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Glaucoma

Measurement of Fixational Eye Movements With the Head-Mounted Perimeter Imo

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Purpose: Although visual field testing is conducted with the subject gazing at a fixation target, constant minute eye movements, called fixational eye movements, do occur during fixation. We examined dynamic changes in fixational eye movements associated with stimulus presentation during visual field testing.

Methods: We used the head-mounted perimeter imo, which is capable of measurement under binocular conditions, with the frame rate of its fixation monitoring camera improved to 300 Hz, to assess fixational eye movements in 18 healthy individuals. We measured changes in fixational eye movements during testing under monocular and binocular conditions and analyzed these changes based on the bivariate contour ellipse area (BCEA). We also assessed the changes in the horizontal and vertical microsaccade rates separately.

Results: Both the BCEA and horizontal microsaccade rates were higher at 400 to 600 msec after stimulus presentation than during stimulus presentation ($P < 0.01$). Additionally, the BCEA and vertical microsaccade rates were significantly lower in the binocular condition than in the monocular condition ($P < 0.01$ and $P < 0.05$, respectively). We did not observe a significant correlation between the test locations and microsaccade direction during visual field testing.

Conclusions: Fixational eye movements, especially vertical microsaccade rates, were lower in the binocular condition than in the monocular condition. Visual field testing under binocular conditions is a useful method for suppressing fixational eye movements and stabilizing the fixation during testing and may improve the reliability of the test results.

Translational Relevance: Visual field testing under binocular conditions can make the fixation more stable during the testing compared with monocular conditions.

Introduction

Standard automated perimetry (SAP) is a subjective test in which the subject responds to a test target presented as they fixate at a fixation target. Stabilization of the subject's fixation during visual field testing is important for obtaining reliable measurements. In general, a threshold variability is observed during visual field testing, even when several measurements are performed at the same location. Furthermore, this threshold variability is more pronounced in the locations where visual field defects have progressed.[1–4] Using high-resolution perimetry with a 0.5° test point interval, Numata et al.[5] reported that the main causes of this variability were minute eye movements that occurred at the locations such as the edge of scotomas during testing.

Even when we attempt to fix our gaze on an object, our eyes continually make micromovements. We cannot perceive these fixational eye movements directly.[6] Fixational eye movements are divided into three

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components: microsaccades, drifts, and tremors.[7–9] As reported by Pritchard,[10] when the image was fixed on the retina, the subject felt that the image had disappeared after a few seconds of viewing, demonstrating that fixational eye movements are necessary for the physiological perception of images on the retina in humans. The role of microsaccades was thought to be limited to correcting deviation of gaze from its target.[11] However, recent studies have demonstrated that microsaccade dynamics are affected by spatial visual attention shifts and conscious control.[12–17]

To increase the reliability of visual field test results, it is necessary to know the changes in the fixation variability during the test. Previous studies on fixational eye movements during visual field testing have used microperimetry with an eye tracking system[18–21] and SAP with eye tracking glasses.[22,23] In patients with conditions such as glaucoma, diabetic retinopathy, and macular holes, fixation stability during visual field testing is lower than in healthy individuals.[18–20] Fixation stability during visual field testing decreases with increasing fixation target size.[21,22] In a study of eye movements in healthy individuals during visual field testing, Hirasawa et al.[23] reported that fixation stability during visual field testing was higher under binocular than under monocular conditions. The engagement of fusion mechanisms in binocular viewing may improve fixation stability. In the many studies cited, fixation stability was quantified through overall visual field testing using the bivariate contour ellipse area (BCEA), which represents the range of eye movement in terms of area.[19–23] These studies did not examine changes in fixational eye movements accurately synchronized with individual stimulus presentations over short periods, such as before, during, or after stimulus presentation. That is, they did not consider fixational eye movements during the test. Fixational eye movements are extremely difficult to control during visual field testing using current eye tracking technology. Additionally, the cameras in these studies did not have a high frame rate, which precluded them from isolating microsaccades. In addition, the perimeter used in these reports clinically performed a test with one eye occluded. Current SAP perimetry is done under monocular conditions, and it does not consider fixation stability or fixational eye movements. There are no studies using a perimeter that can perform a visual field testing of one eye under binocular conditions.

In SAP, a Goldmann size III (0.43° visual angle) test target stimulates the retina for 200 msec at a time. However, because of the effects of fixational eye movements, the test target moves across and stimulates a wider area of the retina than anticipated. To the best of our knowledge, there have been no reports of studies that assessed the range of fixational eye movements during stimulus presentation in this clinical visual field test.

In the present study, using the head-mounted perimeter imo (CREWT Medical Systems, Tokyo, Japan)[24] that enables visual field testing of one eye under binocular conditions, we measured fixational eye movements during visual field testing with a high frame rate under monocular and binocular conditions, to determine changes in fixational eye movements and changes in the rate and direction of microsaccades before, during, and after stimulus presentation. Additionally, we investigated whether the binocular condition or monocular condition is more advantageous for the stability of fixation in the visual field testing.

Methods

Subjects

Visual field testing was conducted on 18 right eyes in 18 healthy individuals (9 men and 9 women, mean age 40.4 ± 8.75 years of age; spherical equivalent right eye: −3.28 ± 3.02 diopters [D], left eye: −3.51 ± 2.94 D). Participants were naive for imo visual field. Exclusion criteria consisted of the following: corrected visual acuity of less than 1.0 in one or both eyes, refractive error of greater than 10 D, astigmatism of greater than 3 D, previous eye surgery, eye disease resulting in an abnormal visual field, systemic diseases with potential effects on visual function, strabismus-induced dysfunction resulting in an abnormal visual field, or poor fixation.

The present cross-sectional study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Institutional Review Board of the Faculty of Medicine, Kindai University (No. 26–239), and all subjects provided informed written consent.

Equipment

In the present study, we used the head-mounted perimeter imo (CREWT Medical Systems). The imo is a portable perimeter that can also test visual fields under binocular conditions, based on standard visual field testing conditions (stimulus size, Goldmann size III; stimulus duration, 200 msec; background luminance, 31.4 asb). Because the imo has independent left and right optical systems, the test target can be displayed separately for the right and left eyes.

Thus, the imo can present the test target randomly to either eye under the binocular condition without the subject being aware of which eye is being tested. During testing, movements in both eyes are observed using a CMOS sensor camera with a frame rate of 30 Hz (Basler AG, Ahrensburg, Germany). In the present study, we changed the CMOS sensor frame rate to 300 Hz (XIMEA, Münster, Germany) to observe fixational eye movements. We secured the imo to a dedicated smart stand and conducted testing with the subject's head fixed, as in typical perimetry.

Procedure

We performed visual field testing under binocular and monocular conditions three times each for all subjects. Under the binocular condition, the subject fixates at the central fixation target displayed on each eye, resulting in binocular fusion. The test target was presented to the right eye of the subject. In testing under the monocular condition, the subject wore an eyepatch on their left eye. After each test, the subjects were given a break of at least 5 minutes. During testing, the subjects were allowed to blink freely.

Test conditions were as follows: stimulus luminance was 100 asb, stimulus size was Goldmann size III, background luminance was 31.4 asb, stimulus duration was 200 msec, and the stimulus interval was 1000 msec. The subjects were presented a test target at test points at 5° intervals on the 45° line, that is, (0°, 0°), (+20°, +20°), (+15°, +15°), (+10°, +10°), (+5°, +5°), (−5°, −5°), (−10°, −10°), (−15°, −15°), and (−20°, −20°); the test target was presented to these locations at random (Fig. 1). Additionally, to assess false-positive responses, we established a time with no stimulus presentation. Figure 2 shows an example of the test data. Figure 3 presents a magnified view of the data, which is divided into five 200-msec time windows for analysis: stimulus presentation, before stimulus presentation 2 (b2), before stimulus presentation 1 (b1), after stimulus presentation 1 (a1), and after stimulus presentation 2 (a2).

Data Analysis

Assessment of Fixational Eye Movements

We quantified fixational eye movements with a BCEA, following the standard method.[25] The equation for calculating the BCEA is as follows:

$$\mathrm{BCEA} = 2 \times \mathrm{k} \times \pi \times \sigma_{\mathrm{H}} \times \sigma_{\mathrm{V}} \times \sqrt{\left(1 - \rho^2\right)},$$

where σ_{H} and σ_{V} are the standard deviations of the fixation points along a vertical and horizontal line, respectively, and ρ represents the product-moment correlation of the two location components. Additionally,

$$\mathrm{p} = 1 - e^{-\mathrm{k}},$$

where e is the base of the natural logarithm. The value of k depends on the area chosen. For this study, fixation data were calculated with P values of 0.95 (k = 3), corresponding with approximately 2 standard deviations of the fixation location data.

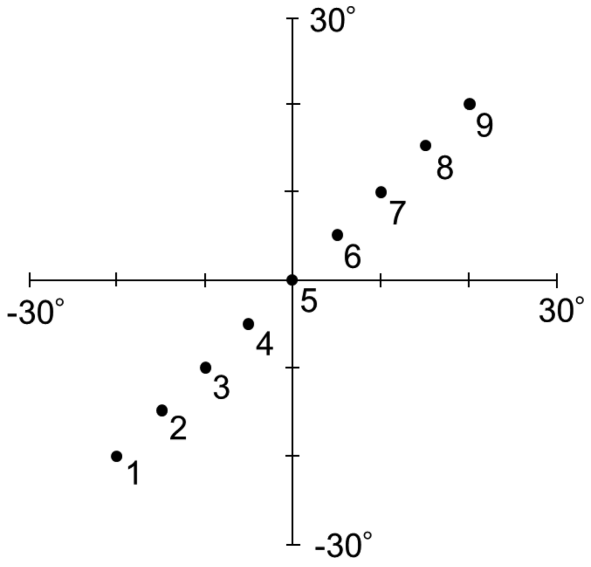

Figure 1. Test locations. Test targets were at 5° intervals on the 45° line.

Detection of Microsaccades

Figure 4 shows how to detect microsaccades. As preprocessing for the detection of microsaccades, we first eliminated noise from measurement data (a) using a five-frame median filter. Next, we deconstructed the measurement data into their horizontal and vertical components and converted them into changes in eye position between each pair of consecutive frames using a differential filter and an absolute value operation.

To examine microsaccades, it is necessary to establish an amplitude threshold for defining microsaccades. Although different researchers have used different thresholds, a threshold of less than 1° has been shown to be practical because it captures 90% of fixational saccades.[26] In the present study, changes in eye movements between frames greater than 0.1° and smaller than 1.0° were counted as microsaccades.

Detection of Blinking

The periods of missing measurement data were considered blinks or saccades. Additionally, as reported in a previous study, microsaccade rate changes for a certain period after a blink.[27] Based

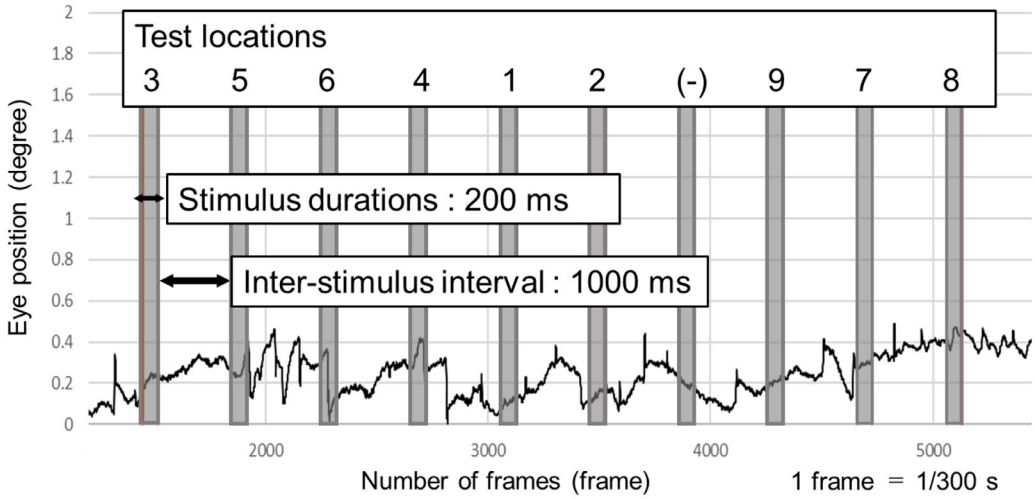

Figure 2. Example of test data (horizontal and vertical components combined). The eye position information during testing is displayed in terms of degrees on the *y*-axis and the number of frames on the *x*-axis; 1 frame = 1/300 s. The gray bars represent the stimulus presentation (= 200 msec). The interstimulus interval was 1000 msec. The test location numbers correspond with the numbers shown in Figure 1. (–) indicates no stimulus location, used to assess false-positive responses.

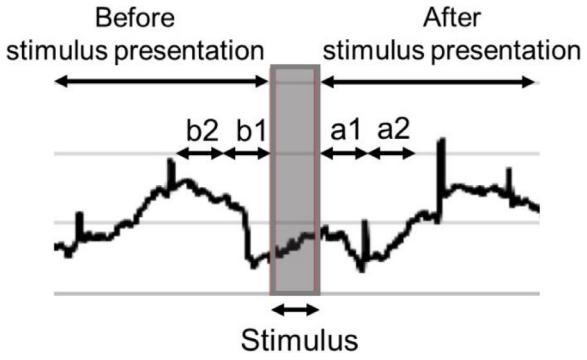

Figure 3. Magnified view of 3000 to 4000 frames shown in Figure 2. The gray bar in the center represents stimulus presentation. The data were divided into five 200-msec time windows for analysis: stimulus presentation, before stimulus presentation 2 (b2), before stimulus presentation 1 (b1), after stimulus presentation 1 (a1), and after stimulus presentation 2 (a2).

on these findings, when a blink occurred during testing in the present study, we deleted all data from 100 msec before the start of the missing measurement data to 400 msec after the missing data.

Statistical Analysis

Data were analyzed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[28] Subjects underwent testing under binocular and monocular conditions three times each, and the means of these three measurements were used for determining the BCEA and microsaccade rate under each condition. We performed multiple comparisons for the BCEA, horizontal microsaccade rate, and vertical microsaccade rate in each time window (200 msec) using the Wilcoxon signed-rank test with Bonferroni correction. Additionally, the BCEA, horizontal microsaccade rate, and vertical microsaccade rate in b2 to a2 (1000 msec) under the binocular and monocular conditions were compared using the Mann–Whitney *U* test.

Results

Comparisons of BCEA Under Binocular and Monocular Conditions

Figure 5 shows BCEA throughout b2 to a2 under binocular and monocular conditions. The BCEA was significantly larger under the monocular condition than under the binocular condition ($P < 0.01$). Figure 6 shows the BCEA during each time window. Under the binocular condition, BCEA during a2 was significantly larger than during b2 ($P = 0.015$). Additionally, the BCEA during a2 was significantly larger than during b1, stimulus presentation, and a1 ($P < 0.01$). Results were nearly identical under the monocular condition: the BCEA during a2 was significantly larger than during any other time window, except for during b2 ($P < 0.01$).

Retinal Area Stimulated by the Test Target

The test target presented to the subjects was Goldmann size III (0.43° visual angle). Assuming that the eye did not move, the retinal area stimulated by the

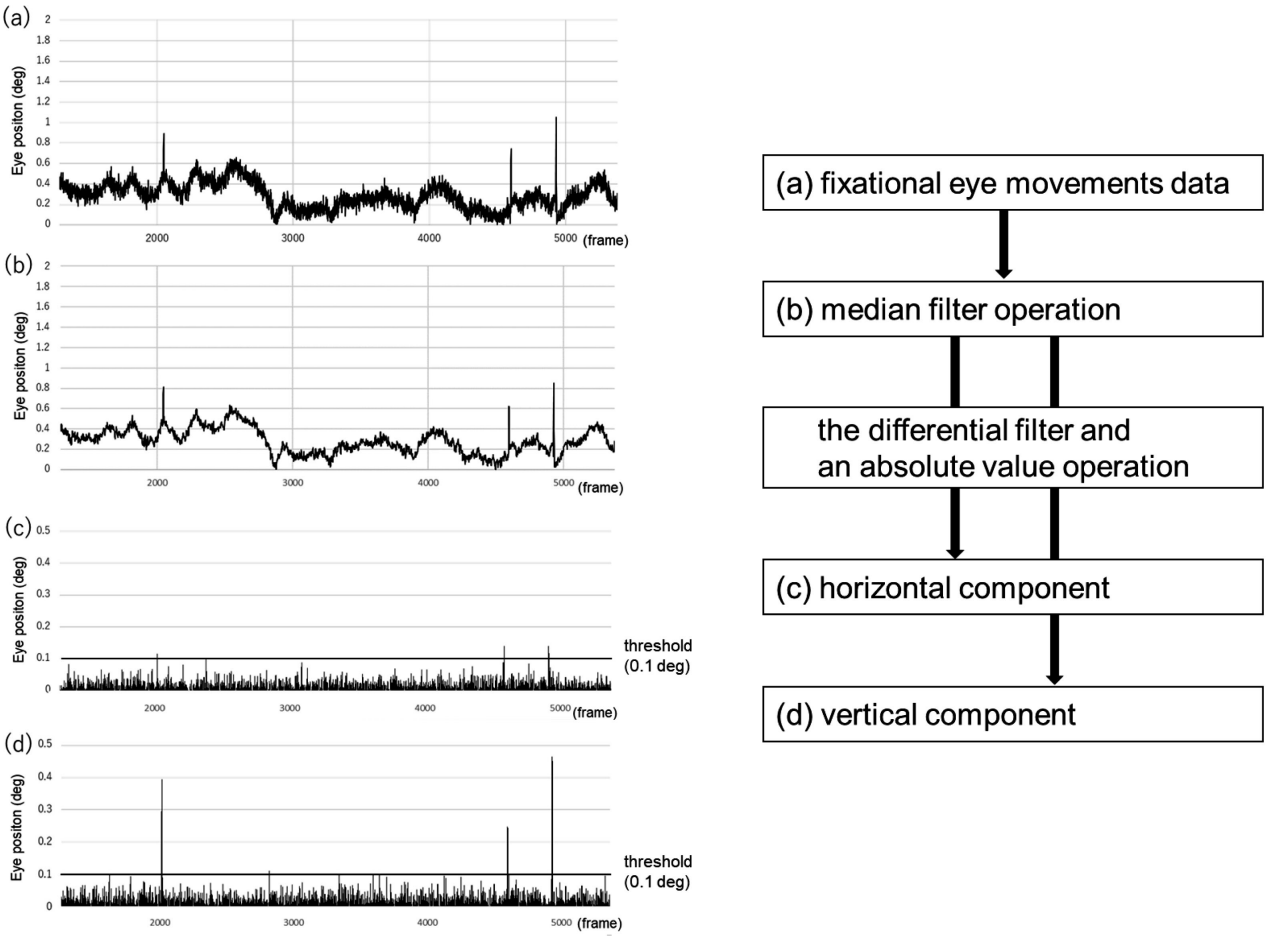

Figure 4. Data analysis procedure. (a) Fixational eye movement data, (b) median filter, (c) horizontal component of change, and (d) vertical component of change. Eye movement changes greater than 0.1° and smaller than 1.0° were counted as microsaccades.

test target would be 0.145°^{2}. The median BCEA during stimulus presentation under the binocular and monocular conditions was 0.031°^{2} and 0.037°^{2}, respectively. If the eye is assumed to move within a perfect circle of the same area as the BCEA, the retinal area stimulated by the test target during stimulus presentation (200 msec) under the binocular and monocular conditions would be 0.311°^{2} and 0.327°^{2}, respectively. Thus, the stimu-

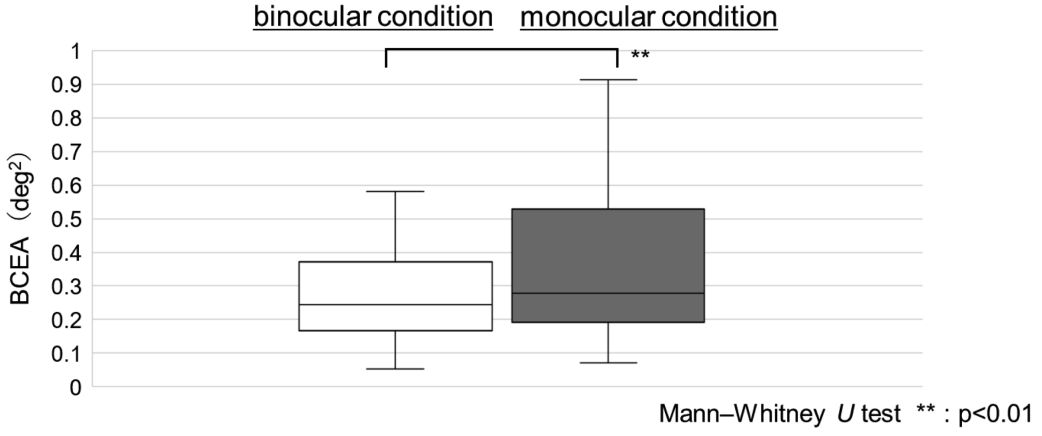

Figure 5. Comparisons of the BCEA throughout b2 to a2 (1000 msec) under the binocular and monocular conditions. The BCEA was significantly larger under the monocular condition than under the binocular condition.

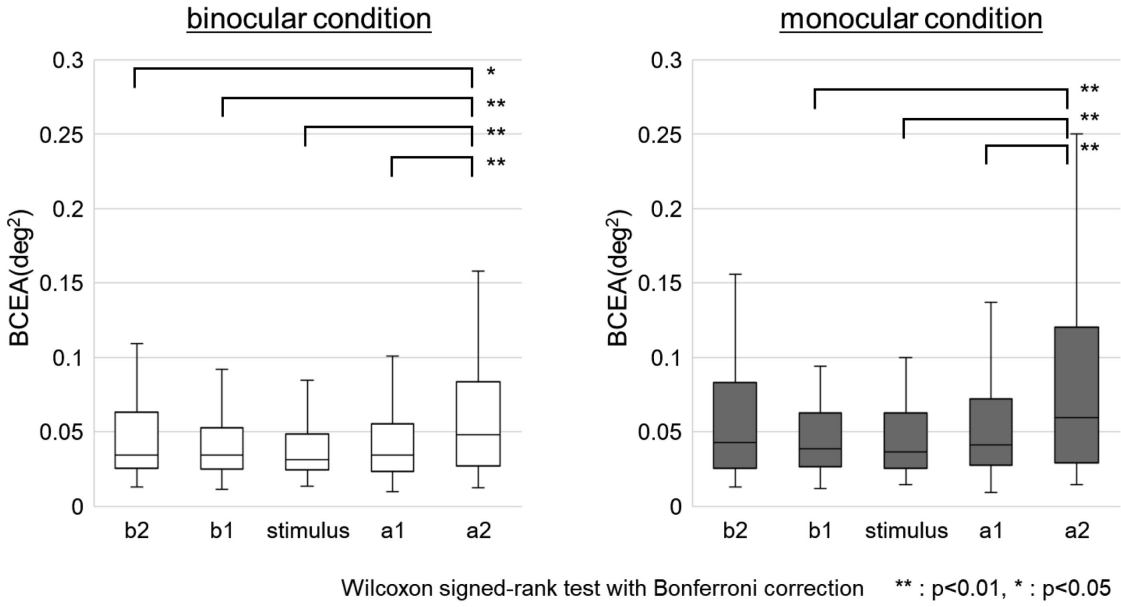

Figure 6. Comparisons of the BCEA in each time window under binocular and monocular conditions. Under the binocular condition, the BCEA was significantly larger during a2 than during any other time window. Under the monocular condition, the BCEA was significantly larger during a2 than during any other time window, except for b2.

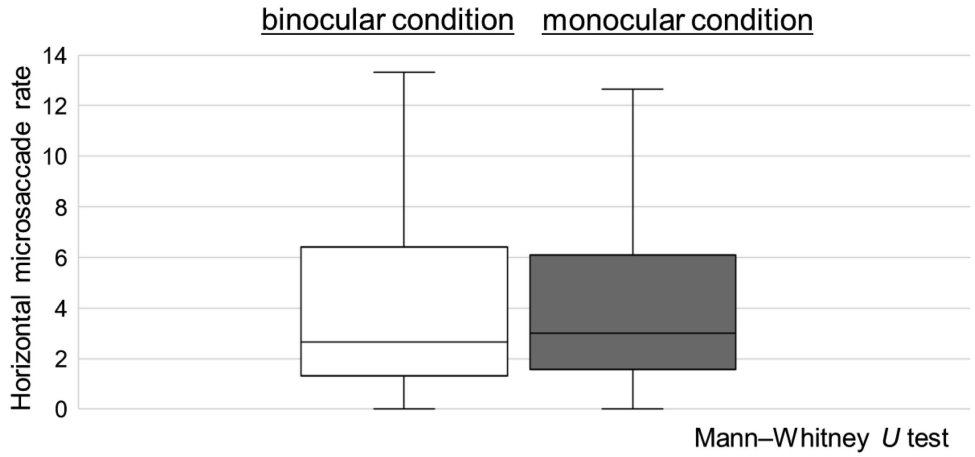

Figure 7. Comparison of horizontal microsaccade rates throughout b2 to a2 (1000 msec) under the binocular and monocular conditions. There was no significant difference in the microsaccade rate between the binocular and monocular conditions.

lated area of the retina was roughly twice that of the original stimulus size.

Microsaccade Rates Under Binocular and Monocular Conditions

Figure 7 shows the horizontal microsaccade rates throughout b2 to a2 under the binocular and monocular conditions. There was no significant difference in the horizontal microsaccade rates between these conditions. Figure 8 shows the horizontal microsaccade rates during each time window. Under both the binocular and monocular conditions, the horizontal microsaccade rates were significantly higher during a2 than during any other time window, except for b2 ($P < 0.01$). Figure 9 shows the vertical microsaccade rates throughout b2 to a2 under the binocular and monocular conditions ($P = 0.015$). The vertical microsaccade rate was significantly higher under the monocular condition than under the binocular condition. Figure 10 shows the vertical microsaccade rates during each time window. There were no significant differences in microsaccade rates between any

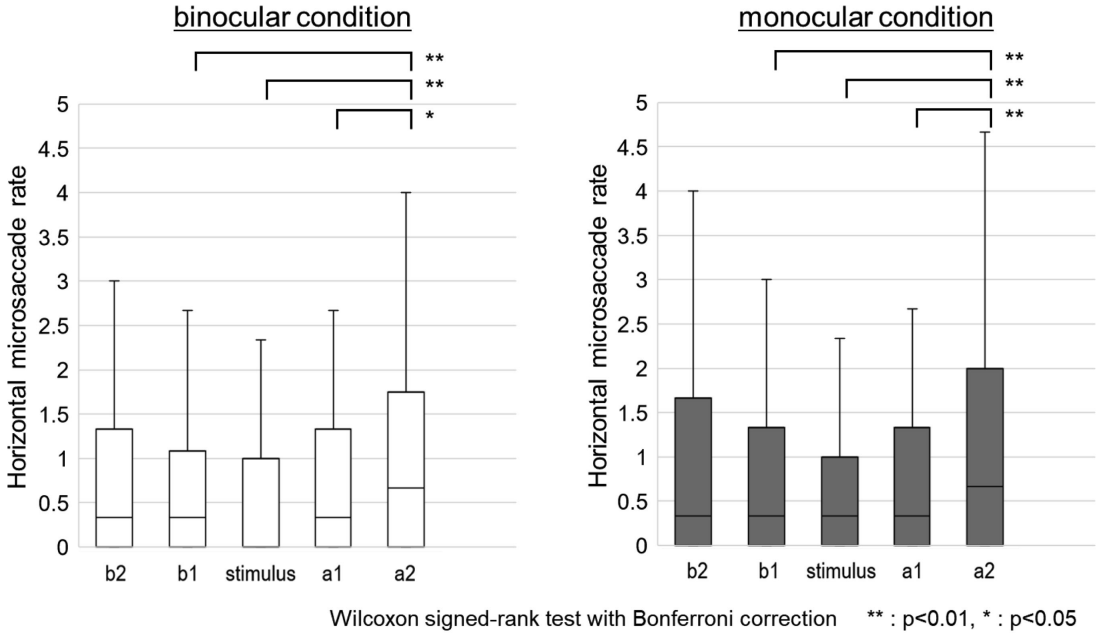

Figure 8. Comparisons of horizontal microsaccade rates in each time window under binocular and monocular conditions. Under both types of conditions, microsaccade rates were significantly higher during a2 than any other time window, except for b2.

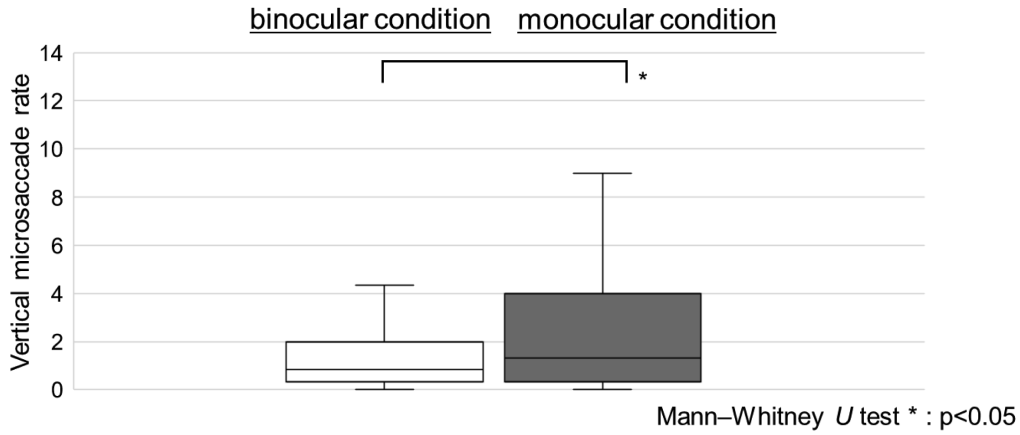

Figure 9. Comparison of vertical microsaccade rates throughout b2 to a2 (1000 msec) under the binocular and monocular conditions. The microsaccade rate was significantly higher under the monocular condition than under the binocular condition.

time windows under either the binocular or monocular conditions.

Comparisons of Horizontal and Vertical Microsaccade Rates

Figures 11 and 12 show comparisons of horizontal and vertical microsaccade rates throughout b2 to a2 (1000 msec). Under both the binocular (Fig. 11) and monocular conditions (Fig. 12), horizontal microsaccades occurred more frequently than did vertical microsaccades ($P < 0.01$).

BCEA and Microsaccade Rates in the False-Positive Interval

To assess false-positive responses, we established a time during visual field testing during which no stimulus was presented. As with actual stimulus presentations, we divided the false-positive interval into five time windows and compared the BCEA and microsaccade rates among those time windows.

Figure 13 shows comparisons of the BCEA (Fig. 13A), horizontal microsaccade rate (Fig. 13B), and vertical microsaccade rate (Fig. 13C) among all time windows during the false-positive interval under

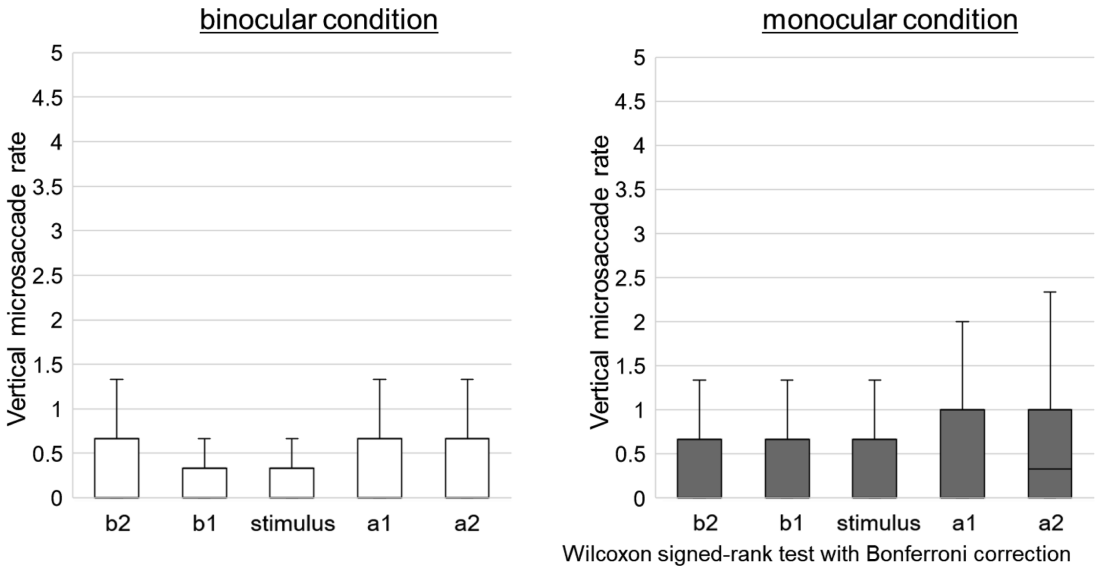

Figure 10. Comparisons of vertical microsaccade rates in each time window under the binocular and monocular conditions. There were no significant differences in the microsaccade rate between any time windows under either the binocular or monocular conditions.

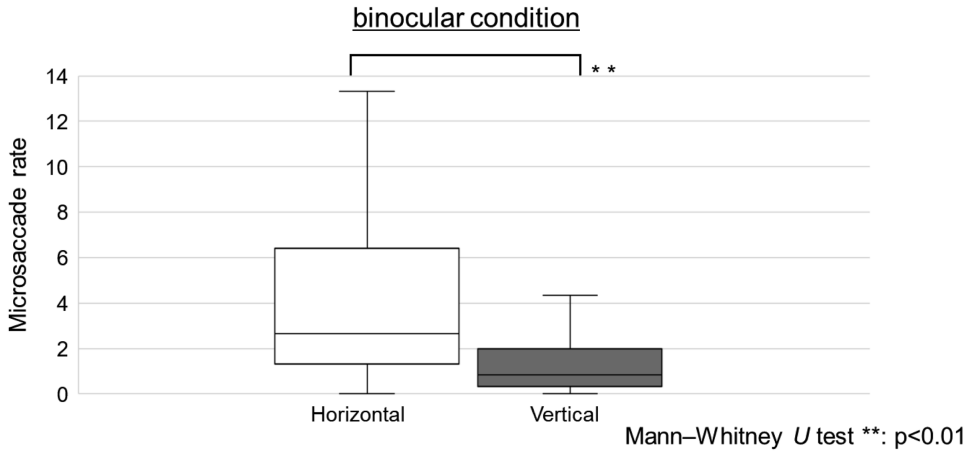

Figure 11. Comparison of horizontal and vertical microsaccade rates throughout b2 to a2 (1000 msec) under the binocular condition. Horizontal microsaccades occurred more frequently than did vertical microsaccades.

the binocular and monocular conditions. There were no significant differences in BCEAs or microsaccade rates between any time windows under either the binocular or monocular conditions.

Directions of Microsaccades

Figure 14 shows the direction of the first microsaccade that occurred in the a2 time window (in which the BCEA and microsaccade rates were significantly high) by test location, as angle histograms. The microsaccade direction was not associated with the test location under either binocular or monocular conditions.

Discussion

The purpose of this study was to measure fixational eye movements during visual field testing under monocular and binocular conditions to determine changes in fixational eye movements and the rate and direction of microsaccades before, during, and after stimulus presentation. Additionally, we investigated whether the binocular condition or monocular condition is more advantageous for the stability of fixation in visual field testing. The BCEA and vertical microsaccade rates were significantly lower in the binocular condition than in the monocular condition. Our results

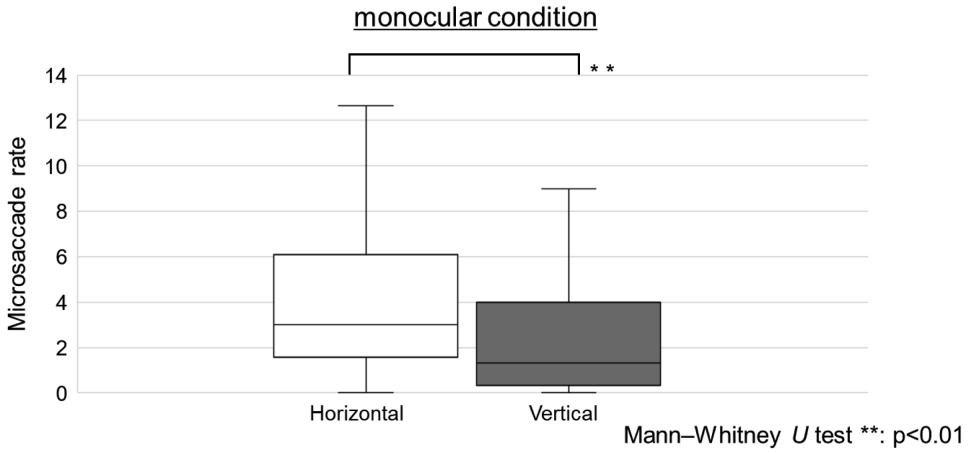

Figure 12. Comparison of horizontal and vertical microsaccade rates throughout b2 to a2 (1000 msec) under the monocular condition. Horizontal microsaccades occurred more frequently than did vertical microsaccades.

showed that the binocular condition improved the stability of fixation compared with the monocular conditions.

BCEA Under Binocular and Monocular Conditions

In the present study, the BCEA was significantly lower before and after stimulus presentation under the binocular than under the monocular condition. In a study conducted with healthy individuals, Hirasawa et al.[23] reported that in a long duration test, such as visual field testing, fixation was more stable under the binocular than under the monocular condition, and there was no significant difference in fixation stability between monocular and binocular condition in a short duration foveal threshold measurement test. Raveendran et al.[29] reported that fixational eye movements in healthy individuals during a 30-s fixation were significantly more stable for binocular than for monocular viewing. The authors surmised that the engagement of fusion mechanisms in binocular viewing improves fixation stability by activating feedback mechanisms within oculomotor control pathways.[29] In the present study, the BCEA was decreased under the binocular condition, conceivably via the same mechanism.

We used the perimeter imo, which has independent left and right optical systems, making it possible to present a test target and a fixation target to the eye being tested, while presenting only a fixation target to the other eye, thus enabling monocular visual field testing under binocular conditions. Fixational eye movements are extremely difficult to control during visual field testing using current eye tracking technology. Thus, visual field testing under binocular conditions, which enable control of fixational eye movements, is a potentially useful technique because it stabilizes fixation.

Increased fixation stability improves the reliability of test results, and it helps us to know the visual field defects as well as to evaluate the progression of disease more precisely. However, if the fixation stability during the visual field testing is higher than that of daily life, the test result may be far from the patient's actual visual function. Patients generally undergo visual field testing under particular conditions such as monocular conditions and in a dark room; it differs greatly from a daily life environment. From this point of view, it is important not to maximize fixation stability, but to test with the same level of stability that occurs in daily life. Visual field testing under binocular conditions that are closer to daily life than monocular patching may be a useful method for evaluating the patient's actual visual function.

Retinal Area Stimulated by a Goldmann Size III Test Target

If fixational eye movements are assumed to occur in a perfect circle of the same area as BCEA during stimulus presentation (200 msec), a Goldmann size III test target would stimulate roughly double the retinal area while moving within it during visual field testing in healthy individuals. In patients with conditions such as glaucoma and diabetic retinopathy, fixation is less stable than in healthy individuals;[18–20] thus, for such patients, a test target would likely stimulate a wider retinal area than that in the present study. Using high-resolution perimetry with a test interval of 0.5° in glaucoma patients, Numata et al.[5]

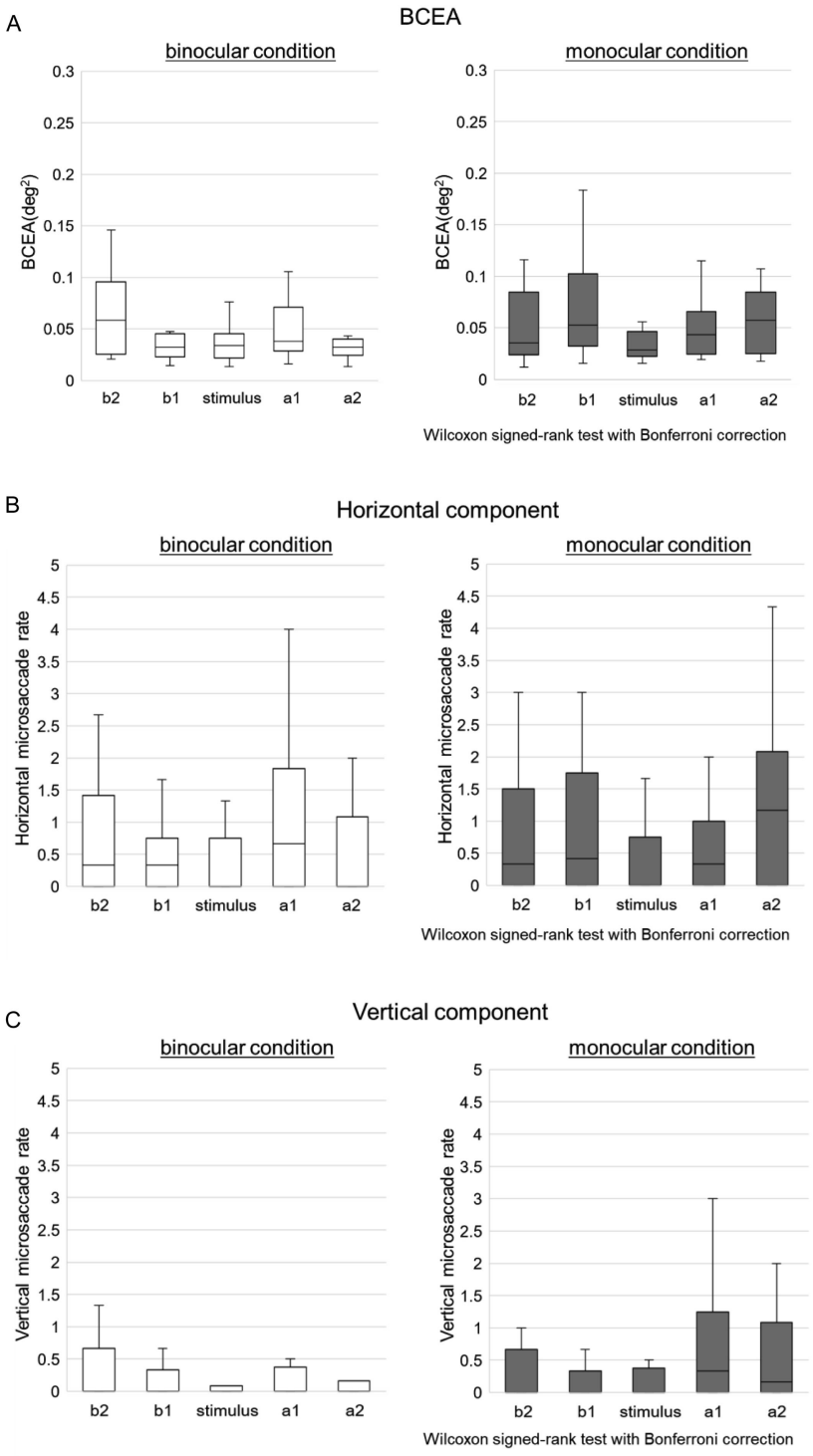

Figure 13. Comparisons of the BCEA (A), horizontal microsaccade rate (B), and vertical microsaccade rate (C) among all time windows in the false-positive interval under binocular and monocular conditions. There were no significant differences in the BCEA or microsaccade rates between any time window under either the binocular or monocular conditions.

reported increased threshold variability at the edges of scotomas, suggesting that fixational eye movements during stimulus presentation greatly affect threshold variability in test locations. However, visual information processing during eye movement involves a control mechanism called "saccadic suppression," which stabilizes jitters in visual information.[30] The same perceptual stabilization mechanism is also reported to be

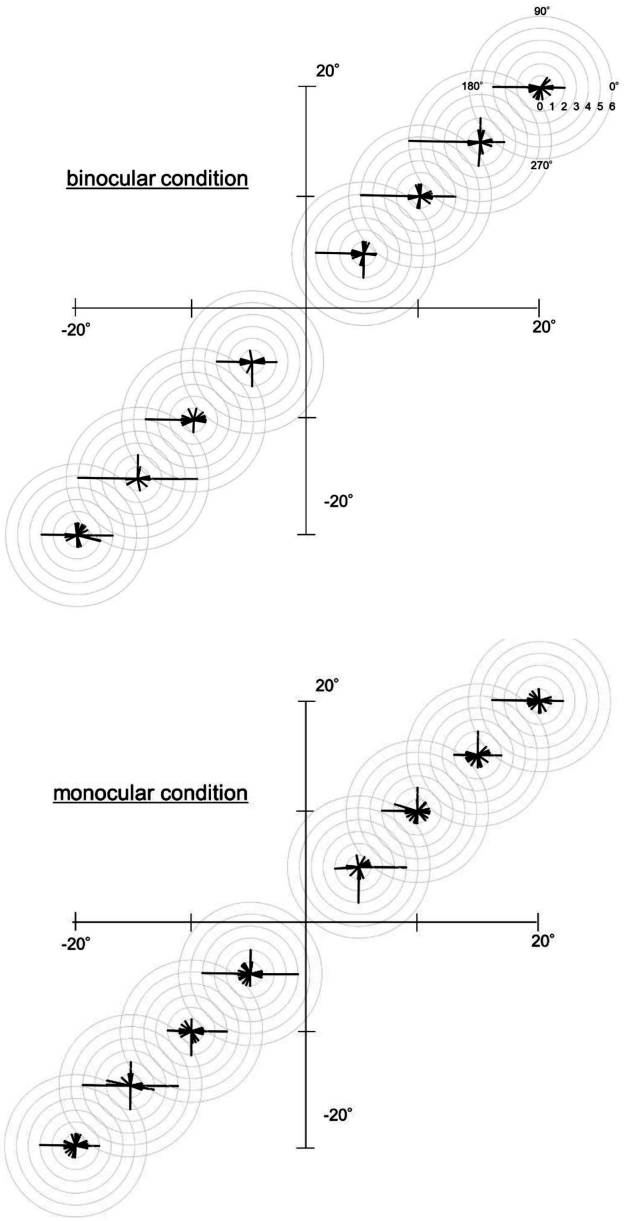

Figure 14. Angle histograms of the first microsaccades to occur in the a2 time window. The concentric circles are 1° intervals at each of the test locations. Axis units and angles are shown on a diagram of binocular condition coordinates (+20° and +20°). There were no significant trends in terms of test locations or microsaccade direction.

involved in minute eye movements, such as microsaccades.[31] The question of how fixational eye movements stimulate a wider retinal area than presumed and ultimately combines with saccadic suppression to affect visual information processing requires further study.

Horizontal and Vertical Microsaccades

Assuming that binocular eye movement is being observed, binocular microsaccades (movement in both eyes simultaneously) occur mainly in a horizontal direction, whereas monocular microsaccades (eye movements in one eye only) occur both in horizontal and vertical directions.[13,32,33] Engbert[14] surmised that binocular microsaccades occur in the horizontal direction to correct binocular disparity caused by drift and tremor, the other components of fixational eye movements. In the present study, we only observed the right eye, and thus we cannot strictly distinguish whether the microsaccades that occurred under the binocular condition were binocular or monocular. However, in our results, the vertical microsaccade rate was significantly higher under the monocular condition than under the binocular condition. Under the monocular condition, only a single eye fixates, causing the monocular microsaccade rate to increase; this factor may explain the increase in the vertical microsaccade rate.

Poststimulus Microsaccadic Inhibition and Rebound

Under both binocular and monocular conditions, the horizontal microsaccade rate was significantly higher during the a2 time window (400–600 msec) than during or before stimulus presentation. In a previous study, optical stimulus perception by subjects induced microsaccadic inhibition (a decrease in the rate of passive microsaccades), followed by a rebound (a subsequent increase in the microsaccade rate).[12] In the present study, the increase in microsaccades during the a2 time window was conceivably due to this rebound effect.

In contrast, although we observed a trend for microsaccadic inhibition, it was not statistically significant. One conceivable reason for the absence of significance in the trend is that there were not enough microsaccades to assess because of the low number of tests conducted.

Poststimulus Presentation Microsaccade Direction

Microsaccade direction is reported to demonstrate the hidden direction of a person's attention.[13–16] When Laubrock et al.[12] presented subjects with squares (1.24° side length) 5° to the left or right of the fixation spot at random times, microsaccades occurred in the direction where the square was presented. However, another study reported that the direction of microsaccades has little relation to the direction of an individual's attention.[34] In the present study, when we examined microsaccade directions and test locations in the a2

time window (400−600 msec), when the microsaccade rate was significantly increased, we did not observe any significant relation to any test target. The results in our study were based strictly on visual field testing measurement conditions used in clinical practice; therefore, we cannot rule out the possibility that the stimulus intensity was too weak to induce visual attention. We may need to conduct further studies with more visible stimulus presentations.

Application of Fixational Eye Movements in Objective Visual Field Testing

Current visual field testing is subjective: the subject responds by pushing a button when they see the test target. For example, in patients with psychogenic disorders and malingering, visual field testing results often suggest that the patient has a visual field defect despite not demonstrating any structural disorders. The results of the present study confirmed that microsaccade rates change significantly in passive attention toward optical stimuli used in visual field testing, even if the subject did not push the button. In the future, a more efficient use of this property of fixational eye movements may lead to their application as an objective indicator independent of the subject's subjective response in visual field testing.

Study Limitations

The present study had some limitations. First, the sample size was small. Owing to the large individual differences in fixational eye movements, assessing the detailed properties of fixational eye movements requires a larger sample size. Second, the subjects in the present study were healthy and relatively young. As clinical application progresses, it may be necessary to assess the properties of fixational eye movements in glaucoma and other disorders that cause visual field defects. Third, there were problems with the frame rate of the testing equipment. The CMOS sensor camera for fixational eye movements, which is built into the perimeter imo, has a sampling rate of 30 Hz, which we improved 10-fold to 300 Hz for analysis. However, detecting microsaccades more accurately requires an even higher frame rate. In the future, we intend to continue our research with equipment capable of assessing eye movements with a higher frame rate.

Conclusion

To our knowledge, there is no previous study to compare the fixational eye movements between the binocular and monocular conditions with the SAP for clinical use. It has been known that fixation stability affects a reliability of visual field test. Our results demonstrate that visual field testing under binocular conditions suppresses fixational eye movements, especially microsaccade rates, and stabilizes fixation during a test. In clinical practice, a highly reliable test result is more beneficial for making a diagnosis and evaluating progression of disease. The binocular visual field test could have a potential for detecting more detailed visual field abnormalities and less test-retest variability than the monocular test.

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