Binocular Therapy for Childhood Amblyopia Improves Vision Without Breaking Interocular Suppression


Abstract

Amblyopia is a developmental disorder of vision with a prevalence of 2% to 5%, defined as a monocular (rarely binocular) reduction of the best-corrected visual acuity (henceforth, acuity) in an otherwise healthy eye. Amblyopia is caused by a prolonged period of abnormal retinal stimulation (mainly) due to strabismus (ocular misalignment), anisometropia (refractive imbalance), or both (combined) and leads to functional deficits, including reduced contrast sensitivity, poor spatial localization, poor stereovision, and foveal crowding.

Typically, amblyopia is treated only if the interocular acuity difference between the amblyopic eye (AE) and the fellow eye (FE) is at least 0.2 logMAR. Current treatment commences with 12 to 24 weeks of wearing prescribed optical correction, which improves AE acuity to normal levels in 27% to 32% of cases. Otherwise, treatment to promote the use of the AE is administered, which consists of patching the FE (2–12 h/d) or blurring the FE with atropine eye drops for up to 24 weeks, which improves AE acuity to normal levels in 27% to 32% of cases.

PURPOSE. Amblyopia is a common developmental visual impairment characterized by a substantial difference in acuity between the two eyes. Current monocular treatments, which promote use of the affected eye by occluding or blurring the fellow eye, improve acuity, but are hindered by poor compliance. Recently developed binocular treatments can produce rapid gains in visual function, thought to be as a result of reduced interocular suppression. We set out to develop an effective home-based binocular treatment system for amblyopia that would engage high levels of compliance but that would also allow us to assess the role of suppression in children’s response to binocular treatment.

METHODS. Balanced binocular viewing therapy (BBV) involves daily viewing of dichoptic movies (with “visibility” matched across the two eyes) and gameplay (to monitor compliance and suppression). Twenty-two children (3–11 years) with anisometropic (n = 7; group 1) and strabismic or combined mechanism amblyopia (group 2; n = 6 and 9, respectively) completed the study. Groups 1 and 2 were treated for a maximum of 8 or 24 weeks, respectively.

RESULTS. The treatment elicited high levels of compliance (on average, 89.4% ± 12.2% of days on treatment) and led to a mean improvement in acuity of 0.27 logMAR (SD 0.22) for the amblyopic eye. Importantly, acuity gains were not correlated with a reduction in suppression.

CONCLUSIONS. BBV is a binocular treatment for amblyopia that can be self-administered at home (with remote monitoring), producing rapid and substantial benefits that cannot be solely mediated by a reduction in interocular suppression.

Keywords: amblyopia, binocular vision, stereoaucuity, visual development

Eye Movements, Strabismus, Amblyopia and Neuro-Ophthalmology

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perform a dichoptic phase-alignment task. Recently, some of us have developed a test measuring the contrast mixture of dichoptically presented letter-pairs that leads observers to switch from using one eye to the other. In terms of physiological mechanism, animal models have shown that prolonged monocular deprivation leads to weakened excitatory drive from the deprived eye and hence imbalanced activation of binocular cortical neurons. The resulting suppression is thought to be the result of an active inhibitory cortical mechanism.

Stronger suppression is associated with more severe amblyopia and has traditionally been viewed as an adaptive mechanism (to avoid double-vision). In contrast, it has been proposed that suppression has a causative role in amblyopia, making it a candidate target for therapy. Notably, Hess and colleagues have developed “antisuppression” therapy, which uses games (with elements split across the eyes to promote binocularity) as a mean of treating amblyopia in adults and children. After 2 to 6 weeks of treatment, visual acuity improves by an average of approximately 0.15 logMAR and stereopsis was measurable in approximately 45% of participants (for the first time in approximately two-thirds of them). However, a randomized controlled trial of an alternative binocular therapy (dBiT) reports only modest success with children (mean acuity gain: 0.08 logMAR). Modern “perceptual learning” treatments have also yielded positive results in adults and older children via monocular training (using the AE) on psychophysical tasks or video-game play. As have hybrid approaches that interleave a monocular task with a drive from the deprived eye and hence imbalanced prolonged monocular deprivation leads to weakened excitatory drive from the deprived eye and hence imbalanced activation of binocular cortical neurons. The resulting suppression is thought to be the result of an active inhibitory cortical mechanism.

METHODS

Participants

Twenty-four children (14 female) aged 3.5 to 11.3 years (mean age: 6.6 ± 2.9 years), with anisometropic (group 1), strabismic, or combined mechanism amblyopia (both in group 2), were recruited from the Richard Desmond Children’s Eye Centre at Moorfields Eye Hospital, London. The treatment was allowed for a maximum of 8 weeks (group 1; pilot study, see Discussion) or 24 weeks (group 2). Our research followed the tenets of the Declaration of Helsinki and we obtained informed consent from caregivers and assent from children before enrollment. Our recruitment procedure and treatment regimen were approved by the local NHS Research Ethics Committee.

Children were included if their amblyopia (defined as an interocular acuity difference of 0.2 logMAR or greater and FE acuity equal or better than 0.2 logMAR) persisted after a minimum of 16 weeks of optical treatment, and if acuity in the AE was unchanged on two consecutive visits, 8 weeks apart. Exclusion criteria included prior amblyopia treatment other than optical correction, presence of paralytic or restrictive squint, other preexisting visual deficit (e.g., cataract) or significant neurological or behavioral problems. Amblyopia was defined as anisometropic if there was a difference of at least 1 diopter (D) in spherical equivalent or 1.5 D in astigmatism between the two eyes. Combined mechanism amblyopia was also associated with heterotropia: either ≤10 D (microstrabismus) or with a larger angle of deviation. Children were classified as strabismic amblyopes if a manifest interocular misalignment greater than 10 D was present (convergent or divergent), but no anisometropia. Participants’ details are summarized in Table 1.

All children received optical treatment before participating in our study. The mean period of optical treatment was 28 ± 12 weeks: 30 ± 16 weeks in children with anisometropia, 25 ± 9 weeks in those with strabismus, and 29 ± 12 weeks in those with combined mechanism amblyopia.

Equipment

Our treatment uses a computer system capable of presenting three-dimensional (3D) movies, which is installed in the child’s home (Fig. 1A). The monitor operates at 1920 × 1080-pixel resolution at 120 Hz (60 Hz per eye). Movies were presented using software written in MATLAB (MathWorks, Ltd., Cambridge, MA, USA) and Psychtoolbox (http://www.psychtoolbox.org, in the public domain). Shutter glasses (Nvidia Corp., Santa Clara, CA, USA) were used to independently control the image presented to the two eyes. These were mounted in a customized children’s ski mask to ensure comfort, while maintaining a snug fit over spectacle correction. The monitor was linearized in software based on a series of luminance measurements (made by placing a Minolta LS110 photometer [Konica Minolta, Tokyo, Japan] behind a single lens of a pair of goggles) to achieve a midgray of 45 cd/m² to each eye. Children were provided with a keypad to make responses to the suppression task, and were encouraged to use the 95-cm-long cable to ensure they maintained viewing distance at approximately 1 m.

TREATMENT REGIMEN

Treatment consisted of 1 hour per day spent viewing movies (selected by children/caregivers) while wearing the goggles. Movies were presented dichoptically and the horizontal offset between the two eyes was continuously modulated to generate a percept of gradually changing depth. A zero-disparity textured background was presented to both eyes to encourage stable vergence. The child’s view of the movie (Fig. 1B, inset) was “balanced” by blurring the image presented to the FE, so that the child’s monocular acuity was matched across eyes. To determine the level of blur required, we ran two tasks. Task 1 (Fig. 2A) quantified AE acuity as the scaling required to support identification of the orientation of a crowded VacMan (“VacMan”). Targets were presented monocularly at 75% contrast with four flanking “ghosts” (spaced at twice the target width). They were masked with a 25% contrast phase-scrambled version of the stimulus that was visible across both eyes (to provide a vergence lock). Stimuli were scaled using an adaptive staircase (QUEST). Over 45 trials, this converged on the scaling that produced 83% correct identification. Task 2 (Fig. 2B) presented similar VacMan stimuli to the FE (scaled with the AE threshold from task 1) and then used QUEST to determine the level of isotropic Gaussian blur that elicited 83% VacMan identification. This level of blur was applied to the image presented to the FE during movie presentation, ensuring that the images presented to the two eyes were equally visible.

During treatment, the movie was interrupted every minute by an interactive game used to measure suppression (Fig. 2C). Two dichoptically presented “ghosts” flanked a central VacMan, either above/below or left/right. We told children “VacMan wants to eat the whitest ghost; which ghost looks the..."
TABLE 1. Baseline Details of Participants (n = 24)

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<th>Participant ID (m/f)</th>
<th>Age, y</th>
<th>Group</th>
<th>Amblyopia Type</th>
<th>Amblyopia Severity</th>
<th>Spectacle Prescription</th>
<th>Best-Corrected VA, logMAR</th>
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<td>plano</td>
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<td>L E comb. (ET – hyperm.)</td>
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<td>mod</td>
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<td>L E strab. (ET)</td>
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<td>L E strab. (ET)</td>
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<td>+6.00/-0.50 x 160</td>
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</table>

Values corresponding to the AE are italicized. Bold indicates “severe” cases (i.e., acuity in the AE > 0.6 logMAR; n = 16). Only participant 8 had mild amblyopia, the remaining had moderate amblyopia (0.3 < acuity in the AE < 0.6 logMAR; n = 7). Participants 7 and 21 did not attend their clinic appointments, hence their data are incomplete and have not been analyzed. aniso, anisometropic; astigm., astigmatism; comb., combined mechanism; CS, convergent strabismus; DS, diopeter sphere; ET, esotropia; hyperm, hypermetropia; LE, left eye; m/f, male/female; mod, moderate; RE, right eye; sev, severe; strab., strabismic.
ghost on the left and a light/dark FE/AE ghost on the right of VacMan.

3. Use $R$ to set ghost component-luminance values. The luminance of the light ghost on one side of VacMan and the dark ghost on the other side are matched increments and decrements: $L_{\text{back}} \pm (R/100)L_{\text{range}}$. For example, in Figure 2C, $R = 75\%$. Thus, for $C = R/100 = 0.75$: $45 \pm C \times 45 = 78.8$ and $11.3$ cd/m$^2$, respectively. Similarly, the light ghost (right) and dark ghost (left) are $L_{\text{back}} \pm (1-C)L_{\text{range}} = 45 \pm 0.25 \times 45 = 56.3$ or $33.8$ cd/m$^2$.

Initially $R$ was set to 80% and then adjusted (by ±10%) on each trial, using a one-up-one-down staircase procedure, according to whether a response was consistent with reliance on the FE or the AE. For $R = 75\%$ (Fig. 2C) the AE sees a substantially stronger white ghost; someone with balanced vision would report that they perceive the whiter ghost on the "left" leading to a reduction in $R$ on the next trial. Thus, $R$ converges on the level necessary for the stimulus delivered to either eye to drive the report with equal probability. For an observer neglecting the AE, $R > 50\%$ indicating that a stronger signal is required in the ambyopic eye for that ghost to be reported as whiter.

Note that each child performed one trial per minute with the procedure restarting each time the child switched movies, so the number of trials contributing to any one suppression estimate varied according to the time spent watching a given movie in one session. If the child chose a location in which no ghost was presented, he or she was either not paying attention or not viewing through the goggles (because balanced ghosts were invisible without the 3D shutter glasses). The number of such errors was used to quantify attention/compliance. The system e-mailed the experimenter a daily update of the time children had spent engaged in movie viewing and their performance on this task.

We treated the first cohort of participants (group 1: $n = 8$, all anisometropes) for a maximum of 8 weeks. At standard orthoptic assessments that occurred alongside BBV (see next section), we observed gains in acuity and stereoacuity that did not reach a plateau. Therefore, for the second group of children (group 2: all combined or strabismic amblyopia) we extended the maximum period of treatment to 24 weeks.

**Orthoptic Assessment**

An experienced orthoptist performed a battery of tests at baseline (pretreatment) and after 4 and 8 weeks of therapy. They assessed best-corrected visual acuity using a crowded logMAR test at 3 m (Thompson v2000 software; Thompson Software solutions, Hertfordshire, UK), stereoacuity using the...
RESULTS

Two children did not attend the 4-week appointment and were excluded from analyses, leaving 22 children. Group 1 thus consisted of seven children with anisometropic amblyopia (mean age 9.5 years; 4 females). A total of 15 children were included in group 2 (mean age 5.2 years), 6 with strabismic amblyopia (mean age 5.75 years; 2 females) and 9 with combined mechanism amblyopia (mean age 4.7 years; 6 females). Where necessary, results are reported separately for children included in group 1 (allowed maximum 8 weeks) or 2 (allowed up to 24 weeks on treatment).

Acuity

Figures 3A and 3B plot the difference in logMAR acuity from baseline (BL), as measured for each child during his or her clinical assessments. Specifically, data for children with pure anisometropic amblyopia (n = 7; square symbols) or strabismic amblyopia (n = 6; triangle symbols) are reported in Figure 3A, whereas those with combined mechanism amblyopia are in Figure 3B (n = 9; circle symbols). Individual declines or improvements in vision are represented by values falling above or below the dashed horizontal line, respectively (no change from BL = 0 logMAR acuity difference). The individual values measured before starting and after completing BBV treatment (entry versus exit logMAR acuity) are plotted in Figure 3C. As per the study protocol, children were treated for up to either 8 weeks (group 1; n = 7; IDs 1–8 in Table 1) or 24 weeks (group 2; n = 15; IDs 9–24). Among children in group 2, 5 did not improve further after 8 weeks (IDs: 9, 10, 17, 19, and 24; making 12 children in total released at this time point), whereas 4 children remained in treatment for 16 weeks (IDs: 11, 16, 18, and 23) and 6 for 24 weeks (IDs: 12–15, 20, 22), depending on the measured improvement in acuity. Note that acuity continued to improve beyond 8 weeks for some children, suggesting that those whose treatment was terminated at this point (because this was the limit of our approved protocol for group 1) would have received further benefit from continued treatment.

When data from all the children were combined (regardless of amblyopia type, n = 22), mean acuity in the AE improved...
from 0.78 ± 0.35 to 0.51 ± 0.34 logMAR, a significant mean gain of 0.27 ± 0.22 logMAR (1-sample paired t-test, t_{6,83}, P < 0.001). Vision in the FE remained stable, improving slightly: the mean gain (−0.05 ± 0.11 logMAR, mean baseline: 0.02 ± 0.15 logMAR) was statistically (P = 0.04) but not clinically (gain < 0.2 logMAR) significant. Mean acuity gain in severe amblyopia (bold in Table 1 for the n = 14 with acuity worse than 0.6 logMAR) was 0.32 ± 0.24 logMAR, versus 0.18 ± 0.14 logMAR in mild-to-moderate amblyopia (n = 8). Acuity gains for group 1 (whose treatment was curtailed at 8 weeks, all anisometropic amblyopes) was 0.26 ± 0.28, and for group 2 (maximum treatment of 24 weeks, combined and strabismic amblyopes) was 0.27 ± 0.19 logMAR. There was no significant difference in acuity gains between group 1 and 2 (2-sample t-test, t_{20}, P = 0.865).

After treatment, 15 children reached IOAD ≤ 0.6 logMAR (6 of whom started with severe amblyopia), including 7 children (1 severe) who recovered to ≤ 0.3 logMAR. No further treatment was required for ID15, whose IOAD improved from 0.34 to 0.1 logMAR and ID1, whose AE acuity reached 0.04 logMAR (although final IOAD was 0.24 logMAR). The mean “proportion of deficit corrected” was 32% ± 26%, with substantial gains (>60%) in two children (IDs 15 and 22, 71% and 69%), and poor (<10%) in three children (IDs 8, 19 and 24). In 7 children, improvement was between 10% and 30%, and in the remaining 10 children, between 50% and 60%.

Maintenance of Acuity Gains After End of Treatment

At the time of writing, clinical follow-up data were available for 11 children, 7 of whom received standard treatment following BBV. Their mean acuity gain was 0.39 ± 0.25 logMAR at completion of BBV treatment and 0.34 ± 0.30 logMAR after an additional mean follow-up time of 47 ± 10 weeks logMAR. Seven children attended a follow-up at 2 years (mean 95 ± 30 weeks after stopping BBV), with +0.01 ± 0.23 logMAR mean change in acuity logMAR from BBV completion (four of seven gained 0.15 ± 0.1 logMAR; three of seven regressed 0.23 ± 0.16 logMAR).

Stereoacuity

Only children with purely anisometropic amblyopia (group 1) had measurable stereoacuity at baseline, with a median of 170 arcsec (interquartile 230 arcsec; Fig. 4). Following treatment, six of seven children had significantly improved stereoacuity. Overall (n = 7), the median stereoacuity value at exit was 85 arcsec (interquartile 30 arcsec) and mean improvement was 165 ± 182 arcsec, significant with a Wilcoxon signed rank test (paired, z = 2.298, P = 0.0215 at α = 0.05). The one participant whose stereoacuity did not improve (ID3) had good stereoacuity at entry. We transformed data to logarithmic seconds of arc to calculate “real change” in stereoacuity and to allow for comparisons between consecutive visits. Prior studies have found the test-retest reliability of stereoacuity measurements using the near Frisby test in children to be 0.3 log arcsec, with “real change” defined as a doubling of stereoacuity expressed in octaves.52 Here, mean stereoacuity gain was 0.40 log arcsec (±0.52), with all but ID3 exhibiting an improvement in stereoacuity ≥ 1 octave (Fig. 4B). Mean improvement was 1.33 octaves (i.e., a factor of 2.6 improvement). Of the children having unmeasurable baseline stereopsis, three showed progression after BBV treatment, reaching 600 (ID9), 85 (ID11), and 110 (ID14) arcsec at 1-year follow-up. For the remaining children, the Frisby measure was inconclusive. The gain in stereoacuity significantly correlated with both the initial level of acuity in the AE (r = 0.97, P = 0.0003) and its absolute improvement (r = 0.85, P = 0.02), but did not correlate with the proportional gain in acuity (r = 0.44, P = 0.32).

Interocular Suppression

Figure 5 shows individual suppression data from the ghost task. Note that ID4 initially did not comply with this task and their (incomplete) data were excluded from the analyses of suppression. The mean suppression at entry was 72.3% (SD 12.02%) and at exit was 72.6% (SD 12.3%). Overall, these values are in line with comparable estimates for adult amblyopes (e.g., 75%) and not significantly different from one another (t-test, t_{20}, P = 0.98). We do not observe the substantial reductions in suppression observed in other studies of binocular therapy.53 Indeed, a statistically significant
A reduction in interocular suppression was observed in only 6 of the 22 children, of whom 4 had combined mechanism and 2 purely strabismic amblyopia. Further, 5 children showed a significant increase in suppression (ID4 excluded), while 10 children showed no significant change. For each individual, we calculated the linear regression trend line (bold lines in Fig. 5) for daily estimates of $R$ (quantifying the patient’s binocularity: 0% fully reliant on AE, 100% fully reliant on the FE).

We performed additional analyses to examine changes within and across sessions. First, for within-session changes, we analyzed runs containing at least 30 trials (“long sessions”; an average of 36.5% of all runs across 21 children) and divided these runs into three parts. We then compared the average stimulus balance in the second and third part (excluding the first part where the staircase may not be close to convergence), computing a linear regression between values to determine if the slope was significantly different from 0. According to this analysis, for each child (excluding ID4) an average of 9% of “long sessions” involved a significant change in suppression within session. However, such changes were not biased toward increasing suppression (49.8% ± 27.8% of cases) or decreasing suppression (50.3% ± 27.8%). Second, across sessions, we note that Kehrein et al. reported an increase in suppression during the first 30 days of occlusion therapy, followed by a return to baseline in the following month. We performed a similar analysis comparing suppression over the first and second 30 days of treatment using regression analysis. Mean slopes over the first and second 30 days were 0.0688 (SD 0.4220) and 0.0018 (SD 0.6245), respectively, a nonsignificant difference ($t_{(20)} = 0.13; P = 0.88$). Thus, occlusion may exert greater (but short-lived) influence on interocular suppression than binocular therapies.

Figure 6A shows suppression at entry versus exit from treatment (ID4 did not have a complete set of data and was excluded). There was no systematic trend in the change of suppression with treatment: suppression decreased in some children (points below the unity line) but increased in others (points above unity). Figure 6B plots improvement in acuity for the AE versus the difference in suppression, obtained by averaging each child’s daily suppression measures. There was a nonsignificant tendency for more improvement in acuity to be associated with modified suppression (Pearson’s $r = 0.19; P = 0.40$; ID4 excluded), especially when suppression significantly changed, either increasing ($r = -0.47; P = 0.80$) or decreasing ($r = -0.13; P = 0.35$). For observers with stable suppression ($n = 10$), we observed a mean gain in acuity of 0.16 ± 0.15 logMAR, whereas for observers whose suppression decreased ($n = 6$) the change in acuity was 0.40 ± 0.15 logMAR and for those whose suppression increased ($n = 5$; ID4 excluded) the change was 0.22 ± 0.18 logMAR. A post hoc power calculation for Pearson’s $r$ supports our analyses being appropriate to detect higher correlations (for $n = 22 - 1_{(df)}$, $r = 0.58$ significant, with 80% power). In Figure 6B, we highlight the range of uncertainty for each child by adding error bars (denoting 95% confidence intervals; horizontal bars for acuity gain, verticals for change in suppression). To do this, we first estimated confidence on acuity gain from the typical test-retest variability of logMAR acuity results in children ($\pm 0.15$ logMAR).
logMAR), and on change in suppression by resampling our indices. We then bootstrapped on pairs of derived values, obtaining at each repetition two sets of changes to find the relative correlation (one set from acuity-paired values and one from suppression-paired values). The mean $r$ across repetitions was 0.161 (mean SD 0.132) confirming the lack of a strong correlation.

**Compliance**

On average, adherence (calculated as the percentage of days when treatment was received) was 68.0% ± 12.2%, meaning that children watched a movie on more than two-thirds of the days on which the equipment was available to them. The mean total dose (across the whole treatment duration) was 75 hours 14 minutes, with a mean daily dose of 54 ± 14.5 minutes (range, 25–89 minutes). Figure 7A shows that none of the children used the system for less than 20 minutes per day (30% of the prescribed dose). Good compliance (20–50 minutes) was demonstrated by 7 children, and excellent compliance (>50 minutes a day) by 15 children, with mean adherence of 63.4% and 70.5%, respectively. Five children exceeded the prescribed dose. A previous study on a monocular video-game therapy for amblyopia showed a marginally significant correlation between gain in acuity and longer daily sessions in children.42 We find that a greater final gain in acuity was not significantly associated with greater daily dose ($r = 0.234$, $P = 0.296$; Fig. 7A) or with a higher percentage of days on treatment ($r = 0.0001$, $P = 0.9998$). One might expect dedication to therapy to improve with age, but we did not find significant correlations of age either with the daily dose ($r = -0.05$, $P = 0.8$) or with the number of treatment days ($r = -0.38$, $P = 0.08$).

As a measure of attention paid to the task, we classified responses on the ghost task either as ‘’valid’’ (the child indicated a ghost in a location where there was one) or as ‘’lapses’’ (the child indicated a position where no ghost was present). On average, 23.1% of responses over all runs were ‘’lapses’’ (SD 20.7%). Figure 7B shows a significant negative correlation between the proportion of ‘’lapses’’ and the age of the child ($r = -0.54$, $P = 0.01$). Although we note a high number of lapses, particularly in some younger children, this

**FIGURE 6.** Estimates of suppression for 21 children (ID4 excluded; IDs numbers to label the correspondent data points; markers colored from blue-younger to red-older children across all recruited children) (A) Suppression ($R$) is similar at entry compared with exit from treatment. (B) There is only a modest correlation of gain in visual acuity (VA) with change in suppression ($r = 0.193$), which does not reach statistical significance ($P = 0.402$). The horizontal dashed line represents the level of “balanced vision.” VA gains outside of the shaded region are considered clinically significant (≥ 0.2 logMAR). Error bars indicate 95% confidence intervals on acuity (horizontal) and suppression (vertical) estimates.

**FIGURE 7.** Compliance and attention. (A) Daily dose in minutes is plotted against acuity (VA) gains in logMAR for the AE. The trend line shows how a higher daily dose (individual mean number of minutes per day spent watching movies) was associated with greater improvement in VA. (B) Percentage of lapse trials on the whitest-ghost task (“invalid responses,” i.e., where the child either indicated a location where a ghost was not present or did not respond at all) as a function of age. Younger children are more prone to lapsing, possibly indicating poorer attention to the task.
### Table 2. Current and Proposed Treatments for Amblyopia

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#### Occlusion, Patching

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#### Game Play and Perceptual Learning

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**Notes:**
- **AE, amblyopic eye; FE, fellow eye.**
- **Variable offspring (e.g., IDs 10, 11). This is because our suppression estimate was noisier than expected (which remains stable across many days; Fig. 5). In particular, although some children with noisier suppression data did make more lapses (e.g., IDs 15, 22), others did not (e.g., IDs 10, 11). This is because our suppression estimate was based on the running average of lapsing generated "no-response" (not a random response) so that the same stimulus level was presented until a valid response was made, and run lengths were long enough (average 30 trials, SD 14.8 trials) that staircases converged even with frequent lapsing. We note that children generally tolerated the interruption of the "ghost" task surprisingly well, possibly because they are accustomed to media content being regularly interrupted by commercials.

**Discussion**

We describe a novel treatment for amblyopia, BBV therapy, which matches stimulation across the eyes and consists of 1 hour per day viewing "binocularly balanced" movies at home through shutter glasses. The procedure involves the blurring of the image received by the FE, at a level such that monocular FE acuity for the blurred stimulus was equal to monocular acuity for the AE (for an unfiltered stimulus as measured at treatment induction). Twenty-two children (3–11 years), with anisotropic, strabismic, or combined amblyopia, completed our study, spending on average 75 hours 14 minutes on treatment, which led to a mean gain in acuity of the AE of 0.27 ± 0.22 logMAR. This gain is clinically significant (i.e., >0.2 logMAR), and matches or exceeds those reported using alternative binocular treatments (Table 2). In terms of rate of improvement, although patching requires 120 hours of treatment for every one line of logMAR acuity gained, our approach is more than four times faster, yielding a similar benefit in only 28 hours of movie viewing.

In terms of stereoacuity, we obtained reliable measures (pre- and posttreatment) only in children with pure anisotropic amblyopia, who frequently maintain a degree of binocularity, especially at low spatial frequencies, which remain visible to both eyes. For these children, stereoacuity reached normal values in all but one child, exceeding reports for occlusion and other binocular therapies (see Table 2).

The treatment duration varied across children, depending on the responsiveness of each child, as evaluated during orthoptic assessment in clinic, and between groups of amblyopia type, to address concerns about inducing diplopia. A pilot group of children (group 1) was treated for 8 weeks only (according to the standard interval adopted in clinic to evaluate a visual treatment). Although acuity improved in six of seven of these children (mean gain: 0.3 ± 0.26 logMAR; ID8 stable), we do not report a significant change in suppression. In the absence of any adverse events, we went on to apply BBV to children in group 2, with strabismic (n = 6) and combined mechanism amblyopia (n = 9), looking at longer-term effects after up to 24 weeks on treatment.

This difference in treatment duration limits the validity of comparing responsivity across children, especially because gains had not plateaued in at least some children who were released from BBV. However, we can still consider the effect of treatment length and compliance on the therapeutic outcome. Standard occlusion therapies, which are likely to improve acuity in 50% to 85% of children, are fundamentally limited by levels of concordance (i.e., agreement on treatment regimen between patient and clinician) falling below 50%, and compliance, especially at a young age (<50% in 4- to 7-year-old children). Recent studies of various binocular treatments have shown that children whose compliance is less than 50% either showed significantly lower gain in logMAR.
Binocular Therapy for Childhood Amblyopia

acuity or required longer treatment durations to reach comparable outcomes. In older children, the success of monocular training (in addition to patching) was related to the total amount of training (across sessions), provided a minimum daily compliance level of 15 minutes of practice per session was met. In our study, on average, children who spent 8 or 16 weeks on BBV showed high levels of compliance (87% ± 21% and 84% ± 28%), with similar gains in AEs acuity (0.2 ± 0.24 and 0.24 ± 0.11 logMAR, respectively). Those eligible for 24 weeks received 98% ± 46% of the prescribed dose and gained 0.41 ± 0.16 logMAR (see also Supplementary Materials). Interestingly, those children whose BBV treatment lasted longer spent a higher proportion of days on treatment (66%, 70%, and 71%, respectively over 8, 16, and 24 weeks). These results suggest that high levels of compliance, as both daily and total perseverance, can produce positive treatment outcomes (although such correlations did not reach significance in our study, perhaps due to the generally high levels of compliance).

More generally, alternative treatments (to replace or augment occlusion) engage higher levels of compliance than occlusion alone. Leaving open the question of whether occlusion is necessary, these studies highlight the importance of compliance in amblyopia treatment. Given the lack of clarity regarding the mechanism supporting improvements in vision, further study is required to determine the extent to which compliance contributes to the superiority of I-Bit (more rapid) therapeutic response from binocular therapies.

Although it is widely assumed that the likelihood of positive treatment outcomes decreases with age, recent interventions have highlighted the possibility of improving vision in amblyopia at almost any age. As highlighted in the introduction, “perceptual learning” (PL) approaches (involving monocular training on gameplay or psychophysical tasks have proven effective in this regard. Gains obtained on the trained task generally transfer to acuity (showing approximately 1–2 logMAR lines of improvement, after approximately 30–50 hours training depending on the severity of amblyopia). Dichoptic PL also has been found to improve stereocuity. Similar improvements have been found with binocular interventions, such as “antisuppression” (AST) or interactive-binocular (I-Bit) therapies that seek to reduce a notional suppressive drive from the FE by equating the visibility of stimuli across the eyes. However, related studies, including games therapy in children and adults did not exclude participants who had previously undergone occlusion therapy. It is impossible to disentangle the influence of previous treatments on outcome. Further, only a few previous studies checked for stable vision before treatment induction. This leaves open the possibility that at least some of the therapeutic benefits of the treatment originate from ongoing benefits of optical treatment. Note that we included only children with no history of occlusion therapy and whose acuity stabilized after minimum 16 weeks of optical treatment.

In terms of stereocuity, only children with measurable (generally poor) stereocuity at entry showed significant improvements following our BBV treatment. This is consistent with earlier work (with occlusion or alternative treatment), which indicated that the initial level of vision may limit treatment outcomes. Among PL approaches, there is evidence for a small advantage of dichoptic game play over monocular movie viewing in improving stereocuity, although monocular game play can also be effective. AST treatment has been shown to significantly improve stereocuity in adults, but not always in children. Further research (e.g., within randomized controlled trials) is needed to determine which components of these therapies are critical for triggering improvements in specific visual functions (such as stereocuity) and to establish the wider applicability of these treatments.

To equalize acuity across the two eyes, we individualized the level of Gaussian blur applied to the image viewed by the FE during movie viewing (i.e., the high spatial frequencies were attenuated in proportion to the AE acuity deficit). This is in contrast to the fixed blur levels used in treatments that rely on, for example, Bargerter translucent filters. In contrast, ASTs manipulate the contrast of the signal to balance visibility across the eyes, and update this level as the child’s vision changes during therapy. The fact that we observe substantial gains in acuity indicates that fixed levels of blur penalization and contrast penalization are both effective for treatment.

Whether and how these methods are related to suppression in amblyopia is hotly debated. Some hold that suppression is a cause of amblyopia and that ASTs strengthen binocular combination by breaking this suppression, allowing monocular and binocular vision to improve. If this were the case, we would expect better outcomes (i.e., improved acuity) to be associated with greater reductions in suppression. We, like an earlier study, do not find strong evidence for such an association, although we note that our approach did not produce substantial changes in suppression at all, unlike at least some binocular gaming therapies or occlusion therapies. That our therapy is effective in the absence of changes in suppression is, however, consistent with the idea that suppression cannot be the sole cause of amblyopic visual loss. An alternative view is that suppression is a consequence of amblyopia to avoid diplopia. If so, a temporary disruption of binocularity (e.g., using repetitive transcranial magnetic stimulation) should have no impact on monocular function. That it does supports the presence of reduced (not lost) functionality of the AE, possibly as a result of suppression.

As mentioned above, there is no consensus as to the best way to quantitate interocular suppression. The method we use to quantify suppression is related to one we have developed previously and uses dichoptic “dark and light” symbol-pairs (“ghosts”). We quantify suppression as the contrast ratio that leads the viewer to be equally likely to report that the symbol presented to either eye is “the whitest.” Although we cannot rule out that the task used to probe suppression will influence the pattern of suppression reported, we think it is unlikely that performance on these different dichoptic tasks is mediated by fundamentally different mechanisms. A further study comparing the currently available methods to measure suppression (clinical and psychophysical) is ongoing. In the present study, we found that the gain in vision achieved under BBV did relate to reduced suppression; however, the correlation was low and failed to reach significance. The absence of a significant relationship between suppression and acuity outcomes greatly limits the risk of inducing intractable diplopia as an adverse side effect from a binocular therapy.

If gains in acuity do not originate from a reduction in suppression, what does produce them? Current theories of the neural basis of amblyopia focus on the consequence of abnormal input from the AE for neural encoding within the lateral geniculate nucleus and primary visual cortex (V1). The following are candidate models: a reduction in the number or/and sensitivity of neurons driven by the AE (undersampling), positional disorganization of visual receptive fields and associated distortions of retinotopic mapping (disarray), and increased variability in the response of binocular cortical neurons. Animal models of amblyopia have produced results to support each of these mechanisms, although the magnitude of these deficits in V1 rarely matches the scale of the behavioral deficits, suggesting an additional role for brain areas beyond V1. In human vision, Clavagnier et al. recently reported findings...
from functional magnetic resonance imaging population receptive field (pRF) mapping (in vivo estimation of visual receptive field size and density)\(^7\)\(^7\)\(^8\) from the FE and AE of patients with amblyopia. They observed larger pRFs in the fovea of amblyopia patients across areas V1 to V3, but normal cortical magnification across these areas, which could arise either through undersampling, positional disarray, or both. This fits with the more general finding of increased receptive field sizes in binocular V1 neurons following retinal lesions.\(^7\)\(^9\)

Given the dependency of the size of RFs (and by extension pRFs) on visual experience in these studies, we consider the reduction in RF size to be the most reasonable current candidate for the mechanism producing therapeutic response. This in turn could be driven by reductions in undersampling and/or disarray within a range of cortical regions, as above. Importantly, the dissociation between suppression and acuity gains in our study suggests that although suppression may play a causal role in these amblyopic deficits,\(^3\)\(^3\) the mechanism underlying such deficits can be altered by treatment without concomitant changes in binocularity that modify suppression.

**CONCLUSIONS**

Our BBV treatment engages high levels of compliance and leads to substantial gains in visual function after a relatively short period of treatment. BBV is currently the only unsupervised binocular vision treatment that also supports remote monitoring of compliance and suppression. Our findings thus far indicate that a reduction in interocular suppression is not the basis of the observed improvements in visual acuity.

**Acknowledgments**

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Binocular Therapy for Childhood Amblyopia Improves Vision without Breaking Interocular Suppression:

Supplemental materials


Visual Outcome: Other Factors

Supplemental Figure 1 summarises how age, type and severity of initial amblyopia and treatment durations influenced outcome. Of the children who stopped after 8 weeks (N=12), 7 from Group 1 were not allowed to continue based on our protocol, while 5 from Group 2 were released due to a lack of further improvement. The mean gain in acuity after 8, 16 or 24 weeks was 0.20±0.24, 0.24±0.11 or 0.41±0.16 LogMAR respectively (see Supp. Fig. 1A). Paired comparisons did not reveal a significant influence of the duration of the treatment on the final gains in acuity (not even between 24 versus 8 weeks, whose relative mean acuity gains showed the largest reciprocal difference; p=0.07). Differences in the maximum permissible period of treatment across groups precludes detailed comparison between groups. However, dependence of treatment response on the type of amblyopia is summarised in Supplemental Figure 1B. Visual acuity improved on average by 0.26 (SD 0.28), 0.34 (SD 0.21) or 0.23 (SD 0.17) LogMAR respectively in children with anisometropic, strabismic or combined-mechanism amblyopia. A two-sample paired t-test indicated there was no statistical significance between the mean-gain achieved for each type of amblyopia (anisometropic vs strabismic, p=0.54; anisometropic vs combined, p=0.80; strabismic and combined, p=0.26). There was no significant dependence of the severity of initial amblyopia with either the final absolute improvement in vision (mean acuity gain in the AE; $R^2=0.13, p = 0.09$; see Supp. Fig. 1C) or the final proportion of deficit corrected ($R^2=0.0006, p = 0.91$).

Lower age has been associated with higher probability of a successful treatment, possibly preventing the applicability of a treatment in adults: compliance (e.g. to patching) reduces with increasing age (Wallace et al. 2013, Stewart et al., 2005, Scheiman et al., 2005) and so does cortical plasticity (Lewis et al., 2005). Using regression analysis (least-squares fitting) we found that the age of participants did not differentially influence the change in acuity in the AE ($R^2= 0.001, p_{(F=0.03)} =0.87$; see Supp. Fig. 1D). Accordingly, there was no dependence of age for children in Group 1 (mean age 9.46±1.93 yrs) or Group 2 (mean age
5.12±1.97 yrs), on the final gain in acuity in the AE (two-sample t-test: p=0.86). Within Group 1, we did however find an effect of age on stereoacuity measurements (Wilcoxon-paired, p=0.02 at α=0.05), though this was not measureable in Group 2. Finally, we considered the possibility that suppression changed with age by taking the individual suppression index averaged over the daily measures, for the duration of BBV treatment. Here we found no significant dependence of age on suppression ($R^2 = 0.14$, p ($F=3.21$) =0.09).

**Supplemental Figure 1** Other factors that may have influenced treatment outcome (A,B: mean improvement or C, D: individual gain). A: Longer treatments led to greater but not significantly different gains in visual acuity. B: Relations between the type of amblyopia and the improvement in VA (none were significant). The dashed lines (in A and B) show the mean test-retest reliability for acuity tests in children. Error bars show one standard error of uncertainty. C: Severity of amblyopia (initial VA in the AE) showed moderate influence on acuity gain in the AE, though this was not significant ($R^2 = 0.134$, p=0.09). D: Age (yrs) was not significantly correlated ($R^2 = 0.001$, p=0.87) with acuity gain in the AE.