Understanding Myopia: Pathogenesis and Mechanisms

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Key Points

- Visual environment (or the quality of the retinal image) modulates the refractive development of the eye.
- Ocular response to form-deprivation and lens induced defocus is evident across a wide range of animal species, including humans.
- The visual system appears to be more sensitive to myopic than hyperopic defocus.
- Evidence suggests that greater time spent outdoors is protective against development and progression of myopia in children.

4.1 Emmetropization and Normal Ocular Growth in Human Eyes

When incident parallel rays of light from distant objects are brought to a focus upon the retina without accommodation, it is known as emmetropia. During postnatal eye growth, the precise matching of the axial length (the distance from the anterior corneal surface to the retina along the visual axis) and the optical power of the eye brings the eye to emmetropia [1, 2]. This active regulatory process that harmonizes the expansion of the eye with the optical power of the cornea and the crystalline lens

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is known as emmetropization [1]. Any disruption to these highly coordinated ocular changes results in the development of refractive errors, wherein distant images are focused either behind (hyperopia) or in front (myopia) of the retina [1].

Human eyes exhibit a distinctive pattern of eye growth during the early period of visual development. The distribution of refractive errors at birth appears to be normally distributed [3, 4]. Apart from some exceptions [5], the majority of newborn infants are moderately hyperopic (~+2.00 to +4.00 D) and this refractive error reduces significantly during the first 18 months of life [3, 6–8] (Fig. 4.1). By about 2–5 years of age, the distribution becomes leptokurtic with a peak around emmetropia to low hyperopia of about +0.50 to +1.00 D [5, 6, 8, 11, 12]. Although studies have reported small reductions in hyperopic refraction until the middle to late teen years [13, 14], emmetropization is believed to be largely completed by 5–6 years of age [5, 6, 8, 14].

Based on the visually guided ocular growth observed in a variety of animal models [15–17] (see Sect. 4.3), the growth of the human eye is also believed to be modulated by an active visual feedback from the hyperopic refractive error in neonatal eyes [18]. Studies have found a strong correlation between the rapid reduction in hyperopia and the changes in axial length during early ocular development [18, 19]. Human eyes are ~17 mm long after birth and grow to about 20 mm after the first year [11, 18–20]. This rapid expansion of the eye is largely attributed to the

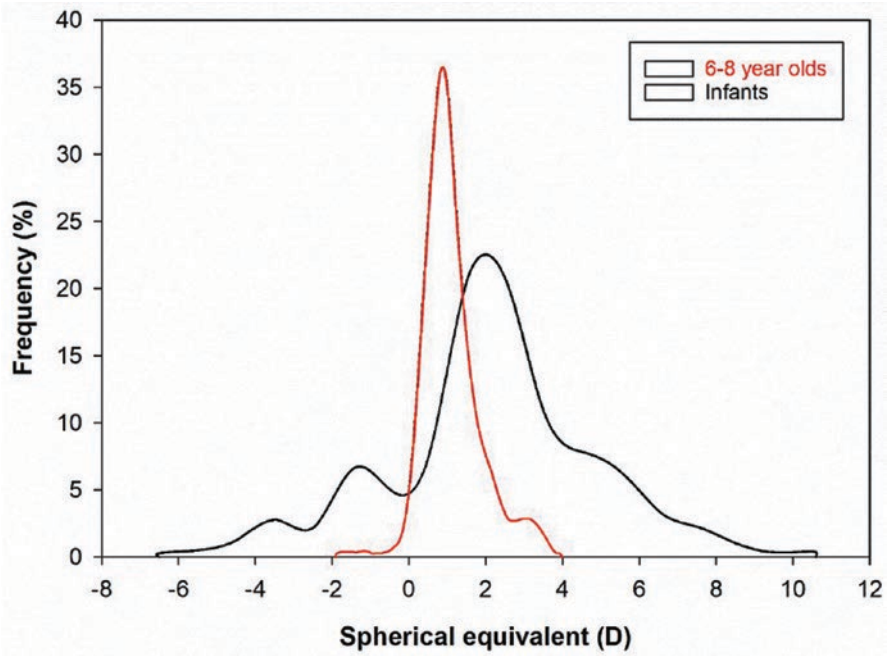

Fig. 4.1 Comparison of refractive error distribution among newborns [3] and 6–8-year-old children [9]. The distribution of refractive errors narrows between infancy to early childhood during the process of emmetropization. Adapted from FitzGerald and Duckman [10]

expansion of the vitreous chamber [18, 21]. From 2–3 years of age, axial elongation slows to approximately 0.4 mm/year until preschool age [11]. Consistent with changes in ocular refraction, the growth of the eye stabilizes further at 5–6 years, and only increases by 1–1.5 mm through the teenage years [11, 20, 21]. Together, these studies suggest that axial length is the most influential factor for emmetropization in human eyes.

In addition to changes in axial length, there is also a significant reduction in the refractive power of the cornea and the crystalline lens that contributes to the overall reduction in hyperopia in the first year of life [11, 18, 22]. Mutti et al. [18] reported a reduction of 1.07 and 3.62 D in corneal and crystalline lens powers, respectively, associated with flattening of the corneal and lens radii in newborn infants, between the ages of 3 and 9 months. Studies have also found higher degrees of corneal astigmatism in newborn infants [23–28], which reduces during the first 4 years of life and is associated with corneal flattening [24, 27, 29, 30]. Overall, these studies suggest that emmetropization in human eyes is largely attributed to the changes in axial length with minor contributions from corneal and crystalline lens powers.

Refractive errors occur as a result of either variations in (a) axial length with respect to the total refractive power of the eye (termed axial myopia or hyperopia) or (b) refractive power of the cornea and the crystalline lens with respect to the axial length of the eye (termed refractive myopia or hyperopia). This chapter focuses on the pathogenesis and potential underlying mechanisms of myopia, and the following section discusses the changes in different ocular parameters during myopic eye growth.

4.2 Ocular Biometric Changes in Human Myopia

As discussed earlier, the axial length of the eye is the primary biometric determinant of refractive error; however, the dimensions, curvature, and refractive index of each individual ocular structure contribute to the final refractive state. Ocular biometrics vary considerably throughout childhood, during the development and progression of myopia, and in response to clinical myopia control interventions.

4.2.1 Cornea

Several cross-sectional analyses have revealed a weak association between increasing corneal power (a steeper radius of curvature) and increasing levels of myopia [31–33], while others report no association [34], or the opposite relationship [35]. Longitudinal studies indicate that changes in corneal curvature during childhood [36–38] and early adulthood [39] are minimal and not associated with the magnitude of myopia progression. However, since the correlation between spherical equivalent refraction (SER) and the axial length to corneal radius ratio is typically stronger than that of axial length alone (by 15–20%) [40–43], corneal curvature does appear to make a modest contribution to the magnitude of myopia. Although

corneal thickness does not vary systematically with refractive error [44–47], a reduction in corneal hysteresis (an estimate of corneal biomechanical strength or viscoelasticity) has been observed with increasing levels of myopia in children [48, 49] and adults [50–52]. However, the causal nature of this relationship remains unclear, or if such corneal metrics correlate with posterior scleral biomechanics.

4.2.2 Crystalline Lens and Anterior Chamber Depth

While the cornea flattens substantially during infancy and then remains relatively stable throughout childhood, the crystalline lens continues to thin, flatten, and reduce in optical power until approximately 10 years (a 0.25–0.50 D reduction per year), concurrent with lens fiber compaction [53–55]. These changes may be part of an emmetropization mechanism to compensate for continued axial elongation or a mechanical consequence of equatorial eye growth. Across a range of ethnicities, Mutti et al. [56] observed that within 1 year of myopia onset, compensatory crystalline lens thinning and flattening abruptly halted compared to children who remained emmetropic (Fig. 4.2), suggesting that childhood myopia is not purely axial in nature, but involves a decoupling of highly correlated anterior and posterior segment eye growth. In Singaporean children, Iribarren et al. [57] reported a transient acceleration in the reduction of lens power during myopia onset when the rate

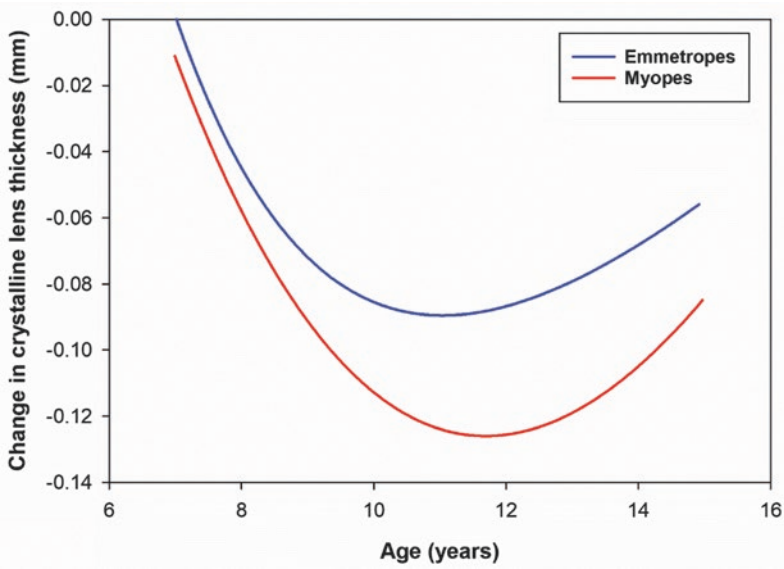

Fig. 4.2 The change in crystalline lens thickness as a function of age in myopes and emmetropes during childhood (after Mutti et al. [56]). Shortly after myopia onset (10–12 years), compensatory crystalline lens thinning abruptly halted compared to children who remained emmetropic suggesting that myopia development involves a decoupling of anterior and posterior segment eye growth

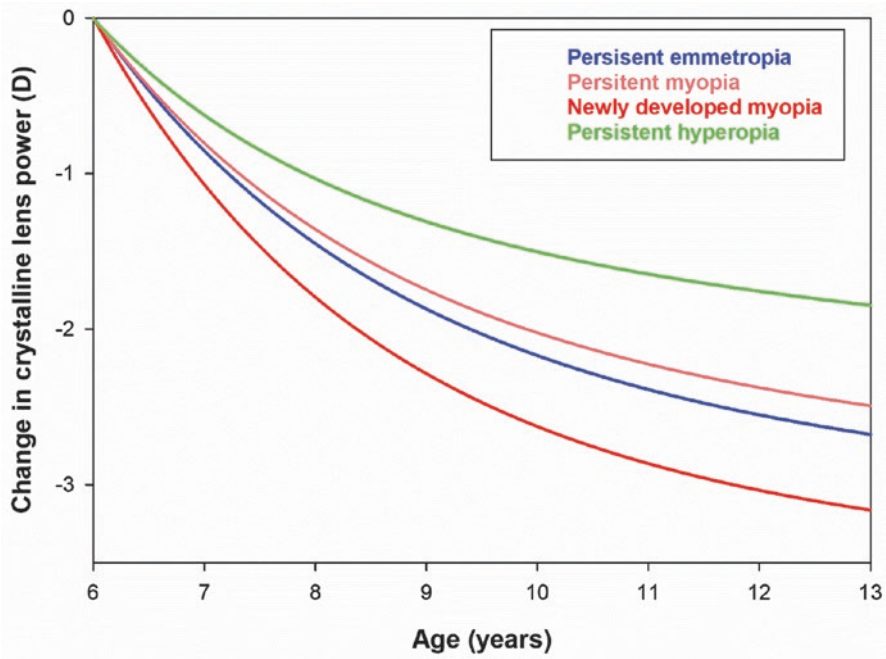

Fig. 4.3 The change in crystalline lens power during childhood (calculated from refraction and biometric measurements) in young Singaporean children for a range of refractive error groups (after Iribarren et al. [57]) The reduction in lens power increases during myopia onset (to a greater extent than other refractive error groups), but is not sustained throughout myopia progression

of axial growth was high, which was not sustained as myopia progressed (Fig. 4.3). Paradoxically, after 10 years of age, the lens continues to thicken and increase in curvature with the bedding down of additional fibers, but reduces in optical power, most likely due to a steepening of the gradient refractive index [58]. Changes in anterior chamber depth throughout childhood are inversely related to changes in lens thickness (as the lens thins, the anterior chamber deepens), and the anterior chamber is typically deeper in myopes compared to emmetropes and vice versa for the crystalline lens [53].

4.2.3 Vitreous Chamber and Axial Length

In contrast to the anterior segment, changes in the posterior segment (particularly, the vitreous chamber, choroid, and sclera) are more pronounced in myopic compared to non-myopic eyes (Fig. 4.4). Axial length, or more precisely, the vitreous chamber depth is the primary individual biometric contributor to refractive error in children, young adults, and the elderly [34, 59, 60], with the vitreous chamber depth accounting for over 50% of the observed variation in SER, followed by the cornea (~15%) and crystalline lens (~1%) [60]. Modeling of cross-sectional and

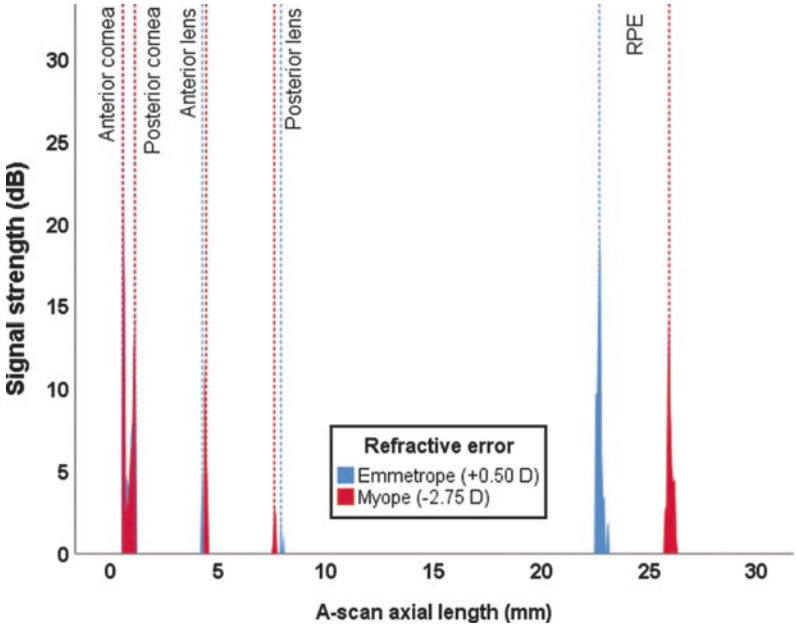

Fig. 4.4 Optical low coherence reflectometry A-Scan output from two 11-year-old males (one myope and one emmetrope). The predominant biometric differences are the deeper vitreous chamber (19.05 mm compared to 15.47 mm) and the longer axial length (25.87 mm compared to 22.69 mm) in the myopic eye. The anterior chamber depth is slightly shallower in the emmetropic eye (by 0.13 mm) while the crystalline lens is thicker (by 0.49 mm) in comparison to the myopic eye. The corneal thickness varies by only 0.04 mm

longitudinal data from emmetropic children indicates that axial length and vitreous chamber depth increase by approximately 0.16 mm per year from age 6–10 years, slowing to 0.05 mm per year from 11 to 14 years [61]. In myopic children aged between 6 and 11 years (corrected with single vision spectacles or contact lenses) average growth rates of approximately 0.30 mm per year have been reported [37, 62, 63], with greater vitreous chamber and axial elongation observed in younger females with myopic parents [37]. A range of myopia control interventions significantly slow the rate of eye growth and myopia progression during childhood, in some cases by up to 50% [64], and this reduction in axial elongation appears to be initially modulated by changes in the choroid underlying the retina.

4.2.4 Choroid

The choroid supplies the outer retina with oxygen and nutrients and regulates intraocular pressure and ocular temperature. The choroid is typically thinner in myopic compared to non-myopic eyes (most pronounced at the fovea [65, 66]) and thins with increasing myopia and axial length in both adults [67–74] and children [75–77]. Significant choroidal thinning is also observed in high myopia (<−6.00 D) or

eyes with posterior staphyloma [78], and has been associated with the presence of lacquer cracks [79], choroidal neovascularization [80], and reduced visual acuity [81]. The choroid also appears to be a biomarker of ocular processes regulating eye growth given that the central macular choroid thins during the initial development and progression of myopia [82–84] and thickens in response to imposed peripheral myopic retinal image defocus [85, 86], topical anti-muscarinic agents [87, 88], and increased light exposure [89] (clinical interventions associated with a slowing of eye growth in children).

4.2.5 Sclera

Scleral thinning associated with axial myopia is primarily restricted to the posterior pole [90–92], due to scleral tissue redistribution [93]. Scleral thinning may alter the tissue strength surrounding the optic nerve head, rendering myopic eyes more susceptible to glaucomatous damage [94, 95]. Consequently, posterior reinforcement surgery using donor scleral tissue has been refined over the years to arrest further axial elongation and scleral thinning in highly myopic eyes [96, 97]. Although anterior scleral thickness is similar between myopic and non-myopic eyes [98–100], there is growing evidence that the anterior sclera thins slightly during accommodation, particularly in myopic eyes [101, 102], most likely due to biomechanical forces of the ciliary muscle. A greater thinning observed in myopic eyes may be a result of a thicker posterior ciliary muscle [103–105] or changes in biomechanical properties of the sclera reported in animal models of form-deprivation myopia [106, 107].

4.3 Visual Environment, Emmetropization, and Myopia: Evidence from Animal Models

Over the last four decades, numerous animal models have provided valuable insight into the mechanisms underlying emmetropization and refractive error development. Much of the knowledge on vision-dependent changes in ocular growth has emanated from animal experiments in which either the quality of image formed on the retina is degraded (known as form-deprivation [FD]), or the focal point of the image is altered with respect to the retinal plane (known as lens induced defocus). Both FD and lens induced defocus result in abnormal eye growth and development of refractive errors. This section summarizes the attributes of experimental ametropias derived from these two visual manipulations, their differences, and significance for understanding refractive error development in humans.

4.3.1 Form-Deprivation Myopia

FD is the most commonly used experimental paradigm to model axial myopia in animals. Depriving the retina of form or patterned vision through eyelid suture

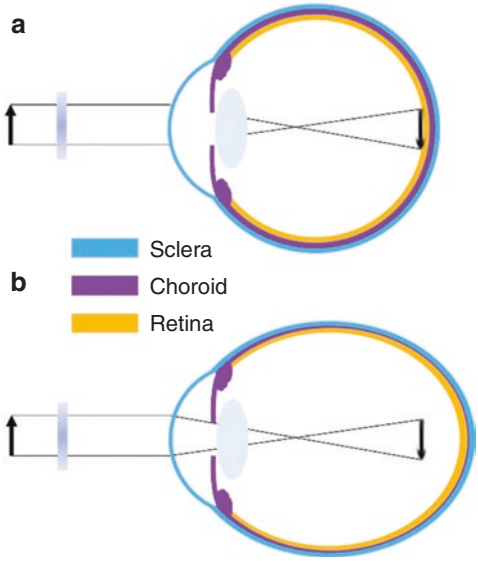

Fig. 4.5 Ocular compensation for form-deprivation (FD). (**a**) A diffuser causes nondirectional blur and a reduction in contrast of the retinal image. (**b**) The absence of visual feedback related to the effective refractive state of the eye causes a thinning of the posterior choroid and an increase in ocular growth, resulting in myopia

[108–110], or translucent diffusers [2, 15, 111–114] consistently produces axial myopia (Fig. 4.5). The use of noncontact translucent diffusers offers a more reliable representation of ocular changes with FD since they do not induce corneal changes (unlike eyelid fusion techniques). The ocular changes observed in response to FD clearly illustrate that degrading retinal image quality can produce robust myopic changes. Schaeffel et al. [115] proposed that FD is an open-loop condition, in which myopia develops as a result of uncoordinated ocular growth due to reduced retinal image contrast (or mid-range spatial frequency vision) [116] and the absence of visual feedback related to the effective refractive state of the eye [117].

The myopic response to FD varies among different animals. It is generally greatest in chickens (−9 D after 5 days of FD) [118], followed by tree shrews (−8 D after 12 days in young animals) [119] and guinea pigs (−6.6 D after 11 days) [113], and is less pronounced and much more variable in marmosets (−8 D after 4.5 weeks) [120] and rhesus monkeys (~−5 to −6 D after 17 weeks) [121, 122]. Variations observed between individual studies and animal models may be due to differences in experimental paradigms, the duration and extent of FD, inherent ocular anatomical variations, and/or differences in susceptibility to environmental myopia. Nevertheless, the myopic response to FD is conserved across a wide range of animal species (including fish, rabbit, mouse, and kestrel) [123]. In all species, axial myopia is predominantly caused by a significant elongation of the vitreous chamber, along with thinning of the choroid and the sclera [16, 17, 113, 124–132]. Few studies have also reported changes in corneal curvature and lens thickness with FD [131, 133–135]. Interestingly, ocular conditions that cause varying degrees of visual deprivation in humans such as ptosis [136], congenital cataract [137], corneal opacity [138], and vitreous hemorrhage [139] are associated with myopia, which may result from mechanisms similar to FD myopia observed in animals.

FD myopia is a graded phenomenon, where increasing degrees of image degradation are positively correlated with the magnitude of induced axial myopia [129, 140]. In addition, the effects of FD declines with age. Younger chicks [141, 142], macaques [143], tree shrews [119], and marmosets [144] show greater ocular changes in response to image degradation compared to older animals, potentially due to age-related reductions in sensory processing of blur stimuli or changes in scleral growth [144].

4.3.2 Lens Defocus Ametropias

Perhaps the strongest evidence of visual regulation of ocular growth comes from animal studies that show eyes can actively compensate for artificially induced myopic and hyperopic defocus by adjusting the axial length to the altered focal plane (i.e., emmetropization through the treatment lenses) (Fig. 4.6) [145]. Myopic defocus with plus lenses simulates artificial myopia that leads to a thickening of the choroid (moving the retina forward) and a reduction in the overall growth of the eye, thus, causing a hyperopic refractive error. Conversely, hyperopic defocus with minus lenses induces artificial hyperopia that leads to a thinning of the choroid

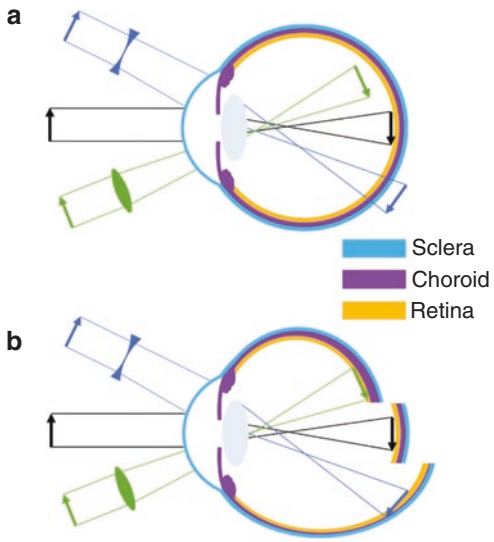

Fig. 4.6 (**a**) Schematic of imposed lens defocus. With no lens (black arrow), incident parallel rays of light from distant objects are focused on the retina. A plus lens (green, convex) causes the retinal image to focus in front of the retina known as myopic defocus, whereas a minus lens (blue, concave) focuses the image behind the retina known as hyperopic defocus. (**b**) A normal eye with no imposed lens defocus (black) exhibits normal ocular growth and choroidal thickness. Myopic defocus with plus lenses (green) causes a thickening of the choroid (moving the retina forward) and a reduction in the overall growth of the eye, causing a hyperopic refractive error. Hyperopic defocus with minus lenses (blue) leads to a thinning of the choroid (moving the retina backward) and an increase in ocular growth, resulting in myopia. Adapted from Wallman J and Winawer J, 2004 [1]

(moving the retina backward) and an increase in ocular growth, resulting in myopia to re-establish the optimal refractive state. This phenomenon was first documented in chicks [145], and has been extensively studied in chicks [16, 17, 146–148], tree shrews [149], rhesus monkeys [15, 150], marmosets [151], guinea pigs [152, 153], and mice [154] thereafter, indicating that the mechanisms regulating ocular growth can distinguish the sign of the imposed defocus in a wide range of animal species.

Chick eyes can compensate for a remarkable range of +15 to −10 D of imposed defocus [16, 147]. However, the operating range of defocus is much smaller for other animal species (monkey: −2 to +8 D [15], marmosets: −8 to <+4 D [151], tree shrew: −10 to +4 D [155], guinea pig: −7 to +4 D) [152, 156]. Compared to birds, the inability of primates to compensate for greater magnitudes of defocus may be due to bigger eye size [15, 150], the process of emmetropization [150], differences in the accommodative response to defocus stimuli, and/or the degree of independent accommodation between fellow eyes [15, 150, 157]. In all animals, the axial response to lens induced defocus is dependent upon the power of the treatment lens [147, 149–152, 158], and is predominantly attributed to the changes in vitreous chamber depth [16, 147, 159]. Similar to FD, the ocular response to lens induced defocus decreases with age [16]. Recent evidence suggests that the human visual system may also be able to detect the sign and magnitude of imposed defocus and make compensatory changes in axial length, similar to other animals. A number of studies have reported small bidirectional changes in axial length and choroidal thickness in response to 1–2 h of myopic and hyperopic defocus in children and young adults [160–165].

Studies have shown that the biological mechanisms underlying alterations in ocular growth to myopic and hyperopic defocus may be completely different (and not merely opposite to each other), and that the visual system is perhaps more sensitive to myopic defocus [166, 167]. In fact, the ocular response to lens induced defocus depends on the frequency and duration of lens wear, and not simply the "total duration" per day [166–169]. These findings argue for a nonlinear processing of myopic and hyperopic defocus signals across the retina [166, 167].

4.3.3 Comparing Form-Deprivation and Lens Defocus

Although FD and lens induced defocus use different visual stimuli to induce compensatory changes in ocular growth, there are features that are common to both visual manipulations. Removal of the visual manipulation triggers "recovery" from both FD and lens induced defocus [16, 17, 170]. During this recovery phase, the eyes quickly return to emmetropia by reversing the changes in choroidal thickness and axial eye growth (mainly by changing the vitreous chamber depth) [16, 17, 119, 150, 151, 170–173].

Further evidence from animal work suggests that the elimination of accommodation by cycloplegia, ciliary nerve section or damage to the Edinger-Westphal nucleus does not prevent the response to imposed FD [145, 174] or lens induced defocus [148, 175]. These results suggest that intact accommodation is not essential for visually guided growth [176] or there might be another accommodative pathway (not through ciliary and iris sphincter muscles) underlying optical defocus induced alterations in ocular growth [175].

Other studies argue that mechanisms underlying the response to FD and lens induced defocus may not be the same [177]. Some studies show different light paradigms selectively disrupt the response to FD or lens induced defocus [178–180]. For instance, high luminance levels inhibit myopia caused by FD in monkeys and chicks, but only slow the response to negative lenses [181, 182]. Furthermore, dopamine (a strong ocular growth inhibitor, see Sect. 4.4.1) may not signal eye growth in a similar manner for these two forms of experimental myopia [183]. While most studies indicate that dopamine agonists block increased axial elongation [177], one study reported that dopamine agonists inhibit FD, but not lens-induced myopia in guinea pigs [184]. More studies are needed to determine if these contradictory results are due to different regulatory mechanisms of eye growth or other parameters of the experimental paradigm.

4.4 Other Visual Cues for Emmetropization

Whilst the clarity of the retinal image dominates the nature of ocular growth, other visual cues may also influence the process of emmetropization. This section examines some of the important cues that could significantly affect retinal image quality, and hence ocular growth in human eyes.

4.4.1 Retinal Physiology

Work from animal models suggests that retinal defocus (or visual blur) initiates a signaling cascade that leads to a number of cellular and biochemical changes in the retina and the retinal pigment epithelium (RPE), which signal changes to the choroid, and eventually the sclera, leading to alterations in the overall growth and refractive state of the eye (Fig. 4.7) [16, 17, 185]. The retina is an integral part of this visual signaling as it is the first layer of photosensory neurons that detect

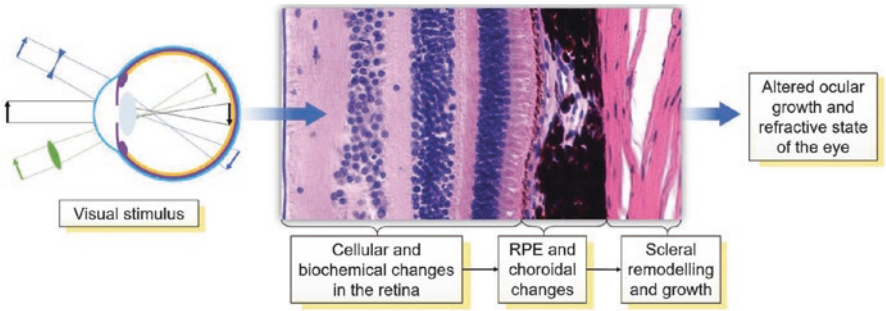

Fig. 4.7 A biochemical signal cascade beginning at the retina and ending at the sclera regulating ocular growth and the refractive state. Retinal defocus may initiate a signaling cascade that leads to a number of cellular and biochemical changes in the retina and the retinal pigment epithelium (RPE), the choroid, and eventually the sclera, leading to alterations in the overall growth and the refractive state of the eye

defocus [186]. Furthermore, ocular compensation for both FD and lens induced defocus are largely regulated at the retinal level. Severing the optic nerve in young chicks does not prevent the development of refractive errors in response to spectacle lenses [16, 187] or diffusers [130]. In both chicks [17, 188, 189] and primates [190], partial diffusers and hemifield spectacle lenses restricted to only half of the visual field cause corresponding myopic changes only in the visually deprived part of the globe. These studies demonstrate that the visual regulation of ocular growth in response to diffusers and lenses primarily occurs within the retina, with minimal input from the brain.

Retinal neurons also secrete a number of growth regulatory neurotransmitters (such as dopamine [191, 192], retinoic acid [153], nitric oxide [193, 194] and glucagon [195]) that can directly alter ocular growth in mammalian eyes. Dopamine, one of the most widely studied neurotransmitters with regard to myopia in animal models, has been implicated as a potent stop signal for myopic eye growth [183, 196]. In both chickens [191, 197] and primates [198], FD myopia is associated with lower levels of 3,4-dihydroxyphenylacetate (DOPAC, the primary metabolite of dopamine) and dopamine in the retina. Although the protective effects of outdoor light exposure on myopia development in children has been hypothesized to be mediated by greater dopamine synthesis in the eye (see Sect. 4.5), the exact mechanisms underlying the protective effects of dopamine on myopia are not fully known. Together, these studies suggest that alterations in normal retinal physiology and/or changes in retinal neurotransmitters may lead to the development of refractive errors, as shown in chickens [186, 199, 200] and mice [201–206]. Some features of retinal abnormalities and refractive errors are evident in humans as well; for instance, NYX [207] and GRM6 [208] retinal ON pathway mutations and retinal degenerations such as cone-rod dystrophy [209] and retinitis pigmentosa [210] are associated with myopia.

4.4.2 Aberrations

A long held belief is that myopia may develop due to the eye's emmetropization response to inherent ocular aberrations that degrade retinal image quality and trigger axial elongation [211]. Since there is minimal variation in longitudinal chromatic aberration between individuals or refractive error groups in humans [212], most investigations have focused on monochromatic higher order aberrations (HOAs) as a potential myopigenic stimulus. Evidence concerning the relationship between HOAs during distance viewing and refractive error from cross-sectional studies is conflicting [211, 213]. However, during or following near work tasks, adult myopic eyes tend to display a transient increase in corneal and total ocular HOAs (Figs. 4.8 and 4.9), suggesting a potential role for near work induced retinal image degradation in myopia development [214, 215]. Longitudinal studies of myopic children also indicate that eyes with greater positive spherical aberration demonstrate slower eye growth [63, 216].

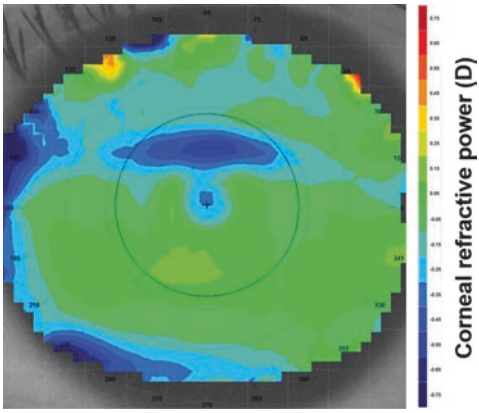

Fig. 4.8 Corneal refractive power difference map following a 10 min reading task at 25° downward gaze. The black circle denotes the pupil outline detected by the video keratoscope. A horizontal band of corneal flattening is observed in the superior aspect of the pupil corresponding to the position of the upper eyelid during downward gaze. This refractive change is equivalent to a 0.20 D hyperopic shift over the central 4 mm

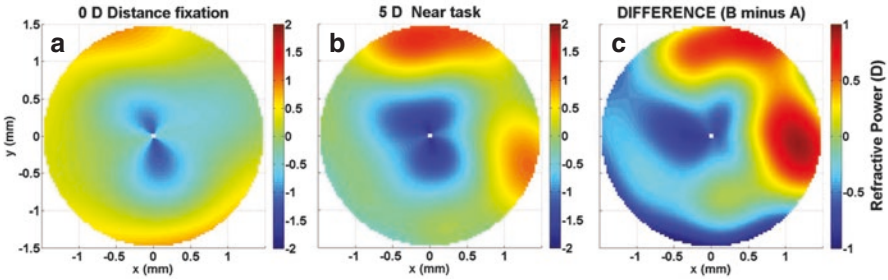

Fig. 4.9 Refractive power maps, a graphical representation of total ocular higher order aberrations, during (**a**) distance fixation (0 D accommodation demand), (**b**) a 5 D accommodation task, and (**c**) the difference (B minus A) over a 3 mm pupil diameter. A significant increase in negative spherical aberration of −0.10 μm is displayed

A number of myopia control interventions also alter the HOA and peripheral refraction profile. While relative peripheral refraction was initially thought to modulate central eye growth, recent longitudinal studies have found no association between peripheral refraction and myopia progression in children [217, 218]. Multifocal soft contact lenses and orthokeratology significantly increase the magnitude of positive spherical aberration [219, 220]. The anticholinergic agent atropine may also provide visual feedback that influences eye growth due to an increase in positive spherical aberration or horizontal coma associated with cycloplegia and pupil mydriasis, respectively [221]. Collectively, these findings suggest that changes in HOAs may influence eye growth and refractive development during childhood.

4.4.3 Accommodation

Given the association between near work and the development and progression of childhood myopia [222], numerous studies have compared various characteristics of accommodation between refractive error groups, typically the accuracy of the accommodation response, since a lag of accommodation (hyperopic retinal defocus) may stimulate axial elongation as observed in animal models. Using a range of experimental approaches, the accommodative response to a 3 D accommodative stimulus is ~0.25 to 1.00 D less in myopic adults compared to emmetropes [223–227]. The slowing of myopia progression during childhood with progressive addition or bifocal lenses, designed to improve accommodation accuracy and minimize a lag of accommodation, adds some weight to the role of accommodation in myopia development and progression [62, 228]. However, the exact underlying mechanism of myopia control with such lenses may be related to imposed peripheral retinal defocus or a reduction in the near vergence demand [229]. In a longitudinal study of young infants [230], a significant relationship was observed between the accommodative response and the reduction in neonatal refractive error in the first 2 years of life, supporting a potential role for accommodation-guided eye growth.

4.4.4 Circadian Rhythms

Like many of the human body's physiological processes, numerous ocular structures and functions exhibit cyclic variations over the course of the day. Visual inputs such as daily patterns of light exposure are considered critical factors in entraining the timing of these circadian rhythms. Findings from animal studies demonstrate that normal eye growth exhibits significant circadian variations, with the eye generally being longest during the day and shorter at night [231]. Choroidal thickness also exhibits a circadian rhythm in normal eyes, which is generally in antiphase to the rhythms in axial length [172]. Similar patterns of diurnal variation in axial length and choroidal thickness have also been documented in normal human eyes [232–234].

It has also been suggested that ocular circadian rhythms may play a role in eye growth regulation and the development of myopia, since altering the visual inputs that drive circadian rhythms (e.g., rearing animals in constant light [235] or constant darkness [236], or exposing the eye to bright light at night time [237]) can result in alterations in normal eye growth in animal models. Furthermore, when refractive errors (both hyperopic and myopic) are induced experimentally in animals, changes in the magnitude and phase of the normal circadian rhythms of axial length and choroidal thickness also occur, which also supports a potential role of circadian rhythms in the development of refractive errors [172, 238]. These findings from animal research were paralleled by studies in young adult humans, where changes in the normal diurnal rhythms of axial length and choroidal thickness occurred in response to short-term (12-h) exposure to monocular myopic [165], and hyperopic blur [163]. Although the exact role played by circadian rhythms in the regulation of

human eye growth is not fully understood, human studies also indicate that myopes exhibit alterations in their systemic melatonin levels [239], and also exhibit altered sleep patterns [240] compared to non-myopic individuals.

4.5 Effects of Key Environmental Factors on Myopia

As discussed in Chaps. 1 and 2, myopia represents a "complex" disorder with both environmental and genetic origins [241, 242]. This section discusses some of the important environmental factors, and their influence on myopia.

4.5.1 Near Work and Education

Since the age when myopia normally develops and progresses coincides with the school years, myopia has long been suggested to be connected with increased levels of education. Indeed, numerous studies conducted across a range of different populations have consistently found that higher levels of education are associated with a higher prevalence of myopia [243–245]. The exact mechanism linking increased education with myopia, however, is less clear. Although it is possible that optical [214, 224] or biomechanical [246, 247] ocular changes associated with near work could potentially promote myopic eye growth in those with higher levels of education (and hence near work demands), population studies examining the link between near work activities and myopia have been conflicting, with some studies suggesting an association between near work and myopia [222, 248], and others indicating no significant effects [249]. The relatively inconsistent findings linking near work with myopia development suggests a potential role for other factors in the association between education and myopia, such as a lack of outdoor light exposure, discussed further below.

4.5.2 Urbanization

Aspects of the living environment may also be involved in the development and progression of myopia, since population-based studies consistently report a higher prevalence of myopia in children living in urban regions, compared to children living in rural regions [250, 251]. These associations between the urban environment and myopia could at least partially be explained by socioeconomic and educational differences between urban and rural regions, which could in turn result in differences in near work and outdoor activities. However, a number of recent studies indicate that a higher population density is significantly associated with increased myopia prevalence in children, independent of near work and outdoor activities [252, 253]. This suggests other aspects of the urban environment may potentially impact upon eye growth. Studies have also reported associations between housing type and myopia, with children living in smaller homes reported to have a significantly higher

prevalence of myopia [253, 254]. Although further research is required to establish the causative nature and mechanisms underlying these associations, it has been hypothesized that a constricted living space may result in an increased exposure to hyperopic blur, thus promoting myopia.

4.5.3 Light Exposure

A number of recent studies report that the time children spend engaged in outdoor activities is negatively associated with their risk of myopia [241, 249, 255–259]. Both cross-sectional and longitudinal studies indicate that greater time spent outdoors is associated with a significantly lower myopia prevalence and reduced risk of myopia onset in childhood. Although some studies report significant associations between myopia progression and outdoor activity [257, 259], this is not a consistent finding across all longitudinal studies [260]. A recent meta-analysis of studies examining the relationship between outdoor time and myopia indicated that there was a 2% reduction in the odds of having myopia for each additional hour per week spent outdoors [261].

These associations [241, 255, 256] have prompted recent interest in the potential influence of light exposure in the regulation of eye growth and myopia. Since outdoor activity typically involves exposure to high intensity light, it has been hypothesized that increased exposure to bright light may be the important factor underlying these protective effects of outdoor activity [256]. Other factors, such as the typical pattern of retinal focus experienced in outdoor environments (which is likely to involve less near focusing and potentially less exposure to hyperopic blur), may also play a role [262].

Light Intensity and Myopia Animal studies indicate that the intensity of daily light exposure can influence refractive development. In normal growing young chickens, rearing animals under a normal daily light-dark cycle, but with daily bright ambient lighting (~10,000 lux) resulted in significantly less myopic refractive errors than when animals were reared under dim ambient lighting during the day (50 lux) [263]. Bright light exposure also inhibits the development of FD myopia in a range of different animal species [114, 181, 264], with the strength of inhibitory effects correlating significantly with the log of the intensity of ambient light exposure [264]. The effects of increased light intensity upon lens induced myopia (through imposing hyperopic defocus) in animals however are less consistent, with either a slowing of lens compensation (with no change in refractive endpoint) [182], or no significant effects on lens compensation reported [265].

Recent observational longitudinal studies in humans utilizing wearable light sensors to assess ambient light exposure have enabled the relationship between light exposure and axial eye growth in childhood to be examined [266, 267]. Similar to findings in animals, both of these recent studies have reported that slower axial eye growth is associated with greater daily ambient light exposure (with a 1-log unit

increase in light exposure being associated with ~0.1 mm/year slower axial eye growth), with this relationship reaching statistical significance in the study with the larger sample size ($n = 102$) [266], and bordering on significance ($p = 0.07$, $n = 60$) in the other study [267]. A recent randomized, controlled trial in Taiwan examined the effect of increasing outdoor time during the school day (an extra 40 min of outdoor time during school recess) upon myopia development and axial eye growth over 12 months [268]. In this study, light exposure was also monitored using wearable light sensors, and a significant association between greater light exposure and slower myopia progression was also documented. Collectively, these studies suggest that increased light exposure is associated with slower axial eye growth in the human eye.

Increased light exposure may also underlie some of the differences in myopia prevalence found in different geographic locations. A recent study compared the habitual ambient light exposure (captured with wearable light sensors) of children living in Singapore (a country with some of the highest reported levels of childhood myopia prevalence [269]) with children living in Australia (where myopia prevalence is generally reported to be relatively low [270]) and found substantially lower levels of outdoor light exposure in the children living in Singapore (Fig. 4.10) [271].

Duration of Light Exposure and Myopia Animal studies examining the effects of increased light exposure upon myopia development have generally used experimental paradigms where elevated light levels were applied continuously for the full day. Lan et al. [272] examined the influence of different daily durations of bright light exposure upon inhibition of myopia in chickens. They found bright light applied for

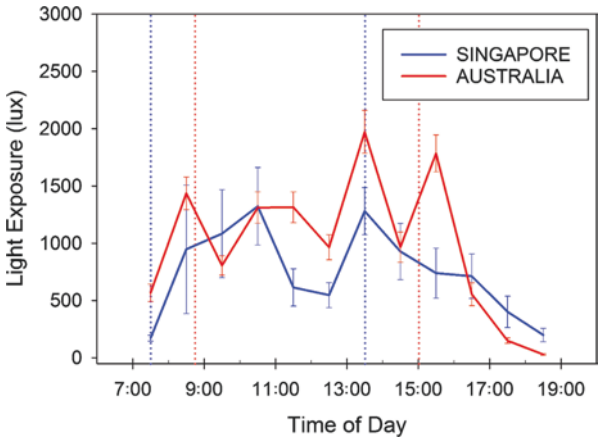

Fig. 4.10 Average hourly light exposure of Australian (red lines) and Singaporean (blue lines) children assessed during school weekdays using wearable light sensors. Note the substantially greater light exposure for the Australian children at a number of periods throughout the day [271]. This lower daily exposure to bright outdoor light may be one factor underlying the higher myopia prevalence typically observed in Singaporean children. Dashed lines indicate the average school start and finish times in Australia (red) and Singapore (blue). Error bars represent the standard error of the mean

only 1 or 2 h per day did not inhibit myopia, but 5 h of exposure did significantly protect against the development of FD myopia. Extending exposure duration further to 10 h per day did not appear to offer further protective benefit.

In a large longitudinal study, Jones et al. [249] reported that children who engaged in outdoor activities for 14 h per week or more, exhibited the lowest odds of developing myopia. A number of recent randomized controlled trials have reported that interventions that increase children's outdoor time (by 40–80 min a day) significantly reduce the onset of myopia in childhood [268, 273, 274]. In the "Role of outdoor activity in myopia study" [266], children who were habitually exposed to low ambient light levels (on average less than 60 min exposure to outdoor light per day) had significantly faster axial eye growth compared to children habitually exposed to moderate and high light levels. These findings from human studies suggest that children who are exposed to less than 60 min a day of bright outdoor light are at an increased risk of more rapid eye growth and myopia development, and that approximately 2 h or more of outdoor exposure each day is required to provide protection against myopia development in the human eye.

Spectral Composition of Light and Myopia Since the spectral characteristics of outdoor light are significantly different to typical indoor light, it has been suggested that the spectral composition of outdoor light may be an additional factor that underlies the protective effects of outdoor activity upon myopia development. Although some studies in humans suggest exposure to short-wavelength light may protect against myopia [275], there has only been limited work in humans examining the possible impact of the spectral composition of light on myopia.

Animal studies do suggest that the spectral content of light can influence the growth of the eye, since altered eye growth is observed in animals reared under narrow band spectral lighting conditions. However, the effects of the spectral content of light shows substantial interspecies differences [276–279]. In chickens and guineas pigs, raising animals in short-wavelength light appears to slow eye growth and reduce myopia development, whereas long-wavelength light appears to increase eye growth and lead to myopia development [276, 279]. Conversely long-wavelength light appears to slow eye growth and reduce myopia development in tree shrews and rhesus monkeys [277, 278]. Further research is required to understand the mechanisms underlying these effects (and interspecies differences) and to establish the impact of the spectral composition of light upon human myopia.

4.6 Conclusion

In conclusion, over the last 40 years, remarkable progress has been made in understanding the possible mechanisms and pathogenesis of myopia, with a large contribution to this knowledge coming from an extensive body of work in animal models. Importantly, laboratory research in animals have shown that the visual environment

(i.e., quality and/or focus of the retinal image) influences ocular growth and refractive development, which has been a key to our current understanding of the process of emmetropization in humans. Similarities in features of defocus induced ocular changes in humans and experimental models of myopia, such as the eye's ability to detect the sign of retinal defocus and make compensatory changes in axial length, suggest that mechanisms of visually guided eye growth and refractive error development in animal models may be present in human eyes as well. Alongside animal research, a large body of clinical and epidemiological research has identified a number of other visual cues (e.g., aberrations, accommodation, and circadian rhythms) and environmental factors (e.g., light exposure, near work, and education) that could affect normal ocular growth and lead to the development of refractive errors. Experimental models continue to provide valuable information on cellular and biochemical mechanisms of eye growth, enabling the identification of potential new therapeutic targets for early diagnosis and treatment of myopia.

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