Dichoptic Spatial Contrast Sensitivity Reflects Binocular Balance in Normal and Stereoanomalous Subjects

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Purpose. To study binocular balance by comparing dichoptic and standard monocular contrast sensitivity function (CSF) in stereonormal and stereoanomalous/stereoblind amblyopic subjects.

Methods. Sixteen amblyopes and 17 controls participated. Using the capability of the passive three-dimensional display, we measured their CSF both monocularly and dichoptically at spatial frequencies 0.5, 1, 2, 4, and 8 cpds using achromatic Gabor patches on a luminance noise background. During monocular stimulation, the untested eye was covered, while for the dichoptic stimulation the untested eye viewed background noise. Dichoptic CSF of both eyes was acquired within one block.

Results. In patients with central fixation, dichoptic viewing had a large negative impact on the CSF of the amblyopic eye, although it hardly affected that of the dominant eye. In contrast, dichoptic viewing had a small but significant effect on both eyes for controls. In addition, all participants lay along a continuum in terms of how much their two eyes were affected by dichoptic stimulation: by using two predefined contrast sensitivity ratios, namely, amblyopic sensitivity decrement and dichoptic sensitivity decrement, not only did we find a significant correlation between these variables among all participants, but also the two groups were identified with minimum error using a cluster analysis.

Conclusions. Dichoptic CSF may be considered to measure visual performance in patients with altered binocular vision, because it better reflects the visual capacity of the amblyopic eye than the standard monocular examinations. It may also be a more reliable parameter to assess the efficacy of modern approaches to treat amblyopia.

Keywords: binocular vision, dichoptic, monocular, spatial contrast sensitivity, area under log contrast sensitivity function (AULCSF)

Conditions affecting binocular vision are often caused by disturbed binocular inputs to the visual cortex during early development.[1–4] For instance, when visual information is compromised to one of the eyes during the critical period (i.e., owing to uncorrected refractive error/manifest strabismus or even deprivation owing to congenital cataract), it alters monocular visual acuity of the affected eye and/or stereo vision, although there is no easily detectable anatomic alteration of the visual system. This condition is referred to as amblyopia. After refractive correction is prescribed and no ophthalmic changes are detected, amblyopia is usually diagnosed by considering the differences in the monocular best-corrected visual acuity (BCVA) of the dominant eye compared with the monocular BCVA of the nondominant (amblyopic) eye.[5,6] Although monocular examinations are considered for the definition of the amblyopic severity, the visual function of the amblyopic eye may be differently affected when both the dominant and the nondominant eyes are simultaneously stimulated in suprathreshold and threshold experimental conditions mimicking everyday vision.[3,7–15] More pronounced visual defects of the amblyopic eye in binocular condition are associated with disturbed interocular interactions.[3,5,16]

Binocular rivalry and interocular suppression are known to be altered in strabismic and amblyopic subjects,[16–23] and even in stereoanomalous subjects with normal monocular vision.[24] The asymmetric interocular suppression of the nondominant eye in amblyopia affects the neural organization required for the proper binocular interactions between the eyes: although most neurons of the visual cortex of animals with normal binocular vision can be stimulated by both eyes similarly and simultaneously with a strong facilitating interaction between them, in strabismic animals, these cortical neurons tend to be segregated into populations of neurons that can only be monocularly stimulated with a suppressive interaction between these populations during binocular vision.[19,25] Accordingly, the greater the magnitude of BCVA alteration the greater the interocular suppression[3,14,23] and the difference between monocular versus dichoptic visual acuity,[10] supporting the need

to examine dichoptic vision in abnormal binocular conditions. Another successful attempt at applying the dichoptic concept in examining amblyopic visual function has been that of Birch et al.,[8] who developed an optotype-based dichoptic eyechart that aimed at assessing suppression. They presented different letters to each eye manipulating their contrast, while keeping the sum constant at 100% contrast, to measure contrast balance, and hence suppression. They found that amblyopic children under dichoptic conditions had their contrast balance elevated by five to six times compared with those of normal children.

BCVA is an important, although somewhat overrated, clinical parameter in amblyopia. However, vision may be assessed in much greater depth in a large range of spatial conditions using discrimination or detection tasks rather than the isolated BCVA measurement. Spatial contrast sensitivity allows a more complete assessment of spatial vision and it is strongly related to the quality of vision,[26] besides providing further information concerning the function of specific visual mechanisms in disturbed binocular vision.[27,28] It can be tested in clinical context through psychophysical procedures. Although recording contrast thresholds at a range of spatial frequencies requires longer examination time than measuring BCVA, it has been included into the visual examination routine by using traditional chart tests[29] and, more recently, computerized tests.[30]

The purpose of this study was to measure dichoptic spatial achromatic contrast sensitivity function (CSF) in stereonormal (control) subjects and stereoanomalous or stereoblind amblyopic patients and compare the results with the monocular measurements of both dominant and nondominant eyes using identical visual stimulation. Traditionally, monocular tests to measure visual acuity and contrast sensitivity are used to verify possible interocular differences in normal and diseased eyes, as well as to study the effects of binocular summation comparing monocular versus binocular thresholds.[15,31] Indeed, subjects with normal binocular vision display similar or slightly different monocular and binocular contrast sensitivity.[32] However, when binocular vision is disturbed, monocular and binocular perception of the amblyopic eye will differ[8,15] as a consequence of a greater binocular imbalance that is more pronounced at high spatial frequencies.[33,34] Jia et al.,[35] for instance, used contrast detection to study interocular inhibition in anisometropic and myopic subjects. The authors measured contrast sensitivities with opaque and translucent patching conditions, and by comparing the two conditions they provided an inhibition index that accurately discriminated amblyopia-related binocular disturbances from visual disturbances caused by myopia, even without optical correction.[35] Here, and using a similar approach, we went a few steps further and instead of using a translucent patch, which lets through diffuse light, we introduced a test in which identical background viewing is delivered to both tested and untested eyes and also extended the investigation to strabismic patients. Therefore, vision was assessed in a broad spectrum by measuring the contrast sensitivity of each eye separately in a true binocular, or rather dichoptic scenario. In our test, both eyes are open, but the target stimulus is seen by only one eye, while the other eye sees the background stimulus. Therefore, separate thresholds are provided for each eye during binocular viewing. In this way, we can yield a better picture of the interocular suppressive mechanisms at play during natural binocular viewing in amblyopia. Our results emphasize the need of dichoptic measurements to better characterize the depth of amblyopia and monitor visual improvements resulting from interventions to treat interocular suppression and to improve monocular BCVA in amblyopic patients.

Methods

Participants

Participants included 17 amblyopic patients (mean age, 35.7 ± 11.2 years, 10 having the right eye as dominant, 7 females) and 17 healthy volunteers (control group; mean age, 28.5 ± 5.7 years, 9 having the right eye as dominant, 6 females). However, one amblyopic patient had to be excluded because he showed better contrast sensitivity in the amblyopic eye compared with the dominant eye. This left 16 patients altogether, whose clinical parameters are detailed in the Table. Six of those 16 patients underwent binocular treatment before, but independent of, the present experiment. Participants gave their informed and written consent to participate in the study, which was performed according to the tenets of the Declaration of Helsinki and was approved by the ethics committee of the National Institute of Pharmacy and Nutrition, Budapest, Hungary (registration number: OGYÉI/42821/2019).

All subjects underwent ophthalmologic examination: refractive error was measured, BCVA was assessed using the electronic visual acuity testing charts in decimals, and the examination of the fundus was performed. Near stereoacuity was also assessed using the graded circles test as in Stereo Fly test (Titmus 1-9, range between 800 and 40 arc seconds) test. Inclusion criteria for patients were as follows: decimal BCVA of 0.8 or worse in the amblyopic eye with at least two lines difference between eyes, abnormal (≥140") or absent stereoacuity, absence of ophthalmologic diseases, other than strabismic and/or anisometropic amblyopia, and the absence of neurologic diseases that could affect the visual system. Inclusion criteria for controls were decimal BCVA at least 1.0 in both eyes, normal stereoacuity, and absence of ophthalmologic or neurologic diseases that could affect the visual system.

Apparatus

The display used for stimulus presentation was a gamma-corrected three-dimensional capable LG D2343 monitor, a 23" Full HD (1920 × 1080 pixel at 60 Hz) IPS panel, which requires polarized glasses for passive three-dimensional viewing. To deliver different images to the right and left eyes, we used interleaved polarization: every even line was visible only to one eye, and every odd line was visible only to the other eye owing to opposite polarization. During the development of the program, calibrations were performed to ensure that the displayed images (to the right and left eyes) were identical at the pixel level. The maximum brightness displayed by the monitor was 96 cd/m^2 in a two-dimensional mode. The software has been developed for Android 6.0 using Android studio and installed on a notebook (4 GB of RAM and Core i7 processor) connected to the monitor by HDMI cable.

Visual Stimuli

Spatial achromatic contrast sensitivity from both eyes was recorded monocularly and dichoptically at spatial

Table. Clinical Parameters of the 16 Amblyopic Patients Included in the Study

N	Etiology	Age/Gender	Refraction		BCVA		Titmus
			Right Eye	Left Eye	Right Eye	Left Eye	Stereoacuity
1	SA	40/M	+2.75 –0.50 20°	–0.50 –1.00 155°	0.5	1.0	140"
2	S	37/M	+0.50 –0.50 120°	plan –0.50 80°	0.5	1.0	200"
3	SA	41/F	+0.50	+3.00 –4.50 10°	1.0	0.2	–
4	SA	15/F	+3.50 +0.50 100°	plan	0.25	1.0	400"
5	SA	36/M	+2.25	+0.50 –1.25 90°	0.05	1.0	–
6	S	58/F	+3.00 –0.25 180°	+4.25 –1.00 180°	1.0	0.03	–
7	SA	39/F	+4.25 –1.25 175°	+0.50 –1.00 160°	0.1	1.0	–
8	SA	28/M	+1.25 –2.75 70°	plan	0.7	1.0	200"
9*	A	39/F	+5.75 –0.75 140°	plan	0.25	1.0	200"
10*	SA	44/F	+3.00 –1.50 5°	+4.25 –1.50 55°	1.0	0.7	–
11*	A	29/M	plan	+5.00 –1.00 175°	1.0	0.1	–
12	A	18/F	plan	+7.00	1.0	0.2	200"
13*	A	43/M	–7.75 –3.75 175°	–3.00 –0.50 25°	0.2	1.0	400"
14*	SA	28/M	–4.75 –1.00 175°	–6.50 –3.25 175°	1.0	0.08	–
15	A	52/M	+2.25 –0.50 50°	+5.25 –0.75 20°	1.0	0.4	800"
16*	S	24/M	+3.25 –2.25 161°	+4.25 –2.75 2°	1.0	0.8	–

A = anisometropic; S = strabismic; SA = strabismic anisometropic. One-half of the patients showed nonmeasurable Titmus stereoacuity (–).

* Patients who underwent binocular treatment before but unrelated to the present study.

frequencies 0.5, 1.0, 2.0, 4.0, and 8.0 cpd. The stimulus consisted of Gabor patches on a luminance noise background that were only distinguishable from the background by their contrast (Fig. 1). The target stimulus was 5° in diameter and was presented for a maximum of 3 seconds randomly on the right or left side of the display. The target was terminated upon response and a homogenous mid-gray background was displayed before starting the next trial. Stimuli were generated in real time.

The starting Michelson contrast was set at 99% for all spatial frequencies tested and was controlled by a staircase procedure. Initially, the staircase ran in a one-down/one-up mode with large step sizes until the subject made two incorrect responses, upon which it changed into a modified two-down/one-up mode with much smaller step sizes. The initial mode was required to quickly reach the threshold, which happened within 10 steps. The step sizes were optimized for the two-down/one-up rule with a $\Delta^-/\Delta^+ = 0.5488$ (García-Pérez, 2011;[36] Garciá-Pérez, 1998[37]), thus, the threshold estimate converged on 80%. The ratio was calculated as follows:

$$0.5488 = \frac{-\log10\,(1-D)}{\log10\,(1+U)}$$

where D is $\text{Step}_D\%/100$, and U is $\text{Step}_U\%/100$. The step sizes were 30% contrast decrement and 91.5% contrast increment and 11% contrast decrement and 23.5% contrast increment for the initial and the two-down/one-up mode, respectively. The staircase ran until it reached eight reversals, out of which the last six happened in the two-down/one-up mode. Contrast thresholds were calculated from the average of the four last reversals.

Procedures

The tests were performed in a dark room with the observer sitting at 91 cm of view distance from the screen. The observers' task was to detect the stimulus and indicate by a button press on which side the target stimulus appeared (2AFC detection task). First, dichoptic stimulation was applied, where contrast sensitivities of both eyes were determined within one block: the target stimulus was only presented to the right or to the left eye in a random order, while the other eye viewed the luminance noise background only. Both eyes were also examined under monocular condition while covering the nonexamined eye. Observers wore passive polarized glasses throughout the experiment to make the visual stimulation identical across conditions (Fig. 1).

Statistical Analysis

For characterizing changes in contrast sensitivity, a broad contrast sensitivity metric, the area under the log CSF (AULCSF) was used.[38] This was calculated by fitting a third-order polynomial to the log contrast sensitivity versus log spatial frequency data of each subject and integrating between the lowest and highest spatial frequencies.[39] For analyzing the contrast sensitivity in the frequency domain, we took the fitted logarithmic CSFs and broke them down to four segments of 0.5 to 1.0, 1 to 2, 2 to 4, and 4 to 8 cpd. Integrating over these segments yielded the corresponding AULCSF segments of low, lower middle, upper middle, and high spatial frequencies, respectively.

Instead of analyzing the AULCSF results in a 2 × 2 repeated measures ANOVA, we calculated two ratios that reflect normalized change in sensitivity along the two separate dimensions: eye and viewing condition. The former was termed amblyopic sensitivity decrement (ASD) and was calculated as one minus the AULCSF of the amblyopic (nondominant [*ND*]) eye divided by that of the dominant eye (*DE*), separately for the monocular and the dichoptic viewing conditions:

$$ASD = 1 - \frac{AULCSF_{ND}}{AULCSF_{DE}}$$

The latter was termed dichoptic sensitivity decrement (DSD) and was calculated as one minus the AULCSF of the

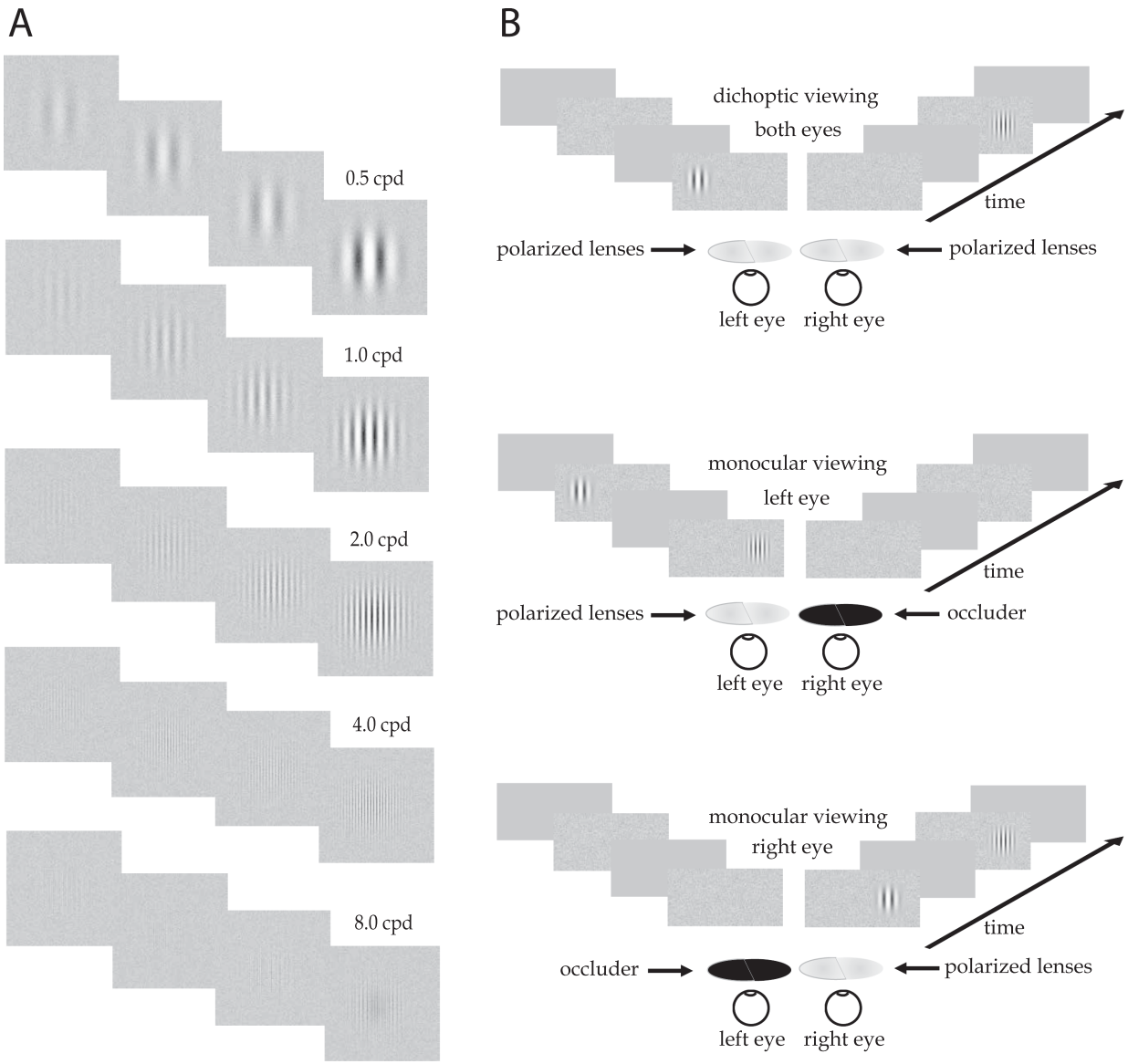

Figure 1. Visual stimuli and test conditions. Gabor patches of achromatic gratings superimposed on a luminance noise background were presented at spatial frequencies of 0.5, 1.0, 2.0, 4.0, and 8.0 cpd displayed here at 99%, 48%, 34%, and 24% contrast (**A**). Both eyes were tested in dichoptic viewing (*top*), followed by the monocular tests of each eye (*middle and bottom*). Spatial frequencies were randomly presented during both dichoptic and monocular viewing conditions.

dichoptic condition divided by that of the monocular condition, separately for dominant and amblyopic/nondominant eye:

$$DSD = 1 - \frac{AULCSF_{Dichoptic}}{AULCSF_{Monocular}}$$

For all ratios, positive values indicated a sensitivity decrease, larger meaning bigger decrement, and zero meant no change. The rationale behind this procedure was to counteract the large variability difference between contrast sensitivity values obtained with the dominant and the amblyopic eye, which would normally preclude the use of ANOVA as a statistical test. Thus, we have succeeded to create ratios with nonsignificantly different variability and could proceed with parametric statistical testing. To analyze these ratios, first, we ran a full model repeated measures ANOVA on each type of ratio with etiology (anisometropic vs. strabismic vs. mixed) and fixation position (central vs. extrafoveal) as between-subject factors, and viewing condition (monocular vs. dichoptic) or eye (dominant vs. amblyopic/nondominant (ND)) as within-subject factors for the ASD and DSD analyses, respectively. We further analyzed the ratios concentrating on the centrally fixating patients and compared them directly via Student *t* tests or Wilcoxon matched pairs test, where the variance was still significantly different between measurements. Furthermore, we compared the AULCSF ratios of centrally fixing amblyopic patients to control subjects using repeated measures ANOVAs with group (patients vs. controls) as a between-subject factor and viewing condition or eye as a within-subject factor for the ASD and DSD analyses, respectively. The AULCSF ratios for the segments were also analyzed

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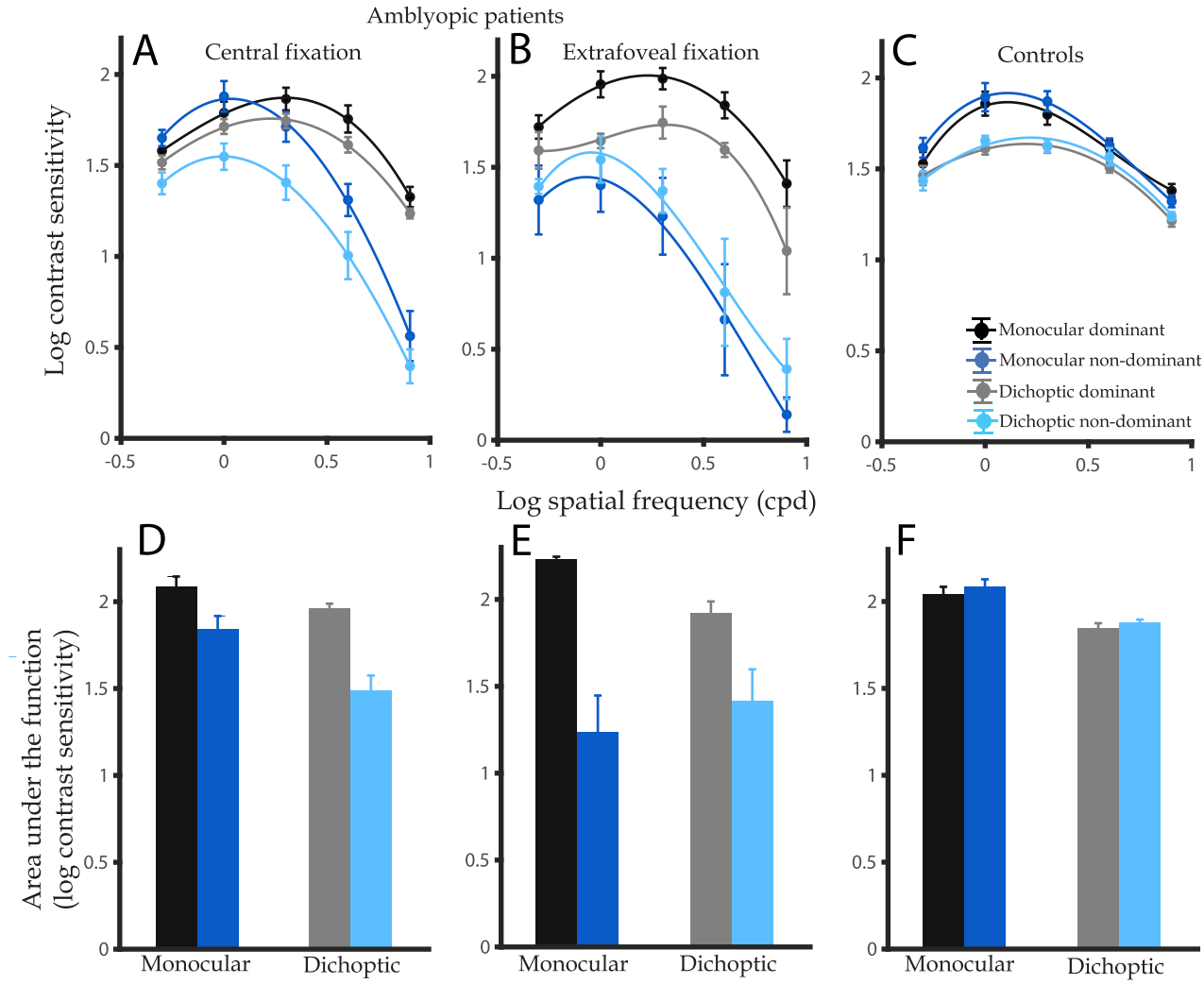

Figure 2. Average (± SEM) log CSFs (*top*) and AULCSF (*bottom*) of, amblyopic patients with central fixation (**A**, **D**; $n = 12$), amblyopic patients with extrafoveal fixation (**B**, **E**; $n = 4$), and controls (**C**, **F**; $n = 16$). Dichoptic CSFs (*grey*, dominant eyes; *light blue*, nondominant or amblyopic eyes); monocular CSFs (*black*, dominant eyes; *dark blue*, nondominant or amblyopic eyes).

by similar repeated measures ANOVAs with an addition of frequency as a within-subject factor. Where the assumption of sphericity was violated owing to the high levels of the SF factor, Greenhouse-Geisser correction was applied to the *P* values.

We investigated the relationship between logMAR visual acuity and the AULCSF ratios using Spearman rank-order correlations. Stereoacuity could not be considered in these correlations because one-half of the patients did not have measurable stereopsis and we could only have assigned an arbitrary number. Because $ASD_{Dichoptic}$ and DSD_{DE} were found to be the two variables along which the patient and controls groups differed the most, we conducted a Spearman rank-order correlation between these variables and a K-means cluster analysis based on these two variables. For the cluster analysis, we were interested in whether the two groups could be deciphered solely based on these measures of contrast sensitivity. Thus, two was chosen as the number of clusters and the unscaled squared Euclidean distance as the distance measure. All statistical analyses were done by Statistica v.13.4.0.14 (Tibco Software Inc., Palo Alto, CA).

Results

Monocular and Dichoptic CSF

Figure 2 summarizes raw data obtained from control and amblyopic subjects. Raw data are shown only for transparency/clarity, because analyses were carried out on derived ratios (see Methods). Averaged monocular and dichoptic CSF (in log scales) of amblyopic patients with central fixation (Fig. 2A; $n = 12$), amblyopic patients with extrafoveal fixation (Fig. 2B; $n = 4$), and controls (Fig. 2C; $n = 17$) are shown in the upper panels for both dominant and nondominant or amblyopic eyes. Dichoptic CSFs (grey, dominant eyes; light blue, nondominant or amblyopic eyes) were lower on average than monocular CSFs (black, dominant eyes; dark blue, nondominant or amblyopic eyes), whereas the amblyopic eyes on average showed decreased CSFs in both viewing conditions. In the bottom panels (Figs. 2D, 2E, amblyopic patients; Fig. 2F, controls), the CSFs of each eye and each viewing condition were assessed as the AULCSF and statistics were carried out on ratios obtained from the AULCSF vales for each condition.

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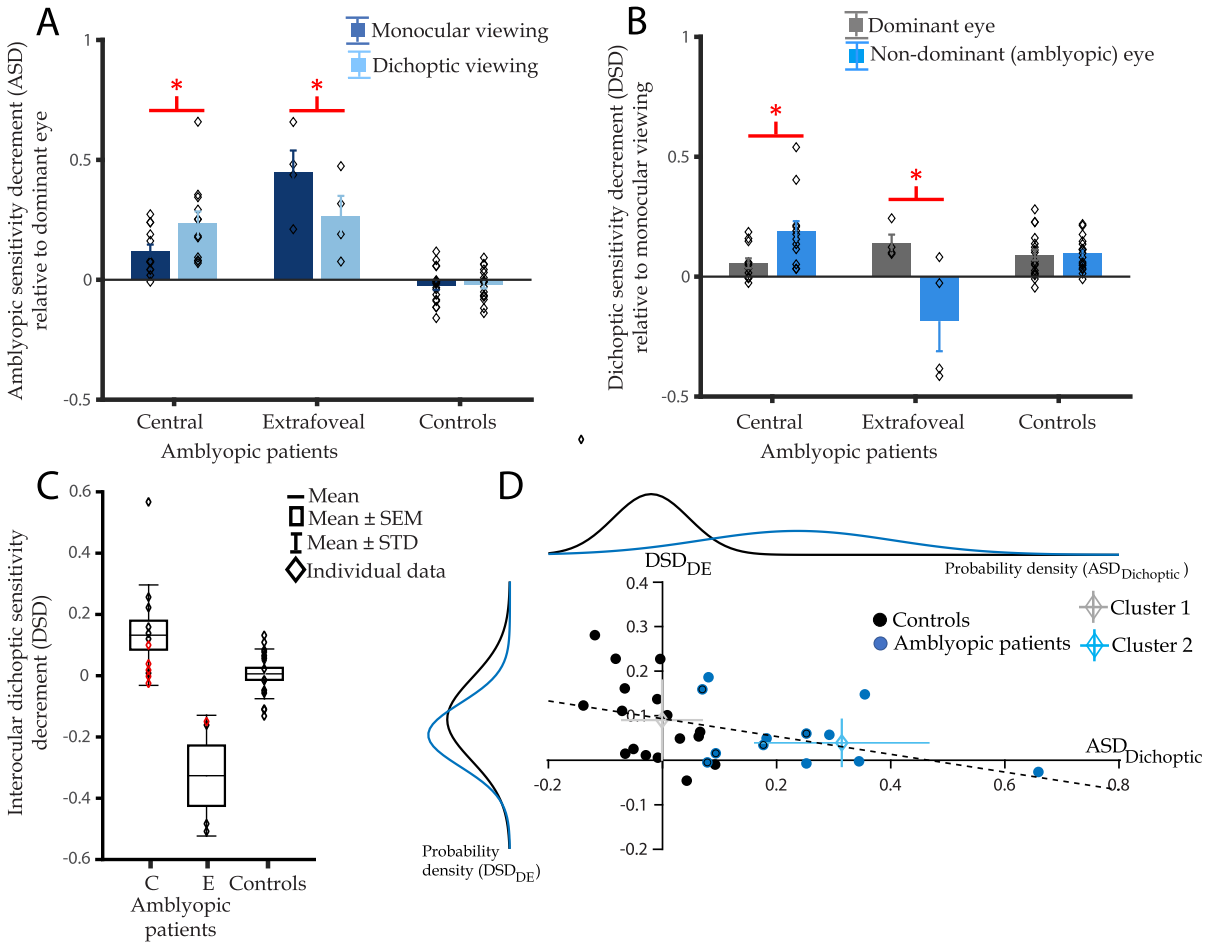

Figure 3. Average (± SEM) and individual results of the ASD and the DSD. (**A**) The monocular viewing condition (*dark blue*) and dichoptic viewing condition (*light blue*) are compared for controls and amblyopic patients using the ASD index, which incorporates AULCSF values from both eyes. (**B**) The dominant eye (*grey*) and nondominant (amblyopic) eye (*blue*) are compared for controls and amblyopic patients using the DSD index, which incorporates AULCSF values from both conditions. Positive values indicate sensitivity decrease. Diamond symbols indicate individual data. Significant ($P < 0.05$) differences are marked with a *red asterisk*. (**C**) The interocular DSD distributions are shown separately for centrally (**C**) and extrafoveally (**E**) fixating patients and controls. Group means are denoted by *vertical lines*, box and whiskers represent SEM and STD, respectively, and *diamond symbols* indicate individual data (*red*, binocularly treated patients). (**D**) DSD_{DE} versus $ASD_{Dichoptic}$ in controls (*black symbols*) and centrally fixating amblyopic patients (*blue symbols*) are plotted. The *light gray cross* represents the centroid ± 1 standard deviation of cluster 1 with all control subjects and four amblyopic patients ($n = 21$) and the *light blue cross* represents the same for cluster 2 with the remaining ($n = 8$) amblyopic patients. *Black outline* indicates patients who have undergone binocular treatment before the experiment.

Contrast Sensitivity of the Amblyopic Eye Is Further Decreased by Dichoptic Viewing in Patients

To combat the large difference in intersubject variability in contrast sensitivity between the amblyopic and the dominant eye, we captured the amblyopic contrast sensitivity deficit by calculating a ratio between the AULCSF of the two eyes that we termed ASD (see Methods). This ratio reflects the normalized change in sensitivity of the amblyopic eye relative to the dominant eye; positive values indicate sensitivity decrease, larger meaning bigger decrement, while zero means no change. The ASD was computed separately for each viewing condition.

First, in a full model we considered the possible effect of fixation and etiology on the relationship between monocular and dichoptic ASD, because these factors can possibly affect contrast sensitivity.[6] Indeed, we found (Fig. 3A) a marked difference in the ASD between centrally and extrafoveally fixating patients, fixation main effect: $F_{(1,\ 12)} = 6.08$, $P = 0.029$; Viewing condition × Fixation: $F_{(1,\ 12)} = 23.690$, $P < 0.001$; those with central fixation showed significantly greater deficit in the dichoptic compared with the monocular condition (post hoc $P = 0.019$), although there was a significant opposite pattern for those with extrafoveal fixation (post hoc $P = 0.036$). Etiology, in contrast, did not have any significant effect on the amblyopic sensitivity deficit, both $F_{(2,\ 12)} \leq 2.10$, $P \geq 0.17$. Thus, it was dropped from the model. Because there were not enough patients with extrafoveal fixation to separately analyze the two subgroups, we focused our further analyses on centrally fixing patients.

The comparison of viewing condition involving the 12 centrally fixing patients corroborated the above finding:

they had significantly more pronounced ASD in the dichoptic compared with the monocular condition, paired t test: $t_{(11)} = 3.09$, $P = 0.010$. To see how they compare with traditional ophthalmologic measurements, we correlated both ASD measures with logMAR visual acuity. However, we found no correlation between either monocular or dichoptic ASD and visual acuity, Spearman both $|rho_{(N = 12)}| \leq 0.064$, $P \geq 0.84$. When centrally fixating patients were compared with the control group, the difference between dichoptic versus monocular ASD became more evident: viewing condition main effect, $F_{(1, 27)} = 8.61$, $P = 0.007$; Viewing condition × Group, $F_{(1, 12)} = 7.31$, $P = 0.012$. There was a large amblyopic deficit in the dichoptic condition relative to that in the monocular condition in patients (post hoc $P = 0.005$), whereas the difference did not exist in the control group (post hoc: $P = 0.99$). Moreover, the ASD differed significantly between patients and controls: group main effect, $F_{(1, 27)} = 37.03$, $P < 0.0001$. In fact, the control group did not have any sensitivity decrement in the nondominant eye compared with the dominant eye, as the ASD did not differ from 0 in either viewing condition: one sample t test both $|t_{(16)}| \leq 1.36$, $P \geq 0.19$.

Contrast Sensitivity of the Dominant Eye Is Affected by Dichoptic Viewing Only in Controls

Similar to the ASD, we created a ratio termed DSD to capture the effect of the dichoptic viewing condition on contrast sensitivity relative to monocular viewing separately for each eye (see Methods). It also reflects the normalized change in sensitivity: positive values indicate sensitivity decrease, larger meaning bigger decrement, and zero means no change. We again started by analyzing the values using a full model with fixation and etiology as categorical factors.

As shown in Figure 3B, fixation significantly affected the DSD in a similar manner to the effect it had on ASD: the DSD in the amblyopic eye was significantly different between centrally and extrafoveally fixating patients: fixation main effect: $F_{(1, 12)} = 9.69$, $P = 0.0089$; Viewing condition × Fixation: $F_{(1, 12)} = 22.13$, $P < 0.001$. In contrast, etiology did not have any effect on DSD, both $F_{(2, 12)} \leq 1.88$, $P \geq 0.19$, and was dropped from the model. Surprisingly, the amblyopic DSD in the extrafoveally fixating group was on average smaller than 0, indicating a sensitivity increase instead of a decrement in the dichoptic compared with the monocular viewing condition. Similar to the ASD analysis, we again focused further DSD analyses on the centrally fixing patients.

A direct comparison of the DSD between eyes in centrally fixating patients yielded a significantly more pronounced DSD in the amblyopic eye compared with the dominant eye, paired t test $t_{(11)} = 2.75$, $P = 0.011$. In fact, the DSD ratio in the dominant eye was slightly, but significantly different from 0, one-sample t test $t_{(11)} = 2.70$, $P = 0.021$). This difference, however, disappeared when the previously trained amblyopic patients were excluded, one sample t test $t_{(6)} = 1.88$, $P = 0.11$, indicating that there was no sensitivity decrease in the dichoptic compared with the monocular viewing condition for the dominant eye of the untrained amblyopic patients. Moreover, correlation between DSD measures and logMAR visual acuity in centrally fixating patients yielded no significant results for either eye, Spearman both $|rho_{(N = 12)}| \leq 1.14$, $P \geq 0.28$. Importantly, when patients were compared with stereonormal controls, a marked difference in the above pattern of DSD emerged between groups, eye main effect: $F_{(1, 27)} = 9.06$, $P = 0.0056$; Group × Eye, $F_{(1, 27)} = 7.55$, $P = 0.011$. Unlike the clear difference between eyes in the amblyopic group (post hoc $P = 0.004$), the DSD of the control group did not differ between eyes (post hoc $P = 0.99$). Nevertheless, the control group did suffer a significant, albeit small, sensitivity loss under dichoptic viewing conditions, because both DSD ratios were significantly larger than 0, one-sample t test both $|t_{(16)}| \geq 4.0$, $P \leq 0.001$, as opposed to the dominant eye DSD effect in the untrained amblyopic patients.

Moreover, we calculated the difference between nondominant and dominant eye DSD values to get a direct measure of interocular balance (Fig. 3C). The distributions of these values showed striking between-group differences. The interocular DSD was 0.006 ± 0.081 in average for controls, with a range of 0.263 [–0.133; 0.130], whereas it was $–0.326 \pm 0.197$ on average for extrafoveally fixating patients, with a range of 0.359 [–0.509; –0.150] and 0.132 ± 0.164 on average for centrally fixating patients, with a range of 0.593 [–0.027; 0.566]. The distributions were completely disjunct between extrafoveally fixating patients and the two other groups. In contrast, there was considerable overlap between centrally fixating patients and controls. However, the overlapping patients included all who have undergone binocular treatment (five of the seven overlapping patients)! Thus, this preliminary interval obtained for control subjects may be considered in future investigations aiming to establish normative values for interocular balance and evaluate the effectiveness of amblyopia therapies.

ASD versus DSD as a Coordinate System to Map Out Binocular (Im)balance

Owing to the marked difference between centrally fixating patients and stereonormal controls in the patterns seen in ASD and DSD, we set out to capture the essence of this difference (Fig. 3D). We correlated the dichoptic ASD with the DSD of the dominant eye from both groups, because these variables showed the greatest difference between groups, essentially creating a coordinate system from these variables. Not only did we find a good separation of the two groups along the combination of these two variables, we also found significant correlation between them (Spearman $rho_{(N = 293)} = –0.41$, $P = 0.026$). All individuals lay along a continuum on the plane determined by these two variables, with only a slight overlap between groups, indicating that this coordinate system could be a promising candidate to map binocular balance. This was corroborated by a K-means cluster analysis, which divided all observations along these axis into a predefined number (two) of clusters: one containing all control subjects plus four amblyopic patients ($n = 21$), and another containing all the other patients ($n = 8$). This solution was reached after one iteration. An interesting aspect of the clustering analysis is that three of the four incorrectly categorized patients had undergone previous binocular treatment. The additional two centrally fixating patients who had also received binocular treatment were located also close to control subjects, indicating that the proposed coordinate system could be helpful in evaluating the effectiveness of future (binocular) therapy.

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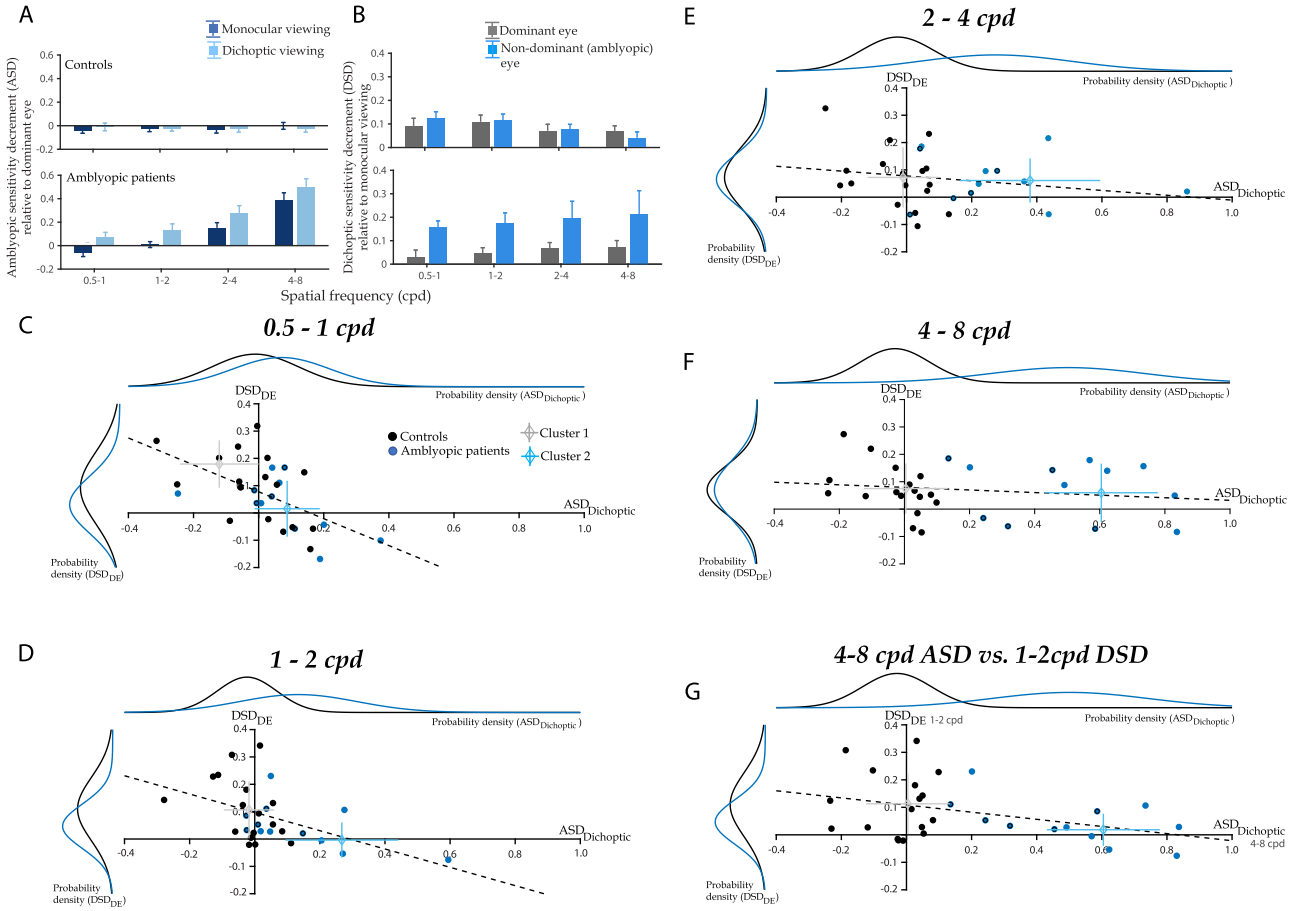

Figure 4. Average (± SEM) results of the ASD and the DSD. AULCSF values were calculated at four segments of 0.5 to 1.0, 1 to 2, 2 to 4, and 4 to 8 cpd. (**A**) Monocular viewing condition (*dark blue*) and dichoptic viewing condition (*light blue*) are shown for controls (*top*) and amblyopic patients (*bottom*) using the ASD index, which incorporates AULCSF values from both eyes, at each of the four segments. (**B**) The dominant eye (*grey*) and nondominant (amblyopic) eye (*blue*) are shown for controls (*top*) and amblyopic patients (*bottom*) using the DSD index, which incorporates AULCSF values from both conditions, at each of the four segments. Positive values indicate sensitivity decrease. (**C–F**) DSD_{DE} versus $ASD_{Dichoptic}$ are plotted for each segment analyzed (C = 0.5–1.0 cpd; D = 1–2 cpd; E = 2–4 cpd; F = 4–8 cpd). (**G**) High spatial frequency (4–8 cpd) dichoptic ASD segment is correlated to lower-middle (1–2 cpd) dominant eye DSD segment. Control subjects and centrally fixating amblyopic subjects are plotted as *black* and *blue dots*, respectively, with a *black outline* indicating those patients who had undergone binocular treatment before the experiment. *Light gray cross* represents the centroid ± 1 standard deviation of cluster 1 and the light blue cross represents the same for cluster 2.

Binocular Imbalance Is Independent of Spatial Frequency

Because amblyopia is known to be more detrimental to contrast sensitivity of higher spatial frequencies,[33,34] we investigated the frequency dependence of the above results. We took the fitted logarithmic CSFs and broken them down to four segments of 0.5 to 1.0, 1 to 2, 2 to 4, and 4 to 8 cpd. Integrating over these segments yielded the corresponding AULCSF segments of low, lower middle, upper middle, and high spatial frequencies, respectively.

Investigation of the ASD ratios yielded a similar pattern of dichoptic versus monocular difference as the whole area under log curve (Fig. 4A). There was a significant main effect of viewing condition for centrally fixing amblyopic patients, main effect of viewing condition: $F_{(1,\ 11)} = 10.70$, $P = 0.0075$, which was independent of spatial frequency, Viewing condition × SF interaction: $F_{(3,\ 33)} = 0.02$, $P_{G-G} = 0.95$. Spatial frequency, however, had a significant overall effect on ASDs, SF main effect: $F_{(3,\ 33)} = 37.52$, $P_{G-G} < 0.0001$; the ASD was significantly bigger for upper middle compared with low and lower middle spatial frequency segments (post hoc both $P \leq 0.017$), while it was more pronounced still for high compared with the upper-middle and the other spatial frequency segments (post hoc all $P \leq 0.0002$). There were no correlations between ASD and logMAR visual acuity in any of the segments, all $|\text{rhos}_{(N\ =\ 12)}| \leq 0.41$, $Ps \geq 0.18$. When analyzed and compared with controls, only the upper middle and high spatial frequency segments showed significant impairments, Group × SF interaction: $F_{(3,\ 81)} = 31.91$, $P_{G-G} < 0.0001$; post hoc $P = 0.99$, $P = 0.34$, $P = 0.00013$, and $P = 0.00012$ for the four SF segments, respectively, which was true for both dichoptic and monocular ASDs. The effect of group on viewing condition was similar to that of the whole AULCSF, Group × Viewing condition interaction: $F_{(1,\ 27)} = 8.29$, $P = 0.0077$, which was again not affected by spatial frequency, Group × Viewing condition × SF interaction: $F_{(2,\ 54)} = 0.11$, $P_{G-G} = 0.82$). In summary,

corresponding with previous results, the amblyopic deficit was only evident at upper middle and even more so at high spatial frequencies. However, the difference in the amblyopic deficit between viewing conditions was similar across spatial frequency segments.

The picture concerning DSD ratios was hardly affected by spatial frequency (Fig. 4B). There was a significant main effect of eye for centrally fixing amblyopic patients, main effect of eye: $F_{(1,\ 11)} = 6.17$, $P = 0.030$, which was also independent of spatial frequency, Viewing condition × SF interaction: $F_{(3,\ 33)} = 0.014$, $P_{G-G} = 0.94$. Neither had spatial frequency an overall effect on DSD ratios, SF main effect: $F_{(3,\ 33)} = 0.81$, $P_{G-G} = 0.42$. There were no correlations between DSD and logMAR visual acuity in any of the segments, all $|\text{rhos}_{(N\ =\ 12)}| \leq 0.42$, $Ps \geq 0.17$). The comparison with controls corroborated the findings with the whole AULCSF (Fig. 4D), Group × Eye interaction: $F_{(1,\ 27)} = 6.36$, $P = 0.017$, although spatial frequency did have a nonsignificantly different trend on overall DSDs of the two groups, Group × SF interaction: $F_{(1,\ 27)} = 3.18$, $P_{G-G} = 0.058$; in the patient group, they tended to increase with SF, whereas in the control group they had a decreasing trend with increasing SF. This generated the highest separation between groups in the lower frequencies for the dominant eye DSD (low and lower-middle SF median not significantly different from zero: Wilcoxon signed rank = 51, $P = 0.38$ and signed rank = 62, $P = 0.08$, respectively) and in the higher frequencies for the nondominant eye DSD (significant group difference for the high SF: Mann-Whitney $U = 2.10$, N1 = 12, N2 = 17; $P = 0.035$), owing to the shift between amblyopic and dominant DSD in the amblyopic group. Spatial frequency had no other effect on DSDs (both main effect and other interactions concerning SF: Fs ≤ 0.26, $Ps \geq 0.67$). Thus, the DSD between eyes was similar across all investigated frequency segments.

However, a different pattern emerged from correlations of dichoptic ASD and dominant DSD ratios separately for each frequency segment (Figs. 4E–H). These ratios showed significant correlations only for low, Spearman $\text{rho}_{(N\ =\ 29)} = -0.57$, $P = 0.0011$, and lower middle spatial frequencies, $\text{rho}_{(N\ =\ 29)} = -0.46$, $P = 0.012$, while there was no detectable correlation either in the upper middle, $\text{rho}_{(N\ =\ 29)} = -0.17$, $P = 0.39$, or the high spatial frequency segments, $\text{rho}_{(N\ =\ 29)} = -0.15$, $P = 0.44$. In contrast, group separation increased from lower to higher spatial frequencies, largely because of the marked decrease in amblyopic contrast sensitivity towards large spatial frequencies. K-means clustering analysis was quite accurate in dividing the group to controls and patients for the high (cluster 1, $n = 20$; cluster 2, $n = 9$; with three amblyopic subjects misplaced, two of whom have undergone binocular treatment) and upper middle spatial frequency segments (cluster 1, $n = 21$ and cluster 2, $n = 8$, with four amblyopic subjects misplaced, three of whom have undergone binocular treatment), whereas it demonstrated worse performance compared with the whole AULCSF analysis in the cases of the lower middle (seven patients and one control misplaced) and low spatial frequency segments (complete mix of controls and patients within clusters). Interestingly, investigation of the relationship between the high frequency dichoptic ASD and the lower-middle dominant eye DSD, those segments that have shown the biggest difference between groups, yielded a unique pattern (Fig. 4G): the cluster analysis results were dominated by the high between-group separation of high frequency dichoptic ASD (cluster 1, $n = 20$ and cluster 2, $n = 9$; with three amblyopic subjects misplaced, two of whom have undergone binocular treatment), while the data points of the previously binocularly treated individuals lay between the two groups, bridging the gap between patients and controls, also creating a week correlative trend, which did not reach significance ($\text{rho}_{(N\ =\ 29)} = -0.24$, $P = 0.22$). Taken together, these results suggest that the absence of DSD effect (i.e., dichoptic masking) in contrast sensitivity of the dominant eye in the low spatial frequency range could be an amblyopic feature to look for especially when evaluating the effectiveness of binocular treatment, other than the well-known and characteristic amblyopic contrast sensitivity deficit in the high spatial frequency range.

Discussion

Using a multispatial frequency luminance contrast detection task, we show a clear dichotomy between normal subjects and stereoanomalous amblyopic patients in how contrast sensitivity of the two eyes behaves under dichoptic viewing conditions, which resembles natural viewing. In patients with foveal fixation, the well-known monocular contrast sensitivity deficit of the amblyopic eye gets even worse under dichoptic viewing conditions, whereas the contrast sensitivity of the dominant eye is only slightly affected by dichoptic viewing. In contrast, in stereonormal controls, there is no contrast sensitivity difference between the eyes in either viewing condition; overall contrast sensitivity, however, gets worse under dichoptic viewing owing to a healthy binocular balance. Moreover, all individuals in both groups lie on a continuum along the above axes, their exact position determined possibly by their binocular balance. The present data emphasize that normal and disturbed binocular vision lead to different normalized dichoptic profiles of contrast sensitivity, which is in line with previous results.[3,7–15,35]

Interocular (or dichoptic) differences activate specific subcortical[40,41] and cortical[42,43] mechanisms, such as those responsible for binocular differencing and summation, during binocular vision that are necessary for perceiving specific attributes of the image.[44–47] These binocular vision-dependent mechanisms influence the establishment of interocular suppression and binocular rivalry during the critical period of development, thus, having great impact on visual acuity, stereopsis, and other visual functions,[24,48–50] which are going to play roles in visual performance during the whole life. Accordingly, evidence of significantly higher ASD in the case of dichoptic compared with monocular viewing condition in patients with foveal fixation supports the hypothesis that disturbed binocular development affects monocular and binocular (dichoptic) discrimination differently and is in close agreement with the findings of Jia et al.[35]

Interestingly, the structural and functional disadvantages of the extrafoveal fixation, in which the amblyopic eye is predictably more suppressed by the dominant eye,[51] result in a different profile: ASD is more pronounced in the monocular compared with the dichoptic viewing condition. This finding is also reflected by the functional advantage during dichoptic viewing condition (i.e., negative mean DSD for the amblyopic eye). We hypothesize that a more variable monocular/binocular retinal preferred loci or fixational area of the amblyopic eye in subjects with extrafoveal fixation could explain, at least partially, these findings. Accordingly, stable fixation during binocular vision condition in normal

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observers is not affected by binocular rivalry, while fixation is less stable when the dominant eye views the target at 0% contrast in subjects with amblyopia.[52] We have not found a direct comparison of monocular versus binocular fixation stability in amblyopic eyes with eccentric fixation in the literature.

In humans, it has been long reported that one eye influences the perception of the other eye in binocular situation via excitatory and inhibitory input between the processing stream of the two eyes.[16,53] This phenomenon normally aids in forming one coherent image from the two slightly different pictures seen by the two eyes when images match in observers with normal binocular vision. However, it is also responsible for the binocular rivalry phenomenon when two mutually exclusive images are presented to the two eyes: the perceived image alternates between the two presented images.[21] This interocular inhibition or suppression is also invoked by presenting background noise to the untested eye,[41,54] which was used in the present experiment. Thus, stimulation of the nontested eye, with identical background delivered to the tested eye, should modulate the monocular sensitivity of the tested eye, which was captured in the ratio termed DSD. The present data agree with previous reports,[35,55] as dichoptic condition indeed changed contrast sensitivity. The extent of the DSD was more or less pronounced based on binocular status: the data showed small but significant DSD in both eyes of stereonormal subjects, while a large DSD was evident in the amblyopic eye of foveally fixating, stereoanomalous amblyopic patients. In contrast, delivering the same background to the amblyopic eye had little influence on discrimination of the contralateral dominant eye in amblyopic subjects. We hypothesize that amblyopic inputs do not provide enough suppressive modulation to the dominant eye as observed in subjects with normal binocular vision between nondominant and dominant eyes. These results are backed by a recent article published by Beylerian et al.,[55] who have conducted a similar experiment with both monocular contrast sensitivity measurement and a dichoptic condition with a noise mask presented to the contralateral eye, called dichoptic masking, which is similar to our noise background seen by the contralateral eye. They showed that dichoptic masking asymmetrically influenced the amblyopic and the nonamblyopic eyes. Namely, there was a significant masking index, analogous to our DSD measure, both when the mask was presented to the contralateral eyes of control subjects and to the nonamblyopic eye of amblyopic subjects, but they failed to see any modulation in contrast sensitivity when the dichoptic mask was shown to the amblyopic eye, supporting a weak suppressive effect exerted by the amblyopic eye.

When broken down to specific spatial frequency ranges, our results have shown two characteristics of amblyopic patients that distinguished them from controls: a large dichoptic amblyopic contrast sensitivity deficit (ASD_{Dich}) in the higher spatial frequency ranges (2–8 cpd) as opposed to zero ASD_{Dich} in the control group and a lack of dominant eye dichoptic contrast sensitivity deficit (DSD_{DE}) in the lower spatial frequency ranges (0.5–2.0 cpd) as opposed to moderate DSD_{DE} in the control group. The first result is not surprising, given the well-known spatial frequency dependence of monocular contrast sensitivity deficits in amblyopic eyes, affecting more the higher frequencies.[56] In the case of dichoptic stimulation, the imbalance of dichoptic masking between eyes further decreases the sensitivity in the amblyopic compared with the dominant eye, thus, possibly enlarging the high-frequency sensitivity deficit in amblyopia. The second result, namely, that the amblyopic eye does not exert dichoptic masking onto the dominant eye in the low frequency range only, might be less readily explainable. One possible explanation would be a spatial frequency tuning of this dichoptic masking as has been shown by Beylerian et al.,[55] which posits that the masking effect is strongest around the spatial frequency of the mask itself. They found that the high-frequency mask presented to one eye had a detrimental effect on contrast sensitivity of the contralateral eye in the high-frequency range, but not in the low-frequency range, and the opposite was true for the low-frequency mask. The luminance noise background employed in the present study might be comparable with the high spatial frequency mask used by the above study, which would explain our findings. However, the problem with this explanation is that Beylerian et al. had concluded based on their results that only the dichoptic masking effect resulting from a mask delivered to the nonamblyopic eye is normal in magnitude and tuned to spatial frequencies similarly to control subjects, whereas dichoptic masking by the amblyopic eye on the nonamblyopic eye is very weak and untuned. Our results, in contrast, showed a similar tuning pattern for both amblyopic and dominant eyes of amblyopic patients, even though the masking effect on the latter was much weaker overall, and we found an opposite masking pattern for both eyes of control subjects. However, there are methodologic differences between the studies and our study was not directly designed to investigate this issue.

Here we also highlight that accessing visual sensitivity at a large range of spatial frequencies gives a better picture of the visual condition compared with the isolated measure of BCVA. Our group and others have found altered contrast sensitivity in young subjects with normal BCVA because of visual pathway-specific conditions[57] or as a result of neurotoxicity.[58] Moreover, normal contrast sensitivity should be considered in addition to normal BCVA as an indicator for treated amblyopia,[59–61] because contrast sensitivity is more related to everyday viewing conditions and, therefore, better correlated with a self-reported quality of vision.[26] In line with this finding, the six patients who have undergone previous binocular treatment clearly showed similarities to the control group in indices derived from their dichoptic contrast sensitivity (e.g., clustering based on $ASD_{Dichoptic}$ vs. DSD_{DE}, distribution of interocular DSD measure), whereas values obtained with traditional visual function measures such as visual acuity and Titmus stereoacuity did not stand out from those of other patients. The main concern regarding contrast sensitivity measurements during clinical examination is the longer time this examination consumes compared with the standard BCVA examination. However, modern approaches have solved this difficulty by implementing psychophysical strategies that enable its clinical applicability.[28,38]

Although it has been demonstrated[8,15,33,34] and also emphasized by the present results that dichoptic detection/discrimination may differ from monocular detection/discrimination in some visual conditions, and perhaps for the early diagnosis and monitoring of ophthalmic conditions,[62,63] dichoptic stimulation is usually not considered in the clinical context. The results of the present study offer multiple possibilities to harvest the potentials of dichoptic stimulation. First, subjects with normal binocular vision displayed similar DSD in both dominant and nondominant eyes; that is, the distribution of their interocular DSD values

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was centered on zero with very little standard deviation. Although the range of the interocular DSD values found in amblyopic subjects overlapped with those of controls, 71% (five of the seven overlapping patients) were those subjects who have undergone binocular treatment before but independent of the present experiment. The other nine patients all displayed a higher absolute difference between the eyes, making this index potentially useful as a clinical parameter for identifying disturbances in contrast sensitivity and/or binocular interactions that arise from developmental or psychiatric disorders.[64,65] Second, patients and controls differed in their overall pattern shown both in dichoptic ASD and dominant eye DSD values. Despite the group differences, all individuals lay along a continuum on the plane determined by these variables, with only a slight overlap between groups, which was again mostly accounted for by the previous binocular treatment (three of four). Thus, the patient's relative position—and the change thereof—in this coordinate system of ASD and DSD could potentially be a good indication of the patient's binocular balance and the success of any therapeutic intervention.

Dichoptic examinations may be a more accurate measure to examine patients with binocular dysfunction. In amblyopia, even though monocular vision is clinically used to establish its severity and to follow-up effects of treatments, there is a current need for a more accurate measure of the visual improvement in binocular condition. Because modern approaches using binocular stimulation, including dichoptic based, have emerged,[66–74] it is now possible to improve monocular BCVA of the amblyopic eye in binocular (dichoptic) condition without penalizing the dominant eye, which in turn brings the possibility of binocular balance restoration. Moreover, monocular discrimination using binocular background is closer to the everyday visual situation than the monocular examination. This approach may be considered by the clinicians when programing and following up therapeutic interventions to stimulate the proper functioning of the amblyopic eye.

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