Higher Contrast Requirement for Letter Recognition and Macular RGC+ Layer Thinning in Glaucoma Patients and Older Adults

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Purpose. Growing evidence suggests the involvement of the macula even in early stages of glaucoma. However, little is known about the impact of glaucomatous macular damage on central pattern vision. Here we examine the contrast requirement for letter recognition and its relationship with retinal thickness in the macular region.

Methods. A total of 40 participants were recruited: 13 patients with glaucoma (mean age = 65.6 ± 6.6 years), 14 age-similar normally sighted adults (59.1 ± 9.1 years), and 13 young normally sighted adults (21.0 ± 2.0 years). For each participant, letter-recognition contrast thresholds were obtained using a letter recognition task in which participants identified English letters presented at varying retinal locations across the central 12° visual field, including the fovea. The macular retinal ganglion cell plus inner plexiform (RGC+) layer thickness was also evaluated using spectral-domain optical coherence tomography (SD-OCT).

Results. Compared to age-similar normal controls, glaucoma patients exhibited a significant increase in letter-recognition contrast thresholds (by 236%, $P < 0.001$) and a significant decrease in RGC+ layer thickness (by 17%, $P < 0.001$) even after controlling for age, pupil diameter, and visual acuity. Compared to normal young adults, older adults showed a significant increase in letter-recognition contrast thresholds and a significant decrease in RGC+ layer thickness. Across all subjects, the thickness of macular RGC+ layer was significantly correlated with letter-recognition contrast thresholds, even after correcting for pupil diameter and visual acuity ($r = -0.65$, $P < 0.001$).

Conclusions. Our results show that both glaucoma and normal aging likely bring about a thinning of the macular RGC+ layer; the macular RGC+ layer thickness appears to be associated with the contrast requirements for letter recognition in central vision.

Keywords: glaucoma, macular function, aging, letter recognition, contrast threshold, retinal layer thickness, structure-function relationship

Glaucoma is a leading cause of blindness, projected to affect 111.8 million people worldwide by 2040.[1] It is characterized by progressive loss of retinal ganglion cells (RGCs) and associated visual field defects. Primary open-angle glaucoma (POAG), the most common form of glaucoma in the United States, affects approximately 2.2 million Americans (2% of the US population 40 years and older).[2]

Glaucoma is traditionally understood as peripheral vision loss and is thought to spare central vision until the end-stage; thus, it hardly affects central visual function.[3–5] However, a growing body of evidence[6–16] suggests that the macula is significantly compromised even in early stages of glaucoma (see Ref. 17 for review). For instance, studies[7,10,11] using optical coherence tomography (OCT) have shown significant thinning of the retinal nerve fiber layer and the ganglion cell layer in the macular region, which likely reflects loss of RGCs and/or significant shrinkage of dendritic structures and cell bodies of the remaining cells.[18] In parallel with physiological evidence, behavioral studies[4,5,19–27] have shown that, even during early stages of the disease, individuals with glaucoma exhibit noticeable dysfunction in various central vision tasks such as reading and object/face recognition. Furthermore, individuals with glaucoma reported a reduced quality of life.[16,21,28–32] In one survey on quality of life, patients stated that their two main priorities were "reading and seeing detail" and "outdoor mobility."[29] Given the view that central vision is spared from glaucomatous injury, it is rather surprising that difficulty reading has been cited as a major complaint among patients with glaucoma.[21,28–34]

While the exact perceptual mechanism limiting central vision tasks in glaucoma remains unclear, evidence hints that reduced contrast sensitivity[35–38] in glaucomatous vision likely plays a limiting role in central vision tasks such as reading. Luminance contrast refers to the difference in intensity between light and dark regions of an image. Contrast information is encoded by contrast-sensitive neurons (e.g., center-surround RGCs) along the visual pathways. The ability to detect differences in contrast is a fundamental building block of human pattern vision and thus crucial to various visual activities.[39] For example, Rubin and Legge[40] found that as the contrast between text and page decreases, reading speed decreases in some people with low vision. Considering the significant macular damage found in glaucomatous eyes, it is reasonable to expect a higher contrast requirement for central

pattern recognition in glaucoma patients. Indeed, a number of studies have reported that decreased contrast sensitivity is present even in early or moderate glaucoma.[35–38] Furthermore, this loss of contrast sensitivity may occur despite normal visual acuity.[37,41] Previous studies[5,40] on the effect of glaucoma on reading further showed that the decrease in reading speed associated with reduced text contrast was significantly more pronounced in people with glaucoma when compared to normal cohorts.

Despite accumulating evidence suggesting the involvement of the macula in all stages of glaucoma, little is known about the impact of glaucomatous macular damage on central pattern vision. Thus, the current study aimed to investigate whether there is a higher contrast requirement for letter recognition in the macular region of glaucomatous eyes and, if so, whether said contrast requirement is related to retinal structural damage (approximated by RGC layer thickness) in the macular region. We chose to examine letter recognition because it is highly relevant to everyday visual activities; it is also one of essential building blocks of reading.

To this end, the contrast threshold for letter recognition (i.e., the minimum contrast required for reliable letter recognition) was measured at nine different retinal locations across the central 12° visual field, including the fovea. In addition, using spectral-domain optical coherence tomography (SD-OCT), we measured the thickness of the retinal ganglion cell plus inner plexiform (RGC+) layer in the macula. In this study, we focused on the RGC+ layer because it is likely to reflect any damage that might have occurred to RGC bodies and their dendritic structures. Both functional and structural data were obtained from and compared among three subject groups: patients with POAG, age-similar normally sighted adults, and young normally sighted adults. We included both young and older normally sighted adults to examine age-related changes in both central pattern vision and retinal thickness in the macular region. To elucidate the structure–function relationship in the macular region, retinal structural data were correlated against letter-recognition contrast thresholds across subjects.

This study will help us understand how glaucoma-related RGC damage undermines central pattern vision, such as letter recognition. In addition, the comparison between young and older normally sighted adults will help us understand how normal aging brings about changes in retinal structure, which may underlie the known contrast-sensitivity deficits in older adults. Taken together, the outcome of this study will provide a better understanding of the structure–function relationship in the macular region of the glaucomatous eye and the aged eye.

Methods

Participants

A total of 40 participants took part in this study: 13 patients with glaucoma (12 patients with POAG and 1 patient with preperimetric glaucoma; mean age = 65.6 ± 6.6 years); 14 age-similar older adults with normal or corrected-to-normal vision (mean age = 59.1 ± 9.1 years); and 13 young adults with normal or corrected-to-normal vision (mean age = 21.0 ± 2.0 years). The study participants were recruited from either the University of Alabama at Birmingham (UAB) Callahan Eye Hospital or the UAB campus.

For the patients with POAG, glaucoma was clinically diagnosed and confirmed through medical records. The patients with POAG in the current study met the following three inclusion criteria: (1) glaucoma-specific changes of optic nerve or nerve fiber layer defect in which the presence of the glaucomatous optic nerve was defined by masked review of optic nerve head photos by glaucoma specialists using previously published criteria;[42] (2) glaucoma-specific visual field defect, defined as having a value on Glaucoma Hemifield Test from the Humphrey Field Analyzer outside normal limits; and (3) no history of other ocular or neurologic disease or surgery that caused visual field loss. The preperimetric glaucoma patient met the inclusion criteria of (1) and (3).

The visual field test was performed with standard automatic perimetry (SAP) using SITA Standard 24-2 tests with a Humphrey Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA, USA). Goldmann size III targets with a diameter of 0.43° were presented for 200 ms at one of 54 test locations in a grid on a white background (10 cd/m^2).

The Table summarizes characteristics of study participants. The average mean deviation (MD) obtained from the Humphrey Field Analyzer in glaucoma patients was –5.9 ± 8.3 dB for the better eye and –11.0 ± 8.4 dB for the worse eye. According to the Hodapp-Anderson-Parrish glaucoma grading system,[43] one patient was a glaucoma suspect, three had mild glaucoma, two had moderate, five had advanced, and two had severe glaucoma. The mean visual acuity (Early Treatment Diabetic Retinopathy Study charts) for glaucoma patients was 0.05 ± 0.10 logMAR (or approximately 20/20 Snellen equivalent) for the right eye and 0.05 ± 0.10 logMAR for the left eye. The mean log contrast sensitivity (Pelli-Robson charts) was 1.50 ± 0.23 for the right eye and 1.56 ± 0.19 for the left eye.

From medical records, we determined that eight of our glaucoma patients had nuclear sclerotic cataracts (NSC) in both eyes of mild to moderate severity (1+ to 2+). One of these eight patients also had cortical cataracts. The remaining five patients all had cataract surgery in both eyes. Furthermore, two patients, G12 and G13, had dry eye. We also confirmed that none of our patients had iatrogenic pupils. From the Humphrey Field Analyzer, we determined the pupil diameter of each of our subjects.

In this study, normal vision was defined as better than or equal to 0.09 logMAR (or 20/25 Snellen equivalent) best-corrected visual acuity in each eye with normal binocular vision and with no history of ocular or neurologic disease other than cataract surgery. For age-similar normal adults, the mean visual acuity was –0.03 ± 0.09 logMAR (or 20/20 Snellen equivalent) for the right eye and –0.05 ± 0.09 logMAR (or 20/20) for the left eye. The mean log contrast sensitivity was 1.81 ± 0.12 for the right eye and 1.75 ± 0.18 for the left eye. For young normal adults, the mean visual acuity was –0.03 ± 0.08 logMAR (or 20/20) for the right eye and –0.04 ± 0.08 logMAR (or 20/20) for the left eye. The mean log contrast sensitivity was 1.83 ± 0.12 for the right eye and 1.80 ± 0.17 for the left eye.

All participants were native or fluent English speakers without known cognitive or neurologic impairments, confirmed by the Mini Mental Status Exam (MMSE; ≥25 MMSE score for those aged 65 and over). Proper refractive correction for the viewing distance was used. The experimental protocols followed the tenets of the Declaration of Helsinki and were approved by the Internal Review Board of the University of Alabama at Birmingham. Written informed consents were obtained from all subjects prior to the experiment and after explanation of the nature and possible consequences of the study.

Measuring Threshold Contrasts for Letter Recognition

Stimuli. To test letter recognition, the 26 uppercase Courier font letters of the English alphabet were used. The x-

Table. Characteristics for Study Participants

Subject ID	Diagnosis	Age, years	Sex	Visual Acuity, logMAR		Contrast Sensitivity, log units		Pupil Diameter, mm		Lens Status		Mean Deviation, dB	
				OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
G1	POAG	56	F	−0.08	−0.08	1.65	1.65	5.5	4.7	NSC 1+ to 2+	NSC 1+ to 2+	−12.20	−9.59
G2	POAG	55	M	0.04	−0.04	1.35	1.50	4.9	5.5	NSC 2+	NSC 2+	−20.91	−27.88
G3	POAG	62	F	0.02	0.06	1.65	1.50	3.4	3.6	IOL	IOL	−0.45	−3.26
G4	POAG	67	F	−0.08	0.04	1.65	1.65	5.2	6.2	NSC 2+	NSC 2+	2.25	−4.07
G5	POAG	66	F	0.12	−0.04	1.65	1.65	7.0	6.9	NSC 2+	NSC 2+	−15.22	−4.22
G6	POAG	74	F	0.04	0.12	1.35	1.35	4.0	5.0	IOL	IOL	−2.28	−7.90
G7	POAG	73	M	0.02	0.00	0.90	1.20	4.6	4.3	IOL	IOL	−23.90	−23.65
G8	POAG	75	F	0.24	0.06	1.65	1.35	3.3	3.8	NSC 1+ to 2+	NSC 1+ to 2+	2.27	−14.22
G9	POAG	61	F	0.02	−0.06	1.35	1.65	4.4	3.6	NSC 1+	NSC 1+	−15.58	−6.11
G10	POAG	63	M	0.12	0.12	1.50	1.65	5.2	4.1	IOL	IOL	−0.61	−2.39
G11	POAG	62	M	0.16	0.26	1.50	1.65	2.5	5.7	NSC 1+	NSC 1+	−9.55	−10.63
G12*	PPG	67	M	−0.08	0.02	1.80	1.95	5.7	5.5	CC & NSC	CC & NSC	1.54	0.58
G13*	POAG	72	M	0.12	0.16	1.50	1.50	3.0	2.7	IOL	IOL	−5.94	−6.94
Mean (±SD)	**POAG & PPG**	65.6	F:M=7:6	0.05	0.05	1.50	1.56	4.5	4.7	-	-	−7.74	−9.25
	(n = 13)	(±6.6)		(±0.10)	(±0.10)	(±0.23)	(±0.19)	(±1.3)	(±1.2)			(±9.12)	(±8.32)
	Normal Old	59.1	F:M=5:9	−0.03	−0.05	1.81	1.75	4.9	4.9	N/A	N/A	0.08	−0.21
	(n = 14)	(±9.1)		(±0.09)	(±0.09)	(±0.12)	(±0.18)	(±1.4)	(±1.4)			(±1.51)	(±1.14)
	Normal Young	21.0	F:M=9:4	-0.03	−0.04	1.83	1.80	5.3	4.9	N/A	N/A	−0.25	−0.54
	(n = 13)	(±2.0)		(±0.08)	(±0.08)	(±0.12)	(±0.17)	(±1.2)	(±1.1)			(±0.86)	(±1.13)

Note that the numbers in parentheses are standard deviations (SD). OD, right eye; OS, left eye; POAG, primary open-angle glaucoma; PPG, preperimetric glaucoma; NSC, nuclear sclerotic cataract; CC, cortical cataract; IOL, intraocular lenses; N/A, not available.

* Denotes an individual with dry eye.

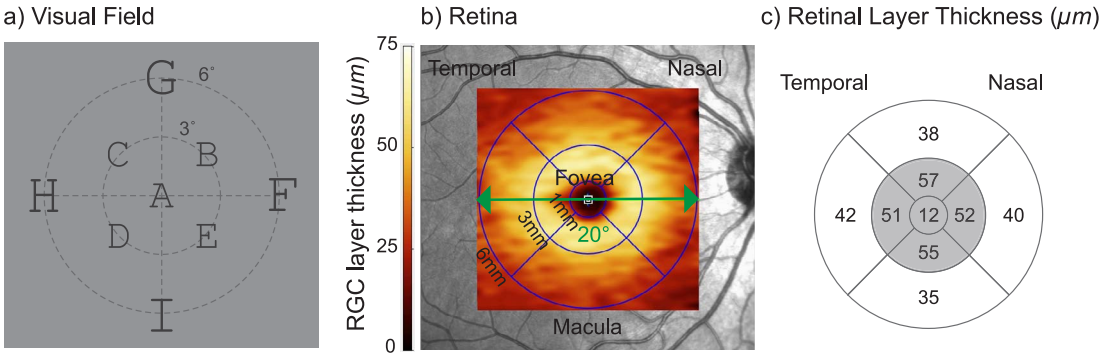

Figure 1. Stimuli for the letter-recognition task and retinal OCT imaging. (**A**) An illustration of the stimulus configuration. A stimulus, a randomly generated letter, was presented in a gaze-contingent manner for 1 second at one of the nine locations shown here. A gaze-contingent display was used to ensure that the target letter was presented at the intended retinal location relative to the fovea. The *dashed lines* represent eccentricities of the target letters and were not shown in the experiment. The size of the target letter (0.8°, 0.8°, 1.1°) in relation to eccentricity was scaled considering the cortical magnification factor.[44] (**B**) Overlay of RGC layer thickness map on a fundus photo. RGC layer thickness map (the heat map) centered on the fovea is overlaid on a fundus image. The diameter of the central, inner, and outer circles are 1, 3, and 6 mm, respectively. The diameter of the outer circle corresponds to the central 20° visual field. The inner and outer circles are divided into four quadrants each. (**C**) Sector map of the average RGC layer thickness. The average RGC layer thickness measurements (in micrometers) are shown for each of the nine subregions defined in (**B**). The center and inner circles (*shaded in gray*) correspond to the central 10° visual field. The thickness of the inner plexiform layer was generated in a similar manner. The RGC+ layer thickness was the sum of the inner plexiform layer and the RGC layer.

height of each letter was 0.8°, 0.8°, 1.1° at eccentricities 0°, 3°, 6°, respectively, at a viewing distance of 57 cm. These letter sizes were chosen considering the cortical magnification factor.[44] A single black letter, with adjustable contrast, was randomly selected and presented on a uniform gray background with a luminance of 159 cd/m^2. The contrast of the letter stimuli was expressed as Weber contrast.

The stimuli were generated and controlled using MATLAB (version 8.3; MathWorks, Inc., Natick, MA, USA) and Psychophysics Toolbox extensions[45,46] for Windows 7, running on a PC desktop computer (Dell Precision Tower 5810; Dell, Inc., Round Rock, TX, USA). Stimuli were presented on a liquid crystal display monitor (Asus VS278H-E; ASUS Computer International, Fremont, CA, USA) with a refresh rate of 144 Hz and resolution of 1920 × 1080, subtending 60° × 34° visual angle at a viewing distance of 57 cm. Stimuli were rendered with 10.8-bit gray-scale levels using the bit-stealing method.[47] Luminance of the display monitor was made linear using an 8-bit look-up table in conjunction with photometric readings from a luminance meter (Minolta LS-110 Luminance Meter; Konica Minolta, Inc., Japan).

Participants' gaze positions were monitored (monocular tracking) using an infrared video-based eye-tracker sampled at 500 Hz (EyeLink 1000 Plus/Desktop Mount, SR Research Ltd., Ottawa, Ontario, Canada) with a maximum spatial resolution of 0.01°. A stimulus was presented in a gaze-contingent manner to ensure that it appeared at the intended retinal location relative to the fovea. The tested eye was tracked while the opposite eye was covered with an eye patch. A nine-point calibration/validation sequence was performed at the beginning of every experimental session that relied on the eye-tracker. Calibration and/or validation were repeated until the validation error was smaller than 0.5° on average. The gaze position error, the difference between the target position and the computed gaze position, was estimated during the nine-point validation process. The average gaze position error was 0.3°. A real-time gaze position was sent to the display computer through a high-speed Ethernet link. The continuous gaze information was used to draw a viewing window on the display screen at a refresh and update rate of 144 Hz.

Task Procedure. The letter-recognition contrast threshold at each of the nine locations (Fig. 1A) was determined for each tested eye. During testing, the nontested eye was covered with an eye patch. The threshold of each testing location was measured by block. One of the nine predetermined locations was randomly selected for each block. Prior to each block, subjects were cued to one of the nine locations. Subjects were instructed to fixate on a cross in the center. Chin and forehead rests were used to minimize head movements and to maintain a fixed viewing distance. Then, using a gaze-contingent display established by the high-speed eye-tracker, a target letter was flashed at the given retinal location for 1 second before being replaced by a set of the 26 letters (i.e., the answer key) presented in a clock face. A subject's task was to determine the identity of the letter that had flashed and to select it with a mouse. Auditory feedback was given for correct answers. Letter-recognition contrast threshold was measured using a 3-down-1-up staircase procedure, which yields a target identification accuracy of 79.4%.[48] Step size of the staircase was 1 dB. The final threshold was determined by taking the geometric average of the last seven staircase reversals. Prior to testing, a practice round was conducted to determine initial contrast of the letters and to familiarize participants with the task procedure.

Measuring Macular RGC+ Layer Thickness With SD-OCT

For each participant, macular retinal layer thickness was measured using SD-OCT (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany).[8,49] The measurement was made in the macula (i.e., the retinal region corresponding to the central 20° visual field). The images were generated using high-resolution volume scan mode with automatic real-time mean value of 15. Macular raster scans (20° × 20°) were acquired with 49 B-scans consisting of 1024 A-scans, resulting in an imaging area of approximately 6 × 6 mm centered on the fovea. Any scan with a quality score less than 20 dB was excluded from analysis. The thickness of each layer was read from the automatic segmentation algorithms provided by the onboard SD-OCT software (version 6.3.1.0). The RGC+ layer thickness was the sum of the ganglion cell layer and inner plexiform layer. The SD-OCT software displays the average retinal thickness and retinal volume of nine subregions of the retina, including a center circle (diameter 1 mm), an inner circle divided into four quadrants (diameter 3 mm), and an outer

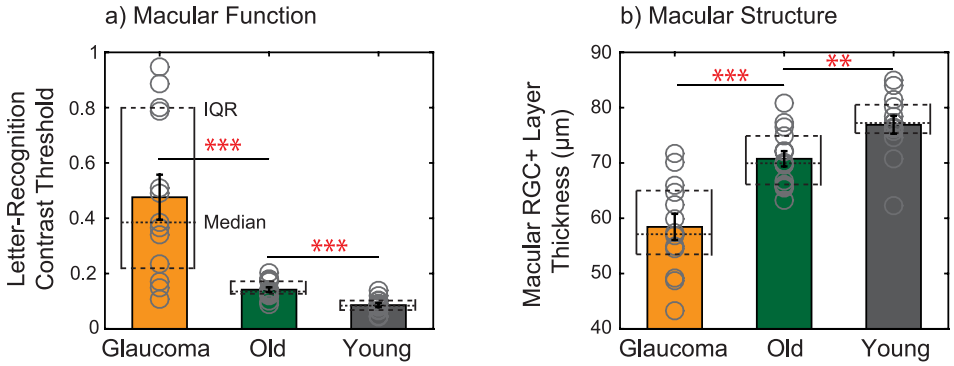

Figure 2. Functional and structural results in the macula. (**A**) Mean letter-recognition contrast threshold for glaucoma patients, normal older adults, and normal young adults. The *orange bar* represents the mean letter-recognition contrast threshold of glaucoma patients, whereas the *green* and *gray bars* represent the thresholds of older and young adults, respectively. (**B**) Mean RGC+ layer thickness for glaucoma patients, normal older adults, and normal young adults. *Gray open circles* represent an individual patient's data point. The two *dashed lines* indicate the interquartile range (IQR), and the *dotted lines* indicate median values. $^{**}P < 0.01$, $^{***}P < 0.001$. *Error bars:* ±1 standard errors of the mean (SEM).

circle divided into four quadrants (diameter 6 mm). The diameters (millimeters) of these circles were transformed to degree units (1 mm ≅ 3.3°). Figures 1B and 1C display the locations of the nine subregions for the thickness measurements.

Data Analysis

For both letter-recognition contrast threshold and macular RGC+ layer thickness data, the averaged value across all retinal locations for each considered eye was used for statistical analyses. The normality of the data was checked using the quantile-quantile plot. To meet the normality assumption, logarithmically transformed letter-recognition contrast thresholds were used. We considered only one eye per participant: the right eye for normally sighted participants or the worse eye for glaucoma patients.

First, to address whether there are any significant differences in either the letter-recognition contrast threshold or macular RGC+ layer thickness among different subject groups (i.e., glaucoma, normal old, and normal young) after controlling for the effects of pupil diameter and visual acuity, we performed the multivariate analysis of covariance (MANCOVA). Here, we used subject group as an independent variable, letter-recognition contrast threshold and macular RGC+ layer thickness as dependent variables, and pupil diameter and visual acuity as covariates in the model. We chose to adjust for pupil diameter and visual acuity because iatrogenic pupils from glaucoma medications[50,51] or other optical characteristics (e.g., senile meiosis, light scattering; see the Discussion for lens opacity) associated with the glaucomatous or aged eye could potentially impact pattern vision. Second, to determine whether macular RGC+ layer thickness plays a crucial role in letter-recognition contrast threshold, we performed multiple regression analysis in which macular RGC+ layer thickness, visual acuity, and pupil diameter were entered as predictors into the model, whereas the letter-recognition contrast threshold served as the dependent variable. To further quantify the relationship between the letter-recognition contrast threshold and macular RGC+ layer thickness, we performed partial correlation analyses between the two variables, after regressing out effects of visual acuity and pupil diameter. For our final test, we used data from both eyes of a single subject. Here, we performed a within-subject correlation[52] on our glaucoma patients, comparing macular RGC+ layer thickness and letter-recognition contrast threshold between the two eyes. Statistical analyses were performed using the *R* software (version 0.98.1091)[53] in combination with MATLAB (R2014b; MathWorks, Inc.).

Results

As described in the data analysis section, our statistical analyses (e.g., MANCOVA) were performed on three subject groups (i.e., glaucoma, normal old, and normal young) to correct for multiple comparisons and control for potential confounding variables. However, as our main goals were to compare glaucoma and age-similar normal old adults (i.e., the effect of glaucoma) and to compare normal old and young adults (i.e., the effect of normal aging), here we report the statistical results of the effect of glaucoma and the effect of aging separately.

The Effects of Glaucoma: Higher Contrast Requirement for Letter Recognition and Thinner Macular RGC+ Layer Thickness in Glaucoma Patients

In this section, we report the effects of glaucoma on the letter-recognition contrast threshold and macular RGC+ layer thickness. Figure 2A plots the mean letter-recognition contrast threshold for each of the three subject groups. Gray open circles represent an individual subject's data point. The two dashed lines indicate the interquartile range (IQR) and the dotted lines indicate median values. There was a significantly higher letter-recognition contrast threshold for glaucoma patients compared to age-similar normal controls (by 236.0%, $F_{(1,23)} = 65.06$, $P < 0.001$) averaged across all testing locations (i.e., nine locations within the central 12° visual field) after controlling for pupil diameter and visual acuity. This pattern of results held when thresholds were considered by retinal eccentricity: glaucoma patients required a significantly higher letter-recognition contrast threshold at the fovea (by 235.7%, $F_{(1,23)} = 7.71$, $P = 0.011$), at 3° (by 227.8%, $F_{(1,23)} = 18.42$, $P < 0.001$), and at 6° (by 243.9%, $F_{(1,23)} = 29.94$, $P < 0.001$). Note that this pattern of results held even after controlling for the age difference (approximately 7 years) between the glaucoma patients and age-similar normal controls ($F_{(1,22)} = 23.02$, $P < 0.001$). Here, we conducted a separate MANCOVA on the data set containing only glaucoma patients and age-similar normal controls using age, visual acuity, and pupil diameter as covariates.

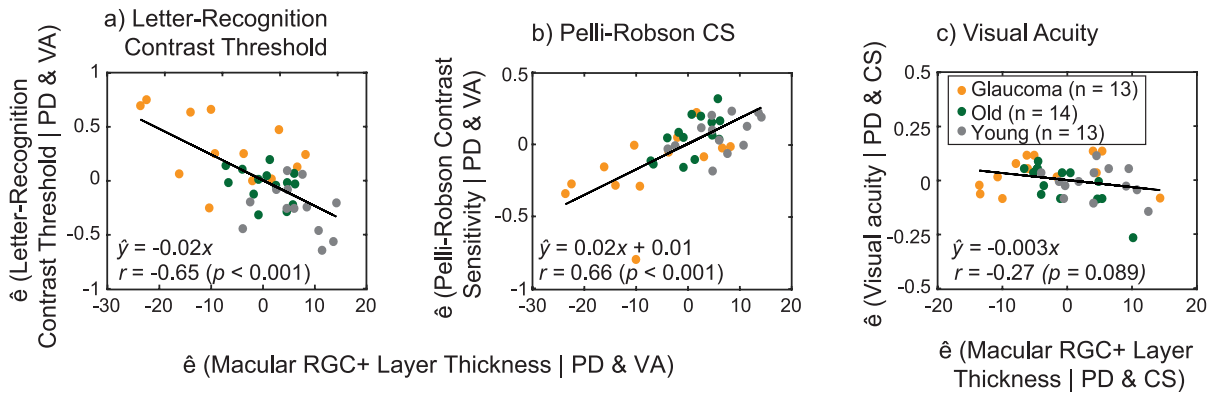

Figure 3. Partial correlations between functional and structural data after controlling for pupil diameter and visual acuity. In the partial correlation plot, $\hat{e}(c|a,b)$ represents the residuals from the regression of the *c* variable on the *a* and *b* variable. The *orange dots* represent data from glaucoma patients ($n = 13$), whereas the *green* and *gray dots* represent data for normal older adults ($n = 14$) and young adults ($n = 13$), respectively. The *black lines* represent the best linear fit to the data. (**A**) Correlation between letter-recognition contrast threshold and macular RGC+ layer thickness after regressing out the effects of pupil diameter (PD) and visual acuity (VA). (**B**) Correlation between Pelli-Robson contrast sensitivity (CS) and macular RGC+ layer thickness after regressing out the effects of PD and VA. (**C**) Correlation between visual acuity (logMAR) versus macular RGC+ layer thickness after regressing out the effects of PD and CS.

Figure 2B plots the mean macular RGC+ layer thickness for each of the three subject groups. There was a decrease in RGC+ layer thickness for glaucoma patients compared to age-similar normal controls (by 17.4%, $F_{(1,23)} = 19.40$, $P < 0.001$) averaged across all testing locations. This pattern of results held for the center and inner circles as well (the shaded area in Fig. 1C); there was a significant decrease for glaucoma patients compared to age-similar normal controls (by 20.1%, $F_{(1,23)} = 19.12$, $P < 0.001$).

The Effects of Aging: Higher Contrast Requirement for Letter Recognition and Thinner Macular RGC+ Layer Thickness in Older Adults

In this section, we report the effects of aging on contrast requirement for letter recognition and RGC+ layer thickness in the macular region of healthy eyes. Thus, we compared both functional and structural data between normally sighted older adults and normally sighted young adults.

As shown in Figure 2A, there was a significantly higher letter-recognition contrast threshold for normal older adults compared to normal young adults (by 65.2%, $F_{(1,23)} = 33.56$, $P < 0.001$) averaged across all testing locations, indicating age-related decline in contrast sensitivity. This pattern of results held even when contrast thresholds were considered by retinal eccentricity: There were significantly higher contrast thresholds for older adults at the fovea (by 66.3%, $F_{(1,23)} = 22.66$, $P < 0.001$), at 3° (by 63.7%, $F_{(1,23)} = 25.29$, $P < 0.001$), and at 6° (by 66.5%, $F_{(1,23)} = 34.66$, $P < 0.001$).

As shown in Figure 2B, we also observed a significant decrease in the macular RGC+ layer thickness for older adults compared to young adults (by 8.0%, $F_{(1,23)} = 9.81$, $P = 0.004$), suggesting age-related changes in retinal structure. The pattern of results remained similar for the center and inner circles (the shaded area region in Fig. 1C); there was a significant decrease in the macular RGC+ layer thickness for older adults compared to young adults (by 6.4%, $F_{(1,23)} = 4.88$, $P = 0.037$).

Relationship Between the Macular RGC+ Layer Thickness and Letter-Recognition Contrast Threshold

Using multiple regression analysis, we aimed to determine the role of macular RGC+ layer thickness in the letter-recognition contrast threshold. Thus, in this model, macular RGC+ layer thickness, visual acuity, and pupil diameter were entered as predictors whereas the letter-recognition contrast threshold was the dependent variable. We found that the macular RGC+ layer thickness was the only significant factor (a coefficient value of –0.02, $P = 0.016$) contributing to the letter-recognition contrast threshold. Neither visual acuity ($P = 0.951$) nor pupil diameter ($P = 0.904$) were statistically significant. Furthermore, this multiple regression analysis revealed that approximately 48% ($F_{(3,36)} = 11.25$, $r^2 = 0.48$, $P < 0.001$) of the variance in letter-recognition contrast threshold was accounted for by this model.

Using a partial correlation analysis, we quantified the correlation between the letter-recognition contrast threshold and macular RGC+ layer thickness after controlling for pupil diameter and visual acuity (Fig. 3A). In the partial correlation plot, $\hat{e}(c|a,b)$ represents the residuals from the regression of the *c* variable on the *a* and *b* variables. Each data point represents the mean of all nine testing locations (or nine subregions) for each subject. Different colors denote different subject groups: orange for glaucoma patients, green for older adults, and gray for young adults. The black solid line represents the best linear fit to the data. We found a significant correlation between RGC+ layer thickness and letter-recognition contrast threshold after regressing out the effects of pupil diameter and visual acuity ($r = –0.65$, $P < 0.001$). When considering data from glaucoma patients only, we found a marginally significant structure–function correlation ($r = –0.53$, $P = 0.060$).

We then examined the relationships between macular RGC+ layer thickness and other functional measures such as Pelli-Robson contrast sensitivity or visual acuity using a partial correlation analysis. Figure 3B shows the relationship between macular RGC+ layer thickness and Pelli-Robson contrast sensitivity after controlling for pupil diameter and visual acuity. Similarly, Figure 3C shows the relationship between macular RGC+ layer thickness and visual acuity (logMAR) after controlling for contrast sensitivity and pupil diameter. We found a significant correlation between macular RGC+ layer thickness and Pelli-Robson contrast sensitivity ($r = 0.66$, $P < 0.001$), even after controlling for pupil diameter and visual acuity. However, we found no significant correlation between macular RGC+ layer thickness and visual acuity after controlling for contrast sensitivity and pupil diameter ($r = –0.27$, $P = 0.089$). Our results suggested that unlike the contrast-

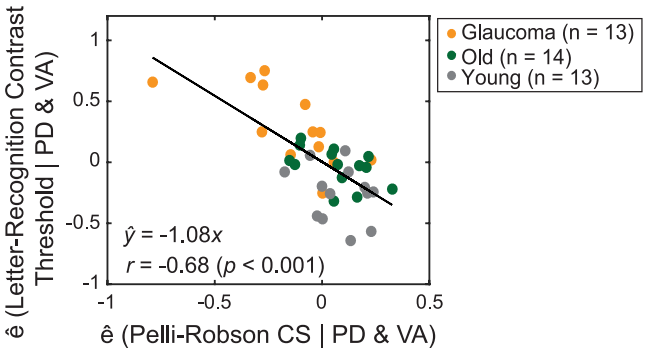

FIGURE 4. Partial correlation between letter-recognition contrast threshold and Pelli-Robson contrast sensitivity. The plot represents a correlation between letter-recognition contrast threshold and Pelli-Robson contrast sensitivity, after controlling for PD and VA. *Orange dots* represent data from glaucoma patients ($n = 13$), whereas *green* and *gray dots* represent data for normal older adults ($n = 14$) and young adults ($n = 13$), respectively. The *black* line represents the best linear fit to the data.

sensitivity measure, the visual acuity measure might not be sensitive enough to capture such macular damage.

Next, we also examined the correspondence between our letter-recognition contrast threshold and foveal Pelli-Robson contrast sensitivity; both methods are designed to assess the contrast required for pattern recognition. As expected, there was a strong correlation between the two measures even after controlling for pupil diameter and visual acuity ($r = -0.68$, $P < 0.001$) (Fig. 4).

DISCUSSION

Primary open-angle glaucoma affects more than 2 million people in the United States.[2] Progressive loss of RGCs and the resulting visual field defects are the major characteristics of glaucoma. Because glaucoma is thought to spare central vision until quite late in the disease progression, it has been long believed that during earlier stages of the disease, glaucoma has little impact on daily central vision tasks, such as reading or object recognition.[3] This view was based on the use of the relatively insensitive Snellen acuity chart to measure central vision and relatively more sensitive perimetry (i.e., visual field test) to measure peripheral vision.[4] Recently, this view has been challenged by converging evidence from both behavioral[19–23] and anatomical/imaging[10,11,13,14] studies that demonstrate that early glaucomatous injury involves the macula.[4,6,7,21] Accumulating evidence also shows that even during the early stage of the disease, persons with glaucoma have a reduced quality of life.[16,28–32] Consistent with patients' subjective self-reports on difficulties in performing everyday activities, recent studies have shown poor objective performance in central vision tasks such as reading[22,23,26] and face recognition.[27]

Consistent with recent findings, the current study showed that, even after controlling for pupil diameter and visual acuity, a higher contrast is required for glaucoma patients to reliably recognize letters in the central 12° visual field, including the fovea. As reliable recognition of individual letters is necessary for successful reading,[54] this increased contrast requirement for letter recognition likely plays a limiting role in reading. In fact, a recent study[5] reported that the decrease in reading rate became much more pronounced as the contrast of text was reduced for glaucoma patients as compared to normal cohorts, suggesting a greater dependence on text contrast for reading. While most visual information necessary for reading is obtained through the central region, parafoveal or peripheral vision is important for efficient reading behaviors, such as optimal saccade planning.[55,56] Thus, it is important to evaluate contrast requirements for letter recognition in the central visual field beyond the foveal region.

Consistent with the functional results, we also observed that glaucomatous eyes exhibit a noticeable shrinkage of macular retinal thickness. We observed a decrease by nearly 20% in the macular RGC+ layer thickness in glaucomatous eyes compared to age-similar healthy eyes. Considering that the majority of our glaucoma patients fall into mild- or moderate-stage glaucoma, the results from our OCT measurements further support the view that the macula is significantly affected, even in relatively early stages of glaucoma.[10,11,13,14]

However, it should be also noted that there were significant variations in both functional and structural data of glaucoma patients. For instance, the standard deviation of letter-recognition contrast thresholds for glaucoma patients was ±0.294 compared to ±0.032 for normal older adults. Similarly, the standard deviation of macular RGC+ layer thicknesses was ±8.50 μm for glaucoma patients and ±5.18 μm for normal older adults. Although speculative, the large variability may be in part due to the various stages of disease progression (from mild to advanced stages). Also, the large variability might have to do with the fact that glaucoma severity was determined by the visual field test (24-2 HFA perimetry), which may not reflect the aspects of visual function required for central letter-recognition tasks. Perimetry (24-2) measured with a light detection task is known to be more sensitive to peripheral visual deficits while underestimating deficits in the central visual field.[4] Therefore, even with the same mean deviation (i.e., a global measure of glaucoma severity), some patients may exhibit more central vision deficits than others, which could lead to considerable individual variability in central vision tasks like ours.

In addition to the effects of glaucoma, we examined the effects of aging upon central pattern vision and macular RGC+ layer thickness in normally sighted individuals. Consistent with the previous findings[57–60] showing age-related decline in spatial contrast sensitivity, we observed a significant increase in letter-recognition contrast threshold for older adults compared to young adults. In parallel with these functional results, we also found a significantly thinner RGC+ layer in older adults compared to young adults. In fact, age-related decrease in retinal (or retinal nerve fiber layer [RNFL]) thickness has been reported in previous studies.[61,62] For example, Alamouti and Funk[61] measured the retinal and RNFL thicknesses in 100 healthy eyes using OCT scans (the age of their participants ranged from 6 to 79 years). They found that both the retinal thickness and the nerve fiber layer thickness were significantly correlated with age: The retinal thickness decreased by 0.53 μm per year and the RNFL thickness decreased by 0.44 μm per year. However, what makes our current study different from these previous studies is that our thickness measurements were made in the macular region whereas others were around the optic nerve head.

The age-related decrease in the retinal layer thickness has been attributed to age-related losses of RGCs.[63–65] The thinning of macular RGC+ layer thickness is likely to reflect age-related losses or shrinkage of RGCs and axons as suggested in histological studies.[66,67] For example, according to a study by Curcio and Drucker,[66] the density of RGCs subserving the central 11° of vision was reduced by 25% in healthy older adults compared to younger adults; Gao and Hollyfield[67] also reported a considerable age-dependent reduction of the ganglion cell layer neurons in the human retina. Taken together, aging appears to produce approximately 15% to 25% loss of RGCs near the fovea.[68] Furthermore, according to a

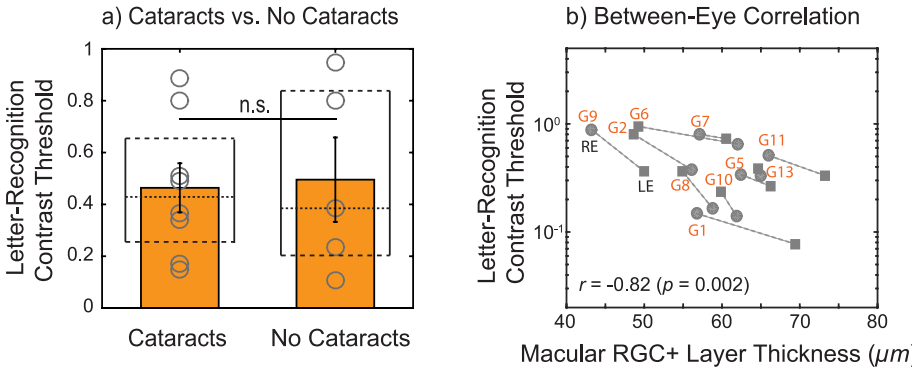

Figure 5. Effect of cataracts on functional data. (**A**) Mean letter-recognition contrast threshold for the glaucoma patients. The *orange bar* on the left represents the mean letter-recognition contrast threshold for glaucoma patients with cataracts, whereas the *orange bar* on the right represents the mean threshold of those without cataracts. *Gray open circles* represent an individual subject's data point. The *dashed lines* indicate the IQR, and the *dotted lines* indicate median values. *Error bars:* ±1 SEM. n.s., no significant difference. (**B**) Between-eye (within-subject) correlation between macular RGC+ layer thickness and letter-recognition contrast threshold was computed using the within-subject correlation measure.[52,76] Only the 10 glaucoma patients who had letter-recognition contrast threshold data from both eyes were included in this analysis. Each *dot* represents measurements from a single eye. *Circles* represent a data point from the right eye whereas *squares* are from the left eye. Measurements between two eyes of a patient are connected by a *gray dashed line*.

recent magnetic resonance imaging study, the volume of the human lateral geniculate nucleus (LGN) that receives information directly from the ascending RGCs via the optic tract was found to decrease by approximately 15% between age 20 and 70, suggesting age-related changes in the human LGN.[69] On the other hand, previous neurophysiological studies of nonhuman primates and cats noted little structural or functional changes in the LGN with aging.[70–72]

Finally, we observed that macular RGC+ layer thickness was significantly correlated with the contrast threshold for letter recognition measured in the central 12° visual field, even after correcting for pupil diameter and visual acuity ($r = -0.65$, $P < 0.001$). Our regression analysis further revealed that deficits in high-level visual function such as letter recognition can be accounted for by structural changes at the level of the RGC layer (more than 40%). We also found a marginally significant structure–function relationship in glaucoma patients, further highlighting the critical role of the functional or structural integrity of RGCs in central pattern vision ($r = -0.53$, $P = 0.060$).

We, however, acknowledge some limitations with our study. First, although we controlled for pupil diameter and visual acuity, we cannot fully rule out the possibility that the optical factors, such as lens opacity, contributed to the higher contrast requirements observed in glaucoma patients and older adults. Cataracts are associated with both aged and glaucomatous eyes.[73–75] As can be seen in the Table, some glaucoma patients exhibited mild cataracts (NSC 1+ or 2+). Unfortunately, lack of lens status information for our normally sighted participants precluded using cataracts as a covariate in our statistical analysis. However, we performed two additional analyses that may help rule out the effect of cataracts. First, as shown in Figure 5A, mean letter-recognition contrast thresholds were compared between glaucoma patients with and without cataracts. We did not find any significant difference between the two groups ($t_{(11)} = 0.18$, $P = 0.860$), suggesting minimal or no effects of cataracts on our functional results. Second, because cataract severity was the same between the two eyes of a single subject (see Table), if a relationship between contrast threshold and RGC+ layer thickness exists between two eyes of a subject, we can conclude that the presence of cataracts is not likely to be a major contributor to our functional data. To test this idea, we computed a between-eye (within-subject) correlation coefficient[52,76] for 10 glaucoma patients who had functional data from both eyes. Figure 5B shows a within-subject correlation between macular RGC+ layer thickness and letter-recognition contrast threshold. Each circle (the right eye, RE) and square (the left eye, LE) represents measurements from a single patient. Measurements between two eyes of a patient are connected by a gray dashed line. We found a significant within-subject correlation between macular RGC+ layer thickness and letter-recognition contrast threshold ($r = -0.82$, $P = 0.002$). Despite considerable between-subject variability, for each individual, as the RGC+ layer thickness decreased in one eye, the letter-recognition contrast threshold of that eye increased accordingly. As there was no difference in cataract severity between two eyes of a single patient, cataracts are not likely to explain our functional results.

Second, dry eye may also explain the observed higher contrast requirements in our glaucoma patients; some medications for glaucoma are known to cause dry eye[77–79] that could reduce contrast sensitivity.[80,81] However, using medical records, we confirmed that only two of our glaucoma patients had dry eye. When these patients' data were excluded from the statistical analyses, we still found that the same pattern of results held. Besides, cataracts or dry eye cannot explain the observed differences in retinal layer thickness among our subject groups and the covarying nature of the macular RGC+ layer thickness and letter-recognition contrast threshold ($r = -0.65$, $P < 0.001$). Taken together, we believe that neither cataracts nor dry eye could explain our functional data and the significant structure–function relationship observed in the current study. This, however, is not to dismiss the potential role of optical characteristics or higher-level cortical mechanisms associated with either glaucoma or normal aging for contrast requirements for pattern recognition in general (see Refs. 39, 68, and 82 for reviews).

Finally, for a better characterization of the age-related structure–function relationship, a wider range of age groups, including individuals aged 70 or older, should be considered in a future study.

To summarize, the results reported in the current study demonstrate that the glaucomatous eye and the aged eye are associated with decreased macular RGC+ layer thicknesses. This decreased macular RGC+ layer thickness appears to be responsible for a higher contrast requirement for pattern recognition in the central visual field. Our findings further

suggest that a progressive reduction of the RGC layer thickness due to either glaucoma or normal aging may undermine central pattern vision.

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