tvst

Refractive Intervention

The Parameters Governing the Anti-Myopia Efficacy of Chromatically Simulated Myopic Defocus in Tree Shrews

Zhihui She[1] **and Timothy J. Gawne**[1]

[1] Department of Optometry and Vision Science, University of Alabama at Birmingham, Birmingham, AL, USA

Correspondence: Timothy J. Gawne, Department of Optometry and Vision Science, University of Alabama at Birmingham, 1716 University Blvd., HPB 528, Birmingham, AL 35295, USA.
e-mail: tgawne@gmail.com

Received: November 13, 2023
Accepted: March 21, 2024
Published: May 9, 2024

Keywords: emmetropization; chromatic aberration; myopia; refractive development

Citation: She Z, Gawne TJ. The parameters governing the anti-myopia efficacy of chromatically simulated myopic defocus in tree shrews. Transl Vis Sci Technol. 2024;13(5):6, https://doi.org/10.1167/tvst.13.5.6

Purpose: We previously showed that exposing tree shrews (*Tupaia belangeri*, small diurnal mammals closely related to primates) to chromatically simulated myopic defocus (CSMD) counteracted small-cage myopia and instead induced hyperopia (approximately +4 diopters [D]). Here, we explored the parameters of this effect.

Methods: Tree shrews were exposed to the following interventions for 11 days: (1) rearing in closed ($n = 7$) or open ($n = 6$) small cages; (2) exposed to a video display of Maltese cross images with CSMD combined with overhead lighting ($n = 4$); (3) exposed to a video display of Maltese cross images with zero blue contrast ("flat blue," $n = 8$); and (4) exposed to a video display of black and white grayscale tree images with different spatial filtering (blue pixels lowpass <1 and <2 cycles per degree [CPD]) for the CSMD.

Results: (1) Tree shrews kept in closed cages, but not open cages, developed myopia. (2) Overhead illumination reduced the hyperopia induced by CSMD. (3) Zero-blue contrast produced hyperopia but slightly less than the CSMD. (4) Both of the CSMD tree images counteracted small cage myopia, but the one low pass filtering blue <1 CPD was more effective at inducing hyperopia.

Conclusions: Any pattern with reduced blue contrast at and below approximately 1 CPD counteracts myopia/promotes hyperopia, but maximal effectiveness may require that the video display be the brightest object in the environment.

Translational Relevance: Chromatically simulated myopic blur might be a powerful anti-myopia therapy in children, but the parameter selection could be critical. Issues for translation to humans are discussed.

Introduction

Normal refractive development (emmetropization) is shaped by the visual environment. This is demonstrated by the well-documented phenomenon that the eyes of many species, including non-human primates,[1–3] tree shrews,[4] guinea pigs,[5] mice,[6] and chicks,[7] can elongate in a controlled manner to reduce imposed optical errors and minimize retinal image blur. The same process also appears to operate in humans: children who are over-corrected (have lenses with excessive negative power) become myopic,[8] and lenses with extra plus power at least partially reduce myopic progression.[9] Additionally, most infants modulate their axial elongation to achieve accurate focus despite a wide spread of initial refractions, which is strong evidence for visually guided emmetropization.[10]

However, increasingly this process is failing, and we are faced with an "epidemic" of myopia.[11] Although the refractive error of myopia can be corrected via spectacles or contact lenses, a myopic eye is excessively elongated and is a major risk factor for later sight-threatening disease.[12,13] Clinical treatments with significant effectiveness exist, but, to date, none of these can completely halt myopic progression.[14–16] There remains a need for new primary and adjunct anti-myopia therapies.

To date, the visual inputs and neural circuitry required for the optically driven process of emmetropization remain poorly understood. One candidate visual cue for emmetropization is the image degradation associated with longitudinal chromatic aberration (LCA). LCA is an optical imperfection that is present in all studied vertebrate camera type eyes.[17] Wavelength-dependent differences in the disper-

sion properties of the ocular media causes the long-wavelength component of an image to focus further away from the front of the eye (i.e. more hyperopic) than the short-wavelength components. In humans, LCA produces approximately a 2 diopter (D) difference in refraction across the visible spectrum.[18] This number is approximately 2.7 D in tree shrews (unpublished data) and 6.2 D for mice (789 nm–457 nm range).[19] This dioptric difference should be sufficient to produce a characteristic difference in color luminance contrast, in which the level of blur of colored image components depends on the sign refractive error – specifically, better long-wavelength ("red") than short-wavelength ("blue") contrast for myopic defocus, and vice-versa for hyperopic defocus.

Recently, our laboratory demonstrated that chromatically simulated myopic defocus (CSMD), created by lowpass-filtering the blue channel of a static image, has a strong axial hyperopic effect on tree shrews, a diurnal mammal closely related to primates[20] that exhibits robust, consistent emmetropizing responses to optical defocus.[4,21] Tree shrews were reared in a fully enclosed box cage and exposed to CSMD-filtered images and developed moderate hyperopia (averaging +4 D) that was accompanied by a reduction in vitreous chamber depth after 11 days, which counteracted the axial myopia that would otherwise develop due to small cage rearing (−2 D).[22]

With its demonstrated potency in counteracting an environmentally induced myopia in a mammalian species, the digital-display-based methodology underlying our previous experiment[22] shows potential for controlling myopia in humans. In this paper we present four parallel experiments conducted as follow-up investigations of our previous work. The purpose of these experiments is to better understand the small-cage model of myopia and the features related to CSMD design and presentation, and to provide insight on its potential translational application for myopia control.

Methods

Animal Subjects

Northern tree shrews (*Tupaia belangeri*) were randomly assigned to six groups in four experiments prior to baseline data collection. Extra reference groups from previous studies in this laboratory were also included in the analysis. No littermates were assigned to the same group, and each group had both male and female tree shrews. All animals were acquired from the Tree Shrew Core at the University of Alabama at Birmingham (UAB). Prior to the onset of the experiment, the animals were reared in standard colony cages under diurnal artificial lighting. All experiments started on the 24th day of visual experience (DVE; defined as the number of days after eye opening, which typically occurs at 3 weeks of age) and ended on 35 DVE (11 days total). All experimental procedures adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were reviewed and approved by the Institutional Animal Care and Use Committee at UAB.

Tree shrews are dichromats. The two cone types in the tree shrew retina are short-wavelength-sensitive (SWS) and long-wavelength-sensitive (LWS) cones, the latter of which is the dominant type (approximately 95%).[23–25] The peak spectral sensitivity of SWS ($\lambda_{max} \approx$ 428 nm) and LWS cones ($\lambda_{max} \approx$ 555 nm) were similar to those of the S-cones ($\lambda_{max} \approx$ 420 nm) and L-cones ($\lambda_{max} \approx$ 560 nm) in humans,[26,27] respectively.

Small Cages

Figure 1 illustrates the small cages used in the experiments. These were identical except for one wall of the cage, that was either open (see Fig. 1A) or covered with an opaque panel (see Fig. 1B) or digital photograph frame. These small cages were cubical boxes with the same internal dimension (28 * 28 * 28 cm) as the cages used in our previous study.[22] The interior of all small cages was painted white with repeated black "Maltese cross" patterns. For the closed cage group (see Fig. 1B), the front opening of the cage was covered using an opaque panel painted white with the same black Maltese cross patterns as the other walls. These cages had a white light-emitting diode (LED) strip attached to the cage ceiling, which provides a diffuse illumination. Both internal and colony lightning ran daily from 8 AM to 10 PM.

The open and closed cages differed in their maximum viewing distances. Whereas animals in open cages had visual access to the colony room through the mesh front (viewing distance > 3 meters [m]), animals in a closed cage had a theoretical maximum viewing distance of 48 cm (assuming an infinitely narrow head!), which equals the space-diagonal of the cage interior. Based on our daily observation through the peepholes that we installed on the cages, the closed cage group of tree shrews typically spent their time on the perching deck viewing the opposite wall. In this circumstance, given the depth of the perching deck, the viewing distance for a tree shrew inside a closed cage was on the order of 28 cm, or approximately 4 D in dioptric distance.

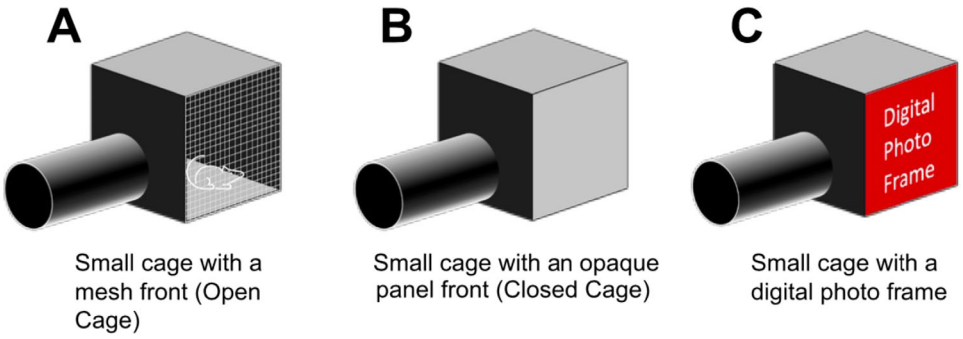

Figure 1. Schematic diagram of the small cages. All cages were made of white-painted panels and had internal dimensions of 28 * 28 * 28 cm. These cages were identical except for the front enclosure and source of illumination. (**A**) Open cages were covered using 30 * 30 cm wired mesh, and illumination was only from the external environment. (**B**) Closed cages were covered using a removable, painted panel, and illuminated via an overhead white LED strip. (**C**) Closed cages with a digital photograph frame. For these animals, the only light source was from the digital photograph frame, except for the CSMD + light group where lighting was supplemented with an overhead white LED strip. Animals reared in open cages (**A**) had visual access to the rest of the housing area with viewing distances of over three meters. Animals reared in closed cages (**B**) and photograph frame cages (**C**) had no visual access to the outside.

Digital Photograph Frame Display

The digital photograph frames have a display area of 25.4 * 14.3 cm and a resolution of 1920 × 1080 (Atatat, Meierjia Technology Co., LTD, Shenzhen, China). The displays were attached to a 30 * 30 cm, black-taped acrylic sheet which fully covered the open side of a small cage and blocked all external light/views. There were two baseline images used: one of high-contrast black and white Maltese cross patterns, and the other a naturalistic black-and-white grayscale image of trees (see Supplementary Fig. S1). The green and red pixels were never modified, but the blue pixels could be filtered in various ways as described in specific experiments. The emission characteristics of the red, green, and blue pixels are given in Supplementary Figure S2. The blue pixels would primarily stimulate the short-wavelength tree shrew cones, and the red and green pixels would primarily stimulate the long-wavelength tree shrew cones. The display was set to show the one image continuously on power-up, and was controlled by a timer on the same 8 AM to 10 PM schedule as the rest of the colony.

Data Collection

Refractive error was defined as the spherical equivalent of the corneal plane corrective prescription measured using an autorefractor (Nidek ARK-700A; Nidek Inc., San Jose, CA, USA). Five independent measurements were averaged and corrected for the small-eye artifact (+4 D) previously determined for tree shrews.[28] Ocular axial dimensions, including anterior chamber depth (anterior corneal surface – anterior lens surface), lens thickness, and vitreous chamber depth (posterior lens surface – internal limiting membrane) were obtained using a low coherence optical biometer (LenStar LS-900; Haag-Streit USA, Inc., Mason, OH, USA) immediately following refractive error measurements. Tree shrews were transported from their home cages in a light-tight nest tube to the measurement room. The measurements were made in dim light with only a small LED reading lamp on one wall and the light from the instrument displays. Measurements would typically take only around 2 minutes per animal, after which they were returned to their nest tubes and then taken back to their home cages.

To correct for the refractive indices of the tree shrew ocular media, physical dimensions of ocular axial separations were calculated from the averaged optical path length using the methodology described by El Hamdaoui et al.[29] All data were acquired from awake animals without cycloplegia, which was estimated to produce a consistent 0.4 D difference in refraction for the tree shrews in comparison to "wet" refraction induced using a topical phenylephrine-atropine compound.[28] All experimental procedures were binocular, and measures from both eyes of each animal were averaged to produce a single data point.

Experimental Design

Experiment 1: Confirm That a Small Cage With One Open Wall Does not Promote Myopia

To determine the role of viewing distance in refractive development, tree shrews were individually reared in small cages that either were fully enclosed (closed cage group, $n = 7$) or that have an open viewing wall on one side (open cage group $n = 6$).

The reference groups consisted of a group of tree shrews previously reared in small cages with a digital photograph frame displaying an unfiltered (maximally sharp) grayscale black and white Maltese cross image (unfiltered control, $n = 7$). We introduced this group to determine if the use of digital photograph frames per se had affected refractive development. We have previously shown that tree shrews in this group developed -1.2 ± 0.4 D (mean $\pm$ SEM) myopia over 11 days.[22] Finally, a group of visually unrestricted tree shrews previously reared in a normal colony environment (colony control, $n = 7$) was used as a reference for this and all other experiments in this study.[30]

Experiment 2: Effect of Overhead Illumination on Chromatically Simulated Myopic Defocus

The test group tree shrews were individually reared in small photograph frame cages from 24 to 35 DVE and were exposed to the CSMD-Maltese cross test image (CSMD + light, $n = 4$). The small cages for the CSMD + light group had white LED strips attached to the top of the cage. Pictures of the inside of the cages with and without overhead lighting are given in Supplementary Figure S3. These LEDs provide concurrent daytime illumination as the photograph frames continuously displaying the CSMD image. Without overhead lighting the white on the photograph display was about 100 cd/m^2, as determined with an LS-110 Spot luminance meter (Minolta, Tokyo, Japan) located outside the cage and with view adjusted with a first surface mirror. With the overhead lights on, the white painted areas on the cage walls half-way up were adjusted to be about 100 cd/m^2, and the white on the photograph display increased to about 137 cd/m^2 – although this varied with position and viewing angle. The control group was the original CSMD group ($n = 8$) (Gawne et al., 2022) in which the cages had

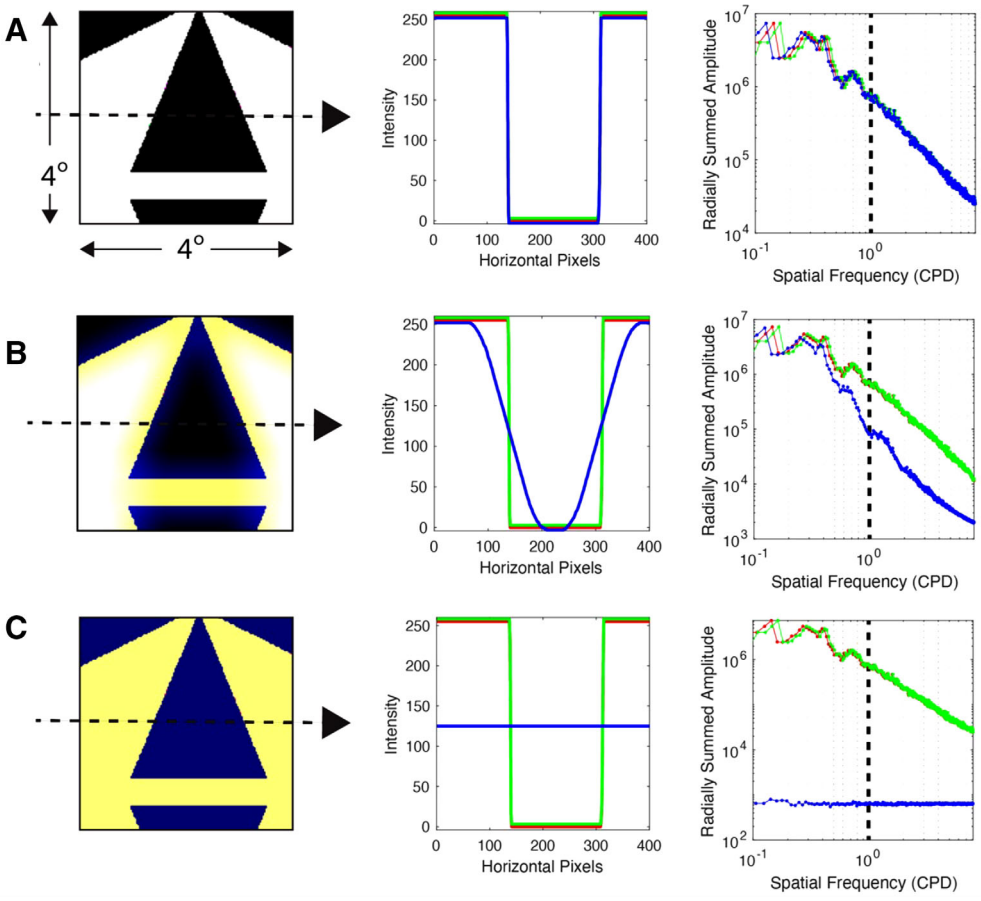

Figure 2. (**A**) *Left* = 4 degrees × 4 degrees image fragment (nominal 28 cm viewing distance) of the unfiltered control pattern. *Middle*: Luminance profiles of red, green, and blue pixels, scanning across a single line of the image (indicated by the *dashed arrow* on the *left*). Profiles were slightly offset in the y axis for clarity. *Right*: Radially averaged spatial frequencies of the image for red, green, and blue components. (**B**) Image fragment of the original CSMD anti-myopia display pattern. The *blue* pixels are spatially blurred relative to the *red* and *green* pixels by convolving with a uniform disk of 40 pixels diameter. (**C**) Flat blue group, with blue contrast eliminated. A small amount of white noise was added to the blue channel to avoid divide by zero errors in the Fourier transform.

no internal light source other than the photograph frame.[22]

Experiment 3: Eliminate all Blue Contrast

We tested an alternative design of simulated myopic defocus. The test group tree shrews ($n = 8$) were individually reared in closed cages and exposed to a test image that had zero blue contrast for 11 days (from 24 DVE to 35 DVE; "flat-blue" group). The flat-blue image, illustrated in Figure 2, was produced by setting the blue pixels to a uniform value equal to the mean of the numeric value (0–255) of all of the blue pixels of the basic CSMD image. By eliminating spatial contrast in the blue pixels, this could also potentially signal myopic defocus, even though it is not a physically plausible result of real-world defocus. This alternative design has a theoretical advantage in that the resulting myopic defocus signal should stay qualitatively consistent regardless of changes in viewing distance and refractive state. The reference group for Flat Blue was the original CSMD group (the same group that served as a positive control in experiment 2), and the unfiltered control group (the same group that served as a negative control in experiment 1).[22] Like other small-cage experiments, the digital photograph frames displayed the image continuously from 8 AM to 10 PM daily, during which there was no additional light source inside the individual cages.

Experiment 4: To Examine the Efficacy of Simulated Myopic Defocus in Natural Images, We Tested the Effects of Two CSMD Variants

These images were produced by applying a blurring filter on the blue channel of a greyscale forest scene image. In the first test group, the forest scene image was filtered by convolving the blue pixels with a circular disk 20-pixels in diameter (20 pixels tree shrew group, $n = 7$; see Fig. 3A). This filter was half the size of that used in the original CSMD-Maltese cross image,[22] and only modestly attenuated spatial frequencies at 1 CPD. In the second test group, the test image was produced by filtering the same greyscale tree image by convolving with the same 40-pixel diameter disk (40 pixels tree shrew group, $n = 6$, see Fig. 3B), and more significantly attenuated spatial frequencies at 1 CPD. For a tree shrew in focus at 28 cm, assuming a pupil size of 3 mm and a 6 mm focal length, the 40 pixels simulated blur would have produced a blur circle on the retina corresponding to approximately 7 D of defocus.

Convolving with an image with a uniform disk simulates the blur created by dioptric defocus, and is in many ways distinct from, for example, convolving with a Gaussian.[31] The motivation of using a natural

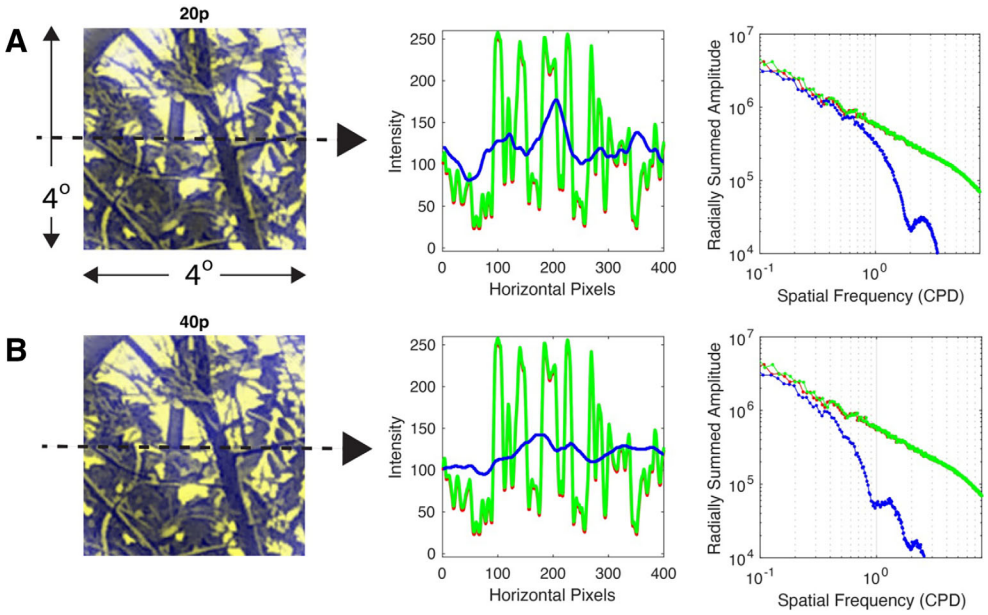

Figure 3. The two gray tree images, arranged as in Figure 2. (**A**) The 20 pixels tree shrew group. *Left*: The 4 degrees × 4 degrees image fragment (nominal 28 cm viewing distance) of the black and white gray trees image (see Supplementary Fig. S1B) was convolved with a circular disk of 20 pixels diameter. *Middle*: Luminance profiles of *red*, *green*, and *blue* pixels, scanning across a single line of the image (indicated by the *dashed arrow* on the *left*). Profiles were slightly offset in the y axis for clarity. *Right*: Radially averaged spatial frequencies of the image for *red*, *green*, and *blue* components. Image (**B**) The 40 pixel tree shrew group. Arranged as in **A**, but the original image was convolved with a uniform disk of 40 pixels in diameter.

image was to expand the application scenario of the already simple blue-blurring processing technique. In particular, does the effect depend on a dense distribution over very high contrast abrupt edges (i.e. high-contrast black and white edges) or the base pattern (the Maltese cross patterns)? Can CSMD also work with the more fractal distribution of features found in naturalistic images? We also sought to narrow down the range of spatial frequencies used by emmetropization. The reference groups were the original CSMD group and the unfiltered control group, both of which were from our previous study[22] and had been used as reference also in our other experiments (see above).

Statistics

We used mixed effect models to determine the effects of our interventions. Specifically, refractive error and axial dimension data were modeled as a quadratic function of the number of days in the experiment. The formulation for these models, expressed in a second-order polynomial function, was:

$$y_{i,j} = \beta_0 + \beta_1\omega_j + \beta_2\omega t_{i,j} + \beta_3\omega t_{i,j}^2 + v_{1j} + v_{2j}t_{i,j} + \in_{i,j}$$

where $y_{i,j}$ is the variable of interest of individual animal j on the i^{th} day of the experiment, β_0 is the model constant, ω_j is a dummy variable for being in specific group(s), t is the number of days in the experiment, v_{1j} and v_{2j} are random intercept and random slope, respectively. β_1, β_2, and β_3 represent the baseline difference and the linear and quadratic component of the time course of development for being in particular groups. Post-estimation Wald's tests were performed to examine the difference in time course between the two groups.[32] One-way ANOVA and post hoc pairwise comparison with Bonferroni correction were used to compare the refraction or ocular dimension across multiple groups at the end of the experiments.

Results

Experiment 1: Rearing in Closed Small Cage, but not Open Ones, Caused Myopia

Figure 4 illustrates the time course of refractive development (see Fig. 4A) and vitreous chamber depth change (see Fig. 4B). As shown Figure 4A, the open cage group (red filled circles) did not develop myopia. The time course of their refractive development and the refractive error at the end of the experiment were both similar to those of the colony control group (black unfilled circles, mean ± SEM: +1.0 ± 0.4 D on 35 DVE). On the other hand, the closed cage group (red filled triangles) became approximately 2 D more myopic than the open cage group at the end of the experiment (−1.1 D vs. +1 D, one-way ANOVA, $F = 10.91$, $P = 0.001$, post hoc comparison $P = 0.007$).

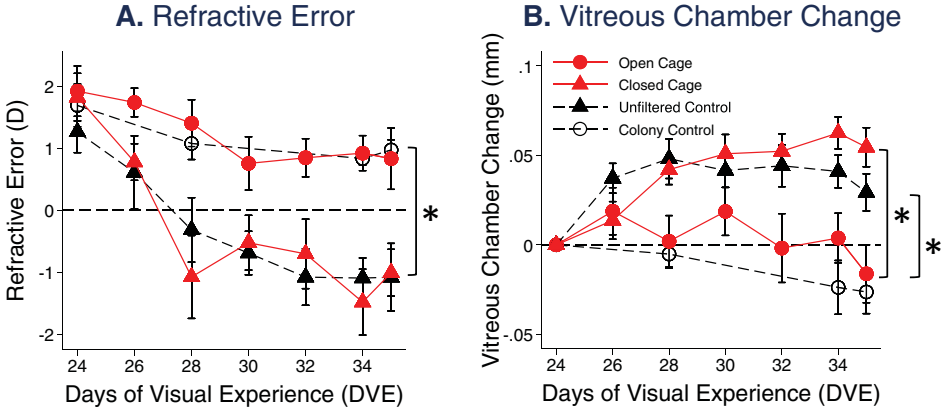

Figure 4. Effects of restricted viewing distance. Panels (**A**) and (**B**) plot the mean ± SEM of refractive error and vitreous chamber depth change, respectively, as a function of days of visual experience (DVE) for the open cage group (*red filled circles*) and closed cage group (*red filled triangles*). The photograph frame unfiltered control group (*black filled triangles*) and the colony control group (*black unfilled circles*) were plotted as references. (**A**) The closed cage group developed small-cage myopia that was similar to those in the photograph frame unfiltered control group, whereas the open cage group exhibited a normal emmetropization pattern and was statistically identical to the colony control group. *Square brackets* and *asterisks* indicate statistical difference between closed and open cages and between colony control and unfiltered control. (**B**) Vitreous chamber depth change was consistent with refractive changes. Vitreous chamber depth change in the open cage group was significantly slower than those in the closed cage and the unfiltered image groups. In both panels, the *square brackets* and *asterisks* indicate statistical differences in the time course of development between the closed and open cages and between the colony control and unfiltered control. The unfiltered control[22] and the colony control[30] data were from previous studies.

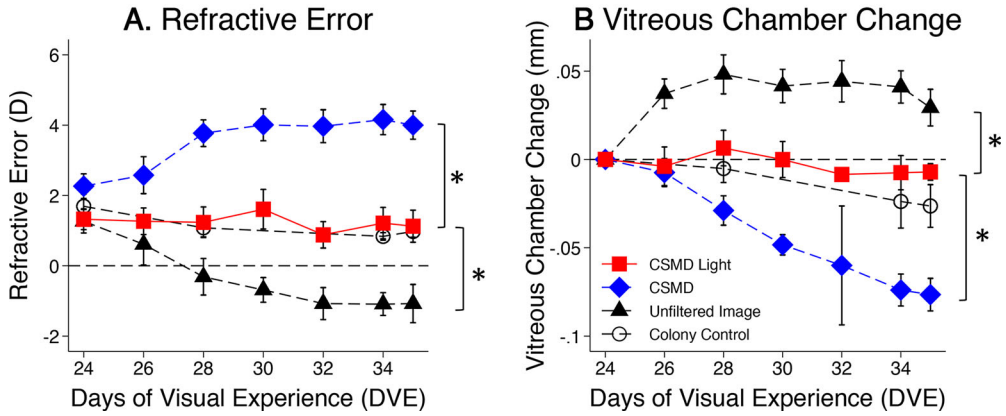

Figure 5. Overhead illumination reduced the efficacy of CSMD. Panels (**A**) and (**B**) plots mean ± SEM refractive error and vitreous chamber depth change as a function of number of days of visual experience (DVE), respectively. (**A**) CSMD with ceiling light (*red filled square*) also prevented the small cage myopia seen in the unfiltered control group (*black filled triangle*). The CSMD + light group developed mild hyperopia by 35 DVE as did the colony controls (*black unfilled circles*), but the magnitude was significantly lower than that in the original CSMD group (*blue filled diamonds*). (**B**) The refractive effect of CSMD + light condition remained consistent with the changes in vitreous chamber depth, suggesting that concurrent overhead illumination reduced, CSMD's efficacy in promoting hyperopia. The *square brackets* and *asterisks* indicate statistically significant difference in the time course of development between the CSMD + light group and the CSMD group/unfiltered controls. The data for the CSMD[22] unfiltered image[22] and colony control[30] came from previous studies.

The time course of refractive development and the refractive error at the end of the experiment in the closed cage group were both similar to those of the unfiltered control group (black filled triangles; refraction at the end of the experiment: −1.1 ± 0.5 D), suggesting that the digital photograph frame itself does not produce any obvious refractive effects. Finally, there was an increase in the vitreous chamber depth in the closed cage group in comparison to the colony control and the open cage groups (see Fig. 4B), which was consistent with the refractive changes.

Experiment 2: Room Illumination Reduced the Hyperopia Produced by CSMD

Figure 5 illustrates the refractive error and changes in vitreous chamber depth for the CSMD + light group. As shown in Figure 5A, the CSMD + light group did not develop small-cage myopia nor progressive hyperopia (Wald's test versus unfiltered control group, χ^2 (1) = 8.69, P = 0.003 for the linear- and χ^2 (1) = 3.99, P = 0.046 for the quadratic components; versus CSMD: χ^2 (1) = 6.92, P = 0.0085 for the linear component). Instead, this group exhibited an emmetropization-like refractive development pattern that is similar to the colony control group (see Fig. 5A, red filled square). On 35 DVE, the CSMD + light group (+1.1 ± 0.9 D) were significantly more hyperopic than the unfiltered control group (−1.1 ± 1.4 D; one-way ANOVA, $F_{(3, 22)}$ = 28.84, P < 0.001; pair-wise comparisons with Bonferroni correction, P = 0.02), but less hyperopic than the CSMD group (+4.0 D; pair-wise comparison between the CSMD and CSMD + light groups with Bonferroni correction, P = 0.001).

Experiment 3: Eliminating Contrast in the Blue Component of Image Counteracts Small-Cage Myopia and Caused Mild Hyperopia

As illustrated in Figure 6A, exposure to the flat blue image (red filled diamonds) prevented small cage myopia (+2.1 ± 1.3 D on 35 DVE, in comparison to −1.1 ± 1.4 D in the unfiltered control group; pair-wise comparison with Bonferroni correction, P = < 0.001). The hyperopic change induced by flat blue was similar in rate of development as that induced by CSMD. However, the flat blue group was less hyperopic than the CSMD group throughout the experiment. The refraction in the flat blue group on 35 DVE was statistically less hyperopic than that in the CSMD group (2.1 ± 1.3 D vs. +4.0 ± 1.1 D; pair-wise comparison with Bonferroni correction, P = 0.02). This difference was partially attributed to the baseline difference between the two groups. The refractive changes in the flat blue group were associated with a reduction in vitreous chamber depth (Fig. 6B), indicating that the flat blue group counteracted small cage myopia and produced hyperopia by slowing axial elongation.

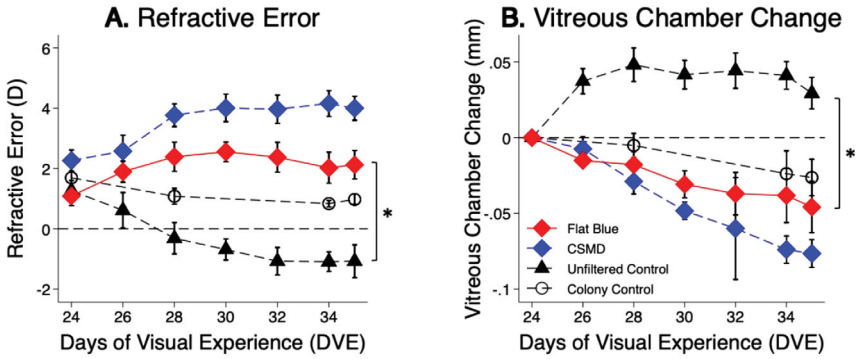

Figure 6. Exposure to the flat blue image counteracted small-cage myopia and produced axial hyperopia. Plots are mean ± SEM as a function of number of days of visual experience (DVE). (**A**) Refractive error. (**B**) Change in vitreous chamber depth. The *square brackets* and *asterisks* denote statistically significant difference in the time course of development between the flat blue group and the unfiltered control group. The data for the CSMD[22] unfiltered control[22] and colony control[30] came from previous studies.

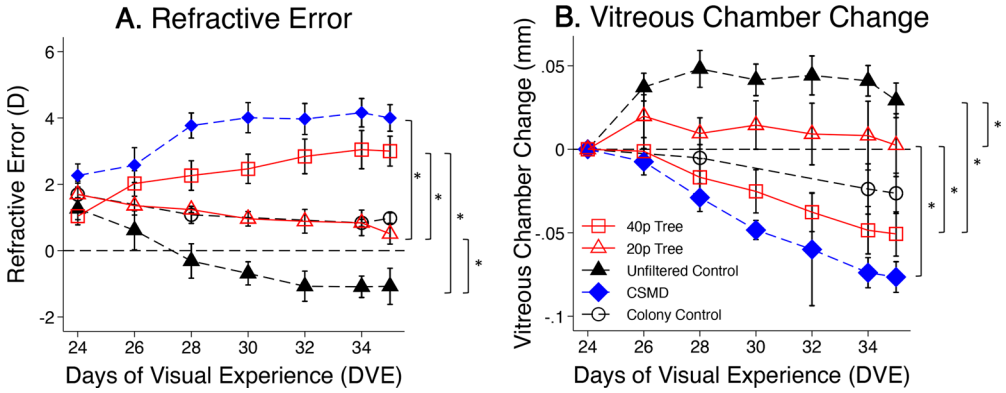

Figure 7. Effects of CSMD-filtered natural images on refractive development. Panels (**A**) and (**B**) plots the mean ± SEM of refractive error and vitreous chamber depth change as a function of days of visual experience (DVE), respectively. (**A**) The 40 pixel tree shrew group (*red unfilled triangle*) and the 20 pixel tree shrew group (*red unfilled square*) images both protected trees shrew from myopia (unfiltered control, *black filled triangles*) and developed hyperopia. The efficacy was similar between the 40 pixel tree shrew group and the CSMD group (*blue filled diamond*) whereas the 20 pixel tree shrew group was weaker than both. (**B**) The changes in vitreous chamber depth were consistent with refractive changes, indicating that both tree images counteracted myopia by slowing axial elongation. The data for the CSMD[22] unfiltered control[22] and colony control[30] came from previous studies.

Experiment 4: CSMD in a Naturalistic Image Is Also Effective Against Small-Cage Myopia

Following a mixed effect model, Wald's tests were performed to compare the rate of refractive change between the two tree shrew image groups and the unfiltered image group. The results showed that exposure to both 40 pixels tree (linear component: χ^2 (1) = 38.16, $P < 0.0001$; quadratic component: χ^2 (1) = 12.03, $P = 0.0005$; Fig. 7, red unfilled triangle) and 20 pixels tree shrew images (linear component: χ^2 (1) = 8.28, $P = 0.004$; quadratic component: χ^2 (1) = 3.94, $P = 0.047$; see Fig. 7, red unfilled square) protected tree shrews from small-cage myopia. With respect to the efficacy of myopia protection, the rate of hyperopic change in the 40 pixel tree shrew group was comparable to those seen in CSMD group, so was the refractive error at the end of the experiment (40 pixels tree shrew versus CSMD: +3.0 ± 1.1 D vs. +4.0 ± 1.13), suggesting that the efficacy was similar between the two interventions. On the other hand, the 20 pixels tree shrew group did not develop progressive hyperopia, which differed from the 40 pixel tree shrew group (Wald's test on the linear component of change rate, χ^2 (1) = 11.65, $P = 0.006$), but exhibited an emmetropization-like refractive development pattern. The refractive error in this group at the end of the experiment (0.5 ± 0.8 D, close to the 1.0 ± 0.4 D of the colony control group) was significantly less hyperopic than the CSMD (pairwise comparison with Bonferroni correction following 1-way ANOVA, $P < 0.0001$) and the 40 pixels tree shrew groups ($P = 0.002$). These refractive obser-

vations were consistent with a difference in vitreous chamber elongation rate (see Fig. 7B), suggesting that, whereas both are sufficient in counteracting small-cage myopia, the 40 pixels tree shrew and the 20 pixels tree shrew images differed in their ability to slow axial elongation.

Discussion

Restricted Viewing Distance Induces Myopia in Tree Shrews

The main finding of experiment 1 was that limited viewing distance associated with fully enclosed small cages caused myopia in tree shrews. This agreed with our previous experiment and the findings in chicks,[33–35] felines,[36] non-human primates,[37–39] and, more recently, guinea pigs,[40] which showed that animals become myopic in a restricted space with short viewing distance. Although myopia induced by small space is well-documented, to date, its underlying mechanism remains unclear. Early investigators, such as Adel[33] and Young,[38,39,41] believed that extended accommodation mediates proximity myopia. Adel (1961) showed that ipsilateral ciliary ganglion ablation, which paralyzes accommodative function, prevented myopic development, suggesting that accommodation is necessary for small-space myopia to develop, as although the large dose of alcohol injection (approximately 1 mL) used to destroy the ciliary ganglion might have also influenced the eyeball and prevented elongation. Wildsoet and Schmid also showed that intact accommodation was required for the correct interpretation of object distance and the development of compensatory myopia.[35] We previously reasoned that "small-cage" myopia in tree shrews was related to proximity hyperopic defocus based on the apparent lack of sustained accommodation in this species and the observation that the magnitude of small-cage myopia was roughly comparable to the dioptric viewing distance inside the cage.[22] Fu et al. similarly suggested that "near work myopia" in guinea pigs was similar to hyperopic defocus myopia due to weak accommodation in that species.[40] The defocus hypothesis, however, remains speculative as neither the present study nor the study of Fu et al.'s study measured accommodative behavior during the experiment. Nevertheless, one notes that in all animals that develop myopia in response to a minus lens, accommodation simply cannot have either the magnitude or the sustained duration to prevent this. A developing eye can only regulate its axial elongation using the local retina image. It has no information about the absolute physical distance to various objects in the environment. An eye in an environment with a restricted viewing distance, will therefore have no method of distinguishing an object at the maximum restricted distance, from an object at optical infinity. It should therefore not be surprising that emmetropization should target sharp focus for the most distant objects.

Additional Lighting Reduced the Efficacy of Chromatically Simulated Myopic Defocus

We showed in experiment 2 that overhead lighting inside small cages greatly reduced the efficacy of CSMD. Illumination is a known environmental modulator of refractive error. Previous studies have consistently found that elevated ambient light level promotes hyperopia in animals.[42–48] However, although our overhead LED did increase the illumination level inside the cage, light level modulation did not seem to explain our observation, because (1) with overhead light, the final degree of hyperopia was decreased, rather than increased; and (2) the illuminance level with the overhead light was within the range that supported normal emmetropization in tree shrews. A possible alternative explanation was that, with additional illumination, tree shrews spent more time viewing other objects inside the cage which are otherwise poorly visible, reducing the time exposed to simulated hyperopic defocus. It is also possible that additional lighting reduced the overall luminance contrast of the displayed image (via reflections off the screen and the protective acrylic panel) and thus reduced the efficacy of the CSMD. Given that ambient lighting is essential for the human environment, further work is required to understand the mechanisms underlying the reduced efficacy of CSMD with overhead lighting. In the meantime, these results suggest that any CSMD display used for human anti-myopia therapy be the brightest object in the room, or perhaps completely fill the visual field as in a virtual reality display.

Elimination of All Image Contrast Across the Blue Pixel Elements can be Interpreted as Myopic Defocus

The main finding of experiment 3 was that it is not necessary to precisely match the chromatic blur caused by myopic defocus: it is only necessary to reduce the short-wavelength contrast relative to the longer wavelength contrast. We note that we have previously shown that ambient narrow-band red light induces hyperopia in tree shrews, but even small amounts of added white (including blue) light greatly reduce this

effect.[49] However, the chromatic simulations of myopic blur used here operate in broad-spectrum light. We hypothesize that, at least for this species, the red light by itself is interpreted as zero blue (short-wavelength) spatial contrast, similar to the flat blue pattern used here. This is not a logical requirement, but may be how the retinal circuitry in this species interprets the artificial situation of an ambient narrow band red light. The red light with some (white) blue light in an otherwise normal cage environment allows the emmetropization system to correctly judge that blue spatial contrast is present, even though the absolute amount of blue light is low relative to the longer wavelengths. With "flat blue" there is no blue spatial contrast in the image, and emmetropization correctly judges that there is no blue spatial contrast, because, in fact, there is no blue spatial contrast in the image.

CSMD Is Effective Even When Applied to Naturalistic Images

The first main finding in experiment 4 was that CSMD filtering was effective in preventing small-cage myopia and producing hyperopia when applied to a naturalistic image. It was not clear from our previous work if there was something special about the high-contrast Maltese cross patterns or not: these results suggest that CSMD can be applied to a wide variety of images and still be effective. Still, it must be considered that some images may be more or less relatively less effective, especially if applied for less than a full day of exposure, or if they contain large colored areas. Additionally, some scenes – such as many manmade ones – may contain different distributions of spatial frequencies than naturalistic images and thus may potentially be less effective when CSMD is applied.[12] Although the results of this study suggest that CSMD does not require specific images, caution should still be exercised in assuming that it will apply to all images.

The second major finding is that the spatial frequency "sweet spot" for emmetropization in tree shrews appears to be roughly in the range of 1 CPD. This is in accord with simulations we have run on this species.[50] It is somewhat paradoxical that, whereas emmetropization exists to enable maximal visual acuity, it does not require high spatial frequencies to operate.[51] After all, it has long been shown in animal models that emmetropization can operate robustly in out-of-focus images when high spatial frequencies are largely absent.[52] We are unaware of any rigorous demonstration of a lower-spatial frequency preference for human emmetropization. However, simulations suggest that this is the case.[53] Additionally, the finding that the fovea is not critical for emmetropization in rhesus monkeys[54] and the heavy reliance of human accommodation (a different system but one that also uses image data to estimate defocus) on the medium spatial frequencies[55] also suggest that high spatial frequencies are not critically important for human emmetropization.

Implications for Myopia Management in Humans

Given the extremely powerful effect of CSMD on restraining axial ocular elongation, one could hypothesize that this method could be effective for controlling myopia in humans. To this end, the following three questions need to be answered: (1) Could findings from tree shrews translate to humans? (2) Could anti-myopia displays work with shorter periods of daily visual exposure? (3) Could an anti-myopia display work for myopic individuals?

Could the Findings in Tree Shrews Translate to Humans?

Animal models are essential for developing new treatments for human diseases, but there are many examples of cases where therapies developed using animal models have not translated to humans. When considering the potential for translating an animal finding to a human therapy, it is absolutely crucial to review the *relevant* similarities and differences between the species. As a trivial example, tree shrews would be a terrible model of red-green opponent color vision, because they do not have the cone photoreceptor classes that would allow then to have red-green opponent color vision. However, as regard to refractive development, we have carefully considered the similarities and differences between tree shrews and humans, and at present have not found any "deal breakers" that would preclude successful translation of the findings shown here. It must be emphasized that translation would not be certain and would likely require considerable effort, but our current state of knowledge does not rule it out.

1. We have modeled the optical parameters likely to govern how chromatic cues are used by emmetropization in both tree shrews[50] and humans[53] and find close parallels.
2. Tree shrews are diurnal, have good visual acuity for a small animal, and the emmetropization mechanism responds to visual conditions in a manner that is rapid (full compensation to a –5 D lens in 11 days), accurate, and consistent across animals.

3. Tree shrews, like most mammals, are dichromatic, whereas most (not all) humans are trichromatic with short (S), medium (M), and long (L) wavelength sensitive cones. Although it has been proposed that interactions between the L and M human cones could affect emmetropization,[56] nevertheless there is considerable evidence that for humans emmetropization is functionally dichromatic like other mammals.[53] There is some evidence that human dichromats are *slightly* less likely to develop myopia than human trichromats[57–59] but it is clear that trichromacy is neither essential for human emmetropization, nor is it the primary cause of the ongoing myopia epidemic.
4. If, for the purposes of emmetropization, human pooled M + L cones are functionally the same as the tree shrew long wavelength cone, then humans and tree shrews have virtually identical cone spectral tuning, as well as similar ocular media absorption. We speculate that a CSMD display for human therapy will not need to differentially blur the green and red pixels.
5. Primates have a fovea, which tree shrews do not, but it has been shown that the primate fovea is not critical for emmetropization – it is the peripheral retina that is key.[54]
6. Tree shrews have extensive binocular vision, about 55 degrees. There is evidence that disorders of binocular vision can affect emmetropization, but this has been proposed to be primarily due to differences in focus between a fixating and non-fixating eye.[60] As emmetropization is mostly local to the retina, and the retina does not itself calculate stereopsis, it does not seem as if binocular vision will be a key variable.
7. Like primates and other vertebrates, tree shrews develop elongated, myopic eyes in response to form deprivation or minus lens wear, show a nearly identical nonlinear response to "STOP" signals produced by interruptions in form deprivation and minus lens wear,[61,62] and show local control of scleral remodeling by the retina.[63]
8. Tree shrews and non-human primates become hyperopic in response to a narrow-band red light but other mammalian and non-mammalian species do not,[16,52] suggesting that how emmetropization uses chromatic signals is especially similar in tree shrews and primates.
9. Although tree shrews have lower visual acuity than human central foveal vision - not quite 3 cycles/degree[64] - the evidence is that it is the middle spatial frequencies that drive emmetropization not the higher ones.[51] Based on our previous work, we hypothesize that in humans the spatial frequency "sweet spot" for emmetropization will be around 4 CPD.[53] However, the findings here that you do not need to perfectly simulate the chromatic effects of optical blur – just eliminate the critical frequencies in the blue – means that the display used here in tree shrews should also be effective in humans – that is, we do not need to precisely identify the spatial frequencies in humans.
10. Tree shrews have a cone-dominated retina,[24] whereas outside of the fovea, humans are rod-dominated. However, as these are both diurnal species, it seems likely that the rods will be saturated under typical daily conditions and that the visual cues used by emmetropization *to evaluate focus* will primarily rely on cones. Outside the fovea, tree shrew and primate retinas have similar *relative* distributions of S and M/L cones.[25,50] On a bright sunny day, everything you see across the entire visual field will be mediated by cones: there are relatively few cones in the periphery relative to rods, but there are still more than enough for all practical purposes, including emmetropization.

Children Could Benefit From an Anti-Myopia Display With Limited Daily Exposure

In multiple species, interrupting the minus lens or form diffuser wear for just 1 or 2 hours a day will drastically reduce if not eliminate the induced myopia.[52] Indeed, for tree shrews, just 45 minutes a day of exposure to a clear in-focus image can prevent the development of myopia in response to wearing a minus lens the entire rest of the day.[65] This well-documented phenomenon had led to the theory that the temporal summation of visually derived signals that lead to ocular elongation (GO) or stop ocular elongation (STOP) are highly nonlinear and that the emmetropization mechanism favors STOP. However, if short periods of STOP signals can veto much longer periods of GO signals, why then do children ever become myopic? We speculate that there is an opposing nonlinearity: short periods of STOP need to be maximally effective: a visual scene stimulus producing weak STOP signals might be ineffective at preventing myopia even if presented for a long time.

It is critical to remember that emmetropization can only evaluate focus indirectly, using the images created on the retina by the combination of the external visual environment and the optics. We have hypothesized that in children developing myopia, the spatial/chromatic/temporal visual environment across

the day is not sufficient to allow the retina to generate quite enough STOP to prevent a slow drift into myopia.[66] This could explain why under-correction of a prescription does not seem to work[67,68]: if the visual environment is impairing the ability of emmetropization to evaluate focus, it will do so across the range of defocus. Current optical anti-myopia therapies, such as multifocal contact lenses,[9] seem to require wearing during a large fraction of the day, but these therapies only slightly alter the retinal image. In principle, myopia could be reduced or eliminated with short periods of daily exposure to a *sufficiently powerful* anti-myopic visual stimulus, if only we knew how to construct such a stimulus. A display derived from CSMD could potentially be such a strong anti-myopia stimulus.

As a general rule, animal eyes adapt to wearing lenses: they become myopic when wearing minus lenses, and hyperopic when wearing plus lenses (with the lenses removed).[52] However, in tree shrews, the ability of the eye to respond to a plus lens declines rapidly with age.[69] An appropriate chromatic stimulus can still create robust hyperopia in older tree shrews - a chromatic stimulus is a more powerful STOP than viewing a normal colony scene through a plus lens.[30] In children that develop myopia, the eye seems to not respond appropriately to myopic defocus, and indeed, "under-correction" of the spectacle or contact lens prescription - the optical equivalent of wearing an additional plus lens - also seems to be ineffective in slowing myopic progression.[68] Perhaps an appropriate chromatic defocus signal could be more powerful in children than plus lenses, even as it is in tree shrews? If nothing else, the ability of chromatic signals to create hyperopia beyond what is needed to create a sharp image in both tree shrews[70] and non-human primates,[71] demonstrates the anti-myopic power of chromatic stimuli for emmetropization.

Could a CSMD Anti-Myopia Video Display Work for Myopic Humans?

Unfortunately, we cannot easily conduct human studies on refractive development – clinical trials in children are extremely expensive and take years, and, for ethical and practical reasons, cannot be randomly explorative of the entire parameter space. However, it has been proposed that acute changes in choroidal thickness changes could be a proxy in humans for longer-term changes in refractive development: visual stimuli that oppose myopia will acutely result in a thicker choroid and vice-versa.[72] A recent study by Swiatczak and Schaeffel in humans found that chromatically simulated myopic blur induced acute choroidal thickening in emmetropes but not in myopes.[73] This suggests that the myopic human retina cannot evaluate chromatic cues for defocus, and that CSMD might not be an effective anti-myopia therapy.

We note that acute choroidal thickness changes are only a proxy for refractive development, and it is not at all clear that this method can reliably predict refractive development in humans.[74]

Swiatczak and Schaeffel also found that myopes had a reduced ability to respond to imposed myopic optical defocus compared to emmetropes[75] but two other independent laboratories have found the opposite results: that the myopic human retina can indeed respond to myopic optical blur.[76,77] To the extent that the response to optical defocus is mediated by chromatic cues, this suggests that human myopes can indeed respond to the chromatic cues for myopic defocus – although perhaps with a reduced gain. Additionally, there are psychophysical studies suggesting that emmetropes process hyperopic and myopic defocus symmetrically, whereas myopes are asymmetrical[78] – although the rules governing central perception might not be identical to those for emmetropization.

Even if under some conditions the myopic human retina has a relatively impaired ability to detect the chromatic cues for myopic defocus, this does not rule out the development of a more powerful version of CSMD that is effective in myopes. Perhaps emmetropization in the myopic human retina is not completely broken, but only needs a booster. Although the study by Swiatczak and Schaeffel is worthy of concern, it does not presently rule out that CSMD could be an effective human therapy in myopes.

Conclusions

CSMD is an extremely powerful stimulus to restrain axial elongation in closely related to primate tree shrews. It shows potential for adaptation as an anti-myopia therapy in humans, although considerably more work needs to be done both in animal models (including non-human primates), and pilot clinical trials.

Acknowledgments

The authors would like to thank Thomas Norton for helpful insight in experimental design and manuscript preparation. We also thank Russel Veal, Johanna Henry, and Jordan Harris for their contribution in care for research animals and data collection.

Supported by NEI grant RO1 EY028578 (T.J.G.) and NEI grant P30 EY003039 (core).

Disclosure: **Z. She**, None; **T.J. Gawne**, holds a provisional patent for control of myopia directly related to the work described in this manuscript (P)

References

1. Hung LF, Crawford ML, Smith EL. Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nat Med*. 1995;1:761–765.
2. Troilo D, Totonelly K, Harb E. Imposed anisometropia, accommodation, and regulation of refractive state. *Optom Vis Sci*. 2009;86:E31–E39.
3. Whatham AR, Judge SJ. Compensatory changes in eye growth and refraction induced by daily wear of soft contact lenses in young marmosets. *Vision Res*. 2001;41:267–273.
4. Norton TT, Amedo AO, Siegwart JT, Jr. The effect of age on compensation for a negative lens and recovery from lens-induced myopia in tree shrews (Tupaia glis belangeri). *Vision Res*. 2010;50:564–576.
5. Howlett MH, McFadden SA. Spectacle lens compensation in the pigmented guinea pig. *Vision Res*. 2009;49:219–227.
6. Tkatchenko TV, Shen Y, Tkatchenko AV. Mouse experimental myopia has features of primate myopia. *Invest Ophthalmol Vis Sci*. 2010;51:1297–1303.
7. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. *Vision Res*. 1988;28:639–657.
8. Chen AM, Erzurum SA, Chandler DL, et al. Overminus lens therapy for children 3 to 10 years of age with intermittent exotropia: a randomized clinical trial. *JAMA Ophthalmol*. 2021;139:464–476.
9. Chamberlain P, Peixoto-de-Matos SC, Logan NS, Ngo C, Jones D, Young G. A 3-year randomized clinical trial of MiSight lenses for myopia control. *Optom Vis Sci*. 2019;96:556–567.
10. Mutti DO, Mitchell GL, Jones LA, et al. Axial growth and changes in lenticular and corneal power during emmetropization in infants. *Invest Ophthalmol Vis Sci*. 2005;46:3074–3080.
11. Dolgin E. The myopia boom. *Nature*. 2015;519:276–278.
12. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res*. 2012;31:622–660.
13. Sankaridurg P, Tahhan N, Kandel H, et al. IMI impact of myopia. *Invest Ophthalmol Vis Sci*. 2021;62:2.
14. Brennan NA, Toubouti YM, Cheng X, Bullimore MA. Efficacy in myopia control. *Prog Retin Eye Res*. 2021;83:100923.
15. Sarkar S, Khuu S, Kang P. A systematic review and meta-analysis of the efficacy of different optical interventions on the control of myopia in children. *Acta Ophthalmol*. 2024;102(3):e229–e244.
16. Sankaridurg P, Berntsen DA, Bullimore MA, et al. IMI 2023 Digest. *Invest Ophthalmol Vis Sci*. 2023;64:7.
17. Mandelman T, Sivak JG. Longitudinal chromatic aberration of the vertebrate eye. *Vision Res*. 1983;23:1555–1559.
18. Charman WN, Jennings JA. Objective measurements of the longitudinal chromatic aberration of the human eye. *Vision Res*. 1976;16:999–1005.
19. Geng Y, Schery LA, Sharma R, et al. Optical properties of the mouse eye. *Biomed Opt Express*. 2011;2:717–738.
20. Cao J, Yang EB, Su JJ, Li Y, Chow P. The tree shrews: adjuncts and alternatives to primates as models for biomedical research. *J Med Primatol*. 2003;32:123–130.
21. Norton TT, McBrien NA. Normal development of refractive state and ocular component dimensions in the tree shrew (Tupaia belangeri). *Vision Res*. 1992;32:833–842.
22. Gawne TJ, She Z, Norton TT. Chromatically simulated myopic blur counteracts a myopiagenic environment. *Exp Eye Res*. 2022;222:109187.
23. Muller B, Peichl L. Topography of cones and rods in the tree shrew retina. *J Comp Neurol*. 1989;282:581–594.
24. Petry HM, Harosi FI. Visual pigments of the tree shrew (Tupaia belangeri) and greater galago (Galago crassicaudatus): a microspectrophotometric investigation. *Vision Res*. 1990;30:839–851.
25. Sajdak BS, Salmon AE, Cava JA, et al. Noninvasive imaging of the tree shrew eye: wavefront analysis and retinal imaging with correlative histology. *Exp Eye Res*. 2019;185:107683.
26. Bowmaker JK, Dartnall HJ. Visual pigments of rods and cones in a human retina. *J Physiol*. 1980;298:501–511.
27. Bowmaker JK, Dartnall HJ, Mollon JD. Microspectrophotometric demonstration of four classes of photoreceptor in an old world primate, Macaca fascicularis. *J Physiol*. 1980;298:131–143.
28. Norton TT, Wu WW, Siegwart JT, Jr. Refractive state of tree shrew eyes measured with cor-

tical visual evoked potentials. *Optom Vis Sci*. 2003;80:623–631.
29. El Hamdaoui M, Gann DW, Norton TT, Grytz R. Matching the LenStar optical biometer to A-scan ultrasonography for use in small animal eyes with application to tree shrews. *Exp Eye Res*. 2019;180:250–259.
30. Gawne TJ, Ward AH, Norton TT. Long-wavelength (red) light produces hyperopia in juvenile and adolescent tree shrews. *Vision Res*. 2017;140:55–65.
31. Strasburger H, Bach M, Heinrich SP. Blur unblurred-a mini tutorial. *Iperception*. 2018;9: 2041669518765850.
32. Rabe-Hesketh S, Skrondal A. *Multilevel and longitudinal modeling using State - Colume I: continuous Responses*. College Station, TX: Stata Press Publication; 2012.
33. Adel NL. Developmental changes in the avian eye. *Optom Vis Sci*. 1964;41:466.
34. Miles FA, Wallman J. Local ocular compensation for imposed local refractive error. *Vision Res*. 1990;30:339–349.
35. Wildsoet CF, Schmid KL. Emmetropization in chicks uses optical vergence and relative distance cues to decode defocus. *Vision Res*. 2001;41:3197–3204.
36. Rose L, Yinon U, Belkin M. Myopia induced in cats deprived of distance vision during development. *Vision Res*. 1974;14:1029–1032.
37. Leng Y, Lan W, Yu K, et al. Effects of confined space and near vision stimulation on refractive status and vitreous chamber depth in adolescent rhesus monkeys. *Sci China Life Sci*. 2010;53:1433–1439.
38. Young FA. The development and retention of myopia by monkeys. *Am J Optom Arch Am Acad Optom*. 1961;38:545–555.
39. Young FA. The effect of restricted visual space on the refractive error of the young monkey eye. *Invest Ophthalmol Vis Sci*. 1963;2:571–577.
40. Fu Q, Zhang Y, Chen L, et al. Near work induces myopia in Guinea pigs. *Exp Eye Res*. 2022;224:109202.
41. Young FA. Primate myopia. *Am J Optom Physiol Opt*. 1981;58:560–566.
42. Ashby R, Ohlendorf A, Schaeffel F. The effect of ambient illuminance on the development of deprivation myopia in chicks. *Invest Ophthalmol Vis Sci*. 2009;50:5348–5354.
43. Ashby RS, Schaeffel F. The effect of bright light on lens compensation in chicks. *Invest Ophthalmol Vis Sci*. 2010;51:5247–5253.
44. Chen S, Zhi Z, Ruan Q, et al. Bright light suppresses form-deprivation myopia development with activation of dopamine D1 receptor signaling in the ON pathway in retina. *Invest Ophthalmol Vis Sci*. 2017;58:2306–2316.
45. Cohen Y, Belkin M, Yehezkel O, Solomon AS, Polat U. Dependency between light intensity and refractive development under light-dark cycles. *Exp Eye Res*. 2011;92:40–46.
46. Cohen Y, Peleg E, Belkin M, Polat U, Solomon AS. Ambient illuminance, retinal dopamine release and refractive development in chicks. *Exp Eye Res*. 2012;103:33–40.
47. Morgan IG, Ashby RS. Bright light blocks the development of form deprivation myopia in mice, acting on D1 dopamine receptors. *Invest Ophthalmol Vis Sci*. 2017;58:2317.
48. Smith EL, 3rd, Hung LF, Huang J. Protective effects of high ambient lighting on the development of form-deprivation myopia in rhesus monkeys. *Invest Ophthalmol Vis Sci*. 2012;53:421–428.
49. Gawne TJ, Samal AV, She Z. The effects of intensity, spectral purity and duty cycle on red light-induced hyperopia in tree shrews. *Ophthalmic Physiol Opt*. 2023;43:1419–1426.
50. Gawne TJ, Norton TT. An opponent dual-detector spectral drive model of emmetropization. *Vision Res*. 2020;173:7–20.
51. Schmid KL, Wildsoet CF. Contrast and spatial-frequency requirements for emmetropization in chicks. *Vision Res*. 1997;37:2011–2021.
52. Troilo D, Smith EL, 3rd, Nickla DL, et al. IMI - report on experimental models of emmetropization and myopia. *Invest Ophthalmol Vis Sci*. 2019;60:M31–M88.
53. Gawne TJ, Grytz R, Norton TT. How chromatic cues can guide human eye growth to achieve good focus. *J Vis*. 2021;21:11.
54. Smith EL, 3rd, Ramamirtham R, Qiao-Grider Y, et al. Effects of foveal ablation on emmetropization and form-deprivation myopia. *Invest Ophthalmol Vis Sci*. 2007;48:3914–3922.
55. Stone D, Mathews S, Kruger PB. Accommodation and chromatic aberration: effect of spatial frequency. *Ophthalmic Physiol Opt*. 1993;13:244–252.
56. Hagen LA, Arnegard S, Kuchenbecker JA, et al. The association between L:M cone ratio, cone opsin genes and myopia susceptibility. *Vision Res*. 2019;162:20–28.
57. Qian YS, Chu RY, He JC, et al. Incidence of myopia in high school students with and without red-green color vision deficiency. *Invest Ophthalmol Vis Sci*. 2009;50:1598–1605.

58. Gan J, Li SM, Atchison DA, et al. Association between color vision deficiency and myopia in Chinese children over a five-year period. *Invest Ophthalmol Vis Sci*. 2022;63:2.
59. Ostadimoghaddam H, Yekta AA, Heravian J, et al. Prevalence of refractive errors in students with and without color vision deficiency. *J Ophthalmic Vis Res*. 2014;9:484–486.
60. Smith EL, 3rd, Hung LF, Harwerth RS. Developmental visual system anomalies and the limits of emmetropization. *Ophthalmic Physiol Opt*. 1999;19:90–102.
61. Shaikh AW, Siegwart JT, Jr., Norton TT. Effect of interrupted lens wear on compensation for a minus lens in tree shrews. *Optom Vis Sci*. 1999;76:308–315.
62. Wensveen JM, Harwerth RS, Hung LF, Ramamirtham R, Kee CS, Smith EL. Brief daily periods of unrestricted vision can prevent form-deprivation amblyopia. *Invest Ophthalmol Vis Sci*. 2006;47:2468–2477.
63. Smith EL, 3rd, Huang J, Hung LF, Blasdel TL, Humbird TL, Bockhorst KH. Hemiretinal form deprivation: evidence for local control of eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci*. 2009;50:5057–5069.
64. Petry HM, Fox R, Casagrande VA. Spatial contrast sensitivity of the tree shrew. *Vision Res*. 1984;24:1037–1042.
65. Norton TT, Siegwart JT, Jr., Amedo AO. Effectiveness of hyperopic defocus, minimal defocus, or myopic defocus in competition with a myopiagenic stimulus in tree shrew eyes. *Invest Ophthalmol Vis Sci*. 2006;47:4687–4699.
66. Khanal S, Norton TT, Gawne TJ. Limited bandwidth short-wavelength light produces slowly-developing myopia in tree shrews similar to human juvenile-onset myopia. *Vision Res*. 2022;204:108161.
67. Tang SM, Zhang XJ, Wang YM, et al. Effect of myopic undercorrection on habitual reading distance in schoolchildren: the Hong Kong children eye study. *Ophthalmol Ther*. 2023;12(2):925–938.
68. Yazdani N, Sadeghi R, Ehsaei A, et al. Undercorrection or full correction of myopia? A meta-analysis. *J Optom*. 2021;14:11–19.
69. Siegwart JT, Jr., Norton TT. Binocular lens treatment in tree shrews: effect of age and comparison of plus lens wear with recovery from minus lens-induced myopia. *Exp Eye Res*. 2010;91:660–669.
70. Gawne TJ, Siegwart JT, Jr., Ward AH, Norton TT. The wavelength composition and temporal modulation of ambient lighting strongly affect refractive development in young tree shrews. *Exp Eye Res*. 2017;155:75–84.
71. Smith EL, 3rd, Hung LF, Arumugam B, Holden BA, Neitz M, Neitz J. Effects of long-wavelength lighting on refractive development in infant rhesus monkeys. *Invest Ophthalmol Vis Sci*. 2015;56:6490–6500.
72. Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res*. 2010;29:144–168.
73. Swiatczak B, Schaeffel F. Myopia: why the retina stops inhibiting eye growth. *Sci Rep*. 2022;12:21704.
74. Ostrin LA, Harb E, Nickla DL, et al. IMI-the dynamic choroid: new insights, challenges, and potential significance for human myopia. *Invest Ophthalmol Vis Sci*. 2023;64:4.
75. Swiatczak B, Schaeffel F. Emmetropic, but not myopic human eyes distinguish positive defocus from calculated blur. *Invest Ophthalmol Vis Sci*. 2021;62:14.
76. Read SA, Collins MJ, Sander BP. Human optical axial length and defocus. *Invest Ophthalmol Vis Sci*. 2010;51:6262–6269.
77. Chiang ST, Phillips JR, Backhouse S. Effect of retinal image defocus on the thickness of the human choroid. *Ophthalmic Physiol Opt*. 2015;35:405–413.
78. Radhakrishnan H, Pardhan S. Contrast detection in noise with positive and negative defocus in myopes. *Vision Res*. 2006;46:2949–2955.