Eye Movements, Strabismus, Amblyopia, and Neuro-Ophthalmology

An Exploratory Study: Prolonged Periods of Binocular Stimulation Can Provide an Effective Treatment for Childhood Amblyopia

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Purpose. The purpose of the present study was to explore the potential for treating childhood amblyopia with a binocular stimulus designed to correlate the visual input from both eyes.

Methods. Eight strabismic, two anisometropic, and four strabismic and anisometropic amblyopes (mean age, 8.5 ± 2.6 years) undertook a dichoptic perceptual learning task for five sessions (each lasting 1 hour) over the course of a week. The training paradigm involved a simple computer game, which required the subject to use both eyes to perform the task.

Results. A statistically significant improvement ($t_{(13)} = 5.46$; $P = 0.0001$) in the mean visual acuity (VA) of the amblyopic eye (AE) was demonstrated, from 0.51 ± 0.27 logMAR before training to 0.42 ± 0.28 logMAR after training with six subjects gaining 0.1 logMAR or more of improvement. Measurable stereofunction was established for the first time in three subjects with an overall significant mean improvement in stereoacuity after training ($t_{(13)} = 2.64$; $P = 0.02$).

Conclusions. The dichoptic-based perceptual learning therapy employed in the present study improved both the monocular VA of the AE and stereofunction, verifying the feasibility of a binocular approach in the treatment of childhood amblyopia. (*Invest Ophthalmol Vis Sci.* 2012;53:817–824) DOI:10.1167/iovs.11-8219

Amblyopia is a common cause of visual impairment that affects approximately 3% to 4% of the population.[1,2] The condition is usually associated with an amblyogenic factor such as strabismus and/or anisometropia and is characterized by reduced VA, despite full optical correction and no physical abnormality of the affected eye.

Amblyopia is the most frequently treated pediatric eye condition in the developed world and imposes a significant economic burden on health care.[3] Recent clinical studies have produced clear protocols for dose, timing, and duration of occlusion therapy.[4–6] However, despite evidence that most improvement in visual function occurs within the first 3 months of treatment,[6] the mean time under specialist care is still approximately 35 months with a typical patching duration of about 18 months.[3] Successful treatment outcomes are limited by poor compliance,[7–9] suboptimal treatment regimens,[10] and regression in VA.[11]

Recent studies using animal models have found that correlated binocular vision is essential for successful recovery from experimentally induced amblyopia[12–16] and that the absence of correlated binocular vision may play a critical role in the development of amblyopia.[13] Other studies have cast doubt on the hypothesis that amblyopes do not possess cortical binocular connections,[17] leading to the suggestion that active binocular suppression causes the amblyopic deficit rather than a reduction in cortical responsiveness to the amblyopic eye.[17] In the clinical domain, it has now been established that correction of refractive error alone can be sufficient to improve visual acuity in strabismic amblyopia despite decorrelated visual inputs.[18,19]

None of the current treatments for amblyopia consider binocular factors; indeed, occlusion/penalization therapy temporarily disrupts correlated binocular vision. A recent large-scale study investigating visual function in amblyopia showed marked intersubject variability in the characteristics of visual loss within the clinically defined categories and reported that the presence of binocular function was a major factor in determining the pattern of the visual deficit.[20,21]

Perceptual learning studies show that repetitive practice of a specific visual task can improve performance in both children and adults with amblyopia, for tasks such as vernier acuity,[22,23] spatial interaction,[24] contrast detection,[25] and letter recognition.[26] It has been found that learning transfers with variable success into improvements in VA[23–25,27–33] and stereopsis.[33,34]

Although most of these studies were performed monocularly, recent research by Hess et al.[35,36] has shown that, when stimuli are equated for visibility between the AE and fellow eye (FE), a binocular approach to treatment can be successful in adult amblyopia.[35,36] Periods of prolonged dichoptic binocular viewing appear to improve monocular VA, reduce suppression, and/or increase binocular interaction. In some subjects, the establishment of stereofunction was found.[35,36] Cleary et al.[37] tested an interactive binocular therapy and found similar results for younger amblyopes (age range, 6.1–11.4 years) who had not complied with or responded to occlusion therapy. More recently, two perceptual learning studies employed paradigms that specifically targeted stereoacuity[38,39] and demonstrated significant improvements in binocular function through repetitive practice.

The results of these studies reflect neural plasticity in amblyopia and suggest that perceptual learning would provide a method for treating amblyopia. Research continues to examine the underlying mechanisms that generate improvement in function with perceptual learning and, importantly, whether these improvements can transfer to other visual functions.[40]

The purpose of the present study was to explore the potential for treating childhood amblyopia with prolonged view-

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ing of a binocular stimulus adapted to correlate the visual input from both eyes.

METHODS

Subjects

Fourteen children with amblyopia (mean age, 8.5 ± 2.6 years) took part in the study. All subjects had undergone occlusion therapy and had been discharged from the Hospital Eye Service when VA improvement reached a plateau, despite ongoing occlusion therapy, for a period of 6 months. All subjects reported good compliance with occlusion therapy with no regression of previous VA gains.

For the purposes of this study amblyopia was defined as a corrected interocular difference of 0.1 logMAR. Clinical diagnosis revealed eight strabismic amblyopes, four strabismic and anisometropic (mixed) amblyopes, and two anisometropic amblyopes. Anisometropia was defined as an interocular difference of greater than 1.00 D in any meridian. Clinical details of all subjects can be found in Table 1.

All experimental procedures were approved by the School of Life Science Ethics Committee and complied with the Declaration of Helsinki. Informed consent was obtained from the parent or guardian and informed assent from the child before testing began.

Procedure

A full optometric and orthoptic examination was undertaken in each subject. This included objective (retinoscopy) and subjective refraction with best VA (logMAR), angle of strabismus with prism cover test, presence or absence of fusion (Bagolini lenses), the area and depth of suppression (prism and Sbiza bar), and stereofunction (TNO and near Frisby). When the Frisby stereotest was used, care was taken to minimize monocular clues.[41]

An additional method of quantifying the density of suppression was undertaken using crossed polarizers. With rotating polarizers in front of the FE, a red filter was placed in front of the AE, and the subject was asked to fixate on a spot light. The front polarizer was rotated until the light changed color. The light transmission through crossed polarizers

TABLE 1. Clinical Characteristics of the Amblyopic Children

Subject	Age (years)	Spectacle Prescription	Visual Acuity (logMAR)	Ocular Alignment	Bagolini Lenses	Stereopsis (seconds of arc)	
						TNO	Frisby
■	6	RE +4.00/+1.50 x110° LE +4.00/+1.50 x 85°	0.22 0.02	10ΔSOT	BV response	240	120
○	7	RE +2.75/+0.50 x 20° LE +3.00/+0.50 x 15°	0.18 0.0	10ΔSOT	Variable BV response	nil	nil
▽	8	RE +2.75DS LE +3.50DS	0.0 0.10	2 ΔSOT	BV response	nil	nil
◇	10	RE +6.25/+1.00 x 85° LE +6.50DS	0.66 0.1	10ΔSOT	Variable BV response	nil	nil
●	8	RE +0.50/+2.75 x 100° LE +1.00DS	0.5 0.0	Straight	BV response	30	30
◁	5	RE +2.00/+0.50 x 180° LE +2.50/+0.50 x 180°	0.2 0.52	25ΔSOT	Suppression	nil	nil
▲	10	RE +5.50/+0.50 x 70° LE +6.00/+0.50 120°	0.0 0.44	10ΔSOT	BV response	240	75
□	11	RE +1.00/+2.50 x 42° LE +0.25/+0.75 x 70°	1.0 0.02	25ΔXOT	Suppression	nil	nil
▷	9	RE +0.50DS LE +0.50/+1.25 x 90°	0.0 0.58	14ΔSOT	Suppression	nil	nil
□	10	RE +0.50DS LE +4.50/+0.50 x 10°	-0.06 0.8	Straight	Suppression	nil	nil
◆	5	RE +4.50/+0.25 x 30° LE +5.25DS	0.20 0.5	2ΔSOT	BV response	60	55
●	11	RE +0.50/+0.25 x 90° LE +5.00/+1.25 x 88°	0.04 0.92	3ΔSOT	BV response	nil	600
✙	14	RE +7.50DS LE +8.50DS	0.0 0.26	4ΔSOT	Suppression	nil	nil
●	6	RE plano LE plano	0.2 0.4	4ΔSOT	BV response	nil	340

Red: strabismic amblyopes; *blue:* anisometropic amblyopes; and *green:* mixed (strabismus and anisometropia) amblyopes. *Open symbols:* subjects with no clinically demonstrable stereofunction before training.

varies nonlinearly with rotation of the anterior polarizing filter and follows a cosine^2 function

$$L = L_{\max} \times \text{cosine}^2\ \Phi$$

where Φ is the angle of rotation.[42] The larger the angle of rotation, the greater the density of suppression, with a value of 0 being equivalent to no suppression.

Apparatus and Stimuli

To assess the initial level of binocular interaction, we used a dichoptically viewed global motion detection paradigm.[35,36,42,43] The paradigm has been refined[44] and validated against traditional clinical methods. Dichoptic presentation of the images was achieved with an augmented reality head-mounted display (Z800 Pro Dual System; eMagin, Bellevue, WA; see Fig. 1 and Appendix A for further details).

Global motion thresholds were measured using a two-alternative, forced choice (2-AFC) discrimination task. Stimulus levels were varied from trial to trial according to an adaptive staircase procedure (three-down, one-up) designed to concentrate observations near the 79% threshold level. The staircase terminated after six reversals, and the threshold of that staircase was averaged over the last five reversals. Visual feedback was given in the form of the fixation dot changing in color to reinforce correct responses. In this well-established paradigm, the signal is created from a percentage of the dots within a random-dot-kinematogram (RDK) moving in the same direction (left or right) among the remaining dots, which move in random directions. For a given presentation, subjects have to discriminate the direction of the coherent global motion of the signal dots. Performance is quantified in terms of the minimum number of signal dots required to enable direction discrimination.

Binocular motion coherence thresholds (with the signal and noise dots presented at 70% contrast to both eyes) were measured for each subject. The mean threshold number of dots was then used in a second program in which the signal dots for motion coherence were presented to the AE only, and the noise dots were presented to the FE. The contrast of the signal to the AE was set at 70%, and the contrast of the noise dots to the FE increased from 0% contrast to threshold. Varying the contrast of the signal and noise independently makes it possible to present stimuli with high contrast to the AE and low contrast to the FE allowing the extent of binocular interaction present to be measured. This technique of matching visibility between eyes allows for maximum binocular combination of the visual stimuli. See Black et al.[44] and Li et al.[45] for further details.

Training Sessions

For the perceptual learning task, the subjects played a simple computer game that involved the manipulation of the position and orientation of falling four-block shapes (Tetris; Honolulu, HI).[46] The purpose of the game is to form a complete wall of blocks with no gaps. This game was modified so that the falling blocks were presented to the AE, and the blocks that formed the wall were presented to the FE via the head-mounted display (HMD) goggles. Interocular contrast thresholds measured previously were used to match the visibility of the blocks in each eye by reducing the contrast of the blocks presented to the FE, and the blocks presented to the AE were maintained at a 70% contrast (Fig. 2). This stimulus arrangement requires binocular interaction to complete the task. The task was performed with full spectacle correction and with the eyes in the habitual viewing position. At the start of the task, the percepts were aligned using crosshairs. The game was self-paced, beginning with slow speeds that could be performed easily and training was for 1 h/d for 5 days. Before each session, the contrast threshold was measured as described above, using the RDK paradigm, and the contrast of the blocks presented to the FE was adjusted accordingly. This quantified improvements in contrast threshold ratio through changes in contrast required to achieve binocularity. At the end of the last training session, all clinical measurements were repeated.

RESULTS

Pretherapy

No significant correlation was found between the interocular contrast ratio and interocular difference (IOD) in traditional VA measures (Fig. 3a; $r = -0.14$; $P = 0.63$).

Previous studies have suggested that the interocular contrast ratio is a reliable objective measure of interocular suppression[35,36]; however, in the present study, no significant correlation was found between the density of suppression (measured with crossed polarizers) and either the interocular contrast ratio (Fig. 3b; $r = -0.003$; $P = 0.99$) or the IOD in VA (Fig. 3c; $r = 0.51$; $P = 0.25$) in the seven subjects with suppression.

Effect of Therapy

Figure 4a shows pre- and posttraining thresholds for VA(AE) in individual subjects. The solid line represents the line of equality, thus values plotted below this line represent an improvement in VA. A statistically significant improvement ($t_{(13)} = 5.46$; $P = 0.0001$) in the mean VA of the AE was demonstrated, from 0.51 ± 0.27 logMAR before training to 0.42 ± 0.28 logMAR after training, with six subjects gaining a clinically significant (outside previously documented limits of test–retest reliability[47]) 0.1 logMAR or more of improvement. Methods of defining outcome in amblyopia therapy have been discussed.[48] If the amblyopic deficit is quantified in terms of the proportion of the deficit corrected, as follows:

$$\frac{\text{VA of AE at start} - \text{VA of AE end of treatment}}{\text{VA of AE at start} - \text{VA of FE end of treatment}}$$

FIGURE 1. A 5-year-old subject comfortably wearing the dual HMD goggles.

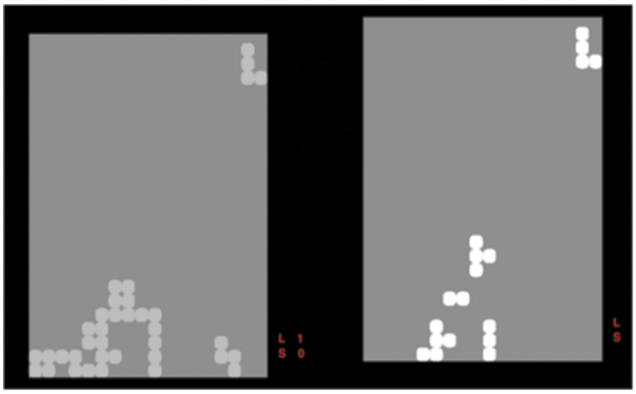

Figure 2. A single frame of the video game, as viewed through the HMD goggles. In this example, the *left* panel represents the image seen by the left eye (in this case the fellow eye). The *right* panel is the high-contrast image seen by the amblyopic eye. Differences in the visibility of the blocks can clearly be seen.

then 22% of the amblyopic deficit in this subject group was corrected by 5 hours of binocular therapy in 1 week and 12 of the 14 subjects showed an improvement in VA (Table 2). Table 2 summarizes individual improvement in visual function after training, and it can be seen that improvement in VA ranged from none measurable to 54%. The subject's age did not correlate significantly with the magnitude of improvement ($r = -0.06$; $P = 0.85$).

Figure 4b shows pre- and posttraining thresholds for the interocular contrast ratio in individual subjects. The solid line represents the line of equality: Values plotted above this line represent improvement in the contrast threshold ratio. Seven subjects showed an improvement in their contrast ratio with three of these subjects (red open circle, red filled triangle, and blue filled circle) improving performance to a level where the two eyes equated with respect to contrast and the interocular contrast ratio was 1. The group mean improvement in interocular contrast ratio after training failed to reach significance ($t_{(13)} = -1.76$; $P = 0.10$).

The effect of training on depth of suppression measured with the cross-polarizer method can be seen in Figure 4c. Very little effect is evident, with no significant difference before and after training ($t_{(13)} = 1$; $P = 0.34$).

Measureable stereofunction was established in three subjects (red open circle, red open inverted triangle, and green open square) for the first time. A further four subjects showed an improvement in stereoacuity, A significant group difference in stereoacuity was found before and after training (Fig. 4d; $t_{(13)} = 2.64$; $P = 0.02$).

It has been shown previously that the type of stereotest influences measurable thresholds and the results from different tests are not interchangeable.[49] The Frisby stereotest was found to be the most appropriate for determining the presence or absence of stereopsis and best measurable stereopsis.[49] In the present study, only 4 of the 14 subjects' stereopsis was measurable by the TNO test; therefore, no posttraining analysis was undertaken on the TNO results.

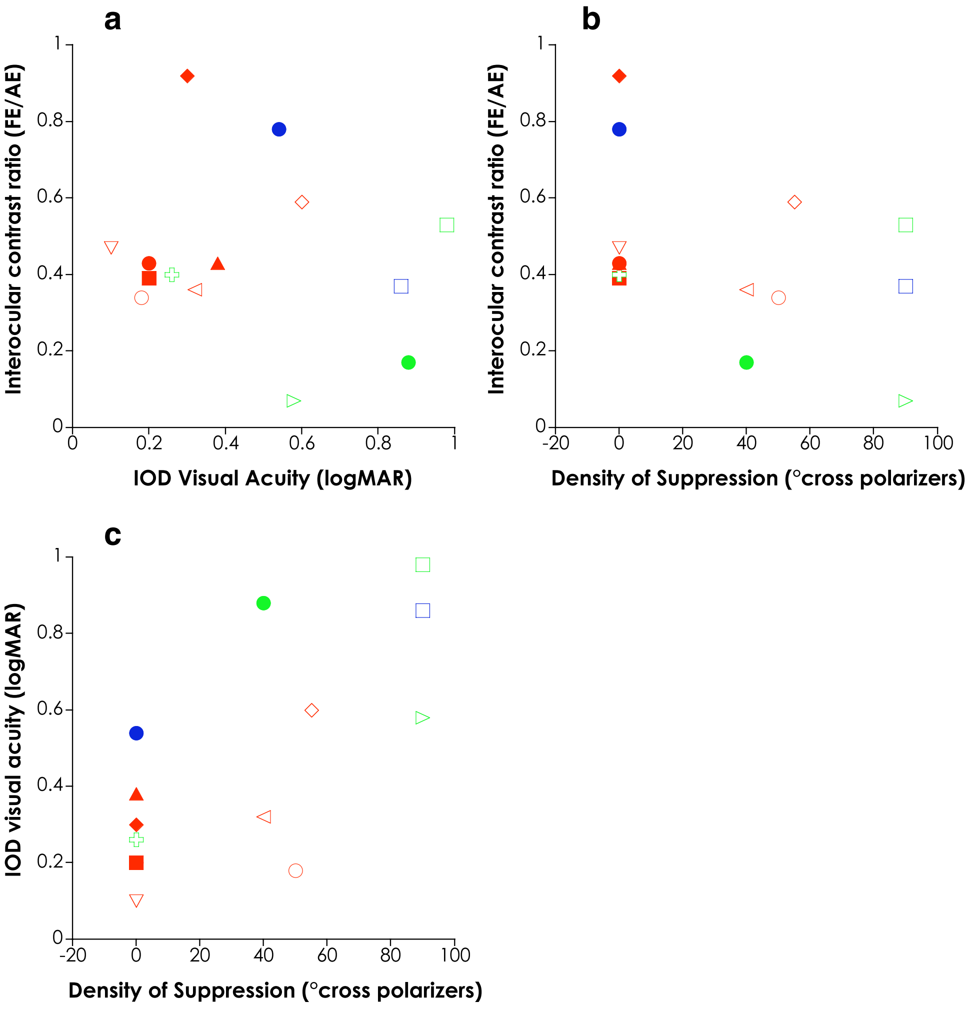

Figure 3. Pretraining. (**a**) The interocular difference in visual acuity (traditional linear logMAR) and the interocular contrast ratio; (**b**) a comparison of the interocular contrast ratio plotted against the density of suppression as measured by the cross-polarizer method; (**c**) the interocular difference in visual acuity (traditional linear logMAR) and the density of suppression as measured by the cross-polarizer method. As a value of 0 indicates no suppression (the greater the angle of rotation the more dense the interocular suppression), these amblyopes were omitted from the statistical analysis and are represented on the graph for illustrative purposes. Symbol nomenclature can be found in Table 1.

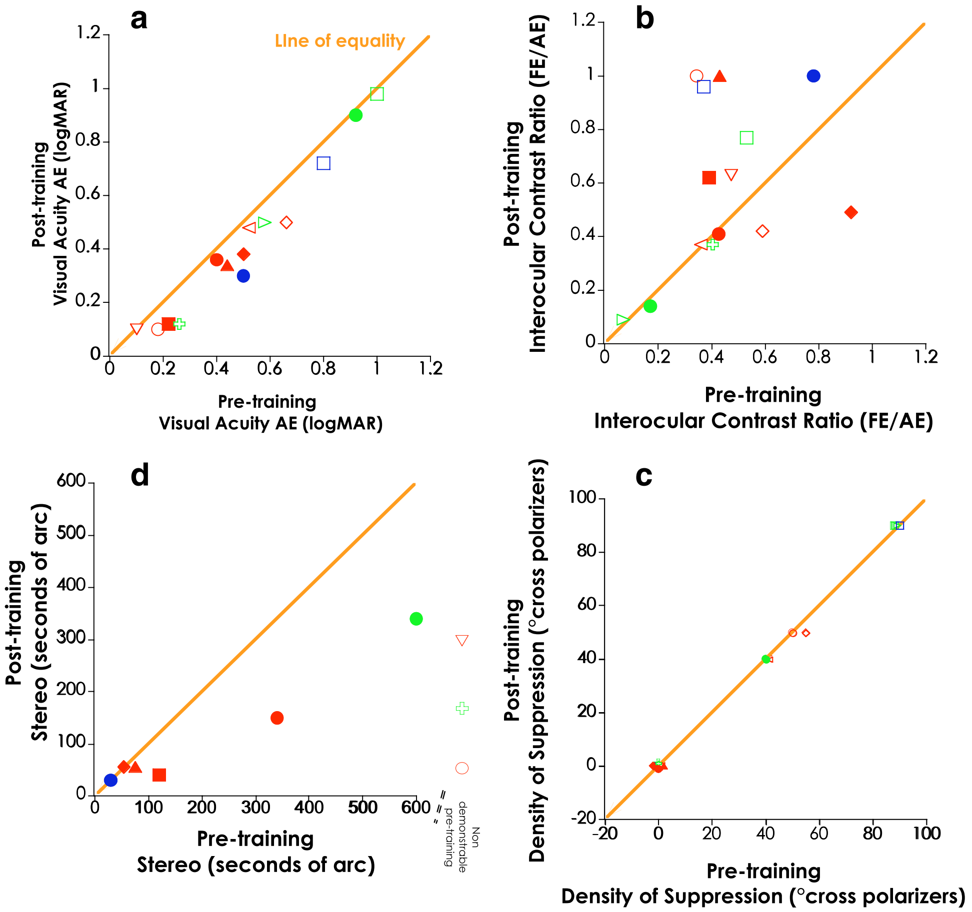

FIGURE 4. Posttraining. A comparison between pre- and posttraining thresholds in visual function. *Solid line:* line of equality. (**a**) logMAR visual acuity of the amblyopic eye. Values lying below the line represent an improvement in visual function. (**b**) The interocular contrast ratio (FE/AE). Values lying above the line represent an improvement in visual function. One subject (*red filled diamond*) showed variability in contrast ratios throughout the week, with the reading taken on the final day being particularly low. (**c**) The density of suppression, as measured by the cross-polarizer method. Most of the subjects lie on the line of equality (the *symbols* have been minimized to clearly display overlapping points) showing no change in measures of interocular suppression with training. (**d**) Stereo function as measured by the Frisby stereotest. Points lying below the line show an improvement in stereo function. There are only nine subjects plotted, as five of the subjects had no measurable stereoacuity before or after training. The three subjects (*red open circle*; *red inverted open triangle*; and *green open triangle*) beyond the *dashed/broken line* on the *x*-axis had no measurable stereopsis pretraining. Symbol nomenclature can be found in Table 1.

The three subjects with large-angle squints (red open left-facing triangle, green open square, and green open right-facing triangle), and the two subjects with the poorest VA(AE) (green open square and green open circle) showed little or no improvement in VA(AE) or in stereofunction. Conversely, the four subjects showing the greatest improvement in VA(AE) (40% or more: red open circle, red filled square, blue filled circle, green open triangle) had small angle strabismus or no deviation when refractive error was corrected, binocular fusion and VA(AE) of no worse than 0.5 logMAR. The three subjects who gained measurable stereoacuity for the first time (red open circle, red inverted triangle, green open square) also had a small-angle strabismus or no deviation when refractive error was corrected, binocular fusion, and a VA(AE) no worse than 0.3 logMAR.

DISCUSSION

In the visual domain perceptual learning is an established phenomenon.[50–53] but in recent years, there has been a resurgence of interest in the application of perceptual learning techniques to the treatment of amblyopia.[38,40,23–31,34,37,54–61] Some studies found that improvements in visual function with training have been generalizable to other tasks.[24,26,28,54] This suggests that perceptual learning protocols might be important in providing a possible alternative or supplement to traditional amblyopia therapy.

Most studies employing perceptual learning techniques in amblyopia have been based on monocular paradigms. The most recent study involving juvenile amblyopes[33] reports similar improvements in overall linear acuity (0.1–0.18 lines) to those found in the present study. Although this study examined children of a different age range from that in the present study, the difference in the amount of training required to produce changes in VA is substantial. The children in the study by Liu et al.[33] underwent 40 to 60 hours of monocular training, whereas in the present study, similar improvements were obtained with five sessions lasting 1 hour over the course of 1 week. Although this appears to be a short training period for a perceptual learning task, a recent study where participants were trained on a motion–color conjunction search task for five consecutive days (also 1 hour per day) showed an increase in the volume of gray matter concurrent with improvements in the task,[62] suggesting that cortical plasticity can be modulated over very short time scales. Whether the gains over a short treatment time observed in the present study resulted from the binocular modality of the training paradigm warrants further investigation.

Recently, two perceptual learning studies have specifically targeted improvements in binocular vision by employing stereotasks. Astle et al.[39] reported an improvement in the binocular function of two adults with anisometropic amblyopia who were trained initially with a monocular task, but whose binocular function improved further with a stereotask, and Ding and Levi[38] reported improvements in stereopsis in five adults with reduced stereoacuity, after perceptual learning with stereoscopic gratings.

Hess et al. [35,36] have extensively used dichoptic stimulation over prolonged periods of viewing with adult amblyopes, using the same RDK paradigm employed in the present study. They reported improvement in VA of the AE, a reduction in suppression and a strengthening of binocular fusion.[35,36] In addition, stereoscopic function was established in the majority of patients tested. They conclude that the basis for a binocular treatment of amblyopia should be aimed at reducing suppres-

Table 2. Improvements in Visual Function

Subject	VA (AE)	Interocular Contrast Ratio	Stereoacuity	% Improvement in VA (AE)
■	✔	✔	✔	44
○	✔	✔	✔	45
▽	✗	✔	✔	0
◇	✔	✗	✗	27
●	✔	✔	✔	26
◁	✔	✗	✗	16
▲	✔	✔	✗	40
□	✔	✔	✗	2
▷	✗	✗	✗	0
□	✔	✔	✗	9
◆	✔	✗	✗	33
●	✔	✗	✔	2
✚	✔	✗	✔	54
●	✔	✗	✔	17

A summary of whether individual subjects showed improvements in VA(AE), interocular contrast threshold ratio, and stereoacuity (Frisby) and the overall percentage of improvement for the VA(AE) deficit after dichoptic training. Nomenclature as in Table 1.

sion as a first step. In the present study no correlation was found between depth of suppression and VA(AE) before training, and there was no reduction in the depth of suppression after training. This result suggests that reduction of suppression may not be necessary before improvements in VA and/or stereoacuity can be obtained. Clinically, it is accepted that suppression can coexist with normal VA (alternating strabismus),[63] and excellent levels of stereoacuity (intermittent strabismus).[64]

The dichoptic-based learning therapy used in the present study appears to be effective in improving monocular VA(AE) and stereofunction in those children who did not have a large-angle squint and who had a VA(AE) no worse than 0.5 logMAR. These results establish the feasibility of employing a binocular stimulus adapted to correlate the visual input to both eyes in the treatment of childhood amblyopia. The heterogeneous nature of amblyopia means that greater numbers of subjects would have to be studied to determine inclusion criteria for successful treatment with respect to type and degree of amblyopia. The results of the present study suggest that the angle of strabismus may be an important consideration.

A limitation of dichoptic stimulation in treating children, who have a manifest strabismus, is that a nonfoveal part of the retina is being stimulated in the AE. It should be possible to use a prism in these strabismic subjects that would align the images into bifoveal positions, but the risk of causing intractable diplopia was perceived to be too great to employ such a strategy in the present study.

All subjects in this study had previously reached a VA plateau under occlusion treatment. It should be emphasized that these children had all been compliant with previous occlusion and are therefore fundamentally different from those reported in the literature to have failed occlusion therapy and demonstrated subsequent improvements in visual function as part of a research trial.

It is possible that some patients who do not respond to existing treatments and/or show regression in visual function after treatment, may obtain an improved outcome with this binocular approach to treatment. The HMD goggles described herein are amenable to children and provide a portable alternative for dichoptic training paradigms in the clinical environment. The task itself is also stimulus nonspecific, and so there would be no reason to doubt that as long as visibility was equated between the AE and FE, similar improvement would be seen in a range of generic gaming platforms.

An understanding of the limits, time course, and mechanisms of perceptual learning is critical for developing a more effective treatment of amblyopia. It is evident from the literature that perceptual learning works in the treatment of adults[24–26,28,29] and children[23,30,33] with amblyopia. To demonstrate the potential of this technique for the clinical treatment of amblyopia, large-scale, randomized, clinical trials are needed to fully explore the validity of this approach.

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APPENDIX A

Images were generated with commercial software (MatLab; The MathWorks, Natick, MA) and displayed using Psychophysics Toolbox routines. Dichoptic presentation of the images was achieved by an augmented reality HMD (Z800 pro dual system; eMagin; Fig. 1). These head-mounted goggles have two high-contrast SVG (scalable vector graphics) OLED (organic light-emitting diode) microdisplays with a resolution of 800 × 600 pixels and a temporal frequency of 60 Hz. Each screen subtends 30° × 40° and has a simulated viewing distance of infinity. The stimulus aperture radius is 11.1°, and the positions of the two screens can be moved manually to align with interpupillary distance and perceptually, using the software, so that the crosshairs of the display are aligned.

Both right and left images contain 100 limited lifetime dots (density 0.26 dots/deg^2) presented on a homogenous medium-gray background. The diameter of each dot was 0.5° with a speed of 4.7 °/s and a stimulus duration of 1 second. Dots were bright against a mean luminance background (35 cd/m^2). The luminance modulation (Michelson contrast) and hence the visibility of the dots could be varied by increasing the luminance of the dots, with respect to the background, according to the following equation:

$$\text{Dot luminance contrast (\%)} = 100[(L_{\text{dots}} - L_{\text{background}})/(L_{\text{background}})]$$

where L_{dots} and $L_{\text{background}}$ are the dot and background luminances, respectively.