SUPRATHRESHOLD VISUAL FUNCTION IN GLAUCOMA

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Suprathreshold Visual Function in Glaucoma

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Abstract

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Keywords: Glaucoma, suprathreshold, visual function, everyday vision, psychophysics, contrast matching, blur, perception, crowding, natural vision

Glaucoma is the leading cause of irreversible blindness worldwide but the effect of glaucoma on patients' vision under suprathreshold conditions relevant to their natural visual environment is poorly understood. This project aimed to investigate and further understand the effects of glaucoma on three aspects of suprathreshold vision; apparent contrast of suprathreshold stimuli, detection and discrimination of image blur and crowding of peripheral vision.

Psychophysical methods were employed to assess these three visual functions by measuring contrast matches of Gabor stimuli, blur detection and discrimination thresholds of edge stimuli and crowding ratios of Vernier targets. These measures were obtained from glaucoma observers tested within and outside of visual field defects and the data compared with healthy controls.

Contrast matching ratios were similar between glaucoma and healthy age-similar controls despite sensitivity loss in the glaucoma group. Blur detection and discrimination thresholds were similar between glaucoma observers' tested within and outside of visual field defects and age-similar controls, though thresholds were slightly elevated for high contrast stimuli in the glaucoma visual field defect group. Crowding ratios were similar between participants with glaucoma and healthy young controls.

The results demonstrate that aspects of suprathreshold visual function can be maintained in early glaucoma despite sensitivity loss at threshold. The results provide empirical evidence as to the asymptomatic nature of the disease in its early stages. It appears that in early glaucoma, there may be compensatory mechanisms at work within the visual system under suprathreshold conditions that can overcome loss of sensitivity at threshold.

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Abbreviations

CCT	Central Corneal Thickness
C/D ratio	Cup/Disc ratio
CPSD	Corrected Pattern Standard Deviation
cpd	cycles per degree
CSF	Contrast Sensitivity Function
dB	Decibel
FDF	Flicker Defined Form
FDT	Frequency Doubling Technology
FN	False Negative
FP	False Positive
FT	Full Threshold
GHT	Glaucoma Hemifield Test
HRP	High pass Resolution Perimetry
IOP	Intraocular Pressure
M	Magnocellular
MD	Mean Deviation
OHT	Ocular Hypertension
OHTS	Ocular Hypertension Treatment Study
ONH	Optic Nerve Head
P	Parvocellular
PD	Pattern Deviation
POAG	Primary Open-Angle Glaucoma
PPA	Peripapillary Atrophy
PSD	Pattern Standard Deviation
RGCs	Retinal Ganglion Cells
SAP	Static Automated Perimetry
SF	Spatial Frequency
SITA	Swedish Interactive Threshold Algorithm
SNR	signal/noise ratio
STF	Short-term fluctuation
SWAP	Short Wavelength Automated Perimetry
SWS	Short Wavelength Sensitive
TD	Total Deviation
VF	Visual Field

Chapter 1

1 Introduction

1.1 Glaucoma

Glaucoma describes a group of progressive optic neuropathies that involve loss of retinal ganglion cells leading to irreversible sight loss (Kwon et al. 2009). Glaucoma is the leading cause of irreversible blindness worldwide and is expected to affect more than 110 million people by 2040 (Quigley and Broman 2006; Tham et al. 2014). Presentation of glaucoma typically includes changes to the optic nerve head and a characteristic pattern of visual field loss (Casson et al. 2012). Intraocular pressure (IOP) is a well-established risk factor in certain types of glaucoma and IOP control is currently the primary route of treatment by which the disease is managed.

Glaucoma can be classified by three categories, anatomy, aetiology and age of onset. The anatomical feature that distinguishes between types of glaucoma is the anterior chamber angle that forms between the iris and cornea. In open-angle glaucoma, the anterior chamber angle is visibly open when viewed using gonioscopy whilst in angle closure glaucoma, the anterior chamber angle is fully or partially closed. The age of onset of the disease can define whether glaucoma is congenital, juvenile or adult-onset glaucoma. The majority of glaucoma cases are acquired in adulthood.

Glaucomatous optic neuropathy in the absence of alternative ocular or systemic causes is known as primary glaucoma. When the anterior chamber angle is open, this can be categorised as Primary Open Angle Glaucoma (IOP > 21mmHg) (POAG) or normal tension glaucoma (IOP ≤ 21mmHg) (Casson et al. 2012; Killer and Pircher 2018). It is estimated that normal-tension glaucoma patients make up 20 to 30% of open-angle glaucoma cases (Sommer 1996). When the anterior chamber angle is partially or fully closed, this is known as Primary Angle Closure Glaucoma (PACG). PACG can be acute or chronic, and is typically associated with elevated IOP. In contrast, when the glaucomatous optic neuropathy is caused by another systemic or ocular condition, the glaucoma is known to be secondary. Examples of secondary open-angle

glaucoma include pseudoexfoliation glaucoma and pigmentary glaucoma. In these cases, pseudoexfoliative material from the lens or pigmentary particles from the iris deposit into the trabecular meshwork and limit aqueous humour outflow. An example of secondary angle closure glaucoma is neovascular glaucoma where new vessels grow on the iris and block the anterior chamber angle causing full or partial angle closure (Rodrigues et al. 2016).

Ocular hypertension describes IOP of above 21mmHg without visual field loss or glaucomatous damage (Gordon et al. 2002). There is a higher risk of developing glaucoma in patients with ocular hypertension. Consequently, ocular hypertensive patients need to be more closely monitored for glaucoma than the general population. Certain factors such as age and cup-to-disc ratio can be used to predict whether an ocular hypertensive patient is likely to progress to POAG (Gordon et al. 2002).

The proportion of the population affected by a disease at a given time is known as prevalence. The global prevalence of glaucoma for adults aged 40 and above is 3.5% (Tham et al. 2014). In 2014, it was estimated that by 2020, there would be 76 million people with glaucoma increasing to 111.8 million by 2040 (Tham et al. 2014). POAG is most prevalent in people with African ancestry (Tham et al. 2014) and is the most common form of glaucoma in western countries (Quigley 1993). Whereas, PACG is most prevalent in south Asians (Tham et al. 2014). Incidence is the number of new cases of a disease that develop from a population at risk during a given time period. The Rotterdam study found the 5 year incidence in an elderly white population as 0.6% definite POAG and 1.2% probable POAG (de Voogd et al. 2005). Additionally, if the first eye was diagnosed with POAG during baseline measurements, the second eye was five times more at risk of developing POAG compared to a person with no POAG on initial measurements (de Voogd et al. 2005). In comparison, the Barbados eye studies found a higher incidence of 2.2% in a black population during a four year period (Leske et al. 2001). The increase in incidence in black populations is expected as the prevalence of POAG is also higher in this group with a prevalence of approximately 5% at 60 years increasing to 12% at 80 years (Kapetanakis et al. 2016).

1.1.1 Risk Factors

A number of risk factors have been identified for glaucoma including age (Mitchell et al. 1996; Kapetanakis et al. 2016), family history (Wolfs et al. 1998), race (Tielsch et al. 1991) and IOP (Sommer et al. 1991). Age is a significant risk factor for developing POAG. As demonstrated in Figure 1.1, it has been previously shown that there is an exponential trend in the prevalence of POAG with increasing age (Iwase et al. 2004; Kapetanakis et al. 2016).

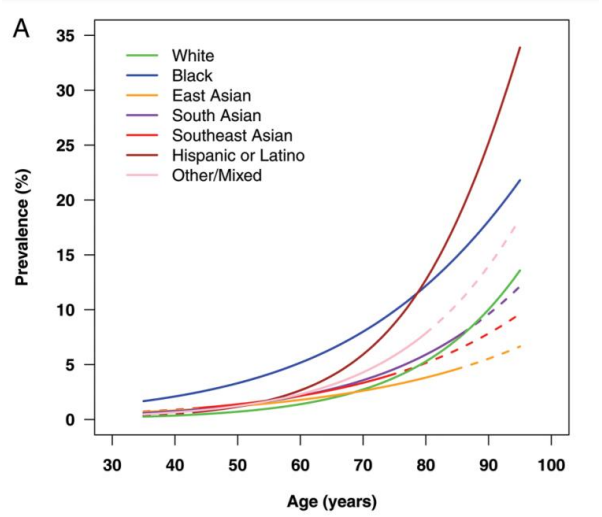


Figure 1.1 Observed prevalence of POAG vs Age in different ethnic groups (Kapetanakis et al. 2016).

Some studies suggest that men are more likely to develop POAG than women. For instance, a meta-analysis found that men were 1.37 times more likely to have POAG than women after accounting for age and racial factors (Rudnicka et al. 2006). Similarly, a more recent study found that men are 1.64 times more likely than women to develop POAG in an African-American population (Khachatryan et al. 2019). However, other studies have found no significant differences in the prevalence rates of POAG in males to females (Tielsch et al. 1991; Bonomi et al. 1998; Quigley and Broman 2006). For instance, Tielsch et al. (1991) found rates of POAG as 2.7% in men compared with 2.35% in women. Overall, it appears that there is currently no clear evidence to show a significant risk factor of a particular gender for POAG.

POAG is more prevalent in people of black racial backgrounds whilst prevalence of PACG is greater in people of Asian ethnicities (Quigley and Broman 2006). For instance, the Baltimore Eye Survey found that the prevalence of POAG was three times higher in black Americans (4.74%)

compared to white Americans (1.29%) (Tielsch et al. 1991). This finding was consistent across gender and age groups. Similarly, a high prevalence of POAG has been found in a black population in Barbados (7%) (Leske et al. 1994). Tielsch et al. (1991) suggest that the difference in prevalence between the two races could be caused by an inherent genetic susceptibility to develop the disease. Prevalence of POAG in Asians has been found to be similar to white individuals. For example, POAG prevalence of 1.62% was found in a south-Indian population compared to 1.4% in an Italian population (Bonomi et al. 1998; Vijaya et al. 2005).

Family history is also a recognised risk factor of POAG. The Rotterdam study found that the lifetime risk of a first-degree relative was 9.2 x the risk of the control group when adjusted for age and gender differences (Wolfs et al. 1998). The Baltimore eye survey found a risk ratio of 2.85 for the association between POAG and a family history in a first-degree relative when adjusting for age and racial differences (Tielsch et al. 1994). The large difference in risk ratios between these two studies could be explained by the differences in populations being studied; the Rotterdam study was of a white population whilst the Baltimore eye survey was of both whites and blacks. The survey also found the highest association of POAG with a family history in siblings (risk ratio of 3.69) compared to parents (2.17) and children (1.12) (Tielsch et al. 1994). Tielsch et al. (1994) suggest that siblings have a higher relative risk than parents or children as siblings share more genetic material than children do with parents. These studies suggest there is a genetic component to developing glaucoma.

IOP is a well-established risk factor for POAG. Table 1.1 shows the increasing prevalence of POAG with an increase in screening IOP (Sommer et al. 1991). The relative risk of POAG was significantly higher with increasing levels of IOP (relative risk of 12.8 in IOPs between 22-29mmHg compared to 2.0 for IOPs between 16-18mmHg) (Sommer et al. 1991).

Table 1.1: The prevalence of POAG compared to screening IOP (Sommer et al. 1991).

IOP (mmHg)	Prevalence (%)	Relative Risk Ratio
≤15	0.65	1.0
16-18	1.31	2.0
19-21	1.82	2.8
22-24	8.30	12.8
25-29	8.33	12.8
30-34	25.37	39.0
≥35	26.09	40.1

Fluctuation in IOP has been found to be a risk factor for POAG in some studies. One study found low mean IOPs with high long term fluctuation had a strong association with glaucomatous visual field progression (Caprioli and Coleman 2008). Bengtsson et al. (2007), on the other hand, found that fluctuation in IOP was not an independent risk factor for glaucoma progression. IOP is currently the only modifiable risk factor for glaucoma and IOP control is the primary route of treatment by which the disease is managed. When measuring IOP, Central Corneal Thickness (CCT) has to be considered. A cornea that is thicker than average may result in an overestimation of the IOP, whereas a thin cornea may result in an underestimation of the IOP reading. In line with the finding that IOP is underestimated in patients with thin corneas, it has been reported that patients with thinner CCTs present to glaucoma specialists with greater glaucomatous damage on the first visit (Herndon et al. 2004). Additionally, the ocular hypertension treatment study (OHTS) has reported that a thin CCT is an independent risk factor for POAG and a significant risk factor for progression of ocular hypertension to POAG (Gordon et al. 2002). Participants with a CCT of 555µm or less were three times more at risk of developing POAG than participants with a CCT greater than 588µm (Gordon et al. 2002).

A significant association between diabetes and POAG has been found in some studies (Bonovas et al. 2004; Rim et al. 2018). The Blue Mountains study found that people with diabetes were twice as likely to develop glaucoma than those without diabetes (odds ratio of 2.12 adjusted for age and gender) (Mitchell et al. 1997). Rim et al. (2018) found lower odds ratio of 1.2 and 1.18 for age groups of 40-59 and 60-79 respectively. Whereas, other studies have found no significant association between diabetes and POAG (Tielsch et al. 1995; Ellis et al. 2000). As a result, the relationship between diabetes and POAG still remains unclear.

1.1.2 Treatment

The aim of treatment in glaucoma is to preserve visual function and involves setting the patient a target IOP. Initially, the target IOP is set based on the patients' individual risk of developing glaucoma and/or the projected rate of disease progression. One method of calculating target IOP is a reduction of 20-50% of the initial IOP that was causing glaucomatous damage (Weinreb and Khaw 2004). In order to achieve this, patients in the United Kingdom are offered selective laser trabeculoplasty or topical medication as a first line treatment (Gazzard et al. 2019). If this treatment is unsuccessful in sufficiently lowering the IOP to target, second line treatment includes alteration or addition of topical medication and/or surgical intervention.

The first line medication chosen depends on the type and severity of the disease as well as taking the patients' medical history into consideration. Prostaglandin analogues, such as latanoprost and travoprost, are a type of topical glaucoma medication that is commonly used in Europe as they are effective in reducing IOP with few systemic side-effects (Weinreb and Khaw 2004). This type of medication works by increasing aqueous outflow through the uveoscleral route (Gabelt and Kaufman 1989). Side effects from this medication include thickening and darkening of the eye lashes and iris hyperpigmentation. Other examples of medication include beta blockers and carbonic anhydrase inhibitors that lower IOP by reducing aqueous secretion. Beta blockers (e.g. Timolol) are used less frequently to treat POAG than prostaglandin analogues as they have more severe systemic side-effects such as bronchospasm, increased asthma and bradycardia (Weinreb and Khaw 2004). Carbonic

anhydrase inhibitors are available in oral and topical form. Examples include Dorzolamide, Brinzolamide (topical) and Acetazolamide (oral). The topical form has fewer side-effects than oral carbonic anhydrase inhibitors but is not as effective in reducing IOP. Side-effects include transient myopia, paraesthesia and renal stones (Weinreb and Khaw 2004). Neuroprotective agents are currently under investigation for use in POAG treatment. The mechanism of the drug involves preventing apoptosis of retinal ganglion cells. Neuroprotective agents are used in Parkinson's disease but there is currently no evidence that these drugs work in POAG treatment (Levin et al. 2017).

As an alternative to topical medication, laser treatment may be used as a first line treatment in the management of POAG. The most common form is laser trabeculoplasty which involves laser burns applied to the trabecular meshwork forming a biological and chemical change that assists aqueous outflow (Weinreb and Khaw 2004). There are two types of laser that can be used in the procedure; argon and selective. Argon laser trabeculoplasty involves a laser beam that can affect all structures in the trabecular meshwork whereas selective laser trabeculoplasty targets only the pigmented structures and leaves the unpigmented structures unscathed (Kramer and Noecker 2001). Selective laser trabeculoplasty has proven to be a successful alternative to drops as a first line treatment (Gazzard et al. 2019). The effects of the procedure usually last between one and five years. Laser diode cyclophotocoagulation is used in advanced POAG cases. The diode laser works by destroying some of the ciliary epithelium involved in secretion and in doing so reduces aqueous secretion (Gaasterland and Pollack 1992). Treatment using a diode laser usually needs repeating as the effects are temporary (Weinreb and Khaw 2004).

Surgery is usually the last route of treatment in POAG, when medical or laser treatment cannot reduce the IOP adequately. Trabeculectomy is the most common type of incisional surgery used to aid aqueous drainage (Weinreb and Khaw 2004). The procedure involves removing part of the sclera or cornea to create another pathway for aqueous humour to leave the anterior chamber. The aqueous humour leaves the anterior chamber and accumulates to form a bleb

between the sclera and conjunctiva. The aqueous humour is then slowly drained from this bleb through the episcleral venous drainage system.

1.2 The Optic Nerve

The optic nerve head (ONH) or optic disc is the point at which retinal ganglion axons gather to form the optic nerve and leave the retina through the scleral canal (Weinreb and Khaw 2004). The ONH is usually oval in shape with a mean vertical diameter of 1.92mm and a mean horizontal diameter of 1.76mm (Jonas et al. 1988). There are approximately 1 million ganglion cell axons passing through the ONH travelling from the retina to the lateral geniculate nucleus. The ONH is also where the main blood vessels enter the eye to supply the retina. At the ONH, axons pass through a series of perforated collagenous connective tissue known as the lamina cribrosa. The ONH has a central depression known as the optic cup that can vary in size and depth. The range of optic cup areas in normal eyes found in one study varied from 0.00mm² to 3.41mm² (Jonas et al. 1988). There is no neural tissue present in the optic cup so it appears paler on examination as the lamina cribrosa is exposed. The neuroretinal rim is pink in colour and surrounds the optic cup. The distribution of the neuroretinal rim area has a distinctive pattern in most healthy eyes; the inferior rim is wider than the superior rim followed by the nasal and is narrowest at the temporal rim (Jonas et al. 1988). This pattern of breadth is known as the ISNT rule. The cup-to-disc (C/D) ratio is a fraction of the cup height/disc height and can be described as vertical or horizontal.

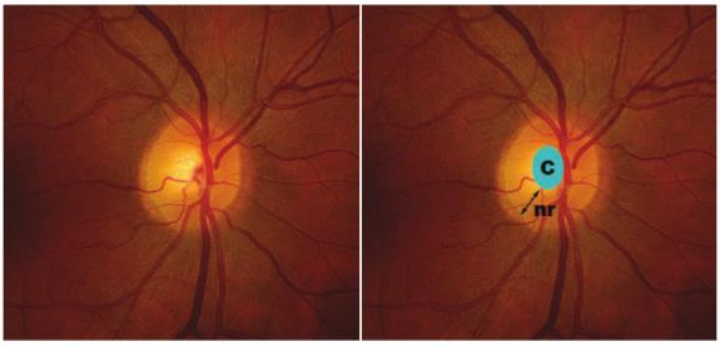


Figure 1.2 A retinal photograph of a healthy right eye ONH (Allingham et al. 2012). C shows the location of the cup and nr is the neuroretinal rim around the cup.

1.2.1 Signs of glaucomatous optic neuropathy

Signs of glaucomatous optic neuropathy may be visible when examining the optic disc. These changes include an enlargement of the optic C/D ratio, alteration to the neuroretinal rim thickness and changes to the lamina cribrosa. Jones et al. (1988) found a Gaussian distribution of the areas of the ONH in normal eyes. Areas of ONHs ranged from 0.80mm² to 5.54mm² (Jonas et al. 1988). More recently, it has been reported that the average ONH size ranged from 1.35mm^2 in eyes with long axial lengths to 2.00mm^2 in eyes with shorter axial lengths (Savini et al. 2012). In addition to variations with axial length, ONH size has been found to vary with race. For example, the mean ONH size was larger in blacks (2.94mm²) compared to whites (2.63mm²) in an American study (Varma et al. 1994). This range in normal ONH size makes it difficult to establish disc size as an independent risk factor for glaucoma.

Furthermore, the presentation of glaucoma is different in smaller ONHs compared to larger discs. A smaller ONH has a larger density of axons passing through whereas a larger ONH has a smaller density. This creates the appearance of a larger physiological cup in a large ONH (Crowston et al. 2004). The Blue Mountains eye study found the median vertical C/D ratio increased from 0.33 in small ONHs (1.2mm) to 0.55 in large ONHs (1.9mm) (Crowston et al. 2004). Consequently, a smaller C/D ratio of 0.2 in a smaller ONH could be considered glaucomatous and a larger C/D ratio of 0.5 in a larger ONH could be healthy. Therefore, the clinical presentation of glaucoma cannot be based on C/D ratio alone and the size of the optic disc needs to be considered when interpreting the significance of the C/D ratio (Crowston et al. 2004).

Although there is a natural reduction of the nerve fibre layer due to ageing, there is a greater loss of the nerve fibre layer and neuroretinal rim (NRR) thickness as glaucoma progresses (Schuman et al. 1995). This reduction in nerve fibre layer thickness was found more frequently in the inferior region in glaucoma patients (Schuman et al. 1995). The inferior and superior regions of NRR are most affected to begin with causing an enlargement of the cup size and increasing the vertical C/D ratio (Jonas et al. 1993) . Early stages of POAG frequently present as diffuse NRR loss which is a general loss of NRR in all sections of the optic nerve (Garway-Heath and Hitchings 1998). Another

common NRR loss is focal loss of the inferior-temporal sector (Garway-Heath and Hitchings 1998). The ISNT rule is a useful indicator when examining for glaucomatous damage. In one study, the ISNT rule was followed in 79% of normal eyes but only 28% of glaucomatous eyes (Harizman et al. 2006). On clinical examination, deviation from the ISNT rule pattern is one of many indicators in determining whether glaucomatous optic neuropathy is present. Figure 1.3 demonstrates deviation from the ISNT rule and the appearance of NRR loss in glaucoma.

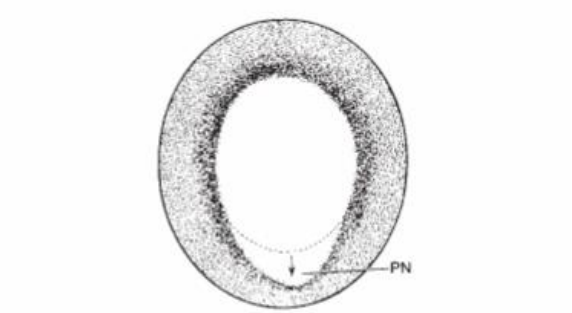


Figure 1.3 A schematic of the enlargement of an optic cup in a glaucomatous disc (Allingham et al. 2012). The dotted line shows the original margin of the cup. PN is the polar notch created as a result of NRR loss.

The retinal ganglion cell axons pass through the lamina cribrosa when entering the scleral canal. Studies suggest that there are morphological changes to the lamina cribrosa in glaucomatous discs. Quigley et al. (1981) found that the posterior movement of the lamina cribrosa in glaucomatous eyes results in a deeper excavated appearance of the optic cup (Figure 1.4). The lamina cribrosa connective tissue plates collapse creating the excavated appearance and this is known as optic nerve pallor. Another study found varying sizes and shapes of focal lamina cribrosa defects in 89% of glaucoma subjects (Kiumehr et al. 2012). Therefore, the lamina cribrosa is also examined when assessing for glaucomatous optic neuropathy.

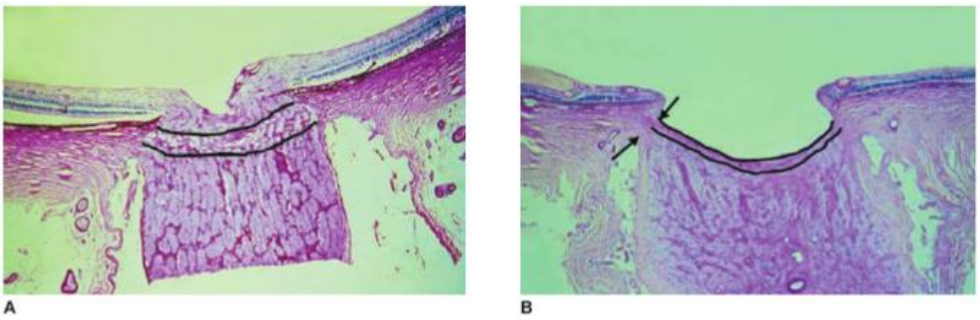


Figure 1.4: A cross section of the optic nerve in a non-glaucomatous eye (A) and a glaucomatous eye (B) (Jonas et al. 2003). The lamina cribrosa is indicated by the black line. The lamina cribrosa is bowed downwards and appears thinner in the glaucomatous eye.

Peripapillary atrophy (PPA) describes the degeneration and thinning of retinal layers surrounding the ONH. PPA is divided into two zones: alpha and beta. The alpha area shows PPA caused by hyper and hypopigmentation of the retinal pigment epithelium. The beta PPA is closest to the ONH and shows degeneration of the chorioretina displaying the sclera and choroidal vessels underneath. PPA is found in both normal ONHs and glaucomatous ONHs. However, PPA progression is more frequent in glaucoma patients. One study found 64% of patients with progressive optic disc damage had progressive PPA (Uchida et al. 1998). The alpha and beta areas of PPA are larger in glaucoma patients compared to healthy individuals (Jonas et al. 1989). The beta PPA is also more frequently found and progresses more in glaucoma patients (Jonas et al. 1989).

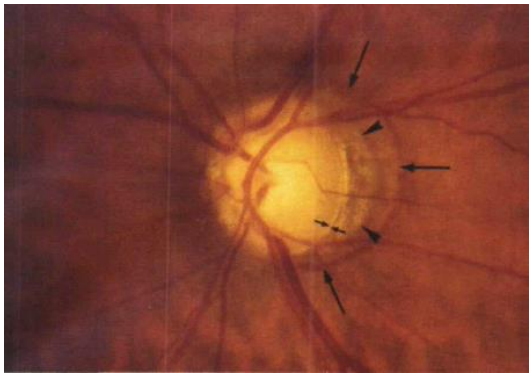


Figure 1.5 A left glaucomatous ONH with peripapillary atrophy (Jonas et al. 1989). Small arrows indicate the scleral ring, large arrows point to alpha PPA zone and arrowheads point to beta PPA zone.

Optic disc haemorrhages are commonly seen in glaucoma patients but are not an exclusive sign of the disease. One study found the incidence of disc haemorrhages in glaucoma patients as high as 30% (Gloster 1981). However, disc haemorrhages are more frequently found in normal-tension glaucoma than POAG (Gloster 1981). The haemorrhage is located between the retinal nerve fibre layers and usually resolves and reappears on the disc. Another non-specific sign of glaucomatous damage is changes to blood vessels on and around the ONH (Figure 1.6). For example, baring and bayonetting of the circumlinear vessels in the superior and inferior quadrants of NRR and narrowing of the retinal arteries near the ONH may commonly be seen on glaucomatous discs.

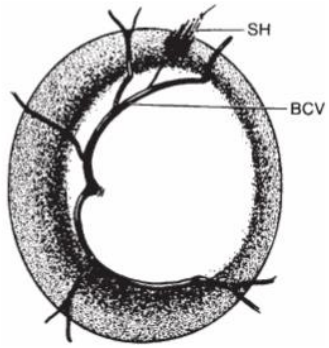


Figure 1.6 An ONH with blood vessel changes & a disc haemorrhage (Allingham et al. 2012). SH is the splinter disc haemorrhage and BCV is baring of a circumlinear blood vessel.

1.3 Visual function in Glaucoma

The visual field (VF) describes the extent of space perceived by a person at a given point. The extent of the monocular VF from the point of fixation is approximately; 50° superiorly, 60° nasally, 70° inferiorly and 100° temporally (Traquair 1939). Traquair (1939) presented the concept of the VF being an island of vision; where the full extent of perceptual vision is represented by the island and the area not perceived represented by the sea. Under photopic conditions, the highest peak of the island represents the fovea and is the most sensitive area of visual perception. From the peak (fovea), the island gradually descends towards the periphery. The ONH is a physiological blind spot represented in this concept as a crater 15° temporally to the peak (fovea). However, under scotopic conditions, the shape of the island changes as the peak sensitivity of photoreceptors shift towards the rods. The island incline is flatter and where the foveal peak is situated; there is now a depression as cone photoreceptors have reduced sensitivity under scotopic conditions. Therefore, the scope of the VF is influenced by the differing peak sensitivities of the photoreceptors.

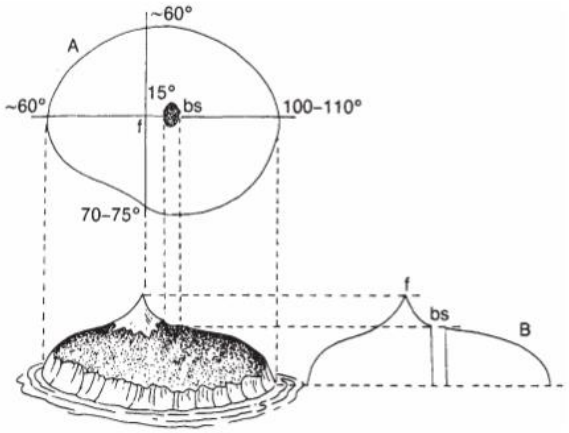


Figure 1.7 A schematic illustrating the island of vision as described by Traquair (1939). Image taken from (Allingham et al. 2012), f is the fovea and bs is the location of the physiological blind spot.

1.3.1 Perimetry

Perimetry is a term used to describe a group of techniques that assess the VF. In static perimetry, the stimuli are presented briefly at pre-determined locations in the VF. In kinetic perimetry, the stimuli are fixed in size and brightness and

move across the VF. The stimulus is moved from an area not detected by the observer to an area within their perceived VF and the observer is asked to indicate when they first detect the stimulus.

Conventional white-on-white perimetry also known as static automated perimetry (SAP) involves the participant being presented with a spot of white light (stimulus) against a dimly lit white background in a number of locations in the VF. SAP is based on measuring contrast sensitivity (see section 1.4.2) also known in perimetry as differential light sensitivity. SAP uses the Weber fraction as a measure of contrast and the decibel scale as the unit of measurement.

The Weber fraction is calculated using the stimulus and background luminance intensities. Weber's law describes the change in contrast necessary for the visual system to discern a difference as being a constant. Weber's law is defined as;

$\Delta L / L = k$

Where ΔL is Contrast or change in luminance, L is the background luminance and k is the Weber fraction. Weber's law is upheld for a range of luminance levels. Weber's fraction is 0.015 under photopic conditions and 0.14 under scotopic conditions.

The decibel (dB) scale is used in perimetry to describe changes in contrast and is a logarithmic scale, dB values are calculated using the following equation:

$dB = 10\log_{10}(Lmax / L)$

where Lmax is the maximum luminance displayed by the perimeter and L is the luminance of the stimulus.

For instance, for a stimulus with luminance of 100cd/m² and a perimeter with a maximum luminance of 10,000cd/m² the decibel value is 20 dB. As perimeters differ in maximum luminance, the dB scale will not be equivalent across manufacturers and therefore comparisons between perimeter results cannot be made using the dB scale. A dB value of 0 represents the maximum luminance of the perimeter. Therefore, an increase in the dB value represents attenuation in luminance of the stimulus and a decrease in the contrast detection threshold.

This means that a higher dB value indicates greater contrast sensitivity of the stimulus at that VF location.

Examples of static automated perimeters used in clinical practice include; Humphrey Field Analyser III, Henson 9000 and Octopus 900. Perimetry is commonly used in clinical practice as any visual defects found can help identify where in the visual pathway there is an abnormality or dysfunction. Furthermore, VF assessment is fundamental in diagnosis and monitoring of glaucoma patients alongside ONH assessment and IOP measurement. This is because glaucomatous VF defects have characteristic patterns of loss identifiable on evaluation of perimetry results.

1.3.2 Interpreting visual field plots

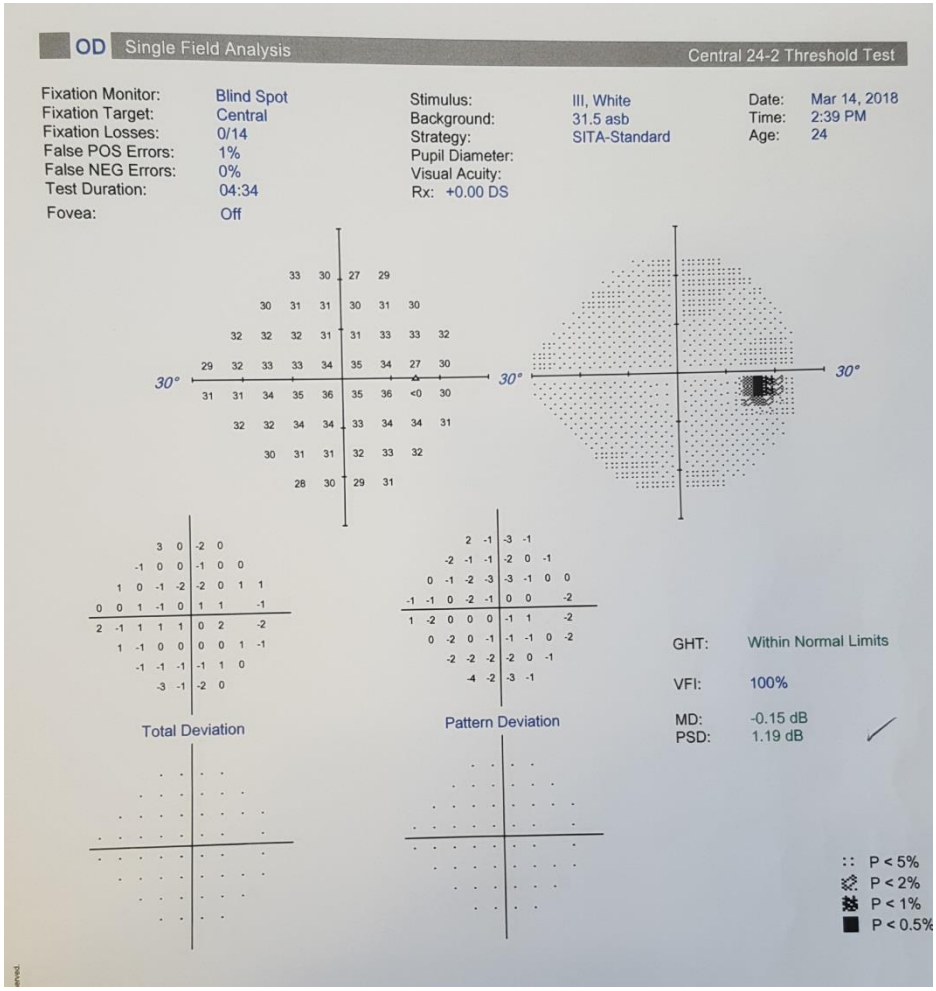


Figure 1.8 An example of a VF plot produced by the SITA Standard 24-2 program on the Humphrey Field Analyser III.

Interpreting VF plots requires a collective evaluation of the various results obtained from the test. The numerical plot (Figure 1.8) gives the threshold value at each location of the VF in decibels. The greyscale plot is not used for interpretation but can be useful when explaining the results to patients. Total deviation (TD) values compare the patient's thresholds to age-matched normal values and are calculated as the patient's threshold minus the age-matched expected threshold at that location. Negative TD values indicate a reduction in sensitivity compared to normative values. Pattern deviation (PD) and TD values are alike but PD first accounts for a generalised loss in sensitivity that could be caused by other factors such as cataracts. The PD plot shows localised loss of sensitivity in the VF. Probability values indicate the probability of a 'normal' patient producing a threshold equal to or worse than this value. For instance, a p value of <5% suggests that less than 5% of age-matched normal individuals would have the same or worse sensitivity value at that location. Both TD and PD values are presented as numerical plots as well as probability maps.

Global indices, such as Mean Deviation and Pattern Standard Deviation, give a single value result from the overall VF test. Mean deviation (MD) is a weighted average of the TD values that shows how the overall VF diverges from age-matched normative data. A MD value of 0 dB indicates no deviation from the normative data and a negative MD value represents a sensitivity loss. MD can be used as a measure of progression of overall sensitivity loss when comparing between VF results over time (Chauhan et al. 2008). The VF printout will display a p value if the MD value is lower than the MD found in 10% of age-matched normative data. Pattern standard deviation (PSD) is a weighted standard deviation that indicates how different the TD values are from each other and describes focal loss after accounting for a general reduction in sensitivity. A small PSD value indicates that the shape of VF ('island of vision') closely corresponds to the shape of a 'normal' VF. A small PSD value is also found in an abnormal VF that deviates from a 'normal' VF similarly across all VF locations tested. A large PSD value, on the other hand, indicates irregularities in the VF that show as localised VF defects.

Short-term fluctuation (STF) is a measure of consistency in the patient's response. STF is calculated from the difference between two threshold

measurements at the same point in 10 VF locations. Corrected pattern standard deviation (CPSD) is the PSD after correcting for STF. STF and CPSD are available on full threshold programmes but not on SITA programmes. The glaucoma hemifield test (GHT) (Åsman and Heijl 1992) gives an indication of asymmetry in VF loss between the superior and inferior regions. Five corresponding sections above and below the horizontal raphe are compared and if significant asymmetry is found, the GHT result states 'outside normal limits' which can be suggestive of glaucomatous damage.

Reliability indices give an indication of how reliable the VF results are and whether further analysis is warranted or whether the results should be disregarded and the test repeated. Fixation losses identify how precise the participant is at keeping their gaze fixed on the central target throughout the test. At the beginning of the test, the blind spot is located and during the test, stimuli are presented in this area. The expectation is, if the participant is fixating correctly, they will not identify these stimuli. However, if the participant does identify these stimuli, a fixation loss is recorded. A VF plot is considered unreliable if fixation losses are above ~20%.

The False Positive (FP) index is calculated from how often the patient presses the response button in the absence of a stimulus or when the patient responds too soon after the stimulus is presented. False positives are an indication that the participant is 'trigger happy' and this may indicate a lack of understanding from the participant. A false positive value of above 15% indicates that the results are unreliable and that the test needs repeating. The False Negative (FN) index may indicate a lack of concentration or if the participant is fatigued. A VF location that has already been assessed is re-tested with a brighter stimulus and if the participant does not respond, it is considered a FN response. However, significantly higher FN values have been found for patients with glaucoma in the affected eye compared to the unaffected eye (Bengtsson and Heijl 2000). This demonstrates that the FN value is not always an indication of a lack of concentration in glaucoma patients but rather a consequence of testing a glaucomatous eye (Bengtsson and Heijl 2000). This finding is thought to be associated with the fact that threshold values are also highly variable in

glaucomatous eyes (Henson et al. 2000). Therefore, the FN index is of less use when interpreting glaucomatous VF plots.

Diffuse sensitivity loss can occur in the disease process (Henson et al. 1999) but diagnosing glaucoma from this type of VF loss is difficult as diffuse loss is also found in other eye anomalies such as cataracts (Anderson and Patella 1999). However, VF loss in glaucoma usually follows a pattern similar to the underlying retinal structures affected by the disease; the retinal nerve fibre layer (Figure 1.9) (Drance 1972). More easily recognisable patterns of VF loss are localised in nature and follow a distinctive arcuate pattern (Anderson and Patella 1999).

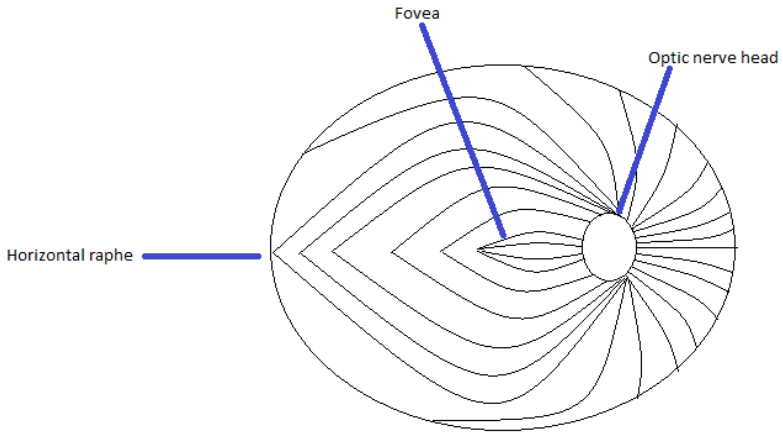


Figure 1.9 A figure illustrating the distribution of the retinal nerve fibre layer.

Paracentral defects present as absolute or relative small localised depressions in sensitivity within the central visual field (Figure 1.10). Arcuate defects begin at the point of the blind spot (ONH) and follow a curved pattern around the fovea then finish at the nasal VF. Arcuate defects can be formed by the combining of paracentral defects. Nasal step defects describe a pattern of glaucomatous loss that is asymmetric above and below the horizontal midline in the nasal VF. This pattern forms as a result of the underlying anatomical structure of the retinal nerve fibre layer.

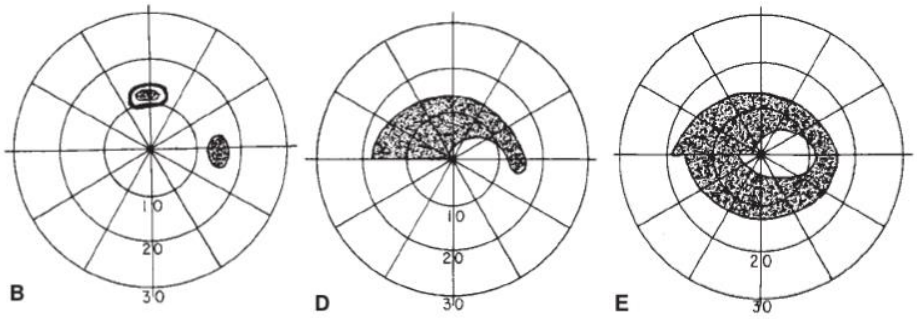


Figure 1.10 Diagrams depicting patterns of glaucomatous VF loss; B is a paracentral superior scotoma, D is a superior arcuate defect and E is an arcuate defect with a nasal step (Allingham et al. 2012).

1.3.3 Developments in perimetry

White-on-white perimetry is currently the conventional method of visual function assessment in glaucoma. However, there are some disadvantages of the technique. Limitations include; high variability in test-retest results (Spry et al. 2001), discordance in the structure-function relationship (Harwerth et al. 1999), limited dynamic range (Artes et al. 2005) and deficiency in indicating sensitivity loss at early stages of the disease (Demirel and Johnson 2001). The signal to noise ratio has been subject to improvement in perimetric techniques (Wild 1988). These improvements have focussed on reducing observer variability by reducing testing times (SITA) (Bengtsson et al. 1997), monitoring fixation and monitoring observer responses (FP, FN). Additionally, software has improved to increase sensitivity specifically to glaucomatous loss (GHT) (Åsman and Heijl 1992). However, despite these improvements, significant variability still remains using conventional perimetry (Chauhan and Johnson 1999; Spry et al. 2001).

Algorithms are used to calculate threshold sensitivities in SAP. The algorithm can affect the variability in test-retest results and the time taken to complete the test. The first method used to calculate contrast detection thresholds in SAP was the Full Threshold staircase strategy. A Full Threshold (FT) program uses the staircase method with a series of reversals to calculate contrast detection thresholds at a fixed number of locations within the VF (Anderson and Patella 1999). The step sizes start with a 4 dB change in luminance until one reversal is obtained and then the step sizes reduce to 2 dB. The contrast detection threshold at each location is calculated after two reversals in the staircase procedure and is taken as the last stimulus intensity that produced a response.

The luminance level chosen as a starting point for each location is based on thresholds obtained for neighbouring points (Anderson and Patella 1999). The FT program has shown to produce greater variability in threshold values for areas where adjacent points have significantly different thresholds such as an area in the VF with a localised depression in sensitivity (Turpin et al. 2003). High variability in threshold values from the FT program has also been found in VF defects of greater depth (Artes et al. 2002). This variability in test-retest results from FT programs can make it difficult to monitor progression of VF loss such as when monitoring glaucomatous field loss. The FT program also has its limitations in that its testing times are significantly longer than other VF programs (Chauhan and Johnson 1999). For this reason, developments to threshold algorithms have focussed on improving the accuracy of the test whilst reducing test times.

The Swedish Interactive Threshold Algorithm (SITA) program was designed to maintain the accuracy of the FT program but significantly reduce the testing time (Bengtsson et al. 1997). The SITA standard program takes around half of the time taken to complete FT test (Bengtsson and Heijl 1998a) whilst SITA Fast takes around a third of the time (Bengtsson and Heijl 1998b). A number of developments contribute to the reduced testing times of SITA programs including developments to the statistical model used in the program. The SITA program estimates thresholds based on probability models of age-matched normal and abnormal field results. As the participant is completing the test, the model continuously updates information of threshold values for the patient to estimate thresholds for the following points being tested. Other methods used in the SITA program to reduce testing times include reducing the number of “catch trials” by calculating the FP reliability index after the test is completed (Bengtsson et al. 1997). The time taken in between presentations can be altered by the SITA program to match the reaction time of the patient; if a patient is quicker at responding, the pace of the test is increased. Similarly, if the patient is slower at reacting to stimuli, the pace of the test is altered to slow down and match the patient. Although SITA programs are used in place of FT, SITA shares a similar disadvantage to FT programs in that it has high variability of test-retest results in locations of reduced sensitivity (Artes et al. 2002).

Suprathreshold perimetry is used to determine whether sensitivity at each location tested is above or below a certain criterion value. Typically, the stimulus intensity chosen for each location is based on the age of the patient (Siatkowski et al. 1996). The advantage of this technique is that it is much quicker than FT testing and can therefore be used as a screening device to check for abnormalities in the VF (Anderson and Patella 1999). This type of test determines where in the VF there is a loss of sensitivity but does not capture the quantity and depth of the defect (Anderson and Patella 1999). As a result, when monitoring disease progression such as glaucoma; the utility of threshold testing outweigh the speed advantage of suprathreshold testing. Artes et al. (2003) have suggested improving suprathreshold testing by the use of a multi-sampling suprathreshold strategy. This strategy works by testing VF locations at suprathreshold levels a number of times. Multi-sampling suprathreshold testing has demonstrated earlier detection of defects than current suprathreshold methods and is more reliable at estimating the spatial extent of the defect (Artes et al. 2003). The authors suggest that this strategy may be more suitable for new patients who are not familiar with threshold testing or those who are not able to concentrate for the length of time required for threshold programs (Artes et al. 2003). The study used computer simulations to collect the results but clinical trials are needed to confirm the results on real patients and determine the practical applicability of multi-sampling suprathreshold testing strategies.

Recent studies have shown promise in reducing test variability by using alternative threshold strategies that take into consideration structural information of the retina (Denniss et al. 2013). Other studies exploring techniques to improve perimetry include fundus-tracked perimetry (Wu et al. 2016) that continuously monitors the retina whilst assessing the VF so that precise locations are tested. These developments intend to reduce test-retest variability but further research is necessary to evaluate their utility.

1.3.4 Developments to stimuli used in static automated perimetry

The first type of stimuli used in SAP were white spots of light that varied in luminance levels presented against a white background; white-on-white perimetry. The shortcomings of using white-on-white perimetry such as in FT

and SITA programs is that these strategies have shown poor test-retest variability in results making it difficult to monitor progression of VF loss in the disease. Furthermore, as one of the main uses of VF testing is monitoring glaucomatous field loss, developments in perimetry have focussed on improving sensitivity in indicating early glaucoma VF loss. Other developments to stimuli have been based around detecting selective loss of a specific subpopulation of retinal ganglion cells.

Frequency doubling technology (FDT) perimetry uses a sinusoidal grating as the stimulus; the grating is of a low spatial frequency (< 1 cpd) and is counterphase flickered at a high temporal frequency (above 15Hz) (Johnson and Samuels 1997). FDT produces a perceptual effect of seeing twice as many bars than are physically present in the stimulus; this is known as the frequency doubling effect (Kelly 1966). The premise for FDT perimetry originates from the hypothesis that glaucoma preferentially affects magnocellular retinal ganglion cells (RGCs) more than other subpopulations of RGCs. The frequency doubling effect was thought to be mediated by magnocellular RGCs (Maddess and Henry 1992) and so initially FDT perimetry assumed to selectively test for magnocellular RGC loss. However, more recent research suggests the frequency doubling effect stems from the cortex and its deficiency in discriminating high temporal frequencies (White et al. 2002). FDT perimetry is similar to SAP in that the participant undergoes a contrast detection task but for a different type of stimulus. FDT also differs from conventional perimetry in that its stimuli cover larger areas of the VF and fewer points are tested. FDT has shown high sensitivity in detecting glaucomatous VF loss (Cello et al. 2000) and has also shown reduced variability in results compared to SAP (Chauhan and Johnson 1999).

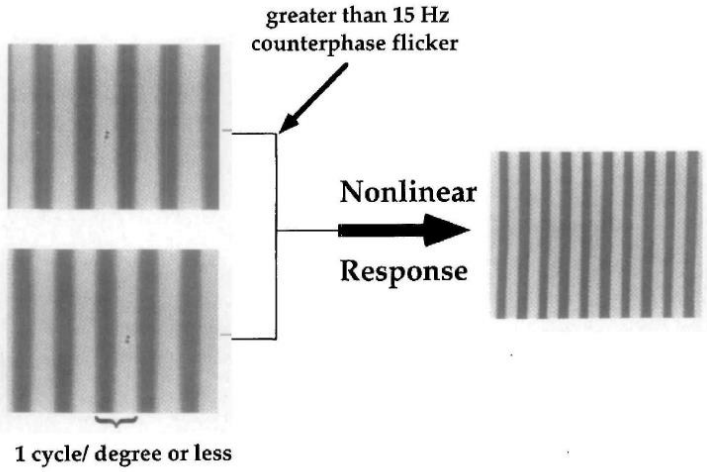


Figure 1.11 A schematic of the FDT stimulus (Johnson and Samuels 1997). A low spatial frequency stimulus that is counterphase flickered at high temporal frequencies is perceived as having twice the amount of bars present in the stimulus.

Flicker perimetry is available in different forms depending on the perimeter. The Octopus perimeter determines the critical flicker fusion frequency (CFF) of a flickering stimulus in different locations of the VF. The CFF is the frequency at which a stimulus of fixed contrast is seen to be a steady light instead of flickering (Figure 1.12). The stimulus is of a Goldmann III size and can flicker at a rate of up to 50 Hz. The observer is asked to respond when the stimulus appears to flicker. The CFF is the threshold sensitivity at a given location and is given in Hertz. Flicker perimetry has shown capability in detecting early glaucoma changes (Nomoto et al. 2009) and is less influenced by optical factors such as refractive error and media opacities compared to conventional white-on-white perimetry (Lachenmayr and Gleissner 1992). Temporal modulation perimetry (TMP) is a type of flicker perimetry available on the Medmont perimeter. TMP differs from CFF in that it measures the contrast detection threshold of a stimulus of fixed temporal frequency. Both TMP and CFF have shown similar results in test-retest reliability but TMP has shown greater capability in detecting glaucomatous field loss compared to CFF (Yoshiyama and Johnson 1997).

Figure 1.12 A diagram illustrating CFF task in flicker perimetry on the Octopus perimeter (Racette et al. 2018). At high temporal frequencies, perceiving flicker becomes more difficult and the stimulus appears as a steady light.

Flicker defined form (FDF) perimetry uses a stimulus created by a temporal illusion (Goren and Flanagan 2008). The stimulus dots are surrounded by counterphase flickered black and white dots creating the illusion of a contour between the stimulus and its background (Figure 1.13) (Goren and Flanagan 2008). The illusion is thought to be driven predominantly by the magnocellular pathway (Quaid and Flanagan 2005). However, an alternative study indicated that perception of the FDF stimulus has some input from the slow surface system driven by the parvocellular pathway (Goren and Flanagan 2008). FDF perimetry has shown the strongest structure-function relationship in glaucoma compared to FDT and SAP (Lamparter et al. 2012); the authors suggest this may be due to reduced variability from FDF perimetry results. FDF perimetry has also shown capability in detecting visual function loss in early glaucoma (Horn et al. 2015). However, the study also found that for subjects with a MD value of more than 5dB on SAP, subjects were not able to see the FDF stimulus at some VF locations (Horn et al. 2015) questioning the utility of FDF perimetry at advanced stages of the disease. The authors suggest using SAP in place of FDF for advanced glaucoma cases. FDF perimetry shows potential in being useful for glaucoma assessment but further research is warranted to show significant improvement in specificity and sensitivity of FDF compared to SAP.

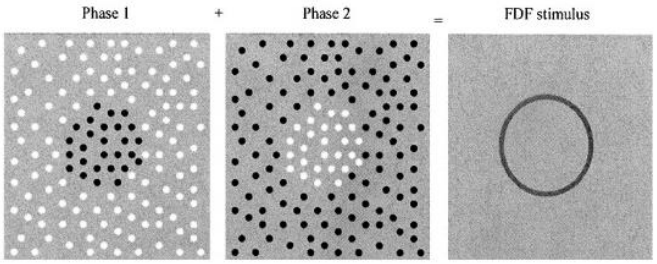


Figure 1.13 A schematic of the FDF stimulus (Quaid and Flanagan 2005). At high temporal frequencies, phase 1 and phase 2 of individual dots are not perceived but an illusion of a ring contour appears; the FDF stimulus.

Short wavelength automated perimetry (SWAP) uses a blue stimulus of Goldmann V size against a yellow adapting background. SWAP is available on the HFA and Octopus perimeters. The principle behind SWAP is to test visual function of the underlying short wavelength sensitive system mediated by the koniocellular pathway (Martin et al. 1997) (see section 1.4.7). SWAP is similar to SAP in that it is a detection task but can take longer to complete as patients require additional time at the beginning of the test to adapt to the yellow background (Racette et al. 2018). SWAP has proven useful in indicating visual function loss of early glaucoma (Johnson et al. 1995) and is capable of detecting glaucomatous field loss before white-on-white perimetry (Demirel and Johnson 2001). However, SWAP has also shown increased variability in test-retest results compared to SAP and this is thought to be caused by the reduced number of neurons sampling the retinal image (Kwon et al. 1998). An additional disadvantage is that SWAP results are affected by refractive error and media opacities unlike flicker perimetry and FDT (Delgado et al. 2002). As the current testing time for SWAP is significantly longer than for SAP, alterations have been made to the threshold algorithm on the HFA to make testing times of SWAP similar to SITA programs (Bengtsson 2003).

High pass resolution perimetry (HRP) uses a high-pass filtered ring stimulus (Frisén 1986) that is of fixed contrast and varies in size (Figure 1.14). HRP determines resolution thresholds for 50 locations within the central 30° of VF and is available on the Ophthimus perimeter (Hi-Tech Vision, Göteborg, Sweden). HRP was designed to selectively test the parvocellular pathway and as an indirect measure of underlying RGC density (Frisén 1995). However, an alternative study suggests resolution thresholds using the HRP stimulus is not

limited by RGCs sampling the retina but rather by optical factors of the eye (Ennis and Johnson 2002). Nevertheless, HRP has proven capable in indicating glaucomatous field loss and shown comparable sensitivity and specificity values with conventional perimetry (Martinez et al. 1995). HRP has also shown to indicate glaucoma progression earlier than conventional perimetry (Chauhan et al. 1999); the authors suggest this method may be useful for future clinical use due to this advantage and significantly shorter testing time compared to conventional perimetry.

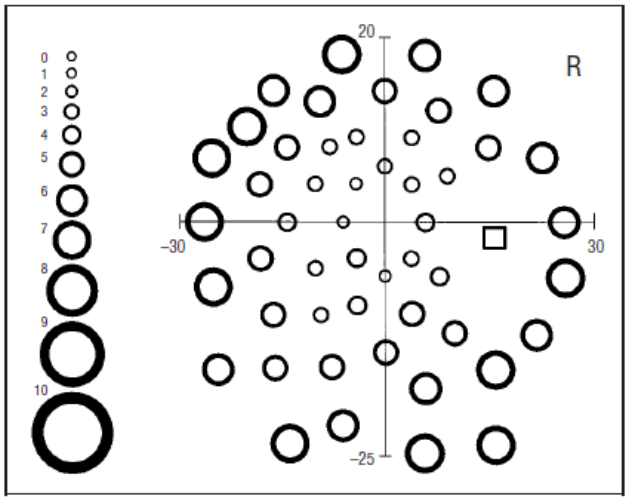


Figure 1.14 A schematic of HRP, the stimulus size changes depending on the VF location being tested (Chauhan et al. 1999).

Current SAP uses a Goldmann III (0.43°) size (Anderson and Patella 1999). SAP using Goldmann III stimulus has shown increased variability in test results in areas of reduced sensitivity (Wall et al. 2009). Furthermore, increased variability of test results and higher pointwise variation of thresholds for areas of reduced sensitivity has been found in glaucoma patients using conventional perimetry (Flammer et al. 1984) making it difficult to monitor progression and obtain an accurate measure of visual function loss from the disease. Therefore, research has investigated the use of different stimulus sizes in SAP to improve variability of test results. Studies have investigated the utility of Goldmann V size (1.72°) and VI size (3.44°) (Wall et al. 2013). Reduced variability in test results for glaucoma patients has been found using the Goldmann V compared to III size (Wall et al. 1997). However, the study used a small cohort of participants; 10 glaucoma participants and 5 controls reducing the strength of

the conclusions drawn. On the other hand, larger stimulus size of Goldmann VI has showed reduced ability in indicating sensitivity loss of glaucoma patients (Wall et al. 2013). Therefore, reduced variability of test results may come at the expense of reduced sensitivity in indicating early visual function loss and the presence of smaller scotomas. An alternative method investigated to overcome this trade-off is Size Threshold Perimetry (STP) (Wall et al. 2013). This method finds thresholds for changes in the size of the stimulus rather than changes in luminance. Wall et al. (2013) found that STP performed just as well as SAP in indicating abnormal locations of VF in glaucoma patients. The authors suggest that a longitudinal study is required to determine if STP has a significant advantage over SAP (Wall et al. 2013).

Testing the macula area for glaucomatous damage has been proposed as studies have found damaged RGCs in the macula region that do not show as a sensitivity loss on the current 24-2 VF program (Hood et al. 2013). As central VF defects correlated strongly with visual experiences of glaucoma patients (Sun et al. 2016); the authors suggest testing the central 10° may be more appropriate than the 24-2 program in assessing visual disability of glaucoma patients. This is further evidenced by findings in one study where 61.5% of glaucoma patients had VF defects detected on the 10-2 program but missed on 24-2 program (De Moraes et al. 2017) highlighting the deficiency of the 24-2 program in indicating a loss of visual sensitivity in the central VF.

However, Wu and Medeiros (2017) point out that these results show an artificial elevation in sensitivity as they are a comparison between a test that examines the whole 24° and one that only tests the central 10°. This means that the 10-2 program is more likely to pick up sensitivity loss in the central 10° as it tests more points within the same VF area compared to the 24-2 program. However, when comparing results from the central 10° of 24-2 program to 10-2 program, a marked increase in sensitivity of 10-2 over 24-2 was not found (Sullivan-Mee et al. 2016). Furthermore, a more sensitive test of the central 10° comes at the expense of not testing peripheral areas that are also affected in glaucoma. Therefore, further research in this area is required to justify a change in the area of VF being tested in glaucoma. But from this research, it is evident that there is

potential for early glaucoma diagnosis by testing the central 10°; so this test could be used in glaucoma clinics in addition to conventional perimetry.

1.3.5 Structure-function relationship in glaucoma

Discordance has been found in some studies between structural ophthalmic changes in glaucoma not relating to functional results produced by conventional perimetry, particularly in early glaucoma (Harwerth et al. 1999). Quigley et al. (1982) demonstrated that a significant number of optic nerve fibres must be damaged in glaucoma before VF results display a sensitivity loss. However, the study used a small sample size of eight glaucomatous and five normal eyes as a comparison so the results cannot be used as a strong reflection of all glaucomatous eyes. A subsequent study found that around 25-35% of RGCs must be lost before conventional perimetry detects an abnormality (Kerrigan–Baumrind et al. 2000). This study compared post-mortem counts of RGCs to SAP VF loss (Kerrigan–Baumrind et al. 2000). However, Hood and Kardon (2007) point out that the loss of 25-35% in RGC count in the glaucoma group compared to the mean count of the control group was still within the 95% confidence interval of normal RGC counts. This may have been down to the large confidence interval range of RGC count in normal eyes (Hood and Kardon 2007). This shows that the results do not support their conclusion as there is a significant overlap in RGC count between the glaucoma and control group. Furthermore, -6dB mean loss of sensitivity was found in the control group who had 100% normal RGC count. Therefore, the results of Kerrigan–Baumrind et al. (2000) actually show support for the opposite conclusion that VF loss precedes RGC loss. As studies have evidenced the misinterpretation of the data (Malik et al. 2012), the results should be interpreted with caution. Hood and Kardon (2007) propose a linear relationship between structural and functional changes in glaucoma and suggest it is the efficacy of the test that determines which is revealed first. Nevertheless, Anderson (2006) points out that novel diagnostic tests need to improve the connection between structural changes in the disease to functional test results.

1.4 Non-clinical measures of visual function

As detailed in section 1.3, conventional perimetry is currently the primary form of visual function assessment in glaucoma. This clinical test is able to detect and monitor glaucomatous visual function changes. However, this clinical test does not show how the disease affects glaucoma patients' 'everyday' visual experiences. This test has also shown reduced capability in indicating loss at early stages of the disease process (Demirel and Johnson 2001) and has shown higher variability in test results compared to other perimetry methods (Spry et al. 2001). Therefore, some research in this area has focussed on alternative measures of visual function that may improve sensitivity in detecting glaucomatous visual loss and reduce variability in test results. Researchers in this field also aim to develop visual function tests that better relate to structural changes in the disease and better relate to the visual symptoms experienced by glaucoma patients.

1.4.1 Patients' perception of vision

Crabb et al. (2013) interviewed patients about their experience of how glaucoma affects their vision. The study also presented a forced-choice task where the participant had to choose a picture from six images that best depicts their perception of vision (Crabb et al. 2013). None of the participants in the study chose the image with the black tunnel effect or black parts (Crabb et al. 2013). The study demonstrates that these types of images are a misrepresentation of vision in glaucoma patients. However, this task is limited in capturing the perception of the patient's vision as the choices were restricted in number and there was no option available for patients to decide none of the images were appropriate representations of their vision. The most common descriptors received from the open-ended questions were 'missing' and 'blur' (Crabb et al. 2013) suggesting that there is more to visual changes in glaucoma than is currently picked up by visual field testing. The participants in the study all had bilateral POAG but it would have been useful to have participants with glaucoma affecting one eye so that the participant could compare vision between the two eyes.

Hu et al. (2014) completed verbal questionnaires on 99 glaucoma patients; 75 of these patients had POAG. 55% of participants reported blurry vision as a visual symptom and 57% described needing more light (Hu et al. 2014). Of the 28 questions included, only 3 questions were open-ended and the remaining 25 questions were forced-choice with a “yes” or “no” response. This style of questionnaire could have been improved by including a gradient of options in order to capture the extent of the visual symptoms impact on the patients’ life.

Fujitani et al. (2017) used a slightly different approach in assessing patients’ perception of vision. Participants with glaucoma were asked to draw their scotoma using an Amsler chart and describe the appearance of the scotoma. 81% of patients in the study were able to describe their scotoma when completing the Amsler grid task suggesting that patients are aware of their scotomas in central and paracentral areas of the visual field affected by the disease. The study also provides evidence that glaucoma does not solely affect peripheral vision but can affect the central visual field in a range patients from those with early-moderate to advanced stages of the disease (Fujitani et al. 2017).

1.4.2 Contrast sensitivity

The range of functional vision in humans can be observed by the contrast sensitivity function (Figure 1.17).The image consists of changes in spatial frequency horizontally and changes in contrast vertically. Spatial frequency (SF) describes the number of sinusoidal cycles in a grating for one degree of visual angle. Consider the two grating images in Figure 1.15; the images are the same size but the number of cycles is greater for the image on the right demonstrating a higher SF. SF is given in cycles per degree of visual angle (cpd).

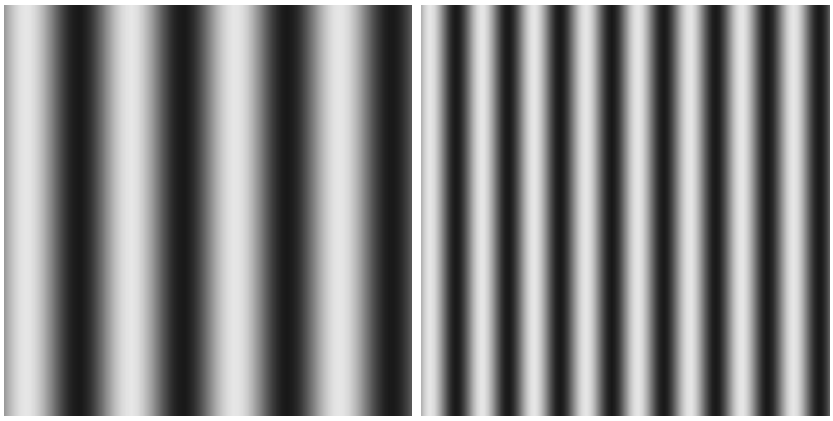


Figure 1.15 Two sinusoidal gratings with the same contrast. The image on the left has a low SF whilst the image on the right has a high SF.

Contrast describes the difference in luminance between the target object and its surround such as other adjacent objects or the background. Contrast can be calculated in various ways including using the Weber and Michelson contrast equations. Weber contrast is defined as: $L - L_b / L_b$ where L is the luminance of the target stimulus and L_b is the luminance of the surrounding background. Weber contrast is usually used as a measure of contrast when a small target is presented on a large uniform background. Grating stimuli such as the gratings in Figure 1.16 are usually defined using Michelson contrast:

$L_{max}-L_{min} / L_{max}+L_{min}$

where L_{max} and L_{min} describe the maximum and minimum luminance of the image.

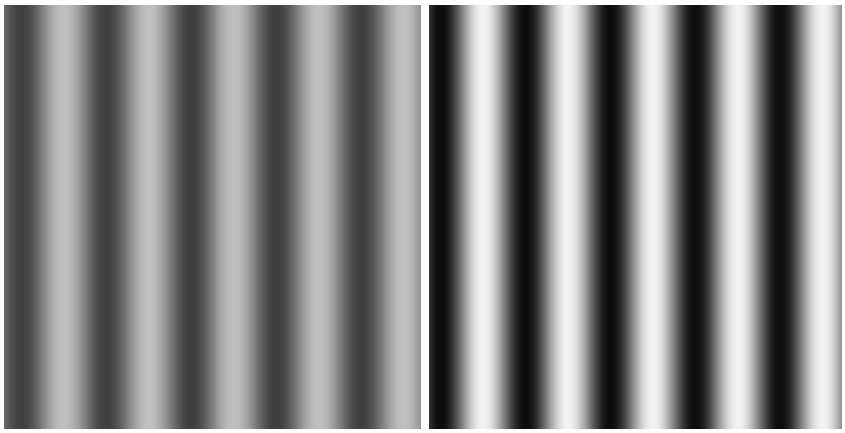


Figure 1.16 Sinusoidal gratings illustrating low (left) and high (right) contrast. The images have the same SF and average luminance but differ in contrast.

The gratings in the figure have the same SF but differ in their respective contrasts. A contrast detection threshold describes the minimum amount of contrast required to detect a stimulus. The threshold is calculated from where the participant is able to detect a stimulus of a given contrast correctly a certain percentage of time. Contrast sensitivity is the reciprocal of contrast threshold. The contrast sensitivity function (CSF) (Figure 1.17) shows the range of functional vision in humans. On the CSF, for a contrast of 100%, the highest SF detected is known as the high SF cut-off. This is the limit of the visual systems ability to resolve the pattern of a stimulus and is referred to as visual acuity.

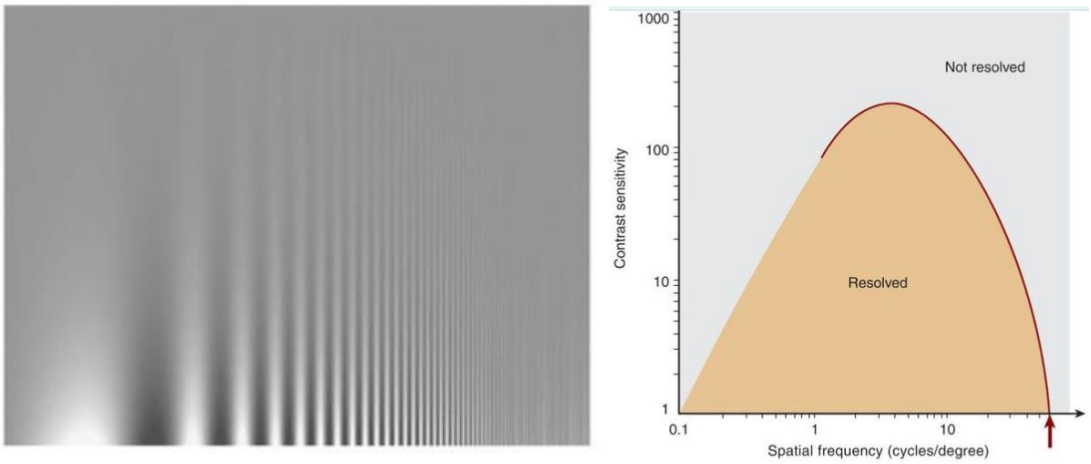


Figure 1.17 On the left, an image illustrating the CSF (Campbell and Robson 1968), SF increases from left to right, contrast increases from the top of image going down. On the right, the human CSF, the arrow points to the high SF cut-off (Schwartz 2009).

Contrast sensitivity, perimetry and visual acuity have been used to investigate visual defects in glaucoma patients (Ross et al. 1984). Contrast sensitivity functions of a static grating (CSF(S)) were categorised into three groups (Figure 1.18). 24 glaucoma patients had reduced CSF(S) for all spatial frequencies. 16 glaucoma patients had reduced sensitivity to mid-range and high spatial frequencies. Only 4 glaucoma patients had reduced CSF(S) for low spatial frequencies only and 6 patients showed no specific loss (Ross et al. 1984).

Advanced visual field loss associated with a general loss of contrast sensitivity whereas mild VF loss associated with specific loss of high spatial frequencies. This result could be explained by mechanisms that process high spatial frequencies being damaged in early stages of glaucoma. This demonstrates the spatial frequency-specific nature of reduced contrast sensitivity in glaucoma patients. Additionally, this finding could explain the increased perception of blur in early glaucoma found by Crabb et al. (2013) as loss of sensitivity to high spatial frequencies would manifest itself as a loss of acuity and potentially as increased blur perception.

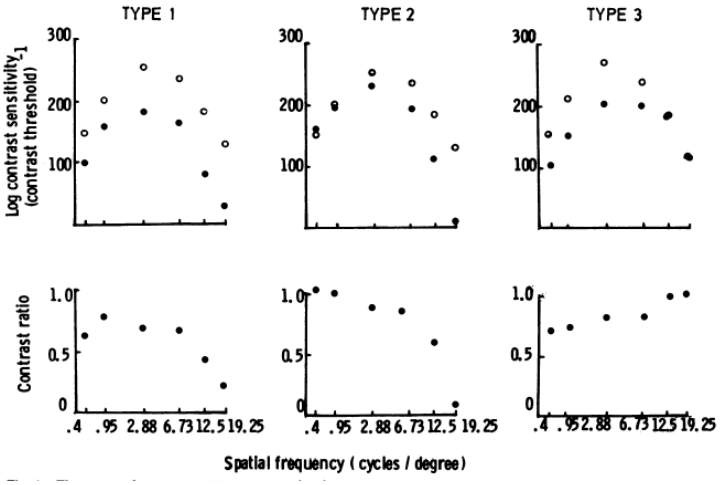


Figure 1.18 Six graphs illustrating the three types of responses in glaucoma patients compared to age-matched healthy controls (Ross et al. 1984). Glaucoma participants have black filled in circles, controls have clear circles.

The study found the most sensitive test in evaluating visual disability was monocular (CSF(S)) of a 2.88 cpd stimulus. 94% of glaucoma participants had a CSF(S) result two standard deviations from the mean CSF(S) of age-matched

controls at this SF (Ross et al. 1984). This information could be utilised when considering what parameters to use to develop new diagnostic tests for POAG. The author suggests CSF(S) could be more sensitive than conventional perimetry in indicating sensitivity loss as 30/37 patients had significantly reduced CSF(S) whilst only having mild VF loss (Ross et al. 1984). One way to test this hypothesis would be by monitoring OHT or suspect glaucoma patients using conventional perimetry and CSF(S) and comparing these results to assess which technique detects visual defects first. Ross et al. (1984) investigated the relationship between testing methods and perceived visual disability in 50 POAG patients. The study found that perceived patient difficulty strongly associated with CSF(S); the authors suggested that this test was the most appropriate method of determining the difficulties experienced by glaucoma patients above perimetry and visual acuity (Ross et al. 1984).

The effects of prolonged viewing of a stimulus on the perception of stimuli seen afterward is known as adaptation (Blakemore and Campbell 1969). Adaptation effects usually require the adapting and test stimuli to have similar properties such as SF and contrast (Greenlee and Heitger 1988). It has been suggested that adaptation is caused by a reduction in contrast gain mechanisms that decrease the signal/noise ratio making it more difficult to complete discrimination tasks (Kulikowski 1976). McKendrick et al. (2010) studied the effects of contrast adaptation on contrast detection and discrimination thresholds in glaucoma patients. The study reaffirmed findings of elevated contrast detection and discrimination thresholds in glaucoma under non-adapt test conditions. However, the study also found that when participants were adapted to a stimulus of a similar SF and contrast, glaucoma participants' discrimination thresholds were less affected by adaptation than controls, particularly at a lower reference contrast of 15%. The study did not find a significant difference in adapted detection thresholds between glaucoma and control participants ($p=0.08$) (McKendrick et al. 2010). However, this could be due to the study being slightly underpowered with the small sample size assessed (15 glaucoma participants and 15 controls). The magnocellular pathway has some involvement in contrast adaptation processing. Therefore, the authors suggest that altered contrast processing in glaucoma could be caused by pathological damage of RGCs that input into the magnocellular

pathway. An additional study of how contrast adaptation affects contrast discrimination and detection thresholds in peripheral locations would be valuable.

Contrast thresholds of sinusoidal interference fringe patterns with a SF of 1 cpd in peripheral locations were elevated in 95% of glaucoma patients in one study (Tochel et al. 2005). However, correspondence between elevated contrast threshold and area of visual field loss was found in only 50% of participants (Tochel et al. 2005). Tochel et al. (2005) suggests that contrast thresholds are not directly linked to visual field loss in glaucoma patients and could represent other functional aspects of damaged retinal ganglion cells. However, strong conclusions cannot be drawn from this study as there were some errors in the methodology. For example, the stimulus used had luminance cues as the background was black and as a result, contrast detection was not isolated during testing. Additionally, there was no form of eye tracking used in the study and as the stimulus was in a peripheral location, the participants would have had an incentive to fixate towards the peripheral stimulus. This could explain why no correspondence was found between contrast thresholds and the visual field result. Furthermore, when analysing the data, the study excluded some results consequently skewing the results. Therefore, this study is likely to be unreliable and does not give strong evidence against the potential relationship between visual field loss and contrast thresholds in glaucoma.

1.4.3 Suprathreshold contrast processing

The human CSF (Figure 1.17) has an inverted U shape with a peak around 4 cpd in the fovea. The ability to detect a stimulus is influenced by the SF content of that stimulus. Mid-range SF stimuli require less contrast to be detected than low or high spatial frequencies. However, visual function above threshold, also known as suprathreshold vision, is very different, as perception of contrast at suprathreshold level becomes independent of the SF content of the stimulus. Under suprathreshold conditions, the contrast level is perceived to be the same over a large range of spatial frequencies (Georgeson and Sullivan 1975). This occurrence is referred to as “contrast constancy” (Georgeson and Sullivan 1975). The human suprathreshold contrast function is flat compared to the

threshold CSF (Figure 1.19). The matched contrast is plotted against the SF of the stimulus for a variety of suprathreshold (standard) contrasts.

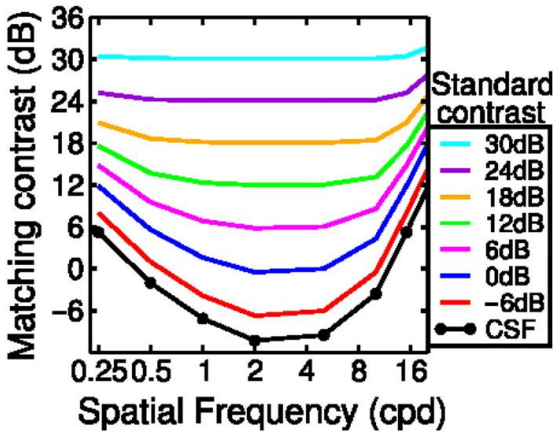


Figure 1.19 A model simulating contrast sensitivity at threshold (black line) and suprathreshold contrast matching functions (coloured lines). At lower levels of suprathreshold (standard) contrast, the contrast matching curves follow a similar pattern to the threshold CSF whereas at higher levels of suprathreshold (standard) contrasts, the curves flatten out (Hess et al. 2008).

This indicates that at suprathreshold level, perceived contrast for high and low spatial frequencies increase more rapidly to match physical contrast than mid-range spatial frequencies. Cannon (1985) found that both foveal and peripheral locations demonstrated contrast constancy even though contrast thresholds significantly increased peripherally. Elevated contrast thresholds in the periphery have been accounted for by effects of cortical magnification (Virsu and Rovamo 1979). This is where a stimulus with the same size of visual angle in the fovea and in the periphery have differing amounts of cortex allocated for processing the information. Cannon (1985) suggests that as cortical magnification factors did not appear to affect perceived contrast in the periphery, mechanisms processing suprathreshold contrast could be different to those mediating contrast detection thresholds.

Several theories have been proposed to explain contrast constancy. Georgeson and Sullivan (1975) proposed that contrast constancy is produced by changes in contrast gain properties at suprathreshold level; where stimuli that have varying levels of input have their outgoing signals made equivalent. These mechanisms within cortical channels compensate for the lack of sensitivity at higher spatial frequencies and therefore suprathreshold contrast sensitivity does

not show the same attenuation that is present under threshold conditions. Brady and Field (1995) discuss a multi-channel model to explain the effects of contrast constancy that does not include changes in contrast gain as a requirement. The authors propose that the visual system has the same peak response regardless of spatial frequency, thus resulting in contrast constancy under suprathreshold conditions (Brady and Field 1995).

Conversely, other studies have found that suprathreshold contrast matches are not constant over a range of spatial frequencies and follow a similar pattern to the CSF at threshold (Bex and Makous 2002; Haun and Peli 2013). Haun and Peli (2013) found that perceived contrast of a natural image was largely influenced by mid-range spatial frequencies and less by high or low spatial frequencies. One explanation for this discrepancy could be the difference in the type of stimuli used between these experiments. Bex and Makous (2002) and Haun and Peli (2013) used natural complex stimuli whereas Bradley and Field (1995) and Georgeson and Sullivan (1975) used simple stimuli such as sinewave gratings and Gabor patches.

1.4.4 Complex vs simple stimuli

Simple stimuli such as sinewave gratings have been used in experiments in order to correctly isolate cortical channels allocated to processing a specific type of information and allow inferences to be made about visual processing of that type of stimuli. Using simple stimuli has allowed components of the stimulus to be controlled such as the spatial frequency content. Research has then compared data sets to build up an understanding of how the visual system processes different types of stimuli. The rationale behind the use of simple stimuli is the notion that the visual system acts as a Fourier analyser by deconstructing any image on the retina into its simpler components and processing all images by these derived simple stimuli.

However, others argue that simple stimuli are not representative of ‘real world’ images where the visual system simultaneously processes a range of stimuli. The challenge of using complex stimuli is not being able to isolate and identify with certainty which components within the complex stimuli are responsible for

the visual systems response. Furthermore, the visual system has mechanisms to suppress subsets of information from complex stimuli and this process is known as “response normalisation” (Graham and Sutter 2000). At threshold, the visual system has shown a suppressive response to low spatial frequencies compared to high spatial frequencies when adapted to complex natural scenes (Bex et al. 2009); this response being quite different to the CSF of simple sinewave grating stimuli. These contrasting results suggest that assessing both simple and complex stimuli in experiments would be valuable in bringing different perspectives to our understanding of how the visual system responds to varying stimulus properties under everyday viewing conditions.

Currently, contrast sensitivity has shown to be useful in assessment of amblyopia, a developmental condition usually affecting one eye and significantly limiting vision. Under threshold conditions, amblyopia has been found to result in reduced contrast sensitivity specifically at high spatial frequencies (Figure 1.20) (Hess and Howell 1977). However, Hess and Bradley (1980) found that under suprathreshold conditions, that is representative of ‘everyday vision’, no contrast coding abnormalities were found in amblyopia suggesting that under suprathreshold conditions, contrast processing is not mediated by the same factors that process contrast at threshold.

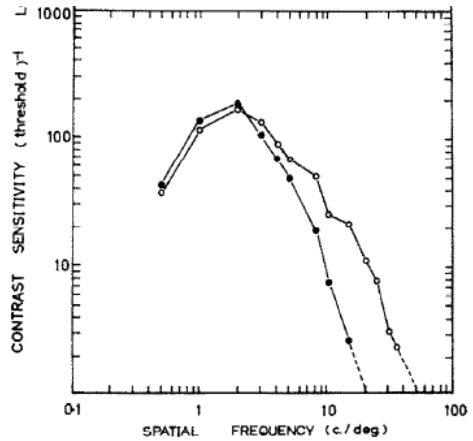


Figure 1.20 A CSF for a participant comparing the healthy eye (open-circles) to the amblyopic eye (filled-circles). The amblyopic eye has reduced sensitivity to high spatial frequencies (Hess and Howell 1977).

As amblyopia is a neural condition, the lack of impairment at suprathreshold level could be explained by neural compensation of contrast processing (Hess and Bradley 1980). Magnocellular RGCs have been shown to play a significant role in contrast adaptation in the macaque (Solomon et al. 2004). This was previously thought to be first processed further along the visual pathway in cortical cells. As RGCs play a significant role in contrast processing and are the

site of damage in glaucoma, suprathreshold contrast processing could be impaired in glaucoma. Furthermore, neural compensation would not be expected in glaucoma as it is a degenerative condition compared to amblyopia that is developed at an early stage but is a stable condition. Impairment of threshold contrast sensitivity has been found in glaucoma and so a subsequent experiment investigating whether suprathreshold apparent contrast is affected by the disease would be valuable.

1.4.5 Selective vs non-selective loss in glaucoma

The magnocellular (M) pathway detects contrast over a large range of luminance levels and is specifically involved in motion processing (Ferrera et al. 1992). Whilst the parvocellular (P) pathway plays an important role in high contrast (Allison et al. 2000) and high SF processing (Merigan et al. 1991). Findings of damage to large axons in glaucoma (Quigley et al. 1987) led to the theory of selective damage to the larger sized magnocellular RGCs in the disease process. As the M pathway is sensitive to high temporal and low SF stimuli (Derrington and Lennie 1984), studies have investigated selective M cell loss by changing testing conditions to isolate the M pathway. Studies have found sensitivity loss in glaucoma patients when using motion perimetry and temporal flickering stimuli (Bosworth et al. 1997; Yoshiyama and Johnson 1997) suggesting specific impairment to the M pathway.

However, when comparing between conventional perimetry and motion perimetry, a greater sensitivity loss using motion perimetry has not been found (Sample et al. 1995). This could suggest that there is no specific loss of the M pathway or that current psychophysical methods assuming to isolate the M pathway are failing to do so. Although the M pathway is known to be sensitive to low spatial and high temporal frequencies, there is considerable overlap between M and P pathway visual functions (Merigan and Maunsell 1993). For instance, Merigan and Maunsell (1993) highlight that there is only 15% difference in peak spatial and temporal frequencies between the two pathways. Definite isolation between M and P pathways has been found in contrast gain properties, colour opponency and the time response of each cell type (Merigan and Maunsell 1993). Alternative psychophysical methods need to be developed

in order to correctly isolate the M pathway to give a true measure of selective loss.

An opposing theory arguing non-selective RGC loss in glaucoma suggests that the apparent loss of larger cells in glaucoma is due to the shrinking of the entire cell population when on examination misleadingly appears to affect the larger RGCs to a greater extent (Morgan 1994). Others suggest that both M and P pathways do not work in isolation but have varying amounts of responsibility in visual processing depending on the properties of the stimulus (Drasdo 1989). Taking these theories into consideration, studies inferring M or P isolation could be alternatively interpreted as predominantly mediated by either pathway.

Pokorny and Smith (1997) investigated if psychophysical tests could demonstrate individual characteristics of M and P pathways in relation to contrast gain signatures using three types of testing conditions. The study found using the steady-pedestal paradigm (Figure 1.21) with a uniform background and a steady incrementing/decrementing stimulus isolated the M pathway whilst the pulsed-pedestal paradigm isolated the P pathway (Pokorny and Smith 1997). Finally, using the pedestal-Δ-pedestal paradigm, both pathways could be inferred as this paradigm assesses both low luminance changes and high luminance changes that are thought to be mediated by the M and P pathways respectively (Pokorny and Smith 1997).

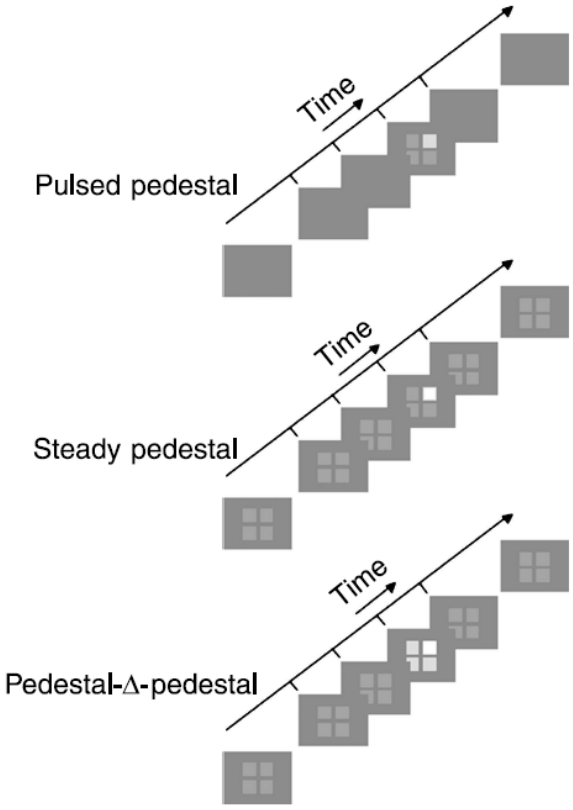


Figure 1.21 A diagram illustrating the three paradigms used to infer underlying M and P pathways (Pokorny 2011). In the pulsed pedestal paradigm, observers viewed a blank screen during the adaptation period and then were presented with a 4-AFC task during the trial. Three of the four squares had equal luminance with the fourth square having an increment/decrement in luminance compared to the other three squares. In the steady pedestal paradigm, observers adapted to four identical squares of equal luminance and in each trial, one of the four squares had a luminance increment or decrement. Finally, in the pedestal-pedestal paradigm, the adaptation period was the same as that of the steady pedestal paradigm. However, for the trial, all four squares had a luminance increment; three squares with an equal increment and the fourth square having a greater increment in luminance compared to the other three.

Sun et al. (2008) investigated contrast gain signatures for inferred M and P pathways in glaucoma patients using the pedestal-Δ-pedestal paradigm technique adapted from Pokorny & Smith(1997). At lower Δ L pedestal, mean foveal contrast discrimination thresholds were significantly higher for glaucoma participants compared to controls (for 0.0 and 0.3 Δ Lpedestal, discrimination thresholds greater by 0.2 & 0.1 log units respectively) indicating greater reduction in contrast sensitivity for the M pathway (Sun et al. 2008). Whereas, at higher Δ Lpedestal, mean contrast discrimination thresholds were similar for glaucoma participants and controls indicating no reduction in sensitivity for the

P pathway. Contrast gain signatures were also significantly reduced for M pathway whilst unchanged for P pathway (25/27 glaucoma patients within 95% CI for P pathway) (Sun et al. 2008).

In contrast, McKendrick et al.(2004) found increased discrimination thresholds for both M and P pathways at foveal and 12.5° eccentricity but no significant difference between the two thresholds for M and P pathways indicating no selective reduction of either pathway in early glaucoma. The difference in results from the Sun et al. (2008) study might be explained by the methodological differences between the two studies. McKendrick et al. (2004) used the steady-pedestal paradigm (for M pathway) and pulsed-pedestal (for P pathway) whilst Sun et al. (2008) used the pedestal-Δ-pedestal paradigm to infer both pathways (methods developed from Pokorny and Smith 1997). Additionally, McKendrick et al. (2004) used incrementing and decrementing interleaving stimuli and a 2-alternative forced choice task whilst Sun et al. (2008) used incrementing stimuli only and a 4-alternative forced choice task.

Additionally, Sun et al. (2008) investigated the causes for change in contrast gain signatures in the M pathway using model simulations of RGC response functions. The study found that an increase in contrast semi-saturation increases contrast discrimination thresholds and decreases contrast gain signatures matching the response of the M pathway. Based on these simulated results and previous histologic findings of reduced dendritic arbor thickness in M cells of glaucomatous primate retina (Weber and Harman 2005), Sun et al. (2008) hypothesised that reduced dendritic complexity and thickness of RGCs in glaucoma patients reduces effective retinal illuminance which increases the semi-saturation contrast and causes a decrease in contrast gain signatures.

1.4.6 Foveal and Peripheral acuity

Detection acuity is the limit of the visual system's ability to detect the presence of a stimulus. Resolution acuity is the limit of the visual system's ability to resolve the pattern/detail of a stimulus. Detection and resolution acuities at the fovea are of a similar value. Whereas, peripheral detection acuities are much higher than peripheral resolution acuities (Figure 1.22) (Thibos et al. 1987a).

Furthermore, peripheral resolution acuities decrease rapidly with eccentricity (14 cpd at 5° eccentricity compared to 2.6 cpd at 35° eccentricity (Thibos et al. 1987a).

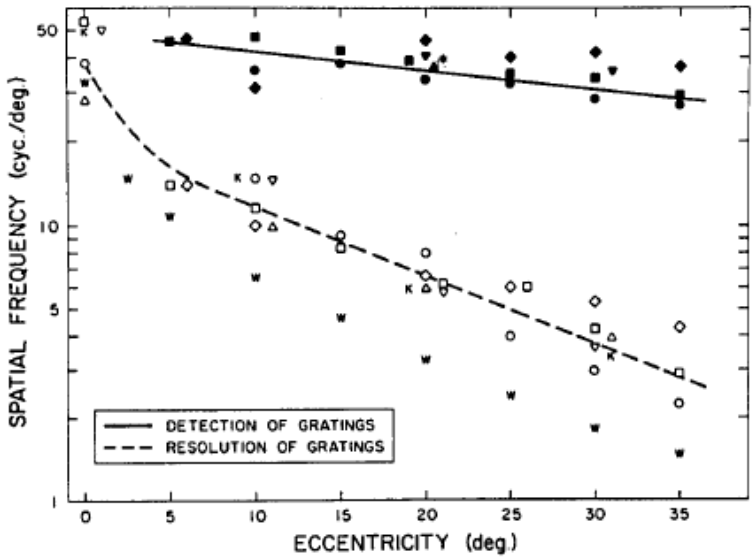


Figure 1.22 shows detection and resolution acuities in relation to eccentricity from the fovea (Thibos et al. 1987a).

Central foveal acuity is limited by a combination of optical and neural factors. Firstly, optical limits are able to reduce foveal acuity. For instance, pupils larger than 2mm result in greater amounts of aberration received by the eye and thereby reduce the quality of the image perceived (Campbell and Green 1965). Thereafter, the spacing between cone photoreceptors was shown as the retinal factor limiting foveal acuity (Hirsch and Curcio 1989). In addition, the optics of the eye act as a filter in the fovea by removing any stimulus with a SF higher than the foveal acuity limit (Campbell and Gubisch 1966) and therefore these stimuli are not perceived.

In the periphery however, neural limits fall off faster than optical limits (Millodot et al. 1975), meaning it is primarily the neurons sampling the retinal image that limit peripheral resolution and not the optics of the eye (Thibos et al. 1987a). This observation is described as sampling limited and is evidenced by the ability to perceive aliasing in the periphery (Thibos et al. 1987b; Anderson and Hess 1990). Aliasing is an illusion whereby stimuli beyond the resolution limit are misrepresented and perceived as a different orientation, direction or lower SF

than the actual stimulus. Thibos et al. (1987a) suggest that peripheral grating detection acuity is limited by the receptive field size of RGCs whilst peripheral resolution acuity is limited by the spacing between RGCs. This was evidenced by the close agreement found between RGC spacing and the minimum angle of resolution (MAR) suggesting the spacing between these cells can be inferred from MAR (Figure 1.23).

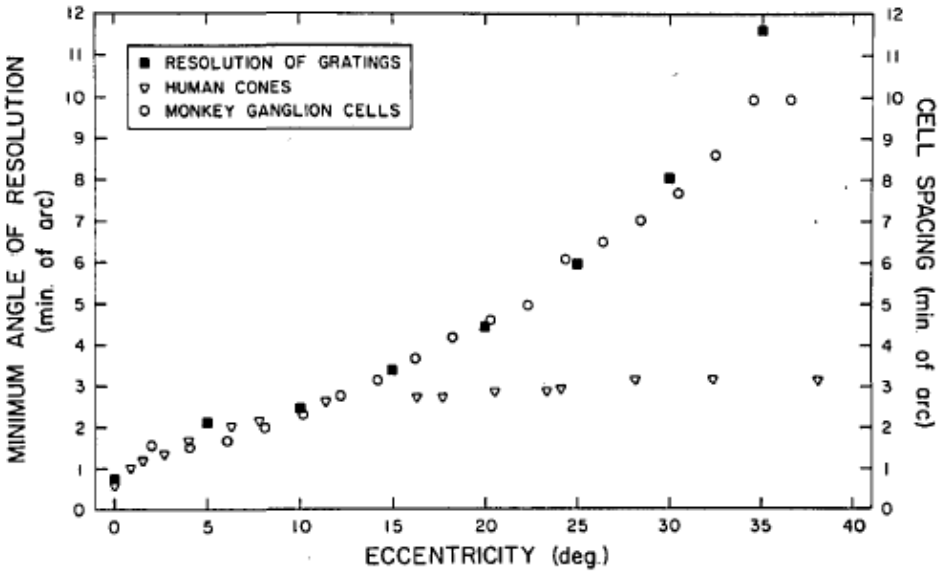


Figure 1.23 A graph showing the correspondence between MAR and RGC spacing (Thibos et al. 1987a).

Therefore, peripheral grating resolution acuity can be used to infer the underlying density of RGCs. Similarly, Thibos et al. (1987) investigated what could be responsible for the retinal limit of detection and found it is due to the largest receptive field size in the system which belongs to the RGCs. Increasing RGC receptive field sizes in the periphery as well as reduced cortex space allocated to processing peripheral vision results in peripheral vision being more blurred than central vision (Anstis 1998).

Achromatic foveal Vernier acuity thresholds were elevated in POAG patients compared to age-matched controls when accounting for contrast detection thresholds ($p=0.04$) (McKendrick et al. 2002). However, no correlation was found between visual field defects and foveal Vernier acuity measurements. This finding could be explained by the fact that current perimetry techniques

need a greater loss of RGCs centrally than peripherally to identify a loss in sensitivity (Garway–Heath et al. 2000). Although the results show that Vernier acuity thresholds can indicate impaired function in POAG patients, it is unclear what underlying mechanisms are responsible for this finding. The authors suggest that Vernier acuity may imply the underlying RGC spatial sampling impairment but currently there is little evidence to support this hypothesis.

Beirne et al. (2003) found that glaucoma patients showed significantly reduced peripheral grating resolution acuities in corresponding areas where significantly reduced sensitivities were not found with perimetry. This supports the argument that areas classed as 'normal' in glaucoma patients according to VF testing could be 'abnormal' (as RGCs have been damaged) but have not been detected yet. This also highlights the utility of peripheral resolution acuity in indicating the presence of glaucomatous damage. On the other hand, Spry et al. (2005) found that resolution acuity perimetry had the lowest level of repeatability (17% confirmation rate) on a one year follow up compared to other perimetric tests. This could suggest resolution acuity perimetry is not as useful as other techniques in monitoring glaucomatous optic neuropathy changes. However, this poor performance could be because of the techniques used to assess resolution acuity perimetry; a 2-alternative forced-choice method was used which can increase the chances of guessing correctly and the number of response errors leading to increased variability in threshold values.

1.4.7 Short wavelength sensitive system

Studies have investigated whether there is a selective loss of certain types of RGCs in POAG. One theory suggests a specific loss of sensitivity of the short wavelength system mediated by bistratified RGCs. Histologic studies have found that there is specific damage to RGCs with larger cell bodies and axons in glaucoma (Glovinsky et al. 1993) that could comprise bistratified RGCs. There is also evidence proposing that bistratified RGCs form a third parallel pathway known as the koniocellular pathway processing blue-yellow opponent information (Martin et al. 1997).

Based on this theory and current evidence, Beirne et al. (2003) investigated whether there is selective death of bistratified RGCs in open-angle glaucoma using psychophysical methods. The study used peripheral chromatic resolution acuities as an inference for the density of underlying bistratified RGCs. The study found that both achromatic and chromatic acuities were lower in glaucoma patients compared to controls (Beirne et al. 2003). However, there was no significant difference in chromatic/achromatic acuity ratios between glaucoma patients and controls indicating no selective loss of bistratified RGC loss in open-angle glaucoma. The authors suggest that there is selective loss of bistratified RGCs in some individuals in the study as significantly lower resolution acuities were found in some retinal locations of some glaucoma patients (Beirne et al. 2003). However, a more likely representation of selective loss in an individual would be findings of significantly reduced resolution acuities in all four locations of the same individual.

SWAP isolates the SWS system by using a yellow background to adapt the medium and long sensitive pathways. As detailed in section 1.3.4, SWAP investigates whether there is selective short wavelength sensitivity (SWS) loss in glaucoma and has demonstrated its ability in producing repeatable visual field defects in glaucoma patients that can be detected earlier than white-on-white perimetry (Sample and Weinreb 1992; Spry et al. 2005). Some may argue that this is evidence for selective damage of bistratified RGCs. However, Johnson (1994) disagrees with this concept and suggests an alternative; the reduced redundancy hypothesis. This hypothesis suggests that visual field defects may be detected earlier using SWAP as the underlying bistratified cells are more sparsely located. These cells therefore have less overlapping receptive fields relative to cells from other subpopulations (Johnson 1994). Furthermore, under white-on-white perimetric conditions, the relative loss of RGCs from the SWS system does not affect overall function as other subpopulations can compensate for the loss of these cells. Johnson (1994) suggests that redundancy as well as the relative loss of a RGC subpopulation must be considered when developing novel clinical testing methods to diagnose POAG.

McKendrick et al. (2002) found increased foveal Vernier acuity thresholds in POAG patients compared to age-matched normals' for the SWS system

(p=0.002) and the M pathway (p<0.001). However, the study did not account for contrast detection thresholds that is known to affect Vernier acuity measurements (Westheimer et al. 1999). As a result, it is unclear how much the reduction in Vernier acuity is mediated by the SWS system alone compared to the reduction in contrast sensitivity.

1.4.8 Blur detection and discrimination

A blur detection threshold describes the minimum amount of blur in a stimulus required to distinguish between a blurred and a clear/sharp stimulus. A blur discrimination threshold is the smallest difference in blur required to distinguish a difference between two blurred stimuli. Typical blur discrimination tasks involve a reference blur that is presented and compared to a test blur with an increment in blur (Figure 1.24). The task is usually a 2 alternative-forced choice method and threshold is taken from around 75% of the blur discrimination function; that is where the observer was able to correctly identify the test blur 75% of the time.

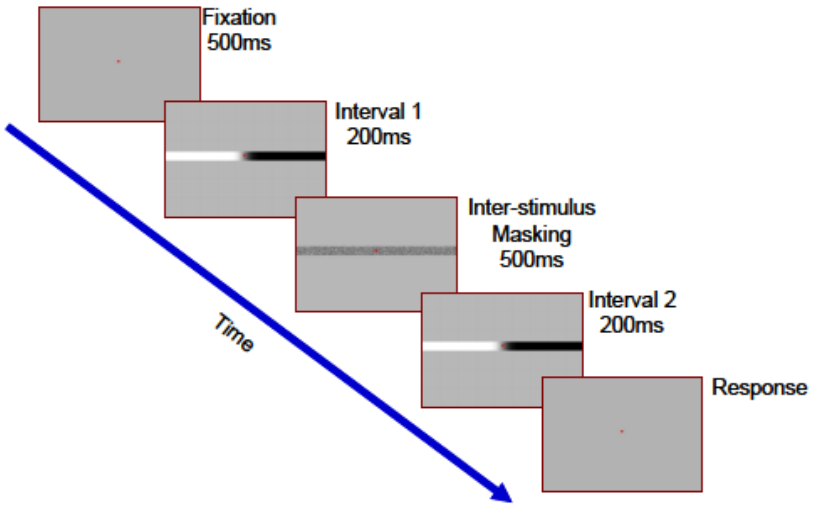


Figure 1.24 A diagram illustrating a psychophysical method used to determine a blur discrimination threshold (Chen et al. 2009). Interval 1 and 2 randomly present either the reference or test blur.

Blur discrimination functions are characteristically “dipper” in shape (Figure 1.25). The y-axis intercept represents the blur detection threshold measured at

the fovea for a reference blur of 0 (clear stimulus) and has a value of around 0.6 arcmin (Hess et al. 1989). Interestingly, as the reference blur increases, the threshold for discrimination decreases for the first part of the dipper function resulting in blur discrimination thresholds being lower than detection thresholds (Hamerly and Dvorak 1981). Blur discrimination thresholds in the fovea have been found as 0.15 arcmin for a reference blur of 1 arcmin for a healthy observer (Watt and Morgan 1983). After this lowest point on the function is reached, blur discrimination thresholds begin to rise with an increment in blur.

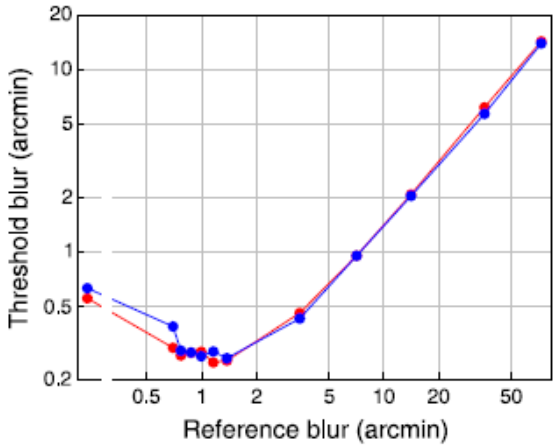


Figure 1.25 A blur discrimination function for two observers. Data from Hess et al. (1989), cited in Watson and Ahumada (2011).

Hess et al. (1989) found that the dipper shape of the blur discrimination function is maintained with eccentricity and the function is vertically displaced (Figure 1.26). This suggests that there is a consistency in how the visual system responds to varying amounts of blur with respect to eccentricity. However, these results need to be interpreted with caution as it is unclear how the authors controlled fixation during the experiment.

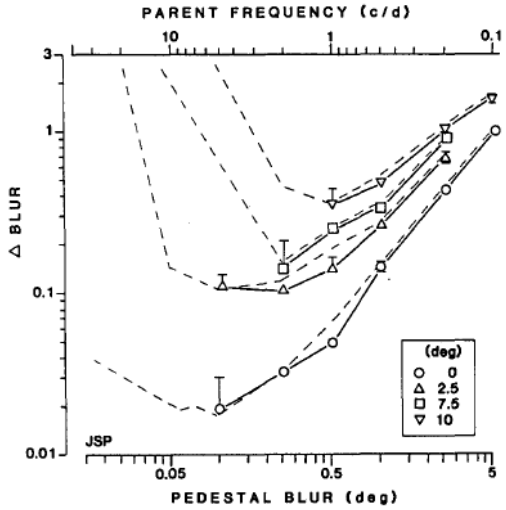


Figure 1.26 A blur discrimination function of the fovea(circle) and eccentricities of 2.5°(triangle), 7.5°(square) and 10°(inverted triangle) (Hess et al. 1989).

It has been reported that mean luminance does not significantly affect blur discrimination thresholds (Chen et al. 2009). Similarly, contrast levels above 30% have little effect on the blur discrimination function. These results indicate that blur discrimination is independent of luminance and high contrast levels (Hess et al. 1989). However, contrast levels below 10% have been shown to displace the blur discrimination function vertically, thereby increasing blur discrimination thresholds (Hess et al. 1989). Chen et al. (2009) propose that reduction in contrast gain properties at low contrast levels account for the vertical displacement of the blur discrimination function at these low contrast levels.

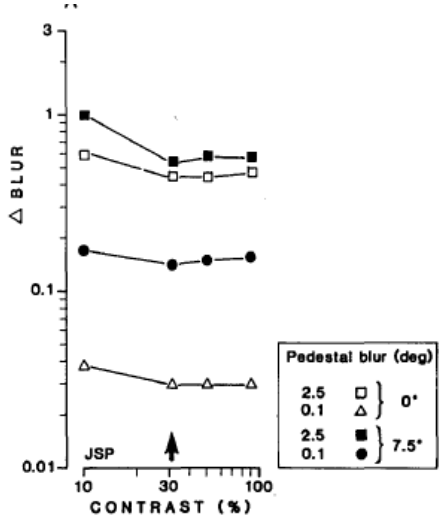


Figure 1.27 Blur discrimination thresholds at varying eccentricities in relation to contrast (Hess et al. 1989). Thresholds level off beyond 30% contrast.

The majority of blur profiles used in blur discrimination experiments are Gaussian derived and some have questioned the effects of different forms of blur on blur detection and discrimination thresholds. However, Watt and Morgan

(1983) have demonstrated that the type of blur used does not affect thresholds as they used three different types of blur formation in their experiments (Gaussian, cosine and rectangular) and did not find a significant difference in thresholds using these different profiles of blur.

Two main models have been proposed to explain the visual systems response to blur; the Weber model and the visible contrast energy (ViCE) model (Watson and Ahumada 2011). The Weber model has been presented in several studies such as Mather and Smith (2002) and Pääkkönen and Morgan (1994) and was originally developed by (Watt 1988). The model describes the blur discrimination threshold being produced when the test blur is a certain multiple of the reference blur. The model incorporates a component of intrinsic blur that is produced within the visual system as well as the contribution of external image blur. However, the concept of intrinsic blur cannot be quantified by the model and as a result; perceived blur cannot be calculated directly from the amount of image blur. Furthermore, Watson and Ahumada (2011) argue that the Weber model does not appropriately account for contrast that is known to affect blur perception at low contrast levels (Hess et al. 1989). The ViCE model describes the blur discrimination threshold being reached when the difference in contrast energy between two blurred stimuli reaches a criterion value (Watson and Ahumada 2011). Instead of incorporating a concept of intrinsic blur, the ViCE model explains blur discrimination with respect to the CSF.

Blur perception has proven important in accommodative processes (Kruger and Pola 1986), motion detection (Harrington and Harrington 1981) and as a cue for depth perception (Mather and Smith 2002). Blur acts as a stimulus for the visual system to accommodate to the position of the image being viewed (Kruger and Pola 1986) as this reduces the amount of blur perceived. Mather and Smith (2002) found that varying levels of blur played a role in the visual systems ability to judge the degree of depth of a retinal image. Moreover, Harrington and Harrington (1981) found that motion perception involves the image of a moving stimulus to be perceived as blurred and the extent of blur is associated with the velocity of the stimulus. In this manner, research into the applicability of blur in other areas of vision processing has been suggested.

As glaucoma patients have highlighted the increase in perception of blur as a visual symptom of the disease (Crabb et al. 2013), experiments of blur discrimination may provide evidence for this perceptual experience. Furthermore, this information could be utilised in novel diagnostic tests for glaucoma as blur is an easy concept to explain to patients and one that they readily understand compared to other visual cues such as contrast that take some explanation and can be misinterpreted by patients.

1.4.9 Spatial Summation

Spatial summation describes the pooling of receptor signals to create a combined single response. For instance, a greater number of rod, relative to cone, photoreceptors connect to a single RGC. This results in greater spatial summation under scotopic conditions causing the scotopic system (mediated by rods) to have greater absolute sensitivity than the photopic system (mediated by cones). Ricco's area describes the perceptive field size where there is complete spatial summation. Within this area, the product of threshold intensity and stimulus area is constant. When the stimulus size is beyond the size of the critical area, complete spatial summation begins to break down and Piper's law of partial summation is followed. Beyond this point, the response follows probability summation where exact summation is not known and is only predicted. The size of Ricco's area increases with eccentricity (Wilson 1970) but decreases with an increase in background intensity (Barlow 1958). Theories explaining the basis of Ricco's law have been disputed. One hypothesis suggests that Ricco's law ceases to exist beyond the critical area as there are spatial inhibition mechanisms at work for stimuli greater than this size. Some propose the inhibitory mechanisms occur at the retinal level mediated by RGC density (Volbrecht et al. 2000) or by the receptive field size of RGCs (Glezer 1965). Others suggest that optical factors contribute to spatial summation limits at the fovea (Dalimier and Dainty 2010). Whilst Swanson et al. (2004) proposed a two-staged neural model to explain spatial summation and suggest the limits of Ricco's area stems from higher cortical levels rather than at the retinal level.

The size of Ricco's area does not change with age under photopic conditions (Redmond et al. 2010b) but has been shown to increase in size in early

glaucoma for achromatic and chromatic (SWS) stimuli (Redmond et al. 2010a). Peripheral resolution acuities were also significantly worse in glaucoma patients compared to age-matched controls indicating reduced RGC densities in glaucoma patients (Redmond et al. 2010a). Fellman et al. (1988) found that increasing the size of a Goldmann stimulus from III to V in perimetry threshold measurements increased sensitivity in glaucoma patients more than increasing the contrast of stimuli. This was not observed in healthy controls suggesting that spatial summation is altered in the disease process. Fellman et al. (1988) suggest that the enlargement of Ricco's area in glaucoma is produced by pathological summation where loss of RGCs causes more widespread located cells to combine signals and produce higher levels of sensitivity than expected for the corresponding physiological area.

As SAP uses a Goldmann III stimulus, only thresholds beyond 15° eccentricity are following Ricco's law and are under complete spatial summation (Redmond et al. 2010a). Within 15° eccentricity, probability summation occurs. Given this information, it is important to recognise that stimulus size and location within the visual field must be taken into consideration when interpreting threshold values for SAP (Redmond et al. 2010a). Whilst probability summation is in place, the exact amount of RGC damage taking place is difficult to predict as there is considerable overlap between the receptive fields of RGCs. On the other hand, under complete spatial summation, better direct estimates are possible for the extent of damage to RGCs. Therefore, interpretation of SAP results when monitoring glaucoma patients' requires some caution and awareness that current stimuli used in SAP do not account for spatial summation properties of the visual system.

Rountree et al. (2018) found that varying the size of a stimulus significantly increased the signal/noise ratio (SNR) in detecting glaucomatous damage more than varying the contrast of a stimulus. The authors suggest that area modulated stimuli are more appropriate for use in SAP than the Goldmann III stimulus currently used. However, on further inspection of the results, it is apparent that improvement in the SNR from area modulated stimuli was small for glaucoma participants with lower and middle TD values and only proved

particularly useful at higher TD values. This indicates that the utility of area modulated stimuli is only proven in advanced stages of the disease.

1.4.10 Crowding

Crowding is a visual phenomenon that describes the difficulty in recognising objects in a cluttered visual environment (Flom et al. 1963; Levi 2008; Whitney and Levi 2011). The perception of crowding has been described as a jumbled appearance where the target stimulus appears more similar to close by flanking (crowding) stimuli (Whitney and Levi 2011). Crowding affects a number of visual function measures including letter recognition/resolution (Astle et al. 2014), orientation acuity (Livne and Sagi 2007) and Vernier acuity (Levi et al. 1985). However, it has been demonstrated that crowding does not affect the detection of stimuli but rather the ability to discriminate between stimuli (Levi et al. 2002a). Therefore, in a crowded visual environment, the observer is able to detect the stimulus but not resolve its detail. Crowding is an important aspect of visual function to consider when investigating suprathreshold visual function as in our natural visual environment, stimuli are not presented in isolation (as we typically measure in psychophysical experiments), but rather, are presented in a complex scene; a cluttered visual environment. Therefore, crowding can affect many aspects of daily visual function by degrading performance of tasks such as reading (Pelli et al. 2007), visual search (Whitney and Levi 2011) and driving (Xia et al. 2020).

It has been demonstrated that for a given target stimulus at E° eccentricity, any flanking stimuli within the distance of 0.5 x E, will induce effects of crowding and degrade performance of the discrimination task (Bouma 1970). This distance is known as critical spacing and has been widely used as a measure of the extent of visual crowding (Astle et al. 2014; Ogata et al. 2019). Furthermore, as flanking stimuli are moved further away from the target stimulus, crowding effects reduce until the critical spacing is reached; at which point, reduction in performance induced by crowding flankers no longer occurs. However, the extent of critical spacing can vary from that defined from Bouma's rule depending on the stimulus and task used (Levi 2008). For instance, it has been shown that the extent of critical spacing can range from 0.1 x E° in the

tangential direction to 0.5 x E° in the radial direction for an eccentricity of 10° and can vary significantly between observers (Toet and Levi 1992). Therefore, Bouma's rule should be used more as an approximation rather than an exact calculation for extent of critical spacing with respect to eccentricity.

Crowding is affected by the position and similarity of flankers to target stimuli. For instance, for horizontal eccentricities, horizontally arranged flankers are more potent than vertically arranged flankers whilst the opposite is true for vertical eccentricities (Toet and Levi 1992). This is known as anisotropies of crowding in the periphery. Further, it has been shown that there is asymmetry in the strength of crowding depending on the direction of eccentricity. For instance, crowding effects are stronger in the superior hemifield compared with the inferior (He et al. 1996). Additionally, two flankers on either side of the target stimulus have a greater crowding effect compared to a single flanker and a single flanker presented more eccentrically has a greater crowding effect than a flanker presented closer the fovea (Bouma 1970).

The effects of various properties of target and flanking stimuli have been investigated and it has been shown that these properties also influence the magnitude of crowding effects including properties such as shape (Levi et al. 1994), contrast (Chung et al. 2001) and colour (Levi et al. 1994) of target and flanking stimuli. Overall, these studies show that the greater the similarity between flanking and target stimuli, the greater the effects of crowding are (Levi et al. 1994). These variations in the strength and extent of crowding show that this aspect of visual function is complex and does not appear to have a simple mechanism involved. These results may indicate that numerous parts of the visual system facilitate crowding.

There has been greater psychophysical investigation into crowding than neurophysiological. For this reason, the precise locus of crowding is not known but evidence from psychophysical research allows us to infer which areas in the visual system are likely to play a significant role in crowding (Whitney and Levi 2011). For instance, it has been demonstrated that crowding occurs under dichoptic viewing conditions (target stimuli presented to one eye, flankers presented to other eye) (Tripathy and Levi 1994) suggesting a cortical locus for crowding. Neurophysiological studies provide strong evidence for cortical loci

including in areas V1, V2 and V3 (Pelli 2008; Bi et al. 2009). However, it is difficult to determine the exact neural locus of crowding as stimuli used in these studies do not solely represent crowding and so it may be that the neural loci involved are also mediating other aspects of the stimulus confounding the results (Whitney and Levi 2011).

Additionally, there does not appear to be an agreed upon model for crowding but various studies have proposed theories such as contrast masking (Levi et al. 2002b) and spatial pooling (Levi et al. 2002a). Contrast masking describes the difficulty in detection and discrimination of stimuli with a second 'masking' stimulus overlying the target stimulus. Levi et al. (2002b) showed that in the fovea, crowding effects can be accurately predicted by masking effects. However, in the periphery, crowding effects could not be predicted by contrast masking and were much stronger than masking effects (Levi et al. 2002a) indicating that these aspects of visual function are not mediated by the same mechanisms.

In particular, spatial pooling has become a widely recognised concept that is described by a two staged model. The first stage of the model involves basic receptors that detect the stimulus (Levi 2008). The second stage involves higher levels in the visual cortex and an integration of information of stimuli appearing within the same receptive fields. Information from multiple stimuli within a receptive field is averaged resulting in a jumbled perception of these stimuli (Pelli et al. 2004). As receptive fields increase in size with eccentricity, the extent of crowding increases in size as well. This concept accounts for why objects are detected but not resolved and accounts for the increasing effect size of crowding with eccentricity. However, Whitney and Levi (2011) point out that this model and various other models proposed to explain crowding do not account for all aspects and requirements for crowding to occur such as the similarity between flankers and target stimuli and the asymmetry in crowding effects between the superior and inferior visual field. Alternatively, it may be that crowding occurs at multiple stages in the visual system. This can be evidenced by multiple factors affecting crowding including factors arising from the target stimulus and flanking stimuli, as well as crowding effects being affected by eccentricity and location within the visual field.

Crowding effects have been investigated in various eye and neurological conditions including amblyopia (Bonneh et al. 2007), dyslexia (Martelli et al. 2009), macular degeneration (Wallace et al. 2017) and glaucoma (Ogata et al. 2019). To date, there has only been one study investigating crowding in glaucoma (Ogata et al. 2019). This study assessed the effects of crowding on letter recognition in participants with early glaucoma. The study showed that critical spacing increases in glaucoma, which demonstrates that the extent of crowding increases in size through the disease process (Ogata et al. 2019). The authors suggest that the results may be explained by a pathological increase in retinal ganglion cell receptive field sizes as glaucoma progresses. However, as the study investigated critical spacing in areas of varying visual field sensitivity, it remains unclear how this change in underlying sensitivity affected measures of critical spacing. It is possible that altering the distance of flanking stimuli could artificially create an uncrowded environment as flanking stimuli could be moved from an area of perceived VF to an area of a VF scotoma that reduces the visibility of flankers and unintentionally creates an uncrowded environment. Therefore, it may be more appropriate to assess a specific visual field location instead of measuring critical spacing and spatially constrain the stimulus-flanker grouping arrangement by measuring the relative crowing effect using fixed flanker distances. This aspect of crowding has not yet been measured in glaucoma patients.

1.5 Aims of the research project

This project aims to explore and further understand how glaucoma affects different aspects of suprathreshold vision. Conventional perimetry is widely used to assess vision in the disease and is based on measuring contrast sensitivity, a measure of threshold visual function. However, as threshold and suprathreshold measures assess different aspects of visual function, perimetry does not tell us about suprathreshold vision, which may be more relevant to patients' daily visual experiences.

Previous studies have used both qualitative and psychophysical approaches to investigate this subject (Anderson 2006; Crabb et al. 2013). Glaucoma patients' have reported perceiving increased blur in their vision and feeling they require more light to see (Crabb et al. 2013; Hu et al. 2014). Furthermore, deficits to aspects of suprathreshold vision have been found such as impairments to achromatic resolution (Beirne et al. 2003), contrast discrimination (McKendrick et al. 2010) and Vernier acuity (McKendrick et al. 2002) that are not identified by current perimetry tests. It could be that other aspects of suprathreshold vision are affected in glaucoma that is currently unknown. These aspects of suprathreshold vision may hold valuable information not currently known about the impact of the disease and could potentially be used as additional forms of visual function assessment alongside perimetry to diagnose and monitor disease progression.

This project aims to investigate the effects of glaucoma on three aspects of suprathreshold visual function using psychophysical methods. The first experiment investigates the effects of glaucoma on apparent contrast of suprathreshold stimuli. It is well known that contrast sensitivity is reduced in glaucoma (Ross et al. 1984; McKendrick et al. 2007) but how the disease impacts contrast perception of high contrast suprathreshold stimuli is unknown. The site of damage in glaucoma is the retinal ganglion cells (Quigley et al. 1982), and these cells play an active role in contrast gain (Solomon et al. 2004). It may be that as cells are destroyed in the disease process, suprathreshold contrast processing becomes affected as well. The first study examines this question by assessing the apparent contrast of suprathreshold stimuli using a contrast matching task.

Furthermore, as retinal ganglion cell receptive fields have been shown to closely correspond to peripheral resolution (Thibos et al. 1987a), and peripheral resolution is reduced in glaucoma (Beirne et al. 2003), it is possible that as cells are destroyed in the disease, patients alternatively experience increased perception of blur as a result. This may evidence the common visual symptom of increased blur reported by patients' (Crabb et al. 2013; Hu et al. 2014). This question will be assessed in the second study (Chapter 4) by measuring blur detection and discrimination thresholds of edge stimuli under both low and high contrast conditions.

Similarly, the premise for the third study is based on investigating if increased blur perception, as reported by patients could be explained by an increased crowding effect in the disease process. Crowding has been suggested to be a result of increased pooling of receptive fields in the visual system (Levi 2008). It is possible that there is pathological pooling of retinal ganglion cell signals as cells are destroyed in the disease and this in turn, increases crowding effects in glaucoma. The final study explores this question by measuring crowding ratios in peripheral vision using a Vernier acuity task.

Suprathreshold visual function in glaucoma is an extensive and complex subject to investigate and is challenging to fully understand. However, we aim to contribute to this field by assessing three aspects of suprathreshold visual function. The studies aim to assess the following three questions:

How does glaucoma affect the apparent contrast of suprathreshold stimuli?

How does glaucoma affect the detection and discrimination of image blur?

How does glaucoma affect crowding?

Chapter 2

2 Optimisation of Stimulus Parameters for Contrast Matching Experiment

2.1 Abstract

Purpose

Studies have shown contrast adaptation affects glaucoma individuals differently to age-matched healthy controls (McKendrick et al. 2010; Lek et al. 2014). As these effects may hamper results by causing confounding group adaptation effects on contrast matching data, it is paramount to account for and minimise effects of adaptation in our future experiment. This study investigates if the stimulus parameters intended for use in the subsequent study induce effects of adaptation on contrast discrimination thresholds.

Methods

Stimuli were Gabors of 50% Michelson contrast (SD 0.5°, random orientation each trial, phase cycling at 1Hz) with a spatial frequency of 2 cpd. Initially, participants viewed a screen under three different adaptation conditions; a blank screen (blank), Gabor stimuli pulsing on/off screen (pulsed) and Gabor stimuli presented steadily on screen (steady). Subsequently, participants completed a contrast discrimination task using a 4-alternative forced choice paradigm. Data were analysed by repeated measures ANOVA in SPSS.

Results

Contrast discrimination thresholds were similar across all three adaptation conditions ($F_{2,8}=0.258$, $p=0.779$). Mean contrast discrimination thresholds ± 95% CI were 7.5 ± 4.0%, 7.1 ± 2.5% and 6.7 ± 1.9% for blank, pulsed and steady adaptation conditions respectively.

Conclusions

The steady stimulus testing parameters do not cause significant effects of adaptation on contrast discrimination thresholds. The results suggest that using these stimulus parameters in the subsequent contrast matching experiment will

not produce confounding effects of group differences in adaptation on contrast matching data.

2.2 Introduction

Contrast adaptation refers to the effects of prolonged viewing of a stimulus to the perception of similar stimuli seen just after (Blakemore and Campbell 1969; Greenlee and Heitger 1988). Adaptation effects typically occur when the adapting and test stimuli contain similar properties, such as spatial frequency and orientation (Blakemore and Campbell 1969; Greenlee and Heitger 1988).

The effects of adaptation are of particular importance for our future contrast matching study as adaptation effects have been shown to be different between glaucoma and age-similar healthy individuals (McKendrick et al. 2010; Lek et al. 2014). Specifically, McKendrick et al. (2010) found that contrast discrimination thresholds were less affected by adaptation in glaucoma individuals compared to age-similar controls. Therefore, it is vital that we minimise and account for effects of adaptation in the contrast matching experiment as the two groups being compared (glaucoma/controls) may adapt differently to stimuli used in the study causing confounding effects on our contrast matching data.

To predict whether stimuli will cause adaptation effects in our future study, we will first consider which type of stimuli and presentation arrangements have induced effects of adaptation in previous studies. Blakemore and Campbell (1969) found an increase in contrast required to detect a stimulus once adaptation had occurred to a stimulus of similar orientation and spatial frequency. This generated interest in this research area and lead to studies investigating if adaptation effects occur on other psychophysical measures (Greenlee and Heitger 1988; Kohn 2007). However, results have been varied (Barlow et al. 1976; Greenlee and Heitger 1988; Wilson and Humanski 1993). For instance, Greenlee and Heitger (1988) found an increase in contrast discrimination thresholds post adaptation for stimuli of lower contrast (<50%) but lower discrimination thresholds for stimuli of higher contrast (>50%) when adapting to a stimulus of vertical orientation, 2 cpd spatial frequency and 80% contrast. However, Määttänen and Koenderink (1991) found no significant

change in contrast discrimination thresholds when participants adapted to Gabor stimuli of varying contrasts. The differences in results between these studies could be explained by the different viewing conditions used in the two studies; Greenlee and Heitger (1988) performed experiments under binocular viewing conditions whilst the experiments of Määttänen and Koenderink (1991) took place under monocular viewing with occlusion of the non-tested eye. To further investigate whether adaptation effects do cause any significant changes in contrast discrimination thresholds, Abbonizio et al. (2002) re-assessed this question by testing observers under varying experimental conditions, exploring differences in stimulus and adaptor contrast and different viewing conditions. The study re-affirmed findings of improvement in contrast discrimination thresholds post adaptation but the authors suggest that these enhancement effects are small.

Wilson and Humanski (1993) found that the effects of adaptation were greater for a longer stimulus presentation time post adaptation; thresholds were elevated significantly more for a presentation duration time of 500ms compared to 30ms. Furthermore, their results suggested that briefly presented stimuli do not necessarily produce significant adaptation aftereffects. Specifically, two out of six observers did not have statistically significantly elevated thresholds when the adapting stimulus was presented for 30ms.These findings suggest that the effects of adaptation are not always consistent but vary depending on the properties of the stimulus, duration of adaptation time/post-adaptation presentation time and the similarity and differences between the adaptor/test stimuli.

Adaptation is mediated by numerous areas in the visual system including cortical neurons (Ohzawa et al. 1985) and earlier in the visual pathway, in retinal ganglion cells (Kim and Rieke 2001; Baccus and Meister 2002). The mechanism suggested to facilitate contrast adaptation is the adjustment in contrast gain where the visual system alters its peak sensitivity to maximise the range of contrast levels to which it can be sensitive (Ohzawa et al. 1985; Solomon et al. 2004).

There are two types of contrast adaptation; slow adaptation effects (duration of seconds to minutes) (Solomon et al. 2004) and fast acting adaptation with a

duration of milliseconds (Baccus and Meister 2002). For this study, we are interested in the former; slow adaptation effects. As contrast adaptation can affect a number of visual measures (Greenlee et al. 1991; McKendrick et al. 2010; McGonigle et al. 2016), and has specifically been shown to be different between the two comparative groups (glaucoma and age-similar controls) (McKendrick et al. 2010; Lek et al. 2014), it is vital that effects of contrast adaptation are controlled and accounted for in our future contrast matching experiment.

Accordingly, the aim of this pilot study was first to investigate whether the stimulus parameters intended to use in our future suprathreshold contrast matching experiment would cause any adaptation effects, and second, to establish optimal stimulus parameters that would control and minimize adaptation effects in our subsequent study. By doing this, we can be confident that we are solely assessing the effect of group on the measure of interest, perceived contrast (glaucoma vs controls) and not differences in image adaptation effects. Three different stimulus conditions were investigated, a control condition (blank) without testing effects of adaptation and two alternative stimuli presentation/adaptation conditions (pulsed, steady stimulus); to elucidate if these stimulus parameters and presentation formats caused effects of adaptation on psychophysical measures of contrast discrimination thresholds.

Based on results from the literature, our hypotheses are as follows;

1.) The steady stimulus adaptation condition would produce effects of adaptation and reduce contrast discrimination thresholds compared to the blank adaptation condition.
2.) These adaptation effects would be reduced by temporally modulating the Gabor stimulus on and off screen and by reducing the duration of presentation time on screen.

2.3 Methods

Observers

Five observers (mean age= 24 years, range= 18 - 28) participated in the study. All participants had healthy eyes with no ocular or systemic condition known to affect visual performance. All observers had visual acuity (Snellen) of 6/6 or better in both eyes. Participants provided written informed consent in accordance with the tenets of the declaration of Helsinki. The study was approved by the University of Bradford Ethics Committee.

Apparatus and stimuli

Gabor stimuli of 50% Michelson contrast (SD 0.5°, random orientation each trial, phase cycling at 1Hz) with a spatial frequency of 2 cpd were used as the adaptor and test stimuli. A contrast of 50% (Michelson units*100) was chosen in this pilot study as this contrast level is likely to be used in the subsequent contrast matching experiment for many observers. Stimulus contrast in the next experiment will vary between observers as it is calculated based on the individual's contrast detection thresholds. For each condition, the contrast will be set at 2x or 4x individual contrast detection thresholds. Therefore, we chose a contrast level that was high enough to induce possible adaptation effects without choosing a very high adaptor contrast that would be unlikely to be presented in the subsequent study. For instance, in the contrast matching experiment, if observers detection thresholds were >= 25%, these observers would not be able to participate in the contrast matching experiment for a reference contrast of 4x detection threshold (see chapter 3). Based on this calculation, we predicted that most observers in the future study would have a contrast match to make for a stimulus of around ~ 50% contrast at either 2x or 4x reference contrast conditions but fewer observers would be making contrast matches for contrast levels beyond this. Stimuli were generated in MATLAB 8.5.0 (R2015a; The Mathworks, Natick, Massachusetts, USA) using Psychtoolbox V3.0.14 (Brainard 1997; Pelli 1997; Kleiner et al. 2007). Stimuli were presented on a 14 bit calibrated display system (resolution 1920x1080, refresh rate 120Hz; Display++, Cambridge Research Systems Ltd, Kent, UK). The mean luminance of the screen was 52.8cd/m². Testing was performed binocularly at a viewing distance of 1m; observers wore appropriate refractive

correction for this viewing distance. Viewing distance was maintained with a chin/forehead rest.

Procedure

Participants completed a contrast discrimination task under three different adaptation conditions; blank, pulsed and steady stimulus. There were two components to the experiment; an initial adaptation period that varied between the three adapting conditions and a subsequent test procedure that measured participants' contrast discrimination thresholds.

Initial adaptation period

At the beginning of each block of trials of the experiment, there was an adaptation period that varied between conditions. The duration of this initial adaptation period was 3 minutes. For the blank (control) adaptation condition, participants viewed a blank grey screen binocularly focussing centrally on a small white fixation spot for 3 minutes prior to completing the contrast discrimination task. For the pulsed adaptation condition, participants viewed the screen with four identical Gabor stimuli surrounding the central white fixation spot at 2.5° eccentricity in ordinal directions pulsing on/off the screen for 3 minutes prior to the contrast discrimination task. The duration of pulsed presentations were 5.5 seconds with contrast ramped on/off according to a raised cosine temporal profile. The initial adaptation period for the steady adaptation condition involved presenting the four Gabor stimuli surrounding the central white fixation spot in ordinal direction at 2.5° eccentricity continuously on screen for 3 minutes prior to the contrast discrimination task. This length of time was chosen as it is longer than the estimated maximum time (~ 1 minute) these Gabor stimuli will be presented continuously in our subsequent contrast matching experiment.

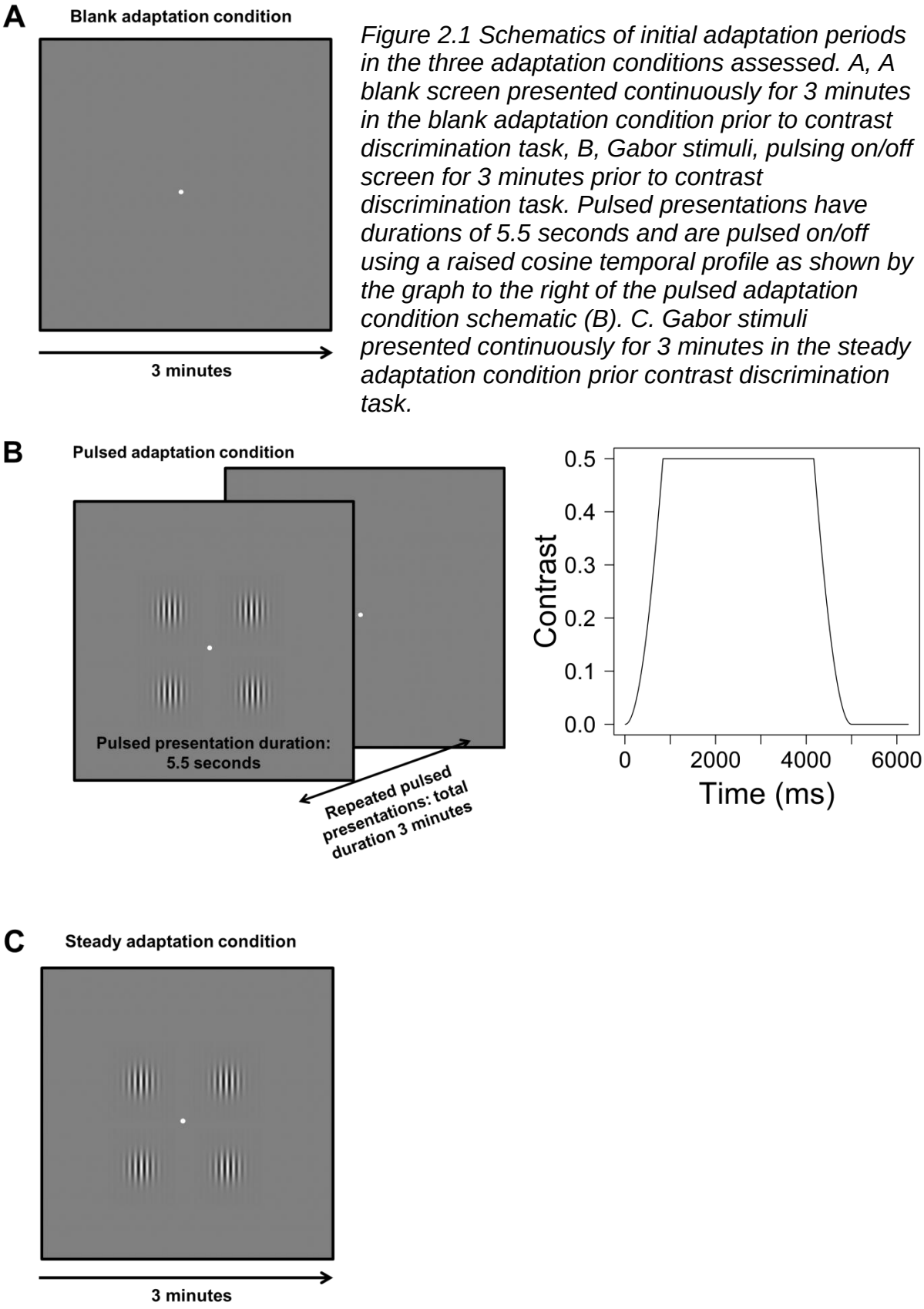


Figure 2.1 Schematics of initial adaptation periods in the three adaptation conditions assessed. A, A blank screen presented continuously for 3 minutes in the blank adaptation condition prior to contrast discrimination task, B, Gabor stimuli, pulsing on/off screen for 3 minutes prior to contrast discrimination task. Pulsed presentations have durations of 5.5 seconds and are pulsed on/off using a raised cosine temporal profile as shown by the graph to the right of the pulsed adaptation condition schematic (B). C. Gabor stimuli presented continuously for 3 minutes in the steady adaptation condition prior contrast discrimination task.

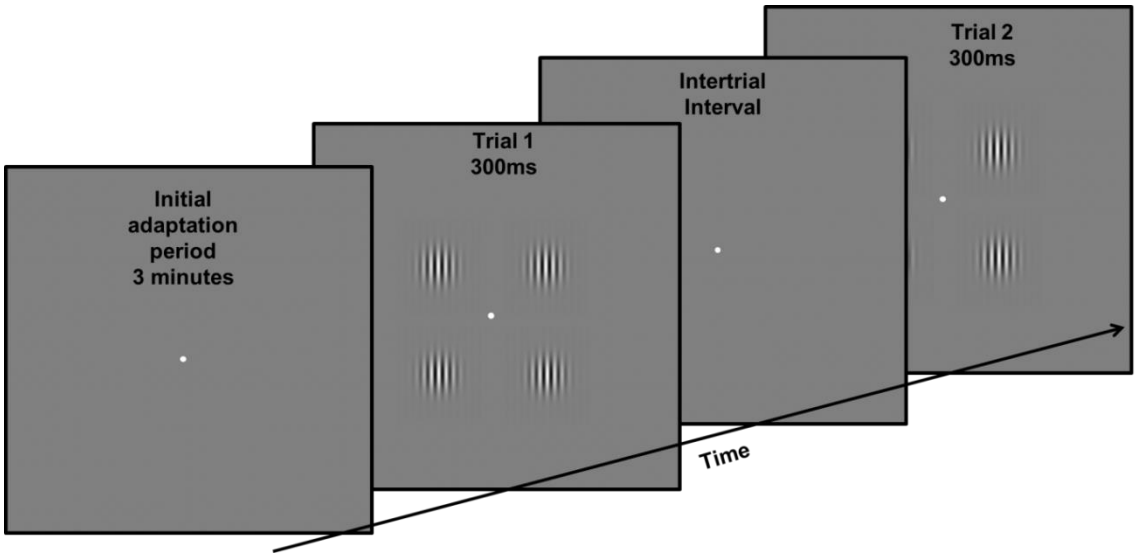


Figure 2.2 A schematic to demonstrate the experiment procedure. First participants viewed the screen under 3 different adaptation conditions. Further depiction of the initial adaptation period in each condition can be seen in Figure 2.1. This initial adaptation period was followed by the contrast discrimination task involving a 4-AFC procedure. The stimulus presentation was the same for all 3 adapting conditions with presentation duration of 300ms. However, the inter-trial interval varied between test conditions. For the blank adaptation condition, inter-trial intervals were presentations of a blank screen for 2000ms. For the two other test conditions, inter-trial intervals involved a top-up 'adaptation' period presenting the Gabor stimuli as pulsing on/off screen (condition 2) or presented steadily (condition 3).

Contrast discrimination task

After these 3 initial adaptation conditions, participants completed the contrast discrimination task using a 4-alternative forced choice procedure. The four Gabors were presented simultaneously in four quadrants at 2.5° eccentricity and were identical with the exception of contrast. Specifically, three of the four Gabors were of a reference contrast (C) whilst one Gabor had contrast of the reference + a contrast increment (C + Δ C). The Gabor with the contrast increment was randomly changed between the four Gabors from trial to trial. The stimulus presentation duration was 300ms for the three adaptation conditions assessed. However, the inter-trial interval duration/stimulus presentation varied between adaptation conditions and was used as a 'top up' adaptation period. For the blank adapting condition, the inter-trial interval was 2000ms showing a blank screen in between presentations. For the pulsed adaptation condition, the inter-trial interval displayed four Gabor stimuli pulsing

on/off screen for 5500ms and then 1000ms of a blank screen to avoid forward masking. For the steady adaptation condition, the inter-trial interval displayed four Gabor stimuli presented continuously for 5500 seconds and then 1000ms of a blank screen before the next presentation.

Observers were asked to determine which of the 4 stimuli had the highest contrast and to give their best guess if they were unsure, responses were recorded with a key press. The method of constant stimuli was utilised to govern task difficulty; a minimum of 20 presentations each of 7 contrast increment levels were assessed. The contrast levels were chosen based on pilot data collected from the initial set up of the experiment. Psychometric functions were plotted as contrast increment (%) vs percentage correctly determined. Contrast discrimination thresholds were taken as the contrast increment correctly determined at 62.5% on the psychometric function. The three adaptation test conditions were completed in a pre-determined randomised order between observers.

2.4 Statistical analysis

Data were analysed in SPSS (version 22; SPSS Inc., Chicago, US). The three adaptation conditions (blank, pulsed stimulus, steady stimulus) were compared by repeated measures ANOVA (within-subject factor: test condition). A value of $\alpha = 0.05$ was used as statistically significant, if Mauchly's test indicated violation of sphericity, Greenhouse-Geisser correction was used.

2.5 Results

Individual observers' results are shown in Figure 2.3 and group mean performance under the three adaptation conditions is shown in Figure 2.4. Specifically, a repeated-measures ANOVA showed no main effect of adaptation condition on contrast discrimination thresholds ($F_{2,8}= 0.258$, $p=0.779$). Mean contrast discrimination thresholds ± 95% confidence intervals for adaptation conditions were 7.5 ± 4.0%, 7.1 ± 2.5% and 6.7 ± 1.9% for blank, pulsed and steady stimulus adaptation conditions respectively.

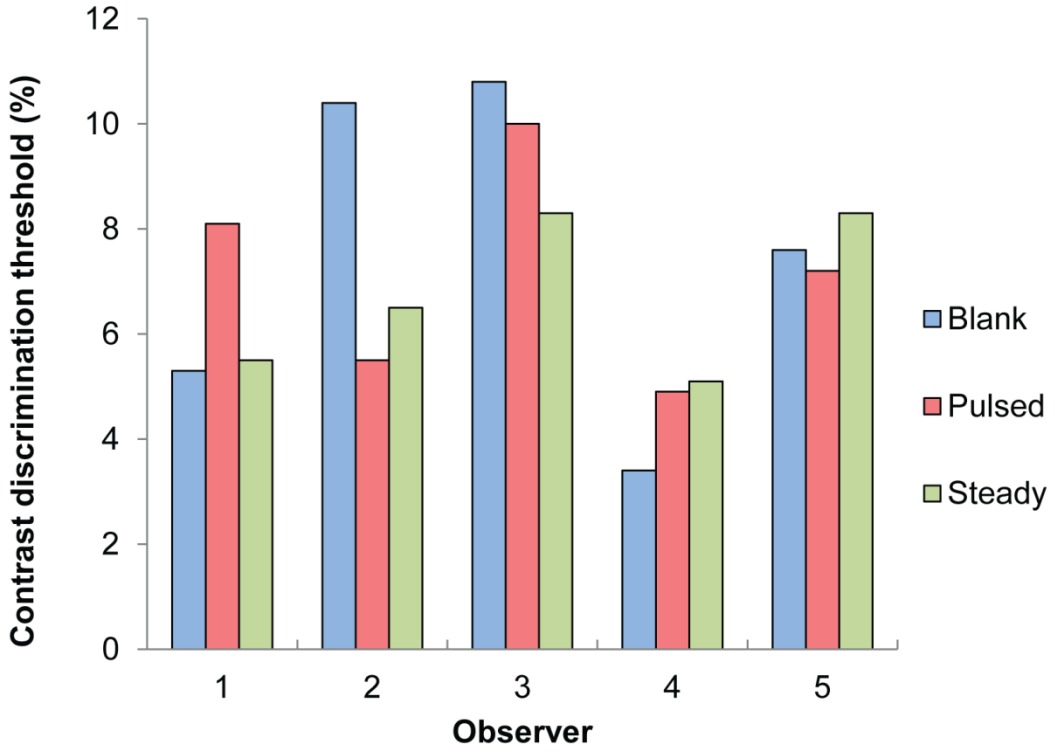


Figure 2.3 Contrast discrimination thresholds for individual observers under the three adaptation conditions; blank (blue), pulsed (pink) and steady (green) stimulus. Individuals' results show no distinct pattern/consistency between adapting conditions.

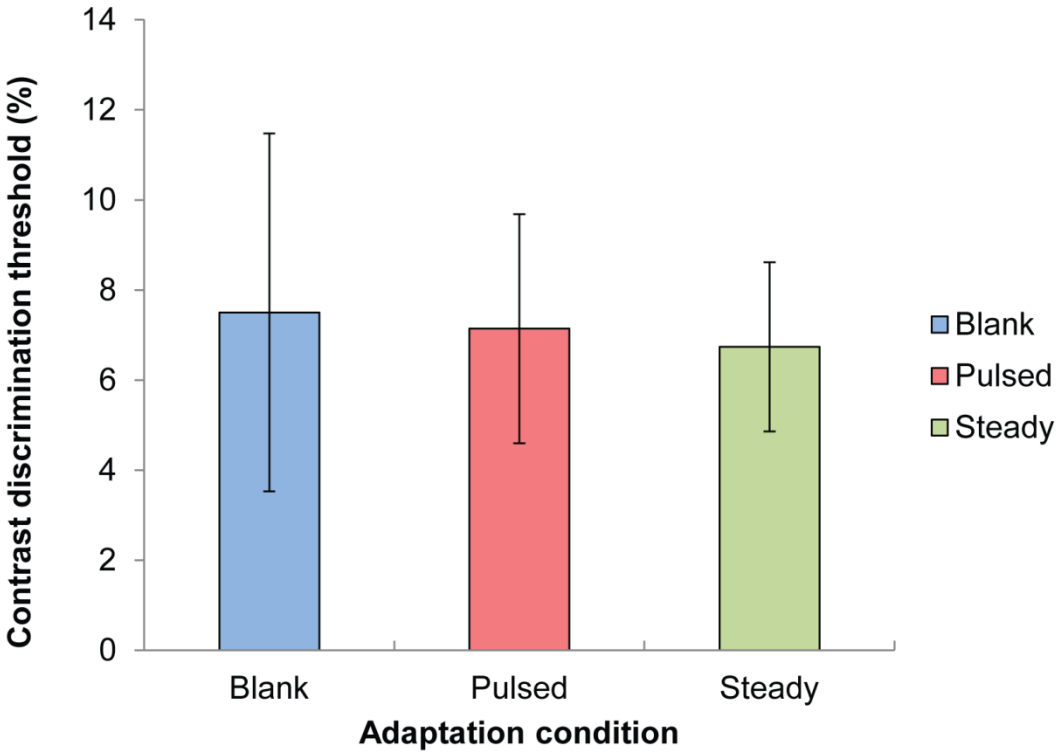


Figure 2.4 The effects of stimulus adaptation condition on contrast discrimination thresholds. Data shown are mean ± 95% CI of the mean. Contrast discrimination thresholds were similar across all three adapting conditions.

2.6 Discussion

We investigated the effects of adaptation on contrast discrimination thresholds under three different adaptation conditions. The results of this pilot study demonstrated that neither pulsing nor steadily presenting the stimulus caused significant effects of adaptation on contrast discrimination thresholds relative to the blank (control) adaptation condition. Furthermore, the results show that there are no additional adaptation effects beyond those induced by the Gabor stimulus itself suggesting that the stimulus has already saturated the effects of adaptation under these testing conditions. These results suggest that using these stimulus parameters, phase-cycling Gabor stimuli of 50% of 2 cpd under steady viewing for ~ 3minutes will not cause significant effects of adaptation on our following contrast matching experiment suggesting that between-group differences in contrast adaptation will have negligible effect on the results of our contrast matching study. These results give us some assurance that we are

solely assessing the effects of glaucoma on contrast matching data compared with age-similar controls and not inducing confounding differing group effects of adaptation on these measures. Further, as this study used an adaptation period (3 minutes) that exceeds the expected time participants will be exposed to stimuli whilst making a contrast match (~ seconds < 1minute), the likelihood of adaptation effects in the future experiment is further reduced.

Our results are consistent with previous studies of minimal effects of adaptation on contrast discrimination thresholds for a stimulus contrast of 50% (Barlow et al. 1976; Greenlee and Heitger 1988). However, Greenlee and Heitger (1988) used an adaptor contrast of 80% whilst Barlow et al. (1976) and the present study used an adaptor contrast of 50%. Greenlee and Heitger (1988) did however, find effects of adaptation for stimuli of greater/lower contrast though in opposing directions; adaptation caused a decrease in discrimination thresholds for test stimuli of higher contrast (>50%) whilst increasing discrimination thresholds for stimuli of lower contrast (<50%). However, the elevation in contrast discrimination thresholds for stimuli of lower contrast was only slight in the first observer whilst more pronounced in the second. Further, their results may be explained by the greater difference in adaptor and test stimulus contrast and the higher adaptor contrast used.

Further, Legge (1981) found no significant effects of adaptation on contrast discrimination thresholds for a 2 cpd stimulus with background contrasts ranging from 0-48% using a range of experimental procedures. For an 8 cpd stimulus, adaptation to a contrast of 24% showed an increase in contrast discrimination for stimuli of lower contrast but no significant difference in contrast discrimination thresholds for stimuli of higher contrast (Legge 1981). Perhaps if the study used an adaptor contrast even higher than this they would have found results more consistent with Greenlee and Heitger (1988). These results suggest that varying the contrast of the adaptor and test stimulus and altering the spatial frequency of the stimulus can significantly impact whether any effects of adaptation on contrast discrimination thresholds occur and the size of the effect. Thus, the effects of adaptation may be specific to the stimulus parameters used in the experiment.

Greenlee et al. (1991) found an increase in adaptation effects on contrast detection thresholds (elevation of contrast detection thresholds) with increase in adaptor contrast and adaptation duration time. Further, the study showed that the recovery time required from adaptation was proportional to the length of adaptation duration for adapting periods ranging from 10-1000 seconds (Greenlee et al. 1991). Additionally, it has been shown that adaptation effects are stronger in the periphery and build up/decay of adaptation are slower in the periphery compared with central viewing (Gao et al. 2019). However, these studies have been completed for contrast detection and have not assessed the same aspect of visual function studied herein of contrast discrimination. Therefore, the results may not be applicable to these experimental conditions.

FMRI studies have demonstrated that contrast discrimination is facilitated early in the visual cortex (e.g. V1, V2d, V3d and V3a) (Boynton et al. 1999). Contrast adaptation, however, is facilitated by a number of areas in the visual system including in the retina, LGN and cortex (Albrecht et al. 1984; Baccus and Meister 2002; Solomon et al. 2004; Gardner et al. 2005). Further, it has been demonstrated that cortical cells are selectively sensitive and tuned to specific spatial frequencies (De Valois et al. 1982). Therefore, our results may be explained by the cortical cells tuned to this specific spatial frequency/contrast remaining robust to effects of adaptation compared to other cortical cells tuned to differing spatial frequencies that may be more susceptible to these adaptation effects. Therefore, these results cannot fully account for or confirm that this experimental set-up would not induce effects of adaptation on other spatial frequencies and contrast levels assessed.

The scope of this study was limited to testing one spatial frequency and contrast level. Gabor stimuli of 2 cpd were chosen as this spatial frequency is intended to be used in the subsequent matching study and is a mid-range spatial frequency likely to be easily detected by most glaucoma and control observers. This is unlike higher spatial frequencies such as the 4 cpd stimulus that was difficult to detect for the majority of glaucoma observers in the contrast matching study (chapter 3). An adaptor contrast of 50% was chosen in this study as a contrast of a similar level is likely to be presented at either reference contrast 2x or 4x for all observers in the subsequent matching study. Fewer observers are

likely to make a contrast match for stimuli of very high contrast due to ceiling effects within the contrast matching experiment (see chapter 3). However, further results of varying spatial frequencies and contrast levels would have been useful as it would have given further assurance of non-significant effects of adaptation on contrast matching data for our future experiment. This study was performed under binocular viewing conditions but as adaptation effects have been shown to be slightly stronger under monocular testing conditions compared with inter-ocular (adapting in one eye and testing in the other eye) (Bjørklund and Magnussen 1981), it may be that adaptation effects also differ between binocular/monocular viewing although there are no studies that have specifically investigated this. However, as no significant adaptation effects on contrast discrimination thresholds under monocular testing conditions have been found previously (Määttänen and Koenderink 1991), it is unlikely that stronger adaptation effects would occur when assessing observers monocularly in the future study. Lengthening the initial adaptation period in this study may have revealed significant adaptation effects; however, the duration time chosen (3 minutes) far exceeds our expected time for observers to produce a match in the subsequent contrast matching experiment so it is unlikely that adaptation effects induced by an adaptation period longer than this would occur.

2.7 Conclusions

Our results suggest that the steady Gabor stimulus was not causing significant effects of adaptation on contrast discrimination thresholds under these experimental conditions. These results support the use of these stimulus parameters in our subsequent contrast matching experiment as our two groups of observers (glaucoma/healthy controls) will not be under confounding differing effects of adaptation whilst completing the task.

Chapter 3

3 Glaucoma affects contrast sensitivity but not apparent contrast of visible stimuli

3.1 Abstract

Purpose

Reduced contrast sensitivity as measured by visual field (VF) tests is a hallmark of glaucoma, but how glaucoma affects the apparent contrast of visible suprathreshold images is unknown. We investigated the effects of glaucoma on the apparent contrast of suprathreshold stimuli of different spatial frequencies, presented both within and outside VF defects.

Methods

Twenty glaucoma participants with partial VF defects (mean age 72, standard deviation [SD] 7 years) and 20 individually age-matched healthy controls (mean age 70, SD 7 years) took part. First, we measured contrast detection thresholds for Gabor stimuli (SD=0.75°, random orientation, phase cycling at 1Hz) of 4 spatial frequencies (0.5, 1, 2, 4 cpd) presented at 10° eccentricity in a 2-interval forced choice procedure. For glaucoma participants, detection was measured both within and outside the VF defect. Participants then completed a contrast matching task using identical Gabor stimuli: Participants adjusted the contrast of a central Gabor to match that of a fixed-contrast reference Gabor presented in the same peripheral locations as for the detection task. Reference Gabor contrast was set at 2x and 4x detection threshold in separate conditions. Data were analysed by linear mixed modelling.

Results

Compared to controls, glaucoma participants' detection thresholds were raised by 0.05 ± 0.025 (Michelson units, ± SE; $p = 0.12$) and by 0.141 ± 0.026 ($p < 0.001$) outside and within VF defects respectively. For reference stimuli at 2x detection contrast, matched contrast ratios (matched/reference contrast) were 0.16 ± 0.039 ($p < 0.001$) higher outside compared to within VF defects in glaucoma participants. Matched contrast ratios within VF defects were similar to

those in controls (mean 0.033 ± 0.066 lower, p = 0.87). For reference stimuli at 4x detection contrast, matched contrast ratios were similar across all 3 groups (p=0.58). Spatial frequency had minimal effect on matched contrast ratios for 2x ($\chi^2(3)=6.4$, p=0.092) and 4x ($\chi^2(2)=5.9$, p=0.054) reference contrasts.

Conclusions

Despite reduced contrast sensitivity, people with glaucoma perceive the contrast of visible suprathreshold stimuli similarly to healthy controls. Our findings contradict common depictions of glaucoma showing areas of reduced contrast and suggest possible compensation for glaucomatous sensitivity loss in the visual system.

3.2 Introduction

Glaucoma is a disease characterized by degeneration and death of retinal ganglion cells (Quigley et al. 1982) leading to irreversible sight loss. The disease is estimated to affect 79.6 million by 2020 (Quigley and Broman 2006) and despite its large prevalence, the effect of the disease on patients' everyday visual experiences is poorly understood.

Previous studies in this area have employed interviews, questionnaires and forced-choice image selection experiments to further understand the perceptual changes experienced by glaucoma patients. These studies have found patients perceive greater amounts of blur in their vision (Crabb et al. 2013), feel they need more light (Hu et al. 2014), and unlike common depictions of visual perception in glaucoma, patients do not describe their vision as 'tunnel vision' (Crabb et al. 2013). However, despite these studies providing some insight, our understanding of how glaucoma affects patients' visual perception is limited.

Current clinical tests for glaucoma predominantly measure contrast detection thresholds across the visual field in the form of static automated perimetry. However, this type of visual assessment does not necessarily reflect how glaucoma patients perceive contrast under more natural 'suprathreshold' viewing conditions. In healthy eyes, the perception of contrast under more natural suprathreshold viewing conditions is considerably different to when

viewed at threshold level. Under threshold viewing conditions, contrast sensitivity is dependent on the spatial frequency content of the stimulus (Campbell and Robson 1968). However, once contrast levels increase above threshold, contrast is perceived consistently and becomes independent of the spatial frequency content of the stimulus (Georgeson and Sullivan 1975; Brady and Field 1995). This consistency in how we perceive contrast under suprathreshold conditions is known as 'contrast constancy' (Georgeson and Sullivan 1975). Furthermore, despite elevation of contrast detection thresholds in the periphery (Wright and Johnston 1983), contrast constancy is maintained with eccentricity (Hess and Bradley 1980; Cannon 1985).

A number of studies have found impairments to visual processes in glaucoma that are not identified by current perimetry tests. For instance, deficits have been found in contrast discrimination (McKendrick et al. 2010) and contrast adaptation (Lek et al. 2014) processes in early glaucoma. Additionally, it has been reported that impairments to contrast gain properties (Sun et al. 2008) and peripheral resolution in glaucoma (Beirne et al. 2003) have been found that are not identified by current perimetry tests (chapter 1.4). These findings suggest that there could be greater impairment to visual function in glaucoma other than reduced contrast sensitivity (Ross et al. 1984). Retinal ganglion cells have some involvement in contrast processing and contrast adaptation (Smirnakis et al. 1997; Solomon et al. 2004) and studies (Beirne et al. 2003; McKendrick et al. 2010) have been developed based on the hypothesis that when retinal ganglion cells degenerate during the course of the disease (Quigley et al. 1981), the visual processes facilitated by these cells become affected as well. These studies have utilised this information by testing specific areas of visual perception that better relate to structural changes in the disease process and have shown that there is potential in testing suprathreshold vision to differentiate between healthy and glaucomatous eyes (Beirne et al. 2003; Sun et al. 2008; McKendrick et al. 2010; Lek et al. 2014).

As most of our visual cues are not at threshold level, investigating the visual system under more natural representative viewing conditions (suprathreshold) could give us a valuable insight into how the disease affects patients' everyday visual experiences. Under suprathreshold viewing conditions, the visual system

compares and contrasts between properties of stimuli rather than just detecting the stimulus, as is measured in contrast sensitivity.

In this study we aimed to investigate how glaucoma affects contrast perception of visible suprathreshold stimuli. To our knowledge this subject has not been previously investigated. Our research question is:

How does glaucoma affect perception of suprathreshold contrast?

3.3 Methods

Participants

Twenty glaucoma observers (mean age ± SD: 72 ± 7 years) and twenty age-matched controls (70 ± 7 years) participated in the study. Glaucoma participants were recruited through local NHS trusts (Leeds teaching hospitals, Bradford teaching hospitals and Calderdale & Huddersfield NHS Foundation trust) and the International Glaucoma Association. In addition, other means of recruitment were used for both glaucoma and control participants including advertisements placed in the University of Bradford Eye Clinic, adverts in local optometric practices, newspapers and local community groups (church groups, rotary clubs, University of the Third Age (U3A) Bradford & Ilkley).

All participants had a visual acuity of better than 6/9.5 in the tested eye and a refractive error of no more than ± 6.00DS and 3.00DC. Participants were only included in the study if they had no ocular or systemic conditions known to affect visual performance, except glaucoma for the glaucoma group and mild cataract (no more than NC3 NO3 C2 P2 on LOCS III grading scale (Chylack et al. 1993)).

All control participants had normal findings on examination of eye health prior to testing. Eye health assessment included applanation tonometry (IOP ≤ 21mmHg and ≤ 3mmHg difference between the eyes), slit lamp biomicroscopy, indirect fundoscopy and perimetry. Visual field testing was completed using the SITA Standard 24-2 test on the Humphrey Field Analyzer III (Carl Zeiss Meditech, Dublin, CA, USA). In this study we defined a ‘visual field defect’ as a cluster of 3 or more adjacent points with a pattern standard deviation of p <5%

and at least 1 point of p < 1% (Anderson and Patella 1999). Control participants were included in the study if visual field results showed no visual field defect and GHT analysis result were ‘within normal limits’.

Only those glaucoma participants with a partial visual field defect were included in the study (one quadrant of the visual field plot must have a visual field defect whilst at least one of the three other quadrants must remain ‘normal’ and without a visual field defect). Glaucoma participants had to have at least one or more sectors of the RNFL scan outside normal limits (p<5%) compared to the age-matched normative database using optical coherence tomography (Spectralis; Heidelberg Engineering GmbH). OCT scans were not a part of the inclusion/exclusion criteria for the control group. Confirmation of glaucoma diagnosis was obtained from the latest Ophthalmology clinic report and/or a reliable history from the patient with evidence of treatment (e.g. drops taken, copy of prescription). If both eyes fit the criteria for the glaucoma group, the tested eye was chosen at random.

Glaucoma participants were tested in 2 locations at 10° eccentricity: one within (red marker) and one outside the visual field defect (green marker) (Figure 3.1). Control participants were tested in a single location at 10° eccentricity; the location tested corresponded to that of their individually age-matched glaucoma participant within an area of a visual field defect. For example, if the glaucoma observer was tested in the right eye superior-nasal quadrant, the age-matched control participant was tested in either the right or left eye in the superior nasal quadrant. A breakdown of glaucoma participants’ perimetry results are shown in Table 3.1.

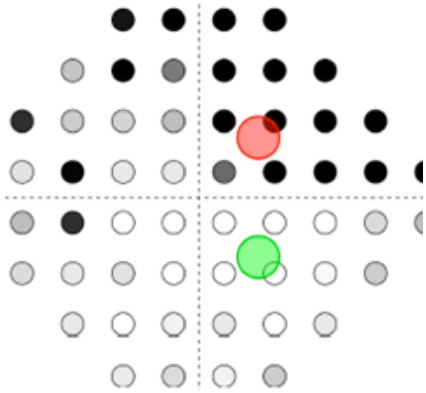


Figure 3.1 A schematic of a VF plot to show the two locations tested in a glaucoma observer. Red marker indicates an area tested within a VF defect, green marker indicates testing a perimetrically normal region.

All participants provided written informed consent before participating in the study. The study was approved by the NHS ethics committee [NHS Reference: 18/LO/0263] and followed the tenets of the Declaration of Helsinki. An inconvenience allowance was given to participants for their time and towards travel expenses.

Table 3.1 A breakdown of individual glaucoma participants' data: ID number, Age, Glaucoma Hemifield Test result, Mean Deviation and Pattern Standard Deviation on Humphrey Field Analyzer III.

Participant ID	Age	GHT Analysis	MD (dB)	PSD (dB)
1	72	Outside normal limits	-4.6	4.34
2	69	Outside normal limits	-1.53	3.94
3	66	Outside normal limits	-3.58	3.87
4	74	Outside normal limits	-2.54	4.34
5	60	Outside normal limits	-4.09	2.69
6	67	Within normal limits	-1.98	2.1
7	73	Outside normal limits	-2.96	4.95
8	90	Outside normal limits	-5.13	10.58
9	73	Outside normal limits	-3.6	6.77
10	75	Within normal limits	-2.18	2.11
11	70	Outside normal limits	-2.92	3.68
12	63	Outside normal limits	-5.85	10.78
13	65	Outside normal limits	-2.5	9.96
14	76	Outside normal limits	-2.25	2.51
15	81	Outside normal limits	-0.38	2.37
16	68	Outside normal limits	-1.73	2.69
17	81	Outside normal limits	-10	11.35
18	76	Outside normal limits	-3.23	5.07
19	66	Borderline	-2.09	1.98
20	65	Outside normal limits	-1.39	2.18

Apparatus and stimuli

Gabor stimuli (SD 0.75°, random orientation each trial, phase cycling at 1Hz) with spatial frequencies 0.5, 1, 2 and 4 cpd were used in the study. Stimuli were generated in MatLab 8.5.0 (R2015a; The Mathworks, Natick, Massachusetts, United States) using Psychtoolbox-3 (V3.0.14). Stimuli were presented on a 14 bit calibrated display system (resolution, 1920x1080; refresh rate, 120Hz; CRS Display++; Cambridge Research Systems Ltd, Kent, UK) viewed from 100cm via a chin/forehead rest. The mean luminance of the screen was 52.8cd/m². Appropriate refractive correction for the screen distance was worn and the non-tested eye was occluded.

Fixation was monitored by eye tracking (CRS LiveTrack-FM) with a recording rate of 60Hz. Central fixation was defined as viewing within the central 5° diameter of the fixation marker/centre of Gabor stimulus. Peripheral stimuli were only presented when central fixation was reported by eye tracking. Lack of fixation was reported using different indicators depending on the task (explained further in procedure section below). Those participants who could not be monitored using the eye-tracker (3 glaucoma observers and 4 controls) were observed using a video monitored by the researcher. Potential reasons the eye-tracker was unable to identify pupils include small pupils and small palpebral apertures (where the lower lid concealed the lower pupil margin and prevented the eye-tracker from identifying the pupil).

Procedure

Contrast detection thresholds

Contrast detection thresholds were obtained to calculate contrast levels required for the subsequent contrast matching task. First, approximation of contrast detection thresholds were obtained for Gabor stimuli using the method of adjustment. Observers focussed on a central fixation target (Figure 3.2) whilst a Gabor stimulus was presented at 10° eccentricity in the specified quadrant/location. The observer was asked to adjust the contrast of the stimulus using a dial (CB7, Cambridge Research Systems, Kent, UK) until they could ‘just see it’ in their peripheral vision. Rotation of the dial clockwise or

anticlockwise resulted in an increase or decrease in contrast respectively. One full rotation of the dial resulted in a 10% change in contrast. These contrast threshold estimates were entered as a starting point for the 2-interval forced-choice procedure used to obtain final detection thresholds. Stimulus contrast throughout the study was defined using Michelson contrast:

(Lmax – Lmin)/(Lmax + Lmin),

where Lmax and Lmin are the maximum and minimum luminance of the stimulus, respectively.

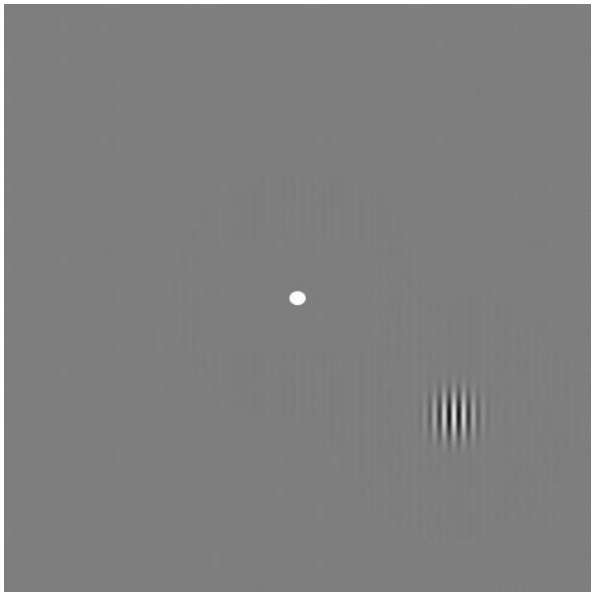


Figure 3.2 A schematic of task 1: Participant fixated centrally on a white spot target (size is not to scale). Contrast of the mid-peripheral stimulus was adjusted using a dial.

Final contrast detection thresholds were measured using a 2-interval forced choice (which interval?) detection task (Figure 3.3). Observers were asked to fixate on the central white spot target; if the observer fixated outside the central 5° diameter of the target, the eye-tracker would alert the lack of fixation by a buzzing sound and peripheral stimuli were not presented until the observer re-fixated centrally. Stimuli were presented in the specified quadrant at 10° eccentricity. Stimuli appeared in one randomly chosen interval for 350ms, ramped on and off according to a raised cosine temporal profile, separated by a 500ms inter-stimulus interval. Stimulus contrast was adjusted according to a 3 down 1 up staircase procedure, with independent staircases randomly interleaved for each spatial frequency. Stimulus contrast was adjusted by 20% before the first reversal and 10% thereafter. Staircases terminated after 6 reversals, with the mean of the last 4 taken as the contrast detection threshold.

Contrast sensitivity was calculated as the reciprocal of contrast detection threshold. Participants were instructed to identify whether the stimulus appeared in interval 1 or 2 and to give their best estimate when they were unsure; responses were recorded with a key press.

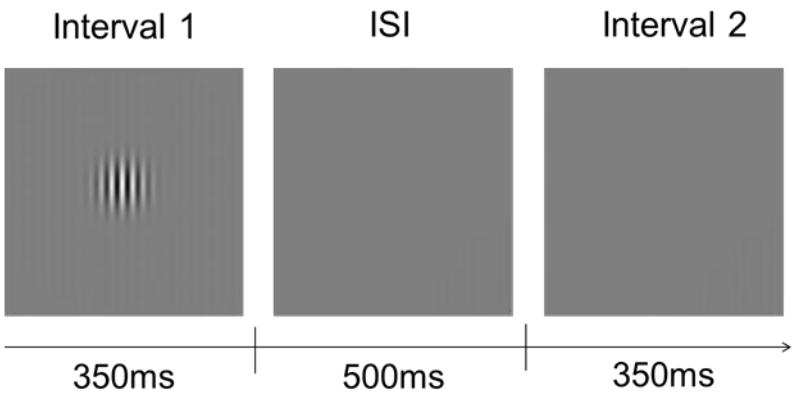


Figure 3.3 Schematic of the 2-interval forced choice procedure used to obtain contrast detection thresholds. Stimuli were presented in the specified quadrant at 10° eccentricity.

Suprathreshold contrast matching

Suprathreshold apparent contrast was measured for each Gabor stimulus in a matching paradigm. Reference contrast levels were calculated as 2x and 4x detection thresholds obtained from the preceding contrast detection experiment. The Gabor stimulus was presented in the mid-peripheral location at 10° eccentricity, whilst a random contrast version of the same stimulus was shown centrally (Figure 3.4). The participant was asked to adjust the contrast of the central Gabor using a dial (method of adjustment) until it matched the peripheral reference Gabor in apparent contrast; participants indicated a match by pressing the dial button. This was repeated twelve times for each stimulus to obtain multiple contrast matches. An average of these 12 matched contrasts was then taken to overcome some of the inherent noise in the method of adjustment, which we used to make the task easier for participants. Matched contrast ratios were calculated from the results as:

Contrast match Ratio = Matched contrast / Reference contrast.

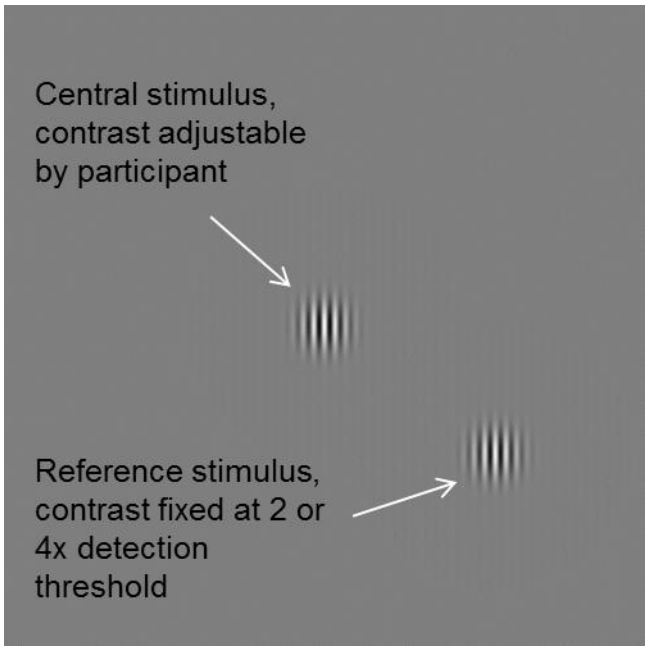


Figure 3.4 A schematic of the contrast matching task: the contrast of the central Gabor stimulus was adjustable; the mid-peripheral Gabor stimulus was of a fixed reference contrast presented in one of four quadrants at 10° eccentricity.

A total of 8 conditions were tested; four spatial frequencies (0.5, 1, 2 & 4 cpd) & 2 reference contrast levels for each spatial frequency (2x and 4x detection threshold). The number of conditions tested depended on the initial detection thresholds; if contrast detection thresholds were greater than or equal to 0.25, not all 8 conditions could be tested as reference contrast levels would equal or exceed the maximum of 100% contrast. The contrast matching task was completed in a predetermined randomised order. Fixation was checked at the beginning of each trial and was monitored via the eye tracker; if participants fixated outside the central 5° diameter, a black cross would appear on screen surrounding the central Gabor stimulus and the peripheral Gabor would disappear. The peripheral stimulus would only reappear once the participant had re-fixated.

Three glaucoma observers were not able to detect the 4 cpd stimulus in the area of a visual field defect at 100% contrast; therefore these data were removed from subsequent analysis. A further 13 glaucoma participants were unable to perform the matching task with reference contrast 4x detection threshold for the 4 cpd stimulus in the visual field defect area due to ceiling effects (4x detection threshold ≥1), therefore this condition was not included in the analysis. To account for ceiling effects among the other conditions, those contrast matching data sets that included more than 4 of 12 matches at the measurement ceiling were removed from the analysis; this applied to 4 control and 6 glaucoma participant data sets. This left only 4 glaucoma participants'

data in the reference contrast 4x detection threshold condition for the 4 cpd stimulus within the visual field defect. This condition was therefore excluded from analysis. A breakdown of the number of data sets removed from 4x reference contrast condition due to ceiling effects is given below in Table 3.2.

Table 3.2 Number of data sets removed from each spatial frequency stimulus in 4x reference contrast condition removed due to ceiling effects. Note, the data for the 4cpd stimulus was removed entirely for the glaucoma VF defect quadrant assessed.

Data sets	0.5cpd	1cpd	2cpd	4cpd
Glaucoma within VF defect	1	0	1	-
Glaucoma outside VF defect	1	0	1	2
Age-similar Controls	2	0	0	1

3.4 Statistical analysis

Data were analysed using linear mixed modelling using R (R Core Team (2017)) and the function “lme4” (Bates et al. 2015). Six separate linear mixed models were used to test each main effect individually on contrast detection thresholds or contrast match ratios at reference contrasts 2x and 4x detection thresholds. Fixed-effects of group (glaucoma participants tested within a VF defect, glaucoma participants tested outside a VF defect and age-matched controls) and spatial frequency were entered into the model. Random effects of participant were included in each model to account for within-participant effects arising from the participants with glaucoma appearing in two of the three groups. Models took the form of:

Contrast detection threshold ~ 1 + Group† + (1|Participant)

Contrast Match Ratios‡ ~ 1 + Group† + (1|Participant)

† The same model arrangement was used to assess Spatial Frequency as the fixed-effect instead of Group.

‡ Contrast match ratios at either 2x or 4x detection contrast level assessed.

A likelihood ratio test was then used to compare the model with and without the fixed-effect in question. If likelihood ratio test results were significant ($p< 0.05$), estimated marginal means were compared by Tukey post-hoc tests using the "emmeans" function (Lenth 2018) to reveal which group caused the effect and the size of the effect.

3.5 Results

Contrast detection thresholds

Detection threshold data are presented as contrast sensitivity functions (log(1/contrast detection threshold)) in Figure 3.5. Mean detection thresholds for the glaucoma group in both locations tested were raised, relative to controls (main effect, $\chi^2(2)= 29.1$, $p<0.001$). Compared to controls, glaucoma participants' detection thresholds were raised by 0.050 ± 0.025 ($p = 0.12$) outside the VF defect area and by 0.141 ± 0.026 ($p < 0.001$) within the VF defect area.

Spatial frequency had a significant effect on contrast detection thresholds ($\chi^2(3)= 89.96$, $p<0.001$). Specifically, thresholds were increased for the 4 cpd stimulus by 0.180 ± 0.024, 0.220 ± 0.024 and 0.221 ± 0.024 compared to 0.5, 1 and 2 cpd stimuli respectively (all $p<0.001$). Contrast detection thresholds for spatial frequencies 1 and 2 cpd were similar (difference in mean detection thresholds, 0.001 ± 0.024, $p = 1.0$) whilst detection thresholds for 0.5 cpd were slightly raised, by 0.040 ± 0.024 ($p=0.33$) and 0.041 ± 0.024 ($p=0.31$) relative to 1 and 2 cpd respectively.

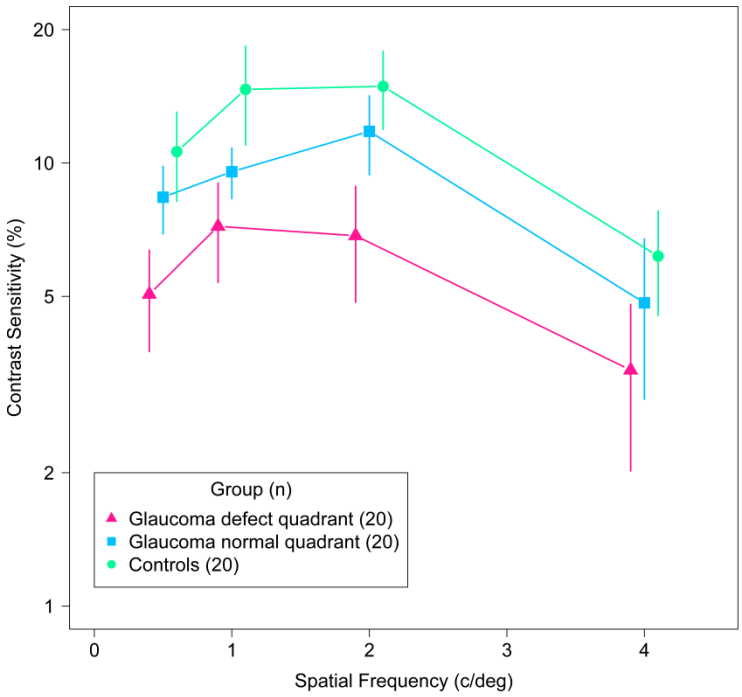
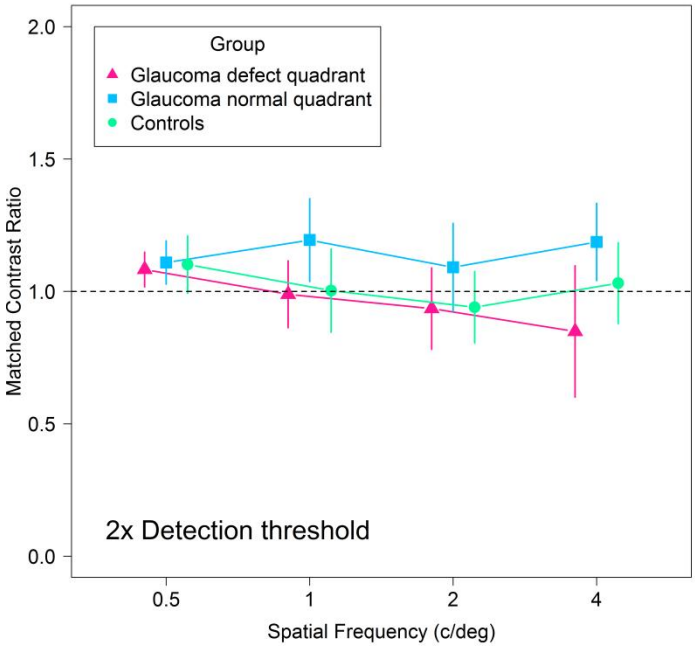


Figure 3.5 Mean contrast sensitivity of four spatial frequencies (0.5, 1, 2 & 4cpd) for the three groups. Error bars show 95% CI of the mean.

Contrast match ratios

Figure 3.6 shows mean group contrast match ratios with 95% CI for the two reference contrast levels (2x and 4x detection thresholds). For reference stimuli at 2x detection contrast, there was a main effect of group on contrast match ratios ($\chi^2(2)= 16.4$, $p < 0.001$). Specifically, matched contrast ratios were 0.16 ± 0.039 ($p< 0.001$) higher outside compared to within VF defects in glaucoma observers. Contrast match ratios were similar between controls and glaucoma observers; both within (matched contrast ratios mean 0.033 ± 0.066 lower; ($p=0.87$) and outside (matched contrast ratios mean 0.126 ± 0.066 higher; $p=0.14$) visual field defects. However, for reference stimuli at 4x detection contrast, contrast match ratios were similar across all 3 groups (grand mean 1.07 [range 1.06-1.10], main effect $\chi^2(2)=1.1$, $p=0.58$).



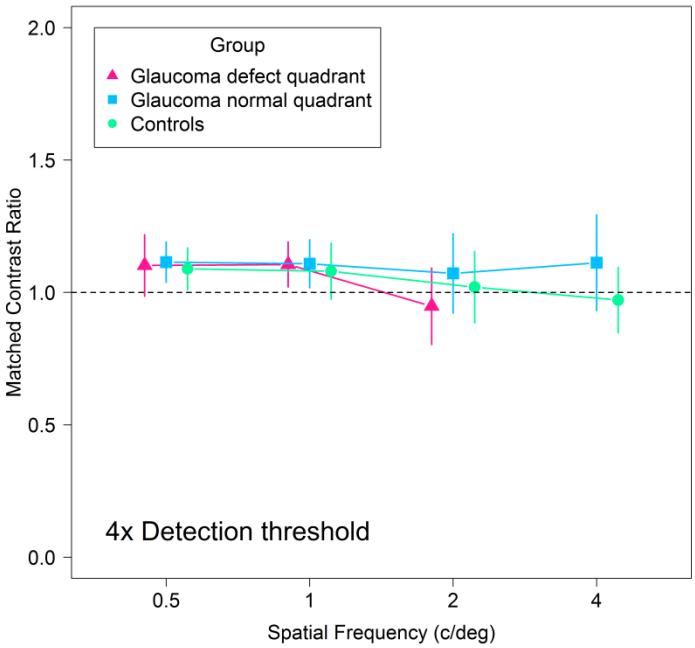


Figure 3.6 Group mean suprathreshold contrast matching functions for reference stimulus contrasts 2x (top) and 4x (bottom) detection threshold. Vertical axes show the ratio between matched and reference contrasts. Horizontal dashed lines indicate where matched contrast equals physical contrast (matched contrast ratio= 1.0). Error bars show 95% CI of the mean.

Figure 3.7 shows individual contrast match data points for each experimental condition. A narrower range of reference contrasts were tested within the visual field defect of the glaucoma group due to elevated detection thresholds. For all conditions, the majority of points lie close to the diagonal, indicating a perceptual match between the foveal and peripheral test locations. Spatial frequency had minimal effect on contrast match ratios for 2x ($\chi^2(3)=6.4$, $p=0.092$) and 4x ($\chi^2(2)=5.9$, $p=0.054$) reference contrasts.

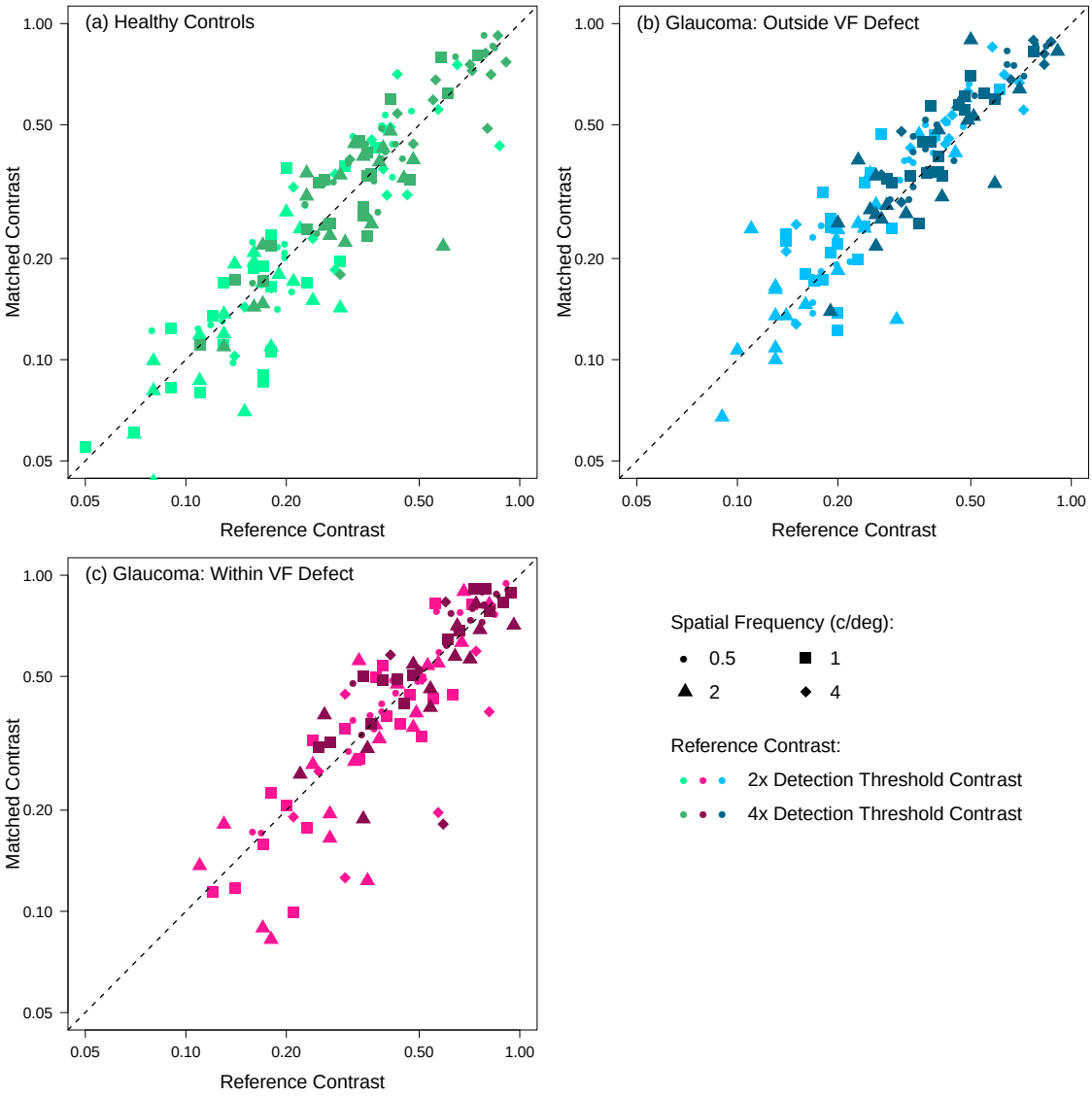


Figure 3.7 Individual suprathreshold contrast matches for the three groups for all four spatial frequencies and both reference contrasts. Data presented are for (a) healthy control participants, (b) glaucoma participants outside their visual field defect and (c) glaucoma participants within their visual field defect. Dashed 1:1 lines indicate veridical perception of suprathreshold contrast (i.e. perceived contrast matches physical contrast).

3.6 Discussion

This study aimed to investigate the effects of glaucoma on contrast perception of suprathreshold stimuli. Detection thresholds were elevated in the glaucoma group when tested within a visual field defect relative to age-matched controls. However, contrast matching data were similar between controls and the glaucoma group both within and outside visual field defects and at low and high contrast levels, despite the glaucoma group having elevated detection

thresholds for these stimuli. These results suggest that common depictions of what glaucoma patients 'see' such as black tunnel effects and greyed-out areas of vision may not accurately represent what glaucoma patients truly perceive. This misinformation to the public may have wider implications in people appropriately understanding how the disease can affect glaucoma patients' vision. Furthermore, these results give some insight into how the disease can be symptomless in nature and go unnoticed in its early stages.

Although the neural mechanisms underpinning suprathreshold contrast perception is undetermined, a number of theories have been proposed to explain this finding (Georgeson and Sullivan 1975; Swanson et al. 1984; Brady and Field 1995). First, it has been proposed that a number of independent channels tuned to different spatial frequencies exist within the visual system to deconstruct and interpret the image (Hubel and Wiesel 1962; Kulikowski and King-Smith 1973). Georgeson and Sullivan (1975) proposed that changes in contrast gain within these channels under suprathreshold conditions could compensate for the attenuation in sensitivity to high and low spatial frequencies at threshold, thus equalising the visual systems response to stimuli of varying spatial frequencies at suprathreshold level. Swanson et al. (1984) extended this concept further by developing a model that could predict contrast matching data from contrast thresholds using a small number of medium bandwidth mechanisms tuned to differing spatial frequencies. The model demonstrated that the visual systems response to varying spatial frequencies could be made equivalent by adjusting the slope of the contrast transfer function (contrast gain) of individual bandwidth mechanisms within the model. Brady and Field (1995) however detracted from this theory and proposed a model that assumes contrast gain remains constant across spatial frequency channels under suprathreshold viewing conditions. The authors suggest that contrast constancy is a result of the visual system's response to the signal alone rather than detection thresholds that are affected by the signal to noise ratio. Brady and Field (1995) propose that higher spatial frequencies respond to noise greater than mid-range spatial frequencies giving channels tuned to higher spatial frequencies a reduced signal to noise ratio and increasing detection thresholds to these stimuli. However, their data showed contrast constancy as soon as stimuli were suprathreshold; this finding was inconsistent with the majority of

literature that showed a gradual flattening of contrast matching functions with increasing suprathreshold contrast (Georgeson and Sullivan 1975; Swanson et al. 1984; Mei and Leat 2007; Mei et al. 2007). McIlhagga (2004), however, proposed that contrast constancy requires noise suppression or denoising mechanisms additional to alterations in contrast gain to maintain contrast constancy. This denoising mechanism allows the visual system to estimate the physical contrast of a stimulus within a noisy internal signal. This theory allows an incorporation of both contrast gain mechanisms as well as accounting for the effects of internal neural noise on perception of contrast and how it may be overcome to uphold contrast constancy.

The results of this study suggest that the mechanisms supporting suprathreshold contrast perception are still active in glaucoma. We suggest that there could be some compensatory mechanisms in place facilitating this contrast constancy response to suprathreshold stimuli. These compensatory mechanisms could be maintained or stretched further to compensate for reduced sensory input at threshold. However, further research is required to investigate the neural mechanisms supporting this visual response in glaucoma.

The results of this study are consistent with previous studies investigating suprathreshold contrast perception in other eye conditions such as amblyopia (Hess and Bradley 1980) and nystagmus (Dickinson and Abadi 1992). However, in atrophic, exudative age-related macular degeneration and juvenile macular degeneration, Mei and Leat (2007) found that despite a flattening of the contrast matching functions, there was still a significant difference in contrast matching data between controls and the maculopathy group. This may be explained by the study not testing observers sufficiently enough above threshold to get a contrast constancy response; the highest contrast level tested for all observers was 0.56. Moreover, the study did not standardise the test between observers as all observers were assessed at the same contrast levels despite the maculopathy group having elevated detection thresholds, relative to controls (Mei and Leat 2007). The study concluded that although slight deficits in suprathreshold apparent contrast were found within the maculopathy group, this was not to the same extent as reduced contrast sensitivity in the maculopathy group. The study draws towards a similar hypothesis of some

compensatory mechanisms at work within the visual pathway under suprathreshold viewing conditions.

The method of adjustment was selected when designing this study as it allowed us to examine a greater number of test conditions within the limited testing time available. This method is also more preferable as it is user-friendly, particularly when assessing inexperienced elderly observers. However, as the method of adjustment is inherently noisier and has greater variability over other psychophysical methods (Wier et al. 1976), contrast matches were repeated twelve times to overcome this limitation. We were restricted to testing a small range of spatial frequencies due to time constraints. Therefore, we assume that beyond our range of 0.5 and 4 cpd, contrast matches would lie close to 1:1 and this may not be accurate. The contrast levels tested were also limited as detection thresholds were high in the glaucoma group so multiples of these detection thresholds reached the limit of 100% contrast causing the test to have a ceiling effect for any observer with detection thresholds of ≥ 0.25. This issue could have been overcome by lowering the multiples to create a greater range of contrast levels.

Participants were assessed under monocular viewing conditions but further assessment under binocular viewing would be valuable as this would be more representative of the daily habitual viewing conditions patients' experience. Further, the contrast matching paradigm employed assumes that participants' central vision was normal given our visual acuity criteria. However, studies have shown changes to central vision in glaucoma, even in the absence of central perimetric defects (McKendrick et al. 2002; McKendrick et al. 2010). Changes to contrast perception in central vision cannot explain our results, because apparent contrast of stimuli both within and outside of visual field defects, where contrast detection thresholds were markedly different, was close to veridical. Reduced apparent contrast of the central stimulus, if it were present, could only explain veridical perception in one, not both visual field regions. Simple Gabor stimuli were used in this study as this type of stimulus enables precise control and restriction of stimulus parameters, thus allowing specific aspects of vision to be examined. However, these stimuli may not accurately reflect natural viewing conditions where observers are subject to concurrent multiple complex stimuli.

Studies have shown the visual system responds differently to complex stimuli and natural scenes compared to simple stimuli (Bex et al. 2009) so further work investigating suprathreshold apparent contrast of natural scenes and complex stimuli in glaucoma would be valuable.

3.7 Conclusions

We have shown that apparent contrast of suprathreshold Gabor stimuli is similar in glaucoma and age-similar healthy observers despite reduced contrast sensitivity in the glaucoma group. This finding is consistent both within and outside of visual field defects measured by perimetry. The results suggest that there could be compensatory mechanisms at work in glaucoma under suprathreshold conditions that are not active under threshold viewing. Further research is required to explore the mechanisms facilitating suprathreshold apparent contrast in glaucoma.

Chapter 4

4 Detection and discrimination of image blur in glaucoma

4.1 Abstract

Purpose

Current clinical tests for glaucoma measure limited aspects of visual function, thus, do not capture all effects of the disease relevant to everyday visual performance. Patients have reported perceiving greater amounts of blur (Crabb et al. 2013) but this has not been measured empirically. In this study, we aimed to investigate the effects of glaucoma on detection and discrimination of image blur.

Methods

Two groups of glaucoma observers with central or non-central visual field defects and an age-similar control group participated. The stimulus was a single horizontal edge bisecting a hard-edged circle of 4.5° diameter. First, we measured contrast detection thresholds for these stimuli centrally using a 2-interval forced choice procedure. Subsequently, we measured blur detection and discrimination thresholds for these stimuli (reference blur 0, 1 arcmin) using a 2-alternative forced choice (which is sharper?) procedure under two contrast conditions; 4x individual detection threshold for the low contrast condition, 95% contrast for the high contrast condition.

Results

Contrast detection thresholds for the glaucoma VF defect group were raised by 0.014 ± 0.004 (mean ± SE) ($p=0.002$) and by 0.011 ± 0.004 ($p= 0.03$) relative to control and glaucoma normal central groups respectively. Blur detection (reference blur 0 arcmin) and discrimination thresholds (reference blur 1 arcmin) were similar between glaucoma VF defect, glaucoma normal central and control groups (reference blur: 0 arcmin, $p=0.29$, 1 arcmin, $p=0.91$). The lower contrast level increased thresholds from the higher contrast level (95% contrast) by 1.30 ± 0.10 arcmin ($p<0.001$) and 1.05 ± 0.096 arcmin ($p<0.001$) for blur detection

and discrimination thresholds respectively. An interaction effect between Group and contrast level was found for blur discrimination thresholds (p= 0.023).

Conclusions

Detection and discrimination of image blur is similar in individuals with early to moderate glaucoma and age-similar healthy controls. The results suggest that blur detection and discrimination in the fovea is primarily limited by optical factors and this remains the case in early to moderate glaucoma.

4.2 Introduction

Current clinical tests for glaucoma are based on measuring contrast detection thresholds in pre-determined locations across the visual field. However, this clinical test does not capture how the disease affects other aspects of visual function relevant to patients' daily visual experiences. Although there are not many symptoms in early stages of the disease, it has been reported that blur is the most common visual symptom that patients' experience (Crabb et al. 2013; Hu et al. 2014). Therefore, assessing blur detection and discrimination thresholds may prove useful in detecting glaucoma and understanding how the early loss of retinal ganglion cells manifests visually.

In the previous chapter (chapter 3) we showed that apparent contrast of suprathreshold stimuli is maintained in early glaucoma and this may be due to an increased pooling of signals from sparser located retinal ganglion cells. It may be that as a consequence of this increased spatial pooling, there is a loss of spatial resolution manifesting as increased blur perception in the disease process. If this is the case, measuring blur detection and discrimination thresholds may prove to be a useful clinical test in diagnosing glaucoma. In peripheral vision, it has been demonstrated that visual acuity is limited by retinal ganglion cell receptive field sizes (Thibos et al. 1987a) and as these cells are destroyed in the disease process, the separation between functioning cells increases resulting in reduced spatial resolution (Beirne et al. 2003) and likely increasing blur perception in glaucoma individuals.

Various aspects of suprathreshold visual perception have been measured in glaucoma to further understand the effects of the disease under more natural visual environments. These studies have found impairment to achromatic and chromatic resolution acuities, deficits in contrast discrimination and reduced Vernier acuity in glaucoma observers (McKendrick et al. 2002; Beirne et al. 2003; McKendrick et al. 2010). These studies evidence that impairment to aspects of natural vision in glaucoma individuals occur that are not identified by current perimetry tests. Blur can be an indicator of visual change and deterioration such as in the cases of uncorrected refractive error (Kandel et al. 2017) and cataract development (Lee et al. 2005). Further, blur acts as a visual cue for various circumstances such as depth (Mather and Smith 2002) and motion (Harrington and Harrington 1981) perception. Assessing blur thresholds may give us further understanding of how the disease impacts patients' vision under their natural suprathreshold environment.

In previous studies, blur perception has been investigated psychophysically by measurement of blur detection and discrimination thresholds (Watson and Ahumada 2011). The stimulus used in these studies is usually an edge that is blurred by a Gaussian kernel; the standard deviation of the kernel is used as a measure of blur and is reported in arcmin. Blur thresholds in healthy individuals are typically around 0.4-0.9 arcmin for blur detection and 0.15-0.4 arcmin for blur discrimination (reference blur 1', 80% contrast) (Watt and Morgan 1983; Mather and Smith 2002). Blur thresholds are affected under different contrast conditions; thresholds significantly increase for lower contrast levels (<30%) but remain similar for contrast levels beyond this (Hess et al. 1989). Under low contrast conditions, it is likely that fewer retinal ganglion cells contribute to the perception of stimuli. As glaucoma pathologically reduces the number of functioning retinal ganglion cells, it may be that the separation between cells is even greater under low contrast causing blur discrimination to be worsened further in individuals with glaucoma. Therefore, we measured blur thresholds under both low and high contrast conditions to investigate if contrast impacts blur detection and discrimination differently between glaucoma and age-similar healthy individuals.

This study will contribute to further understanding how the disease impacts glaucoma patients' daily visual experiences. Here, we investigate the effects of glaucoma on blur detection and discrimination of low and high contrast edge stimuli. Our hypotheses are as follows:

1.) We predict that blur detection and discrimination thresholds will be elevated in the glaucoma group compared with age-similar controls.
2.) We predict that the effect of glaucoma will be greater under low contrast conditions.

4.3 Methods

Participants

32 glaucoma observers (mean age ± SD: 71 ± 6 years) and 18 age-similar controls (70 ± 6 years) participated. Participants were recruited via local NHS trusts, community groups and advertisements in local newspapers. Diagnosis of glaucoma was confirmed by a clinical report from an Ophthalmologist or a reliable self-report with evidence of treatment. In this study, a separate visual field defect criterion was defined for 24-2 and 10-2 SITA Standard tests on HFA III (Humphrey Field Analyzer III, Carl Zeiss Meditec, Jena, Germany). For the 24-2 SITA Standard test, we defined a VF defect as a cluster of 3 or more adjacent non-edge points with $p<5\%$ on the pattern deviation plot. All glaucoma observers had to have a visual field defect on 24-2 SITA Standard test and a sectoral defect ($p< 5\%$) of the retinal nerve fibre layer on a circumpapillary scan using an optical coherence tomographer (Spectralis; Heidelberg Engineering GmbH). Control participants were included in the study if they had no visual field defect on both 24-2 SITA Standard and 10-2 perimetry tests and GHT analysis results were 'within normal limits'.

For the 10-2 SITA Standard test, the criteria for a VF defect were 3 or more adjacent points with $p<5\%$ within the central area of 12 points on the total deviation plot (Figure 4.1). Glaucoma participants were divided into two groups; those with and without central visual field defects on 10-2 SITA Standard test as defined by the above criteria. Glaucoma observers with a visual field defect within the central area of 12 points were grouped into the glaucoma VF defect

group. The second group of glaucoma observers had no visual field defect within this area of points and were classed as glaucoma normal central group. This area of points was chosen as it covers a 6° diameter which is larger than the size of our stimulus used in the study of 4.5° diameter. A power calculation based on pilot data and previous studies determined that a sample size of 18 per group would give 85% power to detect differences (α=0.05) of 1 ± 1 arcmin (mean ± SD). Therefore, the aim of this study was to collect data from a sample size of 18 per group.

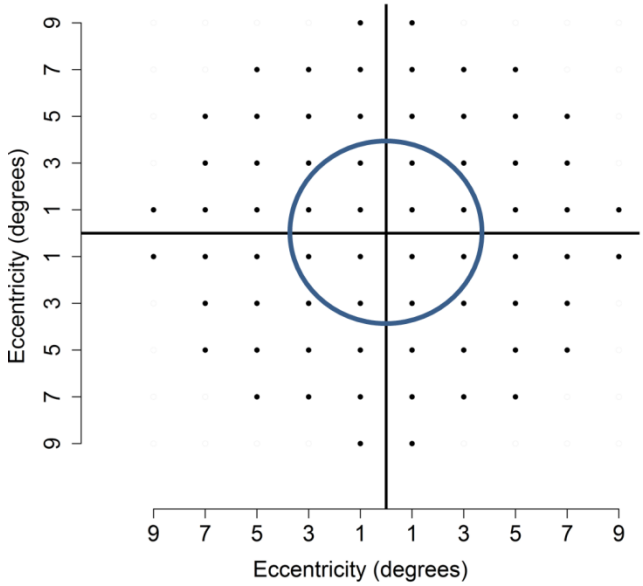


Figure 4.1 A schematic to show the central area of points for the visual field criteria on the total deviation plot of 10-2 SITA Standard test to define the two groups of glaucoma observers; with and without central visual field defects.

All participants had a visual acuity of better than 6/9.5 in the tested eye and a refractive error of no more than ± 6.00DS and 3.00DC. Participants were only included in the study if they had no ocular or systemic condition known to affect visual performance except glaucoma for the glaucoma group and mild cataract (no more than NC3 NO3 C2 P2 on LOCS III grading scale (Chylack et al. 1993)). Control observers were required to have normal findings on eye health assessment prior to testing. These health assessments included slit-lamp biomicroscopy, indirect fundoscopy and Goldmann applanation tonometry (intraocular pressure ≤ 21mmHg and ≤ 3mmHg difference between the eyes for the control group). If both eyes fit the inclusion criteria for any observer, the tested eye was chosen at random. All participants provided written informed consent in accordance with the tenets of the Declaration of Helsinki before

participating in the study. The study was approved by a National Health Service ethics committee. An inconvenience allowance was provided to participants.

Apparatus & stimuli

The stimulus used was a single horizontal edge bisecting a hard-edged circle of 4.5° diameter (Figure 4.2). Stimuli varied in contrast for the low contrast condition (see procedure section) and were of 95% contrast for the high contrast condition. The horizontal edge was blurred by a Gaussian kernel of varying spread that operated as a low-pass spatial filter. In this study, stimulus blur was defined by the spread (standard deviation) of this blurring kernel, reported in arcmin. Two reference blurs were used; 0 arcmin for the blur detection task and 1 arcmin for the blur discrimination task. A third reference blur of 4 arcmin was used initially in contrast detection tasks but not used for subsequent blur discrimination task as testing times were limited to 2.5 hours. This is the duration that most patients can concentrate for with breaks in between in one observation period, and so we did not have sufficient time to incorporate assessing this third reference blur. Stimuli were generated in MatLab 8.5.0 (R2015a; The Mathworks, Natick, Massachusetts, USA) using Psychtoolbox-3 (V3.0.14)(Brainard 1997; Pelli 1997; Kleiner et al. 2007). Stimuli were presented on a 14 bit calibrated display system (resolution, 1920x1080; refresh rate, 120Hz; CRS Display++; Cambridge Research Systems Ltd, Kent, UK) viewed from 127cm via a chin and forehead rest. Appropriate refractive correction was worn for this viewing distance and testing was performed monocularly with occlusion of the non-tested eye. The mean luminance of the screen was 52.8cd/m².

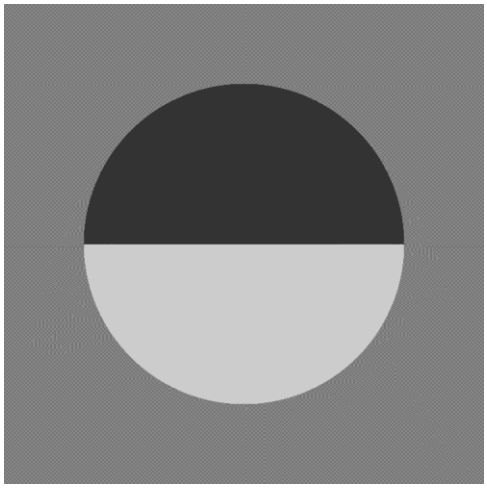


Figure 4.2 An illustration of the stimulus used in the blur experiment. The edge bisected a circle of 4.5° diameter. The stimulus varied in contrast for the low contrast condition and was of a fixed contrast for the high contrast condition (0.95 Michelson units). The edge of the stimulus was blurred using a Gaussian kernel.

Procedure

All participants performed three tasks for these stimuli. Task 1 was used to obtain an approximation of contrast detection thresholds and use this approximate value as a start contrast level for the contrast detection experiment in task 2. Participants fixated on the stimulus (reference blur 0, 1 or 4 arcmin) presented centrally. The observer was asked to adjust the contrast of the stimulus using a dial (CB7, Cambridge Research Systems, Kent, UK) until they could 'just see it'. A rotation of the dial clockwise and anti-clockwise resulted in an increase or decrease in contrast respectively. One full rotation of the dial produced a 10% change in contrast. The results of task 1 were used as a starting point for the contrast detection experiment in task 2. Stimulus contrast in this study was defined as Michelson contrast: (Lmax-Lmin)/(Lmax+Lmin) where Lmax and Lmin are the maximum and minimum luminance of the stimulus respectively.

In task 2, final measures of contrast detection thresholds were obtained using a 2-interval forced choice (which interval?) procedure. Stimuli were presented for 350ms (raised cosine temporal profile), separated by a 500ms interval. Stimulus contrast was adjusted according to a 3 down 1 up staircase procedure; with independent staircases randomly interleaved for each reference blur (0, 1 & 4 arcmin). Easy trials using stimuli of high (95%) contrast were included for the first two presentations and every 10^{th} presentation from then on. These trials were used to maintain observer concentration throughout the experiment. Step sizes for stimulus contrast adjustment were 20% before the first reversal then 10% thereafter. Staircases terminated after 6 reversals, with the mean of the last 4 taken as the detection threshold. Participants were instructed to identify whether the stimulus appeared in interval 1 or 2 and to give their best guess when they were unsure; responses were recorded with a key press.

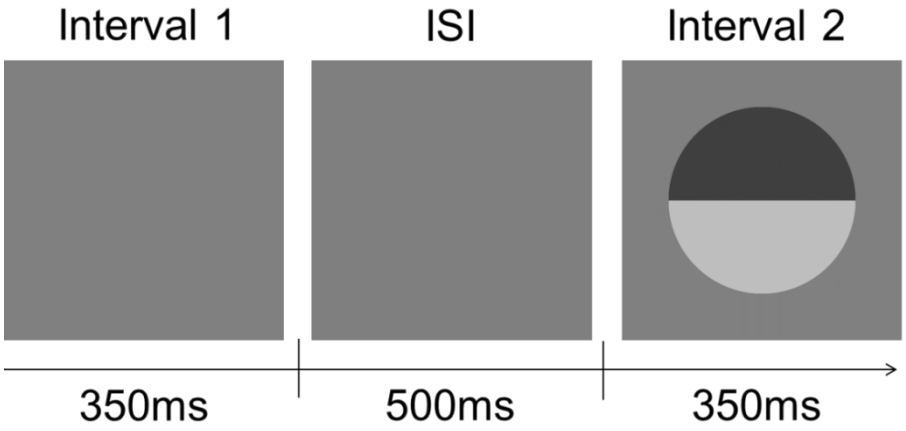


Figure 4.3 Methodology used to obtain contrast detection thresholds for stimuli of reference blur 0, 1 and 4 arcmin. The observer viewed the screen with stimuli displayed centrally. In each trial, stimuli were presented randomly in either interval 1 or 2. Interval duration was 350ms with an inter-stimulus interval (ISI) duration of 500ms. Participants indicated which interval the stimulus appeared in by a key press.

In task 3, blur detection and discrimination thresholds were measured centrally for stimuli of reference blur 0 and 1 arcmin using a 2-alternative forced choice (which is sharper?) procedure. Stimuli were presented side by side separated by 0.5° under free viewing conditions (Figure 4.4). One stimulus had the reference blur (r) and the other stimulus (test stimulus) had blur equal to the reference + a blur increment (r + Δ r). The reference and test stimuli were presented randomly between the two positions on screen; either 0.25° left or 0.25° right from centre of the screen. Participants were instructed to identify which of the two stimuli (left/right) were sharper/clearer and to give their best estimate if they were unsure. Responses were recorded with a key press. Stimuli were presented for 1200ms (raised cosine temporal profile) with a buffer interval between trials of 500ms. Easy trials displaying maximum blur (10 arcmin) were included for the first two presentations and then every 10^{th} presentation thereafter.

A total of 4 test conditions were examined; blur detection (reference blur 0 arcmin) and discrimination (reference blur 1 arcmin) under two contrast conditions; 4x individual contrast detection threshold for the *low contrast* condition and 95% contrast for the *high contrast* condition. Participants performed these tasks in a predetermined randomized order. Test blur was

varied according to randomly interleaved independent 3 down 1 up staircases. These three staircases began randomly between blur levels of 2-6 arcmin. This start blur interval was chosen based on previous pilot data collected from young and elderly healthy observers. Blur was adjusted (increase/decrease) in step sizes of 20% before the first reversal and 10% thereafter. Staircases terminated after 8 reversals and thresholds were calculated as the average of all but the first 2 reversals.

If staircases did not converge or data was of poor quality, the experimental run was repeated and manual levels for the start of staircases were inputted between blur levels of 0-10 arcmin. These start levels were chosen to begin at or above the level of staircase termination from the previous run depending on data quality and convergence of staircases. If data quality was good and staircases showed convergence but did not quite converge, staircases began at a similar level from when the previous staircases terminated. However, if data quality was poor and staircases were not converging, manual start level of staircases began higher than where previous staircases terminated as data appeared not to be sufficiently above threshold for the observer to perform the task appropriately. A maximum of 3 runs per condition were completed.

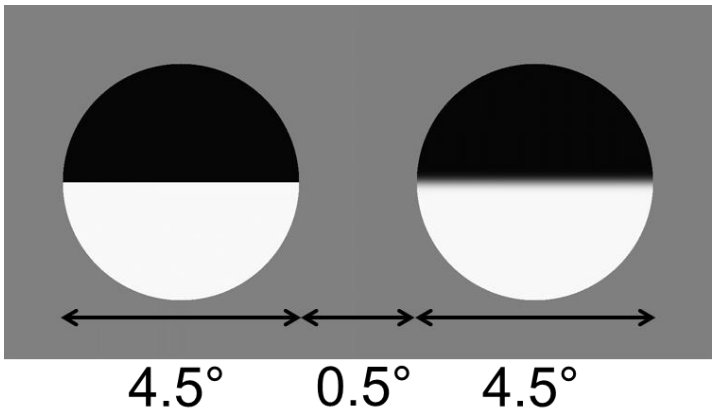


Figure 4.4 Methodology used to obtain blur detection (reference blur 0 arcmin) and discrimination thresholds (reference blur 1 arcmin). A 2-alternative forced choice method was employed under free viewing conditions. Reference and test stimuli were presented randomly either to the left or right hand side of the centre of screen. Participants were instructed to choose which of the two stimuli were clearer. Responses were recorded with a keypress.

4.4 Statistical analysis

Statistical analysis was completed in R (R Core Team (2017)) using lme4 (Bates et al. 2015) and emmeans (Lenth 2018) packages. Data were analysed using linear mixed modelling. For contrast detection data, fixed-effects of Group (glaucoma VF defect, glaucoma normal central, controls) and Reference blur (0, 1, 4 arcmin) and random effect of participant were entered into the model. Models took the form of:

Null:

Contrast detection threshold ~ 1 + (1|Participant)

Fixed-effect of Group:

Contrast detection threshold ~ 1 + Group + (1|Participant)

Fixed-effect of Reference blur:

Contrast detection threshold ~ 1 + Group + Reference Blur + (1|Participant) †

† If likelihood ratio tests showed a significant effect of the first fixed-effect assessed, this fixed-effect remained in the model and a second fixed-effect was added, whereas if likelihood ratio tests showed no significant effect of the first fixed-effect entered into the model, this fixed-effect was removed and a second fixed-effect was added independently. In this case, effect of Group was significant so this fixed-effect remained in the model and an additional fixed-effect of reference blur was entered into the second model.

For blur detection and discrimination data, fixed-effects of Group (glaucoma VF defect, glaucoma normal central, controls) and Contrast level (4x detection threshold, 95% contrast) and random effect of participant were entered into the model. Models took the form of:

Null:

Blur detection threshold ‡ ~ 1 + (1|Participant)

Fixed-effect of Group:

Blur detection threshold ~ 1 + Group + (1|Participant)

Fixed-effect of Contrast:

Blur detection threshold ~ 1 + Contrast + (1|Participant)

‡*The same model arrangement was used for blur discrimination thresholds as the outcome measure instead of blur detection thresholds.*

Null models were compared to alternative models including the fixed-effect in question using χ^2 likelihood ratio test. If likelihood ratio tests were significant ($p<0.05$), Tukey post-hoc test using estimated marginal means separated effects by Group/Reference blur/Contrast and disclosed effect sizes. Interaction effects were also assessed between Group and Reference blur (contrast detection data) and Group and Contrast (blur detection and discrimination data) using linear mixed modelling.

4.5 Results

From the total 32 glaucoma observers, 15 observers were grouped into the glaucoma VF defect group whilst 17 were assigned to the glaucoma normal central group. Tables including perimetry results of individual glaucoma observers in the study are given below. We planned to collect data from a few more observers in each group to complete the same size of 18 participants per group but data collection and recruitment was halted due to COVID-19.

Table 4.1 Individual perimetry results for glaucoma observers' in glaucoma VF defect group:

Participant	Age	MD	PSD	GHT
1	75	-2.57	6.27	Outside normal limits
2	64	-5.64	7.63	Outside normal limits
3	65	-2.69	10.70	Outside normal limits
4	77	-3.33	6.32	Outside normal limits
5	61	-14.95	10.43	Outside normal limits
6	67	-8.62	10.11	Outside normal limits
7	66	-1.92	5.04	Outside normal limits
8	77	-12.77	13.09	Outside normal limits
9	84	-4.34	5.92	Outside normal limits
10	78	-4.53	2.48	General reduction of sensitivity
11	74	-13.08	10.68	Outside normal limits
12	76	-8.00	4.25	Outside normal limits
13	64	-4.50	10.44	Outside normal limits
14	70	-3.21	2.48	Outside normal limits
15	69	-4.83	2.72	Borderline/General reduction

Table 4.2 Individual perimetry results for glaucoma observers' in glaucoma normal central group:

Participant	Age	MD	PSD	GHT
1	73	-4.71	6.15	Outside normal limits
2	78	-6.13	6.04	Outside normal limits
3	70	-2.35	3.66	Outside normal limits
4	61	-6.29	11.17	Outside normal limits
5	70	-3.01	2.20	Outside normal limits
6	74	-1.46	2.77	Outside normal limits
7	67	-5.91	6.57	Outside normal limits
8	69	-1.61	6.50	Outside normal limits
9	69	-3.20	3.05	Outside normal limits
10	73	-5.69	7.18	Outside normal limits
11	83	-3.71	2.34	Within normal limits
12	74	-5.60	10.60	Outside normal limits
13	62	-4.06	8.38	Outside normal limits
14	61	-5.72	9.61	Outside normal limits
15	69	-2.70	2.23	Borderline
16	76	-4.38	7.18	Outside normal limits
17	73	-2.95	4.90	Outside normal limits

Data sets where staircases did not converge even after multiple runs of the experiment or those data sets with poor quality data confirmed by the two investigators were excluded from analyses. This applied to a total of 7 data sets; a breakdown of which data sets were removed for each group can be seen in table 4.3. Two glaucoma observers with central visual field defects could not complete these blur experiment tasks accurately enough for all four conditions and so these two participants' data sets were completely removed and not included within the analysis.

Table 4.3 Data sets removed for each experimental condition due to non-convergent staircases and/or poor quality data confirmed by the two investigators.

Data sets	Ref Blur 0, Low contrast	Ref Blur 0, High contrast	Ref Blur 1, Low contrast	Ref Blur 1, High contrast
Controls	3	0	0	1
Glaucoma normal central VF	0	0	1	0
Glaucoma central VF defect	0	1	1	0

Contrast detection thresholds

Mean group contrast detection threshold for each reference blur is given below in Figure 4.5. Contrast detection thresholds for the glaucoma VF defect group were raised relative to the other two groups (main effect, $\chi^2(2)= 12.6$, $p=0.002$). Specifically, detection thresholds for the glaucoma VF defect group were elevated by 0.014 ± 0.004 ($p=0.002$) (mean ± SE) and by 0.011 ± 0.004 ($p= 0.03$) relative to controls and glaucoma normal central groups respectively. Contrast detection thresholds between control and glaucoma normal central groups were similar (difference in mean detection thresholds, 0.0036 ± 0.004, $p= 0.6$).

Contrast detection thresholds were significantly affected by reference blur ($\chi^2(2)= 20.85$, $p<0.001$). Specifically, contrast detection thresholds were raised for a reference blur of 4 arcmin by 0.0050 ± 0.001 ($p<0.001$) and by 0.0036 ± 0.001 ($p=0.003$) relative to reference blurs of 0 and 1 arcmin respectively. Contrast detection thresholds were similar between reference blur 0 and 1 arcmin (difference in mean detection thresholds, 0.0014 ± 0.001, $p= 0.40$). No significant interaction was found between Group and Reference blur ($\chi^2(4)=1.87$, $p= 0.76$).

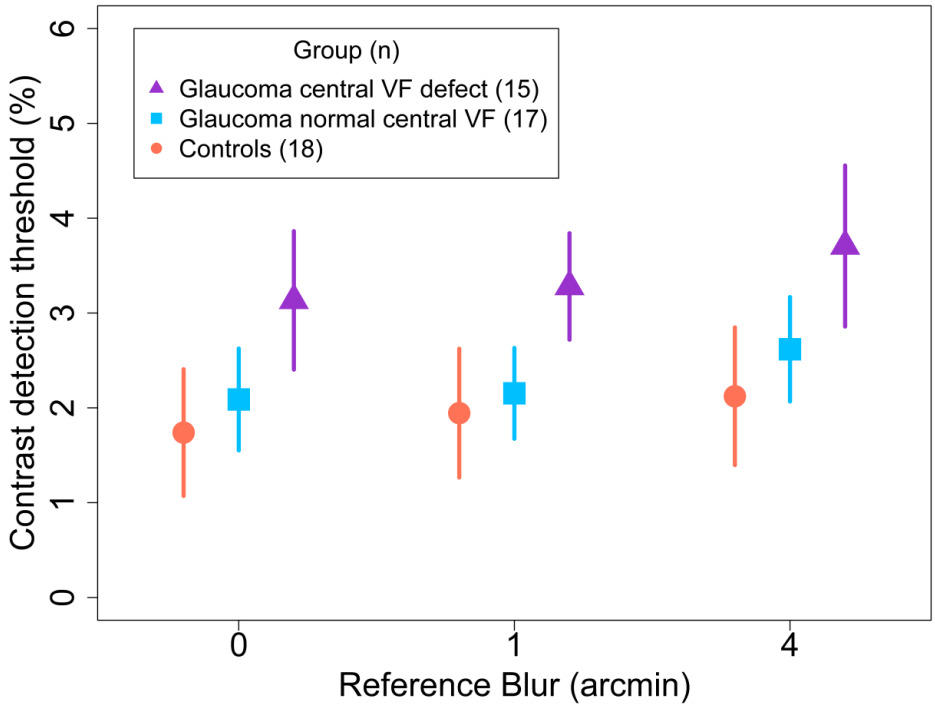


Figure 4.5 Contrast detection thresholds for controls (orange circles), glaucoma observers tested within a VF defect (purple triangles) and glaucoma observers tested in a normal central VF area (blue squares). Thresholds are given as Michelson units converted into percentages. Data shown are mean ± 95% CI of the mean.

Blur detection thresholds

Figure 4.6 shows group mean blur detection thresholds for high (95%) and low (4x detection threshold) contrast levels. Blur detection thresholds were similar across the three groups (main effect of group, $\chi^2(2)=2.46$, $p= 0.29$) with group means ± SE of 2.15 ± 0.18, 2.45 ± 0.18 and 2.53 ± 0.19' for control, glaucoma normal central and glaucoma VF defect groups respectively. There was a main effect of contrast level on blur detection thresholds ($\chi^2(1)=73.49$, $p<0.001$). Specifically, the lower contrast level (4x detection threshold) increased blur detection thresholds by 1.3 ± 0.10' compared with the higher contrast level (95% contrast) assessed.

Although a slightly different trend in blur detection threshold elevation with change in contrast (Figure 4.8) was observed between the three groups, this interaction effect was not significant (interaction of Group and Contrast level,

$\chi^2(2)=5.94$, p= 0.051). Specifically, a decrease in contrast from 95% contrast to 4x detection threshold increased blur detection thresholds by 1.42 ± 0.17, 1.49 ± 0.16 and by 0.94 ± 0.17' for control, glaucoma normal central and glaucoma VF defect groups respectively.

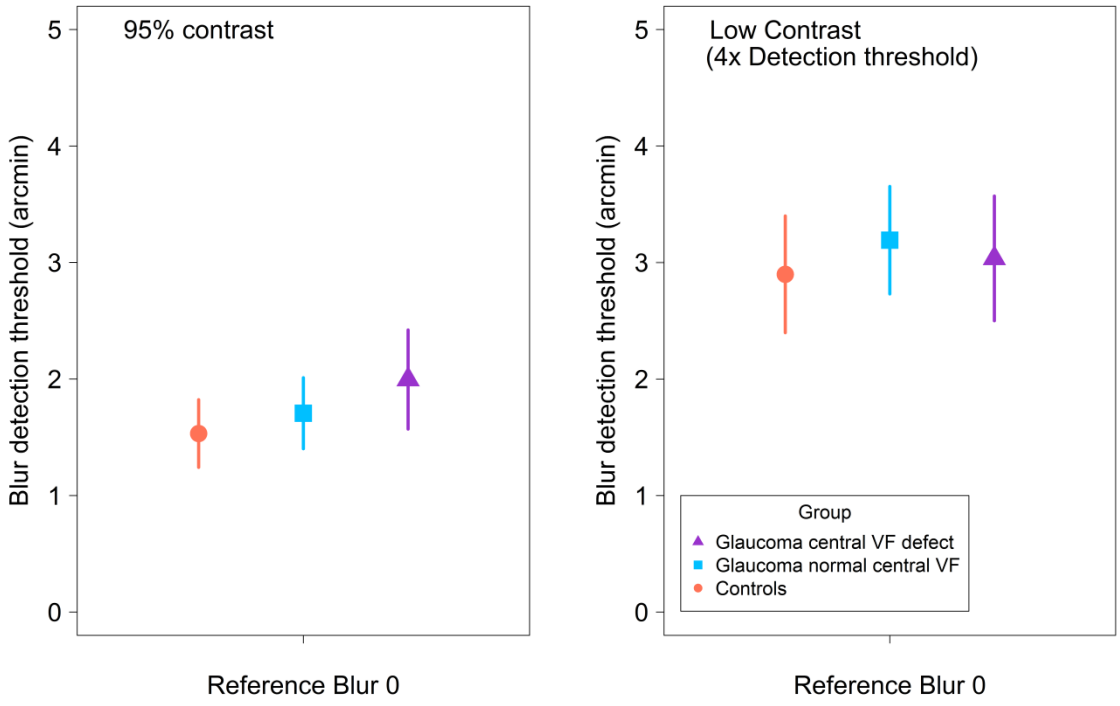


Figure 4.6 Blur detection thresholds (mean ± 95% CI of the mean) for each group for high (left) and low (right) contrast stimuli.

Blur discrimination thresholds

Figure 4.7 shows group mean blur discrimination thresholds for a reference blur of 1 arcmin for both high (95%) and low (4x detection threshold) contrast stimuli. Blur discrimination thresholds were similar across group (main effect of group, $\chi^2(2)= 0.18$, p= 0.91) with group means ± SE of 1.92 ± 0.19, 2.02 ± 0.19 and 2.02 ± 0.21' for control, glaucoma normal central and glaucoma VF defect groups respectively. There was a main effect of contrast level on blur discrimination thresholds ($\chi^2(1)= 60.26$, p<0.001). Similarly, the lower contrast level (4x detection threshold) assessed increased blur discrimination thresholds by 1.05 ± 0.096' compared with the higher contrast level (95% contrast).

There was a main interaction effect between Group and contrast level ($\chi^2(2)= 7.55$, p= 0.023). A decrease in stimulus contrast from 95% contrast to 4x detection threshold increased blur discrimination thresholds to a greater extent for glaucoma normal central and control groups compared with the glaucoma VF defect group (Figure 4.8). Specifically, a decrease in contrast level increased blur discrimination thresholds by 1.26 ± 0.16' for glaucoma normal central compared with 0.68 ± 0.17' for glaucoma VF defect groups (difference in threshold elevation rate between glaucoma normal central and glaucoma VF defect groups, 0.59 ± 0.23, p=0.035) and by 1.17 ± 0.15' for the control group (difference in threshold elevation rate between control and glaucoma VF defect groups, 0.50 ± 0.22, p= 0.075). Increase in blur discrimination thresholds with respect to change in contrast were similar between glaucoma normal central and control groups with a difference in threshold elevation rate of -0.089 ± 0.22 (p= 0.91).

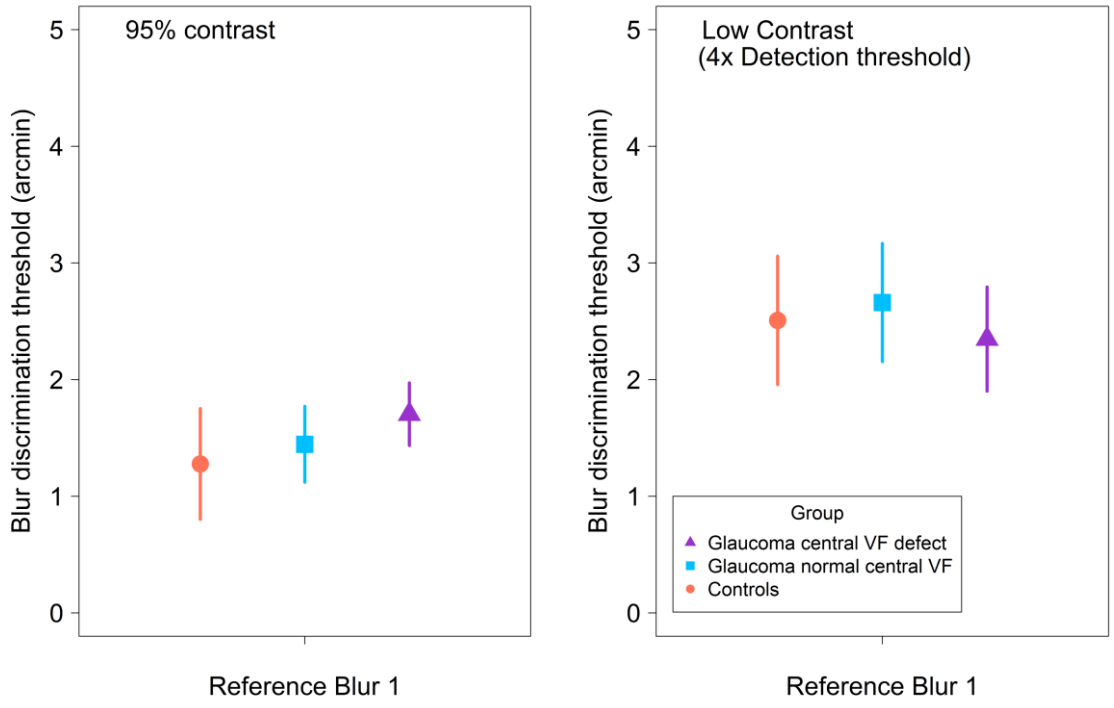


Figure 4.7 Group blur discrimination thresholds (mean ± 95% CI of the mean) for a reference blur of 1 arcmin for high (left) and low (right) contrast stimuli.

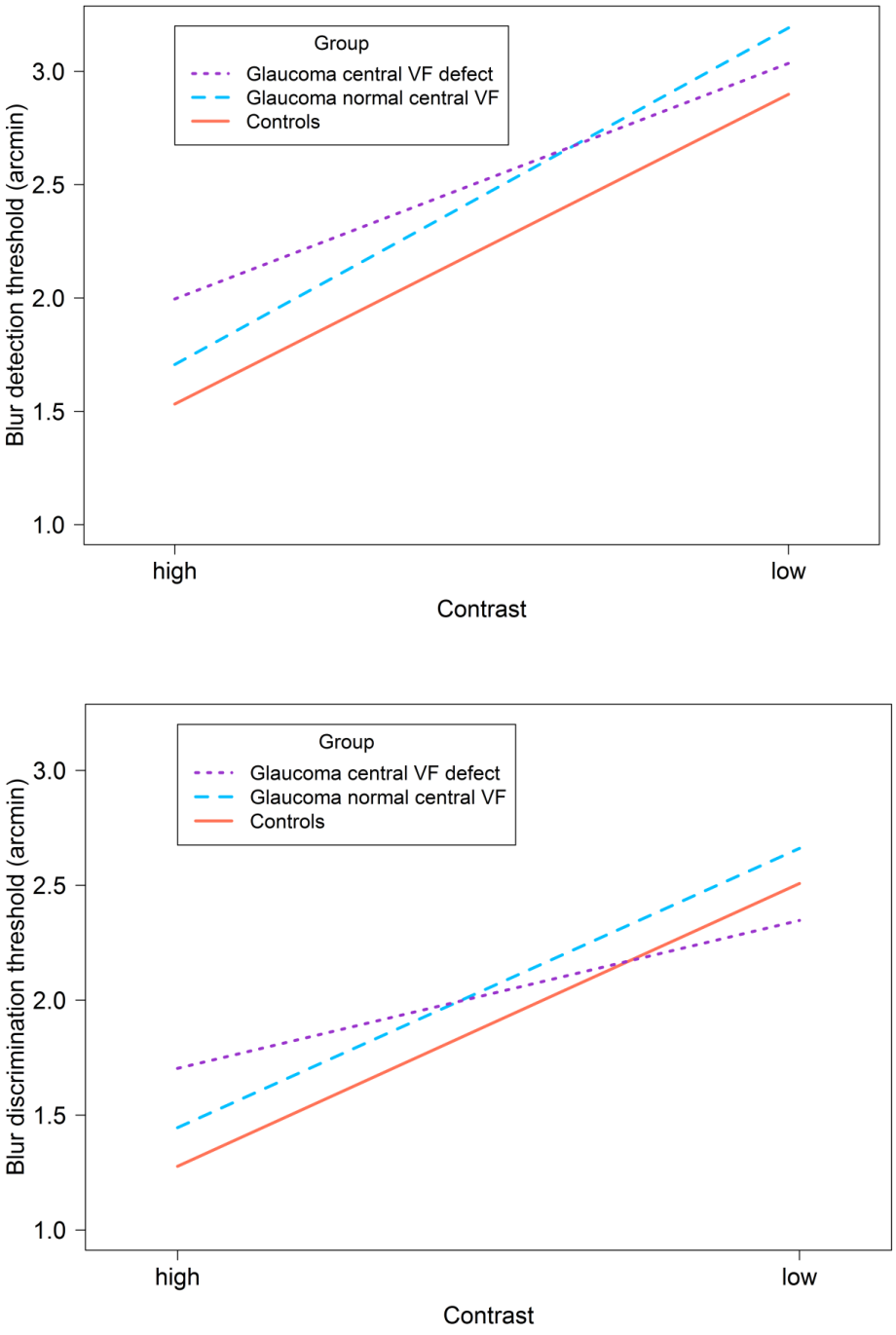


Figure 4.8 : Interaction effects between Group blur detection (top) and discrimination (bottom) thresholds with a change in contrast. For high contrast stimuli, the glaucoma VF defect group had elevated blur detection and discrimination thresholds compared with glaucoma normal central and age-similar control groups. When contrast levels reduce, all groups show an elevation in blur detection and discrimination thresholds, however, the glaucoma VF defect group thresholds are less affected by a change in contrast compared with the other two groups respectively.

4.6 Discussion

The purpose of this study was to test the hypotheses that glaucoma increases blur detection and discrimination thresholds relative to controls, and that the effect would be greater under low contrast conditions. Blur detection and discrimination thresholds were similar between glaucoma and age-similar healthy individuals. The effects of contrast, however, were significant and decreased blur thresholds with an increase in contrast; this finding being in line with previous studies (Hess et al. 1989; Westheimer et al. 1999). Contrary to our initial hypothesis, low contrast stimuli elevated blur discrimination thresholds to a greater extent for glaucoma normal central and control groups compared with the glaucoma VF defect group.

These results suggest that in early to moderate glaucoma, performance in detection and discrimination of image blur in central vision remains intact and relatively unaffected by the disease. These results provide some evidence as to the symptomless nature of the disease in its early stages. The results may suggest that glaucoma individuals that have described perceiving increased blur in their vision (Crabb et al. 2013) may be describing effects of increased neural blur perception in more peripheral locations of the visual field.

Interestingly, the study found a significant interaction effect between contrast and group on blur discrimination thresholds. At high contrast, the glaucoma VF defect group performed slightly worse at blur detection and discrimination compared to the other two groups though this difference was small and statistically non-significant for blur detection. The lack of statistical significance may be due to the smaller than intended sample size. However, at low contrast all three groups performed similarly for blur detection and discrimination thresholds resulting in the glaucoma VF defect group being less affected by a change in contrast than the other two groups. This finding may be explained by neural factors having a greater influence on spatial resolution and blur discrimination under higher contrast conditions. While, under low contrast conditions (closer to threshold), the greater limiting factor for blur discrimination thresholds may be earlier in the visual system, by optical factors of the eye. Under low contrast conditions, the high spatial frequency information may be too low contrast to be detected by all three groups so the reduced resolution

and discrimination ability from the glaucoma VF defect group is overcome by fully sampling the information left in the image of lower spatial frequencies allowing this group to perform similarly to the other two groups assessed. It is possible that assessing blur thresholds to detect glaucoma in the fovea is further limited by resolution and blur thresholds in the fovea being primarily optically limited and so in order to see a significant drop in performance, glaucoma individuals need to have a substantial drop in retinal ganglion cells sampling the retinal image that outweigh the optical limits of the eye. A deficit in performance from glaucoma will only manifest once the task becomes sampling limited and not limited by optical factors. Therefore, a significant elevation in blur detection discrimination thresholds may be seen in the periphery as peripheral resolution, unlike foveal resolution is sampling limited rather than limited by the optics of the eye (Thibos et al. 1987b). However, initial pilot testing showed that the present task was too difficult for the participants to perform in the periphery even in young healthy observers, with most providing unreliable data. This suggests that peripheral blur detection and discrimination are unlikely to be suitable as clinical tests for glaucoma.

Further, it may be that the description of ‘blur’ that is quite commonly used in relation to symptoms described by patients may be attributed to the effects of a different perceptual experience that patients are not able to define such as the effects of crowding (Levi 2008) or aliasing (Thibos et al. 1987b) in the periphery. Patients may be describing their symptom as ‘blur’ when it may be that they have more difficulty in recognising and distinguishing objects in clutter. This visual phenomenon is well known to optical professionals but not commonly known to patients, and could be significantly impaired by the disease as has been shown by a study investigating crowded orientation acuity in glaucoma (Ogata et al. 2019). Crowding affects a range of visual tasks in normal vision (see Levi (2008) for review). Therefore, it could be that these areas of vision are affected to a greater extent in glaucoma, as reduced retinal ganglion cell densities in the disease may cause cells from sparser locations to pool responses and in turn increase crowding effects. As the fovea projects to the greatest density of retinal ganglion cells (Dacey 1993), our results may be explained by an insufficient loss of retinal ganglion cells to show a deficit in performance in this central area assessed in both glaucoma groups (with and

without VF defects), thus allowing glaucoma individuals' blur detection and discrimination to be similar to controls. This is further supported by the cohort of patients examined, most of the individuals in both glaucoma groups had early to moderate stages of glaucoma; evidenced by the majority of observers having a MD better than -10dB in both groups. Further, those with central VF defects in the glaucoma VF defect group had only to meet the minimum criteria of a cluster of 3 points to qualify for this group and so the area assessed may not have had a severe enough scotoma to show a deficit in performance and suggests the underlying retinal ganglion cells assessed may be more preserved allowing glaucoma observers to perform similarly to controls. Perhaps if this task was performed at more eccentric locations with a sparser retinal ganglion cell distribution (Curcio and Allen 1990; Dacey 1993) or in areas with advanced VF defects, we may have seen a drop in performance in glaucoma individuals. This is supported by 2 observers that fit into the glaucoma VF defect group but could not perform the experiment at all or have good enough quality data for all four test conditions to be included in study, showing that in some observers / more advanced glaucoma cases, we would predict a poorer blur detection and discrimination performance.

There are few studies investigating blur perception in various eye conditions, however, a study investigating blur detection and discrimination thresholds in amblyopic individuals found interesting results (Simmers et al. 2003). Blur discrimination thresholds were elevated in amblyopic observers but these individuals were able to match blur veridically under dichoptic viewing conditions (Simmers et al. 2003). The authors suggest that the results show that blur may be processed in the visual system beyond the requirement for high spatial resolution that is lacking in amblyopic individuals. This finding is intriguing, however different to our finding in glaucoma individuals. The authors also suggest the finding of elevated thresholds may be explained by increased noise in the amblyopic visual system.

When compared with previous studies investigating blur detection and discrimination in healthy and usually younger individuals (see Watson and Ahumada (2011) for a comprehensive review), we can observe an elevation in these blur thresholds with respect to ageing. For instance, blur detection and

discrimination thresholds for high contrast (80% contrast) stimuli have been found to be ~ 0.4-0.9 arcmin for blur detection and 0.15-0.4 arcmin for blur discrimination (reference blur 1', 80% contrast) (Watt and Morgan 1983; Mather and Smith 2002) whilst these thresholds in our elderly healthy control observers were 1.53 ± 0.29' and 1.28 ± 0.47' showing a noticeable elevation of these thresholds with ageing. Similarly, for stimuli of lower contrast, our thresholds for elderly healthy observers were 2.90 ± 0.5' and 2.51 ± 0.55' compared with previous studies showing these thresholds as ~ 1-1.4' and 0.4-0.9' for stimuli of 10% contrast (Wuerger et al. 2001; Mather and Smith 2002). Some of these differences may be accounted for by differing psychophysical procedures, for example Wuerger et al. (2001) and Mather and Smith (2002) used a 2-interval forced choice as opposed to a 2-alternative forced choice procedure used in this study. Furthermore, the stimulus used varied between studies, for instance Mather and Smith (2002) used a larger square stimulus with a vertical and horizontal length of 8.72° and a sinusoidal edge whilst the present study used a smaller sized circular stimulus of 4.5° diameter and a straight edge. However, the difference in results may not fully be accounted for by stimulus and procedural differences alone and may evidence an age-related decline in these thresholds. These findings may be attributed to the deterioration of optical factors in the eye that are found with ageing (Artal et al. 1993) but not significantly impacted by a neurodegenerative disease such as glaucoma.

Studies have proposed various models to explain the mechanisms behind blur detection and discrimination thresholds (Wuerger et al. 2001; Mather and Smith 2002; Watson and Ahumada 2011). The model likely to explain blur perception is the visible contrast energy (ViCE) model by Watson and Ahumada (2011); this is the only model that incorporates the effects of both the contrast sensitivity function when stimuli are closer to threshold and the saturation effects of high contrast stimuli on these thresholds. The model predicts blur discrimination thresholds are reached when the visible contrast energy between two stimuli reaches a criterion value. The model shows that its predictions fit the existing data from the literature well following the classic dipper shape and holds for a range of reference blurs.

The ViCE model incorporates the physical difference in reference and test blur by Fourier transforming the spatial information of reference and test stimuli with Gaussian derived blur into their frequency domain and calculating their differences. The model also incorporates the original hard step-edge stimulus to which this Gaussian blur is applied. Additionally, the model incorporates effects of the contrast sensitivity function when reference/test stimuli are of lower contrasts closer to threshold and the saturation effects of contrast when stimuli are of higher contrasts. The model then incorporates these factors to give the local contrast energy difference of the two reference and test stimuli. The ViCE model estimates that when the difference in local contrast energies between reference and test stimuli reach beyond a criterion value ($V \geq 1$), the two stimuli can be discriminated. Therefore, blur discrimination thresholds are obtained at $V=1$.

The model demonstrates its applicability to both blur detection (reference blur 0 arcmin) and a range of reference blurs (0.1-50 arcmin) on the blur discrimination function. The two reference blurs we have assessed, 0 and 1 arcmin follow the general pattern found by many studies, facilitation; blur discrimination being slightly better than blur detection for lower reference blurs. However, we have only tested two points on the blur discrimination function and so it is difficult to predict how age-related decline in blur discrimination would shift the overall function; we may predict a vertical shift in this function with respect to ageing, some of this may be accounted for by a reduction in contrast sensitivity with ageing/glaucoma and therefore increases the requirement for a greater change in blur to reach the criterion value according to the ViCE model. As the relationship between contrast and blur thresholds is non-linear (Hess et al. 1989; Westheimer et al. 1999), it may be that thresholds saturate at a different contrast level in older individuals compared with younger individuals so these factors also need to be considered when using the ViCE model for interpretation that is based on fitting data from younger individuals.

Watson and Ahumada (2011) suggest that age related changes may affect the blur discrimination function due to changes in contrast sensitivity and visual acuity that is well known to decline with ageing (McKendrick et al. 2007; Zhang et al. 2008). According to this ViCE model, blur discrimination thresholds for low

reference blurs are more affected by visual acuity and optical factors whilst thresholds for larger reference blurs are more affected by contrast sensitivity and its attenuation to lower spatial frequencies; our hypothesis of age related elevation in thresholds due to optical ageing factors would support this suggestion. Optical blur from the eye itself is accounted for in the model by the central kernel. There are many age-related changes to the optics of the eye that could occur in our elderly/glaucoma observers including already evidenced early lens changes and possible vitreous changes (Sebag 1987). A likely explanation for elevation in blur detection and discrimination to low reference blurs in both our elderly control and glaucoma observers are a combination of neural and optical factors with more weighting on the latter. Neural factors contributing to this would be an age/glaucoma related decline in retinal ganglion cell density and function and optical factors could include lens, vitreous and other inherent age-related deteriorations in the visual system. Although the point spread function for Gaussian blur is different to that derived from Dioptric blur (Strasburger et al. 2018), it is interesting to consider the dioptric equivalence of these thresholds to give a clinical depiction of the size of blur detection and discrimination thresholds in elderly/glaucoma observers. Using the blur disc diameter equation: $b° = 0.057pD$, where b is the blur disc diameter in degrees of visual angle, p is pupil size in millimetres and D is Dioptric blur.

Our thresholds of blur detection and discrimination in glaucoma and elderly healthy observers are approximately equivalent to ~ 0.25DS for low contrast stimuli and ~0.15DS for high contrast stimuli (pupil size-2-4mm). Therefore, it may be that some elderly observers have a reduced ability to discriminate between blurred images. This may have some clinical relevance as some elderly patients may be less sensitive to changes in blur compared to younger patients. Accordingly, elderly patients may not present to eye examinations with symptoms of increased blur but may show a significant change in eye conditions such as refractive error or cataract development that are typically associated with symptoms of increased blur. However, the initial purpose of this study was to assess if blur detection and discrimination thresholds in central vision could be used to characterise vision in glaucoma and potentially be developed into a clinical test. It is evident that this measure of visual function is

not capable of diagnosing glaucoma in its early stages and so would not be useful as a clinical test in this instance.

Limitations of this study include the experiment being slightly underpowered so increasing the sample size would be beneficial in strengthening our findings and discussion. Moreover, investigating blur detection and discrimination in the fovea does not inform us about more peripheral areas of vision so further examination of these measures would be useful, though we are unsure how this would be possible as we did try to complete this during the pilot phase of this experiment with a 2-IFC procedure and found it was too difficult to complete even for young healthy observers. If the task was completed in the periphery, the stimulus size would need to be significantly larger in order to obtain reliable results and this would result in losing the ability to localise the stimulus that is necessary when assessing glaucoma patients.

In this study, we were limited to testing one reference blur for the blur discrimination task but in order to fully assess the effects of glaucoma and ageing on blur discrimination, it is necessary to assess a range of reference blurs and fit a blur discrimination function. We would then be able to assess how the shape of this function alters with age and glaucoma. This also applies to broadening the range of contrast levels assessed to see how the whole blur discrimination function shifts with respect to a change in contrast and at what point do we find a plateau in blur thresholds with increase in contrast in elderly and glaucoma observers. Further research completing these additional tests would be valuable to get a well-rounded view on blur perception in glaucoma and elderly individuals. However, assessing multiple aspects of blur discrimination would increase observation time significantly and this is not practical for our elderly observers due to patient fatigue in lengthy experiment sessions.

4.7 Conclusions

Blur detection and discrimination in central vision are similar in early glaucoma compared with age-similar healthy individuals. The results suggest that blur discrimination in the fovea is primarily limited by optical factors rather than

neural factors and in order to show a deficit in performance from glaucoma, a greater loss of retinal ganglion cells would be required to exceed these optical limits. Therefore, we would predict a greater decline in performance of blur detection and discrimination in more advanced cases of glaucoma. Further work is required to explore these possibilities.

Chapter 5

5 The effects of glaucoma on crowding of peripheral Vernier acuity

5.1 Abstract

Purpose

Crowding sets a fundamental limit on visual perception under suprathreshold viewing conditions. Crowding may be a result of increased spatial pooling in the periphery (Levi 2008). As retinal ganglion cells are destroyed in glaucoma, it may be that cells from more widespread retinal locations pool responses to maintain the overall response and in turn elevate crowding effects. Here, we investigate the effects of glaucoma on crowding of peripheral Vernier acuity.

Methods

17 participants with glaucoma (mean age ± SD, 70 ± 5 years), 2 age-similar controls (ages 70 and 64 years) and 6 young controls (25 ± 2 years) participated. Crowded (50 arcmin flanker separation) and uncrowded Vernier acuities were measured at 6° eccentricity superior and inferior to central fixation. Data were converted into crowding ratios (crowded / uncrowded Vernier acuity). Additionally, crowding ratios and Vernier acuities were correlated to the Mean Sensitivity of VF locations assessed in participants with glaucoma. Data were analysed by linear modelling and Spearman's correlation.

Results

Crowding ratios were similar between participants with glaucoma and the control group in both superior ($p=0.94$) and inferior test locations ($p=0.29$). Mean sensitivity had a significant negative correlation with uncrowded Vernier acuity ($p=0.002$) in the inferior location assessed. However, there was no significant correlation between Mean Sensitivity and crowded Vernier acuity ($p= 0.06$) or crowding ratios ($p=0.41$) in the inferior test location.

Conclusions

Early glaucoma appears to have a minimal effect on visual crowding. These findings suggest that mechanisms beyond integration of retinal ganglion cell receptive fields play a greater role in facilitating crowding and that the effects of crowding are limited by areas in the visual system beyond the retina, such as within the visual cortex.

5.2 Introduction

Crowding sets a fundamental limit on visual perception under suprathreshold viewing conditions (Levi 2008). The effects of crowding are significant in peripheral vision whereby an object presented in isolation is more easily recognisable than when presented in clutter (Levi 2008). It has been shown that glaucoma affects threshold vison by increasing contrast detection thresholds (Ross et al. 1984; McKendrick et al. 2007) but we have shown in previous studies (chapter 3 & 4) that in early glaucoma, apparent contrast of suprathreshold stimuli and blur detection and discrimination thresholds are relatively unaffected by the disease. These results suggest that there may be some compensatory mechanisms at work in the visual system that maintain visual function under suprathreshold viewing conditions and compensates for loss of sensitivity at threshold.

Previous studies have shown an enlargement in the area of complete spatial summation (Ricco's area) in glaucoma (Redmond et al. 2010a). The authors suggest that this enlargement may be a result of increased spatial pooling of responses in the disease process (Redmond et al. 2010a). Crowding has also been related to spatial summation and its effects have been attributed to greater integration of receptive fields in the periphery compared with the fovea resulting in objects of closer proximity being interpreted within the same receptive field and perceived as a jumble (Levi 2008). However, the mechanisms involved in crowding and Ricco's area differ in that the area of spatial summation can be primarily accounted for by the underlying density of retinal ganglion cells alone (Kwon and Liu 2019) suggesting that these cells are the limiting factor in facilitating spatial summation. However, this study demonstrated that crowding

cannot fully be accounted for by retinal ganglion cell density alone suggesting that other areas in the visual system beyond the retina are also involved in facilitating crowding effects. It is well known that glaucoma affects retinal ganglion cells (Quigley et al. 1995), but glaucoma also affects other areas in the visual system including the LGN (Yücel et al. 2000) and the visual cortex (Williams et al. 2013). As retinal ganglion cells are destroyed in glaucoma (Quigley et al. 1995), it may be that cells from more widespread retinal locations pool responses to maintain the overall signal response and in turn increase crowding effects in the disease.

Further, if crowding effects are elevated in glaucoma, it may explain the predominant visual symptom that patients associate with their disease; increased blur (Crabb et al. 2013; Hu et al. 2014). This visual symptom may actually be attributed to increased crowding effects that patients are unable to identify as the effects of crowding manifest as a loss of resolution.

In this study, we aimed to investigate the effects of glaucoma on crowding. We predicted that crowding effects would be greater in participants with glaucoma compared to age-similar controls.

5.3 Methods

We planned to collect data from 18 participants with glaucoma and 18 age-similar controls. This sample size would have given 85% power to detect a crowding ratio difference (α=0.05) of 1 with a SD of 1. However, data collection and recruitment were halted in March 2020 due to COVID-19. At this point, we had collected data from 17 participants with glaucoma and 2 age-similar controls. Once authorisation to access the lab was granted in August 2020, we were still unable to assess glaucoma and age-similar controls as anyone over the age of 50 was classed as vulnerable to COVID-19; as such, we adapted our methods to the experiment by collecting data from young healthy controls as a replacement for age-similar controls.

Participants with glaucoma & age-similar controls

Inclusion criteria for participants with glaucoma and age-similar controls were in line with previous studies in the research project. All participants included in the study had a visual acuity of better than 6/9.5 (Snellen), refractive error of no more than ± 6.00DS and ±3.00DC and no ocular/systemic condition affecting visual performance apart from mild cataract (no more than NC3 NO3 C2 P2 on the Lens Opacities Classification System III grading scale (Chylack et al. 1993)) and glaucoma for the glaucoma group. Age-similar controls had normal findings on ocular examination including Goldmann applanation tonometry (intraocular pressure ≤ 21mmHg and ≤ 3mmHg difference between the eyes), slit-lamp biomicroscopy and indirect fundoscopy. Visual field testing was performed on the Humphrey Field Analyzer (SITA Standard 24-2, Humphrey Field Analyzer III, Carl Zeiss Meditec, Jena, Germany). Glaucoma observers had to have a VF defect on 24-2 Standard test to be included in the study. VF defect criteria are in line with previous studies in the project; a cluster of 3 or more adjacent non-edge points with p<5% on the pattern deviation plot (Anderson and Patella 1999). Additionally, glaucoma observers had to have a sectoral defect (p< 5%) of the retinal nerve fibre layer on a circumpapillary scan using an optical coherence tomographer (Spectralis; Heidelberg Engineering GmbH). Age-similar controls were included in the study if they had no visual field defect on 24-2 and 10-2 perimetry tests and GHT analysis were ‘within normal limits’. The tested eye was chosen at random if both eyes fit the inclusion criteria.

All observers were assessed in two locations during the experiment; 6° eccentricity superiorly and inferiorly of central fixation. The 10-2 Standard perimetry test was completed on all glaucoma observers to correlate the Mean Sensitivity (MS) of the locations assessed with crowded and uncrowded Vernier acuity measures (Figure 5.1).

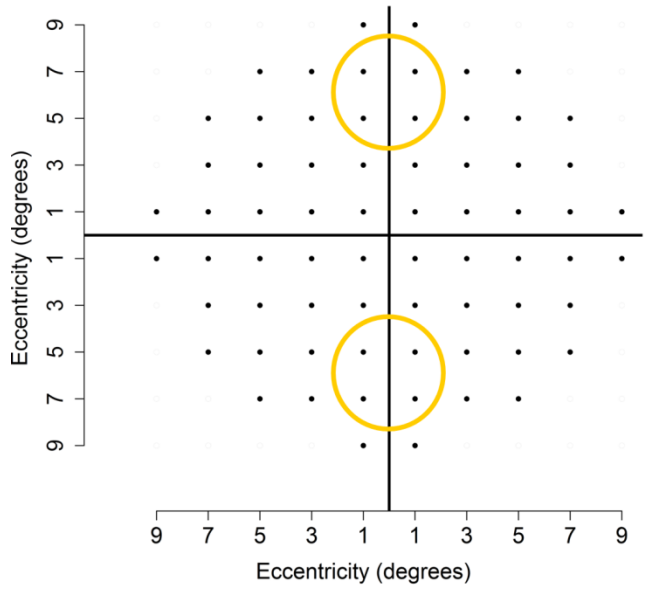


Figure 5.1 A schematic of the 10-2 threshold grid. Stimuli were presented in superior and inferior locations corresponding to the 4 points superiorly/inferiorly on the 10-2 grid (highlighted by yellow rings).

Young controls simulating age-matched control data

Initially, we planned to collect data from age-similar controls and compare these results to data collected from participants with glaucoma. However, as data collection and recruitment of elderly observers was not possible when returning to the campus, we collected data from young healthy controls as an alternative and compared their crowding ratios with the glaucoma group. This method was chosen based on evidence from previous literature investigating the effects of aging on crowding in peripheral vision. These studies demonstrated that the effects of crowding are constant with age despite a decline in other visual function measures with age such as resolution (Scialfa et al. 2013; Astle et al. 2014). Astle et al. (2014) found that crowding ratios were similar across ages ranging from 18- 76 years at 10° eccentricity and three different flanker separations for letter recognition thresholds. Similarly, Scialfa et al. (2013) found that there was no significant difference in crowding ratios between young healthy observers (21 ± 2 years) and elderly observers (70 ± 8 years) assessed at 3 and 6° eccentricity for Landolt C orientation gap acuities. Based on this literature, we converted the young controls data into crowding ratios to simulate an approximation of age-similar control data and this enabled us to complete the experiment, analyse the data and allowed a discussion of the results.

6 young healthy controls participated. All young observers had self-reported healthy eyes and vision with no known ocular or systemic condition that would

affect visual performance and normal findings on their previous eye examination completed within the last 12 months of the visit. We were unable to complete preliminary health assessments on young observers on the day of the experiment visit as the eye clinic was unavailable.

All participants provided written informed consent in accordance with the tenets of the Declaration of Helsinki before participating in the study. The study was approved by a National Health Service ethics committee. An inconvenience allowance was provided to participants.

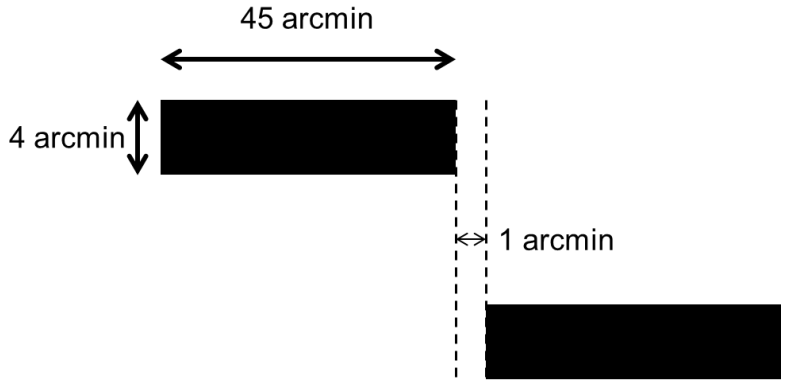
Apparatus & stimuli

The stimulus used was a Vernier target; a pair of horizontal bars, with lengths of 45 arcmin separated by a gap of 1 arcmin (Figure 5.2A). The Vernier bars had a thickness/line width of 4 arcmin. In the crowded testing condition, flanking/crowding bars were placed above and below the Vernier target (Figure 5.2B). The lengths and widths of these flanking bars were 96 arcmin and 2 arcmin respectively. The distances of the crowding bars from the centre of the Vernier target were 50 arcmin above and below the centre of the target. The contrast of the Vernier target was at a maximum (100% Michelson contrast). A Vernier target was chosen as it is a spatially localised stimulus allowing a precise comparison of the Mean Sensitivity of the location assessed with measures of crowded and uncrowded Vernier acuity. Additionally, this target was chosen as Vernier acuity has been shown to be affected by crowding and Vernier targets have been widely used in crowding studies (Levi et al. 1985; Levi 2008; Manassi et al. 2012).

Stimuli were generated in MatLab 8.5.0 (R2015a; The Mathworks, Natick, Massachusetts, USA) using Psychtoolbox-3 (V3.0.14)(Brainard 1997; Pelli 1997; Kleiner et al. 2007). Stimuli were presented on a 14 bit calibrated display system (resolution, 1920x1080; refresh rate, 120Hz; CRS Display++; Cambridge Research Systems Ltd, Kent, UK) viewed from 127cm via a chin and forehead rest. Testing was performed monocularly with occlusion of the non-tested eye. Appropriate refractive correction was worn for the viewing distance. The mean luminance of the screen was 105cd/m^2.

Stimuli were presented at 6° above and below the central fixation marker. Fixation was monitored by eye tracking (LiveTrack FM,Cambridge Research Systems Ltd) with a recording rate of 60 Hz. Central fixation was defined as viewing within a 2.5° radius of the fixation marker. Peripheral stimuli were only presented while central fixation was reported by the eye tracker. Participants that could not be monitored using the eye tracker (7 participants with glaucoma) were observed using live video monitored by the researcher. In these cases, the eye-tracker could not appropriately detect the pupil due to small pupils or small palpebral apertures.

A



B

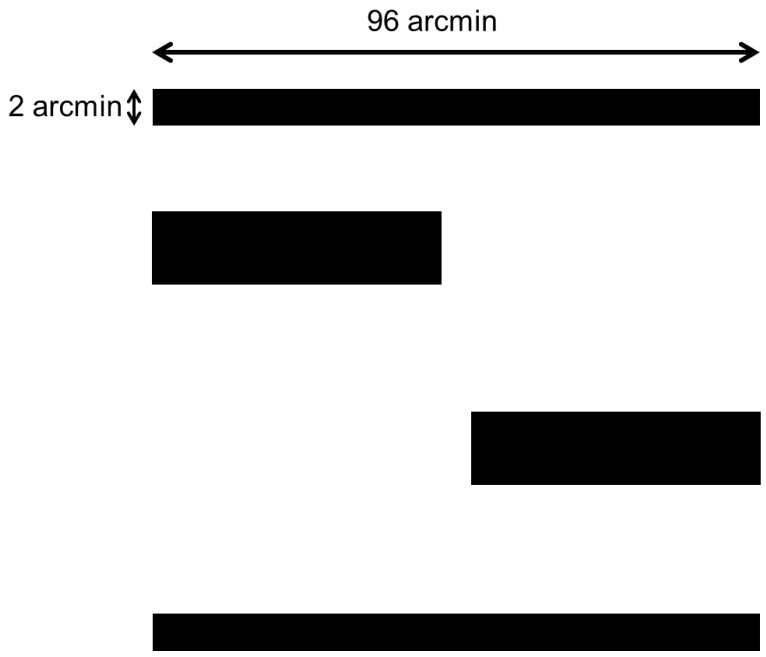


Figure 5.2 A, The stimulus used as a Vernier target in the uncrowded condition, a pair of horizontal bars separated by a distance of 1 arcmin. B, The Vernier

target used in the crowded condition, exact in all respects with figure 5.2A but with additional crowding/flanking bars placed above and below the Vernier target.

Procedure

Observers were instructed to fixate on the central fixation marker throughout the experiment (Figure 5.3). Stimuli were presented randomly from trial to trial at either the superior or inferior location at 6° eccentricity with the total number of presentations in each experimental run being presented equally between the two locations. Vernier acuities were obtained using a 2-alternative forced choice procedure (Figure 5.3). Participants were instructed to identify which of the two Vernier bars (left/right) was higher and to give their best estimate if they were unsure. Responses were recorded with a key press. Vernier targets were presented at each trial for a duration of 250ms with an inter-trial-interval of 500ms. The method of constant stimuli was used to determine task difficulty/ displacement levels of the Vernier target. First, all participants completed a pilot run of each experimental condition (crowded/uncrowded) with a minimum number of presentations of 70 per location (6° superior/inferior of fixation). These data were not used to calculate final Vernier acuities but used to familiarise the observer with the experiment and determine displacement levels for the experimental runs used to obtain final Vernier acuities. To obtain final Vernier acuities, a minimum of 30 presentations of 7 displacement levels (210 trials) were completed in each location. Vernier acuities were obtained under two experimental conditions; with crowding effects (flanking bars placed above/below Vernier target) and without crowding effects (Vernier target presented solely in superior/inferior location). Participants performed these two conditions in a pre-determined randomized order.

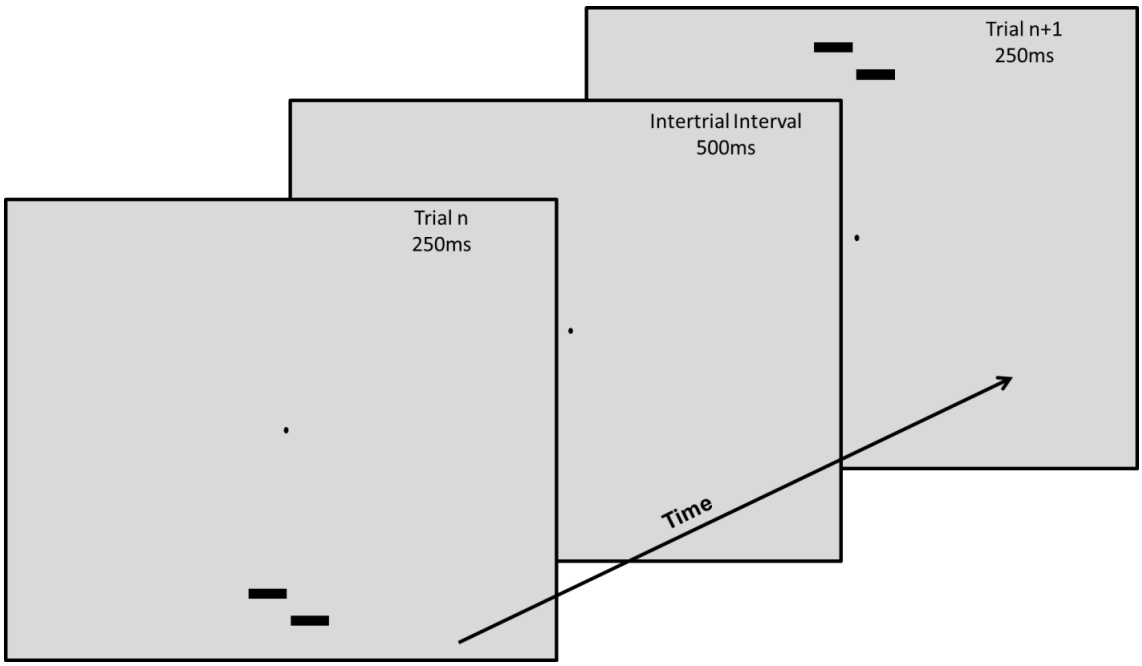
Psychometric functions were plotted as Vernier displacement (arcmin) vs percentage correctly determined. Vernier acuities were taken as the Vernier displacement correctly determined at 80% on the psychometric function. Psychometric functions were fitted using maximum likelihood estimation with the following function:

$$P(c) = 0.5 + (0.5 – LR) \times G(v, m, sd)$$

where c represents the % of correct responses, LR represents the lapse rate that defined the upper asymptote and was allowed to vary between 0 and 0.1. G represents the Gaussian function with mean (m) and standard deviation (sd). Mean and standard deviation were free fitting parameters.

The goodness-of-fit of psychometric functions was assessed by comparing with the model deviance of the distribution of 10,000 Monte Carlo data sets (Wichmann and Hill 2001). The method compares the probability that the data set generated by the function fitted would have a deviance as large or larger than the deviance observed. Higher probabilities of the goodness-of-fit indicate a better fitting dataset. Datasets fitted with a psychometric function with a goodness-of-fit value of < 0.05 and those datasets with no points at or above 90% correctly determined on the psychometric function were considered as poor quality unreliable data and removed from the analysis.

A



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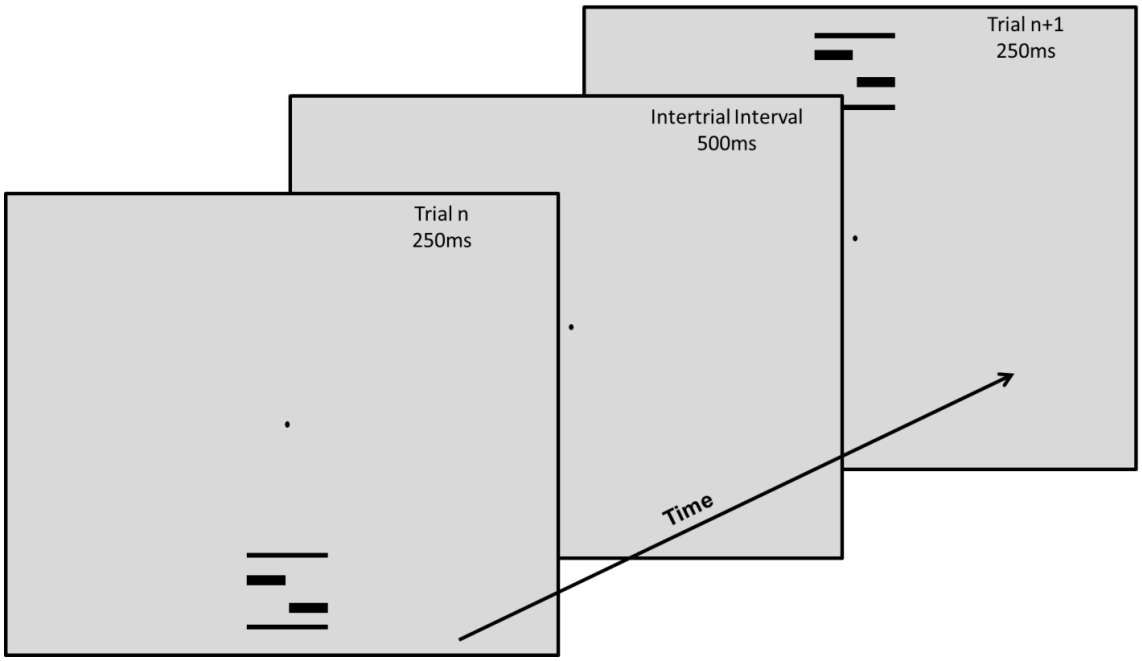


Figure 5.3 Methodology used to determine Vernier acuities under uncrowded (A) and crowded (B) test conditions. Stimuli appeared from trial to trial in either the superior or inferior location at 6° eccentricity. A 2-AFC method was employed (which bar is higher left/right?). Participants indicated their response by a keypress.

5.4 Statistical analysis

Data were analysed in R (R Core Team (2017)). Individual Vernier acuity measurements were converted into crowding ratios:

Crowding ratio = Crowded Vernier acuity / Uncrowded Vernier acuity

Linear modelling was used to assess the effect of group on crowding ratios. Spearman's correlation was used to assess the relationship between mean threshold sensitivity of the location assessed and Vernier acuities (crowded/uncrowded) and crowding ratios in the glaucoma group. A p value of < 0.05 was taken as statistically significant.

To assess the effect of Group (glaucoma vs controls) on crowding ratios, data were split into superior and inferior locations and assessed by linear modelling.

Models took the form of:

Crowding Ratios† ~ Group + c + ε

where c is a constant and ε is random error

†For superior and inferior locations respectively.

Spearman's rho correlation coefficient was used to assess the relationship between the Mean sensitivity of the location assessed (6° superior/inferior of fixation) with crowded/uncrowded Vernier acuities and crowding ratios in participants with glaucoma. Mean sensitivity was calculated using the following method:

1. Threshold sensitivity given in decibels (dB) of the 4 locations (Figure 5.1) were converted into raw threshold values using the following equation:
   Raw threshold (R_t) = 10 ^ $^{dB / 10}$
2. An average of the 4 raw threshold values was calculated:
   Mean threshold (M_t) = (R_t1 + R_t2 + R_t3 + R_t4) / 4
3. The mean threshold was then converted into a decibel value used as mean sensitivity in the correlation analysis:
   Mean sensitivity (dB) = 10 * $\log_{10}(M_t)$

Mean sensitivity is taken as the average of the 4 threshold points of the 10-2 visual field grid (Figure 5.1) that corresponds with the locations assessed in the experiment (6° eccentricity superior / inferior of fixation). These 4 points were

chosen as they cover 2° of visual field that correspond to the maximum size of the stimulus presented (1.67°).

Correlation analyses were as follows:

Mean sensitivity vs Uncrowded Vernier acuity

Mean sensitivity vs Crowded Vernier acuity

Mean sensitivity vs Crowding ratios

5.5 Results

17 glaucoma observers (mean age ± SD, 70 ± 5 years), 2 age-similar controls (ages 70 and 64 years) and 6 young controls (25 ± 2 years) participated. Perimetry results for glaucoma observers are given below in Table 5.1. Of the four experimental conditions assessed (crowded/ uncrowded Vernier acuity at superior/inferior locations), the majority of participants with glaucoma were unable to obtain an accurate psychometric function and sufficient quality data for the superior location assessed, this may have been due to visual field defects corresponding with the location assessed. Some participants with glaucoma mentioned that they could not ‘see’ the stimulus in that location. A breakdown of the number of data sets removed from the analysis with poor quality data for each location and condition assessed is given below in Table 5.2.

Table 5.1 Individual perimetry results for participants with glaucoma.

Participant	Age	Mean Deviation	Pattern standard deviation	GHT
1	76	-2.19	2.56	Outside normal limits
2	67	-3.79	4.78	Outside normal limits
3	70	-2.98	3.27	Outside normal limits
4	61	-5.95	8.36	Outside normal limits
5	74	-4.93	10.65	Outside normal limits
6	62	-7.62	5.72	Outside normal limits
7	62	-4.26	8.04	Outside normal limits
8	70	-1.52	5.82	Outside normal limits
9	70	-2.43	2.35	Outside normal limits
10	76	-3.59	7.07	Outside normal limits
11	71	-1.61	2.46	Borderline
12	68	-2.56	2.33	Borderline
13	73	-3.95	3.24	Outside normal limits
14	75	-1.43	2.92	Outside normal limits
15	67	-3.26	5.40	Outside normal limits
16	69	-1.06	2.36	Borderline
17	74	-4.38	2.70	Outside normal limits

Table 5.2 Data sets removed for each group and test condition due to poor quality data.

Test Condition	Superior, Uncrowded Vernier acuity	Superior, Crowded Vernier acuity	Inferior, Uncrowded Vernier acuity	Inferior, Crowded Vernier acuity
Controls	0	0	0	1
Glaucoma	7	11	1	3

Crowding ratios

Superior location

Mean group crowding ratios for the superior location are given below in Figure 5.4. Crowding ratios were similar between controls and participants with glaucoma in the superior location with a difference in mean crowding ratio of 0.052 ± 0.74 (F(1,12)= 0.005, p=0.94). Individual Vernier acuities for participants with glaucoma and controls under the two test conditions (crowded, uncrowded) are given below in Figure 5.4. Although absolute Vernier acuities are elevated in the glaucoma group for both conditions, the relative crowding effect is similar between groups once elevation in uncrowded Vernier acuities is accounted for in glaucoma observers.

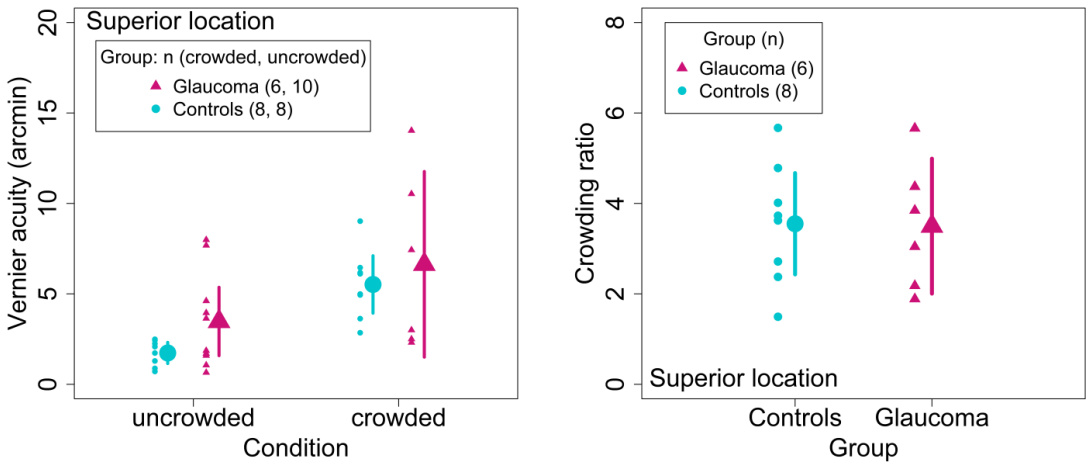


Figure 5.4 Individual Vernier acuities for participants with glaucoma and controls as well as group mean Vernier acuities ± 95% CI for the superior location assessed (left). Mean Crowding ratios ± 95% confidence intervals for controls and participants with glaucoma (right). Crowding ratios appear similar between groups despite sensitivity loss in the glaucoma group.

Inferior location

Group mean crowding ratios for participants with glaucoma and controls in the inferior location is shown below in Figure 5.5. Crowding ratios were slightly raised by 0.73 ± 0.68 in participants with glaucoma compared with controls, though this elevation was not significant (F(1,19)= 1.16, p=0.29). Similarly individual observers' Vernier acuities are shown in Figure 5.5, Vernier acuities

appear raised in participants with glaucoma compared to controls under both crowded and uncrowded conditions, however, once elevation in uncrowded Vernier acuities is accounted for, crowding effects are not significantly greater in the glaucoma group.

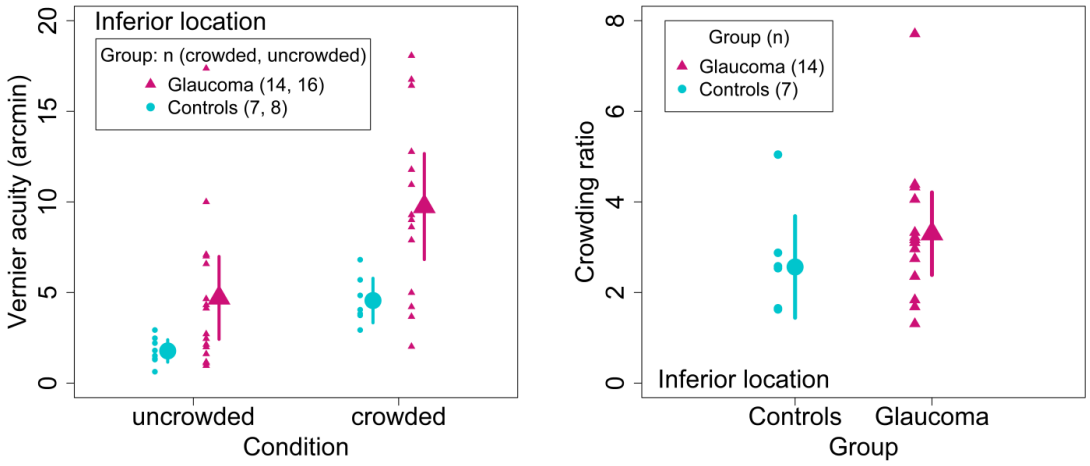


Figure 5.5 : Individual Vernier acuities under crowded and uncrowded test conditions (left). Group mean crowding ratios ± 95% CI for participants with glaucoma and controls in the inferior test location (right).

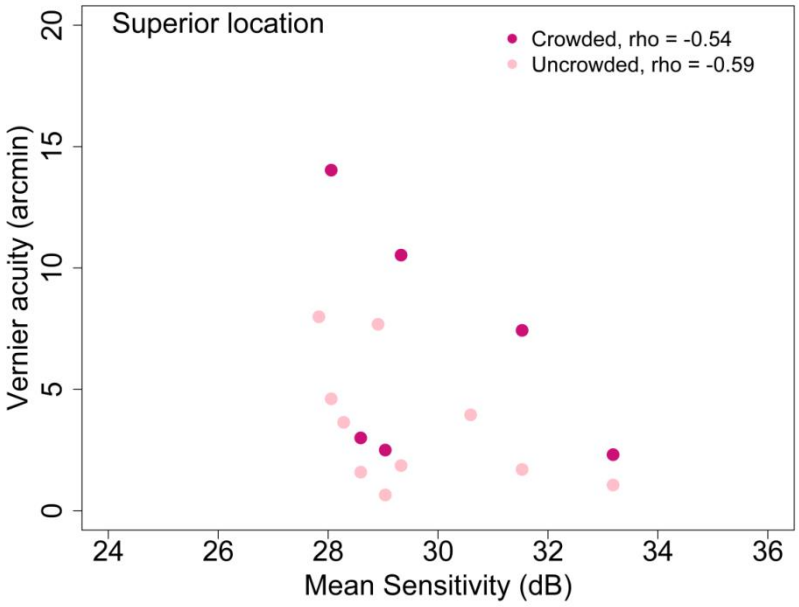
Correlation between Mean Sensitivity and Vernier acuity

Spearman's rho correlation coefficient was used to assess the relationship between Mean Sensitivity (MS) of the location assessed with crowded and uncrowded Vernier acuities in participants with glaucoma. For the superior test location assessed, the sample size is significantly smaller than originally planned, so the results should be interpreted with caution. There was a non-significant relationship between superior uncrowded and crowded Vernier acuities with Mean sensitivity in participants with glaucoma (uncrowded, $r_{S} =$ -0.59, p=0.08, n=10, crowded, $r_{S} =$ -0.54, p=0.30, n=6).

For the inferior location assessed, a significant negative correlation was found between uncrowded Vernier acuities and mean sensitivity in participants with glaucoma ($r_S = -0.72$, p=0.002, n=16). Specifically, an increase in Mean sensitivity was associated with a decrease in uncrowded Vernier acuity. However, a non-significant relationship was found between crowded Vernier

acuity and mean sensitivity for the inferior test location (r_s = -0.53, p= 0.06, n=14).

A



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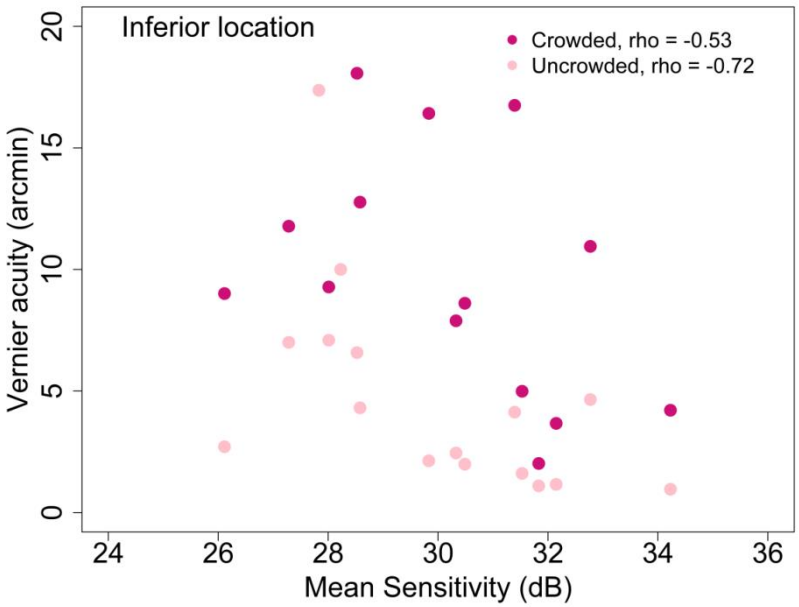

Figure 5.6 Correlation between Mean sensitivity and crowded and uncrowded Vernier acuities in participants with glaucoma for superior (A) and inferior (B) test locations.

Correlation between Mean Sensitivity and Crowding Ratios

A non-significant relationship between Mean sensitivity and crowding ratios were found for both superior and inferior locations assessed (superior, $r_s = 0.26$, p= 0.66, n=6, inferior, $r_s = 0.24$, p= 0.41, n=14).

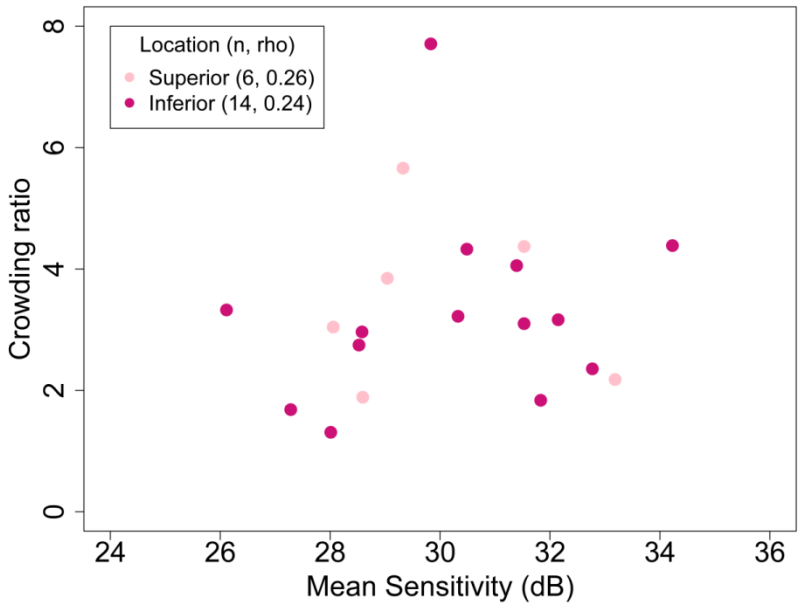

Figure 5.7 Correlation between Mean Sensitivity and crowding ratios for superior (light pink circles) and inferior (dark pink circles) test locations.

5.6 Discussion

This study aimed to investigate the effects of glaucoma on crowding of spatially localised stimulus groups. The preliminary results on participants with glaucoma and young controls suggest that crowding effects are similar between the two groups. Our results suggest that crowding effects on peripheral Vernier acuity are not affected in early stages of the disease. These results were found when data were converted into crowding ratios to account for the elevation of uncrowded Vernier acuity in the glaucoma group.

These results are unlike a previous study that found an increase in crowding effect by an enlargement of critical spacing for a peripheral resolution task in early glaucoma (Ogata et al. 2019). A number of reasons could account for the contrasting results found. First, the task, location and outcome measure were

different between the two studies. Ogata et al. (2019) measured the extent of crowding (critical spacing) of a peripheral resolution task at 10° eccentricity in four ordinal directions whilst the present study used a Vernier acuity task at 6° eccentricity superior/inferiorly and measured the relative crowding effect of a fixed flanker distance for all observers (50 arcmin separation). A fixed flanker distance was chosen in this study as it allows assessment of a precise location and thus, allows an appropriate correlation assessment of the mean sensitivity of the location assessed and Vernier acuity under the two observation conditions.

However, varying the flanker distance that is required to measure critical spacing can be affected by assessing an area that varies vastly in VF sensitivity by moving flankers from within to outside of a VF defect area. For instance, it could be that Ogata et al. (2019) moved the flanking letters from an unaffected VF area allowing it to be perceived by the observer and inducing a crowding effect and then moved the flankers to an area of a complete scotoma, giving rise to no crowding effect and artificially inducing a non-crowded environment and therefore, giving a false estimation of critical spacing as letter recognition will now improve but not due to a lack of crowding but rather an inability to perceive the flanking stimuli altogether. Despite this limitation, critical spacing is another appropriate assessment of crowding and is still valuable assessing in glaucoma as this aspect of vision may be affected by the disease because of the variation in VF sensitivity of the area assessed. However, this limitation does need to be acknowledged when discussing the results.

The results of this study may be explained by the underlying mechanisms of crowding. Indeed, it has been shown in previous studies that crowding effects do not change with age (Scialfa et al. 2013; Astle et al. 2014) despite an age-related decline in other visual function measures such as resolution and contrast sensitivity (McKendrick et al. 2007). It may be that crowding is primarily limited by the visual cortex that may degrade much less than the retina does with age. Some evidence to support this hypothesis is previous findings of unaltered cortical receptive fields with ageing (Mendelson and Wells 2002). Therefore, visual functions limited by the cortex may remain intact whereas visual functions limited by the retina may decline with age.

It has been suggested that crowding has a cortical locus (Pelli 2008) as the phenomenon can still be experienced when presenting flankers and the target stimulus to alternative eyes (Tripathy and Levi 1994). Further, it has been proposed that crowding can be explained by a greater integration of receptive fields in the periphery relative to the fovea (Pelli et al. 2004; Levi 2008). Based on this proposal, it has been suggested that the increased integration of receptive fields due to glaucoma (Redmond et al. 2010a) may result in increased crowding effects (Ogata et al. 2019). It may be that the VF areas assessed in the present study were still functioning relatively well despite some loss of sensitivity giving rise to unchanged crowding ratios. Alternatively, the results may suggest that the underlying mechanisms of crowding are not exclusively dependent on integration of retinal ganglion cell receptive fields and that other neural mechanisms beyond the retina may play a larger role in determining the size of the crowding effect. For instance, a recent paper found that estimated retinal ganglion cell densities mapped well to the size of Ricco's area, however these cell estimates did not fully account for the size of crowding zones (Kwon and Liu 2019). This could suggest that there are distinct neural mechanisms that mediate these two aspects of visual function.

Correlation results in the present study need to be interpreted with caution as sample sizes are much lower than originally planned. No significant correlation between mean sensitivity and uncrowded/crowded Vernier acuity was found for the superior location assessed. This could be explained by the sample size for this location being smaller than anticipated (underpowered). However, an association between uncrowded Vernier acuity and mean sensitivity has been found for the inferior location. Specifically, an increase in mean sensitivity was associated with a reduction in uncrowded Vernier acuity. This result suggests that similar to contrast sensitivity, Vernier acuity may be used as an appropriate measure to infer the underlying density of functioning retinal ganglion cells. A previous study investigating foveal Vernier acuity in glaucoma found no significant correlation between mean deviation and pattern standard deviation of 24-2 full threshold VF results and Vernier acuity in participants with glaucoma (McKendrick et al. 2002). Their correlation results may be explained similarly to ours in that the analysis was underpowered with a smaller sample size. Additionally, their results may be explained by the study correlating global

indices from 24-2 perimetry tests that are affected by overall sensitivity of the whole VF with foveal results rather than using local mean sensitivity from the 10-2 Standard test which appears more appropriate when correlating measures to a specific central VF location.

In line with correlation results from Ogata et al. (2019), we found that crowded Vernier acuities and crowding ratios did not correlate significantly with mean sensitivity in the inferior location. These results give some evidence to suggest that crowding is less related to retinal sensitivity and that crowding effects may be more associated to the cortical receptive fields and overall function of the visual cortex; if cortical cells are well functioning despite retinal sensitivity loss from early glaucoma, it may affect crowding less than other aspects of visual function.

The results suggest that glaucoma appears to have a step like decline in visual function in areas of significantly reduced sensitivity. This can be observed by 7 participants with glaucoma in this study unable to perceive the stimulus and/or complete the task to the required accuracy (most points of psychometric function lie close to the guess rate of 50%) in the superior location for the uncrowded test condition and 11 participants with glaucoma unable to complete the task for the crowded test condition in the superior location. Yet most of these glaucoma observers were able to complete the crowding task inferiorly and perform similarly to controls. This could be explained by the superior location assessed corresponding with a more severe VF scotoma or reduced area of sensitivity compared to the inferior location; evidenced by a lower mean sensitivity for glaucoma observers for the superior location of 28.5dB compared with 30.3dB for the inferior location. These results are similar to Ogata et al. (2019) in that they also found that despite testing participants with glaucoma in 4 quadrants, 20 out of 26 subjects could not perform the task in all four locations.

This study was limited by the situation arising from COVID-19; recruitment and testing of appropriate glaucoma and age-similar controls were halted and the experiment protocol had to be adapted accordingly. As we no longer had access to the eye clinic and were unable to test appropriate age-match controls (an at-risk group of coronavirus), we could not complete further visual field

testing or increase the sample size (power of correlation analysis) that would have been valuable. However, despite this set back, evidence from the literature suggests that crowding ratios are unchanged with age and therefore assessing young healthy controls appeared to be an appropriate alternative. Furthermore, as the study found no significant difference in crowding between individuals with glaucoma and young controls, the results suggest that there would be an even less likely chance of finding a significant difference between participants with glaucoma and age-similar controls.

Crowding is an extensive subject and many factors can affect the area and extent of crowding, therefore it would have been useful to measure other aspects of crowding such as critical spacing and measure various eccentricities and locations to get a more holistic view on crowding effects in glaucoma. It has been suggested that attentional deployment affects performance of letter recognition in the periphery (Talgar et al. 2004) and so it may be that the task was too difficult for participants with glaucoma due to the stimulus appearing randomly between superior and inferior test locations. However, this stimulus presentation set up was used as an additional means to control fixation by preventing the participant from being encouraged to fixate towards one peripheral location of interest and losing central fixation.

The results from this study and previous studies in this research project demonstrate that there is still a long way to go in understanding the effects of glaucoma on suprathreshold visual perception. The visual system appears to have large areas of compensation for loss of retinal input and allows the system to function until significant loss of retinal ganglion cells has occurred.

5.7 Conclusions

Despite participants with glaucoma having reduced Vernier acuity compared to controls, both groups appear to have similar crowding effects. The results suggest that increased spatial summation in the disease process does not fully explain the effects of crowding. The results suggest that mechanisms beyond integration of retinal ganglion cell receptive fields may play a greater role in facilitating crowding effects than first thought.

Chapter 6

6 Discussion & conclusions

6.1 Discussion

The overarching aim of this research project was to investigate the effects of glaucoma on suprathreshold visual function. There has been significant investigation into the effects of the disease on threshold visual function in the form of assessing contrast sensitivity and perimetry (chapter 1) and conventional perimetry is currently the primary form of visual function assessment of glaucoma. However, investigation of suprathreshold visual function, that may reveal information more relevant to understanding how the disease impacts patients' vision under their natural visual environment, has been limited.

Some studies have investigated the effects of glaucoma on patients' visual experiences by using qualitative techniques such as interviews and questionnaires (Crabb et al. 2013; Hu et al. 2014). A recent study asked patients' to draw their paracentral scotoma caused by glaucoma using an Amsler grid (Fujitani et al. 2017). This study showed that the majority of patients were able to describe their scotoma (Fujitani et al. 2017) unlike the common misconception that most patients are unaware of their visual field loss or that peripheral vision loss occurs before paracentral loss. Additionally, studies have shown that patients do not describe their scotomas as a 'black tunnel' effect that is commonly depicted as the visual appearance of the disease (Crabb et al. 2013). These studies have given insight into the effects of the disease from a patient's perspective. However, these studies do not provide empirical evidence to quantify these effects and are subjective to individual patient experiences and rely on the patient's ability to describe their VF defect. Further, it may be that the symptoms experienced by glaucoma patients may be a combination of natural age-related decline in visual function due to lens, vitreous and refractive changes with age and not solely the effects of the disease itself.

Psychophysical studies have had mixed approaches in assessing visual function including assessing specific pathways such as the magnocellular,

parvocellular (Sun et al. 2008) and koniocellular pathways (Beirne et al. 2003) and assessing various suprathreshold psychophysical tasks (Anderson 2006). These studies have had varied results; some studies have found alterations in visual function in glaucoma such as reduced achromatic peripheral resolution (Beirne et al. 2003), alterations to rapid contrast adaptation (Lek et al. 2014), contrast discrimination (McKendrick et al. 2010) and Vernier acuity (McKendrick et al. 2002). Other studies have found no change in some aspects of suprathreshold visual function such as unaltered adaptation effects on contrast detection (McKendrick et al. 2010) and no selective loss of short-wavelength sensitive peripheral resolution (Beirne et al. 2003). These results evidence that not all aspects of suprathreshold visual function are affected early in the disease and suggest that both the state of the disease and the areas within the visual system primarily mediating the visual task influence whether glaucoma alters the suprathreshold visual function task.

This project has assessed three areas of suprathreshold visual function in glaucoma; apparent contrast of suprathreshold stimuli, detection and discrimination of image blur and crowding in peripheral vision. In chapter 3, we measured the apparent contrast of suprathreshold stimuli in participants with glaucoma. Under threshold conditions, it has been found that the ability to detect a stimulus (contrast detection thresholds) is affected by the spatial frequency content of that stimulus (Campbell and Robson 1968) and it is widely known that contrast detection thresholds are elevated across spatial frequencies in participants with glaucoma (Ross et al. 1984; McKendrick et al. 2007). However, we found that when stimuli were of a contrast much higher than threshold, participants with glaucoma were able to perceive the apparent contrast similarly to age-matched healthy controls. The results suggested that reduced retinal input under threshold viewing conditions is compensated for with sufficient increase of the stimulus signal (contrast level) and that within the visual system, there may be compensatory mechanisms at work that can overcome this reduced input under threshold viewing conditions.

The second study (chapter 4) in this project investigated the effects of glaucoma on detection and discrimination of image blur and was devised based on findings from previous qualitative research. These studies found that a common

descriptor used by patients to describe the effects of glaucoma on their vision was increased blur (Crabb et al. 2013; Hu et al. 2014). This second study investigated if this symptom could be evidenced psychophysically by measuring blur detection and discrimination thresholds. Furthermore, as peripheral resolution is limited by reduced retinal ganglion cell density in the periphery (Thibos et al. 1987a), it may be that increased blur perception in the periphery is also linked to the underlying retinal ganglion cell density and as these cells are destroyed in glaucoma (Quigley et al. 1982), a consequence of reduced retinal ganglion cell density could be increased perception of blur. We found that blur detection and discrimination thresholds of high contrast stimuli were slightly elevated in the glaucoma group tested within a VF defect, though the results were not statistically significant. However, when stimuli were of lower contrast and closer to threshold, all observers' (controls and glaucoma participants with and without VF defects) performed similarly; giving rise to a significant interaction effect of group with contrast on blur discrimination thresholds.

It has been suggested (Watson and Ahumada 2011) that the ability to discriminate between blurred images relies on the ability to detect high spatial frequency information from the stimulus and if the signal from high spatial frequencies is not sufficient, the observer perceives the stimulus as blurred. We have shown in the first study that glaucoma individuals were able to detect stimuli of low and mid-range spatial frequencies (0.5- 2 cpd) at 10° eccentricity. However, the majority of glaucoma participants were unable to detect the higher special frequency of 4 cpd stimulus until it was ≥ 0.25 Michelson contrast. It may be that this information holds the key to understanding the results of the second blur discrimination study. Participants with glaucoma tested in a VF defect at high contrast may not have been able to detect the high spatial frequency information of stimuli sufficiently enough to perform as well at discrimination as those glaucoma observers tested in a normal central VF area and healthy controls who could still detect the high SF information more easily allowing these other two groups to perform blur discrimination effectively. However, when tested at lower contrast levels, the high spatial frequency information from all observers became redundant as no observer could detect the high SF information from the stimulus sufficiently at low contrast resulting in

all three groups performing similarly at detection and discrimination of blur at low contrast.

The results from the second study therefore suggest that individuals with glaucoma may be able to retain low and mid-range spatial frequency information from stimuli under their habitual conditions allowing them to discriminate and resolve these stimuli appropriately but lose high spatial frequency information from stimuli resulting in a loss of resolution and a slight increase in blur perception of these stimuli. This can be supported by previous findings of reduced peripheral resolution in glaucoma individuals (Beirne et al. 2003) that assesses the high spatial frequency cut-off of the contrast sensitivity function. However, the results additionally show that the visual system is able to compensate for reduced sensitivity at threshold to some spatial frequencies and that although absolute contrast detection thresholds to these low and mid-range spatial frequencies may be slightly elevated in early glaucoma, once stimuli are sufficiently suprathreshold; glaucoma individuals are able to complete assessment and discrimination of these stimuli similarly to their healthy counterpart. The results give some evidence as to why the nature of the disease can be asymptomatic in its early stages. Moreover, the results show that there may be a vast discrepancy between functional test results and the underlying structures affected by the disease. Retinal ganglion cell count varies widely in healthy eyes (Curcio and Allen 1990) and this variation may affect how well functioning the visual system is under diseased conditions. It may be that although a glaucoma patient loses enough retinal ganglion cells to reduce function under threshold visual conditions, there could still be a sufficient enough cell count for effective suprathreshold visual function when retinal signal input is increased. Alternatively, it could be that the retinal ganglion cell responses follow in line with the contrast gain model proposed by Swanson et al. (1984) where retinal ganglion cell output is amplified downstream once the signal is strong enough at suprathreshold.

The final study, was based on two foundations, first, as crowding has been suggested to be a product of increased integration of receptive fields in the periphery (Levi 2008), and glaucoma is thought to pathologically increase integration of receptive fields evidenced by increased spatial summation in the

disease process (Redmond et al. 2010a), it may be that this pathological integration gives rise to increased crowding effects in glaucoma. Second, if increased crowding effects were found in glaucoma, it may explain the predominant visual symptom of blur experienced by glaucoma patients (Crabb et al. 2013). Perhaps stimuli appearing closer together in the mid-periphery appear more jumbled (crowded) manifesting as a perceived blur to individuals with glaucoma. The results of this final study suggest that at least in early glaucoma, there does not appear to be an increase in crowding effect compared with young controls suggesting that there would be less likely to be a significant difference between glaucoma individuals and age-similar controls. The results follow in line with a hypothesis that the limiting factor in crowding lies beyond the retina. Further evidence to support this hypothesis is a previous study that found a strong agreement between retinal ganglion cell density and the area of spatial summation but less of an agreement between retinal ganglion cell density and crowding zones (Kwon and Liu 2019). Additionally, it has been shown that crowding occurs under dichoptic conditions when target and flanking stimuli are presented to alternate eyes (Tripathy and Levi 1994) suggesting that the retina cannot be the sole limiting factor in crowding.

Together, these studies show that some aspects of suprathreshold visual function such as apparent contrast and blur discrimination may be preserved early in the disease and suggest that there could be compensatory mechanisms at work within the visual system that maintain the overall response under suprathreshold conditions and compensate for reduced retinal input at threshold in early glaucoma. The mechanisms behind these aspects of suprathreshold visual function may be intact allowing some preservation of these functions despite retinal ganglion cell loss. However, the results from these studies additionally show that there is a point at which these compensatory mechanisms break down; as evidenced by observers in the studies unable to complete the experiments at all or to the required accuracy as they could not perceive the stimulus when it was presented. This finding suggests that early sensitivity loss may be compensated for but when sufficient loss of functioning cells has occurred, participants with glaucoma are unable to complete the visual function task altogether as the stimuli are no longer suprathreshold. This was a limitation of the research project as we were unable to assess a range of

glaucoma patients from mild-moderate to advanced cases due to the flooring effects of the visual tests in advanced glaucoma cases.

This project has given some insight into the visual experiences of early-moderate glaucoma patients under suprathreshold viewing conditions and has shown that there is some preservation of visual function despite a loss of retinal ganglion cells. Furthermore, the results demonstrate, that if we would like to develop visual function tests that are able to continuously monitor the progression and loss of retinal ganglion cells in the disease process, we need to assess aspects of visual function that are limited by this site of damage. The results may give an indication as to why structural changes to retinal ganglion cells in glaucoma as measured by optical coherence tomography do not always strongly associate with functional tests since functional tests are a depiction of the state of the whole visual system whereas structural measures are solely assessing one area within the visual system.

Although retinal ganglion cells are the primary site of the disease and clinical assessments should focus on measuring visual function limited by these cells, studies have shown changes to other areas of the visual system in glaucoma that may hold information useful for developing diagnostic and monitoring methods for the disease. fMRI studies have evidenced alterations to neural networks in the visual cortex in individuals with glaucoma (Li et al. 2015). Additionally, changes to sites such as the lateral geniculate nucleus have also been found (Yücel et al. 2000; Yücel et al. 2003). These studies suggest that aspects of visual function limited by retinal ganglion cells do not give the complete view on how the disease impacts patients under their natural visual environment.

Overall, these three studies in conjunction with evidence from other qualitative and psychophysical research show that visual functions' that may be effective as a clinical test in glaucoma such as perimetry may not necessarily be effective in informing us about the daily visual experiences of glaucoma patients. Similarly, assessing suprathreshold visual functions may inform us of the effects of the disease under patients' habitual conditions but may not be practical as diagnostic tests for glaucoma. However, both types of assessment bring further understanding of different aspects of the disease. Glaucoma is an optic

neuropathy that has multifaceted implications in both structural changes to the visual system and varied implications on suprathreshold visual function. These structural and functional aspects may not easily correlate or be explained by one another and until there is a better understanding of the mechanisms facilitating various aspects of suprathreshold visual function, it will be difficult to understand how these visual functions are implicated in the disease process.

6.2 Conclusions

This research project has shown that three aspects of suprathreshold visual function, apparent contrast of suprathreshold stimuli, blur detection and discrimination thresholds and crowding in peripheral vision appear relatively unaffected in early glaucoma. There is still a long way to go in understanding the effects of glaucoma on suprathreshold visual function but it appears that certain features of suprathreshold vision are compensated for in early glaucoma despite sensitivity loss at threshold. The results from the project provide some evidence as to why there is a lack of symptoms in early stages of the disease. Further investigation of which aspects of suprathreshold visual function are affected and alternatively, are maintained in the disease would be valuable to better understand the effects of glaucoma on patients' visual experiences and to determine whether any suprathreshold visual functions may be viable targets for diagnostic clinical tests.

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Appendix A: Conference presentations

Bham, H.A. & Denniss, J. (2018) *Suprathreshold vision in glaucoma*. Crabb Lab meeting, City University, London, UK (talk)

Bham, H.A. & Denniss, J. (2018) *Suprathreshold vision in glaucoma: An untapped source of early diagnostic information?* Faculty of Life Sciences PGR Conference, University of Bradford, Bradford, UK (talk)

Bham, H.A. & Denniss, J. (2018) *Suprathreshold Contrast Perception in Glaucoma: Preliminary Results.* BCOVS, Anglia Ruskin University, Cambridge, UK (poster)

Bham, H.A., Dewsbery, S.D. and Denniss, J. (2019) *Glaucoma Affects Contrast Sensitivity but Not Apparent Contrast of Visible Stimuli.* Association for Research in Vision & Ophthalmology 2019 Annual Meeting, Vancouver, Canada (poster)

Bham, H.A, Dewsbery, S.D. & Denniss, J. (2019) *Detection and discrimination of image blur in glaucoma: Preliminary results*. BCOVS, University of Manchester, Manchester, UK (poster)

Bham, H.A. & Denniss, J. (2019) *Detection and discrimination of image blur in glaucoma.* Faculty of Life Sciences PGR Conference, University of Bradford, Bradford, UK (talk)

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Unaltered Perception of Suprathreshold Contrast in Early Glaucoma Despite Sensitivity Loss

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Purpose. Glaucoma raises contrast detection thresholds, but our natural visual environment is dominated by high contrast that may remain suprathreshold in early to moderate glaucoma. This study investigates the effect of glaucoma on the apparent contrast of visible stimuli.

Methods. Twenty participants with glaucoma with partial visual field defects (mean age, 72 ± 7 years) and 20 age-similar healthy controls (mean age, 70 ± 7 years) took part. Contrast detection thresholds for Gabor stimuli (SD, 0.75°) of four spatial frequencies (0.5, 1.0, 2.0, and 4.0 c/deg) were first measured at 10° eccentricity, both within and outside of visual field defects for participants with glaucoma. Subsequently, the contrast of a central Gabor was matched to that of a peripheral Gabor with contrast fixed at two times or four times the detection threshold. Data were analyzed by linear mixed modelling.

Results. Compared with controls, detection thresholds for participants with glaucoma were raised by 0.05 ± 0.025 (Michelson units, ± SE; $P = 0.12$) and by 0.141 ± 0.026 ($P < 0.001$) outside and within visual field defects, respectively. For reference stimuli at two times the detection contrast, matched contrast ratios (matched/reference contrast) were 0.16 ± 0.039 ($P < 0.001$) higher outside compared with within visual field defects in participants with glaucoma. Matched contrast ratios within visual field defects were similar to controls (mean 0.033 ± 0.066 lower; $P = 0.87$). For reference stimuli at four times the detection contrast, matched contrast ratios were similar across all three groups ($P = 0.58$). Spatial frequency had a minimal effect on matched contrast ratios.

Conclusions. Despite decreased contrast sensitivity, people with glaucoma perceive the contrast of visible suprathreshold stimuli similarly to healthy controls. These results suggest possible compensation for sensitivity loss in the visual system.

Keywords: glaucoma, contrast perception, contrast matching, contrast constancy, suprathreshold

Glaucoma is characterized by the degeneration and death of retinal ganglion cells leading to irreversible sight loss. Many people with early or moderate stage glaucoma do not experience symptoms and as a result may not seek treatment. The lack of symptoms in the early stages of glaucoma is one reason why many cases of glaucoma remain undetected, and why many people with glaucoma already have advanced vision loss upon initial presentation in clinic.[1]

The effect of glaucoma on the everyday visual experience of those with the disease is not well-understood. This incomplete understanding hampers efforts to produce realistic depictions of scenes as they would appear to a person with glaucoma, as well as to explain the likely visual symptoms to those at risk. Previous studies have used interviews, questionnaires, and forced-choice image selection experiments to further understand the perceptual changes experienced by glaucoma patients.[2,3] These studies have found that people with glaucoma perceive increased blur[2,3] and increased glare,[3] and feel that they need more light.[3] Unlike common depictions of scene perception in glaucoma, patients do not perceive "tunnels" or black patches in their vision.[2,3] Despite these studies providing some insight, our understanding of how glaucoma affects patients' visual perception remains limited.

Current clinical vision tests for glaucoma typically measure contrast detection thresholds or the detection of fixed contrast stimuli across the visual field (static automated perimetry). However, scenes from our everyday visual environment predominantly contain suprathreshold contrast. In the healthy visual system, the effect of stimulus properties on the appearance of suprathreshold contrast differs substantially from that on contrast detection thresholds. The minimum contrast required to detect a stimulus (contrast detection threshold) depends on the spatial frequency content and eccentricity of that stimulus. For instance, greater contrast is required to detect stimuli of high or low spatial frequency, compared with stimuli of medium spatial frequency.[4] Further, a stimulus presented centrally can be detected at lower contrast than the same stimulus

presented peripherally.[4,5] However, the apparent contrast of a visible, suprathreshold stimulus is perceived veridically and independently of both spatial frequency and eccentricity, a phenomenon termed "contrast constancy."[6–9] This term was first introduced by Georgeson and Sullivan (1975) in their study comparing perception across spatial frequencies, but may be extended to incorporate the consistent perception of suprathreshold contrast across other properties that affect detection thresholds. Several candidate mechanisms have been proposed to mediate this difference between threshold and suprathreshold vision, including alterations to the contrast gain of spatial frequency-specific channels[6,10] and differences in the influence of neural noise under different conditions.[7]

Although decreases in contrast sensitivity in glaucoma are well-known (e.g.[11–13]), the effects of the disease on the appearance of suprathreshold contrast remain unknown. Retinal ganglion cells play a role in contrast processing and contrast adaptation through alterations to their response gain,[14,15] and changes to contrast gain and adaptation have been demonstrated previously in glaucoma.[16–18] Understanding how these changes impact the appearance of suprathreshold contrast may help to understand the visual experience of people with glaucoma, potentially leading to improved public information and rehabilitation. Alternatively, if contrast constancy is maintained in glaucoma, this knowledge may lead to an improved understanding of possible compensatory mechanisms for decreased sensitivity in the visual system, and provide evidence of another contributory factor for the lack of symptoms in early to moderate glaucoma.

In this study, we explore the effects of glaucoma on the perception of the contrast of visible suprathreshold stimuli both inside and outside of regions of visual field defect as measured by static automated perimetry.

Methods

Participants

Twenty participants with glaucoma (mean age ± SD, 72 ± 7 years) and 20 individually age-matched healthy control participants (70 ± 7 years) participated in the study. Participants were recruited through advertisements in local hospital ophthalmology departments, patient charities, newspapers, and community groups.

All participants had visual acuity better than 6/9.5 (Snellen) in the tested eye and refractive error no greater than 6.00 DS or 3.00 DC. Participants had no ocular or systemic condition known to affect vision except mild cataract (no more than NC3 NO3 C2 P2 on the Lens Opacities Classification System III grading scale[19]) and glaucoma for the participants with glaucoma. Control participants had normal findings on examination of eye health prior to testing. Eye health assessment included perimetry (SITA Standard 24-2, Humphrey Field Analyzer III, Carl Zeiss Meditec, Jena, Germany), Goldmann applanation tonometry (intraocular pressure ≤ 21 mm Hg and difference between the eyes ≤ 3 mm Hg for the control group), slit lamp biomicroscopy, and indirect fundoscopy. We defined a "visual field defect" as a cluster of three or more adjacent points with a pattern deviation P of less than 5% and at least one of which is a P value of less than 1% based on criteria given by Anderson and Patella.[20] Control participants were included in the study if perimetry showed no visual field defect and glaucoma hemifield test analysis was within normal limits.

Only participants with glaucoma with a partial visual field defect were included in the study; at least one quadrant of the visual field plot had a visual field defect as defined earlier while at least one of the three other quadrants was without a visual field defect by the definition. Additionally, participants with glaucoma had at least one sector of the retinal nerve fiber layer with thickness outside normal limits ($P <$ 5%) on an optical coherence tomography circumpapillary scan (Spectralis; Heidelberg Engineering GmbH). Confirmation of glaucoma diagnosis was obtained from the latest ophthalmology clinic report and/or a reliable history from the patient with evidence of current treatment. If both eyes fit the criteria for the glaucoma group, the tested eye was chosen at random. The tested eye for the control group was chosen at random.

Participants with glaucoma were tested in two spatial locations at 10° eccentricity in two of the four ordinal directions. One test location was chosen in a quadrant with a visual field defect, and one test location was chosen in a quadrant without a visual field defect. Control participants were tested in a single location at 10° eccentricity such that the location tested corresponded to that of their individually age-matched glaucoma participant within an area of a visual field defect. For example, if the glaucoma observer was tested in the right eye superior-nasal quadrant, the age-matched control participant was tested in either the right or left eye in the superior nasal quadrant. Supplementary Figure S1 shows each glaucoma participant's visual field and tested locations.

All participants provided written informed consent in accordance with the tenets of the Declaration of Helsinki before participating in the study. The study was approved by a National Health Service ethics committee. An inconvenience allowance was provided to participants.

Apparatus and Stimuli

Gabor stimuli (SD 0.75°, random orientation each trial, phase cycling at 1 Hz) with spatial frequencies of 0.5, 1.0, 2.0, and 4.0 c/deg were used. Stimuli were generated in MATLAB 8.5.0 (R2015a; The MathWorks, Natick, MA) using Psychtoolbox (V3.0.14).[21–23] Stimuli were presented on a 14-bit calibrated display system (resolution 1920 × 1080, refresh rate 120Hz; Display++, Cambridge Research Systems Ltd, Kent, UK). The mean luminance of the screen was 52.8 cd/m^2. Appropriate refractive correction was provided with wide aperture trial lenses for the viewing distance of 100 cm that was maintained using a chin and forehead rest. Monocular testing was performed with occlusion of the nontested eye.

Fixation was monitored by eye tracking (LiveTrack FM, Cambridge Research Systems Ltd) with a recording rate of 60 Hz. Central fixation was defined as viewing within a 2.5° radius of the fixation marker/center of the Gabor stimulus. Peripheral stimuli were only presented while central fixation was reported by the eye tracker. Those participants who could not be monitored using the eye tracker (3 participants with glaucoma and 4 controls) were observed using live video monitored by the researcher. In these cases, eye tracking failed owing to small pupils and/or small palpebral apertures.

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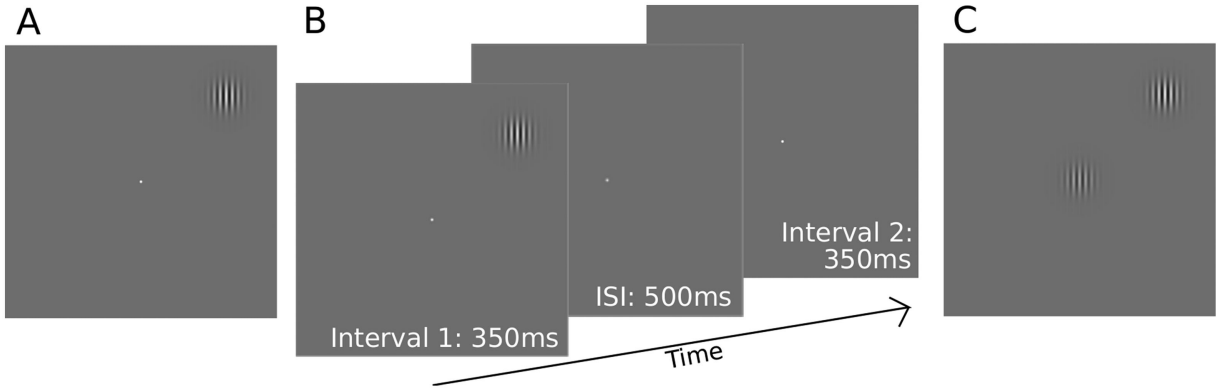

Figure 1. Schematic of the experimental procedures. (**A**) Initial estimates of contrast sensitivity were made by adjusting the contrast of a Gabor stimulus at 10° eccentricity until it was "just visible", while fixating a central target. These estimates were then used as a starting point in a two-interval forced choice procedure used to obtain final contrast detection thresholds (**B**). The Gabor stimulus appeared randomly in either of the two intervals at 10° eccentricity. Participants indicated in which interval the Gabor appeared by a key press. (**C**) Schematic of the contrast matching task. The contrast of the central Gabor stimulus was adjusted by the participant to achieve a perceptual match with the contrast of the midperipheral reference Gabor stimulus, which was fixed at either two times or four times the detection threshold contrast. The reference stimulus was presented at 10° eccentricity in one of the four ordinal directions. ISI, interstimulus interval.

Procedure

Contrast Detection Thresholds. Contrast detection thresholds for the Gabor stimuli were measured using a two-step process. First, approximate thresholds were obtained using the method of adjustment. Participants focused on a central fixation target and a Gabor stimulus was presented at 10° eccentricity in the ordinal direction in the specified quadrant (Fig. 1A). The participant adjusted the contrast of the stimulus using a dial (CB7, Cambridge Research Systems) until they could "just see it." One full rotation of the dial clockwise or anticlockwise resulted in a 10% increase or decrease in contrast, respectively. These contrast detection threshold estimates were used as a starting point for the subsequent two interval forced-choice procedure used to obtain final contrast detection thresholds. Stimulus contrast throughout the study was defined using Michelson contrast: $(L_{max} - L_{min})/(L_{max} + L_{min})$, where L_{max} and L_{min} are the maximum and minimum luminance of the stimulus, respectively. Possible contrasts, therefore, range from 0 to 1.

The final contrast detection thresholds were measured using a two-interval forced choice procedure (Fig. 1B). Observers were asked to fixate on the central white spot target; if the observer fixated outside the central 5° diameter of the target, the eye tracker would alert by a buzzing sound and peripheral stimuli were not presented until the observer refixated centrally. Stimuli appeared in one randomly chosen interval for 350 ms, with contrast ramped on and off according to a raised cosine temporal profile, separated by a 500-ms interstimulus interval. Participants identified whether the stimulus appeared in interval one or two by key press. Stimulus contrast was adjusted according to a three down one up staircase procedure, with independent staircases randomly interleaved for each spatial frequency. Stimulus contrast was adjusted by 20% before the first reversal and 10% thereafter. Staircases terminated after six reversals, with the mean of the last four reversals taken as the contrast detection threshold. Contrast sensitivity was calculated as the reciprocal of contrast detection threshold.

Suprathreshold Contrast Matching. Suprathreshold apparent contrast was measured for each Gabor stimulus in a matching paradigm. Reference contrast levels were set at two times and four times the detection thresholds obtained prior, as described elsewhere in this article. The reference Gabor stimulus was presented in the midperipheral location at 10° eccentricity, whereas a random contrast stimulus, identical in all other respects, was shown centrally (Fig. 1C). Participants adjusted the contrast of the central Gabor using a dial (method of adjustment) until its apparent contrast matched the peripheral reference Gabor, indicating a match by pressing a button. This process was repeated 12 times in a block for each stimulus condition and the mean contrast matched was taken as the measurement of apparent contrast of the peripheral reference stimulus. To account for differences in contrast detection thresholds between participants, matched contrast ratios were calculated as matched contrast/reference contrast.

A total of eight stimulus conditions were tested for control participants; four spatial frequencies (0.5, 1.0, 2.0, and 4.0 c/deg) and two reference contrast levels for each spatial frequency (two times and four times the detection threshold). For participants with glaucoma, these eight conditions were repeated in two locations, within and outside of a visual field defect. The number of conditions tested was restricted for some participants depending on the initial detection thresholds; if contrast detection thresholds for a particular spatial frequency or test location were greater than 0.25, that condition could not be tested because the reference contrast levels would exceed 100% contrast. The contrast matching task for all testable stimulus conditions was completed in a predetermined randomised order. Fixation was monitored via the eye tracker; if participants fixated outside the central 5° diameter, a black crosshair would appear on the screen surrounding the central Gabor stimulus and the peripheral reference Gabor would disappear. The peripheral stimulus would only reappear once the participant had refixated correctly.

Statistical Analysis

Statistical analysis was conducted in R version 3.6.1 using the lme4 and emmeans packages.[24–26] Because data were collected from two spatial locations in the participants with glaucoma, data were not independent between test

locations (within/outside visual field defects) within the glaucoma group. Data were therefore analyzed by linear mixed modelling, accounting for within-subject effects. Six separate linear mixed models were used to test each main effect individually: fixed effects of "group" (three "groups" defined as participants with glaucoma tested within a visual field defect, participants with glaucoma outside the visual field defect, and control participants) and spatial frequency on contrast detection thresholds and contrast match ratios at reference contrasts two times and four times detection thresholds. Random effects of participant were included in each model to account for within-participant effects arising from the participants with glaucoma appearing in two of the three groups. As such, models took the form:

$$y \sim 1 + x + (1|\text{Participant}),$$

where y represents the outcome measure of detection threshold or matched contrast ratio, x represents the fixed effect measure of group or spatial frequency, and 1 represents the intercept, with $(1|\text{Participant})$ denoting random intercepts for individual participants.

Basic models including only intercepts and random effects of participant (i.e., $x = 0$) were compared with models additionally including the fixed-effect parameter in question (x) by χ^2 likelihood ratio test of the nested models. Models were fit to the data by maximum likelihood estimation. If likelihood ratio test results had a P value of less than 0.05, effects were separated by group and spatial frequency by Tukey post hoc tests on estimated marginal means, also revealing effect sizes. Between group differences are reported as mean ± SE.

Results

Contrast Detection Thresholds

Detection threshold data are presented as contrast sensitivity functions (contrast sensitivity = 1/contrast detection threshold) in Figure 2. Detection thresholds for the participants with glaucoma overall were raised relative to controls, main effect, $\chi^2(2) = 29.1$, $P < 0.001$. Compared with controls, the mean detection thresholds for participants with glaucoma were elevated by 0.141 ± 0.026 ($P < 0.001$) within the visual field defect and by 0.050 ± 0.025 ($P = 0.12$) outside the visual field defect area.

Contrast detection thresholds were spatial frequency dependent, $\chi^2(3) = 89.96$, $P < 0.001$. Specifically, thresholds were increased for the 4.0 c/deg stimulus by 0.180 ± 0.024, 0.220 ± 0.024 and 0.221 ± 0.024 compared with 0.5, 1.0, and 2.0 c/deg stimuli, respectively (all $P < 0.001$). Contrast detection thresholds for spatial frequencies of 1 and 2 c/deg were similar (difference in mean detection thresholds, 0.001 ± 0.024, $P = 1.0$), as were detection thresholds for 0.5 c/deg stimuli, 0.040 ± 0.024 ($P = 0.33$) and 0.041 ± 0.024 ($P = 0.31$) higher relative to 1 and 2 c/deg, respectively.

Suprathreshold Contrast Match Ratios

Three participants with glaucoma were unable to detect the 4 c/deg stimulus at maximum contrast within their visual field defect. A further 13 participants with glaucoma were unable to perform the matching task with reference contrast

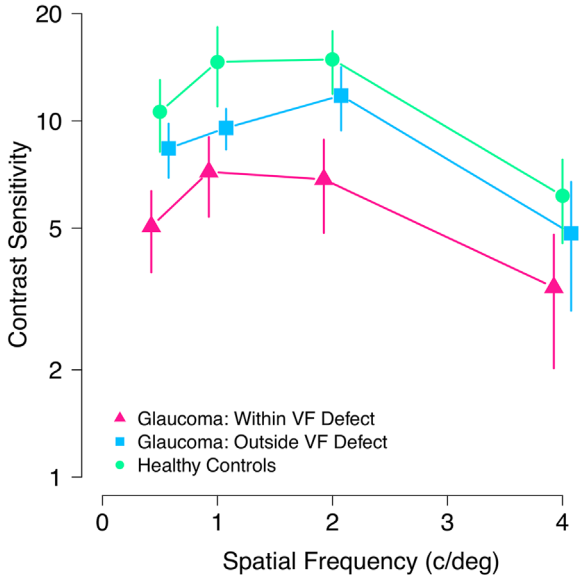

Figure 2. Mean contrast sensitivity for healthy control participants (*green circles*) and participants with glaucoma within their visual field (VF) defect (*pink triangles*) and outside of their visual field defect (*blue squares*). Error bars show 95% confidence interval of the mean.

Table. Distribution of Datasets Removed From the Four Times the Detection Threshold Reference Contrast Condition of the Contrast Matching Task Owing to Ceiling Effects.

Datasets	0.5 c/deg	1 c/deg	2 c/deg	4 c/deg
Healthy controls	2	0	0	1
Glaucoma within VF defect	1	0	1	–
Glaucoma outside VF defect	1	0	1	2

VF, visual field.

Note that the 4 c/deg condition for the participants with glaucoma within their visual field defect was excluded from analysis entirely.

four times the detection threshold for the 4 c/deg stimulus in the visual field defect area owing to ceiling effects (four times the detection threshold ≥ 1). This left only data from four participants with glaucoma in the reference contrast four times the detection threshold condition for the 4 c/deg stimulus within the visual field defect; this condition was therefore excluded from analysis. To account for ceiling effects among the other conditions, those contrast matching datasets that included more than 4 of 12 matches at the measurement ceiling were removed from the analysis; this applied to 4 control and 6 glaucoma participant datasets in total. One of the removed datasets was from a control participant in the two times detection threshold condition with the 4 c/deg stimulus. All remaining removed datasets were from the four times the detection threshold condition and were distributed, as shown in the Table.

Figure 3 shows group mean contrast match ratios for the two reference contrast levels (two times and four times the detection threshold). For reference stimuli at two times detection threshold contrast (Fig. 3a), there was a main effect of group on contrast match ratios, χ^2 (2) = 16.4, $P < 0.001$. This effect was caused by a difference between the two tested locations within the participants with glaucoma; matched contrast ratios were 0.16 ± 0.039 ($P < 0.001$) higher outside compared with within visual field defects in

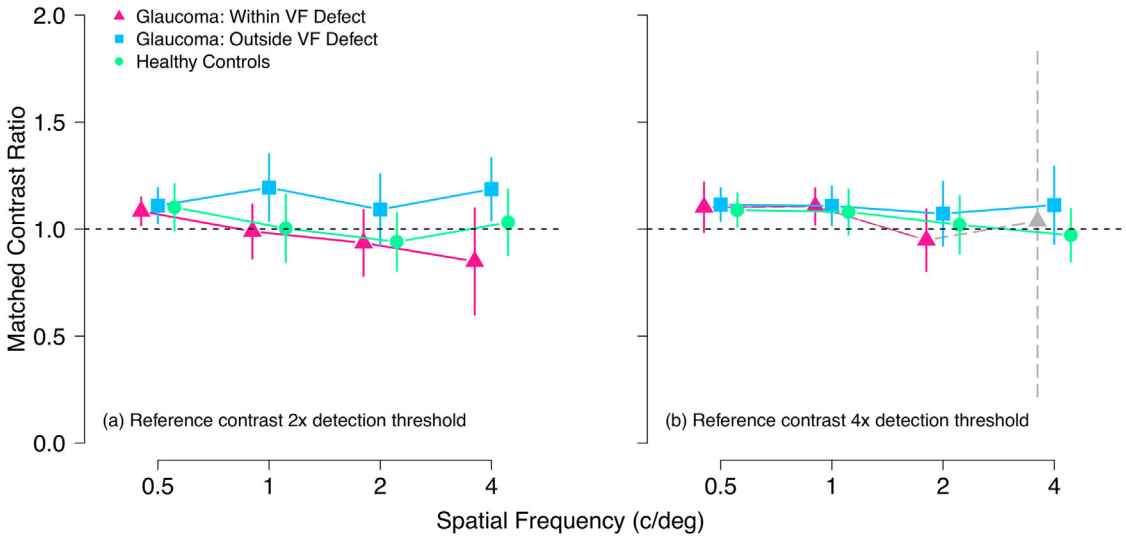

Figure 3. Mean suprathreshold contrast matching functions for reference stimulus contrasts two times (**a**) and four times (**b**) the detection threshold. *Vertical axes* show the ratio between matched and reference contrasts (matched contrast ratio = matched contrast/reference contrast). *Horizontal dashed lines* indicate where matched contrast equals physical contrast (matched contrast ratio = 1.0). Symbols are coded as in Figure 2, except that the *grey triangle* with *dashed error bars* represents the data for the four participants with glaucoma able to complete the 4 c/deg condition at four times the detection threshold. These data were excluded from statistical analysis and are included here for reference only. Error bars show 95% confidence interval of the mean. VF, visual field.

glaucoma observers. Contrast match ratios were, however, similar between controls and participants with glaucoma, both within (matched contrast ratios mean 0.033 ± 0.066 lower; $P = 0.87$) and outside (matched contrast ratios mean 0.126 ± 0.066 higher; $P = 0.14$) visual field defects (Fig. 3a).

For the higher contrast reference stimuli at four times the detection contrast (Fig. 3b), matched contrast ratios were similar between control participants and participants with glaucoma in both tested locations (grand mean 1.07 [range, 1.06–1.10]) main effect of group, $\chi^2(2) = 1.1$; $P = 0.58$. Contrast match ratios were minimally affected by spatial frequency for both two times- $\chi^2(3) = 6.4$; $P = 0.092$, and four times- $\chi^2(2) = 5.9$; $P = 0.054$, reference contrasts.

Figure 4 shows individual participants' contrast matches in each experimental condition. The elevation of detection thresholds in the data for participants with glaucoma can be seen as a relative sparsity of data in the bottom left corner of the plots compared with controls. For all conditions, the majority of points lie close to the diagonal, indicating a perceptual match between the foveal and peripheral locations.

Discussion

This study aimed to investigate the effects of glaucoma on the perception of the contrast of visible, suprathreshold stimuli. Consistent with previous studies, contrast detection thresholds were increased in the glaucoma group within visual field defects relative to age-similar controls.[13,17] However, the perception of suprathreshold contrast was similar between the control and glaucoma groups, particularly in the more suprathreshold higher reference contrast condition. This unaltered perception of suprathreshold stimulus contrast for participants with glaucoma was present both within and outside of visual field defects as measured by perimetry. These results provide further evidence that common depictions of what glaucoma patients see, such as "black tunnel" effects and grayed-out regions, do not accurately represent the perception of scenes by people with glaucoma.[2,3] Further, the unaltered perception of suprathreshold contrast may be a factor in the lack of symptoms experienced by many people with early glaucoma, despite significant sensitivity loss measurable by perimetry.

Our finding of spatial frequency independent, near-veridical perception of suprathreshold contrast in healthy vision is consistent with previous literature where it has been termed "contrast constancy."[6–10,27] Although the neural mechanisms underpinning contrast constancy are undetermined, a number of mechanisms have been hypothesized.[6,7,10] First, it has been widely proposed that a number of independent channels tuned to different spatial frequencies exist within the visual system to deconstruct and interpret the image.[4,28–30] Georgeson and Sullivan proposed that changes in contrast gain within these channels under suprathreshold conditions could compensate for the attenuation in sensitivity to high and low spatial frequencies at threshold, thus equalizing the visual system's response to suprathreshold stimuli of varying spatial frequencies.[6] Swanson et al.[10] extended this concept further by developing a model that could predict contrast matching data from contrast thresholds using a small number of medium bandwidth mechanisms tuned to differing spatial frequencies. The model demonstrated that the visual system's response to varying spatial frequencies could be normalized by adjusting the slope of the contrast transfer function (contrast gain) of individual mechanisms within the model.[10] Brady and Field,[7] however, proposed an alternative model that assumes contrast gain remains constant across spatial frequency channels under suprathreshold viewing conditions. Brady and Field suggested that contrast constancy is a result of the visual system's response to the signal alone rather than detection thresholds that are affected by the signal to noise ratio.[7] Brady and Field proposed that higher spatial

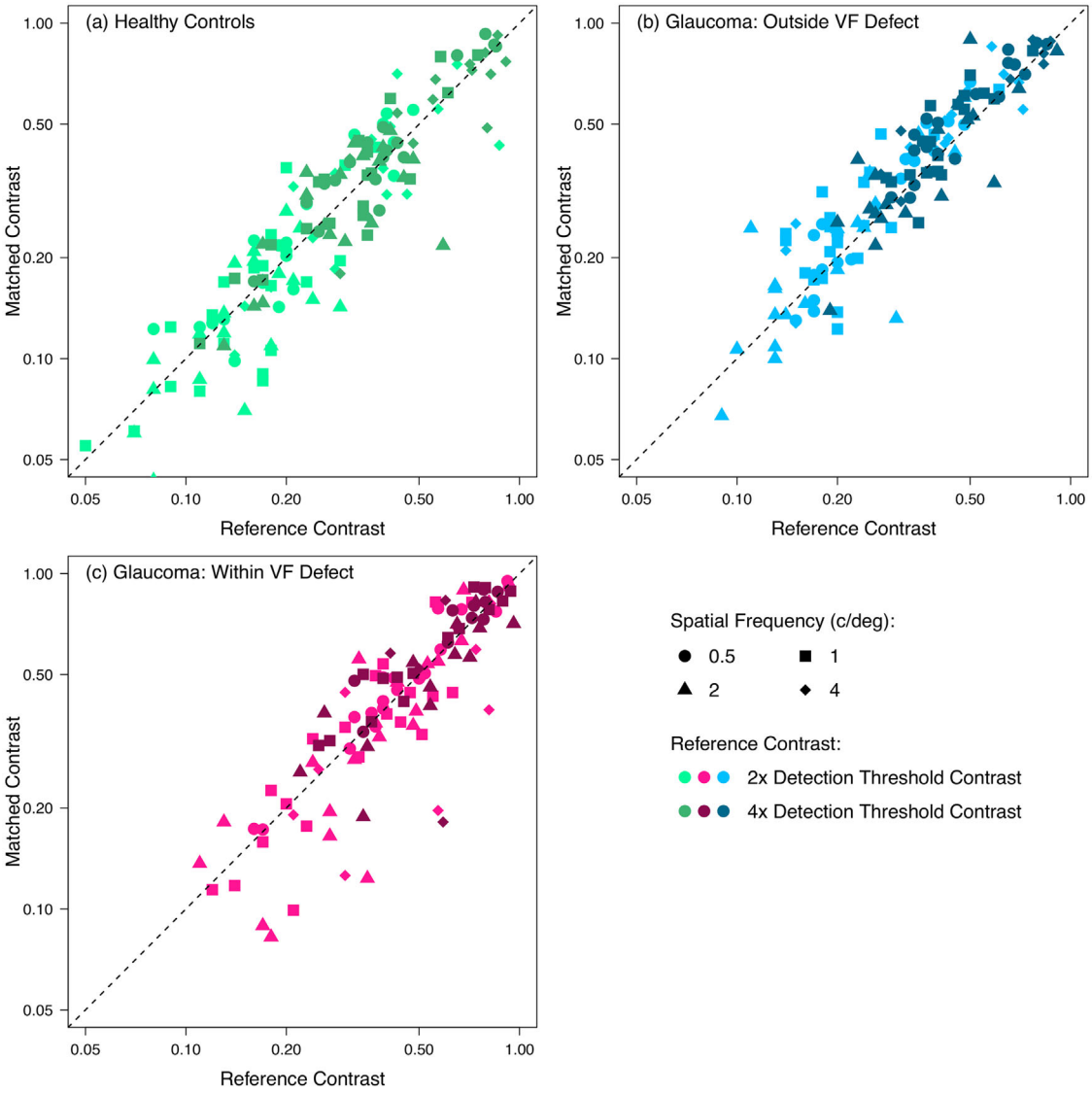

Figure 4. Contrast matches for individual participants in each experimental condition. Data are shown for (**a**) healthy control participants, (**b**) participants with glaucoma outside their visual field (VF) defect, and (**c**) participants with glaucoma within their visual field defect. *Dashed 1:1 lines* indicate perceived contrast matching physical contrast. *Lighter plotting symbols* indicate reference contrasts of two times the detection threshold, and *darker plotting symbols* indicate reference contrasts of four times the detection threshold.

frequency channels respond to noise more than mid-range spatial frequency channels, resulting in a reduced signal-to-noise ratio and increasing detection thresholds for high spatial frequency stimuli.[7] However, their empirical data show contrast constancy as soon as stimuli are suprathreshold, which is inconsistent with other literature showing a gradual flattening of contrast matching functions with increasing suprathreshold contrast.[6,10,27,31]

The results of this study suggest that the mechanisms underlying contrast constancy in the healthy visual system may be intact in glaucoma and able to compensate for pathologic loss of sensitivity. Alternatively, or additionally, further mechanisms may aid compensation for sensitivity loss. It is possible that loss of sensitivity may be accompanied by decreased perceptual surround suppression via alterations to the gain and/or inhibition of downstream visual mechanisms. This may enable an overall perceptual response broadly similar to the predisease state to be maintained despite the decreased sensory input and, combined with existing contrast constancy mechanisms, may be one possible explanation for the present findings. A recent study has investigated two measures of lateral inhibition in the relatively intact central visual field of people with advanced glaucoma, finding no difference from healthy controls.[32] One of their measures, the difference in log contrast sensitivity between 1 and 4 c/deg can also be tested in our data. On this measure we also found no differences between any of the groups ($P = 0.92$, linear mixed model), suggesting that there is no change in lateral inhibition between glaucoma within or outside visual field defects and healthy participants. Further research is needed to explore the mechanisms underlying suprathreshold contrast perception in glaucoma.

The results of this study are consistent with previous studies investigating suprathreshold contrast perception in other disorders of the visual system, including amblyopia[9] and nystagmus.[33] In people with atrophic AMD, exudative

AMD, and juvenile macular degeneration, Mei et al.[31] found that, despite a flattening of the contrast matching functions, there was still a significant difference in contrast matching data between controls and those with maculopathy, although not as large as the difference between detection thresholds. This finding may be explained by not testing participants with maculopathy sufficiently far above threshold to reach contrast constancy; the highest contrast tested was 0.56, and all observers were assessed at the same contrast levels despite the maculopathy group having increased detection thresholds, relative to controls.[31]

Because our everyday visual environment is dominated by suprathreshold contrast, the findings of this study provide some insight into the everyday visual experience of people with glaucoma. However, there are several reasons why our results should be interpreted with caution when considering everyday vision. First, participants were tested monocularly; thus, we are unable to comment on the effects of binocular interactions or the compensation for visual field defects in one eye by relatively intact corresponding visual field in the fellow eye. Further assessment of vision in glaucoma under binocular viewing conditions would be valuable in furthering our understanding of the daily visual experience of those with glaucoma. Second, we used simple Gabor stimuli to enable precise control of stimulus parameters, such as spatial frequency, contrast, and eccentricity. However, findings using these stimuli may not accurately reflect vision under complex natural viewing conditions. Studies have shown that the visual system responds differently to complex stimuli and natural scenes compared with simple stimuli,[34] so further work investigating apparent contrast in natural scenes in glaucoma may be valuable. Finally, a further potential limitation of the present study is that the contrast-matching paradigm used assumes that participants' central vision was normal, but we did not measure foveal contrast sensitivity directly using the Gabor stimulus. Some studies have shown changes to central vision in early glaucoma.[35] Changes to contrast perception in central vision cannot explain our results, however, because apparent contrast of stimuli both within and outside of visual field defects, where contrast detection thresholds were markedly different, was close to veridical (Figs. 3b and 4). Decreased apparent contrast of the central stimulus, if present, could only explain the contrast matches in one, but not both, visual field regions.

The results of this study do not imply that people with glaucoma do not experience visual impairment. Whatever the mechanism of the unaltered suprathreshold contrast perception observed herein, there is no mechanism that could compensate for a total loss of retinal input. Thus, when all retinal ganglion cells signaling a region of visual field are lost, that area becomes blind. Related, we were unable to test most participants with glaucoma within their visual field defect at four times the detection threshold reference contrast with the 4 c/deg stimulus. This was because detection thresholds for this stimulus were elevated beyond 25% contrast; thus, the appropriate reference contrast (>100%) could not be produced. A contrast detection threshold of 25% in this study was approximately four times the mean normal contrast detection threshold for the medium spatial frequencies. In clinical perimetry, a detection threshold four times higher than normal equates to a loss of 6 dB. Although the detection thresholds measured in this study are not directly comparable with perimetric thresholds owing to differences in the stimulus and its presentation, it is clear that many more advanced glaucomatous visual field defects would cause contrast detection thresholds to be increased beyond 25% contrast. Therefore, although our results are consistent with early glaucoma being asymptomatic, they are also compatible with more advanced glaucoma causing visual impairment.

This study has demonstrated that people with glaucoma perceive the contrast of visible, suprathreshold Gabor stimuli similarly to age-similar healthy observers despite decreased contrast sensitivity. This finding is consistent both within and outside of clinically measured visual field defects. The results suggest active or passive compensation for reduced sensory input in the damaged visual system that normalizes responses to suprathreshold contrast, possibly similarly to the mechanisms of contrast constancy in normal vision. The results also provide further evidence for the inaccuracy of common depictions of vision with glaucoma that show black or gray areas obscuring scenes. Further research is required to explore these mechanisms and to better understand the daily perceptual experience of people with glaucoma.

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