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Visual information and the development/control of myopia: Insights from nonhuman primate experiences

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Abstract:

Over the past few decades, primarily by animal studies, correspondingly reinforced by epidemiological, clinical studies and controlled trials, researchers have identified that visual feedback regulates eye refractive developments, with visual image alterations being the most influential myopiagenic environmental factor. This article reviews studies using nonhuman primates to investigate visual risk factors for myopia development and evaluates and summarizes which visual factors contribute to the occurrence and progression of myopia. The possible underlying myopiagenic mechanisms and related myopia prevention/control strategies are also discussed.

Keywords:

Etiology, myopia, primates, treatments, visual

Introduction

For centuries, the close association between near visual work and myopia has been well documented.[1] However, the causal relationship could not be clearly identified due to a lack of prospective well-controlled experiments that deal with multiple near-work-related confounding factors. Compared with studies using human subjects, experiments using animal models provide faster and better control to study the causal relationship. Studying myopia using nonhuman primates, which have the most similar visual system to humans, has greatly improved our understanding of the development and progression of myopia.

Deprivation Myopia

Beginning in the early 1960s, Young conducted a series of studies that raised monkeys in a restricted visual space, produced myopia.[2-6] Near work and accommodation were speculated as the cause.[7] The first clear evidence that visual information in essence can influence the refractive development came from a later observation that young monkeys deprived of normal vision by tarsorrhaphy produced axial myopia.[8] Moreover, subsequent researchers found that raising monkeys with tarsorrhaphy in the dark did not induce deprivation myopia, suggesting that visual stimulation through translucent eyelids (about half a log unit light attenuation) is necessary for the development of deprivation myopia.[9,10]

Over the past several decades, studies in nonhuman primates have explored more about the visual control properties of deprivation myopia:

Age effect

Marmoset monkeys were used to study how age influences the response of deprivation treatment.[11] The study observed that

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increasing vitreous cavity depth and myopia were inversely related to the age at which visual deprivation occurs. This relationship suggests that normal visual information is required to sustain normal eye growth over an extended period of time, and this eye growth mechanism is more sensitive when the monkeys are young.

Graded phenomenon

Using diffusers that produced different degrees of image reduction produced different degrees of myopia that varied directly with the degree of image degradation.[11] This suggests that moderate and high spatial frequency contrast images might provide myopia protection signals.

Recoverability

To examine why deprivation axial myopia can be recovered, monkeys with deprivation myopia were followed by measuring their ocular optical components during the recovery period.[12] It concluded that retarding/stopping the axial growth of the vitreous cavity, concomitant with the normally decreasing refractive power of the anterior segment in young animals, accounts for the hyperopic shift. This explains why myopia in school-age children can not be reversed, but only the rate of myopia progression can be slowed with treatments, since the natural decrease in refractive power developmentally has largely ceased at that age.

Temporal property

As observed in chickens,[13] relatively long periods of visual deprivation can be counterbalanced by short periods of unrestricted vision in rhesus monkeys.[14] One hour of unrestricted vision was sufficient to reduce the degree of deprivation myopia by more than 50%, and 4 h of unrestricted vision almost entirely eliminates deprivation myopia. These results suggest that the visual signals promoting axial elongation can be easily overridden by factors that slow ocular growth.

Local eye growth control

In chicks, deprivation myopia can be produced by optic nerve section[15,16] and corresponding local axial myopia produced by depriving half of the visual field[17] indicates that local eye growth is controlled by local retinal regions. Similarly, evidence of local eye growth control in primates was confirmed in rhesus monkeys reared with diffusers in helmets that deprived the monocular nasal half of the visual field where axial eye elongation developed in the corresponding retinal area.[18] Confirms local eye growth control in primate eyes.

Central retina versus peripheral retinal

Monkeys monocularly treated with fovea laser ablation and diffusers[19,20] or binocularly worn central aperture diffusers still produced axial myopia.[21] These demonstrated that the large peripheral retinal area dominates the fovea on eye growth control.

Effect of light intensity

In contrast to deprivation myopia being in regular room lighting, rearing monkeys in high ambient lighting with diffusers produced axial hyperopia.[22] However, rearing monkeys in dim ambient lighting with diffusers still produced axial myopia, and the degree of myopia is similar to that in regular room lighting.[23] This implies that, under open focus-feedback loop conditions, the eye growth can be regulated by the intensity of light, and high-intensity light can provide anti-myopia signals.

Effect of spectral light

Monkeys wearing diffusers in narrow-band long-wavelength lighting produced hyperopia,[24] whereas wearing diffusers in short-wavelength lighting produced myopia, and the degree of myopia is similar to that in white lighting.[25] These results imply that, under open focus-feedback loop conditions, the eye growth also can be regulated by the spectral light; specifically, long-wavelength light can provide anti-myopia signals.

Focus-driven Mechanism

Lens compensation

Studies imposing positive/negative lenses can produce compensatory eye growth in chicks.[26] Similar lens/defocus compensatory eye growth can also be found in rhesus monkey eyes that were treated monocularly[27] or binocularly[28] and supported by further observations.[27,29-31] These studies indicate that the primate visual system can detect the presence of refractive error and alter its eye growth to eliminate the ametropia, also providing strong evidence that near-work-related hyperopic defocus can cause the development of myopia.

Monocular defocus versus binocular defocus on lens compensation

In chicks, the accommodation of two eyes is completely independent,[26] whereas, in primates, the accommodation of two eyes is largely yoked.[27] As a consequence, binocular imposed equal-powered defocus lenses in monkeys would better simulate the normal emmetropization process, whereas imposing monocular defocus would simulate conditions of anisometropia. The monkey would mostly use the relatively less hyperopically defocused eye to fixate while letting the nonfixating eye be hyperopically defocused.[27] The monocular lens compensation hence can be more specifically termed "isometropization." These results indicate that the focus-driven emmetropization mechanism not only responds to the eye's absolute degree of refractive error

but also to the anisometropic status. This suggests that poor near-work posture, such as head tilted, would create asymmetric dioptric demands of two eyes[32] and promote the development/progress of anisometropic myopia.

Age effect

Using PRK-created hyperopic defocus in 2.0–2.5-year-old monkeys demonstrates that focus-driven eye growth control is still active in adolescent primates.[31,33] These findings support the anti-myopia optical control strategies used in school-age children.

Effects of continuous lighting

To investigate whether interrupting circadian rhythm would influence the vision-dependent eye growth control, monkeys were reared with continuous 24-h light-on per day with either unrestricted vision[34] or with monocular positive/negative lenses.[35] The results showed that focus-driven eye growth control was not noticeably compromised.

Temporal property

Studies found that brief periods of unrestricted vision can prevent myopia produced by long periods of imposed hyperopic defocus in rhesus monkeys.[36,37] These support the general belief that interrupting the near-work activity would benefit myopia control.

Local effect

Infant monkeys wearing spectacle lenses that produced hyperopic defocus in the nasal hemifield with unrestricted vision in the temporal hemifield produced myopia that was restricted to the nasal hemifield.[38] In contrast, wearing positive spectacle lenses that produced relative myopic defocus in the nasal hemifield with unrestricted vision in the temporal hemifield produced compensating hyperopic changes in refractive error in the nasal hemifield.[39] The findings of local effects inspire researchers to investigate which part(s) and how much retinal area(s) are needed for effective anti-myopia treatment.

Central retina versus peripheral retinal control

Studies employing fovea laser with negative lenses or central-aperture negative lenses did not prevent compensating myopic changes in response to imposed hyperopic defocus.[40] This finding demonstrates that the larger area of the peripheral retina dominates the fovea on the focus-driven eye growth control, suggesting that anti-myopia optical strategies can manipulate peripheral optics while maintaining clear central correction.

Simultaneous competing defocus

Following the experiment that imposes simultaneous defusing lens on chicks,[41] rhesus monkeys reared with simultaneous dual focus lenses demonstrated that primate eyes also have a similar mechanism, emphasizing that small lens areas of myopic defocus distributed across the visual field can induce strong signals to slow down eye growth.[42] Further investigation on the spatial integration of the retina[43] provides evidence-based support for the currently available anti-myopia optic lens design.

Effect of high-intensity light

It has long been thought that the protective effect of outdoor activities on myopia is due to a reduction in near work. However, the Sydney Myopia Study, conducted in the late 2000s, showed that outdoor and near work are relatively independent.[44] To examine whether bright light exposure, one of the potential outdoor protection factors, could prevent hyperopic-defocus-induced myopia, rhesus monkeys were reared with monocular negative lenses in high ambient lighting that simulated the intensity and continuous spectrum of sunlight.[45] The results found that, in contrast to the protection effect of high-intensity light found against deprivation myopia,[22] indoor bright light exposure did not alter the compensation to the lens-induced hyperopic defocus. However, monkeys reared in outdoor sunlight with monocular hyperopic defocus imposed by lens or PRK showed myopia protection effects.[46,47] Similar bright light protection effects also be observed in chicks,[48-51]guinea pigs,[52-54] mice,[55,56] and tree shrew.[57] In general, bright light gives stronger protection on deprivation effects than it does on hyperopic defocus effects. Furthermore, hyperopic-defocused monkeys under outdoor sunlight exhibited more protection than monkeys under indoor bright artificial light indicating that outdoor environments contain multiple plausible myopia protection factors, such as encompassing better uniform visual field, containing higher special frequency contrasts, spectrum of light, and circadian rhythms.[32,58,59]

Effect of low-intensity light

Deterioration of visual input in normal monkeys using low ambient lighting did not produce myopia; instead, the eyes maintained hyperopia.[60] This implied that dim light compromises the eye growth directional signals and the efficiency of emmetropization. A further study that reared monkeys with monocular positive/negative lenses in dim lighting showed that the ability to compensate for the induced defocus was decreased.[61] Specifically, two of the seven monkeys developed relative myopia on the positive lens treated eyes indicating that the eyes could not discern the eye growth directional signals and may abnormally choose to fixate with their non-treated eyes. This implies that optical strategies for myopia control could be compromised in dim light environment.

Effect of spectral light

Monkeys reared with binocular/monocular red filters, or reared in narrow-band long-wavelength lighting with

monocular positive/negative lenses or with unrestricted vision,[24] demonstrated that red lighting enhanced the effects of monocular positive lenses and reduced the effects of negative lenses.[62] However, in another study, rearing unrestricted vision monkeys in long-wavelength lighting found that two of the seven monkeys developed myopia.[63] This discrepancy might be due to the two monkeys that initially had a small amount of hyperopic refractive error and received stronger luminance contrast directional signals that cannot be overridden by the hyperopic effect of long-wavelength light, whereas the monocular negative treated monkeys experienced a high degree of anisometropic hyperopia with weaker luminance contrast directional signals that were easily overridden by the hyperopic effects of the long-wavelength light. This implies that the responding dioptric range of focus-driven mechanism might be reduced due to the lack of blue light component required for effective accommodation[64] and relatively more hyperopic defocus according to the property of longitudinal chromatic aberration (LCA).

Regarding the short wavelength spectrum, monkeys reared in narrow-band short-wavelength lighting with monocular positive/negative lenses showed compensating eye growth for those positive lenses treated monkeys but a less consistent response to the negative lenses treated eyes.[65]

These results indicate that long/short-wavelength monochromatic lighting providing no chromatic aberrations may compromise hyperopic-defocus-driven eye growth control which is likely accommodation related.[64]

It has been brought to the research field a puzzle that the eye growth control responses to monochromatic spectral lighting are different across many species.[24,66] In general, chicks and guinea pigs follow the rule of LCA; thus, red lighting results in relatively more hyperopic defocus and produces myopia. On the contrary, blue lighting, on the other hand, produces hyperopia. Whereas, in monkeys and tree shrews, red lighting produces hyperopia and blue lighting acts like white lighting, not promoting myopia. The discrepancy is most likely due to the differences in the visual systems of experimental animals. For example, in chicks, the visual system, like other diurnal birds, has 6 cones and 1 rod.[67] Other than L, M, and S cones, there are double cones and *ultraviolet* cones that likely provide extra luminance contrast information in cloudy days. Their chromatic and luminance detection channels are relatively more spread out in the spectral wavelength domain with good contrast sensitivity and spatial resolution to operate LCA-related focus-driven eye growth control. In contrast, the range of chromatic and luminance channels in trichromatic monkeys is narrower with luminance temporal/spatial contrast weighted more around L/M cones.

Deprivation versus Focus-driven Mechanism

Deprivation studies provided experimental controls eliminating visual optical focus feedback as a confounding factor. The observations of diffuser monkeys in bright light produced hyperopia,[22] and wearing negative lenses in bright light produced myopia suggesting that bright light in essence provides a protective effect. When presented with a negative lens, the protection signals were overridden by stronger hyperopic defocus myopiagenic signals.[45] On the other hand, the red light protective effects found in diffuser monkeys still preserved in negative lens-wearing monkeys suggest that the focus-driven directional signals are weaker and overridden.[24] These results indicate that the myopia-protective effect from high-intensity light and long-wavelength spectrum light is independent of the focus-driven mechanism. Later clinical trials that employ bright light or long-wavelength spectrum light as visual stimulation have shown dramatic myopia protection effects.[68-70]

The Role of Choroidal Thickness

In nonhuman primates, defocus treatment produced choroidal thickness changes in the compensating directions.[71,72] Consequent experiments have persistently shown an association with choroid thinning in conditions related to myopia development, whereas conditions related to hyperopic development have always been associated with choroid thickening.[61,62,66] Because changes of choroidal thickness precede refraction changes, it may play an important role in the visual regulation of axial growth and can be served as a biomarker for predicting long-term refraction outcomes in studies.

Clinical Implication for Myopia Controls

Optical strategies

Due to the similarity of visual systems between human and nonhuman primates, studies investigating focus-driven eye growth controls in monkeys have provided an evidence-based foundation for the current development of anti-myopia optical control strategies. Using multiple small areas of positive defocusing to stimulate the mid-periphery retina has been designed in spectacle lenses, soft contact lenses, and orthokeratology. One constraint of using optical strategies would be the large variations of indoor dioptric stimuli. In addition, since focus-driven eye growth control in primates also

deals with "isometropization," these treatment lenses increase the depth of focus. Careful balancing between two eyes during the refraction procedure should be emphasized to allow isometropization and to prevent anisometropia.

Spectral light remedy

The findings of nonfocus-dependent myopia-protective effects of long-wavelength light in primates inspired using "no focus information" red light for myopia control have demonstrated substantial effects of slowing down the progression of myopia in children.[69] However, further investigation is needed to examine whether combining optical lenses with red lighting therapy provides additive effects. Theologically, this combination might provide additional myopia protection; however, red light hinders the ability of detecting defocus direction and creates a longer posterior focal point (more hyperopic defocus) than white light. Furthermore, compromised accommodation in red light may impede the balance between the eyes' focuses.

High-intensity light and outdoor remedies

Since high-intensity light and other outdoor protection factors are relatively independent of focus factors, patients should be educated not to solely depend on optical anti-myopia strategies. Options of adding bright light/red light treatments for myopia control can be considered.

Conclusion

The most myopiagenic factor is visual image degradation. Out-of-focus images, especially mild-to-moderate central and peripheral hyperopic defocus blur, account for most of the axial eye elongation. While using anti-myopia optical strategies against these risk factors, the protective effects provided by high-intensity/long-wavelength light appear to be independent of defocus control, which is worthy to be further explored.

Data availability statement

The datasets generated during and/or analyzed during the current study are available in the PubMed repository.

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Conflicts of interest

The author declares that there are no conflicts of interest in this paper.

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