Glaucoma

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. 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, visual search, face recognition, watching video, and viewing images (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,19 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. 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-
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 to examine spatial characteristics of eye movements. And we used intersaccadic angle 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 (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 GSS 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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**TABLE 1.** Patient Information and Demographics. Patient ID Colors Correspond to Marker Colors Used Subsequently in Figures 1 and 6

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age, y</th>
<th>Sex</th>
<th>VA, Log</th>
<th>CS, Log</th>
<th>24–2 MD, dB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Left</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>70</td>
<td>F</td>
<td>0.10</td>
<td>0.16</td>
<td>-14.2</td>
</tr>
<tr>
<td>B</td>
<td>44</td>
<td>M</td>
<td>-0.08</td>
<td>0.10</td>
<td>1.45</td>
</tr>
<tr>
<td>C</td>
<td>59</td>
<td>M</td>
<td>-0.04</td>
<td>-0.04</td>
<td>1.90</td>
</tr>
<tr>
<td>D</td>
<td>80</td>
<td>F</td>
<td>0.14</td>
<td>0.14</td>
<td>1.55</td>
</tr>
<tr>
<td>E</td>
<td>64</td>
<td>M</td>
<td>0.18</td>
<td>-0.06</td>
<td>1.95</td>
</tr>
<tr>
<td>F</td>
<td>83</td>
<td>M</td>
<td>0.14</td>
<td>0.14</td>
<td>1.45</td>
</tr>
<tr>
<td>G</td>
<td>65</td>
<td>F</td>
<td>-0.02</td>
<td>0.06</td>
<td>1.95</td>
</tr>
<tr>
<td>H</td>
<td>56</td>
<td>M</td>
<td>-1.00</td>
<td>-1.50</td>
<td>1.95</td>
</tr>
<tr>
<td>I</td>
<td>66</td>
<td>M</td>
<td>0.20</td>
<td>0.04</td>
<td>1.95</td>
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<tr>
<td>J</td>
<td>74</td>
<td>F</td>
<td>0.18</td>
<td>0.14</td>
<td>1.95</td>
</tr>
<tr>
<td>K</td>
<td>60</td>
<td>F</td>
<td>0.02</td>
<td>0.06</td>
<td>1.95</td>
</tr>
<tr>
<td>L</td>
<td>66</td>
<td>M</td>
<td>-0.08</td>
<td>0.16</td>
<td>1.30</td>
</tr>
<tr>
<td>M</td>
<td>66</td>
<td>M</td>
<td>0.04</td>
<td>0.10</td>
<td>1.65</td>
</tr>
<tr>
<td>N</td>
<td>84</td>
<td>M</td>
<td>0.16</td>
<td>0.36</td>
<td>1.65</td>
</tr>
<tr>
<td>O</td>
<td>83</td>
<td>F</td>
<td>0.12</td>
<td>0.08</td>
<td>1.75</td>
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</tbody>
</table>
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 ±17.0° by ±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 ≤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 gray scale 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°/s². Following previous similar studies, 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, , was computed (see Fig. 3B). For example, when two successive saccades moved in the same direction, was close to 0°. In contrast, if two saccades moved in opposition direction, was close to 180°. Across a trial, this resulted in a distribution of values, as shown in Figure 3C. Of these, we were particularly interested in values 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.” We therefore hypothesized that such movements would be particularly elevated when vision was impaired.

To quantify SRR formally, we first measured the proportion of 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 was computed as:

\[
\theta_{agg} = \arctan \left( \frac{s_{y,i} s_{x,i+1}}{s_{x,i} s_{y,i+1}} \right) - \arctan \left( \frac{s_{y,i-1} s_{x,i}}{s_{x,i-1} s_{y,i}} \right),
\]

where and are the y and x components of the th saccade, and where is the preceding saccade. Then, SRR was computed as:

\[
SRR = \frac{\text{Proportion of saccadic reversals}}{\text{Total number of } \theta_{agg}}.
\]
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.
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 $\theta_{\text{diff}}$, the angular difference between successive pairs of saccades. (B) Illustration of how $\theta_{\text{diff}}$ values were computed (measured anticlockwise relative to the horizontal). (C) Polar histogram of $\theta_{\text{diff}}$ values (same data as [A] and [B]). For example, on two occasions $\theta_{\text{diff}}$ 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 $\theta_{\text{diff}}$ 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.
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. 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
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 v3.3.5.25

**RESULTS**

Fifteen patients with glaucoma were recruited (60% men), with a median (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>
<thead>
<tr>
<th></th>
<th>Better Eye, Median (IQR)</th>
<th>Worse Eye, Median (IQR)</th>
<th>Between-Eye Difference, Median (IQR)</th>
<th>Wilcoxon’s P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixation duration, msec</td>
<td>255 (228, 259)</td>
<td>244 (228, 268)</td>
<td>−9 (−16, 11)</td>
<td>0.60</td>
</tr>
<tr>
<td>Fixation count per trial</td>
<td>12.0 (11.6, 13.8)</td>
<td>12.0 (11.25, 13.0)</td>
<td>0 (−1.4, 1.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Saccade velocity, deg/sec</td>
<td>250.0 (182.0, 258.9)</td>
<td>215.0 (169.8, 254.3)</td>
<td>−13.5 (−27.1, 7.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Scanpath length, deg</td>
<td>60.31 (48.0, 64.8)</td>
<td>55.7 (43.2, 59.5)</td>
<td>−6.4 (−14.9, 4.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>SA, deg</td>
<td>3.95 (3.09, 5.42)</td>
<td>3.13 (2.92, 4.66)</td>
<td>0.5 (0.0, 0.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>SRR</td>
<td>0.09 (0.08, 0.12)</td>
<td>0.10 (0.09, 0.12)</td>
<td>−0.014 (−0.021, −0.003)</td>
<td>0.048</td>
</tr>
<tr>
<td>BCEA, deg squared</td>
<td>315 (249, 418)</td>
<td>253 (222, 520)</td>
<td>49 (16, 96)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Statistically significant P values are highlighted in bold.

**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...
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, $P = 0.01$. 

$r = 0.64$

$r = 0.65$
significant differences between glaucoma patients and controls in terms of number of saccades,\textsuperscript{13} fixation rate, fixation duration,\textsuperscript{17} and saccade rate.\textsuperscript{69} One possible reason for this disparity may be due to differences in task. For instance, in the study of Smith et al.,\textsuperscript{17} 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 cuing at more peripheral locations.\textsuperscript{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.\textsuperscript{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).

**References**


