Interocular Suppression as Revealed by Dichoptic Masking Is Orientation-Dependent and Imbalanced in Amblyopia

Ling Gong,[1] Alexandre Reynaud,[2] Zili Wang,[1] Suqi Cao,[1] Fan Lu,[1] Jia Qu,[1] Robert F. Hess,[2] and Jiawei Zhou[1]

[1]School of Ophthalmology and Optometry, Affiliated Eye Hospital, State Key Laboratory of Ophthalmology, Optometry and Vision Science, Wenzhou Medical University, Wenzhou, Zhejiang, China
[2]McGill Vision Research, Department of Ophthalmology and Visual Sciences, McGill University, Montreal, Canada

PURPOSE. We investigate the orientation tuning of interocular suppression using a dichoptic masking paradigm in adult controls and amblyopes.

METHODS. Fourteen adults with anisometropic or mixed amblyopia and 10 control adults participated in our study. Contrast sensitivity was measured by presenting a target Gabor in the tested eye and mean luminance in the untested eye (monocular) and by presenting a target in the tested eye and a bandpass oriented filtered noise in the other eye (masked). Interocular suppression was defined as the thresholds difference between the monocular and masked conditions for each eye. Interocular suppression was measured under parallel and orthogonal suppression configurations. The peak spatial frequency of the target and mask was 0.25 c/d in experiment 1 (low), 1.31 c/d in experiment 2 (mid), and 6.87 c/d in experiment 3 (high).

RESULTS. The masking suppression induced by the amblyopic eye was less strong than that induced by the fellow eye. The suppression from the fellow eye was similar to that observed in the controls. Interocular suppression under parallel configuration was less strong than under orthogonal configuration in amblyopes at low and mid spatial frequency, but not at high spatial frequency.

CONCLUSIONS. We demonstrate that the abnormal interocular masking in amblyopia displays the expected characteristic of orientation selectivity expected of normal controls at low and mid spatial frequency, but not at high spatial frequency. The dichoptic masking imbalance between the eyes of amblyopes results in a net suppression of the amblyopic eye during binocular viewing, modeling clinical suppression.

Keywords: amblyopia, suppression, orientation, dichoptic masking, spatial frequency

Amblyopia, the most frequent cause of monocular visual loss in childhood,[1,2] affects up to 3.6% of the population.[3] It is associated with abnormal visual experience in early development, like strabismus, anisometropia, high refractive error, and cataract.[3–5] Unilateral amblyopia causes monocular vision deficits in visual acuity and contrast sensitivity.[6,7] Amblyopes also suffer from reduced visual performance for stereopsis,[8] binocular combination,[9] face perception,[10] global motion perception,[11] global form perception,[12] and temporal synchrony detection.[13] Recent studies suggest that binocular vision deficits are more impactful than monocular vision deficits in amblyopes' daily life.[3,14]

Interocular suppression plays a key role in the binocular visual deficits of amblyopes.[15,16] Several theoretical models of binocular interactions in amblyopia, for example the two-stage model,[17] multiple-pathway contrast gain control model,[18] and contrast gain control and gain enhancement model,[19] suggest that a disruption to the normally balanced dichoptic inhibitory circuits could provide the basis for understanding suppression in amblyopia. In this case a detailed study of dichoptic masking, which is thought to reflect these inhibitory interocular interactions, has been considered a potentially useful avenue to better understand the phenomenon that under conditions of binocular viewing, information from the amblyopic eye is suppressed[20–23] at an early stage in the visual cortex.[24] Using the dichoptic masking approach, Zhou et al.[23] recently observed less suppression from the amblyopic eye to the fellow eye and a normal suppression from the fellow eye to the amblyopic eye in amblyopic adult patients, resulting in a net suppression of the amblyopic eye under binocular viewing. They also showed that the degree of this net suppression, as assessed by masking, was larger at low spatial frequencies. Furthermore, a better understanding of amblyopic suppression is needed because suppression is now thought to be central in the amblyopic syndrome,[15,25] and training procedures targeting rebalancing the eyes in binocular viewing have been introduced to treat amblyopia.[26–28]

Interocular inhibitory interactions have been found to depend on the orientation, that is, is orientationally tuned,

in the normal visual system by using binocular rivalry[29,30] and dichoptic masking[17] paradigms. The inhibitory strength is strongest when the target and mask are of parallel orientations and is reduced when the orientation of the mask moves away from the orientation of the target. Such orientation-dependent interocular inhibition/suppression is also observed in visual evoked potentials,[31] since a smaller amplitude of the VEP was recorded when the orientation of the target and mask are more similar,[32] likely because of the orientation selectivity of neurons in primary visual cortex.[33] However, the orientation selectivity in systems with abnormal visual experience, for example visual deprivation and amblyopia, is still controversial. The development of orientation selectivity in cat cortical neurons was found to be halted by visual deprivation,[34,35] while there are also reports that no such effect was induced by deprivation.[36,37] In humans, there is evidence that anisometropic amblyopia shows orientation-dependent suppression by using binocular rivalry.[38] Recently, Gao et al.[39] used a continuous flash suppression paradigm to separately investigate the orientation tuning in the fellow the amblyopic eyes. They found that some amblyopes (6 of 9) showed an orientation-independent suppression induced by the fellow eye, and the amblyopic eye showed little or no suppression at 1.6 c/d. These results differ from two previous studies, one by Levi et al.,[40] who used a dichoptic masking paradigm and found that, for a 2 c/d stimulus, the suppression of the fellow eye by the amblyopic eye was orientation dependent, and another by Harrad and Hess,[22] who showed a broader orientation tuning for suppression of the amblyopic eye in dichoptic masking at 5 c/d. These previous studies used single but different spatial frequency stimuli ,and there is a hint that the tuning of dichoptic masking in amblyopia might critically depend on spatial frequency. Here, we directly address this issue by determining whether dichoptic masking, and by implication, interocular suppression, in amblyopia depends on stimulus spatial frequency.

To answer this question, we adopted a dichoptic masking paradigm based on our previous studies.[21,23] In contrast to the studies by Levi et al.[40] and Harrad and Hess[22] and Gao et al.,[39] we used different combinations of target and masks orientations rather than a fixed target orientation with varied mask orientation. We measured subjects' contrast sensitivity for detecting the target in isolation or under various masking conditions for each eye. We used target and noise masks of same peak spatial frequency, because the suppression is known to be greatest when the target and mask are matched in spatial frequency.[21,41,42] Throughout this article, we refer to interocular suppression as the difference between the contrast sensitivity for detecting the target in isolation and that of detecting the target in the presence of the mask in various conditions. We measured interocular suppression under parallel masking conditions (target and mask share the same orientation, 0° with 0° or 90° with 90°) and orthogonal masking conditions (the orientation difference between target and mask is 90°: 0° with 90° or 90° with 0°).

We measured the dichoptic masking suppression both in the fellow eye and the amblyopic eye of 14 amblyopes and compared the data with that of a group of 10 control subjects at low (experiment 1: 0.25 c/d), mid (experiment 2: 1.31 c/d), and high (experiment 3: 6.87 c/d) spatial frequency to investigate the orientation tuning of interocular masking in amblyopes as a way to better understand amblyopic suppression. We hypothesized that the amblyopic visual system exhibits an orientation-dependent interocular suppression. In which case, the interocular suppression would be different under parallel versus orthogonal suppression configurations.

METHODS

Observers

Fourteen adults with anisometropic or mixed amblyopia and 10 control adults (mean age 24.9 ± 1.03 years old; five females) participated in this study. Amblyopia was defined according to the Preferred Practice Patterns of the American Academy of Ophthalmology,[43] with a best-corrected visual acuity in the amblyopic eye between 0.10 (logMAR) and 1.00 (logMAR) and 0.05 (logMAR) or a better vision in the fellow eye. All amblyopes were recruited from Eye Hospital of Wenzhou Medical University, had no obvious structural anomalies or ocular disease, and had normal central fixation; their clinical characteristics are listed in the Table. All amblyopic subjects were instructed to wear spectacles to fully correct their refractive errors in all experiments. All control subjects had normal or corrected to normal visual acuity (0.00 logMAR or better), normal stereoacuity (≤60 arcsecs), minimal (or none) degree of anisometropia (refractive error [spherical equivalent {SE}] difference ≤1.00D), or astigmatism (≤1.00D), and no history of eye disease or surgery. The dominant eye of each subject was determined by a pinhole test.[44] The misalignment of amblyopes was not significantly different from that of controls at horizontal (controls: 13.8 ± 3.67 pixels; amblyopes: 27.1 ± 4.51 pixels; $F_{2,21}$ = 2.51, P = 0.106; one-way ANOVA) or vertical (controls: 0.2 ± 0.20 pixels; amblyopes: 16.4 ± 10.28 pixels; z = –1.091, P = 0.275; Mann-Whitney U test). The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Wenzhou Medical University. All subjects were naive to the purpose of the experiment, and informed consent was obtained from all of them.
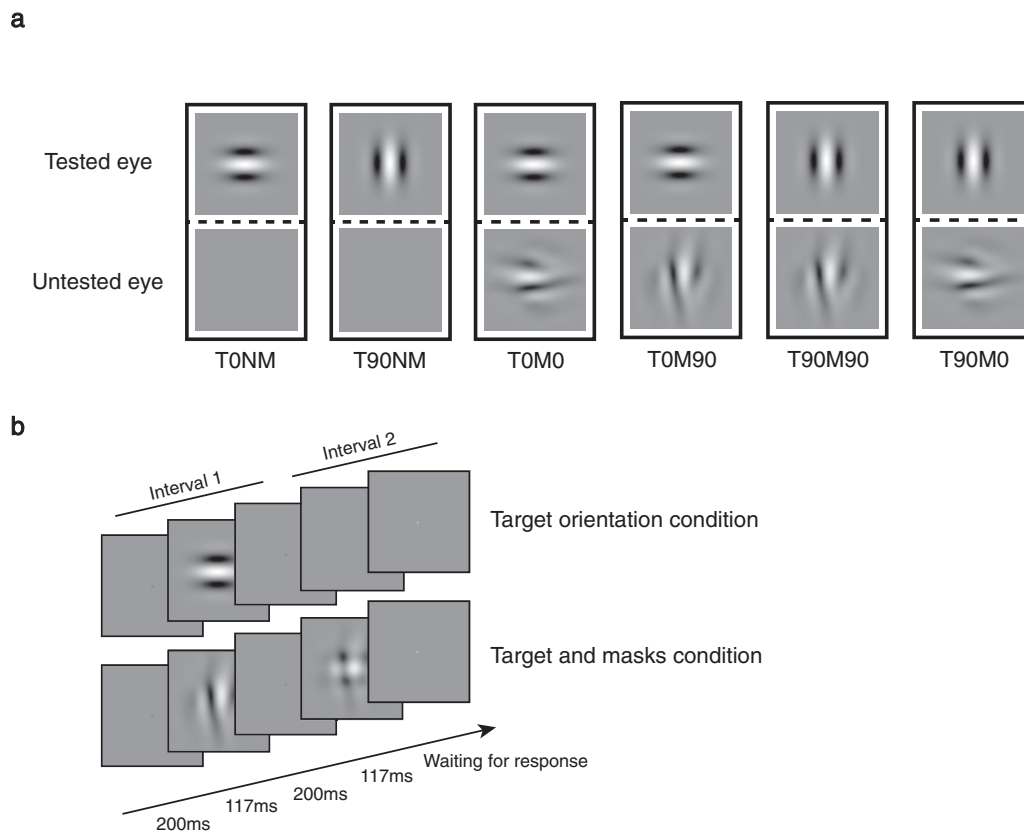
Apparatus

The stimuli used in this study were programmed with MATLAB R2016a (MathWorks, Natick, MA, USA) using the PsychToolBox extension 3.0.14.[45,46] All stimuli were displayed on gamma-corrected head-mounted 3D goggles (GOOVIS Pro; NED Optics, Shenzhen, China). The resolution of the OLED goggles was 1600 × 900 pixels (corresponding to 46° × 26°) for each eye, and the refresh rate was 60 Hz. The maximal luminance of the goggles was 150 cd/m².

Stimulus

Target stimuli were monocular Gabor patches (Gaussian-enveloped gratings: sigma, 1.77°). They were either presented alone (mean luminance background in the other eye) or with a Gaussian-enveloped mask in the other eye. The masks consisted of 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) or 90° (i.e., vertical) and the orientation of the mask was also 0° or 90° depending on the testing condition. The sigma size of mask was 1.5 times larger than that of target to reduce the effect of misalignment. The spatial frequency of the target and mask was

TABLE. Clinical Characteristics of Amblyopies

Subject	Sex/Age	Type	VA AE, logMAR	VA FE, logMAR	Refraction AE	Refraction FE	Squint (OD/OS)	RDS Stereo Acuity, Arc Seconds	History of Treatment
A1	31/M	Anis	0.80	0.00	+5.50/−1.00*170	−2.50/−0.50*90	Ø	600	Detected at 14 years old, glasses since 14 years old, no patching.
A2	20/F	Anis	0.10	0.00	+0.50/−0.50*180	−2.75/−0.50*180	Ø	400	Detected at 11 years old, glasses since 11 years old, patched for 1 year since 13 years old. The refractive error was +3.50/−0.50*10 in AE and 0.00 in FE when this subject was first diagnosed. The refractive error changed during development and treatment. For example, the refractive error was +2.25/−0.50*180 in AE and −0.75 in FE when 16 years old; +0.75 in AE and −2.00 in FE when 19 years old.
A3	25/M	Anis	0.70	0.00	+5.00/−3.00*180	−0.50	Ø	400	Detected at 18 years old, glasses and patched for 2 months since 18 years old.
A4	20/M	Anis	0.10	−0.10	0.00/−1.00*175	+0.25/−0.50*180	Ø	200	Detected at 12 years old, glasses since 12 years old, no patching, PRK surgery at 18 years old.
A5	30/M	Anis	0.10	0.00	−13.25/−2.00*40	−1.50/−1.75*7	Ø	N/A	Detected at 16 years old, glasses since 16 years old, no patching.
A6	22/M	Anis	0.60	−0.10	+5.50	−4.50	Ø	800	Detected at 13 years old, glasses since 13 years old, patched for 1 year since 13 years old.
A7	20/F	Mixed	0.10	0.00	+1.00/−6.50*175	−1.50/−4.50*180	Ø	400	Detected at 10 years old, glasses since 10 years old, strabismus surgery at 10 years old, patched for 3 years since 10 years old.
A8	26/F	Anis	0.22	−0.10	+1.50/−0.50*180	PL	Ø	200	Detected at 15 years old, no treatment.
A9	25/F	Anis	0.50	0.00	+4.50/−0.75*15	PL	Ø	N/A	Detected at 12 years old, no treatment.
A10	22/F	Anis	0.22	−0.08	−5.75/−3.00*75	−6.00	Ø	100	Detected at 13 years old, glasses since 13 years old, patched for 1 year since 13 years old.
A11	24/M	Anis	0.40	−0.10	−14.50/−1.00*180	−7.50/−0.75*10	Ø	400	Detected at 12 years old, glasses since 12 years old, no patching.
A12	22/M	Anis	0.60	−0.10	+5.00	−4.00	Ø	400	Detected at 8 years old, glasses since 8 years old, patched for 1 year since 8 years old.
A13	32/F	Anis	0.70	0.00	+5.00/−1.00*15	+0.25/−0.50*130	Ø	400	Detected at 22 years old, no treatment.
A14	23/F	Anis	0.30	0.00	+2.25	PL	Ø	N/A	Detected at 12 years old, no treatment.

a

b

FIGURE 1. **(a)** Dichoptic stimuli. Contrast sensitivity was measured under (i) T0NM viewing condition: the 0° Gabor target was presented in the tested eye, and a mean luminance background was presented in the untested eye; (ii) T90NM viewing condition: the 90° Gabor target was presented in the tested eye, and a mean luminance background was presented in the untested eye; (iii) T0M0 viewing condition: the 0° Gabor target was presented in the tested eye, and the 0° mask was presented in the untested eye; (iv) T0M90 viewing condition: the 0° Gabor target was presented in the tested eye, and the 90° mask was presented in the untested eye; (v) T90M90 viewing condition: the 90° Gabor target was presented in the tested eye and the 90° mask was presented in the untested eye; (vi) T90M0 viewing condition: the 90° Gabor target was presented in the tested eye, and the 0° mask was presented in the untested eye. **(b)** Time course of the experiment. Each trial began with an orange fixation point appearing for 200 ms. Then the first interval stimulus appeared for 117 ms without fixation point and signaled by a brief tone, followed by a 200 ms interstimulus interval with an orange fixation point, a 117 ms second stimulus interval signaled by a brief tone, and a green fixation point until response. Response correctness was then indicated by another tone.

0.25 c/d in experiment 1, 1.31 c/d in experiment 2, and 6.87 c/d in experiment 3. The contrast of the target was determined with a staircase procedure (see procedures). The contrast of the mask was kept constant at 0.8 through the experiment.

Design

We measured the monocular contrast sensitivity in two target orientation conditions: (i) the orientation of the target was 0° (T0NM, Fig. 1a), and (ii) the orientation of the target was 90° (T90NM). Then, the contrast sensitivity was measured under all possible combinations of the target and masks orientations: (iii) the orientation of the target was 0°, and the orientation of the mask was 0° (T0M0); (iv) the orientation of the target was 0°, and the orientation of the mask was 90° (T0M90); (v) the orientation of the target was 90°, and the orientation of the mask was 90° (T90M90); (vi) the orientation of the target was 90°, and the orientation of the mask was 0° (T90M0). The sensitivity was measured for each eye, thus leading to a total of 12 conditions for each subject in each experiment.

All subjects completed the three experiments in order, first experiment 1, then experiment 2, and last experiment 3. The three experiments were finished in two or three days. In each experiment, the 12 contrast sensitivities were measured in a randomized order. Participants were allowed to take a break after every contrast sensitivity measure and started the next one when they were ready to proceed. Each condition was measured in six to eight minutes; therefore each experiment could be run in one session of one to two hours, with breaks included.

Procedures

Before beginning each experiment, subjects were asked to complete an interocular alignment task to facilitate the fusional alignment between their two eyes. In this task, subjects were instructed to align a vertical red line presented in one eye with a vertical green line presented in the other eye in the middle of the screen. The position of the two lines were then used in the following contrast sensitivity measures.

Contrast thresholds were measured with a two-down one-up staircase procedure using a two-intervals forced

choice (2IFC) paradigm with contrast chosen on a log-scale between 0.001 and 1. The staircase ended after 20 reversals.

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 fixation point and signaled by a brief tone, followed by a 200 ms interstimulus interval with an orange fixation point, a 117 ms second interval signaled by a brief tone, and a green fixation point until response (see Fig. 1b). In the monocular conditions, the target was randomly presented in one of the two intervals, and the other interval was blank. In the masking conditions, the mask was presented in the two intervals, and the target was randomly presented in only one of the two intervals. The subjects were asked to indicate in which interval the target was shown (first or second interval) and press the corresponding key. There was a brief tone after each response to inform the subjects whether their answer was correct. The next trial started immediately after the response.

Data Analysis

The interocular suppression was defined as the dichoptic masking suppression induced by the mask. Interocular suppression was quantified as the threshold elevation between monocular and masked conditions. Threshold elevation was calculated as the contrast sensitivity difference in dB between one masking condition and the target-only condition at matching target orientation for the same test eye, using the following equation:

$$Threshold\ elevation = 20 \times log10 \left(\frac{Thresh_{TxMy}}{Thresh_{TxNM}} \right),$$

where *Thresh* refers to the measured contrast threshold in the viewing conditions indicated as subscripts such that x and y refer to the orientation of the target and mask (0 or 90), respectively. The threshold elevation under T0M0 suppression configuration is the contrast sensitivity of T0M0 viewing condition minus that of T0NM viewing condition; under T0M90 configuration is T0M90 minus T0NM; under T90M90 configuration is T90M90 minus T90NM; and under T90M0 configuration is T90M0 minus T90NM.

The threshold elevation was analyzed: (1) by using repeated-measures ANOVA, with within-subjects factors of suppression configuration (T0M0, T0M90, T90M90 and T90M0) and eye (from dominant eye (DE)/fellow eye (FE) to nondominant eye (NDE)/amblyopic eye (AE) and from NDE/AE to DE/FE), and paired *t*-test as the pairwise post-hoc comparison to examine whether threshold elevation was orientation-dependent and equal between eyes in each group; (2) by mixed repeated-measure ANOVA with a between-subjects factor of group (control and amblyopia) and within-subjects factors of suppression configuration (T0M0, T0M90, T90M90 and T90M0) and eye (from DE/FE to NDE/AE and from NDE/AE to DE/FE), and a mixed repeated-measure ANOVA with a between-subjects factor of group (control and amblyopia) and a within-subjects factor of suppression configuration (T0M0, T0M90, T90M90 and T90M0) as the pairwise post-hoc comparison to examine whether threshold elevation was similar between controls and amblyopes. The degrees of freedom of the F distribution were corrected by an index of deviation to sphericity.[47–49]

The average threshold elevation was calculated as the average under the four suppression configurations. The average threshold elevation was analyzed: (1) by using repeated-measures ANOVA with within-subjects factors of spatial frequency (0.25, 1.31 and 6.87 c/d) and eye (DE/FE and NDE/AE) to examine whether the average threshold elevation was different across the three spatial frequencies and equal between eyes in each group; (2) by mixed repeated-measure ANOVA with a between-subjects factor of group (control and amblyopia) and within-subjects factors of spatial frequency (0.25, 1.31 and 6.87 c/d) and eye (DE/FE and NDE/AE) to examine whether average threshold elevation was similar between controls and amblyopes.

A tuning index was defined as the threshold elevation difference between parallel and orthogonal suppression configurations. The tuning index was analyzed: (1) by using repeated-measures ANOVA with within-subjects factors of spatial frequency (0.25, 1.31 and 6.87 c/d) and eye (DE/FE and NDE/AE) to examine whether the tuning index was different across the three spatial frequency and equal between eyes in each group; (2) by mixed repeated-measure ANOVA with a between-subjects factor of group (control and amblyopia) and within-subjects factors of spatial frequency (0.25, 1.31, and 6.87 c/d) and eye (DE/FE and NDE/AE), to examine whether tuning index was similar between controls and amblyopes; (3) by using the one sample *t*-test to examine whether the tuning index was different from 0.

A two-tailed Pearson correlation analysis was performed between the tuning index, suppression, and the visual acuity, as well as between contrast sensitivity and suppression. Analyses were performed with SPSS Statistics Version 25 (IBM, Armonk, NY, USA), with $P < 0.05$ as the criterion for statistical significance.

RESULTS

Experiment 1 — The Orientation Selectivity at Low Spatial Frequency (0.25 c/d)

In experiment 1, we measured contrast sensitivity under six viewing conditions (see Fig. 1) for the two eyes in controls and amblyopes with a spatial frequency of 0.25 c/d. The threshold elevation between monocular and masking conditions (see Methods) for the four suppression configurations are plotted in Figure 2.

Figures 2a and 2b show the threshold elevation of each control adult and the average threshold elevation of controls, respectively. A repeated-measures ANOVA revealed that the effect of suppression configuration was significant ($F_{3,27} = 35.68$, $P < 0.001$), and that the effect of eye was not significant ($F_{1,9} = 0.22$, $P = 0.654$). The pairwise post-hoc comparison showed a significant difference between T0M0 and T0M90 ($P < 0.001$), as well as T90M90 and T90M0 ($P < 0.001$) suppression configurations. However, no significant difference was found between T0M0 and T90M90 ($P = 0.384$), or T0M90 and T90M0 ($P = 0.167$) suppression configurations. In general, threshold elevation of controls was similar in the two eyes and was smaller under orthogonal condition than parallel condition.

The threshold elevation of each amblyopic subject and the average threshold elevation of amblyopes are plotted on Figures 2c and 2d, respectively. When a repeated-measure ANOVA was performed, the effect of suppression configuration ($F_{1.6,21.4} = 19.00$, $P < 0.001$) and eye
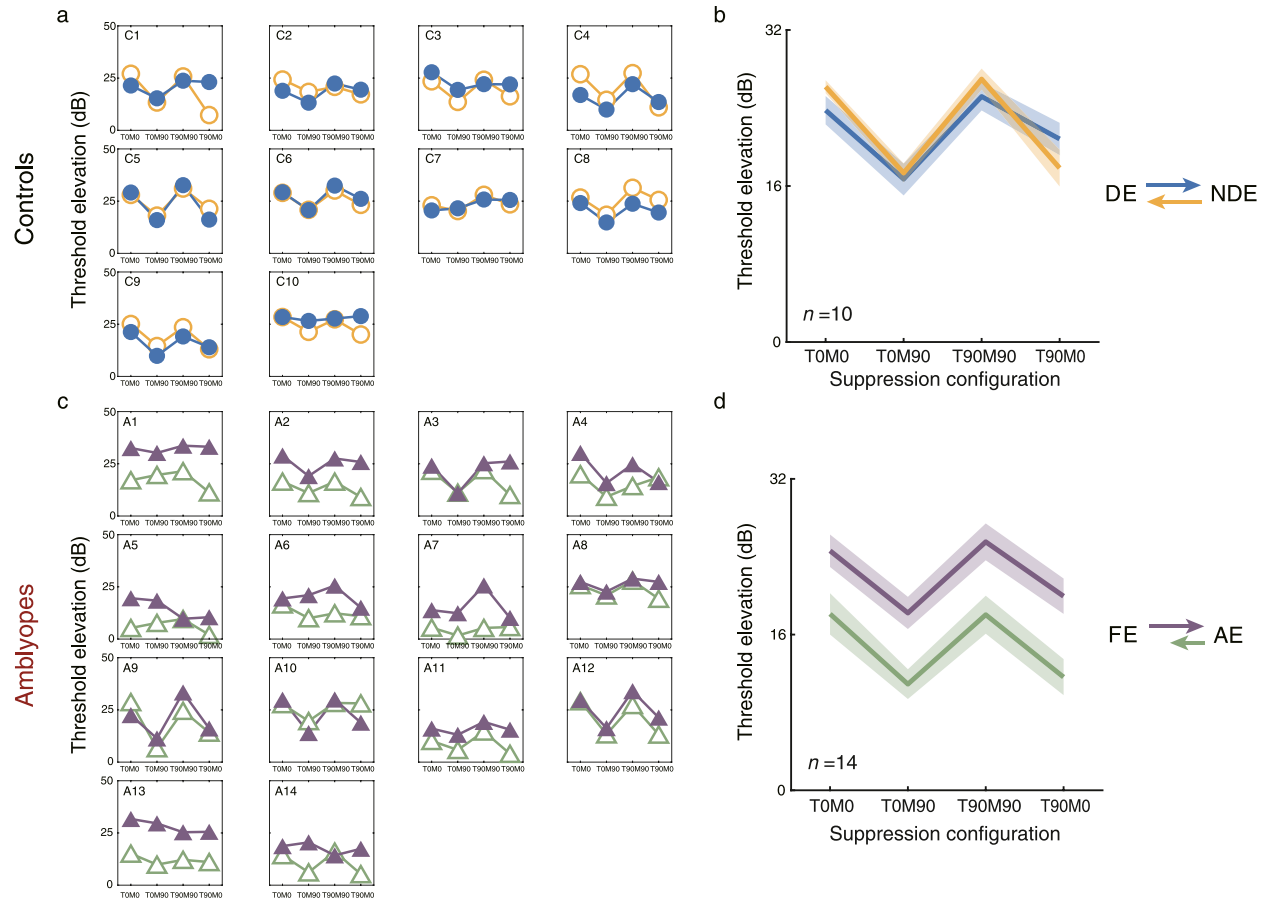
FIGURE 2. The threshold elevation of controls and amblyopes at 0.25 c/d. **(a)** The threshold elevation of each control adult under four suppression configurations (i.e., T0M0, T0M90, T90M90, and T90M0). The *solid blue circles* represent the threshold elevation from DE to NDE. The *hollow yellow circles* represent the threshold elevation from NDE to DE. **(b)** The average threshold elevation of controls (n = 10). The *blue line* and *yellow line* represent the threshold elevation from DE to NDE and from NDE to DE, respectively. The *shaded areas* show the range ± SEM. **(c)** The threshold elevation of each amblyopic subject. The *solid purple triangles* represent the threshold elevation from FE to AE. The *hollow green triangles* represent the threshold elevation from AE to FE. **(d)** The average threshold elevation of amblyopes (n = 14). The *purple line* and *green line* represent the threshold elevation from FE to AE and from AE to FE, respectively. The *shaded areas* show the range ± SEM.

($F_{1,13}$ = 30.23, P < 0.001) was significant. A pairwise post-hoc comparison showed a significant difference between T0M0 and T0M90 (from FE to AE, P = 0.002; from AE to FE, P = 0.001), as well as T90M90 and T90M0 (from FE to AE, P = 0.009; from AE to FE, P = 0.001) suppression configurations. However, no significant difference was found between T0M0 and T90M90 (from FE to AE, P = 0.592; from AE to FE, P = 0.925), or T0M90 and T90M0 (from FE to AE, P = 0.307; from AE to FE, P = 0.607) suppression configurations. In short, threshold elevation of amblyopes was different in the two eyes and was smaller under the orthogonal condition compared with the parallel condition.

To compare the threshold elevation between controls and amblyopes, we performed a mixed repeated-measure ANOVA and revealed that the effect of eye ($F_{1,22}$ = 14.81, P = 0.001), suppression configuration ($F_{1.9,41.9}$ = 46.24, P < 0.001), and that interaction between eye and group ($F_{1,22}$ = 18.98, P < 0.001) was significant. The effect of group was not significant ($F_{1,22}$ = 3.51, P = 0.074). The pairwise post-hoc comparison showed that the threshold elevation from FE to AE in amblyopes was similar to the threshold elevation from DE to NDE eye in controls (P = 0.820). However, the threshold elevation

from AE to FE in amblyopes was found significantly lower than the threshold elevation from NDE to DE in controls (P = 0.002).

Experiment 2 — The Orientation Selectivity at Mid Spatial Frequency (1.31 c/d)

In experiment 2, we measured the contrast sensitivity under six viewing conditions for the two eyes in controls and amblyopes when spatial frequency was 1.31 c/d. The threshold elevation for the four suppression configurations is plotted in Figure 3.

Figures 3a and 3b show the threshold elevation of each control subject and the average threshold elevation of controls, respectively. A repeated-measure ANOVA revealed that the effect of suppression configuration was significant ($F_{2.0,17.9}$ = 36.35, P < 0.001), and that the effect of eye was not significant ($F_{1,9}$ = 0.29, P = 0.602). A pairwise post-hoc comparison showed a significant difference between T0M0 and T0M90 (P < 0.001), as well as T90M90 and T90M0 (P < 0.001) suppression configurations. However, no significance difference was found between T0M0 and T90M90
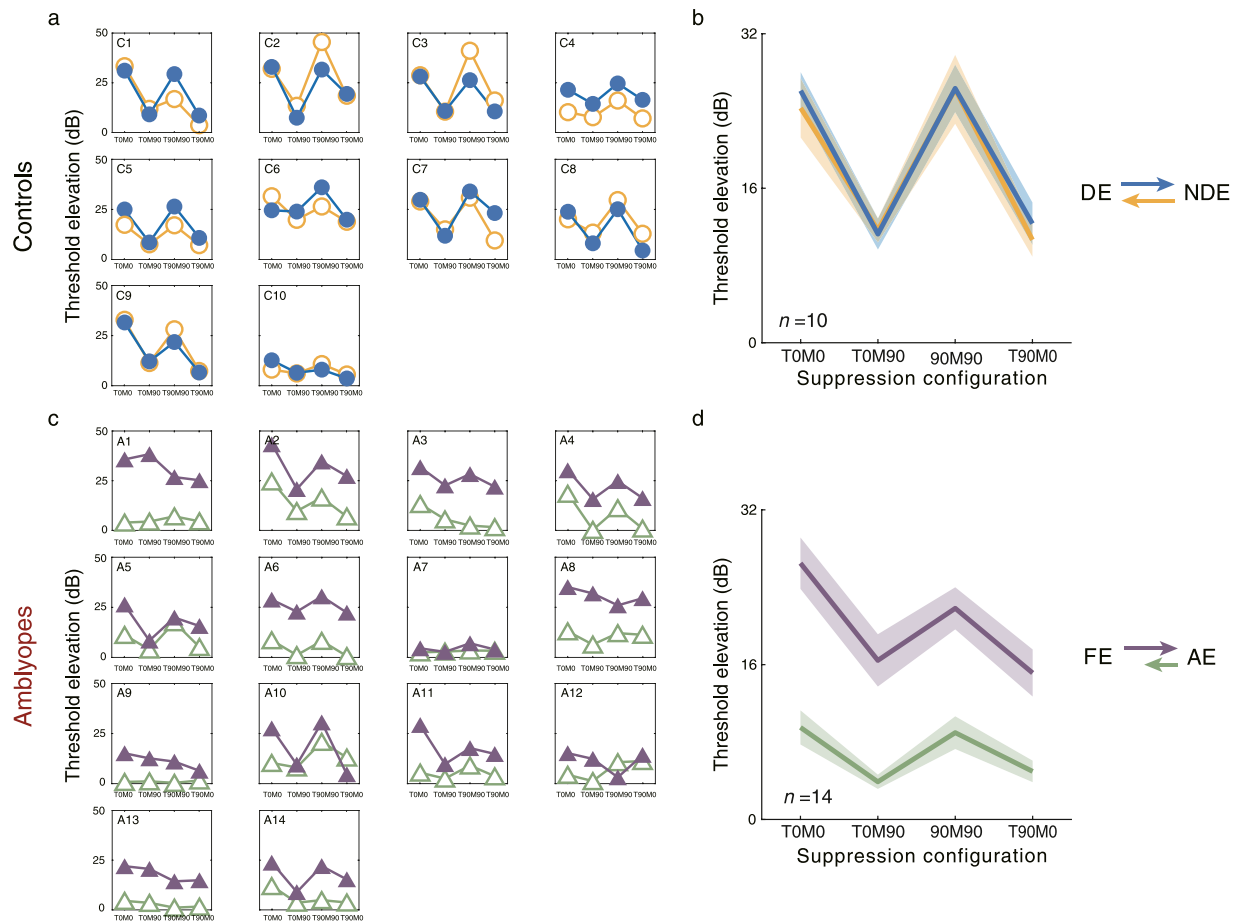
FIGURE 3. The threshold elevation of controls and amblyopes at 1.31 c/d. **(a)** Threshold elevation of each control adult under four viewing condition (i.e., T0M0, T0M90, T90M90 and T90M0). The *solid blue circles* represent the threshold elevation from DE to NDE. The *hollow yellow circles* represent the threshold elevation from NDE to DE. **(b)** Average threshold elevation of control adults (n = 10). The *blue line* and *yellow line* represent the threshold elevation from DE to NDE and from NDE to DE, respectively. The *shaded areas* show the range ± SEM. **(c)** Threshold elevation of each amblyopic subject. The *solid purple triangles* represent the threshold elevation from FE to AE. The *hollow green triangles* represent the threshold elevation from AE to FE. **(d)** Average threshold elevation of amblyopic subjects (n = 14). The *purple line* and *green line* represent the threshold elevation from FE to AE and from AE to FE, respectively. The *shaded areas* show the range ± SEM.

($P = 0.539$), or T0M90 and T90M0 ($P = 0.980$) suppression configurations. In general, threshold elevation of controls was similar in the two eyes and was smaller under orthogonal condition than parallel condition.
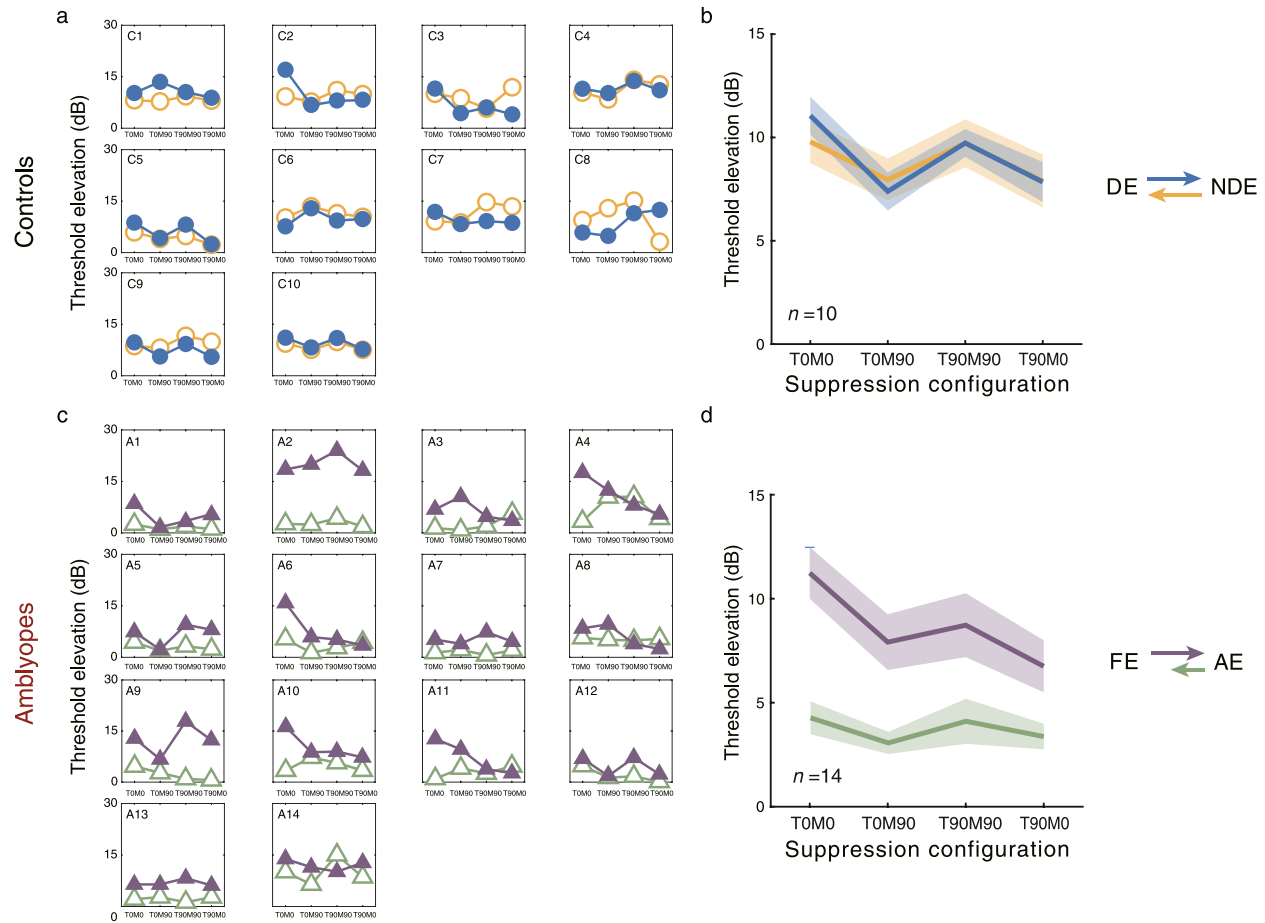
The threshold elevation of each amblyopic subject and the average threshold elevation of amblyopes are plotted in Figures 3c and 3d, respectively. When a repeated-measure ANOVA was performed, the effect of suppression configuration ($F_{1.9,24.7} = 13.62$, $P < 0.001$) and eye ($F_{1,13} = 47.47$, $P < 0.001$) were significant. The interaction between suppression configuration and eye was also significant ($F_{3,39} = 4.38$, $P = 0.009$). The pairwise post-hoc comparison showed a significant difference between T0M0 and T0M90 (from FE to AE, $P = 0.001$; from AE to FE, $P = 0.003$), as well as T90M90 and T90M0 (from FE to AE, $P = 0.006$; from AE to FE, $P = 0.007$) suppression configurations. Also, a significant difference was found between T0M0 and T90M90 in the fellow eye ($P = 0.004$), but not in the amblyopic eye ($P = 0.750$). And no significant difference was found between T0M90 and T90M0 (from FE to AE, $P = 0.414$; from AE to FE, $P = 0.277$) suppression configurations. In short, threshold elevation of amblyopes was different in the two eyes, and was

smaller under orthogonal condition than parallel condition.

To compare the threshold elevation between controls and amblyopes, we performed a mixed repeated-measure ANOVA and revealed that the effect of eye ($F_{1,22} = 29.08$, $P < 0.001$), suppression configuration ($F_{2.0,43.1} = 49.48$, $P < 0.001$), group ($F_{1,22} = 5.61$, $P = 0.027$), and that interaction between eye and group ($F_{1,22} = 22.85$, $P < 0.001$), between suppression configuration and group ($F_{3,66} = 7.46$, $P < 0.001$) was significant. The pairwise post-hoc comparison showed that the threshold elevation from FE to AE in amblyopes was similar to the threshold elevation from DE to NDE eye in controls ($P = 0.745$). However, the threshold elevation from AE to FE in amblyopes was found significantly lower than the threshold elevation from NDE to DE in controls ($P < 0.001$).

Experiment 3 — The Orientation Selectivity at High Spatial Frequency (6.87 c/d)

In experiment 3, we measured the contrast sensitivity under six viewing conditions for the two eyes in controls and

FIGURE 4. The threshold elevation of controls and amblyopes at 6.87 c/d. **(a)** The threshold elevation of each control adult under four suppression configurations (i.e. T0M0, T0M90, T90M90 and T90M0). The *solid blue circles* represent the threshold elevation from DE to NDE. The *hollow yellow circles* represent the threshold elevation from NDE to DE. **(b)** The average threshold elevation of controls (n = 10). The *blue line* and *yellow line* represent the threshold elevation from DE to NDE and from NDE to DE, respectively. The *shaded areas* show the range ± SEM. **(c)** The threshold elevation of each amblyopic subject. The *solid purple triangles* represent the threshold elevation from FE to AE. The *hollow green triangles* represent the threshold elevation from AE to FE. **(d)** The average threshold elevation of amblyopes (n = 14). The *purple line* and *green line* represent the threshold elevation from FE to AE and from AE to FE, respectively. The *shaded areas* show the range ± SEM. Note the different scale compared to Figures 2 and 3.

amblyopes when spatial frequency was 6.87 c/d. The threshold elevation for the four suppression configurations is plotted in Figure 4.

Figures 4a and 4b show the threshold elevation of each control subject and their average, respectively. A repeated-measure ANOVA revealed that the effect of suppression configuration was significant ($F_{3,27} = 7.36$, $P = 0.001$), and that the effect of eye was not significant ($F_{1,9} = 0.04$, $P = 0.854$). A pairwise post-hoc comparison showed a significant difference between T0M0 and T0M90 ($P < 0.001$), as well as T90M90 and T90M0 ($P = 0.022$) suppression configurations. However, no significant difference was found between T0M0 and T90M90 ($P = 0.394$), or T0M90 and T90M0 ($P = 0.787$) suppression configurations. In general, threshold elevation of control adults was similar in the two eyes and was smaller under orthogonal configuration than parallel configuration.

The threshold elevation of each amblyopic subject and their average are plotted in Figures 4c and 4d, respectively. When a repeated-measure ANOVA was performed, the effect of suppression configuration ($F_{3,39} = 6.41$, $P = 0.001$)

and eye ($F_{1,13} = 20.03$, $P < 0.001$) was significant. A pairwise post-hoc comparison showed a significant difference between T0M0 and T0M90 ($P = 0.008$), as well as between T90M90 and T90M0 ($P = 0.009$) suppression configurations in the fellow eye. However, the difference between T0M0 and T0M90 ($P = 0.140$), or between T90M90 and T90M0 ($P = 0.372$) suppression configurations was not significant in the amblyopic eye. And no significant difference was found between T0M0 and T90M90 (from FE to AE, $P = 0.107$; from AE to FE, $P = 0.359$), or T0M90 and T90M0 (from FE to AE, $P = 0.786$; from AE to FE, $P = 0.595$) suppression configurations in either of the eyes. In short, threshold elevation of amblyopic patients was different in the two eyes. It was smaller under the orthogonal configuration compared with the parallel configuration only for the fellow eye, but not for the amblyopic eye.

To compare the threshold elevation between controls and amblyopes, we performed a mixed repeated-measure ANOVA with suppression configuration and revealed that the effect of eye ($F_{1,22} = 11.51$, $P = 0.003$), suppression configuration ($F_{3,66} = 12.91$, $P < 0.001$), group ($F_{1,22} = 7.21$,
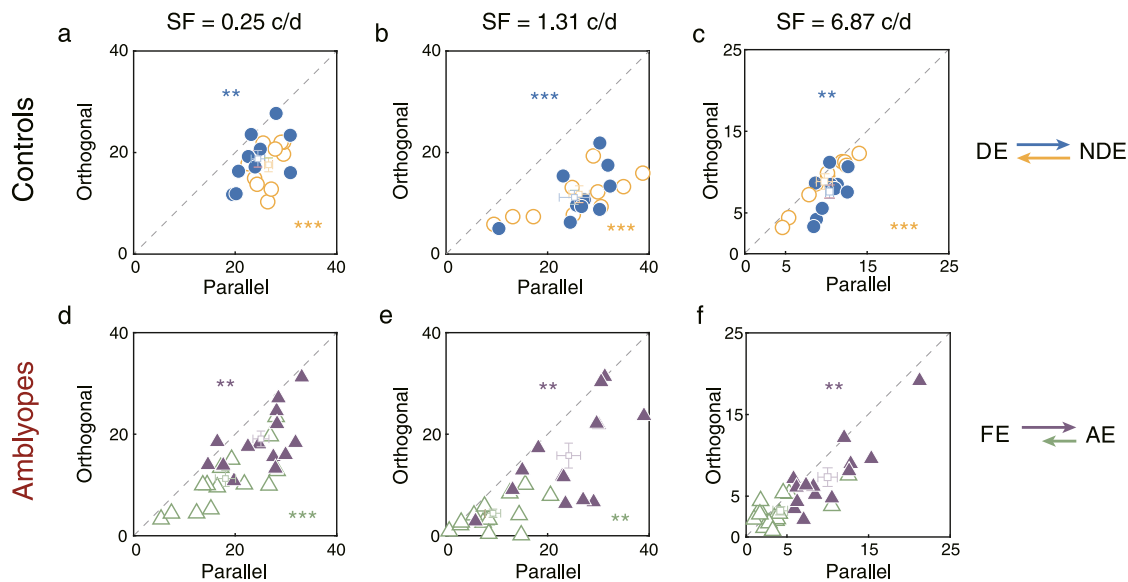
FIGURE 5. Threshold elevation under parallel and orthogonal suppression configurations. The average threshold elevation under two parallel configurations (i.e., T0M0 and T90M90 suppression configurations, x-axis) is plotted against the average threshold elevation under two orthogonal configurations (i.e., T0M90 and T90M0 suppression configurations, y-axis). **(a)** The results of controls at 0.25 c/d. **(b)** The results of control adults at 1.31 c/d. **(c)** The results of control adults at 6.87 c/d. Each *solid blue dot* represents the threshold elevation from DE to NDE of one control adult. Each *hollow yellow dot* represents the threshold elevation from NDE to DE of one control adult. **(d)** The results of amblyopes at 0.25 c/d. **(e)** The results of amblyopes at 1.31 c/d. **(f)** The results of amblyopes at 6.87 c/d. Each *solid purple triangle* represents the threshold elevation from FE to AE of one amblyopic patient. Each *hollow green triangle* represents the threshold elevation from AE to FE of one amblyopic patient. The average results were plotted with the *solid square symbol*. *Error bars* represent standard errors. Results of two-tailed paired-samples *t*-test are presented in each panel to show the difference of threshold elevation between parallel and orthogonal suppression configurations: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

$P = 0.014$), and interaction between eye and group ($F_{1,22} = 10.07$, $P = 0.004$) were significant. The pairwise post-hoc comparison showed that the threshold elevation from FE to AE in amblyopic patients was similar to the threshold elevation from DE to NDE eye in controls ($P = 0.810$). However, the threshold elevation from AE to FE in amblyopes was found to be significantly lower than the threshold elevation from NDE to DE in controls ($P < 0.001$).

The Orientation Selectivity at 3 Spatial Frequencies

As described above, an orientation-dependent interocular suppression had been observed both in controls and amblyopes. To better present the orientation selectivity, Figure 5 shows the threshold elevation of controls and amblyopes at 0.25, 1.31, and 6.87 c/d, where the abscissa represents the average threshold elevation under the two parallel suppression configurations (T0M0 and T90M90), and the ordinate represents the average threshold elevation under the two orthogonal suppression configurations (T0M90 and T90M0). The symbols represent the threshold elevation from DE to NDE (solid blue circle), from NDE to DE (hollow yellow circle), from FE to AE (solid purple triangle) and from AE to FE (hollow green triangle). Confirming previous observations, the threshold elevation under orthogonal configuration was less than that under parallel configuration (the symbols fall below or near the unity line) both in control adults and amblyopic subjects, except for the suppression from the amblyopic eye at 6.87 c/d. These observations are confirmed by statistical analysis (paired *t*-test). In controls, the threshold elevation under orthogonal suppres-

sion configuration was significantly less than that under parallel suppression configuration at 0.25 (DE, $t_9 = 4.10$, $P = 0.003$; NDE, $t_9 = 7.25$, $P < 0.001$), 1.31 (DE, $t_9 = 8.44$, $P < 0.001$; NDE, $t_9 = 6.46$, $P < 0.001$), and 6.87 (DE, $t_9 = 4.34$, $P = 0.002$; NDE, $t_9 = 5.41$, $P < 0.001$) c/d. In amblyopes, the threshold elevation under orthogonal suppression configuration was significantly less than that under parallel suppression configuration at 0.25 (FE, $t_{13} = 4.14$, $P = 0.001$; AE, $t_{13} = 5.52$, $p < 0.001$), 1.31 (FE, $t_{13} = 4.11$, $P = 0.001$; AE, $t_{13} = 3.89$, $P = 0.002$). And at 6.87 c/d, the significant difference was found only in FE ($t_{13} = 4.48$, $P = 0.001$), but not in AE ($t_{13} = 1.43$, $P = 0.177$).

Our findings demonstrate that the reduced suppression from AE to FE in amblyopes is orientationally-dependent at low (0.25 c/d) and mid (1.31 c/d) spatial frequencies. At high spatial frequency (6.87 c/d), amblyopes show orientation-dependent suppression by the fellow eye, but orientation-independent suppression by the amblyopic eye. To further investigate the orientation tuning of interocular suppression, the tuning indexes of controls and amblyopes at 0.25, 1.31, and 6.87 c/d are shown in Figure 6. The tuning index was defined as the threshold elevation difference between parallel and orthogonal suppression configurations. Blue and yellow boxes illustrate the tuning indexes of controls (blue: DE; yellow: NDE). Purple and green boxes illustrate tuning indexes of amblyopes (purple: FE; green: AE).

In controls, the effect of spatial frequency was significant ($F_{2,18} = 21.76$, $P < 0.001$), but the effect of the eye was not significant ($F_{1,9} = 1.01$, $P = 0.342$), when a repeated-measure ANOVA was performed. In amblyopes, the effect of spatial frequency ($F_{1.4,18.0} = 6.24$, $P = 0.015$) was significant, and the interaction between spatial frequency and eye was also significant ($F_{2,26} = 3.94$, $P = 0.032$), when a repeated-
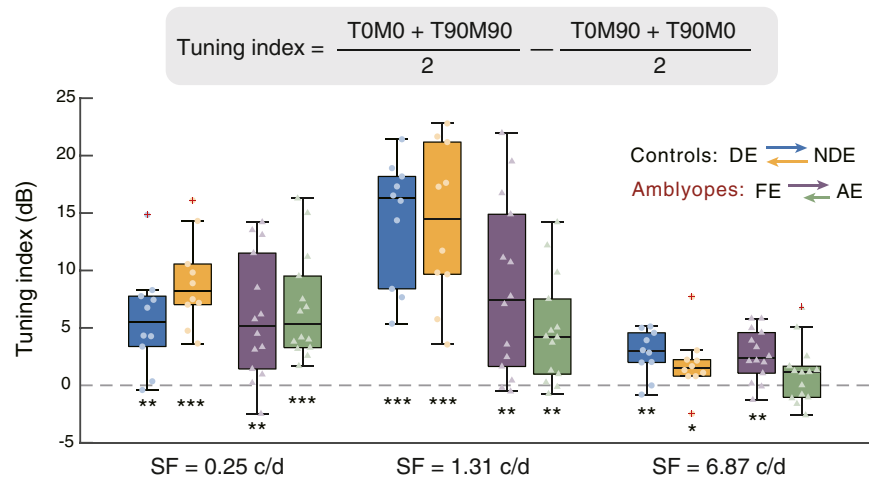
FIGURE 6. Boxplots of tuning index in controls and amblyopes. The tuning indexes at 0.25, 1.31, and 6.87 c/d are illustrated. *Blue* and *yellow boxes* represent the tuning indexes of DE and NDE in controls, respectively. *Purple* and *green boxes* represent the tuning indexes of FE and AE in amblyopes, respectively. Individual data points are represented by a *circle* (controls) or a *triangle* (amblyopes). The *black solid line* within each box represents the median. The box represents the interquartile range (IQR) of the data (25th to the 75th percentile). The *whiskers* represent 1.5 × IQR either above the third quartile or below the first quartile. The data points with *red crosses* represent outliers. The *gray dashed line* indicates 0 dB tuning index level. *Asterisks* indicate significant differences from 0. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

measure ANOVA was performed. To compare the tuning indexes between controls and amblyopes, we performed a mixed repeated-measure ANOVA and revealed that the effect of spatial frequency ($F_{1.4,31.4} = 24.99$, $P < 0.001$) and group ($F_{1,22} = 9.24$, $P = 0.006$), and that interaction between spatial frequency and group ($F_{1.4,31.4} = 5.74$, $P = 0.014$), between spatial frequency and eye ($F_{2,44} = 5.59$, $P = 0.007$) was significant. A pairwise post-hoc comparison showed that the tuning index of amblyopes was significantly different from that of controls at 1.31 c/d ($P = 0.004$), but not at 0.25 ($P = 0.562$) or 6.87 c/d ($P = 0.475$).

The tuning index of controls was determined to be significantly different from 0 by a one sample *t*-test (0.25 c/d: DE, $t_9 = 4.10$, $P = 0.003$; NDE, $t_9 = 7.25$, $P < 0.001$; 1.31 c/d: DE, $t_9 = 8.44$, $P < 0.001$; NDE, $t_9 = 6.46$, $P < 0.001$; 6.87 c/d: DE, $t_9 = 4.34$, $P = 0.002$; NDE, $t_9 = 2.29$, $P = 0.048$). Tuning index of amblyopes was significantly different from 0 at 0.25 c/d (FE, $t_{13} = 4.14$, $P = 0.001$; AE, $t_{13} = 5.52$, $P < 0.001$), 1.31 c/d (FE, $t_{13} = 4.11$, $P = 0.001$; AE, $t_{13} = 3.88$, $P = 0.002$). However, the tuning index of the fellow eye was significantly different from 0 ($t_{13} = 4.78$, $P = 0.001$), but that of the amblyopic eye was not ($t_{13} = 1.43$, $P = 0.177$) at 6.87 c/d.

In short, amblyopes and controls showed positive tuning index (i.e., larger suppression under parallel than orthogonal configurations) at 0.25 and 1.31 c/d. At 6.87 c/d, the tuning index of controls and amblyopes was greatly reduced. It was still positive for the two eyes of controls. However, for amblyopes, it remained significantly positive only for the fellow eye, not for the amblyopic eye.
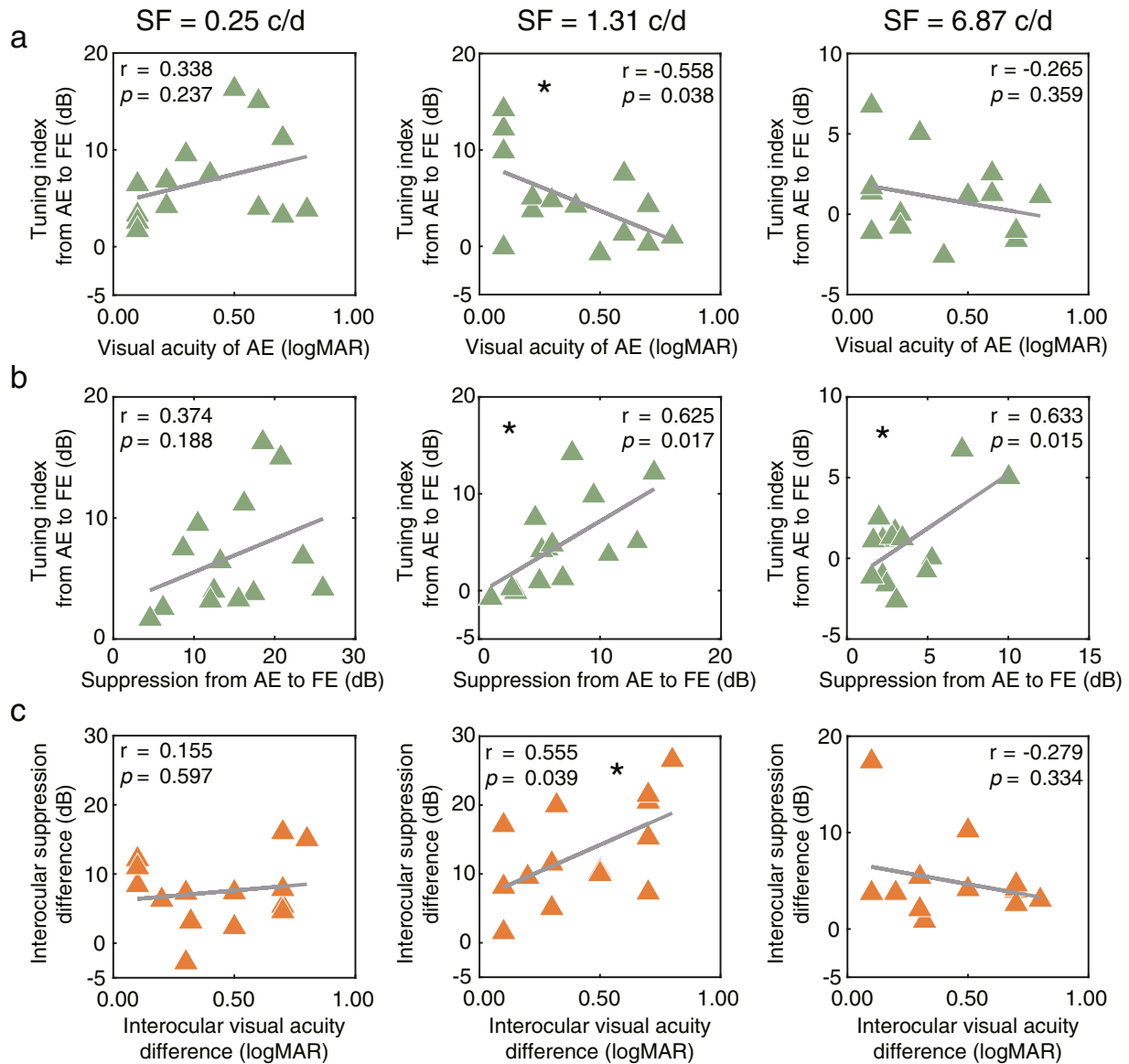
The Correlation Between Tuning Index, Visual Acuity and Suppression

To examine the relationship between tuning index, visual acuity, and suppression, some correlations are plotted in Figure 7. The tuning index from AE to FE is plotted against the visual acuity of AE in Figure 7a. A two-tailed

Pearson correlation analysis found that correlation between tuning index and visual acuity was significant at 1.31 c/d ($r = -0.558$, $P = 0.038$), but not at 0.25 c/d ($r = 0.338$, $P = 0.237$) or 6.87 c/d ($r = -0.265$, $P = 0.359$). The tuning index from AE to FE is plotted against the suppression from AE to FE in Figure 7b. A two-tailed Pearson correlation analysis found that correlation between tuning index and suppression was significant at 1.31 c/d ($r = 0.625$, $P = 0.017$) and 6.87 c/d ($r = 0.633$, $P = 0.015$), but not at 0.25 ($r = 0.374$, $P = 0.188$). The interocular suppression difference is plotted against the interocular visual acuity difference in Figure 7c. The interocular suppression difference was calculated as the suppression from FE to AE minus the suppression from AE to FE (i.e., (FE→AE) – (AE→FE)). A two-tailed Pearson correlation analysis found that the correlation between interocular suppression and interocular visual acuity was significant at 1.31 c/d ($r = 0.555$, $P = 0.039$), but not at 0.25 c/d ($r = 0.155$, $P = 0.597$) or 6.87 c/d ($r = -0.279$, $P = 0.334$).

DISCUSSION

In this study, as a means of better understanding suppression in amblyopia, we assess the relative strengths of interocular masking between controls and amblyopes and between the fellow and amblyopic eyes of amblyopes. We assume, as others have,[20–23] that the reciprocal interocular inhibitory networks that modulate the combination of information between the eyes[50,51] underlies suppression in amblyopia. We investigated the orientation tuning of interocular masking in controls and amblyopes. We measured interocular suppression at low (0.25 c/d, experiment 1), mid (1.31 c/d, experiment 2), and high (6.87 c/d, experiment 3) spatial frequencies. We have two interesting findings that could potentially influence the way in which we think about suppression in amblyopia; first, the interocular masking by the fellow eyes of amblyopes is comparable to that of controls for all spatial frequencies, while that of the amblyopic eye is weaker at all spatial frequencies. The net imbalance in dichoptic masking between the eyes that results from

Figure 7. Relationship between tuning index, visual acuity, and suppression. **(a)** Correlation between tuning index and visual acuity. The abscissa represents the visual acuity of AE, and the ordinate represents the tuning index from AE to FE. **(b)** Correlation between tuning index and suppression. The abscissa represents the suppression (i.e., average suppression under four suppression configurations) from AE to FE, and the ordinate represents the tuning index from AE to FE. **(c)** Correlation between interocular suppression and interocular visual acuity difference. The abscissa represents the interocular visual acuity difference (i.e., visual acuity difference between two eyes), and the ordinate represents the interocular suppression difference (i.e., suppression difference between the two eyes). Each *triangle* represents one amblyopic subject's data. *Asterisks* indicate significant correlations. * *P* < 0.05.

this, which supports its potential basis in amblyopic suppression,[21–23] is reduced at high spatial frequencies. Second the interocular masking between the eyes of amblyopes is orientationally tuned at low-mid spatial frequencies but not at high spatial frequencies for the amblyopic eye (i.e., when information in the amblyopic eye is suppressing information in the fellow eye).

The Orientational Tuning of Dichoptic Masking in Amblyopia

In all three experiments, similar masking suppression strength was found in the two eyes of controls. These results

agree with previous studies.[17,23,30] However, unequal interocular masking was observed in amblyopes: suppression strength from the amblyopic eye to the fellow eye was much weaker than that from the fellow eye to the amblyopic eye. This is consistent with previous findings in animal neurophysiological[24,52] and human psychophysical[21,23] studies. In experiment 1 and experiment 2, we showed that orthogonal masking has less effect than parallel masking in both amblyopic and control groups. This reveals that interocular masking suppression exhibits orientation tuning in both eyes of amblyopes at low and mid spatial frequency. In experiment 3, the same results as that found in experiments 1 and 2 were found for the fellow eye, however, the inhibitory influence that the amblyopic eye exerted on the fellow eye was

similar under parallel and orthogonal configurations. Thus amblyopes exhibit orientationally dependent interocular inhibition, except at a high spatial frequency for the amblyopic eye.

Our results are different from the findings of Gao et al.[39] This difference could not be caused by the different spatial frequencies used,[41,42] because Gao et al.[39] and the present study both measured interocular suppression at a mid-spatial frequency (Gao et al.'s study with 1.6 c/d and the present study with 1.31 c/d in experiment 2). It might be because of the different paradigms used: dichoptic masking paradigm versus continuous flash suppression paradigm. The mask used in the continuous flash suppression paradigm is a spatially broadband noise refreshing at 10 Hz, while we used a static bandpass noise with a peak spatial frequency matched to that of the target. The different spatiotemporal composition of the masks might result in a difference in the measured suppression. Thus the orientation selectivity of interocular suppression might not be general for very different measurements. Another possible explanation could be that different categories of amblyopic subjects were recruited in these two studies. Most subjects (13 of 14) are anisometropic amblyopes in our study, and all amblyopes had only minimal (or none) misalignment. However, Gao et al.[39] measured mostly strabismic and mixed amblyopes. Although they did not find any relationship between strabismus and orientation tuning of interocular suppression, the orientation selectivity might still be affected to some extent by amblyopia type. Indeed, it has been reported that anisometropic amblyopia shows orientation-dependent interocular suppression,[38,40] whereas unilateral strabismus (associated with amblyopia) shows less orientation tuning.[38,53]

Levi et al.[54] found an orientation tuning function for Vernier acuity and line detection in amblyopia by using a masking paradigm and suggested that the organization of the underlying mechanisms is normal in the amblyopic visual system (both in fellow eye and amblyopic eye). However, a broader orientation tuning width in amblyopic eyes has been reported by some studies. For example, Faulkner et al.[55] used optical imaging of intrinsic signals and single-cell recording in anesthetized cats and found that, compared with the deprived eye (i.e., amblyopic eye), the orientation tuning of neurons dominated by the nondeprived eye (i.e., fellow eye) is narrower. Huang et al.[56] also came to a similar conclusion through psychophysical measures and computational modeling in adult amblyopia. The present results relate to the tuning of the inhibitory interocular influences and may not necessarily correspond to the orientational tuning of purely monocular processes described above. Interestingly, we do show a correlation between the lack of orientation tuning and the strength of the interocular inhibition emanating from the amblyopic eye (Fig. 7b).

The Dichoptic Masking Imbalance in Amblyopia at Higher Spatial Frequencies

The degree of suppression strength in amblyopes found in this masking study at high spatial frequencies (Supplementary Figure S3) is at odds with a number of previous reports. A reduced masking imbalance between the fellow eye and amblyopic eyes was previously shown at high spatial frequencies in the masking study of Zhou et al.[23] However, using a different approach, one involving suprathreshold stimuli, Kwon et al.,[57] Reynaud and Hess,[58] and Mao et al.[59] found an increased binocular imbalance at high spatial frequency. They measured balance points using fusion/matching tasks under suprathreshold conditions (i.e., the contrasts in both eyes were well above the detection thresholds), whereas Zhou et al.[23] and the present study measured suppression at detection threshold (i.e., target in tested eye was at threshold, and mask in untested eye was suprathreshold). It is known that amblyopes have monocular deficits in contrast sensitivity at high frequency[60,61] but normal suprathreshold contrast perception from suprathreshold contrast matching studies.[6,62–64] Hence, this disagreement about whether the degree of suppression increases with spatial frequency at higher spatial frequencies is likely to be different for threshold and suprathreshold processing. The fact that amblyopes have raised thresholds inevitably means that using a threshold-based approach will introduce floor effects that will act to reduce the degree of suppression measured. Or to put this another way, the degree of suppressive imbalance observed could just be a consequence of the raised thresholds of the amblyopic eye. However, we did not observe any correlation between the amblyopic eye contrast sensitivity and the induced suppression (Supplementary Figure S2).

At high spatial frequency, the suppression measurement might be affected when the contrast threshold of AE became close to the contrast of the mask. Whereas the masking effect is still credible because the contrast threshold under target orientation conditions was still lower than 0.8 for all participants (i.e., the contrast sensitivity was larger than 1.94 dB, see Supplementary Figure S1). For some amblyopic subjects, the suppression measurement might have been reduced in magnitude by the reduced suprathreshold contrast of the mask. This could have possibly, because of a floor effect, resulted in less-clear orientational tuning. Thus the lack of orientation selectivity for masking observed at high spatial frequency could potentially be the consequence of a reduced masking effect. This would be supported by the fact that some amblyopic subjects like A14 show strong suppression and orientation tuning and by the correlations reported between tuning index and suppression in Figure 7.

In summary, by using a dichoptic masking paradigm as a model for amblyopic suppression, we observed that masking strength by amblyopic eye is smaller than that by fellow eye, resulting in imbalanced interocular masking and a net suppression of information in the amblyopic eye across all spatial frequencies. This particular imbalance is greatest at low-mid spatial frequencies. Furthermore, the interocular masking emanating from the amblyopic eye was found to be orientation-tuned at low and mid spatial frequencies, but untuned at higher spatial frequencies.

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