Temporal Constraints on Experimental Emmetropization in Infant Monkeys

Chea-su Kee,[1] *Li-Fang Hung,*[1,2] *Ying Qiao-Grider,*[1,2] *Ramkumar Ramamirtham,*[1,2] *Jonathan Winawer,*[3] *Josh Wallman,*[4] *and Earl L. Smith III*[1,2]

Purpose. To characterize the temporal integration properties of the emmetropization process, the authors investigated the effects of brief daily interruptions of lens wear on the ocular compensation for negative lenses in infant rhesus monkeys.

Methods. Eighteen monkeys wore –3 D lenses binocularly starting from approximately 3 weeks of age. Six of these monkeys wore the lenses continuously. For the other animals, the –3 D lenses were removed for four 15-minute periods each day. During these periods, the monkeys viewed through either zero-power lenses ($n = 6$) or +4.5 D lenses ($n = 6$). Three monkeys reared with binocular plano lenses and 16 monkeys reared normally served as controls. Refractive development was assessed by cycloplegic retinoscopy and A-scan ultrasonography.

Results. As expected, the group of animals that wore the –3 D lenses continuously exhibited clear evidence of compensating axial myopia. These predictable myopic changes were mostly eliminated by the brief, daily periods of viewing through plano lenses. Interestingly, brief periods of viewing through +4.5 D lenses produced weaker protective effects.

Conclusions. Brief periods of unrestricted vision can prevent the axial myopia normally produced by long daily periods of imposed hyperopic defocus. Thus, the temporal integration properties of the emmetropization process normally reduce the likelihood that transient periods of hyperopic defocus will cause myopia. (*Invest Ophthalmol Vis Sci.* 2007;48:957–962) DOI:10.1167/iovs.06-0743

Evidence from a wide range of animal species has demonstrated that emmetropization is an active process that is regulated by visual feedback associated with the eye's effective refractive state.[1–3] In particular, it has consistently been shown that early in life optically imposed alterations in the eye's refractive state can produce predictable compensating changes in axial growth. For example, negative lenses that displace the eye's secondary focal point beyond the retina (imposing hyperopic defocus) can increase axial growth rates, resulting in a reduction in the optical error that exists when viewing through the negative lens. Conversely, positive lenses that impose myopic defocus (shifting the focal point in front of the retina) can slow axial growth and promote hyperopic shifts in the eye's refractive state that compensate for the lens-imposed optical error (e.g., chickens,[4] guinea pigs,[5] tree shrews [Venkataraman S, et al. *IOVS* 2005;43:ARVO E-Abstract 1973], and New World [marmosets][6] and Old World [macaque] monkeys[7,8]). This pattern of results indicates that visual experience plays a critical role in normal refractive development and probably also in the genesis of common refractive errors such as juvenile-onset myopia.

During normal development, the eye, largely irrespective of its natural refractive state, experiences many interleaved periods of alternating hyperopic and myopic defocus and periods of well-focused retinal images. These fluctuations in focus result from accommodation and from the fact that we live in a three-dimensional world with objects located at different viewing distances. The manner in which these experiences are integrated over time determines the course of refractive development and is a fundamental operational property of the mechanisms that regulate emmetropization. In this respect, three series of observations indicate that different aspects of visual experience are weighed differently by the mechanisms regulating eye growth. First, observations in chickens[9,10] and monkeys[11] indicate that brief daily periods of unrestricted vision, in essence periods of potentially in-focus retinal images, effectively counteract the dramatic myopiagenic effects of much longer daily periods of form deprivation. For example, providing an infant monkey with only 1 hour of unrestricted vision during the middle of the daily light cycle reduces the amount of axial myopia produced by continuous deprivation by more than 65%.[11] Second, brief daily interruptions of negative lens wear, in which chickens[12] or tree shrews[13,14] are allowed unrestricted vision, greatly reduce the impact of optically imposed hyperopic defocus on refractive development. In chickens, only 3 hours of unrestricted vision counterbalance the myopiagenic effects of wearing negative lenses for the rest of the day.[12] Third, positive lenses appear to have a stronger impact on refractive development, and their effects follow a different time course from those for negative lenses. In particular, longer daily periods of unrestricted vision are required to prevent compensation for positive lenses than for negative lenses.[12] When chicks wear positive and negative lenses successively, their eyes exhibit preferential compensating growth for the positive lens, even when the negative lens is worn for periods five times longer than for the positive lens.[15–17] Thus, the emmetropization process does not appear to integrate visual signals in a simple linear manner over time.

The nonlinear temporal integration properties of the emmetropization process have important implications for understanding the role of visual experience in normal and abnormal

From the [1]College of Optometry, University of Houston, Houston, Texas; [2]Vision CRC, University of New South Wales, Sydney, Australia; [3]Department of Psychology, Stanford University, Stanford, California; and [4]Department of Biology, City College, New York, New York.

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Corresponding author: Chea-su Kee, New England College of Optometry, 424 Beacon Street, Boston, MA 02115; keec@neco.edu.

refractive development. In particular, knowledge of how different visual signals are integrated over time is essential for defining the nature of the visual experience required to ensure normal refractive development and the extent to which visual experience can produce anomalous refractive errors. Moreover, this information is likely to be critical for optimizing the design of any optical treatment regimens for preventing or slowing the progression of common refractive errors.

Despite substantial differences in the normal rates of ocular development across species commonly used in refractive error experiments, some aspects of the temporal integration properties of the emmetropization process are quantitatively similar. For example, in chicks and monkeys, the effects of 12 hours of form deprivation are decreased more than 50% by only 1 hour of unrestricted vision.[9–11] Although the underlying mechanisms responsible for form deprivation myopia and negative lens–induced myopia may be different[18–20]; data from chicks and tree shrews show quantitatively similar effects of interruptions of form deprivation and hyperopic defocus.[9–13] These similarities suggest that mechanisms that promote axial myopia in response to these visual manipulations have been conserved across species. To examine whether similar parallels exist in primates, we investigated how brief periods of unrestricted vision influenced the myopic compensation typically produced by hyperopic defocus. In addition, because myopic defocus in chicks is more effective in blocking myopic growth than unrestricted vision,[15–17] we also examined how brief periods of viewing through positive lenses influenced the myopic compensation normally produced by hyperopic defocus.

Methods

Animal Subjects

The subjects were 37 infant rhesus monkeys (*Macaca mulatta*) obtained at approximately 2 to 3 weeks of age and housed in adult-size cages in our primate nursery on a 12-hour light/12-hour dark lighting cycle.[8] All rearing and experimental procedures were reviewed and 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.

After the initial biometric measurements performed at approximately 3 weeks of age, the monkeys were randomly assigned to the control group ($n = 19$) or to one of the three treatment groups ($n = 6$ in each group). For all three treatment groups, a relative hyperopic defocus was optically imposed by securing –3.0 D spectacle lenses in front of both eyes using a lightweight helmet system that has been described previously.[7,8] A binocular rather than a monocular treatment regimen was used to provide a more consistent optical stimulus over time and to eliminate the possibility that interocular alternating fixation patterns would influence the nature and temporal pattern of visual experience. We used –3.0-D lenses because our previous studies[8,21] have demonstrated that 3-week-old monkeys consistently exhibit compensating axial growth in response to negative lenses of this power. During the treatment period, one group of experimental animals wore the –3.0-D lenses continuously. For the other 2 groups of experimental animals, the negative lenses were removed and replaced with either zero-power lenses (–3 D/plano group) or +4.5 D lenses (–3 D/+4.5 D group) for four 15-minute periods each day. These four 15-minute exposure periods occurred at equally spaced intervals beginning at the start of the daily lighting cycle (8:00–8:15, 12:00–12:15, 16:00–16:15, 19:45–20:00). This time sequence was used because we have previously found that 1 hour of unrestricted vision can greatly reduce the amount of form deprivation myopia in monkeys[11] and because in chicks multiple periods of unrestricted vision were more effective in counteracting a myopiagenic stimulus than a single period of the same total duration.[15] The lens-switching process was accomplished by changing the helmets worn by the animals and was completed in a matter of a few seconds. The zero-powered substitution lenses were used for one experimental group to simulate the effects of unrestricted vision. For the other experimental group, +4.5-D substitution lenses were chosen to increase the likelihood that the substitution lenses would produce absolute myopic defocus (at least for distant targets) and because we had previously found that infant monkeys typically showed hyperopic compensation for +4.5-D lenses worn continuously.[8] Thus, at the start of the rearing period, the monkeys in the –3 D/plano and the –3 D/+4.5 D groups experienced a relative 3-D hyperopic shift in their refractive status for 11 hours each day (vs. 12 hours per day for the continuous –3.0 D group) and either 1 hour of unrestricted (and presumably clear) vision or 1 hour of relative myopic defocus (the exact amount and sign of defocus depended on an animal's natural refractive error and its fixation behavior). The animals rapidly adapted to the lens-rearing strategy; we did not observe any obvious differences in the fixation behavior among experimental groups or any of the individual animals in a group. The control group consisted of 16 normally reared monkeys (no optical interventions) and 3 monkeys that wore binocular plano lenses. The data from the control monkeys have been reported in our previous studies.[8,22,23]

Optical and Biometric Measurements

Biometric measurements were performed every 2 to 3 weeks during the treatment period, which lasted for an average of 14.2 ± 0.4 (SD) weeks. The details of our biometric measurements have been described elsewhere.[8,24] Briefly, to perform the measurements, the animals were anesthetized (intramuscular injection: 15–20 mg/kg ketamine hydrochloride, 0.15–0.2 mg/kg acepromazine maleate; topical injection: 1–2 drops 0.5% tetracaine hydrochloride) and subjected to cycloplegia (multiple drops of 1% tropicamide topically 20–30 minutes before retinoscopy). Refractive errors along the pupillary axis were determined independently by two skilled investigators using streak retinoscopy and handheld trial lenses, averaged,[25] and specified as spherical-equivalent, spectacle-plane refractive corrections. We have previously estimated that the 95% limit of agreement for our retinoscopy measures (spherical-equivalent refractive error) was ±0.6 D.[24] Ocular axial dimensions were measured by A-scan ultrasonography implemented with a 7-MHz transducer (Image 2000; Mentor, Norwell, MA). Intraocular distances were calculated from the average of 10 separate measurements using a weighted average velocity of 1550 m/s.

Statistical Analysis

Statistical analyses were performed using statistical software (Release 12.21, Minitab Inc., State College, PA). Paired *t*-tests were used for interocular comparisons. Two-sample *t*-tests and nonparametric Mann–Whitney *U* tests were used to test for significant differences among the right eyes of the treatment groups. The variability of the data within each group was represented by standard deviations.

Results

At the start of the lens-rearing period, the eyes of the control and experimental monkeys were, on average (± SD), moderately hyperopic (right eye control monkeys, +3.65 ± 1.87 D; right eye experimental monkeys, +3.75 ± 1.21 D), and no significant interocular differences were observed in refractive error or vitreous chamber depth in control or experimental groups (paired *t*-tests; $P = 0.12–0.88$). There were also no significant differences in the initial refractive errors or vitreous chamber depths between the control group and any of the three experimental groups (two-sample *t*-tests for right eye data; $P = 0.43–0.91$).

Emmetropization proceeded rapidly in the control animals (Fig. 1, thin lines) with both eyes of each control monkey growing in a coordinated manner toward a low degree of hyperopia. By approximately 18 weeks of age (127 ± 7 days), the mean right eye refractive error for the control monkeys had

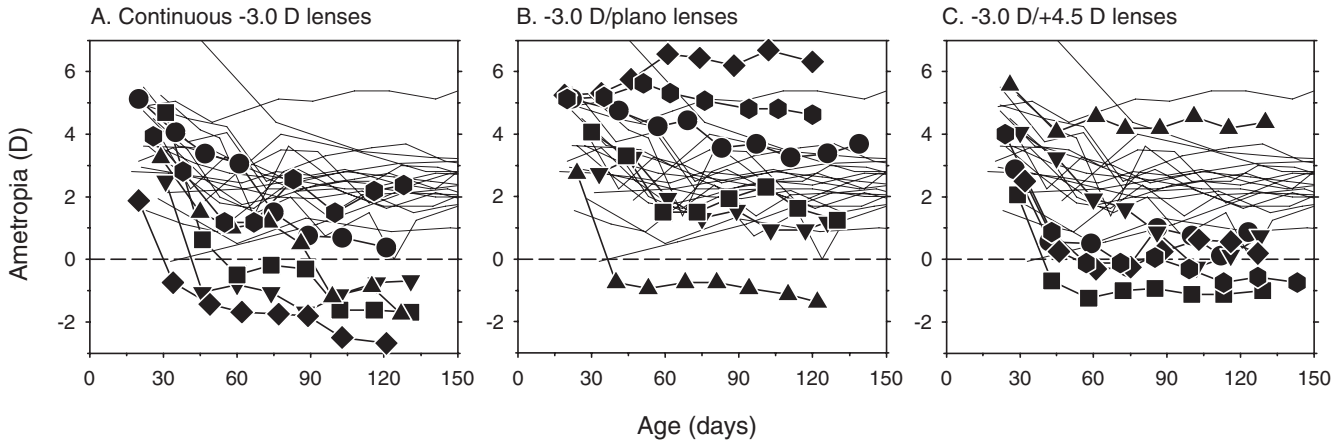

FIGURE 1. Longitudinal changes in the spherical-equivalent refractive errors of the right eyes for infant monkeys in the –3.0 D (**A**), the –3.0 D/plano (**B**), and the –3.0 D/+4.5 D lens groups (**C**). *Thin solid lines*: data from the right eyes of control monkeys.

decreased to +2.49 ± 0.99 D; 17 of the 19 control monkeys exhibited ametropia between +1.25 and +3.69 D.

Continuously wearing of –3.0 D lenses altered the course of emmetropization in a predictable manner (Fig. 1A). Toward the end of the rearing period, 5 of the 6 experimental monkeys in the –3 D treatment group exhibited refractive errors that were less hyperopic or more myopic than in any of the control animals. At the end of the treatment period (126 ± 4 days of age), no systematic interocular differences were observed in refractive errors in the –3 D experimental group (paired *t*-test; $P = 0.56$); the mean right eye refractive error for the –3 D animals was –0.68 ± 1.82 D, which was –3.17 D more myopic than the age-matched control animals. Thus, on average, compared with controls, the animals in the –3 D group had completely compensated for the optically imposed hyperopic errors.

In contrast, four daily 15-minute periods of unrestricted vision largely eliminated the predictable refractive compensation for the –3 D treatment lenses (Fig. 1B). Only one of the six animals in the –3 D/plano group showed evidence of compensating for the optically imposed hyperopic defocus. Three of the –3 D/plano animals exhibited refractive error changes that were comparable to those observed for most of the control animals, and two of the –3 D/plano animals showed relative hyperopic shifts in refractive error. Consequently, at the end of the treatment period, one of the –3 D/plano animals exhibited relative myopia that was outside the control range, three of the experimental monkeys exhibited refractive errors within 2 SD of the control mean, and 2 of the –3 D/plano monkeys had hyperopic errors that were more than 2 SD above the control mean.

The four daily 15-minute periods of viewing through +4.5 D lenses had a smaller effect on the refractive compensation for the –3 D treatment lenses (Fig. 1C). Although one of the –3 D/+4.5 D animals maintained a moderate degree of hyperopia throughout the observation period, five of the six monkeys in this group exhibited evidence of lens compensation. At the end of the lens-rearing period, two of these five animals exhibited absolute myopic ametropias, and three more of these animals had refractive errors that were less hyperopic or more myopic than in the control animals.

Figure 2 summarizes the refractive development for the control and experimental animals. The left panel shows refractive error growth curves for each subject group determined using a locally weighted regression, scatter plot–smoothing algorithm (LOESS plots[26]), and the right panel includes individual and mean refractive errors for the control and experimental subjects at the end of the treatment period. The pattern of refractive development for the –3 D monkeys showed a clear myopic trajectory compared with that in control animals. At the end of the treatment period, the average ametropia for the –3 D group was significantly more myopic than that for the control monkeys (–0.68 vs. +2.49 D; two-sample *t*-test, T = –4.06, $P = 0.01$). On the other hand, the pattern of refractive development for the –3 D/plano monkeys was comparable to that for the controls, and the average end-of-treatment refractive error for the –3 D/plano animals was not different from that for the control monkeys (+2.56 vs. +2.49 D; two-sample,

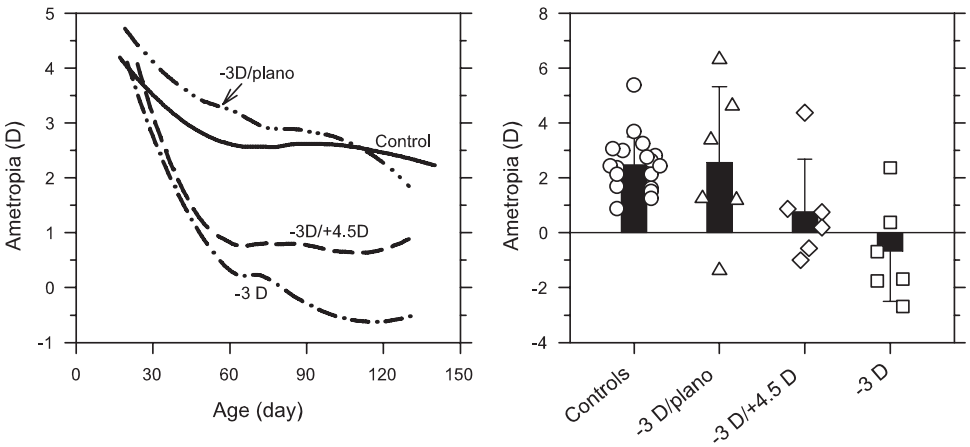

FIGURE 2. *Left*: longitudinal changes in the spherical-equivalent refractive errors for the different treatment groups. Growth curves were generated using a locally weighted, nonlinear-smoothing algorithm. *Right*: spherical-equivalent refractive errors for treated animals at the end of the treatment period and for control animals at equivalent ages. *Filled bars*: Mean ± SD. Different symbols represent individuals in the different treatment groups.

t-test, T = 0.07, $P = 0.95$), but it was significantly more hyperopic than that for the –3 D monkeys (+2.56 vs. –0.68 D; two-sample *t*-test, T = 2.67, $P = 0.04$). The refractive error growth curve for the –3 D/+4.5 D group exhibited an initial myopic growth trajectory that was similar to the that for the –3 D group, but the function leveled off at a more hyperopic level. As a result, over the course of the treatment period, the average changes in refractive error for the –3 D/+4.5 D group (–2.74 D) were intermediate compared with those for the –3 D animals (–4.24 D) and for the –3 D/plano (–1.61 D) and control (–1.14D) groups. At the end of the treatment period, the differences in the average refractive errors for the control and –3 D/+4.5 D groups approached statistical significance (+2.49 vs. +0.77 D; two-sample *t*-test, T = –2.11, $P = 0.09$) and the median refractive errors for these groups were significantly different (+2.44 vs. +0.47 D; Mann–Whitney *U* test, $P = 0.01$). However, neither average (+0.77 vs. –0.68 D; two-sample *t*-test, T = –1.34, $P = 0.21$) nor median (+0.47 vs. –1.19 D; Mann–Whitney *U* test, $P = 0.17$) refractive errors for the –3 D/+4.5 D monkeys were significantly different from those for the –3 D animals or from those for the –3D/plano animals (average: +0.77 vs. 2.56 D; two-sample *t*-test, T = 1.31, $P = 0.23$; median: +0.47 vs. 2.32 D; Mann–Whitney *U* test, $P = 0.17$).

Differential effects of the treatment regimens on refractive development were largely axial in nature and specifically associated with differences in vitreous chamber depth. Figure 3 illustrates the vitreous chamber growth curves for each subject group (left panel) and the relationship between vitreous chamber depth and refractive error for individual subjects at the end of the treatment period (right panel). Compared with control monkeys, the animals in the –3 D and –3 D/+4.5 D groups exhibited faster vitreous chamber growth rates and, on average, longer vitreous chamber depths at the end of the treatment period (–3 D group, 10.04 ± 0.52 mm; –3 D/+4.5 D group, 10.06 ± 0.67 mm; controls, 9.68 ± 0.25 mm). However, these differences were not statistically significant (two-sample *t*-tests, $P = 0.16$ and 0.23). On the other hand, the vitreous chamber growth curve for the –3 D/plano monkeys was similar to that for the control animals. At the end of the treatment period, the average vitreous chamber depth for the –3 D/plano monkeys (9.72 ± 0.68 mm) was comparable to that for the control animals. Although the variance of the vitreous chamber depths in the experimental groups prevented the average differences from reaching statistical significance, when the data for all subjects were analyzed together, refractive error was significantly correlated with vitreous chamber depth (Pearson $r = -0.65$; $P = 0.004$).

Discussion

Our main finding was that brief, daily periods of viewing through zero-power lenses greatly reduced the predictable axial myopia caused by prolonged periods of negative lens wear in infant monkeys. Even though the total time spent viewing through the plano lenses amounted to only approximately 8% of the total daily light cycle, the protective effects of these brief periods were robust and were manifested in the refractive development of individual monkeys and the average refractive errors at the end of the treatment period. The weaker protective effects in the –3 D/+4.5 D group indicated that the nature of the visual experience during the interruptions in negative lens wear was critical to prevent myopic compensation. Overall, our results demonstrate that brief periods of unrestricted vision can counterbalance the myopiagenic effects of much longer periods of hyperopic defocus.

These results extend our current understanding of the temporal integration properties of the vision-dependent mechanisms that regulate refractive development in primates. We have previously demonstrated that single daily periods of unrestricted vision are effective in reducing the amount of form deprivation myopia in infant monkeys.[11] Thus, as in chicks,[9,10,12] brief daily periods of unrestricted vision can reduce the myopiagenic effects of form deprivation and imposed hyperopic defocus in infant primates. This is significant because several observations suggest that the processes responsible for form deprivation myopia and lens-induced myopia are not identical.[18–20] In this respect, our current results indicate that the mechanisms responsible for these two forms of experimental myopia in monkeys have similar temporal integration properties, probably because these processes share components, possibly a final common pathway in which the signals that influence eye growth are integrated over time.

The protective antimyopic effects of single daily periods of unrestricted vision are quantitatively and qualitatively similar across species. In form deprived chicks[9,10] and monkeys[11] and negative lens–reared chicks[12] and tree shrews,[13] the degree of relative myopia decreases exponentially with increasing durations of the daily period of unrestricted vision, with a time constant of approximately 65 minutes. In all these species, a daily 1-hour period of unrestricted vision reduces the amount of myopia by at least 50% compared with animals that experienced continuous form deprivation or hyperopic defocus. In chicks,[10,15] multiple daily periods of unrestricted vision are even more effective in preventing myopia than a single period of the same total duration, which is another indication of the nonlinear manner in which growth signals are integrated over time. For example, Napper et al.[10] found that whereas one continuous 30-minute period of unrestricted vision reduced

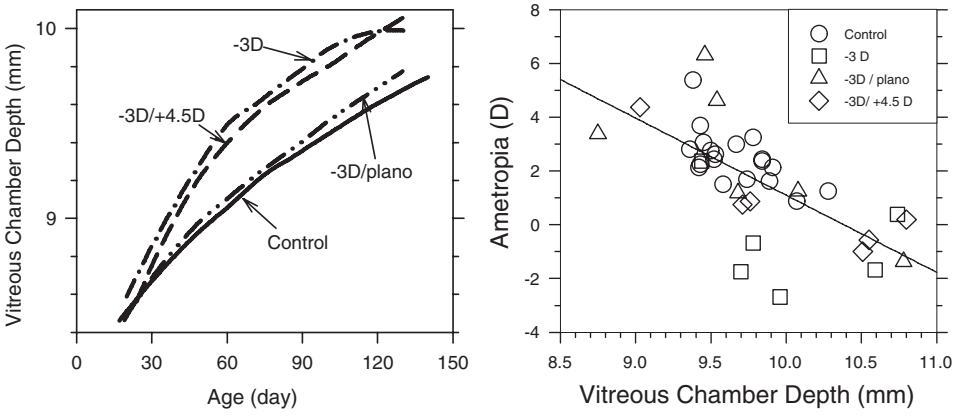

Figure 3. *Left*: longitudinal changes in vitreous chamber depth for the treatment groups. Growth curves were generated using a locally weighted, nonlinear-smoothing algorithm. *Right*: spherical-equivalent refractive error for each monkey is plotted as a function of vitreous chamber depth. Monkeys from different treatment groups are represented by different symbols, as shown in the legend. *Solid line*: linear regression values.

form deprivation myopia by 65% in chicks, dividing the 30 minutes of normal vision into three 10-minute episodes reduced the resultant myopia by 84%. It appears that similar nonlinearity exists in primates. Whereas a single 1-hour period of unrestricted vision reduced the amount of form deprivation myopia in infant monkeys by an average of 65%,[11] in the present study, four daily 15-minute periods of unrestricted vision eliminated any systematic myopic compensation induced by relative hyperopic defocus. The average ametropia in the –3D/plano group was actually slightly more hyperopic than in the control group. One possibility is that the apparently greater antimyopic effects of multiple daily periods of unrestricted vision result because the effects of the unrestricted vision are strongest at the onset of the period of unrestricted vision.

The pattern of results observed in monkeys and other species indicate that the signals or processes that promote axial elongation are comparatively weak or easily overridden by factors that slow ocular growth. It appears that different types of visual experience are weighted differently by the vision-dependent mechanisms that regulate eye growth. Specifically, in infant monkeys, the effects of unrestricted vision are effectively stronger or persist to a greater extent beyond the exposure period than the responses to form deprivation[11] or to the relative hyperopic defocus produced by viewing through negative lenses. This bias in the effective temporal integration properties of the mechanisms that regulate refractive development help ensure the development of emmetropia and greatly reduce the likelihood that transient periods of image degradation or hyperopic defocus result in axial myopia.

In chicks, several observations suggest that the emmetropization process weighs the effects of hyperopic and myopic defocus differently. For example, in a series of experiments, Wallman et al.[15–17] showed that when chicks are exposed to alternating periods of myopic and hyperopic defocus, eye growth is dominated by myopic defocus, even when short periods of myopic defocus are intermixed with much longer periods of hyperopic defocus. These results are in agreement with the hypothesis that the emmetropization process in chicks can distinguish myopic from hyperopic defocus, though it is unclear what cues are used to make this discrimination. Given the many similarities between the emmetropization process in chicks and monkeys, we had hypothesized that viewing through +4.5-D lenses during the four daily 15-minute interruptions in the –3 D rearing schedule would have a greater protective effect than viewing through plano lenses. However, the opposite was observed with five of the six monkeys in the –3 D/+4.5 D group— evidence of compensation for the –3 D lenses. Similarly, Norton et al.[14] report that in tree shrews, brief daily periods of unrestricted vision are more effective in counteracting the myopiagenic effects of negative lens wear than similar periods of imposed myopic defocus.

It is not clear why the +4.5 D lenses were less effective than plano lenses in preventing myopic compensation. Although it is possible that the emmetropization process in monkeys cannot discriminate the sign of defocus, it is also possible that the degree of imposed myopic defocus was too large. Although we have previously demonstrated that animals reared with +4.5 D lenses typically exhibit hyperopic compensation,[8] the emmetropization process in infant monkeys has a limited operating range, and our alternating lens paradigm might have reduced the effective range of refractive errors that normally produce compensating growth. In this respect, several of the monkeys in the –3 D/+4.5 D group exhibited myopic changes shortly after the onset of lens wear, which effectively increased the degree of myopic defocus, potentially resulting in an optical error outside the operating range of the emmetropization process. However, in this study, we did not control viewing distance or accommodative status. As a consequence, the absolute amount of imposed defocus was unknown. We have previously argued that animals reared with positive lenses were likely to reduce the amount of imposed myopic defocus by habitually viewing near objects.[7] Near fixation during the period of viewing through +4.5 D lenses would have eliminated or greatly reduced the amount of myopic defocus. However, viewing through –3 D lenses for most of the day might have interfered with this adaptive viewing behavior. It is also possible that the stop signals produced by myopic defocus in primates are weaker than those produced by unrestricted vision or that the vision-dependent mechanisms in primates require a longer integration period for myopic defocus than for normal unrestricted vision. In the latter, it is known that in chickens, reducing the duration of exposure to less than 2 minutes per episode prevents compensation for imposed myopic defocus.[15] Parametric investigation of the effects of different lens powers and viewing durations in monkeys is required to address this apparent difference between chickens and primates.

Although the average refractive error at the end of the treatment period for the –3 D/plano monkeys was similar to that for the control animals, the range of refractive errors was larger in the –3 D/plano group. Thus, the brief daily periods of unrestricted vision were sufficient to eliminate the predictable myopic compensation produced by hyperopic defocus; however, these periods of unrestricted vision were not sufficient to ensure normal refractive development. It is particularly interesting that half the animals in this group maintained high degrees of hyperopia throughout the rearing period, despite their experiencing substantial amounts of hyperopic defocus, especially when viewing through the –3-D treatment lenses. The source of the variability is unknown. Perhaps the high degree of variability reflects individual differences in the integration properties of the emmetropization process or the sensitivity of the process to defocus. However, some of the variability is likely to reflect individual differences in visual experience. The function describing the protective, antimyopic effects of different durations of daily periods of unrestricted vision is steep.[11] Consequently, small individual differences in exposure history or in behavior (e.g., differences in fixation patterns and average viewing distances) could have resulted in significant differences in outcomes. These kinds of behavioral differences, however, could not account for the relative hyperopic changes found in several of the –3D/plano monkeys.

Although many aspects of the operational properties of the emmetropization process are still not well understood, the results of these experiments have important implications concerning the role of visual experience in the genesis of common refractive errors such as juvenile-onset myopia. In particular, integration nonlinearities such as those observed in the present study would greatly constrain the effects of visual experience on the development of myopia, which may explain why it has been so difficult to establish a quantitative relationship between visual experience and the degree of myopia, at least on an individual basis. For example, several lines of evidence suggest that chronic hyperopic defocus associated with underaccommodation during near work may promote the development of myopia[27,28] (see, however, Mutti et al.[29]). On a population basis, a clear association exists between the amount of time spent on near work and the prevalence and degree of myopia.[30,31] However, on an individual basis, near work is only weakly correlated with myopia.[32–34] These weak correlations may reflect the fact that commonly used metrics of near work, such as the so-called diopter hour or the number of books read per week, do not take into consideration the manner in which different types of visual experience are integrated over time. For example, consider the differences in the calculated di-

opter-hour units of myopiagenic visual experience for the animals in the –3 D and the –3 D/plano groups. With control animals as a reference (i.e., zero diopter hours), the monkeys in the –3 D and the –3 D/plano groups experienced, respectively, 36 and 33 diopter hours per day of viewing conditions that would promote myopic growth. Considering the different outcomes for these two experimental groups, it is clear that diopter-hour units did not capture the critical aspects of visual experience that contribute to myopia. In normal eyes (i.e., normal temporal integration properties), idiosyncratic behaviors that result in short interruptions in near work may counterbalance any stimulus for myopic growth. As a consequence, measures that are commonly used to quantify near work may not be appropriate. As Wallman and Winawer[2] have argued, the way in which one reads may be an important factor in determining whether near work promotes the development of myopia.

In summary, our results have demonstrated that temporal changes in visual error signals are not integrated in a simple linear fashion. Our results indicate that to stimulate myopic growth, a myopiagenic visual stimulus would have to be present almost constantly. Perhaps in searching for experiential factors that contribute to myopia, we should concentrate on factors that are relatively constant over time.

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