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. Recently, we reported that dichoptic de-masking training can further boost stereoacuity, but not visual acuity, in adults with amblyopia after extensive monocular perceptual training. Here, we investigated whether this dichoptic training targets on interocular suppression directly, or improves vision through high-level brain mechanisms.

. Eleven adults with amblyopia first used amblyopic eyes (AEs) to perform contrast ($n = 6$) or orientation ($n = 5$) discrimination training, while resisting dichoptic noise masking from fellow eyes (FEs). Learning was indicated by increased maximal tolerable noise contrast (TNC) for AE contrast/orientation discrimination. After dichoptic training, six observers continued to use AEs to perform monocular training for nine sessions.

. (1) Training of dichoptic de-masking doubled maximal TNC, but learning did not transfer much to the same task at an orthogonal orientation or a different task, showing orientation/task specificities. (2) Following a training-plus-exposure (TPE) protocol, AEs then received exposure of the orthogonal orientation by performing the other orientation/contrast discrimination task at the orthogonal orientation. After this TPE training, dichoptic learning with the original discrimination task transferred to the orthogonal orientation. (3) Dichoptic training improved AE's acuity (1.2 lines), stereoacuity (60.2%), and contrast sensitivity (mainly at higher spatial frequencies). (4) Additional monocular training did not produce further acuity and stereoacuity gains.

. The initial orientation/task specificities exclude the possibility that dichoptic training reduces physiological interocular suppression. The later transfer of learning to an orthogonal orientation with TPE training suggests improvement in high-level brain processing. Dichoptic training may strengthen top-down attention to AEs to counter the impacts of attentional bias to FEs and/or physiological interocular suppression and improve stereoacuity.

Keywords: amblyopia, dichoptic training, perceptual learning, orientation specificity, task specificity

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Amblyopia is a developmental visual disorder due to abnormal binocular visual experience (e.g., strabismus and anisometropia) in early childhood that disrupts the development of the visual cortex.[1,2] Imbalanced visual inputs from two eyes may lead to interocular suppression or inhibition of the amblyopic eye (AE) by the strong fellow eye (FE).[3] As a consequence, visual acuity, stereoacuity, as well as many other visual functions, are compromised.[4,5]

Many studies have demonstrated that perceptual learning improves vision in adults with amblyopia.[6,7] Although amblyopia affects both binocular and monocular visual functions, earlier perceptual learning studies mostly perform monocular training in the AE with the FE patched. More recent studies employ dichoptic training, targeting abnormal binocular functions directly via reducing interocular suppression, strengthening binocular fusion, and promoting binocular vision. Many dichoptic training studies use signal integration training paradigms, in which the task elements are separated between the two eyes and must be integrated for successful task completion.[8–15] Dichoptic training may assist information integration from the two eyes to help recover stereovision in amblyopic patients.[6]

In a previous study, we adopted a different dichoptic de-masking training paradigm (details provided in Methods and Results sections), in which the observers were trained to discriminate the contrast or orientation of a Gabor stimulus presented to the AE while discounting the masking effect from a noise masker presented to the FE.[16] Dichoptic de-masking training was performed by a group of monocularly well-trained adult amblyopic observers to isolate the effects of dichoptic training. The observers were significantly more capable of discounting dichoptic noise masking after training. Moreover, dichoptic training produced extra gains of stereoacuity, but not visual acuity, in these monocularly well-trained amblyopic observers, supporting Levi et al.[6] on the potential advantages of dichoptic training.

Like in adults with normal vision, monocular perceptual learning in those with amblyopia is often specific to the trained orientation. The orientation specificity has been attributed to training induced neural plasticity in the amblyopic early visual

. The Characteristics of the Amblyopic and Fellow Eyes

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S1	24	F	A	None	AE (L)	Plano	0.602	0.523	200	70
					FE (R)	−2.25	0.000	0.000		
S2	24	M	A	None	AE (L)	+3.75	0.398	0.398	F	30
					FE (R)	−3.25	−0.079	−0.079		
S3	19	F	A & S	R 2$^{\Delta}$ EsoT	AE (R)	Plano	0.398	0.301	200	70
					FE (L)	−2.75	0.000	0.000		
S4	26	F	A	None	AE (L)	+1.75/−0.50×75	0.602	0.398	400	140
					FE (R)	−2.25/−0.50×85	0.000	0.000		
S5	22	F	A & S	Alter EsoT	AE (L)	+1.00/+1.50×100	0.824	0.699	F	200
					FE (R)	−2.75	0.000	0.000		
S6	25	M	A	None	AE (L)	+2.50/−2.50×160	0.921	0.699	F	250
					FE (R)	−3.50	0.000	−0.079		
S7	28	M	A	None	AE (L)	Plano	0.699	0.523	F	250
					FE (R)	−1.75/−0.50×85	−0.176	−0.176		
S8	20	F	A	None	A[illegible] (L)	+4.00/−1.50×180	0.301	0.301	50	20
					[illegible]E (R)	+3.00/−2.50×85	−0.176	−0.176		
S9	23	M	A	None	AE (L)	+2.75/−1.00×75	0.097	0.000	70	50
					FE (R)	−0.25/−0.50×90	−0.079	−0.079		
S10	19	F	A	None	AE (L)	+2.25	0.824	0.602	F	200
					FE (R)	−1.75	0.000	−0.176		
S11	24	M	A & S	R 7$^{\Delta}$ E[illegible]	AE (L)	+5.00/−2.00×55	1.301	1.222	F	400
					FE (R)	−1.25/−0.50×85	0.000	0.000		

Strabismus was diagnosed by the cover test a[illegible] distance of 33 cm. The visual acuity was measured by a clinical E-chart. The stereoacuity w[illegible] evaluated with the Randot Stereo Test. ExoT, ex[illegible]pia; EsoT, esotropia; Δ, prism diopters; A, anisometropic; S, strabismic; R, right; L, left; F, fa[illegible] (>500).

areas that are most orientation s[illegible]tive.[17,18] However, orientation specificity in AE mo[illegible]ar learning can be abolished with a training-plus-ex[illegible]re (TPE) protocol,[19] consistent with findings in nor[illegible] vision.[20–23] Specifically, orientation, contrast, and Verni[illegible]rning can transfer to an orthogonal orientation compl[illegible] when either AE or FE receives exposure to the ortho[illegible]l orientation via performing an irrelevant task that alone c[illegible]ot affect the performance of the trained task at the orth[illegible]al orientation. The complete learning transfer suggests [illegible]E monocular learning is more likely a result of cog[illegible] compensation. That is, the performance improvem[illegible] not caused by plasticity in the amblyopic visual cor[illegible]r se, which would not predict orientation transfer. R[illegible] high-level brain areas may learn the rules of reweighting [illegible]oisy visual inputs from the amblyopic visual cortex for b[illegible]eadout. These rules can be applied to untrained orient[illegible]to enable learning transfer with TPE training, so as [illegible]pensate the functional deficits of the amblyopic vis[illegible]em.[19] The initial orientation specificity may be cause[illegible] lack of functional connections between high-level le[illegible]and new orientation inputs, which can be [illegible]via botto[illegible] [illegible]isual co[illegible] tions in [illegible] TPE p[illegible]

In t[illegible]ent study, we investigated the mechanisms of ambly[illegible]choptic de-masking learning by testing two confl[illegible]hypotheses. The low-level hypothesis supposes tha[illegible]ptic training reduces physiological interocular su[illegible]n in the amblyopic visual cortex, which restores at l[illegible]functionality of binocular vision. T[illegible] [illegible]e[illegible] [illegible]siol[illegible] [illegible]nt,[24,[illegible] relat[illegible] indicate learning of different rules for different tasks.[22] In contrast, the high-level hypothesis supposes that dichoptic training improves rules of reweighting visual input[illegible] specific task. This hypothesis would predict initial o[illegible] specificity that needs to be overridden by TPE traini[illegible] as task specificity. Our results demonstrated ori[illegible] task specificity with dichoptic de-masking lear[illegible] with amblyopia, which is consistent with [illegible] hypothesis rather than the low-level one. [illegible] demonstrated that the abolishment of ori[illegible] with TPE training, again consistent [illegible] hypothesis. We speculate that dichopti[illegible] may strengthen task-specific top-down[illegible] counter the impacts of attentional [illegible] physiological interocular suppre[illegible] stereoacuity.

Eleven amblyopic obs[illegible] [illegible] greater be[illegible] psychop[illegible] befo[illegible] [illegible] in the Table. Informed consent was collected from each observer prior to data collection. The study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board of Peking University.

The basic experimental design is represented schematically in Figure 1A. Prior to training the visual acuities and contrast sensitivity functions for both amblyopic and fellow eyes, as well as the stereoacuity, were measured. Eleven observers were assigned into two groups randomly. Following a dichoptic TPE protocol: (1) The first group ($n = 6$) practiced contrast discrimination at a vertical orientation for nine sessions. Then they received exposure to the orthogonal orientation through an irrelevant orientation discrimination task for five sessions. (2) The second group ($n = 5$) first practiced orientation discrimination at a horizontal orientation for five sessions. Then they received exposure to the orthogonal orientation through an irrelevant contrast discrimination task for another five sessions. After the dichoptic TPE training, the visual acuities, contrast sensitivity functions, and stereoacuity were remeasured. A subset of observers ($n = 6$; S1, S2, S3, S5, S7, and S11 in the Table) then performed monocular orientation training for nine sessions. After this monocular training the visual acuities and stereoacuity were remeasured.

The setup was identical to that in Liu and Zhang.[16] The stimuli were generated with Psychtoolbox-3 software[27] and presented on a 21-in Sony G520 CRT monitor (2048 × 1536 pixel, 0.19 × 0.19 mm/pixel, and 75-Hz frame rate). The head of the observer was stabilized by a chin-and-head rest. Experiments were run in a dimly lit room. For grating acuity and contrast sensitivity testing, a 14-bit look-up table achieved with a video attenuator was used to linearize the luminance of the monitor (mean luminance = 27 cd/m^2), and for other tasks an 8-bit look-up table was used (mean luminance = 50 cd/m^2).

The dichoptic stimuli (Fig. 1B) consisted of a pair of collinear vertical or horizontal Gabors (Gaussian windowed sinusoidal gratings) presented in AE and a band-pass filtered white noise masker in FE. The two Gabors had the same spatial frequency at 40% of AE's cut-off frequency, standard deviation at 1 wavelength (the reciprocal of spatial frequency), orientation at 0° or 90°, phase at 90°, and a center-to-center distance of 4 wavelengths. The cut-off frequency of AE (Mean = 14.4 cpd, SD = 3.6 cpd) was assessed by a grating acuity test for each observer before training. The viewing distance was 1.2 m. In contrast discrimination trials, one Gabor's contrast was set at 0.80, and the other Gabor's contrast was 0.80 − 1.414 × contrast discrimination threshold (with no masker presented in FE). The contrast discrimination threshold was premeasured for each observer with the same Gabor stimulus at a reference contrast of 0.80 (AE's contrast just-noticeable difference (JND) threshold: mean = 0.189, SD = 0.031). In orientation discrimination trials, the global orientation of two always aligned Gabors were tilted upper or lower from horizontal. The orientation offset was 1.414 times the orientation discrimination threshold premeasured for each observer with no masker presented in FE (AE's orientation JND threshold: mean = 1.5°, SD = 0.3°). The contrast of two Gabors was identical at 0.80.

The band-pass filtered noise masker was 512 × 512 pixels (4.4° × 4.4°) in size. To create the noise masker, a 512 × 512 pixels zero-mean white noise field was first generated, with each element being 2 × 2 pixels. The white noise field was then filtered in the frequency domain by a 1-octave band-pass filter centered at the same frequency of the Gabors. A new noise masker was generated every trial.

observer pressed the space bar to initiate the trial as soon as the whole cross appeared stable. Immediately after the key press, a black square contour (1.5° × 1.5°, the contour lines were 2-arcmin thick) was presented for 200 ms to prime attention to AE. After that the Gabor stimuli and the noise masker were presented dichoptically for 200 ms.

In the contrast discrimination trials, the observers were asked to judge which Gabor had a higher contrast. In the orientation discrimination trials, they were asked whether the 2-Gabor stimuli tilted upper or lower from horizontal. A staircase varied the root mean square contrast of the noise masker upon AE's contrast or orientation judgment. The staircase followed a 3-up-1-down rule that resulted in a 79.4% convergence rate. Specifically, three consecutive correct responses would raise the noise contrast by one step, and one incorrect response would lower the noise contrast by one step. The step size of the staircase was 0.05 log units. Each staircase consisted of eight reversals (∼40–50 trials). The geometric mean of the last six reversals was taken as the maximal tolerable noise contrast (TNC) for successful contrast or orientation discrimination.

To ensure effective noise masking (i.e., an observer did not close his/her fellow eye), in 20% of the trials a white digit ("1" or "2," 1.1° × 1.7° in size) was centered on the noise masker in FE while a blank screen was presented in AE. The observer needed to report the digit by key press (the mean correct rate = 95.5 ± 1.5%). Auditory feedback was given on incorrect responses in all trials.

The dichoptic TPE protocol consisted of a first training phase and a second exposure phase. Before and after the first training phase (i.e., contrast/orientation discrimination training), the following conditions were tested to evaluate the learning and transfer effects: (1) maximal TNC for AE's contrast/orientation discrimination at the trained orientation (groups 1, 2), and (2) maximal TNC for AE's contrast (group 1) or orientation discrimination (group 2) at an untrained orthogonal orientation. Each condition was measured for five staircases (∼200–250 trials). After the second exposure phase (orientation/contrast discrimination training at an orthogonal orientation), only condition (2) was re-tested to evaluate the learning and transfer effects. All staircases were run following a randomly permuted table for each observer. The duration varied from 1 to 2 hours, depending on the conditions. In the training and exposure phases, each daily session consisted of 20 staircases (for a total number of 800∼1000 trials) and lasted for approximately 2 hours. More details can be found in the Results section below.

During monocular training, orientation discrimination threshold was measured with a 2AFC staircase procedure in AE. In each trial, a foveal fixation cross was flashed for 400 ms before the onset of the stimulus. Then the reference and the test stimuli were presented separately in two 200-ms stimulus intervals in a random order, separated by a 500-ms interstimulus interval. Threshold was estimated following a 3-down-1-up staircase rule that resulted in a 79.4% convergence rate. The step size of the staircase was 0.05 log units. Each staircase consisted of two preliminary reversals and six experimental reversals. The geometric mean of the experimental reversals was taken as the threshold for each staircase run. Each session consisted of 20 staircases (for a total number of 800∼1000 trials) and lasted for approximately 2 hours.

Several studies have suggested that the interocular contrast ratio is a reliable objective measurement of interocular suppression.[9,28] Therefore, we adopted the interocular contrast ratio, which was the maximal TNC for AE divided by the maximal TNC for FE, to assess the strength of interocular suppression. Specifically, in the pre- and posttests, the Gabors and the noise masker were switched between eyes, so that the noise masker was presented to AE and the Gabor stimuli were presented to FE. Thus, the maximal TNCs for FE contrast

. The stereoacuity was evaluated using the Randot Stereo Test (Stereo Optical Co., Inc., Chicago, IL, USA) with polarizing glasses at a 40-cm viewing distance under normal room lighting. The stereo test was administered and scored according to the manufacturer's instructions. A graded sequence test was provided by contoured circles at 10 levels of disparity ranging from 400 to 20 arcsec. Randot forms with disparities at 500 and 250 arcsec were also used to provide additional steps of disparity.

Eleven adult amblyopic observers with no prior monocular training experience were randomly divided into two groups. The first group of six initially practiced AE contrast discrimination at a vertical orientation with dichoptic noise masking for nine sessions (Fig. 2A). We used the percent improvement (PI = [threshold_post/threshold_pre-1] × 100) to index the learning and transfer effects. After the first training phase, the maximal TNC for AE contrast discrimination was significantly improved by 173.1 ± 39.8% ($t_5 = 4.35$, $P = 0.007$, Cohen's $d =$ 1.78; 2-tailed paired t-test in this and later analyses unless

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suggests that dichoptic de-masking learning
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TPE training
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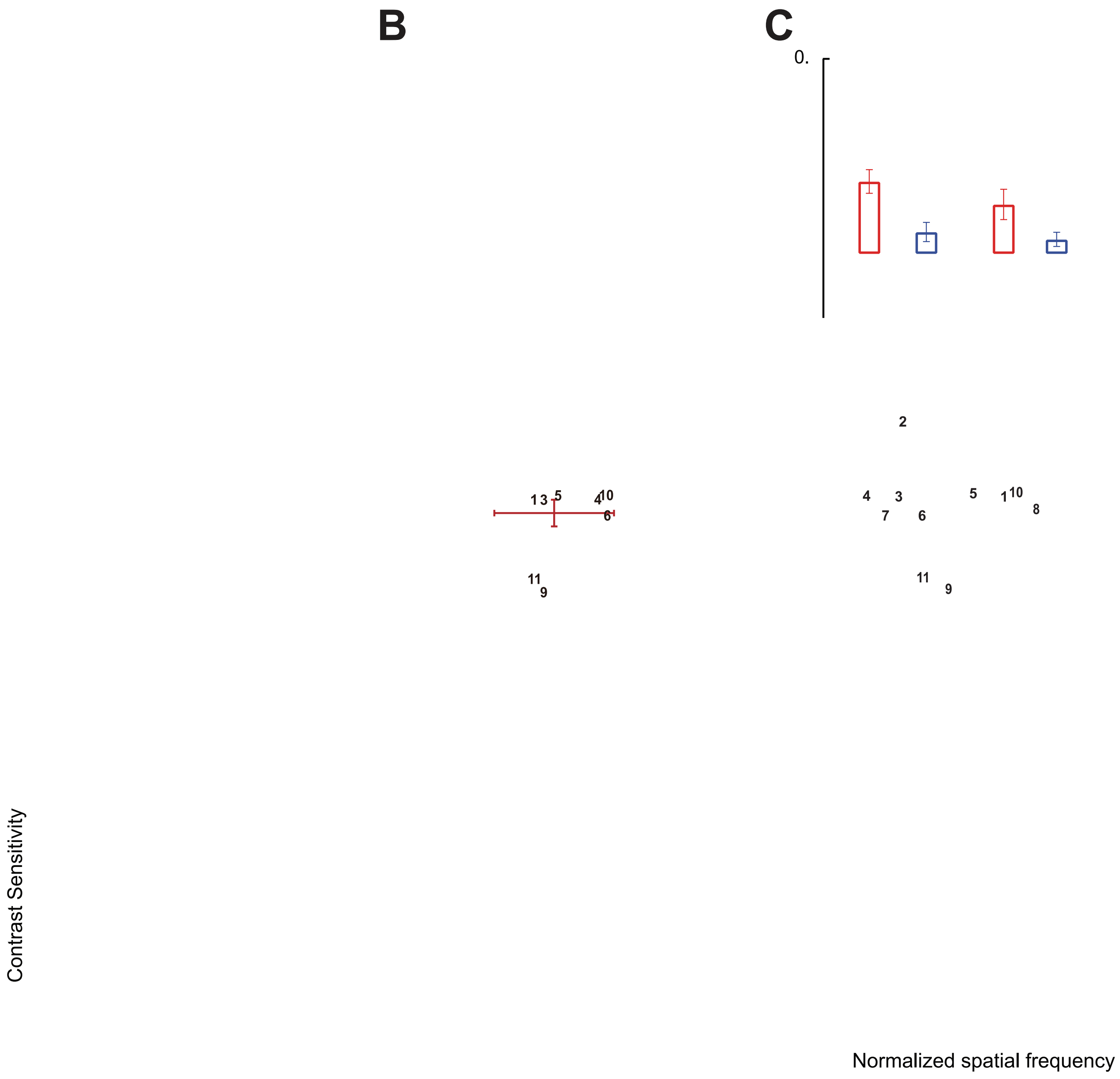
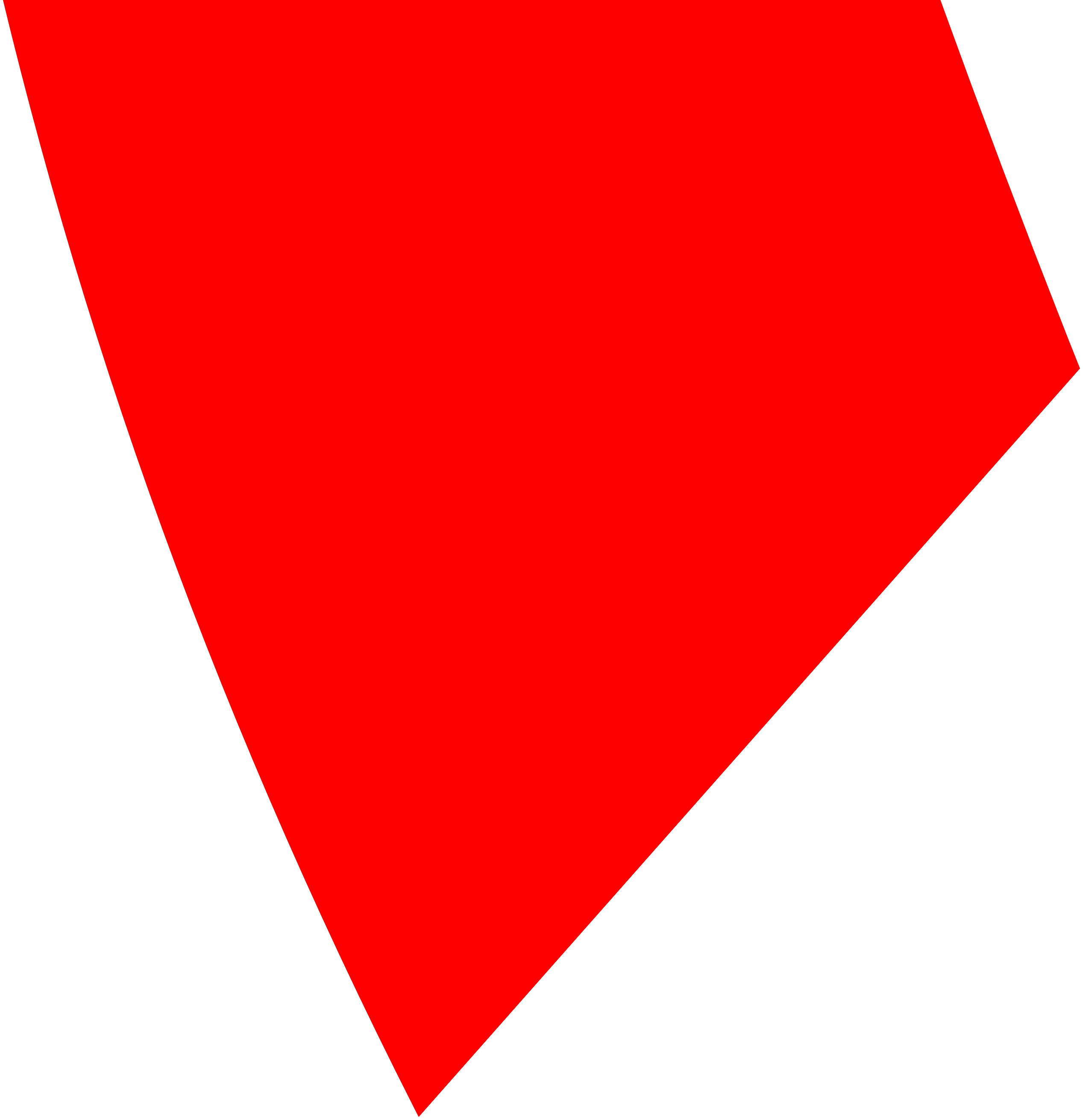


stereoacuity was neither significantly correlated with the pretraining stereoacuity ($r = -0.07$, $P = 0.84$), nor was it with the E-chart acuity improvement (Fig. 3E, $r = -0.22$, $P = 0.52$). In addition, there was no significant correlation between the improvement of stereoacuity and the improvement of the dichoptic de-masking learning at the trained orientation (Fig. 3F, $r = -0.28$, $P = 0.41$).

. The pre- and posttraining contrast sensitivity functions measured in AEs and FEs were shown in Fig. 3G. Before training, the mean AE cut-off spatial frequency was 14.4 ± 1.1 cpd, lower than the mean FE cut-off spatial frequency at 25.0 ± 1.7 cpd ($P < 0.001$). After training, contrast sensitivity functions in AEs were improved but still showed contrast sensitivity loss, primarily at higher spatial



the binocular vision impairments caused by strabismic amblyopia. A recent hypothesis is that training leads to better attention to the AE, so as to ease the effects of direct interocular suppression in a top-down manner to improve vision.[33] In general, this hypothesis is consistent with our claim that perceptual learning in amblyopic observers, like in normals, is a high-level learning process,[19] which may involve improved attention to the AE. In our dichoptic learning, the observers are purposely trained to counter the masking effects from the FE. Therefore, the improved attention to the AE would reduce the attentional bias to the FE, and/or counterbalance the low-level physiological interocular suppression in V1.[25] This would result in a lower interocular suppression index that may reflect both high-level attentional bias and low-level physiological interocular suppression, as shown in our data.

We understand that our current study has its limitations. First, it is possible that the results are specific to our particular dichoptic training paradigm. We present a masker in one eye and a target in the other eye. The training principles and underlying mechanisms may be distinct from other dichoptic training studies in which the task elements are separated between the two eyes and must be integrated for successful task completion.[8–13] Second, our results are largely based on anisometropic amblyopes (>70%). It is suggested that the mechanisms underlying strabismic and anisometropic amblyopia are different.[34,35] The applicability of our conclusions to other types of amblyopia needs to be experimented. Third, more observers need to be included to confirm the results that monocular training would bring no more benefits after dichoptic training.

In our study, six of 11 observers received new lenses, which they wore only during the training sessions for a total of 20 to 28 hours, while the other five wore their existing lenses. We found no significant difference of E-chart acuity improvements in AEs between these two subgroups of observers ($P = 0.08$). There are reports that for adults with amblyopia, refractive adaptation has limited and insignificant effects on visual acuity and stereoacuity.[36,37] Therefore, we assume that the refractive adaptation effects from 20 to 28 hours of new lens wearing would have very small effects on acuity and stereoacuity improvements in these six observers, and the overall effects would be minimal when all 11 observers' results are considered together.

We did not perform follow-up measurements in the current study. However, follow-up measurements were carried out in a previous study of ours using the same training paradigm.[16] In that study, seven of 13 amblyopic observers were retested 10 months (mean = 10.3 months, SD = 0.9 months) after they finished dichoptic training. The maximal tolerable noise contrasts were not significantly different from those measured immediately after training ($t_6 = 0.06$, $P = 0.96$, Cohen's $d = 0.03$). The stereoacuities were not significantly different either ($t_6 = 0$, $P > 0.99$, Cohen's $d = 0$). These results indicate that the dichoptic training effects can persist for an extended period.

We demonstrated that dichoptic de-masking learning of visual discrimination in adults with amblyopia can transfer nearly completely to an orthogonal orientation with a TPE protocol, and that the learning is task specific. These results suggest high-level dichoptic learning, in which the amblyopes may learn the rules of reading out orientation or contrast signals from dichoptically presented noise, so that learning is transferrable across orientations. Dichoptic training may improve top-down attention to the amblyopic eye, so as to counter attentional bias to the FE and/or physiological interocular suppression.

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