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Effects of Local Myopic Defocus on Refractive Development in Monkeys

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Abstract

Purpose—Visual signals that produce myopia are mediated by local, regionally selective mechanisms. However, little is known about spatial integration for signals that slow eye growth. The purpose of this study was to determine whether the effects of myopic defocus are integrated in a local manner in primates.

Methods—Beginning at 24±2 days of age, seven rhesus monkeys were reared with monocular spectacles that produced 3 D of relative myopic defocus in the nasal visual field of the treated eye, but allowed unrestricted vision in the temporal field (NF monkeys). Seven monkeys were reared with monocular +3 D lenses that produced relative myopic defocus across the entire field of view (FF monkeys). Comparison data from previous studies were available for 11 control monkeys, 8 monkeys that experienced 3 D of hyperopic defocus in the nasal field, and 6 monkeys exposed to 3 D of hyperopic defocus across the entire field. Refractive development, corneal power, and axial dimensions were assessed at 2- to 4-week intervals using retinoscopy, keratometry, and ultrasonography, respectively. Eye shape was assessed using magnetic resonance imaging.

Results—In response to full-field myopic defocus, the FF monkeys developed compensating hyperopic anisometropia, the degree of which was relatively constant across the horizontal meridian. In contrast, the NF exhibited compensating hyperopic changes in refractive error that were greatest in the nasal visual field. The changes in the pattern of peripheral refractions in the NF monkeys reflected interocular differences in vitreous chamber shape.

Conclusions—As with form deprivation and hyperopic defocus, the effects of myopic defocus are mediated by mechanisms that integrate visual signals in a local, regionally selective manner in primates. These results are in agreement with the hypothesis that peripheral vision can influence eye shape and potentially central refractive error in a manner that is independent of central visual experience.

Lens compensation experiments have provided the strongest and most clinically relevant evidence that refractive development is regulated by visual feedback associated with the eye's effective refractive state.^{1–3} In every species that has been studied in a systematic manner, these experiments have demonstrated that optically imposed changes in the eye's refractive state predictably alter refractive development in a manner that reduces the optically imposed error.^{4–9} In particular, these experiments have shown that the eye is capable of determining whether it is myopic or hyperopic and within a moderate range of optical errors is able to alter vitreous chamber elongation rates to re-establish emmetropia.

The results from lens compensation experiments are significant because they indicate that optical defocus could play a critical role in the genesis of common refractive errors in children. Moreover, these experiments indicate that optically imposed defocus could be used to effectively manage refractive development and, specifically, that imposed myopic defocus could be used to reduce myopic progression.^{2, 3, 10} However, in order to develop the optimal optical treatment strategies for myopia, it is important to understand how visual signals from across the retina are integrated.

Visual signals that accelerate axial growth are mediated by mechanisms that operate in a local, regionally selective manner.^{11–16} For example, when either form deprivation or hyperopic defocus is imposed across half the visual field, the infant monkey eye develops axial myopia in the treated hemi-retina, but not in the untreated half of the eye.^{15, 16} However, relatively little is known about how the signals produced by myopic defocus are integrated across the retina. In the only published study to date, Diether and Schaeffel¹⁴ showed that positive lenses that produced relative myopic defocus over half the retina produce hyperopic shifts in refractive error that were largely restricted to the treated half of the chicken eye, in agreement with the hypothesis that the effects of myopic defocus are also mediated by local, regionally selective, retinal mechanisms. However, no changes in eye shape were associated with these regional alterations in refractive error.

A key issue is whether myopic and hyperopic defocus are mediated by the same mechanism with the same spatial integration properties. A number of observations suggest that myopic and hyperopic defocus are mediated by the same mechanism. In addition, to the obvious complimentary anatomical changes produced in choroidal thickness and axial length by myopic and hyperopic defocus,^{9, 17} several putative components in the signaling cascade that regulates refractive development are modulated in a bidirectional manner that is correlated with the sign of imposed optical defocus.^{18–21}

However, potential differences in the mechanisms underlying the effects of positive- and negative-lens-induced defocus have been observed. For example, experimental manipulations employed to localize the mechanisms responsible for lens compensation have yielded qualitatively different results for imposed myopic and hyperopic defocus. In particular, in chickens, colchicine, a neurotoxin, disrupts compensation to negative-lenses without producing substantial alterations in the hyperopic shifts induced by positive lenses.²² In guinea pigs sectioning the optic nerve retards compensation for positive lenses without significantly altering the myopic changes produced by negative lenses, which suggests that extraocular mechanisms are involved in compensation for positive lenses.²³ As a consequence, it is not prudent to assume that the spatial integration properties for myopic and hyperopic defocus are the same. Therefore, the goals of this study were to characterize the effects of hemiretinal myopic defocus on ocular growth and the pattern of peripheral refractions in infant monkeys and to compare these results to the effects of full-field myopic defocus and to the effects previously obtained with hemiretinal hyperopic defocus.¹⁶

METHODS

Subjects

Data are presented for 29 infant rhesus monkeys (*Macaca mulatta*) that were obtained at 2 to 3 weeks of age and housed in our primate nursery that was maintained on a 12-hour light (~350 lux) / 12-hour dark cycle. All of the 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 National Institutes of Health Guide for the Care and Use of Laboratory Animals.

The primary subjects were 7 infant monkeys that were reared wearing goggles that secured a zero-powered lens in front of the fellow control eye and a spectacle lens that produced 3 D of relative myopic defocus in the nasal visual field of the treated eye ("NF" monkeys). The treatment lenses were Franklin-type bifocals that were oriented so that the transition between the near and far segments of the lens was oriented vertically. The nasal and temporal segments of the lenses had refracting powers of +3 D and 0 D, respectively, and the vertical transition between the two power zones was positioned approximately 1 mm to the temporal side of the center of the treated eye's entrance pupil. The effects of full-field myopic defocus were investigated in 7 animals ("FF" monkeys), which were reared with zero-powered lenses over the fellow control eyes and +3 D single-vision spectacles over the treated eyes that imposed relative myopic defocus over the entire field of view (vertical field = 87°; horizontal field = 80°). The treatment lenses were worn continuously from 24 ± 2 to 142 ± 10 days of age. The details of the nursery care for our infant monkeys and our goggle-rearing methods have been described previously.²⁴

Comparison data for peripheral refractions were available from previous studies for 8 animals reared with -3 D of hyperopic defocus imposed over the nasal hemifield,¹⁶ 6 infants reared with monocular -3 D lenses that produced hyperopic defocus across the entire field of view,¹⁶ and 11 normal monkeys reared with unrestricted vision.^{25, 26} Eye shape information was available for 6 of the normal monkeys and all of the infants reared with hyperopic defocus.¹⁶

Ocular Biometry

The refractive status, corneal power and axial dimensions were measured using methods described previously. The first measurements were obtained at ages corresponding to the onset of lens wear and then at approximately two- or four-week intervals thereafter. To obtain the ocular measurements, the animals were anesthetized (ketamine hydrochloride, 15–20 mg/kg; acepromazine maleate, 0.15–0.2 mg/kg) and cycloplegia was induced using 1% tropicamide. The refractive status of each eye was measured independently by two experienced, but unmasked, investigators using a streak retinoscope and averaged.²⁷ An eye's refractive error was defined as the spherical-equivalent, spectacle-plane refractive correction;²⁸ no corrections were made for the small-eye artifact associated with retinoscopy.²⁹ Central refractions were determined along the pupillary axis (i.e., the first Purkinje image produced by the retinoscope beam was observed in the center of the subject's entrance pupil). Following measurements of the central refraction, retinoscopy was performed at 15° intervals along the horizontal meridian out to a maximum eccentricity of 45°.²⁵ Throughout the paper, the eccentricities for refractive errors are specified with respect to the visual field (e.g., temporal field measurements correspond to refractive errors for the nasal retina). The anterior radius of curvature of the cornea was measured by keratometry (Alcon, Inc; Hand-held Auto-keratometer) and central corneal power was calculated from the average of three readings using an assumed refractive index of 1.3375.³⁰ Ocular axial dimensions were measured by A-scan ultrasonography implemented with a 13-MHz transducer (OTI Scan 1000; OTI Ophthalmic Technologies, Inc, Ontario, Canada). Intraocular distances were calculated from the average of 10 separate measurements using velocities of 1532, 1641, and 1532 m/sec for the aqueous, lens, and vitreous, respectively.

Magnetic Resonance Imaging

To assess the effects of the treatment regimens on the shape of the posterior globe, magnetic resonance images (MRI) were obtained near the end of the lens-rearing period using a 7T horizontal bore scanner (Biospec USR70/30; Bruker, Karlsruhe, Germany). The details of our MRI procedures have been described previously.^{16, 26}

The acquired axial MR images were reconstructed using in-house software (MATLAB; MathWorks, Natick, MA), which identified the horizontal plane image that contained the approximate optical axis of the eye (defined as the perpendicular through the midpoint of the line connecting the equatorial poles of the lens in the horizontal slice that showed the greatest lens thickness). The software interpolated between the axial image slices to produce a uniform resolution of 0.195 mm in the three dimensional matrix, which, in terms of vitreous chamber depth, corresponded to a dioptric interval of about 1 D.²⁶

The intersection of the presumed optical axis and the posterior lens surface was considered to be the approximate position of the second nodal point and was used as the reference for specifying retinal eccentricities. The primary measure of interest was the vitreous chamber depth, which was defined as the distance between the approximate position of the second nodal point and the retina. Vitreous chamber depth in the horizontal meridian was determined as a function of eccentricity in 15° intervals out to eccentricities of 45°. ^{16, 26}

Statistical Analyses

Mixed-design, repeated-measures ANOVAs (SuperANOVA; Abacus Concepts, Inc, Berkeley, CA) and multiple comparisons were used to determine if there were differences in refractive error or vitreous chamber depth as a function of eccentricity or differences in the patterns of peripheral refraction between subject groups. For the repeated measures analyses within subjects, the probability values were adjusted using the Geisser-Greenhouse correction. For individual parameters, two-sample t-tests were used to compare mean values between subject groups and paired t-tests were employed for interocular comparisons. The relationship between vitreous chamber depth and refractive error was analyzed using linear regression (Minitab Inc. State College, PA).

RESULTS

Prior to the onset of the lens-rearing regimens, there were no systematic interocular differences in central refractive error or ocular dimensions in either the NF and FF monkeys. The treated and control eyes exhibited similar refractive corrections, corneal powers, lens thicknesses, and vitreous chamber depths ($T = -2.03$ to 1.03 ; $P = 0.09$ to 0.88). The anterior chamber depths for the treated eyes of the FF monkeys were shallower (2.43 ± 0.12 mm vs 2.59 ± 0.18 mm; $T = -2.94$, $P = 0.03$) than those in their fellow control eyes. However, it is likely that this difference was a statistical anomaly since two weeks later the depths of the anterior chamber in the two eyes of the FF monkeys were similar (2.68 ± 0.15 vs 2.62 ± 0.08 ; $T = 1.18$, $P = 0.28$). In addition, there were no systematic between group differences in central refractive errors (control-eye averages: NF = $+3.96 \pm 1.44$ D; FF = $+4.68 \pm 1.25$; $T = 1.01$, $df = 11$, $P = 0.33$) or any ocular dimensions (control eyes; $T = -1.60$ to 2.23 , $df = 7$ to 11 , $P = 0.06$ to 0.79).

Both lens-rearing strategies altered central refractive development and, especially in the case of the NF monkeys, the pattern of peripheral refractions. Figure 1 shows the longitudinal changes in the patterns of peripheral refraction for representative FF and NF monkeys. As illustrated by the left plots, which were obtained at the start of the lens-rearing period, the patterns of peripheral refractions along the horizontal meridian were initially well-matched in the two eyes of individual monkeys. With time, the FF monkeys manifested relative hyperopic anisometropias that were relatively constant across the horizontal meridian and that came about primarily because the treated eyes maintained the moderate degrees of hyperopia normally found in neonates while the fellow control eyes exhibited systematic reductions in hyperopia that were comparable to the emmetropizing changes in control monkeys.^{25, 31} The NF monkeys also developed hyperopic anisometropias; however, the degree of relative hyperopia in their treated eyes was greatest in the nasal visual fields. The

interocular refractive-error differences in the NF monkeys developed as a result of absolute hyperopic shifts in the refractions of the treated eyes, in combination with emmetropizing changes in the control eyes. In both subject groups, the interocular differences in refractive error, which became apparent after 2 to 4 weeks of lens wear, were relatively stable after about 100 days of age.

Figures 2 and 3 illustrate the patterns of peripheral refraction at the end of the lens-rearing period for individual monkeys in the FF and NF groups, respectively. Specifically, the average ($\pm$ SE) ametropias obtained during the last three measurement sessions of the lens-rearing period are plotted as a function of horizontal field eccentricity. In the FF group (Figure 2), the central refractions in the treated eyes were significantly more hyperopic than those in their fellow control eyes ($+4.96 \pm 1.03$ D vs $+3.27 \pm 0.89$ D; $T = 12.43$, $P < 0.001$). The results were very consistent in the FF group; every monkeys exhibited relative hyperopic errors in their treated eyes and, as emphasized by the average data in panel H, the interocular differences were relatively constant across the horizontal meridian. Repeated-measures ANOVA indicated that the differences in refractive error between the treated and fellow eyes of the FF monkeys were significant ($F = 58.77$; $df = 1$; $GG = 0.0003$), but they did not vary with eccentricity ($F = 3.11$; $df = 6$; $P = 0.08$).

At the end of the treatment period, the central refractive errors in the treated eyes of the NF monkeys (Figure 3) were also significantly more hyperopic than those in their fellow control eyes ($+4.80 \pm 1.52$ D vs $+3.95 \pm 1.61$ D; $T = 4.14$, $P = 0.006$). In some cases (panel A), the relative hyperopic errors in the treated eyes were restricted to the nasal visual field. However, all 7 NF animals exhibited relative hyperopia in their treated eyes and as reflected in the individual data and the average data in panel H, the degree of relative hyperopia was typically smallest in the temporal field and greatest in the nasal visual field. For the group, the interocular differences in refractive error were significant ($F = 61.43$; $df = 1$; $GG = 0.0002$) and there were significant variations in these differences as a function of eccentricity (i.e., the patterns of peripheral refraction were different; $F = 13.56$; $df = 6$; $GG = 0.005$).

The different effects of the FF and NF rearing procedures on the pattern of peripheral refractions is illustrated in Figure 4, which shows the interocular differences in refractive error plotted as a function of eccentricity for individual animals. For the FF monkeys, the degree of anisometropia was relatively constant across the horizontal meridian and for the majority of animals the interocular differences in refractive error fell outside the range of interocular differences for control monkeys at all eccentricities (shaded areas). In contrast, the NF monkeys exhibited systematic changes in the degree of anisometropia with eccentricity. At the 45° temporal field eccentricity, the anisometropias for all of the NF monkeys were within the normal range. The interocular differences in refractive error in the NF monkeys became more hyperopic in the central and nasal visual fields and at the 45° nasal field eccentricity the anisometropias fell outside the normal range for all of the NF animals. Comparisons between the FF and NF groups revealed that the differences in the degree of anisometropia varied significantly with the eccentricity between the two subject groups ($F = 3.20$; $df = 6$; $GG = 0.04$).

The induced central anisometropias were primarily axial in nature. At the end of the lens-rearing period, the central vitreous chamber depths of the treated eyes were significantly shorter than those in their fellow control eyes in both the FF (9.58 ± 0.34 mm versus 9.91 ± 0.36 mm; $T = -12.15$, $P < 0.001$) and NF monkeys (9.70 ± 0.42 mm versus 9.92 ± 0.39 mm; $T = -5.20$, $P = 0.002$). However, in addition both experimental groups exhibited small, but statistically significant, anterior segment alterations that contributed to the hyperopic anisometropias. Specifically, at the end of the treatment period, the corneas of the treated

eyes were slightly flatter than the corneas of the control eyes in both the FF ($+55.32 \pm 1.38$ D versus $+55.75 \pm 1.13$ D; $T = -3.20$, $P = 0.02$) and NF monkeys ($+54.40 \pm 0.85$ versus $+54.73 \pm 0.73$ D; $T = -2.70$, $P = 0.04$) and in the FF monkeys, the anterior chamber was slightly deeper in the treated eyes (3.06 ± 0.07 mm versus 3.03 ± 0.07 mm; $T = 3.67$, $P = 0.01$). No interocular differences in lens thickness were observed in either treatment group (FF monkeys: 3.51 ± 0.17 mm versus 3.53 ± 0.19 mm, $T = -1.66$, $P = 0.15$; NF monkeys: 3.60 ± 0.13 mm versus 3.59 ± 0.10 mm, $T = 0.35$, $P = 0.74$).

The differences in the patterns of peripheral refractions between the FF and NF monkeys were due to differences in the shapes of the posterior globe. Figure 5 illustrates the vitreous chamber depths obtained from the MR images near the end of the treatment period for the treated (filled circles) and control eyes (open circles) of representative animals from the FF (top rows) and NF subject groups (bottom rows). The interocular differences in vitreous chamber depth are shown below the treated- and control-eye plots. In the FF monkeys, all of the treated eyes had shorter central axial lengths than their fellow eyes. However, as reflected in the data from individual subjects, the interocular differences in vitreous chamber depth varied with eccentricity. The greatest differences were found in the near nasal retinas of the FF monkeys; the interocular differences in vitreous chamber depth were typically smaller in the temporal retina. As in the FF monkeys, all of the NF animals exhibited relatively shorter central axial lengths in their treated eyes. However, in contrast to the FF monkeys, the interocular differences in vitreous chamber depth for the NF monkeys were smallest in the nasal retina and generally largest in the near temporal retina.

Figure 6 shows the average ($\pm$ SE) interocular differences in vitreous chamber depth plotted as a function of horizontal eccentricity for the FF (left) and NF monkeys (right). The shaded areas represent the average ± 2 SEs for the interocular differences in control monkeys. For the FF monkeys, the average interocular difference in vitreous chamber depth were more than 2 standard errors away from the average interocular differences observed in normal monkeys at all eccentricities. However, the effects of full-field hyperopic defocus on the relative ocular growth of the treated eyes varied with eccentricity ($F = 12.42$; $df = 6$; $GG = 0.006$). Specifically, the reductions in axial growth were largest in the central and nasal retina and decreased with eccentricity in the temporal retina. The reductions in axial growth produced by the NF treatment regimen also varied with eccentricity ($F = 17.58$; $df = 6$; $GG = 0.002$), but the pattern of change was very different from that observed in the FF monkeys. In contrast to the FF monkeys, the interocular differences at the 45° nasal retinal eccentricity were within 2 SEs of the average for normal monkeys. The magnitude of the interocular differences in vitreous chamber depth at the 45° temporal retina eccentricity in the NF monkeys was similar to that in the FF monkeys. However, unlike in the FF monkeys, the interocular differences in vitreous chamber depth in the NF monkeys became smaller from the 30° temporal retinal eccentricity to the 45° nasal retinal eccentricity. In essence, the primary differences between the FF and NF monkeys were in the nasal retina, which is the part of the retina that received unrestricted vision in the NF monkeys.

The alterations in the peripheral refraction of the NF monkeys were associated with alterations in eye shape. In Figure 7 interocular differences in refractive error are plotted as a function of interocular differences in vitreous chamber depth for the control (small circles), FF (left) and NF monkeys (right). Data are shown for all eccentricities. As represented by the regression function, the degree of relative hyperopia in the NF monkeys was negatively correlated with the relative vitreous chamber depths of their treated eyes ($r^2 = 0.20$; $P < 0.001$). However, as shown in the left panel of Figure 7, the interocular differences in refractive error were not systematically associated with the interocular differences in vitreous chamber depth ($r^2 = 0.00$; $P = 0.74$). In other words, the interocular differences in

the pattern of peripheral refractions in the FF monkeys did not simply reflect the interocular differences in vitreous chamber shape.

DISCUSSION

The key finding of this study was that relative myopic defocus that was restricted to the nasal visual field produced regionally selective compensating hyperopic changes in refractive error. These relative hyperopic changes reflected local reductions in vitreous chamber elongation in the temporal retina. These results, which are similar in nature to the effects of hemi-field myopic defocus in chickens,¹⁴ indicate that the mechanisms that mediate the effects of myopic defocus in primates, like those responsible for the axial myopia produced by optically imposed hyperopic defocus,¹⁶ function in a local, regionally selective manner.

Overall, the effects of myopic defocus on the patterns of peripheral refraction, both full-field and nasal-field, are complimentary to those produced by hyperopic defocus. Figure 8 compares the patterns of peripheral refractions for monkeys reared with optically imposed hyperopic and myopic defocus. Data are shown for both full-field and nasal-field defocus. The degree of imposed defocus (± 3 D) and the onset and duration of lens wear were similar in all subject groups. For reference, the shaded areas represent the average (± 2 SEs) refractive errors for the right eyes of age-matched control monkeys. An obvious feature of the Figure is the mirror-image nature of the plots for hyperopic and myopic defocus. For example, for both groups of NF monkeys, interocular differences in refractive error were smallest in the temporal visual field; however, whereas the -3 D NF monkeys (panel 9B) exhibited relative myopia in the nasal fields, the $+3$ D NF monkeys (panel 9D) showed relative hyperopia in the nasal fields of their treated eyes. The average degree of anisometropia in the nasal visual fields in the two groups of NF monkeys was comparable, but the $+3$ D NF regimen appeared to have a greater effect on the treated eyes' refractions in the temporal field. Whereas, the data for the treated and control eyes of the -3 D NF monkeys overlapped throughout the temporal field, the temporal field refractions for the treated eyes of the $+3$ D NF monkeys were consistently more hyperopic than those for their fellow control eyes in the near temporal field. It is possible that the spatial spread of visual signals for positive-lens-induced myopic defocus is greater than that for hyperopic defocus, resulting in a more gradual transition between the nasal and temporal fields. However, it is also possible that behavioral/fixation differences between the two subject groups contributed to the more spatially diffuse changes in the $+3$ D NF monkeys. In particular, while the -3 D NF animals were unlikely to fixate through the powered portion of the lens because it required higher than normal accommodative efforts, there were some incentives for the $+3$ D NF animals to fixate through the powered portion of the lenses, especially at near fixation distances. If that was the case, the position of the transition between the two power zones of the treatment lenses relative to the pupils of the treated eyes may have been more variable in the $+3$ D NF monkeys, which would be expected to result in a blurring of the transition between the nasal and temporal hemi-fields.

Another important finding is that the pattern of peripheral refractions in the treated eyes of the $+3$ D FF monkeys (panel 8C) was different from that found in control monkeys and in the -3 D FF monkeys (panel 8A). For example, in addition to the compensating central hyperopia, the treated eyes of the $+3$ D FF monkeys exhibited relative peripheral myopia, which was most obvious at the 45° eccentricities. In contrast, the treated eyes of -3 D FF monkeys exhibited central myopia and relative peripheral hyperopia. In essence, with full-field defocus the largest compensating changes were observed in the central and near-central retina and generally decreased with eccentricity in both the negative- and positive-lens-reared monkeys. The different patterns of peripheral refraction observed in eyes with

experimentally induced myopia and hyperopia are similar to those found along the horizontal meridian of humans with naturally occurring myopia and hyperopia.^{32, 33}

Due to optical and neural concerns, it would be expected that the effects of a given degree of optical defocus would vary with eccentricity in the monkey eye. In particular, because the depth of field increases in the periphery, the ability of a given degree of imposed defocus to alter ocular growth would decrease with eccentricity. Thus, the smaller refractive changes observed in the treated-eye peripheries could simply reflect an eccentricity dependent decrease in the visual growth signal or growth-stopping signal. However, severe form-deprivation, which would presumably have relatively comparable visual effects across a very large part of the retina, like hyperopic defocus, produces central myopia and relative peripheral hyperopia.^{16, 26} Thus, it is likely that anatomical and biological factors also contribute to the eccentricity dependent differences in the degree of compensation. Regardless, there is much interest in the different patterns of peripheral refraction found in hyperopic and myopic eyes. In particular, because imposed defocus in the periphery can alter central refractive development in animals,^{16, 34–36} it has been speculated that the pattern of peripheral refraction could influence central refractive development.² Specifically, it is possible that relative peripheral hyperopia typically exhibited by myopic eyes (at least in the horizontal meridian)^{32, 37} could serve as a stimulus for myopia progression. In an analogous manner, the relative peripheral myopia found in hyperopic eyes could potentially retard emmetropization. While we did not directly investigate the potential causal relationship between the pattern of peripheral refraction and central refractive development, the results of this study show that alterations in the pattern of peripheral refraction can accompany compensating changes produced by both optically imposed full-field myopic and hyperopic defocus. In other words, the association between relative peripheral myopia and central hyperopia or between relative peripheral hyperopia and central myopia is not necessarily causal in nature.

It is interesting that in the +3 D FF monkeys, the interocular differences in refractive error, especially in the nasal visual field, were not correlated with interocular differences in vitreous chamber depth. While the interocular differences in refractive error in the +3 D FF monkeys did not vary significantly with eccentricity, these animals exhibited clear nasal-temporal asymmetries in the interocular differences in vitreous chamber depth. On the other hand, in monkeys reared with –3 D full-field lenses or full-field form deprivation, we previously found that the relative changes in refractive error were correlated with relative changes in vitreous chamber depth, i.e., the observed changes in the pattern of peripheral refractions were correlated with changes in the shape of the vitreous chamber.^{16, 26} However, as Verkicharla et al.³⁸ have discussed, both the eye's optics and vitreous chamber shape contribute to the pattern of peripheral refraction and one must be cautious inferring the shape of the retina from the pattern of peripheral refractions. The results obtained in our +3 D FF monkeys provide a clear example of the potential disconnects between peripheral refraction and eye shape. In this respect, several observations indicate that imposed myopic defocus altered the optics of the treated eyes. Specifically, the treated eyes of the +3 D FF subject had flatter corneas and deeper anterior chambers than their fellow control eyes. Possibly the alterations in anterior chamber depth were also associated with changes in the alignment of the crystalline lens resulting in nasal-temporal differences in effective power. If that was the case, the fact that the degree of anisometropia did not vary with eccentricity suggests that the asymmetries in ocular shape may have been compensating for the asymmetries in refracting power. We have observed increases in corneal power in eyes with relatively high degrees of form deprivation myopia.²⁶ However, no interocular differences in corneal power, anterior chamber depth or lens thickness were observed in animals with myopia produced by –3 D FF lenses.¹⁶

The relative peripheral hyperopia commonly found in humans with myopia is associated with more prolate or less oblate shaped eyes, although there is considerable variability in eye shape between myopic individuals.³⁹ However, comparatively little is known about eye shape in humans with hyperopia. Several studies have indicated that hyperopic eyes, like emmetropic eyes, are more oblate than myopic eyes,^{40–42} but there have not been any systematic studies of the nasal temporal symmetries in eye shape in hyperopic eyes. Nasal-temporal asymmetries in vitreous chamber depth have been observed in animals with vision-induced refractive errors. In particular in marmosets with lens-induced myopia, the increases in vitreous chamber depth were primarily restricted to the temporal retina/nasal field.⁴³ In macaques, the largest increases in vitreous chamber depth in response to FF form deprivation and full-field hyperopic defocus are also found in the temporal retina/nasal field,^{16, 26} however, the nasal-temporal asymmetries are small compared to those in marmosets. As shown in Figure 7, with FF +3 D lenses the greatest reductions in vitreous chamber depth were observed in temporal field/nasal retina. Perhaps the nasal retina is more sensitive to signals that slow eye growth or perhaps the temporal retina is more sensitive to signals that increase vitreous chamber growth.

The fact that local alterations in the effective focus of the eye can produce regional changes in eye growth and refractive error indicate that peripheral vision can influence eye shape and potentially produce changes in central refractive error⁴⁴ that are independent of the nature of central visual experience. In other words, peripheral treatment strategies may be effective in controlling central refractive development without interfering with central vision. However, the results also imply that correcting strategies for myopia or hyperopia that involve variations in refractive power across the visual field could potentially alter the shape of the eye and the pattern of peripheral refractive errors.

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REFERENCES

1. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. *Vision Res.* 1988; 28:639–657. [PubMed: 3195068]
2. Smith EL 3rd. Prentice Award Lecture 2010: A case for peripheral optical treatment strategies for myopia. *Optom Vis Sci.* 2011; 88:1029–1044. [PubMed: 21747306]
3. Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. *Neuron.* 2004; 43:447–468. [PubMed: 15312645]
4. Howlett MH, McFadden SA. Spectacle lens compensation in the pigmented guinea pig. *Vision Res.* 2009; 49:219–227. [PubMed: 18992765]
5. Hung LF, Crawford ML, Smith EL. Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nat Med.* 1995; 1:761–765. [PubMed: 7585177]
6. Shaikh AW, Siegwart JT Jr, Norton TT. Effect of interrupted lens wear on compensation for a minus lens in tree shrews. *Optom Vis Sci.* 1999; 76:308–315. [PubMed: 10375247]
7. Whatham AR, Judge SJ. Compensatory changes in eye growth and refraction induced by daily wear of soft contact lenses in young marmosets. *Vision Res.* 2001; 41:267–273. [PubMed: 11164443]
8. Shen W, Sivak JG. Eyes of a lower vertebrate are susceptible to the visual environment. *Invest Ophthalmol Vis Sci.* 2007; 48:4829–4837. [PubMed: 17898310]
9. Wildsoet C, Wallman J. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. *Vision Res.* 1995; 35:1175–1194. [PubMed: 7610579]
10. Smith EL III. Optical treatment strategies to slow myopia progression: Effects of the visual extent of the optical treatment zone. *Exp Eye Res.* 2013 [Epub ahead of print].

11. Wallman J, Gottlieb MD, Rajaram V, Fugate-Wentzek LA. Local retinal regions control local eye growth and myopia. *Science*. 1987; 237:73–77. [PubMed: 3603011]
12. Norton TT, Siegwart JT Jr. Animal models of emmetropization: matching axial length to the focal plane. *J Am Optom Assoc*. 1995; 66:405–414. [PubMed: 7560727]
13. McFadden SA. Partial occlusion produces local form deprivation myopia in the guinea pig eye. *Invest Ophthalmol Vis Sci*. 2002; 43 E-Abstract 189.
14. Diether S, Schaeffel F. Local changes in eye growth induced by imposed local refractive error despite active accommodation. *Vision Res*. 1997; 37:659–668. [PubMed: 9156210]
15. Smith EL 3rd, Huang J, Hung LF, Blasdel TL, Humbird TL, Bockhorst KH. Hemiretinal form deprivation: evidence for local control of eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci*. 2009; 50:5057–5069. [PubMed: 19494197]
16. Smith EL 3rd, Hung LF, Huang J, Blasdel TL, Humbird TL, Bockhorst KH. Effects of optical defocus on refractive development in monkeys: evidence for local, regionally selective mechanisms. *Invest Ophthalmol Vis Sci*. 2010; 51:3864–3873. [PubMed: 20220051]
17. Hung LF, Wallman J, Smith EL 3rd. Vision-dependent changes in the choroidal thickness of macaque monkeys. *Invest Ophthalmol Vis Sci*. 2000; 41:1259–1269. [PubMed: 10798639]
18. McFadden SA, Howlett MH, Mertz JR. Retinoic acid signals the direction of ocular elongation in the guinea pig eye. *Vision Res*. 2004; 44:643–653. [PubMed: 14751549]
19. Mertz JR, Wallman J. Choroidal retinoic acid synthesis: a possible mediator between refractive error and compensatory eye growth. *Exp Eye Res*. 2000; 70:519–527. [PubMed: 10866000]
20. Zhang Y, Liu Y, Wildsoet CF. Bidirectional, optical sign-dependent regulation of BMP2 gene expression in chick retinal pigment epithelium. *Invest Ophthalmol Vis Sci*. 2012; 53:6072–6080. [PubMed: 22879416]
21. Fischer AJ, McGuire JJ, Schaeffel F, Stell WK. Light- and focus-dependent expression of the transcription factor ZENK in the chick retina. *Nat Neurosci*. 1999; 2:706–712. [PubMed: 10412059]
22. Choh V, Padmanabhan V, Li WS, Sullivan AB, Wildsoet CF. Colchicine attenuates compensation to negative but not to positive lenses in young chicks. *Exp Eye Res*. 2008; 86:260–270. [PubMed: 18078935]
23. McFadden, SA.; Zengi, G.; Bowrey, H.; Leotta, A.; Wildsoet, CF. Location of signals which control ocular growth in the mammalian eye: Symposium 10 paper 1. In: Tarutta, E.; Chua, WH.; Young, T.; Goldschmidt, E.; Saw, SM.; Rose, KA.; Smith, EL., 3rd; Mutti, DO.; Ashby, R.; Stone, RA.; Wildsoet, C.; Howland, HC.; Fischer, AJ.; Stell, WK.; Reichenbach, A.; Frost, M.; Gentle, A.; Zhu, X.; Summers-Rada, J.; Barathi, V.; Jiang, L.; McFadden, S.; Guggenheim, JA.; Hammond, C.; Schippert, R.; To, CH.; Gwiazda, J.; Marcos, S.; Collins, M.; Charman, WN.; Artal, P.; Tabernero, J.; Atchison, DA.; Troilo, D.; Norton, TT.; Wallman, J., editors. *Myopia: Why Study the Mechanisms of Myopia? Novel Approaches to Risk Factors Signalling Eye Growth- How Could Basic Biology Be Translated into Clinical Insights? Where Are Genetic and Proteomic Approaches Leading? How Does Visual Function Contribute to and Interact with Ametropia? Does Eye Shape Matter? Why Ametropia at All?* Optom Vis Sci; 2011. p. 429
24. Smith EL 3rd, Hung LF. The role of optical defocus in regulating refractive development in infant monkeys. *Vision Res*. 1999; 39:1415–1435. [PubMed: 10343811]
25. Hung LF, Ramamirtham R, Huang J, Qiao-Grider Y, Smith EL 3rd. Peripheral refraction in normal infant rhesus monkeys. *Invest Ophthalmol Vis Sci*. 2008; 49:3747–3757. [PubMed: 18487366]
26. Huang J, Hung LF, Ramamirtham R, Blasdel TL, Humbird TL, Bockhorst KH, Smith EL 3rd. Effects of form deprivation on peripheral refractions and ocular shape in infant rhesus monkeys (*Macaca mulatta*). *Invest Ophthalmol Vis Sci*. 2009; 50:4033–4044. [PubMed: 19420338]
27. Harris WF. Algebra of spherocylinders and refractive errors, and their means, variance, and standard deviation. *Am J Optom Physiol Opt*. 1988; 65:794–802. [PubMed: 3207150]
28. Kee CS, Hung LF, Qiao-Grider Y, Roorda A, Smith EL 3rd. Effects of optically imposed astigmatism on emmetropization in infant monkeys. *Invest Ophthalmol Vis Sci*. 2004; 45:1647–1659. [PubMed: 15161822]

29. Hung LF, Ramamirtham R, Wensveen JM, Harwerth RS, Smith EL 3rd. Objective and subjective refractive error measurements in monkeys. *Optom Vis Sci.* 2012; 89:168–177. [PubMed: 22198796]
30. Kee CS, Hung LF, Qiao Y, Habib A, Smith EL 3rd. Prevalence of astigmatism in infant monkeys. *Vision Res.* 2002; 42:1349–1359. [PubMed: 12044741]
31. Qiao-Grider Y, Hung LF, Kee CS, Ramamirtham R, Smith EL 3rd. Normal ocular development in young rhesus monkeys (*Macaca mulatta*). *Vision Res.* 2007; 47:1424–1444. [PubMed: 17416396]
32. Millodot M. Effect of ametropia on peripheral refraction. *Am J Optom Physiol Opt.* 1981; 58:691–695. [PubMed: 7294139]
33. Mutti DO, Sholtz RI, Friedman NE, Zadnik K. Peripheral refraction and ocular shape in children. *Invest Ophthalmol Vis Sci.* 2000; 41:1022–1030. [PubMed: 10752937]
34. Liu Y, Wildsoet C. The effect of two-zone concentric bifocal spectacle lenses on refractive error development and eye growth in young chicks. *Invest Ophthalmol Vis Sci.* 2011; 52:1078–1086. [PubMed: 20861487]
35. Tepelus TC, Vazquez D, Seidemann A, Uttenweiler D, Schaeffel F. Effects of lenses with different power profiles on eye shape in chickens. *Vision Res.* 2012; 54:12–19. [PubMed: 22186225]
36. Woods J, Guthrie SE, Keir N, Dillehay S, Tyson M, Griffin R, Choh V, Fonn D, Jones L, Irving E. Inhibition of defocus-induced myopia in chickens. *Invest Ophthalmol Vis Sci.* 2013; 54:2662–2668. [PubMed: 23471891]
37. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res.* 2006; 46:1450–1458. [PubMed: 16356528]
38. Verkicharla PK, Mathur A, Mallen EA, Pope JM, Atchison DA. Eye shape and retinal shape, and their relation to peripheral refraction. *Ophthalmic Physiol Opt.* 2012; 32:184–199. [PubMed: 22486366]
39. Atchison DA, Jones CE, Schmid KL, Pritchard N, Pope JM, Strugnell WE, Riley RA. Eye shape in emmetropia and myopia. *Invest Ophthalmol Vis Sci.* 2004; 45:3380–3386. [PubMed: 15452039]
40. Schmid GF. Variability of retinal steepness at the posterior pole in children 7–15 years of age. *Curr Eye Res.* 2003; 27:61–68. [PubMed: 12868010]
41. Zhou, X-D.; Wang, F-R.; Zhou, S-Z.; Shi, J-S. A computed tomographic study of the relation between ocular axial biometry and refraction. In: Tokoro, T., editor. *Myopia Updates: Proceedings of the 6th International Conference on Myopia*. New York: Springer; 1998. p. 112–116.
42. Lim LS, Yang X, Gazzard G, Lin X, Sng C, Saw SM, Qiu A. Variations in eye volume, surface area, and shape with refractive error in young children by magnetic resonance imaging analysis. *Invest Ophthalmol Vis Sci.* 2011; 52:8878–8883. [PubMed: 22003110]
43. Totonelly K, Troilo D. Eye shape and off-axis refractive state following induced axial refractive errors in marmoset monkeys. *Invest Ophthalmol Vis Sci.* 2008; 49 E-Abstract 3589.
44. Seidemann A, Schaeffel F, Guirao A, Lopez-Gil N, Artal P. Peripheral refractive errors in myopic, emmetropic, and hyperopic young subjects. *J Opt Soc Am A Opt Image Sci Vis.* 2002; 19:2363–2373. [PubMed: 12469730]

Figure 1.

Spherical-equivalent refractive corrections obtained at different times during the treatment period for representative monkeys in the FF +3 D and NF +3 D subject groups plotted as a function of horizontal visual field eccentricity. The open and filled symbols represented the control and treated eyes, respectively. The plots on the left were obtained at the onset of the treatment period; the ages for the subsequent measures are shown in each plot. Zero eccentricity represents the pupillary axis.

Figure 2.

Spherical-equivalent refractive corrections plotted as a function of horizontal visual field eccentricity for the treated (filled symbols) and fellow eyes (open symbols) of individual monkeys treated with full-field +3 D lenses (panels A–G). The data points represent the mean $\pm$ SE for the final three measurement sessions of the lens-rearing period. Panel H shows the group means ($\pm$ SE) for the FF +3 D monkeys at the end of the treatment period.

Figure 3.

Spherical-equivalent refractive corrections plotted as a function of horizontal visual field eccentricity for the treated (filled symbols) and fellow eyes (open symbols) of individual monkeys treated with nasal-field +3 D lenses (panels A–G). See Figure 2 legend for other details.

Figure 4.

Interocular differences in refractive error (treated eye – control eye) plotted as a function of horizontal visual field eccentricity for individual monkeys that were reared with full-field (A) and nasal-field defocus (B). The shaded area represents the range of anisometropias (right eye – left eye) for age-matched normal animals.

Figure 6.

Mean ($\pm$ SE) interocular differences in vitreous chamber depth obtained from MR images near the end of the treatment period plotted as a function of horizontal retinal eccentricity for the FF (left) and NF subject groups (right). The shade area represents the mean ± 2 SEs for the interocular differences in the vitreous chamber depths of age-matched normal monkeys.

Figure 7.

Interocular differences in refractive error are plotted as a function of interocular differences in vitreous chamber depth (treated or right eye – fellow or left eye) for all eccentricities along the horizontal meridian for both the full-field (left) and nasal-field subject groups (right). Data are also shown for the age-matched normal controls (small circles). The solid lines represent the best fitting regression lines for the treated monkeys.

Figure 8.

Average ($\pm$ SE) refractions plotted as a function of horizontal eccentricity for monkeys were reared with full-field -3 D lenses (A), nasal field -3 D lenses (B), full-field +3 D lenses (C), and nasal field +3 D lenses (D). The filled and open symbols represent the treated and fellow eyes, respectively. The average ($\pm$ 2 SE) ametropias for age-matched normal monkeys are indicated by the shaded areas in each plot. The data for the monkeys treated with -3 D lenses were replotted from Smith et al.¹⁶