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 11.18 million people worldwide by 2040. 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 suggests that the macula is significantly compromised even in early stages of glaucoma (see Ref. 17 for review). For instance, studies 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.6 In parallel with physiological evidence, behavioral studies 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 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.35 For example, Rubin and Legge\(^{36}\) 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.5,39,40 Furthermore, this loss of contrast sensitivity may occur despite normal visual acuity.57,41 Previous studies5,46 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 12º 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;45 (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 0.43º were presented for 200 ms at one of 54 test locations in a grid on a white background (10 cd/m²).

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,44 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 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-
### Characteristics for Study Participants

<table>
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<tr>
<th>Subject ID</th>
<th>Diagnosis</th>
<th>Age, years</th>
<th>Sex</th>
<th>Visual Acuity, logMAR</th>
<th>Contrast Sensitivity, log units</th>
<th>Pupil Diameter, mm</th>
<th>Lens Status</th>
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**Mean (±SD)** POAG & PPG 65.6 (±6.6) F:M=7.6 0.05 (±0.10) 1.50 (±0.23) 4.5 (±1.3) N/A

**Normal Old (n = 14)** 59.1 (±9.1) F:M=5.9 -0.03 (±0.09) 1.81 (±0.12) 4.9 (±1.4) N/A

**Normal Young (n = 13)** 21.0 (±2.0) F:M=9.4 0.03 (±0.08) 1.83 (±0.12) 5.3 (±1.2) N/A

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.
tested eye. During testing, the nontested eye was covered with
physics Toolbox extensions45,46 for Windows 7, running on a
letter stimuli was expressed as Weber contrast.
plexiform layer was generated in a similar manner. The RGC
ground with a luminance of 159 cd
randomly selected and presented on a uniform gray back-
Hz and resolution of 1920
International, Fremont, CA, USA) with a refresh rate of 144

Round Rock, TX, USA). Stimuli were presented on a liquid
8
8
3

Luminance of the display monitor was made linear using an 8-

height of each letter was 0.8

8
8
8
8
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stimuli were generated and controlled using MATLAB
version 8.3; MathWorks, Inc., Natick, MA, USA) and Psycho-
Factor.44 A single black letter, with adjustable contrast, was
randomly selected and presented on a uniform gray back-
ground with a luminance of 159 cd/m². 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 Psycho-

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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. 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 identifi-
cation 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 1](http://arvojournals.org/)
The relationship between the letter-recognition contrast threshold and macular RGC+ layer thickness is an important aspect of understanding the effects of glaucoma. In our study, we aimed to investigate these relationships and their implications for pattern vision.

**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 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 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 was 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 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) 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) 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 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 was 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 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) in combination with MATLAB (R2014b; MathWorks, Inc.).

**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 237.7%, \( F_{(1,23)} = 18.42, P < 0.001 \)), 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.
Contrast Requirement for Letter Recognition in Glaucoma

In this section, we report the effects of aging on contrast sensitivity and thinner macular RGC layer thickness in older 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%, $F_{(1,23)} = 53.56, P < 0.001$) 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 66.5%, $F_{(1,23)} = 34.66, P < 0.001$), at $3^\circ$ (by 65.7%, $F_{(1,23)} = 25.29, P < 0.001$), and at $6^\circ$ (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 for glaucoma patients compared to age-similar normal controls (by 20.1%, $F_{(3,13)} = 4.88, P = 0.013$), at $3^\circ$ ($r = -0.27, P = 0.089$) versus macular RGC+ layer thickness after regressing out the effects of PD and VA.

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% ($F_{(3,13)} = 11.25, r^2 = 0.48, P < 0.001$) 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, $\hat{c}(a,b)$ represents the residuals from the regression of the $c$ variable on the $a$ and $b$ variables. 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 $(n = 15)$, 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 3**. Partial correlations between functional and structural data after controlling for pupil diameter and visual acuity. In the partial correlation plot, $\hat{c}(a,b)$ 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 $(n = 15)$, 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.
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. 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. This view was based on the use of the relatively insensitive Snellen acuity chart to measure central vision with a light detection task known to be more sensitive to peripheral visual deficits while underestimating deficits in the central visual field. 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 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 nerve fiber layer (RNFL) thickness has been reported in previous studies. For example, Alamouti and Funk 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 $0.53\, \mu m$ 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. 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. For example, according to a study by Curcio and Drucker, 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 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. Furthermore, according to a
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.73-75 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 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.

Figure 5A, mean letter-recognition contrast thresholds were calculated for glaucoma patients with and 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

Second, dry eye may also explain the observed higher contrast requirements in our glaucoma patients; some medications for glaucoma are known to cause dry eye77-79 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 = -0.82, P = 0.002). Despite considerable between-subject variability, for each individual, 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 unlikely to explain our functional results.

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 increased macular RGC+ layer thickness. This increased 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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