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Effect of Sensitivity Disparity Between the Two Eyes on Pointwise Monocular Sensitivity Under Binocular Viewing in Patients With Glaucoma

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Précis: A difference between monocular sensitivities measured with and without occlusion was observed in glaucoma. Monocular sensitivity without occlusion could have been affected differently by binocular interaction due to the sensitivity disparity between both eyes.

Purpose: To investigate the influence of sensitivity disparity between both eyes on visual field results under binocular viewing in glaucoma.

Materials and Methods: Thirteen glaucoma patients tested by Humphrey Field Analyzer (HFA) and imo were reviewed retrospectively. On the basis of their HFA results, we defined the eye with a better HFA-MD as "the better eye" and the fellow eye with a worse HFA-MD as "the worse eye." Depending on the pointwise pattern deviation (PD) of both eyes, all evaluated test points were classified into 4 groups: normal PD in both eyes (N/N), normal PD in the better eye but abnormal in the worse eye (N/A), abnormal PD in the better eye but normal in the worse eye (A/N), and abnormal PD in both eyes (A/A). Using imo, which can measure sensitivity with and without occluding the nontested eye, the better eye's sensitivities with and without occlusion were compared in each group using weighted data. The weight was derived by applying the inverse probability weighting.

Results: Monocular sensitivity without occlusion was higher than that with occlusion in N/N ($P < 0.01$) and the opposite was observed in A/A ($P < 0.05$). No significant sensitivity difference between both conditions was seen in N/A or A/N. In N/A, the points showing a higher sensitivity without occlusion decreased as the sensitivity difference between both eyes increased.

Conclusions: A difference between sensitivities measured with and without occlusion was observed in glaucoma. Owing to the sensitivity disparity between both eyes, monocular sensitivity without occlusion could have been affected differently by binocular interaction.

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Visual field (VF) testing is essential for diagnosis and assessment of glaucoma progression. Clinically, the nontested eye is usually occluded with an opaque occluder during VF testing. Although the influences of occlusion on sensitivity have been reported,[1–4] monocular sensitivity measurement without occluding the nontested eye remains difficult and comparison of monocular sensitivities measured under both conditions (with and without occlusion) has not been made.

A head-mounted perimeter "imo" (CREWT Medical Systems Inc., Tokyo, Japan) that enables VF testing without occluding the nontested eye has been developed recently. This perimeter has an optical system which is completely separated for the right and left eyes. The backgrounds for the 2 eyes are fused and a target is projected on the fused background.[5] Using imo, we have compared monocular sensitivities measured with and without occlusion and investigated the influence of binocular interaction on monocular sensitivity in normal volunteers.[6] Our previous results indicate that without occlusion, binocular interaction is activated and affects not only binocular sensitivity but also monocular sensitivity. Because the imo backgrounds for the 2 eyes are fused as 1, it is important to further investigate if the sensitivity difference between the 2 eyes that correspond under binocular viewing affects monocular sensitivity measurements. This is particularly important in patients with glaucoma because the backgrounds will be fused in the 2 eyes with sensitivity disparity.

Previous studies have used imo to evaluate monocular sensitivities in glaucoma eyes. Reportedly, the mean sensitivity obtained by imo correlates with the mean sensitivity by the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec Inc., Dublin, CA) in patients with glaucoma.[5] Under binocular viewing, the central sensitivity of glaucoma patient's better eye is higher and that of the worse eye is lower as compared with the measurements with occlusion.[7] To assess glaucomatous VF progression, not only overall but also local sensitivity changes should be investigated. It is therefore essential to evaluate how sensitivity change at each test location can be affected by binocular viewing condition. However, to our knowledge, pointwise sensitivity comparison between both conditions has not been made. Furthermore, it is unknown whether sensitivity disparity

between the 2 eyes has an impact on the pointwise sensitivity measured under binocular viewing in eyes with VF defects.

This study aimed to investigate if pointwise monocular sensitivity measured without occluding the nontested eye in patients with glaucoma is affected by the sensitivity disparity between the 2 eyes that correspond under binocular viewing.

MATERIALS AND METHODS

Subjects

We retrospectively reviewed the medical records of 13 patients (5 males and 8 females; mean age, 56.1 ± 11.7 y, range, 35 to 79 y) with glaucoma (8 patients with primary open-angle glaucoma and 5 patients with normal tension glaucoma), who had visited the outpatient clinic of Kindai University Hospital between June 2017 and June 2018 and had been tested by both imo and HFA. The diagnosis of glaucoma was based on the presence of typical glaucomatous optic disc changes, nerve fiber layer defects, and corresponding glaucomatous VF abnormalities by HFA (SITA standard 30-2, 24-2). VF abnormality was evaluated using the pattern deviation (PD) probability plot that showed a cluster of 3 or more nonedge-contiguous points having sensitivity with a probability of <5% in the upper or lower hemifield with at least 1 point with a probability of <1%. In this study, patient's HFA results were only used to determine the better/worse eyes using the mean deviation (HFA-MD) and for group classification using the pointwise PD (HFA-PD). We defined the eye with a better HFA-MD score as "the better eye" and the fellow eye with a worse HFA-MD score as "the worse eye." The exclusion criteria were refraction of <−6.00 D, visual acuity worse than 0.3 logMAR, ocular diseases other than glaucoma that might affect the VF, and unreliable VF test results with a false-positive rate of ≥15%.

This retrospective study was approved by the Ethics Committee of Kindai University Faculty of Medicine (No. 30-146) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained for all patients.

Classification of 4 Groups

VF abnormalities were evaluated by HFA-PD plots with a 5% abnormal level. Depending on the HFA-PD of the better and worse eyes that corresponded at each test point under binocular viewing, all the evaluated test points were classified into 4 groups (Fig. 1):

(1) the HFA-PD was normal in both eyes (the N/N group),
(2) the HFA-PD was normal in the better eye but abnormal in the worse eye (the N/A group),
(3) the HFA-PD was abnormal in the better eye but normal in the worse eye (the A/N group), and
(4) the HFA-PD was abnormal in both eyes (the A/A group).

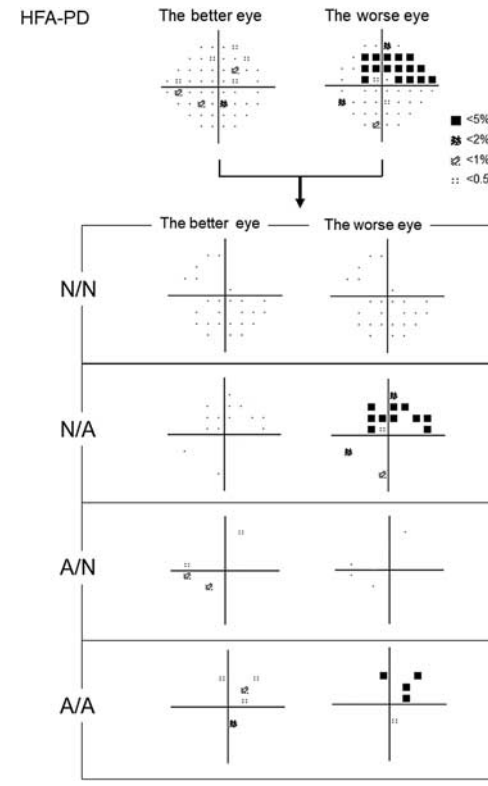

FIGURE 1. The group classification. Using the HFA-PD plots with a 5% abnormal level, all the test points in the better and worse eyes were classified to 4 groups. As an example, the PD plots for case 11 are shown. HFA indicates Humphrey Field Analyzer; PD, pattern deviation.

The Imo Examinations

In this study, the monocular sensitivities under both conditions were compared using the better eye's measurements by imo ("imo-sensitivity"). Under the condition with occlusion, the nontested eye was occluded with a white occluder and no background illumination was present. The details of the perimeter imo were described elsewhere.[5] Imo has 2 separate displays for the right and left eyes, and this enables a VF test to be performed either with or without occluding the nontested eye. The target is projected on a background that is fused in the 2 eyes. The pupil monitoring is independently performed for each eye. As a special feature of imo, the binocular random single eye test (the imo monocular test without occlusion) can randomly present a test target on the display for the right or left eye and the examinee cannot be aware of which eye is being tested.[5] In this study, the imo-sensitivities with and without occlusion were respectively obtained using the monocular test and the binocular random single eye test. The subjects included in this retrospective study were tested by a 30-2 (same as the HFA 30-2 program) or 24plus program (with additional test points in the central 10 degrees of the HFA 24-2 pattern) using target size III (visual angle of 0.431 degrees). A maximum target luminance of 3183 cd/m^2 (0.1 to 10,000 asb) with a background luminance of 10 cd/m^2 (31.4 asb) and a stimulus duration of 200 ms were used. Test strategy used the Ambient Interactive Zippy Estimation by Sequential Testing algorithm for all the tests. Ambient Interactive Zippy Estimation by Sequential Testing is a method of determining threshold value by adding Zippy Estimation by Sequential Testing to the effect of the periphery of the test point.[8,9]

Data Analysis

The sensitivity difference between both conditions was calculated for each group using both weighted and nonweighted data. Because the nonweighted mean difference could be strongly affected by a patient with a large number of data in the group, by applying a weight we created a

TABLE 1. Mean Deviations for the Better and Worse Eyes by HFA and Imo in Individual Cases

	HFA		Imo		
			Better Eye		Worse Eye
Patient No.	Better Eye	Worse Eye	With Occlusion	Without Occlusion	With Occlusion
1	−0.35	−1.59	−0.31	0.52	−2.83
2	−5.13	−5.82	−1.92	−1.52	−1.58
3	0.06	−5.24	−0.55	−0.49	−4.33
4	−2.84	−7.95	−4.66	−2.16	−9.06
5	−0.51	−15.25	0.30	−0.82	−14.15
6	−1.55	−2.83	−0.24	0.29	−1.23
7	−1.07	−1.08	−0.27	0.14	−0.25
8	−1.87	−18.23	−2.56	−3.28	−15.58
9	−1.67	−8.38	−0.74	−0.44	−4.14
10	−13.81	−26.49	−13.42	−12.72	−21.94
11	0.18	−7.65	−0.29	−0.13	−7.19
12	−1.84	−22.33	−1.67	−3.19	−18.68
13	−1.25	−3.32	−2.75	−3.23	−4.21

The numbers are mean deviations (dB).
HFA indicates Humphrey Field Analyzer.

pseudo-population[10] in which the number of data for every patient in the group was the same. This could avoid the problem with the nonweighted data. The weight was derived by applying the inverse probability (stabilized) weight,[10] which was calculated by dividing the proportion of the number of data in a group g (g = N/N, N/A, A/N, or A/A) for all the patients by that for the kth patient (k indicates the patient number); that is, the stabilized weight can be expressed as $P_r\ (G=g)/P_r\ (G=g|K=k)$. For comparison, both weighted and nonweighted results were shown. To see how sensitivity differences varied among the 4 groups, the sensitivity differences between both conditions were expressed as percentages for comparison.

Statistical Analysis

Data were analyzed using BellCurve for Excel (Social Survey Research Information Co. Ltd). Monocular sensitivity differences between both conditions were analyzed using paired t test, which assume data are from a normal distribution. The relationship between the worse eye's imo-sensitivity and the better eye's imo-sensitivity difference between both conditions was analyzed for the N/A group using Spearman rank correlation coefficient. Probability <0.05 was considered statistically significant.

RESULTS

Among the studied 13 patients with glaucoma, 7 patients had the right eye and 6 patients had the left eye as the better eye. By HFA, the mean (range) MD values were −2.43 (0.18 to −13.81) dB for the better eye and −9.70 (−1.08 to −26.49) dB for the worse eye. By imo, the mean (range) MD values for the better eye were −2.08 (0.52 to −12.72) dB without occlusion and −2.24 (0.30 to −13.42) dB with occlusion; and −8.09 (−0.25 to −21.94) dB for the worse eye with occlusion (Table 1). The mean (range) visual acuities were −0.2 (0 to −0.2) logMAR for the better eye and −0.1 (0.3 to −0.2) for the worse eye. All VF results had a false-positive rate of 15% or lower.

By imo, 11 patients were tested using the 24plus program (78 test points excluding the fovea) and 2 patients were tested using the 30-2 program (76 test points excluding the fovea). The HFA and imo test locations matched at 672 test points and of 672, 624 test points excluding the test points at the blind spots and those without correspondence between both eyes were evaluated. Of the 624 (13 patients) evaluated test points, 325 (13 patients) test points had a normal HFA-PD in both eyes (the N/N group) and 59 (9 patients) test points had a 5% abnormal level of the HFA-PD in both eyes (the A/A group). The HFA-PD was normal in the better eye but abnormal in the worse eye at 203 (13 patients) test points (the N/A group) and was abnormal in the better eye but normal in the worse eye at 37 (10 patients) test points (the A/N group). Table 2 shows the weighted and nonweighted mean imo-sensitivities and confidence intervals for the 4 groups. The mean foveal imo-sensitivities for the better eye were 33.4 ± 1.8 dB with occlusion and 32.9 ± 2.4 dB without occlusion ($P = 0.51$).

Figure 2 shows the comparison between imo-sensitivities with and without occlusion in each group. The imo-sensitivity difference was analyzed using weighted data. In the N/N group, the imo-sensitivity without occlusion was significantly higher than that with occlusion ($t = -5.57$, $P < 0.01$). On the contrary, the imo-sensitivity with occlusion was significantly

TABLE 2. Mean Imo-Sensitivities for the Better and Worse Eyes in Each Group

	N/N (n = 325)	N/A (n = 203)	A/N (n = 37)	A/A (n = 59)
Better eye				
With occlusion				
Weighted	27.8 (27.4-28.1)	27.7 (27.3-28.1)	22.0 (19.1-25.0)	23.5 (21.2-25.8)
Nonweighted	27.7 (27.4-28.0)	27.5 (27.1-27.9)	23.0 (20.5-25.4)	14.9 (11.7-18.0)
Without occlusion				
Weighted	28.5 (28.2-28.8)	27.4 (26.9-28.0)	22.6 (19.5-25.7)	22.0 (19.4-24.6)
Nonweighted	28.4 (28.1-28.7)	26.7 (26.1-27.3)	23.2 (20.7-25.7)	13.6 (10.5-16.8)
Imo-sensitivity difference between both conditions				
Weighted	−0.71 (−0.96 to −0.46)	0.26 (−0.23 to 0.75)	−0.58 (−1.78 to 0.61)	1.47 (0.11-2.83)
Nonweighted	−0.72 (−0.98 to −0.46)	0.79 (0.29-1.30)	−0.24 (−1.61 to 1.13)	1.22 (−0.09 to 2.53)
Worse eye				
Without occlusion	25.5 (24.7-26.3)	12.7 (11.0-14.4)	24.9 (22.3-27.6)	9.2 (6.1-12.3)

The numbers are mean imo-sensitivities (dB) (95% confidence interval). The better eye, the eye with a better HFA-MD; the worse eye, the eye with a worse HFA-MD. The sensitivities under both conditions were compared using the better eye's imo measurements.

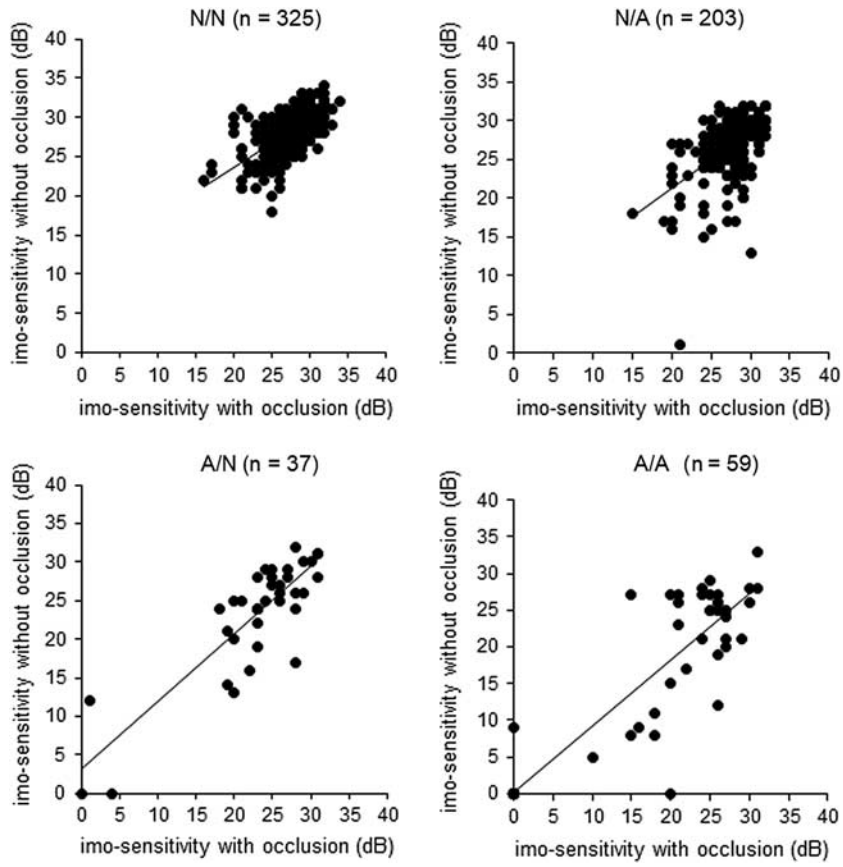

FIGURE 2. Comparison between the better eye's imo-sensitivities with and without occlusion in each group. Although the N/N and A/A groups showed opposite results, no significant sensitivity difference was observed in the N/A or A/N group between both conditions.

higher than that without occlusion in the A/A group ($t = 2.17$, $P < 0.05$). No significant imo-sensitivity difference was seen in the N/A or A/N group ($t = 1.04$, $P = 0.30$ for N/A and $t = -0.99$, $P = 0.33$ for A/N).

Figure 3 shows the distributions for the imo-sensitivity differences between both conditions (imo-sensitivity with occlusion minus imo-sensitivity without occlusion) in each group using the weighted and nonweighted data. A negative sensitivity difference value indicates a higher imo-sensitivity without occlusion. The percentages for a higher imo-sensitivity without occlusion and a higher sensitivity with occlusion were 46.3% and 24.9% in the N/N group, 42.7% and 39.9% in the N/A group, and 46.4% and 31.4% in the A/N group. The N/N group clearly showed a sensitivity difference between both conditions. Although the N/N, N/A, and A/N groups showed similar distributions for the weighted and nonweighted data, the A/A group had very different distributions, indicating a variation in the data.

Figure 4 shows a negative correlation between the worse eye's imo-sensitivity and the better eye's imo-sensitivity difference between both conditions (imo-sensitivity with occlusion minus imo-sensitivity without occlusion) in the N/A group (r's $= -0.26$, $P < 0.01$). The higher the worse eye's imo-sensitivity, the smaller the sensitivity difference between the 2 eyes was. On the contrary, the sensitivity difference between both eyes increased when the worse eye's imo-sensitivity decreased. Among the test points with a worse eye's imo-sensitivity of ≥ 25 dB (70 points), 51.4%, 20.0%, and 28.6% of these points showed a higher, equal, and lower imo-sensitivity without occlusion than that with occlusion, respectively. Among the test points with a 0 dB imo-sensitivity in the worse eye (82 points), respectively, 22.0%, 15.8%, and 62.2% of these points showed a higher, equal, and lower imo-sensitivity without occlusion (Fig. 4). The percentage of the points with a higher sensitivity under binocular viewing decreased as the sensitivity difference between both eyes increased.

DISCUSSION

This study demonstrated that in patients with VF defects, monocular sensitivity measured without occluding the nontested eye is affected by the sensitivity disparity between the 2 eyes that correspond under binocular viewing. This indicates the involvement of different binocular interactions caused by the sensitivity disparity in monocular sensitivity measurement under binocular viewing.

One of the factors for the influence of binocular viewing on sensitivity is binocular interaction. Binocular interaction is achieved when the visual cortex of the eye receives visual information from the retinal corresponding points. Binocular interaction has 2 main functions, binocular summation and binocular rivalry. Depending on how the stimulus is presented under binocular viewing, either binocular summation or binocular rivalry will be triggered. Binocular summation occurs when the same stimulus is presented to both eyes and that results in increased sensitivity.[11–13] Conversely, binocular rivalry occurs when

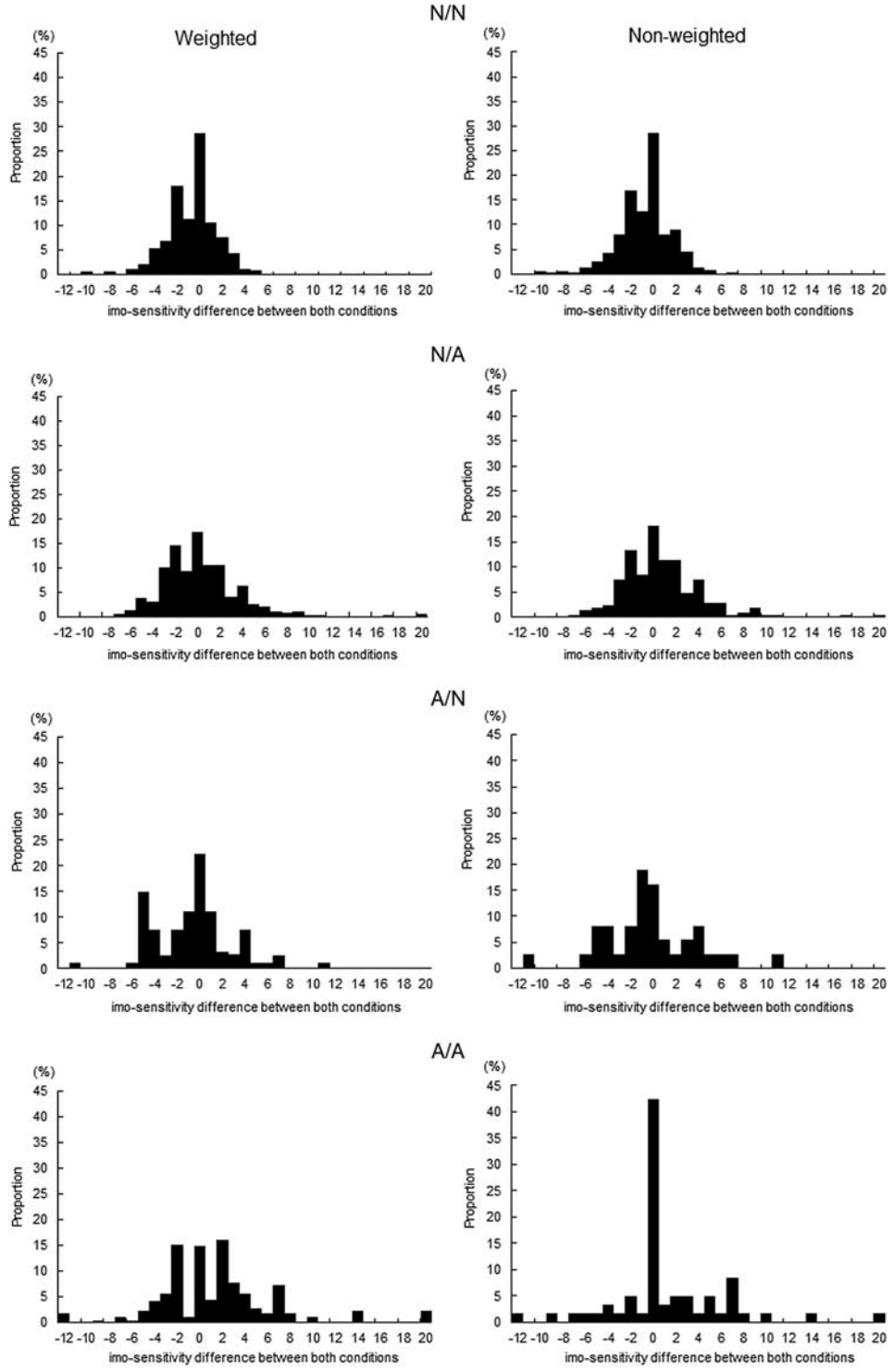

FIGURE 3. Distributions for the better eye's imo-sensitivity differences between both conditions using weighted and nonweighted data. A positive value in the *x*-axis (sensitivity with occlusion minus sensitivity without occlusion) indicates a better imo-sensitivity with occlusion.

different stimuli are presented to both eyes and sensitivity decreases.[1,4,14,15] These previous results demonstrate the effects of binocular interaction on binocular sensitivity. When monocular sensitivity is measured without occlusion by imo (the binocular random single eye test), binocular fusion is in action to fuse the backgrounds in the 2 eyes. Our current results showed that when monocular sensitivity was measured without occlusion, the influence of occlusion on

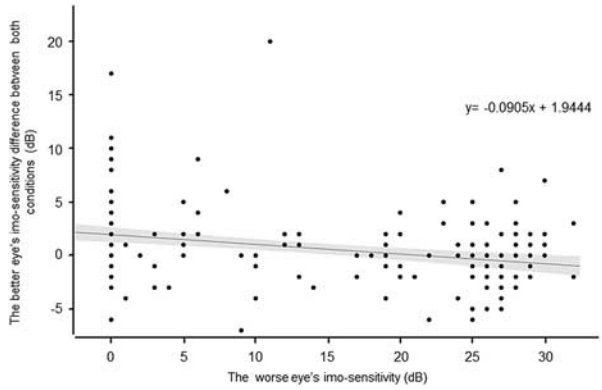

FIGURE 4. The relationship between the worse eye's imo-sensitivity and the better eye's imo-sensitivity difference between both conditions in the N/A group. A negative value in the *y*-axis indicates a better imo-sensitivity without occlusion. A negative correlation was observed (r's = −0.26, $P < 0.01$). The shaded area indicates the 95% confidence limits about the regression line.

the tested eye's sensitivity could be eliminated but the binocular fusion in action could also trigger binocular interaction. Moreover, the triggered binocular interaction functioned differently in the 4 groups. This suggested that in addition to its influence on binocular sensitivity, binocular interaction also affected monocular sensitivity under binocular viewing, and that either binocular summation or binocular rivalry would be triggered depending on how the sensitivities of the 2 corresponding eyes were related.

In the N/N and A/A groups, sensitivities with and without occlusion were significantly different. In the N/N group, the monocular sensitivity without occlusion was higher than that with occlusion. Our previous study also showed a higher monocular sensitivity without occlusion in visually normal volunteers and the involvement of binocular summation.[6] We therefore considered that in a glaucomatous VF with test locations showing mixed normal and abnormal sensitivities, binocular summation might have been activated at the test locations where both eyes had normal sensitivities just like in normal eyes. Conversely, the monocular sensitivity without occlusion was lower than that with occlusion in the A/A group. As fluctuation of sensitivity observed in the area with a low sensitivity has been previously reported,[16,17] it is difficult to conclude whether the lower sensitivity without occlusion observed in the A/A group was due to the involvement of binocular interaction or other causes. Further investigation will be necessary.

The sensitivity difference between both conditions however was not clear in the N/A and A/N groups (Fig. 2). One possible explanation might be the level of sensitivity difference between the 2 eyes in these 2 groups. In the N/A group, the points with an imo-sensitivity of ≥ 25 dB in the worse eye had a small sensitivity difference between both eyes, and 51.4% of these points had a higher sensitivity without occlusion as compared with the points with a higher sensitivity with occlusion (28.6%, Fig. 4). On the contrary, the sensitivity difference between both eyes increased as the worse eye's imo-sensitivity decreased, and the percentage of the points with a higher sensitivity with occlusion was the highest (62.2%) when the worse eye had an imo-sensitivity of 0 dB. These results indicated how monocular sensitivity measured without occlusion was affected by the level of sensitivity difference between both eyes. When the worse eye in the N/A group had an imo-sensitivity of 0 dB, the visual information from the worse eye was not transmitted to the visual cortex. Theoretically, the monocular sensitivities of the 2 eyes should be about the same regardless of whether the nontested eye was occluded or not. However, the sensitivity without occlusion decreased as the worse eye's sensitivity decreased and was lower than the sensitivity with occlusion when the worse eye's sensitivity reached 0 dB. We suspected that binocular rivalry might have occurred at the test locations showing decreasing sensitivity without occlusion. Past studies reported that binocular summation decreases as the sensitivity difference between both eyes increases, and that different stimuli presented to both eyes can induce binocular rivalry.[18–21] We therefore considered that in the N/A and A/N groups, the different sensitivities in the 2 eyes might have created different stimulation and caused binocular rivalry when the backgrounds in both eyes were fused under binocular viewing. Regarding the A/N group, a detailed investigation could not be made in this study due to the small number of the test points (37 points) in this group.

Another possible explanation for the sensitivity results could be the influence of background adaption levels in the 2 eyes. Using frequency doubling technology, previous studies reported that the second eye tested has slightly lower sensitivity than the first eye because the second eye (the nontested eye) has been occluded and experienced dark adaptation.[22,23] In the present study, the background adaptation levels might not be the same under the occluded/nonoccluded test conditions and thus affected the sensitivity results in the 4 groups. Future studies using different occluding methods to investigate the influence of light and dark adaptation will be necessary.

Treatment of glaucoma requires long-term assessment of VF progression. On the basis of the current results, monocular sensitivities obtained under binocular viewing can vary if the sensitivity disparity between the 2 eyes changes over the course of treatment (for instance, from N/N to N/A). Therefore, attention should be paid to any variation in the sensitivity measurements when VF progression is assessed. In addition, it is well-known that glaucoma compromises patient's vision-related quality of life (QOL). To evaluate patient's vision-related QOL, the conventional method usually estimates the binocular VF from monocular VF results.[24] Our results suggested that VF tests under binocular viewing would be closer to patient's actual sight than VF tests under monocular condition, but the impact of binocular viewing condition on VF results should be considered.

This study however has some limitations. Because the test-retest variability of the VF results under binocular viewing could not be investigated in this retrospective study, further studies will be necessary. In addition, this study investigated pointwise sensitivities and only 13 cases that fulfilled the inclusion criteria were included in this retrospective study. Although we used weighted data to prevent data bias, these test locations were not independent. In the future, we would like to conduct studies on the effects of binocular viewing condition on monocular sensitivity measurement over a longer time span as well as in a large group of patients with different stages of glaucoma.

In the future, we would like to conduct studies on the effects of binocular viewing condition on monocular sensitivity measurement over a longer time span as well as in a large group of patients with different stages of glaucoma.

In conclusion, we have demonstrated that monocular sensitivity measured with occlusion is different from that

without occlusion in patients with glaucoma. Moreover, the sensitivity measured without occlusion is affected by the level of sensitivity disparity between the 2 eyes. To better assess patient's vision-related QOL, the impact of binocular interaction on VF test results should be considered.

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