Binocular Interactions in Glaucoma Patients With Nonoverlapping Visual Field Defects: Contrast Summation, Rivalry, and Phase Combination

Catarina A. R. João,[1,2] Lorenzo Scanferla,[1,2] and Nomdo M. Jansonius[1,2]

[1]Department of Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[2]Graduate School of Medical Sciences (Research School of Behavioural and Cognitive Neurosciences), University of Groningen, Groningen, The Netherlands

Correspondence: Nomdo M. Jansonius, Department of Ophthalmology, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands; n.m.jansonius@umcg.nl.

Received: May 3, 2021
Accepted: August 19, 2021
Published: September 10, 2021

Citation: João CAR, Scanferla L, Jansonius NM. Binocular interactions in glaucoma patients with nonoverlapping visual field defects: Contrast summation, rivalry, and phase combination. *Invest Ophthalmol Vis Sci.* 2021;62(12):9. https://doi.org/10.1167/iovs.62.12.9

Purpose. In glaucoma, visual field defects in the left and right eye may be nonoverlapping, resulting in an intact binocular visual field. In clinical management, these patients are often considered to have normal vision. However, visual performance also relies on binocular processing. The aim of this study was to evaluate binocular visual functions in glaucoma patients with intact binocular visual field, normal visual acuity, and stereoscopy.

Methods. We measured in 10 glaucoma patients and 12 age-similar controls: (1) monocular and binocular contrast sensitivity functions (CSF) using a modified quick CSF test to assess binocular contrast summation, (2) dominance during rivalry, and (3) contrast ratio at balance point with a binocular phase combination test. A mirror stereoscope was used to combine the left and right eye image (each 10° horizontally by 12° vertically) on a display.

Results. Area under the monocular and binocular CSF was lower in glaucoma compared to healthy ($P < 0.001$), but the binocular contrast summation ratio did not differ ($P = 0.30$). For rivalry, the percentage of time of mixed percept was 9% versus 18% ($P = 0.056$), the absolute difference of the percentage of time of dominance between the two eyes 19% versus 10% ($P = 0.075$), and the rivalry rate 8.2 versus 12.1 switches per minute ($P = 0.017$) for glaucoma and healthy, respectively. Median contrast ratio at balance point was 0.66 in glaucoma and 1.03 in controls ($P = 0.011$).

Conclusions. Binocular visual information processing deficits can be found in glaucoma patients with intact binocular visual field, normal visual acuity, and stereoscopy.

Keywords: binocular vision, contrast summation, rivalry, phase combination, glaucoma

In healthy individuals, signals from both eyes are integrated to create a single and stable image of the outside world that permits binocular vision. Glaucoma is a neurodegenerative disease characterized by progressive damage of the retinal ganglion cells, leading to loss of retinal sensitivity. In early and moderate glaucoma, this loss of sensitivity results in apparently localized visual field defects.[1] Often, the location of these defects differs between the eyes (nonoverlapping visual field defects), resulting in an intact binocular visual field. In clinical management, these patients are often considered to have normal vision, and some authors advocate to base treatment decisions on the binocular visual field. This approach may avoid overtreatment but may also threaten visual performance. After all, visual performance also relies on binocular visual information processing. Therefore, even at relatively early stages, the degradation of monocular visual functions may impact the visual quality of life of glaucoma patients.[2,3] Binocular visual performance in glaucoma patients has been explored before,[4–7] but the understanding of binocular visual information processing in glaucoma is far from complete.

Our brain is able to integrate information received by each eye, even if the inputs are different. At least four different mechanisms exist: stereoscopy (depth information from disparity),[8,9] contrast summation (lower binocular detection threshold in case of identical monocular spatial inputs),[10–15] rivalry (handling of conflicting spatial information),[16–19] and phase combination (monocular inputs differ but are sufficiently equal to result in a stable, single percept.[20–22] In this study we focus on the last three mechanisms. To date, some studies have shown separately how glaucoma patients integrate two identical monocular spatial inputs (binocular contrast summation)[4,5,23,24] and how they deal with conflicting information in binocular rivalry.[25,26] However, phase combination seems thus far largely unexplored in glaucoma.

Recently, it was argued that assessment of binocular function, specifically binocular contrast summation, is dependent on multiple factors and requires standardization.[27] Therefore, to complement what has been done already, our arti-

cle focuses on the use of new methodological guidelines suggested to precisely assess binocular functions in clinical research, in our case in glaucoma patients. These guidelines comprise the avoidance of an eye patch and, related to that, unawareness regarding the stimulated eye, the use of an alternative forced choice psychophysical method, and a standardized analysis of summation. Additionally, measuring a contrast sensitivity function (CSF; contrast sensitivity as a function of spatial frequency), a comprehensive assessment of spatial vision used to assess binocular summation, is very time consuming, and this hampers its use in clinical research. Thus a further goal of this article was to measure contrast sensitivity in glaucoma patients using an adapted quick CSF method,[28–30] which allows for a fast estimate of the entire CSF with a reasonable precision.

The aim of our study was to provide a more complete picture of the influence of glaucoma on binocular visual information processing. For this purpose, we measured, in a group of glaucoma patients and controls, monocular and binocular contrast sensitivity functions (CSF) to assess binocular contrast summation, eye dominance duration in rivalry, and perceived contrast in phase combination. All participants had an intact binocular visual field (VF), a normal visual acuity in both eyes, and stereoscopy. In addition, all glaucoma patients had nonoverlapping VF defects in the area of the VF relevant to the dichoptic experiments.

Methods

The ethics board of the University Medical Center Groningen approved the study protocol (NL70288.042.19). All participants provided written informed consent. The study followed the tenets of the Declaration of Helsinki.

Participants

We recruited 10 glaucoma patients and 12 age-similar healthy subjects between 50 and 80 years old. Glaucoma patients were selected from the ophthalmic outpatient department of the University Medical Center Groningen, using the visual field database of the Groningen Longitudinal Glaucoma Study.[31] In the Groningen Longitudinal Glaucoma Study, to be included as a glaucoma patient, reproducible VF loss had to be present in at least one eye. The VF loss had to be compatible with glaucoma and without any other explanation. Those with pseudoexfoliative or pigment dispersion glaucoma or a history of angle closure or secondary glaucoma were excluded, leaving primary open-angle glaucoma cases. Intraocular pressure (IOP) was not part of our glaucoma definition. The VF loss had to be measured with standard automated perimetry; in our study we used the Humphrey field analyzer (HFA; Carl Zeiss Meditec, Dublin, CA, USA) with 30-2 grid and SITA fast strategy. The mean deviation (MD) had to be between −3 and −18 dB (thus allowing for early, moderate, and severe glaucoma cases), and the foveal sensitivity had to be ≥30 dB (normal or near-normal performance—sufficient to fixate reliably). Patients had to have nonoverlapping visual field (VF) defects in at least two of the four central test locations of the 30-2 grid (with coordinates [±3, ±3] deg eccentricity). This is essentially the area where we conducted our dichoptic experiments (see below). A nonoverlapping VF defect was defined as a sensitivity with $P < 0.5\%$ (sensitivity below the 0.5th percentile of the built-in normative database) in the total deviation probability plot in one eye combined with $P > 2\%$ (sensitivity above the 2nd percentile of the built-in normative database) the corresponding test location in the other eye. No requirements were formulated regarding the more peripherally located test locations.

Healthy subjects were recruited by advertisement and were included only if they had no positive family history of glaucoma, or glaucoma themselves or any other eye disease, other than refractive error, as assessed by a questionnaire. Healthy subjects underwent a screening examination, in which they were required to have an IOP below 21 mm Hg, normal mean peripapillary retinal nerve fiber layer thickness and a normal thickness of the retinal ganglion cell layer in the macular area, as assessed by optical coherence tomography (Canon HS-100 OCT, software version 4.1.0; Canon, Inc., Tokyo, Japan). Visual fields were screened using frequency doubling technology (C20-1 screening mode; Carl Zeiss, Jena, Germany); any reproducibly abnormal test location at $P < 0.01$ was considered abnormal. A normal frequency doubling technology test result, especially in a population with a low baseline risk of glaucoma (normal IOP, negative family history of glaucoma, normal OCT findings), makes the presence of glaucoma very unlikely.[32]

All participants had to have a best-corrected visual acuity (BCVA) of 0.1 logMAR or better in both eyes and normal stereoscopy (using the four-circle targets of the Fly Stereo Acuity Test; Vision Assessment Corporation, IL; normal stereoscopy defined as 40 arc seconds or better). For the patients, the better eye was defined as the eye with the higher (less negative MD) value; for the healthy subjects, the better eye was defined as the dominant eye. Ocular dominance was determined using the Worth 4-dot test (chrome flashlight + pair of red-green spectacles) combined with hole-in-the-hand test.[33]

Apparatus and Procedures

Stimuli were displayed on a BenQ XL2540 monitor driven by the Psychophysics Toolbox (PTB-3)[34,35] with Octave (version 4.0.0; available in the public domain at www.gnu.org/software/octave/) on a computer running GNU/Linux (Ubuntu 16.04 LTS). Monitor resolution was 1920 × 1080 pixels with a refresh rate of 240 Hz and a mean background luminance of 100 cd/m^2. Luminance was measured with a Minolta luminance meter with a built-in photometric filter (LS-110; Minolta Camera Co. Ltd., Tokyo, Japan). Participants viewed, in a dimly lit room, the monitor screen through a commercially available mirror stereoscope (Geoscope Economy) supported in a homebuilt apparatus (light path divider and chin rest), at a viewing distance of 1.45 m. Figure 1A shows the experimental setup. The setup allowed for trial frame glasses to be used, and all experiments were performed with optimal correction for the viewing distance. While resting their head in the chin rest, participants could see the monitor screen divided into two halves, presenting an area of 10° horizontally and 12° vertically to each eye, resulting in binocular viewing. The advantage of this setup is that participants are not aware which eye was being tested, and it avoids the use of an eye patch during the experiments.[27]

Before each experiment, the participant's eyes were carefully aligned. We presented a black fixation dot (5 cd/m^2) and a 6° × 6° high contrast Perlin noise frame to each eye to help fuse the dichoptic displays. Table, chin rest, and the stereoscope mirrors were adjusted to allow for

Investigative Ophthalmology & Visual Science

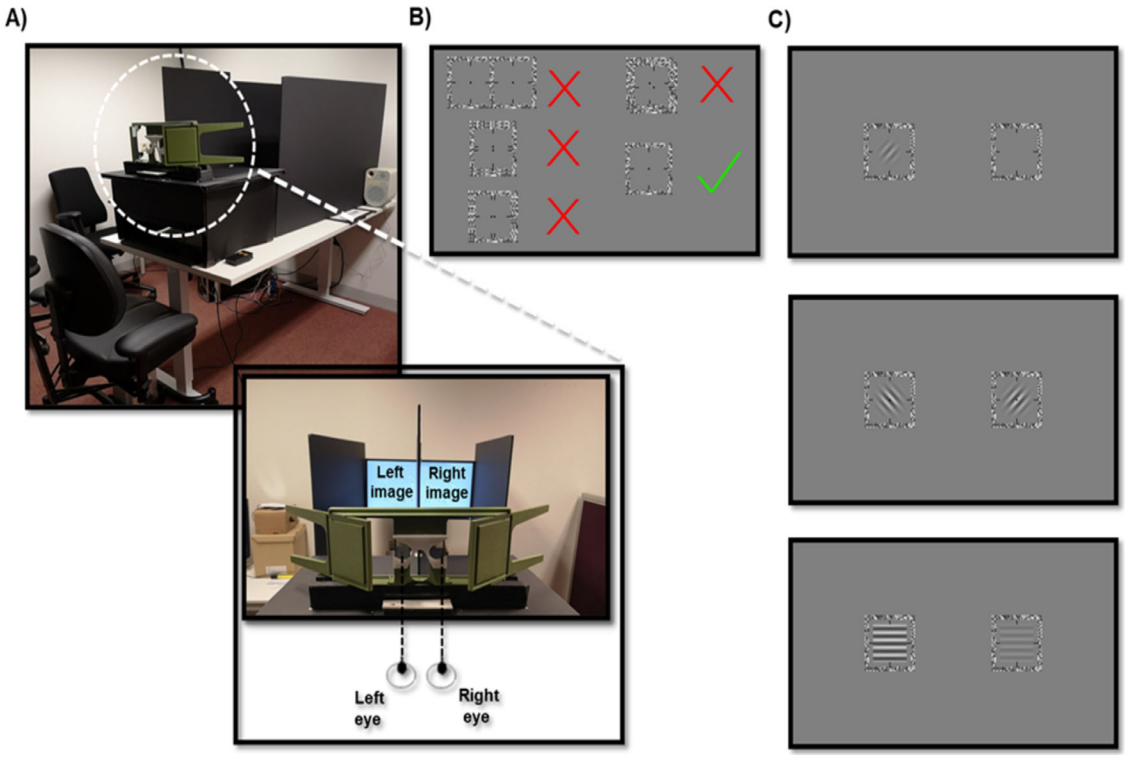

Figure 1. **(A)** Schematic illustration of the experimental setup. **(B)** Illustration of the instructions given to the participant: Two frames were dichoptically displayed to the left and right eye and the subject adjusted the stereoscope to fuse the two images into a single dot with four lines. **(C)** Example of each visual stimulus (not to scale); from top to bottom: quick CSF test, rivalry test, and phase combination test.

fusion of the frames and the fixation dots (Fig. 1B). After achieving stable fusion, the participants pressed the spacebar on the computer keyboard to initiate the experimental tests described below. The experiments were performed in a random order, preceded by a practice run, during one visit lasting approximately two hours, including breaks.

Adapted Quick CSF Test. We measured monocular and binocular CSFs by using a quick CSF test originally designed by Lesmes et al.[28] and adapted (and renamed to adapted quick CSF test) by Farahbakhsh et al.[30] It consists of a 3-parameter CSF model fitted using QuestPLUS (Matlab implementation of QUEST+ freely available at: https://github.com/petejonze/QuestPlus. The essence of this method is that the curve fitting process is part of the actual measurement: stimuli are dynamically chosen to optimize the fit of a (predefined) model. The algorithm (a) varies dynamically properties of the stimulus (spatial frequency and contrast), (b) fits a model (a CSF described by three parameters) to the raw trial-by-trial data, and (c) evaluates the estimated likelihoods of all possible parameter values to determine the most informative stimulus to present on the next trial. The three parameters were (1) peak contrast sensitivity, (2) peak frequency, and (3) rate of fall-off at high spatial frequencies, expressed as the logarithmic increase in spatial frequency needed to halve sensitivity. Stimulus was a 2.5° diameter oblique gabor patch with contrast ranging from 1 to 100% and spatial frequency from 1 to 15 cpd, both logarithmically spaced, with step sizes of 0.1 and 0.084 log, respectively. Each trial consisted of the initial one-second fixation dot in the center of the fusion frames followed by the stimulus with a response window of one second. A brief tone signaled the onset of each stimulus. The gabor was displayed to the left, right or both eyes depending on the trial being tested (Fig. 1C, upper panel). Subjects were asked to indicate the orientation of the grating (right or left tilt) by pressing a key on the keyboard. Right eye, left eye, and binocular testing were performed in a random order, assigned before testing, and not disclosed to the participant. In total, 450 trials were performed (150 per CSF [left eye, right eye, binocular]).

Rivalry Test. Rivalry was assessed using two 2.5° × 2.5° orthogonal gabor patches (±45°) of 50% contrast and 1 cpd spatial frequency. The right-tilted patch was shown to the right eye and the left-tilted patch to the left eye (Fig. 1C, middle panel). We used eight trials lasting 30 seconds each, with a blank display of one second between trials to reduce after effects from the previous trial. In each trial, subjects viewed the stimuli while continuously holding the key corresponding to the current dichoptic percept, being a grating tilted either 45° to the right or to the left. If no clear orientation could be observed, no key was held, and this was counted as mixed percept.

Phase Combination Test. To quantify the relative contribution of each eye to the binocularly fused percept (ocular dominance), we adopted a binocular phase combination paradigm.[21,22,36] The Stimulus consisted of two horizontal gratings of 1 cpd, each subtending 2.5° × 2.5°, with equal and opposite phase-shifts of 1/16 of a cycle (22.5°) relative to a reference line, resulting in a 45° phase difference between the gratings (Fig. 1C, lower panel). The contrast of the stimulus presented to the worse eye was fixed at 50%, whereas the contrast of the stimulus in the fellow eye varied with a contrast ratio (better/worse eye) of 0.01, 0.2, 0.5, 0.8, 1.1, 1.4, 1.7, or 2.0. To avoid any potential bias, the experiments were also performed with swapped phase

Investigative Ophthalmology & Visual Science

shifts. This resulted in 16 conditions (8 interocular contrast ratios × 2 phase combinations), and each condition was tested five times, yielding 80 trials. During a trial, the gratings were presented simultaneously and continuously until the subject's decision was made; the subject had to report the perceived phase by reporting, using the keyboard keys, whether the central dark band appeared above or below the reference line. Each trial was followed by a one-second blank display.

Data Analysis

The subject characteristics were described with mean and standard deviation (SD) for normally distributed variables; for skewed distributions we used median and interquartile range (IQR; range from 25th to 75th percentile). Groups were compared using a Student *t*-test or Mann Whitney U test (Wilcoxon Rank Sum test); proportions were compared using a χ^2 test.

For characterizing the VFs of the glaucoma patients, we estimated the patient's binocular visual field from their monocular Humphrey field analyzer measurements (the most recent test available from clinical care) using the integrated visual field (IVF) method.[37,38] In short, IVF was calculated by using the monocular total deviation values. For each test location, the total deviation value of the IVF was defined as the higher value of the corresponding two monocular values. The mean visual field defect was defined as the unweighted mean of the total deviation values of all test locations within the 30-2 grid. To characterize the depth of our nonoverlapping visual field defects in the four central test locations, we calculated, for each of the four central test locations, the absolute difference between the corresponding sensitivities of both eyes and averaged the resulting four absolute differences.

For binocular summation, we determined the area under the log contrast sensitivity function (AULCSF) above log CS = 0, in the spatial frequency range between 1.5 and 18 cpd.[29] Binocular summation was then calculated by considering the ratio of the binocular AULCSF to that of the average of both monocular AULCSFs.[27]

For quantifying rivalry, we calculated, for the eight trials together, the percentage of time during which one of the buttons was pressed, indicating dominance, and none of the buttons was pressed, considered mixed percept. Dominance was further classified as belonging to either the better or worse eye, depending on the button pressed. We compared, between the two groups, (1) the percentage of time of mixed percept, (2) the absolute difference of the percentage of time of dominance between the two eyes, and (3) the number of complete switches (from left to right eye or vice versa) per minute (rivalry rate).

For quantifying phase combination, we calculate the contrast ratio at balance point for each group.[22] This variable shows how much contrast has to differ between eyes to the point at which both eyes are equally balanced (eyes make equal contributions to binocular combination). A value of 1 indicates perfect balance between the two eyes. To determine the contrast ratio at balance point for a subject, we fitted the number of trials in which the subject reported the better eye dominated as a function of the interocular contrast ratio, using a cumulative normal distribution function and the nonlinear least squares method from the statistical toolbox of MATLAB (version R2018a; Mathworks, Natick, MA, USA). From this, the contrast ratio corresponding to 50% probability of being seen with the better eye (contrast ratio at the balance point) was derived.

All other analyses were performed using R (version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria). $P \leq 0.05$ was considered statistically significant.

Results

Table 1 shows the demographic and clinical characteristics of the glaucoma patients and controls. Groups were similar with regard to age and sex, visual acuity, and stereo acuity. The average MD in glaucoma patients was −5.2, −9.3, and −2.7 dB in the better eye, worse eye, and IVF, respectively. The median (IQR) absolute difference in sensitivity averaged over the four central test locations was 4.1 (2.9 to 7.2) dB.

Monocular and Binocular CSFs

For each participant, the full set of CSFs (monocular left eye, monocular right eye, binocular) was successfully concluded in only 15 min using the quick CSF test, including breaks between trials. Figure 2 shows the comparisons for both groups, for the mean monocular and binocular CSF parameters obtained, which included the AULCSF, peak contrast sensitivity, peak spatial frequency, and β. For each CSF parameter we conducted an analysis of variance (ANOVA), each with one between-subject variable (glaucoma or healthy) and one within-subject variable (monocular or binocular). Table 2 presents the results. As can be seen in this table, glaucoma patients had a lower AULCSF than the controls and the monocular condition differed from the binocular condition regarding AULCSF and peak sensitivity. These effects did not differ between glaucoma and healthy (no significant interactions). In line with this, the binocular contrast summation ratio did not differ between the groups ($P = 0.30$). It was 1.27 ± 0.06 for the glaucoma patients and 1.20 ± 0.02 for the healthy subjects (see Discussion section). Table 3 presents the mean, standard error, and 95% confidence interval of the four CSF parameters, per group (glaucoma and healthy) and condition (monocular and binocular), calculated using bootstrapping (10,000 cycles; bias-corrected accelerated percentile method).

Eye Dominance in Rivalry

Figure 3 shows the results of the rivalry experiment. It shows, for each individual subject, the percentage of time of dominance of the better eye, dominance of the worse eye,

Table 1. Characteristics of the Study Population

	Glaucoma (N = 10)	Controls (N = 12)	*P* Value
Age, years	65 (7)	68 (5)	0.23
Sex, Male, N (%)	5 (50%)	5 (42%)	1.0
Stereo acuity, log arc seconds	1.9 (0.4)	1.7 (0.1)	0.11
Visual acuity, logMAR	0.02 (0.06)	−0.02 (0.04)	0.13
HFA MD (dB) 30-2 grid			
Better eye	−5.2 (5.3)	—	—
Worse eye	−9.3 (4.6)	—	—
IVF	−2.7 (2.9)	—	—

HFA, Humphrey field analyzer.
Mean (standard deviation) unless stated otherwise.

Investigative Ophthalmology & Visual Science

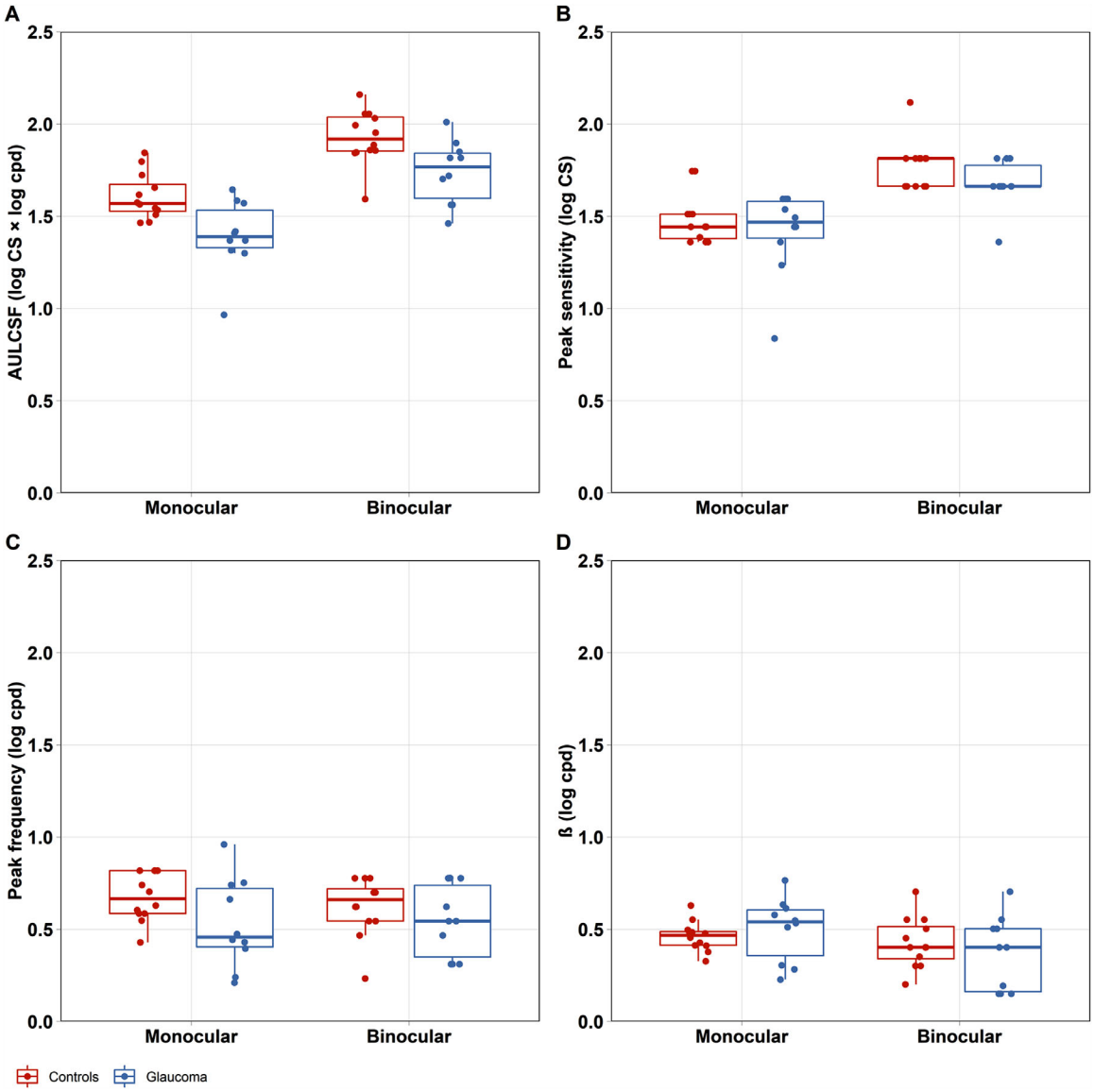

Figure 2. Boxplot with jitter of the monocular and binocular group comparisons of contrast sensitivity function (CSF) parameters, including area under the log CSF (AULCSF; **A**), peak sensitivity (**B**; log units), peak spatial frequency (**C**; log cpd), and β (**D**; log unit of cpd [to convert to octave, this number should be multiplied by log10/log2 = 3.32]), for glaucoma patients (*blue*) and controls (*red*).

Table 2. ANOVA Results (*P* Values) for CSF Parameters (for Details See Main Text)

Factor	AULCSF	Peak Contrast Sensitivity	Peak Frequency	β
Glaucoma	1.5×10^{-4}	0.09	0.05	0.85
Eye condition (monocular/binocular)	2.3×10^{-8}	1.0×10^{-6}	0.68	0.10
Glaucoma × eye condition	0.79	0.79	0.55	0.30

and mixed percept. The median (IQR) percentage time of mixed percept was 9% (7% to 16%) for the patients and 18% (9% to 28%) for the controls. This apparent difference did not reach statistical significance (P = 0.056). For the absolute difference of the percentage of dominance time between the eyes, this was 19% (13% to 29%) for the patients and 10% (7% to 14%) for the controls ($P = 0.075$). The mean (SD; range) rivalry rate of the glaucoma patients was 8.2 (3.5; 2–13) switches per minute, which was significantly lower than the rivalry rate of the controls (12.1 [3.5; 7–19] switches per minute; $P = 0.017$).

As can be seen in Figure 3, in eight of 10 glaucoma patients, the highest percentage of time corresponded to dominance of the better eye (eye with higher MD value); in the remaining two patients, the highest percentage corresponded to dominance of the worse eye. In 11 of 12 controls, the highest percentage of time corresponded to dominance of the better eye (dominant eye); in the remaining

Investigative Ophthalmology & Visual Science

Table 3. Bootstrapped Mean ± SE and 95% CI (Bias-Corrected Accelerated Percentile Method; 10,000 Cycles), Calculated Per Group (Glaucoma/Controls) and Per Eye Condition (Monocularly/Binocularly), for Each of the Four CSF Parameters

	Glaucoma		Controls	
	Monocular	**Binocular**	**Monocular**	**Binocular**
AULCSF	1.39 ± 0.06 [1.25–1.49]	1.74 ± 0.05 [1.64–1.84]	1.61 ± 0.03 [1.55–1.69]	1.93 ± 0.04 [1.84–1.99]
Peak contrast sensitivity	1.41 ± 0.07 [1.20–1.51]	1.68 ± 0.04 [1.56–1.74]	1.48 ± 0.04 [1.43–1.58]	1.78 ± 0.04 [1.71–1.87]
Peak frequency	0.53 ± 0.07 [0.40–0.68]	0.54 ± 0.06 [0.43–0.66]	0.67 ± 0.04 [0.60–0.74]	0.62 ± 0.04 [0.50–0.69]
β	0.49 ± 0.05 [0.39–0.59]	0.37 ± 0.06 [0.26–0.49]	0.46 ± 0.02 [0.42–0.50]	0.43 ± 0.04 [0.36–0.51]

SE, standard error; CI, confidence interval.

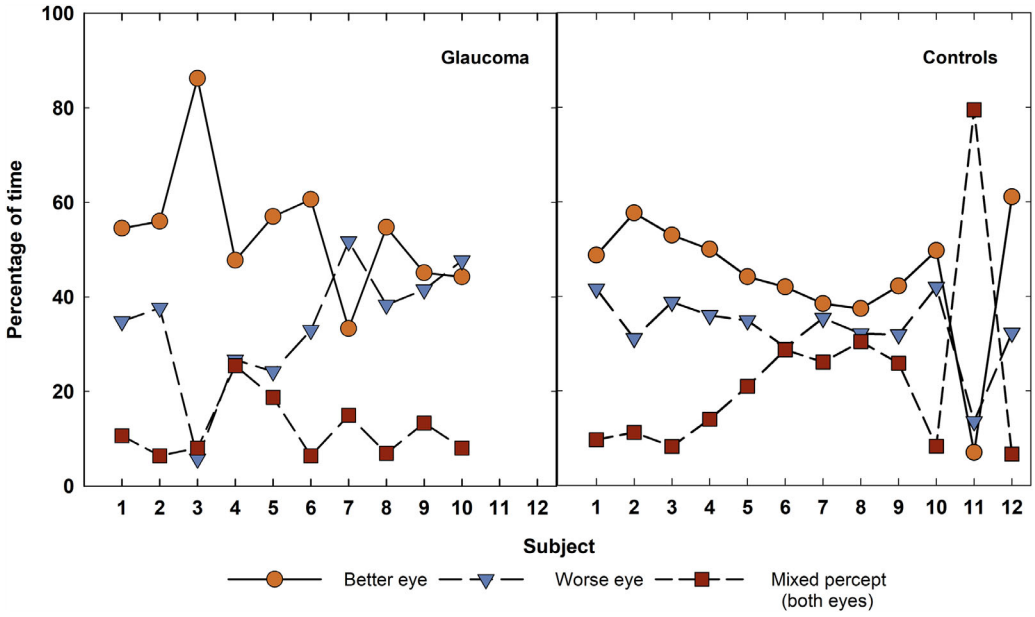

Figure 3. Percentage of time, corresponding to dominance of the better eye (*orange*), dominance of the worse eye (*blue*), and mixed percept (*red*) for each individual subject. *Left panel* corresponds to the glaucoma patients, *right panel* to the controls.

single control, the highest percentage corresponded to mixed percept.

Binocular Phase Combination

We measured the interocular contrast difference that is needed to result in a balanced binocular combination in six glaucoma patients and seven healthy subjects; unlike the first two experiments, this specific test was revealed to be difficult to understand and perform for both the patients and the controls. Figure 4 shows the contrast ratio at balance point for each group. The median (IQR) balance point of the glaucoma patients was 0.66 (0.52 to 0.81), to be compared to 1.03 (0.87 to 1.13) in the controls ($P = 0.011$). The results suggest a balanced contribution from each eye in healthy subjects, but not in glaucoma patients.

Discussion

Glaucoma patients showed a lower AULCSF than controls, both monocularly and binocularly; the corresponding contrast summation ratio was not affected. In the rivalry experiment, the percentage of time of mixed percept and the difference of time dominance between the better and worse eye did not differ between glaucoma patients and controls. However, the number of complete percept switches per unit time was significantly lower in glaucoma patients than in controls. We uncovered significant differences in perceptual eye dominance between glaucoma patients and controls with the binocular phase combination experiment. This suggests that the binocular percept is built less balanced in glaucoma patients compared to controls.

Glaucoma has been shown to affect monocular contrast sensitivity over a wide range of spatial frequencies (see Bierings et al. for a recent review).[39] The difference between monocular and binocular contrast sensitivity has been addressed extensively in healthy subjects, but is, to our knowledge, not so well understood in glaucoma. In healthy subjects, binocular contrast sensitivity is typically greater than the monocular contrast sensitivity of either eye. Campbell and Green[12] reported, for contrast sensitivity on a linear scale, a binocular contrast summation ratio of

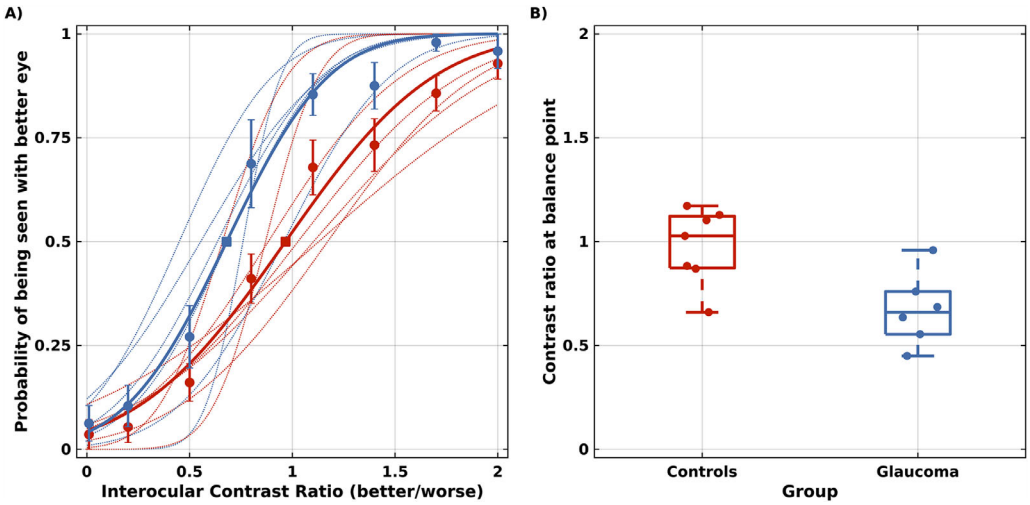

Figure 4. (**A**) Average psychometric functions for the two groups and the corresponding individual data, showing the probability of the better eye being stronger as a function of interocular contrast ratio. (**B**) Boxplot with jitter of the contrast ratio at balance point. Glaucoma patients (*blue*) and controls (*red*).

1.4 (on average, a monocularly presented stimulus requires a contrast 1.4 times higher than the same stimulus presented binocularly in order to be equally detectable). After this publication, a similar difference in monocular and binocular contrast sensitivity has been reported several times.[11,14,40–42] In a recent meta-analysis involving 65 studies, Baker et al.[27] found binocular contrast summation ratios ranging from approximately 1.4 to 2, with a weighted average of 1.5, close to, but significantly larger than the abovementioned value of 1.4. Among others, the ratio was influenced by differences between the eyes (imbalance) and the spatial and temporal frequency of the stimulus. The binocular contrast summation ratio found in our controls was 1.20. However, this value is based on the AULCSF, that is, on the area under the CSF on a log-log scale. Thus far, only one study used the quick CSF method to determine the binocular contrast summation ratio, in young healthy subjects.[43] Their ratio was 1.15 (based on binocular viewing versus the dominant eye). Following the recommendations of Baker et al.,[27] we used the mean of both monocular viewing conditions rather than the dominant eye. For the dominant eye, our ratio would have been 1.19, which is in good agreement with the results of Dorr et al.[43] If we would have used a linear scale, for example applied to the peak CS as displayed in Fig. 1B, then the binocular contrast summation ratio of the controls would have been 2.02, which is at the upper limit of the range as reported in the abovementioned meta-analysis.[27] In glaucoma, the ratios between binocular and monocular contrast sensitivity were previously reported by El-Gohary et al.[44] using contrast grating charts. They found a decreased ratio in glaucoma at spatial frequencies of 1.5, 3, and 18 cpd. On the contrary, Essock et al.,[5] using a Pelli-Robson chart and various temporally modulated stimuli, did not find any significant decrease in binocular summation ratios in early glaucoma. We were not able to find any other study that has reported on contrast summation in glaucoma ever since. In our study, glaucoma patients showed a binocular advantage similar to that of controls. This seems counterintuitive, given that they had nonoverlapping VF defects, hampering the ability to integrate information from two eyes from overlapping points in space. However, their binocular VF was intact whereas the monocular VFs were not, suggesting that their binocular advantage was based on integration of information from different points in space. This explanation agrees with previous research linking stimulus size to contrast sensitivity.[45]

The study of binocular rivalry provides insights into the dynamics of the visual system, and several pathological conditions have been shown to cause abnormal rivalry patterns compared to healthy subjects.[46–53] However, despite its long history and clinical relevance, information regarding rivalry processing has not been studied intensively in glaucoma patients. Tarita-Nistor et al.[25,26] studied changes in the dominance wave propagation during binocular rivalry and differences in the binocular rivalry rate between glaucoma patients and age-similar controls. Our results can, to some extent, be compared to the latest study of Tarita-Nistor et al.,[25] in which rivalry rate and the percept dominance were measured using a static, horizontal and vertical, sine wave grating (presented dichoptically with a double-mirror stereoscope). In their study, the rivalry rate was lower in glaucoma patients compared to that of controls, which agrees with our results. With regard to the percept dominance, no group differences were found between glaucoma and controls, which is also in agreement with our results. The mixed percept was perceived slightly less, a trend also found in our results.

The binocular phase combination experiment quantified the contribution of each eye to the binocular percept. Our results showed that, in healthy subjects, the average balance point was close to one, indicating a balanced contribution from each eye. These findings are in good agreement with literature; a comparable mean ± SD balance point (0.91 ± 0.05) has been reported in young healthy participants, using a similar methodology.[54] We extended the previous experiments to older healthy subjects and to glaucoma. To the best of our knowledge, these extensions have not yet been reported. In glaucoma, the contrast ratio at the balance point was much lower compared with that of controls. This indicates that, even if glaucoma patients appear to be binocularly normal in terms of visual and stereo acuity, they may have significant interocular imbalances, in which one eye contributes much more to binocular processing than the other.

A few limitations of our study must be acknowledged. Our sample size was relatively small, especially for the phase combination experiment; although the phase combination experiment provides a precise way for measuring the binocular eye balance, it turned out to be a difficult task for our elderly participants. Nevertheless, the effects were strong and appeared to be significant in our small sample. Possibly, with some modifications, the experiment could be transformed into an easy, effective tool for quantifying binocular eye balance in clinical practice. In a pilot preceding the current study, a range of spatial frequencies was used, and 1 cpd seemed optimal. At higher spatial frequencies, even young subjects, for whom 1 cpd was easy to do, were not always able to perform the task. Further studies should elucidate whether lower spatial frequencies, not used in the pilot, could be easier for the elderly, and still convey useful information. Another limitation is that we used—inevitably—a different better eye definition in both groups. In the healthy subjects, this was the dominant eye; in the glaucoma patients, we used the better MD eye. Obviously, because of the cross-sectional study design, it was not possible to determine the dominant eye in the patients before their disease onset. We performed, however, the tests for uncovering the dominant eye also in the glaucoma patients. Interestingly, the "dominant" eye according to the tests corresponded for all except one patient with the better MD eye. This could be either chance or the case that patients without a clear dominance before their glaucoma onset develop a preference for their less-affected eye. A strength of our study is that our tests were performed with a mirror stereoscope to avoid the use of an eye patch, because the effects of interocular brightness differences on binocular performance are well documented.[12,55–57] Likewise, we tried to cover all the other recently suggested guidelines for measuring binocularly in clinical populations.[27] Finally, we assured nonoverlapping VF defects by requiring non-overlapping VF defects in at least two of the four central test locations of the 30-2 grid (with coordinates [±3, ±3] deg eccentricity). These four test locations essentially demarcate the region where we conducted our dichoptic experiments but do not fully characterize it (that is, the region is undersampled). For that reason, parts of the region could have had either overlapping defects or normal sensitivities in both eyes. Therefore, our results presumably underestimate the binocular deficits in patients or VF areas with purely nonoverlapping VF defects. Future studies should use perimetric grids with a higher spatial resolution to fully characterize the testing area, possibly combined with personalized stimuli.

What is the clinical meaning of our observations? As outlined in the Introduction section, the location of visual field defects, especially in early and moderate glaucoma, may differ between the eyes (nonoverlapping visual field defects), resulting in an intact binocular visual field. In clinical management, these patients are often considered to have normal vision, and some authors advocate basing treatment decisions on the binocular visual field. This approach may avoid overtreatment but may also compromise visual performance and thus quality of life if binocularity is beneficial for the patient. Regarding binocular contrast summation, in the normal, physiological situation, identical images offered to the two eyes are combined, resulting in an improved contrast sensitivity. Although this mechanism was still intact in our patients, a further increase in asymmetry could result in inhibition: the worse eye disturbs the better eye.[58] This is a common complaint of patients in more advanced disease. Further studies should elucidate at what stage summation is replaced by inhibition. On the other hand, binocular rivalry occurs when conflicting information is displayed to each eye; this requires the brain to resolve the conflicting signals, resulting in the dominance of one image and suppression of the other. A typical situation yielding rivalry, is the blockage of the image of one eye by a nearby object, while looking at an object at distance. Here, glaucoma patients might be hindered by the lower rivalry rate we found. Importantly, rivalry comprises much more than our foveal vision experiment; target size is important[59] and, especially for peripheral vision in glaucoma, things are complicated by, amongst others, filling-in.[60,61] This should be addressed in further studies. Finally, binocular phase combination refers to the situation where two slightly different monocular spatial patterns are combined into a single percept (as opposed to binocular contrast summation, where the monocular spatial patterns are identical, and rivalry, where the patterns are too different to be integrated successfully). Binocular phase combination reflects the (im)balance between the sensory inputs of the eyes, i.e., it provides a quantitative measure of the magnitude of asymmetry in binocular visual processing. Most of the healthy population has a weak eye dominance, that is, their sensory inputs are balanced.[62] In glaucoma, we found a clear interocular imbalance. A similar imbalance was reported in patients with amblyopia, anisometropia, and strabismus.[36,54,63] A visual function that depends on ocular balance is global motion perception.[64] Interestingly, a reduced global motion perception has been reported in glaucoma previously.[65,66]

The binocular visual phenomena rely on excitation and inhibition mechanisms in our brain. For example, the dynamics of the cortex during the rivalry process depends on the balance between the levels of excitatory (glutamate) and inhibitory (GABA) neurotransmitters across neuronal populations that encode the percept of each eye at multiple stages of the visual processing. Neural mechanisms of eye dominance are mediated by GABAergic inhibition (I. Betina Ip et al. bioRxiv 2020.09.10.291047; preprint available),[67] and higher GABA concentrations in the visual cortex have been related to a lower rivalry rate.[68] Hence, even though a possible neurotransmitter dysregulation in the patient's visual cortex cannot be detected psychophysically, our results suggest higher GABA concentrations in glaucoma. Interestingly, a recent pathway analysis linked GABA to glaucoma.[69] As such, our article supports the view that neurotransmitter dysregulations might underlay the perceptual deficits observed in glaucoma patients.

In conclusion, binocular visual information processing deficits can be found in glaucoma patients with intact binocular visual field, normal visual acuity, and intact stereoscopy. This implies that patients with non-overlapping visual field defects cannot plainly be considered to have normal vision. Further research should extend the studies toward the peripheral visual field and relate the findings to visual complaints of patients. This could provide better insight in mechanisms of visual information processing and result in more specific tools for clinical decision making.

Acknowledgments

The authors thank Kim Westra and Helmy Douma for assistance with the recruitment of subjects, and all participants in this study.

Supported by The European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 661883.

Disclosure: **C.A.R. João,** None; **L. Scanferla,** None; **N.M. Jansonius,** None

References

1. Kim JM, Kyung H, Shim SH, Azarbod P, Caprioli J. Location of initial visual field defects in glaucoma and their modes of deterioration. *Invest Ophthalmol Vis Sci*. 2015;56:7956–7962.
2. McKean-Cowdin R, Wang Y, Wu J, Azen SP, Varma R; Los Angeles Latino Eye Study Group. Impact of visual field loss on health-related quality of life in glaucoma: the Los Angeles Latino Eye Study. *Ophthalmology*. 2008;115:941–948.
3. Yanagisawa M, Kato S, Kobayashi M, Watanabe M, Ochiai M. Relationship between vision-related quality of life and different types of existing visual fields in Japanese patients. *Int Ophthalmol*. 2012;32:523–529.
4. Bassi CJ, Galanis JC. Binocular visual impairment in glaucoma. *Ophthalmology*. 1991;98:1406–1411.
5. Essock EA, Fechtner RD, Zimmerman TJ, Krebs WK, Nussdorf JD. Binocular function in early glaucoma. *J Glaucoma*. 1996;5:395–405.
6. Musch DC, Niziol LM, Gillespie BW, Lichter PR, Janz NK. Binocular measures of visual acuity and visual field versus binocular approximations. *Ophthalmology*. 2017;124:1031–1038.
7. Elgohary AA, Elshazly LHM, Fahmy IA. Glaucoma functional damage and comparative psychophysical studies. *Int J Ophthalmol Clin Res*. 2015;2(4):039
8. Marr D, Poggio T. A computational theory of human stereo vision. *Proc R Soc Lond B Biol Sci*. 1979;204(1156):301–328.
9. Blakemore C, Hague B. Evidence for disparity detecting neurons in the human visual system. *J Physiol*. 1972;225:437–455.
10. Frisén L, Lindblom B. Binocular summation in humans: evidence for a hierarchic model. *J Physiol*. 1988;402:773–782.
11. Legge GE. Binocular contrast summation–II. Quadratic summation. *Vision Res*. 1984;24:385–394.
12. Campbell FW, Green DG. Monocular versus binocular visual acuity. *Nature*. 1965;208(5006):191–192.
13. Smith EL, 3rd, Y Chino, Ni J, Cheng H. Binocular combination of contrast signals by striate cortical neurons in the monkey. *J Neurophysiol*. 1997;78:366–382.
14. Anderson PA, Movshon JA. Binocular combination of contrast signals. *Vision Res*. 1989;29:1115–1132.
15. Arditi AR, Anderson PA, Movshon JA. Monocular and binocular detection of moving sinusoidal gratings. *Vision Res*. 1981;21:329–336.
16. Baker DH, Graf EW. On the relation between dichoptic masking and binocular rivalry. *Vision Res*. 2009;49:451–459.
17. Blake R, Fox R. Adaptation to invisible gratings and the site of binocular rivalry suppression. *Nature*. 1974;249(456):488–490.
18. Kovács I, Papathomas TV, Yang M, Fehér A. When the brain changes its mind: interocular grouping during binocular rivalry. *Proc Natl Acad Sci U S A*. 1996;93:15508–15511.
19. Lee SH, Blake R, Heeger DJ. Hierarchy of cortical responses underlying binocular rivalry. *Nat Neurosci*. 2007;10:1048–1054.
20. Huang CB, Zhou J, Zhou Y, Lu ZL. Contrast and phase combination in binocular vision. *PLoS One*. 2010;5(12):15075.
21. Ding J, Sperling G. A gain-control theory of binocular combination. *Proc Natl Acad Sci U S A*. 2006;103:1141–1146.
22. Wang Y, He Z, Liang Y, Chen Y, Gong L, Mao Y, et al. The binocular balance at high spatial frequencies as revealed by the binocular orientation combination task. *Front Hum Neurosci*. 2019;13:196.
23. Wood JM, Collins MJ, Carkeet A. Regional variations in binocular summation across the visual field. *Ophthalmic Physiol Opt*. 1992;12:46–51.
24. Nelson-Quigg JM, Cello K, Johnson CA. Predicting binocular visual field sensitivity from monocular visual field results. *Invest Ophthalmol Vis Sci*. 2000;41:2212–2221.
25. Tarita-Nistor L, Samet S, Trope GE, González EG. Intra- and inter-hemispheric processing during binocular rivalry in mild glaucoma. *PLoS One*. 2020;15(2):0229168.
26. Tarita-Nistor L, Samet S, Trope GE, González EG. Dominance wave propagation during binocular rivalry in mild glaucoma. *Vision Res*. 2019;165:64–71.
27. Baker DH, Lygo FA, Meese TS, Georgeson MA. Binocular summation revisited: Beyond $\sqrt{2}$. *Psychol Bull*. 2018;144:1186–1199.
28. Lesmes LA, Lu ZL, Baek J, Albright TD. Bayesian adaptive estimation of the contrast sensitivity function: the quick CSF method. *J Vis*. 2010;10(3):17.
29. Hou F, Lesmes LA, Kim W, et al. Evaluating the performance of the quick CSF method in detecting contrast sensitivity function changes. *J Vis*. 2016;16(6):18.
30. Farahbakhsh M, Dekker TM, Jones PR. Psychophysics with children: Evaluating the use of maximum likelihood estimators in children aged 4–15 years (QUEST+). *J Vis*. 2019;19(6):22.
31. Heeg GP, Blanksma LJ, Hardus PJ, Jansonius NM. The Groningen Longitudinal Glaucoma Study. I. Baseline sensitivity and specificity of the frequency doubling perimeter and the GDx nerve fibre analyser. *Acta Ophthalmologica Scandinavica*. 2005;83:46–52.
32. Stoutenbeek R, Heeg GP, Jansonius NM. Frequency doubling perimetry screening mode compared to the full-threshold mode. *Ophthalmic Physiol Opt*. 2004;24:493–497.
33. Roper-Hall G. The "Worth" of the Worth Four Dot Test. *American Orthoptic Journal*. 2004;5:112–119.
34. Brainard DH. The Psychophysics Toolbox. *Spat Vis*. 1997;10:433–436.
35. Pelli DG. The VideoToolbox software for visual psychophysics: transforming numbers into movies. *Spat Vis*. 1997;10:437–442.
36. Huang CB, Zhou J, Lu ZL, Feng L, Zhou Y. Binocular combination in anisometropic amblyopia. *J Vis*. 2009;9:1–16.
37. Crabb DP, Viswanathan AC. Integrated visual fields: a new approach to measuring the binocular field of view and visual disability. *Graefes Arch Clin Exp Ophthalmol*. 2005;243:210–216.
38. Asaoka R, Crabb DP, Yamashita T, Russell RA, Wang YX, Garway-Heath DF. Patients have two eyes: binocular versus better eye visual field indices. *Invest Ophthalmol Vis Sci*. 2011;52:7007–7011.
39. Bierings RAJM, Overkempe T, van Berkel CM, Kuiper M, Jansonius NM. Spatial contrast sensitivity from star- to sunlight in healthy subjects and patients with glaucoma. *Vision Res*. 2019;158:31–39.
40. Tyler CW, Chen C-C. Spatial summation of face information. *J Vis*. 2006;6(10):11.
41. Meese TS, Georgeson MA, Baker DH. Binocular contrast vision at and above threshold. *J Vis*. 2006;6:1224–1243.
42. Baker DH, Meese TS, Summers RJ. Psychophysical evidence for two routes to suppression before binocular summation of signals in human vision. *Neuroscience*. 2007;146:435–448.
43. Dorr M, Kwon M, Lesmes LA, et al. Binocular summation and suppression of contrast sensitivity in strabismus, fusion and amblyopia. *Front Hum Neurosci*. 2019;13:234.

44. El-Gohary AA, Siam GA. Stereopsis and contrast sensitivity binocular summation in early glaucoma. *Res J Med Med Sci*. 2009;4:85–88.
45. Howell ER, Hess RF. The functional area for summation to threshold for sinusoidal gratings. *Vision Res*. 1978;18:369–374.
46. Pettigrew JD, Miller SM. A "sticky" interhemispheric switch in bipolar disorder? *Proc Biol Sci*. 1998;265:2141–2148.
47. Miller SM, Gynther BD, Heslop KR, et al. Slow binocular rivalry in bipolar disorder. *Psychol Med*. 2003;33:683–692.
48. Nagamine M, Yoshino A, Miyazaki M, Takahashi Y, Nomura S. Difference in binocular rivalry rate between patients with bipolar I and bipolar II disorders. *Bipolar Disord*. 2009;11:539–546.
49. Robertson CE, Kravitz DJ, Freyberg J, Baron-Cohen S, Baker CI. Slower rate of binocular rivalry in autism. *J Neurosci*. 2013;33:16983–16991.
50. Vierck E, Porter RJ, Luty SE, Moor S, Crowe MT, Carter JD, et al. Further evidence for slow binocular rivalry rate as a trait marker for bipolar disorder. *Aust N Z J Psychiatry*. 2013;47:371–379.
51. Jia T, Ye X, Wei Q, Xie W, Cai C, Mu J, et al. Difference in the binocular rivalry rate between depressive episodes and remission. *Physiol Behav*. 2015;151:272–278.
52. Ye X, Zhu R-L, Zhou X-Q, He S, Wang K. Slower and Less Variable Binocular Rivalry Rates in Patients with Bipolar Disorder, OCD, Major Depression, and Schizophrenia. *Front Neurosci*. 2019;13:514.
53. Xiao G, He K, Chen X, et al. Slow Binocular Rivalry as a Potential Endophenotype of Schizophrenia. *Front Neurosci*. 2018;12:634.
54. Zhou J, Feng L, Lin H, Hess RF. On the maintenance of normal ocular dominance and a possible mechanism underlying refractive adaptation. *Invest Ophthalmol Vis Sci*. 2016;57:5181–5185.
55. Home R. Binocular summation: a study of contrast sensitivity, visual acuity and recognition. *Vision Res*. 1978;18:579–585.
56. Horowitz MW. An analysis of the superiority of binocular over monocular visual acuity. *J Exp Psychol*. 1949;39:581–596.
57. Wildsoet C, Wood J, Maag H, Sabdia S. The effect of different forms of monocular occlusion on measures of central visual function. *Ophthalmic Physiol Opt*. 1998;18:263–268.
58. Howard IP. Depth Perception. In: Pashler H , ed. *Stevens' Handbook of Experimental Psychology*. Hoboken: John Wiley and Sons; 2002.
59. Howard IP. *Seeing in depth, Vol. 1: Basic mechanisms*. Toronto: University of Toronto Press; 2002.
60. He S, Davis WL. Filling-in at the natural blind spot contributes to binocular rivalry. *Vision Res*. 2001;41:835–840.
61. Tong F, Engel SA. Interocular rivalry revealed in the human cortical blind-spot representation. *Nature*. 2001;411:195–199.
62. Li J, Lam CSY, Yu M, et al. Quantifying sensory eye dominance in the normal visual system: a new technique and insights into variation across traditional tests. *Invest Ophthalmol Vis Sci*. 2010;51:6875–6881.
63. Feng L, Zhou J, Chen L, Hess RF. Sensory eye balance in surgically corrected intermittent exotropes with normal stereopsis. *Sci Rep*. 2015;5:13075.
64. Hess RF, Hutchinson CV, Ledgeway T, Mansouri B. Binocular influences on global motion processing in the human visual system. *Vision Res*. 2007;47:1682–1692.
65. McKendrick AM, Badcock DR, Morgan WH. The detection of both global motion and global form is disrupted in glaucoma. *Invest Ophthalmol Vis Sci*. 2005;46:3693–3701.
66. Shabana N, Cornilleau Pérès V, Carkeet A, Chew PTK. Motion perception in glaucoma patients: a review. *Surv Ophthalmol*. 2003;48:92–106.
67. Sengpiel F. Motion perception is learned, not innate. *Nature Neuroscience*. 2006;9:591–592.
68. Robertson CE, Ratai E-M, Kanwisher N. Reduced GABAergic Action in the Autistic Brain. *Curr Biol*. 2016;26:80–85.
69. Bailey JN, Yaspan BL, Pasquale LR, et al. Hypothesis-independent pathway analysis implicates GABA and acetyl-CoA metabolism in primary open-angle glaucoma and normal-pressure glaucoma. *Hum Genet*. 2014;133:1319–1330.

Investigative Ophthalmology & Visual Science