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Perceptual Learning Improves Adult Amblyopic Vision Through Rule-Based Cognitive Compensation

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Purpose. We investigated whether perceptual learning in adults with amblyopia could be enabled to transfer completely to an orthogonal orientation, which would suggest that amblyopic perceptual learning results mainly from high-level cognitive compensation, rather than plasticity in the amblyopic early visual brain.

Methods. Nineteen adults (mean age $=$ 22.5 years) with anisometropic and/or strabismic amblyopia were trained following a training-plus-exposure (TPE) protocol. The amblyopic eyes practiced contrast, orientation, or Vernier discrimination at one orientation for six to eight sessions. Then the amblyopic or nonamblyopic eyes were exposed to an orthogonal orientation via practicing an irrelevant task. Training was first performed at a lower spatial frequency (SF), then at a higher SF near the cutoff frequency of the amblyopic eye.

Results. Perceptual learning was initially orientation specific. However, after exposure to the orthogonal orientation, learning transferred to an orthogonal orientation completely. Reversing the exposure and training order failed to produce transfer. Initial lower SF training led to broad improvement of contrast sensitivity, and later higher SF training led to more specific improvement at high SFs. Training improved visual acuity by 1.5 to 1.6 lines ($P < 0.001$) in the amblyopic eyes with computerized tests and a clinical E acuity chart. It also improved stereoacuity by 53% ($P < 0.001$).

Conclusions. The complete transfer of learning suggests that perceptual learning in amblyopia may reflect high-level learning of rules for performing a visual discrimination task. These rules are applicable to new orientations to enable learning transfer. Therefore, perceptual learning may improve amblyopic vision mainly through rule-based cognitive compensation.

Keywords: amblyopia, perceptual learning, orientation

Amblyopia is a developmental visual disorder caused by early abnormal binocular visual experience (e.g., strabismus and anisometropia) that disrupts the development of neural circuitry in the visual cortex. It is an ideal model for understanding when and how brain plasticity may be harnessed for recovery of visual function lost. There is a widespread belief that amblyopia is irreversible beyond 6 to 7 years of age (the upper limit of the sensitive period).[1] However, studies have reported that perceptual learning, a process in which training improves discrimination of basic visual features, can improve adolescent and adult amblyopic vision.[2–8] These results, along with neurophysiological findings that the adult visual cortex retains a certain amount of plasticity,[9–11] raise hope that perceptual learning may be able to take advantage of the cortical plasticity to improve amblyopic vision.

Similar to normal perceptual learning, amblyopic perceptual learning is at least partially and sometimes completely specific to the trained orientation[3,12,13] (also see Figs. 2–4 of the present study). Many researchers take orientation specificity as evidence that perceptual learning reflects plasticity in early visual cortical areas[14–16] where neurons are most selective for orientation.[17,18] Others assume that perceptual learning is based on reweighting the responses of neurons activated by the trained stimulus, in that the brain assigns greater weights to the responses of more relevant visual neurons to improve readout.[19–21] Here the reweighting results in more precise stimulus templates, which also leads to orientation specificity.[22]

However, recently we developed a training-plus-exposure (TPE) technique to demonstrate that orientation-specific perceptual learning in foveal vision can transfer completely to a new orientation in normal vision, provided that the observers are exposed to the new orientation through an irrelevant task.[23] This finding, along with our demonstration that perceptual learning can transfer completely to untrained retinal locations,[24–26] indicates that normal perceptual learning may occur in high-level brain areas beyond the orientation-selective and retinotopic visual cortex, and it may be through a process in which the brain first learns the rules for reweighting the visual inputs and can then apply these rules to other orientations after exposure to them.

This finding also raises fundamental issues to the understanding of amblyopic perceptual learning. Does perceptual learning improve amblyopic vision through similar rule-based high-level mechanisms, which could be regarded as cognitive compensation for the disrupted visual cortical functions in amblyopia? Or does training indeed rewire the amblyopic visual cortex to restore at least part of the functionality, or improve the response reweighting for a limited set of neurons activated

TABLE. The Characteristics of the Amblyopic and Nonamblyopic Eyes

Subject	Age, y	Sex	Refractive Error	Acuity	Strabismus	Type	Patching Treatment
a	23	F	R: −1.00/−3.00 × 175	20/40	R 30^{Δ} EsoT	Aniso and Strab	No
			L: −6.00/−0.75 × 175	20/25			
b	24	M	R: −2.75	20/20	None	Aniso	Yes
			L: +1.00/−1.00 × 10	20/40			
c	19	F	R: +2.00	20/20	None	Aniso	No
			L: Plano	20/40			
d	19	M	R: Plano	20/20	L 15^{Δ} ExoT	Aniso and Strab	No
			L: +2.50	20/80			
e	27	M	R: −0.25/−0.50 × 75	20/20	L 25^{Δ} EsoT	Strab	Yes
			L: +0.75/−0.25 × 165	20/167			
f	23	F	R: −2.00/−0.50 × 90	20/20	L 30^{Δ} EsoT	Aniso and Strab	No
			L: +2.00	20/200			
g	23	M	R: +2.00	20/20	None	Aniso	Yes
			L: +5.00/−0.50 × 170	20/40			
h	25	F	R: Plano	20/30	None	Aniso	No
			L: +5.00/−1.00 × 45	20/20			
i	22	F	R: −1.00/−1.25 × 45	20/25	None	Aniso	No
			L: −4.50/−1.25 × 150	20/50			
j	23	M	R: +4.50	20/133	None	Aniso	No
			L: Plano	20/170			
k	22	M	R: −2.75	20/25	None	Aniso	No
			L: +1.50	20/40			
l	24	F	R: Plano	20/25	R 30^{Δ} EsoT	Aniso and Strab	Yes
			L: +3.00	20/133			
m	21	M	R: +4.00/+1.00 × 75	20/20	None	Aniso	No
			L: −1.50/+0.50 × 50	20/66			
n	22	F	R: −0.25	20/16	None	Aniso	No
			L: +5.00/−1.25 × 10	20/80			
o	23	M	R: −4.00/+0.75 × 110	20/66	R 20^{Δ} ExoT	Strab	Yes
			L: −4.00/+0.75 × 80	20/20			
p	19	F	R: −0.25	20/20	None	Aniso	Yes
			L: +4.50/+0.50 × 100	20/40			
q	20	F	R: +2.25	20/40	None	Aniso	No
			L: −3.00/+0.75 × 60	20/20			
r	23	M	R: +0.50/0.25 × 170	20/16	None	Aniso	Yes
			L: +5.25/+0.75 × 155	20/50			
s	22	M	R: −0.25	20/20	R 30^{Δ} ExoT	Aniso and Strab	Yes
			L: +3.50/+1.25 × 130	20/400			

Aniso, anisometropia; Strab, strabismus; XT, exotropia; ET, esotropia; Δ, prism diopters.

by the trained stimulus? For practical purposes, orientation specificity limits the use of perceptual learning as a potential therapeutic tool to improve amblyopic vision. Thus, learning transfer would certainly increase the training efficiency. We addressed these issues here by applying TPE to enable learning transfer to an orthogonal orientation in adults with amblyopia.

MATERIALS AND METHODS

Observers

Nineteen amblyopic observers aged 19 to 27 years old (mean = 22.5 years) with anisometropic and/or strabismic amblyopia participated in this study (Table). Eight of them had a previous history of patching treatment, but they and the other 11 observers, who had no previous patching history, had similar visual acuities (15.6 ± 3.7 arcmin vs. 16.7 ± 2.2 arcmin, $P = 0.79$, two-tailed two-sample *t*-test). Each observer's vision was best corrected before training by an ophthalmologist. The study followed the tenets of the Declaration of Helsinki and was approved by the IRB of Peking University. Informed consent was obtained from each observer prior to data collection.

Apparatus

The stimuli were generated by a Matlab-based WinVis program (Neurometrics Institute, Oakland, CA, USA) and were presented on a 21-inch Sony G520 color monitor (Sony, Tokyo, Japan; for contrast, Vernier and orientation tasks: 2048 pixel × 1536 pixel, 0.19 mm × 0.19 mm per pixel, 75 Hz frame rate; for E acuity, grating acuity, and contrast sensitivity testing: 1024 pixel × 768 pixel, 0.38 mm × 0.38 mm per pixel, 120 Hz frame rate). For grating acuity and contrast sensitivity testing, a 14-bit look-up table achieved with a video attenuator[27] 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). Viewing was monocular with the nontested eye covered by a translucent eye patch. A chin-and-head rest helped stabilize the head of the observer. Experiments were run in a dimly lit room.

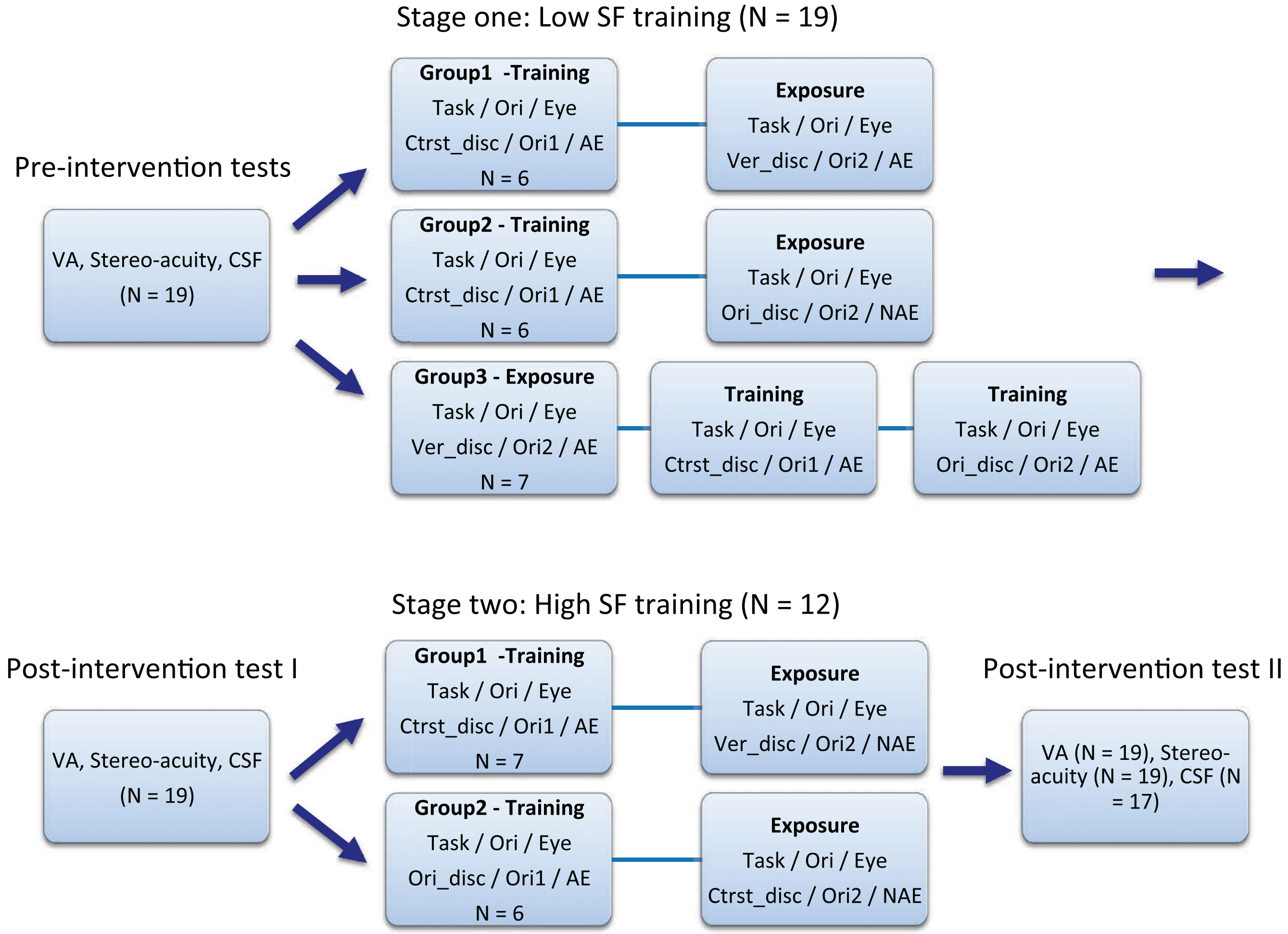

Figure 1. A flowchart of the study design. VA, visual acuity; CSF, contrast sensitivity function; SF, spatial frequency; Ctrst, contrast; Ori, orientation; Ver, Vernier; disc, discrimination. One observer was in both groups in the second stage training.

Stimuli

The experiments consisted of two training stages (Fig. 1). The first used a low spatial frequency (mean = 2.4 cycles per degree [cpd], SD = 0.7 cpd) that was approximately 2.7 octaves below the cutoff frequency of the amblyopic eye, and the second used a higher spatial frequency (mean = 8.2 cpd, SD = 1.8 cpd) that was approximately 0.9 octaves below the same cutoff frequency of the amblyopic eye. Various visual functions were assessed before and after each training stage.

In the first low spatial frequency training stage, a pair of identical and collinear Gabors (Gaussian windowed sinusoidal gratings) centered on a mean luminance screen background were used for contrast discrimination, Vernier, and orientation discrimination tasks (Fig. 2a). The two Gabors had the same spatial frequency, standard deviation (one wavelength), contrast (80%), orientation (horizontal or vertical), and phase (180°) unless otherwise specified. The center-to-center distance between the two Gabors was five wavelengths. The Vernier offset was always perpendicular to the orientation of the Gabors and was achieved by shifting each Gabor half of the total offset in opposite directions. In contrast discrimination trials the alignment of two Gabors was randomly jittered by ±50 arcmin (±2 times the mean wavelength). In orientation discrimination trials the two Gabors were always aligned, and the phase, which was equal in two Gabors, was randomized from 0° to 180° for every presentation. The stimulus was viewed through a circular opening (diameter = 17° at a viewing distance of 2 m) of a black cardboard that covered the monitor surface. This helped mask the straight edges of the monitor that the observers might use as cues for orientation and Vernier judgments. The viewing distance was 1.6 m.

In the second training stage the center-to-center distance of the two high spatial frequency Gabors was four wavelengths. Other stimulus parameters were unchanged except when specified. In addition, a single Gabor (36° or 126° orientation) with a random phase was used for orientation and contrast discrimination training (Fig. 4). The contrast for the orientation discrimination task was 80%. The viewing distance was 2 m.

Visual Function Assessments

Visual Acuity. Single-E acuity was measured with a tumbling letter E (a minimal luminance black letter on a full-luminance white background). Crowded-E acuity was tested with a tumbling E letter target surrounded by four same-sized tumbling E flankers in the four cardinal directions, with an edge-to-edge gap of one letter size. The crowded-E acuity may be influenced by the crowding effect. The stroke and opening width of the E letter was one fifth of the letter height. Besides computerized single-E and crowded-E acuities, visual acuity was also measured with a clinical E acuity chart, the standard

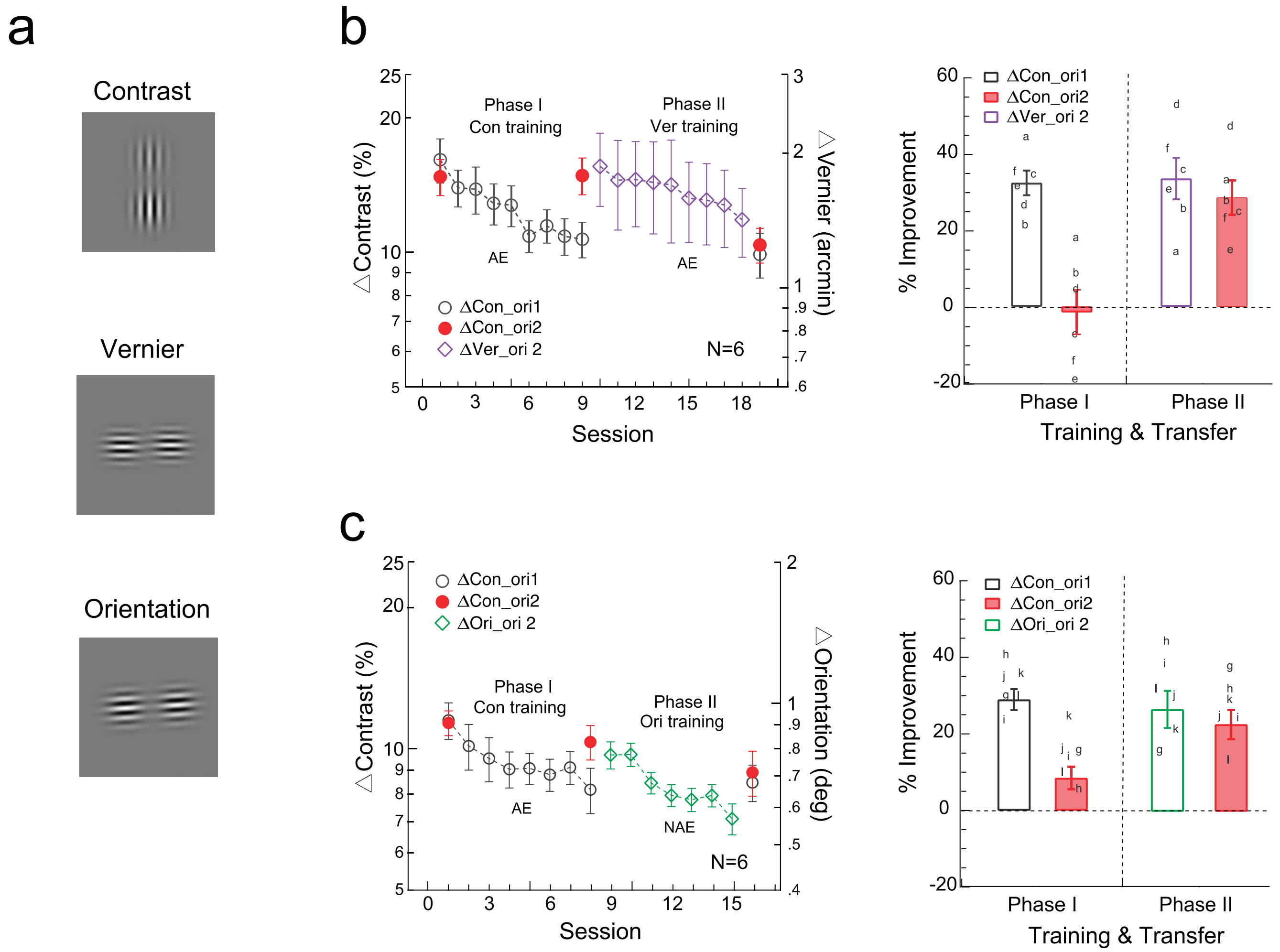

Figure 2. Contrast learning and its transfer to an orthogonal orientation with TPE at low spatial frequencies. (**a**) The two-Gabor stimulus configurations for contrast, Vernier and orientation discrimination, respectively. The contrast task was to judge which Gabor had higher contrast. The Vernier task was to judge whether the right Gabor was higher or lower than the left Gabor in the shown stimuli. The orientation task was to judge whether the global orientation of two Gabors tilted clockwise or anticlockwise from the vertical or horizontal (horizontal in the shown stimuli). (**b**, **c**) *Left panels*: TPE procedure. Observers first practiced contrast discrimination with their amblyopic eyes at one orientation (ΔCon_ori1, *gray circles*; contrast thresholds indicated by the left ordinate) in phase I. The transfer of learning was tested at an untrained orthogonal orientation (ΔCon_ori2, the left two *red circles*). Observers were then exposed to the orthogonal orientation through either Vernier training with the amblyopic eyes (ΔVer_ori2, *purple diamonds*; Vernier thresholds indicated by the right ordinate; [**b**]) or orientation training with the nonamblyopic eyes (ΔOri_ori2, *green diamonds*; orientation thresholds indicated by the right ordinate; [**c**]) in phase II. The transfer of contrast learning to the orthogonal orientation was then remeasured (ΔCon_ori2, the right two *red circles*). The thresholds are averaged over all observers, with error bars representing one standard error of the mean. The left and right ordinates have the same scale factor in log units. *Right panels*: A summary of learning and transfer for phase I and phase II training. Each lower-case letter indicates the improvement of a different observer (see Table).

visual acuity chart in China. Grating acuity was tested with a 0.29° × 0.29° sharp-edged, full contrast, square-wave grating tilted ±45° from vertical. The viewing distance with these tasks was 4 m.

Contrast Sensitivity. Contrast sensitivity was measured with a Gabor stimulus ($\sigma = 0.9°$, orientation $= \pm 45°$ from vertical). The spatial frequencies were 1/16, 1/8, 1/4, 1/2, 3/4, and 1 times the cutoff frequency of the amblyopic or nonamblyopic eye predetermined with a grating acuity task. Three staircase thresholds were collected to determine the sensitivity to each spatial frequency. The testing order of all staircases for all spatial frequencies followed a random permutation table. Different tables were used for amblyopic and nonamblyopic eyes. Staircases were run consecutively for one eye to finish one repeat before switching to the other eye. The viewing distance was 4 m.

Stereoacuity. The Randot Stereo Test (Stereo Optical Co., Inc., Chicago, IL, USA) with form stimuli was used to test stereoacuity under normal room lighting (around 30 cd/m^2).

Procedures

The contrast discrimination, Vernier discrimination and orientation discrimination thresholds with the two-Gabor stimuli were all measured with a single-interval staircase procedure. In each trial, a foveal fixation cross was flashed for 400 ms, followed by a 200-ms presentation of the stimuli. An observer judged with key press which Gabor had a higher contrast, whether the right Gabor was higher or lower than the left

Gabor for a horizontal Vernier, or the lower Gabor was to the left or right of the upper Gabor for a vertical Vernier, or whether the two-Gabor stimuli tilted clockwise or counterclockwise from the vertical or horizontal. Auditory feedback was given on incorrect responses in these and other tasks through pretraining tests, training, and posttraining tests.

The orientation and contrast thresholds with the single-Gabor stimulus were measured with a two-interval forced-choice staircase procedure. In each trial, the foveal fixation cross was flashed for 400 ms before the onset of the stimulus. Then the reference and the target were presented separately in two 200-ms stimulus intervals in a random order, separated by a 500-ms interstimulus interval. The observer's task was to judge in which stimulus interval the Gabor orientation was more clockwise or the contrast was higher.

The E acuities, grating acuity, and contrast sensitivity were all measured with a single-interval staircase procedure. The stimulus stayed on until a key press by the observer. The task was to judge the orientation of the grating (tilted to the left or right from vertical) or the tumbling E (left, right, up, or down).

All thresholds were estimated following a 3-down-1-up staircase rule that resulted in a 79.4% convergence level. Each staircase consisted of two preliminary reversals and six experimental reversals (four experimental reversals for E acuity measurements) with approximately 40 to 50 trials. The step size of the staircase was 0.05 log units (0.03 log units for E acuity measurements). The geometric mean of the experimental reversals was taken as the threshold for each staircase run.

Statistical Analyses

The performance improvement due to training or transfer was represented by percent improvement (PI); $\mathrm{PI} = 100\% \times (\mathrm{Th}_{\mathrm{post}} - \mathrm{Th}_{\mathrm{pre}})/\mathrm{Th}_{\mathrm{pre},}$ in which $\mathrm{Th}_{\mathrm{pre}}$ stood for pretraining threshold, and $\mathrm{Th}_{\mathrm{post}}$ stood for posttraining threshold.

A transfer index (TI) defined by $\mathrm{TI} = \mathrm{MPI}_{\mathrm{transfer}}/\mathrm{MPI}_{\mathrm{trained}}$ was used to compare the transfer of learning among different training conditions, in which MPI stood for mean percent improvement; $\mathrm{TI} = 1$ indicated complete transfer, and $\mathrm{TI} = 0$ indicated no transfer.

One-tailed paired *t*-tests were used unless specified to test the possibility that the MPI due to training or transfer was significantly larger than zero.

When the pre- and posttraining contrast sensitivities were compared over multiple spatial frequencies, a repeated-measures ANOVA was used to test the main effect of training and the interaction between training and spatial frequency.

Study Design

The flowchart in Figure 1 provides an overview of the study design. Prior to training the contrast sensitivity functions and visual acuities for both amblyopic and nonamblyopic eyes, as well as the stereoacuity, of all observers were measured. The first stage of training was performed in all 19 observers at a low spatial frequency to reveal the general learning effects. This stage consisted of three independent experiments, each was run by six to seven observers. All observers then participated in a second stage of training at a high spatial frequency, but only a subset of them ($N = 12$) completed it. This high spatial frequency training was directly targeted at the high spatial frequency deficits of amblyopia. The second stage consisted of two independent experiments, each was run by six to seven observers. After training the contrast sensitivity functions, visual acuities, and stereoacuity were remeasured.

RESULTS

The Transfer of Amblyopic Perceptual Learning Enabled by TPE at a Low Spatial Frequency

The first stage of training was performed at a low spatial frequency (2.4 ± 0.7 cpd; Fig. 5a, red arrow), approximately 2.7 octaves below the amblyopic eye's cutoff frequency, where contrast sensitivities of the two eyes were similar. This low-spatial frequency training was aimed at revealing any general learning effects associated with training in amblyopic eyes.

The 19 amblyopic observers were divided into three groups. The first group ($N = 6$) practiced a contrast discrimination task using amblyopic eyes for 8 to 10 2-hour sessions on different days. The local and global orientations of the two collinear Gabors were either both at 0° or both at 90° orientation (Fig. 2a). Training significantly improved contrast discrimination at the trained orientation (ΔCon_ori1, indicating contrast discrimination at orientation 1; Fig. 2b), with the mean contrast threshold reduced from 16.1 ± 1.8% to 10.7 ± 1.0%. The MPI was 32.5 ± 3.2% ($P < 0.001$), and the improvement range was 21.5% to 44.7%. However, learning did not transfer to the orthogonal orientation when the whole stimulus pattern rotated by 90° (ΔCon_ori2, MPI = –1.5 ± 5.9%, $P = 0.41$; range, –19.1% to 18.1%), demonstrating strong orientation specificity.

Following the TPE protocol, the same observers were then exposed to the orthogonal orientation by practicing a Vernier discrimination task, which was irrelevant to contrast discrimination, with their amblyopic eyes for nine additional sessions (ΔVer_ori2, MPI = 33.6 ± 5.4%, $P < 0.001$; range, 14.4%–53.1%). After this exposure, contrast discrimination at the orthogonal orientation was significantly improved, with the contrast threshold reduced from 14.9 ± 1.4% to 10.4 ± 0.9% (ΔCon_ori2, MPI = 29.3 ± 3.8%, $P < 0.001$; range, 18.6%–44.9%). The overall MPI after training and exposure was 28.6 ± 4.5% (range, 15.0%–47.4%), not significantly different from the MPI at the trained orientation ($P = 0.50$, two-tailed paired *t*-test). Thus TPE enabled complete transfer of contrast perceptual learning in amblyopic eyes. In the initial training phase, the mean TI was –0.04 ± 0.18. However, after the orthogonal orientation exposure the TI increased to 0.94 ± 0.20, which was not significantly different from $\mathrm{TI} = 1$ ($P = 0.39$), suggesting complete learning transfer.

We reasoned that since there might still be binocular neurons in the amblyopic visual cortex, it might not matter whether the orthogonal orientation exposure was through the amblyopic eye or the fellow nonamblyopic eye. Training with the nonamblyopic eye would have the advantage of easing the stress on the fatigue-prone amblyopic eye. To test this, a second group ($N = 6$) practiced contrast discrimination with amblyopic eyes at one orientation, which reduced the contrast threshold from 11.5 ± 1.0% to 8.1 ± 0.9% (ΔCon_ori1, MPI = 29.0 ± 2.7%, $P < 0.001$; range, 18.9%–38.2%; Fig. 2c). Learning transferred slightly this time to an orthogonal orientation with reduced threshold from 11.3 ± 0.7% to 10.3 ± 0.5% (ΔCon_ori2, MPI = 8.5 ± 3.0%, $P = 0.018$; range, –1.5% to 20.1%, TI = 0.31 ± 0.09). The observers were then exposed to the orthogonal orientation through irrelevant orientation discrimination training with their nonamblyopic eyes (ΔOri_ori2, MPI = 26.7 ± 4.9%, $P = 0.001$; range, 10.4%–42.5%). This measure further reduced contrast thresholds to 8.9 ± 1.0% at the orthogonal orientation in the amblyopic eyes (ΔCon_ori2, MPI = 14.9 ± 5.6%, $P = 0.023$; range, –3.1% to 32.9%). The overall MPI of contrast performance at the orthogonal orientation was 22.7 ± 3.8% (range, 7.3%–35.2%), not significantly different from the MPI at the trained orientation ($P = 0.11$, two-tailed paired *t*-test). The overall TI

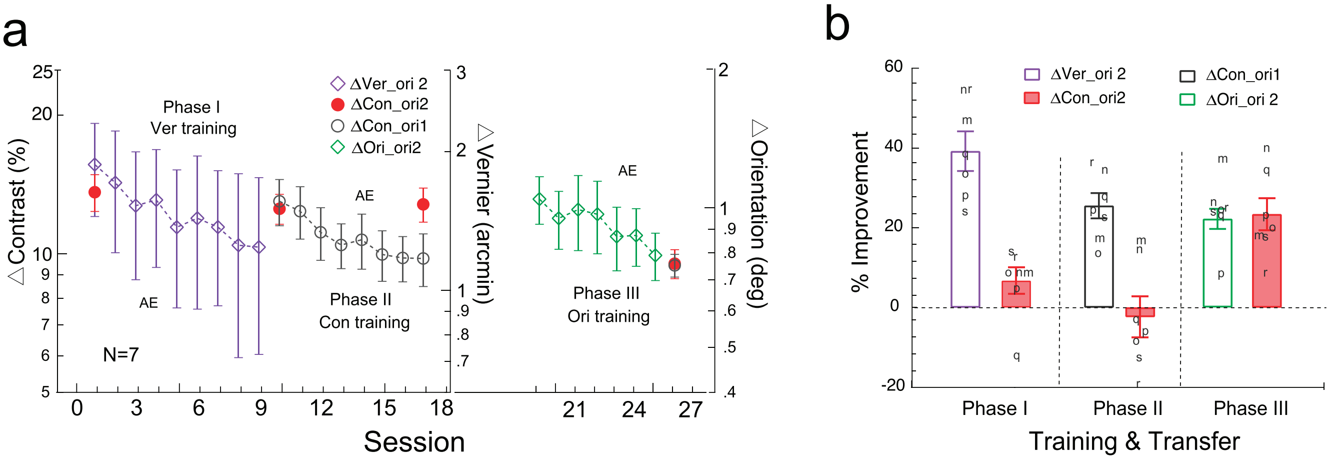

Figure 3. The effect of rTPE and subsequent TPE on learning transfer. (**a**) rTPE (phases I and II) and subsequent TPE (phases II and III). Phase I (sessions 1–9): Observers were exposed to the orthogonal orientation with Vernier training with the amblyopic eyes (ΔVer_ori2, *purple diamonds*, thresholds indicated by the middle ordinate). Contrast discrimination thresholds (left ordinate) at the same orientation (ΔCon_ori2) are shown by the leftmost two *red circles*. Phase II (sessions 10–17): Contrast discrimination was practiced at ori1 (ΔCon_ori1, *gray circles*). The transfer of learning to the orthogonal orientation (ΔCon_ori2) is shown by the middle two *red circles*. Phase III (sessions 19–26): Observers were exposed to the orthogonal orientation again with orientation discrimination training (ΔOri_ori2, *green diamonds*, thresholds indicated by the right ordinate). The impact of orientation exposure on contrast discrimination at the orthogonal orientation (ΔCon_ori2) is shown by the rightmost two *red circles*. (**b**) A summary of training and transfer with rTPE and subsequent TPE.

was 0.81 ± 0.15, not significantly different from TI = 1 ($P = 0.12$). These results indicate that exposing the nonamblyopic eye to an orthogonal orientation can enable the transfer of contrast learning to this orthogonal orientation in the amblyopic eye.

In the TPE procedure described above, training was followed by orthogonal orientation exposure. A third group ($N = 7$) performed reversed-order TPE (rTPE), in which the orthogonal orientation exposure preceded training, to test the order effect of TPE. Specifically, in the initial exposure phase the amblyopic eye was exposed to the orthogonal orientation through Vernier learning (ΔVer_ori2, MPI = 40.4 ± 4.7%, $P < 0.001$; range, 24.3%–55.0%; Fig. 3), which slightly reduced the contrast threshold from 13.7 ± 1.3% to 12.6 ± 1.0% at the same orientation (ΔCon_ori2, MPI = 6.7 ± 3.3%, $P = 0.044$; range, −11.9% to 14.2%). This task specificity thus provided a useful baseline for the TPE results in the first two groups of observers, indicating that the improved contrast performance at the orthogonal orientation was mainly not a result of Vernier or orientation training at the same orthogonal orientation per se. The amblyopic eye then practiced contrast discrimination at the training orientation, which further reduced the contrast threshold from 13.1 ± 1.5% to 9.8 ± 1.3% (ΔCon_ori1, MPI = 25.5 ± 3.2%, $P < 0.001$; range, 13.8%–36.7%). However, this rTPE did not improve contrast performance at the orthogonal orientation (ΔCon_ori2, MPI = −2.4 ± 5.1%, $P = 0.14$; range, −19.1% to 17.0%, TI = −0.09 ± 0.22), similar to the outcome of rTPE in observers with normal vision.[23] In order to better understand this order effect, the amblyopic eye went through a third practice phase in which the orthogonal orientation was exposed again with orientation training (ΔOri_ori2, MPI = 24.3 ± 2.5%, $P < 0.001$; range, 8.7%–37.5%). Here the second and third practice phases together constituted the regular TPE, and contrast learning transferred completely to the orthogonal orientation, where the contrast threshold was reduced from 12.9 ± 1.1% to 9.6 ± 0.7% (ΔCon_ori2, MPI = 23.4 ± 4.1%, $P = 0.001$; range, 8.9%–40.3%), with the overall TI = 0.98 ± 0.15. These order effects indicate that learning has to be established before it can be made transferrable with orthogonal orientation exposure. The order effects also rule out the possibility that the TPE-enabled learning transfer may result from cross talks between neurons tuned to orthogonal orientations in the early visual cortex, even if a temporal delay (i.e., the time gap between training and exposure phases) of such putative cross talks is allowed.

The Transfer of Amblyopic Perceptual Learning Enabled by TPE at a High Spatial Frequency

The results of the first stage of training suggest that perceptual learning in the amblyopic visual system, as in the normal visual system,[23] can transfer completely to an orthogonal orientation once the observer has learned the task and is then exposed to the orthogonal orientation. However, one might argue that since the learning was done at a low spatial frequency, where the amblyopic deficits were small or none, these results might simply reflect normal perceptual learning. In order to assess learning under conditions where there was a substantial loss of visual functions, all 19 observers were given a second TPE at a high spatial frequency (8.2 ± 1.8 cpd, or 0.9 octaves below the cutoff frequency) where the amblyopic deficits were substantial. Among them, 12 observers completed all conditions and the training results below were based on their data. The other seven observers did not complete the exposure phase for various reasons. One observer among the 12 who completed all conditions, and 1 observer among the 7 who did not complete all conditions, did not perform the posttraining contrast sensitivity function test, but all finished visual acuity and stereoacuity tests (see the posttraining statistics later).

Seven observers completed contrast discrimination training at an oblique orientation (45° or 135°) with amblyopic eyes, which reduced the contrast threshold from 17.8 ± 1.8% to 13.5 ± 1.3% (ΔCon_ori1, MPI = 24.1 ± 2.9%, $P < 0.001$; range, 10.1%–32.1%; Fig. 4a). Again contrast learning did not transfer to the orthogonal orientation (ΔCon_ori2, MPI = −0.6 ± 4.6%, $P = 0.45$; range, −16.6% to 18.2%). Their fellow nonamblyopic eyes were then exposed to the orthogonal orientation with Vernier training (ΔVer_ori2, MPI = 29.6 ± 1.0%, $P < 0.001$; range, 25.5%–33.0%). After the TPE, contrast learning transferred significantly to the orthogonal orientation, reducing the contrast threshold from 17.1 ± 1.6% to 14.1 ± 0.9% (ΔCon_ori2, MPI = 16.6 ± 3.1%, $P = 0.001$; range, 4.2%–

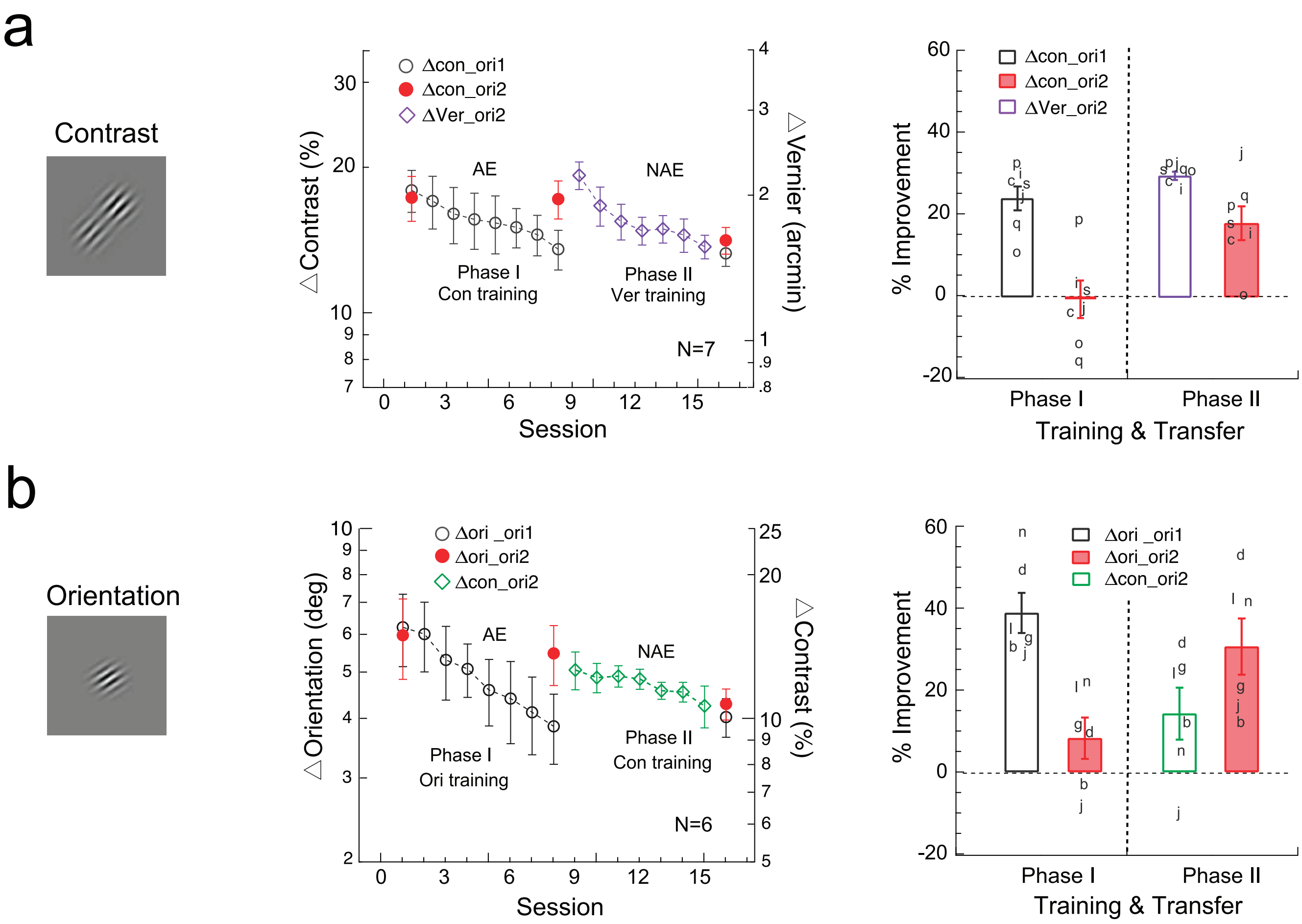

Figure 4. Perceptual learning and its transfer to an orthogonal orientation with TPE at high spatial frequencies. (**a**) *Left*: Oblique stimuli for contrast discrimination. *Middle*: TPE procedure. phase I (sessions 1–8): Observers practiced contrast discrimination using their amblyopic eyes at an oblique orientation (45°/135°, ΔCon_ori1, *gray circles*; contrast thresholds indicated by the left ordinate), and the transfer of learning was tested at an orthogonal orientation (135°/45°, ΔCon_ori2, *red circles*). Phase II (sessions 9–16): Nonamblyopic eyes were exposed to the orthogonal orientation with Vernier training (ΔVer_ori2, *purple diamonds*; thresholds indicated by the right ordinate), and the transfer of contrast learning was remeasured. *Right*: A summary of training and transfer effects with TPE. (**b**) *Left*: Oblique stimuli for orientation discrimination. *Middle*: TPE procedure. Phase I (sessions 1–8): Orientation discrimination was practiced using the amblyopic eyes at an oblique orientation (45°/135°, ΔOri_ori1, *gray circles*; orientation thresholds indicated by the left ordinate) and the transfer of learning was tested at an orthogonal orientation (135°/45°, ΔOri_ori2, *red circles*). Phase II (sessions 9–16): The nonamblyopic eyes were exposed to the orthogonal orientation with contrast training (ΔCon_ori2, *green diamonds*; contrast thresholds indicated by the right ordinate), and the transfer of orientation learning was remeasured. *Right*: A summary of training and transfer effects with TPE. Observer j shown in (**a**, **b**) participated in both experiments.

29.5%). The overall MPI was 18.0 ± 4.1%, with the range 0.1% to 35.5%. The difference between MPIs with trained ΔCon_ori1 and untrained ΔCon_ori2 after the TPE was insignificant ($P = 0.13$, two-tailed paired *t*-test). The overall TI was 0.73 ± 0.19, not significantly different from TI = 1 ($P = 0.11$). Therefore, further TPE at high spatial frequencies continued to enable significant transfer of contrast learning.

Five new observers and one from the experiment described above (Fig. 4a) practiced a new orientation discrimination task with their amblyopic eyes, which reduced the orientation threshold at the trained orientation (36°/126°) from 6.2° ± 1.1° to 3.8° ± 0.6° (ΔOri_ori1, MPI = 38.8 ± 4.9%, $P = 0.001$; range, 28.6%–58.3%; Fig. 4b). Learning showed similar orientation specificity, with no significant transfer to the orthogonal orientation (ΔOri_ori2, MPI = 8.3 ± 5.1%, $P = 0.44$; range, –8.9% to 21.6%). However, additional exposure of the orthogonal orientation through irrelevant contrast training with the fellow nonamblyopic eyes (ΔCon_ori2, MPI = 14.2 ± 6.3%, $P = 0.038$; range, –10.6% to 31.1%) resulted in orientation learning transfer to the orthogonal orientation (ΔOri_ori2, orientation threshold changed from 5.5° ± 0.8° to 4.3° ± 0.3°, MPI = 24.7 ± 5.3%, $P = 0.003$; range, 10.6%–47.9%). The overall MPI was 30.6 ± 6.9%, range was 11.6% to 52.7%, and TI was 0.76 ± 0.13. Again the difference between MPIs with trained ΔOri_ori1 and untrained ΔOri_ori2 was insignificant ($P = 0.18$, two-tailed paired *t*-test). These results indicate that the TPE-enabled transfer of learning in amblyopia is not limited to contrast learning and may not be a task-specific effect.

The Impact of TPE on Contrast Sensitivity, Visual Acuity, and Stereoacuity

Contrast Sensitivity Functions. The contrast sensitivity functions measured before training showed the well-documented loss of contrast sensitivity in the amblyopic eyes, mainly at high spatial frequencies[28,29] (Fig. 5a). The mean cutoff spatial frequency of the amblyopic eyes determined with grating acuity measurements was 15.3 ± 1.0 cpd, lower than

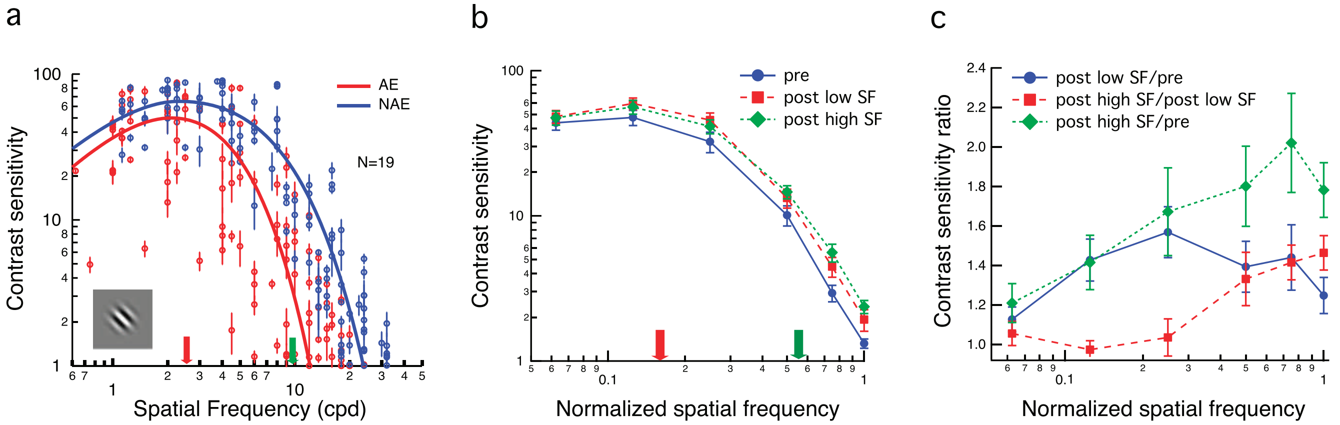

Figure 5. The impact of TPE on contrast sensitivity functions in amblyopic eyes. (**a**) The mean contrast sensitivity functions of the amblyopic eyes (AE; *red curve*) and nonamblyopic eyes (NAE; *blue curve*) prior to training, along with individual data points. Each curve is the best fitting Difference-of-Gaussian 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. The arrows on the *x*-axis indicate the mean low (*red*) and high (*green*) spatial frequencies used in the first and second stages of training. (**b**) The mean contrast sensitivity functions pretraining, post low-spatial frequency training, and post high-spatial frequency training. The arrows on the *x*-axis indicate the normalized mean low (*red*) and high (*green*) spatial frequencies used in the first and second stages of training. Stimulus spatial frequencies were normalized by the cutoff spatial frequency. (**c**) The ratios of the three curves shown in panel (**b**).

the mean cutoff spatial frequency of the fellow nonamblyopic eyes at 24.9 ± 1.2 cpd ($P < 0.001$).

Figure 5b shows the amblyopic eyes' contrast sensitivity functions before training and after each stage of TPE with the stimulus spatial frequencies normalized by the cutoff spatial frequency. The impact of each stage of training can be seen more clearly in Figure 5c that shows the ratios of the three pre- and posttraining contrast sensitivity functions. A repeated-measures ANOVA analysis compared the contrast sensitivities at six normalized spatial frequencies before training (Fig. 5b, blue curve) and after the first stage of TPE (Fig. 5b, red curve). The results showed a significant main effect of training ($F_{1,18} = 14.93$, $P = 0.001$), suggesting significantly improved contrast sensitivity functions in the amblyopic eyes. There was also a significant interaction between training and spatial frequency ($F_{5,90} = 7.36$, $P < 0.001$). These effects can be better appreciated in Figure 5c (blue curve) in that there was an overall improvement of the contrast sensitivity function over a broad range of spatial frequencies, with slightly greater gains near the trained spatial frequency. This is similar to previous reports that perceptual learning improves a broad range of spatial frequencies in adult amblyopic eyes.[5,30,31] The effects of subsequent TPE at a high spatial frequency were analyzed with three lower spatial frequencies and three higher ones, respectively. A repeated-measures ANOVA analysis compared the contrast sensitivities at three lower spatial frequencies after the first and second stages of TPE (Fig. 5b, the left three datum points in red and green curves, respectively), which showed no significant main effect of training ($F_{1,16} = 0.55$, $P = 0.47$). However, the same comparison of contrast sensitivities at three higher spatial frequencies including the cutoff frequency (Fig. 5b, the right three datum points in red and green curves, respectively) showed a significant main effect of training ($F_{1,16} = 9.54$, $P = 0.007$), suggesting further improvement in contrast sensitivity at higher spatial frequencies. Overall, the TPE improved the contrast sensitivity function significantly, with the most prominent effects on high spatial frequencies near the cutoff frequency (Fig. 5c, green curve).

Visual Acuity. After the first stage of TPE at a low spatial frequency (30–45 hours), the visual acuity of amblyopic eyes improved significantly. The single-E acuity was improved from 16.2 ± 1.9 arcmin to 13.1 ± 1.5 arcmin (MPI = 16.7 ± 3.2%, $P < 0.001$; Fig. 6a, red dots), and the crowded-E acuity was improved from 24.0 ± 4.8 arcmin to 19.5 ± 3.8 arcmin (MPI = 15.1 ± 3.2%, $P < 0.001$; Fig. 6b, red dots). After the second stage of TPE at a high spatial frequency (15 hours), the single-E acuity and crowded-E acuity were further improved to 10.7 ± 0.9 arcmin (MPI = 14.9 ± 2.8%, $P < 0.001$) and 15.6 ± 2.6 arcmin (MPI = 14.5 ± 2.9%, $P < 0.001$), with overall improvements by 29.0 ± 3.8% (range, −13.8% to 52.8%) and 27.0 ± 4.0% (range, −11.5% to 69.4%), respectively (Figs. 6a, 6b, green dots). Both improvements were approximately equivalent to 1.6 lines on a visual acuity chart. There was no difference of acuity improvement between the 12 anisometropic amblyopes and the seven strabismic or anisometropic/strabismic amblyopes ($P = 0.62$, two-tailed two-sample *t*-test). The overall visual acuity improvement obtained with the clinical E acuity chart was similar at 1.5 ± 0.2 lines. Additionally, the single- and crowded-E acuities improved by an average of 8.4 ± 2.0% (0.4 lines) in the nonamblyopic eyes. The crowded-E acuity was lower than the single-E acuity in both pre- and posttraining conditions ($F_{1,18} = 6.37$, $P = 0.021$), and there was no significant interaction between training and acuity type, suggesting that training did not significantly reduce crowding ($F_{1,18} = 3.56$, $P = 0.075$).

The initial single-E acuity and crowded-E acuity improvements after low spatial frequency TPE were not significantly correlated with the pretraining acuity level ($r = 0.33$, $P = 0.19$ and $r = 0.40$, $P = 0.09$, respectively). However, the acuity improvements following the subsequent high spatial frequency TPE were significantly correlated with the pretraining acuity level ($r = 0.65$, $P = 0.003$ and $r = 0.69$, $P = 0.001$, respectively). That is, those with deeper amblyopia gained greater improvement of visual acuity. In addition, there was a marginally significant effect of previous patching treatment. The acuity improved by 24.1% in observers ($n = 8$) who had been previously patched, less than the 35.4% in those ($n = 11$) who had not ($P = 0.053$, one-tailed two-sample *t*-test), similar to the report in an earlier study.[6]

Stereoacuity. Stereoacuity improved from 415.3 ± 44.1 arcsec to 244.2 ± 32.3 arcsec (MPI = 39.2 ± 5.2%, $P < 0.001$) after the initial low spatial frequency TPE, and further to 190.0

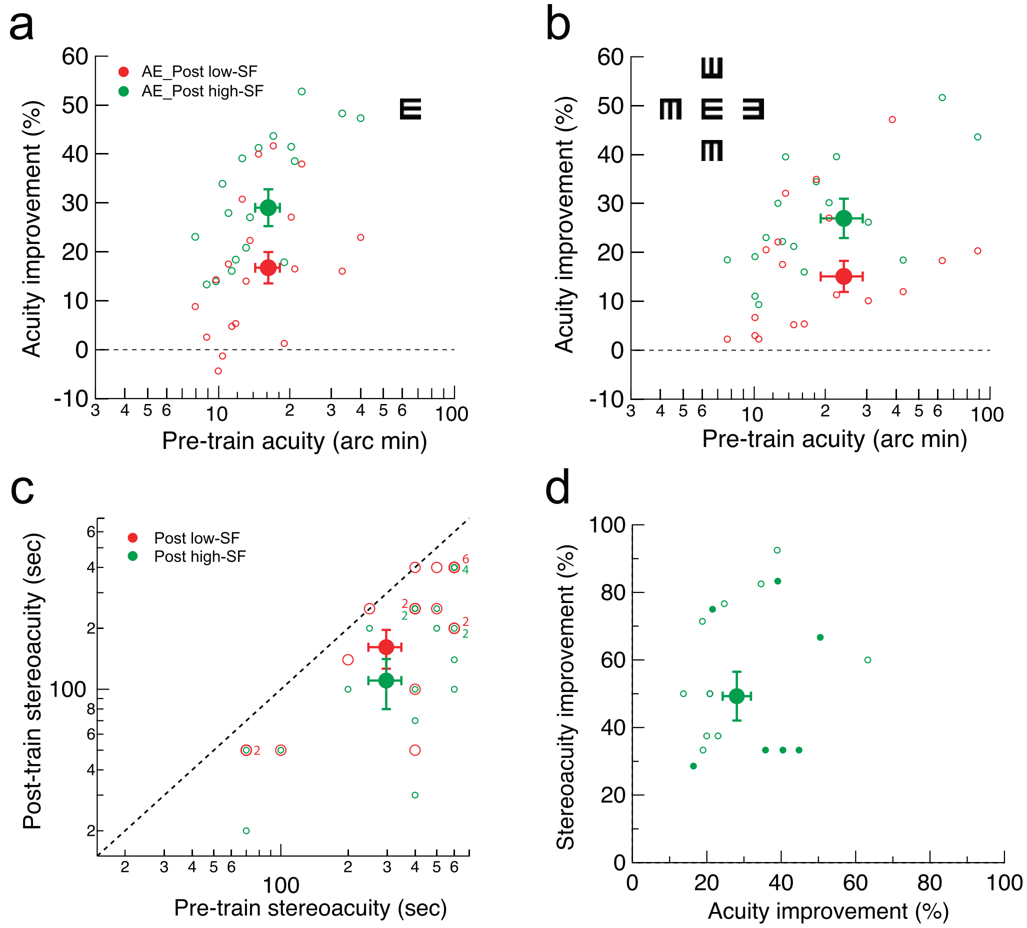

FIGURE 6. The impact of TPE on visual acuity and stereoacuity. (**a**, **b**) Single- and crowded-E acuity improvements after initial low spatial frequency and later high spatial frequency training plotted against the pretraining acuity. The larger dots show the mean improvements at the mean pretraining acuity level. (**c**) Stereoacuity after initial low spatial frequency and later high spatial frequency training plotted against the pretraining stereoacuity level. Each colored digit indicates the number of overlapping data points after one round of TPE. (**d**) The stereoacuity improvement plotted against acuity improvement (averaged over single and crowded-E acuity improvements) after two rounds of training. The small *solid dots* represent the data of amblyopes who were stereoblind pretraining.

± 30.7 arcsec (MPI = 22.8% ± 5.8%, $P < 0.001$) after the subsequent high spatial frequency TPE. The total improvement was 53.4% ± 5.1%, with a range of 20.0% to 92.5% (Figs. 6c, 6d). Note that in Figure 6c, and for the data analysis, when observers were initially stereoblind (unable to see stereopsis at the largest test disparity at 500 arcsec), we arbitrarily designated their stereoacuity to be 600 arcsec. All seven stereoblind observers showed measureable stereoacuity after training. The 12 anisometropic amblyopes and the 7 strabismic or anisometropic/strabismic amblyopes showed similar stereoacuity improvement after the first stage of training (40.5 ± 8.3% vs. 36.9 ± 2.3%, $P = 0.75$). But after the second stage of training, the anisometropic amblyopes showed more additional improvement than did the strabismic or anisometropic/strabismic amblyopes (32.0 ± 7.1% vs. 7.1 ± 7.1%, $P = 0.034$, two-tailed two-sample t-test). The improvement in stereoacuity was not significantly correlated with the pretraining stereoacuity level ($r = 0.085$, $P = 0.73$), even excluding those who were stereoblind pretraining ($r = 0.32$, $P = 0.35$, $n = 11$) since we did not know their actual improvement. The stereoacuity improvement was also not significantly correlated with the averaged single- and crowded-E acuity improvement ($r = 0.38$, $P = 0.11$), but the correlation became marginally significant when those who were stereoblind pretraining were excluded from data analysis ($r = 0.59$, $P = 0.056$, $n = 11$).

DISCUSSION

In this study we demonstrate that perceptual learning in adults with amblyopia can be rendered significantly and sometimes completely transferrable to an orthogonal orientation with TPE. Moreover, the rTPE suggests that the observers must first learn a task before the learning can be enabled to transfer to an orthogonal orientation through exposure. We have previously reported similar TPE and rTPE results in normal foveal vision with orientation discrimination learning.[23] Therefore, perceptual learning in amblyopia appears to be no different from normal perceptual learning in these aspects, even at high spatial frequencies at which amblyopic deficits are most prominent.

Previous studies have attributed amblyopic perceptual learning, like normal perceptual learning, to low-level neural plasticity in the early visual cortex,[2,3] or to more efficient use of the stimulus information through response reweighting.[19,20] These explanations are either inspired or constrained by the specificity of perceptual learning. However, the complete learning transfer enabled with TPE does not favor the early cortical plasticity explanation because neurons belonging to orthogonal orientation channels in the early visual cortex rarely connect to each other. The rTPE data, which shows that learning must precede exposure in order for transfer to occur, also rule out the roles of cross talks between these orthogonal neurons even if such putative cross talks exist.

The complete learning transfer rather favors a higher-level learning process that is more general and versatile than simple response reweighting. Indeed, reweighting of specific orientation signals would make learning more specific, rather than less so.[22] Therefore, amblyopic perceptual learning, just like normal perceptual learning, is more likely a rule-based cognitive learning process.[23] In the amblyopic perceptual learning case the brain learns the rules to reweight the noisy visual inputs due to amblyopia. These general rules can be applied to other orientations with proper training procedures to enable learning transfer, so as to compensate the deficits of the amblyopic visual system.

An important outcome of the training, consistent with many previous studies of perceptual learning in amblyopia,[7,8] is the transfer of improvement to untrained tasks: contrast sensitivity, visual acuity, and stereoacuity. Our results show that TPE improved contrast sensitivity in the amblyopic eyes. The initial low spatial frequency training resulted in an improvement over a broad range of spatial frequencies, consistent with previous reports.[5,30] However, the further improvement achieved through the subsequent high spatial frequency training was limited to the trained and nearby high frequencies (Fig. 5). Interestingly, Huang et al.[5] reported a broad bandwidth of improvement after training their observers to detect a high spatial frequency grating (near the cutoff spatial frequency of the amblyopic eye). Together these results suggest a broad improvement through either low or high spatial frequency training. However, on top of this broad improvement, subsequent training at high spatial frequencies can further improve the sensitivities of the high spatial frequency channels, where amblyopic visual deficits are most pronounced. Similarly, visual acuity improvement after the initial low spatial frequency training is uncorrelated with pretraining acuity, but the overall improvement after the subsequent high spatial frequency training is strongly correlated with pretraining acuity (Figs. 6a, 6b). Like contrast sensitivity, the acuity improvement appears to be a broad learning effect initially, and then a high spatial frequency specific effect.

Our study may have important clinical implications. Perceptual learning has not yet entered clinical practice for the treatment of amblyopia. One of the main reasons is the well-known "curse" of specificity. Our TPE results point to important principles in the design of perceptual learning as a treatment that can readily generalize, and we show that some of the burden can be borne by the fellow nonamblyopic eye.

SUMMARY

We demonstrated that perceptual learning of various visual discrimination tasks in adults with amblyopia can transfer completely to an untrained orthogonal orientation with TPE. These results suggest that perceptual learning improves amblyopic vision, at least in large measure, through high-level cognitive compensation, rather than through early plasticity in the amblyopic visual brain.

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