Improved Binocular Outcomes Following Binocular Treatment for Childhood Amblyopia

Krista R. Kelly,[1] Reed M. Jost,[1] Yi-Zhong Wang,[1,2] Lori Dao,[3] Cynthia L. Beauchamp,[3] Joel N. Leffler,[4] and Eileen E. Birch[1,2]

[1]Retina Foundation of the Southwest, Dallas, Texas, United States
[2]Department of Ophthalmology, UT Southwestern Medical Center, Dallas, Texas, United States
[3]ABC Eyes Pediatric Ophthalmology, PA, Dallas, Texas, United States
[4]Children's Eye Care of North Texas, PA, Plano, Texas, United States

Correspondence: Krista R. Kelly, Crystal Charity Ball Pediatric Vision Evaluation Center, Retina Foundation of the Southwest, 9600 N. Central Expressway, Suite 200, Dallas, TX 75231, USA; kkelly@rfsw.org.

KRK and RMJ contributed equally to the work presented here and should therefore be regarded as equivalent authors.

PURPOSE. Childhood amblyopia can be treated with binocular games or movies that rebalance contrast between the eyes, which is thought to reduce depth of interocular suppression so the child can experience binocular vision. While visual acuity gains have been reported following binocular treatment, studies rarely report gains in binocular outcomes (i.e., stereoacuity, suppression) in amblyopic children. Here, we evaluated binocular outcomes in children who had received binocular treatment for childhood amblyopia.

METHODS. Data for amblyopic children enrolled in two ongoing studies were pooled. The sample included 41 amblyopic children (6 strabismic, 21 anisometropic, 14 combined; age 4–10 years; ≤ 4 prism diopters [PD]) who received binocular treatment (20 game, 21 movies; prescribed 9–10 hours treatment). Amblyopic eye visual acuity and binocular outcomes (Randot Preschool Stereoacuity, extent of suppression, and depth of suppression) were assessed at baseline and at 2 weeks.

RESULTS. Mean amblyopic eye visual acuity ($P < 0.001$) and mean stereoacuity improved ($P = 0.045$), and mean extent ($P = 0.005$) and depth of suppression ($P = 0.003$) were reduced from baseline at the 2-week visit (87% game adherence, 100% movie adherence). Depth of suppression was reduced more in children aged <8 years than in those aged ≥ 8 years ($P = 0.004$). Worse baseline depth of suppression was correlated with a larger depth of suppression reduction at 2 weeks ($P = 0.001$).

CONCLUSIONS. After 2 weeks, binocular treatment in amblyopic children improved visual acuity and binocular outcomes, reducing the extent and depth of suppression and improving stereoacuity. Binocular treatments that rebalance contrast to overcome suppression are a promising additional option for treating amblyopia.

Keywords: binocular amblyopia treatment, amblyopia, binocular outcomes, interocular suppression, stereoacuity

Amblyopia is traditionally viewed as a monocular disorder, with the current standard of care being patching of the fellow eye to force use of the amblyopic eye. Patching can improve visual acuity for 73%–90% of amblyopic children, but between 15% and 50% do not achieve normal visual acuity even after years of treatment.[1-6] Furthermore, 19%–50% of successfully treated children will experience a recurrence of amblyopia.[2,7,8] In addition to decreased visual acuity, amblyopia is accompanied by binocular dysfunction, including nil or impaired stereoacuity and interocular suppression.[9-14] Yet, rarely is normal binocularity restored following patching treatment, even when normal visual acuity is achieved.[2,3,7,15-18] Because amblyopia arises from binocular discordance when pediatric eye disorders such as strabismus and/or anisometropia are present, binocular treatments may yield better vision outcomes.

Recent psychophysical and physiologic research has revealed a structurally intact binocular visual system despite the presence of amblyopia, although this system is rendered functionally monocular because of active interocular suppression.[19-22]

Several binocular treatment approaches have been developed that promote recovery of not only visual acuity, but also binocular vision.[19,23-38] One approach is to reduce suppression by decreasing the contrast of stimuli presented to the fellow eye to allow binocular combination during treatment with dichoptic games or dichoptic movies (i.e., contrast rebalanced treatment).[24-26,30-36] Our lab reported that 2 to 4 weeks of binocular treatment with games (Tetris, Dig Rush) or movies resulted in mean visual acuity improvements of 0.15 to 0.20 logMAR (1.5–2 Snellen lines) in amblyopic children.[24,26,30,32] Furthermore, the improvement with game play was significantly more than found with patching treatment for 2 weeks.[24]

Similar improvements in visual acuity have been found in amblyopic adults using the contrast rebalancing approach to amblyopia treatment, along with improved stereoacuity.[25,33-35] However, most studies, but not all,[12,24,36] assessing binocular treatment, including those from our lab, have either not reported binocular outcomes, or have shown no improvement of binocular outcomes in amblyopic children.[24-26,30-32] Some of these studies had small sample sizes, some included children

with large tropias, and most had low treatment adherence or used suppression assessment techniques that were not child-friendly. Thus, it remains to be determined whether binocularity in children benefits from binocular amblyopia treatments.

We evaluated the following binocular outcomes: stereoacuity, extent of suppression scotoma, and depth of suppression following 2 weeks of binocular treatment in amblyopic children. To increase our sample size, we pooled data from two of our binocular treatment studies: a randomized clinical trial of binocular game treatment[24] versus patching, and a single-arm study of binocular movie treatment.[26] These treatments both have the same contrast-rebalancing paradigm, have previously been reported to improve visual acuity by 1.5 to 2 lines with 2 weeks of treatment, and have good adherence rates. By overcoming limitations of previous studies, we aim to determine whether binocular deficits in amblyopia can be ameliorated by binocular treatment.

METHODS

The research protocol observed the tenets of the Declaration of Helsinki, was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and conformed to the requirements of the United States Health Insurance Portability and Privacy Act. Child assent (aged ≥10 years) and parental/legal guardian consent was obtained prior to testing and after explanation of the nature and possible consequences of the study.

Participants

Data were pooled from two ongoing studies of binocular treatment for childhood amblyopia. A total of 41 amblyopic children were enrolled; 20 game, 21 movies. Data from all children treated with the game were gathered from an ongoing randomized clinical trial comparing binocular game treatment to patching treatment (clinicaltrials.gov, study identifier NCT02365090). Children in this study were randomized to game treatment or patching at a 1:1 ratio. Visual acuity, stereoacuity, and depth of suppression data from 13 of the 20 (65%) children treated with the game in the current study have previously been published as Part A of this clinical trial (1 of 14 children enrolled in Part A who were randomized to the game missed the 2-week visit).[24] Children treated with the movies were drawn from an ongoing single-arm open-label study. Data from 6 of the 21 (29%) children treated with the movies have previously been published.[26] All inclusion/exclusion criteria were the same, and all vision assessments were conducted in a similar manner for both forms of treatment.

Inclusion Criteria. Eligible children aged 4 to 10 years were diagnosed with amblyopia due to a history of strabismus, anisometropia, or both, and referred to the Retina Foundation of the Southwest by 9 pediatric ophthalmologists in the Dallas-Fort Worth area. Eligible children had amblyopic eye best-corrected visual acuity (BCVA) of 0.3 to 0.8 logMAR (20/40–20/125), 0.1 logMAR (20/25) or better fellow eye BCVA (0.2 logMAR or better for 4-year-olds), and an interocular difference of ≥0.3 logMAR (≥3 lines). Visual acuity was stable prior to binocular treatment (i.e., ≥8 weeks in glasses, if needed)[24] OR no change in BCVA with glasses at two visits separated by 4 to 6 weeks (three children had glasses for 8 to <12 weeks, two children had glasses for 12 to <16 weeks, 35 children had glasses for ≥16 weeks, and one child had low refractive error and was not prescribed glasses prior to initiation of binocular treatment). Strabismic children were initially diagnosed with esotropia, but were aligned with surgery and/or spectacle correction to within 4 PD of orthotropia at distance and near.

Anisometropic children had ≥1.0 diopter difference in spherical equivalent or astigmatism with or without microtropia. Combined mechanism children had a history of acquired esotropia and anisometropia.

Exclusion Criteria. None of the children were born <32 weeks postmenstrual age, or had coexisting ocular or systemic disease, congenital infections/malformations, or developmental delay. English was the primary language for all children. Medical records were obtained from referring ophthalmologists to extract diagnosis, current alignment, cycloplegic refraction, and prior treatment plan.

PROCEDURE

Vision Assessment

Vision assessments were conducted at baseline and at the 2-week visit, and included:

1. Crowded monocular BCVA using the electronic visual acuity electronic Early Treatment Diabetic Retinopathy Study protocol[39,40] for children aged ≥7 years, or the Amblyopia Treatment Study HOTV protocol for children aged <7 years.[41,42]
2. Stereoacuity using Randot Preschool and Randot Butterfly tests (Stereo Optical Co., Inc., Chicago, IL, USA).
3. Extent of suppression scotoma using the Worth 4-Dot test at seven different distances. A flashlight with four equidistant lights (one white, one red, two green) was shown at seven different distances (cm) while the child wore red-green anaglyph glasses. The maximum distance at which the child could see all four lights (fusion) was noted, providing an estimate of suppression scotoma size (log deg) and fusion category.[43] (See Supplementary Table S1).
4. Depth of suppression was measured either by using a dichoptic motion coherence test that determines the maximum contrast of randomly moving dots in the fellow eye that still allows the child to discriminate the direction of coherent motion dots in the amblyopic eye[20,30] or using a dichoptic eye chart that determines the contrast ratio at which the child reports letters presented to each eye with equal likelihood.[12]

Availability and child's ability to comprehend the test determined which suppression test was completed. Note that, both techniques measure the ratio of amblyopic eye to fellow eye contrast that allows the child to simultaneously perceive images from both eyes, and were highly correlated in a pilot study in which 31 children aged 4 to 10 years completed both tests on the same day ($r = 0.89$, $P < 0.001$).

Binocular Treatment

Game. We loaned 20 children an iPad with a touch-sensitive screen and asked them to play a game at home for 1 hour a day, 5 days a week for 2 weeks (10 hours total). *Dig Rush*, an engaging action-oriented game, requires the child to use their finger to manipulate miners and their surroundings to dig for gold and return it to a cart as quickly as possible while avoiding obstacles such as fire, lava, and monsters (described in Ref. 24). There are 42 levels that increase in difficulty and the child can earn up to three stars per level (maximum star count = 126). The child can use gold to purchase items to help them dig faster and carry more gold, as well as more miners and digging tools (Fig. 1A).

Children played the game while wearing red-green anaglyphic glasses that separated game elements seen by each eye. Reduced
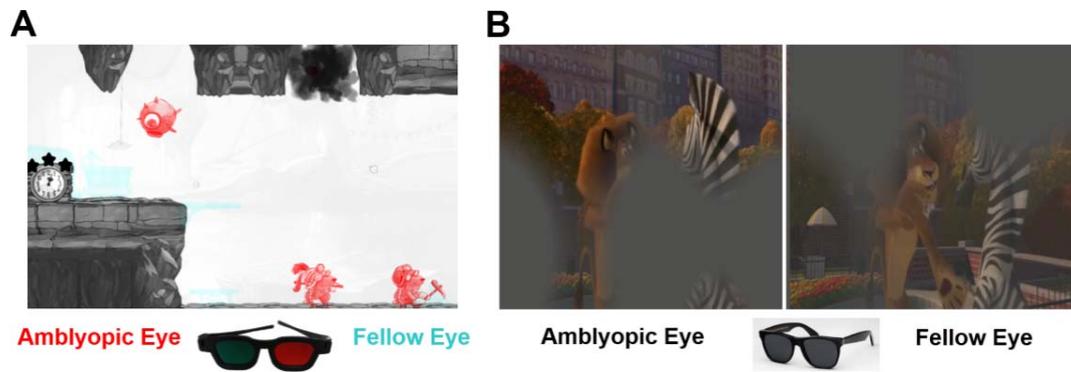
FIGURE 1. (A) Screenshot from the binocular game. Red-green anaglyph glasses separate the images. High-contrast red elements (miners, fireball) are seen by the amblyopic eye. Low-contrast blue elements (gold, cart) are seen by the fellow eye. Gray elements (rocks, ground) are seen by both eyes. (B) Monocular components of a movie showing the areas of high contrast visible only to the amblyopic eye and areas of low contrast visible only to the fellow eye, and areas visible to both eyes. Views from each eye are shown side by side for clarity but were presented superimposed on a passive 3D monitor. Polarized glasses separate the images, with high-contrast images (*left*) seen by the amblyopic eye and low-contrast images (*right*) seen by the fellow eye.

contrast elements (e.g., gold, fire) are seen by the fellow eye, high contrast elements (e.g., miners, monsters) are seen by the amblyopic eye, and high contrast background elements (e.g., ground, rocks) are seen by both eyes. In order for the child to play the game successfully, both eyes must see their respective game components. Contrast in the amblyopic eye remained at 100% contrast, while contrast in the fellow eye started at 20% but increased with game success (i.e., a star earned). At least 18 hours of game play was required to reach 100% contrast, thus ensuring no child maxed out at 100% after 2 weeks (10 hours) of treatment. If game play was unsuccessful for 30 minutes (no stars earned), fellow eye contrast was reduced. Prior to enrollment, the experimenter ensured that the child could see all elements of the game wearing the red-green glasses. Children were familiarized with the game and practiced until the experimenter was confident in their ability to understand and play the game.

Movies. Twenty-one children came to the laboratory to watch one movie per visit during the 2-week treatment period (6 visits total, approximately 9 hours of treatment). Movies were presented on a passive three-dimensional (3D) display (LG Electronics USA; Englewood, NJ, USA) and children wore polarized glasses that separate images between the two eyes. Dichoptic versions of 18 popular animated Disney/Pixar movies were created by multiplying elements presented to the amblyopic eye by a patterned mask that consisted of irregularly shaped blobs (described in Ref. 26). Elements presented to the fellow eye were multiplied by the inverse pattern mask (Fig. 1B). The blob's location and shape dynamically varied at 10 second intervals. Similar to the binocular game treatment, high-contrast elements were seen by the amblyopic eye, reduced contrast elements were seen by fellow eye, and some elements were seen by both eyes. In order for the child to appreciate the movies, both eyes must see their respective movie elements. Initial fellow eye contrast was customized based on each child's dichoptic motion coherence threshold minus 10% contrast (minimum 20%, maximum 60% initial contrast)[20,30] and incremented by 10% of the previous contrast for each subsequent movie (e.g., initial movie fellow eye contrast of 20%, subsequent movie fellow eye contrasts of 22%, 24.2%, 26.6%, 29.3%, and 32.2%).

Adherence to Protocol

Adherence with game play was obtained from an iPad log file that contained the amount of time played and the fellow eye

contrast for each play session. Movie treatment adherence was calculated by the number of hours the child watched in-lab movies. The child was monitored by at least one parent or legal guardian to ensure they were watching the movie and wearing their polarized glasses, and by study personnel who checked in on the child at 15- to 30-minute intervals.

Statistical Analyses

Stereoacuity was converted to log arcsec for analyses. Nil stereoacuity was arbitrarily assigned a value of 4 log arcsec. For extent of suppression (i.e., Worth 4-Dot), the furthest distance at which the child reported 4 dots (fusion) was converted into size of suppression scotoma in degrees, which was then converted to log degrees (log deg).[43] If no fusion was present at the shortest distance (16 cm), an arbitrary value of 1.2 log deg was given. For depth of suppression (i.e., dichoptic motion coherence or dichoptic eye chart), the minimum contrast ratio (amblyopic eye contrast/fellow eye contrast) at which the amblyopic eye was not suppressed was determined.[12,20] All analyses were conducted with an intent-to-treat approach.

Paired *t*-tests were conducted to determine whether amblyopic eye BCVA, stereoacuity, extent of suppression scotoma, and depth of suppression improved significantly from baseline to the 2-week visit. Secondary analyses included independent *t*-tests for BCVA and binocular outcomes to determine whether game treatment differed from movie treatment, and whether amblyopia types (anisometropic, strabismic + combined) or age groups (<8 years, ≥8 years) differed. Pearson *r* correlations were also conducted to determine whether baseline factors (amblyopic eye BCVA, stereoacuity, extent of suppression scotoma, and depth of suppression) were predictive of improvement in binocular outcomes. All tests were performed using a 2-tailed alpha with a significance level of 0.05.

RESULTS

A total of 6 (15%) children were diagnosed with strabismic amblyopia; 21 (51%) with anisometropic amblyopia; and 14 (34%) with combined mechanism amblyopia. The mean ± SD age was 7.0 ± 1.8 years (range, 4.4–10.7 years). Mean amblyopic eye BCVA ± SD at enrollment was 0.51 ± 0.17 logMAR (20/65 ± 1.7 lines; range, 0.3–0.8 logMAR; 20/40–20/125). Moderate amblyopia (0.3–0.6 logMAR; 20/40–20/80) was present in 30 (73%) children and severe amblyopia (0.7–

TABLE. Baseline Characteristics for All Children Who Completed 2 Weeks of Binocular Treatment

	Total ($N = 41$)	Game Treatment ($n = 20$)	Movie Treatment ($n = 21$)
Sex: F, n (%)	15 (37)	5 (25)	10 (48)
Age, y			
4 to 7, n (%)	31 (76)	15 (75)	16 (76)
8 to 10, n (%)	10 (24)	5 (25)	5 (24)
Mean ± SD	6.96 ± 1.78	6.71 ± 1.92	7.20 ± 1.64
AE BCVA, logMAR (Snellen equivalent)			
Moderate amblyopia: 0.3 to 0.6 (20/40 to 20/80), n (%)	30 (73)	15 (75)	15 (71)
Severe amblyopia: 0.7 to 0.8 (20/100 to 20/125), n (%)	11 (27)	5 (25)	6 (29)
Mean ± SD	0.51 ± 0.17	0.50 ± 0.17	0.52 ± 0.17
	(20/65 ± 1.7 lines)	(20/63 ± 1.7 lines)	(20/66 ± 1.7 lines)
FE BCVA, logMAR (Snellen equivalent)			
Mean ± SD	0.01 ± 0.09	0.02 ± 0.09	0.00 ± 0.10
	(20/20 ± 0.9 lines)	(20/21 ± 0.9 lines)	(20/20 ± 1.0 lines)
Prior amblyopia treatment			
No, n (%)	9 (22)	7 (35)	2 (10)
Yes, n (%)	32 (78)	13 (65)	19 (90)
Glasses wear prior to treatment, wk			
8 to <12 weeks, n (%)	3 (7)	3 (15)	0 (0)
12 to <16 weeks, n (%)	2 (5)	2 (10)	0 (0)
≥16 weeks, n (%)	35 (85)	14 (70)	21 (100)
Not prescribed	1 (2)	1 (5)	0 (0)
Cause of amblyopia			
Strabismus, n (%)	6 (15)	4 (20)	2 (10)
Anisometropia, n (%)	21 (51)	9 (45)	12 (57)
Combined, n (%)	14 (34)	7 (35)	7 (33)

AE, amblyopic eye; FE, fellow eye; BCVA, best-corrected visual acuity.

0.8 logMAR; 20/100–20/125) was present in 11 (27%) children. A total of 32 (78%) children had received prior amblyopia treatment. Baseline characteristics are provided in the Table.

Adherence to Protocol

In total, children completed 8.9 ± 2.2 hours of binocular treatment (94% prescribed treatment time; range, 2.7–16.3 hours). Fellow eye contrast was 28% ± 15% at baseline and 53% ± 25% at the 2-week visit. Separated into treatment type, children with game treatment completed 8.7 ± 3.0 hours (87% prescribed treatment time; range, 2.7–16.3 hours). Fellow eye contrast was 20 ± 0% at baseline and 49% ± 19% at the 2-week visit. Children with movie treatment completed 9.1 ± 0.8 hours (100% prescribed treatment time; range, 7.0–10.9 hours). Fellow eye contrast was 36% ± 18% at baseline and 58% ± 29% at the 2-week visit.

Visual Acuity

Mean ± SD amblyopic eye BCVA improvement from baseline to the 2-week visit with binocular treatment was 0.14 ± 0.09 logMAR (1.4 ± 0.9 lines), and this improvement was significant (mean BCVA ± SD at baseline, 0.51 ± 0.17 [20/65 ± 1.7 lines] versus 2-week, 0.37 ± 0.17 [20/47 ± 1.7 lines], $t_{40} = 9.55$, $P < 0.001$; Fig. 2). Improvement ranged from 0.0–0.4 logMAR; 35 children (85%, 95% confidence interval [CI_{95}]: 72%–93%) improved by 0.1 logMAR or more (2 improved 0.4 logMAR [4 lines]; 15 improved 0.2 logMAR [2 lines]; 18 improved 0.1 logMAR [1 line]); and 6 (15%, $CI_{95} = 7\%–28\%$) children did not improve. Ten children (24%, $CI_{95} = 14\%–39\%$) reached 0.2 logMAR (20/32) or better BCVA. No difference for change in BCVA was found between the game and movie treatments ($P = 0.92$).

Binocular Outcomes

Twenty-six children had no measurable stereoacuity at baseline and at the 2-week follow-up. Despite this, mean stereoacuity significantly improved from baseline to the 2-week visit with binocular treatment (mean ± SD = 3.56 ± 0.77 log arcsec versus 3.46 ± 0.79 log arcsec; $t_{40} = 2.06$, $P = 0.046$; Fig. 3). A nonparametric Wilcoxon signed rank test including all patients confirmed this significant mean stereoacuity improvement ($P = 0.045$). Eight children (20%, $CI_{95} = 10\%–34\%$) improved from baseline to the 2-week visit (4/11 and 4/30 with or without measurable stereoacuity at baseline, respectively); 30 children
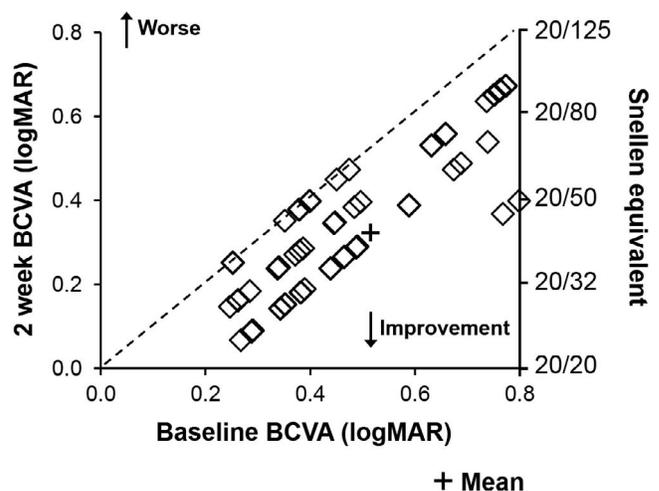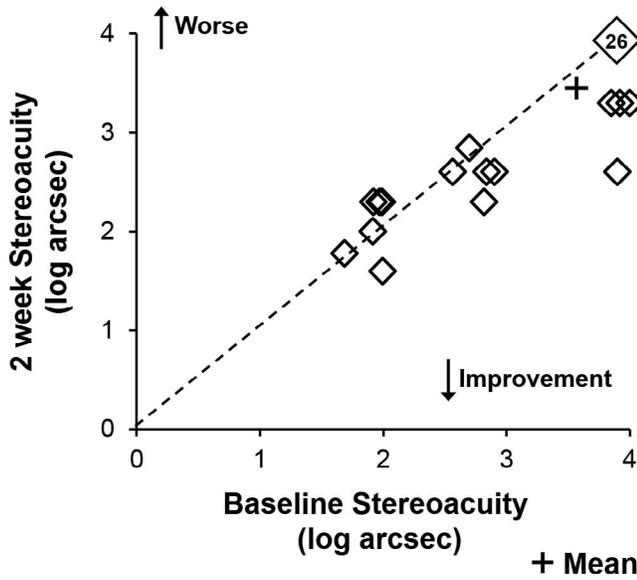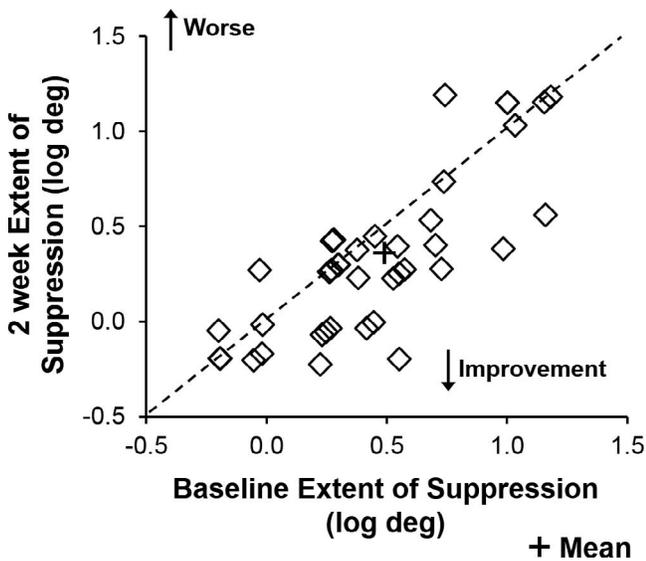

FIGURE 2. Scatterplot showing amblyopic eye BCVA at baseline versus at the 2-week visit for individual participants undergoing binocular treatment (*black diamonds*). Data points below the dotted line indicate improvement. Overlapping symbols are slightly shifted for clarity. Group mean is also shown (+).
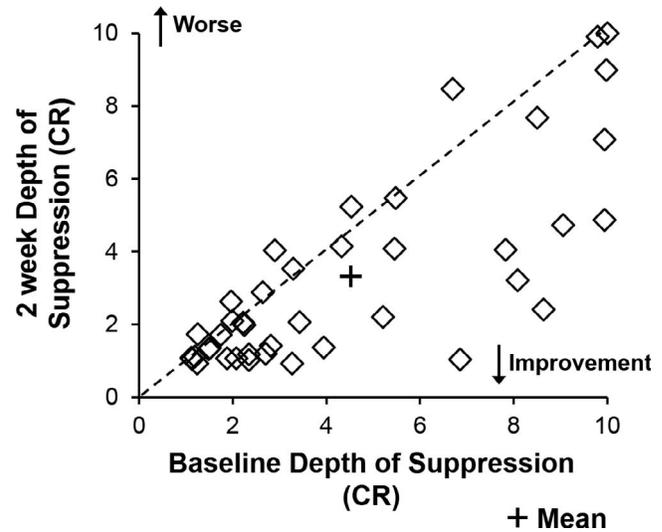
FIGURE 3. Scatterplot showing stereoacuity at baseline versus at the 2-week visit for individual participants undergoing binocular treatment (*black diamonds*). Data points below the *dotted line* indicate improvement. Overlapping symbols are slightly shifted for clarity. The number within the data point at baseline 4 log arsec and 2-week 4 log arcsec indicates the number of children with no measurable stereoacuity at baseline and no improvement at the 2 week visit. Group mean is also shown (+).

(73%, CI_{95} = 58%–84%) did not change from baseline to the 2-week visit (4/11 and 26/30 with or without measurable stereoacuity at baseline, respectively), and 3 children (7%, CI_{95} = 3%–19%) with measurable stereoacuity at baseline scored 1 level worse at the 2-week visit. No difference for change in stereoacuity was found between the game and movie treatments (P = 0.28).

Extent of suppression scotoma (Worth 4-Dot) was significantly reduced from baseline to the 2-week visit with binocular

FIGURE 4. Scatterplot showing extent of suppression scotoma (Worth 4-Dot) at baseline versus at the 2-week visit for individual participants undergoing binocular treatment (*black diamonds*). Data points below the dotted line indicate improvement. Overlapping symbols are slightly shifted for clarity. Group mean is also shown (+).

FIGURE 5. Scatterplot showing depth of suppression (contrast ratio: CR) at baseline versus at the 2-week visit for individual participants undergoing binocular treatment (*black diamonds*). Data points below the dotted line indicate improvement. Overlapping symbols are slightly shifted for clarity. Group mean is also shown (+).

treatment (mean ± SD = 0.49 ± 0.38 log deg versus 0.37 ± 0.41 log deg; t_{40} = 3.00, P = 0.005; Fig. 4). Twenty (49%, CI_{95} = 34%–64%) children improved at least one level (0.15 log deg) from baseline to the 2-week visit (6 children improved 1 level, 7 children improved 2 levels, and 7 children improved ≥3 levels); 14 (34%, CI_{95} = 22%–49%) children did not change from baseline to the 2-week visit; and 7 (17%, CI_{95} = 9%–31%) children worsened from baseline to the 2-week visit (6 children worsened 1 level, 1 child worsened 2 levels). No difference for change in extent of suppression scotoma was found between the game and movie treatments (P = 0.60).

Depth of suppression measured by contrast ratio significantly improved from baseline to the 2-week visit with binocular treatment (mean ± SD = 4.52 ± 3.08 vs. 3.33 ± 2.64; t_{40} = 3.99, P = 0.0003; Fig. 5). Twenty-six (63%, CI_{95} = 48%–76%) children improved at least 0.15 (9 children improved <1.00, 8 children improved 1.00–1.99, and 9 children improved >2.00); 8 (20%, CI_{95} = 10%–34%) children did not improve from baseline to the 2-week visit; and 7 (17%, CI_{95} = 8%–31%) children worsened at least 0.15 from baseline to the 2-week visit. No difference for change in depth of suppression was found between the game and movie treatments (P = 0.32).

Factors Predicting Improvement in Binocular Outcomes With Amblyopia Treatment

No differences were found between children with anisometropic amblyopia and children with strabismic + combined amblyopia for change in binocular outcomes (P ≥ 0.10). Interestingly, depth of suppression was reduced more in children aged <8 years than in those aged ≥8 years (mean improvement ± SD = 1.48 ± 2.07 vs. 0.20 ± 0.62; t_{39} = 3.04, P = 0.004; Fig. 6). No age effect was found with binocular treatment for change in stereoacuity (P = 0.80) or change in extent of suppression (P = 0.60). Controlling for age, worse depth of suppression at baseline was significantly correlated with a larger reduction in depth of suppression at the 2-week visit for binocular treatment (r = 0.48, P = 0.002, CI_{95} = 0.23–0.70; Fig. 7). No other baseline factors were predictive of changes in binocular outcomes following binocular treatment.
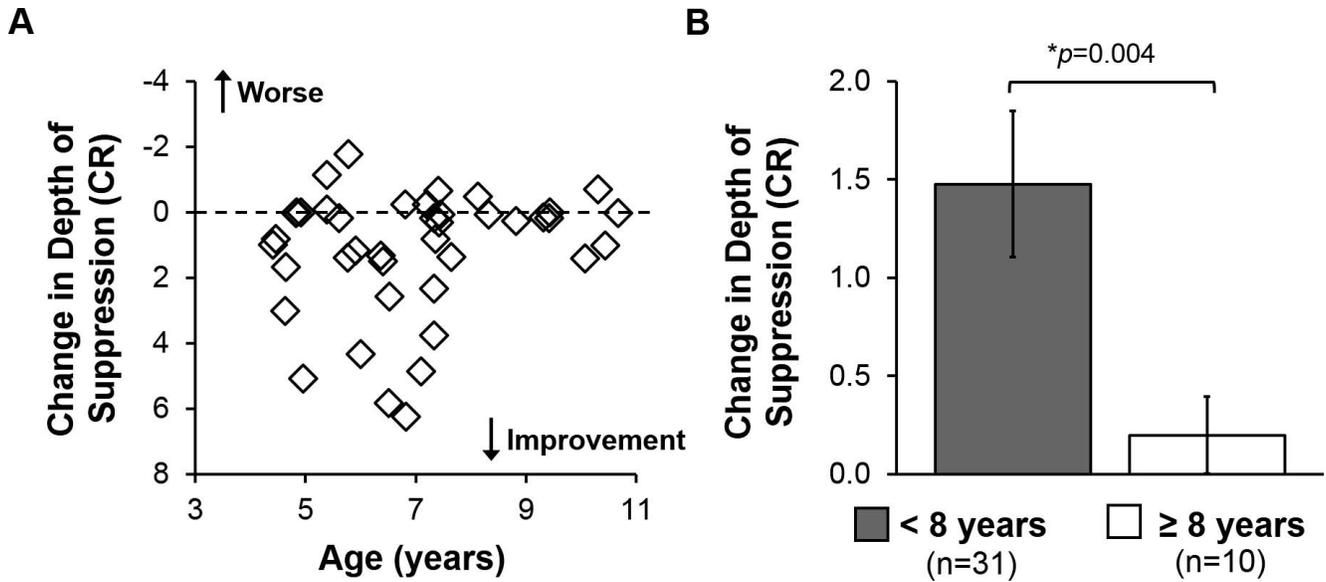
A

B

FIGURE 6. (A) Scatterplot showing change in depth of suppression (CR) by age at the 2-week visit for individual participants (*black diamonds*). Overlapping symbols are slightly shifted for clarity. Data points below the *dotted line* indicate improvement. (B) *Bar graph* showing a significantly larger improvement in depth of suppression (CR) for younger children (*gray*, aged <8 years) versus older children (*white*, aged ≥8 years). *Error bars* represent ± standard error.

Since many children had extremely poor values for all binocular measures at baseline, we assessed regression to the mean using Bland Altman[44] analyses. For all three binocular outcomes, the slope of the regression line was not significantly different from zero (stereoacuity, slope = −0.02, $P = 0.79$, CI_{95} = 0.53–0.82; extent of suppression, slope = −0.09, $P = 0.40$, $CI_{95} = 0.45–0.71$; depth of suppression, slope = 0.17, $P = 0.13$, $CI_{95} = 3.61–5.59$), indicating that regression to the mean was not a major factor in the observed improvements.

DISCUSSION

In addition to visual acuity gains, improved binocular function has been a major goal of amblyopia treatment, yet it is difficult
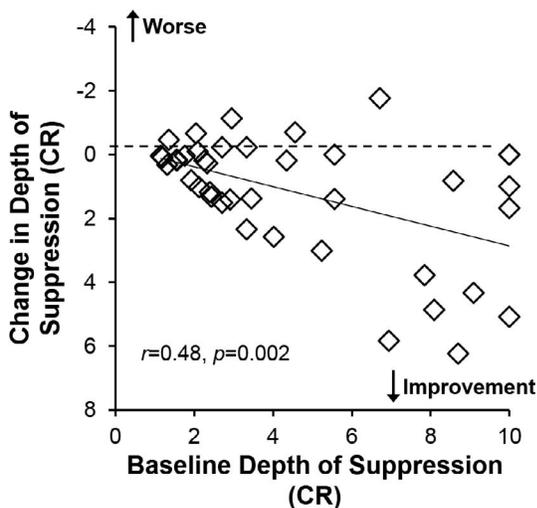

FIGURE 7. Scatterplot showing a significant correlation between baseline depth of suppression (CR) and change in depth of suppression at the 2-week visit for individual participants (*black diamonds*). Data points below the *dotted line* indicate improvement. The *solid line* indicates the trend.

to attain normal binocularity even after years of treatment. In our study, binocular outcomes in amblyopic children improved with 2 weeks of binocular treatment using a dichoptic game or dichoptic movies that rebalance contrast, consistent with data from children[12,24,36] and adults[25,33–35] with binocular treatment. Alternate forms of binocular treatment using virtual reality[23] and perceptual learning[29] have also shown improved Randot stereoacuity in amblyopic adults. Most children in our study with nil stereo at baseline remained at nil stereo after 2 weeks of binocular treatment (26/30). The Randot Preschool and Randot Butterfly tests measure stereoacuity up to 3.3 log arcsec. It is therefore possible that the limitations of our test range prevented our ability to appreciate improvements from nil stereoacuity. Nil stereopsis with random dot stereograms also may occur because the dots are small and dense, low in contrast, and static.[29,45,46]

Only 20% of children in our study experienced a stereoacuity improvement following binocular treatment. One child had normal stereoacuity at baseline and at the 2-week outcome visit, and one child improved 3 levels to achieve normal stereoacuity; no other child achieved normal stereoacuity. Further, baseline stereoacuity was not correlated with visual acuity improvement, and has never been reported to be a predictive factor for visual acuity improvement following binocular treatment. While short-term dichoptic treatment improves visual acuity, it may not be effective in restoring normal stereoacuity in amblyopic children, possibly due to the treatment type, treatment duration, or both. The key to binocular improvement may lie in the release of interocular suppression (i.e., using contrast rebalancing games or movies) prior to a yet-to-be developed treatment specifically designed to improve stereoacuity. It is also possible that a longer period of binocular treatment may yield larger stereoacuity improvements. While research shows some improvement in stereoacuity in amblyopic children following monocular treatment (patching, atropine), these improvements occur following months of treatment and normal stereoacuity is rarely achieved.[2,3,7,15–18]

We also found that both the extent of suppression and depth of suppression reduced significantly from baseline for the binocular treatment group. Apart from two studies,[12,24]

reduced interocular suppression has not yet been reported in children following binocular amblyopia treatment, possibly due to small sample sizes and/or children's difficulty with the psychophysical task used to measure suppression.[25,26,30] Here, we found that worse baseline depth of suppression was related to a larger reduction in suppression following binocular treatment. Reduced suppression was more striking in children under 8 years of age in our study, in line with data showing that visual acuity in amblyopic children under 7 years improved more with binocular treatment than older children.[31] Converging evidence suggests that interocular suppression plays a key role in the etiology of amblyopia,[12,19,47–49] and early binocular treatment that reduces or eliminates suppression may be the key to amblyopia treatment. Child-friendly tasks that possess the ability to quantify the degree of suppression in amblyopia have only recently been available.[12,47] Using these tests in conjunction with other tasks that show the presence or extent of suppression (i.e., Randot Suppression Test, Worth 4-Dot) may provide more information regarding treatment success.

Similar to previously published binocular treatment studies from our lab using movies[26] and the *Dig Rush* game,[24] we found that 2 weeks of binocular treatment improved amblyopic eye visual acuity by 0.14 logMAR (1.4 lines). Previously, in a randomized clinical trial, we have shown that the visual acuity improvement following 2 weeks of binocular treatment was almost double that found with patching, and was achieved with <50% treatment time required for patching (approximately 10 vs. 28 hours assigned treatment). In fact, 10 (24%) children in the current study reached 20/32 or better with binocular treatment. Binocular treatment may yield faster visual acuity gains than patching; after just 2 weeks, binocular treatment resulted in half of the maximum visual acuity improvement of two to three lines previously found with 6 months of patching.[3,50] However, 31 (76%) children still had residual amblyopia after 2 weeks of binocular treatment. Thus, a longer treatment period may be required to reach normal visual acuity levels, and for other binocular outcomes such as stereoacuity and suppression to also reach normal levels. It remains to be determined whether long-term binocular treatment is as effective in remediating amblyopia as patching.

Recent psychophysical and physiologic findings point to a structurally intact binocular visual system that is rendered functionally monocular by suppression that occurs in amblyopia.[19–22] The neural basis of amblyopia is yet to be fully elucidated; thus the mechanism responsible for treatment success is not yet known. Rapid vision gains with just 2 weeks of binocular treatment may reflect metaplasticity in visual cortex. Contrast rebalancing may act to decrease the strong activation provided by the fellow eye, allowing the weak inputs from the amblyopic eye to initiate long-term potentiation via synaptic metaplasticity.[19,51] The permanence of vision gains following binocular treatment has yet to be fully ascertained; however, stable visual acuity gains one year after 4 to 8 weeks of binocular treatment have been reported for eight children.[37]

Visual acuity and binocularity gains with binocular treatment did not differ between children treated with the at-home game compared to children treated with the in-lab movies, suggesting that treatment can be effective regardless of whether active engagement (i.e., screen manipulation using fingers) or passive viewing occurs. However, binocular amblyopia treatment is relatively novel and must be examined further to ascertain the feasibility and success of long-term treatment, to investigate the most effective methods of contrast manipulation for maximum improvement, and to develop a variety of engaging games and movies that can be taken home for treatment.

The current study pooled data from two ongoing studies of binocular treatment and was limited in that there was no control group. Pilot data for depth of suppression from 11 untreated age-similar amblyopic children whose visual acuity remained stable (no change greater than 0.1 logMAR) and who were tested on two visits ≥2 weeks apart show a mean ± SD improvement in depth of suppression contrast ratio of 0.23 ± 1.03. This learning effect is a factor of 5.2 smaller than the magnitude of treatment effect for depth of suppression found in amblyopic children participating in binocular treatment (treatment change = 1.19 ± 1.90). This suggests that a learning effect cannot fully explain the change in depth of suppression at 2 weeks. While binocular amblyopia treatment has proven effective in improving amblyopia for children ages 4 to 10 years with anisometropia and treated strabismus, our findings cannot be generalized to strabismic children with angles greater than 4 PD, older children, or to other forms of amblyopia such as deprivation amblyopia due to congenital cataract.

Conclusions

Although not all children had improved binocular outcomes during a short 2-week period of binocular amblyopia treatment, the group as a whole had improved mean stereoacuity and improved mean extent and depth of suppression. Binocular movies and games that rebalance contrast to overcome suppression provide a promising additional option for treating amblyopia.

References

1. Repka MX, Beck RW, Holmes JM, et al.; Pediatric Eye Disease Investigator Group. A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Arch Ophthalmol*. 2003;121:603–611.

2. Repka MX, Wallace DK, Beck RW, et al. Two-year follow-up of a 6-month randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Arch Ophthalmol*. 2005;123:149–157.

3. Pediatric Eye Disease Investigator Group. A randomized trial comparing Bangerter filters and patching for the treatment of moderate amblyopia in children. *Ophthalmology*. 2010;117:998–1004.

4. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). *Invest Ophthalmol Vis Sci*. 2004;45:3048–3054.

5. Pediatric Eye Disease Investigator Group. A randomized trial to evaluate two hours of daily patching for amblyopia in children. *Ophthalmology*. 2006;113:904–912.

Investigative Ophthalmology & Visual Science

6. Woodruff G, Hiscox F, Thompson JR, Smith LK. Factors affecting the outcome of children treated for amblyopia. *Eye*. 1994;8:627–631.

7. Saxena R, Puranik S, Singh D, Menon V, Sharma P, Phuljhele S. Factors predicting recurrence in successfully treated cases of anisometropic amblyopia. *Indian J Ophthalmol*. 2013;61: 630–633.

8. Pediatric Eye Disease Investigator Group. Risk of amblyopia recurrence after cessation of treatment. *J AAPOS*. 2004;8:420–428.

9. Birch EE, Stager DR. Long-term motor and sensory outcomes after early surgery for infantile esotropia. *J AAPOS*. 2006;10: 409–413.

10. Birch EE, Stager DR, Berry P, Leffler J. Stereopsis and long-term stability of alignment in esotropia. *J AAPOS*. 2004;8:146–150.

11. Birch EE. Marshall Parks lecture. Binocular sensory outcomes in accommodative ET. *J AAPOS*. 2003;7:369–373.

12. Birch EE, Morale SE, Jost RM, et al. Assessing suppression in amblyopic children with a dichoptic eye chart. *Invest Ophthalmol Vis Sci*. 2016;57:5649–5654.

13. Levi D, Knill D, Bavelier D. Stereopsis and amblyopia: a mini-review. *Vision Res*. 2015;114:17–30.

14. Li J, Thompson B, Lam CSY, et al. The role of suppression in amblyopia. *Invest Ophthalmol Vis Sci*. 2011;52:4169–4176.

15. Stewart CE, Wallace MP, Stephens DA, Fielder AR, Moseley MJ. The effect of amblyopia treatment on stereoacuity. *J AAPOS*. 2013;17:166–173.

16. Birch EE, Wang J. Stereoacuity outcomes after treatment of infantile and accommodative esotropia. *Optom Vis Sci*. 2009; 86:647–652.

17. Wallace DK, Lazar EL, Melia M, et al. Steroacuity in children with anisometropic amblyopia. *J AAPOS*. 2011;15:455–461.

18. Pediatric Eye Disease Investigator Group. Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial. *Arch Ophthalmol*. 2008;126:1634–1642.

19. Hess RF, Thompson B. Amblyopia and the binocular approach to its therapy. *Vision Res*. 2015;114:4–16.

20. Mansouri B, Thompson B, Hess RF. Measurement of supra-threshold binocular interactions in amblyopia. *Vision Res*. 2008;48:2775–2784.

21. Baker DH, Meese TS, Mansouri B, Hess RF. Binocular summation of contrast remains intact in strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 2007;48:5332–5338.

22. Sengpiel F, Jirmann KU, Vorobyov V, Eysel UT. Strabismic suppression is mediated by inhibitory interactions in the primary visual cortex. *Cereb Cortex*. 2006;16:1750–1758.

23. Vedamurthy I, Knill DC, Huang SJ, et al. Recovering stereo vision by squashing virtual bugs in a virtual reality environment. *Philos Trans R Soc Lond B Biol Sci*. 2016;371:20150264.

24. Kelly KR, Jost RM, Dao L, Beauchamp CL, Leffler JN, Birch EE. Binocular iPad game vs patching for treatment of amblyopia in children: a randomized clinical trial. *JAMA Ophthalmol*. 2016; 134:1402–1408.

25. Knox PJ, Simmers AJ, Gray LS, Cleary M. An exploratory study: prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia. *Invest Ophthalmol Vis Sci*. 2012;53:817–824.

26. Li SL, Reynaud A, Hess RF, et al. Dichoptic movie viewing treats childhood amblyopia. *J AAPOS*. 2015;19:401–405.

27. Žiak P, Holm A, Halička J, Mojžiš P, Piñero DP. Amblyopia treatment of adults with dichoptic training using the virtual reality oculus rift head mounted display: preliminary results. *BMC Ophthalmol*. 2017;17:105.

28. Herbison N, MacKeith D, Vivian A, et al. Randomised controlled trial of video clips and interactive games to improve vision in children with amblyopia using the I-BiT system. *Br J Ophthalmol*. 2016;100:1511–1516.

29. Ding J, Levi DM. Recovery of stereopsis through perceptual learning in human adults with abnormal binocular vision. *Proc Natl Acad Sci*. 2011;108:E733–E741.

30. Li SL, Jost RM, Morale SE, et al. A binocular ipad treatment for amblyopic children. *Eye (Lond)*. 2014;28:1246–1253.

31. Holmes JM, Manh VM, Lazar EL, et al. Effect of a binocular iPad game vs part-time patching in children aged 5 to 12 years with amblyopia. *JAMA Ophthalmol*. 2016;33647:1–9.

32. Birch EE, Li SL, Jost RM, et al. Binocular iPad treatment for amblyopia in preschool children. *J AAPOS*. 2015;19:6–11.

33. Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of Amblyopia in adults well beyond the critical period of visual development. *Restor Neurol Neurosci*. 2010;28:793–802.

34. Li J, Thompson B, Deng D, Chan LYL, Yu M, Hess RF. Dichoptic training enables the adult amblyopic brain to learn. *Curr Biol*. 2013;23:R308–R309.

35. Hess RF, Babu RJ, Clavagnier S, Black J, Bobier W, Thompson B. The iPod binocular home-based treatment for amblyopia in adults: efficacy and compliance. *Clin Exp Optom*. 2014;97: 389–398.

36. Webber AL, Wood JM, Thompson B. Fine motor skills of children with amblyopia improve following binocular treatment. *Invest Opthalmol Vis Sci*. 2016;57:4713–4720.

37. Li S, Jost R, Morale S, et al. Binocular iPad treatment of amblyopia for lasting improvement of visual acuity. *JAMA Ophthalmol*. 2015;133:479–480.

38. Ooi TL, Su YR, Natale DM, He ZJ. A push-pull treatment for strengthening the "lazy eye" in amblyopia. *Curr Biol*. 2013; 23:R309–310.

39. Beck R, Moke P, Turpin A, et al. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. *Am J Ophthalmol*. 2003;135:194–205.

40. Cotter SA, Chu RH, Chandler DL, et al. Reliability of the electronic early treatment diabetic retinopathy study testing protocol in children 7 to <13 years old. *Am J Ophthalmol*. 2003;136:655–661.

41. Moke PS, Turpin AH, Beck RW, et al. Computerized method of visual acuity testing: adaptation of the amblyopia treatment study visual acuity testing protocol. *Am J Ophthalmol*. 2001; 132:903–909.

42. Holmes JM, Beck RW, Repka MX, et al. The amblyopia treatment study visual acuity testing protocol. *Arch Ophthalmol*. 2001;119:1345–1353.

43. Rosenbaum AL, Santiage AP, eds. *Clinical Strabismus Management*. Philadelphia: WB Saunders; 1999.

44. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307–310.

45. Simons K. A comparison of the Frisby, Random-Dot E, TNO, and Randot circles stereotests in screening and office use. *Arch Ophthalmol*. 1981;99:446–452.

46. Westheimer G. Clinical evaluation of stereopsis. *Vision Res*. 2013;90:38–42.

47. Narasimhan S, Harrison ER, Giaschi DE. Quantitative measurement of interocular suppression in children with amblyopia. *Vision Res*. 2012;66:1–10.

48. Li J, Hess RF, Chan LYL, et al. Quantitative measurement of interocular suppression in anisometropic amblyopia: A case-control study. *Ophthalmology*. 2013;120:1672–1680.

49. Birch EE. Amblyopia and binocular vision. *Prog Retin Eye Res*. 2013;33:67–84.

50. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch Ophthalmol*. 2002;120:268–278.

51. Bear MF. Bidirectional synaptic plasticity: from theory to reality. *Philos Trans R Soc Lond B Biol Sci*. 2003;358:649–655.