Eye Movements, Strabismus, Amblyopia and Neuro-Ophthalmology

The Orientation Selectivity of Dichoptic Masking Suppression is Contrast Dependent in Amblyopia

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Purpose. We aimed to study the effect of stimulus contrast on the orientation selectivity of interocular interaction in amblyopia using a dichoptic masking paradigm.

Methods. Eight adults with anisometropic or mixed amblyopia and 10 control adults participated in our study. The contrast threshold in discriminating a target Gabor in the tested eye was measured with mean luminance in the untested eye, as well as with a band-pass oriented filtered noise in the other eye at low spatial frequency (0.25 c/d). Threshold elevation, which represents interocular suppression, was assessed using a the dichoptic masking paradigm (i.e. the contrast threshold difference between the target only and masked conditions), for each eye. Orientation selectivity of the interocular suppression as reflected by dichoptic masking was quantified by the difference between the parallel and orthogonal masking configurations. Two levels of mask's contrast (3 times or 10 times that of an individual's contrast threshold) were tested in this study.

Results. The strength of dichoptic masking suppression was stronger at high, rather than low mask contrast in both amblyopic and control subjects. Normal controls showed orientation-dependent dichoptic masking suppression both under high and low contrast levels. However, amblyopes showed orientation-tuned dichoptic masking suppression only under the high contrast level, but untuned under the low contrast level.

Conclusions. We demonstrate that interocular suppression assessed by dichoptic masking is contrast-dependent in amblyopia, being orientation-tuned only at high suprathreshold contrast levels of the mask.

Keywords: amblyopia, interocular suppression, orientation selectivity, contrast, dichoptic masking

Amblyopia is a neurodevelopmental disorder associated with abnormal visual experience early in life, such as strabismus, anisometropia, high refractive error, and cataract.[1–4] It is the most common cause of monocular visual loss in children,[5,6] affecting approximately 1% to 5.5% of the population.[2,7] Amblyopes suffer from poor monocular visual functions[8–10] (e.g. reduced visual acuity and contrast sensitivity), as well as poor binocular visual functions[11,12] (e.g. reduced stereopsis and abnormal binocular combination). Binocular vision deficits are reported to be more impactful than monocular vision deficits in amblyopia daily life.[2,13]

Interocular suppression has been considered to be central to the mechanisms underlying amblyopia.[14] It has been reported that the interocular suppression induced by amblyopic eye stimulation was much weaker than that by fellow eye stimulation.[15,16] This imbalanced interocular suppression is thought to have a causative role in the binocular visual deficits of amblyopia.[17–20] In addition, a recent study has shown that there are residual binocular visual deficits (i.e. the sensory eye dominance is abnormally biased toward the fellow eye at a wide spatial frequency ranges from 0.5 to 8 cycles/degree) even when amblyopes have regained normal visual acuity.[21] Thus, binocular therapy targeting rebalancing the interocular suppression has been introduced to treat amblyopia.[14,22–26]

These previous studies highlighted the importance of interocular suppression in amblyopia. However, our understanding of interocular suppression in amblyopia is not complete. To illustrate, the orientation selectivity of interocular suppression in amblyopia is still controversial. Levi et al.,[27] found that the suppression induced by the fellow eye (i.e. from the fellow eye to the amblyopic eye) was strongest when target grating and mask grating were at the same orientation, and suppression was reduced when there was an increased difference between target and mask orientation by using a dichoptic masking paradigm with spatial frequency of 2 c/d in one subject with amblyopia. Harrad and Hess[28] also used dichoptic masking paradigm and observed orientation dependent but broader tuning suppression by the fellow eye to the amblyopic eye in one strabismic amblyope at 5 c/d. However, Gao et al.,[29] found that 6 of 9 amblyopes showed an orientation untuned dichoptic masking suppression induced by the fellow eye, and the amblyopic eye showed little or no masking effect at 1.6 c/d by continuous flash suppression paradigm. The paradigms and spatial frequencies used in these previous studies were different. In our recent study,[30] we used a dichoptic masking paradigm and measured interocular suppressive interaction of both eyes for a range of spatial frequencies in amblyopes and found that such orientationally tuned interocular suppression was observed in low to mid spatial frequency in both eyes, but not at high spatial frequency for the amblyopic eye. These studies suggest that the orientation selectivity of interocular suppression in amblyopia is spatial frequency dependent.

It should be noted that in these previous studies, a fixed level of suprathreshold contrast mask was normally used for measuring the interocular suppressive interaction. It is known that amblyopes' contrast deficits are strongly spatial frequency dependent, for example, the contrast sensitivity function was significantly reduced at high spatial frequency.[9,31–35] This means that the measurement of interocular suppressive interaction might have been affected (i.e. reduced in magnitude) by the reduced level of suprathreshold contrast of the mask as a consequence of the elevated contrast threshold of the amblyopic eye at high spatial frequency. Therefore, one important question that needs to be answered is whether the mask stimulus suprathreshold contrast (i.e. relative to threshold) affects the orientation selectivity of interocular interaction in amblyopia. This is an important issue because, as pointed out above, the unselective masking at high spatial frequency in amblyopia previously reported could be due to either the high spatial frequency per se or the reduced suprathreshold contrast resulting from the elevated contrast threshold. To answer this question, we used the dichoptic masking paradigm[30] with masks at different suprathreshold contrast levels (3 times or 10 times of individual's contrast threshold) to measure orientation selectivity of interocular interaction in amblyopes and normal controls. The contrast threshold for each eye was measured under the target condition, as well as under parallel (the target and mask share the same orientation, 0° target with 0° mask) or orthogonal (the orientation difference between the target and the mask is 90°, 0° target, with 90° mask) masking conditions. Threshold elevation, which represents interocular suppressive interaction, was defined as the contrast threshold difference between the target and masking conditions, as for previous studies.[15,30] We specifically used a low spatial frequency stimulus (i.e. 0.25 c/d) because amblyopes usually have normal contrast threshold in this frequency range. This allowed us to use mask contrasts that were of the same absolute and relative (i.e. suprathreshold) contrast for normal controls and amblyopes. We found that orientation tuning was greater at the higher mask contrast condition. The orientation selectivity was significant both under 3 times and 10 times mask contrast in control adults, whereas it was significant only under 3 times mask contrast (not under 10 times mask contrast) in amblyopes.

METHODS

Participants

Eight adults with anisometropic or mixed amblyopia and 10 control adults (mean age = 22.8 ± 1.32 years old; 5 females) participated in this study. Amblyopia was defined according to the Preferred Practice Patterns of the American Academy of Ophthalmology[36] with an interocular best-corrected visual acuity (BCVA) difference of two or more logMAR lines. Participant A7 is a clinically treated amblyope[2,37] with one logMAR line difference of interocular BCVA. Participant A7 was included as she had a pattern of amblyopic interocular suppression even with recovered monocular visual acuity. All amblyopes were recruited from Eye Hospital of Wenzhou Medical University, and had no obvious structural anomalies or ocular disease, and had normal central fixation; their clinical characteristics are listed in the Table. All control participants had normal or corrected-to-normal visual acuity (≤0.00 logMAR), normal stereoacuity (≤60 arcsecs), minimal (or none) degree of anisometropia (refractive error [spherical equivalent, {SE}) difference ≤1.00 D) or astigmatism (≤1.00 D), and no history of eye disease or surgery. The dominant eye of each participant was determined by a pinhole test.[38] All participants were instructed to wear spectacles to fully correct their refrative errors in the experiment. The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Wenzhou Medical University. All participants were naive to the purpose of the experiment and informed consent was obtained from all of them.

Apparatus

The stimuli used in this study were programmed with MATLAB R2016a (MathWorks, Natick, MA, USA) using the PsychToolBox extension 3.0.14.[39,40] All stimuli were displayed on head-mounted 3D goggles (GOOVIS Pro, NED Optics, Shenzhen, China) with gamma-correction. The refresh rate was 60 Hz, and the resolution of the OLED goggles was 1600 × 900 pixels (corresponding to 46 × 26 degrees) for each eye. The maximal luminance of the goggles was 150 cd/m^2.

Stimulus

Target stimuli were monocular Gabor patches (Gaussian-enveloped gratings: sigma = 1.77°) that were presented to one eye. A mean grey background (monocular target condition) or a Gaussian-enveloped mask (dichoptic masking condition) was presented to the other eye. The masks were oriented noise patterns, created by convolving a white noise by a Gabor filter with a half-response spatial frequency of 1.84 octaves and orientation bandwidth of 65° in the space domain. The orientation of the target was 0° (i.e. horizontal) and the orientation of the mask was either 0° (i.e. horizontal) or 90° (i.e. vertical) depending on the testing condition. The sigma size of mask was 1.5 times larger than that of the target to reduce the effect of misalignment. The spatial frequency of the target and mask was 0.25 c/d. The contrast of the target was determined with a staircase procedure (see Procedures). The contrast of the mask was 3 times or 10 times higher than the monocular contrast threshold measured in the target condition.

Design

We first measured the monocular contrast threshold in the target only condition. Then, the contrast threshold was measured under 2 threshold mask conditions: 3 times and 10 times the threshold mask conditions. Each threshold mask condition included 2 mask orientations: (1) the orientation of the mask was 0° (parallel); and (2) the orientation of the mask was 90° (orthogonal). The contrast threshold was measured for each eye, and for two threshold mask conditions, and for two mask orientation conditions, thus leading to a total of 10 conditions for each participant (Fig. 1A).

Table. Clinical Characteristics of Amblyopes

Subject	Gender/ Age	Type	VA, logMAR (AE/FE)	Refraction (AE/FE)	Squint (OD/OS)	RDS Stereo Acuity, Arc Seconds	History of Treatment
A1	26/F	Anis	0.22 −0.08	+1.50/−0.50 × 180 PL	Ø	200	Detected at 15 years old, no treatment
A2	25/M	Anis	0.70 0.00	+5.00/−3.00 × 180 −0.50	Ø	400	Detected at 18 years old, no treatment
A3	25/F	Anis	0.50 0.00	+4.50/−0.75 × 15 PL	Ø	N/A	Detected at 12 years old, no treatment
A4	22/M	Anis	0.60 −0.08	+5.00 −4.00	Ø	400	Detected at 8 years old, glasses since 8 years old, patched for 1 year since 8 years old
A5	28/M	Anis	0.42 0.14	+4.00 +2.25	Ø	200	Detected at 11 years old, glasses since 13 years old
A6	23/F	Mixed	0.22 −0.08	−6.00/−3.00 × 75 −6.00	XP 10	100	Detected at 13 years old, glasses since detection, patched occasionally for 1 year
A7	20/F	Mixed	0.10 0.22	+1.00/−6.50 × 175 −1.50/−4.50 × 180	X(T) 15	400	Detected at 12 years old, then received strabismus surgery for X(T), glasses since detection, patched occasionally for 6 months
A8	22/M	Anis	0.60 −0.08	+5.50 −4.50	Ø	800	Detected at 13 years old, glasses since 13 years old, patched for 1 year since 13 years old

Anis, anisometropic amblyopia; Mixed, amblyopia with both strabismus and anisometropia; VA, visual acuity; AE, amblyopic eye; FE, fellow eye; PL, plano, emmetropia pd, prism diopters; OD, right eye; OS, left eye; Ø, without strabismus; XP, exophoria; X(T), intermittent exotropia; RDS, randot stereotest.

In all subjects, the left eyes (6 non-dominant eyes and 6 amblyopic eyes) were measured first, then the right eyes. For each eye, the contrast threshold under the target condition was measured first, and then under the mask conditions. The threshold mask conditions (i.e. 3 times and 10 times the threshold mask conditions) were randomized in all subjects. In addition, the orientations of the mask (i.e. parallel and orthogonal) were measured randomly in each threshold mask condition. Participants were allowed to take a break after every contrast threshold measure and started the next one when they were ready to proceed. Each condition was measured in 6 to 8 minutes, therefore the experiment was finished in 1 to 2 hours, with breaks included.

Procedures

Before beginning the experiment, an interocular alignment task was needed to be completed by facilitating the fusional alignment between the participants' two eyes. Participants were asked to align a vertical red line with a vertical green line presented to each eye in the middle of the screen. The position of the two lines were then used for presenting stimuli in the two eyes (without shifting the phase of Gabors) in the following contrast threshold measures.

Contrast thresholds were measured with a two-down one-up staircase procedure using a 2-interval forced choice (2IFC) paradigm with contrast chosen on a log-scale between 0.001 and 1. The staircase ended after 20 reversals.

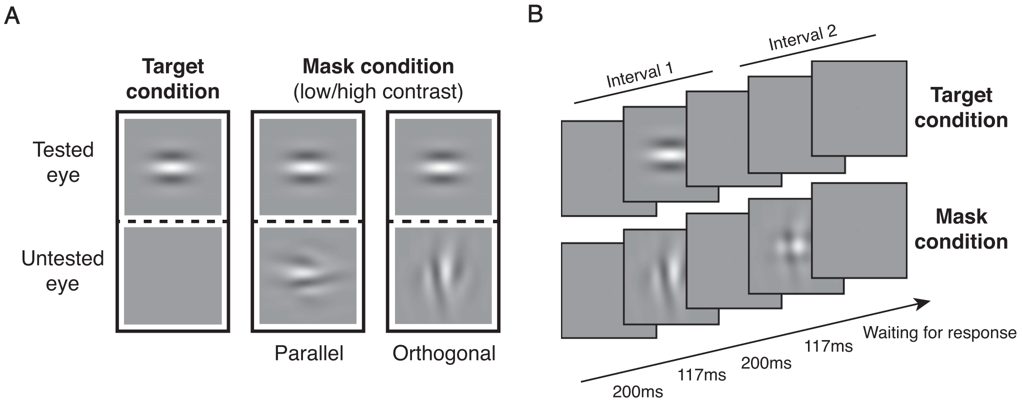

Figure 1. (**A**) Dichoptic stimuli. Target condition included one viewing condition: the 0° Gabor target was presented to the tested eye and a mean luminance background was presented to the untested eye. Mask condition included 2 threshold mask conditions: (1) low contrast: the mask contrast was 3 times higher than the individual's contrast threshold; and (2) high contrast: the mask contrast was 10 times higher than the individual's contrast threshold. Each threshold mask condition included 2 orientation conditions: (1) parallel condition: the 0° Gabor target was presented to the tested eye and the 0° mask was presented to the untested eye; and (2) orthogonal condition: 0° Gabor target was presented to the tested eye and the 90° mask was presented to the untested eye. (**B**) Time course of the experiment. Each trial began with an orange fixation point (radius 0.1°) appearing for 200 ms. The first interval stimulus appeared for 117 ms without fixation point and signaled by a brief tone, followed by a 200 ms inter-stimulus interval with an orange fixation point. Then a 117 ms second stimulus interval appeared signaled by a brief tone, and a green fixation point until response. Response correctness was then indicated by another tone.

In each trial, the presentation sequence was as follows: an orange fixation point (radius 0.1°) appeared for 200 ms at the beginning, then the first interval stimulus appeared for 117 ms without a fixation point and signaled by a brief tone, followed by a 200 ms inter-stimulus interval with an orange fixation point, a 117 ms second interval signaled by a brief tone, and a green fixation point until response (Fig. 1B). In the target condition, the target was randomly presented in one of the two intervals and the other interval was blank. In the mask condition, the mask was presented in both the two intervals and the target was randomly presented in only one of the two intervals. The participants were asked to indicate the target that was shown in which interval (first or second interval) and to press the corresponding key. There was a brief tone following each response to inform the correctness. The next trial started immediately after the response.

Data Analysis

The effect of interocular suppressive interaction was defined as the dichoptic masking suppression induced by the mask. It should be noted that the effect of dichoptic masking might involve both the interocular suppression (e.g. when the mask is orthogonal) as well as within-channel pedestal or noise type masking (e.g. when the mask is parallel). For clarity and consistency with both our previous studies[15,30] and those of others,[41,42] we have referred to the change in detectability due to masking in terms of elevated contrast thresholds rather than reduced contrast sensitivity. Threshold elevation was quantified as the difference of contrast threshold in dB between one mask condition and the target condition for the same test eye, using the following equation:

$$Threshold\ elevation = 20 \times \log_{10}\left(Thresh_{Mask}\right) - 20 \times \log_{10}\left(Thresh_{Target}\right) \quad (1)$$

where *Thresh* refers to the measured contrast threshold in mask or target condition. For example, the threshold elevation under 3 times the parallel mask condition is the contrast threshold in dB of 3 times the parallel mask condition minus that of the target condition.

Analysis was performed with SPSS Statistics version 25 (IBM, Armonk, NY, USA) and Matlab 2018a (Mathworks, Natick, MA, USA), with $P < 0.05$ as the criterion for statistical significance. The Shapiro-Wilks test was used to assess the normality of the dataset.[43] The degrees of freedom of the F distribution were corrected by an index of deviation to sphericity.[44–46] The Bayes factor (BF) was calculated to quantify the relative predictive performance of two rival hypotheses ($\mathcal{H}0$: no significant difference; $\mathcal{H}1$: significant difference)[47] in one-sample *t*-test:

$$\underbrace{\frac{p(\mathcal{H}0)}{p(\mathcal{H}1)}}_{Prior\ odds} \times \underbrace{\frac{p(D|\mathcal{H}1)}{p(D|\mathcal{H}0)}}_{BF_{10}} = \underbrace{\frac{p(\mathcal{H}1|D)}{p(\mathcal{H}0|D)}}_{Posterior\ odds} \quad (2)$$

A Bayes factor (BF_{10}) of 1 indicates that both hypotheses predicted the data equally well. The $0 < BF_{10} < 1$ can be interpreted as evidence for the alternative $\mathcal{H}0$ relative to the null hypothesis $\mathcal{H}1$. The $1 < BF_{10} < 3$, $BF_{10} > 3$, $BF_{10} > 10$, and $BF_{10} > 100$ can be interpreted as anecdotal, moderate, strong, and extreme evidence for $\mathcal{H}1$, respectively.[48]

RESULTS

Monocular Contrast Threshold With no Mask

Figure 2 shows the contrast threshold of the controls and the amblyopes. Mixed repeated-measures analysis of variance (ANOVA) with a between-subjects factor of group (controls and amblyopes), with a within-subjects factor of eye (dominant eye [DE]/fellow eye [FE] and non-dominant eye [NDE]/amblyopic eye [AE]) was performed to examine whether contrast threshold was different between normal controls and amblyopes, and between DE (FE) and NDE (AE). The effect of group (F[1,16] = 0.933, $P = 0.348$), eye (F[1,16] = 0.001, $P = 0.981$), or the interaction between the group and eye (F[1,16] = 0.303, $P = 0.589$) was not significant. This result demonstrated that the contrast threshold of each eye was not different between controls and amblyopes at the spatial frequency we studied (i.e. 0.25 c/d).

Threshold Elevation With Dichoptic Masking

We measured contrast threshold under five conditions (see Fig. 1) for the two eyes in controls and the amblyopes. The threshold elevation (i.e. interocular interaction, the difference of contrast threshold in dB between the target and mask conditions, see Methods) under the two threshold mask conditions (each mask contrast including 2 orientations) are plotted in Figure 3. Figures 3A and 3B show the threshold elevation of controls and that of amblyopes, respectively.

Mixed repeated-measures ANOVA with a between-subjects factor of group (controls and subjects amblyopes), with within-subjects factors of eye (from DE/FE to NDE/AE and from NDE/AE to DE/FE), mask contrast (3 times and 10 times), and orientation (parallel and orthogonal) was performed to examine whether threshold elevation was different between normal controls and amblyopes, between low and high mask contrast, between parallel and orthogonal, and between DE/FE and NDE/AE. The effects of eye (F[1,16] = 6.059, $P = 0.026$), mask contrast (F[1,16] =

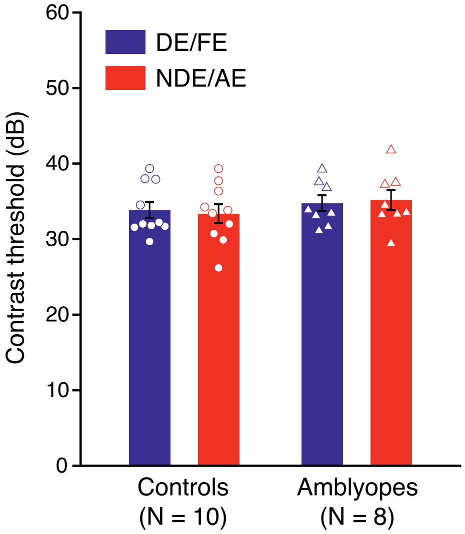

FIGURE 2. Contrast threshold of each eye in controls and amblyopes at 0.25 c/d. Blue and red bars represent the contrast threshold of DE/FE and NDE/AE in controls and amblyopes, respectively. Individual data point is represented by a circle (controls) or a triangle (amblyopes).

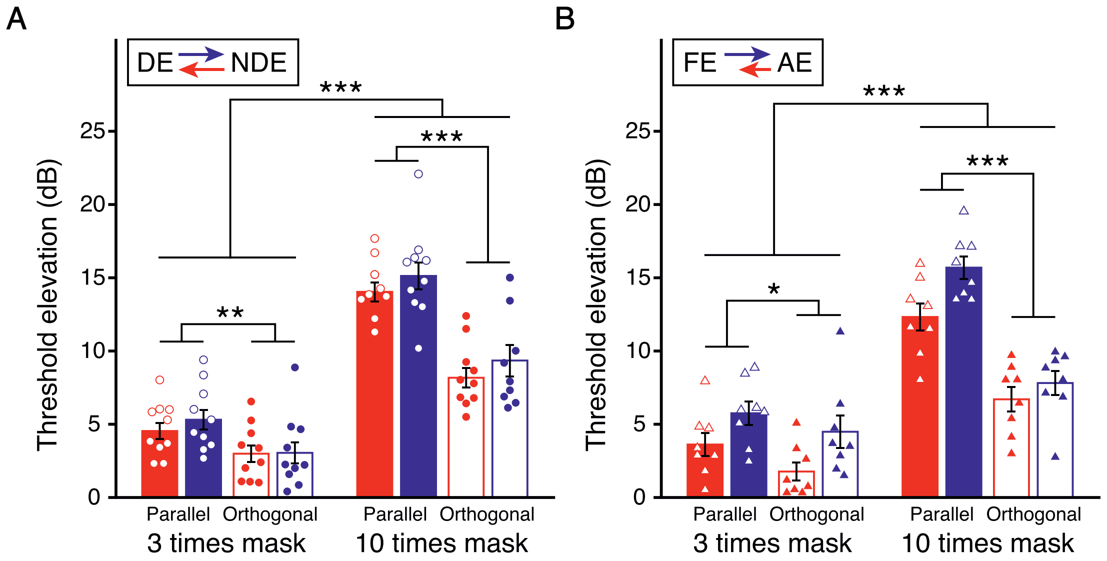

Figure 3. Threshold elevation in controls (**A**) and amblyopes (**B**). Blue and red bars represent the threshold elevation from DE/FE to NDE/AE and from NDE/AE to DE/FE in controls and amblyopes, respectively. Solid and hollow bars represent the threshold elevation measured under parallel and orthogonal conditions, respectively. Individual data point is represented by a circle (controls) or a triangle (amblyopes). *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

328.798, $P < 0.001$), and orientation (F[1,16] = 195.850, $P < 0.001$) and the interaction between mask contrast and orientation (F[1,16] = 181.706, $P < 0.001$) were found to be significant. But the effect of group was not significant (F[1,16] = 1.905, $P = 0.186$). The interactions between other factors were not significant (all, $P > 0.170$).

Threshold Elevation in Normal Controls. In controls (see Fig. 3A), repeated measure ANOVA with within-subjects factors of eye (from DE to NDE and from NDE to DE), mask contrast (3 times and 10 times), and orientation (parallel and orthogonal) was performed to examine whether the threshold elevation was different between the two eyes, under different threshold mask conditions, and under different orientations. The effects of mask contrast (F[1,9] = 278.769, $P < 0.001$) and orientation (F[1,9] = 95.995, $P < 0.001$), and interaction between the mask contrast and orientation (F[1,9] = 21.438, $P = 0.001$) were found to be significant. But the effect of the eye (F[1,9] = 0.590, $P = 0.462$), or the interaction between the eye and mask contrast (F[1,9] = 0.764, $P = 0.405$), between eye and orientation (F[1,9] = 0. 042, $P = 0.843$), or among the eye, mask contrast, and orientation (F[1,9] = 0.505, $P = 0.495$) was not significant. The post hoc analysis showed that the threshold elevation was significantly different between parallel and orthogonal conditions both under 3 times ($P = 0.001$) and 10 times ($P < 0.001$) the threshold mask conditions.

Threshold Elevation in Amblyopes. In amblyopes (see Fig. 3B), repeated measure ANOVA with within-subjects factors of eye (from FE to AE and from AE to FE), mask contrast (3 times and 10 times), and orientation (parallel and orthogonal) was performed to examine whether the threshold elevation was different between the two eyes, under different threshold mask conditions, and under different orientations. The effects of eye (F[1,7] = 14.938, $P = 0.006$), mask contrast (F[1,7] = 97.186, $P < 0.001$), and orientation (F[1,7] = 103.783, $P < 0.001$), and interaction between mask contrast and orientation (F[1,7] = 58.553, $P < 0.001$) were found to be significant. But the interaction between the eye and mask contrast (F[1,7] = 0. 020, $P = 0.891$), between the eye and orientation (F[1,7] = 0. 568, $P = 0.475$), or among the eye, mask contrast, and orientation (F[1,7] = 2.351, $P = 0.169$) was not significant. The post hoc analysis showed that the threshold elevation was significantly different between parallel and orthogonal conditions both under 3 times ($P = 0.011$) and 10 times ($P < 0.001$) the threshold mask conditions.

These findings indicated that the dichoptic masking suppression was similar in the two eyes in the controls, whereas it was different between the eyes in amblyopes. Dichoptic masking suppression was larger under parallel condition than under orthogonal condition. In addition, we demonstrated that larger dichoptic masking suppression could be found with higher mask contrast.

Results of Tuning Index (Orientation Selectivity of Interocular Suppression)

To better represent the orientation selectivity, the tuning index (the threshold elevation difference between the parallel and orthogonal conditions) of controls and amblyopes are plotted in Figures 4A and 4B, respectively.

Tuning Index in Normal Controls. In the controls (see Fig. 4A), repeated-measures ANOVA with within-subjects factors of eye (from DE to NDE and from NDE to DE) and mask contrast (3 times and 10 times) was performed to examine whether the tuning index was different between the two eyes, or under different threshold mask conditions. The effect of mask contrast was found to be significant (F[1,9] = 21.438, $P = 0.001$). But the effect of the eye (F[1,9] = 0.042, $P = 0.843$), or the interaction between the eye and mask contrast (F[1,9] = 0.505, $P = 0.495$) was not significant. One sample *t*-test was performed, and BF_{10} was calculated (see Methods-Data analysis). Tuning index of the two eyes was found to be significantly different from 0 both under

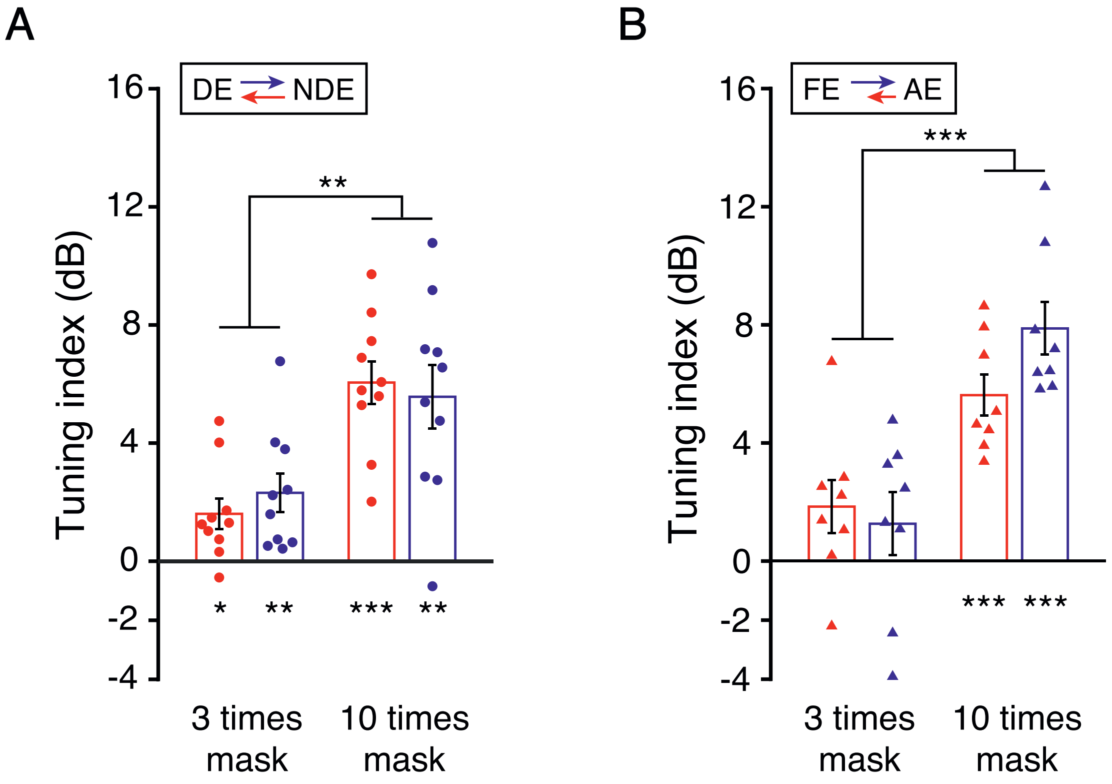

Figure 4. Tuning index of controls (**A**) and amblyopes (**B**). Blue and red bars represent the tuning index of DE/FE and NDE/AE in controls and amblyopes, respectively. Individual data point is represented by a circle (controls) or a triangle (amblyopes). *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

3 times and 10 times the mask contrast (3 times: from NDE to DE, $BF_{10} = 5.455$, $P = 0.012$, from DE to NDE, $BF_{10} = 9.486$, $P = 0.006$; 10 times: from NDE to DE, $BF_{10} > 100$, $P < 0.001$, from DE to NDE, $BF_{10} = 66.035$, $P < 0.001$).

Tuning Index in Amblyopes. In amblyopes (see Fig. 4B), repeated-measures ANOVA with within-subjects factors of the eye (from FE to AE and from AE to FE) and mask contrast (3 times and 10 times) was performed to examine whether the tuning index was different between the two eyes, or under different threshold mask conditions. The effect of the mask contrast was found to be significant ($F[1,7] = 58.553$, $P < 0.001$). But the effect of the eye ($F[1,7] = 0.568$, $P = 0.475$), or the interaction between the eye and mask contrast ($F[1,7] = 2.351$, $P = 0.169$) was not significant. One sample *t*-test was performed, and BF_{10} was calculated. Tuning index of the two eyes was found to be significantly different from 0 under 10 times the threshold mask condition (from AE to FE, $BF_{10} > 100$, $P < 0.001$; from FE to AE, $BF_{10} > 100$, $P < 0.001$) but not under 3 times threshold mask condition (from AE to FE, $BF_{10} = 1.340$, $P = 0.080$; from FE to AE, $BF_{10} = 0.579$, $P = 0.274$).

These results indicated that the tuning index was similar in the two eyes, in both normal controls and amblyopes. In addition, the tuning index was significantly larger with higher mask contrast, in both subjects with amblyopia and normal vision. Significant tuning index was observed in the controls and amblyopes under the 10 times threshold mask condition. However, under 3 times threshold mask condition, the tuning index of controls was significant, while that of amblyopes trended to be different from 0 with 3 times contrast mask but without statistically significant.

DISCUSSION

In this study, we evaluated the interocular suppressive interaction by using a dichoptic masking paradigm. The contrast of mask was set at either 3 times or 10 times the level of the monocular target grating contrast threshold to produce a weaker and a stronger suppressive effect. The threshold elevation at these different mask contrast suprathreshold levels was measured. An imbalanced dichoptic masking suppression was observed in amblyopes, whereas a balanced dichoptic masking suppression was observed in normal controls (i.e. the masking effect from the amblyopic eye to the fellow eye was less than that from the fellow eye to the amblyopic eye in amblyopes, while it was similar in the two eyes of control adults). This result was consistent with previous studies.[15,16,30,49,50] Also, the imbalanced dichoptic masking suppression was not the result of the monocular deficits, as the contrast threshold of the amblyopes was not different between the two eyes at the low spatial frequency used (i.e. 0.25c/d). This supports the proposition that the interocular suppressive imbalance in amblyopia at low spatial frequency is not a simple consequence of threshold attenuation in the interocular contrast gain control mechanism.[51,52] In addition, parallel masking was shown to have more effect than orthogonal masking in both control and amblyopic subjects at 10 times the mask contrast level. This result agreed with our previous study[30] and other studies,[27,53] suggesting that amblyopes exhibit normal orientation-tuned interocular suppressive interactions in both eyes when there is a strong dichoptic mask.

The strength of dichoptic masking suppression was found to be stronger at high mask contrast compared with low mask contrast both in amblyopes and normal controls. This result agreed with previous studies using binocular rivalry paradigm,[54] continuous flash suppression paradigm,[29] and dichoptic masking paradigm.[52] For example, Meese et al.,[52] used a contrast masking paradigm with a spatial frequency matched mask and target, and found an increased test contrast at higher mask contrasts. The slope of function of the test contrast and the mask contrast was found to be a close to unity at moderate and higher mask contrasts, which was consistent with Weber's law. Here, we found that the orientation selectivity of dichoptic masking suppression in amblyopia was also affected by the mask contrast. At the 3 times mask contrast threshold condition, the parallel and orthogonal masking effects were similar in both eyes in amblyopes, whereas the parallel masking effect was stronger than the orthogonal masking effect in normal controls. One patient (subject A1) showed strong masking effect from FE to AE under both the 3 times and 10 times mask contrast conditions. This did not affect our results and the main conclusion as the amblyopic subjects still showed orientation untuned interocular suppression under the low mask contrast even if we excluded the data of this subject (tuning index was not significantly different from 0; from AE to FE: $BF_{10} = 1.359$, $P = 0.084$; from FE to AE: $BF_{10} = 0.929$, $P = 0.144$). This reveals that the orientation selectivity of interocular interaction was different between amblyopes and normal controls at mask contrasts close to threshold.

The correlations between the strength of dichoptic masking suppression (i.e. the threshold elevation) and the tuning index (i.e., the orientation selectivity of dichoptic masking suppression), between the tuning index and visual acuity were not found either for 3 times or 10 times threshold mask conditions (see Supplementary Material). These results agreed with our previous study, in which significant correlation was not found at 0.25 c/d.[30] Even though the contrast of the mask was set at 0.8 in our previous study and it was set at various contrast levels in the present study, similar correlation results were observed. We conclude that the anomalous orientation selectivity of interocular interaction at 0.25 c/d in amblyopes for the 3 times threshold mask condition was not a consequence of neither the monocular visual acuity deficits nor the imbalanced interocular interaction.

More importantly, our results also suggested that one needs to take the contrast of the mask into consideration (i.e. fixed contrast or visibility level), when investigating the properties of interocular suppression in amblyopia. The fact that the orientation tuning properties depend on the suprathreshold contrast level clearly indicates that suppression in amblyopia cannot be simply regarded as exaggerated normal dichoptic masking. It might also indicate that the contributions of overlay/surround inhibitory interactions underlie the interocular suppression in amblyopia.[55] One prediction that we are currently investigating is whether this lack of orientation tuning depends on the visual field extent of the mask.

Rebalancing the interocular suppression has been considered as a potential treatment for binocular deficits in amblyopia. For example, Bossi et al.[14] used a blurring of the fellow eye and normal image in the amblyopic eye (binocularly balanced movie) to treat amblyopia. Patients received clinically significant improvement of visual acuity, and pure anisometropic amblyopia also received stereoacuity improvement. Blurring reduces the contrast preferably for stimuli of higher spatial frequencies. Here, we show that contrast is an important factor when considering interocular suppressive effects in amblyopia even at very low spatial frequencies, suggesting that a therapeutic manipulation based on contrast rather than lowpass filtering might be more optimal. Also, different contrast and orientation conditions, as well as other stimuli settings might need to be considered when training based on contrast modulation is designed to benefit visual functions using training tasks. In addition, it is also suggested that contrast might play a key role in training, as our present study and those of other studies[11,19,56,57] have observed.

In conclusion, the interocular interaction and its orientation selectivity were assessed by dichoptic masking paradigm at a low and a high mask contrast level for a low spatial frequency stimulus. The dichoptic masking suppression and orientation selectivity were both contrast dependent in adults with amblyopia and normal vision. In normal adults, the dichoptic masking suppression showed orientation tuning both under high and low mask contrasts. However, in amblyopia, the dichoptic masking suppression was found to be orientation-tuned at high mask contrast, but untuned at low mask contrast.

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