Animal Models Paper

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Animal Models

- Macaque and marmoset monkeys, tree shrews, guinea pigs, mice, chickens, fish, and squid
- Emmetropization
- Form deprivation myopia
- Lens-induced myopia and hyperopia

Special Issue

IMI – Report on Experimental Models of Emmetropization and Myopia

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The results of many studies in a variety of species have significantly advanced our understanding of the role of visual experience and the mechanisms of postnatal eye growth, and the development of myopia. This paper surveys and reviews the major contributions that experimental studies using animal models have made to our thinking about emmetropization and development of myopia. These studies established important concepts informing our knowledge of the visual regulation of eye growth and refractive development and have transformed treatment strategies for myopia. Several major findings have come from studies of experimental animal models. These include the eye's ability to detect the sign of retinal defocus and undergo compensatory growth, the local retinal control of eye growth, regulatory changes in choroidal thickness, and the identification of components in the biochemistry of eye growth leading to the characterization of signal cascades regulating eye growth and refractive state. Several of these findings provided the proofs of concepts that form the scientific basis of new and effective clinical treatments for controlling myopia progression in humans. Experimental animal models continue to provide new insights into the cellular and molecular mechanisms of eye growth control, including the identification of potential new targets for drug development and future treatments needed to stem the increasing prevalence of myopia and the vision-threatening conditions associated with this disease.

Keywords: myopia, emmetropization, animal models, visual regulation, eye growth

1. Introduction

Emmetropization refers to the developmental process that matches the eye's optical power to its axial length so that the unaccommodated eye is focused at distance. Investigations using animal models have informed our understanding of the role of vision in postnatal eye growth, the mechanisms and operating characteristics of emmetropization, and the development of refractive errors (myopia, where the eye is typically too long for its optical power; and hyperopia, where the eye is too short for its optical power). Animal models have established the existence of visual regulation of eye growth and refractive development as well as local retinal control of eye growth. They have also revealed biochemical signaling cascades that transduce visual stimuli related to the sign of defocus into cellular and biochemical changes in the retina, which, in turn, signal changes in the retinal pigment epithelium (RPE), choroid, and eventually sclera, leading to altered eye growth and changes in refractive state. These studies provide a framework for the development of optical and pharmacologic treatments that can be used to effectively reduce the prevalence and progression of myopia, which has become a major public health concern.[1]

In this paper, the findings of investigations using experimental animal models to study emmetropization and myopia development are reviewed. The contributions that studies with experimental animal models have made to understanding the mechanisms of emmetropization, the development of myopia, and new treatments to reduce myopia progression are summarized. Current models of eye growth control, areas of investigation and major findings, and frameworks for the

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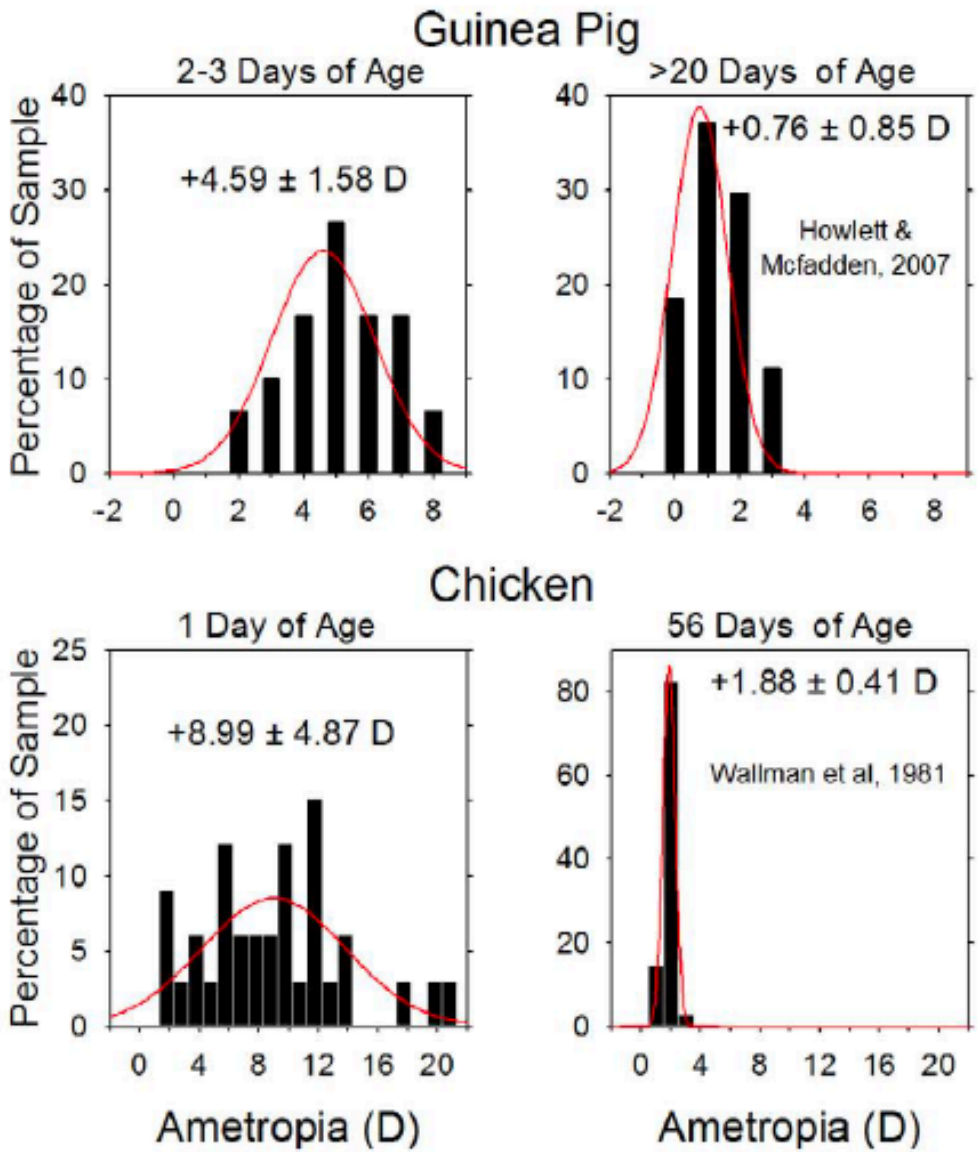
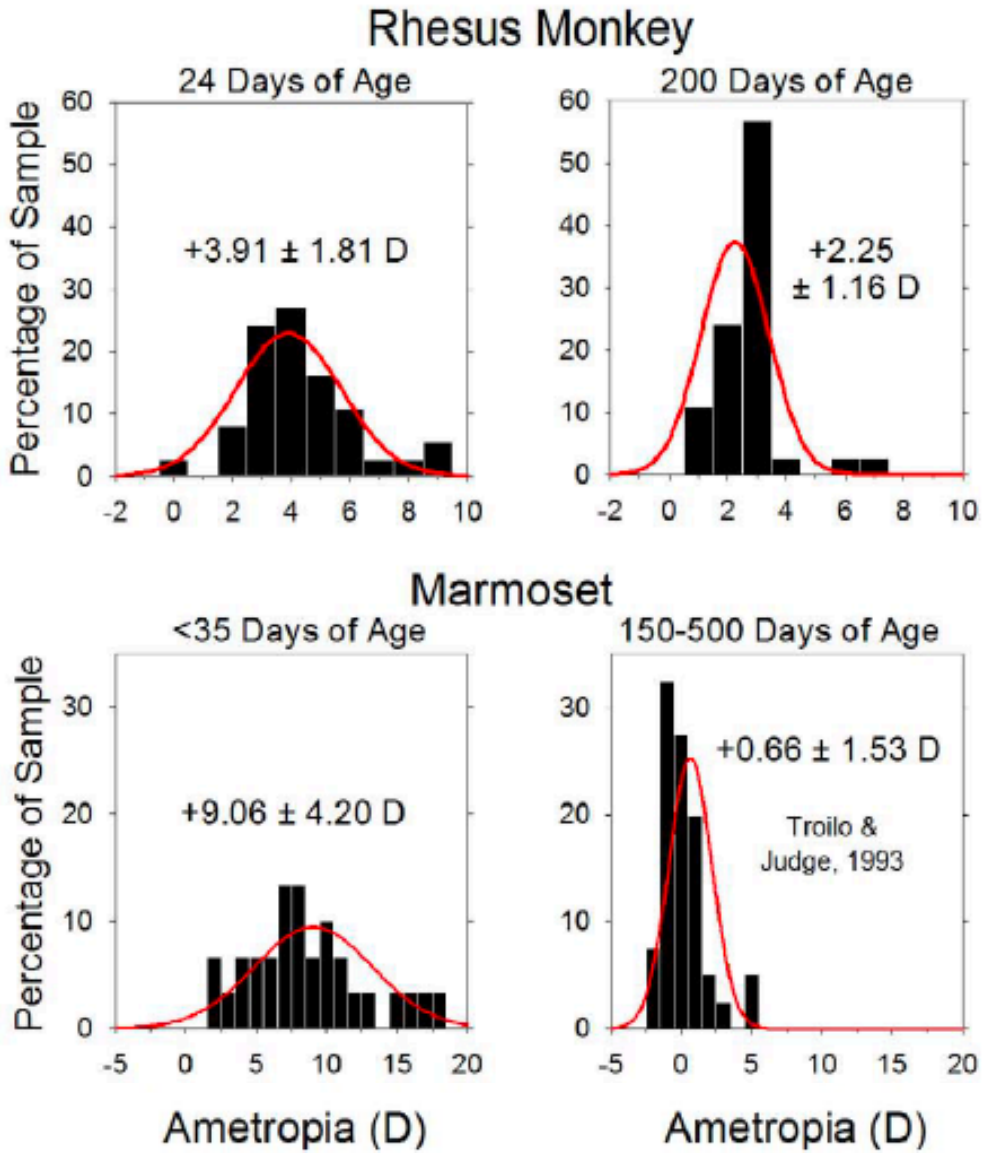
Emmetropization in Animals





Emmetropization in Human Infants

Axial Growth and Changes in Lenticular and Corneal Power during Emmetropization in Infants

Donald O. Mutti,[1] G. Lynn Mitchell,[1] Lisa A. Jones,[1] Nina E. Friedman,[2] Sara L. Frane,[2] Wendy K. Lin,[2] Melvin L. Moeschberger,[3] and Karla Zadnik[1,3]

Purpose. To evaluate the contribution made by the ocular components to the emmetropization of spherical equivalent refractive error in human infants between 3 and 9 months of age.

Methods. Keratophakometry in two meridians was performed on 222 normal-birthweight infant subjects at 3 and 9 months of age. The spherical equivalent refractive error was measured by cycloplegic retinoscopy (cyclopentolate 1%). Anterior chamber depth, lens thickness, and vitreous chamber depth were measured by A-scan ultrasonography over the closed eyelid.

Results. Both the mean and SD for spherical equivalent refractive error decreased between 3 and 9 months of age (+2.16 ± 1.30 D at 3 months; +1.36 ± 1.06 D at 9 months; $P < 0.0001$, for the change in both mean and SD). Average ocular component change was characterized by increases in axial length, thinning, and flattening of the crystalline lens, increases in lens equivalent refractive index, and decreases in lens and corneal power. Initial refractive error was associated in a nonlinear manner with the change in refractive error ($R^2 = 0.41$; $P < 0.0001$) and with axial growth ($R^2 = 0.082$; $P = 0.0005$). Reduction in hyperopia correlated significantly with increases in axial length ($R^2 = 0.16$; $P < 0.0001$), but not with changes in corneal and lenticular power. Decreases in lenticular and corneal power were associated with axial elongation ($R^2 = 0.40$, $R^2 = 0.12$, respectively; both $P < 0.0001$).

Conclusions. Modulation in the amount of axial growth in relation to initial refractive error appeared to be the most influential factor in emmetropization of spherical equivalent refractive error. The associations between initial refractive error, subsequent axial growth, and change in refractive error were consistent with a visual basis for emmetropization. The cornea and crystalline lens lost substantial amounts of dioptric power in this phase of growth, but neither appeared to play a significant role in emmetropization. (*Invest Ophthalmol Vis Sci.* 2005;46:3074–3080) DOI:10.1167/iovs.04-1040

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Refractive error represents a mismatch between the eye's focal length and its axial length. Infant eyes undergo a process of emmetropization whereby both the average amount and the variance in the distribution of refractive errors are reduced. The precise mechanisms coordinating the optical and structural development of the eye are not completely understood. Results of animal experiments suggest that this process is guided by feedback from visual input.[1–5] The current model of human emmetropization from animal studies is that hyperopic defocus caused by an infant's hyperopic refractive error modulates the growth of the eye to reduce refractive error.[4,6]

Also poorly understood is the role played in emmetropization by the ocular components, such as the cornea or crystalline lens. The visual feedback model of emmetropization holds that defocus modulates the axial growth of the eye to reduce refractive error. Visual guidance of ocular growth might therefore be termed an "active" mechanism. In contrast, the cornea and lens could be important contributors to emmetropization if the eye grew at a certain random rate, but changes in the power of the cornea and crystalline lens occur in appropriate proportion to the initial refractive error. The crystalline lens loses substantial amounts of power during infancy.[7] If the crystalline lens and cornea lost relatively small amounts of power in comparison with the dioptric effect of axial growth, then highly hyperopic infants would lose hyperopia quickly and move rapidly toward emmetropia. Infants with little initial hyperopia could move more slowly toward emmetropia if lenticular or corneal power decreased by a large number of diopters per millimeter of axial growth. Emmetropization could therefore result from the loss of anterior segment power at different rates, depending on initial refractive error. Variation in the contribution of the equatorial gradient index profile to power changes during axial growth has been proposed as a source of graded changes in lenticular power.[7] Emmetropization resulting from this type of optical coordination between lenticular power change, corneal power change, and initial refractive error might therefore be termed "passive," because visual guidance of axial growth would not be necessary. This particular type of passive emmetropization would be distinct from a previously described passive mechanism for emmetropization due to scaling—the decrease in refractive error as a proportion of the decreasing power of the eye.[8]

The purpose of the Berkeley Infant Biometry Study (BIBS) is to document the development of the major optical ocular components during emmetropization. The purpose of this report is to examine how the major ocular components—namely, axial length, corneal power, and crystalline lens power—change to produce emmetropia and whether that process operates more by an active or passive process. Support for an active mechanism would come from evidence of emmetropization through modulation of axial growth, analogous to that seen in animal experimentation, whereas a passive mechanism would be inferred from emmetropization occurring primarily through modulation of corneal and lenticular power.

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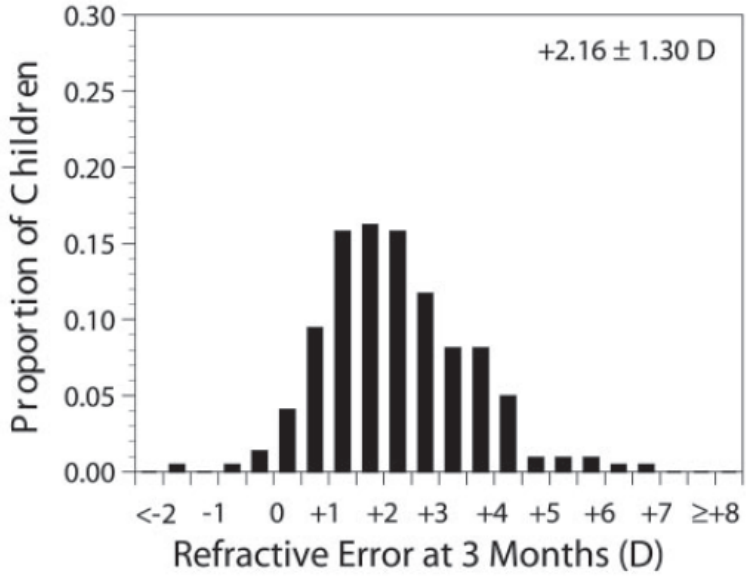

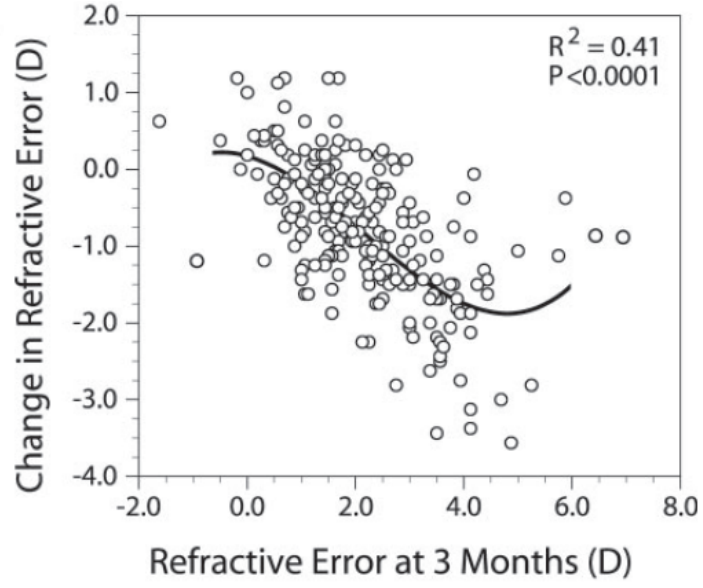

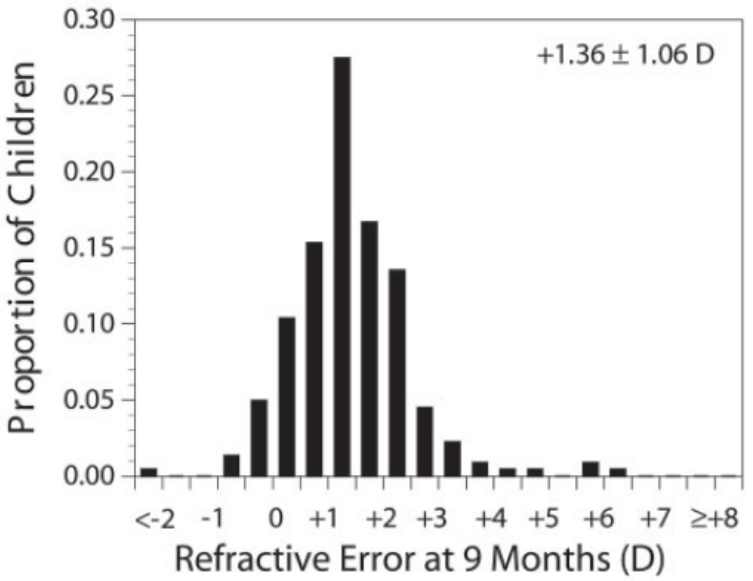

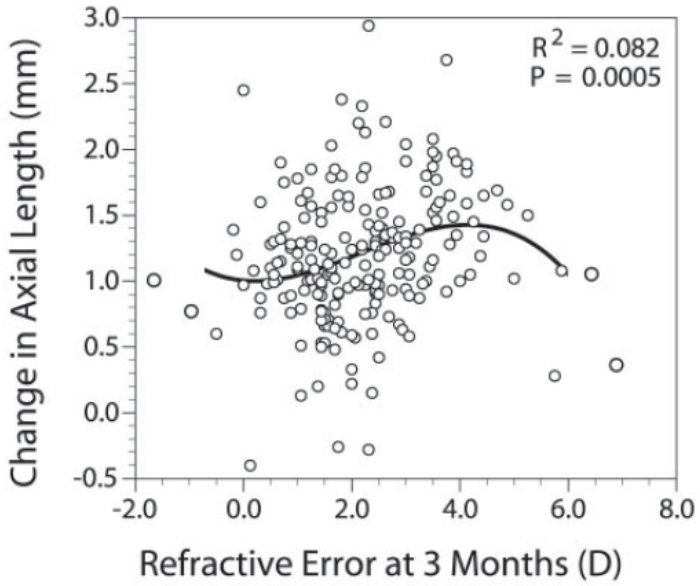

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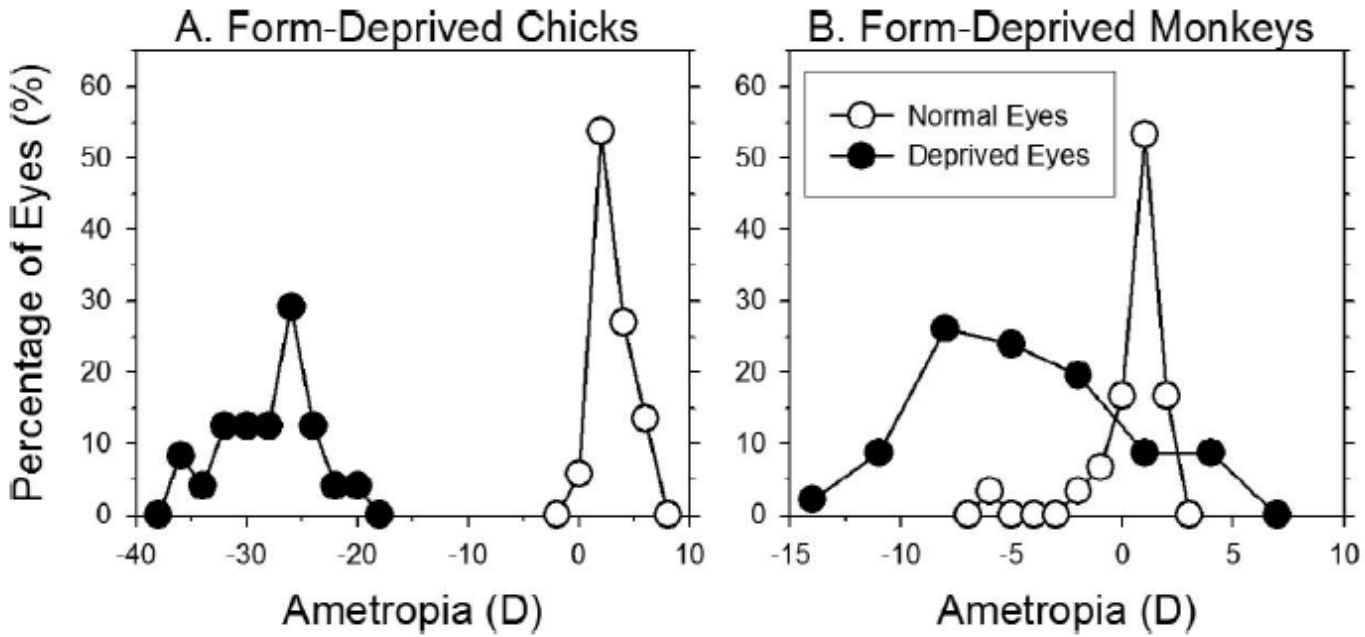

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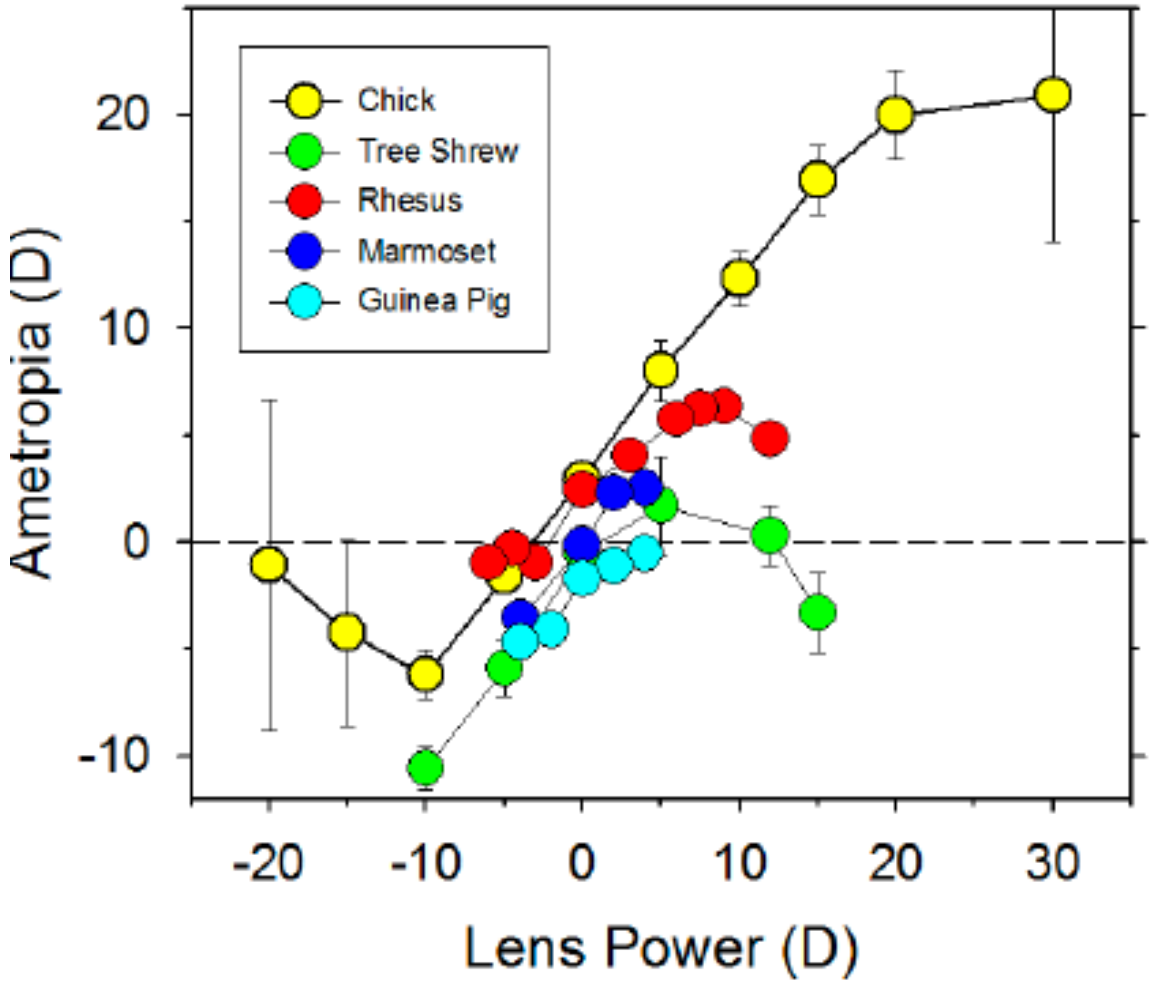

Competing Peripheral vs. Central Signals

1. Peripheral hyperopia imposed in both eyes of 8 infant monkeys by –3 D spectacle lenses with 6 mm circular apertures
   - Unrestricted field of view = 10 deg
2. Ablated central 10 deg of retina of one eye of 6 infant monkeys
   - Peripheral hyperopia imposed by full aperture –3 D lenses

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Relative peripheral hyperopic defocus alters central refractive development in infant monkeys

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Emmetropization

ABSTRACT

Understanding the role of peripheral defocus on central refractive development is critical because refractive errors can vary significantly with eccentricity and peripheral refractions have been implicated in the genesis of central refractive errors in humans. Two rearing strategies were used to determine whether peripheral hyperopia alters central refractive development in rhesus monkeys. In intact eyes, lens-induced relative peripheral hyperopia produced central axial myopia. Moreover, eliminating the fovea by laser photoablation did not prevent compensating myopic changes in response to optically imposed hyperopia. These results show that peripheral refractive errors can have a substantial impact on central refractive development in primates.

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1. Introduction

Visual feedback associated with the eye's effective refractive state regulates emmetropization (Norton, 1999; Smith, 1998; Wallman & Winawer, 2004). In many species, including primates, the effects of vision on refractive development appear to be mediated primarily by local retinal mechanisms that integrate visual signals in a spatially restricted manner and that exert their influence selectively on the subjacent sclera (Diether & Schaeffel, 1997; Hodos & Kuenzel, 1984; Siegwart & Norton, 1993; Smith et al., 2009; Wallman, Gottlieb, Rajaram, & Fugate-Wentzek, 1987). Although it has generally been assumed that visual signals from the fovea or central retina dominate refractive development in primates (Stone & Flitcroft, 2004), several lines of evidence indicate that peripheral visual signals can have a substantial effect on axial growth and central refractive development.

Clinical observations provide support for the idea that visual signals from the peripheral retina can have a significant impact on emmetropization at the fovea and possibly the genesis of common refractive errors. For example, patients who have natural or treatment-induced peripheral retinal abnormalities frequently exhibit larger than normal ranges of central refractive errors and, on average, larger central refractive errors (Connolly et al., 2002; Knight-Nanan & O'Keefe, 1996; Nathan, Kiely, Crewther, & Crewther, 1985; Nissenkorn, Yassur, Mashkowski, Sherf, & Ben-Sira, 1983; Sieving & Fishman, 1978). It is possible that these central refractive errors come about because the treatment and/or disease processes interfere with the mechanisms responsible for emmetropization. In this respect, children who have conditions or diseases that primarily affect the peripheral retina usually exhibit larger central refractive errors than children with eye diseases that primarily affect central vision (Nathan et al., 1985).

The most direct evidence that peripheral vision can influence central refractive development come from animal experiments in which the visual signals from the fovea were eliminated or from experiments in which peripheral vision was selectively manipulated. For example, laser photoablation of the fovea in infant monkeys does not (1) interfere with emmetropization in animals reared with unrestricted vision, (2) prevent form-deprivation from producing central axial myopia, or (3) alter the recovery from experimentally induced refractive errors (Smith, Kee, Ramamirtham, Qiao-Grider, & Hung, 2005; Smith et al., 2007). These results demonstrate that visual signals from the fovea are not essential for many vision-dependent changes in refractive development and that visual signals from the periphery, in isolation, can be used to determine the direction of axial growth required to eliminate central refractive errors and to determine when ocular growth has eliminated that refractive error, i.e., when emmetropia has been established. Moreover, when experimental manipulations impose conflicting visual signals between the central and peripheral retina, peripheral vision can dominate overall ocular growth. For example, chicks and monkeys that were reared with diffuser lenses that selectively deprived the peripheral retina of form vision, but allowed unrestricted central vision, typically developed central axial

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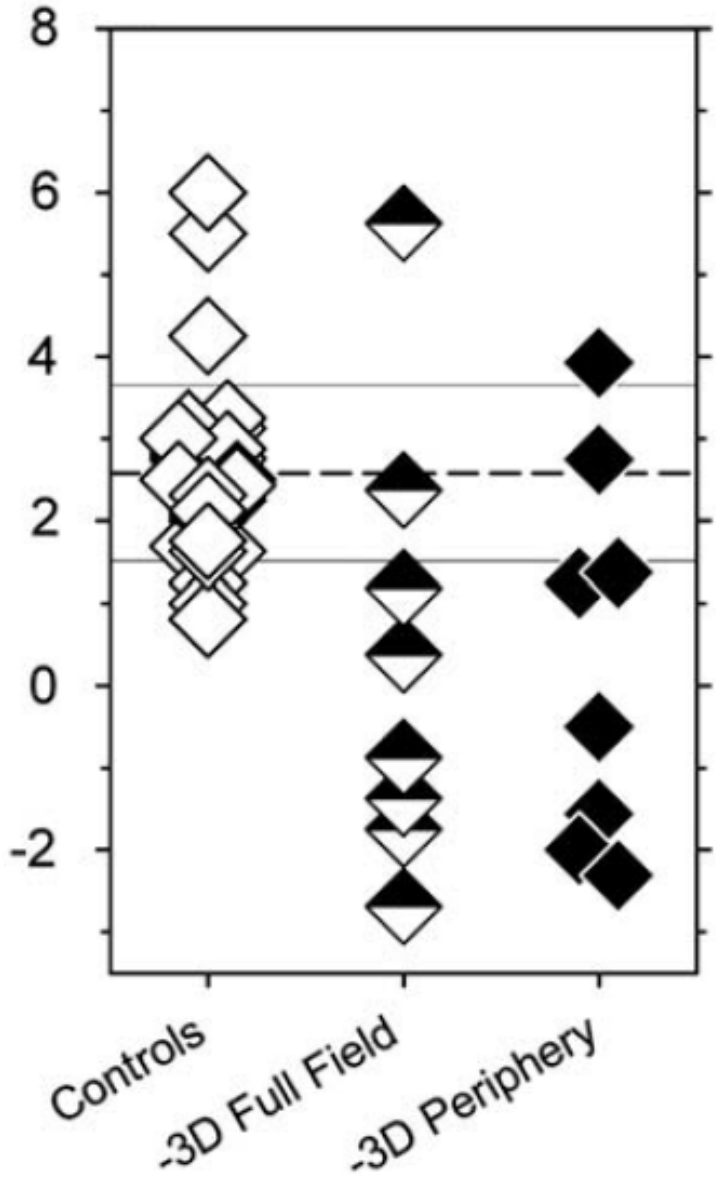
Competing Peripheral vs. Central Signals

1. Peripheral hyperopia imposed in both eyes of 8 infant monkeys by –3 D spectacle lenses with 6 mm circular apertures
   - Unrestricted field of view = 10 deg
2. Ablated central 10 deg of retina of one eye of 6 infant monkeys
   - Peripheral hyperopia imposed by full aperture –3 D lenses



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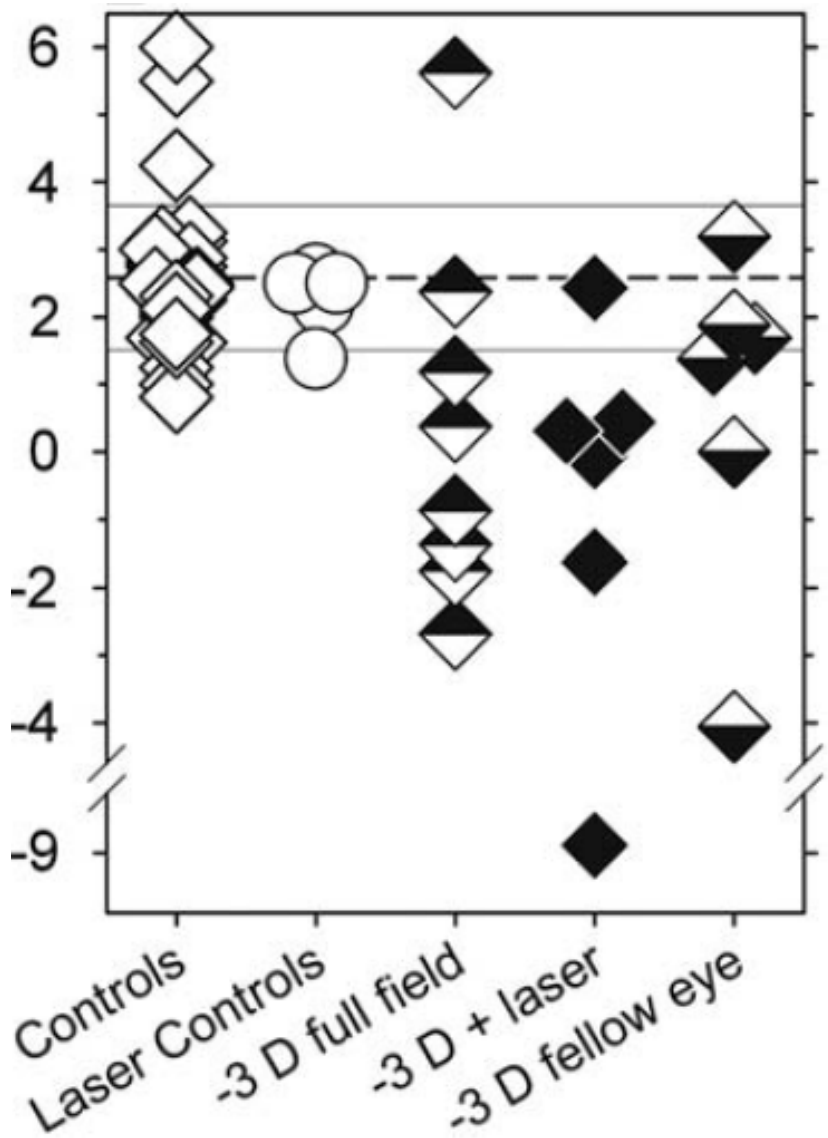


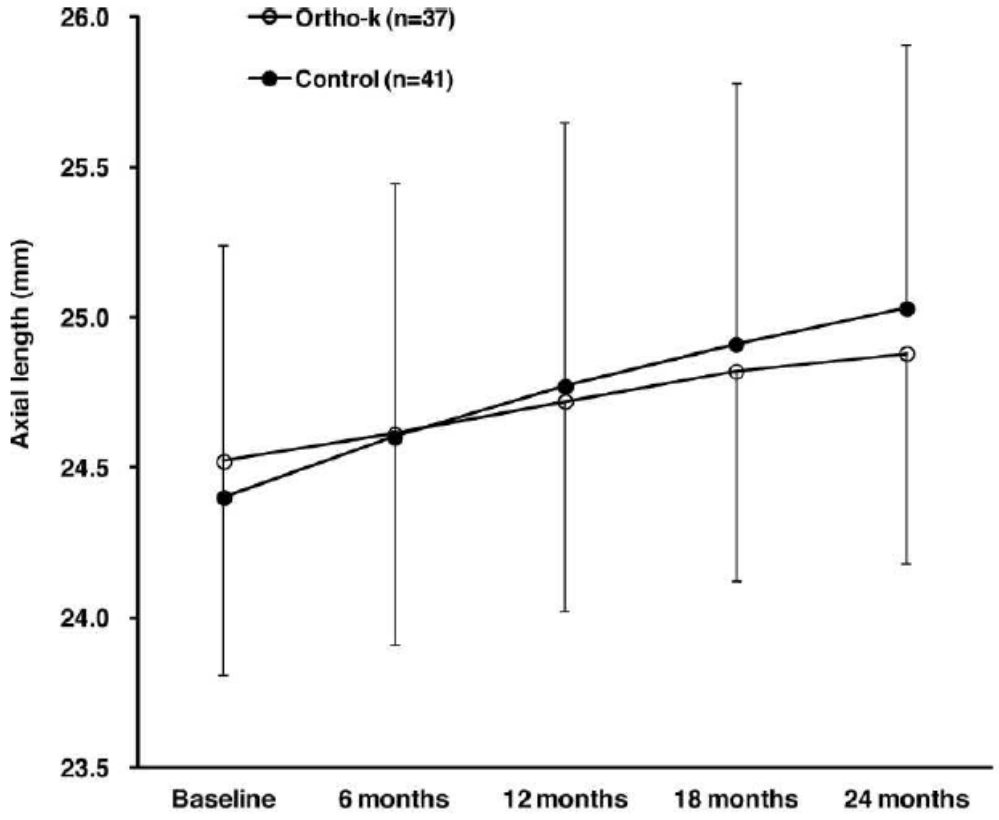
Supports Use of Peripheral Positive Defocus

Overnight Orthokeratology

Clinical Trials

Retardation of Myopia in Orthokeratology (ROMIO) Study: A 2-Year Randomized Clinical Trial

Pauline Cho and Sin-Wan Cheung

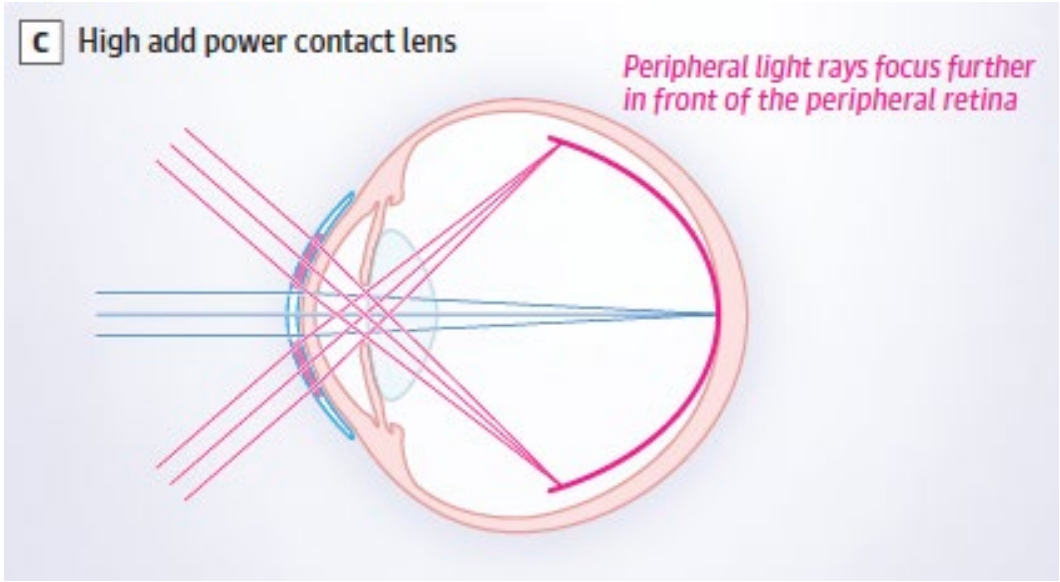


Distance-Center Multifocal Contact Lenses

JAMA | Original Investigation

Effect of High Add Power, Medium Add Power, or Single-Vision Contact Lenses on Myopia Progression in Children
The BLINK Randomized Clinical Trial

Jeffrey J. Walline, OD, PhD; Maria K. Walker, OD, PhD; Donald O. Mutti, OD, PhD; Lisa A. Jones-Jordan, PhD; Loraine T. Sinnott, PhD; Amber Gaume Giannoni, OD; Katherine M. Bickle, OD, MS; Krystal L. Schulle, OD; Alex Nixon, OD, MS; Gilbert E. Pierce, OD, PhD; David A. Berntsen, OD, PhD; for the BLINK Study Group



Refractive Development with Dual-Focus Lenses

- Macaques reared with binocular dual-focus spectacles
- Lenses had central 2-mm clear zones and concentric annular zones with alternating powers:
  - +3 and 0 D (+3 D/0) or
  - –3 and 0 D (–3 D/0)
- Relative widths of powered and plano zones varied from 50:50 to 18:82
- Comparison data from monkeys reared with binocular full-field single-vision lenses (FF +3 D, FF –3 D, n = 10) and 35 controls

Anatomy and Pathology/Oncology

The Effects of the Relative Strength of Simultaneous Competing Defocus Signals on Emmetropization in Infant Rhesus Monkeys

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Purpose. We investigated how the relative surface area devoted to the more positive-powered component in dual-focus lenses influences emmetropization in rhesus monkeys.

Methods. From 3 to 21 weeks of age, macaques were reared with binocular dual-focus spectacles. The treatment lenses had central 2-mm zones of zero-power and concentric annular zones that had alternating powers of either +3.0 diopters (D) and 0 D (+3 D/pL) or −3.0 D and 0 D (−3 D/pL). The relative widths of the powered and plano zones varied from 50:50 to 18:82 between treatment groups. Refractive status, corneal curvature, and axial dimensions were assessed biweekly throughout the lens-rearing period. Comparison data were obtained from monkeys reared with binocular full-field single-vision lenses (FF+3D, n = 6; FF−3D, n = 10) and from 35 normal controls.

Results. The median refractive errors for all of the +3 D/pL lens groups were similar to that for the FF+3D group (+4.63 D versus +4.31 D to +5.25 D; P = 0.18–0.96), but significantly more hyperopic than that for controls (+2.44 D; P = 0.0002–0.003). In the −3 D/pL monkeys, refractive development was dominated by the zero-powered portions of the treatment lenses; the −3 D/pL animals (+2.94 D to +3.13 D) were more hyperopic than the FF−3D monkeys (−0.78 D; P = 0.004–0.006), but similar to controls (+2.44 D; P = 0.14–0.22).

Conclusions. The results demonstrate that even when the more positive-powered zones make up only one-fifth of a dual-focus lens' surface area, refractive development is still dominated by relative myopic defocus. Overall, the results emphasize that myopic defocus distributed across the visual field evokes strong signals to slow eye growth in primates.

Keywords: emmetropization, hyperopia, myopia, Fresnel lens, refractive error, eye growth

Myopia has reached epidemic proportions in many parts of East Asia[1–5] and it appears that the prevalence of myopia is rapidly increasing in the United States[6] and other non-Asian countries.[7–9] Moreover, in recent decades, the onset of myopia has shifted to younger ages,[10] which has ultimately led to an increased prevalence of high degrees of myopia.[1,11] This increase in highly myopic eyes, which has been dramatic in many countries,[1,11,12] is a significant economic burden[13–15] and a major public health concern because of the associated sight-threatening conditions of myopic macular degeneration, retinal detachment, cataract, and glaucoma.[16–20] Unfortunately, it has been estimated that the retinal complications due to myopia will increase dramatically over the next few decades as the prevalence and degree of myopia continues to increase and as the population around the world ages.[9,21] In this respect, treatment strategies that could effectively reduce myopia progression and/or delay the onset of myopia could have substantial therapeutic benefit.[22–24]

Fortunately, research conducted on laboratory animals has provided the scientific foundation for potential optical treatment strategies to reduce the burden of myopia. Specifically, in a wide variety of animal species it has been demonstrated that ocular growth and refractive development are regulated by visual feedback associated with the eye's effective refractive state, in essence optical defocus.[25–32] Most importantly, optically imposed myopic defocus has been shown to consistently slow ocular growth and produce hyperopic shifts during emmetropization in young animals.[32–35] This pattern of results indicates that optical correction strategies that produce myopic defocus in children should be effective in reducing myopia progression. In this respect, recent clinical trials have shown that a variety of lens designs that correct distance vision while simultaneously imposing relative myopic defocus over a large part of the retina[22] can produce clinically meaningful reductions in myopia progression in children.[36–41]

In particular, traditional multifocal spectacles[42–44] and aspheric spectacle lenses that were designed to produce relative myopic defocus primarily in the periphery[36] have been shown to reduce myopia progression in children, with Franklin-style bifocals, which typically impose myopic defocus over a

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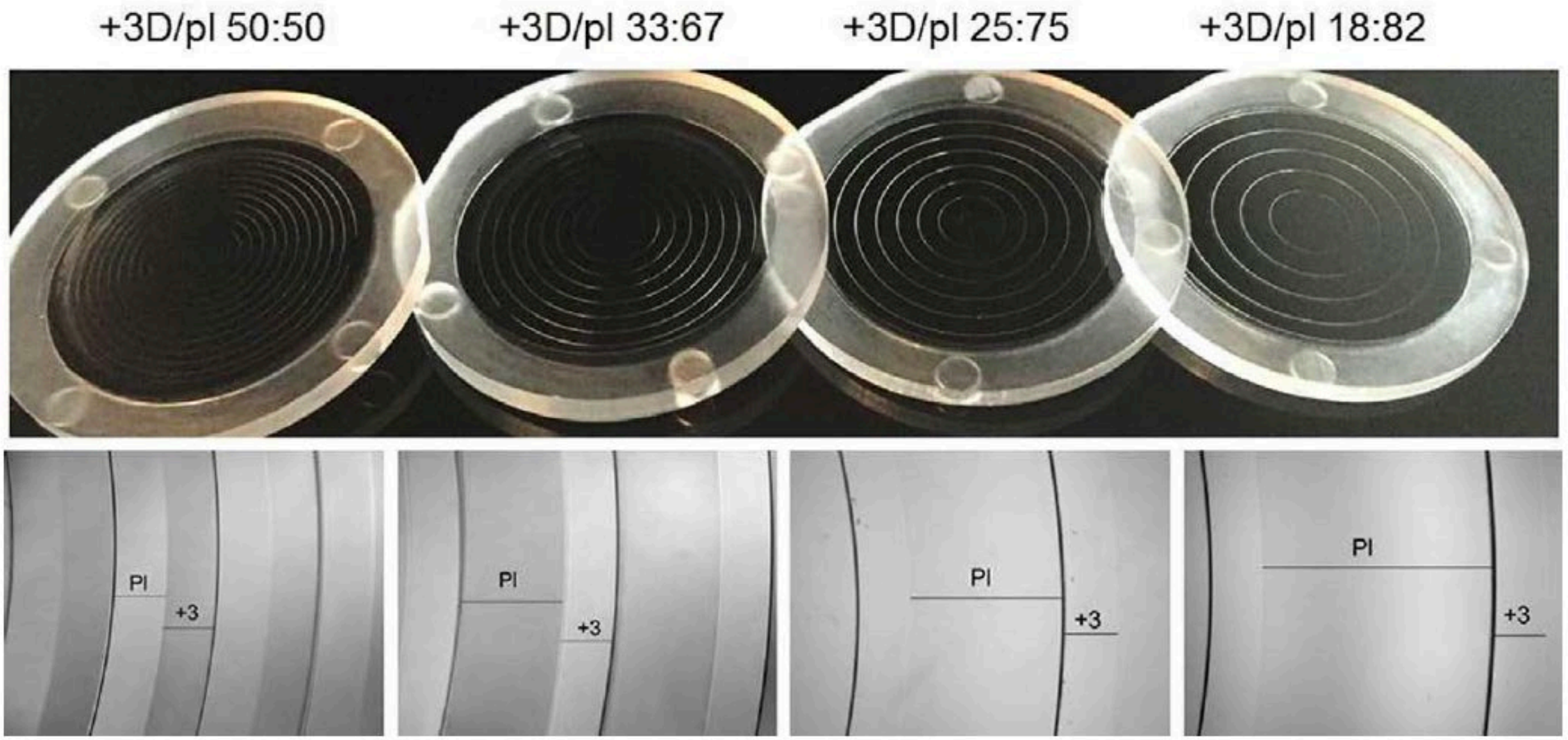
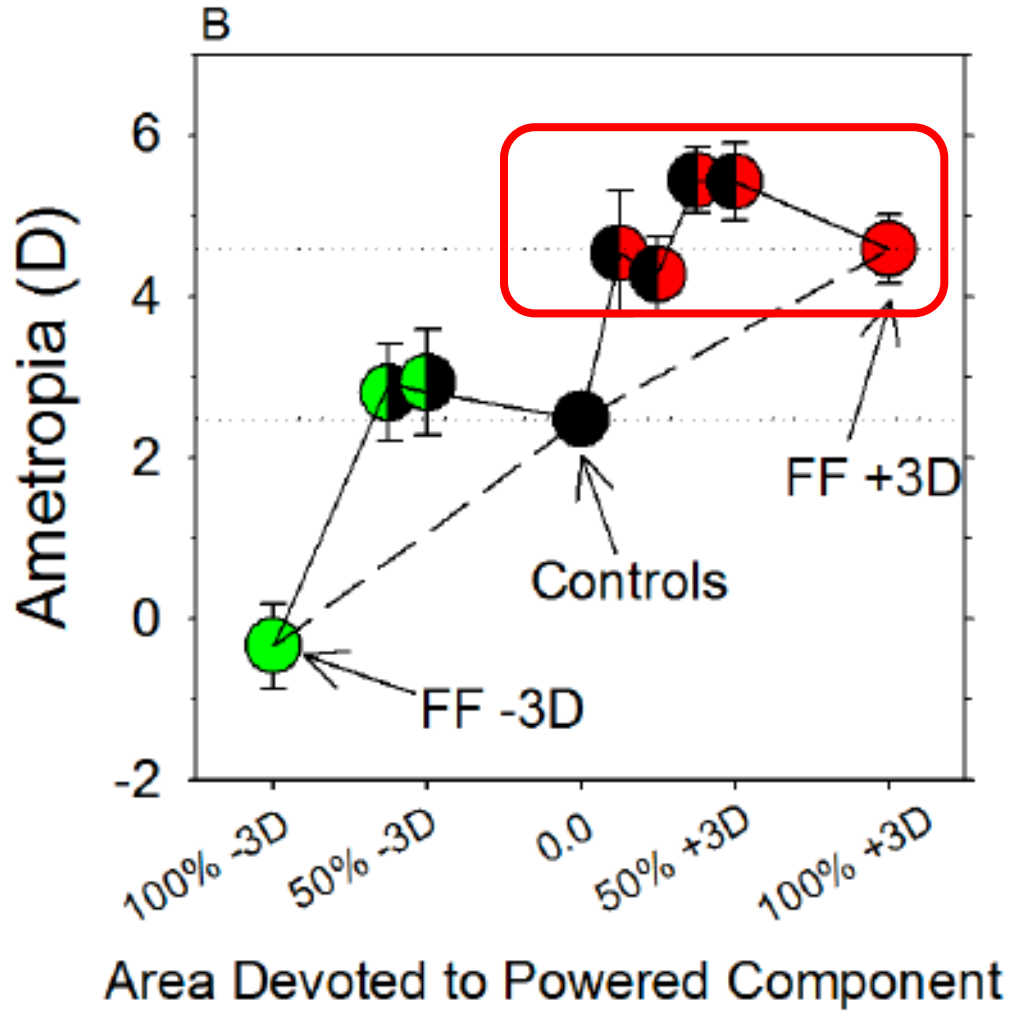
Refractive Development with Dual-Focus Lenses



Refractive Development with Dual-Focus Lenses

- Refractive errors for +3 D/0 group similar to FF +3 D group
- But more hyperopic than controls
- Refractive errors for –3 D/0 group, similar to controls
- But less myopic than FF –3D group



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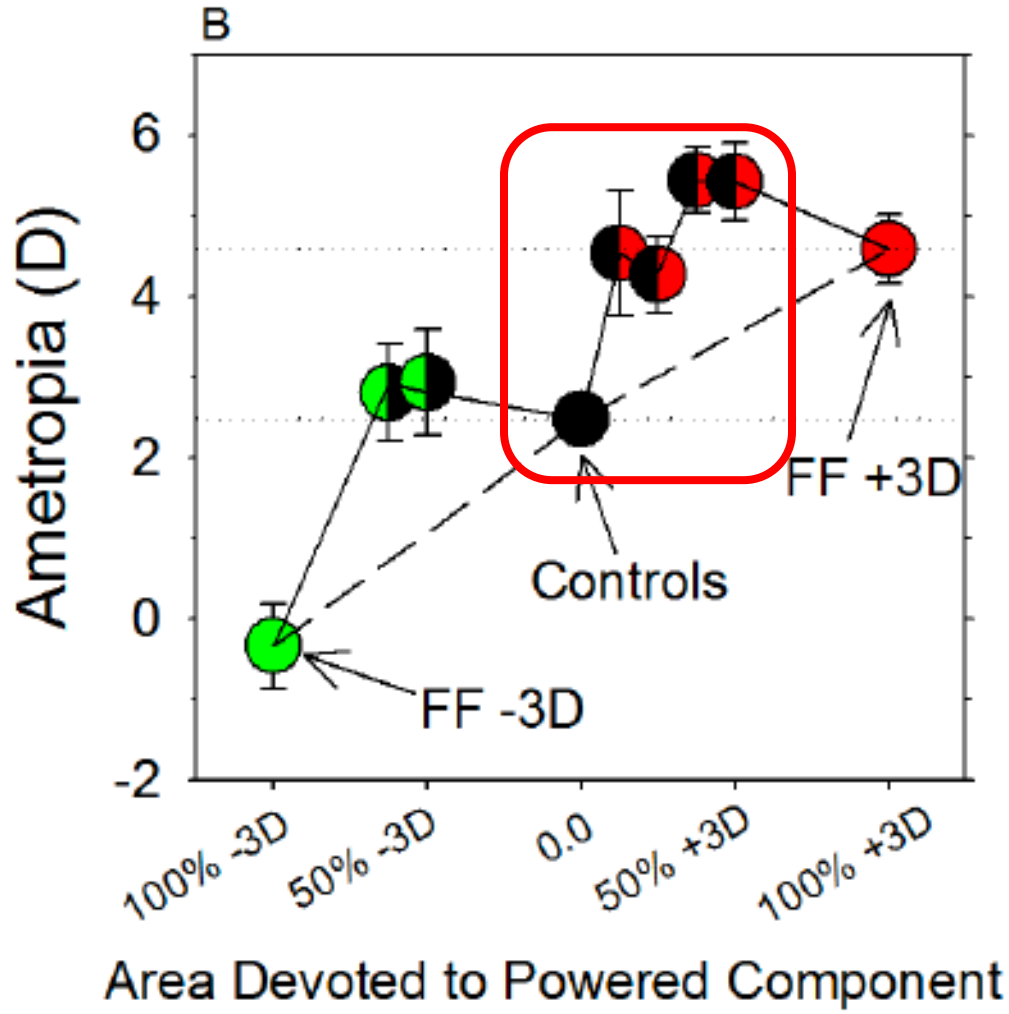

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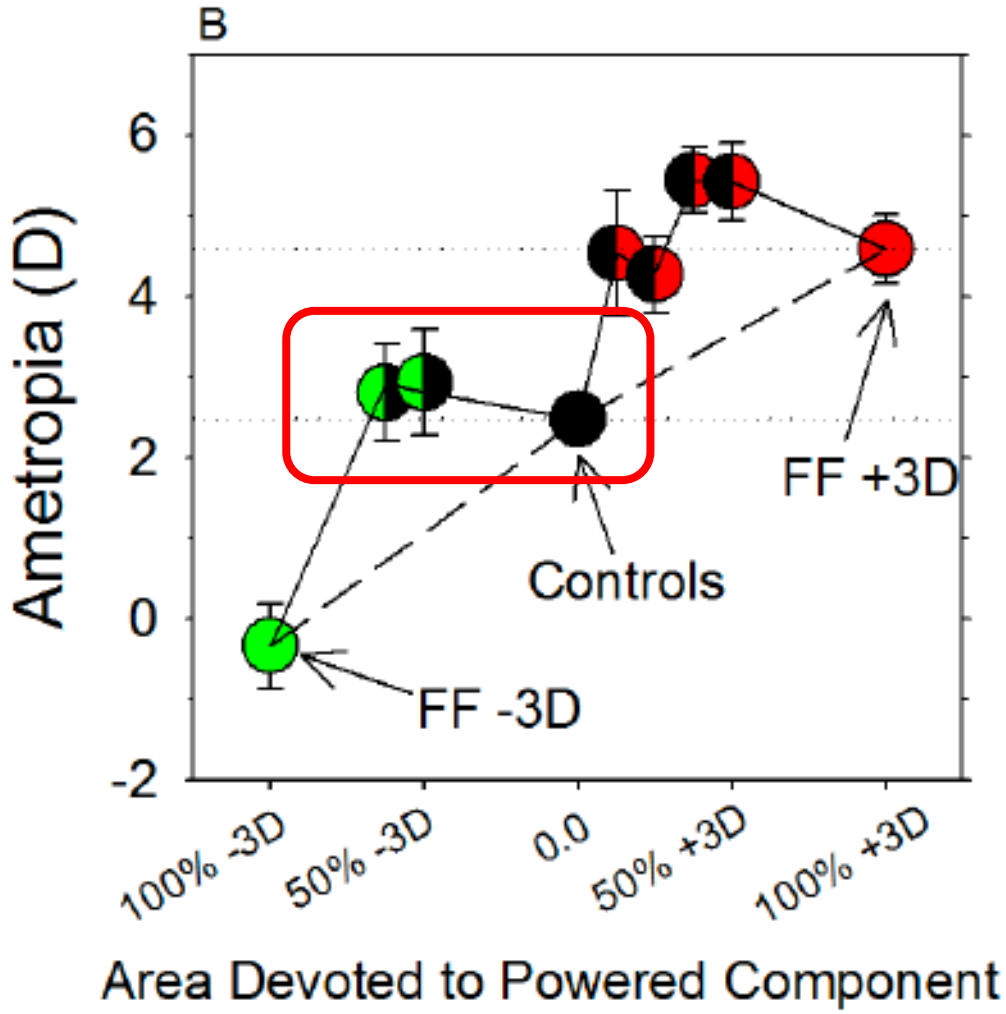

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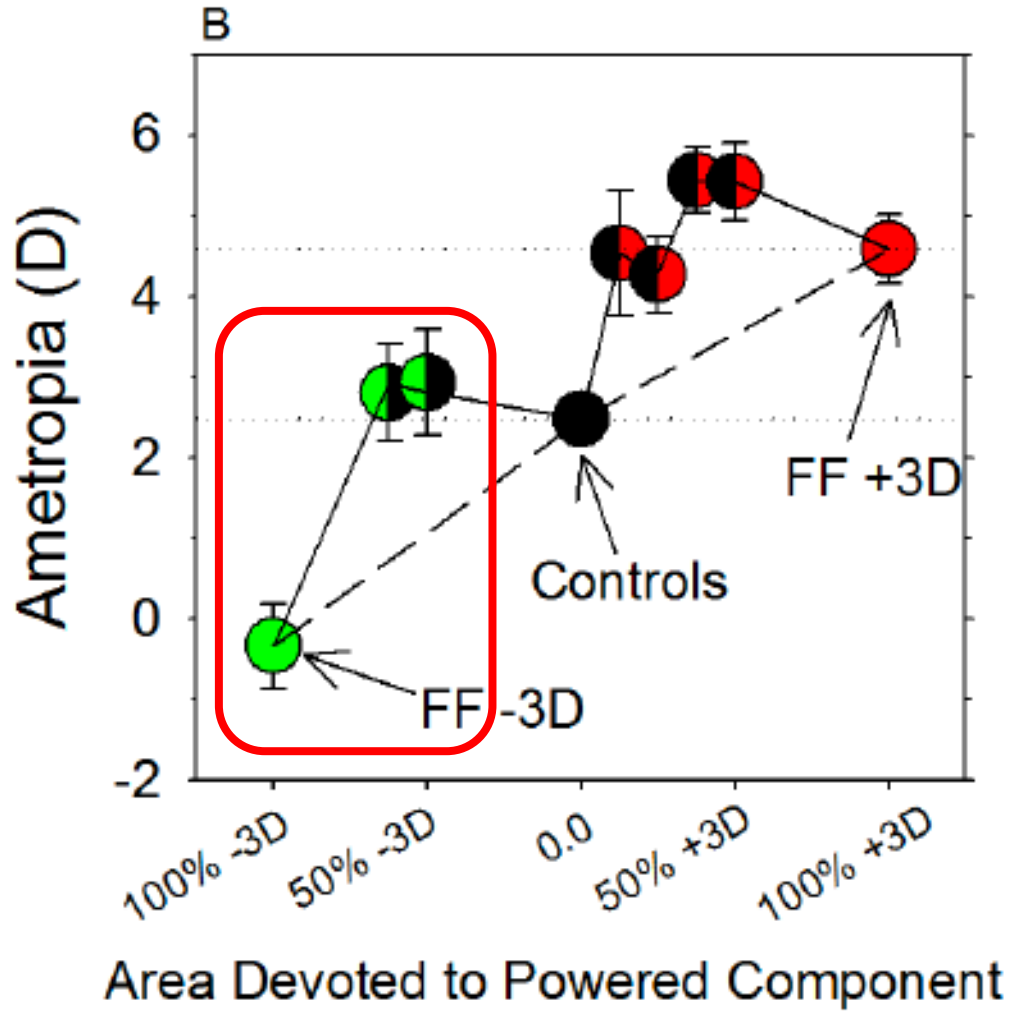
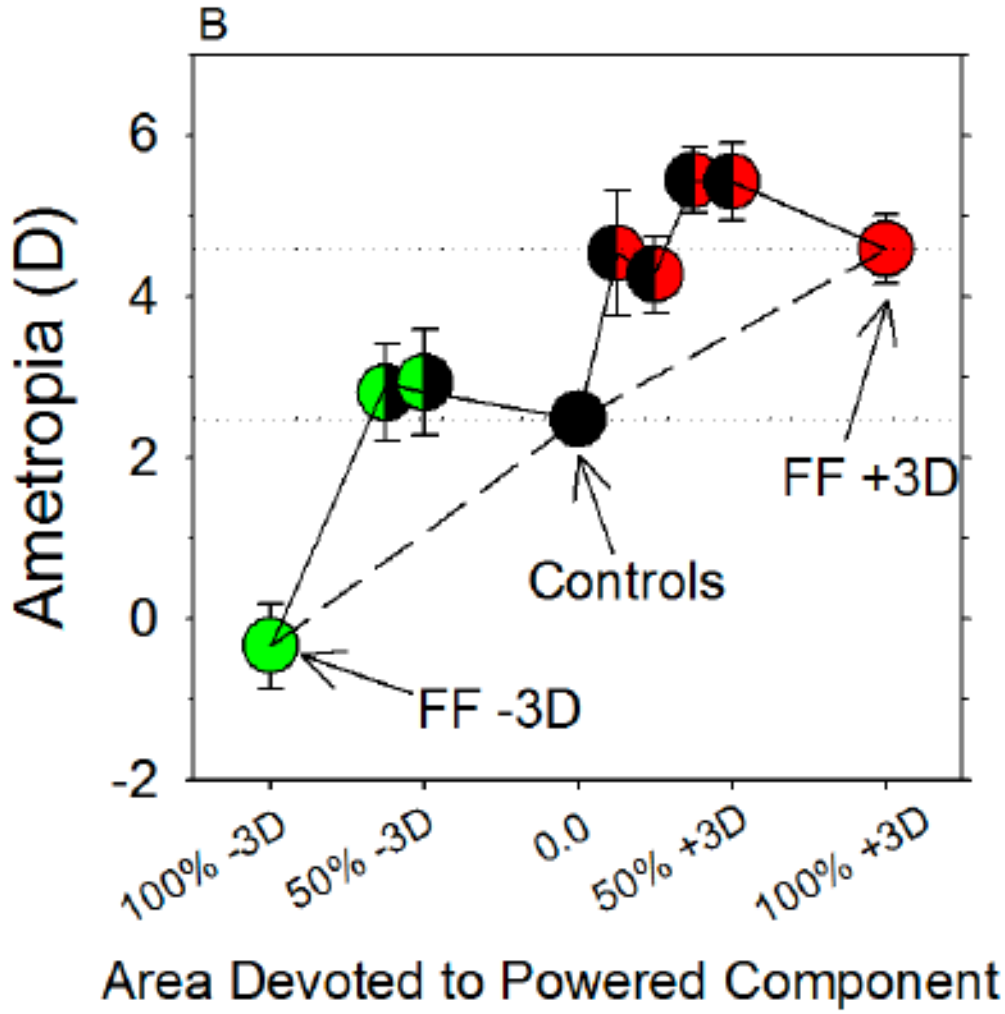


Refractive Development with Dual-Focus Lenses

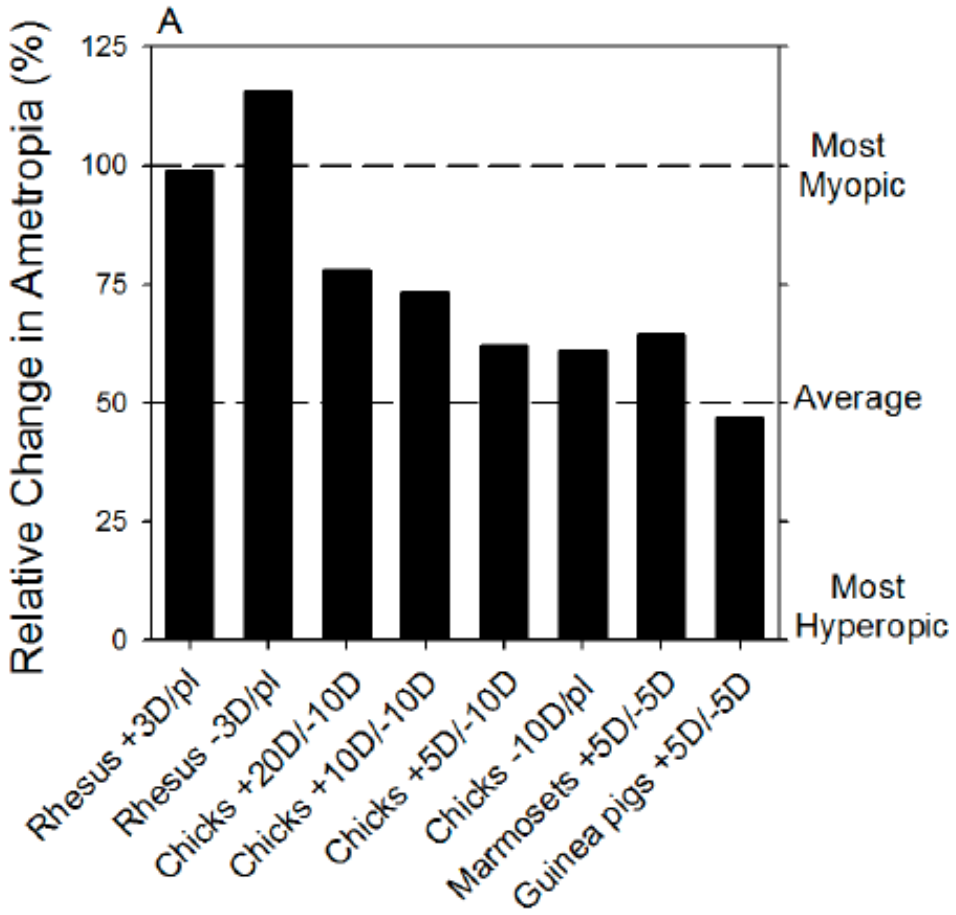
- In monkey eyes, refractive development driven by more positive area of lens



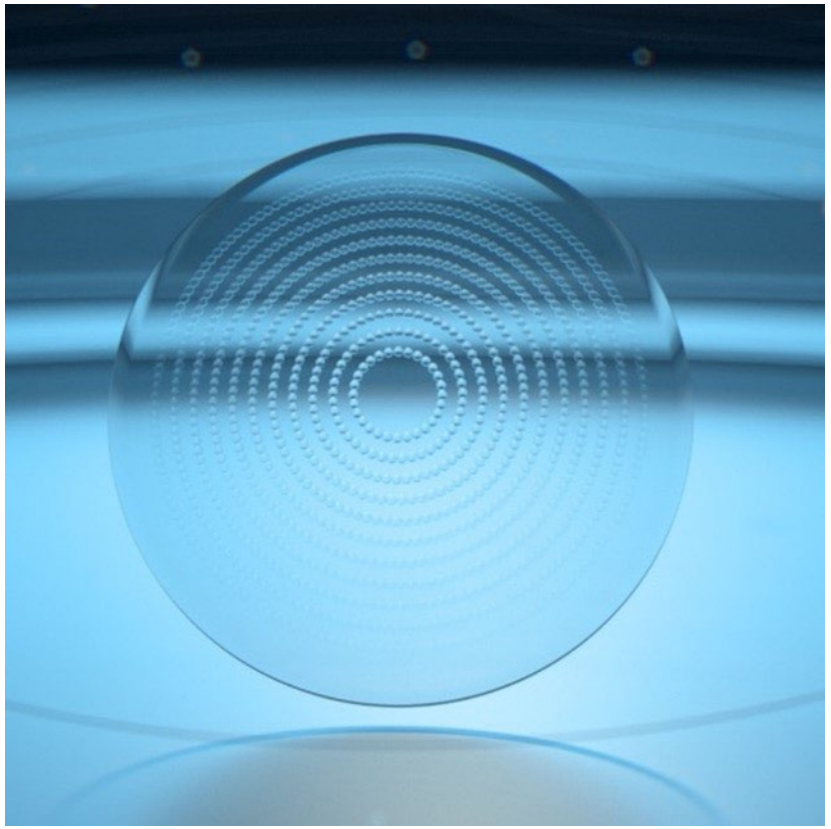
Refractive Development with Dual-Focus Lenses

- In monkey eyes, refractive development driven by more positive area of lens

- In other animal models, refractive development driven by average power of lens



Supports Use of Dual-Focus with Plus Power

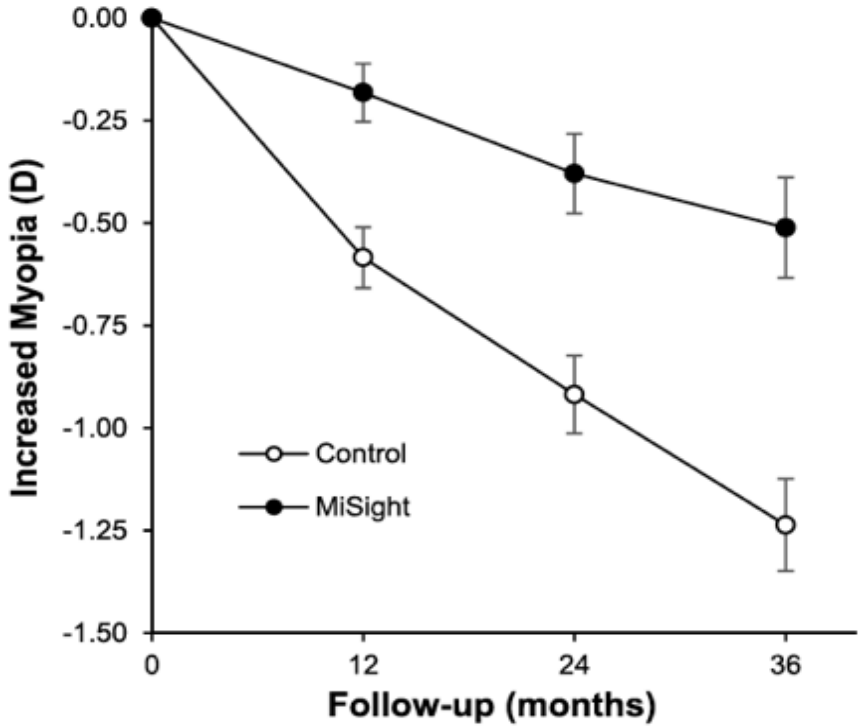


Supports Use of Dual-Focus with Plus Power

CLINICAL TRIAL

A 3-Year Randomized Clinical Trial of MiSight Lenses for Myopia Control

Paul Chamberlain, BSc,[1]* Sofia C. Peixoto-de-Matos, MSc,[2] Nicola S. Logan, PhD,[3] Cheryl Ngo, MBBS, MMed,[4] Deborah Jones, BSc, FAAO,[5] and Graeme Young, PhD, FAAO[6]

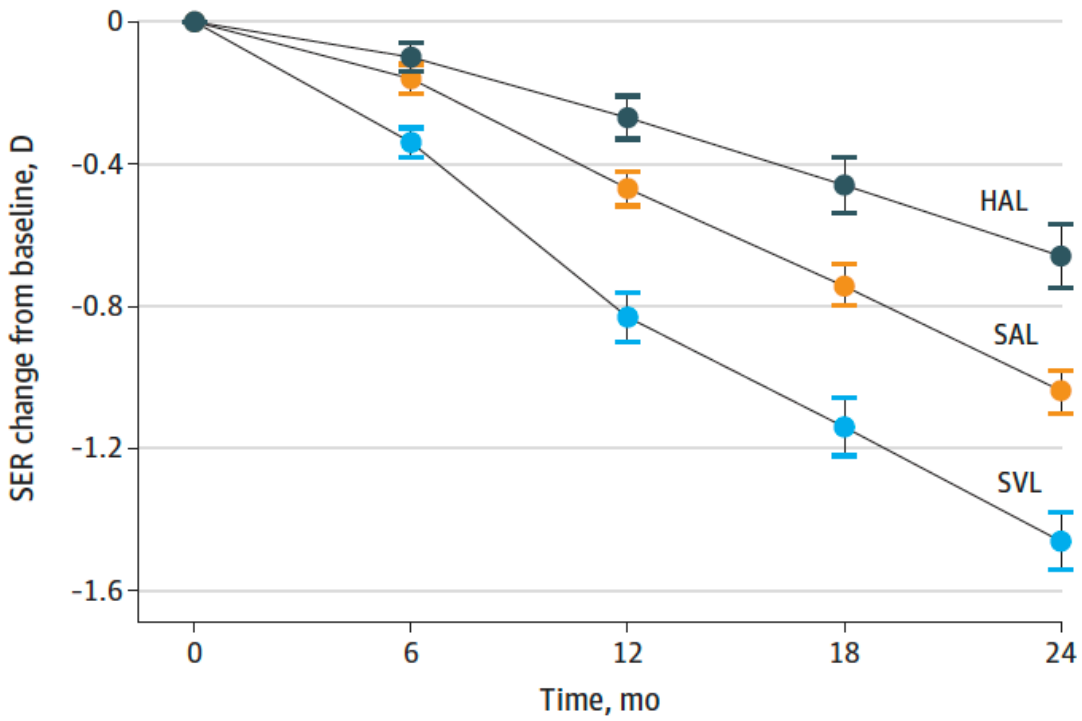


JAMA Ophthalmology | Original Investigation

Spectacle Lenses With Aspherical Lenslets for Myopia Control vs Single-Vision Spectacle Lenses

A Randomized Clinical Trial

Jinhua Bao, PhD; Yingying Huang, MD; Xue Li, PhD; Adeline Yang, MSc; Fengchao Zhou, BSc; Junqian Wu, BSc; Chu Wang, BSc; Yuhao Li, BSc; Ee Woon Lim, BSc; Daniel P. Spiegel, PhD; Björn Drobe, PhD; Hao Chen, MD, OD



Zadnik and Mutti (1995)

- Critical review of how animal myopia data relate to human condition
- Concerns about application of animal models of myopia to etiology of human juvenile onset myopia including:
  1. No deprivation of form vision in environment of school-aged child as severe as that required to induce myopia in animals
  2. Sensitive period for deprivation myopia in animals appears to be too early to account for human juvenile onset myopia
  3. Studies in chicken using spectacle lenses to create dioptric blur involve choroidal thickness modulation that has no human analog

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How Applicable are Animal Myopia Models to Human Juvenile Onset Myopia?

KARLA ZADNIK,* DONALD O. MUTTI*

Received 2 February 1994; in revised form 27 April 1994

Investigations into the plasticity of eye growth and refractive error development have significantly expanded our knowledge of animal models of myopia in the last 15 yr. The applicability of this information is as yet undetermined, but hopefully this information will be useful in learning more about human myopia. This paper presents a critical review of the animal myopia literature as those data relate to the human condition. Differences between the chicken, tree shrew, and primate animal models of myopia are outlined, and the various experimental paradigms used to investigate refractive error development and ocular growth in the chicken are compared. Specific arguments against the application of animal models of myopia to the etiology of human juvenile onset myopia include the following: (1) there is no deprivation of form vision in the environment of the school-aged child as severe as that required to induce myopia in animals; (2) the sensitive period for deprivation myopia in animals appears to be too early to account for human juvenile onset myopia; and (3) studies in the chicken using spectacle lenses to create dioptric blur involve a choroidal thickness modulation that has no human analog. Ultimately, the results of investigations into the cellular and biochemical modulation of eye growth in animals may be the most relevant to human myopia.

Myopia Deprivation Animal myopia Emmetropization Juvenile onset myopia Heredity Environment

Various aspects of human myopia have been studied for at least 80 yr (Steiger, 1913; Working Group on Myopia Prevalence and Progression, 1989). That research has produced evidence for a genetic-based etiology of myopia as well as for an environmental-based theory of myopia centered on accommodation and near work (McBrien & Barnes, 1989). It is as yet unknown what relative roles these "nature" and "nurture" components play in the onset and progression of human myopia, and there are many limitations in attempting to discern their relative roles through epidemiologic and clinical research. The fortuitous discovery that abnormal axial length elongation occurs in certain animal species during visual deprivation is largely responsible for the resurgence of research interest in myopia as experimental manipulation became possible in the study of the etiology of myopia (Wallman, Turkel & Trachtman, 1978; Wiesel & Raviola, 1977). The three species most often studied are: (1) the chicken, with visual deprivation resulting in marked elongation of the globe (Wallman & Adams, 1987), even when applied regionally (Wallman, Gottlieb, Rajaram & Fugate-Wentzek, 1987), (2) the tree shrew, with visual deprivation resulting in marked globe elongation and resultant myopia (McKanna & Casagrande, 1978; Marsh-Tootle & Norton, 1989), and (3) non-human primates, with disruption of normal visual input resulting in moderate axial growth and moderate myopia in some studies (Raviola & Wiesel, 1985; Tigges, Tigges, Fernandes, Eggers & Gammon, 1990; Wiesel & Raviola, 1977, 1979).

Troilo and Wallman (1991) have recently drawn parallels between three lines of evidence from animal experimentation, relating the plasticity of refraction and the influence of the environment in animals to an environmental etiology for human myopia: (1) refraction can be tuned to partially compensate for the defocus induced by spectacle lenses (Irving, Sivak & Callender, 1992; Schaeffel, Glasser & Howland, 1988; Schaeffel & Howland, 1991; Schaeffel, Troilo, Wallman & Howland, 1990; Wallman, Xu, Wildsoet, Krebs, Gottlieb, Marran & Nickla, 1992); (2) a physically near environment produces myopia and is presumed to be analogous to prolonged near work in humans (Miles & Wallman, 1990; Young, 1961); and (3) form deprivation produces myopia both in animal species (McKanna & Casagrande, 1978; Raviola & Wiesel, 1985; Wallman *et al.*, 1978) and in humans (Gee & Tabbara, 1988; Miller-Meeks, Bennett & Keech 1989; Rabin, Van Sluyters & Malach, 1981; Robb, 1977; von Noorden & Lewis, 1987).

Given the vast array of information on experimental myopia available from the animal models, especially the

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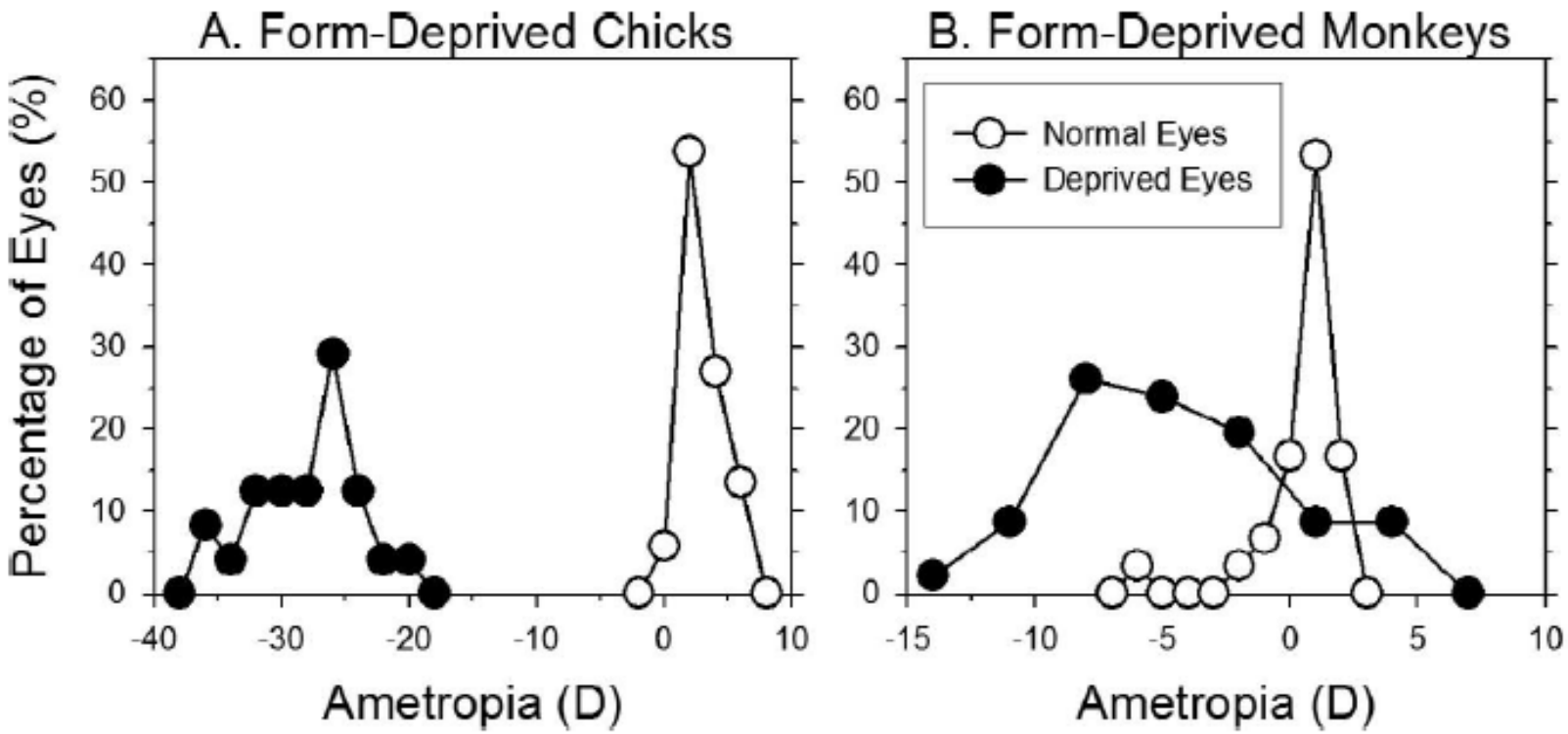
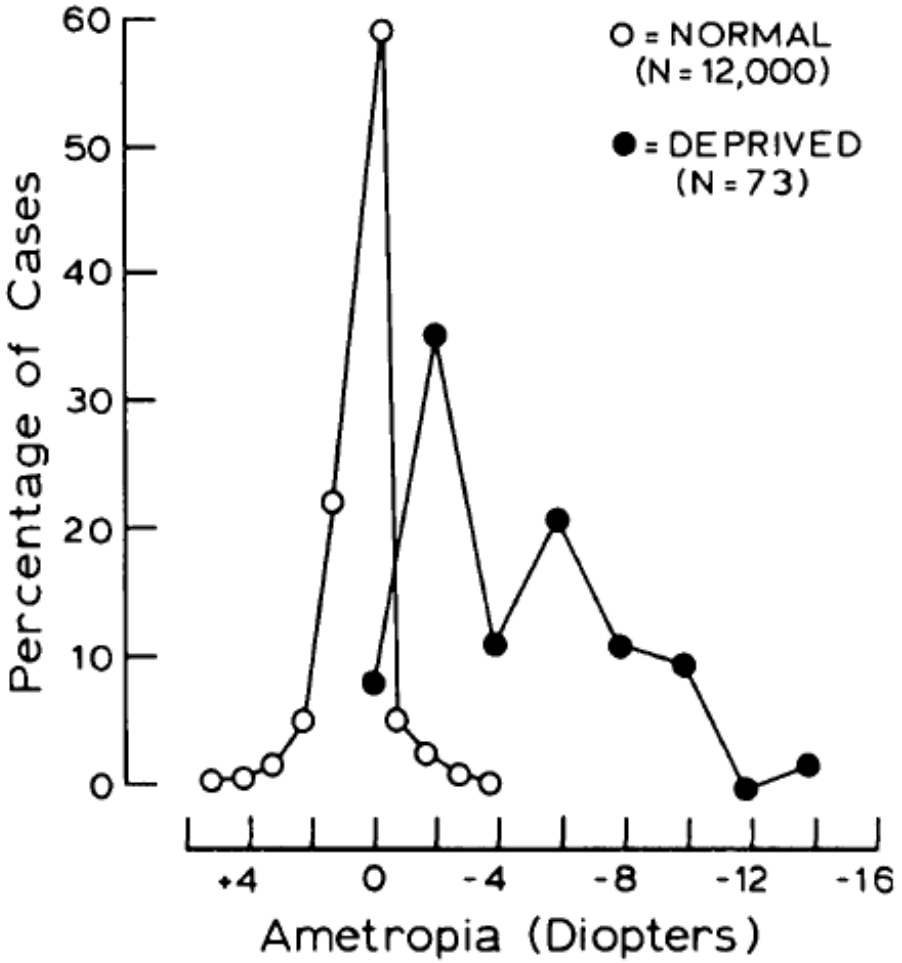
Form Deprivation Myopia



Emmetropization: a vision-dependent phenomenon

- Retrospective analysis of refractive error among humans subjected to various ocular anomalies that disrupt pattern vision
- Revealed significant degree of myopia
- Suggests that emmetropization is vision-dependent phenomenon

Emmetropization: a vision-dependent phenomenon. JEFF RABIN, RICHARD C. VAN SLUYTERS, AND RAFI MALACH.



Emmetropization and Retinal Disease

- Retrospective data on 256 children from low vision clinic
- Control data from 1,023 normally-sighted children
- Low vision children grouped according to disease classification and onset
- Overall inability to emmetropize and trend towards myopia
- Peripheral retinal diseases associated with more myopia
- If fovea primarily impaired, hyperopic trend

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Disease-Associated Visual Image Degradation and Spherical Refractive Errors in Children

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ABSTRACT

Retrospective clinical data from 496 eyes of 256 children attending a low vision clinic were analyzed to determine the relation between disease states which involve visual image degradation and refractive error. Refractive data from 1023 normal vision children were used as a control. The low vision children were grouped according to their disease classification and the acknowledged age-of-onset of their visual disability. It was found that there was an overall inability to emmetropize and a trend towards myopia. It was also observed that the diseases which led to myopia were associated with a peripheral or peripheral plus central impairment of vision and that those conditions in which foveal vision was primarily impaired showed a mild hypermetropic trend. Eyes in which the visual impairment was not congenital but occurred before the age of 3 years tended to develop hypermetropia. The deviation from emmetropia decreased with increasing age-of-onset of the visual impairment, as did the variation about the mean refraction. The plastic period for emmetropization is estimated to end at 8 to 9 years of age.

Key Words: image degradation, low vision, age-of-onset of disease, emmetropization, myopia, hypermetropia

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Ocular diseases which cause severe visual loss in early infancy have been noted to be associated with high refractive errors, and in particular, myopia. There have been numerous reports with respect to lid hemangioma,[1] retinitis pigmentosa,[2,3] ptosis,[4] retinopathy of prematurity,[5] cataract,[5,6] optic atrophy,[5] macular dystrophy,[5] rupture of Descemet's membrane,[7] and neonatal lid closure.[8] In addition, casual reference to the occurrence of myopia in association with some of the rarer forms of ocular disease afflicting infants has frequently been made in case reports.

In the present study, using retrospective human data retrieved from records of patients attending a children's low vision clinic, the differences between specific classes of disease and the refractive states are explored and these are related to the age-of-onset of visual deprivation.

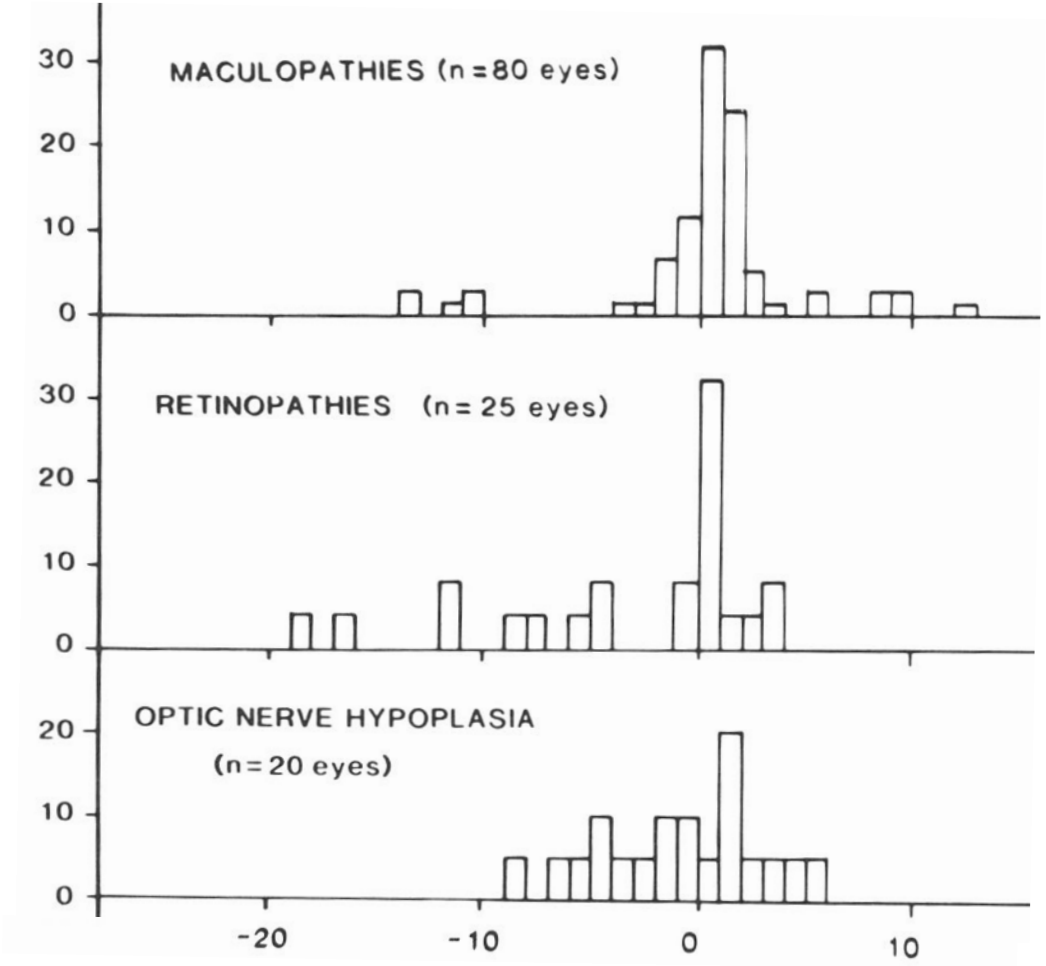
METHODS

A retrospective study was made of refractive errors of 433 children between the ages of 1 and 16 years who attended a multidisciplinary low vision clinic in Melbourne, Australia.

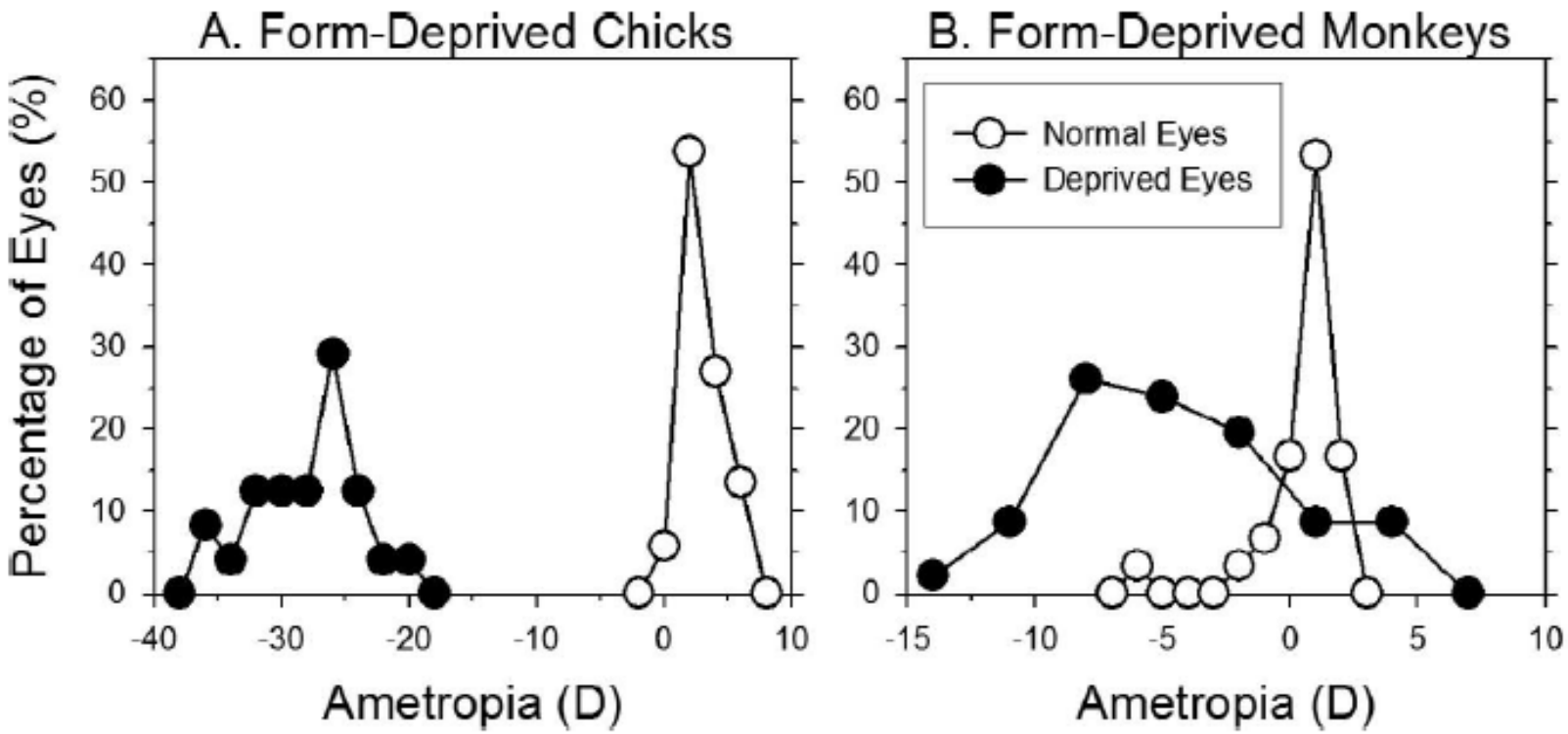
For various reasons not all eyes of the 433 low vision children were included in the analysis of data, in some cases refraction results were incomplete or unclear. The eyes of children with cataract (207), subluxated lens (19), or corneal opacification (3) were excluded from the sample as refraction in these cases was considered to be too unreliable. Additionally, eyes were excluded if there had been any surgery or laser or radiation therapy because of the possible effects upon refractive error. Lastly, refraction details were also unavailable for 65 eyes, thus reducing the number of children for whom reliable refractive data could be obtained to 256 with a total of 496

Emmetropization and Retinal Disease

- Retrospective data on 256 children from low vision clinic
- Control data from 1,023 normally-sighted children
- Low vision children grouped according to disease classification and onset
- Overall inability to emmetropize and trend towards myopia
- Peripheral retinal diseases associated with more myopia
- If fovea primarily impaired, hyperopic trend



Form Deprivation Myopia



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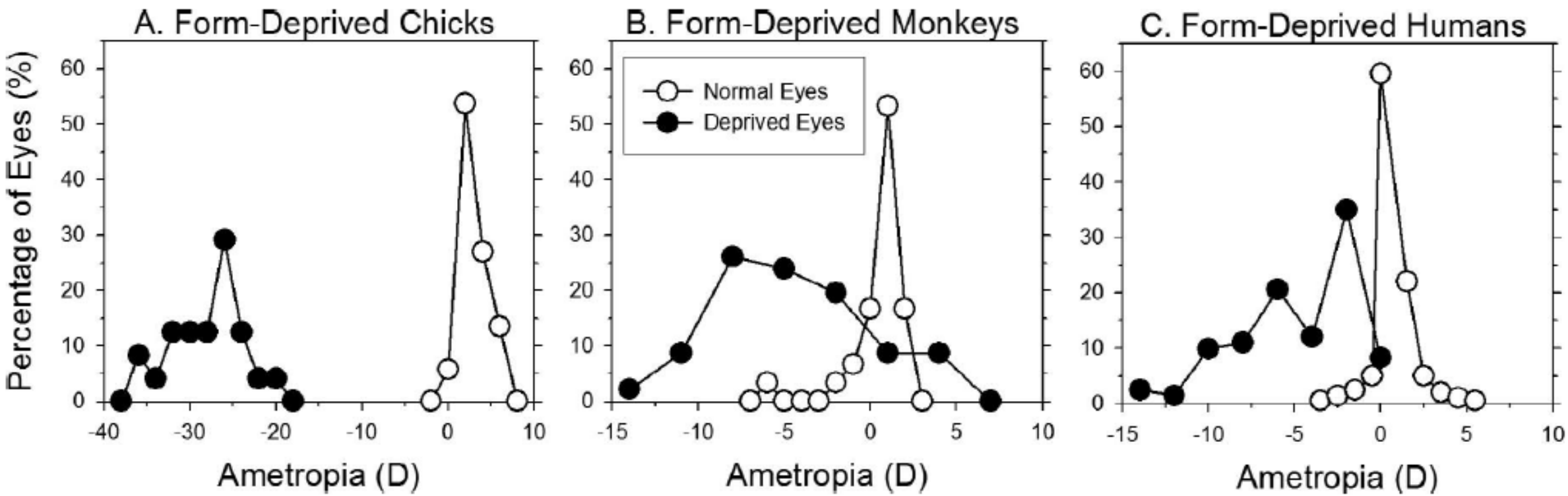

How Applicable are Animal Myopia Models?

- Critical review of how animal myopia data relate to human condition
- Concerns about application of animal models of myopia to etiology of human juvenile onset myopia including:
  1. No deprivation of form vision in environment of school-aged child as severe as that required to induce myopia in animals
  2. Sensitive period for deprivation myopia in animals appears to be too early to account for human juvenile onset myopia
  3. Studies in chicken using spectacle lenses to create dioptric blur involve choroidal thickness modulation that has no human analog

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How Applicable are Animal Myopia Models to Human Juvenile Onset Myopia?

KARLA ZADNIK,* DONALD O. MUTTI*

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Investigations into the plasticity of eye growth and refractive error development have significantly expanded our knowledge of animal models of myopia in the last 15 yr. The applicability of this information is as yet undetermined, but hopefully this information will be useful in learning more about human myopia. This paper presents a critical review of the animal myopia literature as those data relate to the human condition. Differences between the chicken, tree shrew, and primate animal models of myopia are outlined, and the various experimental paradigms used to investigate refractive error development and ocular growth in the chicken are compared. Specific arguments against the application of animal models of myopia to the etiology of human juvenile onset myopia include the following: (1) there is no deprivation of form vision in the environment of the school-aged child as severe as that required to induce myopia in animals; (2) the sensitive period for deprivation myopia in animals appears to be too early to account for human juvenile onset myopia; and (3) studies in the chicken using spectacle lenses to create dioptric blur involve a choroidal thickness modulation that has no human analog. Ultimately, the results of investigations into the cellular and biochemical modulation of eye growth in animals may be the most relevant to human myopia.

Myopia Deprivation Animal myopia Emmetropization Juvenile onset myopia Heredity Environment

Various aspects of human myopia have been studied for at least 80 yr (Steiger, 1913; Working Group on Myopia Prevalence and Progression, 1989). That research has produced evidence for a genetic-based etiology of myopia as well as for an environmental-based theory of myopia centered on accommodation and near work (McBrien & Barnes, 1989). It is as yet unknown what relative roles these "nature" and "nurture" components play in the onset and progression of human myopia, and there are many limitations in attempting to discern their relative roles through epidemiologic and clinical research. The fortuitous discovery that abnormal axial length elongation occurs in certain animal species during visual deprivation is largely responsible for the resurgence of research interest in myopia as experimental manipulation became possible in the study of the etiology of myopia (Wallman, Turkel & Trachtman, 1978; Wiesel & Raviola, 1977). The three species most often studied are: (1) the chicken, with visual deprivation resulting in marked elongation of the globe (Wallman & Adams, 1987), even when applied regionally (Wallman, Gottlieb, Rajaram & Fugate-Wentzek, 1987), (2) the tree shrew, with visual deprivation resulting in marked globe elongation and resultant myopia (McKanna & Casagrande, 1978; Marsh-Tootle & Norton, 1989), and (3) non-human primates, with disruption of normal visual input resulting in moderate axial growth and moderate myopia in some studies (Raviola & Wiesel, 1985; Tigges, Tigges, Fernandes, Eggers & Gammon, 1990; Wiesel & Raviola, 1977, 1979).

Troilo and Wallman (1991) have recently drawn parallels between three lines of evidence from animal experimentation, relating the plasticity of refraction and the influence of the environment in animals to an environmental etiology for human myopia: (1) refraction can be tuned to partially compensate for the defocus induced by spectacle lenses (Irving, Sivak & Callender, 1992; Schaeffel, Glasser & Howland, 1988; Schaeffel & Howland, 1991; Schaeffel, Troilo, Wallman & Howland, 1990; Wallman, Xu, Wildsoet, Krebs, Gottlieb, Marran & Nickla, 1992); (2) a physically near environment produces myopia and is presumed to be analogous to prolonged near work in humans (Miles & Wallman, 1990; Young, 1961); and (3) form deprivation produces myopia both in animal species (McKanna & Casagrande, 1978; Raviola & Wiesel, 1985; Wallman *et al.*, 1978) and in humans (Gee & Tabbara, 1988; Miller-Meeks, Bennett & Keech 1989; Rabin, Van Sluyters & Malach, 1981; Robb, 1977; von Noorden & Lewis, 1987).

Given the vast array of information on experimental myopia available from the animal models, especially the

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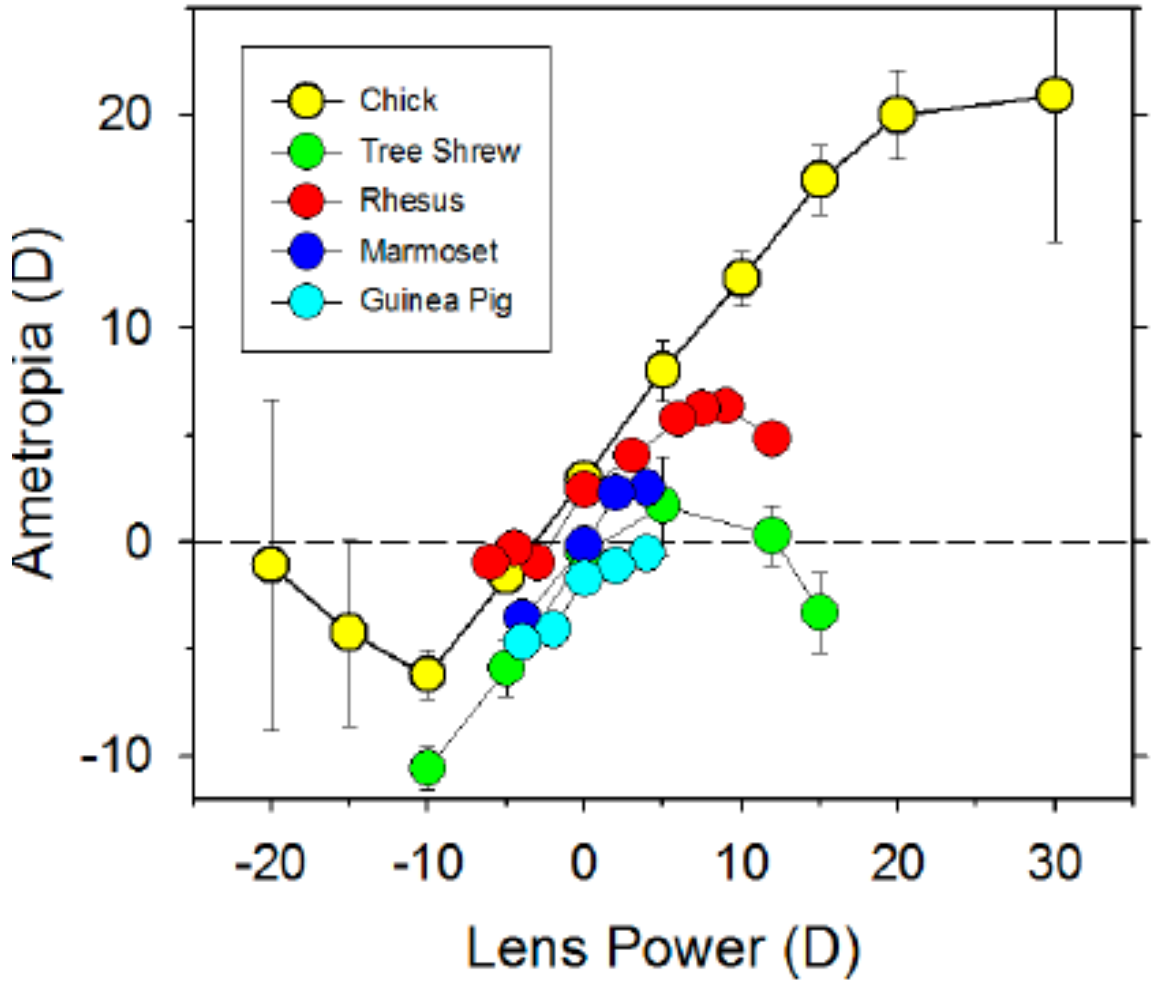
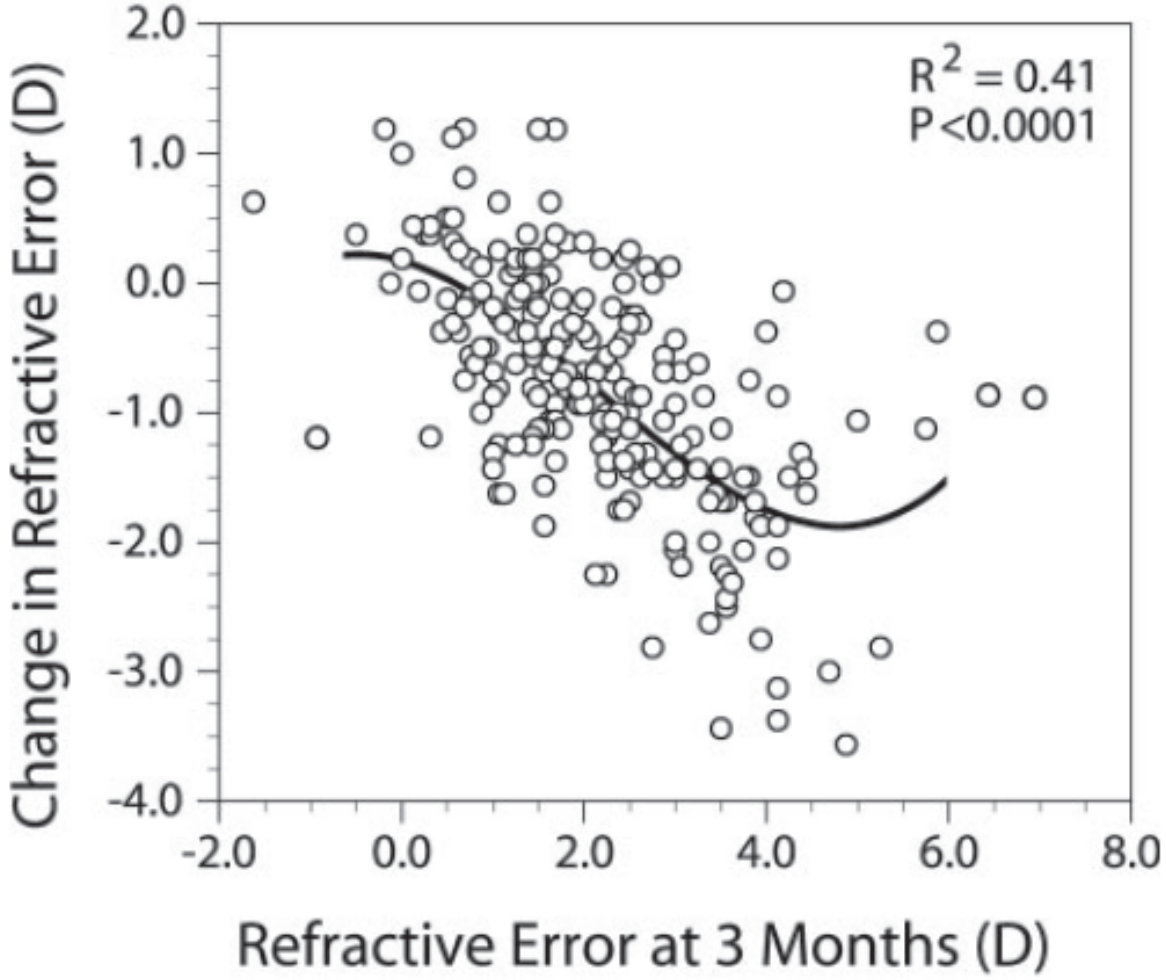
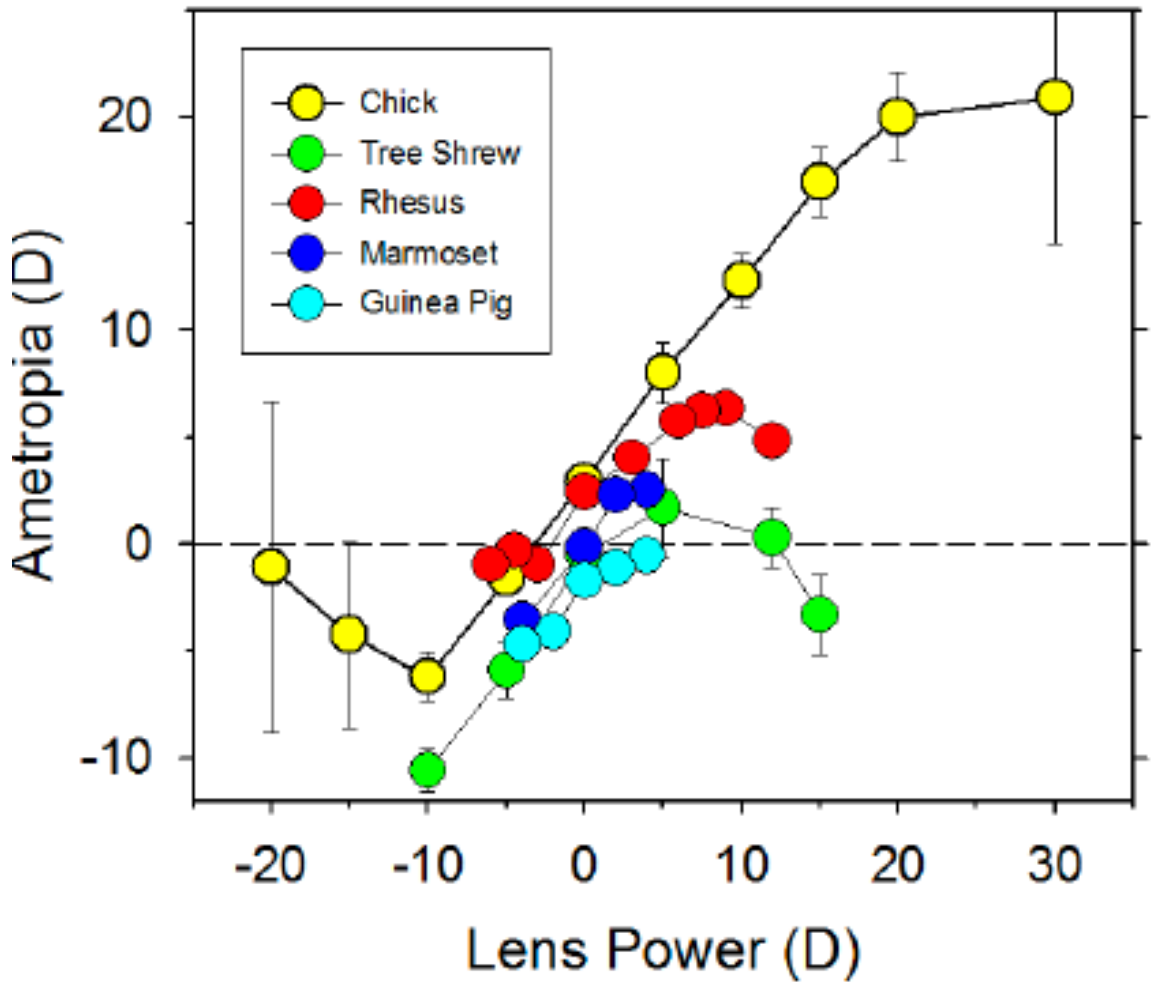
Lens-Induced Myopia and Hyperopia

- Macaque and marmoset monkeys, tree shrews, guinea pigs, mice, chickens, fish, and squid
- Emmetropization
- Form deprivation myopia
- Lens-induced myopia and hyperopia



Lens-Induced Myopia and Hyperopia





Monocular Overplus Spectacles

- 11-year-old myopic children, –1.00 to –3.00 D
- Dominant eye corrected for distance
- Fellow eyes were uncorrected or undercorrected by 2 D
- Interocular difference in myopia progression = 0.36 D/year
- Interocular difference in axial elongation = 0.13 mm/year
- After refitting with conventional spectacles, anisometropia at baseline levels within 18 months
- Sustained myopic defocus slows axial elongation

1196

EXTENDED REPORT

Monovision slows juvenile myopia progression unilaterally

J R Phillips

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See end of article for authors' affiliations

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Aim: To evaluate the acceptability, effectivity, and side effects of a monovision spectacle correction designed to reduce accommodation and myopia progression in schoolchildren.

Methods: Dominant eyes of 11 year old children with myopia (−1.00 to −3.00 D mean spherical equivalent) were corrected for distance; fellow eyes were uncorrected or corrected to keep the refractive imbalance ≤2.00 D. Myopia progression was followed with cycloplegic autorefraction and A-scan ultrasonography measures of vitreous chamber depth (VCD) for up to 30 months. Dynamic retinoscopy was used to assess accommodation while reading.

Results: All children accommodated to read with the distance corrected (dominant) eye. Thus, the near corrected eye experienced myopic defocus at all levels of accommodation. Myopia progression in the near corrected eyes was significantly slower than in the distance corrected eyes (inter-eye difference = 0.36 D/year (95% CI: 0.54 to 0.19, p = 0.0015, n = 13); difference in VCD elongation = 0.13 mm/year (95% CI: 0.18 to 0.08, p = 0.0003, n = 13)). After refitting with conventional spectacles, the resultant anisometropia returned to baseline levels after 9–18 months.

Conclusions: Monovision is not effective in reducing accommodation in juvenile myopia. However, myopia progression was significantly reduced in the near corrected eye, suggesting that sustained myopic defocus slows axial elongation of the human eye.

Animals raised wearing lenses which impose hyperopic retinal defocus (plane of focus located behind the retina) develop axial myopia.[1 2] In line with these animal studies it has been suggested[3] that focusing errors associated with prolonged accommodation, in particular lag of accommodation (plane of focus behind the retina), might explain the link between prolonged near work and the development of axial myopia in humans. Attempts to reduce accommodative lag by prescribing progressive addition lenses (PALs) to children in order to reduce myopia progression have had limited success.[4–6] Although PALs may slow progression somewhat, the effect is insufficient to control myopia progression in the clinical situation.[6 7] Whether results from animal models are directly applicable to naturally occurring myopia in humans is questionable.[8] A study of undercorrection of myopia[9] found that myopia progressed significantly more rapidly in children who were undercorrected compared to those wearing a full correction, implying that myopic defocus in humans increases the rate of myopia progression. However, in animals myopic defocus slows elongation of the eye and causes hyperopia.[1 2] Animal studies also predict that overcorrection of myopia might accelerate myopia progression in children. However, attempts to manage exotropia,[10] or to slow myopia progression with overcorrection,[11] do not appear to increase myopia progression.

Alternative theories[12] linking near work and myopia development have proposed that intraocular forces associated with sustained accommodation might lead to eye enlargement, perhaps by "stretching" the sclera. The human eye elongates slightly during accommodation,[13 14] suggesting that prolonged accommodation might lead to a permanent increase in eye length and myopia. On this basis, reducing accommodative effort might act to reduce myopia progression.

A prescription that is widely used to provide a near addition for presbyopic contact lens wearers is monovision, in which one eye is corrected for distance vision while the other is corrected for near vision. In principle, a monovision correction prescribed to children with myopia could reduce accommodative effort during near work and potentially slow myopia progression. Although some aspects of visual function may be compromised with monovision,[15 16] most presbyopic monovision wearers perceive a clear image of the world at distance and at near and are unaware of the anisometropic blur.[17]

The aims of this study were to determine whether children could successfully wear a monovision spectacle correction and whether it would reduce accommodative effort at near. A further aim was to investigate possible side effects of monovision wear, particularly whether it might induce some anisometropia over time. Monovision was prescribed as spectacles rather than contact lenses because the procedure was aimed at 11 year old children for whom spectacles are more universally applicable.

METHODS

Participants were 18 children (11 female, seven male, mean age 11.6 years) with a variety of ethnic origins (10 east Asian, the remainder included white, south Asian (Indian), and Maori/Pasifica). Inclusion criteria were (i) 10–13 years of age, (ii) no previous spectacle or contact lens wear, (iii) both eyes having subjectively determined best sphere refractions between −1.00 D to −3.00 D with astigmatism ≤−1.00 DC and initial anisometropia ≤1.00 D, (iv) both eyes correctable to 6/6 Snellen acuity, and (v) no binocular vision abnormality or ocular pathology. Stereopsis was assessed using the Wirt circles of the Stereotest (Stereo Optical Inc, Chicago, IL, USA). Eye dominance was determined using a simple sighting test.[18]

Abbreviations: ACD, anterior chamber depth; AXL, axial length; LT, lens thickness; PALs, progressive addition lenses; REML, restricted maximum likelihood; SER, spherical equivalent refraction; VCD, vitreous chamber depth

Binocular Overminus Spectacles

- To evaluate effectiveness of overminus spectacles to improve distance intermittent exotropia (IXT) control
- 386 children with IXT, aged 3 to 10 years (mean = 6.3 years), +1.00 to –6.00 D
- Randomly assigned to
  - –2.50 D for 12 months, then –1.25 D for 3 months or
  - Regular spectacle use

Research

JAMA Ophthalmology | Original Investigation

Overminus Lens Therapy for Children 3 to 10 Years of Age With Intermittent Exotropia
A Randomized Clinical Trial

Angela M. Chen, OD, MS; S. Ayse Erzurum, MD; Danielle L. Chandler, MSPH; Amra Hardnovic, MPH; B. Michele Mella, ScM; Amit R. Bhatt, MD; Donny W. Suh, MD; Marilyn Vricella, OD; John W. Erickson, OD; Aaron M. Miller, MD; Justin D. Marsh, MD; Marie I. Bodack, OD; Stacy R. Martinson, OD; Jenna R. Tittelbaum, OD; Michael E. Gray, MD; Hannah L. Holfort, OD; Lingkun Kong, MD; Raymond T. Kraker, MSPH; Bahram Rahmani, MD; Birva K. Shah, OD; Jonathan M. Holmes, BM, BCh; Susan A. Cotter, OD, MS; for the Pediatric Eye Disease Investigator Group

IMPORTANCE This is the first large-scale randomized clinical trial evaluating the effectiveness and safety of overminus spectacle therapy for treatment of intermittent exotropia (IXT).

OBJECTIVE To evaluate the effectiveness of overminus spectacles to improve distance IXT control.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial conducted at 56 clinical sites between January 2017 and January 2019 associated with the Pediatric Eye Disease Investigator Group enrolled 386 children aged 3 to 10 years with IXT, a mean distance control score of 2 or worse, and a refractive error between 1.00 and −6.00 diopters (D). Data analysis was performed from February to December 2020.

INTERVENTIONS Participants were randomly assigned to overminus spectacle therapy (−2.50 D for 12 months, then −1.25 D for 3 months, followed by nonoverminus spectacles for 3 months) or to nonoverminus spectacle use.

MAIN OUTCOMES AND MEASURES Primary and secondary outcomes were the mean distance IXT control scores of participants examined after 12 months of treatment (primary outcome) and at 18 months (3 months after treatment ended) assessed by an examiner masked to treatment group. Change in refractive error from baseline to 12 months was compared between groups. Analyses were performed using the intention-to-treat population.

RESULTS The mean (SD) age of 196 participants randomized to overminus therapy and 190 participants randomized to nonoverminus treatment was 6.3 (2.1) years, and 226 (59%) were female. Mean distance control at 12 months was better in participants treated with overminus spectacles than with nonoverminus spectacles (1.8 vs 2.8 points; adjusted difference, −0.8; 95% CI, −1.0 to −0.5; $P < .001$). At 18 months, there was little or no difference in mean distance control between overminus and nonoverminus groups (2.4 vs 2.7 points; adjusted difference, −0.2; 95% CI, −0.5 to 0.04; $P = .09$). Myopic shift from baseline to 12 months was greater in the overminus than the nonoverminus group (−0.42 D vs −0.04 D; adjusted difference, −0.37 D; 95% CI, −0.49 to −0.26 D; $P < .001$), with 33 of 189 children (17%) in the overminus group vs 2 of 169 (1%) in the nonoverminus group having a shift higher than 1.00 D.

CONCLUSIONS AND RELEVANCE Children 3 to 10 years of age had improved distance exotropia control when assessed wearing overminus spectacles after 12 months of overminus treatment; however, this treatment was associated with increased myopic shift. The beneficial effect of overminus lens therapy on distance exotropia control was not maintained after treatment was tapered off for 3 months and children were examined 3 months later.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02807350

Invited Commentary page 476
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Binocular Overminus Spectacles

- Distance IXT control at 12 months was better with overminus spectacles
- At 18 months, little or no difference
- Myopic shift greater in overminus than nonoverminus group:
  –0.42 D vs –0.04 D
- 33 of 189 children (17%) in overminus group vs 2 of 169 (1%) in nonoverminus group had myopic shift > 1.00 D

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Overminus Spectacles in Myopic Children

- In intervention group with myopia
- Mean progression = −1.07 ± 0.76 D
- 51% showed more than 1.0 D

"first randomized clinical trial of the lens paradigm, where rearing nonmyopic animals with negatively-powered lenses leads to myopia"

Letters

COMMENT & RESPONSE

Broader Implications of Overminus Lens Therapy in Relation to Myopia Management

To the Editor Chen and colleagues' article[1] on overminus lens therapy for intermittent exotropia (IXT) raises many questions regarding this condition but has implications for the management of childhood myopia. To our knowledge, this study is also the first randomized clinical trial of the so-called lens-paradigm, where rearing nonmyopic animals with negatively powered lenses leads to myopia.[2]

This study appears to have 2 clear clinical implications: (1) inadvertently overminusing children who have myopia due to noncycloplegic refraction may increase myopic progression and (2) that overminus therapy is unjustified for IXT, especially in children with myopia. In the intervention group, 51% showed more than -1.0 diopter (D) of progression compared with only 2% of the control group. A recent article reported an additional -1 D of myopia carries an increased risk of 57%, 20%, 21%, and 30% of myopic maculopathy, open-angle glaucoma, posterior subcapsular cataract, and retinal detachment, respectively, and potentially an additional year of visual impairment in later life.[3] Thus, the transient improvements in IXT control are far outweighed by the potential risks associated with increased myopic progression.

The trial also raises several questions. The mean age of participants was 6.3 years, yet 87 of 358 participants (24%) had myopia. This is a far higher proportion of children with myopia than expected in the general US population at this age,[4] indicating that this was an intrinsically unusual group of children from a refractive, as well as oculomotor, perspective. The controls also showed an unusually small rate of progression (−0.16 D/y). Does this suggest that impaired binocularity from IXT reduces myopic progression? Animal studies suggest this may be a possibility. Monkeys that failed to show compensatory eye growth to imposed anisometropia were found to have developed amblyopia in the noncompensated eye.[5] Although trial participants did not have amblyopia by conventional criteria (interocular difference of distance visual acuity less than or equal to 0.2 logMAR or approximately 2 lines on a standardized chart), some of the marked difference in myopic progression between the overminus and control groups may be attributable to improved binocularity in the intervention group. This question would appear to merit further clinical investigation.

In light of these results, we believe that clinicians should be wary of using overminus therapy in myopic children with IXT. If such treatment is considered justifiable by the treating clinician, careful monitoring of refraction and axial length should be performed to ensure that myopic progression and axial elongation do not exceed population norms.

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Undercorrection: Two Randomized Trials

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Undercorrection of myopia enhances rather than inhibits myopia progression

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Abstract

The effect of myopic defocus on myopia progression was assessed in a two-year prospective study on 94 myopes aged 9–14 years, randomly allocated to an undercorrected group or a fully corrected control group. The 47 experimental subjects were blurred by approximately +0.75 D (blurring VA to 6/12), while the controls were fully corrected. Undercorrection produced more rapid myopia progression and axial elongation (ANOVA, $F(1,374) = 14.32$, $p < 0.01$). Contrary to animal studies, myopic defocus speeds up myopia development in already myopic humans. Myopia could be caused by a failure to detect the direction of defocus rather than by a mechanism exhibiting a zero-point error.

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Keywords: Emmetropization; Refractive error; Myopia

1. Introduction

The refractive development of the eye is under the influence of a feedback mechanism known as emmetropization where optical defocus guides the growth of the eye so that there is no refractive error (Hung, Crawford & Smith, 1995; Schaeffel, Glasser & Howland, 1988; Troilo & Wallman, 1991). This requires that the visual system is able to distinguish between myopic defocus (where the optical image is formed in front of the retina) from hypermetropic defocus (where the image plane is behind the retina).

When the primate emmetropic eye is deprived of form vision by degrading the optical image, it becomes myopic (Raviola & Weisel, 1977; Wallman & McFadden, 1995) and restoring an undegraded image results in a growth of the eye towards emmetropia again. A similar response has been found in most (but not all) species examined.

Although there is general agreement that growth of the young human eye is regulated by an emmetropization mechanism, refractive errors occur in between 20% of the adult population in European populations, and up to 80% of the population in some Asian countries. The reason for this anomaly is not clear, as the retinal image is defocussed in myopes rather than degraded. Possibly the error detection system in these individuals is flawed, or the eye may be growing towards an "incorrect" zero (Medina, 1987a,b).

If the emmetropization mechanism is defective in detecting the sign of defocus, then it is possible that human myopia is an inappropriate response to a signal, which would better result in a growth response in the hypermetropic direction. If the mechanism is merely showing a zeroing error then undercorrecting myopia should slow down or halt the progression of eye growth. There is little reliable information on the effect of undercorrection in humans. Only one poorly controlled clinical trial has been carried out on myopes (Tokoro & Kabe, 1965). However where spectacles are not worn for close work there was no significant effect on myopia progression (Ong, Grice, Held, Thorn & Gwiazda, 1999).

We report here the results of a randomised controlled clinical trial to determine the effects of undercorrection on the rate of progression of myopia. Our results show that undercorrection speeds up the rate of myopia progression in myopic children, which supports the idea that their emmetropization mechanism is defective in detecting blur.

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CLINICAL AND EXPERIMENTAL
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ORIGINAL PAPER

The possible effect of undercorrection on myopic progression in children

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Background: Undercorrection has recently been found to enhance the rate of progression of myopia. This result was thought to be controversial as it contrasted with expectations based on animal studies, as well as the results found wearing progressive addition lenses. The aim of the present study was to again determine the effect of undercorrection on the progression of myopia in a random population of children who are known to be very susceptible to myopia.

Methods: A cohort of 48 myopic children, aged six to15 years was randomly assigned to either a fully corrected group (n = 23) or to an undercorrected group (n = 25). The subjects in the latter group were blurred by +0.50 D. The prospective study extended over a period of 18 months. Optometric examinations were carried out at the beginning of the study, then at six-month, 12-month and 18-month follow-up.

Results: Undercorrection produced a slight but not statistically significant increase in myopic progression over the 18-month period equal to 0.17 D, compared to full correction. A similar trend towards an increase in progression was noted in females and in children with near esophoria.

Conclusion: This study supports the evidence that undercorrection does not represent an effective therapy to slow the rate of early-onset myopic progression, regardless of near heterophoria.

Key words: myopia, myopic progression, retinal defocus, under correction

Once myopia appears in children, it tends to progress up to the late teenage years.[1] Thus, there have been numerous attempts at finding therapies that could reduce the rate of progression in those individuals susceptible to environmental factors, as opposed to those in whom the progression is programmed genetically. These therapeutic methods are reviewed elsewhere.[2] One of the various methods proposed consists of prescribing single vision lenses with an undercorrection. The rationale for this procedure is that it reduces the accommodative response for near vision. Moreover, it has been established in animal studies that a myopic defocus (when the retinal image is formed in front of the retina) halts ocular elongation and its consequent myopic progression in chicks,[3] tree shrews,[4] marmosets[5] and infant monkeys.[6] However, extrapolating from animal experiments, in which myopia is induced, to children with existing myopia demands great caution, especially as many of these animal experiments are carried out monocularly,[7] thus avoiding binocular interaction.

Nevertheless, it is surprising that so little research has been devoted to undercorrection as a possible method of slowing the progression of myopia. One clinical study was carried out by Tokoro and Kabe,[8] who found a significantly smaller rate of myopic progression with undercorrection than with full correction over a three-year period. That study suffered

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Undercorrection: Two Randomized Trials

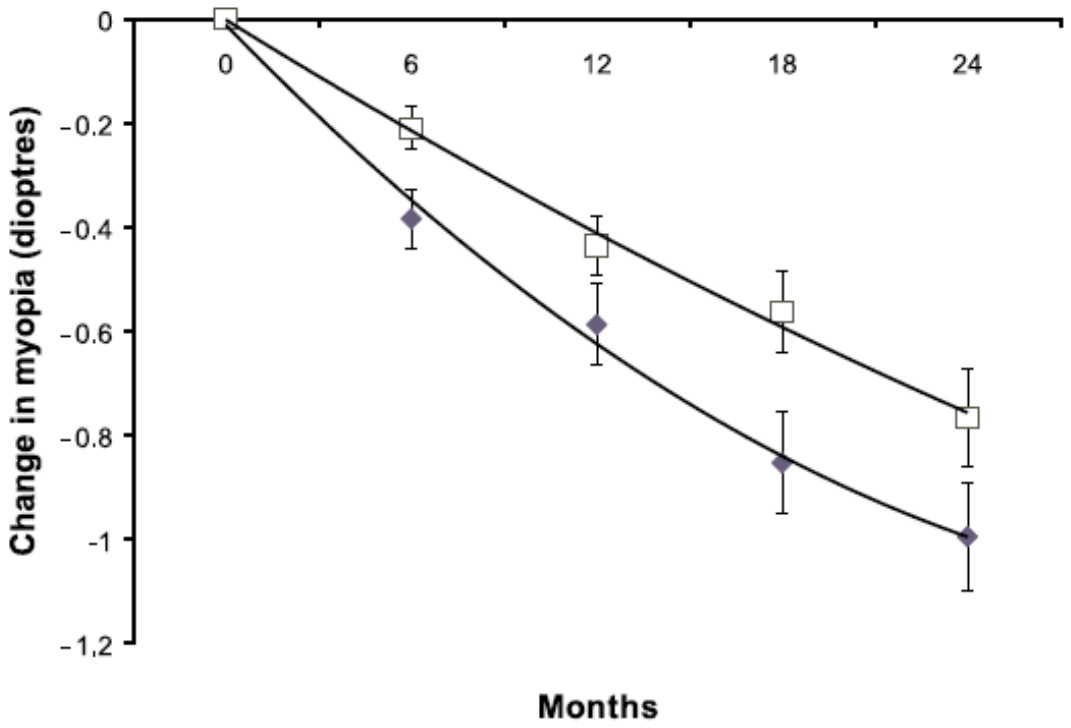

Fig. 1. Mean changes (vertical bars show ±1 SEM) in refractive error for the undercorrected group (filled symbols) and the fully corrected group (open symbols) over the two-year period of the study. There were 47 subjects in each group. The undercorrected group showed a greater rate of progression as compared to the fully corrected group (univariate ANOVA, $F(1, 374) = 14.32$, $p = 0.001$).

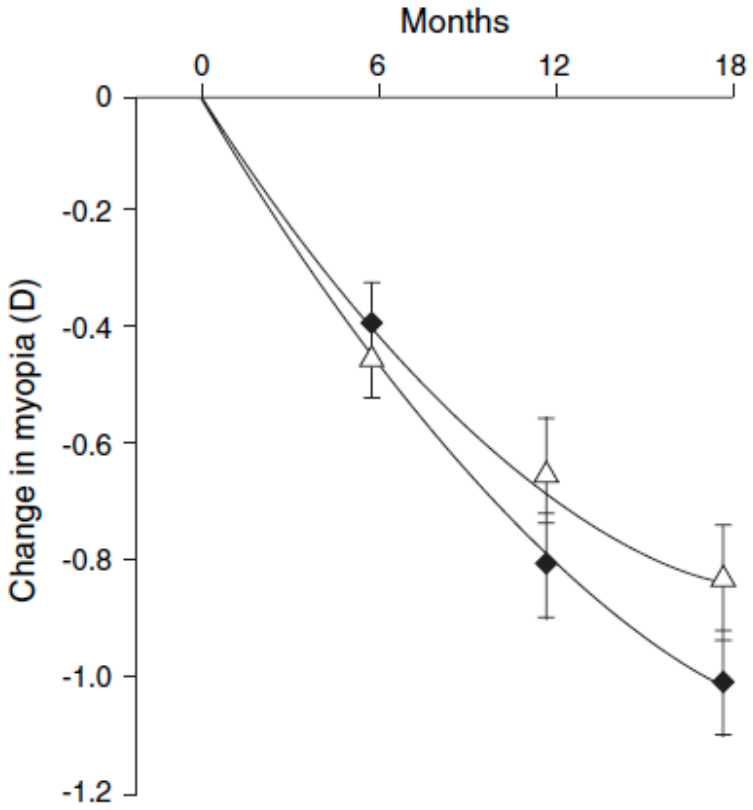

Figure 1. Mean changes in myopia for the fully-corrected group (open triangles) and the under-corrected group (filled diamonds) over the 18-month period of the study. The vertical bars show ±1 SEM.

How Applicable are Animal Myopia Models?

- Critical review of how animal myopia data relate to human condition
- Concerns about application of animal models of myopia to etiology of human juvenile onset myopia including:
  1. No deprivation of form vision in environment of school-aged child as severe as that required to induce myopia in animals
  2. Sensitive period for deprivation myopia in animals appears to be too early to account for human juvenile onset myopia
  3. Studies in chicken using spectacle lenses to create dioptric blur involve choroidal thickness modulation that has no human analog

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How Applicable are Animal Myopia Models to Human Juvenile Onset Myopia?

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Investigations into the plasticity of eye growth and refractive error development have significantly expanded our knowledge of animal models of myopia in the last 15 yr. The applicability of this information is as yet undetermined, but hopefully this information will be useful in learning more about human myopia. This paper presents a critical review of the animal myopia literature as those data relate to the human condition. Differences between the chicken, tree shrew, and primate animal models of myopia are outlined, and the various experimental paradigms used to investigate refractive error development and ocular growth in the chicken are compared. Specific arguments against the application of animal models of myopia to the etiology of human juvenile onset myopia include the following: (1) there is no deprivation of form vision in the environment of the school-aged child as severe as that required to induce myopia in animals; (2) the sensitive period for deprivation myopia in animals appears to be too early to account for human juvenile onset myopia; and (3) studies in the chicken using spectacle lenses to create dioptric blur involve a choroidal thickness modulation that has no human analog. Ultimately, the results of investigations into the cellular and biochemical modulation of eye growth in animals may be the most relevant to human myopia.

Myopia Deprivation Animal myopia Emmetropization Juvenile onset myopia Heredity Environment

Various aspects of human myopia have been studied for at least 80 yr (Steiger, 1913; Working Group on Myopia Prevalence and Progression, 1989). That research has produced evidence for a genetic-based etiology of myopia as well as for an environmental-based theory of myopia centered on accommodation and near work (McBrien & Barnes, 1989). It is as yet unknown what relative roles these "nature" and "nurture" components play in the onset and progression of human myopia, and there are many limitations in attempting to discern their relative roles through epidemiologic and clinical research. The fortuitous discovery that abnormal axial length elongation occurs in certain animal species during visual deprivation is largely responsible for the resurgence of research interest in myopia as experimental manipulation became possible in the study of the etiology of myopia (Wallman, Turkel & Trachtman, 1978; Wiesel & Raviola, 1977). The three species most often studied are: (1) the chicken, with visual deprivation resulting in marked elongation of the globe (Wallman & Adams, 1987), even when applied regionally (Wallman, Gottlieb, Rajaram & Fugate-Wentzek, 1987), (2) the tree shrew, with visual deprivation resulting in marked globe elongation and resultant myopia (McKanna & Casagrande, 1978; Marsh-Tootle & Norton, 1989), and (3) non-human primates, with disruption of normal visual input resulting in moderate axial growth and moderate myopia in some studies (Raviola & Wiesel, 1985; Tigges, Tigges, Fernandes, Eggers & Gammon, 1990; Wiesel & Raviola, 1977, 1979).

Troilo and Wallman (1991) have recently drawn parallels between three lines of evidence from animal experimentation, relating the plasticity of refraction and the influence of the environment in animals to an environmental etiology for human myopia: (1) refraction can be tuned to partially compensate for the defocus induced by spectacle lenses (Irving, Sivak & Callender, 1992; Schaeffel, Glasser & Howland, 1988; Schaeffel & Howland, 1991; Schaeffel, Troilo, Wallman & Howland, 1990; Wallman, Xu, Wildsoet, Krebs, Gottlieb, Marran & Nickla, 1992); (2) a physically near environment produces myopia and is presumed to be analogous to prolonged near work in humans (Miles & Wallman, 1990; Young, 1961); and (3) form deprivation produces myopia both in animal species (McKanna & Casagrande, 1978; Raviola & Wiesel, 1985; Wallman *et al.*, 1978) and in humans (Gee & Tabbara, 1988; Miller-Meeks, Bennett & Keech 1989; Rabin, Van Sluyters & Malach, 1981; Robb, 1977; von Noorden & Lewis, 1987).

Given the vast array of information on experimental myopia available from the animal models, especially the

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Choroidal Changes in Chickens

- Chick eye able to change refractive state by up to 7 D changes in choroidal thickness
- Eyes recovering from form-deprivation myopia show choroidal thickening
- In chick eyes presented with myopic or hyperopic defocus, choroid expands or thins to compensate for imposed defocus
- After lenses removed, choroidal thickness again compensates

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Moving the Retina: Choroidal Modulation of Refractive State

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The chick eye is able to change its refractive state by as much as 7 D by pushing the retina forward or pulling it back; this is effected by changes in the thickness of the choroid, the vascular tissue behind the retina and pigment epithelium. Chick eyes first made myopic by wearing diffusers and then permitted unrestricted vision developed choroids several times thicker than normal within days, thereby speeding recovery from deprivation myopia. Choroidal expansion does not occur when visual cues are reduced by dim illumination during the period of unrestricted vision. Furthermore, in chick eyes presented with myopic or hyperopic defocus by means of spectacle lenses, the choroid expands or thins, respectively, in compensation for the specific defocus imposed. Consequently, when the lenses are removed, the eye finds its refractive error suddenly of opposite sign, and the choroidal thickness again compensates by changing in the opposite direction. If a local region of the eye is made myopic by a partial diffuser and then given unrestricted vision, the choroid expands only in the myopic region. Although the mechanism of choroidal expansion is unknown, it might involve either a increased routing of aqueous humor into the uveoscleral outflow or osmotically generated water movement into the choroid. The latter is compatible with the increased choroidal proteoglycan synthesis either when eyes wear positive lenses or after diffuser removal.

Accommodation Chicken Choroid Myopia Refractive error

INTRODUCTION

Like most other optical devices, eyes are generally thought to focus by lens adjustments that optically move the image plane. During ocular accommodation, most vertebrates move the image plane by rapidly adjusting the optical power of the eye, for example by increasing the curvature of the lens for near objects. Variants of this mechanism are found in fish, which displace the lens, and in birds, which alter the curvature of the cornea as well as the lens (Sivak, 1980; Schaeffel & Howland, 1987; Troilo & Wallman, 1987). A second, slower, way that vertebrates bring images into focus on the retina is by adjusting the growth of the eye as a whole so that its length becomes appropriate for the resting optical power of the eye (emmetropization) (Van Alphen, 1961, 1986; Schaeffel & Howland, 1988a; Troilo & Wallman, 1991). The strongest evidence for this emmetropization process is that, in the chick, the eye grows in compensation for defocus produced by spectacle lenses (Schaeffel, Glasser & Howland, 1988; Irving, Sivak & Callender, 1992). In this paper, we present evidence for a third focusing mechanism—intermediate in speed—in which the retina is moved forward and back by changes in the thickness of the choroid.

The choroid in chickens, as in other vertebrates, consists of two parts: the choriocapillaris, a network of fenestrated capillaries just behind the retinal pigment epithelium, and the main portion of the choroid, which contains numerous larger blood vessels, and, at least in birds, large lacunae. These structures are supported by an intervascular suspensory system comprised of extracellular matrix, smooth muscle fibers, fibroblasts and pigmented cells (Meriney & Pilar, 1987). The choroid supplies the outer retina with oxygen and nutrients and also functions as a heat sink (Bill, 1985). It is under the control of the autonomic nervous system, and is innervated from many divergent sources, including the oculomotor, trigeminal and facial nerves, as well as the ciliary, superior cervical and pterygopalatine ganglia (Bill, 1985). In addition, a plethora of putative transmitters have been localized to these terminals, including acetylcholine, VIP, substance P

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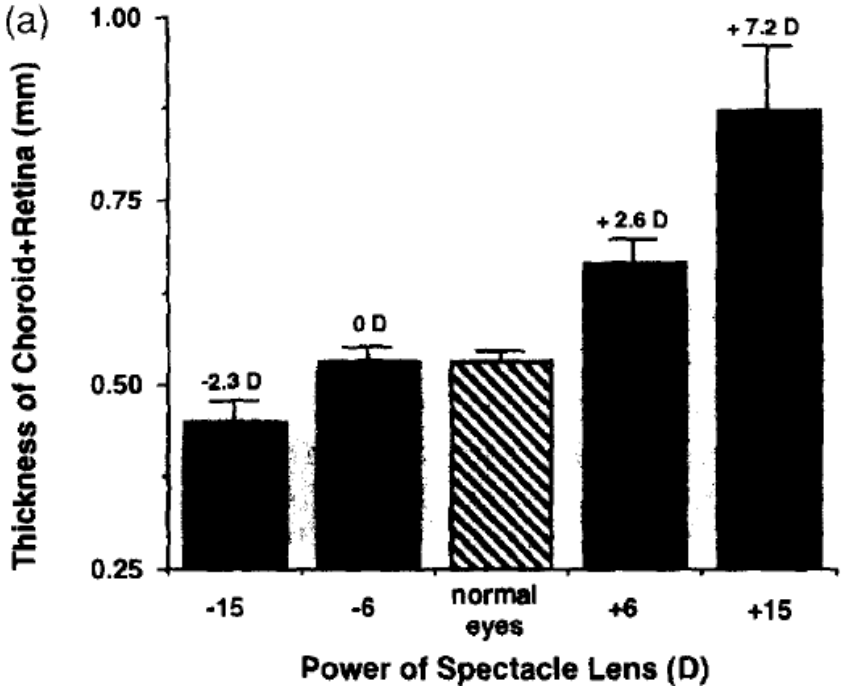

Short-Term Choroidal Changes in Humans

- 28 young adults
  (14 myopes, 14 emmetropes)
- Ocular biometry measured before and after 60-minutes of monocular defocus
  - control (no defocus),
  - myopic (+3 D defocus),
  - hyperopic (–3 D defocus), and
  - diffuse defocus (0.2 Bangerter filter)
- Fellow eye optimally corrected

Clinical and Epidemiologic Research

Human Optical Axial Length and Defocus

Scott A. Read, Michael J. Collins, and Beata P. Sander

Purpose. To investigate the short-term influence of imposed monocular defocus on human optical axial length (the distance from anterior cornea to retinal pigment epithelium) and ocular biometrics.

Methods. Twenty-eight young adult subjects (14 myopes, 14 emmetropes) had eye biometrics measured before and 30 and 60 minutes after exposure to monocular (right eye) defocus. Four different monocular defocus conditions were tested, each on a separate day: control (no defocus), myopic (+3 D defocus), hyperopic (−3 D defocus), and diffuse (0.2 density Bangerter filter) defocus. The fellow eye was optimally corrected (no defocus).

Results. Imposed defocus caused small but significant changes in optical axial length ($P < 0.0001$). A significant increase in optical axial length (mean change, +8 ± 14 μm; $P = 0.03$) occurred after hyperopic defocus, and a significant reduction in optical axial length (mean change, −13 ± 14 μm; $P = 0.0001$) was found after myopic defocus. A small increase in optical axial length was observed after diffuse defocus (mean change, +6 ± 13 μm; $P = 0.053$). Choroidal thickness also exhibited some significant changes with certain defocus conditions. No significant difference was found between myopes and emmetropes in the changes in optical axial length or choroidal thickness with defocus.

Conclusions. Significant changes in optical axial length occurred in human subjects after 60 minutes of monocular defocus. The bidirectional optical axial length changes observed in response to defocus implied the human visual system is capable of detecting the presence and sign of defocus and altering optical axial length to move the retina toward the image plane. (*Invest Ophthalmol Vis Sci.* 2010; 51:6262–6269) DOI:10.1167/iovs.10-5457

It is now generally accepted that the quality of the retinal image can influence axial eye growth. A number of different experimental paradigms, applied on a range of different species have illustrated that altering retinal image quality can lead to consistent and predictable changes in eye growth (for reviews, see Refs. 1–3). Disrupting form vision through the use of lid suture[4] and translucent goggles/diffusers[5–7] or manipulating the contrast of the visual environment[8] has been shown to lead to axial elongation and myopia development, proportional to the degree of image disruption,[6–8] that recovers once normal vision is returned.[5] Furthermore, defocus of the retinal image in both chick and primate animal models, through positive (myopic defocus) or negative lenses (hyperopic defocus), is known to lead to predictable (both direction and magnitude of eye growth) changes in eye growth consistent with the eyes growing to compensate for the imposed defocus.[9–12]

Changes in eye length associated with defocus are modulated by changes in both scleral growth and choroidal thickness, the net effect of which results in an anterior or a posterior movement of the retina toward the image plane.[13–16] Myopic defocus, therefore, leads to a thickening of the choroid and to a decreased scleral growth rate (which results in anterior movement of the retina), and hyperopic defocus leads to a thinning of the choroid and an increase in scleral growth rate (which results in posterior movement of the retina). Choroidal thickness changes in response to imposed defocus have been observed in both avian[14,15] and primate animal[17,18] models and have been demonstrated to occur rapidly and to precede scleral-mediated changes in eye size. Recent studies investigating the time course of choroidal thickness changes in response to defocus have illustrated that these changes can occur remarkably quickly, with only minutes of exposure to defocus required to elicit a response.[19–22]

The majority of work that has contributed to the current understanding of the influence of retinal image quality on eye growth has involved research with animal models. Although similar ocular responses to imposed defocus have been demonstrated in a number of different species, there has been relatively limited research investigating the influence of defocus on eye length in human subjects. There is some evidence, though, that supports the notion that retinal image quality can influence eye length in humans. A variety of different ocular conditions that lead to a disruption in form vision, such as ptosis,[23,24] congenital cataract,[25,26] corneal opacity,[27,28] vitreous hemorrhage,[29] and other ocular diseases,[30] have been found to be associated with abnormal eye growth in young humans, which suggests that relatively large alterations in retinal image quality may influence eye growth in human subjects. However, the influence of more subtle retinal image changes on eye growth in humans remains to be determined.

The relatively recent introduction of highly precise, noncontact methods for measuring eye dimensions has led to the finding that a number of factors can lead to short-term changes in optical axial length, hereafter referred to as axial length (the axial distance from the anterior cornea to the retinal pigment epithelium) of human subjects. Changes in accommodation[31,32] and IOP[33,34] have both been found to be associated with short-term changes in axial length. Furthermore, small but significant diurnal variations have also been noted to occur in human axial length[35–37] that may be mediated by changes in choroidal thickness.[38] Although the use of these highly precise methods of measuring axial length has led to an improved understanding of a number of short-term factors that can influence eye length in humans, no previous study has investigated the influence of defocus on axial length in human eyes. In this study we aimed to examine whether imposing defocus on

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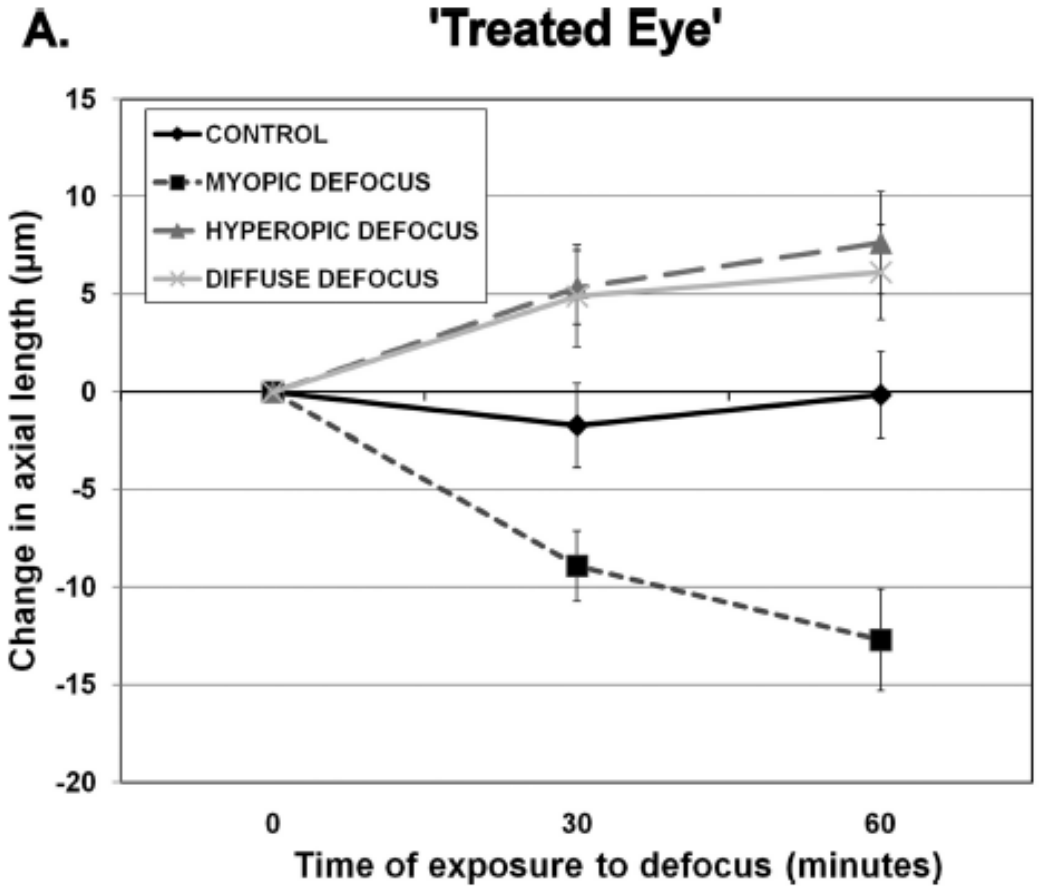
Short-Term *Axial Length* Changes in Humans

- Myopic defocus (+ lens) induced
  –13 µm decrease in axial length
- Hyperopic defocus (– lens) induced
  +8 µm increase in axial length
- Diffuse defocus induced borderline
  +6 µm increase in axial length



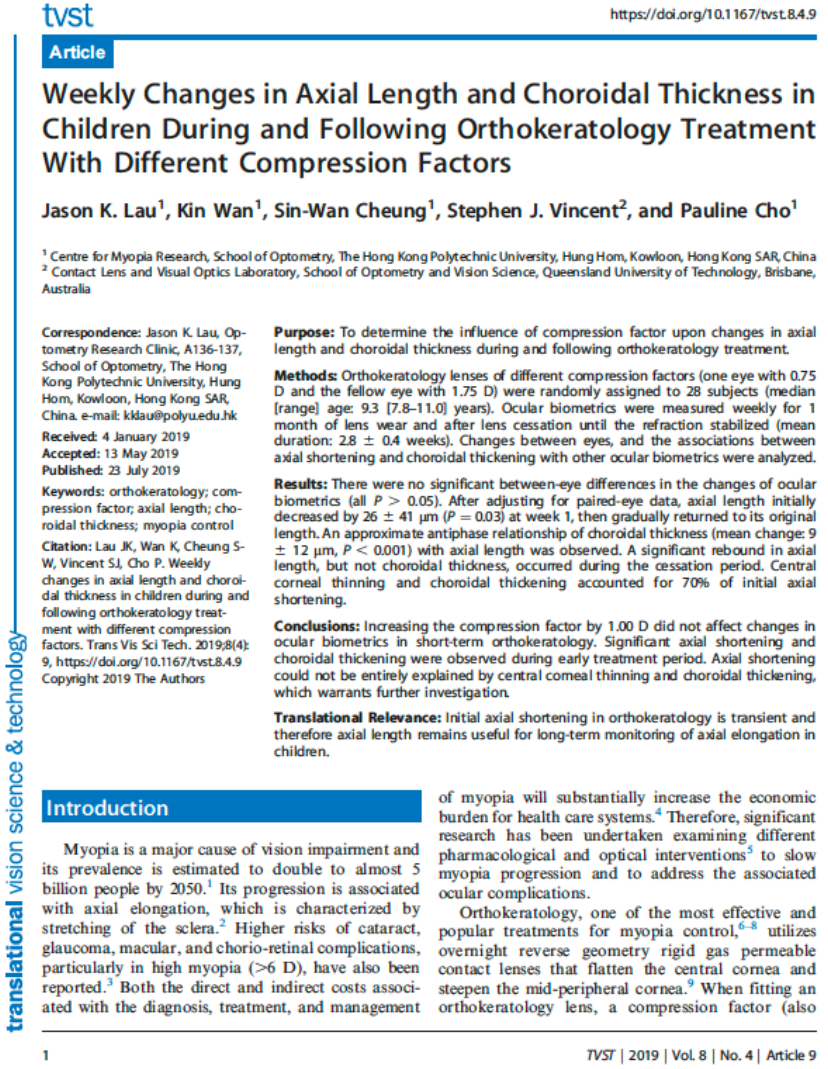
Short-Term Choroidal Changes in Humans

TABLE 1. Change in Ocular Biometrics from Baseline after 30 and 60 Minutes of Exposure to Defocus

	Change from Baseline (μm) Mean ± SD			
	Control (no defocus)	3 D Myopic Defocus	3 D Hyperopic Defocus	Diffuse Defocus
Axial length (n = 28)				
30 min	−2 ± 11	−9 ± 10*	5 ± 10*	5 ± 14
60 min	0 ± 12	−13 ± 14*	8 ± 14*	6 ± 13
Retinal thickness (n = 24)				
30 min	0 ± 5	−1 ± 5	−1 ± 4	−1 ± 4
60 min	−1 ± 7	−2 ± 5	−1 ± 4	−2 ± 4
Choroidal thickness (n = 23)				
30 min	2 ± 15	7 ± 13	−8 ± 16	1 ± 11
60 min	5 ± 15	12 ± 16*	−3 ± 14	−6 ± 12

Choroidal Changes with Myopia Control

- 28 myopic children, 7 to 11 years
- Fit with orthokeratology lenses
- 1 month of wear
- Biometry measured weekly
- Axial length decreased by 26 µm at week 1
- Choroidal thickness increased by 9 µm



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Article

Weekly Changes in Axial Length and Choroidal Thickness in Children During and Following Orthokeratology Treatment With Different Compression Factors

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Purpose: To determine the influence of compression factor upon changes in axial length and choroidal thickness during and following orthokeratology treatment.

Methods: Orthokeratology lenses of different compression factors (one eye with 0.75 D and the fellow eye with 1.75 D) were randomly assigned to 28 subjects (median [range] age: 9.3 [7.8–11.0] years). Ocular biometrics were measured weekly for 1 month of lens wear and after lens cessation until the refraction stabilized (mean duration: 2.8 ± 0.4 weeks). Changes between eyes, and the associations between axial shortening and choroidal thickening with other ocular biometrics were analyzed.

Results: There were no significant between-eye differences in the changes of ocular biometrics (all $P > 0.05$). After adjusting for paired-eye data, axial length initially decreased by 26 ± 41 µm ($P = 0.03$) at week 1, then gradually returned to its original length. An approximate antiphase relationship of choroidal thickness (mean change: 9 ± 12 µm, $P < 0.001$) with axial length was observed. A significant rebound in axial length, but not choroidal thickness, occurred during the cessation period. Central corneal thinning and choroidal thickening accounted for 70% of initial axial shortening.

Conclusions: Increasing the compression factor by 1.00 D did not affect changes in ocular biometrics in short-term orthokeratology. Significant axial shortening and choroidal thickening were observed during early treatment period. Axial shortening could not be entirely explained by central corneal thinning and choroidal thickening, which warrants further investigation.

Translational Relevance: Initial axial shortening in orthokeratology is transient and therefore axial length remains useful for long-term monitoring of axial elongation in children.

Introduction

Myopia is a major cause of vision impairment and its prevalence is estimated to double to almost 5 billion people by 2050.[1] Its progression is associated with axial elongation, which is characterized by stretching of the sclera.[2] Higher risks of cataract, glaucoma, macular, and chorio-retinal complications, particularly in high myopia (>6 D), have also been reported.[3] Both the direct and indirect costs associated with the diagnosis, treatment, and management of myopia will substantially increase the economic burden for health care systems.[4] Therefore, significant research has been undertaken examining different pharmacological and optical interventions[5] to slow myopia progression and to address the associated ocular complications.

Orthokeratology, one of the most effective and popular treatments for myopia control,[6–8] utilizes overnight reverse geometry rigid gas permeable contact lenses that flatten the central cornea and steepen the mid-peripheral cornea.[9] When fitting an orthokeratology lens, a compression factor (also

Choroidal Changes with Myopia Control

- 28 myopic children, 7 to 11 years
- Fit with orthokeratology lenses
- 1 month of wear
- Biometry measured weekly
- Axial length decreased by 26 µm at week 1
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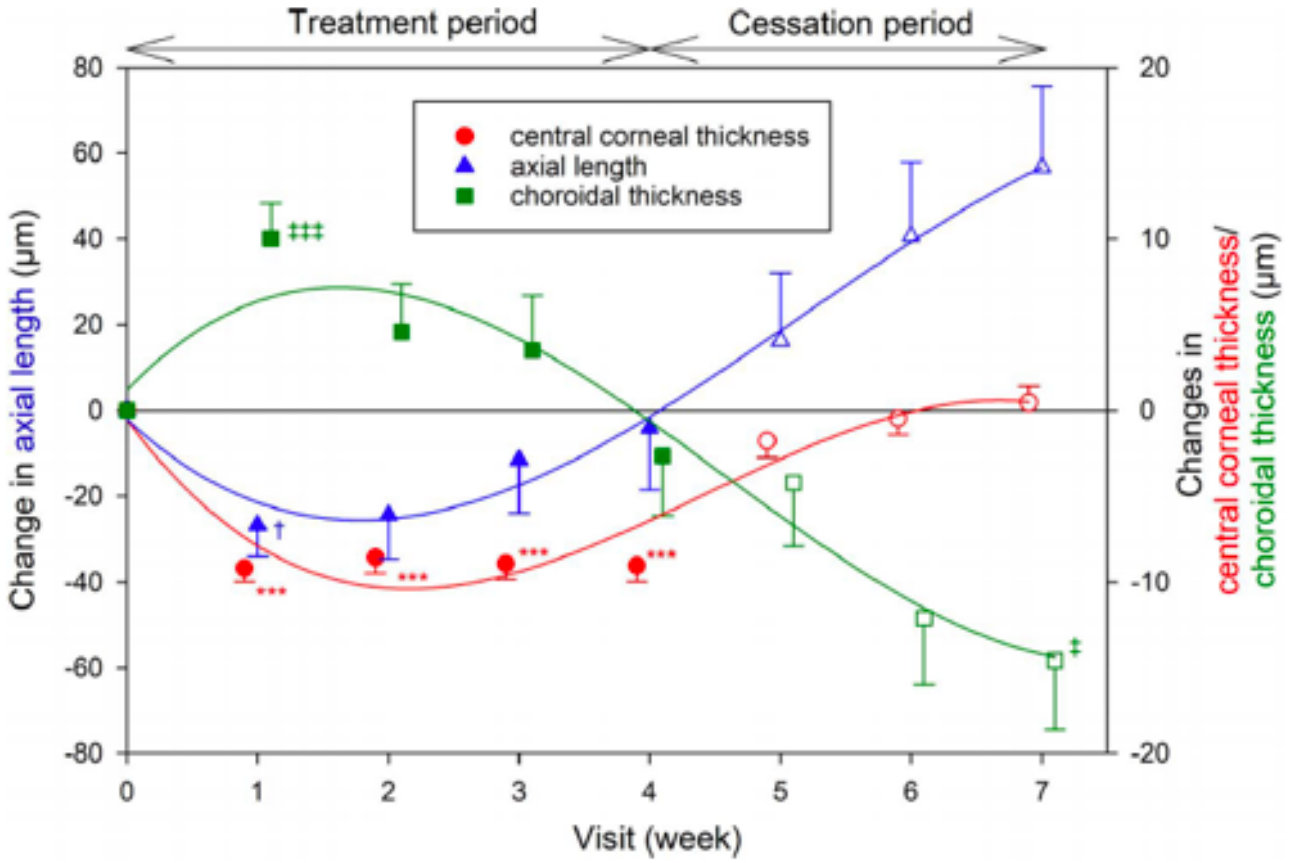

Inconsistencies

…among animal models

- Influence of constant light
- Spectral composition of ambient lighting
- Anterior segment involvement
- Influence of dual-focus lenses

…with human school-age myopia

- Plus lenses don’t prevent/slow
- Temporal integration and periods of distance/clear vision
- Effect of caffeine

Thank you

bullers2020@gmail.com
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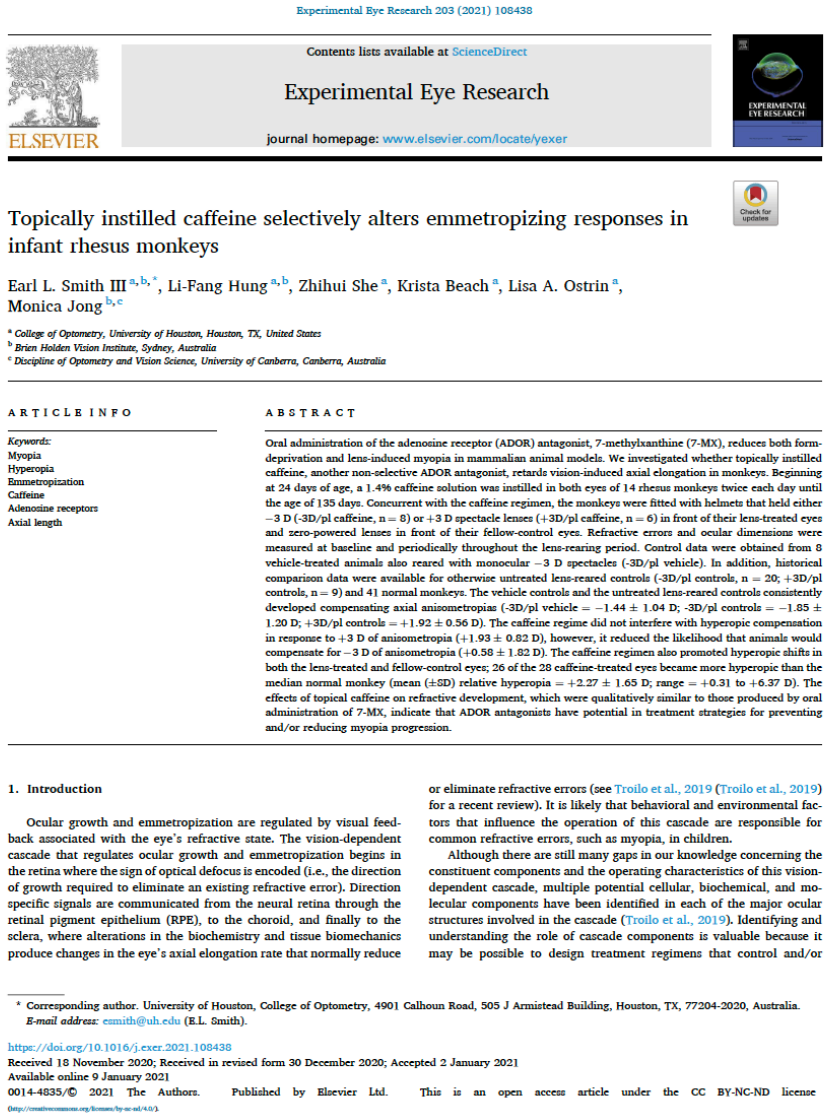
Caffeine Eye Drops

- 14 rhesus monkeys
- 1.4% caffeine solution
- Instilled in both eyes twice/day
- From 24 to 135 days of age
- Concurrently, wore either –3 D or +3 D spectacle lenses monocularly
- –3 D lens induced –1.44 D anisometropia with vehicle
- –3 D lens induced +0.58 D anisometropia with caffeine



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Topically instilled caffeine selectively alters emmetropizing responses in infant rhesus monkeys

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ABSTRACT

Oral administration of the adenosine receptor (ADOR) antagonist, 7-methylxanthine (7-MX), reduces both form-deprivation and lens-induced myopia in mammalian animal models. We investigated whether topically instilled caffeine, another non-selective ADOR antagonist, retards vision-induced axial elongation in monkeys. Beginning at 24 days of age, a 1.4% caffeine solution was instilled in both eyes of 14 rhesus monkeys twice each day until the age of 135 days. Concurrent with the caffeine regimen, the monkeys were fitted with helmets that held either −3 D (-3D/pl caffeine, n = 8) or +3 D spectacle lenses (+3D/pl caffeine, n = 6) in front of their lens-treated eyes and zero-powered lenses in front of their fellow-control eyes. Refractive errors and ocular dimensions were measured at baseline and periodically throughout the lens-rearing period. Control data were obtained from 8 vehicle-treated animals also reared with monocular −3 D spectacles (-3D/pl vehicle). In addition, historical comparison data were available for otherwise untreated lens-reared controls (-3D/pl controls, n = 20; +3D/pl controls, n = 9) and 41 normal monkeys. The vehicle controls and the untreated lens-reared controls consistently developed compensating axial anisometropias (-3D/pl vehicle = −1.44 ± 1.04 D; -3D/pl controls = −1.85 ± 1.20 D; +3D/pl controls = +1.92 ± 0.56 D). The caffeine regime did not interfere with hyperopic compensation in response to +3 D of anisometropia (+1.93 ± 0.82 D), however, it reduced the likelihood that animals would compensate for −3 D of anisometropia (+0.58 ± 1.82 D). The caffeine regimen also promoted hyperopic shifts in both the lens-treated and fellow-control eyes; 26 of the 28 caffeine-treated eyes became more hyperopic than the median normal monkey (mean (±SD) relative hyperopia = +2.27 ± 1.65 D; range = +0.31 to +6.37 D). The effects of topical caffeine on refractive development, which were qualitatively similar to those produced by oral administration of 7-MX, indicate that ADOR antagonists have potential in treatment strategies for preventing and/or reducing myopia progression.

1. Introduction

Ocular growth and emmetropization are regulated by visual feedback associated with the eye's refractive state. The vision-dependent cascade that regulates ocular growth and emmetropization begins in the retina where the sign of optical defocus is encoded (i.e., the direction of growth required to eliminate an existing refractive error). Direction specific signals are communicated from the neural retina through the retinal pigment epithelium (RPE), to the choroid, and finally to the sclera, where alterations in the biochemistry and tissue biomechanics produce changes in the eye's axial elongation rate that normally reduce or eliminate refractive errors (see Troilo et al., 2019 (Troilo et al., 2019) for a recent review). It is likely that behavioral and environmental factors that influence the operation of this cascade are responsible for common refractive errors, such as myopia, in children.

Although there are still many gaps in our knowledge concerning the constituent components and the operating characteristics of this vision-dependent cascade, multiple potential cellular, biochemical, and molecular components have been identified in each of the major ocular structures involved in the cascade (Troilo et al., 2019). Identifying and understanding the role of cascade components is valuable because it may be possible to design treatment regimens that control and/or

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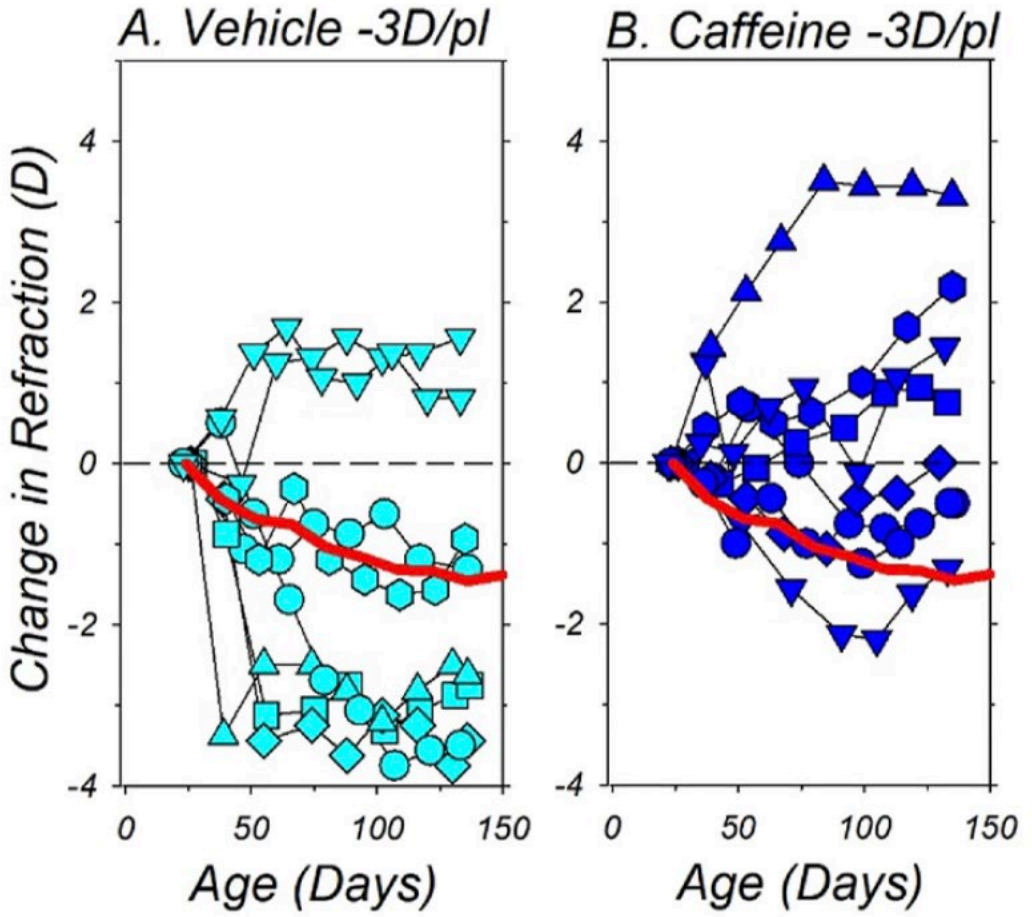

The Future of Myopia Control?

Myopia Control with Topical Caffeine with/without Atropine

- 96 Vietnamese myopic children (10.4 ± 2.0 years, –4.1 ± 1.3D)
- Randomized to nightly:
  - 2% Caffeine,
  - 0.02% Atropine + 2% Caffeine, or
  - 0.02% Atropine
- 86 children with myopia (10 ± 2.1 years, –3.3 ± 1.4 D) enrolled concurrently in parallel group to wear spectacles only

	ΔMyopia	ΔAxial
• Control	–0.76 D	0.37 mm
• Caffeine	–0.70 D	0.35 mm
• Atr. + Caffeine	–0.47 D	0.23 mm†
• Atropine	–0.46 D†	0.24 mm†

† significant after adjusting for confounders

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