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Dichoptic training in adults with amblyopia: Additional stereoacuity gains over monocular training

1. Introduction

Amblyopia is a developmental visual disorder that often results from imbalanced binocular visual inputs due to anisometropia, strabismus, or form deprivation (Holmes & Clarke, 2006). It is the most common cause of vision loss in infants and young children, with an estimated prevalence of 3% in the population (Webber & Wood, 2005). Amblyopia is thought to reflect alternations in the properties of neurons in early visual areas (Chino, Bi, & Zhang, 2004; Kiorpes, 2006). As a result, visual acuity and stereoacuity, along with many other visual functions, are compromised. Although amblyopia is commonly treated before the children reach an age of six to seven years old when the visual cortical development is still within the sensitive period, not everyone responds to the treatment and regains normal visual acuity. Therefore, many adults with amblyopia have to live with impaired visual acuity and stereopsis.

Repetitive practice can improve performance of various visual tasks in adults and juvenile with amblyopia (Chung, Li, & Levi, 2006; Levi & Polat, 1996; Li & Levi, 2004; Liu, Zhang, Jia, Wang, & Yu, 2011; Polat, Ma-Naim, Belkin, & Sagi, 2004; Zhang, Cong, Klein, Levi, & Yu, 2014; Zhou et al., 2006). Learning also generalizes with a variable success to visual acuity and stereopsis (see Levi, Knill, and Bavelier (2015) for a comprehensive review). In a recent report, of which the current study is a follow-up, we found that extended (60 h) monocular training of contrast, orientation, and Vernier discrimination tasks improved amblyopic eye visual acuity by 28% (1.6 lines in a visual acuity chart) and stereoacuity by 53% improvement in 19 adult amblyopic participants (Zhang et al., 2014).

In typical perceptual learning experiments involving participants with amblyopia, training is monocular in the amblyopic eyes while the fellow eyes are covered. Nevertheless, the amblyopic eyes are actively inhibited by the dominant non-amblyopic eyes (Baker, Meese, Mansouri, & Hess, 2007; Huang, Zhou, Lu, & Zhou, 2011; Mansouri, Thompson, & Hess, 2008). This interocular suppression is not directly targeted by monocular training. A number of recent studies trained adult amblyopic participants with dichoptic stimuli and reported that dichoptic training also improves visual acuity and stereoacuity (Astle, McGraw, & Webb, 2011; Ding & Levi, 2011; Hess, Mansouri, & Thompson, 2010a, 2010b; Li et al., 2013; Ooi, Su, Natale, & He, 2013; Xi, Jia, Feng, Lu, & Huang, 2014). The effectiveness of dichoptic training is also evident in animal experiments. Murphy, Roumeliotis, Williams, Beston, and Jones (2015) found that after monocular deprivation, visual recovery was promoted by binocular training of detection of orientation signals imbedded in noise. Moreover, binocular

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training was still effective when it started after the peak of the critical period for ocular dominance plasticity in the visual cortex.

Regardless of these interesting findings, it is important to investigate whether dichoptic training has any advantage over conventional monocular perceptual learning in improving adult amblyopic vision, for both theoretical and practical considerations. In the current study, we designed a dichoptic de-masking training method (Fig. 1a) and applied it to a group of monocularly well-practiced adult amblyopic participants. These amblyopic participants had completed prolonged monocular training (60 h) with various visual tasks, and their visual acuity in the amblyopic eyes and stereoacuity had been significantly improved and mostly saturated (Zhang et al., 2014). We were particularly interested in whether additional dichoptic training could translate to additional gains in visual acuity and stereoacuity, two common clinical measures to evaluate monocular and binocular vision.

2. Method

2.1. Participants

Thirteen amblyopic participants (9 anisometropic, 1 strabismic, and 3 mixed) aged 21–29 years (mean = 24 yrs) participated in the study (Table 1). They were among 19 amblyopic participants who completed prolonged monocular contrast, orientation and Vernier training for 30 sessions (60 h) in our previous study (Zhang et al., 2014). Three of the remaining six amblyopic participants were unable to align the nonius lines due to large angle strabismus, and the other three could not come due to time constraints. The study followed the tenets of the Declaration of Helsinki and was approved by the IRB of Peking University. Written consent was obtained from each participant before training.

During previous monocular training the visual acuity of these 13 amblyopic eyes was improved by 18.5 ± 4.3% (0.8 logMAR unit), 21 ± 4.4% (0.9 logMAR unit), and 26% ± 4.7% (1.3 logMAR unit) by the 10th, 20th, and 30th (last) session, respectively (replotted in Fig. 2a). There was no significant visual acuity change from the 20th to the 30th session ($t_{12} = 1.39$, $p = 0.19$). Individually only three participants (S2, S11, S13) showed visual acuity improvement from the 20th to 30th session. The stereoacuity was improved by 39.1% ± 4.6%, 46.8 ± 5%, and 54.6% ± 5.6% by the 10th, 20th, and 30th session (replotted in Fig. 2b). There was no significant change from the 20th to the 30th session either ($t_{12} = -1.92$, $p = 0.08$). Individually only four participants (S1, S5, S7, S9) showed stereoacuity improvement from the 20th to 30th session. These results suggested that the monocular training had largely saturated the visual acuity and stereoacuity.

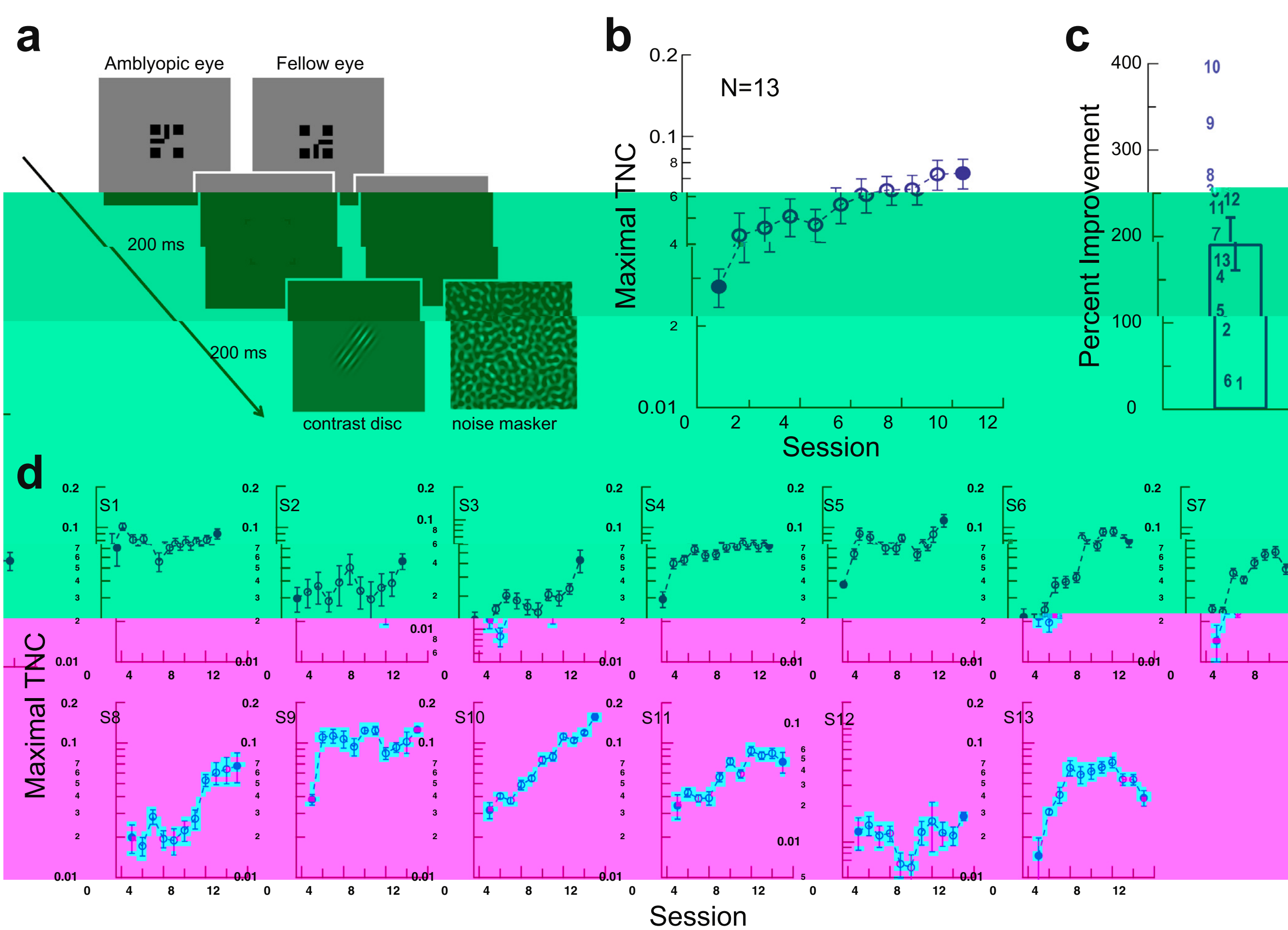
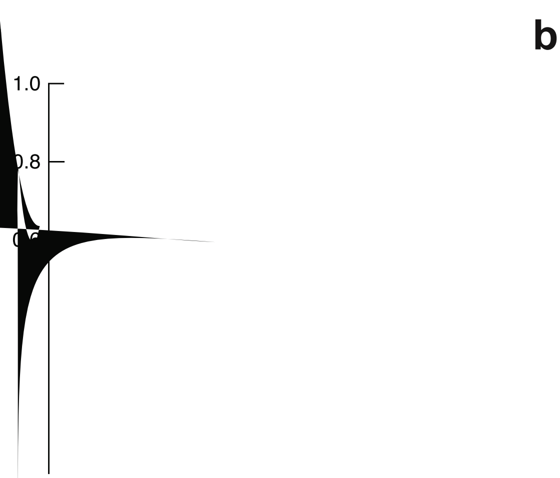


Fig. 1. The effect of dichoptic training on maximal tolerable noise contrast for the amblyopic eyes to perform a contrast discrimination task after prolonged monocular training. (a) The dichoptic training paradigm. From top-left to bottom-right: Binocular fusion was first achieved with the help of two assisting half-crosses. A cue was then presented for 200 ms to prime the amblyopic eye. After that a pair of Gabors were presented to amblyopic eye for another 200 ms while a bandpass noise masker was presented to fellow eye at the same time. Participants judged which Gabor had higher contrast. (b) Session by session changes of maximal tolerable noise contrast (TNC) for successful contrast discrimination as a result of dichoptic training averaged over all amblyopic participants. Solid circle represent performance tested in the pre- and post-training session. Open circles represent performance tested in the training sessions. (c) Mean and individual percent improvement of performance. Each digit indicates a different participant. (d). Individual learning curves. Error bars representing one standard error of the mean.

s of amblyopic participants.

e (y)	Gender	Type of amblyopia	Strabismus (Dist)	Eye	Refractive Error	Visual Acuity (log MAR)			Stereoacuity (arcsec)		
						PreMono	PostMono	PostDicho	PreMono	PostMono	PostDicho
	F	A	None	AE (R)	+2.25	0.301	0.222	0.222	70	20	20
				FE (L)	−3.00/+0.75 × 60	0.000	0.000	0.000			
	F	A	None	AE (L)	+5.00/−1.25 × 10	0.602	0.301	0.301	F	100	100
				FE (R)	−0.25	−0.079	−0.176	−0.176			
	F	A	None	AE (R)	+4.50/+0.50 × 100	0.222	0.097	0.097	100	50	40
				FE (L)	−0.25	0.000	−0.079	−0.079			
	M	A	None	AE (L)	+5.00/−0.50 × 170	0.301	0.222	0.222	400	70	40
				FE (R)	+2.00	0.000	0.000	0.000			
	F	A	None	AE (L)	Plano	0.301	0.301	0.301	200	100	30
				FE (R)	+2.00	0.000	0.000	0.000			
	M	A	None	AE (L)	+1.50	0.301	0.222	0.222	70	50	30
				FE (R)	−2.75	−0.079	−0.176	−0.176			
	M	A	None	AE (L)	+1.00/−1.00 × 10	0.301	0.301	0.301	200	70	70
				FE (R)	−2.75	0.000	0.000	−0.079			
	M	A	None	AE (R)	+4.50	0.824	0.602	0.602	400	200	200
				FE (L)	Plano	−0.079	−0.079	−0.079			
	F	A	None	AE (L)	−4.50/−1.25 × 150	0.398	0.301	0.301	F	100	70
				FE (R)	−1.00/−1.25 × 45	0.097	0.097	0.097			
	F	A & S	R 19Δ EsoT	AE (L)	+3.00	0.824	0.602	0.602	F	400	250
				FE (R)	Plano	−0.079	−0.176	−0.176			
	M	S	R 20Δ ExoT	AE (R)	−4.00/+0.75 × 110	0.523	0.301	0.301	400	250	140
				FE (L)	−4.00/+0.75 × 80	−0.079	−0.079	−0.079			
	M	A & S	L 15Δ ExoT	AE (L)	+2.50	0.602	0.398	0.398	400	250	100
				FE (R)	Plano	−0.176	−0.176	−0.176			
	M	A & S	L 25Δ EsoT	AE (L)	+0.75/−0.25 × 165	0.824	0.699	0.699	400	250	250
				FE (R)	−0.25/−0.50 × 75	0.000	−0.079	−0.079			

amblyopia: A, anisometropic; S, strabismic. Strabismus: ExoT, exotropia; EsoT, esotropia; Δ, prism diopters. Eye: AE, amblyopic eye; FE, fellow eye. (unable to see stereopsis at the largest test disparity at 500 arcsec). PreMono: pre-monocular training; PostMono: post-monocular training; PostDicho: g.



2.2. Apparatus and stimuli

The stimuli were generated by a Matlab-based WinVis program (Neurometrics Institute, Oakland, CA) and presented on a 21-in. Sony G520 CRT monitor (2048 pixel × 1536 pixel, 0.19 mm × 0.19 mm per pixel, 75 Hz frame rate, 58.2 cd/m^2 mean luminance). The head of the participant was stabilized by a chin-and-head rest. Experiments were run in a dimly lit room.

The dichoptic stimuli (Fig. 1a) consisted of a pair of aligned Gabors (Gaussian windowed sinusoidal gratings) presented in the amblyopic eye and a band-pass filtered white noise masker in the non-amblyopic fellow eye. The two Gabors had the same spatial frequency at 40% of the amblyopic eye cutoff frequency, standard deviation at one wavelength (the reciprocal of spatial frequency), orientation at 45° or 135° (counter-balanced across participants), phase at 90°, and a center-to-center distance of 4 wavelengths. The cutoff frequency of the amblyopic eye (Mean = 16.4 cpd, SD = 3.6 cpd) was assessed in advance by a grating acuity task for each participant. The viewing distance was 1.2 m. For contrast discrimination trials, one Gabor's contrast was set at 0.80, and the other Gabor's contrast at 0.80–1.414 times the contrast discrimination threshold (pre-measured when no masker was presented in the fellow eye). The mean contrast discrimination threshold was 16.2% (SE = 1.5%).

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

2.3. Procedures

In the dichoptic training task, a trial began with binocular-fusion of two half-crosses (contrast 100%), each with four assisting squares, to align the two eyes in a 4-mirror stereoscope (Fig. 1a). 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 participants whose visual acuity difference between the two eyes was greater than 4 lines, the contrast of the half cross and four assisting squares in the fellow eye was reduced to 60% to facilitate binocular fusion. The participant pressed the space bar to initiate the trial as soon as the whole cross appeared stable. Immediately after the key press, a 1.5° × 1.5° black empty square (edge width = 2 arcmin, Fig. 1a) was presented for 200 ms to prime attention to the amblyopic eye. After that the Gabor stimuli and the noise masker were presented dichoptically for 200 ms.

During training the participants were asked to judge which Gabor had a higher contrast with key press. A staircase varied the root mean square contrast of the noise masker following a 3-up-1-down rule that resulted in a 79.4% convergence rate. The step size of the staircase was 0.05 log units. Each staircase consisted of 8 reversals (approximately 40–50 trials). The geometric mean of the last 6 reversals was taken as the maximal tolerable noise contrast for successful contrast discrimination.

To ensure that the participants did not close the fellow eye when seeing the stimuli, in 20% of the trials a white digit ("1" or "2", 1.1° × 1.7° in size) was centered in the noise masker in the fellow eye while a blank screen was presented in the amblyopic eye. The participants needed to report the digit by key press (the mean correct rate = 98.0 ± 0.3%). Auditory feedback was given on incorrect responses in all trials.

The pre- and post-training performance was measured for five staircases (approximately 200–250 trials). Each of nine training sessions consisted of 20 staircases (800–1000 trials) and lasted for approximately 2 h on a single day. More details can be found in the Results section below.

2.4. Visual acuity assessments

All participants were refracted with a Snellen E light box at the designated viewing distance of 5 m before and after training (results are summarized in Table 1 and Fig. 2a).

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 the tumbling E target was 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 since 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 amblyopic eye cut-off spatial frequency. The stimulus was 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.

For visual acuity measurements the stimuli were presented for an unlimited time until a key press. The participant judged the orientation of the tumbling E target: left, right, up, or down. A single-interval staircase varied the letter size (width) following a 3-down-1-up rule with 0.03 log units step size. For grating acuity measurement the task was to judge whether the grating tilted toward to the left or right from vertical, while a staircase varied the spatial frequency of the grating following a 3-up-1-down rule with a 0.05 log units step size. Each staircase consisted of 8 reversals, with the geometric mean of the last 6 reversals taken as the visual acuity or grating acuity (cut-off spatial frequency).

2.5. Stereoacuity assessments

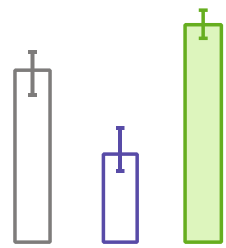
The stereoacuity was tested with the Randot Stereo Test (Stereo Optical Co, Inc, Chicago, IL) under normal room lighting. Contoured circles at ten levels of disparity ranging from 400 to 20 arcsec provide a graded sequence for testing. In addition, Randot Forms with disparities at 500 and 250 arcsec were also used to provide additional steps of disparity. Participants wore polarizing glasses and looked at the test material at a viewing distance of 40 cm. Lighting level was kept the same across tests. Note that in Figs. 2 and 3, 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.

3. Results

The dichoptic training started one month after the previous monocular training ended. During dichoptic training, the amblyopic eye performed contrast discrimination under dichoptic noise masking from the fellow eye (Fig. 1a). After nine sessions (18 h) of training, the maximal tolerable noise contrast was significantly improved by 191.4 ± 30.5% after training (t_{12} = 6.278, $p < 0.001$, Cohen's d = 1.74), from 0.028 ± 0.004 to 0.076 ± 0.011 (Fig. 1b, c). These amblyopic participants thus were significantly more capable of discounting dichoptic noise masking after training.

Fig. 2 plotted the individual visual acuity and stereoacuity data measured during previous monocular training and current dichoptic training. The visual acuity and stereoacuity increased slightly in a few participants before dichoptic training from the end of monocular training. To be conservative, the dichoptic training effects were assessed using data at the end of monocular training as baselines. Fig. 2 shows after dichoptic training stereoacuity was improved in more than half of the participants but visual acuity was improved in only one participant. Here the stereoacuity gains were all from those who did not show stereoacuity improvements from the 20th to 30th session during previous monocular training. The four participants (S1, S5, S7, S9) who did show improvements from the 20th to 30th session previously had no more stereoacuity gain. Therefore, the current stereoacuity gains were most likely a result of further dichoptic training, rather than a result of remaining potentials of improvement not completely saturated by previous monocular training.

Confirming these observations, on the average the dichoptic training improved stereoacuity from 146.9″ ± 31.2″ to 103.1″ ± 22.9″ (Fig. 3a). This amounted to a 26.5% ± 6.9% improvement (t_{12} = 3.83, $p = 0.002$, Cohen's d = 1.1; Fig. 3b) on top of the 54.6% ± 5.6% gain from previous monocular training. The total improvement was 68.2% ± 4.4% (t_{12} = 15.47, $p < 0.001$, Cohen's d = 4.29). On the average, the stereoacuity improvement was 1.14 octaves after previous monocular training, which



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135 min in total) of monocular contrast training, further nine 10-min sessions (90 min in total) dichoptic disparity training (detecting depth in random dot stereograms) produced additional improvement in stereoacuity, but not in visual acuity. Although the results of Astle et al. (2011) appear similar to ours, the scarce number of participants (N = 2) makes it difficult to draw any statistically meaningful conclusion. Moreover, the initial monocular training of Astle et al. (2011) may not saturate the stereoacuity improvement due to the limited number of training time. It may take 10–14 h to saturate a visual function in normals, and more hours in amblyopes (Li, Klein, & Levi, 2008). In contrast, significantly more training time (60 h, approximately 48,000 trials) were involved in monocular training preceding the current dichoptic training study.

Our results show substantial perceptual learning of discounting dichoptic noise masking with a contrast discrimination task (Fig. 1). Like in normals, perceptual learning is often specific to the trained orientation in amblyopic participants. Such orientation specificity has been attributed to training induced neural plasticity in the amblyopic early visual areas that are most orientation selective (Levi & Polat, 1996; Li, Levi, & Klein, 2004). However, neurophysiological evidence for V1 plasticity with perceptual learning is mixed at best. Schoups, Vogels, Qian, and Orban (2001) reported that monkey orientation learning accompanies with steeper V1 orientation tuning functions, but the same changes were not repeated by Ghose, Yang, and Maunsell (2002) in either V1 or V2 neurons. Rather more significant orientation tuning changes are evident in V4 neurons (Raiguel, Vogels, Mysore, & Orban, 2006; Yang & Maunsell, 2004), which, however, can only account for a small portion of behavioral learning effects (Raiguel et al., 2006). Psychophysically, we used a Training-plus-Exposure (TPE) protocol to remove orientation specificity in normal and amblyopic perceptual learning (Xiong, Zhang, & Yu, 2016; Zhang et al., 2010, 2014). For example, contrast and orientation learning in the amblyopic eye can transfer to an untrained orthogonal orientation completely when either the amblyopic eye or the non-amblyopic fellow eye is also exposed to the orthogonal orientation through an irrelevant task (Zhang et al., 2014). The complete learning transfer suggests that perceptual learning in amblyopic vision, as in normal vision, involves high-level neural processing, which may compensate functional deficits in amblyopic early visual areas (Zhang et al., 2014). Specific to our dichoptic training task, we have preliminary data indicating that the learning can also transfer to an orthogonal orientation through TPE training, which suggests that the current dichoptic learning may also involve high-level learning. We will present the results in a future paper.

One puzzling issue with perceptual learning in adults with amblyopia is that although learning is orientation specific with convention training (Levi & Polat, 1996; Li et al., 2004), and is task specific (Cong, Wang, Yu, & Zhang, 2016; Zhang et al., 2014), it does transfer to clinical visual acuity and stereoacuity tests. Perceptual learning often produces more significant improvement of the trained task (e.g., tripled maximal tolerable noise contrast in Fig. 1) than of visual acuity and stereoacuity. We suspect that the visual acuity and stereoacuity improvements in adult amblyopic participants may be attributed to the general components of perceptual learning, such as improved attention to the amblyopic eyes, while more task-specific learning components are responsible for addition improvement of the trained task.

We are aware the limitations of the current study. First, our results are largely based on anisometropic amblyopic participants (9 out of 13). Further evidence from other types of amblyopia is necessary for a more balanced evaluation of the efficiency of dichoptic training. Second, our results may be specific to the particular dichoptic training paradigm used. In other dichoptic training studies each eye is presented with a part of the stimuli and the observer must integrate the stimuli dichoptically for successful task completion (Hess et al., 2010b; Li et al., 2013). The training principles and the underlying mechanisms may be distinct between these two paradigms (van Boxtel, van Ee, & Erkelens, 2007). We do not know at this point which paradigm is more efficient in dichoptic training. Third, because of the small sample size, we did not run a control group with further monocular training to contrast the current training group that switched to dichoptic training after monocular training. Although we have confidence that previous prolonged monocular training has maximized its impacts on visual acuity and stereoacuity, adding the control group would be a stricter test for our conclusion that dichoptic training results in additional gains of stereoacuity. Eventually large-scale randomized clinical trials are necessary to confirm the potential advantages of dichoptic training for clinical treatment of adult amblyopia.

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