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Integration of Defocus by Dual Power Fresnel Lenses Inhibits Myopia in the Mammalian Eye

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Purpose. Eye growth compensates in opposite directions to single vision (SV) negative and positive lenses. We evaluated the response of the guinea pig eye to Fresnel-type lenses incorporating two different powers.

Methods. A total of 114 guinea pigs (10 groups with 9–14 in each) wore a lens over one eye and interocular differences in refractive error and ocular dimensions were measured in each of three experiments. First, the effects of three Fresnel designs with various diopter (D) combinations (−5D/0D; +5D/0D or −5D/+5D dual power) were compared to three SV lenses (−5D, +5D, or 0D). Second, the ratio of −5D and +5D power in a Fresnel lens was varied (50:50 compared with 60:40). Third, myopia was induced by 4 days of exposure to a SV −5D lens, which was then exchanged for a Fresnel lens (−5D/+5D) or one of two SV lenses (+5D or −5D) and ocular parameters tracked for a further 3 weeks.

Results. Dual power lenses induced an intermediate response between that to the two constituent powers (lenses +5D, +5D/0D, 0D, −5D/+5D, −5D/0D and −5D induced +2.1 D, +0.7 D, +0.1 D, −0.3 D, −1.6 D and −5.1 D in mean intraocular differences in refractive error, respectively), and changing the ratio of powers induced responses equal to their weighted average. In already myopic animals, continued treatment with SV negative lenses increased their myopia (from −3.3 D to −4.2 D), while switching to SV positive lenses or −5D/+5D Fresnel lenses reduced their myopia (by 2.9 D and 2.3 D, respectively).

Conclusions. The mammalian eye integrates competing defocus to guide its refractive development and eye growth. Fresnel lenses, incorporating positive or plano power with negative power, can slow ocular growth, suggesting that such designs may control myopia progression in humans.

Keywords: myopia, Fresnel lens, spectacle lens compensation, guinea pig

Myopia occurs when the eye is too long for its optical power and arises from excessive axial elongation during development. Interest in controlling myopia progression has been spurred in recent years by the rapid rise in its prevalence, especially in East Asian countries.[1–3] Studies involving animal models have provided convincing evidence that ocular growth is guided by vision and, of relevance to avenues for myopia control, ocular growth has been shown to be sensitive to optical defocus. Specifically, hyperopic defocus imposed by negative lenses accelerates ocular growth while myopic defocus imposed with positive spectacle lenses slows it,[4–7] in each case counteracting the imposed defocus. Therefore, it is of interest to know how the eye responds to a combination of myopic and hyperopic defocus and whether inclusion of positive power in multifocal corrective lens designs might also slow myopic progression.

Two dual power concentric lens designs have been studied. The first design incorporated relative positive power restricted to the periphery of the lens surrounding a central zone of opposite or less power.[8,9] Such designs have produced positive myopia control treatment outcomes in humans[10–12] and while they at least partially counteract the relative peripheral hyperopia present in myopic eyes,[13,14] recent evidence questions whether this relationship is causal.[15,16] It is possible they partially act because of altered ocular spherical aberration or increased depth of focus[17] and/or imposed on-axis myopic defocus (Tarrant J, et al. *IOVS* 2007;48:ARVO E-Abstract 1510). A second design based on the Fresnel principle incorporates alternating annuli of different powers throughout the lens so that two focal planes are simultaneously experienced on- and off-axis (Wildsoet CF, et al. *IOVS* 2000;41:ARVO Abstract 3930). Myopia progression has been found to regress in chicks wearing a dual focus Fresnel lens incorporating competing positive and negative defocus.[18] Relative differences in eye growth were also reduced in some marmosets wearing a dual-powered contact lens on one eye when compared with the growth induced by single vision negative lenses found in earlier studies.[19] However, substantial individual variability and unexpected contralateral effects in which 8/10 marmosets developed some myopia in their untreated (non–lens-wearing) eyes confound these results.[19] In chicks, the effect of imposed myopic defocus (positive power) was found to dominate when combined with an equivalent proportion of imposed

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hyperopic defocus (negative power).[18] This dominance of myopic defocus also occurs in chicks exposed to defocus stimuli of opposite sign using fixed focal planes in lens/cone devices[20,21] or intermittent lens-wearing paradigms.[22]

The avian eye differs from mammalian and primate eyes in several important ways. First, in response to myopic defocus, the chick eye rapidly and significantly expands its choroid,[23] allowing it to compensate for significant amounts of imposed defocus within hours. Although choroid thickness is also modulated by defocus in primates[24] and mammals,[4] the amplitude of the response is too small to affect significant refractive error changes (<1 diopter [D] in the guinea pig).[4] Second, the decay of the myopic effect of repeated exposures to hyperopic defocus given in isolation, takes 0.4 hours in the chick, but over 30 hours in guinea pigs.[25] Third, in mammalian and primate eyes, significant remodeling occurs in the fibrous sclera that affects the shape of the eye and the progression of myopia.[26,27] However, the avian sclera includes a cartilaginous layer[28] that imparts greater rigidity,[29] and thus the potential to support more localized ocular shape changes and necessarily involves different mechanisms by which the chick eye alters its size.

The guinea pig study described here specifically investigated the responses of a small mammalian eye to exposure to various dual defocus Fresnel lenses in two situations. In the first approach, young animals wore lenses containing different combinations of defocus for several weeks during which ocular changes were tracked. In the second approach, eyes were first made myopic with a SV negative lens, which was then replaced in one group with a Fresnel lens incorporating positive power. We found that the eyes of young guinea pigs integrated the competing imposed defocus stimuli. Importantly, in terms of myopia control, initially myopic animals show regression in their relative myopia in the presence of non-myopiagenic defocus presented in a Fresnel lens format. Some of these data have been previously reported (Tse DY, et al. *IOVS* 2010;51:ARVO E-Abstract 1727).[30]

Materials and Methods

Animals and Housing

Pigmented guinea pigs (*Cavia porcellus*) were housed with their mothers and littermates as previously described[31] in opaque plastic boxes (65 × 45 × 20 cm) with wire lids. The light from overhead white light emitting diodes was evenly diffused through a 3-mm translucent white PMMA acrylic sheet (Opal Perspex; Lucite International, Mitchell Plastics, Melbourne, Australia) located 200 mm above the boxes. The luminance was 400 lux at the center of each box. Lights were on a 12-hour day/12-hour night cycle. All procedures were approved by the University of Newcastle Animal Care and Ethics Committee and were in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Lenses and Their Application

All three experiments described here included dome-shaped Fresnel (dual power) lenses incorporating annuli of alternating power. When worn, their optical effect for distant objects is to produce two distinct image planes extending over the entire visual field[18] (Fig. 1). Their design was optimized to minimize spherical aberration using optical design software (Zemax; Zemax Design Corp., Bellevue, WA). Lens specifications, including center thickness, diameter and base curve, are listed in Supplementary Table S1. Single vision (SV) lenses, matched to the average center thickness, diameter, and base curve of the Fresnel lenses, were included as controls. The distance of the lens apex to the cornea (d) was 6 mm, changing slightly the effective power (F_e) of the lenses at the cornea (+5.15D for +5D lens and −4.85 D for −5D lens; $F_e = F/(1 - d \times F)$; where F is the nominal power of the lens). Lenses were mounted onto plastic washers backed with hook fasteners and attached to mating arcs made of loop fastener (Birch Haberdashery and Craft, Melbourne, Australia) that had been previously glued to the fur, well above and below the eye (Fig. 1B).[4] Lenses were replaced with clean lenses each day under dim light and carefully centered on the pupil. Regardless of centering the Fresnel lenses, the combination of eye movements and the presence of 17 annuli ensured that all retinal regions experienced both focus conditions.

Experiment 1: Ocular Response to Competing Defocus During Emmetropization

In this experiment, the effects of three Fresnel dual power lenses (+5D/0D, −5D/0D or −5D/+5D, ratio of 50:50 for each) were compared with two SV lenses (+5D or −5D) and the attachment mount without a lens (control, 0D; Table, total of 56 animals with 9–10 in each lens group). Lenses (or lens mount only) were worn on one eye for 11 days from age 3 to 14 days, when emmetropization is ongoing and eye growth rapid.[32] At the end of the lens-wearing period (at age 14 days), ocular parameters were measured in both eyes in the following order. First, corneal curvatures were measured in awake handheld animals using videokeratometry. Next, refractive error was measured using streak retinoscopy 1.5 hours after instillation of 1 to 2 drops of 1% cyclopentolate hydrochloride solution (Cyclogyl). Finally, ocular length and the component axial distances were measured with high frequency A-scan ultrasonography under gaseous anesthesia (1.5% isoflurane in oxygen). Measurement protocols were the same as previously described.[31,33]

Experiment 2: Effect of Different Ratios of Competing Defocus

In this experiment, the ocular response to Fresnel lenses varying in the area dedicated to +5D and −5D powers were examined: ratios of either 50:50 or 62.5:37.5 (referred to as 60:40) were tested (Table, 9 and 11 animals in each ratio group, respectively). The timing of lens wear and measurements were the same as in Experiment 1.

Experiment 3: Influence of Competing Defocus on Myopia Recovery

This experiment studied the effects of three different lens designs on recovery from induced myopia (Table, total of 38 animals with 11–14 in each lens condition). Four-day-old guinea pigs first wore a −5D lens over one eye for 4 days to induce relative myopia. Typically, when such lenses are then removed and unimpeded vision is restored, the induced myopia rapidly regresses and the interocular differences disappear.[33–35] At the end of the initial 4-day lens treatment period (at 8 days old), the −5D lens was changed to either a +5D SV lens or a Fresnel dual power lens (−5D/+5D of ratio 50:50) or left in place (control group). Ocular parameters were measured in all eyes at the end of the first 4 days of lens wear and again after 1 and 2 weeks during the "recovery" period (at age 8, 15, and 22 days, Table). Measurements were the same as in Experiment 1.

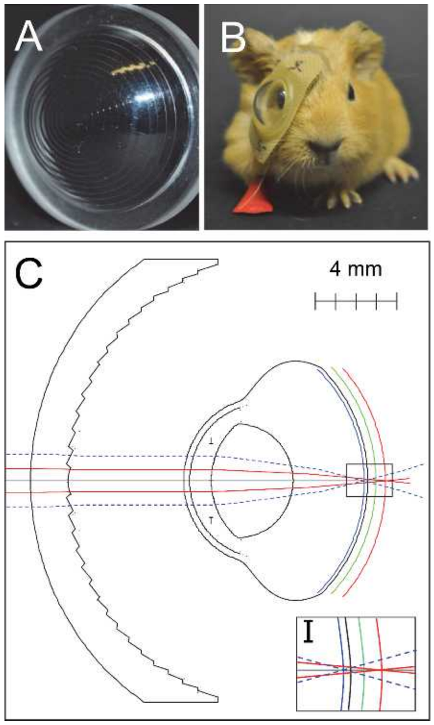

Figure 1. Fresnel lens. (**A**) Unmounted lens showing 16 concentric rings of alternating power. (**B**) Guinea pig wearing a mounted lens. Red bootie is worn on the nearest foot to buffer potential damage to the lens from scratching. (**C**) Diagrammatic representation of the two focal planes induced by a −5D/+5D dual power Fresnel lens in the nonaccommodated guinea pig eye. Without the lens, the eye is hyperopic at this age (*green line*). The +5D powered rings (+5.12 D effective power) foci is myopic, just in front of the retina (*blue line*). The −5D powered rings (−4.89 D effective power) foci is hyperopic and behind the retina (*red line*), exaggerating the preexisting hyperopia. The average of these two foci (+2.5 D) is shown by the hyperopic green plane (see *Inset I* for enlargement; eye and lens drawn to scale but focal planes exaggerated for clarity).

Data Analysis and Presentation

Interocular differences between the lens-wearing and fellow (non–lens-wearing) eye (referred to as "relative" myopia or "relative" ocular length, etc.) were calculated and are reported as means ± SE. Differences between groups were analyzed by one-way ANOVA (Experiment 1) or two-way mixed ANOVA (Experiment 3). Comparison of different lens groups at particular time points used Holm-Sidak multiple comparisons to control for family-wise errors. In Experiments 1 and 2, one-sample *t*-tests were used to compare the mean responses to dual-powered lenses, relative to the arithmetic mean of the responses to the defocus components presented as SV lenses. Statistical analyses used statistical software (SPSS version 19; IBM Corp., Armonk, NY, and SigmaPlot version 11; Systat Software, Inc., Chicago, IL). To determine if refractive error was predicted by the changes in ocular length observed, the following formulae was applied: $y = 21.2674 + 5.8738 \times (1 - e^{-0.1428x}) + 4.9387 \times (1 - e^{-0.0123x})$ where y is the change in ocular length which produces 1 D of defocus; and x is equal to days of age.[32]

Results

Experiment 1: Ocular Response to Competing Defocus During Emmetropization

Compensation to Defocus in Single Vision Lenses. After 11 days of wearing a +5D or a −5D SV lens, the lens-treated eyes showed the expected hyperopic and myopic changes in refractive error relative to their fellow eyes (+2.1 ± 0.6 D and −5.2 ± 0.8 D, respectively, $P < 0.001$ in both cases, Fig. 2, Supplementary Table S2). These changes represent compensation for 41% and 106% of the imposed effective positive (+2.1 of +5.15 D) and negative lens powers (−5.2 of −4.85 D), respectively. This smaller response to positive compared with negative lenses reflects the smaller response range to myopic than to hyperopic defocus in young primates[36] and mammals[4,37] (McFadden SA, et al. *IOVS* 2008;49:ARVO Abstract 3713). The refractive errors underlying these mean differences are shown for each eye in individual animals in Figure 3. Single vision positive lenses induced a hyperopic shift in the treated eye in 8/10 animals while all animals wearing SV negative lenses show a clear myopic shift (compare Figs. 3A, 3C). On average, eyes exhibiting relative hyperopia were shorter than their fellows (−47 ± 20 μm, $P = 0.04$, Fig. 2B), while those showing relative myopia were longer (92 ± 16 μm, $P < 0.001$, Fig. 2B). The ocular lengths and refractive errors of eyes wearing a lens mount only (0D, control group) were not significantly affected (Fig. 2) and the two eyes of individual animals were well matched in refractive error in 9/10 cases (Fig. 3E).

Compensation to Fresnel Lenses. In animals wearing a −5D/+5D lens, the mean refractive errors of treated and fellow eyes were not significantly different (difference of −0.3 ± 0.8 D, $P = 0.73$, Fig. 2A striped bars, Supplementary Table S2), nor were the lens-wearing eyes significantly different in average length relative to their fellow eyes (ocular length difference of

Table. Experimental Paradigms Showing Lens Types Worn, Age When Worn (in Days [d]), and Number of Animals (n) in Each Group

Experiment	Group	Lens Type	Age During Lens Wear, d	Length of Lens Wear, d	Age When Measured, d	*n*
Exp. 1: Ocular response to competing defocus during emmetropization	1	+5D	3–14	11	14	10
	2	+5D/0D				9
	3	0D				9
	4	−5D/+5D				9
	5	−5D/0D				10
	6	−5D				9
Exp. 2: effect of different ratios	7	−5D/+5D ratio 50:50	3–14	11	14	9
	8	−5D/+5D ratio 40:60				11
Exp. 3: influence of competing defocus on myopia "recovery"	9	−5D, continue with −5D	4–8, 8–22	4, 14	8, 15, 22	14
	10	−5D, switch to +5D				13
	11	−5D, switch to −5D/+5D				11

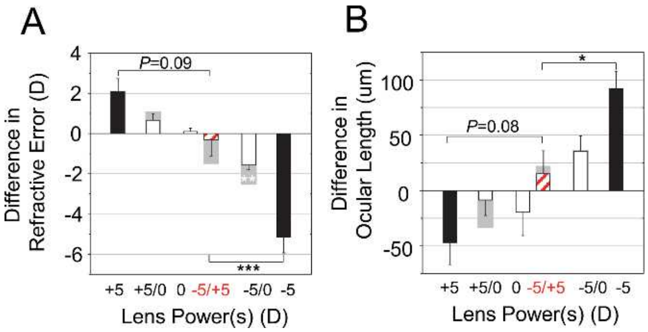

FIGURE 2. Mean difference between the lens-wearing and fellow eyes at the end of the lens-wearing period for each 50:50 dual lens power (plano combinations, *white*; power combination, *striped red*) and their corresponding single vision controls (*black bars*). (**A**) Difference in spherical equivalent refractive error. (**B**) Difference in ocular length measured with ultrasound. *Grey bars* show the arithmetic mean of the response to the two underlying single vision powers in each dual power lens. *White asterisks* indicate if this hypothetical average is significantly different from what was actually found. *Bars* are SE. The significant difference between each powered single vision control and the –5D/+5D Fresnel lens is shown by the square brackets. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

15 ± 20 μm, $P = 0.48$, Fig. 2B striped bars, Supplementary Table S2). This response pattern contrasts with the significant changes just described for eyes wearing +5D or –5D SV lenses and is consistent with the dual imposed defocus stimuli being integrated by the underlying emmetropization mechanism. The changes induced by the –5D/+5D Fresnel lens were not significantly different from the average of the responses to the two constituent powers presented as SV lenses (refractive error: +1.2 D more hyperopic than the predicted linear average, $P = 0.17$; ocular length: –7 μm shorter than the average, $P = 0.74$; grey bars in Fig. 2). Such a pattern might emerge if half of the animals responded to the positive power and half to the negative power component of the Fresnel lens. Inspection of the responses of individual animals (Fig. 3B) revealed a hyperopic shift in 2/9 animals, consistent with that expected if the response was guided only by the positive power in the –5D/+5D Fresnel lens. The remaining 7/9 animals showed either no change or a very small myopic shift (Fig. 3B) and no animal showed a strong myopic shift comparable with the response to the –5D SV lens. The mean difference in refractive error excluding the two hyperopic responders was –1.42 ± 0.06 D, very similar to the average of responses to the –5D and +5D lenses (–1.52 D).

The results for the two other Fresnel lenses are also consistent with the eye being influenced by both defocus stimuli. Thus, although a –5D/0D Fresnel lens induced significantly more myopia (–1.6 ± 0.2 D) and elongation (35 ± 14 μm) relative to their untreated eyes (details in Supplementary Table S2), these changes were respectively 70% (3.6 D) and 62% (57 μm) less than the comparable changes seen with SV –5D lenses (–1.6 vs. –5.2 D, $P = 0.34$ and 35 vs. 96 μm, $P < 0.001$, respectively, Fig. 2). The dampening of the refractive error response to –5D rings when interlaced with plano zones was a consistent pattern in all animals (compare Figs. 3C, 3F). This reduction was slightly greater than might be expected from a simple linear average of the responses to the SV –5D lens and control 0D (mount only) condition (grey bars in Fig. 2), suggesting a small bias toward the plano component: Only one animal responded to the plano component (compare Figs. 3E, 3F). Overall, when plano and negative powers were combined, 90% of animals did not respond exclusively to either of the constituent powers, but responded to their combination. While the overall changes induced by wearing the +5D/–0D lens were not statistically significant (+0.7 ± 0.3 D, –9 ± 14 μm, Fig. 2, Supplementary Table S2), individual responses were interesting. Specifically, 5/9 animals showed hyperopic shifts, but these responses were distinctly muted relative to that induced by +5D SV lens wear (compare Figs. 3D, 3A), while the responses of the remaining animals were similar to those wearing plano lenses (compare

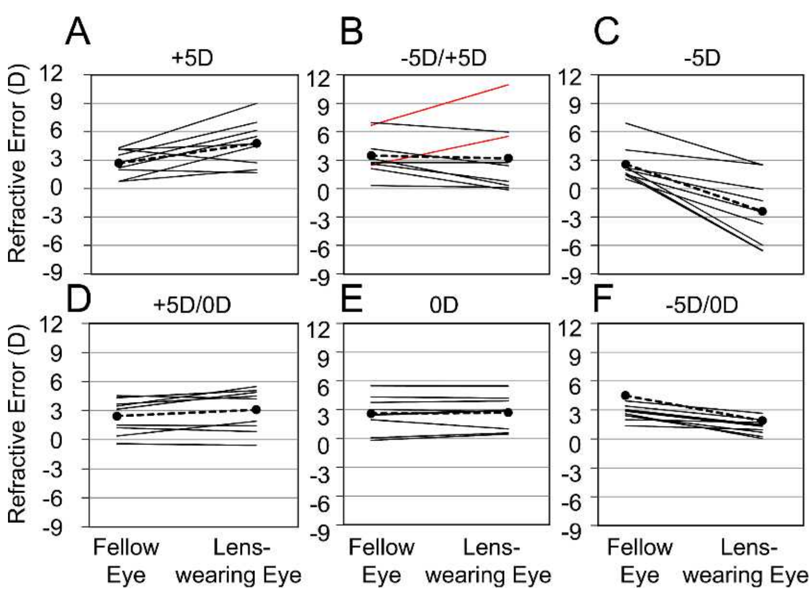

FIGURE 3. Refractive errors in each eye in individual animals in Experiment 1 after 11 days of wearing a (**A**) +5D SV lens, (**B**) –5D/+5D Fresnel lens, (**C**) –5D SV lens, (**D**) +5D/0D Fresnel lens, (**E**) lens holder only, or a (**F**) –5D/0D Fresnel lens.The mean for each group is shown by the *filled circles* and *dashed lines*. *Linked lines* show each animal's response in the fellow eye and in the eye wearing a lens (or lens holder, 0D). Note that the mean differences observed between the two eyes do not arise because of any effect on the fellow eyes which remain relatively consistent between the different lens groups ($F_{5,50} = 0.6$, $P = 0.8$). *Red lines* in (**B**) show two animals that responded to the positive power only.

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Figs. 3D, 3E). In other words, "diluting" a +5D lens with plano zones attenuated the usual response to imposed myopic defocus, and resulted in an intermediate response between that normally induced by the two constituent powers in isolation.

Given that adding either positive or plano power diluted the response to −5D and adding negative or plano power diluted the response to +5D, the question arises as to whether adding power is more effective as a diluent than adding plano. We found that combining −5D power with either +5D or 0D power in equal proportions (50% ratio) reduced the induced relative myopia by +4.9 D and +3.6 D (reductions of 94% and 70%, respectively) when compared with the response to a SV −5D lens (−5D/+5D: −0.29 ± 0.73 D; −5D/0D: −1.56 ± 0.25 D; −5D: −5.15 ± 0.78 D). Comparable reductions of 77 μm and 57 μm in relative ocular elongation were also observed (84% and 62% reductions for adding +5D or 0D, respectively, −5D/+5D: 15 ± 0.18 μm; −5D/0D: 35 ± 0.14 μm; −5D: 92 ± 0.16 μm). Similar comparisons of the response to the SV +5D lens with the responses to −5D/+5D or +5D/0D Fresnel lenses, reduced the degree of induced relative hyperopia (by −2.4 D and −1.5 D, respectively) and relative ocular shrinkage (by +62 μm and +39 μm, respectively). Although adding zones of opposite power had a consistently larger dilution effect, it was not statistically greater than the attenuation from adding plano zones (−5D: $P = 0.14$ and $P = 0.42$; +5D: $P = 0.29$ and $P = 0.34$; for refractive error and ocular length, respectively).

Changes in Other Ocular Components. The opposing increase and decrease in relative ocular length seen with SV −5D and +5D lens wear (relative to 0D) was paralleled by similar changes in other ocular parameters relative to 0D controls (vitreous chamber depth: +50 μm vs. −37 μm, Fig. 4A; crystalline lens thickness: +38 μm vs. −39 μm, Fig. 4B; for −5D and +5D respectively; details in Supplementary Table S2). However, with the −5D/+5D lens, relative vitreous chamber elongation was more similar to that seen with the SV −5D lens ($P = 1.0$, Fig. 4A) and longer than that induced by the +5D lens (by +102 μm, Fig. 4A). The relative crystalline lens response to the Fresnel lenses was also intermediate between the responses to each constituent power presented in SV lens format (Fig. 4B). A small amount of anterior segment deepening was seen with the SV lenses, but not with the Fresnel lenses (Fig. 4C). The layers of the posterior eye wall (retina, choroid and sclera), did not significantly change in relative thickness in any lens-wearing group (Fig. 4D).

Experiment 2: Effect of Different Ratios of Competing Defocus

When the lens area devoted to positive power was decreased in the dual-powered −5D/+5D lens design, the induced interocular differences in refractive error were slightly biased toward the positive component, although not significantly so (60:40, $P = 0.09$; 50:50, $P = 0.17$; one sample *t* relative to the predicted weighted linear average; Fig. 5A). This apparent bias arose because, like the effect of the 50:50 −5D/+5D lens, the 60:40 lens induced relative hyperopia (+1.7 D and +1.9 D) in 2/11 animals (18%). Despite the greater proportion of the 60:40 lens dedicated to negative power, no animal showed a myopic shift comparable with that induced by the SV −5D lens. The mean interocular difference, excluding the two hyperopic responders, was −2.16 ± 0.54 D, almost identical to the weighted linear average of responses to the constituent powers (−2.25 D). Statistical comparisons of results for ocular length with the predicted weighted dose–responses for both 60:40 and 50:50 lens designs also suggest that the competing defocus experiences are somehow integrated during ocular growth regulation ($P = 0.59$ and 0.75 respectively; relative to dashed

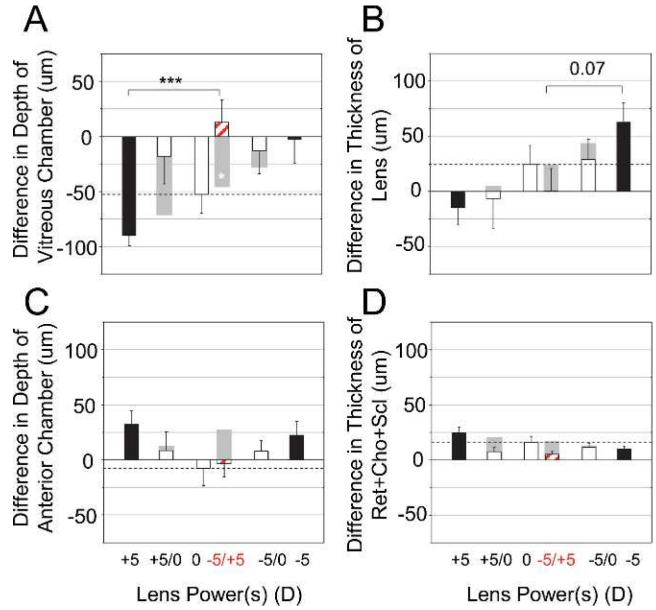

Figure 4. The effect of different lens types on the mean difference between the lens-wearing and fellow eye. (**A**) Difference in vitreous chamber depth. (**B**) Difference in lens thickness. (**C**) Difference in anterior chamber depth. (**D**) Difference in the combined thickness of the retina, choroid, and sclera. *Grey bars* show the arithmetic mean of the response to the two underlying single vision powers in each dual power lens. *Bars* are SEM. Statistical and shading conventions are the same as in Figure 2.

lines in Fig. 5B). Similarly, the interocular differences in vitreous chamber and anterior chamber depths induced by the 60:40 Fresnel lens design were similar to the weighted average of the responses to the two underlying SV powers (vitreous: −35 ± 7 μm vs. −44 ± 7 μm, $P = 0.71$; anterior chamber: +26 ± 4 μm vs. +31 ± 4 μm, $P = 0.72$; for 60:40 versus weighted average, respectively).

Experiment 3: Influence of Competing Defocus on Myopia Recovery

To appreciate the absolute effects of the different lens-wear paradigms, the main parameters are plotted separately for each eye in Figure 6 (all parameters are in Supplementary Table S2). Typically, in monocular lens paradigms, the effect of a lens is measured relative to the untreated fellow eye. These interocular differences were calculated for each animal, and the derived mean data are shown in Figures 7 and 8.

Effects of 4 Days of −5D SV Lens Wear. In young guinea pigs, briefly wearing a −5D lens induced significant myopia and an increase in ocular length relative to untreated fellow eyes, which were still hyperopic at 8 days of age (4.55 ± 0.25 D, Fig. 6A). In contrast, the lens-wearing eyes show reduced hyperopia at this time (to 1.48 ± 0.36 D, Fig. 6A). After just 4 days, the interocular difference in refractive error, averaged across all three groups in this experiment, was −3.1 ± 0.3 D ($P < 0.001$, Fig. 7A), representing 62% compensation for the imposed effective lens power (−3.1 D vs. −4.85 D). The corresponding relative difference in ocular length was +32 ± 12 μm ($P < 0.01$, Fig. 7B) arising from elongated vitreous chambers (by +13 ± 6 μm, $P < 0.05$, Fig. 8A) and anterior chambers (by +24 ± 10 μm, $P < 0.01$, Fig. 8C). These changes, together with a small nonsignificant corneal power increase (average difference of 1.57 ± 0.8 D, $P = 0.06$) predicted the

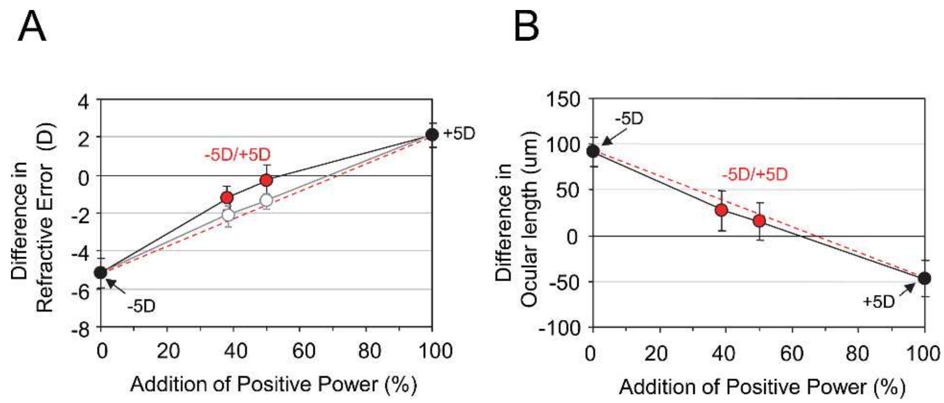

Figure 5. Comparison of the response of the eye to wearing lenses with different ratios of alternating −5D/+5D power (50:50 and 60:40) relative to SV controls. Mean difference between the lens-wearing and fellow eye is shown. (**A**) Spherical equivalent refractive error. (**B**) Ocular length. *Bars* are SE. The response of the eye is not significantly different from the expected response for a perfect integrator (*dashed line*). *Grey-filled circles* and *grey lines* show the average excluding the two animals that responded purely to the positive power.

measured refractive error difference within 0.27 D using the model eye for an 8-day-old guinea pig.[32] All three groups showed similar responses to a −5D lens for all ocular variables except for the retina, which thinned slightly in the treated eye in two of the three groups ($P < 0.05$ for the retina, $P > 0.05$ for all other variables; see Fig. 8D at 8 days and Supplementary Table S3).

Progression of Myopia With Continued −5D SV Lens Wear. Continued wear of the −5D lenses beyond day 4 led to more myopia progression over the following week in the lens-wearing eyes (to −2.1 D, Fig. 6A, left panel) and relative to the changes in the fellow eyes (interocular difference increased by −1.9 ± 0.5 D, $P < 0.05$ between age 8 and 15 days; Fig. 7A). Eyes achieved full compensation after 11 days of lens wear (relative myopia of −5.2 ± 0.6 D). Over the same period, relative ocular length increased by +41 ± 17 μm (Fig. 7B) primarily due to elongation in the vitreous chamber depth by +40 ± 12 μm between 8 and 15 days ($P < 0.05$, Fig. 6B left panel and Fig. 8A). These changes, together with a nonsignificant corneal power increase (average difference of 1.08 ± 1.5 D, $P = 0.47$) predicted the measured refractive error difference within 0.21 D using the model eye for a 22-day-old guinea pig.[32]

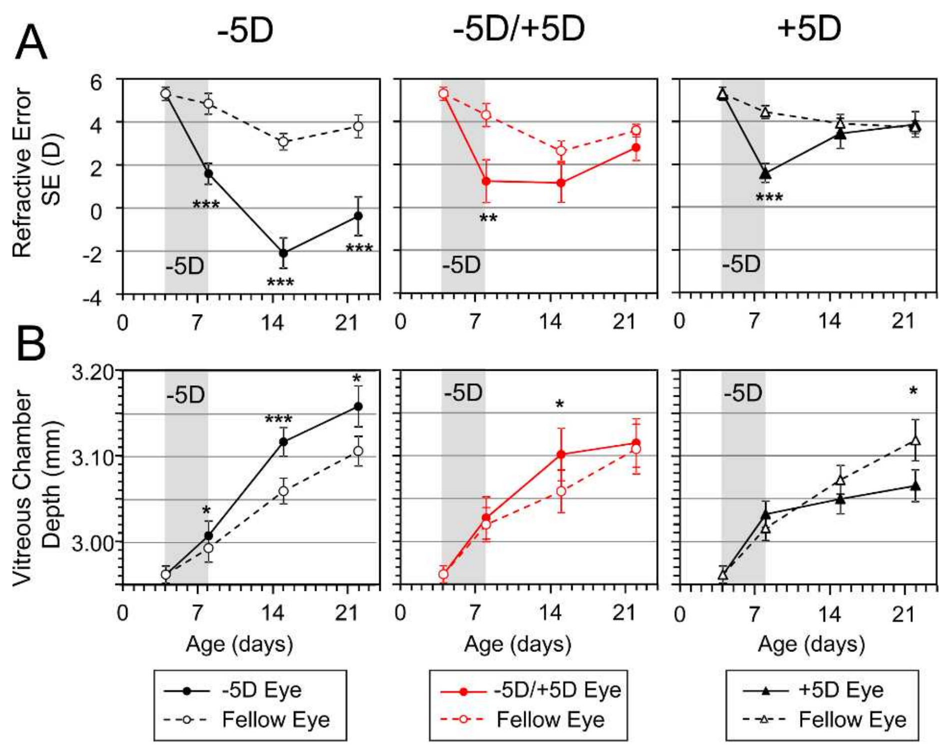

Figure 6. Average lens-wearing and fellow eye responses. (**A**) Refractive error. (**B**) Vitreous chamber depth; during the period after the induction of myopia with a −5D lens worn on one eye for 4 days. At age 8 days, the lens either remained a −5D lens (*left panel*) or was swapped with a −5D/+5D (*middle panel*) or a +5D lens (*right panel*). *Bars* are SEM. Values at age 4 days were not measured in these animals but are based on the average taken from our database of untreated eyes at this age ($n > 100$). The statistical difference between the eyes is shown. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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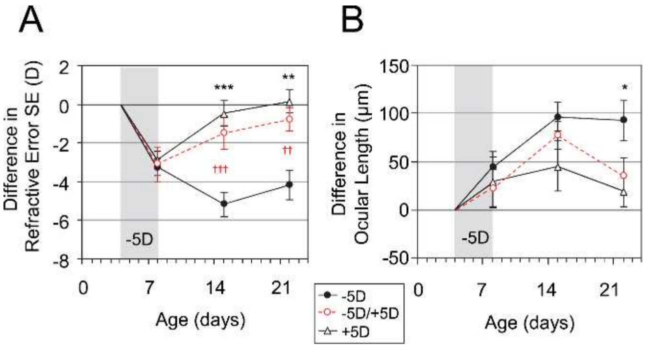

FIGURE 7. Animals were first made myopic by wearing −5D lenses on one eye for 4 days (*grey zone*). At age 8 days, the lens remained as a −5D lens or was swapped to a −5D/+5D or +5D lens. The mean difference between the two eyes is shown for 0, 1, and 2 weeks after the lens swap. (**A**) Spherical equivalent refractive error. (**B**) Ocular length measured with ultrasonography. *Bars* are SEM. *P* values from Holm-Sidak comparisons (between age 8 and 22 days) are shown for the difference between the response to: −5D and +5D SV lenses (*), and −5D/+5D and −5D lens designs (†). Three symbols (*** or †††), $P <$ 0.001; two symbols (** or ††), $P < 0.01$; one symbol (* or †), $P < 0.05$.

Regression of Relative Myopia With Switch to +5D SV Lens Wear. Exchanging the −5D SV lens for a +5D SV lens after relative myopia had been induced resulted in its rapid regression (loss of 3 ± 0.9 D of relative myopia between 8 and 22 days, Fig. 6A right panel and Fig. 7A). This is reflected in a gradual reduction in ocular elongation differences (Fig. 7B) due to a relative shortening of the vitreous chamber in lens-wearing eyes (−69 ± 30 µm change between 8 and 22 days, $P < 0.01$; cf. Fig. 6B, left, and Fig. 8A). The retina, choroid, and sclera all showed rapid thickening over the first week after lens exchange (+5 µm, +15 µm, and +13 µm changes, respectively, $P < 0.01$ in all cases, Figs. 8D–F).

Regression of Relative Myopia With Switch to a Fresnel −5D/+5D Lens. Exchanging the −5D SV lens for a −5D/+5D lens also led to regression of the induced relative myopia, which decreased by 2.3 ± 0.9 D over the subsequent 2 weeks ($P < 0.01$, Figs. 6A, 7A). These animals also developed significantly less myopia than those continuing to wear the −5D SV lens (−0.8 D vs. −4.2 D after 2 weeks, Fig. 7A). Their "recovery" was 77% of that recorded in animals switched to a +5D SV lens (who decreased their relative myopia by +2.87 ± 0.94 D, Fig. 7A). Similarly, the interocular difference in ocular length for the −5D/+5D lens at the end of the monitoring period was intermediate between that induced by the two constituent SV lenses (Fig. 7B). This primarily reflected the change in the relative vitreous chamber depth which was 52 µm less than in animals switched to a −5D lens and 53 µm more than those switched to a +5D lens (Fig. 7A, Supplementary Table S3). Neither lens thickness nor anterior chamber depth was differentially affected by the different types of lens treatment applied over the final 2 weeks ($P = 0.4$, Fig. 8B; $P =$ 0.8, Fig. 8C). That refractive error changes over this period largely reflect vitreous chamber changes was also evidenced by the significant correlation between these two parameters ($r^2 =$ 0.33, $P < 0.001$).

Changes in the Retina, Choroid, and Sclera After Lens Switching. Replacing the −5D SV lens with a +5D SV lens caused the retina, choroid, and sclera to significantly thicken in treated eyes relative to their fellow eyes (Supplementary Table S3), increasing the interocular differences relative to those animals continuing to wear −5D lenses (Fig. 8D–F). The shorter

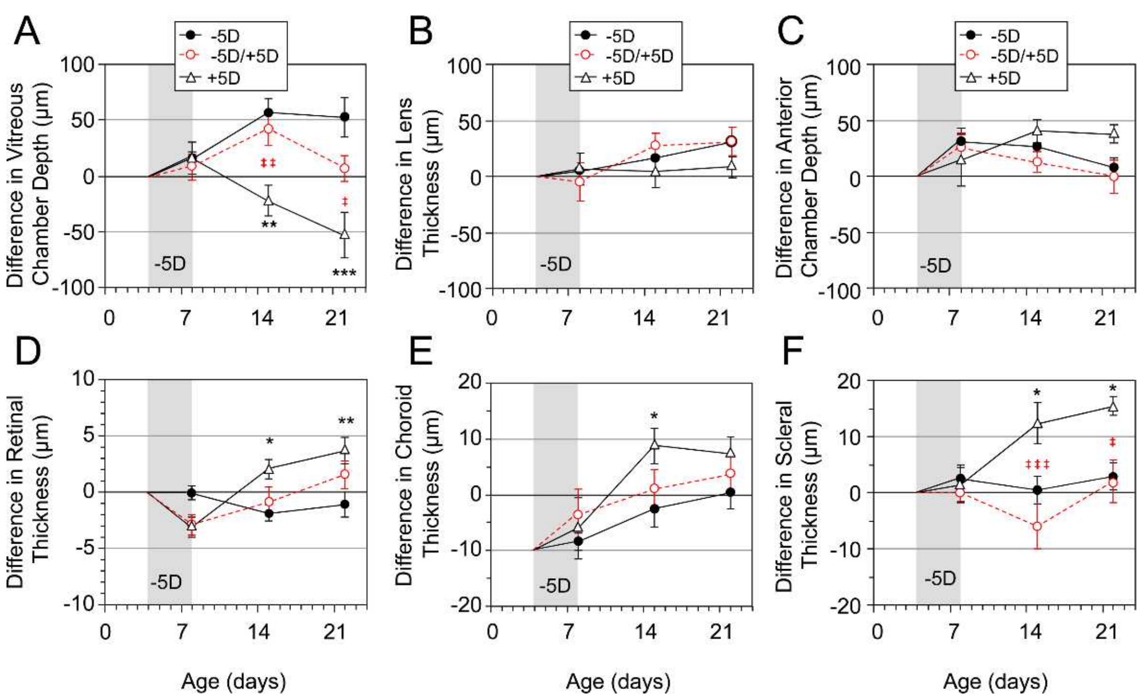

FIGURE 8. The mean difference between the two eyes in underlying ocular distances on axis at 0, 1, and 2 weeks after the lens swap occurred at 8 days of age following 4 days of −5D lens-wear (*grey zone*). (**A**) Vitreous chamber depth. (**B**) Crystalline lens thickness. (**C**) Anterior chamber depth. (**D**) Retinal thickness. (**E**) Choroid thickness. (**F**) Sclera thickness. After 2 weeks, the +5D/−5D Fresnel lens evoked an intermediate response in vitreous elongation, and retinal and choroidal thickening, while the remaining ocular components responded similarly to that induced by continuous SV negative lens-wear. *Bars* are SEM. *P* values from Holm-Sidak comparisons (between age 8 and 22 days) are shown for the difference between the response to: −5D and +5D SV lenses (*), and −5D/+5D and +5D (‡) lens designs. Three symbols (*** or ‡‡‡), $P < 0.001$; two symbols (** or ‡‡), $P < 0.01$; one symbol (* or ‡), $P < 0.05$.

the vitreous chamber, the thicker these layers became (retina: $r^2 = 0.28$, $P < 0.001$; choroid: $r^2 = 0.26$, $P < 0.001$; sclera, $r^2 = 0.22$, $P < 0.001$). Relative to the effect of these two SV lenses, switching to a −5D/+5D Fresnel lens caused an intermediate change in the relative thickness of the retina and choroid (Figs. 8D, 6E). However, scleral thickness was similar to the response to −5D lenses, as if it only responded to the negative power component (imposed hyperopic defocus) of the −5D/+5D lens (Fig. 8F).

Discussion

We find that mammalian refractive error development is guided by mechanism(s) that integrate competing defocus stimuli simultaneously presented to the same retinal areas. This mechanism appears to be ubiquitous as avian eyes exhibit similar behavior, although with subtle differences. In chicks there is a consistent response bias in which myopic defocus dominates.[18,21] For example, when chicks view through a 50:50 Fresnel lens, the response shows a significant bias toward that typical of a positive lens.[18] In one such study, 100% of chicks showed such biases for three different 50:50 Fresnel combinations: −10D/+20D, −10D/+10D, and −10D/+5D, with an average bias of +10.5 D, +5.4 D, and +2.7 D more than the weighted average of the constituent SV responses respectively.[18] In contrast, only 2/9 guinea pigs showed a similar biased response in favor of the positive power in the 50:50 −5D/+5D lens. Such individual sensitivity to positive power is reminiscent of the way some monkeys prefer to use the eye wearing a positive lens for fixation[36]; and the posturing of accommodation toward the most myopic meridian within an astigmatic eye.[36] Interestingly, when the responses of the remaining guinea pigs wearing a −5D/+5D lens were examined, no apparent bias was detected; instead their responses approximated the average of the constituent powers.

Species differences were also observed when the percentage of positive power was reduced below 50%. In chicks, reductions to 33% or 25% completely eliminated the positive bias[18] and instead eyes showed an intermediate response with a 20% to 30% bias in the opposite direction toward myopia. In contrast, no such bias towards myopia was seen in the guinea pigs in the current study, when the area devoted to positive power was reduced to 37.5%. Like the response to 50:50 lenses, two animals responded as if only detecting the positive power, with the remaining animals exhibiting responses approximated by the weighted linear average of the responses to the constituent powers. If the human eye responds like the guinea pig, it suggests that an anti-myopic effect might be reliably produced with Fresnel dual power lenses incorporating 50% or 37.5% of relative positive power.

The refractive changes observed reflect underlying changes in ocular growth as a similar integration was found for ocular length on axis, primarily arising from changes in the depth of the vitreous chamber. The crystalline lens also contributed to the responses elicited by defocusing lenses, becoming thicker in enlarged myopic eyes and thinner in eyes that show reduced elongation. Intriguingly, in the presence of Fresnel lenses, the crystalline lens changes reflected the average imposed power. Although a thicker crystalline lens on its own would increase ocular power,[32] we do not know if refractive index or surface curvatures might also have changed. In normal early development in these small eyes (axial length 7.3 mm), the lens contributes approximately 70% of the total optical power and continually thickens as the eye grows.[32] The decrease in ocular power (loss of 19 D over 100 days) is mostly accounted for by corneal flattening rather than through a decline in lens power.[32] In humans in early childhood, the lens initially thins before thickening from age 10 years,[38] but lens power continuously declines with age.[39,40] The onset of myopia in children correlates with significant changes in lens power and thickness, although the significance of these changes remains to be resolved.[39,40] It is possible these lens changes in myopic guinea pig eyes are simply a passive consequence of eye shape changes. For example, a reduction in equatorial diameter in myopic guinea pig eyes (Zeng G, et al. *IOVS* 2011;52:ARVO E-Abstract 3923) could underlie the increases in lens thickness that we observed.

The posterior layers of the eye wall also appeared to be modulated by imposed defocus, although not under all conditions. Eyes recovering from myopia showed the greatest changes. Specifically, the sclera rapidly thickened when an SV-positive lens was substituted for the myopia-inducing SV-negative lens, and the adjacent choroidal and retinal layers also thickened (Supplementary Table S3). It is not clear whether the thickening of the inner layers is secondary to the scleral changes or vice versa. It has been speculated that there may be independent signal pathways modulating choroidal and scleral changes, at least in the chick.[41] Interestingly, changes in the thickness of the sclera did not accompany the regression of induced relative myopia triggered by substitution of the −5D SV lens with a Fresnel lens incorporating positive power. As the accompanying changes in ocular dimensions were relatively small, it is possible that a minimum change in eye size is required to elicit remodeling of the sclera. It is also plausible that the dilution of the negative power with positive power, as in the Fresnel lens design, slowed the temporal response dynamics of the sclera.[27]

In introducing this study, we presented the possibility that a Fresnel lens design incorporating relative positive power might be used to control myopia in humans. A potential concern with this design is that the combination of two different focusing powers in the one lens might lead to image degradation—for example, through increased higher order aberrations and reduced spatial contrast. However, spatial contrast degradation induces myopia in guinea pigs (McFadden SA, et al. *IOVS* 2012; 53:ARVO E-Abstract 346) as in other species,[42,43] rather than triggering the reduction in relative myopia that we observed with our Fresnel lens designs. The Fresnel lens designs used here were also optimized to minimize spherical aberration, yet the −5D/0D and +5D/0D lenses induced opposite changes in ocular growth (Fig. 2). These data from guinea pigs suggest that incorporating relative positive power within a lens design may inhibit myopia progression in humans.

In Experiment 3, including 50% of positive power in the lens design resulted in substantial regression of relative myopia, compared with those animals that continued to wear an SV −5D lens, and 77% of the recovery achieved with an SV +5D lens. We do not know if the recovery response with a 50:50 Fresnel lens is any different from that which would occur if the lens was simply removed from an eye previously made myopic,[33,34,44] or if the same effect might also be achieved if plano segments were incorporated into the Fresnel lens. However, our results clearly show that including a non-myopiagenic component has the potential to dilute or cancel the effect of a myopiagenic component.

The response profiles reported here for the guinea pig differ from the consistent bias in the chicks' response to competing myopic and hyperopic defocus when presented in equal proportions simultaneously[18,21] or successively.[22] The origin of the strong response to positive lenses in the chick may reflect the large capacity of its choroid to thicken in compensation for myopic defocus, which induces a significant hyperopic refractive shift[41] prior to changes in eye length.[23] The choroidal response in mammals and primates is much smaller and may explain their more limited ability to respond to positive lenses.[45] In a previous study of chicks wearing −10D/+20D Fresnel lenses, choroidal thickening accounted for 57% of the positive bias (unpublished biometric data[18]) and four different Fresnel lenses containing both positive and negative power significantly influenced choroidal thickening in chicks (Wildsoet CF, et al. *IOVS* 2000;41:ARVO Abstract 3930). Species differences have also been observed in that brief periods of monocular positive lens wear appear no more effective than plano lenses in protecting against the myopiagenic effect of negative lenses in tree shrews[46] and monkeys[47] unless lenses are worn binocularly.[48] Interestingly, when comparisons were made between the guinea pig responses to plano and positive lens additions in Fresnel lens format, there was little advantage of one over the other (e.g., Fig. 2). Nonetheless, using positive power may have clinical relevance, and greater effects might be expected if lenses are worn binocularly, as would commonly be required in human treatments.

The current study also examined the effect of manipulating the proportion of lens area devoted to positive versus negative power. Decreasing the area assigned to positive power decreased its influence in a manner predicted by the weighted linear average of the two powers. This finding is of potential clinical relevance in that it offers a potential mechanism for improving retinal image quality and thus visual acuity in lenses designed for human myopia control. For example, a Fresnel lens design incorporating an addition (myopic defocus) occupying ~50% of the optical zone is currently undergoing clinical trials. Preliminary results show that such lenses are well tolerated by children and produce significant retardation in myopia progression.[49] Although high contrast acuity appears relatively unaffected, low contrast visual acuity is reported to be slightly reduced.[49] In light of the results from the current study, it may be possible to minimize the latter effect by reducing the area assigned to relative myopic defocus while maintaining a myopia retardation effect, albeit reduced.

In conclusion, our results imply that refractive development in the growing mammalian eye is guided by a mechanism with the capacity to integrate dual defocus stimuli. Including positive power or plano components in a Fresnel-type lens design leads to less ocular growth and less myopia compared to single vision negative lenses. Fitted to already relatively myopic eyes, these lenses also may facilitate its regression. Our experiments tested young guinea pigs aged between 14 and 22 days, approximately equivalent to children aged between 2.5 and 5 years.[32] Thus, they have greatest predictive value for early onset myopia, which typically starts in children aged approximately 7 years,[50] with even earlier onset reported in several major population studies[51,52] (although poor cycloplegia may underlie these latter findings[53]). Our findings may also apply to juvenile onset myopia if the years preceding onset are critical to its development. Furthermore, given the positive benefits of multifocal contact lenses in older children,[10–12] it is not unreasonable to assign broader translational value to the current results. Indeed, although inhibitory effects on eye growth would be expected to reduce as the eye growth rate decreases, the notion that the eye integrates defocus to guide its growth is likely to apply to any growing eye and progressive myopia is synonymous with increased growth. Therefore, lens treatments with growth inhibitory elements, alone or combined with myopia corrections, can be expected to help limit both the development and/or the progression of human myopia.

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