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The effect of amblyopia treatment on stereoacuity

Catherine E. Stewart, BMedSci (Orthoptics), PhD,[a] Michael P. Wallace, MA, MSc,[a] David A. Stephens, BSc, PhD,[b] Alistair R. Fielder, FRCS, FRCOphth,[a] Merrick J. Moseley, BSc, PhD,[1] on behalf of the MOTAS Cooperative

Author affiliations: [a]Division of Optometry & Visual Science, City University, London, UK; [b]Department of Mathematics and Statistics, McGill University, Montreal, Canada

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Correspondence: Catherine E. Stewart, Division of Optometry & Visual Science
City University, Northampton Square, London, EC1V 0HB, UK (email: c.e.stewart@city.ac.uk).

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Abstract

Purpose

To explore how stereoacuity changes during amblyopia treatment.

Methods

The Monitored Occlusion Treatment for Amblyopia Study (MOTAS) comprised three distinct phases. In the first, baseline, phase two assessments of visual function were made to confirm the initial visual and binocular visual deficit. The second phase, refractive adaptation, now commonly termed "optical treatment," was an 18-week period of spectacle wear with measurements of logMAR visual acuity and stereoacuity with the Frisby test at weeks 0, 6, 12, and 18. In the third phase, occlusion, participants were prescribed 6 hours of patching per day.

Results

A total of 85 children were enrolled (mean age, 5.1 ± 1.5 years). In 21 children amblyopia was associated with anisometropia; in 29, with strabismus; and in 35, with both. At study entry, poor stereoacuity was associated with poor visual acuity ($P < 0.001$) in the amblyopic eye and greater angle of strabismus ($P < 0.001$). Of 66 participants, 25(38%) participants who received refractive adaptation and 19 (29%) who received occlusion improved by at least one octave in stereoacuity, exceeding test–retest variability. Overall, 38 (45%) improved one or more octaves across both treatment phases. Unmeasureable stereoacuity was observed in 56 participants (66%) at study entry and in 37 (43%) at study exit.

Conclusions

Stereoacuity improved for almost half of the study participants. Improvement was

observed in both treatment phases. Factors associated with poor or nil stereoacuity at study entry and exit were poor visual acuity of the amblyopic eye and large-angle strabismus.

Amblyopia is the most common cause of visual morbidity in childhood, with a prevalence of 1.6% to 3.5%.[1] It occurs during the sensitive period for visual development[2] and is characterized by deficits in spatial vision, including stereovision, usually unilateral, and is associated with one or more sensory obstacles, such as ametropia, strabismus, or a form vision–depriving condition such as cataract.

Although many components of spatial vision can be modulated by amblyopia therapy, including contrast sensitivity[3,4] and positional acuity,[5] visual acuity assessed by letter optotypes remains the principal means of monitoring change. There is, however, little information on how binocular vision changes during amblyopia therapy. This is of particular importance because stereopsis is a binocular visual function that is necessarily interrupted during occlusion.

From a functional viewpoint, the condition best suited to promoting normal visual development and the attainment of full binocular vision is when the visual input from each eye is equal.[6] Binocular function emerges around 3 to 4 months of age, along with maturation of other components of the visual system, including vergence control and cortical development.[7] Stereoacuity increases from 800 arcsec at 4 months to 110 arcsec by 12 months and approaching near adult levels by 24 months,[8] although not attaining full adult levels until around 8 to 9 years.[9]

Mainstream treatment for unilateral amblyopia has two principal components: refractive correction, usually by spectacles, and occlusion by patching or penalization (atropine cycloplegia) of the fellow eye. Both interventions individually generate an improvement in visual acuity.[6]

In this study we examined the changes in stereoacuity that occurred during

amblyopia treatment in the Monitored Occlusion Treatment for Amblyopia Study (MOTAS). This study was designed to explore the dose–response function of occlusion with respect to, primarily, visual acuity, with secondary outcomes including stereoacuity and contrast sensitivity. The principal findings of MOTAS have been published elsewhere.[6,10-12]

Methods

MOTAS comprised three discrete phases: baseline, refractive adaptation, and occlusion. Refractive adaptation is now more commonly referred to as "optical treatment," but here we retain use of the former term for consistency with the original publications.[10-12] Henceforth we refer to refractive adaptation and occlusion as the "treatment phases." See Stewart and colleauges[10] for full details of MOTAS methods

The baseline phase comprised a minimum of two consecutive vision assessments. The primary MOTAS outcome measure was logMAR visual acuity. Three letter logMAR visual acuity charts were employed: ETDRS, crowded, and single logMAR. The chart used depended on the reading ability of the child and was generally age-dependent. To ensure consistency, the visual acuity test employed at the first study session was used throughout the study period. A secondary visual outcome measure of MOTAS was stereoacuity as measured with the Frisby stereotest.[13] The Frisby test was chosen as a test that all children are able to perform in the age range studied (3-7 years) and also because of its fine incremental scale. The test equipment consists of transparent plates, each subdivided into four squares with different sized and randomly placed arrowheads printed onto one surface and with one square containing a circular target of arrowheads printed onto the other surface. The target, which can only be identified in the presence of

stereopsis, appears to emerge out of the plate. The Frisby test has three plates of 6 mm, 3 mm, and 1.5 mm thickness that determine the magnitude of disparity for each test distance (20–80 cm), as listed in Table 1.

The test procedure was as follows. The test cards were presented perpendicular to the child's visual axis at 30 cm. Commencing with the 6 mm plate, if the child correctly identified the target on at least twice in three presentations, the thinner plates were then presented (avoiding overlapping testing of the same disparity on different plates), and if these were also correctly identified the test distance was increased to 40 cm, 50 cm, and so on. The test continued with the presentation of progressively finer plates at greater distances until the child was unable to identify the target. At this point the tester reverted to the previous plate to confirm the end point, the child's stereoacuity being the finest plate correctly identified at the farthest test distance. If the child failed the thickest plate at 30 cm, then the thickest plate was presented at 20 cm. Children who could not resolve the thickest plate at 20 cm were recorded as having nil stereoacuity.

Ocular alignment was assessed using the cover-uncover test to observe the presence of heterotropia and the alternate cover test to observe any increase in angle on dissociation or presence of heterophoria and recovery upon removing the cover. The angle of deviation was measured by the prism and alternate cover test at near (1/3 m) and distance (6 m).

Refractive error was assessed by one author (ARF) using cycloplegic retinosocopy. Significant refractive error was considered to be ≥1.50 D bilateral hypermetropia; ≥ 1.50 D bilateral myopia; ≥0.75 D bilateral astigmatism and ≥ 1.00 D anisometropia.

Children who required spectacle correction entered the refractive adaptation phase, whereas those not requiring spectacle correction entered the occlusion phase. All children with significant refractive error were instructed to wear spectacles full-time and were scheduled to return for four vision assessments at 6-week intervals from week 0 (onset of spectacle wear) until 18 weeks of refractive adaptation was completed—a period that our previous research indicated would allow for all significant improvement attributable to spectacle wear to have occurred.[14] Children remaining eligible for occlusion (see below for inclusion criteria) entered the occlusion phase and were prescribed 6 hours occlusion per day (a dose considered moderate, allowing for under- and over-concordance). Occlusion episodes received were recorded to the nearest minute by an occlusion dose monitor.[15] Both visual function and the monitored occlusion dose were recorded at 2-week intervals until visual acuity ceased to improve (two inflexions on a visual acuity versus time plot or change not exceeding ± 0.02 log units difference on three consecutive visits). This sensitive measure was used to ensure that treatment was not stopped before all reasonable gains had occurred (see Stewart and collegues[10]). On completion of the occlusion phase, participants left the study and were returned to standard clinical care. No patient had any other ophthalmic intervention, including surgery, during the study period.

Inclusion eligibility criteria were age 3 to 8 years, anisometropia and/or strabismus, an interocular acuity difference of at least 0.1 logMAR, written parental consent, no previous occlusion, and the absence of either ocular pathology or learning difficulties. The study was administered according to the Helsinki Declaration II and approved by Hillingdon and St Mary's Hospital, London, NHS Trusts' Local Research

Ethics Committees.

Statistical Analysis

The cohort for our analyses consisted of participants who had a stereoacuity measurement at both the start and end of one or both treatment phases. Using multivariate linear regression models, we investigated what factors are associated with stereoacuity, conducting two main analyses: an analysis of associations with baseline stereoacuity, and an analysis of associations with stereoacuity at the end of (each phase of) treatment. The following covariates were considered: age, visual acuity in the amblyopic eye, the presence of anisometropia, and the angle of any strabismus (the last two being measured only at study entry). In addition, models of stereoacuity at end of treatment phase controlled for stereoacuity at the start of that particular treatment phase. Two-way interaction terms were considered, and backward selection based on the Akaike Information Criterion was used for final model selection.[16] Time in treatment was not included in the models of outcome stereoacuity.

Due to evidence of nonlinear relationships with stereoacuity at study entry and end of treatment, age and the amount of anisometropia were categorized. Age was divided into three categories: <48 months, ≥48 to <72 months, and ≥72 months.[6] Amblyopia type was classified as with anisometropia (≥ 1 D) and with only strabismus; therefore, our new anisometropia group consisted of those with mixed amblyopia as well as those with purely anisometropic amblyopia. Although this seemingly provides less information than the trichotomy of anisometropia/mixed/strabismus used to identify patient characteristics, we considered it important to include angle of strabismus, which was categorized into three levels: slight (<10°), moderate (≥10° and <25°), and

large (≥25°).

The lowest possible measure of stereoacuity was 1,200 arcsec and participants not attaining this level were recorded as having 'nil' stereoacuity which were assigned the next octave value of 2,400 arcsec in the analysis.[17] Sensitivity to this procedure was investigated by performing analyses with extreme values for nil stereoacuity of 1,500 and 10,000 arcsec. All analyses were performed with stereoacuity log-transformed (to base 10) and were implemented in the statistical software package R. Mann-Whitney-Wilcoxon tests were used to identify whether changes in stereoacuity were significant in and between study phases.

Results

Primary Analysis

A total of 85 children were included (mean age, 5.1 ± 1.5 years). In 21 children (mean age, 5.6 ± 1.2 years), amblyopia was associated with anisometropia; in 29 (mean age, 4.7 ± 1.2 years), with strabismus; and in 35 (mean age, 5.3 ± 1.5 years), with both anisometropia and strabismus (mixed). Of the 85, 50 completed both treatment phases, 16 received refractive adaptation, and 19 received occlusion only (8 had no refractive error and 11 had undergone full refractive adaptation prior to study entry). The characteristics of individuals at study entry are summarized in Table 2, where we consider first the entire cohort and second those with measurable stereoacuity at study entry. Of the 85 participants, 56 (66%) had nil stereoacuity at study entry. Details of strabismus classification are shown in Table 3. Further details of baseline characteristics of participants have been published elsewhere.[11] Mean concordance with the prescribed occlusion dose rate (6 hours/day) was 2.8 hours (48%). Only 10 (14%) of participants

achieved an average concordance within 30 minutes of the prescribed dose rate.

Figure 1A summarizes stereoacuity at start and end of each treatment phase; Figure 1B represents the progress of those with measureable stereopsis at the start and end of each phase to enable visualization of progression through the study.

Refractive Adaptation Phase

In the 66 children who entered the refractive adaptation phase, the median (IQR) visual acuity for amblyopic eyes improved from 0.56 ± 0.41 to 0.34 ± 0.54 logMAR, a mean improvement of 0.22 ± 0.18; (range, 0.0 to 0.6). Following refractive adaptation, 13 study participants (16.7%) no longer had amblyopia according to the study definition.

The median (IQR) change in stereoacuity during refractive adaptation was as follows: for all children (n = 66), 3.38 ± 0.60 to 2.78 ± 1.31 (P = 0.006); for the 21 children with stereoacuity at the outset, 2.23 ± 0.74 to 2.04 ± 0.49 (P = 0.01); for the 14 children who gained stereoacuity during this phase (n = 14), 2.78 ± 0.49 arcsec. (These values equate to 2,400 to 600 and 170 to 110 and 600 log arcsec, respectively.) Thirty-one continued to have nil stereoacuity.

Occlusion

During the occlusion phase (n = 69) median (IQR) visual acuity for amblyopic eyes improved from 0.48 ± 0.49 to 0·15 ± 0.35 logMAR: a mean improvement of 0·33 ± 0·18 (range, 0.0-1.2]. Analyzing the change in stereoacuity during the occlusion phase was as follows: for all children (n = 69), 3.38 [1.15] to 2.78[1.51] (P = 0.21); those with stereoacuity at the start of the phase (n = 32), 2.18 [0.60] to 1.88 [0.49] (P = 0.01); those that gained stereoacuity in this phase (n = 6), achieved 2.78 [0.23] log arcsec. (These values equate to 2,400 to 600 and 170 to 75 and 2,400 to 600 log arcsec, respectively.)

Thirty-one continued to have nil stereoacuity.

Change in Stereoacuity

Figure 2 summarizes the change in stereoacuity during each treatment phase in terms of octave steps (improvement of 1 octave equivalent to a decrease in 0.3 log arcsec or simply a halving of stereoacuity on its original, arcsec scale). Improvement by at least one octave, the amount required to exceed test–retest variability,[17] was achieved by 25 children (38%) who received refractive adaptation, 19 (28%) who received occlusion, and 38 (45%) who underwent refractive adaptation and/or occlusion. Only 6 children (15%) improved by at least 1 octave in each phase of treatment. One participant in the refractive adaptation phase and 2 participants in the occlusion phases demonstrated a deterioration of stereopsis by 1 octave. Seven participants with measureable stereopsis demonstrated improvements <1 octave in each phase and overall. Thirty-seven (44%) had nil stereoacuity throughout the study. Table 4 summarizes characteristics of participants at study exit.

Regression Analysis

For the purposes of fitting multivariate normal linear regression models, age at study entry was categorized into the three groups: <48 months (n = 27), ≥48 and <72 months (n = 33), and ≥72 months (n = 35). Those with anisometropic and mixed amblyopia were grouped into a single anisometropia group (to be compared with those with purely strabismic amblyopia). Absolute angle of strabismus was categorized into three groups: slight (<10°, n = 48), moderate (≥10° to <25°, n = 19), and large (≥25°, n = 18). Results of the model for stereoacuity at study entry are summarized in Table 5. All two-way interaction terms were eliminated during the model selection procedure, as was

anisometropia, which was not found to contribute significantly to the model ($P = 0.176$).

At study entry, controlling for age ($P > 0.25$ for both categories), poor stereoacuity was associated with poor visual acuity in the amblyopic eye, with a 1 logMAR decline of visual acuity on average corresponding to a decline in stereoacuity of 0.51 log arcsec. Relative to those with mild strabismus, poor stereoacuity was not significantly associated with moderate strabismus ($P = 0.083$) but was with severe strabismus ($P = 0.007$). After controlling for the other variables, those with severe strabismus had, on average, 0.38 log arcsec worse stereoacuity than those with mild strabismus. A separate analysis did not find a significant difference in stereoacuity between those with moderate and severe strabismus ($P = 0.341$). Analyses carried out with values of 1,500 and 10,000 for nil stereoacuity returned similar results.

Outcome stereoacuity was modeled across the entire cohort of 85 individuals, with those 50 who received both treatments contributing to the model twice (once as refraction and once as occlusion patients). As with our multivariate linear model of stereoacuity at study entry, all two-way interaction terms were eliminated during model selection, as was anisometropia ($P = 0.696$). The results of fitting our final model are summarized in Table 6. After controlling for stereoacuity at start of treatment ($P < 0.001$) and age ($P = 0.264$ and $P < 0.001$ for the 48-72 and >72 age categories, respectively), worse stereoacuity was again associated with worse visual acuity in the amblyopic eye at start of treatment ($P < 0.001$), with a 1 logMAR worsening of visual acuity on average corresponding to a worsening in stereoacuity of 0.30 log arcsec. Relative to those with mild strabismus, those with moderate ($P = 0.01$) and severe ($P < 0.001$) strabismus were found to have poor stereoacuity (0.20 and 0.33 log arcsec, respectively). Again, there was

no significant difference in stereoacuity between those with moderate and severe strabismus (P = 0.138).

A mixed effects model approach that accounted for the repeated-measure aspect of the dataset (with most participants contributing two sets of covariate and outcome measurements) returned similar results, as did analyses with extreme values of 1,500 and 10,000 for nil stereoacuity.

Discussion

This study(MOTAS) examined factors influencing changes in stereopsis during amblyopia treatment. The study participants represent a typical population of children with amblyopia undergoing treatment. We found that severe amblyopia and a greater angle of strabismus were associated with reduced or absent stereoacuity. Stereoacuity can improve in either the refractive adaptation and occlusion phases of treatment; however, most individuals improve during one or the other.

At study entry, patients with anisometropia were more likely to have better stereopsis than those with strabismus. This finding is consistent with Loudon and colleagues,[18] who showed those children with strabismus detected by screening had a lower binocularity score compared to those with anisometropia. However, by study exit this was not the case in our cohort, indicating that initial visual acuity and the angle of strabismus were the most important factors associated with improvement in stereoacuity.

Optical treatment of amblyopia is now well documented to improve visual acuity for all types of amblyopia.[19-21] The present study demonstrates that stereoacuity not only improves during this phase of treatment for individuals with anisometropia, reported recently by Richardson and colleagues, [22] but also that individuals with all three types of

amblyopia demonstrate significant improvements in stereoacuity.

Documentation of stereoacuity improvement during each treatment phase is sparse, mainly because until recently optical treatment and occlusion were not fully differentiated. In MOTAS, for some individuals stereoacuity improved during the occlusion phase. The data suggest that improvement in stereoacuity was more likely in the refractive adaptation phase rather than the occlusion phase; however, the data was biased by those that improved sufficiently in this first phase to make continued treatment unnecessary, and further studies, with larger numbers of patients, are required. By definition, occlusion precludes form vision of the fellow eye and thus disrupts any potential binocular vision. It therefore might be speculated that for those participants with amblyopia and with measureable stereopsis, occlusion treatment could cause a deterioration of this aspect of spatial vision. Yet experimental work has shown that short daily periods of binocular vision, if concordant and continuous, outweigh or protect against much longer daily periods of monocular deprivation (allowing the development of normal visual acuity in both eyes of kittens).[23] On this basis, for the human condition, providing that occlusion is not full-time (ie, all waking hours) it is likely that some period of monocular viewing can be tolerated without negatively affecting the potential for improved binocular function. It could be instructive to observe changes in stereoacuity after occlusion is discontinued; unfortunately, the study design did not permit continued observation. We postulate that stereoacuity might continue to improve following acquisition of better visual acuity in the occlusion phase and discontinuation of treatment that could disrupt or prevent improvement of stereoacuity.

Superior stereoacuity was associated with superior visual acuity at the start and

end of each treatment phase. Superior visual acuity and reduction in the difference between the visual inputs of each eye are likely to allow for better discrimination of stereoacuity images—a finding reported for those with anisometropic amblyopia by Wallace and colleagues,[24] who also found a relationship between better stereoacuity and less anisometropia at baseline. Induced anisometropia of as little as 1.0 D has been reported to degrade stereopsis.[25] Due to the small numbers in our study cohort, we were unable to explore the relationship between amount of anisometropia and stereoacuity.

We observed a correlation between logMAR visual acuity and log stereoacuity. This has also been documented by Lee and Isenberg,[26] who reported a significant linear relationship between stereoacuity improvement with occlusion and visual acuity improvement, irrespective of presence of small-angle or intermittent strabismus. When visual acuity is degraded with the use of fogging plus lenses, stereoacuity is reported to decrease approximately proportionally to the reduction of visual acuity.[27] This raises the questions, What level of interocular difference is consistent with good stereopsis? How much difference causes degradation of stereopsis? Odell[25] report that visual acuity deficits degrade stereoacuity more severely when using random dot rather than with real depth (Frisby, FD2) tests. Odell and colleagues[25] reported good stereopsis on the Frisby test until visual acuity degrades to 20/100 (0.70 logMAR equivalent), with most subjects maintaining gross stereoacuity at 20/320 (1.2 logMAR equivalent). In MOTAS, those without stereoacuity at study exit had a median [IQR] consistent with these values (0.70 [0.51] logMAR).

Visual acuity of the amblyopic eye and angle of strabismus are strong predictors of improvement in stereoacuity during treatment. Individuals with angles of strabismus

>25 D are unlikely to achieve stereoacuity. This will consolidate the belief that early surgery to reduce the angle of strabismus is beneficial provided patients have good visual acuity and achieve successful alignment.[9,28,29] Analysis of angle of strabismus and stereoacuity was limited to three groups (<10 D, 10 D to <25 D and >25 D) in the present study, but did not distinguish between manifest and latent strabismus due to the small sample size. Therefore within the <10 D and 10 to <25 groups there were some individuals that had no mainifest deviation. Further modeling of the effect of angle of strabismus on stereoacuity and improvement during treatment warrants discrimination between latent and manifest deviations as well as angle size. Furthermore, recovery of fusion[30,31,29] and stereopsis has been observed even in those who had strabismus onset before visual maturity (<9 years). The visual outcomes of patients with infantile esotropia have been reported to be substantially improved if the misalignment is corrected surgically, early in life.[9,32-34] Drover and colleagues[9] also suggest that early muscle surgery could be associated with greater prevalence of stereopsis and be beneficial to subsequent motor development.

In conclusion, stereoacuity improved for almost half of the study participants, even for a proportion of those without stereopsis at the outset. Improvement can occur during both refractive adaptation and occlusion. Children in whom stereoacuity did not improve had significantly poorer visual acuity at the start and end of treatment and a larger angle of strabismus.

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Table 1. Disparities in arcsec for each Frisby test plate, as a function of test distance.

Table 2. Characteristics of MOTAS participants at study entry. With the exception of amblyopia type, entries are of the form "median (interquartile range)." Note, the angle of strabismus in measured with alternate prism cover test.

Table 3. Ocular alignment at baseline. Range = angle of deviation at near and distance fixation, with and without refractive correction. PCT = Prism Cover Test (using alternate prism cover testing); BO = Base Out; BI = Base In. N.B. The corrected column includes measurements from children with insignificant refractive error (defined previously in the Method).[10]

Table 4. Characteristics of MOTAS study participants at study exit. With the exception of amblyopia type, entries are of the form "median (interquartile range)". Note that 3.38 log stereoacuity is an arbitrary assignment for those with nil stereoacuity.

Table 5. Multivariate linear regression model of (log transformed) stereoacuity at study entry. Age categories are relative to those under 48 months, anisometropia compares those classified as having anisometropia to those with purely strabismic amblyopia (n = 85). Regression coefficients translate to the increase in stereoacuity at study exit for either a one unit increase in the corresponding variable or, for categorical variables, relative to its baseline.

Table 6. Multivariate linear regression model of (log transformed) stereoacuity at end of treatment phases. Age categories are relative to those under 48 months, anisometropia compares those classified as having anisometropia to those with purely strabismic amblyopia, phase compares occlusion phase with refraction phase. Stereoacuity, age and visual acuity measured at start of treatment phase, all other measurements taken at study

entry (n = 85). Regression coefficients translate to the increase in stereoacuity at study exit for either a one unit increase in the corresponding variable or, for categorical variables, relative to its baseline.

Legends

FIG 1. A, Stereoacuity at start and end of refraction (n = 66) and occlusion (n = 69) treatment phases. Note that participants with unmeasurable stereoacuity were assigned 2400 arcsec (3.38 log arcsec). Stereoacuity is poor at the start of the occlusion phase compared to the end of the refractive adaptation due to some patients leaving the study at this point (n = 16) and others (n = 19) starting the study at the beginning of the occlusion phase. B, Stereoacuity at start and end of refraction (n = 21) and occlusion (n = 32) treatment phases, excluding those with unmeasurable stereoacuity at the start of each treatment phase. Boxes indicate 25% and 75% quartiles; whiskers extend to the most extreme point not more than 1.5 times the interquartile range from the median.

FIG 2. Change (improvement) in stereoacuity during treatment phases and treatment as a whole. An improvement of 1 octave corresponds to a halving of stereoacuity on its original, arcsec, scale, or a decrease of 0.3 log arcsec.