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Dichoptic training improves contrast sensitivity in adults with amblyopia

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A B S T R A C T

Dichoptic training is designed to promote binocular vision in patients with amblyopia. Initial studies have found that the training effects transfer to both binocular (stereopsis) and monocular (recognition acuity) visual functions. The aim of this study was to assess whether dichoptic training effects also transfer to contrast sensitivity (CS) in adults with amblyopia. We analyzed CS data from 30 adults who had taken part in one of two previous dichoptic training studies and assessed whether the changes in CS exceeded the 95% confidence intervals for change based on test–retest data from a separate group of observers with amblyopia. CS was measured using Gabor patches (0.5, 3 and 10 cpd) before and after 10 days of dichoptic training. Training was delivered using a dichoptic video game viewed through video goggles ($n = 15$) or on an iPod touch equipped with a lenticular overlay screen ($n = 15$). In the iPod touch study, training was combined with anodal transcranial direct current stimulation of the visual cortex. We found that dichoptic training significantly improved CS across all spatial frequencies tested for both groups. These results suggest that dichoptic training modifies the sensitivity of the neural systems that underpin monocular CS.

1. Introduction

For many years amblyopia was thought to be untreatable in older children and adults who were past the critical period of visual cortex development (Epelbaum et al., 1993). However, it is now evident that visual function can improve in adults with amblyopia. The gold-standard amblyopia treatment for children consists of optical correction followed by occlusion therapy (Holmes & Clarke, 2006) and there is evidence that similar approaches can also improve visual acuity in at least a subset of older children and adults with amblyopia (Kupfer, 1957; Scheiman et al., 2005; Simmers & Gray, 1999; Wick et al., 1992). These effects seem to be particularly reliable when occlusion of the fellow eye is combined with visual perceptual learning paradigms. Perceptual learning refers to an improvement in the performance of a psychophysical task after training on the task. Perceptual learning has been found to improve a range of visual functions in adults with amblyopia including Vernier acuity (Levi, Polat, & Hu, 1997) and contrast detection (Huang, Zhou, & Lu, 2008; Polat et al., 2004) (for recent reviews see Astle, Webb, & McGraw, 2011b; Levi & Li, 2009b). Perceptual learning promotes plasticity within the amblyopic visual system and the typical approach of conducting the training in a supervised laboratory setting ensures compliance with fellow eye occlusion, which can be challenging for adults.

Perceptual learning can also improve visual task performance in observers with normal vision (Epstein, 1967; Gibson, 1969, 1991). These improvements are often specific to the trained stimulus with only limited transfer of learning to other stimuli and tasks (Ball & Sekuler, 1982, 1987; Fiorentini & Berardi, 1980). However, considerable transfer of perceptual learning to other visual abilities can occur in adults with amblyopia (Levi & Li, 2009a). For example, perceptual learning of a contrast detection task at a fixed spatial

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frequency transferred to a broader range of adjacent spatial frequencies for adults with amblyopia than for controls (Huang et al., 2008). Furthermore, a variety of studies have found that monocular training on specific tasks such as Vernier acuity (Levi et al., 1997) or contrast detection (Huang et al., 2008; Polat et al., 2004) transfers to recognition acuity in adults with amblyopia. Similar effects have been achieved by combining occlusion with other visual activities such as playing video games (Li, Ngo, et al., 2011). In some cases, monocular training can also transfer to stereoacuity (Astle, McGraw, & Webb, 2011a; Li & Levi, 2004; Li, Ngo, et al., 2011).

An alternative approach to treating amblyopia that focuses on improving binocular vision has recently been proposed (Hess, Mansouri, & Thompson, 2011; Hess & Thompson, 2013). This approach, referred to here as dichoptic training, does not employ monocular occlusion. Instead, high contrast stimuli are presented to the amblyopic eye and lower contrast stimuli are presented to fellow eye in order to balance the input from the two eyes and enable binocular integration (in clinical terms this can be thought of as overcoming suppression of the amblyopic eye) (Mansouri, Thompson, & Hess, 2008). The approach is based on the hypothesis that patients with amblyopia possess an intact binocular visual system, which is rendered functionally monocular by an imbalance in the inputs from the two eyes (clinically thought of as suppression). Evidence supporting this hypothesis originates from animal models and human psychophysics. Animal neurophysiology has shown that a stronger imbalance of information between the two eyes is correlated with deeper amblyopia (Bi et al., 2011) and that antagonizing inhibitory GABA-A receptors can enhance the binocular responses of cells in the striate cortex of cats with an experimentally induced strabismus (Sengpiel et al., 2006). Comparable results have been found in humans; a larger imbalance between the two eyes (suppression) is associated with poorer visual acuity in adults and children with amblyopia (Kwon et al., 2014; Li et al., 2013a, 2013b; Li, Thompson, Lam, et al., 2011; Narasimhan, Harrison, & Giaschi, 2012) and preliminary evidence suggests that larger imbalances may also be associated with poorer outcomes following occlusion therapy (Li et al., 2013b; Narasimhan, Harrison, & Giaschi, 2012). In addition, non-invasive brain stimulation of the visual cortex, which is thought to alter neural inhibition (Fitzgerald, Fountain, & Daskalakis, 2006; Spiegel et al., 2012; Stagg et al., 2009), can improve contrast sensitivity in adults with amblyopia (Clavagnier, Thompson, & Hess, 2013; Spiegel, Byblow, et al., 2013; Thompson et al., 2008).

Initial studies have demonstrated that dichoptic training can lead to significant improvements in stereopsis and acuity without the need for occlusion of the amblyopic eye (Birch, 2013; Black et al., 2012; Hess, Mansouri, & Thompson, 2010a, 2010b; Hess et al., 2012; Knox et al., 2011; Li, Thompson, et al., 2013; Li et al., 2014; Spiegel, Li, et al., 2013; To et al., 2011). The first studies of dichoptic training used dichoptic random dot kinematograms as training stimuli whereby signal dots were presented to one eye and noise dots to the other (Hess, Mansouri, & Thompson, 2010a, 2010b). In order to make the training more engaging, more recent studies have used modified video games (Knox et al., 2011; Li, Thompson, et al., 2013; Li et al., 2014; To et al., 2011). One of these games requires the tessellation of falling blocks. Some blocks are presented to the amblyopic eye at high contrast and others are presented to the fellow eye at low contrast. Training using this approach results in patients being able to play the game with progressively less interocular contrast difference reflecting a stronger contribution of the amblyopic eye to binocular vision. Importantly, this improvement in binocular combination transfers to improved stereopsis and amblyopic eye visual acuity. The transfer of dichoptic training to monocular acuity is surprising because the dichoptic training does not involve occlusion of the fellow eye. This pattern of transfer raises the possibility that binocular imbalance plays a role in both the binocular and monocular losses that occur in amblyopia and also suggests that rebalancing the two eyes may enable plasticity within the amblyopic visual cortex (Li, Thompson, et al., 2013).

The aim of this study was to further investigate the transfer of dichoptic training to monocular visual function by assessing amblyopic eye contrast sensitivity before and after training. There are a number of reasons why it is important to know whether contrast sensitivity is improved by rebalancing the eyes and restoring binocular vision. The first is that impaired contrast sensitivity, particularly for high spatial frequencies, is a fundamental component of amblyopia (Bradley & Freeman, 1981; Hess & Howell, 1977; Levi & Harwerth, 1977) that is thought to reflect reduced responses from striate cortex neurons corresponding to the fovea (Kiorpes et al., 1998; Kiorpes & McKee, 1999). Therefore improved contrast sensitivity after treatment would implicate changes at the level of the striate cortex. Secondly, patients with amblyopia also report spatial distortions (Hess, Campbell, & Greenhalgh, 1978) that are thought to underlie the differences between grating and letter acuity in this condition. Improved letter acuity that has already been reported as a consequence of binocular treatment could reflect reduced spatial distortions rather than a direct improvement in sensitivity and spatial resolution. On the other hand, contrast sensitivity measurements are not contaminated by distortions (Hess et al., 1978), therefore an improvement in contrast sensitivity would be consistent with a specific improvement in sensitivity.

We analyzed contrast sensitivity data collected as part of two previous studies of dichoptic training for which stereopsis and visual acuity outcomes have been published (Li, Thompson, et al., 2013; Spiegel, Li, et al., 2013). Both studies found significant improvements in visual acuity and stereopsis after 10 days of training (5 days per week over 2 weeks) using the falling blocks videogame. Li, Thompson, et al. (2013) compared dichoptic training to monocular training and found that dichoptic training resulted in significantly greater improvements in visual function. Spiegel, Li, et al. (2013) found that visual cortex anodal transcranial direct current stimulation (a-tDCS) enhanced dichoptic training induced improvements in stereopsis. tDCS is a non-invasive technique for stimulating the human brain (Nitsche & Paulus, 2000). Magnetic resonance spectroscopy studies have found that a-tDCS of the human motor cortex reduces the concentration of GABA within the stimulated region (Kim et al., 2014; Stagg et al., 2009). This indicates that a-tDCS may temporarily reduce inhibitory/suppressive interactions within specific brain areas. Results from combined psychophysics and tDCS studies on participants with normal vision (Spiegel et al., 2012) and observers with amblyopia (Spiegel, Byblow, et al., 2013) suggest that a-tDCS may have a similar effect when delivered to the visual cortex. This previous work provided the motivation for testing whether combining dichoptic training with a-tDCS would lead to greater improvements than dichoptic training alone. The results showed that a-tDCS potentiated the effect of dichoptic training on stereopsis but not on acuity (Spiegel, Li, et al., 2013). Our new analysis of previously unpublished data collected during these two dichoptic training studies revealed that dichoptic training improved amblyopic eye contrast sensitivity in the majority of participants.

2. Methods

2.1. Participants

Thirty adults with amblyopia (mean age 22.2 ± 3.5 years SD) were recruited from the ophthalmology clinic at Zhongshan Ophthalmic Center, Guangzhou, China. Amblyopia was defined as an interocular acuity difference of at least 0.2 logMAR and 0 logMAR or better visual acuity in the fellow eye. Further inclusion criteria were a history of anisometropia, strabismus or both with an absence of ocular pathology. The participants had taken part in one of two studies investigating dichoptic training for which acuity and stereopsis outcomes have been published (Li, Thompson, et al., 2013; Spiegel, Li, et al., 2013) (n = 15 from each study). Contrast sensitivity data were not included in the earlier reports as they were not available for all participants in each study and test–retest reliability data were not available. Participant details are summarized in Table 1 and their training history in Fig. 1. Tables 2 and 3 include the baseline, interim and post-training results for visual acuity, stereopsis and suppression for each participant in each group. All procedures were carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and were approved by the Zhongshan Ophthalmic Center Ethics Committee. Informed consent was obtained from all participants prior to data collection.

2.1.1. The iPod/tDCS group (participants from Spiegel, Li, et al., 2013)

Fifteen participants had taken part in a study investigating the effects of a-tDCS on dichoptic training (Spiegel, Li, et al., 2013). This study involved 10 days of dichoptic training (5 days per week over 2 weeks) using the falling blocks videogame presented on iPod touch device equipped with a prismatic overlay. This training duration was based on previous work, which used similar (To et al., 2011) or shorter (Knox et al., 2011) durations. To ensure accurate alignment of the lenticular screen, iPods were placed in holders,

Table 1

Clinical details of the study participants. See main text and Fig. 1 for group definitions. Aniso = anisometropic amblyopia, Strab = strabismic amblyopia, mixed = combined mechanism (both anisometropic and strabismic) amblyopia, AmE = amblyopic eye, FFE = fellow fixing eye, VA = visual acuity.

Group/participant	Age	Type	Previous treatment	AmE VA Pre [logMAR]	FFE VA [logMAR]	Refraction OD	Refraction OS	Deviation
iPod-AS1	18	Aniso	Patching	0.7	0	Plano	5.75–1.25 × 5	Ortho
iPod-AS2	20	Strab	None	1	0	+0.25	Plano	ESO 8.5°
iPod-AS3	22	Aniso	Patching	0.4	0	−1.50	+3.00	Ortho
iPod-AS4	22	Aniso	None	0.22	0	+5.0–0.5 × 35	+2.5–0.5 × 155	Ortho
iPod-AS5	25	Strab	Surgery	0.73	−0.1	−1.25	−0.75	ET 10°
iPod-AS6	31	Strab	None	0.42	−0.1	−3.25	−2.25	ET 15°
iPod-AS7	20	Aniso	Patching	1	0	+1.25–0.75 × 15	+6.5–1.0 × 95	Ortho
iPod-SA1	21	Aniso	None	0.15	−0.1	−0.50	+3.25–1.0 × 80	Ortho
iPod-SA2	23	Strab	Patching	1	−0.1	+4.75–1.0 × 10	+4.5–1.25 × 5	ESO 14°
iPod-SA3	17	Mixed	None	1	0	+4.25–0.5 × 50	−0.25	ESO 11°
iPod-SA4	31	Aniso	None	0.57	0	+5.0–2.0 × 120	+7.75–1.0 × 30	Ortho
iPod-SA5	19	Strab	Surgery	0.55	−0.1	0.0–0.5 × 165	−1.00–0.75 × 15	XT 5°
iPod-SA6	24	Strab	None	0.38	−0.1	−5.0–0.75 × 180	−4.00–1.25 × 170	ET 17°
iPod-SA7	19	Aniso	None	0.7	0	+8.00–2.00 × 175	+3.25–1.0 × 85	Ortho
iPod-SA8	29	Aniso	None	1	−0.1	−1.25–1.00 × 85	+3.75–0.75 × 75	Ortho
Goggles-D1	26	Strab	Surgery and patching	0.52	−0.10	−2.00/−0.50 × 15	−1.50/−1.00 × 5	EX 5°
Goggles-D2	24	Aniso	Patching	0.44	−0.04	+3.25	+1–0.75 × 10	Ortho
Goggles-D3	22	Aniso	Patching	0.66	−0.08	−1.0	+1.75–0.5 × 90	Ortho
Goggles-D4	22	Aniso	None	0.44	−0.20	+6.25–2.0 × 105	+1.0	Ortho
Goggles-D5	21	Aniso	None	0.48	0.00	+3.0	−1.25–0.5 × 170	Ortho
Goggles-D6	22	Aniso	None	0.58	−0.10	+3.0	+7.0–0.5 × 90	Ortho
Goggles-MD1	19	Strab	None	0.68	−0.20	+3.25–2.75 × 85	−0.50	ES 11°
Goggles-MD2	22	Aniso	None	0.54	−0.14	+7.75–2.0 × 35	+3.5–1.5 × 135	Ortho
Goggles-MD3	24	Aniso	None	0.52	−0.08	+5.25–0.75 × 175	+1.5–0.75 × 5	Ortho
Goggles-MD4	21	Strab	None	0.44	−0.06	−2.5	+4.75–1.25 × 165	EX 10°
Goggles-MD5	19	Aniso	None	0.42	−0.12	+6.75–1.25 × 75	+2.0–0.75 × 25	Ortho
Goggles-MD6	19	Aniso	None	0.54	−0.18	−3.50	+1.0–0.5 × 180	Ortho
Goggles-MD7	20	Aniso	None	0.60	0.06	+4.0–3.5 × 175	+1.25–0.75 × 5	Ortho
Goggles-MD8	22	Aniso	None	0.40	0.04	+2.75	−0.75–0.5 × 180	Ortho
Goggles-MD9	23	Aniso	None	0.56	−0.08	−0.5–1.50 × 180	+5.0–1.0 × 175	Ortho

Table 2

Individual participant data for the iPod/tDCS group. Pre = baseline, Post 5 = measurements made after 5 sessions of dichoptic training, Post 10 = measurements made after 10 sessions of dichoptic training. Visual acuity (VA) is shown in logMAR units, stereo in arc seconds and suppression in % contrast tolerated in the fellow eye. Larger contrast values indicate weaker suppression. AmE = amblyopic eye. See Fig. 1 for group definitions.

Participant	AmE VA Pre	AmE VA Post 5	AmE VA Post 10	Stereo Pre	Stereo Post 5	Stereo Post 10	Suppression Pre	Suppression Post 5	Suppression Post 10
iPod-AS1	0.7	0.48	0.48	Nil	800	800	0	28	22
iPod-AS2	1	0.57	0.55	Nil	Nil	Nil	10	29	38
iPod-AS3	0.4	0.21	0.21	Nil	Nil	Nil	2	15	20
iPod-AS4	0.22	0.12	0.08	800	200	200	32	65	77
iPod-AS5	0.73	0.57	0.3	Nil	800	800	28	36	40
iPod-AS6	0.42	0.33	0.18	Nil	800	400	45	100	100
iPod-AS7	1	0.7	0.42	Nil	Nil	Nil	0	13	14
iPod-SA1	0.15	0.05	0.03	800	200	100	2	33	41
iPod-SA2	1	0.57	0.55	Nil	Nil	800	19	100	100
iPod-SA3	1	0.6	0.55	Nil	Nil	800	2	15	20
iPod-SA4	0.57	0.35	0.27	Nil	Nil	800	26	37	69
iPod-SA5	0.55	0.33	0.17	Nil	Nil	400	25	37	54
iPod-SA6	0.38	0.25	0.15	800	400	200	35	48	51
iPod-SA7	0.7	0.42	0.25	Nil	Nil	800	24	29	40
iPod-SA8	1	0.7	0.48	Nil	Nil	Nil	0	16	19

Table 3
Individual participant data for the goggles group. Pre monocular = baseline measurements for the participants who completed 10 sessions of monocular training before being crossed over to dichoptic training. Pre = pre dichoptic training baseline. Post 10 = post 10 sessions of dichoptic training. Visual acuity (VA) is shown in log MAR units, stereo in arc seconds and suppression in % contrast tolerated in the fellow eye. Larger contrast values indicate weaker suppression. AmE = amblyopic eye. N/A = not applicable; pre monocular measurements were only made for the Goggles-MD group. The Goggles-D group did not complete any monocular training. See Fig. 1 for group definitions.

Participant	AmE VA pre monocular	AmE VA Pre	AmE VA Post 10	Stereo pre monocular	Stereo Pre	Stereo Post 10	Suppression pre monocular	Suppression Pre	Suppression Post 10
Goggles-D1	N/A	0.52	0.28	N/A	800	400	N/A	20	66
Goggles-D2	N/A	0.44	0.32	N/A	Nil	400	N/A	11	54
Goggles-D3	N/A	0.66	0.46	N/A	Nil	800	N/A	18.5	59
Goggles-D4	N/A	0.44	0.30	N/A	Nil	800	N/A	17	100
Goggles-D5	N/A	0.48	0.28	N/A	800	200	N/A	13.5	50
Goggles-D6	N/A	0.58	0.46	N/A	Nil	Nil	N/A	26.5	100
Goggles-MD1	0.68	0.60	0.44	Nil	Nil	Nil	13.5	24	39
Goggles-MD2	0.54	0.50	0.36	Nil	Nil	800	21	50	59
Goggles-MD3	0.52	0.56	0.28	800	800	400	19	26	100
Goggles-MD4	0.44	0.38	0.20	800	400	100	15	19	37
Goggles-MD5	0.42	0.34	0.18	Nil	Nil	400	37	51	54
Goggles-MD6	0.54	0.46	0.26	Nil	Nil	400	35	17	100
Goggles-MD7	0.60	0.60	0.40	Nil	Nil	Nil	9	12	42
Goggles-MD8	0.40	0.34	0.18	800	400	200	22	38	42
Goggles-MD9	0.56	0.58	0.42	Nil	Nil	800	10.5	10	26

controlled using a wireless keyboard and participant's heads were restrained using a head and chin rest. The study adopted a cross-over design that required two groups of participants. The first group (denoted iPod-AS; see Fig. 1) completed 5 days of dichoptic training combined with a-tDCS followed by 5 days of dichoptic training combined with sham tDCS. The second group (denoted iPod-SA; see Fig. 1) completed 5 days of dichoptic training combined with sham-tDCS followed by 5 days of dichoptic training combined with a-tDCS. A detailed description of the tDCS parameters is provided by Spiegel, Li, et al. (2013). Contrast sensitivity measurements were made at baseline (Pre), after 5 days of training (Post 5) and after 10 days of training (Post 10). Seven participants were from the group that received a-tDCS followed by sham tDCS (iPod-AS) and eight participants were from the group that received sham tDCS followed by a-tDCS (iPod-SA). It is important to note that all participants had received equal amounts of real and sham tDCS at the Post 10 time-point.

2.1.2. The goggles group (participants from Li, Thompson, et al., 2013)

The second set of fifteen participants had taken part in a study comparing dichoptic and monocular training (Li, Thompson, et al., 2013). This study involved two groups of participants, one trained dichoptically and one trained monocularly using the falling blocks videogame. Training was conducted using head-mounted video goggles (eMagin™ Z800 3DVisor) and lasted for 10 days (5 days per week over 2 weeks). The primary aim of this experiment was to directly compare dichoptic and monocular training. However, because improvements were small in the monocular group, this group was crossed over to dichoptic training for a further 10 days once the monocular training was complete to assess whether additional improvements would occur. Of the fifteen participants for whom contrast sensitivity data were available, six were from the group who received dichoptic training only (denoted Goggles-D; see Fig. 1). These participants completed contrast sensitivity measurements at baseline (Pre) and after 10 days of dichoptic training (Post 10). The remaining nine participants were from the group that received monocular training followed by dichoptic training (denoted Goggles-MD; see Fig. 1). These participants completed contrast sensitivity measurements at baseline (pre monocular), after monocular training (Pre; this measure was used as the pre dichoptic training baseline) and after 10 days of dichoptic training (Post 10).

2.2. Test–re-test reliability

A separate group of twelve participants with amblyopia who had not participated in any dichoptic training studies completed two sets of contrast sensitivity measurements separated by at least 24 h. On average these participants were 6 years younger than the participants that completed dichoptic training (mean age 16 years, range 13–22 vs. mean age 22, range 18–31). The range of amblyopic eye visual acuities was the same for the test–retest

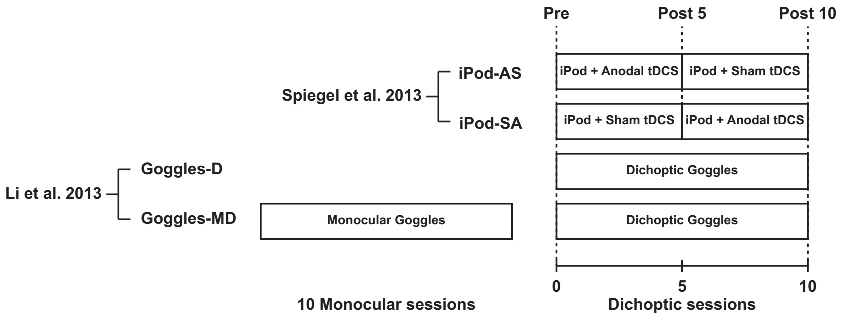

Fig. 1. The two sets of participants for which contrast sensitivity data were available. Fifteen of the participants took part in a study investigating the combination or anodal or sham tDCS on dichoptic training and fifteen participants took part in a study comparing monocular and dichoptic training. iPod-AS refers to a group of 7 participants who completed 5 sessions of dichoptic training on an iPod device combined with anodal tDCS followed by 5 sessions of dichoptic training combined with sham tDCS. iPod-SA refers to a group of 8 participants who received sham stimulation followed by anodal stimulation. Note that after 10 sessions both groups had received equal amounts of anodal and sham tDCS. Goggles-D refers to a group of 6 participants who received 10 sessions of dichoptic training only. Goggles-MD refers to a group of 9 participants who received 10 sessions of monocular training followed by 10 sessions of dichoptic training. The iPod-AS and iPod-SA groups trained using an iPod device whereas the Goggles-D and Goggles-MD groups trained using head-mounted video goggles. See Section 2.1 for further details.

participants and the dichoptic training participants (0.2–1 log MAR) although the mean visual acuity was better for the test–retest group (0.4 log MAR vs. 0.59 log MAR).

2.3. Contrast sensitivity

Contrast sensitivity was assessed at 0.5, 3, and 10 cpd using a two-alternative, forced-choice method whereby participants had to judge the orientation of Gabor patches (spatial sigma 2°, temporal sigma 500 ms embedded in a cosine envelope) as vertical or horizontal. Contrast was expressed as a Michelson Contrast percentage (Formula 1).

$$C = 100 \times \frac{(I_{\max} - I_{\min})}{(I_{\max} + L_{\min})} \tag{1}$$

Stimuli were generated using a MacBook Pro laptop (Apple Inc., California, USA) with Psykinematix software (KyberVision, Quebec, Canada), which allows for 10.8 bits of contrast resolution, and presented using a linearized 17″ CRT screen (Philips 107S61, Amsterdam, Netherlands; refresh rate = 85 Hz, mean luminance 200 cd/m^2) at a viewing distance of 60 cm. Following a familiarization procedure, participants completed a threshold measurement for each spatial frequency in a random sequence. Seventy-five percent correct thresholds were estimated for each measurement using a Bayesian adaptive staircase run over a maximum of 100 trials, which generated data that were fit by a Weibull function. The adaptive staircase was based on the algorithm proposed by Kontsevich and Tyler (1999) and implemented in Psykinematix.

2.4. Visual acuity measurements

For the participants trained using video goggles and the test–retest participants, visual acuity was tested using a log MAR chart with 0.1 log MAR steps viewed from a distance of 4 m. The participants trained on the iPod devices were tested using a Topcon ACP-8 projector with decimal progression viewed from a distance of 3 m. Tumbing E symbols were used for both charts and a four-alternative forced-choice method was adopted. Acuity thresholds were determined by subtracting the appropriate number of log MAR units for each correctly identified optotype. Note that the chart with decimal progression had a lower resolution on a log MAR scale than the log MAR chart. Stereopsis was assessed using the Randot Stereo Test at a 40-cm viewing distance.

2.5. Dichoptic training

Dichoptic training was administered under supervision in a clinical research room at Zhongshan Ophthalmic Center. As described previously (Li, Thompson, et al., 2013; Spiegel, Li, et al., 2013; To et al., 2011), the training was delivered using a video-game that required falling blocks to be tessellated together. Some blocks were presented at high contrast to the amblyopic eye, some blocks were presented at a low contrast to the fellow eye, and some blocks were presented to both eyes to aid binocular combination. The game could only be played successfully if the images shown separately to the two eyes were combined. The contrast of the blocks shown to the fellow eye was set at the start of each session by measuring interocular suppression using an established psychophysical technique (Black et al., 2011, 2012) modified for use in cases of high anisometropia (Li et al., 2013b). The blocks seen by the amblyopic eye were always presented at 100% contrast.

The participants who took part in the study comparing monocular and dichoptic training (Goggles-D and Goggles-MD in Fig. 1) were trained using video goggles for 60 min per session. The participants who took part in the study investigating the effect of a-tDCS on dichoptic training (iPod-AS and iPod-SA in Fig. 1) were trained using iPod touch devices equipped with a lenticular overlay for 75 min per session. Anodal or sham tDCS was administered for the first 15 min of each training session for these participants.

2.6. Data analysis

All contrast detection thresholds were converted to log contrast sensitivity. The 95% CIs for the difference in means between test 1 and test 2 for the test–retest group were calculated for each spatial frequency. The change in contrast sensitivity for amblyopic eyes for each spatial frequency as a result of dichoptic training were compared to these 95% CIs as the upper (positive) CI indicated the estimated improvement from test–retest variability alone. ANOVAs were also conducted on the log contrast sensitivity scores separately for the Goggles, the iPod/tDCS and the test–retest group to test for changes in contrast sensitivity across sessions. Finally, Pearson's correlation coefficients were used to assess whether changes in contrast sensitivity were correlated with changes in acuity, stereopsis or suppression. These analyses were conducted separately for the Goggles and iPod/tDCS groups.

3. Results

3.1. The iPod/tDCS Group (participants from Spiegel, Li, et al., 2013)

Pre and post 10 contrast sensitivity functions along with plots of the difference between the two functions are shown for each individual participant in Fig. 2. The dashed lines in the difference plots represent the upper and lower 95% CIs from the test–retest data. Individual thresholds for each participant for all time-points are provided in Table 4. Improvements in CS that exceeded the upper 95% CI were more common for the higher spatial frequencies (4/15 participants improved at 0.5 cpd; mean improvement for all participants = 0.13 log units, 95% CI 0.12; 8/15 for 3 cpd; mean improvement = 0.30 log units, 95% CI 0.27 and 12/15 for 10 cpd; mean improvement = 0.33 log units, 95% CI 0.13). Interestingly, when improvements for the 3 cpd stimulus did occur, they tended to be larger than the improvements for the 10 cpd stimulus (e.g. Fig. 2, participants i-AS3 and i-SA3). Two participants showed reductions in CS that exceed the lower CI, one for the 3 and 10 cpd stimuli (0.36 and 0.27 log units, respectively) and one for the 3 cpd stimulus only (0.4 log units). A mixed ANOVA with factors of Spatial Frequency, Time (Pre, Post 5 and Post 10) and Stimulation Order (anodal-sham vs. sham-anodal) revealed significant effects of Spatial Frequency ($F_{1,16} = 13.5$, $p = 0.001$, degrees of freedom corrected for sphericity) and Time ($F_{2,26} = 83.1$, $p < 0.001$), but no interactions ($p > 0.05$). This indicates that tDCS order (anodal followed by sham vs. sham followed by anodal) did not significantly influence the improvement of contrast sensitivity. The average CS values for each spatial frequency at baseline (Pre) after 5 sessions (Post 5), and after 10 sessions (Post 10) are shown in Fig. 3. Results for the two groups (iPod-AS and iPod-SA) are shown separately. The average plots reflect the trend for greater improvements at the higher spatial frequencies of 3 and 10 cpd.

3.2. The Goggles group (participants from Li, Thompson, et al., 2013)

Individual participant data illustrating the effects of dichoptic training only are shown in Fig. 4 in the same format as Fig. 2. Individual data are also provided in Table 5. For this group, the greatest number of participants exhibited reliable CS improvements for the 3 cpd stimulus (6/15 participants improved at 0.5 cpd; mean improvement for all participants = 0.13, 95% CI

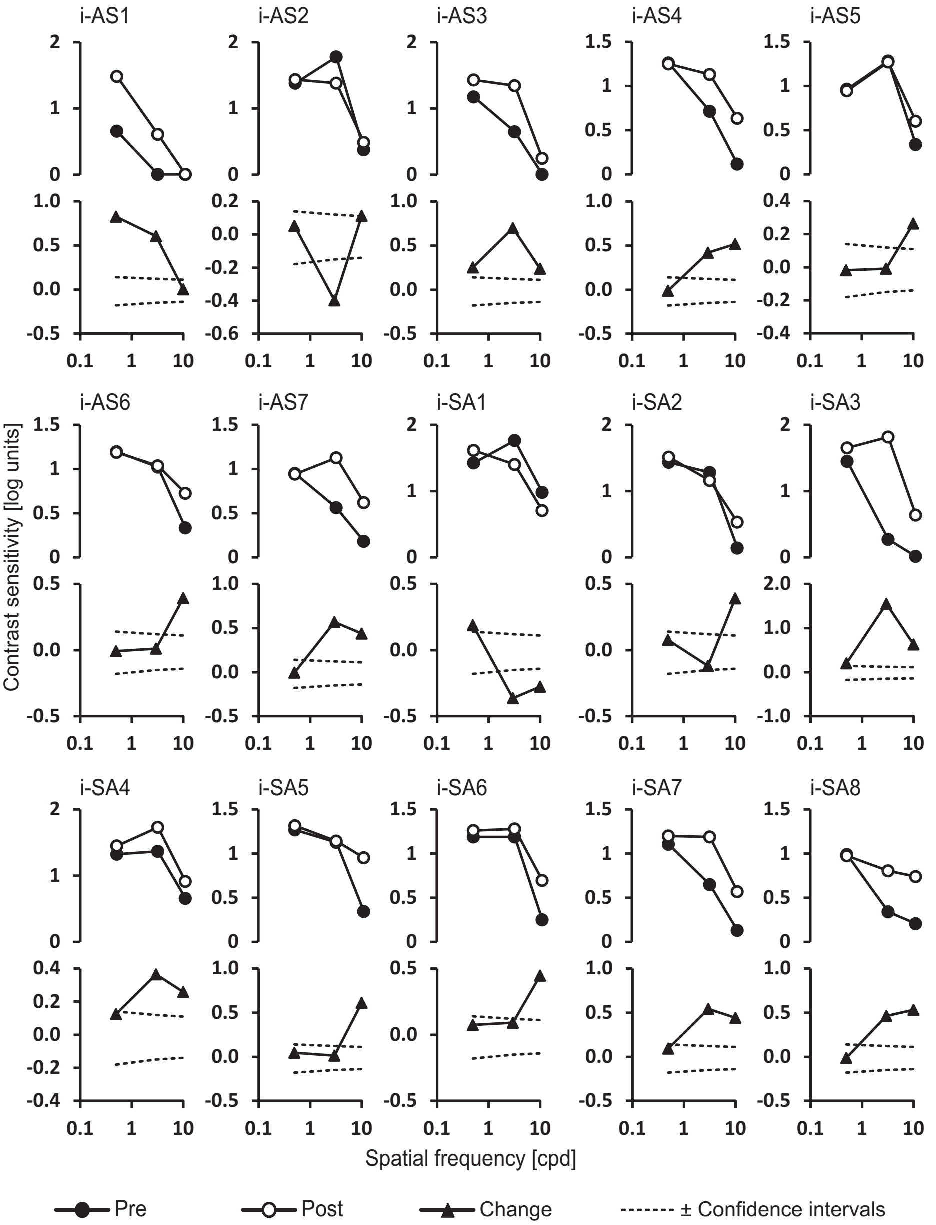

Fig. 2. Individual contrast sensitivity functions for each participant trained using the iPod device. The top portions of each panel show the pre (filled circles) and post (open circles) training contrast sensitivity functions. The lower portions show the difference between the two functions with positive values indicating a contrast sensitivity improvement. The dashed lines show the estimated 95% confidence intervals for change for the test–retest group. Data points falling outside these confidence intervals represent a change that cannot be directly explained by test–retest variability. Note that the *y*-axis scales vary to account for differing contrast sensitivities and training effects.

0.08, 11/15 at 3 cpd; mean improvement = 0.22 log units, 95% CI 0.08 and 7/15 at 10 cpd; mean improvement = 0.15 log units, 95% CI 0.12). No participants exhibited a reliable decrease in CS. A mixed ANOVA with factors of Spatial Frequency (0.5, 3 and 10 cpd), Time (Pre and Post 10) and Group (Goggles-D vs. Goggles-MD) revealed significant main effects of Spatial Frequency ($F_{2,26} = 84.5$, $p < 0.001$) and Time ($F_{1,13} = 87.0$, $p < 0.001$) as well as a significant interaction between Time and Group ($F_{1,13} = 11.9$, $p = 0.004$). There were no other significant main effects or interactions. The mean CS values for each spatial frequency and time point for each group are shown in Fig. 5.

The interaction between Time and Group reflected smaller improvements after dichoptic training for participants who had completed two weeks of monocular training prior to dichoptic training (the Goggles-MD group). The overall mean improvement for the Goggles-MD group was 0.1 (SE 0.06) log units compared to 0.2 (SE 0.09) log units for the Goggles-D group. This suggests that monocular training may have led to CS improvements that reduced the subsequent response to dichoptic training. This effect is evident in Fig. 5 for the 10 cpd stimulus. However, a direct comparison between the dichoptic training results for the Goggles-D group and the monocular training results for the Goggles-MD group revealed a significant interaction between Time and Group ($F_{1,13} = 13.6$, $p = 0.003$), whereby the dichoptic training generated significantly greater improvements in CS than monocular training. This suggests that dichoptic training was more effective at improving contrast sensitivity than monocular training. For this comparison, the overall mean monocular training improvement was 0.1 (SE 0.07) log units compared to 0.2 (SE 0.09) log units for dichoptic training.

Table 4
Log sensitivity for each spatial frequency tested for each participant in the iPod/tDCS group. Pre = baseline, Post 5 = post 5 sessions of dichoptic training, Post 10 = post 10 sessions of dichoptic training. See Fig. 1 for group definitions.

Participant	CS 0.5 cpd Pre	CS 3 cpd Pre	CS 10 cpd Pre	CS 0.5 cpd Post 5	CS 3 cpd Post 5	CS 10 cpd Post 5	CS 0.5 cpd Post 10	CS 3 cpd Post 10	CS 10 cpd Post 10
iPod-AS1	0.66	0.01	0.00	1.30	0.65	0.00	1.48	0.61	0.01
iPod-AS2	1.38	1.78	0.38	1.48	1.60	0.35	1.44	1.38	0.49
iPod-AS3	1.18	0.65	0.01	1.42	1.36	0.38	1.43	1.34	0.24
iPod-AS4	1.26	0.71	0.11	1.36	0.91	0.36	1.25	1.13	0.63
iPod-AS5	0.96	1.28	0.34	1.03	1.35	0.50	0.95	1.27	0.60
iPod-AS6	1.20	1.02	0.33	1.27	1.07	0.54	1.19	1.03	0.72
iPod-AS7	0.95	0.56	0.18	0.98	0.84	0.36	0.94	1.13	0.62
iPod-SA1	1.43	1.76	0.98	1.63	1.33	0.54	1.61	1.40	0.70
iPod-SA2	1.43	1.28	0.14	1.53	1.33	0.67	1.51	1.16	0.53
iPod-SA3	1.45	0.27	0.01	1.61	1.60	0.39	1.65	1.82	0.64
iPod-SA4	1.32	1.37	0.66	1.39	1.38	0.68	1.45	1.73	0.91
iPod-SA5	1.27	1.13	0.34	1.19	1.16	0.64	1.32	1.14	0.95
iPod-SA6	1.19	1.19	0.25	1.36	1.21	0.47	1.26	1.28	0.70
iPod-SA7	1.11	0.65	0.13	1.20	0.85	0.39	1.20	1.19	0.57
iPod-SA8	0.99	0.34	0.21	1.03	0.51	0.49	0.98	0.80	0.74

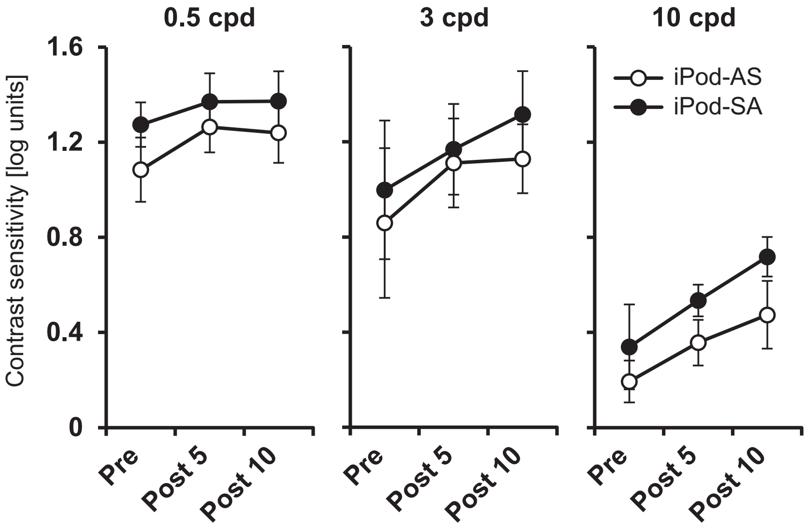

Fig. 3. The group mean contrast sensitivity before (Pre), after 5 sessions (Post 5) and after 10 sessions (Post 10) of iPod-based dichoptic training with anodal or sham tDCS. iPod-AS denotes the group that received anodal tDCS for 5 sessions followed by sham tDCS, iPod-SA denotes the group who received sham tDCS followed by anodal tDCS. Error bars show between subjects 95% confidence intervals (note that statistical analyses were within subjects).

3.3. Correlations among improvements in CS, visual acuity, suppression and stereopsis

There were no significant correlations between the change in CS at a specific spatial frequency and changes in visual acuity or suppression for either the iPod/tDCS group or the goggles group. There was a negative correlation between CS improvement and stereopsis improvement for the 3 cpd stimulus in the goggles group, however this relationship was not significant for any of the other spatial frequencies and did not occur for the iPod/tDCS group suggesting that this may be a type 1 error. Correlations are summarized in Table 6.

3.4. Test–retest measurements

The average contrast sensitivity functions for the test–retest group are shown in Fig. 6. A repeated measures ANOVA with factors of Spatial Frequency (0.5, 3 and 10 cpd) and Time (test 1 and test 2) revealed the expected significant main effect of Spatial Frequency ($F_{2,22} = 44.0$, $p < 0.001$) but no main effect of Time ($F_{1,11} = 0.9$, $p = 0.8$) and no interaction ($F_{2,22} = 0.02$, $p = 1$). The mean differences in log contrast sensitivity (test 2 minus test 1) with 95% CIs for each spatial frequency were: 0.5 cpd, −0.02 (−0.18–0.14); 3 cpd, −0.02 (−0.15–0.12); 10 cpd, −0.01 (−0.14–0.11). The negative mean differences show that contrast sensitivity tended to decrease from test 1 to test 2. Univariate ANOVAs conducted on the difference scores for each spatial frequency with covariates of age and amblyopic eye visual acuity revealed no significant effect of age for any spatial frequency ($p > 0.05$). There were no significant effects of visual acuity for the 0.5 and 10 cpd stimuli ($p > 0.05$) but there was a significant effect for the 3 cpd stimulus ($F_{1,12} = 8.9$, $p = 0.02$) whereby participants with poorer visual acuity tended to show greater reductions in contrast sensitivity at test 2 relative to test 1.

4. Discussion

Previous studies of dichoptic training delivered in a videogame format have found that the training effects transfer to both stereopsis and visual acuity in adults with amblyopia (Hess, Mansouri, & Thompson, 2010a, 2010b; Knox et al., 2011; Li, Thompson, et al., 2013; Spiegel, Li, et al., 2013; To et al., 2011).

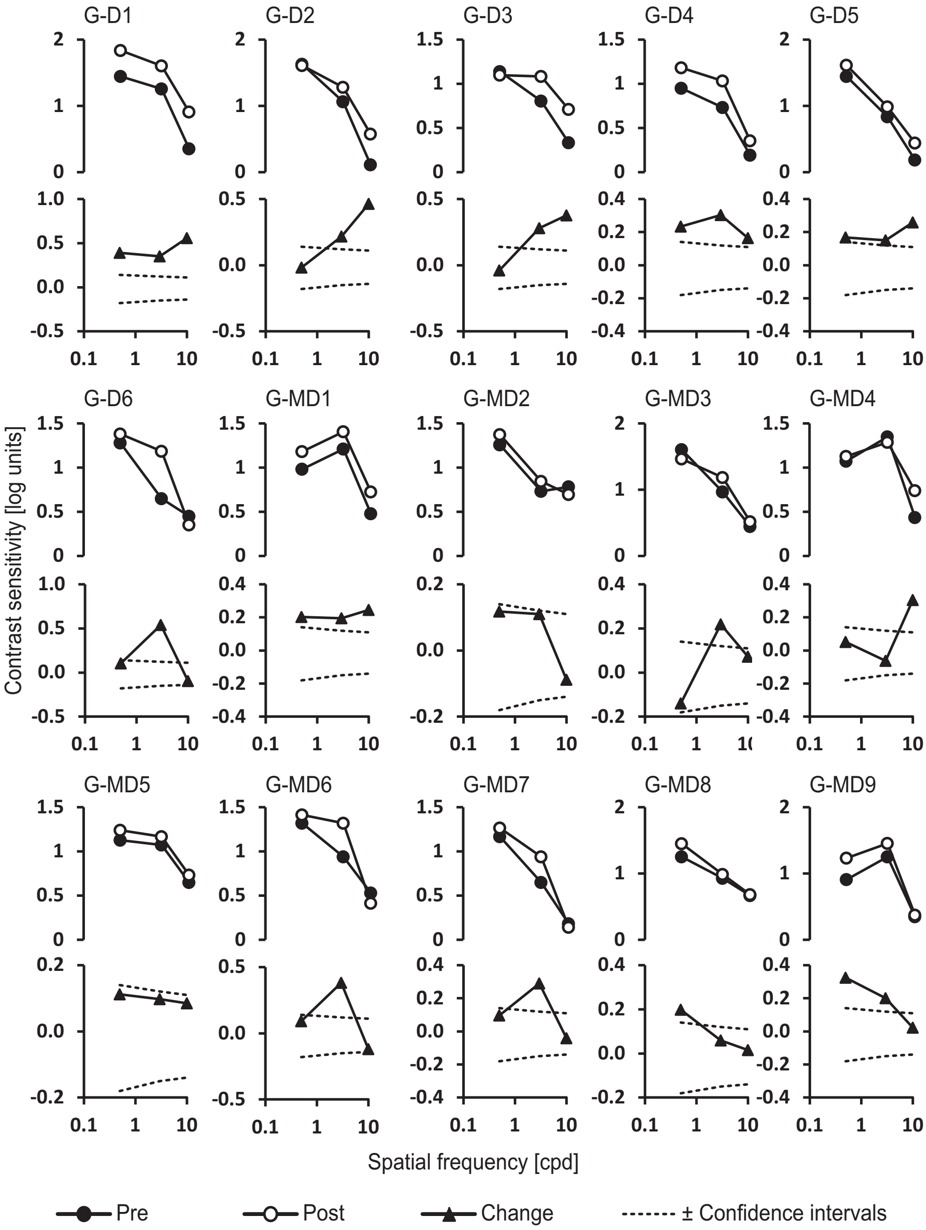

Fig. 4. Individual contrast sensitivity functions for each participant trained using the video goggles. The data are presented in the same way as Fig. 2.

Here we show that dichoptic training effects also transfer to amblyopic eye contrast sensitivity in at least a subset of observers.

Substantial improvements in amblyopic eye contrast sensitivity have previously been reported in adults with amblyopia following perceptual learning of a monocular contrast detection task performed at the cutoff spatial frequency (Huang et al., 2008; Zhou et al., 2006). Overall we found a 2-fold improvement in contrast sensitivity across all spatial frequencies and observers. This is less than the approximately 3-fold improvement for a fixed high spatial frequency induced by direct monocular training at that specific frequency (Huang et al., 2008; Zhou et al., 2006). However, our improvement is comparable to that reported after monocular training of contrast detection across a range of spatial frequencies presented with flanking stimuli (Polat et al., 2004). The distinguishing feature of our study is that participants were not explicitly trained on monocular contrast sensitivity. Rather, they were trained on a task that targeted binocular function.

4.1. Comparison of the iPod/tDCS and goggles groups

There were some differences for the results of patients trained using the video goggles and those trained using an iPod whereby iPod patients tended to show larger improvements. However, due to differences in the design of these experiments, it is not possible to attribute these effects to the difference in training device alone.

The iPod/tDCS group had slightly longer training sessions and also received one week of a-tDCS. The latter is an important factor as a-tDCS has been previously shown to temporarily improve CS in both healthy (Kraft et al., 2010) and amblyopic observers (Spiegel, Byblow, et al., 2013). In addition, a-tDCS administered with dichoptic training enhanced training related improvements in stereopsis (Spiegel, Li, et al., 2013). The analyses presented here did not detect any differences in the time course of contrast sensitivity improvement between the group that received a-tDCS

Table 5
Log sensitivity for each spatial frequency tested for each participant in the goggles group. Pre monocular = baseline measurements for the participants who completed 10 sessions of monocular training before being crossed over to dichoptic training. Pre = pre dichoptic training baseline. Post 10 = post 10 sessions of dichoptic training. N/A = not applicable; pre monocular measurements were only made for the Goggles-MD group. The Goggles-D group did not complete any monocular training. See Fig. 1 for group definitions.

Participant	CS 0.5 cpd pre monocular	CS 3 cpd pre monocular	CS 10 cpd pre monocular	CS 0.5 cpd Pre	CS 3 cpd Pre	CS 10 cpd Pre	CS 0.5 cpd Post 10	CS 3 cpd Post 10	CS 10 cpd Post 10
Goggles-D1	N/A	N/A	N/A	1.45	1.26	0.35	1.84	1.60	0.91
Goggles-D2	N/A	N/A	N/A	1.63	1.06	0.11	1.61	1.28	0.58
Goggles-D3	N/A	N/A	N/A	1.14	0.80	0.33	1.10	1.08	0.71
Goggles-D4	N/A	N/A	N/A	0.95	0.73	0.19	1.18	1.03	0.35
Goggles-D5	N/A	N/A	N/A	1.45	0.84	0.18	1.61	0.99	0.44
Goggles-D6	N/A	N/A	N/A	1.28	0.65	0.45	1.38	1.19	0.35
Goggles-MD1	0.94	1.28	0.35	0.98	1.21	0.48	1.18	1.41	0.72
Goggles-MD2	1.38	0.61	0.59	1.26	0.73	0.78	1.37	0.84	0.69
Goggles-MD3	1.45	0.73	0.18	1.60	0.97	0.45	1.46	1.18	0.52
Goggles-MD4	0.90	1.26	0.35	1.07	1.35	0.43	1.13	1.29	0.74
Goggles-MD5	1.05	0.78	0.59	1.13	1.07	0.65	1.24	1.17	0.73
Goggles-MD6	1.25	0.73	0.45	1.32	0.94	0.53	1.41	1.32	0.41
Goggles-MD7	1.18	0.45	0.10	1.17	0.65	0.18	1.26	0.94	0.14
Goggles-MD8	1.34	0.76	0.45	1.25	0.93	0.66	1.45	0.99	0.68
Goggles-MD9	0.99	1.07	0.23	0.91	1.25	0.35	1.23	1.45	0.37

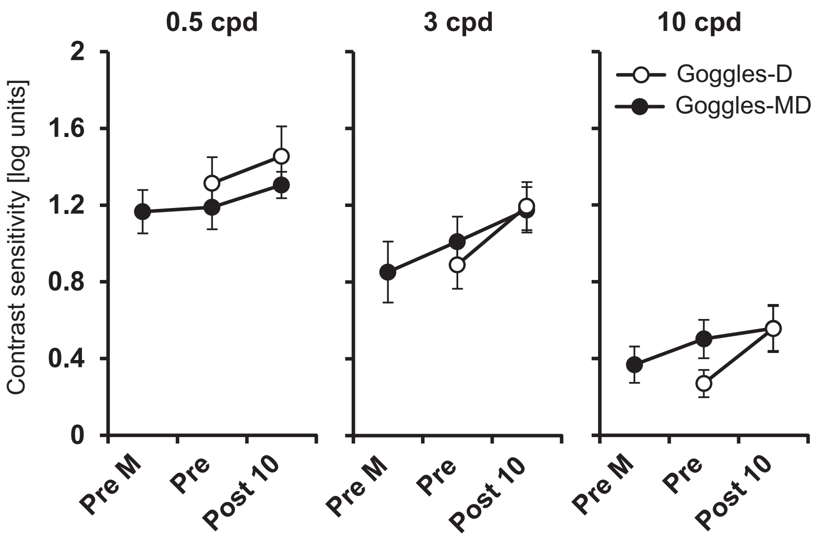

Fig. 5. The group mean contrast sensitivity before monocular training (Pre M), before dichoptic training (Pre) and after dichoptic training (Post 10) for the goggles group. Note that only the Goggles-MD participants (filled circles) completed monocular training. Error bars show between-subjects 95% confidence intervals.

Table 6
Pearson's correlations between CS changes and changes in visual acuity, stereopsis and suppression. Data within each group were pooled. *Significant correlation. There were no systematic patterns in the correlations.

Group	SF [cpd]	VA change [logMAR]	Stereo sensitivity change [arc sec]	Suppression change [% contrast]
iPod	0.5	$r = -0.336$, $p = 0.221$	$r = -0.001$, $p = 0.999$	$r = -0.136$, $p = 0.628$
iPod	3	$r = 0.232$, $p = 0.406$	$r = -0.388$, $p = 0.153$	$r = -0.399$, $p = 0.140$
iPod	10	$r = 0.483$, $p = 0.68$	$r = -0.441$, $p = 0.1$	$r = -0.063$, $p = 0.824$
Goggles	0.5	$r = -0.029$, $p = 0.92$	$r = -0.04$, $p = 0.888$	$r = 0.09$, $p = 0.750$
Goggles	3	$r = -0.029$, $p = 0.919$	*$r = -0.616$, $p = 0.014$	$r = 0.473$, $p = 0.075$
Goggles	10	$r = 0.289$, $p = 0.269$	$r = -0.363$, $p = 0.183$	$r = 0.17$, $p = 0.545$

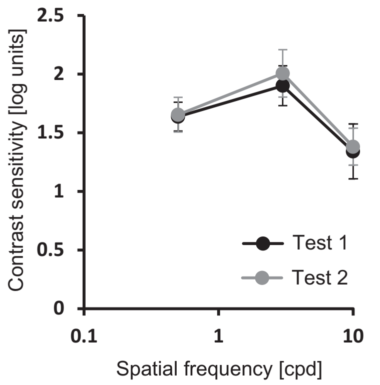

Fig. 6. Contrast sensitivity measurements for twelve observers with amblyopia made at least 24 h apart. Error bars show 95% confidence intervals.

first followed by sham and the group that had sham followed by anodal tDCS. This is consistent with the previously reported acuity results (Spiegel, Li, et al., 2013) and suggests that the beneficial effects of dichoptic training on monocular functions may be strong enough to mask any improvements related to anodal tDCS. Because both groups had received the same dose of tDCS at the end of the

10 days of training, we cannot rule out more general effects of tDCS on the contrast sensitivity improvements observed for the tDCS/iPod group. However, it is clear from the Goggles group (who did not receive any tDCS) that tDCS is not necessary for contrast sensitivity improvements to occur following dichoptic training.

Another difference was that 9/15 participants in the Goggles group had previously received training using a monocular version of the video game and their post-monocular training thresholds were used as the baseline for the dichoptic training analysis. This is important to emphasize as monocular training has been associated with improvements in monocular function in amblyopia (Levi & Li, 2009b). Indeed, the group who received monocular training showed less improvement in CS after subsequent dichoptic training than the group that received dichoptic training alone (improvements of 0.17 vs. 0.30 log units at 3 cpd and 0.06 vs. 0.29 log units at 10 cpd for the Goggles-MD and Goggles-D groups, respectively). This suggests that monocular training led to improvements in contrast sensitivity that reduced the subsequent response to dichoptic training. However, it is important to emphasize that a direct between-groups comparison of monocular and dichoptic training, which was the primary purpose of the original experiment, revealed that dichoptic training resulted in significantly greater improvements than monocular training.

Overall, there are three complimentary results indicating that dichoptic training was chiefly responsible for the CS improvements found in both groups of participants. Firstly, while CS improved in the iPod/tDCS group, tDCS had no statistically significant effect, leaving dichoptic training as the primary cause of the CS improvement. Secondly, a direct comparison of monocular and dichoptic training for the goggles group showed that dichoptic training induced significantly greater CS improvements than monocular training. Thirdly, dichoptic training led to additional improvements in participants who had already received monocular training.

4.2. General discussion

It is clear from Figs. 2 and 4 that there was substantial individual variability in the magnitude and spatial frequency specificity of CS changes across participants in both groups. This is not surprising as contrast sensitivity was not directly trained and therefore it is reasonable to assume that transfer effects may vary considerably across participants. This variability may underlie the lack of a systematic pattern of correlations between CS improvements and improvements in visual acuity, stereopsis and suppression (Table 6).

As a whole, our results are consistent with the hypothesis that treatment approaches designed to rebalance inputs from the amblyopic and fellow eyes can lead to wide-ranging improvements in visual function in adult patients with amblyopia (Hess, Mansouri, & Thompson, 2011; Hess & Thompson, 2013). The transfer of dichoptic training effects to binocular vision (stereopsis and binocular combination) and visual acuity (Li, Thompson, et al., 2013; Spiegel, Li, et al., 2013) as well as contrast sensitivity is notable as these are thought to be the primary deficits experienced by patients with amblyopia (McKee, Levi, & Movshon, 2003). Furthermore, because contrast sensitivity is a fundamental component of vision that allows for the detection and recognition of visual stimuli across a wide range of spatial scales, improvements in contrast sensitivity are desirable. Such widespread transfer of learning is not typical of monocular training studies. For example, while monocular training on contrast sensitivity tasks can transfer to letter acuity (Huang et al., 2008; Polat et al., 2004), training on letter acuity tasks does not necessarily transfer to contrast sensitivity (Astle, Webb, & McGraw, 2011c).

What mechanisms might underlie the transfer of learning induced by dichoptic training? One possibility relates to the nature of the training stimulus. The moving blocks in the video game are dynamic, spatially broadband and crowd one another. Monocular training on spatially broadband stimuli (Astle et al., 2011c) and tasks that target crowding (Chung, Li, & Levi, 2012; Hussain, Webb, Astle, & McGraw, 2012) have both been shown to result in transfer of learning to letter acuity in adults with amblyopia. Furthermore, monocular training using commercially available videogames has been found to transfer to a range of visual functions including spatial attention and positional acuity in observers with amblyopia (Li et al., 2011b). These effects may reflect modulation of abnormal spatial integration by neural mechanisms subserving the amblyopic eye (Hussain et al., 2012) and/or reductions in both external and internal noise (Huang, Lu, & Zhou, 2009; Li & Levi, 2004; Li et al., 2011b). However, these mechanisms cannot account for all of the learning we observed because dichoptic training effects were larger than those induced by monocular training with the same videogame stimulus (see also Li, Thompson, et al., 2013). Therefore, binocular mechanisms are likely to be involved in the learning experienced by our participants. As described above, binocular imbalance appears to play an important role in the amblyopia syndrome. Therefore, a rebalancing of the eyes' inputs may confer improvements in both binocular and monocular function by allowing for latent abilities to be expressed and/or by removing an impediment to visual cortex plasticity that subsequently allows for broad improvements in visual function. These two possibilities are not mutually exclusive and may work together during dichoptic training.

This study has a number of limitations. Firstly, data were combined from two different studies that used different experimental designs. This prevents direct comparisons between the contrast sensitivity results from the two sets of participants. However, contrast sensitivity improvements were evident in both datasets. Secondly, the group of participants that provided test–retest data was not directly matched to the trained participants in terms of age and amblyopic eye visual acuity. Despite these differences between the groups, it is notable that on average the test–retest group did not show significant improvements from test 1 to test 2 even though the two tests were separated by a relatively short interval to maximize any possible learning effects. This was not the case for the trained participants who exhibited significant improvements in contrast sensitivity. It is also notable that we measured contrast sensitivity at a relatively high mean luminance of 200 cd/m^2. The advantage of using a higher mean luminance is that contrast sensitivity at high spatial frequencies is higher (although low spatial frequencies remain unaffected) (Van Nes & Bouman, 1967; Van Nes, Koenderine, Nas, & Bouman, 1967). Therefore, using a relatively high mean luminance increased our ability to detect any changes in contrast sensitivity at high spatial frequencies.

The finding that contrast sensitivity was improved helps us to better understand the neural site and neural basis of the previously reported improvements in letter acuity as a consequence of dichoptic training (Birch, 2013; Black et al., 2012; Hess, Mansouri, & Thompson, 2010a, 2010b; Hess et al., 2012; Knox et al., 2011; Li, Thompson, et al., 2013; Li et al., 2014; Spiegel, Li, et al., 2013; To et al., 2011). Contrast sensitivity is understood in terms of V1 function where animal studies have shown a direct relationship between the reduced sensitivity of foveal cells receiving amblyopic eye input and behavioral contrast sensitivity at high spatial frequencies (Kiorpes et al., 1998; Kiorpes & McKee, 1999). Therefore the improvements in contrast sensitivity reported here raise the possibility that that the acuity improvements are, at least partly, a consequence of improved sensitivity of cells within V1. However, another explanations are possible. These include a reduction in internal noise (Dosher & Lu, 1998; Li, Levi, & Klein, 2004) or a change in the readout of signals from early visual areas by higher-level decision-making areas (Law & Gold, 2008).

In summary, this study showed that dichoptic training, while not directly targeting monocular function, improved contrast sensitivity in the amblyopic eye. Although the exact mechanisms underlying these improvements remain to be fully elucidated, this finding further supports the idea that amblyopia is primarily a disorder of binocular vision.

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RFH and BT are named inventors on two patents concerning the treatment approach that was used in this study. The remaining authors have no conflicts of interest to declare.

References

Astle, A. T., McGraw, P. V., & Webb, B. S. (2011a). Recovery of stereo acuity in adults with amblyopia. *BMJ Case Reports*, 2011.

Astle, A. T., Webb, B. S., & McGraw, P. V. (2011b). Can perceptual learning be used to treat amblyopia beyond the critical period of visual development? *Ophthalmic and Physiological Optics, 31*(6), 564–573.

Astle, A. T., Webb, B. S., & McGraw, P. V. (2011c). The pattern of learned visual improvements in adult amblyopia. *Investigative Ophthalmology & Visual Science, 52*(10), 7195–7204.

Ball, K., & Sekuler, R. (1982). A specific and enduring improvement in visual motion discrimination. *Science, 218*(4573), 697–698.

Ball, K., & Sekuler, R. (1987). Direction-specific improvement in motion discrimination. *Vision Research, 27*(6), 953–965.

Bi, H., Zhang, B., Tao, X., Harwerth, R. S., Smith, E. L., 3rd, & Chino, Y. M. (2011). Neuronal responses in visual area V2 (V2) of macaque monkeys with strabismic amblyopia. *Cerebral Cortex, 21*(9), 2033–2045.

Birch, E. E. (2013). Amblyopia and binocular vision. *Progress in Retinal and Eye Research, 33*, 67–84.

Black, J., Maehara, G., Thompson, B., & Hess, R. F. (2011). A compact clinical instrument for quantifying suppression. *Optometry and Vision Science, 88*(2), 334–342.

Black, J. M., Hess, R. F., Cooperstock, J. R., To, L., & Thompson, B. (2012). The measurement and treatment of suppression in amblyopia. *Journal of Visualized Experiments, 70*, e3927.

Bradley, A., & Freeman, R. D. (1981). Contrast sensitivity in anisometropic amblyopia. *Investigative Ophthalmology & Visual Science, 21*(3), 467–476.

Chung, S. T., Li, R. W., & Levi, D. M. (2012). Learning to identify near-acuity letters, either with or without flankers, results in improved letter size and spacing limits in adults with amblyopia. *PLoS ONE, 7*(4), e35829.

Clavagnier, S., Thompson, B., & Hess, R. F. (2013). Long lasting effects of daily theta burst rTMS sessions in the human amblyopic cortex. *Brain Stimulation*.

Dosher, B. A., & Lu, Z. L. (1998). Perceptual learning reflects external noise filtering and internal noise reduction through channel reweighting. *Proceedings of the National academy of Sciences of the United States of America, 95*(23), 13988–13993.

Epelbaum, M., Milleret, C., Buisseret, P., & Dufier, J. L. (1993). The sensitive period for strabismic amblyopia in humans. *Ophthalmology, 100*(3), 323–327.

Epstein, W. (1967). *Varieties of perceptual learning*. New York, St. Louis, San Francisco, Toronto, London, Sydney: McGraw-Hill Book Company.

Fiorentini, A., & Berardi, N. (1980). Perceptual learning specific for orientation and spatial frequency. *Nature, 287*, 43–44.

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology, 117*(12), 2584–2596.

Gibson, E. J. (1969). *Principles of perceptual learning and development*. New York: Appleton-Century-Crofts (pp. viii, 537).

Gibson, E. J. (1991). *An odyssey in learning and perception*. Cambridge, Massachusetts, London, England: A Bradford Book, The MIT Press.

Hess, R. F., Campbell, F. W., & Greenhalgh, T. (1978). On the nature of the neural abnormality in human amblyopia; neural aberrations and neural sensitivity loss. *Pflugers Archiv European Journal of Physiology, 377*(3), 201–207.

Hess, R. F., & Howell, E. R. (1977). The threshold contrast sensitivity function in strabismic amblyopia: Evidence for a two type classification. *Vision Research, 17*(9), 1049–1055.

Hess, R. F., Mansouri, B., & Thompson, B. (2010a). A binocular approach to treating amblyopia: Antisuppression therapy. *Optometry and Vision Science, 87*(9), 697–704.

Hess, R. F., Mansouri, B., & Thompson, B. (2010b). A new binocular approach to the treatment of Amblyopia in adults well beyond the critical period of visual development. *Restorative Neurology and Neuroscience, 28*, 1–10.

Hess, R. F., Mansouri, B., & Thompson, B. (2011). Restoration of binocular vision in amblyopia. *Strabismus, 19*(3), 110–118.

Hess, R. F., & Thompson, B. (2013). New insights into amblyopia: Binocular therapy and noninvasive brain stimulation. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 17*(1), 89–93.

Hess, R. F., Thompson, B., Black, J. M., Maehara, G., Zhang, P., Bobier, W. R., et al. (2012). An iPod treatment for amblyopia: An updated binocular approach. *Optometry, 83*(2), 87–94.

Holmes, J. M., & Clarke, M. P. (2006). Amblyopia. *Lancet, 367*(9519), 1343–1351.

Huang, C. B., Lu, Z. L., & Zhou, Y. (2009). Mechanisms underlying perceptual learning of contrast detection in adults with anisometropic amblyopia. *Journal of Vision, 9*(11), 2421–2514.

Huang, C. B., Zhou, Y., & Lu, Z. L. (2008). Broad bandwidth of perceptual learning in the visual system of adults with anisometropic amblyopia. *Proceedings of the National academy of Sciences of the United States of America, 105*(10), 4068–4073.

Hussain, Z., Webb, B. S., Astle, A. T., & McGraw, P. V. (2012). Perceptual learning reduces crowding in amblyopia and in the normal periphery. *Journal of Neuroscience, 32*(2), 474–480.

Kim, S., Stephenson, M. C., Morris, P. G., & Jackson, S. R. (2014). TDCS-induced alterations in GABA concentration within primary motor cortex predict motor learning and motor memory: A 7T magnetic resonance spectroscopy study. *Neuroimage, 99*, 237–243.

Kiorpes, L., Kiper, D. C., O'Keefe, L. P., Cavanaugh, J. R., & Movshon, J. A. (1998). Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *Journal of Neuroscience, 18*(16), 6411–6424.

Kiorpes, L., & McKee, S. P. (1999). Neural mechanisms underlying amblyopia. *Current Opinion in Neurobiology, 9*(4), 480–486.

Knox, P. J., Simmers, A. J., Gray, L. S., & Cleary, M. (2011). An exploratory study: Prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia. *Investigative Ophthalmology & Visual Science, 53*(2), 817–824.

Kontsevich, L. L., & Tyler, C. W. (1999). Bayesian adaptive estimation of psychometric slope and threshold. *Vision Research, 39*(16), 2729–2737.

Kraft, A., Roehmel, J., Olma, M. C., Schmidt, S., Irlbacher, K., & Brandt, S. A. (2010). Transcranial direct current stimulation affects visual perception measured by threshold perimetry. *Experimental Brain Research, 207*(3–4), 283–290.

Kupfer, C. (1957). Treatment of amblyopia exanopsia in adults: A preliminary report of seven cases. *American Journal of Ophthalmology, 43*(6), 918–922.

Kwon, M., Lu, Z. L., Miller, A., Kazlas, M., Hunter, D. G., & Bex, P. J. (2014). Assessing binocular interaction in amblyopia and its clinical feasibility. *PLoS ONE, 9*(6), e100156.

Law, C. T., & Gold, J. I. (2008). Neural correlates of perceptual learning in a sensory-motor, but not a sensory, cortical area. *Nature Neuroscience, 11*(4), 505–513.

Levi, D. M., & Harwerth, R. S. (1977). Spatio-temporal interactions in anisometropic and strabismic amblyopia. *Investigative Ophthalmology & Visual Science, 16*(1), 90–95.

Levi, D. M., & Li, R. W. (2009a). Improving the performance of the amblyopic visual system. *Philosophical Transactions of the Royal Society of London. Series B, Biological sciences, 364*(1515), 399–407.

Levi, D. M., & Li, R. W. (2009b). Perceptual learning as a potential treatment for amblyopia: A mini-review. *Vision Research, 49*(21), 2535–2549.

Levi, D. M., Polat, U., & Hu, Y. S. (1997). Improvement in Vernier acuity in adults with amblyopia. Practice makes better. *Investigative Ophthalmology & Visual Science, 38*(8), 1493–1510.

Li, J., Hess, R. F., Chan, L. Y., Deng, D., Chen, X., Yu, M., et al. (2013a). How best to assess suppression in patients with high anisometropia. *Optometry and Vision Science, 90*(2), e47–e52.

Li, J., Hess, R. F., Chan, L. Y. L., Deng, D., Yang, X., Chen, X., et al. (2013b). Quantitative measurement of interocular suppression in anisometropic amblyopia: A case-control study. *Ophthalmology, 120*(8), 1672–1680.

Li, J., Thompson, B., Deng, D., Chan, L., Yu, M., & Hess, R. F. (2013). Dichoptic training enables the adult amblyopic brain to learn. *Current Biology, 23*(8), R308–R309.

Li, J., Thompson, B., Lam, C. S. Y., Deng, D., Chan, L. Y. L., Maehara, G., et al. (2011). The role of suppression in amblyopia. *Investigative Ophthalmology & Visual Science, 52*(7), 4167–4176.

Li, R. W., & Levi, D. M. (2004). Characterizing the mechanisms of improvement for position discrimination in adult amblyopia. *Journal of Vision, 4*(6), 476–487.

Li, R. W., Levi, D. M., & Klein, S. A. (2004). Perceptual learning improves efficiency by re-tuning the decision 'template' for position discrimination. *Nature Neuroscience, 7*(2), 178–183.

Li, R. W., Ngo, C., Nguyen, J., & Levi, D. M. (2011). Video-game play induces plasticity in the visual system of adults with amblyopia. *PLoS Biology, 9*(8), e1001135.

Li, S. L., Jost, R. M., Morale, S. E., Stager, D. R., Dao, L., Stager, D., et al. (2014). A binocular iPad treatment for amblyopic children. *Eye (London)*.

Mansouri, B., Thompson, B., & Hess, R. F. (2008). Measurement of suprathreshold binocular interactions in amblyopia. *Vision Research, 48*(28), 2775–2784.

McKee, S. P., Levi, D. M., & Movshon, J. A. (2003). The pattern of visual deficits in amblyopia. *Journal of Vision, 3*(5), 380–405.

Narasimhan, S., Harrison, E. R., & Giaschi, D. E. (2012). Quantitative measurement of interocular suppression in children with amblyopia. *Vision Research, 66*, 1–10.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology, 527*(Pt 3), 633–639.

Polat, U., Ma-Naim, T., Belkin, M., & Sagi, D. (2004). Improving vision in adult amblyopia by perceptual learning. *Proceedings of the National academy of Sciences of the United States of America, 101*(17), 6692–6697.

Scheiman, M. M., Hertle, R. W., Beck, R. W., Edwards, A. R., Birch, E., Cotter, S. A., et al. (2005). Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Archives of Ophthalmology, 123*(4), 437–447.

Sengpiel, F., Jirmann, K. U., Vorobyov, V., & Eysel, U. T. (2006). Strabismic suppression is mediated by inhibitory interactions in the primary visual cortex. *Cerebral Cortex, 16*(12), 1750–1758.

Simmers, A. J., & Gray, L. S. (1999). Improvement of visual function in an adult amblyope. *Optometry and Vision Science, 76*(2), 82–87.

Spiegel, D. P., Byblow, W. D., Hess, R. F., & Thompson, B. (2013). Anodal transcranial direct current stimulation transiently improves contrast sensitivity and normalizes visual cortex activation in individuals with amblyopia. *Neurorehabilitation and Neural Repair*.

Spiegel, D. P., Hansen, B. C., Byblow, W. D., & Thompson, B. (2012). Anodal transcranial direct current stimulation reduces psychophysically measured surround suppression in the human visual cortex. *PLoS ONE, 7*(5), e36220.

Spiegel, D. P., Li, J., Hess, R. F., Byblow, W. D., Deng, D., Yu, M., et al. (2013). Transcranial direct current stimulation enhances recovery of stereopsis in adults with amblyopia. *Neurotherapeutics*.

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., et al. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *Journal of Neuroscience, 29*(16), 5202–5206.

Thompson, B., Mansouri, B., Koski, L., & Hess, R. F. (2008). Brain plasticity in the adult: Modulation of function in amblyopia with rTMS. *Current Biology, 18*(14), 1067–1071.

To, L., Thompson, B., Blum, J. R., Maehara, G., Hess, R. F., & Cooperstock, J. R. (2011). A game platform for treatment of amblyopia. *IEEE Transactions on Neural Systems and Rehabilitation Engineering: A Publication of the IEEE Engineering in Medicine and Biology Society, 19*(3), 280–289.

Van Nes, F. L., & Bouman, M. A. (1967). Spatial modulation transfer in the human eye. *Journal of the Optical Society of America, 57*(3), 401–406.

Van Nes, F. L., Koenderine, J. J., Nas, H., & Bouman, M. A. (1967). Spatiotemporal modulation transfer in the human eye. *Journal of the Optical Society of America, 57*(9), 1082–1087.

Wick, B., Wingard, M., Cotter, S., & Scheiman, M. (1992). Anisometropic amblyopia: Is the patient ever too old to treat? *Optometry and Vision Science, 69*(11), 866–878.

Zhou, Y., Huang, C., Xu, P., Tao, L., Qiu, Z., Li, X., et al. (2006). Perceptual learning improves contrast sensitivity and visual acuity in adults with anisometropic amblyopia. *Vision Research, 46*(5), 739–750.