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Horizontal Gaze Tolerance and Its Effects on Visual Sensitivity in Glaucoma

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Purpose. This study evaluates the effect of 6° horizontal gaze tolerance on visual field mean sensitivity (MS) in patients with glaucoma using a binocular head-mounted automated perimeter, following findings of structural changes in the posterior globe from magnetic resonance imaging and optical coherence tomography.

Methods. In this cross-sectional study, a total of 161 eyes (85 primary open-angle glaucoma [POAG] and 76 healthy) from 117 participants were included. Logistic regression and 1:1 matched analysis assessed the propensity score for glaucoma and healthy eyes, considering age, sex, and axial length as confounders. Visual field tests were performed with the imo perimeter (CREWT Medical Systems, Inc., Tokyo, Japan) at central gaze, 6° abduction, and 6° adduction positions as fixation points. A mixed-effects model was used to compare MS under all conditions.

Results. The analysis included a total of 82 eyes, with 41 POAG and 41 healthy after matching. The mean (standard deviation) age was 68.0 (11.0) years, with a mean deviation of −9.9 (6.6) dB for POAG and −1.0 (1.9) dB for healthy eyes using Humphrey field analysis 24-2. MS did not significantly differ among central gaze (27.0 [1.8] dB), abduction (27.1 [1.9] dB), and adduction (26.9 [2.2] dB) in healthy eyes ($P = 0.650$). However, MS was significantly lower for adduction (17.2 [5.9] dB) compared to central gaze (18.1 [5.9] dB) and abduction (17.9 [5.9] dB) in glaucoma eyes ($P = 0.001$ and $P = 0.022$, respectively).

Conclusions. Horizontal gaze, especially in adduction, significantly reduces visual sensitivity in glaucoma, suggesting a specific vulnerability associated with eye movement. This finding highlights the importance of eye positioning in glaucoma, warranting further investigation of its clinical significance.

Keywords: visual sensitivity, horizontal duction, perimeter, cross-sectional study

Glaucoma, the leading cause of irreversible blindness worldwide, is a progressive optic neuropathy characterized by a progressive loss of retinal ganglion cells and their axons.[1] Although IOP-related mechanical stress is a key risk factor, primary open-angle glaucoma (POAG) can develop within normal IOP ranges, so-called normal-tension glaucoma (NTG), which predominates in East Asians.[2,3] The factors contributing to optic nerve damage beyond elevated IOP are not fully understood.[4,5]

The idea that gaze could strain the optic nerve and the eye wall traces back to Purkinje and von Helmholtz,[6] who each suggested that pulling on the optic nerve could trigger gaze-evoked phosphenes. Subsequent studies on biomechanical models have shown that mechanical factors, along with elevated IOP, may contribute to optic nerve damage, as observed in glaucoma.[5,7–9] These models indicate the potential for optic nerve damage to arise from stress (i.e., force/area) and strain (i.e., local deformation induced by stress) in tissues bearing the load of the optic nerve head (ONH), including the peripapillary sclera, lamina cribrosa, and scleral canal wall.[10] Moreover, a recent study reveals that during eye adduction, the optic nerve sheath is tethered, restricting optic nerve movement, as demonstrated by magnetic resonance imaging (MRI).[11] Furthermore, ONH changes associated with eye movements have been reported using optical coherence tomography (OCT). Lee et al.[12] also demonstrated that abduction causes translation stress, while adduction induces shear stress, suggesting that observing structural changes is useful for inferring the stress on the ONH associated with eye movements. Such stress may be greater in glaucoma eyes than in healthy eyes due to remodeling of connective tissue.[13] However, no studies have investigated functional changes associated with eye movements in patients with glaucoma.

To date, only a few instruments have been available to measure visual sensitivity during horizontal movement.[14] In a prior study, we developed a new static program that incorporates adduction and abduction tolerance, named the

horizontal gaze tolerance test, demonstrating the feasibility of quantifying visual field (VF) sensitivities with horizontal ductions tolerance in healthy eyes.[14] The aim of this study was to investigate whether horizontal gaze alters sensitivities differently between glaucoma and healthy eyes.

Methods

Participants

This cross-sectional study included healthy participants and patients with POAG who underwent imo perimetry (CREWT Medical Systems, Tokyo, Japan) from April 2019 to December 2020. The research protocol followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Saitama Medical University. All study participants provided written informed consent.

Comprehensive ophthalmic examinations were conducted for all participants, including slit-lamp biomicroscopy, IOP measurement with Goldmann applanation tonometry and noncontact tonometry (Tonoref II; Nidek Co., Ltd., Aichi, Japan), and fundus photography (CX-1; Canon, Tokyo, Japan). Axial length and central corneal thickness measurements were obtained using the Optical Biometer OA-2000 (Tomey, Nagoya, Japan). VF testing utilized the 24-2 Swedish interactive threshold algorithm (SITA) standard strategy on the Humphrey field analyzer (Carl Zeiss Meditec, Dublin, CA, USA) to diagnose and evaluate glaucoma severity. All participants had previous experience with VF examinations, and unreliable VFs (defined as fixation losses >25% or false positive >15%) were excluded.

Healthy participants had an IOP of 21 mm Hg or lower, no history of elevated IOP, normal optic discs upon review by a glaucoma specialist (T.S.), and normal VF tests. VFs were conducted with program 24-2 SITA using a Humphrey Visual Field Analyzer (Zeiss Meditec, San Leandro, CA, USA). A normal examination was a pattern standard deviation (PSD) within the 95% confidence limits and glaucoma hemifield test (GHT) result within normal limits. Glaucoma diagnosis required (1) ONH changes confirmed by fundus photography or biomicroscopy with a handheld lens, including a vertical cup-to-disc ratio $\geq$0.7, rim notch with rim width $\leq$0.1, or a retinal nerve fiber layer defect originating at the ONH and extending in an arcuate or wedge shape and (2) glaucomatous VF defects consistent with ONH changes and meeting one of Anderson and Patella's criteria,[15] such as a cluster of $\geq$3 nonedge points with $P < 0.05$, out of which at least one point has a P value of less than 1% in a single hemifield, a GHT result out of limits, or an abnormal PSD with $P < 0.05$.

Inclusion criteria also included the following: age greater than 20 years, open angles on gonioscopy, best-corrected visual acuity of 20/40 or better, spherical refractive error within −9.0 to +3.0 D (this will be explained in the next section), cylinder refractive error within ±3.0 D, and axial length less than 26 mm. Systemic hypertension and diabetes were not exclusionary unless accompanied by respective retinopathies. Exclusion criteria also included systemic or ocular conditions affecting VF, a history of intraocular surgery (excluding uncomplicated cataract surgery), concurrent retinal pathologies, nonglaucomatous optic neuropathy, uveitis, ocular trauma, strabismus, fusion disorders, or a history of Parkinson disease, Alzheimer disease, dementia, or stroke.

Imo Perimetry

We assessed VF testing under various gaze conditions utilizing the imo head-mounted binocular automated perimeter.[14,16–18] In brief, the imo test presents targets to either eye through a high-definition transmissive liquid crystal display that is illuminated by a high-intensity light-emitting diode. It incorporates dual optical and pupil-monitoring systems for each eye, alongside an automatic eye-tracking feature that compensates for eye movements by adjusting target location. The eye tracking utilizes three near-infrared LEDs (950 nm) for monitoring, and real-time image capture is achieved with an SXVGA-resolution (1280 × 960 pixels) CMOS sensor, operating up to 54 frames per second. The imo can test the right and left eyes separately and can also present the test object to either eye randomly in an nonocclusion manner without the examinee being aware of which eye is being tested.[16] This provides an examination environment close to daily vision and has been reported to stabilize fixation and enhance patient satisfaction.[19,20] The imo comes with an attachment lens, but it can correct for spherical power within the range of −9.0 D to 3.0 D using the adjustment knobs for each eye. This internal optical adjustment ensures no positional shift due to decentration. Although not used in this study, when using the attachment lens, the target position is adjusted based on the added power for central gaze (CREWT, personal communication, July 11, 2024).

This study evaluated 36 points within the central 30° VF using 24plus (1) Ambient Interactive Zippy Estimated by Sequential Testing (AIZE)–Rapid,[21,22] with Goldmann size III stimuli (0.431° visual angle). AIZE utilizes Bayesian inference and maximum likelihood methods for threshold determination,[22] and it reduces test time by around 70% compared to the traditional 4–2 dB bracketing method.[16] AIZE begins testing at randomly selected initial positions and updates the prior probability mass function not only for the tested location but also for neighboring locations within each quadrant based on the subject's response. The first 50 stimuli are randomly selected from test locations within 15°, regardless of the quadrant.[22] Initial measurements for this study were taken at the central gaze fixation point, followed by tests at 6° abduction and 6° adduction, as shown in Figure 1.[14] Abduction and adduction were tested in a random sequence. Using the "Random Uniform" function in JMP, the allocation was conducted to determine whether to perform adduction or abduction first. This allocation was carried out by an independent individual (S.T.) who was unaware of the patients' backgrounds. To minimize test time and reduce participant fatigue, Ex-mode was employed for abduction and adduction measurements.[14] Unlike standard VF tests that rely on a normative database potentially increasing stimulus presentations for patients with glaucoma, Ex-mode leverages the previous patient's test result (in this case, the result of central gaze) to search for a threshold, reducing the amount of target presentations while maintaining accuracy. VFs were considered unreliable and excluded if fixation losses were >25% or false-positive responses were >15%. Mean sensitivity (MS) was calculated in dB using individual test points, where each point was converted to a linear scale and averaged to obtain the values.

Propensity Score Matching

With age, remodeling occurs in the ocular tissues, leading to mutual influences on the stiffening and softening

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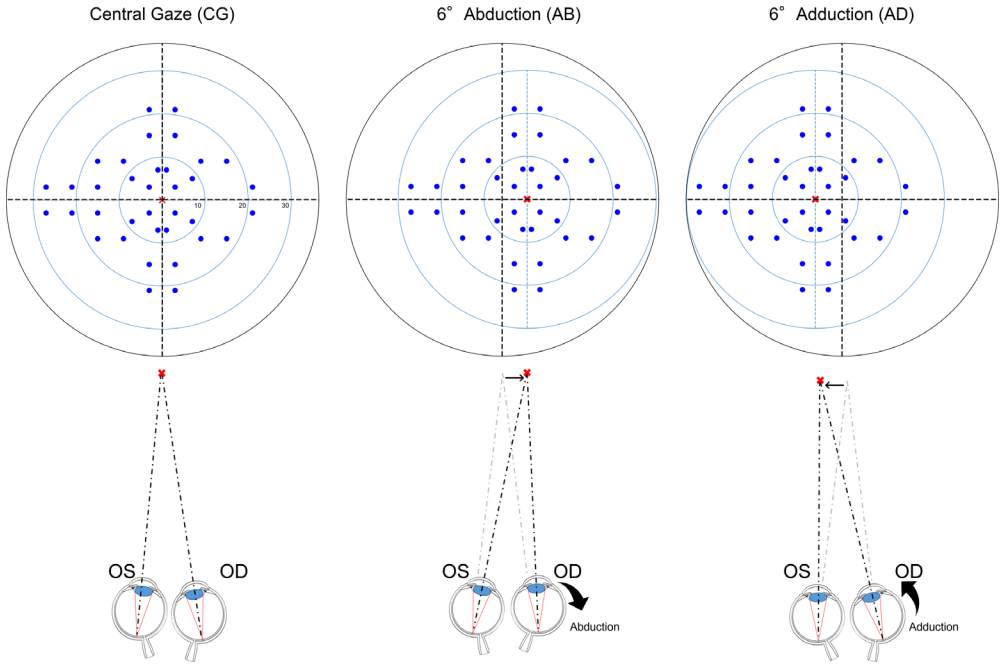

Figure 1. Schematic explanation of the CG, 6° AB, and 6° AD as fixation points for the right eye. Test points were adjusted according to the fixation point. In the figure, the scale of the axial length and the distance of the target presentation are exaggerated for simplification and emphasis for readability. The convergence shown in central gaze does not occur (the adduction angle is at most 2°).

of tissues surrounding the ONH and strain on connective tissues.[5,23] Since it was unclear whether the main effects and interactions among variables such as age and axial length were linearly associated with functional changes caused by eye movement, propensity score matching was performed to examine differences between glaucoma and healthy eyes. A random seed was used to ensure consistent results. Specifically, logistic regression and 1:1 matching analysis were conducted, considering age, sex, and axial length as confounding factors.

Statistical Analysis

Participant and eye characteristic data were presented as mean (SD) for continuous variables and counts for categorical variables. Categorical variables were compared using the Fisher exact test. Mixed-effects modeling was used to compare ocular parameters among healthy participants and patients with glaucoma. Models were fitted with ocular measurements as the response variable, considering diagnostic group as fixed effects. To account for the similarity in measurements between the bilateral eyes of a participant, measurements from both eyes were nested within participant. A mixed-effects model was also used to compare global VF parameters under all gaze conditions (i.e., central gaze, abduction, and adduction). The distribution of residuals, one of the assumptions of the linear model, was visually assessed using a Q-Q plot. Additionally, a residuals versus fitted values plot was examined to evaluate linearity and to check for homoscedasticity. To account for the multiple comparisons made in the analysis, the critical P value was divided by the number of comparisons to adjust the significance level. The effect of horizontal eye movements on disease severity was assessed using a Bland–Altman plot to provide 95% limits of agreement, and regression analysis was performed to compare MS for central gaze with abduction and adduction. Point-by-point analysis of sensitivities at each test location was also conducted by comparing central gaze with abduction and adduction to investigate the geographic characteristics on the eye movements. Although not initially planned in the study design, we performed an additional analysis to investigate a discrepancy between our previously published work and the primary analysis in the current study: specifically, that horizontal gaze altered visual sensitivity in older healthy controls previously but not in our current analysis. Linear mixed-effects analyses were conducted on the combined data from both studies, using the mean sensitivity of central gaze as the dependent variable, with mean sensitivity in abduction/adduction and study group (current study versus data from previous study)[14] as independent variables. Multivariable models also included diagnosis, an interaction term between mean sensitivity in abduction/adduction and diagnosis, age, an interaction term between mean sensitivity in abduction/adduction and age, an interaction term between mean sensitivity in abduction/adduction and study group, sex, axial length, spherical refractive error, central corneal thickness, best-corrected visual acuity, and IOP. Full models including all these variables were constructed separately for abduction and adduction. Additionally, stepwise regression was applied to identify and report parsimonious models for each. Statistical significance was determined based on the adjusted threshold for multiple comparisons, with a two-sided P value of <0.05 used as the threshold unless otherwise specified. All statistical analyses were performed using JMP version 10.1 software (SAS Institute, Inc., Cary, NC, USA) and Stata software version 16 (StataCorp LP, College Station, TX, USA).

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Results

Demographic and Clinical Characteristics

In this cross-sectional study, a total of 161 eyes (85 POAG and 76 healthy) from 117 participants were included. All participants were able to complete the test without binocular fusion issues or fatigue from horizontal eye movements. After matching, the analysis included a total of 82 eyes, with 41 POAG and 41 healthy. There was no significant difference in the test order (z statistic = −1.249, P = 0.211). The mean (SD) age was 68.0 (11.0) years. Mean (SD) deviation was −9.9 (6.6) dB for POAG eyes and −1.0 (1.9) dB for healthy eyes. Mean (SD) spherical refractive error was −2.4 (0.4; range, −6.5 to 2.75) for POAG eyes and −1.7 (0.3; range −6.0 to 2.5) for healthy eyes. Demographic and clinical characteristics between POAG and healthy groups are shown in Table 1.

Comparison of the VF Parameters Among the Three Different Fixation Points

MS (SD) did not significantly differ among central gaze (27.0 [1.8] dB), abduction (27.1 [1.9] dB), and adduction (26.9 [2.2] dB) in healthy eyes (P = 0.650). However, MS was significantly lower for adduction (17.2 [5.9] dB) compared to central gaze (18.1 [5.9] dB) and abduction (17.9 [5.9] dB) in eyes with glaucoma (P = 0.001 and P = 0.022, respectively). For comparison, Table 2 also presents the results of mean deviation, visual field index, and foveal threshold values among three different fixation points, in addition to those for MS. Figure 2 illustrates the differential MS analyses in glaucoma and healthy eyes: (A) abduction (AB) – central gaze (CG) and (B) adduction (AD) – CG. These comparisons were made between eyes with glaucoma (blue) and healthy (orange). The Bland–Altman analysis comparing abduction to central gaze showed a mean difference of −0.13 (95% confidence interval [CI], −3.04 to 2.78). The regression analysis indicated a slope of 0.03 (Fig. 3A). In contrast, for the comparison of adduction to CG, the analysis revealed a mean difference of −0.56 (95% CI, −3.50 to 2.38). The regression line had a slope of 0.07, indicating greater differences in more damaged eyes (Fig. 3B).

Analysis of Sensitivities at Each Test Location by Comparing Fixation Points

Figure 4 illustrates the point-by-point comparison between central gaze with abduction and adduction at each location. No specific geometric trends were observed between abduction and central gaze, such as sensitivity differences in eccentricity or in certain directions, in both healthy and glaucoma eyes (Figs. 4A–D). Comparing adduction with central gaze, in healthy eyes, adduction showed lower sensitivity in general (i.e., cooler colors), but the absolute differences were minimal (Fig. 4B). Conversely, in glaucoma eyes, adduction generally demonstrated lower sensitivity with larger absolute differences compared to healthy eyes (Fig. 4D).

Analysis to Investigate the Difference Between a Previous Study (Shoji et al.[14]) and the Current Study

Table 3 presents the demographic and clinical characteristics of participants in current and previous studies. In the previ-

Table 1. Demographic and Clinical Characteristics of the Participants

Characteristic	Overall	POAG	Control	*P* Value
Participants, No.	69	34	35	
Age, y	68.0 (11.0)	67.9 (9.2)	68.0 (12.7)	0.962
Sex, male/female, No.	36/33	17/17	19/16	0.722
Eyes, No.	82	41	41	
Axial length, mm	24.1 (1.2)	24.1 (1.2)	24.1 (1.2)	0.811
Spherical refractive error	−1.5 (2.4)	−1.8 (2.8)	−1.2 (2.0)	0.284
Central corneal thickness, µm	523.4 (30.7)	524.8 (32.1)	522.0 (29.5)	0.709
BCVA, logMAR	−0.01 (0.11)	0.03 (0.13)	–0.04 (0.06)	0.002
IOP, mm Hg	14.1 (3.4)	13.5 (3.6)	14.7 (3.2)	0.165
HFA 24-2 mean deviation, dB	−5.5 (6.6)	−9.9 (6.6)	−1.0 (1.9)	<0.001

Data are given as mean (SD), unless otherwise indicated. Categorical variables were compared using the Fisher exact test. Mixed-effects modeling was used to compare ocular parameters among groups. BCVA, best-corrected visual acuity; HFA, Humphrey Field analyzer.

Table 2. Comparison of the Mean Sensitivity, Mean Deviation, and Visual Field Index and Foveal Threshold Among the Three Different Fixation Points

Variable	Central Gaze (CG)	Abduction (AB)	Adduction (AD)	*P* Value	Post Hoc
POAG (n = 41)					
Mean sensitivity (dB)	18.6 (5.9)	18.2 (5.9)	17.6 (6.0)	0.001*	CG, AB > AD
Mean deviation (dB)	−10.1 (6.2)	−10.5 (6.3)	−11.2 (6.3)	0.002*	CG, AB > AD
Visual field index (%)	70.1 (20.7)	69.3 (20.5)	68.1 (21.1)	0.037*	CG > AD
Foveal threshold (dB)	29.5 (5.8)	29.9 (3.4)	29.9 (3.0)	0.838	
Healthy (n = 41)					
Mean sensitivity (dB)	27.0 (1.8)	27.1 (1.9)	26.9 (2.2)	0.650	
Mean deviation (dB)	−1.3 (1.5)	−1.2 (1.7)	−1.4 (1.9)	0.768	
Visual field index (%)	97.7 (3.0)	97.6 (3.1)	97.4 (4.8)	0.881	
Foveal threshold (dB)	31.8 (3.2)	31.9 (3.6)	31.5 (2.6)	0.749	

* Post hoc adjustment for multiple comparisons.

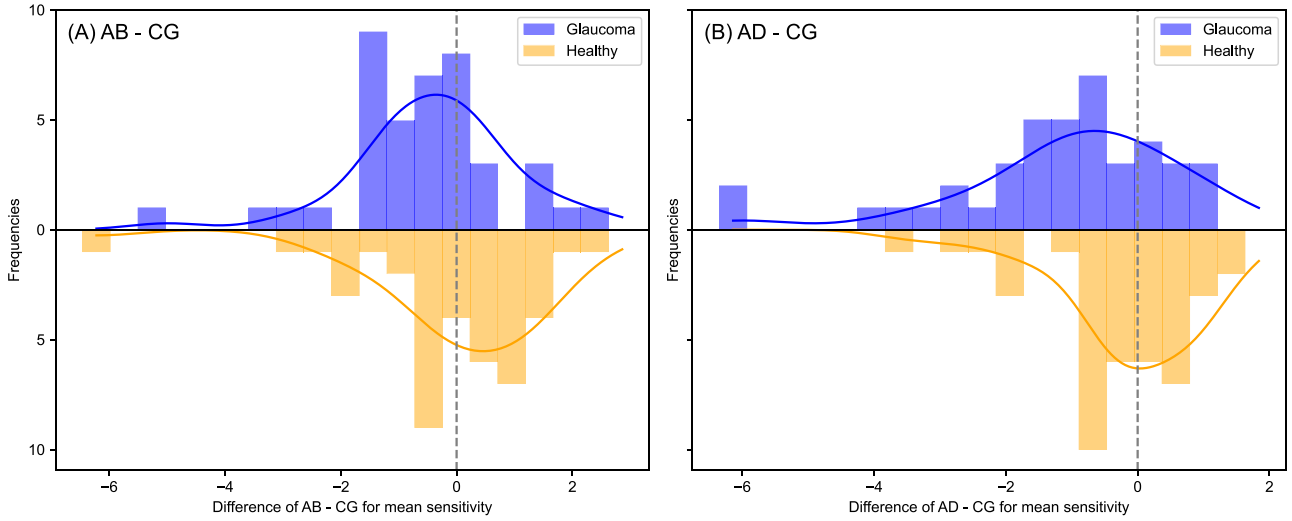

Figure 2. Differential mean sensitivity analyses in glaucoma and healthy eyes. (**A**) Histogram and kernel density estimation of mean sensitivity between 6° AB and CG in eyes with glaucoma (*blue*) and healthy (*orange*). *Bars* represent histogram data, while the *solid lines* indicate the smoothed probability density. (**B**) Histogram and kernel density estimation of mean sensitivity between 6° AD and CG in eyes with glaucoma and healthy eyes. The color scheme and axes representations are consistent with (**A**).

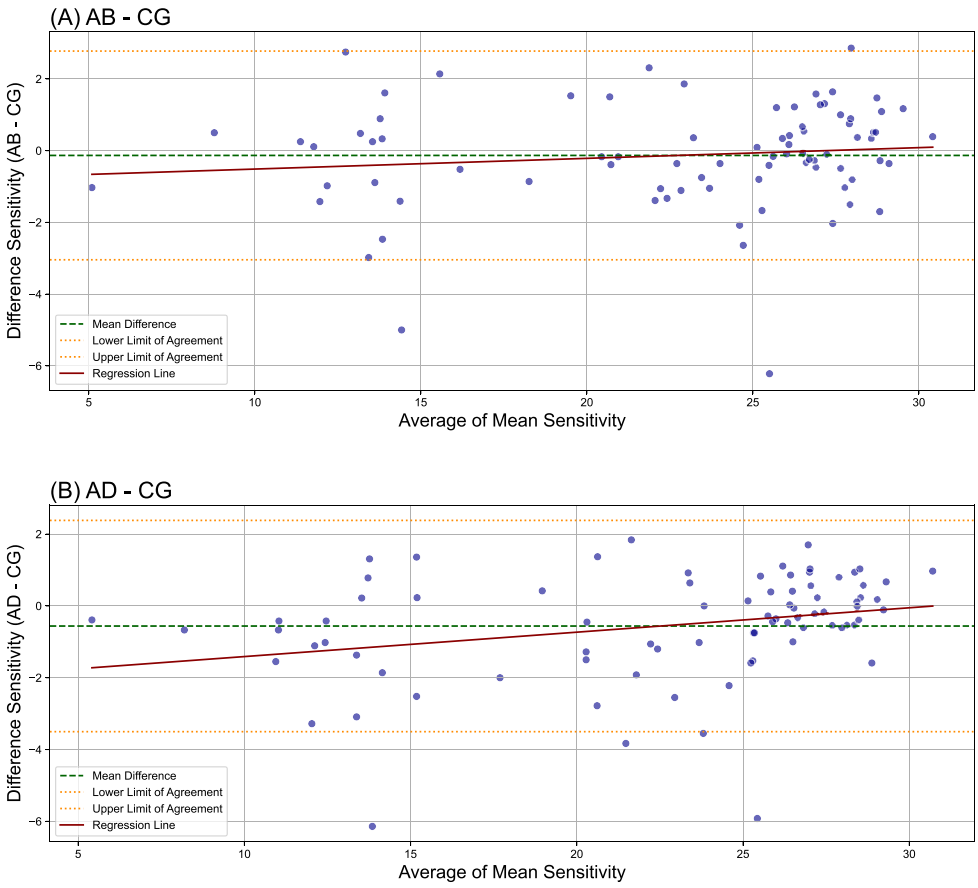

Figure 3. Bland–Altman plots with mean difference and agreement limits (including 95% of all difference values). The *solid line* represents the line of best fit from linear regression.

ous study, all 57 eyes were controls. Additionally, the mean (SD) age differed significantly between the current study (68.0 [11.0]) and the previous study (47.9 [20.5]; $P < 0.001$). We performed a multivariable analysis using the combined data sets from both studies (Table 4). In the multivariable models, eye movement and age were significant factors in

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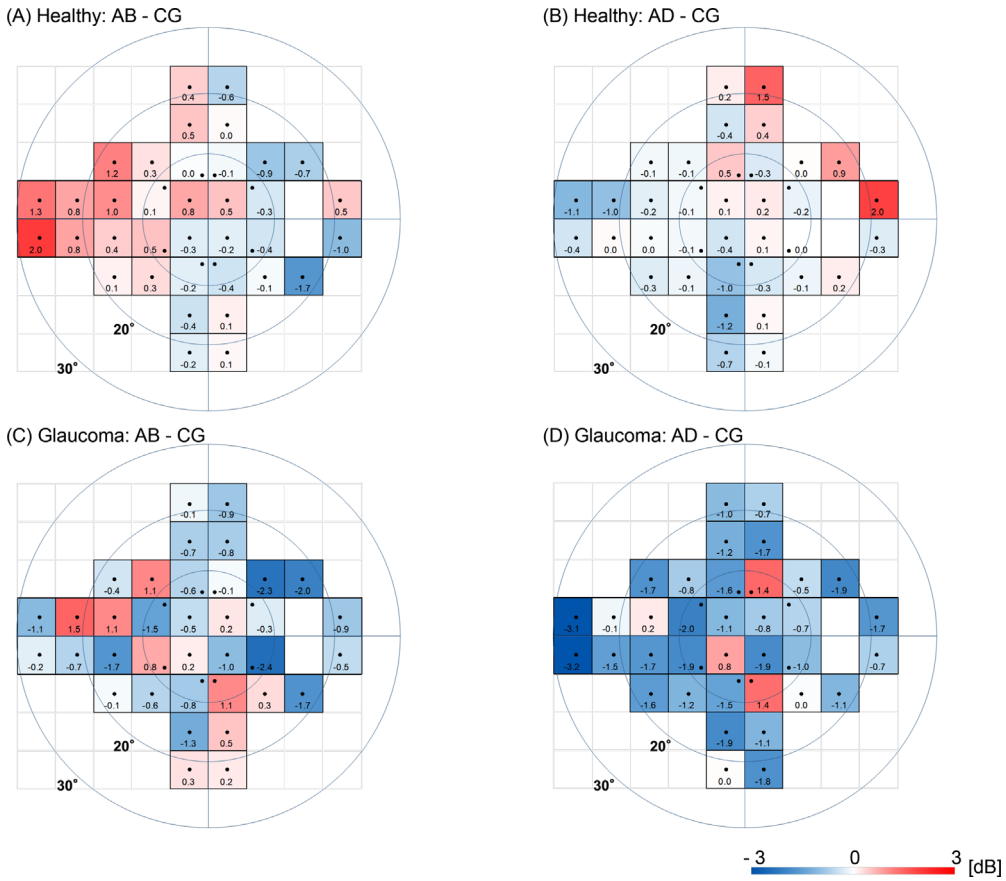

Figure 4. Analysis of sensitivities at each test location by comparing CG with AB and AD, plotting all eyes as the right eye. Graphs illustrate average differences: (**A**) AB minus CG in healthy eyes, (**B**) AD minus CG in healthy eyes, (**C**) AB minus CG in glaucoma eyes, and (**D**) AD minus CG in glaucoma eyes. *Warmer colors* indicate higher sensitivity in CG, while *cooler colors* indicate vice versa. Testing points for visual field are overlaid with *black dots*.

Table 3. Demographic and Clinical Characteristics of the Participants of the Current Study and the Previous Study (Shoji et al.[14])

Characteristic	Current Study	Shoji et al.[14]	*P* Value
Participants, No.	69	48	
Age, y	68.0 (11.0)	47.9 (20.5)	<0.001
Sex, male/female, No.	36/33	25/23	1.000
Eyes, No.	82	57	
Diagnosis, POAG/control, No.	41/41	0/57	<0.001
Axial Length, mm	24.1 (1.2)	24.5 (1.1)	0.046
Spherical refractive error	−1.5 (2.4)	−2.4 (2.1)	0.463
Central corneal thickness, µm	523.4 (30.7)	529.6 (32.9)	0.261
BCVA, logMAR	−0.01 (0.11)	−0.07 (0.04)	<0.001
IOP, per 1 mm Hg higher	14.1 (3.4)	14.7 (2.7)	0.222
Mean sensitivity (dB)			
Central gaze	27.0 (1.8)	28.8 (1.6)	<0.001
Abduction	27.1 (1.9)	29.1 (1.6)	<0.001
Adduction	26.9 (2.2)	28.7 (1.9)	<0.001

Data are given as mean (SD) unless otherwise indicated. Categorical variables were compared using the Fisher exact test. Mixed-effects modeling was used to compare ocular parameters between the current and previous studies.

both the full and parsimonious models (*P*s < 0.05). The results indicate that the study group itself did not significantly influence mean sensitivity. Furthermore, the analysis demonstrated that age was an independent factor affecting mean sensitivity, separate from the influence of horizontal eye movements. This finding aligns with previous studies, which have reported a decrease in retinal nerve fiber with increasing age.[24,25]

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Table 4. Multivariable Linear Mixed-Effect Model Results for the Effect of Study and Gaze Direction (Abduction and Adduction) on Central Gaze Sensitivity, $n = 139$ Eyes

	Abduction				Adduction			
	Model 1 (Full Model)		Model 2 (Parsimonious Model)		Model 3 (Full Model)		Model 4 (Parsimonious Model)	
Variable	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
Eye movement, abduction or adduction	0.47 (0.22 to 0.72)	<0.001	0.65 (0.42 to 0.88)	<0.001	0.41 (0.21 to 0.6)	<0.001	0.54 (0.42 to 0.65)	<0.001
Diagnosis, glaucoma	−6.14 (−14.52 to 2.24)	0.149	−7.93 (−14.28 to −1.58)	0.015	−9.67 (−15.08 to −4.26)	0.001	−10.14 (−13.73 to −6.55)	<0.001
Eye movement × diagnosis	0.23 (−0.08 to 0.53)	0.142	0.30 (0.07 to 0.52)	0.011	0.37 (0.17 to 0.58)	0.001	0.40 (0.25 to 0.54)	<0.001
Age, per 1 year older	−0.11 (−0.22 to −0.01)	0.039	−0.03 (−0.05 to −0.02)	<0.001	−0.11 (−0.21 to −0.01)	0.033	−0.03 (−0.04 to −0.02)	<0.001
Eye movement × age	0.00 (0.00 to 0.01)	0.165			0.00 (0.00 to 0.01)	0.102		
Study, current study	−1.24 (−10.15 to 7.67)	0.782			1.59 (−4.12 to 7.31)	0.580		
Eye movement × study	0.04 (−0.28 to 0.36)	0.799			−0.07 (−0.27 to 0.14)	0.507	−0.01 (−0.02 to 0.00)	0.021
Sex, female	−0.45 (−0.85 to −0.06)	0.026			−0.23 (−0.62 to 0.16)	0.238		
Axial length, per 1 mm longer	−0.09 (−0.23 to 0.05)	0.201			−0.04 (−0.19 to 0.12)	0.649		
Spherical refractive error, per 10 D higher	0.00 (−0.02 to 0.03)	0.771			−0.02 (−0.02 to −0.01)	<0.001	−0.02 (−0.02 to −0.01)	<0.001
Central corneal thickness, per 100 µm thicker	−0.01 (−0.02 to 0.00)	0.177			0.00 (−0.01 to 0.01)	0.777		
BCVA, per 1 logMAR higher	−1.09 (−4.31 to 2.13)	0.504			−4.06 (−7.14 to −0.99)	0.010	−4.10 (−7.34 to −0.87)	<0.001
IOP, per 10 mm Hg higher	0.02 (−0.01 to 0.05)	0.262			0.03 (0.02 to 0.05)	<0.001	0.04 (0.02 to 0.06)	<0.001

Discussion

In this study, we conducted VF testing using imo and evaluated horizontal duction tolerance, encompassing fixation in a horizontally moved eye position. No significant differences were found in MS between central gaze with abduction and adduction in healthy participants. However, patients with glaucoma exhibited lower MS during adduction when compared to central gaze, while no significant differences were found in abduction, suggesting that the effects of adduction might be more clinically relevant than those of abduction in the context of glaucoma.

Eye Movement and Optic Nerve Head Deformation

There is an increasing interest in investigating whether ONH deformations, resulting from the traction force exerted on the optic nerve, could initiate the development and advancement of optic neuropathies, including glaucoma.[11,26–29] Wang et al.[8] reported that optic nerve tortuosity was reduced in adduction compared to baseline gaze. This finding is intuitive, as the optic nerve is highly stretched in adduction. The shape of the anterior lamina cribrosa, as measured by OCT, underwent greater changes in glaucoma eyes than in healthy eyes after an acute increase in IOP.[30] These results reinforce our observation that MS was worse during adduction in glaucoma compared to healthy eyes, suggesting that the decrease in visual sensitivity aligns with structural stress load, especially during adduction. Notably, our finding that horizontal gaze did not alter visual sensitivity in our healthy control group is at odds with previous work showing horizontal gaze did significantly alter visual sensitivity in healthy older controls.[14] Therefore, we pooled the data from both studies to see whether an effect of horizontal gaze in healthy controls is supported when both studies are combined and, importantly, whether the presence of glaucoma significantly alters any effect. As shown in models 2 and 4 in Table 4, horizontal eye movement was significantly associated with visual sensitivity in the pooled data set. Furthermore, the presence of glaucoma and its interaction with eye movement were significantly associated with visual sensitivity. Individuals with glaucoma had significantly reduced central gaze sensitivity compared to healthy participants. While the interaction term between eye movement and glaucoma diagnosis was statistically significant, its small magnitude suggests that the effect is clinically nonsignificant. Importunately, we found no interaction between the effect of age and the effect of horizontal gaze on visual sensitivity, in contrast with the previous work,[14] suggesting healthy aging might not be associated with a gaze effect on visual sensitivity.

Differential Effects of Adduction and Abduction Angles

Demer[11] demonstrated that, in healthy eyes, the optic nerve experiences tethering, leading to straightening when the adduction angle ranges from 22° to 26°. Further adduction from this range stresses the junction of optic nerve, its sheath, and the sclera. This stress propagates widely from the temporal peripapillary region to a broad zone of the temporal inner sclera, including the macula.[31] Suh et al.[32] found that gradually increasing the angles of adduction and abduction led to angle-dependent misalignment of Bruch's membrane opening and ONH tilt. However, this misalignment was less in abduction than in adduction,[32] which might

explain the nonsignificant sensitivity reduction observed in abduction in our study. The angles of adduction and abduction used in our study were relatively small. However, understanding the differences in reference positions and how they may influence the result is important to accurately interpret these previous studies. The previously reported increase in sensitivity during abduction was small (approximately 0.4 dB), and this effect size is smaller than the observed effect of adduction in glaucomatous eyes in the current study. While the previous study indicated a slight increase in sensitivity during abduction, it is possible that this observation was due to experimental variability or other uncontrolled factors. The findings of the current study, particularly the decrease in sensitivity during adduction in glaucomatous eyes, might be more mechanistically plausible considering biomechanical stress imparted by straightening and stretching the optic nerve and therefore carry more weight in understanding disease mechanisms.

Reference Positions and Their Influence on Study Outcomes

In this regard, our study employed a VF test focused on a distance of 1 m at central gaze, compared with the 33 cm used in a traditional perimeter, thereby requiring little (<2°) adduction to view this test. In contrast, some studies using OCT required up to 17° of adduction to center the optic disc in the scan, thus establishing a different baseline gaze.[26,32] These studies did not compensate for the internal fixation target offset with OCT, resulting in an nasal fixation bias. Consequently, the adduction angle was overestimated, and the abduction angle was underestimated. Similar to our study, with central gaze as the reference point, a 13° adduction was shown to cause deformation around the optic nerve and peripapillary tissue through finite element modeling, even without optic nerve tethering.[33] Despite the smaller angle of eye movement in our study, we observed a decrease in VF sensitivity in glaucoma eyes during adduction.

Dynamics of Eye Movements and Optic Nerve Strain

In contrast to the continuous nature of elevated IOP, large adduction represents intense, transient phenomena that occur frequently. Humans perform saccadic eye movements, which are rapid shifts of the fovea toward points of interest, about three times per second. This enables high-resolution visual processing while maintaining stable perception. Although most naturally occurring human saccades have magnitudes of 15° or less,[34] large gaze saccades, coordinated with head movement, involve eye movements averaging 25° to 45°.[35,36] The strain on the optic nerve during saccades or binocular convergence, such as during reading, is likely less severe than during the largest and fastest adductions associated with tracking visual targets or coordinating with head turns.[31] Nevertheless, a recent study by Wang et al.[8] confirmed the hypothesis that horizontal eye movements exert strain on the ONH region. Their research, derived from theoretical modeling of a single subject, showed that even modest 13° abductions, which MRI revealed to keep the optic nerve slack, could induce more strain in the lamina cribrosa and papillary sclera than significant IOP elevations to 50 mm Hg. Further studies are required to determine whether the transient deformations of the prelamina ONH and peripapillary tissues, observed by structural and functional tests, lead to long-term damage of these tissues.

Exploring Physiologic Differences in IOP-Based Glaucoma Subtypes

Recently, Chuangsuwanich et al.[37] investigated the relationship between ONH strain measured by OCT and VF sensitivity after an acute increase in IOP. They reported a significant negative association between ONH strain and VF sensitivity in high-tension glaucoma compared to NTG. This may suggest physiologic differences between these glaucoma subtypes. Although our study did not differentiate between NTG and high-tension glaucoma due to limitations in sample size, it raises interest in whether there is a difference in VF sensitivity changes after horizontal eye movement between NTG and high-tension glaucoma.

ONH Blood Flow During Horizontal Ocular Duction

Our findings align with a recent study by Kawai et al.,[38] which observed ONH blood flow decreased during horizontal ocular duction in both healthy and glaucomatous eyes. Specifically, during adduction, a significant decrease in blood flow using laser speckle flowgraphy was noted in healthy eyes, while POAG eyes showed a decrease in both adduction and abduction. NTG eyes also exhibited a significant reduction in blood flow during adduction compared to central gaze. These findings suggest that mechanical compression and deformation during eye movements, particularly adduction, can influence blood flow in the ONH.

Temporal Changes in the Optic Nerve Head Due to Horizontal Eye Movements

Horizontal eye movements, such as adduction, rapidly impose mechanical stress on the optic nerve head and surrounding tissues.[33,39] This stress may temporarily alter the shape of the posterior eye, potentially affecting blood flow to the retina and neural transmission.[38] In glaucomatous eyes, we observed a diffuse decrease in sensitivity across 24plus points with adduction compared to central gaze within a short period of 4 to 6 minutes for VF testing. The slight differences in peripheral and central sensitivity are unlikely due to fatigue, considering the characteristics of AIZE. In our study, the changes between central gaze and adduction in glaucomatous eyes were statistically significant, but their impact on clinical practice remains unclear. Nevertheless, the long-term effect of horizontal eye movement might pose a potential risk for glaucoma. Activities requiring extended periods of adduction, such as using smartphones, may be potentially linked to the onset of glaucoma. There is currently insufficient scientific evidence to establish a definitive causal relationship, warranting future investigation. The potential connection between prolonged adduction and change in IOP,[40] as well as the progression of myopia due to near work,[41] further complicates this issue. Therefore, it is essential to design appropriate studies to specifically address these factors and accurately assess their impact.

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Limitations

This study has several limitations. First, our analysis was confined to small-angle horizontal eye movements. A previous study using OCT has demonstrated that the ONH deviation increased with larger angles, exhibiting a piecewise linear relationship in adduction.[32] Specifically, deviations for adductions greater than 25° showed a fourfold increase compared to smaller angles.[32] This raises the question of whether sensitivity reductions are exacerbated at larger angles. However, our preliminary findings indicated that a horizontal tolerance exceeding 10° induced severe fatigue among participants, resulting in low reproducibility due to the physical strain.[14] Therefore, further investigations, possibly incorporating alternative methodologies such as electroretinography, are needed to assess tolerance at wider angles. Second, during adduction, the eyeball may retract in high myopic eyes[11] or in glaucoma eyes.[42] If this recession causes the measured hill of vision to shift nasally (i.e., the optic nerve moves nasally to alleviate tethering), a systematic increase in temporal sensitivity and a decrease in nasal sensitivity would be expected. Nonetheless, since the present study did not include eyes with high myopia and the retraction was minimal in eyes with glaucoma,[42] it is unlikely to have influenced the position of the VF measurement in the current study. This finding suggests that a more accurate assessment can be achieved by using a fundus tracking perimeter. To ensure the robustness of our findings, we randomized the order of adduction and abduction testing to minimize learning and fatigue effects and confirmed that the test order did not influence MS differences. However, we acknowledge that it is not possible to eliminate all confounding factors. Moreover, while no current device can measure visual sensitivity during gaze shifts, we recognize that unknown factors might still impact the results. Third, the use of hypotensive eyedrops may have impacted our results. Eyedrops can lead to corneal thinning and reduced periocular adipose tissue, potentially altering the biomechanics of eye movements.[43] Fourth, the sample size of the current study was relatively small. To examine whether extreme values influenced the results, we repeated the analysis for Table 2 by excluding values that were ±3 SD from the mean for both "AD minus CG" and "AB minus CG." This included 39 patients with POAG and 40 healthy participants. The results showed CG > AD for both MS and MD ($P < 0.05$, respectively), which did not alter the interpretation of the results. Fifth, in our previous study, we included healthy individuals registered between October 2017 and September 2020.[14] The goal was to compare young healthy eyes with older healthy eyes, so we recruited participants from among the families of patients and volunteers through website postings and outpatient clinic notices. In older healthy eyes, higher MS was observed in abduction compared to adduction and central gaze (28.1 dB, 27.5 dB, and 27.7 dB, respectively).[14] In contrast, there was no significant difference in MS between abduction and central gaze positions in the current control group, even though the group was also elderly. Upon further analysis, combining data from both studies, we found that older age was independently associated with decreased MS, separate from the effects of horizontal eye movements (Tables 3 and 4). This analysis suggests that, based on the combined evidence from both studies, previous findings indicating that healthy older observers exhibit a change in visual sensitivity with horizontal gaze may require reconsideration in light of current findings, highlighting the importance of age in interpreting visual sensitivity differences.[24,44] Sixth, we did not use the attachment lens, so there were no effects of minification, magnification, or prismatic effects due to decentration. However, since the optical system of the device remains proprietary to CREWT Medical Systems, detailed information has not yet been disclosed. These potential effects should be clarified in future studies to better understand their impact. Lastly, we did not compare our result with test–retest variability. This is important to ensure that the measured differences are outside the range of variability. We are planning to study test–retest variability, and this will be reported in future research.

In conclusion, MS with adduction was significantly worse than with both central gaze and abduction in glaucoma. This raises the possibility of eye positioning having a contributory role in glaucoma pathophysiology, perhaps due to mechanical stress on the optic nerve. Further studies are needed to better understand its implications for clinical management. In healthy individuals, sensitivity remained consistent with horizontal gaze. While this appears to contrast with previously published work, our reanalysis of the earlier data suggests that the conclusion that horizontal gaze alters visual sensitivity in older adults may require reevaluation.

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