Brief Daily Periods of Unrestricted Vision Preserve Stereopsis in Strabismus

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PURPOSE. This study examines whether brief periods of binocular vision could preserve stereopsis in monkeys reared with optical strabismus.

METHODS. Starting at 4 weeks of age, six infant monkeys were reared with a total of 30 prism diopters base-in split between the eyes. Two of the six monkeys wore prisms continuously, one for 4 weeks and one for 6 weeks. Four of the six monkeys wore prisms but had 2 hours of binocular vision daily, one for 4, one for 6, and two for 16 weeks. Five normally reared monkeys provided control data. Behavioral methods were used to measure spatial contrast sensitivity, eye alignment, and stereopsis with Gabor and random dot targets.

RESULTS. The same pattern of results was evident for both local and global stereopsis. For monkeys treated for 4 weeks, daily periods of binocular vision rescued stereopsis from the 10-fold reduction observed with continuous optical strabismus. Six weeks of continuous strabismus resulted in stereo blindness, whereas daily periods of binocular vision limited the reduction to a twofold loss from normal. Daily periods of binocular vision preserved stereopsis over 16 weeks of optical strabismus for one of the two monkeys.

CONCLUSIONS. Two hours of daily binocular vision largely preserves local and global stereopsis in monkeys reared with optical strabismus. During early development, the effects of normal vision are weighed more heavily than those of abnormal vision. The manner in which the effects of visual experience are integrated over time reduces the likelihood that brief episodes of abnormal vision will cause abnormal binocular vision development. (*Invest Ophthalmol Vis Sci.* 2011;52:4872–4879) DOI:10.1167/iiov.10-6891

Visual experience plays an important role in the development of both normal and abnormal binocular vision. Both monkey and human infants are born with basic visual capabilities and require normal visual experience early in life to reach optimal levels of visual functioning as adults.^{1,2} Disorders such as strabismus can, at least during the early critical period of visual development, disrupt the function of binocular mechanisms necessary for the development of normal stereopsis in monkeys and humans.^{3,4}

Current research indicates that infants have the potential for stereopsis at a very early age. Infant monkeys as young as

the sixth postnatal day have been shown to have adult-like proportions of binocular neurons in primary visual cortex (V1) that are sensitive to interocular disparity.¹ Over the first 4 postnatal weeks the immaturities that limit disparity sensitivity, namely, poor contrast sensitivity to higher spatial frequencies and low response amplitudes to disparity, rapidly improve, resulting in increases in sensitivity to disparity at the cellular level.¹ It is after this period of maturation, at 3 to 4 weeks of age, that infant monkeys respond behaviorally to binocular disparities in stereoscopic targets.⁵ Similarly, human infants demonstrate behavioral responses to stereoscopic targets starting at 3 to 4 months of age.^{6–9} Human infants can demonstrate sensitivity to disparity on the order of approximately 8 arc-minutes, and as the sensitivity to contrast matures, stereopsis improves to adult levels of approximately 5 to 10 arcseconds of stereopsis.¹⁰

Infantile esotropia, or an inward turning eye, is the most common strabismus occurring from birth to approximately 5 to 6 months of age in human infants.^{11–14} While variable and/or small-angle esotropias observed in younger infants often resolve spontaneously,¹⁴ constant larger-angle (≥ 40 prism diopters) esotropias are unlikely to resolve spontaneously^{14,15} and present an impediment to the development of normal stereopsis.

At 3 to 4 months of age, early in the time course for the emergence of measureable stereopsis, prism-corrected human infantile esotropes have been shown to demonstrate stereopsis in the same proportions as normal infants.^{2,12,16} The proportion of normal infants responding to disparity increases to 100% by 7 months of age, while infantile esotropes lose the ability to distinguish between disparate and nondisparate targets beyond 5 months of age.²

Current treatment for infantile esotropia is generally early surgical alignment, though the best functional binocular outcome remains “the monofixation syndrome,”^{11,17–23} or “sub-normal binocular vision,”^{24,25} where there is invariably reduced stereopsis due to suppression of the fovea of the previously deviated eye.²⁶

Although the effects of temporal variations in eye alignment during the period of binocular visual development have not been previously examined systematically, a few observations suggest that the constancy of strabismus over time has a significant effect on the degradation of stereopsis. For example, adults with constant strabismus are not likely to demonstrate stereopsis, while those with intermittent strabismus or strabismus that manifests only at certain viewing distances often demonstrate stereopsis under conditions of binocular fusion.²⁷ In addition, Blakemore²⁸ demonstrated that strabismic kittens reared with normal binocular stimulation retain disparity sensitive neurons.

Our goal was to determine whether the early potential for normal stereopsis can be preserved by providing brief periods of normal binocular visual experience throughout a limited duration of strabismus. Our previous work has shown that brief periods of unrestricted vision can prevent amblyopia

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Supported by National Eye Institute (NEI) Grants R01 EY03611 (ELS) and R01 EY01139 (RSH), and NEI Core Grant P30 EY007551 to UHCO.

Submitted for publication November 14, 2010; revised January 13 and February 16, 2011; accepted February 23, 2011.

Disclosure: J.M. Wensveen, None; E.L. Smith III, None; L.-F. Hung, None; R.S. Harwerth, None

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despite much longer periods of form deprivation.²⁹ Both monocular spatial vision and binocular stereoscopic vision require normal visual experience early in life to develop normally. However, there are inevitably periods of blur and periods of diplopia, even when the visual system is functioning normally. For normal vision to develop, it may be that the mechanisms that control visual development are influenced to a lesser degree by periods of abnormal visual experience and to a greater degree by periods of normal visual experience.

MATERIALS AND METHODS

Subjects

Data are presented for 11 rhesus monkeys (*Macaca mulatta*). All infants were obtained at 1 to 3 weeks of age and reared in the university primate nursery that was maintained on a 12-hr light:12-hr dark lighting cycle. All rearing and experimental procedures were approved by the University of Houston's Institutional Animal Care and Use Committee and were in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Optical strabismus was produced in six infant monkeys by securing 15 diopter prisms oriented base-in in front of each eye by means of a lightweight helmet, in the manner previously described.^{30–32} Prism rearing was initiated at 4 weeks of age for monkeys JOB, JAR, KER, and OLI, at 3 weeks for monkey UME, and at 5.3 weeks for monkey IGO. The prism-rearing regime was purposefully delayed until the subjects were 3 to 4 weeks old because visual manipulations like optical strabismus that are initiated in infant monkeys after 3 weeks of age are unlikely to result in a frank misalignment once the prisms are removed.^{33–35}

Two monkeys wore the prisms continuously, one for 4 weeks (JOB) and the other for 6 weeks (IGO). Two other experimental monkeys also wore the prisms for 4 weeks (JAR) or 6 weeks (KER) but were allowed 2 hours of normal binocular vision each day by replacing the prisms with clear plano lenses. Two monkeys (OLI and UME) were also allowed 2 hours of normal binocular vision each day, but their treatment was continued for an extended duration of 16 weeks. These periods of normal binocular vision were centered near the midpoint of the normal 12-hr lights-on cycle. At the end of the rearing period, the helmets were removed to allow normal vision. Five normally reared monkeys provided control data (monkeys AND, MAR, QUI, QUE, and JUS). The behavioral data for some of these monkeys have been previously reported in abstract form (Wensveen JM, et al. *IOVS* 2007; ARVO E-abstract 5884).³⁶

Apparatus and Visual Stimuli

Behavioral training and testing were initiated after the monkeys had experienced one year of unrestricted vision after the treatment period ensuring that any observed deficits in visual function were permanent. During the daily experimental sessions, the monkeys were seated in a primate chair fitted with a response lever on the waist plate and a drink spout on the neck plate. The animal's optimal spectacle correction, which was determined for each eye independently by retinoscopy and a subjective refraction procedure,³⁵ was held in a facemask at about a 14-mm vertex distance for all training and testing procedures. For monocular viewing, the lens well for one of the eyes was occluded with an opaque disc.

Spatial Contrast Sensitivity

Knowledge of the integrity of monocular spatial vision mechanisms was crucial for the interpretation of the binocular stereoscopic data. Consequently, to determine whether the prism-rearing paradigm had compromised our subjects' spatial visual development, spatial contrast sensitivity functions were determined for each eye of each monkey. The basic apparatus and operant procedures were similar to those used in previous investigations.^{29,33,35,37,38}

The Gabor detection stimuli consisted of sine-phase vertical sinusoidal gratings windowed by a 2° Gaussian envelope and were presented on an 11° × 14° video monitor with a space-averaged luminance of 60 cd/m². The stimulus contrast was defined as $(L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$, where $L_{\max}$ and $L_{\min}$ represent the maximum and minimum luminances of the grating, respectively. The behavioral paradigm was a temporal-interval detection task that required the monkey to press and hold down the response lever to initiate a trial and then to release the lever within a criterion response interval of 900 ms after the presentation of the grating stimulus to score a "hit." Data were collected using an adaptive decreasing-contrast staircase procedure where each hit was followed by a 0.1 log unit reduction in contrast, and two consecutive misses were followed by a 0.6 log unit increase in contrast, causing staircase reversals to converge to a contrast where the probability of a hit was 29%, and this contrast was taken as the threshold. Contrast detection thresholds were measured as a function of grating spatial frequency from 0.25 to 16 cyc/deg in 0.15 log unit steps.

Contrast sensitivity functions were generated from the geometric means of a minimum of 30 threshold measurements at each spatial frequency. Each contrast sensitivity function was fitted with the following double exponential function using an iterative routine that minimized the sum of squared errors³⁹:

$$\text{Contrast sensitivity} = [ks(sf * kf) ^ al] \exp(-ab * sf * kf)$$

where sf is the spatial frequency; al and ab are parameters that reflect the slopes of the low and high spatial frequency portions of the function, respectively; and ks and kf are proportional to the peak contrast sensitivity and the optimum spatial frequency, respectively.

Fixation Disparity and Interocular Alignment

Eye alignment information was also critical for the interpretation of the stereoscopic threshold data. To ensure that no strabismus was manifest, fixation disparities were measured behaviorally as a function of prism-induced forced vergence.^{40,41} In essence, the monkeys made dichoptic nonius judgments for line stimuli presented against a background that promoted binocular fusion. The offset of the dichoptically viewed line stimuli at perceptual alignment (fixation disparity) was determined over a range of horizontal prism powers. The plot of prism power (forced vergence) versus fixation disparity provided an indication of the monkey's motor fusion capabilities⁴² and, more importantly, the prism power that minimized the monkey's fixation disparity to zero (the associated phoria).

Local and Global Stereopsis

Stereoscopic stimuli were generated by computer graphics (VSG 2/3; Cambridge Research Systems, Cambridge, England) and dichoptically viewed through liquid-crystal shutters (model LV 100P; DisplayTech Inc., Longmont, CO) synchronized with the video frames to present alternate, noninterlaced frames at 60 Hz to each eye. The generation of the local stereoscopic stimuli has been described previously.^{38,40} Briefly, stereoscopic stimuli were one-dimensional Gabor patches with four cycles of the vertical sine-phase sinusoidal grating visible for all grating spatial frequencies.⁴³ The upper reference Gabor was presented with no horizontal disparity and was separated from the lower test Gabor by a 2 arcmin gap. The lower test Gabor was presented with crossed or uncrossed disparity. The disparity threshold was measured for grating spatial frequencies ranging from 0.25 to 16.0 cyc/deg in half-octave steps.

To test global stereopsis, the display consisted of a top and bottom band of random dots 4.5° (200 pixels) in height and 17.9° (800 pixels) in width separated by an 8 arcmin (6 pixels) gap of average luminance. The band on the top of the display was seen by both eyes with zero disparity and constituted the reference area. The band on the bottom was the test area and was dichoptically displayed with a positional disparity. Each band was a full density stereogram, where the band was

FIGURE 1. The reciprocal of the average threshold contrast for each eye was plotted as a function of spatial frequency to generate monocular spatial contrast sensitivity functions. *Open symbols:* right eye sensitivities; *filled symbols:* left eye sensitivities of these normally reared monkeys; *error bars:* standard deviations; *lines:* best-fitting double exponential functions.³⁹

divided into elements that were 6.7 arcminutes square (5×5 pixels) and were either black or white. The stereograms were dynamic. Disparity thresholds were measured across a range of interocular correlations from 100% to 10% in half-octave steps. With 100% correlation, the black and white dots in the stereo half-image seen by the right eye exactly matched the polarity of dots in the same relative positions in the stereo half-image seen by the left eye. At 50% correlation, half of the black and white dots in the stereo half-image seen by the right eye were forced to match the polarity of the dots in the same positions in the stereo half-image seen by the left eye, and the remaining half of the total number of dots were left free to vary randomly. At 0% correlation, none of the dots in the right eye stereo half-image were forced to match their positional partner in the left eye stereo half-image, but by chance, 50% of the pairs would have matched polarity.

To measure disparity thresholds with either Gabor or random dot stimuli monkeys performed a "go/no-go" discrimination task that incorporated the essential features of a two-alternative forced-choice paradigm. An 8 Hz clicker prompted the monkey to press down on the lever to initiate a 1 second fixation cue, followed by the 1 second presentation of the reference and test stimuli. Correct behavior was defined as a lever release (a "go" response) if the test stimulus was perceived as closer than the reference due to the positional offset in crossed disparity, or a maintained lever press (a "no-go" response) if the test stimulus was perceived as farther than the reference due to the positional offset in uncrossed disparity. Each correct response was reinforced with a tone, and every second to third correct response was reinforced with orange drink.

During a daily experimental session a single grating spatial frequency was incorporated into the Gabor stimuli, or a single percentage correlation was presented in the random dot bands. Regardless of the visual stimulus configuration, the method of constant stimuli was used with five values of crossed and five values of uncrossed disparity equally spaced along the disparity continuum. Psychometric functions were fitted with a logistic function and the semi-intraquartile range was taken as the threshold.⁴⁴ The results reported are the means of at least four threshold determinations. We were certain that monkeys were basing their responses on binocular disparity because, when one of the monkey's eyes was occluded, performance always fell to chance levels.

RESULTS

Spatial Contrast Sensitivity

The contrast sensitivity functions for normally reared monkeys AND, MAR, QUI, QUE, and JUS (Fig. 1) and prism-reared monkeys JAR, UME, JOB, and KER (Fig. 2) were comparable in all major aspects. The contrast sensitivities for the two eyes of any given monkey were well matched, and the functions for each monkey exhibited the characteristic bandpass shape. The average maximum contrast sensitivity for these nine monkeys was 143 ± 52 for optimal spatial frequencies between 2.2 and 3.7 cyc/deg, and the mean extrapolated cutoff spatial frequency was 23.3 ± 4.4 cyc/deg.

Monkey IGO (constant optical strabismus for 6 weeks) and monkey OLI (optical strabismus with daily periods of normal vision for 16 weeks) showed lower than normal maximum contrast sensitivities, peak spatial frequencies, and cutoff spatial frequencies. Monkey IGO was the more severely affected (OD maximum sensitivity, 64 for 0.8 cyc/deg and 4.1 cyc/deg cutoff spatial frequency; OS maximum sensitivity, 103 for 1.1 cyc/deg and 5.9 cyc/deg cutoff spatial frequency) than monkey OLI (OD maximum sensitivity, 73 for 2.1 cyc/deg and 11.6 cyc/deg cutoff spatial frequency; OS maximum sensitivity, 69 for 1.5 cyc/deg and 8.5 cyc/deg cutoff spatial frequency).

All monkeys showed normal refractive errors at the beginning of prism rearing by retinoscopy.³⁵ However, monkey IGO exhibited a high bilateral hyperopia (OU, +11.00 D), and monkey OLI showed an anisometropia (OD, -1.00 D; OS, +3.00 D) at 18 months of age when behavioral testing was initiated. Each animal's optimal spectacle correction was held in a facemask for all training and testing procedures.

Fixation Disparity and Interocular Alignment

All the monkeys were nonstrabismic, based on inspection of the positions of the first Purkinje images produced by a bright fixation target. In addition, all monkeys performed dichoptic nonius alignment discriminations through an array of prisms to generate forced vergence-fixation disparity functions. No mon-

Prism Reared Monkeys

FIGURE 2. Monocular spatial contrast sensitivity functions of prism-reared monkeys. See Figure 1 for details.

key required prisms to perceptually align physically aligned targets, which was consistent with normal interocular alignment in all animals.^{38,41,45}

Local and Global Stereopsis

Depth discrimination thresholds are plotted against the grating spatial frequency of the Gabor stimuli for the normally reared monkeys only on the left panel in Figure 3. Normal monkeys showed decreasing disparity thresholds over low to midspatial frequencies to an average minimum of 0.15 arcmin (8.9 arcsec) at around 2.82 cyc/deg, and then the disparity thresholds remained relatively constant, with a slight increase at higher spatial frequencies. The right panel of Figure 3 shows disparity thresholds as a function of grating spatial frequency for the prism-reared monkeys compared with the disparity average ± 2 standard deviations (99% confidence interval) of the normally reared monkeys, represented as the shaded area. Experimental monkeys showed the same pattern of results as the normal monkeys, except that the disparity thresholds were shifted to

larger values. The monkey reared with 4 weeks of continuous strabismus (JOB, filled hexagons) showed a 10-fold reduction in local stereopsis across all spatial frequencies, and his best stereopsis was 16.0 arcmin (960 arcsec) with the 2.82 cyc/deg target. Monkey JAR, who was also prism-reared for 4 weeks but who had daily periods of unrestricted vision, showed near normal stereopsis (filled squares) and, for comparison, had 0.53 arcmin (31.8 arcsec) stereopsis with the same 2.82 cyc/deg target. Monkey KER, reared with daily periods of unrestricted vision but for 6 weeks, showed only a one-octave reduction in stereopsis across all spatial frequencies (filled diamonds), and her best stereopsis was 0.64 arcmin (38.4 arcsec) with the 2 cyc/deg Gabor target. Monkey UME (open circles), showed local stereopsis comparable to these other two monkeys that were allowed daily periods of unrestricted vision even though her treatment period was for a much longer duration of 16 weeks. Monkey UME demonstrated her best stereopsis of 0.83 arcmin (49.7 arcsec) with the 2.82 cyc/deg target.

FIGURE 3. *Left:* Depth discrimination thresholds as a function of spatial frequency of the carrier grating of the Gabor stimuli for normally reared monkeys (AND, squares; MAR, circles; QUI, diamonds; QUE, triangles; JUS, inverted triangles). Data points: average of four threshold determinations; error bars: standard deviations. *Right:* The shaded area represents the average depth discrimination thresholds ± 2 standard deviations (99% confidence interval) for normally reared monkeys as a function of spatial frequency of the carrier grating of the Gabor stimuli; symbols represent disparity thresholds of the prism-reared monkeys (JOB, hexagons, 4 weeks of continuous prism; KER, filled diamonds, 6 weeks of prism with breaks; UME, open circles, 16 weeks of prism with breaks; JAR, filled squares, 4 weeks of prism with breaks).

FIGURE 4. Depth discrimination thresholds as a function of the correlation of dot polarity between right and left eye random dot stimuli. *Data points:* average of four threshold determinations; *error bars:* standard deviations. *Open symbols* are data from normally reared monkeys (MAR, circles; JUS, inverted triangles). Data from prism-reared monkeys are shown by *filled symbols* (JOB, hexagons, 4 weeks of continuous prism; KER, diamonds, 6 weeks of prism with breaks; UME, circles, 16 weeks of prism with breaks; JAR, squares, 4 weeks of prism with breaks).

Monkeys IGO (continuous prism for 6 weeks) and OLI (daily periods of unrestricted vision for 16 weeks) could not discriminate depth despite performing over 60,000 training trials each spanning disparities from a minimum of 1 arcmin to a maximum of 250 arcmin, exceeding the upper value represented on Figure 3.

Figure 4 shows depth discrimination thresholds as a function of the correlation in polarity between random dots seen by the right and left eyes. Two normally reared monkeys MAR and JUS contributed data, which are shown by the open circles and open triangles, respectively. The disparity threshold decreased linearly with increasing percent correlation on log-log axes. The experimental monkeys showed the same pattern of results except that the disparity thresholds were shifted to larger values. The relative order of the performance of the animals with random dot stimuli mirrored the order seen in Figure 3 describing their performance with Gabor stimuli. The monkey reared with 4 weeks of continuous strabismus (JOB, filled hexagons) showed more than a log unit reduction in global stereopsis. The other monkey who was prism reared for 4

weeks but who had daily periods of unrestricted vision (JAR, filled squares), showed global stereopsis that was closest to that of the normally reared monkeys. Monkey UME (filled circles), who also received daily periods of unrestricted vision but was treated for an extended duration of 16 weeks, showed larger reductions in stereopsis across correlations compared with the normal monkeys. The monkey reared with periods of unrestricted vision during 6 weeks of optical strabismus (KER, filled diamonds) showed disparity thresholds that were approximately 10-fold higher than normal. In comparison to the deficit in local stereopsis, monkey KER showed a more dramatic loss in global disparity sensitivity. Because monkeys IGO and OLI could not discriminate depth with the Gabor stimuli, they were not trained or tested with the random dot stimuli.

To determine whether monkey IGO could not discriminate depth because of his reduced contrast sensitivity, monkey JAR, who did exhibit stereopsis, was blurred with plus powered lenses so that her contrast sensitivity for the Gabor targets was essentially the same as that of monkey IGO. In the left panel of Figure 5 the fitted monocular contrast sensitivity functions for monkey IGO are reproduced from Figure 2, and the blurred monocular contrast sensitivity measures for monkey JAR are superimposed (open squares). The right panel of Figure 5 shows disparity thresholds for monkey JAR with the blurring lenses (open squares) compared with her data without the blurring lenses (filled squares) and that of all other prism-reared monkeys (solid lines) and normal monkeys (shaded area) replotted from Figure 3. Over lower spatial frequencies the disparity thresholds are not significantly diminished by the blur, and only above 1 cyc/deg does the disparity threshold increase. Only at spatial frequencies above 4 cyc/deg were the stimuli too blurred for the performance of depth discriminations. These results indicate that the inability of monkey IGO to perform depth discriminations was not because of his reduced contrast sensitivity.

DISCUSSION

To characterize how the mechanisms responsible for the development of stereopsis integrate the effects of normal and abnormal binocular vision over time, we investigated the effect on stereopsis of interrupting otherwise continuous strabismus with a single brief daily period of normal binocular vision. Optical strabismus imposed by base-in prisms is ideal for these experiments because the sensory experiences of diplopia and confusion and the constancy of the image dissociation with viewing direction and distance mimic that of a large-angle

FIGURE 5. *Left:* The fitted spatial contrast sensitivity functions for monkey IGO are replotted from Figure 2, but the *open squares* are contrast sensitivity measures for monkey JAR through blurring lenses. *Right:* The *shaded area* represents the average disparity thresholds ± 2 standard deviations of all normally reared monkeys, and the *lines* represent the disparity thresholds of all prism-reared monkeys across spatial frequency of the Gabor gratings (replotted from Fig. 3), with the disparity thresholds for monkey JAR through blurring lenses (*open squares*) and without blurring lenses (*filled squares*).

esotropia. However, the true value in employing optical strabismus in these experiments is that removal of the prisms restores the potential for normal binocular visual interactions immediately, and to a degree that is unlikely to be achieved with a surgical or pharmacological model of strabismus. Consequently, the timing and degree of the imposed image dissimulation can be precisely controlled.

The main finding was that a brief daily period of binocular vision during otherwise constant optical strabismus largely preserved both local and global stereopsis in infant monkeys. The three monkeys (KER, UME, and JAR) that were allowed 2 hours of unrestricted vision during otherwise constant optical strabismus demonstrated local stereopsis that exceeded 50 arcseconds, which is considered the "highest quality" stereopsis and is rare among surgically corrected human strabismics.^{21,46,47} The fact that comparatively short periods of unrestricted vision offset the damaging effects of much longer daily periods of strabismus indicates that the mechanisms responsible for stereopsis development do not weigh the effects of normal and abnormal binocular visual experience equally. These mechanisms integrate the effects of normal versus abnormal binocular visual experience in a nonlinear manner over time, and/or the response of these mechanisms to normal binocular vision is much stronger or persists to a greater extent beyond the exposure period than the response to abnormal binocular visual experience. This bias in the temporal integration properties of the vision-dependent mechanisms responsible for stereopsis would help ensure the development of normal stereopsis and would greatly reduce the likelihood that transient periods of diplopia would have a lasting impact on binocular vision.

It must be emphasized that the brief daily periods of binocular vision during otherwise constant optical strabismus acted to preserve and promote stereopsis that had already begun developing during the first 3 weeks of life, before prism rearing.¹ Likewise, human infants do not routinely demonstrate esotropia at birth, but do so more commonly at 3 to 4 months of age, when stereopsis is normally emerging.¹⁴ That esotropic infants can respond to binocular disparity early in the time course for the emergence of stereopsis^{2,12,16} confirms that the abnormal visual experience imposed by constant esotropia destroys what stereopsis had developed.

Our results secondarily show the effect of duration of abnormal vision on the development of stereopsis. Both monkeys reared with 4 weeks of optical strabismus had better stereopsis than their counterparts reared with 6 weeks of optical strabismus. Of the two monkeys prism reared for 16 weeks, one demonstrated stereopsis while the other did not. In sum, these results indicate that longer durations of abnormal vision are more likely to negatively impact the development of stereopsis. This result is in agreement with previous research indicating that shorter durations of abnormal visual experience interfere less with the development of normal binocular vision^{13,48} and support surgical alignment of strabismus at as early an age as is possible.

The monkey reared with 6 weeks of constant strabismus (monkey IGO) developed high bilateral hyperopia and showed bilaterally reduced contrast sensitivity and no measurable stereopsis with Gabor stimuli. Although we cannot conclude that optical strabismus caused the hyperopia, it makes sense that the uncorrected bilateral hyperopia during the early critical period of spatial vision development had a negative impact on spatial contrast sensitivity. The results of the control experiment indicate that the stereo blindness was not due to poor contrast sensitivity and must be a direct result of the abnormal binocular visual experience produced by prism rearing, as the equivalent blur in a monkey sensitive to disparity had little effect on disparity thresholds with low spatial frequency Gabor

targets. Constant optical strabismus during this early critical period of vision development is known to severely degrade stereopsis, and so the inability of monkey IGO to discriminate depth from binocular disparity represents success of this control experiment and not failure.³⁰⁻³²

Of the two monkeys prism reared for 16 weeks with daily periods of binocular vision, one (monkey UME) demonstrated stereopsis, whereas the other (monkey OLI) did not. The monkey that did demonstrate stereopsis (monkey UME) also showed normal monocular contrast sensitivity and had equal refractive errors in the two eyes. Monkey OLI had poor but equal monocular contrast sensitivity and had developed an anisometropia (OD, -1.00 D; OS, $+3.00$ D) by the time behavioral training and testing were initiated at 18 months of age. Refractive error had been checked by retinoscopy before prism rearing and was equal for the two eyes and slightly hyperopic, which is normal for an infant monkey.⁴⁹⁻⁵² The anisometropia did not cause a relative unilateral loss of contrast sensitivity and so must have either developed after the critical period for form vision development or the refractive errors in each of the eyes allowed the monkey to use each eye independently during vision development, but not together even during the 2 hours of daily binocular vision during prism rearing or during the year after prism rearing. If the anisometropia developed after the prism rearing, it could have disrupted any stereopsis that had been preserved by the 2 hours of daily binocular vision during prism rearing.

There have been previous experiments on the effects of daily brief periods of binocular vision during visual manipulations designed to interrupt normal binocular visual development in cats. The results of this study are not directly comparable to those reported by Mitchell et al.⁵³ in cats because of differences in methodology, in particular, the nature of the visual manipulations, but more critically because our use of control conditions allows a clearer understanding of the effects of the imposed visual manipulations. In the Mitchell study two of three kittens did not demonstrate stereopsis after a rearing protocol of 2 hours of binocular vision followed by 5 hours of monocular occlusion, then 17 hours of darkness each day from 4 to 8 weeks of age. Although the authors concluded that 2 hours of daily binocular exposure was not sufficient to allow the development of stereopsis when animals were otherwise monocularly occluded, there were only three experimental animals and no control experiments had been performed to investigate the impact on stereopsis of the exceedingly long duration of darkness the kittens experienced each day.

Prior research has established that prism-reared infant monkeys are a good model for human concomitant strabismus,^{4,30-32,38,45} affording a level of confidence when extrapolating experimental findings in nonhuman primates to the human condition. The results from our experimental monkeys have implications for human infants with infantile esotropia. Our findings clearly show that to prevent stereopsis from developing, the strabismus must be essentially constant over time. In this way our study supports the observation that adults with constant strabismus are less likely to have measurable stereopsis, while adults with intermittent strabismus, or who are nonstrabismic at a particular viewing distance, will have stereopsis, though it may be degraded compared with normal. More importantly, our results suggest that the vision-dependent mechanisms controlling the development of stereopsis in infants can function effectively with only brief daily periods of normal binocular vision. Consequently, efforts to provide even brief daily periods of normal binocular vision could have substantial therapeutic value in the management of children with infantile esotropia before alignment surgery. These interventions may take the form of prism neutralization of the deviation and/or

providing a bold repeating visual stimulus that can be superimposed regardless of inaccurate binocular alignment.⁵⁴

Our findings also show that preservation of stereopsis can be accomplished very early in the course of binocular visual development. Four of our monkeys were prism reared up to 8 to 10 weeks of age, which is equivalent to approximately 8 to 10 months in human infants.^{55,56} Although both monkey and human infants are very susceptible to the damaging effect of abnormal binocular vision during this time when stereopsis normally emerges and rapidly develops, the mechanisms supporting stereopsis are extremely sensitive to the protective effects of periods of normal binocular vision. Early detection and management of strabismus is critical for the preservation of normal binocular visual function. A large-angle esotropia may be noticed by parents, but the implication of an eye turn for the long-term visual prognosis is not usually recognized, and diagnosis may be delayed until their school screening. Our results strongly support early screening and exams by eye doctors to detect and manage strabismus during early childhood.

Because only a very few weeks of constant strabismus during early life can result in stereo blindness, surgical eye alignment at the earliest possible age is the best option for preserving normal binocular vision. However, if it is not possible to achieve surgical alignment immediately, temporary manipulations that provide as close to normal binocular vision as possible, even for short periods during the day may be sufficient to maintain normal binocular function.

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