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Purpose

ethods. 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

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$^{\Delta}$ 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$^{\Delta}$ ExoT	Aniso and Strab	No
			L: +2.50	20/80			
e	27	M	R: −0.25/−0.50 × 75	20/20	L 25$^{\Delta}$ EsoT	Strab	Yes
			L: +0.75/−0.25 × 165	20/167			
f	23	F	R: −2.00/−0.50 × 90	20/20	L 30$^{\Delta}$ 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$^{\Delta}$ 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$^{\Delta}$ 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$^{\Delta}$ 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

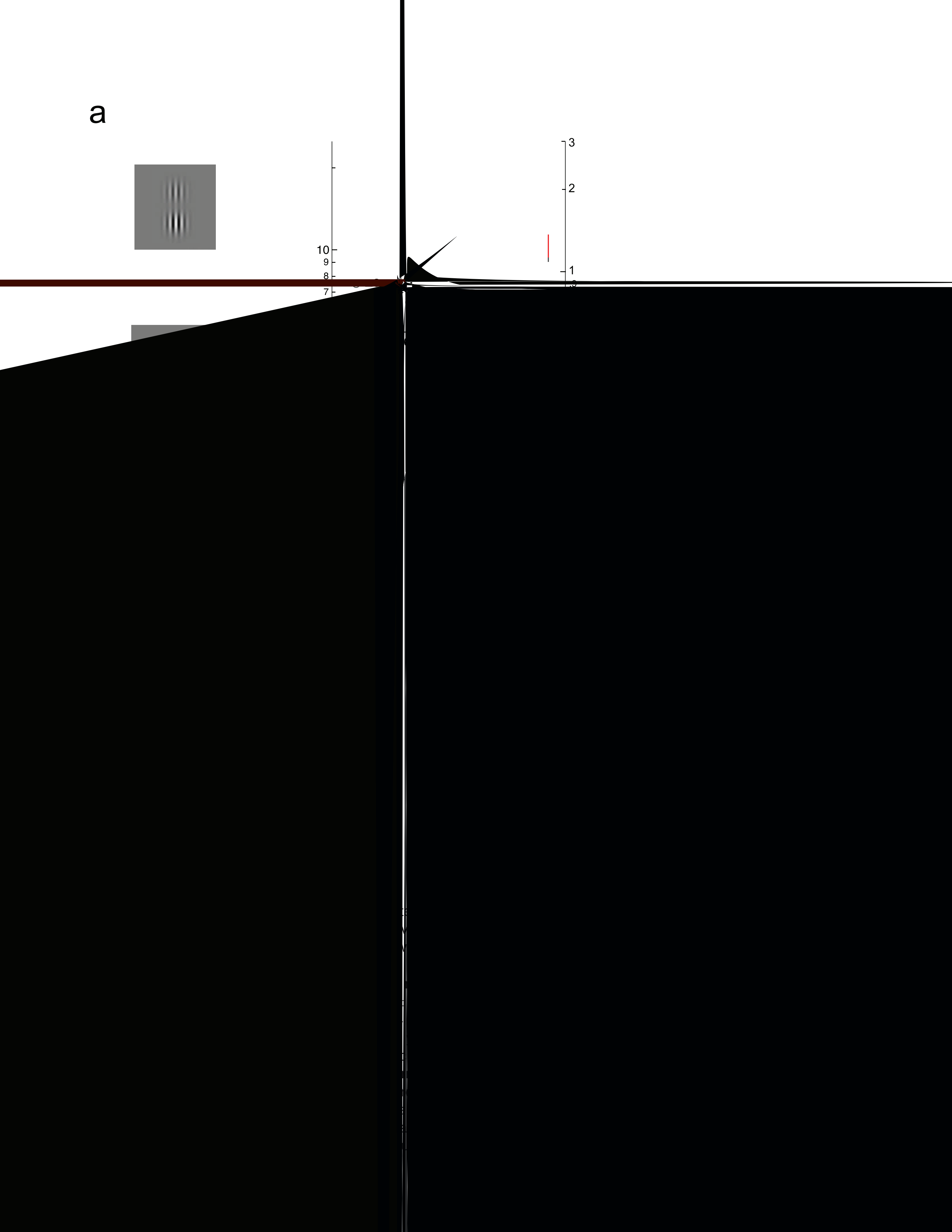
The stimuli were generated by a Matlab-based WinVis program (Neurometrics Institute, Oakland, CA, USA) and were presented on a 21-inch Sony G520 color monitor (Sony, Tokyo, Japan; for contrast, Vernier and orientation tasks: 2048 pixel × 1536 pixel, 0.19 mm × 0.19 mm per pixel, 75 Hz frame rate; for 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.

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)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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 counter-clockwise 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); $PI = 100\% \times (Th_{post} - Th_{pre})/Th_{pre}$, in which Th_{pre} stood for pretraining threshold, and Th_{post} stood for posttraining threshold.

A transfer index (TI) defined by $TI = MPI_{transfer}/MPI_{trained}$ was used to compare the transfer of learning among different training conditions, in which MPI stood for mean percent improvement; TI = 1 indicated complete transfer, and 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 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 a

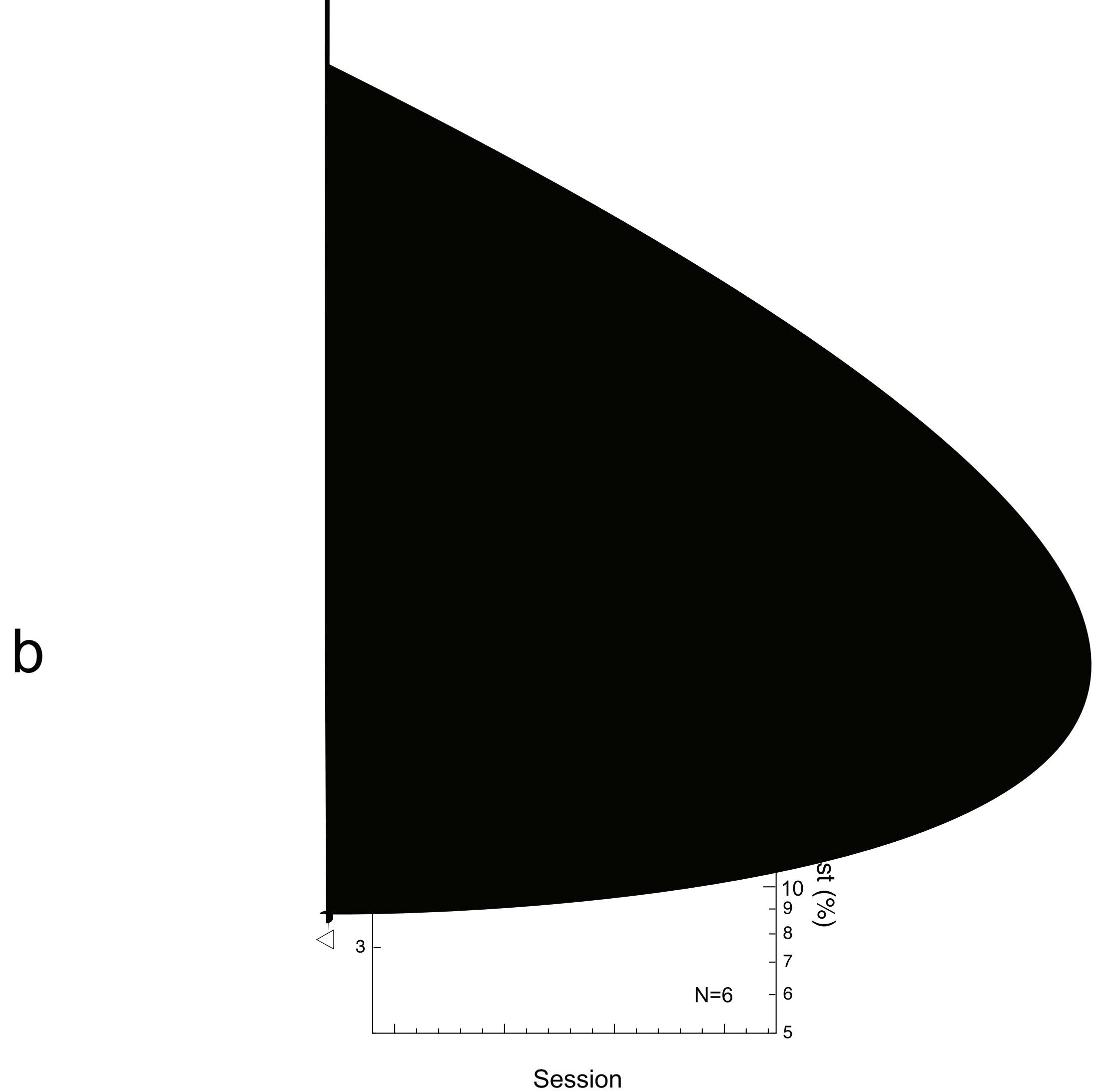
was 0.81 ± 0.15, not significantly different from TI = 1 (P = 0.12). These results indicate that exposing the nonamblyopic eye to an orthogonal orientation can enable the transfer of contrast learning to this orthogonal orientation in the amblyopic eye.

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%–



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 the mean cutoff spatial frequency of the fellow nonamblyopic eyes at 24.9 $\pm$ 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

$\pm$ 30.7 arcsec (MPI

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.

Summar

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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