to discern the impact of covariates, the distribution around mean group performance was statistically significant between groups (F (1, 49) = 5.29, p = 0.026). As shown in Figure 5.5, the average speech perception score was lower in glaucoma participants compared to controls, accounting for a 7.05% decline. Furthermore, 9/25 glaucoma ears (36%) fell below the 90th percentile of control performance range (equated to 3/25 control ears) (see Figure 5.6). No significant impact of age or average hearing level was identified in these sample groups.
Figure 5.5: Individual raw scores with overlying mean (middle interval bar) and standard deviations (upper and lower bars) for speech perception in groups at SNR 0 dB; glaucoma 36.48% ± 11.86% versus control 45.53% ± 7.91%.

Figure 5.6: Individual raw scores for speech perception at SNR 0 dB for the glaucoma group highlighting 9/25 (36%) (represented by pink circles) fall outside the lower 90th percentile value of control performance (i.e. <34%).

5.5 Additional analyses

5.5.1 Disease severity in Glaucoma Participants

No significant main effect of stage of disease was found for glaucoma participants on the majority of auditory function tasks. However using an adjusted model, speech perception scores were significantly influenced by stage of disease (F (1, 49) = 2.87, p = 0.034). In support of this finding, increasing disease stage was significantly correlated with decreasing speech perception score in glaucoma participants (rho: -0.346, p = 0.041). No other visual
function indices (mean defect, pattern sensitivity deviation, retinal nerve fibre layer thickness) were found to correlate with auditory outcomes.

### 5.5.2 Inter-ear and inter-eye group comparisons

Given that the majority of glaucoma participants had asymmetrical disease stages between eyes (60%) separate analysis looking at a ratio of performance (best ear/eye ÷ worst ear/eye) was conducted. The mean group ratio was then compared to determine whether the degree of asymmetry varied between groups on select tasks. As shown in Appendix 7, no significant differences were found in the magnitude of inter-ear/eye performance between groups across selected tasks except for auditory speech perception scores. Specifically, glaucoma participants displayed a 32% inter-ear difference in speech recognition compared with 14% in controls (F (1, 48) = 6.69, p =0.013). Despite not reaching statistical significance, observation of the proportion of participants in each group with a difference in ear/eye performance showed that the number was generally higher in the glaucoma group compared to controls for the other tasks.

### 5.5.3 Correlations between auditory tasks

Significant correlations were identified between auditory tasks for both groups with preponderance for stronger correlations in glaucoma participants. In both groups, amplitude modulation thresholds were moderately associated with frequency difference limens at 500 Hz (glaucoma> rho: 0.524, p = 0.012; control> rho: 0.514, p = 0.009 - see Figure 5.6). As shown in Figures 5.7, amplitude modulation detection was also moderately correlated with speech perception ability (rho: -0.478, p = 0.016) in the glaucoma group. In glaucoma participants, average hearing sensitivity threshold moderately correlated with frequency difference limens at 4 kHz (0.517, p = 0.012).
Figure 5.7: Correlation between amplitude modulation threshold (Y axis) and frequency difference limens at 500 Hz (X axis) for the control group in blue, correlation coefficient 0.514, \( p = 0.009 \); and glaucoma group in red, correlation coefficient 0.524, \( p = 0.012 \).

Figure 5.8: Correlation between temporal amplitude modulation threshold (Y axis) and speech perception score (X axis) for the glaucoma group; correlation coefficient -0.478, \( p = 0.016 \).

5.6 Auditory Results Summary

Based on the results to Experiment 2, there is mild evidence for auditory processing disturbances in glaucoma individuals compared to age and gender equivalent controls as reflected by impaired speech perception capabilities under competing noise. The hypothesis of selective auditory processing dysfunction is supported by confirmation of a speech
perception deficit in OAG individuals along with observing a trend in right ears for impaired frequency difference limens at 500 Hz (Appendix 8). Overall, results to this experiment suggest a similar trend to Experiment 1 and further imply that auditory neuronal signal disruption may be specific to tasks requiring a greater degree of temporal processing precision.

5.6 Visual assessment results

The visual baseline characteristics of the samples are shown in Table 5.1. Data represent 25 pairs of left eyes. In subsequent analyses two participant pairs had missing vision data therefore each sample reduced to 23 participants. In addition, two left eyes of two glaucoma participants were excluded from statistical analysis due to central acuity not meeting inclusion criteria and/or visual field loss impacting on central vision within 5 degrees of central fixation. Therefore results from a total of 21 pairs of left eyes are reported with results for 23 pairs of right eyes reported in Appendix 7.

As shown in Table 5.1, visual function measures were significantly poorer in glaucoma participants with the majority of glaucoma participants having minimal or moderate stages of visual field loss (grade 0 = 48% minimal, grade 2 = 20% moderate). Within the control group, 4 participants (16%) had mild patterns of visual field loss consistent with the clinical findings of cataract formation. The median central acuity was 0.04 logMAR units (Snellen equivalent 6/5) in the glaucoma group and 0.00 logMAR units (6/6) in the control group. No significant difference was identified in median central visual acuity between groups (p = 0.477). As previously mentioned, the median values for optic nerve structure and function are as expected for both older, healthy eyes and eyes with early staged glaucomatous optic neuropathy (Blumenthal et al., 2000).

5.6.1 Temporal Contrast Detection

Temporal contrast detection ability was evaluated for two temporal frequencies, namely for a 10 Hz and 30 Hz flickering stimulus. The minimum percentage contrast for 10 Hz stimulus was lower (better) than that for a 30 Hz stimulus for both groups. In the glaucoma group, mean percentage contrast (± standard deviation) for a 10 and 30 Hz stimulus were 1.47% (0.80) and 8.08% (3.93) whilst in the control group they were 1.10% (0.33) and 6.71% (2.73),
respectively. This threshold estimate pattern of a more elevated threshold level with higher temporal frequency is consistent with reported data (Kelly, 1961; Waugh & Hess, 1994).

Examining group performance (converting thresholds into log units) across these two levels was investigated using a 2 x 2 repeated measures ANOVA model. Temporal contrast detection thresholds were found to be significantly different between groups across the two levels \( F(1, 40) = 5.90, p = 0.020 \). In addition, a significant interaction was identified within groups between performance and age \( F(1, 40) = 5.65, p = 0.022 \).

Examining group performance at each individual temporal contrast detection level revealed poorer detection ability in the glaucoma group compared to controls at 10 Hz \( F(1, 43) = 6.78, p = 0.013 \) but similar performance at 30 Hz \( F(1, 43) = 1.31, p = 0.259 \), adjusted for age and vision (see Figures 5.9 and 5.10). Inspection of Figure 5.10 shows one control performer with exceptionally good temporal contrast detection ability at 30 Hz. Removing this result did not change the statistical outcome. These data suggest that contrast detection thresholds are comparable between groups at fast flicker rates but poorer in glaucoma participants at moderate flicker rates. Age was shown to have a statistically significant impact upon group performance at 30 Hz only \( F(1, 43) = 7.58, p = 0.009 \).

![Figure 5.9: Individual raw values with overlying mean (middle interval bar) and standard deviations (upper and lower bars) for temporal contrast detection thresholds at 10Hz; glaucoma -0.21 ± 0.13 and control -0.33 ± 0.15.](https://example.com/figure5.9.png)
Figure 5.10: Individual raw values with overlying mean (middle interval bar) and standard deviations (upper and lower bars) for temporal contrast detection thresholds at 30Hz; glaucoma 0.86 ± 0.13 and control 0.78 ± 0.20.

5.6.2 Speed Discrimination

Speed discrimination ability evaluated the smallest perceivable difference in targets moving at slow and fast velocities, reference speeds 2 degrees per second and 8 degrees per second respectively. The ratio (Weber fraction) of mean performance ± standard deviations for speed discrimination for slow speeds was 0.69 ± 0.28 in the glaucoma group and 0.48 ± 0.15 in controls. For fast speeds, the mean performance ratios were 0.42 ± 0.19 and 0.33 ± 0.14 respectively (see Figures 5.11 and 5.12). The values in the control group are near those reported for older adults using similar methodology (Raghuram et al., 2005; Snowden & Kavanagh, 2006). Using a 2 x 2 repeated measures ANOVA model, performance across reference speeds was significantly different across groups (F (1, 40) = 8.29, p = 0.006). Comparing Figures 5.11 and 5.12 shows a greater difference in mean group performance at slow speeds.
Figure 5.11: Individual raw scores with overlying mean (middle interval bar) and standard deviations (upper and lower bars) for speed discrimination ability for each group, reference speed 2 deg/s; glaucoma 0.69 ± 0.28 versus control 0.48 ± 0.15.

Figure 5.12: Individual raw scores with overlying mean (middle interval bar) and standard deviations (upper and lower bars) for speed discrimination ability for each group, reference speed 8 deg/s; glaucoma 0.42 ± 0.19 versus control 0.33 ± 0.14.

The interaction between speed rate and group was investigated further in separate ANCOVA models which confirmed the difference in group performance was significant at slow velocities, adjusted for age and central acuity (F (1, 43) = 8.29, p = 0.006). Glaucoma group performance remained poorer than controls removing the one glaucoma outlier with a score of 1.73 (see Figures 5.11 and 5.13). Discrimination of faster velocities was found to be similar between groups (F (1, 43) = 2.99, p = 0.092). However a notable proportion of glaucoma participant’s displayed results outside the lower limit (90th percentile) of the range.
in control performance for both reference speeds. Specifically, 9 out of 21 glaucoma eyes (42.86%) for slow speed discrimination and 6 out of 21 glaucoma eyes (28.57%) for fast speed discrimination revealed significant threshold elevations above the 90\textsuperscript{th} percentile for average control discrimination (versus 10% control eyes) (see Figure 5.14). The magnitude of the difference across velocities was also supported by effect size calculation using Cohen’s \( d \) (Cohen, 1988).

Figure 5.13: Individual raw scores with overlying mean (middle interval bar) and standard deviations (upper and lower bars) for speed discrimination ability for each group, reference speed 2 deg/s less one glaucoma outlier; glaucoma 0.64 ± 0.17 versus control 0.48 ± 0.15.

Figure 5.14: Individual raw scores for glaucoma participants for speed discrimination at 2 deg/s highlighting a proportion of eyes, 9/21 (42.86%) (pink circles), fall outside the upper limit of control range performance (90\textsuperscript{th} percentile value equating to >0.68 Weber Fraction).
### 5.6.2.1 Effect size for speed discrimination performance across tasks

Using the means and standard deviations for each group at each reference speed level, an estimate of effect size was calculated (Cohen, 1988). Table 5.3 illustrates and confirms the magnitude of the group difference for speed discrimination at slow velocities was larger than at fast velocities. For the glaucoma group, the ‘large’ effect size 0.85 indicates the mean is located around the 80th percentile of the control group distribution with 49.5% of non-overlapping group values (Cohen, 1988).

Table 5.3: Cohen's effect size calculation for speed discrimination at two levels across groups.

<table>
<thead>
<tr>
<th>Reference Speed (deg/s)</th>
<th>Glaucoma N=23</th>
<th>Control N=23</th>
<th>Cohen's d</th>
<th>Effect size correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± standard deviation (Weber Fraction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.00</td>
<td>0.69 ± 0.29</td>
<td>0.49 ± 0.16</td>
<td>0.853</td>
<td>0.393</td>
</tr>
<tr>
<td>8.00</td>
<td>0.43 ± 0.20</td>
<td>0.33 ± 0.14</td>
<td>0.579</td>
<td>0.278</td>
</tr>
</tbody>
</table>

Key: Deg/s = degrees per second. Note: Calculations made using an online calculator. URL: http://www.uccs.edu/~faculty/lbecker/

### 5.6.3 Coherent Motion Detection

Global motion detection is a higher order temporal processing visual task and within this study was estimated based on the smallest number of targets required to perceive coherent motion. Median coherent motion detection thresholds were 26.50% (IQR: 16.75% - 33.94%) in the glaucoma group and 20.88% (IQR: 15.94% - 28.88%) in the control group. As illustrated in Figure 5.15, global motion threshold performance was statistically poorer in the glaucoma group (Kristal Wallis test: H = 4.32, df = 1, p = 0.040) and remained poorer following adjustment for age and central acuity (F (1, 42) = 5.69, p = 0.025). In the glaucoma group, 5 out of 21 (23.81%) exhibited significant threshold elevations above the 90th percentile for the median control score (also same % for confidence limit of control mean).
5.7 Correlations between visual tasks

Few correlations were identified between visual tasks with the significant correlations isolated to performance on temporal contrast detection for both groups. Specifically, log temporal contrast detection at 10 Hz was found to be correlated strongly with speed discrimination at slow velocities for both groups (glaucoma: rho 0.940, p = 0.000; control: rho 0.978, p = 0.000). However no significant correlations were identified between log temporal contrast at 30 Hz and speed discrimination at faster velocities for either group.

No significant correlations were identified between visual function indices (mean defect, pattern sensitivity deviation and average retinal nerve fibre thickness) and any visual processing measure. Nor were any significant performance relationships identified between tasks that were statistically significantly different that is speed discrimination at slow velocities and coherent global motion detection (glaucoma: rho 0.201, p = 0.395; control: rho 0.289, p = 0.191). Despite this result it was observed that within the glaucoma group, 3 out of the 11 participants (27.27%) revealed both abnormal slow speed discrimination and global coherent motion detection above the 90th percentile limit for control range performance.

5.8 Visual Results Summary

Based on the results to Experiment 2, there is strong evidence to suggest that glaucoma participants have poorer visual temporal processing compared to age and gender equivalent controls. This was exemplified for tasks requiring a high degree of temporal precision such
as speed discrimination and global motion detection. Furthermore, these tasks were conducted stimulating central (foveal) retina or areas found to demonstrate normal central acuity and flicker sensitivity on visual field testing. Thus findings for glaucoma subjects suggest perceptual deficits in visual neural signaling occurring along the visual pathway to the visual cortex. Results were gathered from sample sizes below target however there was still statistical evidence of impairment to visual temporal processing in glaucoma subjects.

5.9 Correlations between auditory and visual tasks

The design of the study was such that levels of temporal processing, from low to high (more complex), were examined in both the auditory and visual systems. Correlations between the temporal processing levels, for example between auditory frequency discrimination and visual speed discrimination tasks, were not significant suggesting relative independence of temporal processing between the two sensory systems. Observation of the data supported these findings with no clear trends between poor performing ears with poor performing eyes. However, all participants with abnormal results had at least 1 abnormal result in both auditory and visual testing such that those with impaired speech perception had either impaired coherent global motion or impaired speed discrimination. Overall, within the total sample of glaucoma participants, 5 revealed poorer speech perception scores, 11 had elevated slow speed discrimination ability and 5 had elevated coherent motion detection thresholds compared to controls.

An association between eye and ear performance was also approached from examining any relationships between right and left sides. In line with the current study hypothesis of a central susceptibility to neural disturbance in both visual and auditory systems, it may be anticipated that it would be more likely to witness contra-lateral patterns over ipsi-lateral patterns in poor performance. To explore this further, background evaluation was made using two sensory comparisons to explore the potential of an association between ear and eye function. From results in Appendix 7, comparison of average hearing level and stage of disease in the glaucoma group showed a trend for contra-lateral performance matching right ear and left eye and vice versa. Of note was in conjunction with this contra-lateral sensory function trend, a notable proportion of the glaucoma group had poorer left ear hearing matched with more advanced disease in their left eyes. With respect to the control group, most had comparable visual function stage (as expected) that was matched with poorer hearing in the left ear.
Overall, findings suggest no definite patterns in eye-ear associations however most glaucoma participants have greater asymmetry in sensory function between right and left sides compared with controls but this trend did not reach statistical significance. Taken together, auditory and visual temporal processing impairment is concurrent in a significant proportion of glaucoma participants with the pattern of disruption, or the specific tests that reveal an abnormality, varying between individuals. Performance on auditory processing tasks is not predictive of performance on visual processing tasks, or vice versa.
Chapter 6 : Discussion of findings

6.1 Auditory temporal processing

To my knowledge, this is the first study to examine auditory processing ability in patients with glaucoma. It was demonstrated that auditory processing performance correlated strongly across functional measures for both groups. Despite finding that the majority of participants in both groups had comparable test results for both experiments, a higher proportion of the OAG group fell outside the upper limit of the control performance on select tasks. The results obtained for this sub-group of glaucoma participants broadly fit with the pattern of responses expected in support of the hypothesis that some individuals may be more susceptible to auditory dysfunction than others of a similar age and this may reflect an underlying increased vulnerability of their central nervous system to stress and injury.

Similar auditory brainstem response (ABR) measures were identified between groups in this study. Absolute latencies for ABR waves I and III were close to identical between groups but a trend for a mild delay in wave V was found in the glaucoma group but this was not statistically significant. As a result of the trend in wave V, the overall neural conduction time reflected by the wave I-V interpeak interval was longer in the glaucoma group compared to controls. As with previously reported literature, a delay in the interpeak latency between waves I-V is particularly suggestive of a central lesion affecting the auditory pathway (Chiappa, 1982; Starr & Achor, 1975; Starr et al., 2000). However, results for this task do not clearly demonstrate abnormal ABRs in the majority of glaucoma participants. There was a sizable proportion, 26.2%, of OAG individuals who displayed a greater delay in their interpeak conduction time outside the upper limit (90th percentile) of the control range performance who were among the group who subsequently were identified to have auditory processing difficulty on other functional measures.

Previous research has shown correlations between ABR abnormalities and disruptions to auditory neural temporal processing (Rance et al., 2004; Starr et al., 1991; Zeng et al., 2005). In support of these reports, significant relationships between amplitude modulation detection and ABR interpeak latencies were identified in both groups. Elevated amplitude modulation detection was uncovered in a significant proportion, 28.5%, of OAG individuals in the first experiment. Compared to controls and other members of the OAG cohort,
impaired amplitude modulation detection in these OAG individuals suggests that they possess a poorer ability in recognizing the temporal aspects of a modulated sound signal. Specifically, as highlighted in the first experiment involving the larger samples, the glaucoma group overall required a larger amplitude modulation depth to detect a difference in the signal level, namely 25.12% compared to 18.84% in controls. Performance on this task is influenced by how effectively the auditory system can produce a high level of dynamic temporal precision in encoding envelope changes cycling at a rate of 6.7 milliseconds. Therefore findings suggest that a proportion of glaucoma individuals have auditory neurons that are less efficient in executing fine temporal processing.

These findings confirm previous reports examining auditory processing function in older adults and suggest that alterations in temporal acuity (or temporal resolution ability) may occur independently of age-related hearing loss and age-related auditory function decline in individuals suspected of having central auditory processing dysfunction (Fitzgibbons & Gordon-Salant, 1996; Gordon-Salant & Fitzgibbons, 1993; Humes & Christopherson, 1991; Schneider & Hamstra, 1999). In other words, individuals with temporal processing impairment within their auditory neural pathway display relatively intact loudness discrimination, pitch discrimination at high frequencies and sound localization but impaired perception relating to the timing of auditory cues. Examples of this processing error in perceiving temporal information include poor gap detection, temporal modulation detection, low frequency discrimination and signal detection in noise (Zeng et al., 2005; Zeng et al., 1999). A critical functional consequence linked with having auditory temporal processing impairment is difficulty with speech understanding. As was shown in the current study, the severity of the temporal processing abnormality found in amplitude modulation detection strongly correlated with speech perception ability in OAG individuals. This supports previous research correlating various functional measures, including speech perception, in patients suspected of having auditory neural temporal processing deficits (Rance, 2005; Rance et al., 2004; Zeng et al., 2005).

A proportion of OAG individuals were found to have poorer speech perception abilities compared to age equivalent controls in Experiment 2. Namely 36% (9/25 ears) of the glaucoma participants displayed speech recognition scores outside the lower limit of the control performance range (90th percentile) when the signal in noise ratio was 0 dB. However this finding was not similarly evident in Experiment 1, despite the same
experimental task and samples involving larger numbers of participants. This inconsistency in speech perception results is surprising given that both the glaucoma and control samples, across experiments, were independently similar in age, hearing sensitivity and average temporal processing ability (as determined by amplitude modulation detection). One possibility for these findings may have been that the testing conditions were not identical between experiments. Specifically, whilst testing for both experiments was conducted under non-sound proof conditions, the levels of background noise or extraneous masking variables during testing may have varied given the different testing sites used. Despite these procedural differences, if the results are combined from both experiments (n=67) the data support a trend toward a higher number of glaucoma participants having speech perception scores that fall outside the 90th percentile of the control range performance (12/67 glaucoma ears (18%); t (1, 66) = 1.72, p = 0.08).

Speech perception is a dynamic task that is reliant on multiple sources of signal information and processes including adequate auditory temporal processing ability (see review (Moore, 2008) (Bailey & Snowling, 2002; Kral, 2000). For instance, extracting the temporal information in running speech allows the listener to discriminate rapid changes in amplitude and frequency and better interpret speech units such as phonemes and syllables (Rance et al., 2004). It has been shown that speech perception deficits frequently emerge in individuals with central auditory processing dysfunction (Rance, 2005; Rance et al., 2007; Zeng & Liu, 2006; Zeng et al., 1999). Recently a few investigators have shown speech understanding difficulties in patients with Friedreich’s ataxia (FRDA), an inherited motor and sensory neuropathy associated with both visual and auditory impairments (see review (Delatycki et al., 2000).

Studies have shown that individuals with FRDA display variable degrees of central processing abilities in their auditory systems (Amantini et al., 1984; Lopez-Diaz-de-Leon et al., 2003; Rance et al., 2010a; Rance et al., 2008). Specifically, some less affected FRDA patients may have normal ABR potentials but poor speech discrimination, most marked under competing background noise (Rance et al., 2008). In comparison, more affected FRDA individuals reveal severe speech perception deficits in conjunction with strikingly abnormal or absent ABR recordings (Rance et al., 2010a), hallmark signs of auditory neuropathy / auditory dysynchrony (AN/AD) (Berlin et al., 2003; Starr et al., 1996). Evidence for AN/AD was not specifically found in the current study, however comparing results to the research
performed with FRDA individuals provides insight into the progressive nature of mild to severe auditory central processing dysfunction. Of note, in the current study a correlation between stage of disease and speech perception ability in glaucoma subjects was found. However, to draw conclusions regarding the impact of stage of glaucomatous disease on auditory dysfunction, a study involving a larger number of individuals with advancing disease would need to be considered.

The speech perception deficit uncovered in a proportion of OAG individuals was evident under exigent listening conditions that replicate everyday listening conditions (Crandell & Smaldino, 2000). Whilst the mechanisms underlying the impact of noise on speech perception are not reportedly clear, there is strong evidence suggesting individuals with auditory neural deficits are particularly affected by simultaneous noise masking or when the stimulus and noise are presented at the same time (Kraus et al., 2000; Lorenzi et al., 2009; Zeng et al., 2005). Specifically, in ears with compromised auditory temporal processing function, auditory neurons are less efficient in discriminating differences in temporal cues under simultaneous noise conditions. Given that levels of background noise fluctuate in everyday listening conditions, it may be likely that speech perception deficits shown here in select OAG participants are exacerbated in instances where multiple noise distracters are present and the reliance on temporal processing mechanisms is heightened. However, it is also likely that OAG individuals will show varying degrees of ‘real life’ difficulty in understanding speech in noisy environments given the individual differences in using the many cues that assist speech perception (Massaro, 1974).

There are a number of experimental procedures that can be employed to explore the functions that support speech and auditory perception including techniques that exploit fine auditory temporal processing mechanisms (Fitzgibbons & Gordon-Salant, 1996). Among these techniques are tests to assess frequency discrimination ability. In the current study frequency discrimination ability was conducted to evaluate how well auditory neurons capture the temporal aspects of a signal through ‘phase locking’ capabilities at low frequencies (Malone et al., 2010; Moore, 1973). Specifically, discrimination of frequencies less than 4 kHz is contingent upon auditory neurons reflecting the timing of the signal in the pattern of neural firing (Sachs & Young, 1979). In contrast to the study hypothesis, glaucoma participants in Experiment 2 did not reveal poorer frequency discrimination for difference limens at 500 Hz compared to controls. This suggests that groups had
comparable and adequate ‘phase-locking’ ability to allow the resolution of small
discriminate changes for frequencies cycling around 2 milliseconds. Overall, frequency
discrimination for both low and high frequencies were similar between study groups which
likely explains the absent relationship between speech perception ability and frequency
discrimination in glaucoma participants for Experiment 2.

Results to this point suggest that not all auditory functions requiring adequate temporal
processing ability were impaired in the glaucoma cohort (across experiments). Within both
study groups a proportion of participants displayed performance that was outside the
central tendency but with a trend for a higher number in the glaucoma group on tasks
requiring high temporal resolution. Overall, the data suggests a mild deficit in auditory
temporal processing in individuals with OAG who have normal to near normal sound
detection thresholds. The clinical implications of the auditory findings suggest that whilst
not every patient with OAG should be referred for audiometric assessment, central auditory
dysfunction needs to be ruled out in those patients complaining of poor hearing or difficulty
hearing especially out in public arenas. Standard audiometric protocols are based on
detecting sound which is an inappropriate test for investigating auditory central processing
dysfunction as highlighted in this study and others (Rance, 2005). Therefore assessments,
such as speech understanding in noise, which are not routine tests, would be recommended.

Like the auditory system, the visual system has temporal processing strategies (Eagleman et
al., 2005). The correspondence between how the auditory and visual systems handle
temporal information was examined specifically in Experiment 2. This part of the study
explored the hypothesis that highly active neurons in both visual and auditory systems may
show signs of functional deficit if they are particularly vulnerable to shared centralized
stressors. Damage to the temporal properties of visual perception have been shown to
result from early retinal ganglion cell injury (Yucel et al., 2003) and this implies that temporal
processing and integration pathways are particularly vulnerable to damage in glaucomatous
optic nerve injury (Breton et al., 1991; McKendrick et al., 2004; McKendrick et al., 2005;
Trick, 1985; Tyler, 1981)

6.2 Visual temporal processing

To evaluate generalized temporal processing impairment in glaucoma patients this study
was designed to assess visual perceptual function in an analogous and hierarchical manner
to auditory perceptual function. Evidence of visual pathway processing dysfunction was identified in a significant proportion of the OAG cohort on tests that selectively assessed neural processing following stimulation of the central (foveal) retina. In the context of normal foveal visual function (optimal visual acuity and intact central visual field) results for a subgroup of glaucoma participants suggest a disruption of central processing streams. This disruption was shown across psychophysical tasks exploring stages of visual temporal processing.

In the presence of normal high contrast foveal visual function, glaucoma participants overall were found to have impaired low level, or early neural pathway, temporal processing function. This was reflected by poorer average temporal contrast detection at a 10 Hz flicker rate in glaucoma participants compared to control counterparts. This finding supports previous studies showing that disrupted foveal contrast sensitivity functions are frequently observed in early glaucoma (Ansari et al., 2002; Battista et al., 2009; Hawkins et al., 2003; McKendrick et al., 2004; McKendrick et al., 2007). In opposition to these results were the outcomes obtained for temporal contrast detection for a 30 Hz flicker stimulus. As expected both groups had increased difficulty with contrast detection at a higher flicker rate of 30 Hz compared to a 10 Hz flicker rate but unexpectedly groups had generally comparable performance at the former level. Indeed any differences observed in contrast detection at 30 Hz were found to be attributable to age, namely the observation of poorer performance in older participants within groups, and not the presence/absence of glaucoma per se. The decline of spatial and temporal contrast ability at the fovea with increasing age in itself was not a surprising finding (see review (Spear, 1993) (Zhang et al., 2008).

Poor performance on temporal contrast detection strongly correlated with poor performance on speed discrimination. For example, those OAG individuals with impaired temporal contrast detection at 10 Hz were more likely to also show impaired speed discrimination for slow velocities (2 deg/s or 4 hertz) compared to controls. With regard to speed discrimination for slow velocities it was found that, on average, glaucoma individuals required a 17% greater inter-velocity difference between targets than controls to perceive a difference in temporal motion rates around 4 Hz. The capacity to discriminate targets moving at faster speeds did not seem to be any less for glaucoma participants than that displayed by controls with similar speed discrimination abilities for targets moving around 16 hertz.

82
This later finding is in contrast to the study hypothesis which postulated that eyes with visual temporal processing disruption would manifest impaired speed discrimination for faster velocities in line with requiring a higher degree of temporal resolving power. In effect this was not shown however these findings raise the question regarding the sensitivity of this temporal processing task. Firstly, it may be argued that performance was influenced by test stimulus duration. Namely, the stimulus duration adopted was brief (500 ms) thereby restricting the length of time permitted to detect and encode motion cues. Stimulus duration impacts upon the motion energy generated from spatial and temporal aspects of a stimulus. With this in mind less motion energy is produced in a 4 Hz drifting stimulus than a 16 Hz drifting stimulus within 500ms if the spatial properties are the same (Adelson & Bergen, 1985; Smith & Ledgeway, 2001). As a result, if select glaucoma eyes have decreased sensitivity to motion, a short stimulus presentation may have restricted the interval in which enough information could be accumulated to assist with discrimination of the slower moving stimuli. Alternatively, given that the faster stimulus was more suprathreshold in terms of motion energy, it would be anticipated that subjects temporal sensitivity was less affected by the stimulus presentation interval (Adelson & Bergen, 1985).

Another possible explanation for the speed discrimination patterns observed in groups may be related to the spatial characteristics of the stimulus. This second argument surrounds the notion that the perception of faster moving stimuli is enhanced by spectral contrast cues, namely by the apparent narrowing and dimming of stimuli with increasing speed (on par with the frequency doubling illusion) (Fredericksen & Hess, 1999; Hess & Plant, 1985). If this were the case then the results may in fact indirectly support the hypothesis where perception of slow moving targets is purely reliant on temporal processing in the absence of other perceptual speed ‘clues’. Thus assessing visual discrimination of slow velocities may be a more sensitive test to isolate temporal processing mechanisms involved in the perception of speed.

The pattern of speed discrimination ability, specifically reduced sensitivity with decreasing speed demonstrated by both groups, has been shown in previous studies involving older adult based populations examining speed discrimination behavior (Raghuram et al., 2005; Snowden & Kavanagh, 2006). Results also support the principal observation of a reduction in visual performance the closer the discriminatory task is to threshold perception for glaucoma individuals (McKendrick et al., 2005; McKendrick et al., 2010). However, despite
the current study highlighting these speed-performance patterns, the actual speed discrimination threshold estimates for both study groups at each of these rates are considerably more elevated than those reported by Raghuram et al. (Orban et al., 1984; Raghuram et al., 2005). Whilst the stimulus design for the current study was based on Raghuram et al. (2005) the threshold algorithm was different. As a result, expected differences in threshold estimates were observed relative to the underlying point on the psychometric curve function being assessed.

In conjunction with impaired speed discrimination, a significant proportion of OAG individuals displayed impaired coherent motion detection compared to controls. With respect to foveal motion sensitivity in OAG participants, these findings broadly support a number of studies suggesting that glaucoma development produces early impairment in coding temporal cues for motion detection (Bullimore et al., 1993; Silverman et al., 1990; Trick et al., 1995; Wall & Ketoff, 1995). However directly comparing results across studies is difficult owing to different experimental procedures triggering different receptors for motion sensitivity and neural mechanisms responsible for visual temporal and motion processing. Experimental procedures for global motion detection in the current study were adopted from McKendrick et al. (2005). Specifically the previous study found that overall coherent global motion detection was impaired in the periphery in their glaucoma subjects whereas the current shows impairment in the foveal region.

Pooling results, the current study found evidence of central visual pathway disruption characterised by neural temporal processing impairment in a proportion of OAG individuals. Specifically in the setting of normal retinal visual field sensitivity, impairments in foveal temporal contrast detection, slow speed discrimination and coherent motion detection were identified in a group of OAG individuals. Given the hierarchical nature of the experimental protocol, these results also suggest that evidence of neural pathway disruption can be reflected on tasks exploring various stages of visual processing from fovea to cortex. Collectively findings support previous studies that suggest deficits in visual temporal processing can manifest from retinal areas with normal visual function capacity as measured on standard automated perimetry (McKendrick et al., 2004). This is of particular significance as it would be expected that a greater impairment in temporal processing ability would arise from areas of the retina undergoing visual field loss. Therefore by highlighting evidence of neural processing dysfunction along the visual pathway emanating from the central retina
(area spared of retinal visual function loss), this study is better poised to support the hypothesis that neural processing deficits found in glaucoma may be due to a more widespread centralized nervous system vulnerability to dysfunction.

Complex neural functions such as temporal processing are difficult to localize in any sensory domain, including visual and auditory, owing to the lack of a specific cortical area in the brain responsible for decoding and processing temporal properties of sensory stimulation (Eagleman et al., 2005; Mauk & Buonomano, 2004). However within the visual system, a number of key cortical areas have been identified that contribute to the overall perception of visual temporal information. The visual tasks chosen predominately targeted the M pathway to the level of the LGN. This pathway is particular sensitive for coding temporal frequency and motion signals to the visual cortex (see review McKendrick & Johnson, 2011). However both M and P pathways are involved in transmitting temporal frequency and motion signals with neural channels converging and communicating within and beyond the primary visual cortex (Andersen et al., 1990; Maunsell & Newsome, 1987; Maunsell et al., 1991; Merigan & Maunsell, 1993; Merigan et al., 1993). Rather than implying selective M and P cell neural loss or implicate specific cortical regions, results suggest disrupted visual processing within cortical neural circuits involved in visual temporal processing.

The design of Experiment 2 was such that levels of temporal processing, from low to high (more complex), were examined in both the auditory and visual systems. Correlations between the temporal processing levels, for example between amplitude modulation detection and visual speed discrimination tasks, were not significant suggesting relative independence of temporal processing between the two sensory systems. Observation of the data supported these findings with no clear trends between poor performing ears with poor performing eyes however all participants with abnormal results had at least 1 abnormal result in both auditory and visual testing. Taken together, auditory and visual temporal processing impairment is concurrent in a significant proportion of glaucoma participants with the pattern of disruption, or the specific tests that reveal an abnormality, varying between individuals.

One interpretation of these findings may be that different cortical sites and mechanisms, other than temporal processing, are likely to contribute to the results. The finding of concurrent but asymmetrical visual and auditory temporal processing impairment in a
proportion of OAG individuals may suggest a common, albeit disproportionate, mechanism affecting visual and auditory ganglion cells. It may be postulated, for example, that neural firing patterns may be affected by the spread of neurodegeneration via transsynaptic processes such as through synaptic deactivation and neurotransmitter substance loss; processes implicated in the spread of dysfunction in other CNS based neurodegenerative conditions (Scheff et al., 1993; Stevens et al., 2007).

Alternatively, results may simply demonstrate that psychophysical evidence of neural temporal processing loss varies between glaucoma participants and performance on one task is not predictive of performance on other tasks for all owing to individual variations in the capacity of neurons to met neural processing demands (Sample et al., 2000a) or differences in limits of neural redundancy (Johnson, 1994). To support this, no phenotypic or historical factors could be identified that united those glaucoma participants who performed less well than other glaucoma participants in the study such as average retinal nerve fibre layer thickness, number and type of glaucomatous risk factors, degree of visual field loss, age, years on medical treatment or baseline IOP. Overall, performance on auditory processing tasks was not predictive of performance on visual processing tasks, or vice versa.
Chapter 7: Conclusions

This study showed that a mild impairment exists within neural temporal processing, in both the visual and auditory systems in individuals suffering from OAG. The extent and nature of this sensory impairment was found to be much greater than that which occurred in individuals not suffering from OAG. The deficits, in relation to visual processing, predominantly showed signs of weakened speed detection when tested at slow rates, and a reduced ability to detect global motion coherence; whilst those associated with auditory processing, showed that both the ability to detect amplitude modulation and to recognise speech whilst under challenging listening conditions was found to be greatly impaired. Given that neural processing deficits were uncovered in the presence of intact peripheral sensory receptor function, namely normal ‘seeing’ foveal retina (optimal visual field sensitivity) and normal ‘hearing’ cochlea (standard sound detection sensitivity), deficits observed suggest the possibility of a central systemic neuronal impairment. Given that there was no correlation between auditory and visual impairment in those affected, results may suggest generalised systemic neuronal vulnerability to injury from quite possibly different mechanisms.

The current study highlights the use of assessing a range of visual and auditory temporal processing tasks to explore whether sensory neural deficits exist and if present, whether it's specific to low, intermediate or high level processing areas within their respective neural pathways. This addresses the finding that among OAG individuals with generally early staged disease, a variety of perceptual deficits and combinations of processing deficits can be detected. Also it allows consideration of whether neural disruption or damage is either local or more generalized accounting for the different pathway mechanisms that handle fine and gross temporal cues in both visual and auditory systems. With regard to glaucoma disease monitoring (e.g. for progression) these tests would need to be repeated on a larger sample of patients with and without glaucoma to ensure they had low test-retest variability.

Overall the current study suggests the potential of generalized neural processing impairment outside the visual pathways in individuals with glaucoma on functional measures without recourse to the underlying cause. The presence of both auditory and visual processing dysfunction supports the hypothesis that in some susceptible individuals a proportion of nerves within their CNS are particularly vulnerable to damage from any number of factors,
the functional consequences of which are varied and may represent innate differences in neural resilience or redundancy against injury.

7.1 Major Limitations

To date the research exploring auditory problems in glaucoma individuals has focused on whether there is an accelerated loss of hearing at the cochlear level. The reported results thus far have been equivocal with consensus confined to cases of secondary types of open angle glaucoma with a known systemic aetiology (Aydogan Ozkan et al., 2006; Detorakis et al., 2008; Kremmer et al., 2004; Shapiro et al., 1997). The current study selected all participants on the basis of self reported normal hearing and they were subsequently included in the study if their average hearing level threshold was less than 30 dB. This selection bias, in conjunction with the non-random selection of OAG participants, reduces the generalisability of results to the entire OAG population at large. It is for these reasons that comments regarding the prevalence of hearing loss in open angle glaucoma patients cannot be made on the basis of findings from this study albeit to report the novel findings that without evidence of overall hearing impairment, a proportion of glaucoma patients do show specific signs of mild auditory neuropathy.

Other limitations in this study include missing visual psychophysical data which could have lead to some of the statistical analyses being underpowered to find a difference in the central tendency between groups. In addition, as this was a cross sectional based study no conclusions can be drawn regarding any variation in the degree or rate of change in sensory processing disruption. Lastly, the degree to which current findings relate to ‘real world’ experiences may be limited due experimental procedures being conducted unilaterally rather than in conjunction with bilateral testing.

7.2 Future directions

The current study could lead to several key directions for future research. Firstly, it highlights the areas for more appropriate management of glaucoma patients who do display temporal processing impairment. With respect to vision, it may suggest further study examining the impact of impaired speed and global motion detection on perceptual judgments that underpin everyday activities such as navigation and driving. With respect to auditory function, it may suggest methods to improve language and speech perception ability in noisy environments such as enhancing lip reading skills.
Secondly, this was a cross sectional study so conclusions relating to temporal recovery ability of visual and auditory neurons cannot be made. This would be an area for further research which, through a prospective and longitudinal study, could address questions regarding the prospect of sensory neural plasticity and recovery over time given the research done in perceptual learning in adults (see reviews (Gilbert et al., 2009; Moucha & Kilgard, 2006; Pienkowski & Eggermont, 2011)).

Thirdly, this study raises the question regarding which test is the most sensitive in uncovering sensory temporal processing impairment. Sensory evoked potential measures are gaining increasing interest in neurological diagnosis and management (Mastaglia & Carroll, 1982). In particular, a great deal of research has been conducted in examining visual evoked potentials (VEP) in ocular disease and in individuals suspected of other central nervous system pathology (Halliday, 1981; Halliday et al., 1973; Shahrokhi et al., 1978). Pattern VEP has been particularly useful in detecting early glaucomatous change (Bach, 2001; Bach et al., 2006) and assessing whether results on this measure correlate with auditory evoked potential findings in glaucoma suspects may strengthen the argument pertaining to a widespread disturbance of neural signaling efficiency within the CNS.

Utilizing the most sensitive and most appropriate measure of sensory temporal processing is critical. To explore fine auditory temporal processing further an examination of harmonic tone testing could be considered. This testing has been shown to assess the sensitivity of auditory neurons in detecting complex tones and discriminating temporal fine structure at high frequencies (Moore et al., 2006b). Analogous in the visual system, further investigation into the temporal dynamics may be gained from exploring speed discrimination ability in more detail, such as testing peripheral retina. This is especially constructive given the previous literature that suggests peripheral RGCs are more susceptible to damage before more centrally located cells (Burgoyne et al., 1995; Yan et al., 1994).

Lastly, this study creates a platform from which to consider whether functional deficits in neural responsiveness to fine temporal features of auditory and visual stimuli are primarily caused by a glaucomatous process or whether there are secondary to a fundamental vulnerability within the central nervous system to injury. Localizing and quantifying the changes anatomically would provide physiological evidence to support pathogenic mechanisms and this may be assisted by combining psychophysical testing with functional magnetic imaging.
Overall this research study has paved a new direction in which to investigate the provenance of other non-visual sensory deficits in glaucoma and in doing so has attempted to broaden the understanding behind the pathophysiology of glaucoma within the central nervous system. Ultimately work in this direction will allow greater insight into whether glaucoma is a multisensory disease which ultimately may direct more specific intervention strategies.
Chapter 8: References


Shatz, C. J. (1997). Form from function in visual system development. *Harvey Lect* 93, 17-34.


APPENDIX 1

Example of Audiogram assessment form
APPENDIX 2

Conversion dB to %

Hugh McDermott’s Formula:

\[ P = 10^{\frac{dB}{20}}, \]

where \( P \) is the proportion, which can be expressed in %, and dB is the dB value.

The \(^\wedge\) means to-the-power-of.

Thus -27dB gives 4.47%.

<table>
<thead>
<tr>
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<th>AM%</th>
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<td>-3</td>
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</tr>
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<td>-33</td>
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Reference: (McKay & McDermott, 1998)
APPENDIX 3

Consonant-Nucleus-Consonant Word list

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<tr>
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<th>r</th>
<th>i</th>
<th>p</th>
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<td>b</td>
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<td>BALL</td>
<td>b</td>
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</table>

Word score = /50 = ____________
Phoneme score = /150 = ____________
Vowel score = /50 = ____________
Consonant score = /100 = ____________
**APPENDIX 4**

Key Findings from Pilot testing of Psychophysical Vision Model
N = 8 subjects, Mean age 36 years ± 10.6 years

<table>
<thead>
<tr>
<th>Vision Protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Temporal Amplitude Detection</td>
<td></td>
</tr>
<tr>
<td>Hertz (Hz)</td>
<td></td>
</tr>
<tr>
<td>Minimum contrast detection at specified temporal frequencies.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image1" alt="Scatterplot of temporal amplitude threshold at various frequencies" /></td>
<td>Monocular psychometric function curve for a normal adult shown. As temporal amplitude increases the contrast threshold is elevated.</td>
</tr>
<tr>
<td>2. Temporal Amplitude at select frequencies</td>
<td></td>
</tr>
<tr>
<td>Contrast threshold detection when using a flickering patch at 10Hz and 30Hz.</td>
<td></td>
</tr>
<tr>
<td><img src="image2" alt="Dotplot of 10Hz and 30Hz temporal contrast thresholds; N = 8" /></td>
<td>I will assess contrast thresholds at two temporal frequencies, 10 Hz and 30 hertz. Data involving 8 normal adults confers with reported literature that contrast detection is 1% for 10 Hz stimulus and 5% for a 30 Hz stimulus for normal adults (Tyler, 1989; Tyler, 1991).</td>
</tr>
</tbody>
</table>

120
### 3. Speed Discrimination

The minimum perceivable difference in speed (%) of two moving targets.

Two testing conditions: speed discrimination thresholds under slow and fast speeds.

Deg/s = degrees per second

Foveal speed discrimination thresholds are around 3% for target gratings with a reference speed of 2 deg/s and around 10% for target gratings with a reference speed of 8 deg/s. This pilot data confers with reported literature in normal adults for slow and fast speeds (Lakshminarayanan et al., 2005; Raghuram et al., 2005). Temporal sensitivity is homogenous across the retina and to account for likely differences in visual field losses, central testing will be performed.

### 4. Global Motion

Measuring the minimum number of dots (%) required to detect coherent motion.

Target is 100 white dots on black background

Global motion detection for high contrast stimuli was 16% ± 5.4% in the pilot group. This is close to reported normal foveal thresholds for younger and older adults in the literature which is between 10%-20% and 10-30% respectively (Ellemberg et al., 2004; McKendrick et al., 2005).

<table>
<thead>
<tr>
<th>Velocity of 1st and 2nd grating</th>
<th>% difference in velocity detected</th>
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</thead>
<tbody>
<tr>
<td>2-16</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td></td>
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<td>2-8</td>
<td></td>
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<tr>
<td>8-16</td>
<td></td>
</tr>
<tr>
<td>8-32</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dotplot of speed discrimination thresholds across a range of velocities</th>
</tr>
</thead>
</table>

(Figure from McKendrick et al, 2005 reprinted with permission)

The results show the dotplot of speed discrimination thresholds across different velocities.
APPENDIX 5: Background analyses for Experiment 1

A ratio (best ear ÷ worst ear) of performance was conducted to explore the degree to which right and left eye performance compared for each subject with 1.0 representing no difference in performance and < or > 1.0 indicating a difference. A ratio less than 1.0 is generated when a lower numerical outcome variable, closer to 0, signifies better task performance and vice versa. The rationale behind this analysis was to determine whether the degree of asymmetry varied between groups on select tasks.

Table 5.1 Examination of symmetry ratio of performance between right and left ears across groups; n = 42.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glaucoma</th>
<th>Control</th>
<th>P Value†</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean ± standard deviation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4FA</td>
<td>0.85 ± 0.14</td>
<td>0.83 ± 0.11</td>
<td>0.541</td>
</tr>
<tr>
<td>TAM</td>
<td>1.26 ± 0.28</td>
<td>1.21 ± 0.24</td>
<td>0.529</td>
</tr>
<tr>
<td>ABR wave V</td>
<td>0.97 ± 0.03</td>
<td>0.98 ± 0.03</td>
<td>0.475</td>
</tr>
<tr>
<td>ABR wave I-V</td>
<td>0.95 ± 0.04</td>
<td>0.97 ± 0.02</td>
<td>0.029*</td>
</tr>
<tr>
<td>Speech 0 SNR</td>
<td>1.24 ± 0.36</td>
<td>1.27 ± 0.30</td>
<td>0.800</td>
</tr>
</tbody>
</table>

Key: †One-way ANOVA; * Significant at p>0.05; TAM = temporal amplitude modulation, 4FA = 4-frequency average hearing level, ABR = auditory brainstem response, SNR = signal to noise ratio.

Comments:

No significant differences are evident between overall ear performances across the majority of tasks between groups. However, glaucoma participants had a slightly higher proportion of asymmetrical ABR interpeak latency ability with a tendency for right ears to be more prolonged than left ears.

As highlighted above, both groups had a trend for asymmetrical average hearing levels and temporal amplitude modulation detection. However the degree of asymmetry was found to be greater in the glaucoma group. Consequently analyses were conducted to explore the strength of the relationship between the ears of glaucoma participants. The table below displays the varying degrees of correlation between the ears across auditory tasks in glaucoma participants. Results are only shown for glaucoma participants as it was found the degree of asymmetry in control participants right and left ears were smaller, resulting in higher correlations. In contrast the majority of glaucoma
participants did not have significant correlations in ear performance. This analysis assisted with the decision to report data for each ear separately as opposed to randomized data or data for both ears in total. This inter-ear difference is likely due to asymmetrical disease stage in 28/42 (66.67%) of glaucoma participants.

Table 5.3 Correlation between right and left ears for glaucoma participants; N=84.

<table>
<thead>
<tr>
<th>Auditory Task</th>
<th>P value</th>
<th>Pearson’s r</th>
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</thead>
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<td>0.867</td>
</tr>
<tr>
<td>Temporal Amplitude Threshold</td>
<td>0.762</td>
<td>0.482</td>
</tr>
</tbody>
</table>

**Auditory Brainstem Response**

<table>
<thead>
<tr>
<th></th>
<th>P value</th>
<th>Pearson’s r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency – wave I</td>
<td>0.396</td>
<td>0.282</td>
</tr>
<tr>
<td>Latency – wave III</td>
<td>0.026*</td>
<td>0.832</td>
</tr>
<tr>
<td>Latency – wave V</td>
<td>0.075</td>
<td>0.508</td>
</tr>
<tr>
<td>Difference I-III</td>
<td>0.627</td>
<td>0.672</td>
</tr>
<tr>
<td>Difference III-V</td>
<td>0.475</td>
<td>0.342</td>
</tr>
<tr>
<td>Difference I-V</td>
<td>0.347</td>
<td>0.576</td>
</tr>
<tr>
<td>Amplitude – wave I</td>
<td>0.657</td>
<td>0.375</td>
</tr>
<tr>
<td>Amplitude - wave V</td>
<td>0.066</td>
<td>0.650</td>
</tr>
</tbody>
</table>

**Speech Perception (decibels)**

<table>
<thead>
<tr>
<th>SNR</th>
<th>P value</th>
<th>Pearson’s r</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR +20</td>
<td>0.952</td>
<td>0.803</td>
</tr>
<tr>
<td>SNR +10</td>
<td>0.074</td>
<td>0.733</td>
</tr>
<tr>
<td>SNR +5</td>
<td>0.830</td>
<td>0.808</td>
</tr>
<tr>
<td>SNR =0</td>
<td>0.982</td>
<td>0.527</td>
</tr>
</tbody>
</table>

*Significant p <0.05

Key: SNR = Signal to noise ratio, Latency in milliseconds, Amplitude in microvolt
APPENDIX 6: Results for right ears Experiment 1

Table 6.1 Baseline and visual function characteristics for each group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glaucoma N=42</th>
<th>Control N=42</th>
<th>P Value#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (interquartile range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>59.50 (54, 65.25)</td>
<td>60.00 (54.75, 64.25)</td>
<td>0.802</td>
</tr>
<tr>
<td>Central VA</td>
<td>0.00 (-0.10, 0.00)</td>
<td>-0.10 (-0.20, 0.00)</td>
<td>0.005*</td>
</tr>
<tr>
<td>MD</td>
<td>-2.74 (-5.77, -1.78)</td>
<td>-0.42 (-1.35, 0.57)</td>
<td>0.000*</td>
</tr>
<tr>
<td>PSD</td>
<td>2.88 (1.63, 6.98)</td>
<td>1.47 (1.22, 1.83)</td>
<td>0.000*</td>
</tr>
<tr>
<td>RNFL</td>
<td>74.92 (63.71, 90.61)</td>
<td>94.96 (86.01, 102.22)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Stage of disease† – number (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No VF loss</td>
<td>13 (30.95)</td>
<td>35 (83.33)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>14 (33.33)</td>
<td>7 (16.67)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (14.29)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>6 (14.29)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (4.76)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>End Stage</td>
<td>1 (2.38)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>42 (100)</td>
<td>42 (100)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 6.2 Overall sound detection levels for each group

<table>
<thead>
<tr>
<th>Frequency (KHz)</th>
<th>Glaucoma N=42</th>
<th>Control N=42</th>
<th>P Value#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (Interquartile range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td>10.00 (5.00, 11.25)</td>
<td>15.00 (10.00, 15.00)</td>
<td>0.117</td>
</tr>
<tr>
<td>0.50</td>
<td>10.00 (10.00, 15.00)</td>
<td>15.00 (10.00, 20.00)</td>
<td>0.075</td>
</tr>
<tr>
<td>1.00</td>
<td>10.00 (10.00, 15.00)</td>
<td>13.75 (15.00, 20.00)</td>
<td>0.018*</td>
</tr>
<tr>
<td>2.00</td>
<td>15.00 (10.00, 20.00)</td>
<td>17.50 (13.75, 25.00)</td>
<td>0.030*</td>
</tr>
<tr>
<td>4.00</td>
<td>22.50 (15.00, 38.50)</td>
<td>25.00 (15.00, 35.00)</td>
<td>0.974</td>
</tr>
<tr>
<td>8.00</td>
<td>40.00 (13.75, 62.50)</td>
<td>30.00 (20.00, 45.00)</td>
<td>0.378</td>
</tr>
<tr>
<td>4FA</td>
<td>16.25 (10.00, 22.50)</td>
<td>12.50 (10.00, 17.50)</td>
<td>0.185#</td>
</tr>
<tr>
<td></td>
<td>Mean ± Standard Deviation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4FA</td>
<td>17.72 ± 9.230</td>
<td>18.80 ± 7.00</td>
<td>0.476†</td>
</tr>
</tbody>
</table>

4FA = average of 0.5, 1.0, 2.0 and 4.0 Kiloertz (kHz). #Kruskal-Wallis test †ANOVA
*Significant p<0.05

### Table 6.3 Significance levels for auditory task outcomes

<table>
<thead>
<tr>
<th>RIGHT EARS n=42</th>
<th>Kruskal Wallis &gt;Group</th>
<th>ANCOVA &gt;Group &gt;Age &gt;4FA</th>
<th>Repeated Measures ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.842</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Average Hearing Level</td>
<td>0.305</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Temporal Amplitude</td>
<td>0.199</td>
<td>0.056 0.000* 0.971</td>
<td>-</td>
</tr>
</tbody>
</table>
### Speech Perception \( n = 42 \)

|  | 0.026* | 0.549 | **Within Factors:** |  
|---|---|---|---|---|---|---|
| Speech | 0.026* | 0.549 | **Within Factors:** |  
| SNR +20 | 0.441 | 0.010* | SNR | 0.003 |  
| Speech | 0.879 | 0.453 | SNR x Age | 0.002* |  
| SNR +10 | 0.952 | 0.006 | SNR x 4FA | 0.275 |  
| Speech | 0.199 | 0.647 | SNR x Group | 0.379 |  
| SNR +5 | 0.127 | 0.014* | **Between Factors:** |  
| Speech | 0.932 | 0.758 | Age | 0.323 |  
| SNR +0 | 0.059 | 0.255 | Ear 4FA | 0.013* |  
|  |  |  | Group | 0.969 |  

### ABR Latency \( n = 42 \)

|  | 0.989 | 0.556 | **Within Factors:** |  
|---|---|---|---|---|---|---|
| Wave I | 0.989 | 0.556 | **Within Factors:** |  
| 0.015* | 0.027* | Latency | 0.000 |  
| Wave III | 0.019* | 0.048* | Latency x Age | 0.056 |  
| 0.029* | 0.597 | Latency x 4FA | 0.115 |  
| Wave V | 0.006 | 0.015* | Latency x Group | 0.009* |  
| 0.000* | 0.923 | **Between Factors:** |  
| Wave I-III | 0.034 | 0.037* | Age | 0.000 |  
| 0.802 | 0.053 | Ear 4FA | 0.632 |  
| 0.266 | 0.214 | Group | 0.049* |  
| 0.009* | 0.631 |  | - |  
| Wave III-V | 0.266 | 0.214 | - |
Wave I-V | 0.016* | 0.010 | 0.056 | 0.232 | -

**ABR Amplitude n = 42**

<table>
<thead>
<tr>
<th>Wave</th>
<th>Amplitude</th>
<th>SNR x Age</th>
<th>Amplitude x 4FA</th>
<th>Amplitude x Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wave I</td>
<td>0.285</td>
<td>0.241</td>
<td>0.011*</td>
<td>0.054</td>
</tr>
<tr>
<td>Wave V</td>
<td>0.345</td>
<td>0.370</td>
<td>0.090*</td>
<td>0.287</td>
</tr>
<tr>
<td>Wave V/I</td>
<td>0.820</td>
<td>0.565</td>
<td>0.609</td>
<td>0.042*</td>
</tr>
</tbody>
</table>

*Significant at p<0.05

Repeated Measures in participants with normal hearing at SNR 0 decibels:

**Within Factors:**
- SNR: 0.013
- SNR x Age: 0.798
- SNR x Group: 0.058

**Between Factors:**
- Age: 0.981
- Group: 0.249
Table 6.4 Significant correlation coefficients between auditory tasks by group.

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Glaucoma</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman’s rho</td>
<td>Spearman’s rho</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td>AM + Speech SNR 5 dB</td>
<td>-0.389</td>
<td>-0.369</td>
</tr>
<tr>
<td></td>
<td>0.011</td>
<td>0.016</td>
</tr>
<tr>
<td>AM + Speech SNR 0 dB</td>
<td>-0.286</td>
<td>-0.406</td>
</tr>
<tr>
<td></td>
<td>0.067 (trend)</td>
<td>0.008</td>
</tr>
<tr>
<td>AM + ABR I-V latency</td>
<td>0.366</td>
<td>0.601</td>
</tr>
<tr>
<td></td>
<td>0.017</td>
<td>0.000</td>
</tr>
<tr>
<td>AM + ABR V latency</td>
<td>(Not significant)</td>
<td>0.567</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.000</td>
</tr>
</tbody>
</table>

Key: AM = amplitude modulation detection, ABR = Auditory brainstem response, SNR = signal in noise, 4FA = 4-frequency average hearing threshold.

Summary of statistically significant findings for right ears:

Glaucoma participants displayed a significantly prolonged ABR interpeak latency between waves I and V compared to controls, evidence of slower neural conduction in the auditory pathway. This was associated with a trend toward poorer amplitude modulation detection in the glaucoma group. Performance on ABR testing also correlated moderately with speech perception ability in both groups. These findings confirm and an expected relationship between temporal processing coding and neural conduction efficiency.
APPENDIX 7

The same background analysis performed in Experiment 1 was performed for Experiment 2 with the same intention of evaluating the degree of correspondence in the ratio of performance between the best and worst ear for each participant. Results were evaluated in terms of groups and displayed below.

Table 7.1 Examination of symmetry versus asymmetry in average hearing level between groups; n = 25.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glaucoma</th>
<th>Control</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± standard deviation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4FA</td>
<td>0.79 ± 0.18</td>
<td>0.76 ± 0.17</td>
<td>0.461</td>
</tr>
<tr>
<td>AM</td>
<td>1.20 ± 0.21</td>
<td>1.12 ± 0.19</td>
<td>0.157</td>
</tr>
<tr>
<td>500 DLF</td>
<td>0.70 ± 0.29</td>
<td>0.79 ± 0.21</td>
<td>0.208</td>
</tr>
<tr>
<td>Speech 0 SNR</td>
<td>1.32 ± 0.81</td>
<td>1.14 ± 0.18</td>
<td>0.013*</td>
</tr>
<tr>
<td>Slow SD</td>
<td>0.76 ± 0.21</td>
<td>0.81 ± 0.16</td>
<td>0.382</td>
</tr>
<tr>
<td>Global Motion</td>
<td>0.76 ± 0.15</td>
<td>0.75 ± 0.15</td>
<td>0.823</td>
</tr>
</tbody>
</table>

Key: †One-way ANOVA; * Significant at p>0.05; 4FA = 4-frequency hearing threshold average, AM = amplitude modulation detection, DLF = discrimination limens for frequency, SNR = signal to noise, SD = speed discrimination.

Comments:

The degree of asymmetry as determined by the ratio of performance between ears was found to be similar between groups across the majority of tasks for Experiment 2. However, glaucoma participants were found to have a greater degree of asymmetry between speech perception scores with a trend for poorer scores in left ears than right ears.
Background analyses comparing ear and eye performance on select tasks in Experiment 2.

Prior to the conduct of this study, anecdotal notes were made based on glaucoma patients who I treat commenting that they felt that their hearing was poorer on the same side as their most affected glaucoma eye. In line with the current study hypothesis of a central susceptibility to neural disturbance in both visual and auditory systems, it may be anticipated that it would be more likely to witness contra-lateral patterns over ipsi-lateral patterns in poor performance. To explore this further, background evaluation was made using two sensory comparisons to explore the potential of an association between ear and eye function. The first comparison is between auditory function (i.e. average hearing level) and visual stage of disease. The second comparison is between auditory performance (i.e. temporal amplitude modulation) and visual performance (i.e. speed discrimination).

Table 7.2 Comparison of average hearing level and stage of glaucoma disease across group; n=25.

<table>
<thead>
<tr>
<th>Worst ear versus worst eye</th>
<th>Glaucoma</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td></td>
<td>Ipsi-lateral performance</td>
<td></td>
</tr>
<tr>
<td>Right ear / Right eye stage</td>
<td>0 (0.00)</td>
<td>1 (4.00)</td>
</tr>
<tr>
<td>Left ear / Left eye stage</td>
<td>5 (20.00)</td>
<td>3 (12.00)</td>
</tr>
<tr>
<td>Contra-lateral performance trend</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ear / Left eye stage</td>
<td>5 (20.00)</td>
<td>1 (4.00)</td>
</tr>
<tr>
<td>Left ear / Right eye stage</td>
<td>5 (20.00)</td>
<td>1 (4.00)</td>
</tr>
<tr>
<td>Other trend</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ear less / eyes same</td>
<td>3 (12.00)</td>
<td>4 (16.00)</td>
</tr>
<tr>
<td>Left ear less / eyes same</td>
<td>6 (24.00)</td>
<td>11 (44.00)</td>
</tr>
<tr>
<td>Ears same / eyes same</td>
<td>1 (4.00)</td>
<td>4 (4.00)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>25 (100.00)</td>
<td>25 (100.00)</td>
</tr>
</tbody>
</table>
Comments:
Comparison of average hearing level and stage of disease in the glaucoma group showed a trend for contra-lateral performance between the poorer hearing of the right ear and disease stage of the left eye and vice versa. A similarly notable proportion of the glaucoma group had poorer left ear hearing matched with similar stage of disease. With respect to the control group, most had comparable visual function stage (as expected) that was matched with poorer hearing in the left ear.
In addition to the above, investigation into any performance trends between ears and eyes was performed between perceptual processing tasks. See Table 7.6 below.

Table 7.6 Comparison of auditory amplitude modulation and visual speed discrimination at 2 degrees per second for each group.

<table>
<thead>
<tr>
<th>Worst ear versus worst eye</th>
<th>Glaucoma</th>
<th></th>
<th>Control</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ipsilateral performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ear / Right eye</td>
<td>2 (9.52)</td>
<td>7 (30.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ear / Left eye</td>
<td>7 (33.33)</td>
<td>3 (13.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Contra-lateral performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ear / Left eye</td>
<td>4 (19.04)</td>
<td>6 (26.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ear / Right eye</td>
<td>6 (28.57)</td>
<td>7 (30.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other trend</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ear / Eyes equal</td>
<td>1 (4.77)</td>
<td>0 (0.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ear / Eyes equal</td>
<td>1 (4.77)</td>
<td>0 (0.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ears equal / Eyes equal</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>21 (100.00)</td>
<td>23 (100.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments:
No definite trends in this table can be observed for either group albeit confirming most glaucoma participants have asymmetrical sensory function between right and left sides with a slightly higher proportion having contra-lateral performance matching, for
example the lesser performing side being right ear and left eye or left ear and right eye. This later trend was apparent for both groups but overall it may be concluded that there is variety of possible outcomes suggesting that, reflecting upon the anecdotal notes mentioned above, that some glaucoma patients have a ‘same-sided’ bias but not all.
**APPENDIX 8: Results for right ears / eyes for Experiment 2**

Table 8.1 Baseline and visual function characteristics for each group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glaucoma N=25</th>
<th>Control N=25</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (interquartile range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>61.00 (57.50, 65.50)</td>
<td>61.00 (58.00, 64.50)</td>
<td>0.977</td>
</tr>
<tr>
<td>Central VA</td>
<td>0.06 (0.00, 0.13)</td>
<td>0.04 (-0.06, 0.10)</td>
<td>0.477</td>
</tr>
<tr>
<td>MD</td>
<td>-0.86 (-2.92, -0.10)</td>
<td>-0.38 (-1.06, 0.33)</td>
<td>0.059*</td>
</tr>
<tr>
<td>PSD</td>
<td>2.04 (1.39, 5.12)</td>
<td>1.41 (1.25, 1.74)</td>
<td>0.019*</td>
</tr>
<tr>
<td>RNFL</td>
<td>88.06 (70.35, 103.47)</td>
<td>94.41 (90.36, 119.10)</td>
<td>0.048*</td>
</tr>
</tbody>
</table>

**Stage of disease† – number (%)**

| Stage | Glaucoma | Control | |
|-------|----------|---------|
| No VF loss | 15 (60.00) | 23 (92.00) |
| Mild | 6 (24.00) | 2 (8.00) |
| Moderate | 2 (8.00) | - |
| Advanced | 1 (4.00) | - |
| Severe | 1 (4.00) | - |
| End Stage | - | - |
| **Total** | **25 (100.00)** | **25 (100.00)** |

†Reference: Modified glaucoma staging system proposed by Mills et al (2006)

*Kruskal-Wallis test; *Significant. Key: VA = visual acuity, MD = mean defect, PSD = pattern sensitivity deviation, RNFL = mean retinal nerve fibre layer, VF = visual field. Measurement scales: Central VA in log units, MD and PSD in decibels, RNFL in microns.
Table 8.2 Overall sound detection levels for each group

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>Glaucoma N=25</th>
<th>Control N=25</th>
<th>P Value#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (Interquartile range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td>15.00 (10.00, 20.00)</td>
<td>15.00 (10.00, 20.00)</td>
<td>0.866</td>
</tr>
<tr>
<td>0.50</td>
<td>15.00 (10.00, 27.50)</td>
<td>15.00 (10.00, 20.00)</td>
<td>0.757</td>
</tr>
<tr>
<td>1.00</td>
<td>15.00 (10.00, 20.00)</td>
<td>10.00 (10.00, 15.00)</td>
<td>0.461</td>
</tr>
<tr>
<td>2.00</td>
<td>15.00 (5.00, 17.50)</td>
<td>10.00 (5.00, 12.50)</td>
<td>0.152</td>
</tr>
<tr>
<td>3.00</td>
<td>20.00 (5.00, 27.50)</td>
<td>15.00 (5.00, 20.00)</td>
<td>0.448</td>
</tr>
<tr>
<td>4.00</td>
<td>20.00 (10.00, 35.00)</td>
<td>20.00 (7.50, 27.50)</td>
<td>0.374</td>
</tr>
<tr>
<td>6.00</td>
<td>30.00 (20.00, 40.00)</td>
<td>25.00 (18.75, 36.25)</td>
<td>0.282</td>
</tr>
<tr>
<td>8.00</td>
<td>35.00 (27.50, 55.00)</td>
<td>35.00 (17.50, 52.50)</td>
<td>0.533</td>
</tr>
<tr>
<td>4FA</td>
<td>16.25 (10.00, 22.50)</td>
<td>12.50 (10.00, 17.50)</td>
<td>0.137</td>
</tr>
<tr>
<td></td>
<td>Mean ± Standard Deviation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4FA</td>
<td>16.40 ± 8.09</td>
<td>13.85 ± 5.50</td>
<td>0.116†</td>
</tr>
</tbody>
</table>

Key: 4FA = average of 0.5, 1.0, 2.0 and 4.0 Kilohertz (kHz). ≠Kruskal-Wallis test. †ANOVA
### Table 8.3 Significance levels for auditory (top) and visual (bottom) task outcomes

<table>
<thead>
<tr>
<th>RIGHT EARS n=25</th>
<th>Kruskil Wallis &gt;Group</th>
<th>ANCOVA &gt;Group &gt;Age &gt;4FA</th>
<th>Repeated Measures ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.748</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Average Hearing Level</td>
<td>0.116</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Amplitude Modulation</td>
<td>0.826</td>
<td>0.982</td>
<td>-</td>
</tr>
<tr>
<td>0.388</td>
<td>0.109</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Frequency Discrimination (FD)**

<table>
<thead>
<tr>
<th>500 Hz</th>
<th>0.046*</th>
<th>0.027*</th>
<th>0.377</th>
<th>0.622</th>
<th>0.474</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>FD</td>
<td>FD x Age</td>
<td>FD x 4FA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.093</td>
<td>0.082</td>
<td>0.970</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FD x Group</td>
<td>0.075</td>
<td></td>
</tr>
</tbody>
</table>

**Between Factors:**

<table>
<thead>
<tr>
<th>Age</th>
<th>0.075</th>
</tr>
</thead>
<tbody>
<tr>
<td>4FA</td>
<td>0.074</td>
</tr>
<tr>
<td>Group</td>
<td>0.538</td>
</tr>
</tbody>
</table>

**Speech Perception**

<table>
<thead>
<tr>
<th>SNR 0 dB</th>
<th>0.025*</th>
<th>0.032*</th>
<th>0.275</th>
<th>0.064</th>
<th>-</th>
</tr>
</thead>
</table>

**Repeated Measures**

<table>
<thead>
<tr>
<th>RIGHT</th>
<th>Kruskil Wallis</th>
<th>ANCOVA</th>
<th>Repeated Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
<td>Group</td>
<td>ANOVA</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>VA</td>
<td>VA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>Age</td>
<td></td>
</tr>
</tbody>
</table>

| Age                      | 0.748   | -       | -             |
| Central Visual Acuity    | 0.436   | -       | -             |

**Temporal Contrast Detection (TCD)**

<table>
<thead>
<tr>
<th>Temporal Contrast Detection</th>
<th>0.052</th>
<th>0.750</th>
<th>Within Factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>10Hz</td>
<td>0.250</td>
<td>0.127</td>
<td>TCD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TCD x Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TCD x VA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TCD x Group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temporal Contrast Detection</th>
<th>0.652</th>
<th>0.059</th>
<th>Between Factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>30Hz</td>
<td>0.187</td>
<td>0.591</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group</td>
</tr>
</tbody>
</table>

**Speed Discrimination (SD)**

<table>
<thead>
<tr>
<th>Speed Discrimination</th>
<th>0.002*</th>
<th>0.009*</th>
<th>Within Factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow: reference at 2 degrees per second</td>
<td>0.326</td>
<td>0.748</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD x Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD x VA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD x Group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fast: reference at 8 degrees per second</th>
<th>0.652</th>
<th>0.599</th>
<th>Between Factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.187</td>
<td>0.591</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group</td>
</tr>
</tbody>
</table>

**Global Motion**

| Global Motion | 136 |
**Global Motion less outlier x 1 control**

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>Glaucoma N=25</th>
<th>Control N=25</th>
<th>Cohen’s d</th>
<th>Effect size correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>14.61 ± 7.11</td>
<td>10.48 ± 3.47</td>
<td>0.738</td>
<td>0.346</td>
</tr>
<tr>
<td>4.00</td>
<td>82.27 ± 27.42</td>
<td>72.00 ± 26.14</td>
<td>0.383</td>
<td>0.188</td>
</tr>
</tbody>
</table>

**Key:** 4FA = average of 0.5, 1.0, 2.0 and 4.0 Kilohertz (kHz), VA = Visual Acuity, * Significant at p<0.05

**Effect size for frequency discrimination right ears**

Using the means and standard deviations for each group at frequency discrimination levels an estimate of effect size was calculated (Cohen, 1988). Comparing figures 5.2 and 5.3 illustrates the magnitude of the group difference for frequency discrimination at 500 Hz was larger than at 4 kHz. For the glaucoma group, the effect size 0.74 indicates the mean is located around the 77th percentile of the control group distribution with 45% of non-overlapping group values (Cohen, 1988). This analysis confirms a large effect size at 500 Hz and not at 4 kHz and supports the finding that that within the glaucoma group, 13 out of 25 (52%) exhibited threshold elevations at 500 Hz above the normal limits of mean control performance (above 95% confidence limits).

**Table 8.4 Cohen’s effect size calculation for frequency discrimination at two levels across groups.**

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>Glaucoma N=25</th>
<th>Control N=25</th>
<th>Cohen’s d</th>
<th>Effect size correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>14.61 ± 7.11</td>
<td>10.48 ± 3.47</td>
<td>0.738</td>
<td>0.346</td>
</tr>
<tr>
<td>4.00</td>
<td>82.27 ± 27.42</td>
<td>72.00 ± 26.14</td>
<td>0.383</td>
<td>0.188</td>
</tr>
</tbody>
</table>

Note: Calculations made using an online calculator. URL http://www.uccs.edu/~faculty/lbecker/
Table 8.5 Significant correlation coefficients for auditory (top) and visual (bottom) tasks by group.

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Glaucoma Spearman’s rho</th>
<th>Glaucoma P value</th>
<th>Control Spearman’s rho</th>
<th>Control P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auditory tasks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4FA + FD 4 kHz</td>
<td>0.497</td>
<td>0.019</td>
<td>(Not significant p = 0.087)</td>
<td></td>
</tr>
<tr>
<td>AM + FD 500 Hz</td>
<td>0.452</td>
<td>0.030</td>
<td>0.558</td>
<td>0.003</td>
</tr>
<tr>
<td>AM + Speech score</td>
<td>-0.529</td>
<td>0.008</td>
<td>(Not significant p = 0.424)</td>
<td></td>
</tr>
<tr>
<td><strong>Visual tasks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log TCD 10 Hz + Slow SD</td>
<td>0.414</td>
<td>0.040</td>
<td>0.521</td>
<td>0.011</td>
</tr>
<tr>
<td>Slow SD + MD</td>
<td>(Not significant p = 0.698)</td>
<td></td>
<td>-0.535</td>
<td>0.009</td>
</tr>
</tbody>
</table>

No significant correlation between speed discrimination and global coherent motion

Note: No significant correlations between levels of temporal processing between auditory and visual tasks.

Key: 4FA = 4-frequency average hearing threshold, AM = amplitude modulation detection, FD = Auditory frequency discrimination, TCD = visual temporal contrast detection, SD = speed discrimination; PSD = pattern sensitivity deviation (from visual field testing)

**Summary of statistically significant findings for right ears and eyes:**

With regard to auditory processing function, a significant subset of glaucoma participants displayed poorer speech perception ability and poorer low frequency discrimination compared to age and gender equivalent controls. A similar proportion of OAG individuals also revealed visual processing deficits as reflected by impaired speed discrimination at slow velocities and elevated global coherent motion thresholds. Within both groups, significant correlations were identified across tasks within each sensory domain but no relationships were found between performances across sensory systems.