

Dichoptic De-Masking Learning in Adults With Amblyopia and Its Mechanisms

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PURPOSE. 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.

METHODS. 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.

RESULTS. (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.

CONCLUSIONS. 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

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



TABLE. The Characteristics of the Amblyopic and Fellow Eyes

Observer	Age, y	Sex	Type of Amblyopia	Strabismus, Distance	Eye	Refractive Error	Visual Acuity, logMAR		Stereoaucuity, arcsec	
							PreDicho	PostDicho	PreDicho	PostDicho
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 ^Δ 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	AE (L)	+4.00/-1.50×180	0.301	0.301	50	20
					FE (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 ^Δ EsoT	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 at a distance of 33 cm. The visual acuity was measured by a clinical E-chart. The stereoaucuity was evaluated with the Randot Stereo Test. ExoT, exotropia; EsoT, esotropia; Δ, prism diopters; A, anisometropic; S, strabismic; R, right; L, left; F, failed (>500).

areas that are most orientation selective.^{17,18} However, orientation specificity in AE monocular learning can be abolished with a training-plus-exposure (TPE) protocol,¹⁹ consistent with findings in normal vision.²⁰⁻²³ Specifically, orientation, contrast, and Vernier learning can transfer to an orthogonal orientation completely when either AE or FE receives exposure to the orthogonal orientation via performing an irrelevant task that alone does not affect the performance of the trained task at the orthogonal orientation. The complete learning transfer suggests that AE monocular learning is more likely a result of cognitive compensation. That is, the performance improvement is not caused by plasticity in the amblyopic visual cortex per se, which would not predict orientation transfer. Rather, high-level brain areas may learn the rules of reweighting the noisy visual inputs from the amblyopic visual cortex for better readout. These rules can be applied to untrained orientations to enable learning transfer with TPE training, so as to compensate the functional deficits of the amblyopic visual system.¹⁹ The initial orientation specificity may be caused by a lack of functional connections between high-level learning and new orientation inputs, which can be remedied via bottom-up stimulation and top-down modulation of early visual cortical neurons representing the new orientations in a TPE protocol.²³

In the current study, we investigated the mechanisms of amblyopic dichoptic de-masking learning by testing two conflicting hypotheses. The low-level hypothesis supposes that dichoptic training reduces physiological interocular suppression in the amblyopic visual cortex, which restores at least part of the functionality of binocular vision. This hypothesis would predict no orientation specificity because physiological interocular suppression is orientation invariant,^{24,25} and no task specificity because the task specificity is related to high-level attentional mechanisms,²⁶ and may indicate learning of different rules for different tasks.²² In contrast, the high-level hypothesis supposes that dichoptic

training improves rules of reweighting visual inputs for a specific task. This hypothesis would predict initial orientation specificity that needs to be overridden by TPE training, as well as task specificity. Our results demonstrated orientation and task specificity with dichoptic de-masking learning in adults with amblyopia, which is consistent with the high-level hypothesis rather than the low-level one. Our results also demonstrated that the abolishment of orientation specificity with TPE training, again consistent with the high-level hypothesis. We speculate that dichoptic de-masking training may strengthen task-specific top-down attention to the AE to counter the impacts of attentional bias to the FE and/or physiological interocular suppression, so as to improve stereoaucuity.

METHODS

Observers

Eleven amblyopic observers (8 anisometropic, and 3 anisometropic and strabismic) aged 19 to 28 years (mean = 23 years) participated. All had a visual acuity of 0 logMAR or better in FEs, and a visual acuity difference of two lines (0.2 logMAR) or greater between the AEs and FEs. They were new to psychophysical experiments. Their vision was best corrected before training by an ophthalmologist. Five of eleven observers wore their existing lenses during training, which were worn for a period of at least 6 months. The other six observers received new lenses during training, which were worn only when they undertook the experiments (20~28 hours). Full ophthalmic histories were obtained. Clinical details of all observers are summarized 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

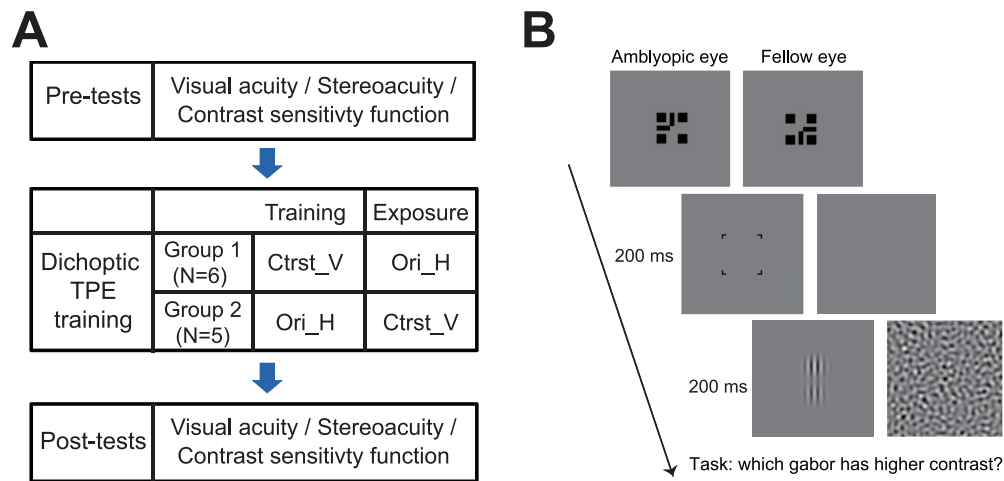


FIGURE 1. (A) A flowchart of the study design. Ctrst_V: contrast discrimination at a vertical orientation; Ori_H: orientation discrimination at a horizontal orientation. (B) The dichoptic training paradigm of a contrast discrimination task. From *top-left* to *bottom-right*: binocular fusion was first achieved with the assistance of two half-crosses. Then a cue was presented for 200 ms to prime the AE. A pair of collinear Gabors were later presented to AE for 200 ms while a bandpass noise masker was presented to FE at the same time. Observers were asked to judge which Gabor had higher contrast.

was approved by the institutional review board of Peking University.

Study Design

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.

Apparatus and Stimuli

The setup was identical to that in Liu and Zhang.¹⁶ The stimuli were generated with Psychtoolbox-3 software²⁷ 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 $0.80 - 1.414 \times$ 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 ($4.4^\circ \times 4.4^\circ$) 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.

The stimulus for monocular orientation discrimination training was a single Gabor with the orientation at 36° , contrast at 80%, spatial frequency at 40% of AE cut-off frequency, and phase randomized. The stimulus was viewed at a distance of 2 m through a circular opening (diameter 17°) of a black cardboard covering the rest of the monitor screen.

Procedures

In the dichoptic training task, each trial began with binocular fusion of two half-crosses (contrast 100%), each with four assisting squares, to align the two eyes in a four-mirror stereoscope (Fig. 1B). A whole cross was perceived when correct vergence was achieved. The contrast of the half-crosses and four assisting squares were 100%. But for those observers whose visual acuity difference between the two eyes was greater than four lines, the contrast of the half cross and four assisting squares in FE was reduced to 60% while the contrast in AE was kept at 100% to facilitate binocular fusion. The

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 ($1.5^\circ \times 1.5^\circ$, 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," $1.1^\circ \times 1.7^\circ$ 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 = $95.5 \pm 1.5\%$). 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.

Interocular Suppression

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 discrimination (group 1) and orientation discrimination (group 2) at the trained orientation were measured. Each condition was measured for five staircases (~200–250 trials). In contrast discrimination trials, one Gabor's contrast was set at 0.80, and the other Gabor's contrast was $0.80 - 1.414 \times$ the FE contrast discrimination threshold with no masker presented in AE. The FE contrast discrimination threshold was premeasured for each observer with the same Gabor stimulus at a reference contrast of 0.80 (FE contrast threshold: mean = 0.131, SD = 0.027). In orientation discrimination trials, the orientation offset was 1.414 times the FE orientation discrimination threshold premeasured for each observer with no masker presented in AE (FE orientation threshold: mean = 0.9° , SD = 0.1°).

Visual Function Assessments

Visual Acuity. All observers were refracted with a Snellen E-chart light box at the designated viewing distance of 5 m before and after training (Table). In addition, single-E and crowded-E visual acuities were tested with a custom computerized program. For single-E acuity testing, the stimulus was a tumbling letter E (a minimal luminance black letter on a full-luminance white monitor screen). For crowded-E acuity testing, the stimuli were a tumbling E target surrounded by four additional same-sized tumbling E letters, one on each side at an edge-to-edge gap of one letter size. The crowded-E acuity was functionally similar to the conventional visual chart acuity because both were influenced by visual crowding. The stroke and opening width of the E letters was one-fifth of the letter height. In addition, a grating acuity task was performed to measure the AE cut-off spatial frequency in each observer. The stimulus was a $0.29^\circ \times 0.29^\circ$ full-contrast square-wave grating tilted $\pm 45^\circ$ from vertical. The viewing distance with these tasks was 4 m.

For visual acuity measurements the stimuli were presented for an unlimited time until a key press. The observer judged the orientation of the tumbling E target as left, right, up, or down. Visual acuities were estimated with a single-interval staircase procedure following a 3-down-1-up staircase rule. The step size of the staircases was 0.03 log units. For grating acuity measurement, the task was to judge whether the grating tilted to the left or right from vertical, while a staircase varied the spatial frequency of the grating following a 3-up-1-down rule. The step size of the staircases was 0.05 log units. Each staircase consisted of eight reversals, with the geometric mean of the last six reversals taken as the visual acuity or grating acuity (i.e., cut-off spatial frequency).

Contrast Sensitivity. Contrast sensitivity was measured with a Gabor stimulus ($\sigma = 0.9^\circ$, orientation = $\pm 45^\circ$ from vertical). The spatial frequencies were 1/16, 1/8, 1/4, 1/2, 3/4, and 1 times the pretraining cut-off spatial frequency. Three staircases were run to measure the sensitivity to each spatial frequency. The order of all staircases for all spatial frequencies followed a randomly permuted table. Each observer's AE and FE had different tables. Staircases were run consecutively for each eye before switched to the other eye. The viewing distance was 4 m.

The mean contrast sensitivity functions were fitted with a Difference of Gaussians function: $y = A_1 e^{-(x/\sigma_1)^2} - A_2 e^{-(x/\sigma_2)^2}$. Here, y stood for the contrast sensitivity, x for the spatial frequency of the grating, A_1 and A_2 for the amplitudes of the Gaussians, and σ_1 and σ_2 for the standard deviations of the Gaussians.

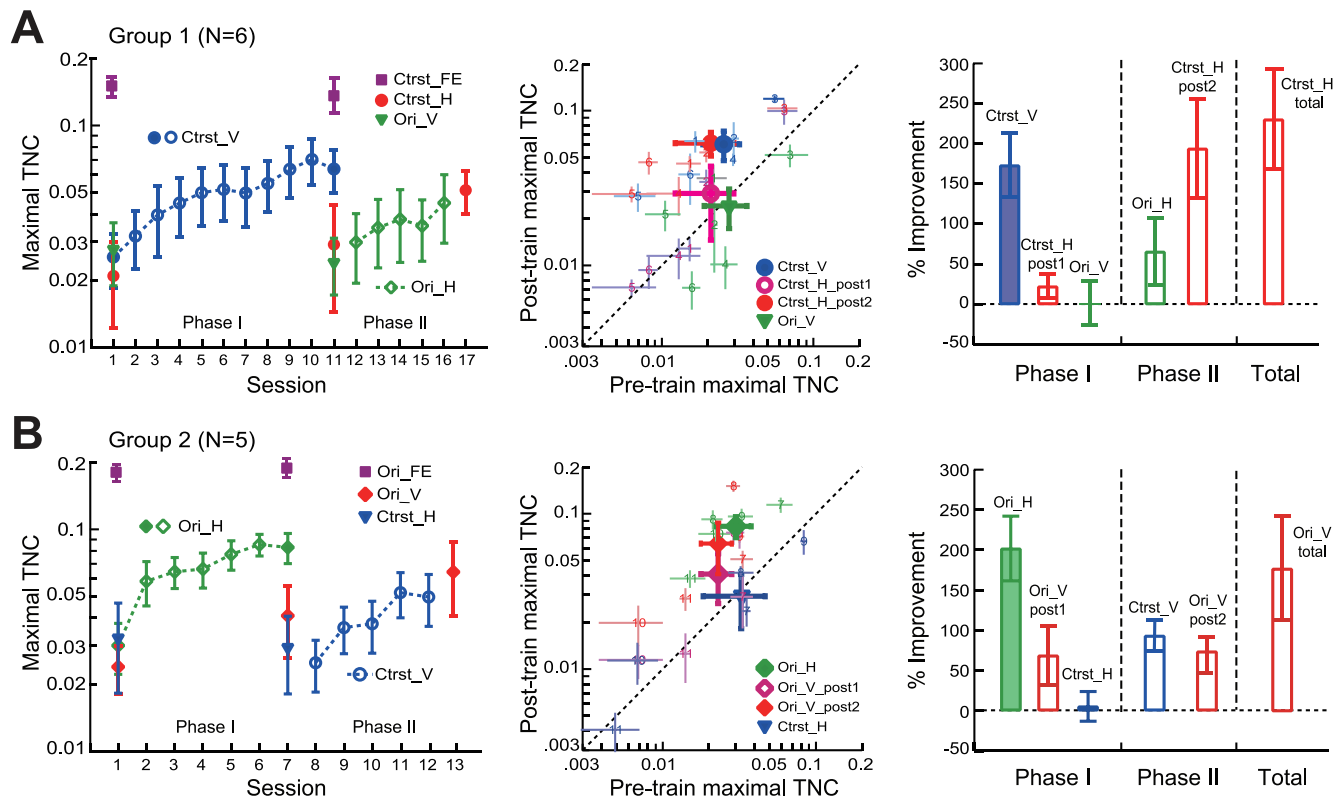


FIGURE 2. The transfer characteristics of dichoptic de-masking learning. **(A) (Left)** The transfer of dichoptic learning for AE contrast discrimination with TPE training. In the first training phase (sessions 2~10), AE contrast discrimination at 90° (Ctrst_V) under dichoptic noise masking was practiced. In post-test1 (session 11), learning and transfer effects were tested for the following conditions: maximal TNCs for AE contrast discrimination at the trained orientation (Ctrst_V) and the untrained orthogonal orientation (Ctrst_H), maximal TNC for AE orientation discrimination at the trained orientation (Ori_V), and maximal TNC for FE contrast discrimination at the trained orientation (Ctrst_FE). In the second exposure phase (sessions 12~16), AEs were exposed to transfer orientation at 0° while performing an irrelevant orientation discrimination task with dichoptic noise masking (Ori_H). The transfer of dichoptic learning for contrast discrimination to 0° was remeasured (Con_H) (session 17). **(Middle)** Comparisons of mean (circle) and individual post- and pretraining maximal TNCs. Each number indicates a different observer (see Table). Ctrst_H_post1: the improvement of Ctrst_H after the first training; Ctrst_H_post2: the improvement of Ctrst_H after the second exposure phase; Ctrst_H_total: the overall improvement of Ctrst_H after TPE training. **(Right)** A summary of learning and transfer results. **(B) (Left)** The transfer of dichoptic learning for AE orientation discrimination with TPE training. In the first training phase (sessions 2~6), AE orientation discrimination at 0° with dichoptic noise masking was practiced (Ori_H). Learning and transfer effects were tested (session 7): maximal TNCs for AE orientation discrimination at the trained (Ori_H) and untrained orthogonal orientation (Ori_V), maximal TNC for AE contrast discrimination at the trained orientation (Ctrst_H), and maximal TNC for FE orientation discrimination at the trained orientation (Ori_FE). In the second exposure phase (sessions 8~12), AEs received exposure to the transfer orientation 90° while performing an irrelevant contrast discrimination task with dichoptic noise masking (Con_V). The transfer of dichoptic de-masking learning for orientation discrimination to 90° was remeasured (Ori_V) (session 13). **(Middle)** Comparisons of mean and individuals post- and pretraining maximal TNCs. Each number indicates a different observer (see Table). Ori_V_post1: the improvement of Ori_V after the first training phase; Ori_V_post2: the improvement of Ori_V after the second exposure phase; Ori_V_total: the overall improvement of Ori_V after TPE training. **(Right)** A summary of learning and transfer results.

Stereoacuity. 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.

RESULTS

Dichoptic De-Masking Learning Showed Orientation and Task Specificity

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 discrim-

ination at a vertical orientation with dichoptic noise masking for nine sessions (Fig. 2A). We used the percent improvement ($PI = [\text{threshold_post}/\text{threshold_pre} - 1] \times 100$) to index the learning and transfer effects. After the first training phase, the maximal TNC for AE contrast discrimination was significantly improved by $173.1 \pm 39.8\%$ ($t_5 = 4.35$, $P = 0.007$, Cohen's $d = 1.78$; 2-tailed paired t -test in this and later analyses unless specified), from a root mean square contrast of 0.026 ± 0.007 to 0.060 ± 0.013 . Another group of five observers first practiced AE orientation discrimination at a horizontal orientation with dichoptic noise masking for five sessions, which improved maximal TNC by $201.8 \pm 40.3\%$ (Fig. 2B, $t_4 = 5.01$, $P = 0.007$, Cohen's $d = 2.24$), from a root mean square contrast of 0.030 ± 0.008 to 0.083 ± 0.013 .

In the pre- and posttests, the maximal TNC for FE contrast discrimination (group 1) remained unchanged (Fig. 2A, mean percent improvement (MPI) = $-11 \pm 7.9\%$, $t_5 = -1.41$, $P = 0.22$, Cohen's $d = 0.57$). Likewise, the maximal TNC for FE orientation discrimination (group 2) was not significantly

changed either (Fig. 2B, $MPI = 11.39 \pm 18.51\%$, $t_4 = 0.62$, $P = 0.57$, Cohen's $d = 0.28$). In the pretest, the interocular contrast ratio, which we used as an index for interocular suppression (see Methods), was 0.18 for the two groups when data were averaged, suggesting strong interocular suppression. In the posttest, the interocular contrast ratio was significantly increased to 0.56 ($t_{10} = 3.53$, $P = 0.005$, Cohen's $d = 1.06$), suggesting reduced interocular suppression. As would be discussed later, this reduction does not necessarily suggest reduced physiological interocular suppression, but is likely a result of reduced interocular functional imbalance due to cognitive learning effects.

For contrast discrimination learning (group 1), when the stimulus was switched to an orthogonal orientation after the first training phase, no significant change of maximal TNC was observed ($MPI = 22.2 \pm 15\%$, $t_5 = 1.48$, $P = 0.20$, Cohen's $d = 0.61$, the first two red solid circles in Fig. 2A). Similarly, the maximal TNC for AE orientation discrimination (group 2) was not significantly changed at an orthogonal orientation either ($MPI = 68.5 \pm 36.3\%$, $t_4 = 1.89$, $P = 0.13$, Cohen's $d = 0.85$, the first two red solid diamonds in Fig. 2B). When data from two groups were combined, there was significant difference between the improvements at the trained orientation and the untrained orthogonal orientation ($t_{10} = 5.37$, $P < 0.001$, Cohen's $d = 1.62$), showing orientation specificity in dichoptic de-masking learning.

In addition, we found that dichoptic de-masking learning was mostly specific to the trained task. When the test task was switched to untrained orientation discrimination in group 1, there was no significant change of maximal TNC for AE orientation discrimination after dichoptic contrast discrimination training ($MPI = 1.8 \pm 27.7\%$, $t_5 = 0.07$, $P = 0.95$, Cohen's $d = 0.03$, the first two green solid triangles in Fig. 2A). Likewise, dichoptic learning of orientation discrimination transferred little to contrast discrimination in group 2 ($MPI = 5.1 \pm 18.6\%$, $t_4 = 0.27$, $P = 0.80$, Cohen's $d = 0.12$, the first two blue solid triangles in Fig. 2B). When data from two groups were combined, there was no significant difference between the improvements at the trained task and the untrained task ($t_{10} = 0.20$, $P = 0.84$, Cohen's $d = 3.44$), suggesting that dichoptic learning was specific to the trained task.

The orientation specificity and task specificity may not fit the predictions of reduced physiological interocular suppression in dichoptic learning. Next, we explored whether the learning effects may result from changes in high-level brain processing.

Transfer of Dichoptic De-Masking Learning to an Orthogonal Orientation With TPE Training

Previously, we have shown that the orientation specificity in perceptual learning of normal vision may result from insufficient bottom-up or top-down stimulation of the untrained orientation, and that additional exposure of the untrained orientation can enable learning transfer.^{20,23} Such a TPE protocol has also been applied successfully to abolish orientation specificity in monocular AE learning.¹⁹ Here, we tested whether the same protocol also worked on orientation specificity in dichoptic de-masking learning. After initial contrast discrimination training, the amblyopic observers in group 1 continued to practice an AE orientation discrimination task with the same stimuli at an orthogonal orientation, also under dichoptic noise masking. The new orientation task alone had no impact on AE contrast discrimination because of the task specificity, but it exposed the observers to the orthogonal transfer orientation. After five sessions of orientation exposure, which improved maximal TNC for AE orientation discrimination by $65.5 \pm 41.9\%$ (Fig. 2A, $t_5 =$

1.56 , $P = 0.18$, Cohen's $d = 0.64$), the maximal TNC for AE contrast discrimination at the same orthogonal orientation was further improved by $193.9 \pm 61.5\%$ ($t_5 = 3.15$, $P = 0.03$, Cohen's $d = 1.29$). The total improvement was $230.3 \pm 62.6\%$ ($t_5 = 3.71$, $P = 0.01$, Cohen's $d = 1.52$), which was not significantly different to the total improvement at the trained orientation ($t_5 = 1.02$, $P = 0.35$, Cohen's $d = 0.42$), indicating complete de-masking learning transfer of dichoptic learning for AE contrast discrimination to an orthogonal orientation. Moreover, the task specificity results ruled out the possibility that the improved contrast discrimination at the orthogonal transfer orientation resulted from orientation training around the same orientation alone.

The transfer effects were replicated in group 2. After initial orientation training, the observers received exposure to the orthogonal transfer orientation through an irrelevant contrast discrimination training task under dichoptic noise masking. After that, the maximal TNC for AE orientation discrimination at the orthogonal orientation was further improved by $73.6 \pm 22.1\%$ (Fig. 2B, $t_4 = 3.34$, $P = 0.03$, Cohen's $d = 1.49$). In general, the total improvement was as much as that at the trained orientation ($t_4 = 0.86$, $P = 0.44$, Cohen's $d = 0.38$), showing substantial and nearly complete learning transfer. The consistent and nearly complete learning transfer shown in these two groups suggests that dichoptic de-masking learning in adults with amblyopia is mainly a high-level process, which will be further elaborated in the Discussion section.

The Impacts of Dichoptic De-Masking Training on Visual Acuity, Stereoacuity, and Contrast Sensitivity

Visual Acuity. For the eleven observers, after dichoptic TPE training (13~17 sessions), the visual acuity measured by a clinical E-chart was improved by 1.2 ± 0.2 logMAR lines in AEs (Fig. 3A, from 0.63–0.51 logMAR, $t_{10} = 4.90$, $P = 0.001$, Cohen's $d = 1.48$) and 0.2 ± 0.2 lines in FEs (from -0.05 to -0.07 logMAR, $t_{10} = 1.38$, $P = 0.20$, Cohen's $d = 0.41$). The acuity improvement in AEs was neither significantly correlated with the pretraining acuity ($r = -0.47$, $P = 0.14$), nor with the dichoptic de-masking learning effects at the trained orientation ($r = -0.34$, $P = 0.30$). When measured with a computerized acuity test (Figs. 3B, 3C), the AE single-E acuity was improved by 1.2 ± 0.3 lines (acuity threshold from 21.7 ± 3.8 to 16.7 ± 2.6 arcmin, $t_{10} = 4.05$, $P = 0.002$, Cohen's $d = 1.22$), and AE crowded-E acuity by 0.8 ± 0.3 lines (acuity threshold from 32.2 ± 11.2 to 28.3 ± 10.5 arcmin, $t_{10} = 2.69$, $P = 0.02$, Cohen's $d = 0.81$). The average improvement over both types of acuities was equivalent to approximately 0.9 ± 0.2 lines ($t_{10} = 3.46$, $P = 0.006$, Cohen's $d = 1.04$), not significantly different from that measured with a clinical E-chart acuity ($t_{10} = 1.01$, $P = 0.34$, Cohen's $d = 0.31$). The same training had much less impacts on FE single- and crowded-E acuities, with an improvement of 0.2 ± 0.1 lines on the average ($t_{10} = 1.83$, $P = 0.10$, Cohen's $d = 0.55$). The mean crowding index for AEs (crowded-E acuity/single-E acuity) was not significantly changed after dichoptic training (from 1.30 ± 0.21 to 1.50 ± 0.37 , $t_{10} = -1.24$, $P = 0.24$, Cohen's $d = 0.37$), indicating that training improved uncrowded acuity slightly more than crowded acuity.

Stereoacuity. The dichoptic training improved stereoacuity from $410.9'' \pm 70.7''$ to $152.7'' \pm 35.9''$, or by $60.2 \pm 4.9\%$ (Fig. 3D, $t_{10} = 9.04$, $P < 0.001$, Cohen's $d = 2.72$). Note that in Figure 3D, observers S2, S5, S6, S7, S10, and S11 were initially stereoblind (unable to see stereopsis at the largest test disparity of 500 arcsec). For data analysis, we arbitrarily designated his/her stereoacuity to be 600 arcsec. The improvement of

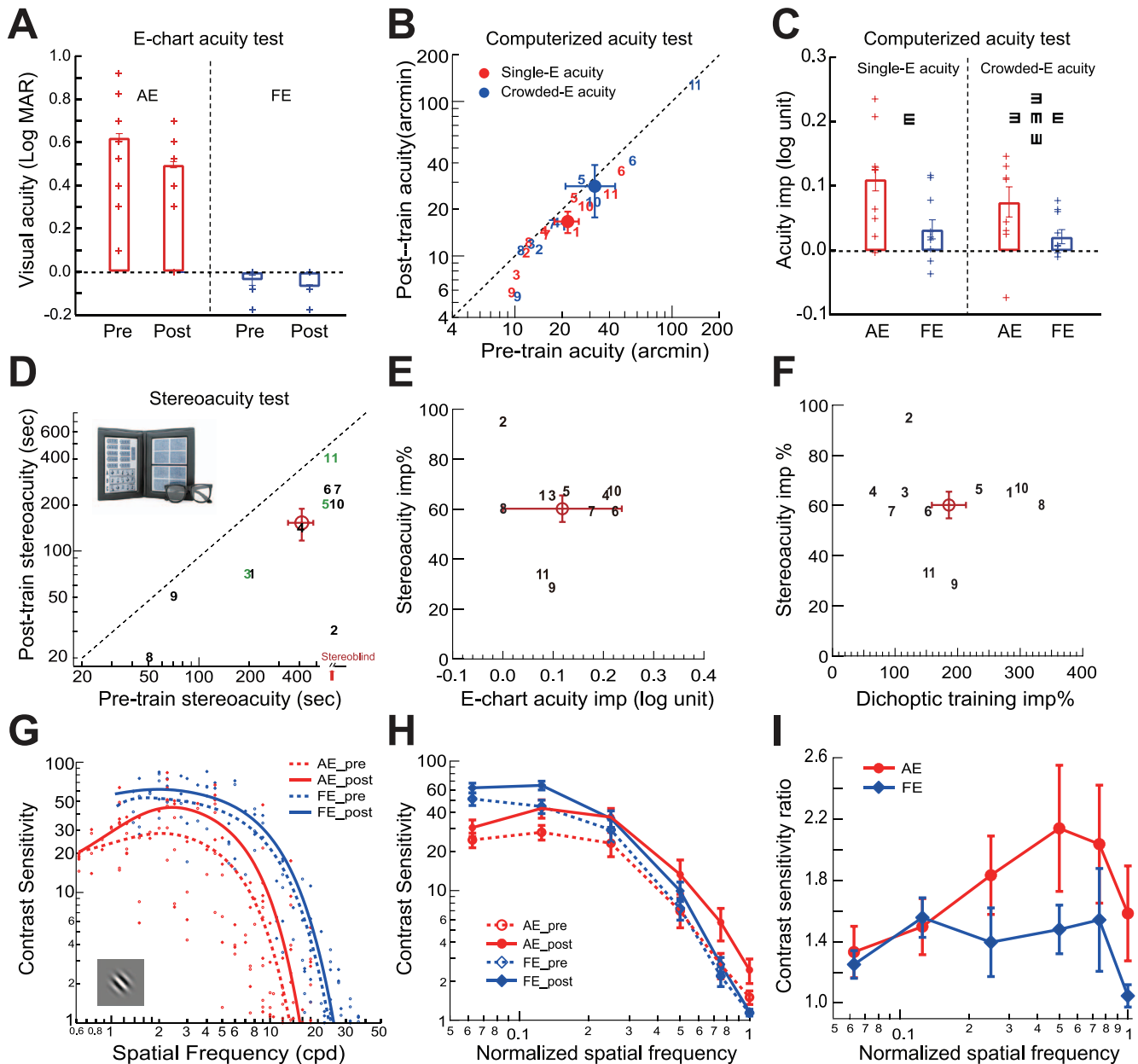


FIGURE 3. The impact of dichoptic TPE training on visual functions. (A) E-chart acuity in AEs and FEs before and after dichoptic training. (B) Comparisons of individual and mean AE single- and crowded-E acuity before and after dichoptic training. The circles with error bars indicate mean single- and crowded-E acuity. Each number indicates a different observer (see Table). (C) Single- and crowded-E improvements in AEs and FEs. (D) Individual and mean post- versus pretraining stereoacuity. The circle indicates the group mean. The arrows on the x-axis indicate the amblyopic observers who were stereoblind before training. Three green numbers indicate strabismic observers. (E) The stereoacuity improvement versus clinical E-chart acuity improvement. (F) The improvement of stereoacuity versus the improvement of dichoptic de-masking training at the trained orientation. The large symbol indicates the group mean. Each number indicates a different observer (see Table). (G) The mean contrast sensitivity functions of AEs (red curves) and FEs (blue curves) before (dashed curves) and after training (solid curves), along with individual data points. Each curve is the best fitting of a Difference-of-Gaussian function. Insert: A Gabor patch used for contrast sensitivity measurement. The task was to judge whether the Gabor was tilted toward the left or right from vertical. (H) The mean pre- and posttraining contrast sensitivity functions for AEs (red curves) and FEs (blue curves). Stimulus spatial frequencies were normalized by the corresponding cut-off spatial frequencies. (I) The ratios of the pre- and posttraining contrast sensitivity functions in AEs and FEs.

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, $r = -0.28, P = 0.41$).

Contrast Sensitivity. 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

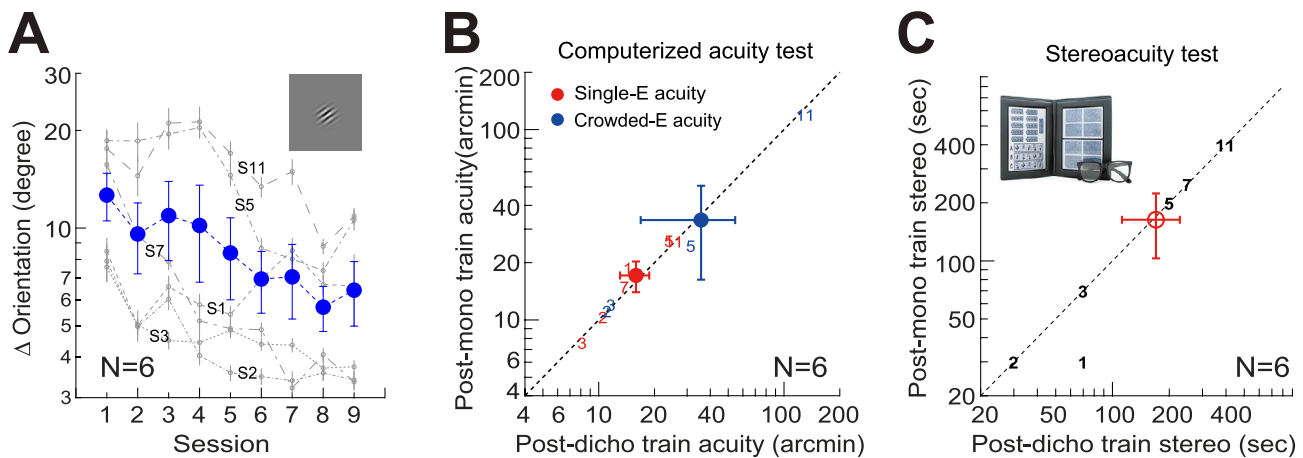


FIGURE 4. The effects of additional monocular training after dichoptic training. **(A)** Monocular training of AE orientation discrimination. *Insert:* the Gabor stimulus (36°) used for orientation training. The *gray lines* indicate individuals' data. **(B)** Comparisons of individual and mean AE single- and crowded-E acuity after dichoptic training and after additional monocular training. The *large symbol with error bars* indicate mean single- and crowded-E acuity. **(C)** A comparison of individual and mean stereoacuity after dichoptic training and after additional monocular training. The *large symbol with error bars* indicates the mean stereoacuity.

frequencies, when compared with those in FEs. We replotted the AE and FE contrast sensitivity functions with the spatial frequencies normalized by each observer's pretraining cut-off spatial frequencies (Fig. 3H) and presented the ratios of the pre- and posttraining AE and FE normalized contrast sensitivity functions (Fig. 3I). A repeated-measures ANOVA compared the contrast sensitivities at six normalized spatial frequencies before training (Fig. 3H, dashed curve) and after training (Fig. 3H, solid curve). The results showed a significant main effect of training for AEs ($F_{1,10} = 13.51$, $P = 0.004$, $\eta^2 = 0.58$) and FEs ($F_{1,10} = 29.89$, $P < 0.001$, $\eta^2 = 0.75$), suggesting improved contrast sensitivity functions in both eyes. There was also a significant interaction between training and spatial frequency for AEs ($F_{5,50} = 7.70$, $P < 0.001$, $\eta^2 = 0.44$) and FEs ($F_{5,50} = 10.51$, $P < 0.001$, $\eta^2 = 0.51$). These effects can be appreciated in Figure 3I in that there was an overall improvement of the contrast sensitivity function over a broad range of spatial frequencies for both eyes. However, AEs showed much more prominent effects on medium and high spatial frequencies compared with FEs (Fig. 3I).

No Additional Benefits of Monocular Training After Dichoptic Training

We reported previously that dichoptic training leads to further boost of stereoacuity, but not visual acuity, following extensive monocular training.¹⁶ Here, we investigated whether additional monocular training could generate any extra benefits of visual acuity and stereoacuity after dichoptic training, with the hypothesis that dichoptic training may have taken full care of visual acuity and stereoacuity. We were able to call back six dichoptically trained amblyopic observers (Fig. 4), so the following results should be considered having less statistical power. The six observers further practiced a monocular AE orientation discrimination task for nine sessions (for a total number of 7200~9000 trials). This monocular training reduced the orientation discrimination threshold by $46.9 \pm 8.6\%$ (Fig. 4A, $t_5 = 6.64$, $P = 0.001$, Cohen's $d = 2.71$) from $12.9 \pm 2.2^\circ$ to $6.8 \pm 1.5^\circ$. However, no significant extra gains in E-chart acuity ($t_5 = -1.0$, $P = 0.36$, Cohen's $d = 0.68$), AE single-E acuity (Fig. 4B, $t_5 = -1.66$, $P = 0.16$, Cohen's $d = 0.68$), crowded-E acuity (Fig. 4B, $t_5 = 1.12$, $P = 0.31$, Cohen's $d = 0.46$), and stereoacuity (Fig. 4C, $t_5 = 1.0$, $P = 0.36$, Cohen's $d = 0.41$) were evident.

Therefore, at least for these adults with amblyopia, additional monocular training following dichoptic training could not further improve visual acuity and stereoacuity.

DISCUSSION

In this study, we demonstrate that dichoptic de-masking learning for contrast and orientation discrimination in adults with amblyopia can transfer nearly completely to an orthogonal orientation with a TPE protocol, as well as task specificity in dichoptic de-masking learning.

What is learned in dichoptic learning of adult amblyopic observers? Our results show that dichoptic learning does not transfer to untrained orthogonal orientation (before TPE protocol) and untrained task with the same visual stimuli. Neurophysiological evidence suggests that physiological interocular suppression is invariant to stimulus orientation.²⁴ A recent psychophysical study also reported a lack of orientation specificity in suppression of the AE.²⁹ Therefore, if the amblyopic observers learn to discount interocular suppression directly through dichoptic training, learning should have transferred to a new orientation or task. More likely the amblyopic observers may learn to be more capable of picking up the trained orientation or contrast signals under the influence of dichoptic noise. This learning shall not occur only in a subgroup of visual neurons that directly respond to the stimuli. The complete learning transfer across orientations with TPE training suggests that the amblyopic observers may learn the rules of reading out orientation or contrast signals from dichoptic noise, and this rule-based learning can transfer to an orthogonal orientation, so that new orientation or contrast signals can be readout from noise equally effectively. This learning may not transfer to a new task because the rules are task specific even if the stimuli share the same orientation.^{22,26}

Why dichoptic learning, which is specific to the trained orientation (at least initially) and task, can lead to improved visual acuity, stereoacuity, and contrast sensitivity? There have been reports that attentional deficiencies may add to direct interocular suppression to compromise visual functions of amblyopes.³⁰⁻³² For example, Chow et al.³² reported that a FE bias in the interocular allocation of attention may contribute to

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 counter-balance 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 anisometric amblyopes (>70%). It is suggested that the mechanisms underlying strabismic and anisometric 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 stereoacuties 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.

CONCLUSIONS

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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