The Degree of Image Degradation and the Depth of Amblyopia

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PurpOse. To determine whether the depth of monocular form-deprivation amblyopia is dependent on the degree of retinal image degradation.

Methods. Chronic monocular form deprivation was produced in nine infant rhesus monkeys by securing one of three different strengths of diffuser spectacle lenses in front of the treated eye and a clear zero-powered lens in front of the fellow eye. Three infant monkeys reared with plano lenses in front of both eyes provided control data. The treatment lenses were worn continuously from approximately 3 weeks of age for periods ranging between 11 and 19 weeks. When the monkeys were approximately 18 months of age, psychophysical procedures were used to measure the effects of the rearing procedures on the spatial contrast sensitivity function for each eye.

Results. The treated eyes of all nine diffuser-reared monkeys showed contrast sensitivity deficits that were indicative of amblyopia. On average, the interocular grating acuity difference increased systematically from 0.6 octaves for the weakest diffuser lens to $2.3 \pm 0.7$ and $3.5 \pm 0.8$ octaves for the intermediate and strongest diffuser lenses, respectively. There was a close correspondence between the magnitude of the amblyopic deficits and the reduction in retinal image contrast produced by the diffuser lenses.

Conclusions. The results demonstrate that the depth of monocular, nonstrabismic amblyopia is strongly influenced by the degree of retinal image degradation experienced early in life. (Invest Ophthalmol Vis Sci. 2000;41:3775–3781)
exact role that the degree of image degradation plays in non-strabismic amblyopia is speculative.

The goal of this investigation was to provide insight into the pathophysiology of amblyopia by investigating the effect of the degree of image degradation on the depth of amblyopia. Specifically, we studied the effects of varying degrees of monocular image degradation on the development of spatial vision in infant monkeys.

**METHODS**

**Subjects**

Twelve infant rhesus monkeys (Macaca mulatta) were subjects. The infant monkeys were obtained at 1 to 3 weeks of age and were hand reared in our primate nursery that was maintained on a 12-hour light/12-hour dark lighting cycle. All the 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.

The effects of chronic unilateral retinal image degradation were investigated in nine infant monkeys. Beginning at approximately 3 weeks of age (24 ± 2.5 days), the infant monkeys were fit with a lightweight helmet that held a diffuser spectacle lens in front of the treated eye and a clear, zero-powered lens in front of the fellow eye. Diffuser lenses were used to degrade the retinal image, because unlike the unilateral optical defocus imposed by anisometric spectroscopic lenses, the degree of image degradation produced by diffusers cannot be improved by accommodation, changes in fixation distance, or compensating ocular growth. The diffusers consisted of a zero-powered carrier lens that was covered with a commercially available occlusion foil (Bangerter Occlusion Foils; Fresnel Prism and Lens, Scottsdale, AZ). These occlusion foils are available in a range of strengths, three of which were used in the present experiments. The relative changes in spatial contrast sensitivity produced by viewing through these specific three diffuser lenses are illustrated in Figure 1 for two human observers. These data provide a practical measure of the spatial-frequency-dependent reductions in retinal image contrast created by our treatment lenses.

Three infant monkeys were treated with the strongest diffuser lenses, which limited adult human vision to spatial frequencies below approximately 1 cyc/deg. The intermediate diffusers, which reduced contrast sensitivity from approximately 0.5 log units at 0.125 cyc/deg to more than 2 log units at 8 cyc/deg, were worn by four infant monkeys. The weakest diffuser lenses, which were fitted to two infant monkeys, produced reductions in contrast sensitivity that ranged from 0.1 log units at 0.125 cyc/deg to an average of 0.75 log units at 8 cyc/deg. To control for potential effects associated with the helmet-rearing procedures, three infant monkeys were reared with helmets that held clear, zero-powered lenses over both eyes. Behavioral data for one of the plano control animals has been previously reported. For both the plano control and diffuser-reared monkeys, the lenses were worn continuously for periods ranging between 11 and 17 weeks (mean duration, 100 ± 12.6 days). At the end of the rearing period, the helmets were removed, and the animals were housed in a normally lighted environment.

Although form deprivation initiated at or within 2 to 3 days of birth frequently produces strabismus in infant monkeys, similar procedures initiated after approximately 3 weeks of age rarely produce strabismus. As expected, observations of the positions of the first Purkinje images relative to the centers of the entrance pupils indicated that none of our treated animals had strabismus.

The diffuser lenses altered the course of emmetropization in the treated monkeys. During the treatment period, in many of the form-deprived animals, axial myopia developed in the treated eyes, the degree of which varied directly with the strength of the diffuser lenses. However, after lens removal, all the treated monkeys exhibited recovery from the induced form-deprivation myopia. At the time of the behavioral testing only two animals (MKY JAS and MKY LAR) showed more than 1.0 D of anisometropia.

**Psychophysical Methods**

When the animals had grown sufficiently to fit comfortably into our behavioral apparatus (approximately 18 months of age, i.e., after at least 1 year of visual experience without the treatment lenses), spatial contrast sensitivity functions were measured behaviorally for each eye. The basic apparatus and operant procedures were similar to those used in previous investigations.

During the daily experimental sessions, the monkeys were seated in a primate chair inside a light-proof, sound-attenuating chamber. The primate chair was fitted with a response lever on the waist plate and a drink spout on the neck plate through which orange drink reinforcement was delivered. The animal’s optimal spectacle correction, which was determined for each eye independently using a subjective refraction procedure, was held in a face mask at approximately a 14-mm vertex distance. For monocular viewing, the lens well for one of the eyes was occluded with an opaque disc.

The detection stimuli were vertical sinusoidal gratings that were generated using a graphics board (VSG; Cambridge Research Systems, McLean, VA) on a 20-inch video monitor (Flex-
FIGURE 2. Mean contrast sensitivity (±SD) plotted as a function of spatial frequency for the left (○) and right eyes (●) of the three control monkeys reared with plano lenses in front of both eyes. The smooth lines drawn through the data represent the best-fitting exponential functions. Data for MKY HT2 (left) replotted from Smith et al.18

Scan 9080; EIZO Nanao, Cypress, CA) that operated at a 100-Hz frame rate. The usable display subtended a visual angle of 11 × 14° at the 114-cm viewing distance and had a space-averaged luminance of 60 candelas (cd)/m². The grating stimuli were presented as Gabor patches, which consisted of a carrier grating presented in cosine phase with the center of the display. The contrast of the grating was attenuated by a two-dimensional Gaussian envelope and declined to a value of 1/e of the maximum contrast at 4° from the Gabor’s center. The number of grating cycles within the Gabor varied as a function of spatial frequency. As a result, at low spatial frequencies when a small number of grating cycles were presented, probabilistic concerns may have limited absolute sensitivity by a small amount.28 However, for spatial frequencies above the peak of the monkey’s contrast sensitivity function, the number of grating cycles exceeded the number required for optimal performance. A photometer (Spectra; Pritchard, Photo Research Corp., Burbank, CA) equipped with an automated scanning spot was used to calibrate the luminance and contrast of the display. The contrast of the grating pattern 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 after the presentation of the grating stimulus. The duration of the grating stimuli was 500 msec. Contrast detection thresholds were measured as a function of spatial frequency from 0.125 or 0.25 cyc/deg to 16 cyc/deg in 0.15 log unit intervals. Data were collected using an adaptive staircase procedure. The decision rules (a 0.05 log unit reduction in contrast after each hit and a 0.6 log unit increase in contrast after two consecutive misses) converged to a contrast threshold on the step increasing part of the psychometric function that corresponded to a 25% detection rate. During a given experimental session, the staircases for five to seven different spatial frequencies were simultaneously interleaved.

Contrast sensitivity functions were generated from the geometric means of a minimum of 10 threshold measurements at each spatial frequency. For descriptive purposes and to calculate an eye’s grating visual acuity, each contrast sensitivity function was fit with a double exponential function29

Contrast sensitivity = \((k_s f/k_f)^{a_l}\) exp\((-ab\cdot s f/k_f)\)

where \(s f\) is spatial frequency; \(a_l\) and \(a b\) are parameters that reflect the slopes of the low- and high-spatial frequency portions of the function, respectively; \(k_s\) and \(k_f\) are proportional to the peak contrast sensitivity and the optimum spatial frequency, respectively. An iterative routine was used that minimized the sum of squared errors.

RESULTS

As observed previously in normal monkeys,30 the contrast sensitivities for the left and right eyes of the plano control monkeys were well matched across the range of spatial frequencies tested (Fig. 2). For both eyes of each plano control monkey, the peak contrast sensitivity was found at approximately 2.0 to 3.0 cyc/deg, and there was a progressive decline in sensitivity for higher and lower spatial frequencies. The optimum spatial frequencies and peak contrast sensitivities for all three plano control monkeys (Table 1) were within the range of values for normal monkeys.31 The extrapolated grating acuities were close to 20 cyc/deg, which is near the lower limit for gratings that we have obtained previously in older adult monkeys using similar behavioral methods.31 However, it should be noted that the exponential function that was fit to the data consistently yields lower cutoff spatial frequency values than the linear regression methods52 that we used in our previous studies. Overall, the contrast sensitivity data for the three control subjects demonstrate that the helmet-rearing procedures per se did not produce permanent alterations in our infant monkeys’ spatial vision.

The results for the three diffuser groups were qualitatively similar (Figs. 3, 4, and 5). For each diffuser-reared monkey, the contrast sensitivity function for the fellow nontreated eye exhibited the normal band-pass shape. The peak contrast sensitivities and the optimal and cutoff spatial frequencies for the nontreated eyes were generally comparable to those for normal and plano control monkeys (Table 1); however, several diffuser monkeys showed somewhat low grating acuities in their nontreated eyes (e.g., MKY LIS and MKY LAR). The monkeys that exhibited the low acuities for their nontreated eyes also tended to exhibit large spatial vision deficits in the deprived eyes. Although we have too few subjects to rigorously address this issue, amblyopic humans, including those who experienced monocular form deprivation, frequently exhibit mild visual deficits in their nonamblyopic, fellow eyes.33–36 In comparison to the nontreated fellow eyes, the treated eyes of all nine of the diffuser-reared monkeys showed obvious relative contrast sensitivity deficits that were indicative of amblyopia. As typically observed in human am-
The deficits in contrast sensitivity were smallest at low spatial frequencies and increased in magnitude with increasing spatial frequency.

The depth of the amblyopia was the primary difference between the results for the three diffuser groups. For the treated eyes, the peak contrast sensitivities and the optimal and cutoff spatial frequencies varied according to the degree of image degradation (Table 1). Specifically, the lowest values for all three of these spatial parameters were consistently found in infant monkeys that were treated with the strongest diffuser lenses (Fig. 3). The monkeys that wore the weakest diffuser lenses (Fig. 5) exhibited the most normal spatial parameters, with the monkeys treated with the intermediate diffusers (Fig. 4) showing amblyopic deficits that were between those observed in the other two diffuser groups.

To quantify the overall reductions in spatial vision, the area under the contrast sensitivity functions plotted on log–log coordinates was determined by integrating the fitted exponential functions from 0.2 cyc/deg to the cutoff spatial frequency. This procedure provides a single quantity that characterizes the overall visual performance of the eye. Figure 6 shows the area under the log contrast sensitivity functions for each eye of the deprived and control subjects and the interocular area ratios for individual monkeys. Inspection of Figure 6 reveals that the depth of the contrast sensitivity deficits was consistent within each group and that between diffuser groups there was no overlap in the descriptive parameters for the treated-eye contrast sensitivity functions. As a group, the areas under the log contrast sensitivity functions were significantly lower in the treated versus the nontreated eyes (paired t-test, \( df = 8, T = -5.98, P < 0.0001 \)), and the depth of amblyopia as reflected by the interocular area ratios varied systematically with the degree of image degradation (ANOVA, \( df = 11, F = 63.4, P < 0.0001 \)).

Figure 7 compares the spatial vision deficits in the treated eyes of the deprived monkeys with the reductions in spatial vision produced by the diffuser lenses in normal human observers. For the form-deprived monkeys, the amblyopic deficits are represented by the interocular differences in log contrast sensitivity determined from the exponential functions fitted to the contrast sensitivity data (solid lines). For all three diffuser groups, the spatial-frequency-dependent amblyopic deficits roughly paralleled the reductions in contrast sensitivity produced by the diffuser lenses in normal observers (dashed lines). However, for all diffuser groups the functions for the experimental monkeys were located below the human data, indicating that the amblyopic contrast sensitivity deficits were generally smaller than the reductions in retinal image contrast produced by the treatment lenses in a normal adult eye.

### Table 1. Results by Subject

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Peak Contrast Sensitivity (cyc/deg)</th>
<th>Optimum Spatial Frequency (cyc/deg)</th>
<th>Cutoff Spatial Frequency (cyc/deg)</th>
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<tr>
<td></td>
<td>Nontreated Eye</td>
<td>Treated Eye</td>
<td>Nontreated Eye</td>
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<td>Strongest diffuser</td>
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<td>MKY MIG</td>
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<td>Intermediate diffuser</td>
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<td>MKY AXE</td>
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Figure 3. Mean contrast sensitivity (±SD) plotted as a function of spatial frequency for the treated (●) and nontreated eyes (○) of the three monkeys reared with the strongest diffuser lenses in front of the treated eyes and clear plano lenses in front of the fellow eyes.
DISCUSSION

The main finding of this study was that the depth of amblyopia produced by early form deprivation is dependent on the degree of monocular image degradation. On average, the interocular grating acuity differences of our monocularly form-deprived monkeys increased systematically from 0.6 octaves for the weakest diffuser lenses to 2.3 ± 0.7 and 3.5 ± 0.8 octaves for the intermediate and strongest diffuser lenses, respectively. Although the depth of amblyopia produced by our strongest diffuser lenses was substantial, the visual deficits exhibited by our diffuser-reared monkeys were not as great as those produced in infant monkeys by early monocular eyelid closure.6,19 For example, when monocular form deprivation is initiated by lid suture at approximately 1 month of age, the grating acuities for the deprived eyes are typically more than six octaves lower than those for the nondeprived eyes.6,19 However, based on the graded deficits observed in the present study, it is reasonable to expect milder deficits in our diffuser-reared monkeys because even our strongest diffuser would degrade the retinal image less than eyelid closure.

Human infants that experience form deprivation as a result of congenital cataracts exhibit rapid improvements in visual acuity after restoration of clear visual inputs.39 Because our monkeys were allowed a substantial period of unrestricted vision between the end of the rearing period and the start of the behavioral experiments, it is possible that the measured visual acuities for our monkeys were better than those manifested immediately at the end of the treatment. However, any recovery of spatial vision was probably limited. Unlike monocularly form-deprived human infants, the refractive errors in the treated eyes of our monkeys were not corrected after the period of deprivation, nor was recovery promoted by patching the fellow nontreated eye. Moreover, little passive recovery, either behavioral or neurophysiological, has been previously observed in form-deprived monkeys.19,40

The visual deficits produced by unilateral retinal image degradation are generally attributed to a combination of two amblyogenic factors, direct deprivation effects and asymmetric binocular competitive interactions. For several reasons, it is
likely that the visual deficits in our diffuser-reared monkeys were caused primarily by asymmetric binocular competition. Based on the relative rates of visual system development for monkeys and humans, our lens-rearing period corresponded to the ages when both direct effects and binocular competitive factors are active in human infants. When form deprivation is initiated in infant monkeys by eyelid closure at ages that are similar to the onset of the lens-rearing procedures in this study, monocular form deprivation produces dramatically greater visual deficits than binocular form deprivation, a hallmark sign of asymmetric binocular competition. In this respect, the visual deficits produced by our intermediate and strongest diffuser lenses are greater than those produced by binocular lid suture, even though our lenses do not degrade the retinal image as much as lid closure. In addition, experimental manipulations that minimize the potential for competitive binocular interactions during a comparable period of early development dramatically reduce the effects of monocular lid suture on the spatial vision of infant monkeys.

The close correspondence between the amblyopic deficits exhibited by our diffuser-reared monkeys and the lens-induced reductions in retinal image contrast is compelling and has implications for the process of binocular competition. There are several potential explanations for this close agreement. First, because spatial resolution is low at birth and rapidly improves with age, it could be argued that at a given spatial scale a stronger diffuser lens would effectively impact development at an earlier age than a weaker diffuser lens. Assuming that the sensitivity of spatial vision mechanisms to monocular form deprivation decreased during our lens-rearing period, then the stronger diffusers would be expected to produce larger abnormalities on the basis of their earlier effective onset ages. However, delaying the age of onset of monocular eyelid closure from 1 to 5 months of age, essentially from the beginning to the end of our treatment period, does not influence the depth of amblyopia in young monkeys. Therefore, it seems unlikely that the variations in amblyopia produced by our different diffusers were due to differences in the effective age of onset of anomalous competitive interactions. Alternatively, it seems more likely that the variation in the depth of amblyopia simply reflects the different ranges of spatial vision mechanisms that were compromised by the diffuser-induced reductions in image contrast. As the strength of the diffuser was increased, the reduction in retinal image contrast increased in magnitude and extended to lower spatial frequencies. Consequently, the stronger diffuser lenses would impact development over a wider range of spatial frequency mechanisms, as observed in our population of diffuser-reared monkeys. This scenario implies that the competitive binocular interactions that contribute to amblyopia take place in a spatial frequency-specific manner rather than an overall eye-specific manner. This explanation is in agreement with the results from a number of neurophysiological studies that indicate that competitive binocular interactions take place on a cell-by-cell basis.

Our results provide support for the hypothesis that the depth of monocular form-deprivation amblyopia or anisometric amblyopia is influenced by the degree of retinal image degradation experienced early in life. These findings provide an explanation, at least in part, for the positive association between the depth of anisometropia amblyopia and the magnitude of anisometropia and the common observation that the unilateral amblyopias produced by media opacities are generally more severe than those typically observed in anisometric amblyopia. Our findings emphasize that, in addition to factors such as the age of onset and the duration of anomalous vision, the degree of retinal image degradation experienced by infants should influence the prognosis for regaining normal vision.

References


