Does Glaucoma Alter Eye Movements When Viewing Images of Natural Scenes? A Between-Eye Study

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Purpose. To investigate whether glaucoma produces measurable changes in eye movements.

Methods. Fifteen glaucoma patients with asymmetric vision loss (difference in mean deviation [MD] $>$ 6 dB between eyes) were asked to monocularly view 120 images of natural scenes, presented sequentially on a computer monitor. Each image was viewed twice—once each with the better and worse eye. Patients' eye movements were recorded with an Eyelink 1000 eye-tracker. Eye-movement parameters were computed and compared within participants (better eye versus worse eye). These parameters included a novel measure: saccadic reversal rate (SRR), as well as more traditional metrics such as saccade amplitude, fixation counts, fixation duration, and spread of fixation locations (bivariate contour ellipse area [BCEA]). In addition, the associations of these parameters with clinical measures of vision were investigated.

Results. In the worse eye, saccade amplitude($P = 0.012; -13\%$) and BCEA ($P = 0.005; -16\%$) were smaller, while SRR was greater ($P = 0.018; +16\%$). There was a significant correlation between the intereye difference in BCEA, and differences in MD values (Spearman's $r = 0.65; P = 0.01$), while differences in SRR were associated with differences in visual acuity (Spearman's $r = 0.64; P = 0.01$). Furthermore, between-eye differences in BCEA were a significant predictor of between-eye differences in MD: for every 1-dB difference in MD, BCEA reduced by 6.2% (95% confidence interval, 1.6%–10.3%).

Conclusions. Eye movements are altered by visual field loss, and these changes are related to changes in clinical measures. Eye movements recorded while passively viewing images could potentially be used as biomarkers for visual field damage.

Keywords: glaucoma, eye tracking, automated perimetry, eye movements, visual field

Visual field (VF) assessments are critical for the detection and management of glaucoma. Current methods of VF assessment (automated perimetry) are demanding for patients to perform, and are often problematic to organize and interpret in busy clinics.[1,2] Alternative measures of the visual function in glaucoma are therefore needed, potentially suitable for use at home or in community settings.

One possibility may be to measure a person's natural eye movements. Glaucoma patients have been shown to have altered eye movements as compared to peers with normal vision when performing everyday tasks, such as reading,[3–5] visual search,[6] face recognition,[7] watching video,[8] driving,[9–12] and viewing images[13] (for a review, see Kasneci et al.[14]). Furthermore, it has been recently reported that people with early-stage glaucoma, with no detectable visual field loss, exhibit altered eye-movement behavior.[15] More recently there have even been reports of a possible link between optic nerve head strain induced by eye movements and axonal loss in glaucoma.[16]

However, existing studies disagree about precisely how eye movements are altered by glaucomatous field loss. For instance, Crabb et al.[17] have found that glaucoma patients make more saccades, fixations, and smooth pursuit eye movements per second than controls when watching a movie depicting real-world driving. In contrast, Wiecek et al.[18] have reported that peripheral VF loss does not influence saccade amplitude (SA), fixation duration, and number of saccades during visual search tasks. Instead, they observed a significant difference in the direction of saccades between patients and controls. Other studies have variously reported difference in saccade rate but not amplitude,[6] number of saccades and spread of fixations but not saccade amplitude,[13] and saccade amplitude but not fixation rate or duration.[19] Some of these ambiguous results may be due to differences in task. However, previous studies also suffer from two limitations, both of which we address in the present study.

First, previous studies have exhibited imperfect matching between cases and controls. Most previous studies have compared eye movements between independent groups of glaucoma patients and age-similar controls. Individual differences in factors such as cognitive skills, visual acuity (VA), sex, culture, and health status are therefore confounding factors that could have affected eye movements between participants.[5,20] Accordingly, in this study we investigated people with asymmetrical visual field loss between eyes. The better (less affected) eye was used as the control for the worse eye. Comparing performance within a patient (i.e., between eyes), instead of comparing across patients and controls, allowed us to control individual differences, resulting in a purer measure of how VF loss affects eye movements.

Second, many previous studies have used only a small subset of relatively simple metrics to describe patients' eye move-

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Table 1. Patient Information and Demographics. Patient ID Colors Correspond to Marker Colors Used Subsequently in Figures 1 and 6

Patient ID	Age, y	Sex	VA, Log		CS, Log		24–2 MD, dB	
			Right	Left	Right	Left	Right	Left
A	70	F	0.10	0.16	1.65	1.35	−14.2	−4.1
B	44	M	−0.08	0.10	1.45	1.80	−31.1	−14.6
C	59	M	−0.04	−0.04	1.90	1.95	1.9	−7.0
D	80	F	0.14	0.14	1.55	1.65	−7.7	−3.0
E	64	M	0.18	−0.06	1.95	1.95	−9.8	−1.2
F	83	M	0.14	0.14	1.45	1.50	−20.7	−4.9
G	65	F	−0.02	0.06	1.95	1.95	−19.5	−6.0
H	56	M	−1.00	−1.50	1.95	1.95	−19.9	−4.8
I	66	M	0.20	0.04	1.95	1.95	−1.2	−7.8
J	74	F	0.18	0.14	1.95	1.95	−9.8	−3.0
K	60	F	0.02	0.06	1.95	1.95	−5.7	−17.9
L	66	M	−0.08	0.16	1.30	1.95	−15.9	−5.9
M	66	M	0.04	0.10	1.65	1.65	−3.3	−12.1
N	84	M	0.16	0.36	1.65	1.35	−0.9	−19.1
O	83	F	0.12	0.08	1.75	1.65	−22.4	−8.4

ments (e.g., saccade count, fixation count, saccade rate, and fixation duration). These metrics do not capture the spatial or temporal characteristics of the scanpath, and so may be relatively insensitive to the effects of VF loss. Accordingly, in the present work we also quantified the spread of fixations[17] to examine spatial characteristics of eye movements. And we used intersaccadic angle[21] (difference in direction between successive saccades) to examine temporal characteristics of saccadic movements.

In short, the current study examined how eye movements are affected by VF loss due to glaucoma. The goal was to understand whether, and in what way, our eye movements adapt to visual field loss: differences which, in the longer term, might lead to a novel paradigm for identifying such loss. Analyses were performed within-subject, using patients with asymmetric VF, in order to isolate the specific impact of VF loss on behavior, and novel metrics were used to characterize each eye's spatiotemporal profile. Furthermore, we investigated the relationships between eye-movement metrics and common clinical measures (e.g., visual acuity, contrast sensitivity). Given previous reports, our main hypothesis was that patients' eye movements would be altered in their worse eye compared to their better eye. However, given the lack of agreement between previous studies (see above), we were unable to predict which eye-movement metrics would differ between eyes, or the direction of these differences.

Methods

Participants

Fifteen patients with a clinical diagnosis of primary open-angle glaucoma, and no other ocular diseases, were recruited from a database of volunteers (see Table 1 for patient details). All participants had a distinct asymmetry in their visual field loss, as defined by (1) a between-eyes difference in mean deviation (MD) of at least 6 dB or more, and/or (2) a between-eyes difference in glaucoma severity of at least one stage, as measured by the Glaucoma Staging System 2[22] (GSS2). All but one of the patients satisfied both criteria, as detailed in Clinical Testing. The between-eye difference in MD for this patient (Table 1, patient D) was 4.7 dB. However, when staged using the GSS2 grading, one eye was scored at stage 2 and the fellow eye at stage 4, and so was still included in the study.

The study was approved by the Ethics Committee for the School of Health Sciences, City, University of London. The research was carried out in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants.

Clinical Testing

Visual Fields. Static threshold perimetry (24-2) was performed monocularly in each eye, using a Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA, USA) running

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the SITA-Standard algorithm. MD values for each eye/test are given in Table 1 and were used to determine the "worse eye" and "better eye." HFA grayscales for the 24-2 VF test are shown for each individual in Figure 1.

Visual Acuity. Recognition acuity was measured monocularly by using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. As shown in Table 1, all participants (except left eye of patient *N*) exhibited a VA of 0.18 logMAR or better (Snellen equivalent of 6/9).

Contrast Sensitivity (CS). CS was measured monocularly by using Pelli-Robson charts.

Apparatus

The test apparatus is shown in Figure 2A. Stimuli were presented on a 56-cm CRT computer monitor (Iiyama Vision Master Pro 514; Iiyama Corporation, Tokyo, Japan) running at 100 Hz with a resolution of 1600 by 1200 pixels. Given the viewing distance of 60 cm, the visual angle of the screen was $\pm 17.0°$ by $\pm 13.4°$ (i.e., when fixating centrally). Participants' head position was stabilized by using a chin rest, and participants wore the same set of trial frames to ensure that any restriction to the field of view due to spectacle frames was equivalent for each person. Eye-movement positions were recorded by using the Eyelink 1000 remote eye tracker (SR Research Ltd., Ottawa, ON, Canada), which records at 1000 Hz with a spatial precision of $\leq 0.5°$. Before the study commenced, a nine-point calibration grid—the default calibration method of the device—was performed and repeated until the result was rated "good" by the instrument. Between each trial, a drift check was also performed and a recalibration was carried out if substantial drift was detected. Although no keypresses were required during the test trials, participants used a keyboard between trials to indicate when they were ready to continue (see Procedure).

Stimuli

The stimuli consisted of 39 color images and 81 grayscale images (see Supplementary Fig. S1 for the complete set of images). The images were taken from a nature documentary (Planet Earth; BBC Television, London, UK) and depicted outdoor natural scenes, featuring animals, flowers, and underwater images. Images were displayed full screen (1600 by 1200 pixels).

Procedure

Before each trial, participants were asked to fixate on a central cue (Fig. 2B) and to press the spacebar when ready to continue. The keypress allowed participants to take breaks in between trials, and they were encouraged to do so as required.

On each trial, the participant was shown 1 of 120 images for a mean duration of 4 seconds (SD, 0.6 second; range, 3–5 seconds). A small amount of random jitter was added to the duration of each image, to encourage participants to remain engaged/attentive throughout the study (it was observed during piloting that a minority of participants, when presented with a precisely regular sequence of images, eventually stopped looking at the screen, and learnt to simply press the spacebar every *N* seconds). During the trial, participants were not required to make an explicit, button-press response, but were instead asked simply to freely view the images as a slideshow.

A complete test run consisted of 120 images, presented sequentially in random order (Fig. 2C). Participants completed two test runs in a single session: once for each eye. The starting eye was randomized among participants. The entire session on average lasted approximately 25 minutes, including breaks.

Eye-Movement Analysis

Identifying Saccades. An example scanpath for a single trial/participant is shown in Figure 3A. Raw gaze samples were recorded at 1000 Hz and were classified as saccadic if both (1) velocity $> 30°/s$; and (2) acceleration $> 8000°/s^2$. Following previous similar studies,[13] small saccades of amplitude $< 0.5°$ were discarded post hoc. This resulted in the exclusion of 5.8% of saccades for the worse eye and 6.0% for the better eye. Eye-movement data were analyzed with a bespoke software program written in MATLAB R2017a (MathWorks, Inc., Natick, MA, USA).

Saccadic Reversal Rate (SRR). To understand the temporal dynamics of a scanpath, we derived a novel metric that we term "saccadic reversal rate." This was computed as follows. For each successive pair of saccades, the angular difference in direction, θ_{diff}, was computed (see Fig. 3B). For example, when two successive saccades moved in the same direction, θ_{diff} was close to 0°. In contrast, if two saccades moved in opposite direction, θ_{diff} was close to 180°. Across a trial, this resulted in a distribution of θ_{diff} values, as shown in Figure 3C. Of these, we were particularly interested in values of θ_{diff} between 170°–190°, which we here term "saccadic 'reversals.'" In healthy eyes, such reversals are relatively common (5%) and are thought to represent a strategy of revisiting positions "where some information may have been lost or overlooked."[21] We therefore hypothesized that such movements would be particularly elevated when vision was impaired.

To quantify SRR formally, we first measured the proportion of θ_{diff} values falling within a 20° bin centered on 180° (Fig. 3C, red shaded bin). The choice of bin size was arbitrary. However, changing the bin width to 30° or 60° did not affect the overall pattern of results. The angle between saccades (θ_{diff}) was computed as:

$$\theta_{diff} = \arctan\left(s_{i,y}/s_{i,x}\right) - \arctan\left(s_{i-1,y}/s_{i-1,x}\right), \quad (1)$$

where $s_{i,y}$ and $s_{i,x}$ are the y and x components of the i^{th} saccade, and where s_{i-1} is the preceding saccade. Then, SRR was computed as:

$$\text{SRR} = \frac{\text{Proportion of saccadic reversals}}{\text{Total number of } \theta_{diff}}. \quad (2)$$

SRR was computed at the end of each run (i.e., the rightmost panel in Fig. 4). This analysis produced one SRR value for each eye, for each participant.

Bivariate Contour Ellipse Area (BCEA). The spread of fixation locations was computed as the BCEA. The BCEA provides a summary measure of the spread of a participant's gaze over the visual field (in degrees visual angle, squared). Previous studies have used BCEA to study fixation stability in patients with macular degeneration[23,24] and to analyze eye movement of bilateral glaucomatous participants when viewing driving scenes in a hazard perception test[17] and when viewing everyday scenes.[13] Note that in the present study—unlike in perimetry—participants were not instructed to fixate a particular location. BCEA should therefore be interpreted simply as a measure of spread, not accuracy, and a bigger value should not necessarily be considered "worse."

To compute BCEA, fixation positions were first transformed into a location in a new plane (Fig. 5; first column, $N = 1$). This was done by aligning fixation positions based on their relative position to the preceding fixation. This transformation

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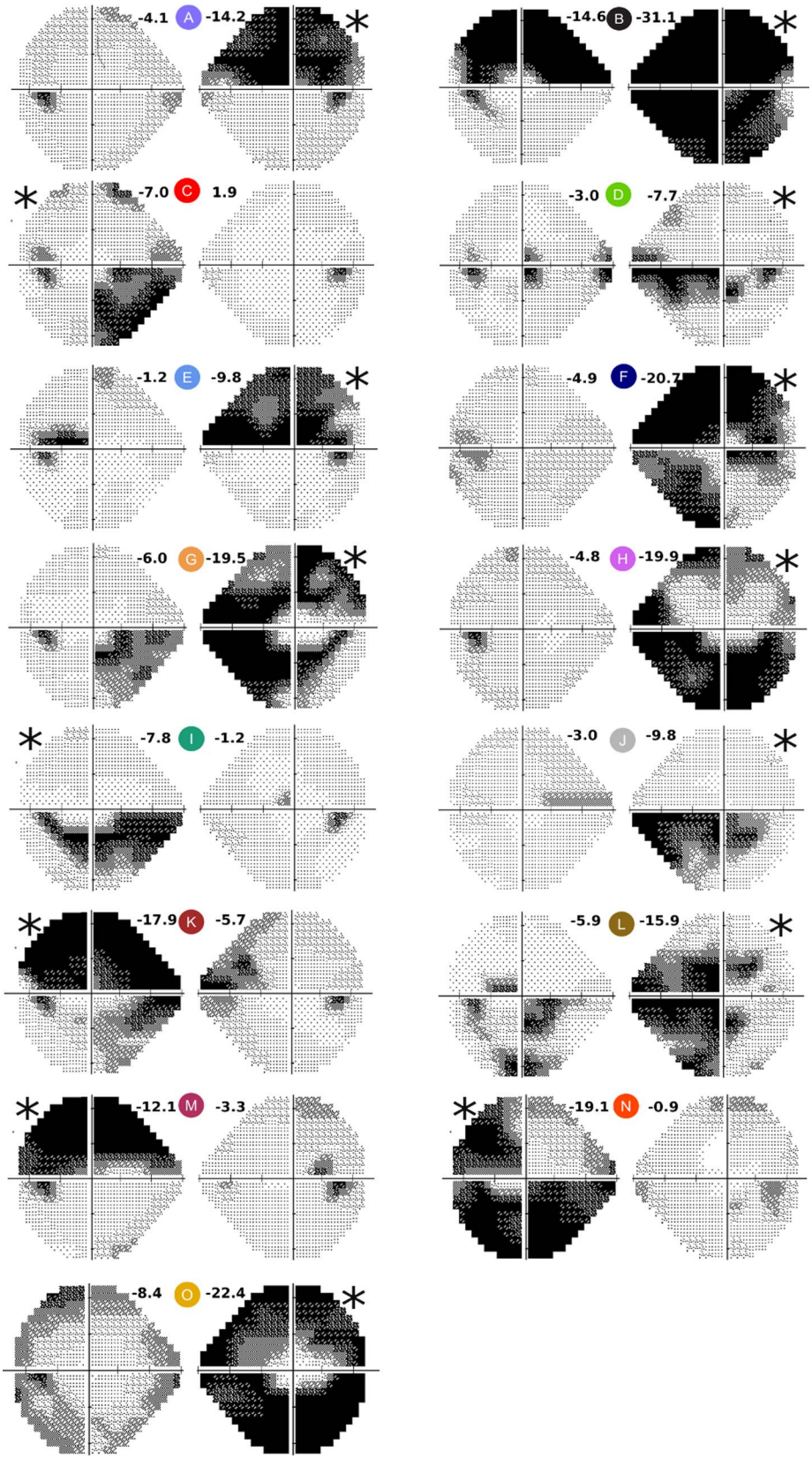


Figure 1. HFA Grayscales of monocular visual fields for all 15 participants measured by using the 24-2 algorithm (SITA). HFA MD values (dB) are given for each image and were used to classify the eye as better or worse. The worse eye in each image is indicated by an *asterisk*.

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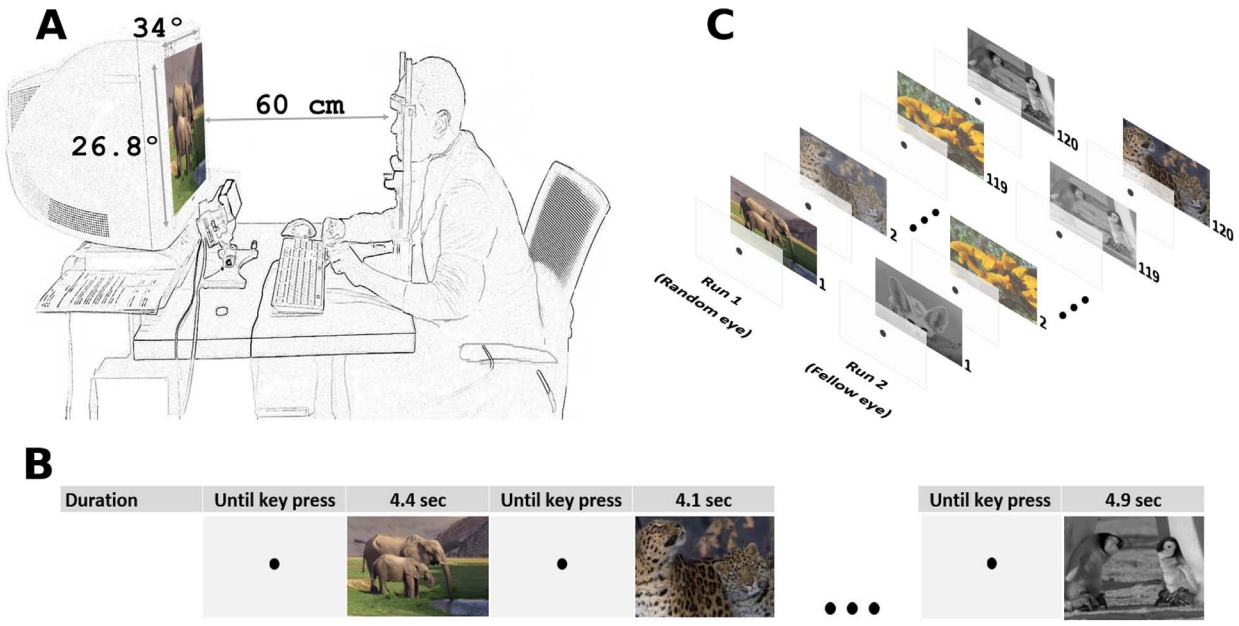


FIGURE 2. Stimuli, apparatus, and procedures. (**A**) Participants were seated 60 cm from the screen (distance constrained by using the chin/head rest), and viewed the stimuli monocularly. An eye tracker was mounted below the monitor and recorded eye movements during test trials. Participants used a computer keyboard to initiate each trial. (**B**) The stimuli were displayed for a random duration between 3 and 5 seconds. Before each trial a black central fixation point, on a white background, was presented. (**C**) During each run a patient watched 120 images monocularly, and each patient completed two runs (one per eye).

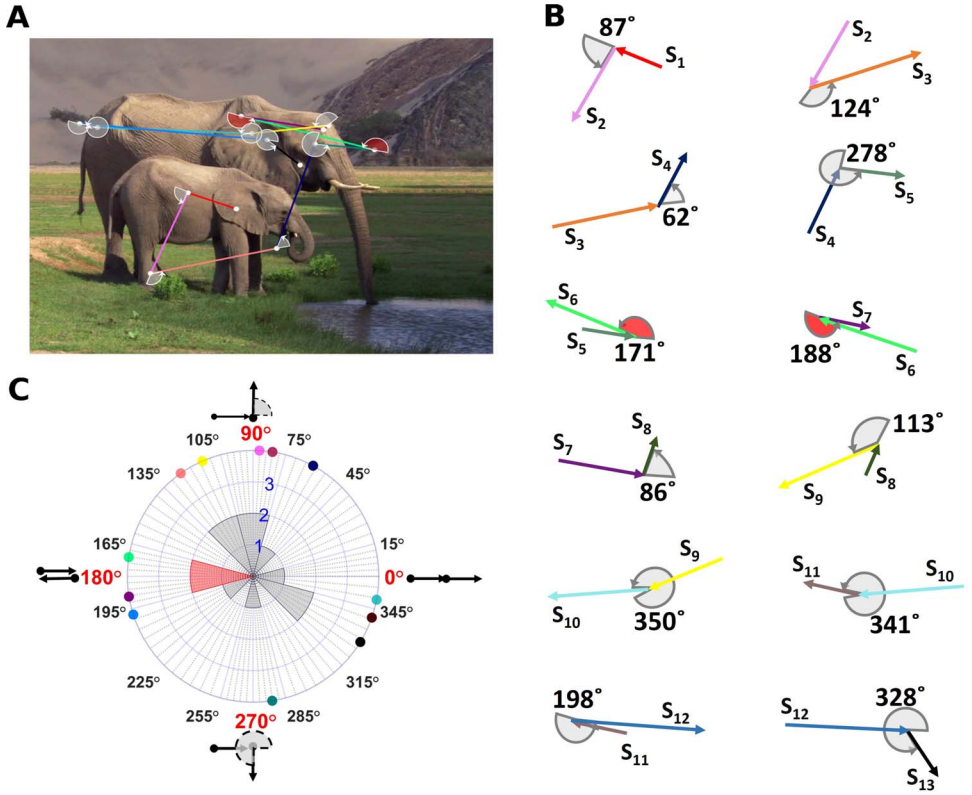


FIGURE 3. Computation of the novel eye-movement metric: SRR. (**A**) Example eye-movement data from a single trial. *White dots* represent fixations, and *vectors* represent saccades. The arcs represent θ_{diff}, the angular difference between successive pairs of saccades. (**B**) Illustration of how θ_{diff} values were computed (measured anticlockwise relative to the horizontal). (**C**) Polar histogram of θ_{diff} values (same data as [**A**] and [**B**]). For example, on two occasions θ_{diff} fell within 165°–195°, while on one occasion the angular difference was very small (close to zero). The saccadic reversals are highlighted in *red*. *Colored dots* around the periphery of the histogram show each of the individual θ_{diff} values computed in (**B**). Note that for illustration purposes, the bins shown here are 30° wide, and include data from a single trial only. However, in the final analysis bins of 20° were used, and data were concatenated across all 120 trials.

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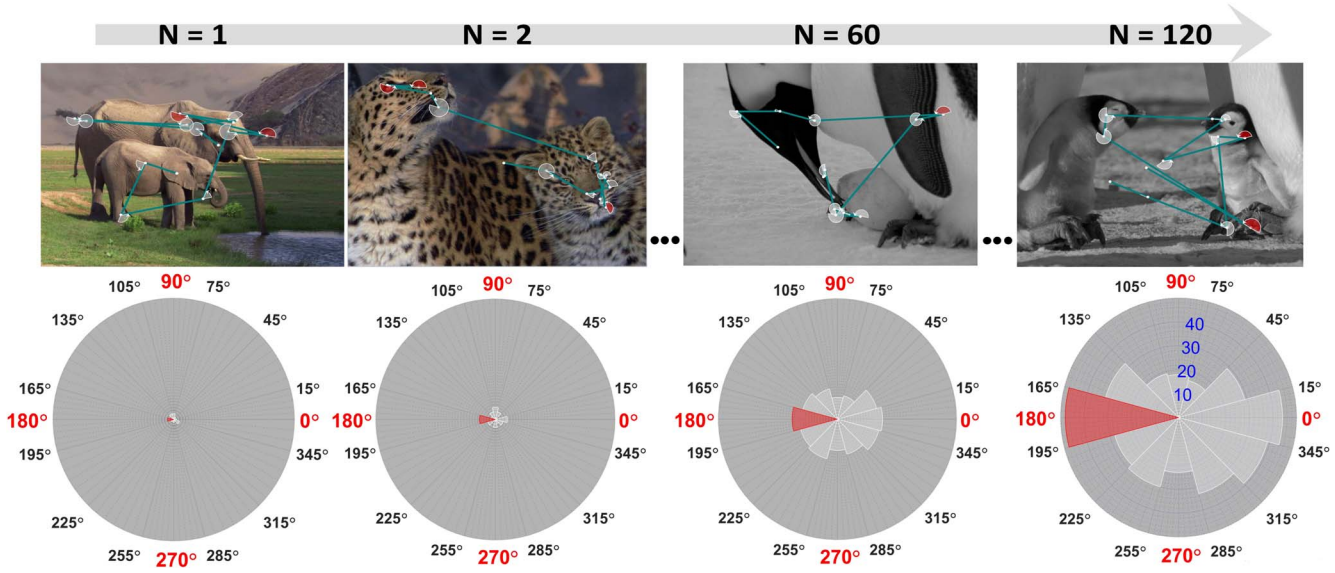


FIGURE 4. SRR analysis (left eye of patient ID *K*). The *upper row* illustrates the raw scanpaths for individual trials (fixations and saccades represented as *points* and *vectors*, respectively). The *bottom row* shows the corresponding cumulative count of θ_{diff} values from trials 1 (*leftmost*) to 120 (*rightmost*). SRR was computed at the end of a run and was defined as the proportion of θ_{diff} values that fell in the red bin to the total count of θ_{diff}. Shown here: SRR = 0.13.

maintains the corresponding saccade amplitudes. One BCEA value was computed for each eye at the end of each run (Fig. 5; last column, $N = 120$).

Additional Eye-Movement Metrics. In addition to SRR and BCEA, we also computed other common metrics, widely used in previous similar studies.[13] These were (1) number of fixations, (2) fixation duration, (3) SA, (4) saccade velocity (speed of saccade), and (5) total scanpath length. The distributions of the parameters were non-Gaussian; therefore, we considered median values for our statistical analysis. In each case, we computed one value for each eye, for each participant. Note that several of these parameters are likely to covary (e.g., saccade amplitude and total scanpath length), but they are not redundant. For example, two observers could have the same fixation duration, saccade count, and scanpath length, but a different median saccade amplitude.

Statistical Analyses. Each metric (SRR, BCEA, additional eye-movement metrics) provided a single pair of values for each patient (i.e., one value for the better eye and one value for the worse eye). Pairwise statistical analyses were performed to ascertain any significant differences between the better eye and worse eye. Since the distribution of the data was non-Gaussian, we used nonparametric paired analyses (Wilcoxon's test). Multiple regression analysis was used to explore if any of

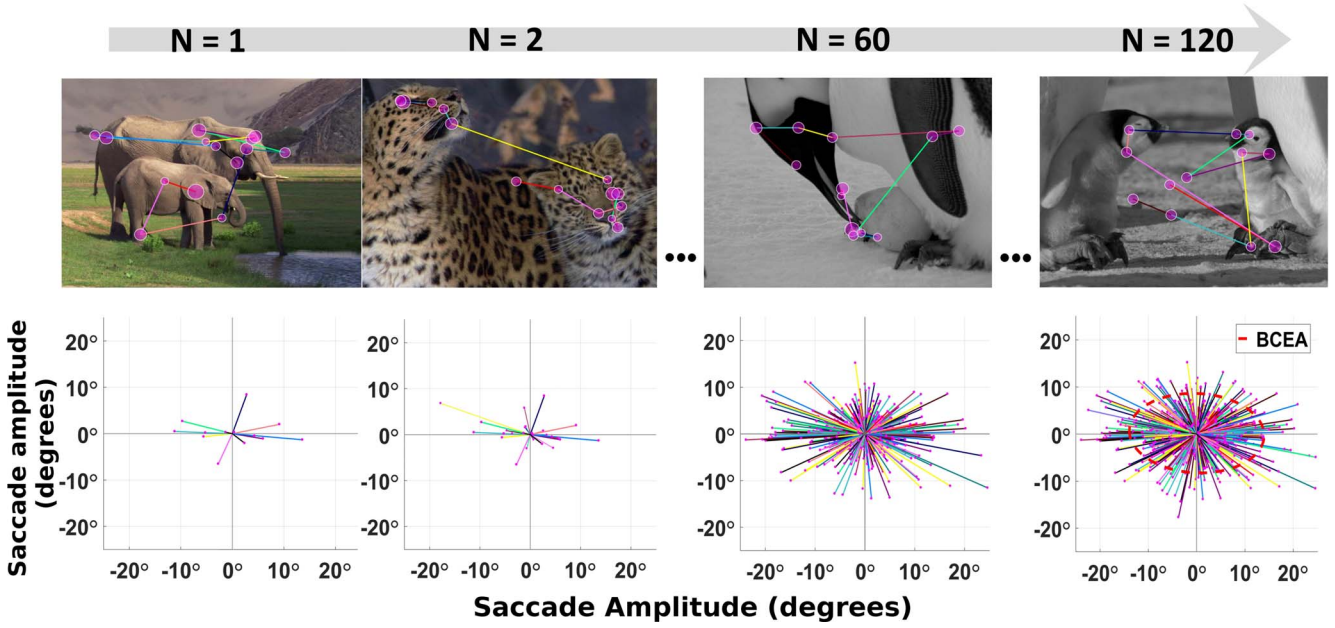


FIGURE 5. BCEA computation across a run (left eye of patient ID *k*). The *upper row* illustrates the raw scanpaths for individual trials (fixations and saccades represented as *points* and *vectors*, respectively). Each saccade is colored uniquely to match the plots at the bottom. The *bottom row* shows the aligned saccades/fixations. BCEA was computed at the end of a run from the best-fitting ellipse (*red dashed line*).

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Table 2. Comparison of the Difference Between Worse and the Better Eyes in Different Eye-Movement Features

	Better Eye, Median (IQR)	Worse Eye, Median (IQR)	Between-Eye Difference, Median (IQR)	Wilcoxon's *P* Value
Fixation duration, msec	235 (228, 259)	244 (228, 268)	−9 (−16, 11)	0.60
Fixation count per trial	12.0 (11.6, 13.8)	12.0 (11.23, 13.0)	0 (−1.4, 1.0)	0.67
Saccade velocity, deg/sec	230.0 (182.0, 258.9)	215.0 (169.8, 254.3)	−13.5 (−27.1, 7.0)	0.18
Scanpath length, deg	60.31 (48.0, 64.8)	55.7 (43.2, 59.3)	−6.4 (−14.9, 4.3)	0.15
SA, deg	3.95 (3.09, 5.42)	3.13 (2.92, 4.66)	0.5 (0.0, 0.9)	**0.013**
SRR	0.09 (0.08, 0.12)	0.10 (0.09, 0.12)	−0.014 (−0.021, −0.003)	**0.018**
BCEA, deg squared	313 (249, 418)	253 (222, 320)	49 (16, 96)	**0.005**

Statistically significant *P* values are highlighted in bold.

the parameters, or combination of parameters, were predictive for the between-eye differences as measured by between-eye difference in MD. All statistical analyses were conducted using R v3.3.3.[25]

Results

Fifteen patients with glaucoma were recruited (60% men), with a median (interquartile range [IQR]) age of 68 (61, 79) years. The median (IQR) HFA MD value was −4.1 (−5.9, −1.7) dB for the better eyes, and −15.9 (−19.8, −9.8) dB for the worse eyes. The median between-eye difference in MD value was −10.1 (−14.8, −8.6) dB, reflecting a pronounced asymmetry in VF loss within this group of patients. Between eyes (better versus worse), there were no significant differences in logMAR VA ($P = 0.814$) or Pelli-Robson CS values ($P = 0.362$). The right eye was the "worse eye" in 10 of the 15 participants.

Table 2 shows median (IQR) values for each of the various eye-movement parameters. There was no statistically significant difference, between eyes, in terms of fixation duration, fixation count, saccade velocity, or scanpath length. However, as shown in Figure 6, better eyes made larger saccades (Wilcoxon signed rank test; $P = 0.012$), exhibited greater BCEA (Wilcoxon signed rank test; $P = 0.005$) and lower SRR (Wilcoxon signed rank test; $P = 0.018$). The median (IQR) between-eye difference (better eye - worse eye) in SA was 0.49° (0.0°–0.9°); the median (IQR) difference in SRR and BCEA was −0.014 (−0.003, −0.023) and 49.0 (16.1–95.8) deg squared. There was no correlation between the intereye difference in BCEA and intereye difference in SA (Spearman's $r = 0.16; P = 0.56$).

To investigate the presence of possible practice effects, we compared eye movements between the eye tested first versus second (i.e., instead of the better versus the worse eye). No significant differences were observed for any of the eye-movement metrics tested (fixation duration, $P = 0.84$; saccade count, $P = 0.52$; saccade velocity, $P = 0.44$; scanpath length, $P = 0.97$; SA, $P = 0.09$; SRR, $P = 0.42$; BCEA, $P = 0.38$). This indicates that there was no substantial order-effect.

Table 3 shows the univariate associations, after corrections for multiple comparison, between each eye-movement parameter and various common clinical measures (MD, CS, and VA; Bonferroni correction for four comparisons). There was some indication of a linear relationship between age and SA but it was not statistically significant after correcting for multiple comparisons (Spearman's correlation; $r = 0.62, P = 0.02$) (Fig. 7A). There was a statistically significant association between the differences in SRR (between the better and the worse eyes) and differences in logMAR VA ($r = 0.64, P = 0.01$) (Fig. 7B). Furthermore, a statistically significant association was observed between differences in BCEA and differences in MD values ($r = 0.65, P = 0.01$) (Fig. 7C). There was no significant association between any other eye-movement parameters and any clinical measures (see Table 2).

Stepwise multiple regression analysis (Backward elimination) showed that between-eye differences in BCEA alone were a statistically significant predictor of between-eye differences in MD values ($F = 7.37, R^2 = 0.36, P = 0.01$): for every 1-dB difference in MD, BCEA decreased by an average of 6.2% (95% confidence interval, 1.6%–10.3%) between eyes. This indicates that as the VF worsens the spatial extent of eye movements reduces.

Discussion

This study assessed the effect of glaucomatous VF damage on eye movements. In patients with between-eye asymmetric VF loss, median SAs were smaller in the worse eye, and the total spread of fixations (BCEA) was reduced. Although both metrics relate to the spread of the data, BCEA separated "better" and "worse" eyes more consistently than SA. This is likely because BCEA is dependent on both the direction and amplitude of the saccades, and provides a more direct measure of the extent to which observers explored the visual scene. In addition, we computed SRR: a novel eye-movement parameter that considers the geometric relationship between temporal sequences of saccades. SRR was significantly greater in the worse eye, indicating that the worse eye exhibited more back-and-forth saccadic movements than the fellow, better eye. There were also significant relationships between eye-movement parameters and clinical measures. Specifically, between-eye differences in BCEA were correlated with MD, while SRR was correlated with VA. In terms of more basic eye-movement metrics, such as saccade count, fixation count, fixation duration, and scanpath length, this study did not find a significant difference between worse and the better eyes.

Comparison With Previous Findings

Our findings of smaller saccades and reduced spread of fixations are consistent with previous reports. Thus, BCEA has been reported to be smaller in glaucoma patients than age-similar healthy controls.[13,26] Similarly, SAs in glaucoma patients have been reported to be smaller than in controls in some,[15,19] though not all (Smith et al.[13]; Wiecek et al.[18]) previous studies. To the best of our knowledge, this is the first study that analyzed the angle between saccades to evaluate eye movements of patients with visual field loss. Taken together, these results provide novel and compelling evidence that eye movements are altered after VF damage.

We did not find statistically significant differences between the worse and better eye in terms of more basic parameters, such as saccade count, fixation count, saccade rate, and fixation duration. In contrast, some (though not all; Prado Vega et al.[11]; Wiecek et al.[18]) previous studies have reported

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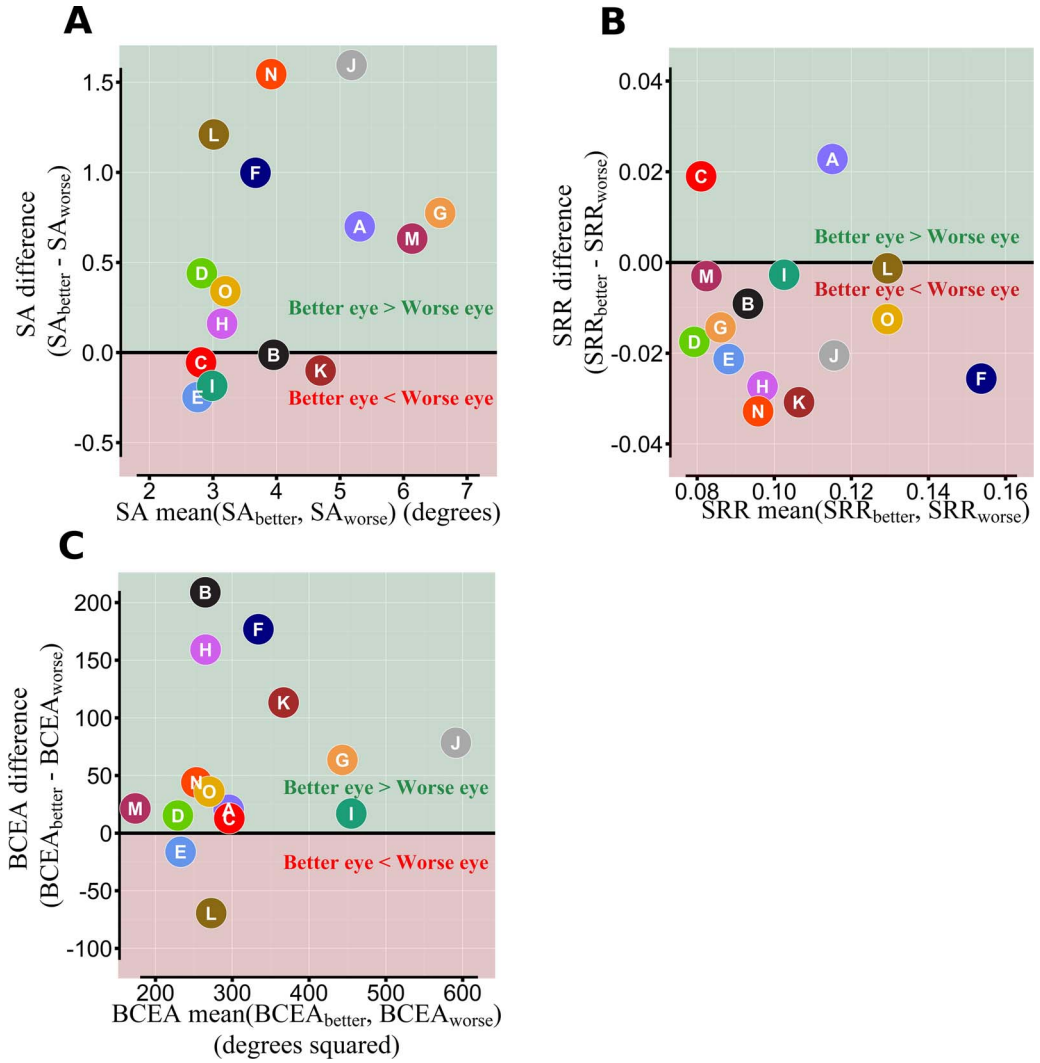


Figure 6. Plots of difference between the better and the worse eye in (**A**) median value of a saccade amplitude, (**B**) saccadic reversal rate, and (**C**) BCEA. The *black solid line* in each plot marks the null hypothesis ("no difference between the eyes").

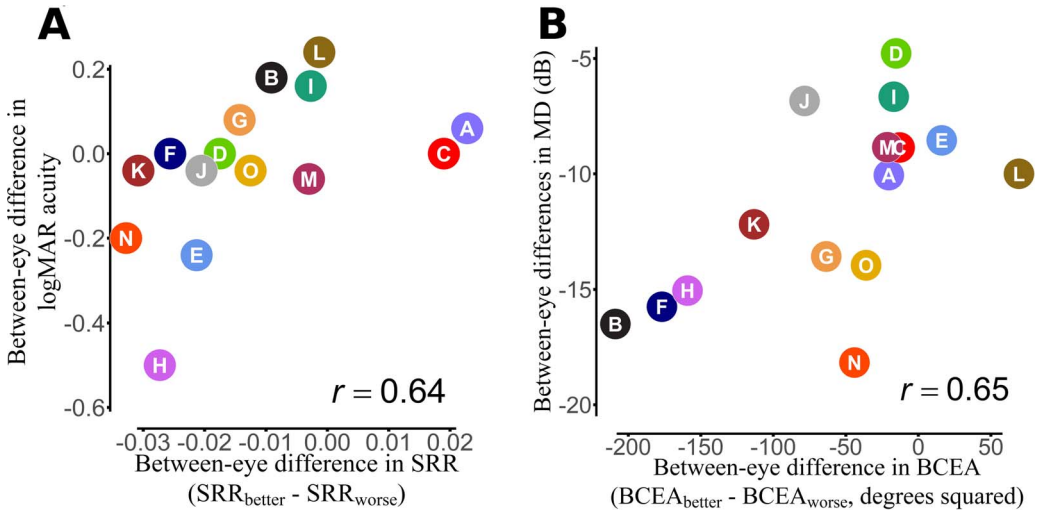


Figure 7. Plot depicting relationships between (**A**) between-eye differences in SRR and VA, $P = 0.01$; and (**B**) between-eye differences in BCEA and 24-2 MD values, $P = 0.01$.

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Table 3. Spearman's *r* Correlations Comparing Between-Eye Differences in SA, BCEA, and SRR With Clinical Measures and Age

	Clinical Measures			
Eye Movement	**MD**	**VA**	**CS**	**Age**
SA				
r	0.23	0.13	0.30	0.62
P value	0.42	0.66	0.28	0.02
SRR				
r	−0.36	**0.64**	−0.30	0.15
P value	0.18	**0.01**	0.28	0.59
BCEA				
r	**0.65**	0.03	−0.08	0.10
P value	**0.01**	0.93	0.78	0.73

Statistically significant associations are highlighted in bold. Following Bonferroni correction for four comparisons, the criterion for significance was $P < 0.013$.

significant differences between glaucoma patients and controls in terms of number of saccades,[13] fixation rate, fixation duration,[17] and saccade rate.[6] One possible reason for this disparity may be due to differences in task. For instance, in the study of Smith et al.,[6] participants were asked to search for targets in photographs. However, in this study, participants were asked to view photographs freely. Another possible reason is that the effects of these parameters are very small, and we lacked the statistical power in the present study to detect them reliably. Finally, it may be that these simple eye-movement metrics are more susceptible to individual differences and do not always occur reliably.

Relationship Between Eye Movements and Common Clinical Measures

When using their worse eye, patients made more spatially restricted eye movements (i.e., SA and BCEA of worse eye were smaller). Since other possible factors that affect eye movements (such as cognitive skills, age, personal preference) were controlled for, these differences in eye movements are likely due to their visual impairment. For example, since the worse eye typically exhibited substantial VF loss (see Fig. 1), the spatial narrowing of eye movements might be explained by an absence of exogenous cueing at more peripheral locations.[27–29] If this were the case, one would expect a relationship between measurements of VF loss and the spread of fixations. Consistent with this, our data showed that decreases in VF MD values were positively correlated with reductions in the spread of fixations (BCEA).

When viewing a scene, it is normal for normally sighted observers to make a number of saccadic reversals.[21] However, our data showed that saccadic reversal rates were increased on average in glaucomatous eyes, and this was statistically significant. As with the other eye-movement parameters (BCEA, SA), this may be primarily a consequence of their restricted VF, with patients opting to revisit parts of the image in the absence of any peripheral cues to attract their attention. If this is the case, one could similarly predict that a normal eye may exhibit greater SRRs when viewing a visual stimulus where all salient information is confined to a narrow spatial region. Alternatively (or in addition), it may be that increased SRRs represent an adaptive strategy to cope with reductions in acuity, with patients "revisiting" parts of the image in order to gain more information ("resampling"). Consistent with this, increases in SRR (between the eyes) were correlated with decreases in VA (Fig. 7B).

Between eyes, there was a positive association between BCEA (spread of fixations) and MD values, and also between SRR and VA. This is encouraging, as it suggests that natural eye movements could in future provide complementary biomarkers to traditional clinical measurements. This would have substantial practical advantages, owing to the ease with which it would be possible to collect large amounts of data with minimal burden or discomfort to patients.[8]

Implications and Future Work

The present work could be developed in a number of ways. First, this study showed eye-movement parameters (SA, SRR, and BCEA) are altered by worsening VF loss, but we cannot say, based on the present results, whether these measures could be used to detect VF loss. To answer this, one would have to build a model that can discriminate patients from healthy subjects and evaluate its diagnostic sensitivity and specificity in an appropriately designed study.[30,31] Second, the present work showed a relationship between eye movements and summary metrics of visual impairment, such as VA and MD. However, the small sample size precludes any investigation into the relationship between eye movement and different patterns or location of VF loss.

Conclusions

When viewing images monocularly, patients with asymmetric VF loss exhibited systematically different eye movements in their worse eye. Specifically, eye-movements in the worse eye were shown to be restricted in spatial extent, and to exhibit more frequent back-and-forth ("reversal") saccades. These differences in eye movements were shown to correlate with common clinical measures, with differences in BCEA and SRR associated with changes in MD and VA, respectively. This work introduces a novel eye-movement summary statistic, SRR, which could be applied to analyze eye movements of patients with other ophthalmic or neurodegenerative conditions.

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References

1. Malik R, Baker H, Russell RA, Crabb DP. A survey of attitudes of glaucoma subspecialists in England and Wales to visual field test intervals in relation to NICE guidelines. *BMJ Open*. 2013; 3:e002067.
2. Glen FC, Baker H, Crabb DP. A qualitative investigation into patients' views on visual field testing for glaucoma monitoring. *BMJ Open*. 2014;4:e003996.
3. Burton R, Crabb DP, Smith ND, Glen FC, Garway-Heath DF. Glaucoma and reading: exploring the effects of contrast lowering of text. *Optom Vis Sci*. 2012;89:1282–1287.
4. Ishii M, Seki M, Harigai R, Abe H, Fukuchi T. Reading performance in patients with glaucoma evaluated using the MNREAD charts. *Jpn J Ophthalmol*. 2013;57:471–474.
5. Smith ND, Glen FC, Mönter VM, Crabb DP. Using eye tracking to assess reading performance in patients with glaucoma: a within-person study. *J Ophthalmol*. 2014;2014:e20528.

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6. Smith N, Glen F, Crabb D. Eye movements during visual search in patients with glaucoma. *BMC Ophthalmol*. 2012;12:45.
7. Glen FC, Smith ND, Crabb DP. Saccadic eye movements and face recognition performance in patients with central glaucomatous visual field defects. *Vision Res*. 2013;82:42–51.
8. Crabb DP, Smith ND, Zhu H. What's on TV: detecting age-related neurodegenerative eye disease using eye movement scanpaths. *Front Aging Neurosci*. 2014;6:1–10.
9. Bowers A, Peli E, Elgin J, McGwin G, Owsley C. On-road driving with moderate visual field loss. *Optom Vis Sci*. 2005; 82:657–667.
10. Medeiros FA, Weinreb RN, Boer ER, Rosen PN. Driving simulation as a performance-based test of visual impairment in glaucoma. *J Glaucoma*. 2012;21:221–227.
11. Prado Vega R, van Leeuwen PM, Rendón Vélez E, Lemij HG, de Winter JCF. Obstacle avoidance, visual detection performance, and eye-scanning behavior of glaucoma patients in a driving simulator: a preliminary study. *PLoS One*. 2013;8: e77294.
12. Glen FC, Smith ND, Crabb DP. Impact of superior and inferior visual field loss on hazard detection in a computer-based driving test. *Br J Ophthalmol*. 2015;99:613–617.
13. Smith ND, Crabb DP, Glen FC, Burton R, Garway-Heath DF. Eye movements in patients with glaucoma when viewing images of everyday scenes. *Seeing Perceiving*. 2012;25:471–492.
14. Kasneci E, Black AA, Wood JM. Eye-tracking as a tool to evaluate functional ability in everyday tasks in glaucoma. *J Ophthalmol*. 2017;2017:e6425913.
15. Najjar RP, Sharma S, Drouet M, et al. Disrupted eye movements in preperimetric primary open- angle glaucoma. *Invest Ophthalmol Vis Sci*. 2017;58:2430–2437.
16. Wang X, Beotra MR, Tun TA, et al. In vivo 3-dimensional strain mapping confirms large optic nerve head deformations following horizontal eye movements. *Invest Ophthalmol Vis Sci*. 2016;57:5825–5833.
17. Crabb DP, Smith ND, Rauscher FG, et al. Exploring eye movements in patients with glaucoma when viewing a driving scene. *PLoS One*. 2010;5:e9710.
18. Wiecek E, Pasquale LR, Fiser J, Dakin S, Bex PJ. Effects of peripheral visual field loss on eye movements during visual search. *Front Psychol*. 2012;3:472.
19. Lee SSY, Black AA, Wood JM. Effect of glaucoma on eye movement patterns and laboratory-based hazard detection ability. *PLoS One*. 2017;12:e0178876.
20. Coutrot A, Hsiao JH, Chan AB. Scanpath modeling and classification with hidden Markov models. *Behav Res Methods*. 2017;50:362–379.
21. Amor TA, Reis SDS, Campos D, Herrmann HJ, Andrade JS. Persistence in eye movement during visual search. *Sci Rep*. 2016;6:20815.
22. Brusini P, Filacorda S. Enhanced Glaucoma Staging System (GSS 2) for classifying functional damage in glaucoma. *J Glaucoma*. 2006;15:40–46.
23. Bellmann C, Feely M, Crossland MD, Kabanarou SA, Rubin GS. Fixation stability using central and pericentral fixation targets in patients with age-related macular degeneration. *Ophthalmology*. 2004;111:2265–2270.
24. González EG, Teichman J, Lillakas L, Markowitz SN, Steinbach MJ. Fixation stability using radial gratings in patients with age-related macular degeneration. *Can J Ophthalmol*. 2006;41: 333–339.
25. R Core Team. R: a language and environment for statistical computing. Available at: https://www.r-project.org/. Accessed January 10, 2018.
26. Cheong AMY, Geruschat DR, Congdon N. Traffic gap judgment in people with significant peripheral field loss. *Optom Vis Sci*. 2008;85:26–36.
27. Thorpe SJ, Gegenfurtner KR, Fabre-Thorpe M, Bülthoff HH. Detection of animals in natural images using far peripheral vision. *Eur J Neurosci*. 2002;14:869–876.
28. Larson AM, Loschky LC. The contributions of central versus peripheral vision to scene gist recognition. *J Vis*. 2009;9(10): 6.
29. Kwon MY, Legge GE. Spatial-frequency requirements for reading revisited. *Vision Res*. 2012;62:139–147.
30. Bossuyt PM, Reitsma JB, Bruns DE, et al. Toward complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Clin Chem Lab Med*. 2003;41:68–73.
31. Fidalgo BMR, Crabb DP, Lawrenson JG. Methodology and reporting of diagnostic accuracy studies of automated perimetry in glaucoma: evaluation using a standardised approach. *Ophthalmic Physiol Opt*. 2015;35:315–323.

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