
Myopia progression - a review of current fundamental research
Frank Schaeffel
no conflicts of interest
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Myopia Research Group

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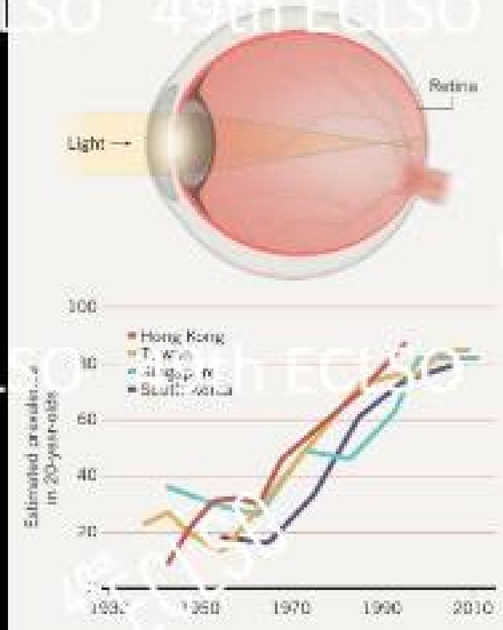
The myopia boom

Short-sightedness is reaching epidemic proportions. Some scientists think they have found a reason why.

The "myopia boom" in the last decades is not genetic



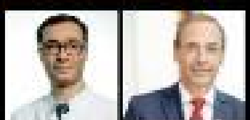
NATURE | VOL 519 | 19 MARCH 2015

THE MYOPIA BOOM

SHORT-SIGHTEDNESS IS REACHING EPIDEMIC PROPORTIONS. SOME SCIENTISTS THINK THEY HAVE FOUND A REASON WHY.

BY ELIE DOLGIN

2014



The most consistent correlation of myopia is with the level of education

Gutenberg study (Mainz, Germany):
the level of education determines myopia

Myopia and Level of Education
Results from the Gutenberg Health Study

Alireza Mirshahi, MD,[1] Katharina A. Ponto, MD,[1] René Hoehn, MD,[1] Isabella Zwiener, PhD,[2] Tanja Zeller, PhD,[3] Karl Lackner, MD,[4] Manfred E. Beutel, MD,[5] Norbert Pfeiffer, MD[1]

Participants: A cohort of the Gutenberg Health Study, including 4658 eligible enrollees between 35 and 74 years of age.

Rhine-Main Region in mid-western Germany with a total of 15 010 participants and follow-up after 5 years

Results:
- Individuals who graduated from school after 13 years were more myopic
  - than those who graduated after 10 years
  - than those who graduated after 9 years
  - and than those who never finished secondary school
- Of persons who graduated from school after 13 years, 50.9% were myopic (SE ≤ −0.5 D)
- In university graduates, the proportion of myopic persons was higher (53%)

Conclusions: Higher levels of school and postschool professional education are associated with a more myopic refraction. Participants with higher education ... more often were myopic ...

Ophthalmology 2014;121:2047-2052 © 2014 by the American Academy of Ophthalmology.

clear demonstration that education induces myopia

2018

Education and myopia: assessing the direction of causality by mendelian randomisation

Edward Mountjoy,[1,2] Neil M Davies,[1,2] Denis Plotnikov,[3] George Davey Smith,[1,2] Santiago Rodriguez,[1,2] Cathy E Williams,[2] Jeremy A Guggenheim,[3] Denize Atan[4]

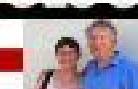
n = 69,798

genetic variants associated with myopia (44, explain 4.32% of myopia)	genetic variants associated with education (69, explain 0.71% of years of education)
more years of education ?	more myopia ?

Result

myopia has no effect of education	but -0.27 D more myopia ... of education

BMJ 2018;361:k2022 doi: 10.1136/bmj.k2022 (Published 6 June 2018)



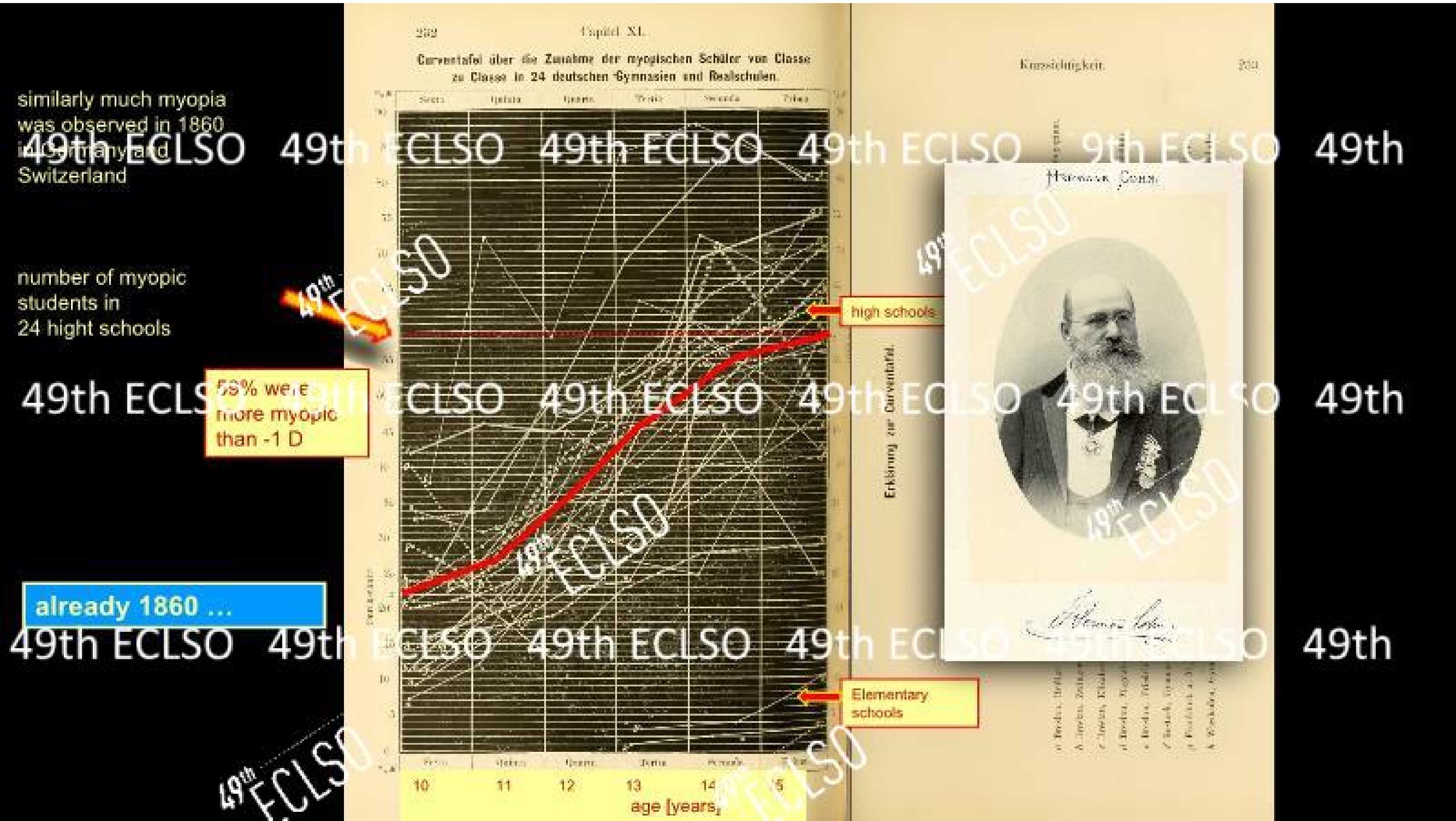
EDITORIALS

Intense schooling linked to myopia

Education systems must change to protect children's vision

Ian G Morgan professor[1], Amanda N French lecturer[2], Kathryn A Rose professor[2]

the bmj

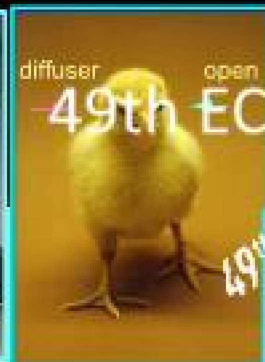

similarly much myopia was observed in 1860 in Germany and Switzerland
number of myopic students in 24 hight schools
58% were more myopic than -1 D
already 1860 …
232 Capitel XI.
Curventafel über die Zunahme der myopischen Schüler von Classe zu Classe in 24 deutschen Gymnasien und Realschulen.
high schools
Elementary schools
10
11
12
13
14
15
age [years]
Kurzsichtigkeit. 233
Erklärung zur Curventafel.
Hermann Cohn

learning about the biological mechanisms of myopia:

experiments in animal models

a new experimental aera to study myopia started in the late 70's

a poor image on the retina makes the eye long
first discovered in rhesus monkeys in 1977,
and about the same time in the chicken:
"**deprivation myopia**"



the biological sense of
"deprivation myopia"
is not really clear
it is "open loop eye growth"

(but it is present in all models)

Torsten N. Wiesel
Elio Raviola
Departments of Neurobiology and Anatomy, Harvard Medical School, Boston, Massachusetts 02115

Nature Vol. 266 3 March 1977

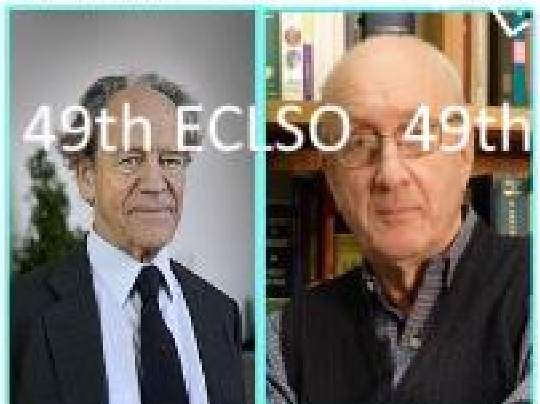


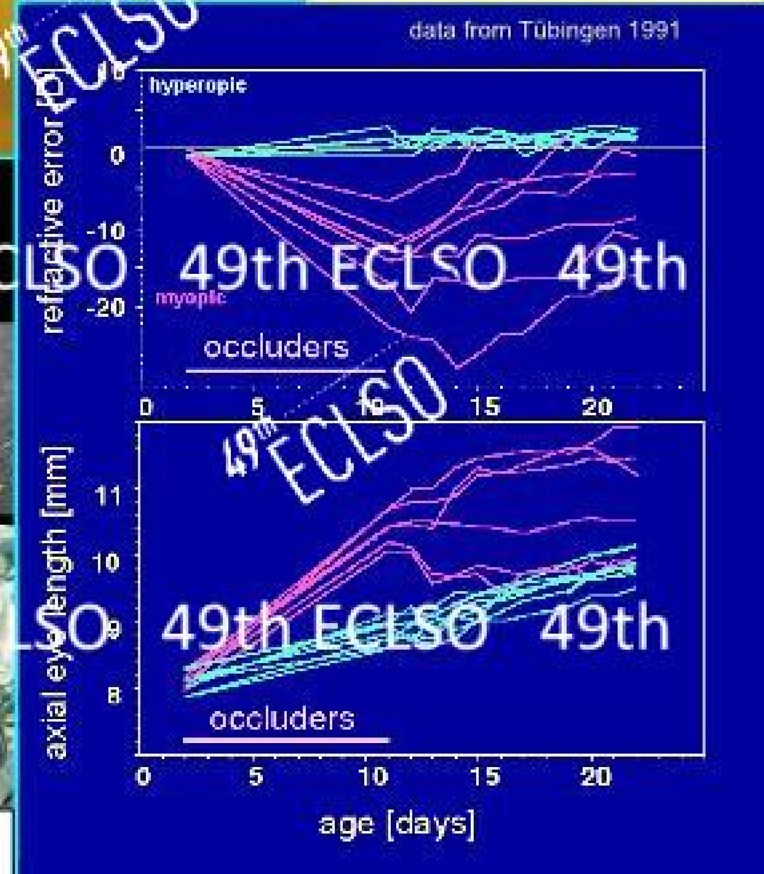
Fig. 1 Eyes of a rhesus monkey in which the lids on the right (b) were fused at the age of 2 weeks and opened 18 months later (experiment 5 in Table 1). Suture threads mark the insertions of the extrinsic ocular muscles. The left eye (a) was normal

Myopia and eye enlargement after neonatal lid fusion in monkeys

The aetiology of myopia has been studied mainly by investigating the distribution of refractive errors in human populations[1]. No clear conclusion has emerged, however, so the prevailing clinical attitude is that myopia can neither be prevented nor cured, but only corrected with appropriate

of a 1% solution of homatropine and the refraction of both eyes determined by using a streak retinoscope and hand-held trial case lenses. The corneal curvature was measured with a keratometer and the fundus was examined. At various times after lid opening, animals were refracted again, used for electrophysiological studies on the visual pathways and finally perfused through the heart with 10%

Josh Wallman
Science 1978

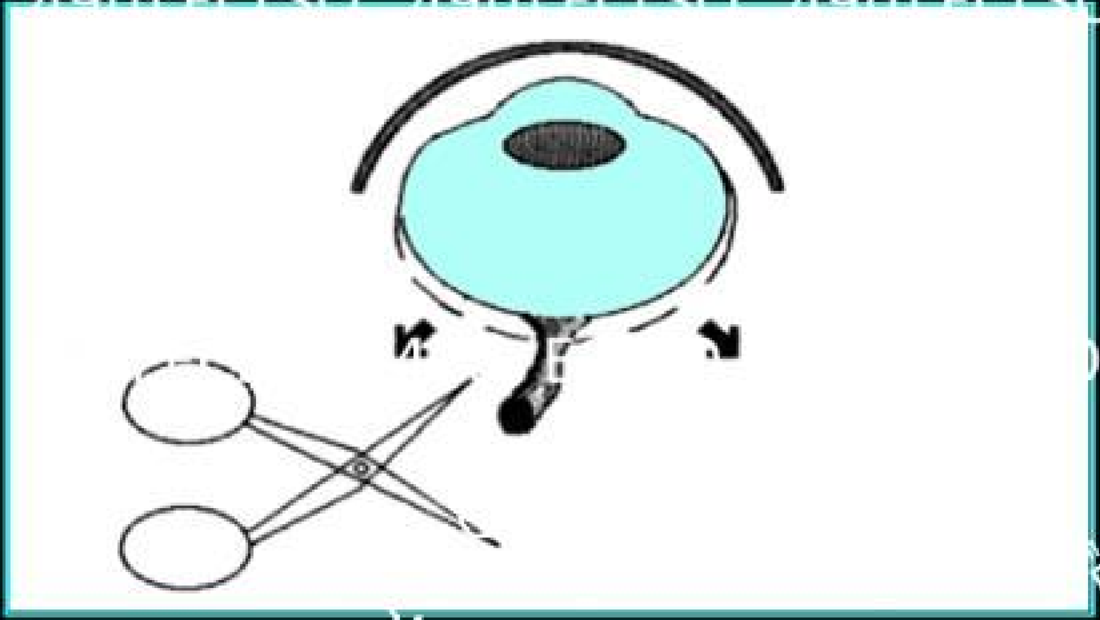


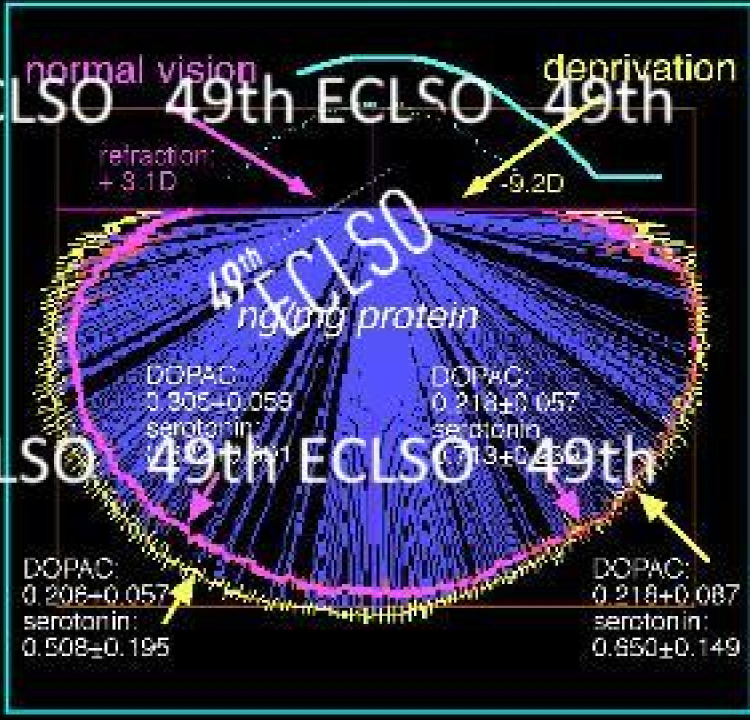
unexpected: intact optic nerve not needed and there is local control of eye growth


Wallman et al, Science 1987

and there are local changes in eye growth and retinal dopamine metabolism

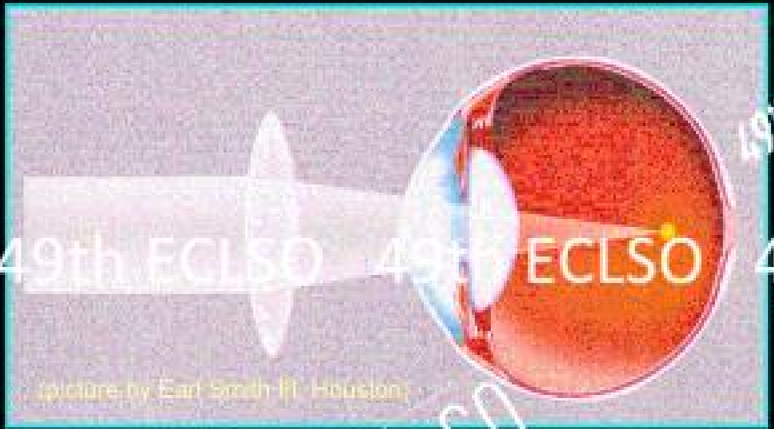
Ohngemach et al, Vis Neurosci 1997

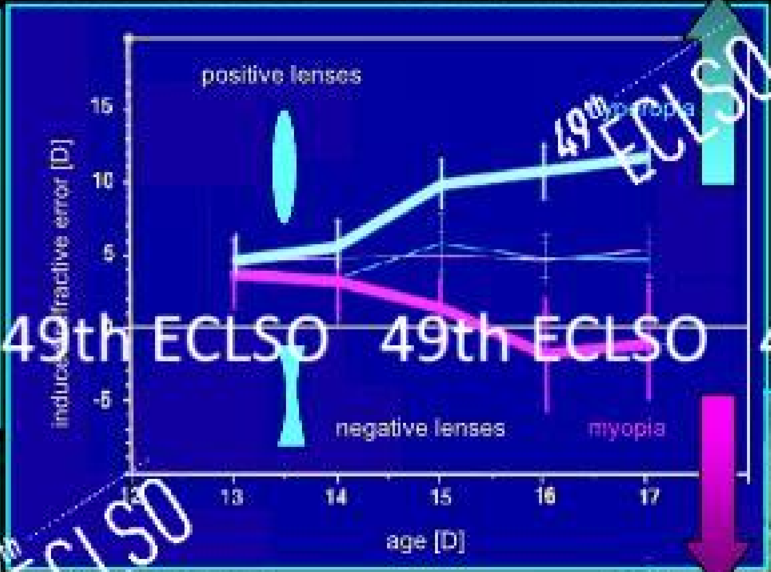




and there is more than deprivation myopia (which is an open-loop condition): a "closed loop" feedback mechanism for emmetropization

shifting the focal plane induces compensatory eye growth



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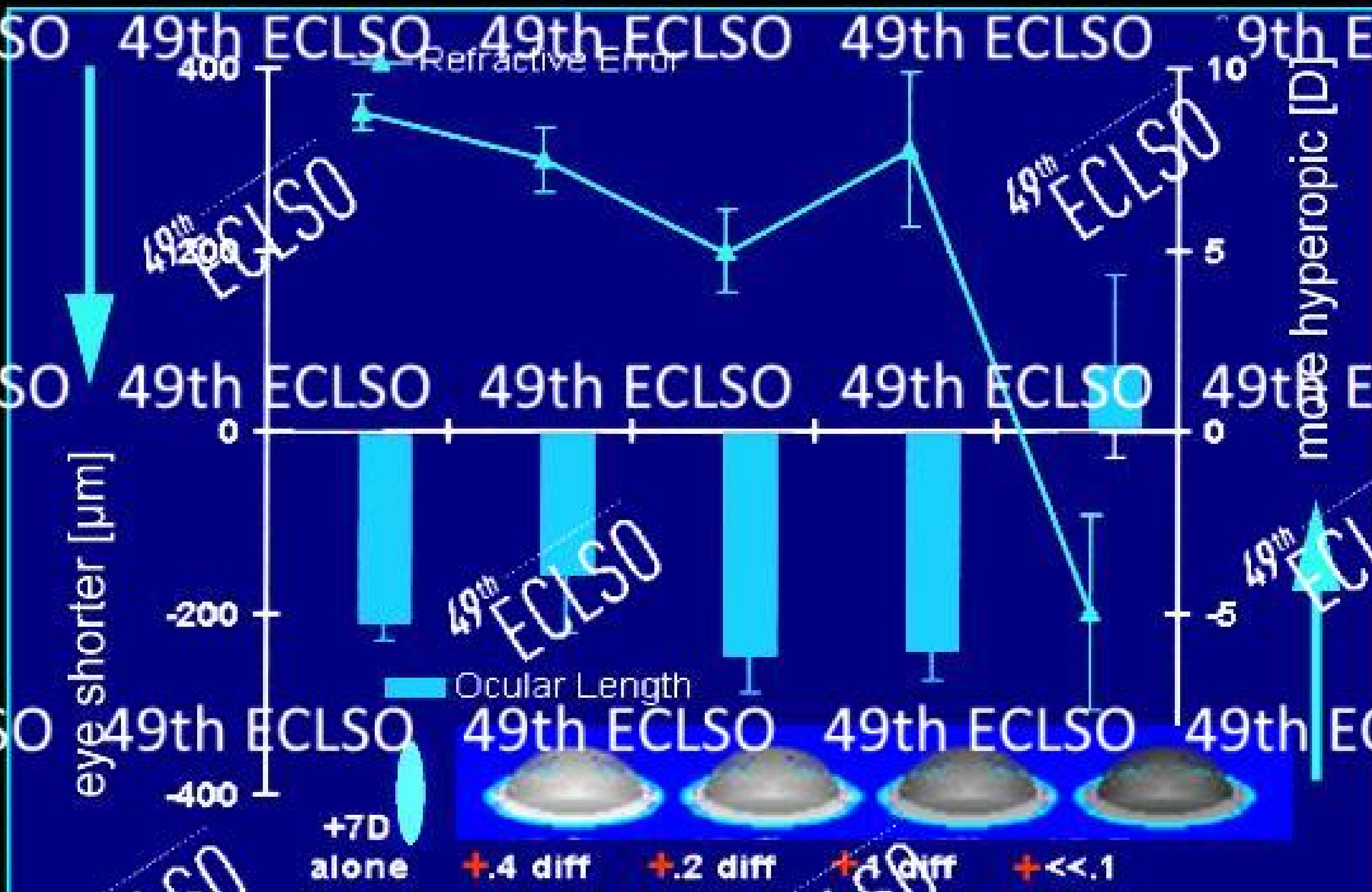
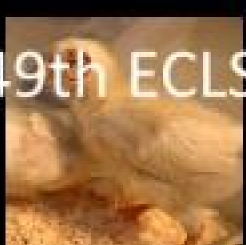
ACCOMMODATION, REFRACTIVE ERROR AND EYE GROWTH IN CHICKENS

works also in monkeys, tree shrews, guinea pigs, fish, mice and children

helmets with spectacle lenses (Smith et al. IOVS 1999)

very robust inhibitory signal for eyes growth:
positive lenses cause hyperopia despite diffusing Bangerter foils on top





Bangerter foils with different levels of diffusion

Park, Winawer, Wallman, IOVS 2003

... "2" mechanisms of emmetropization (hypothesis Swiatczak/Schaeffel)

(everything works in the low spatial frequency range (< 10 cyc/deg) and without accommodation, and both mechanisms act at the same time)

retina

- low pass WITHOUT PLUS DEFOCUS
- slow response, prolonged exposure needed
- atropine, pirenzepine, dopamine, NO, bright light
- inhibited by ON stimuli and short duty cycles, > 5 Hz

- low pass WITH PLUS DEFOCUS
- fast response, short exposure time sufficient
- NOT atropine, pirenzepine, dopamine, NO, bright light
- OFF stimulus inhibited

... have different genetic networks with little overlap

choroid

- bi-directional signals ZENK/Egr1, RA, BMP2, ...

- default growth, low energy, choroidal thinning

oxygen

- inhibition has high energy consumption, choroidal thickening

oxygen

sclera

scleral fibroblasts

and … do we know now how emmetropization works?

… no … these are the problems:

myopia does not inhibit itself
(as would be expected from a closed loop feedback system)

undercorrection has little effect
(undercorrection should act like a positive lens)

Is positive defocus (necessary to inhibit eye growth) detected by the human retina at all?

(note that we would not need this for vision or accommodation)

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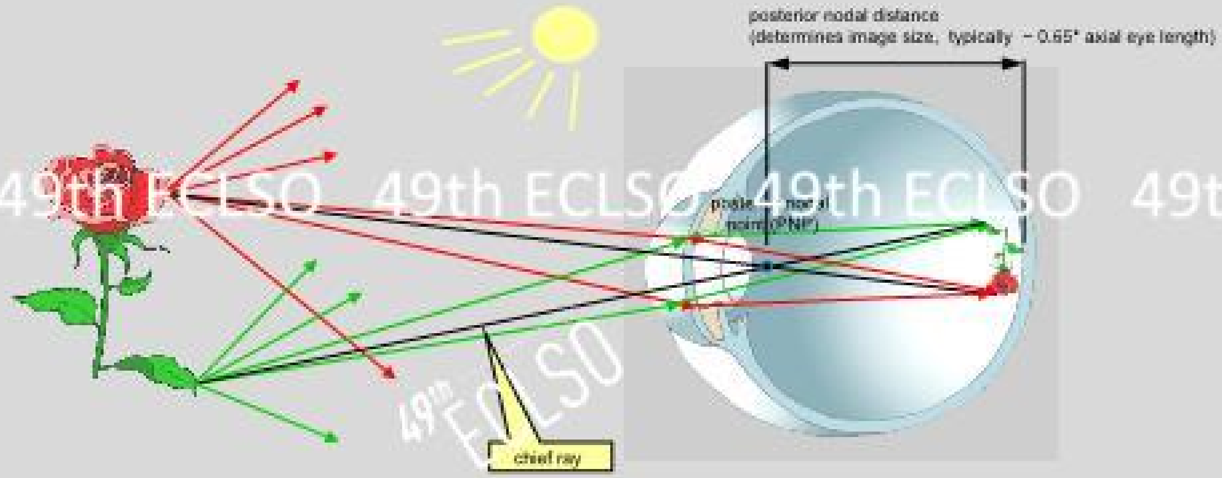
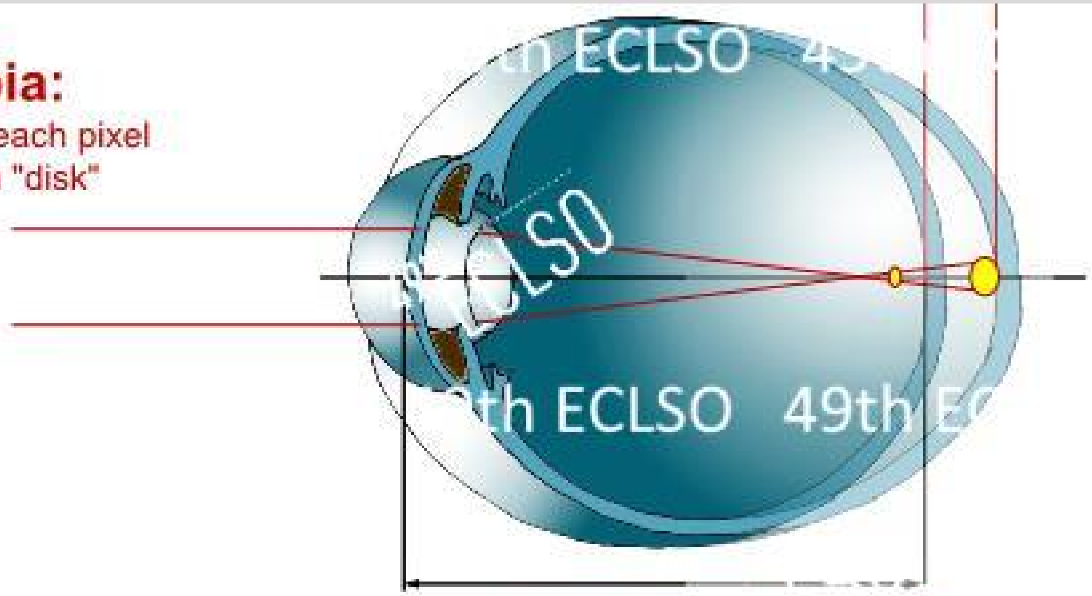
how does the image get on the retina ?



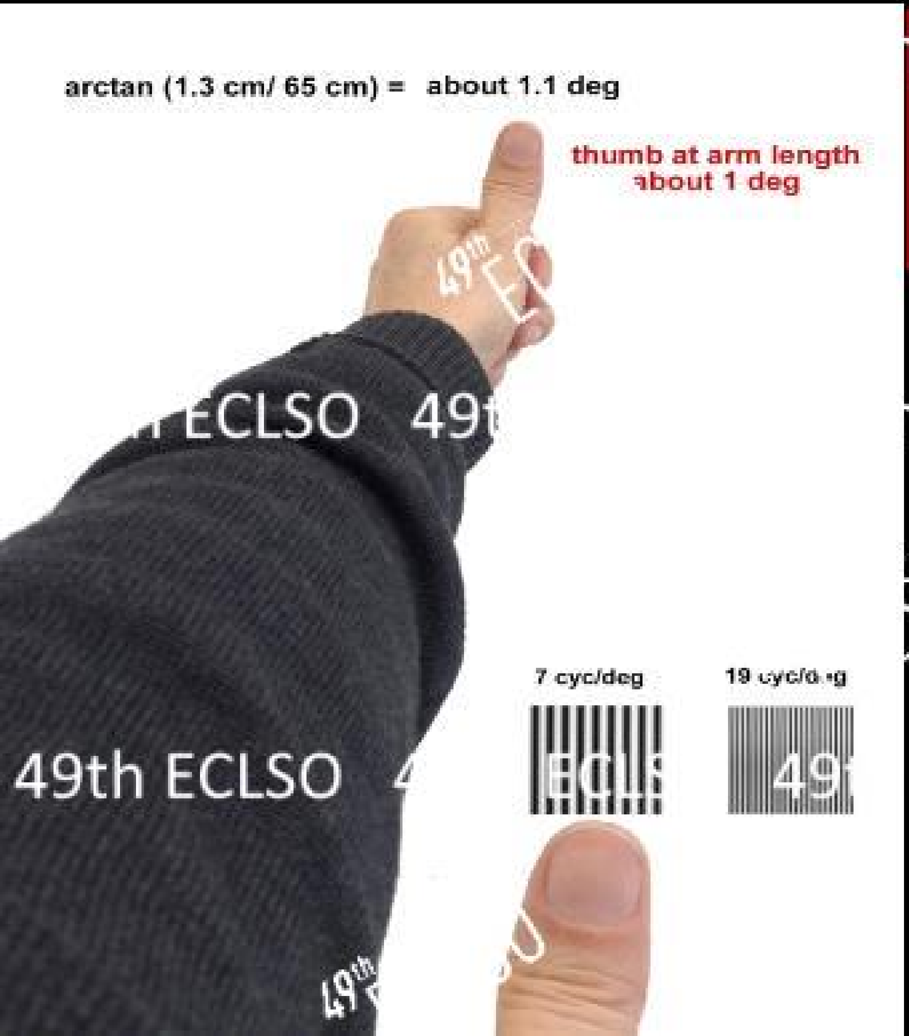
myopia:

eye too long, each pixel becomes a "disk"



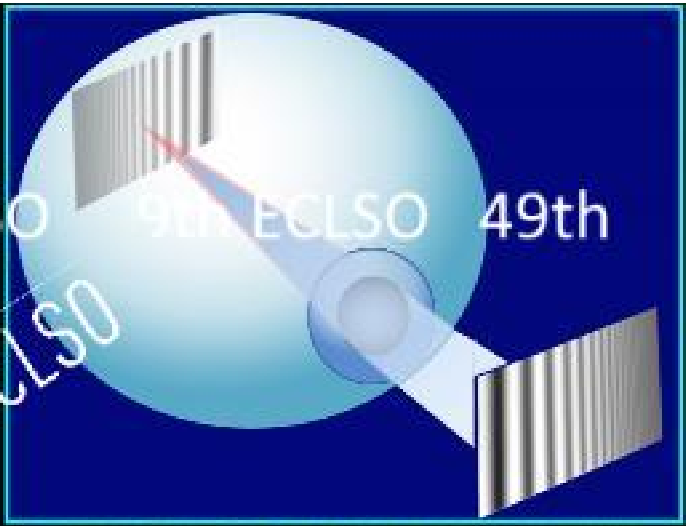
typical axial length approx. 24 mm

How can the sharpness of movie be quantified? Comparing the modulation transfer function –
the spatial frequency distribution [cyc/deg] (after Jean Baptiste Fourier, born 1768)
illustrated:

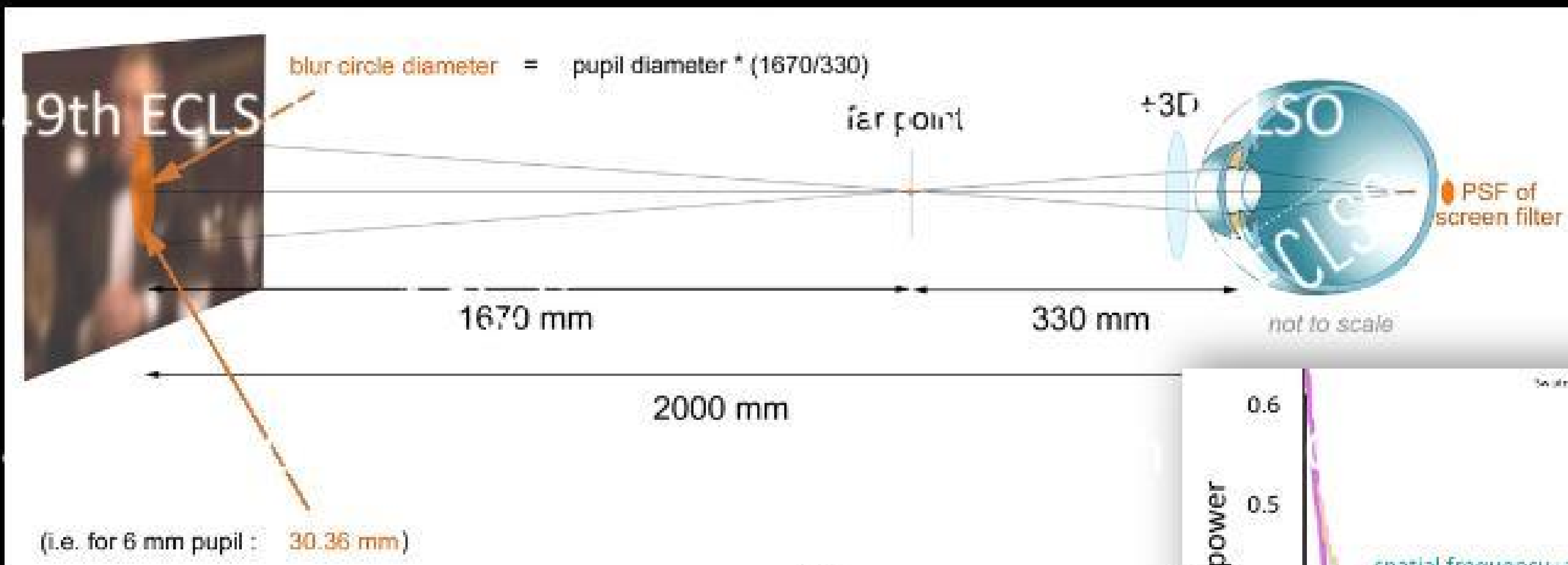


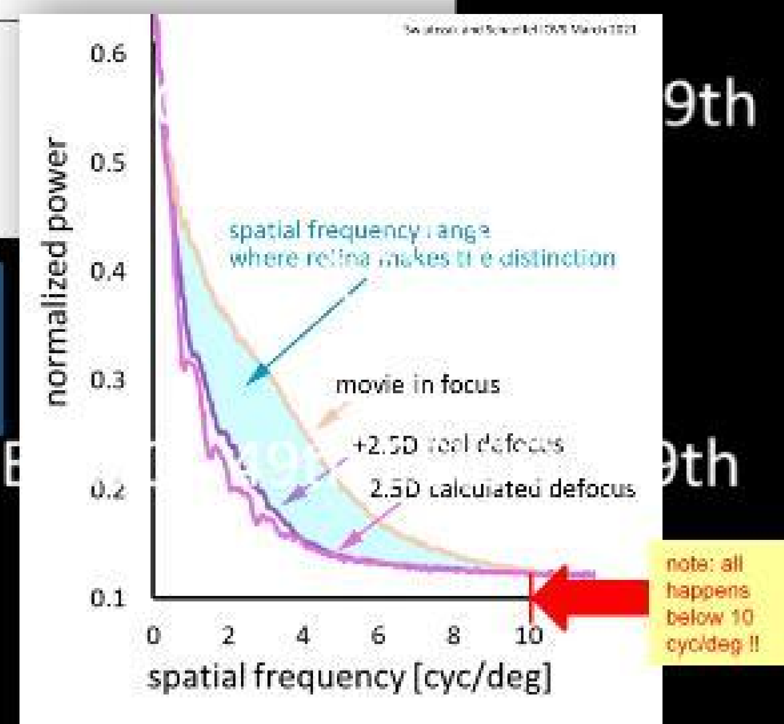
optics of the eye is not perfect and therefore a low pass filter for spatial frequencies

defocus increases low pass filtering following a well defined function (first Bessel function)



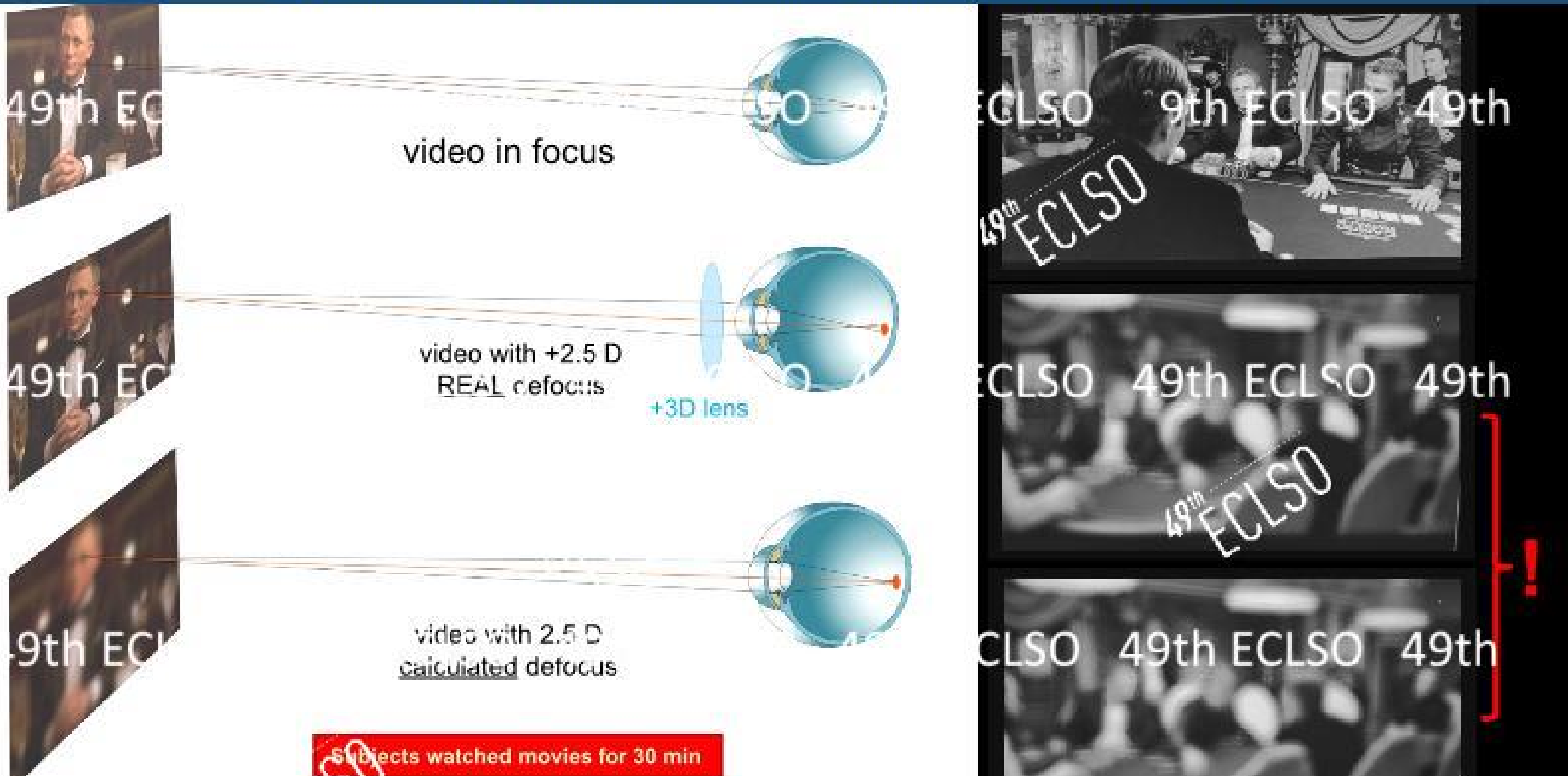
simulating defocus to find out whether human retina distinguish positive defocus from (flat) calculated defocus





a close match of the modulation transfer with calculated defocus to real defocus was achieved by converting pixels into discs of defined diameter

experiment: young adult human subjects watch movies at 2 m distance



Software (visual C++) was written for realtime spatial filtering of any movie at ≈ 25 Hz

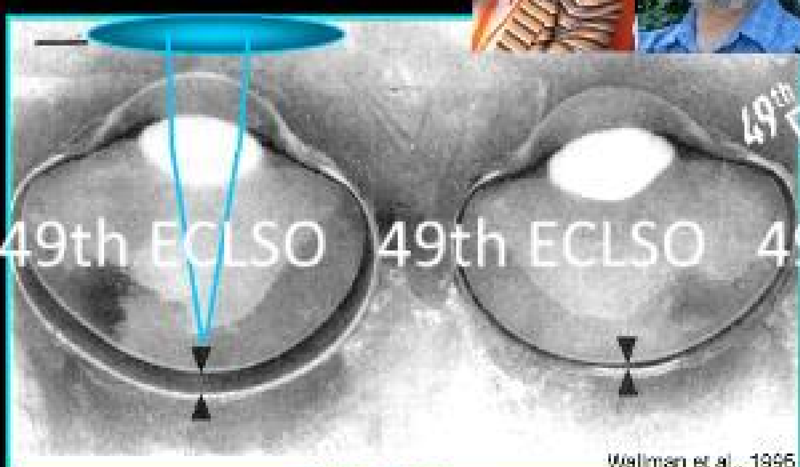
how can we measure the output of the retina on short time scales?

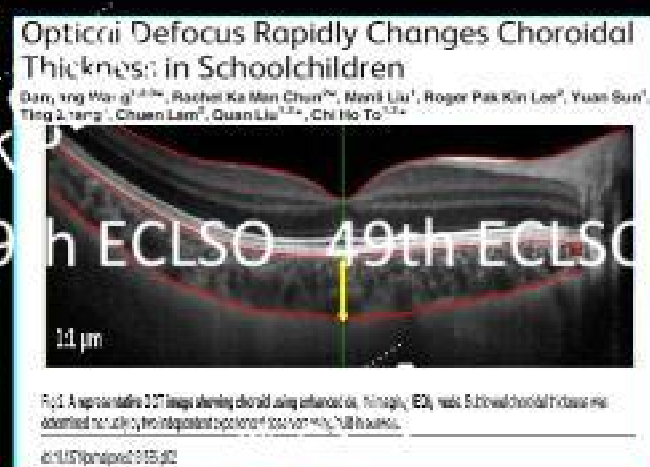
a predictor of future myopia - changes in choroidal thickness

also in children, choroidal thickness changes in both directions when lenses are used to shift the focal plane

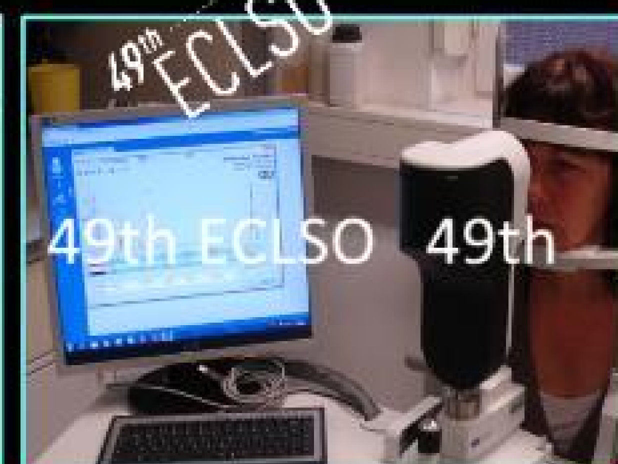
choroidal thickness changes can also be inferred "indirectly" from short-term changes in axial length

(using low coherence interferometry, the Lenstar LS900)




Optical Defocus Rapidly Changes Choroidal Thickness in Schoolchildren

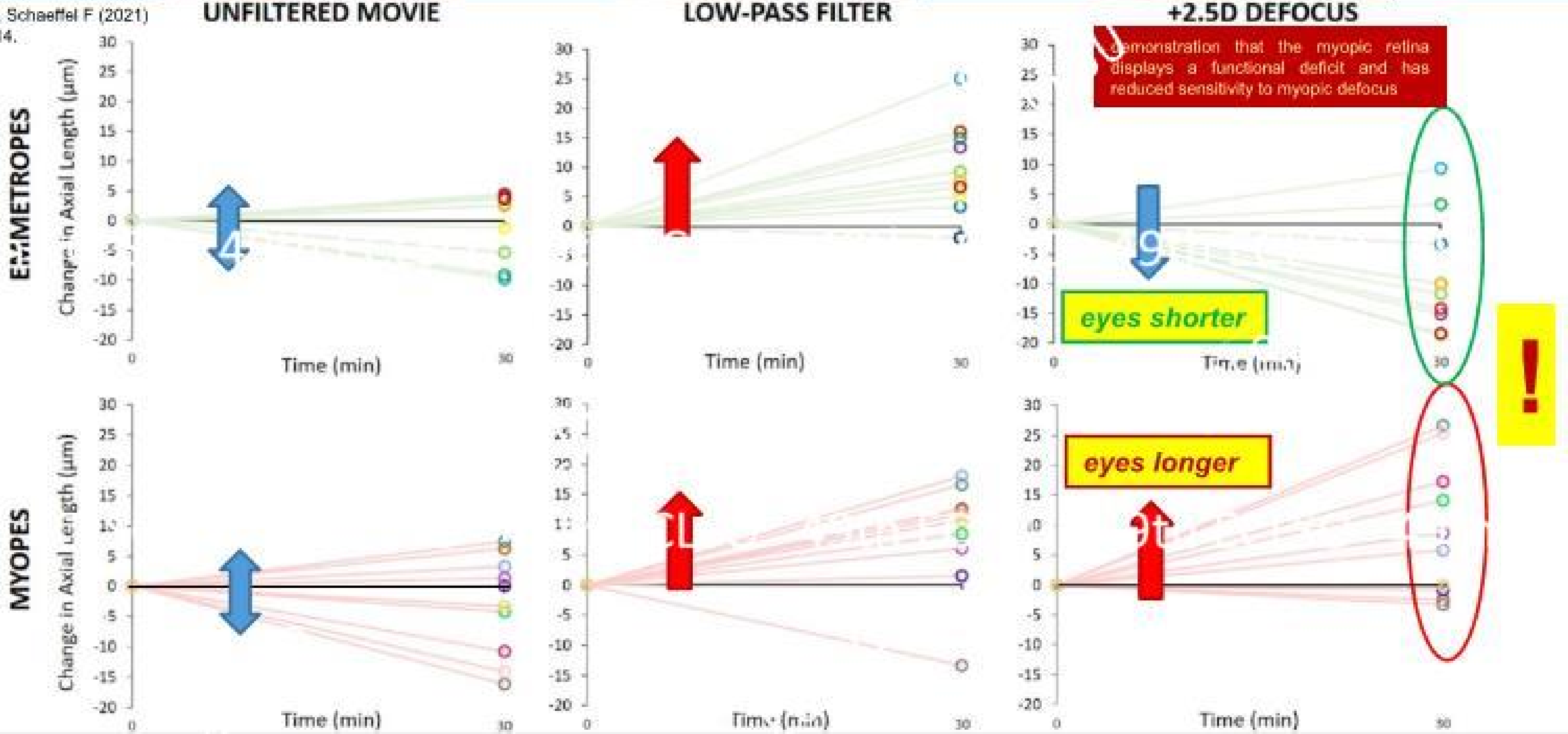
Dan, ing Wang, Rachel Ka Man Chun, Manli Liu, Roger Pak Kin Lee, Yuan Sun, Ting Zhang, Chuen Lam, Quan Liu, Chi Ho To



Results

- changes in ocular axial length after 30 min

Swiatczak B, Schaeffel F (2021) IOVS 62(3):14.



so the myopic retina does not detect positive defocus …

… or could it be that the <u>biochemical signalling cascade</u> for growth inhibition from retina to choroid and sclera is no longer functional in myopic people?

… use other known tricks to make the choroid thicker by retinal stimulation

SCIENTIFIC REPORTS

OPEN Reading and Myopia: Contrast Polarity Matters

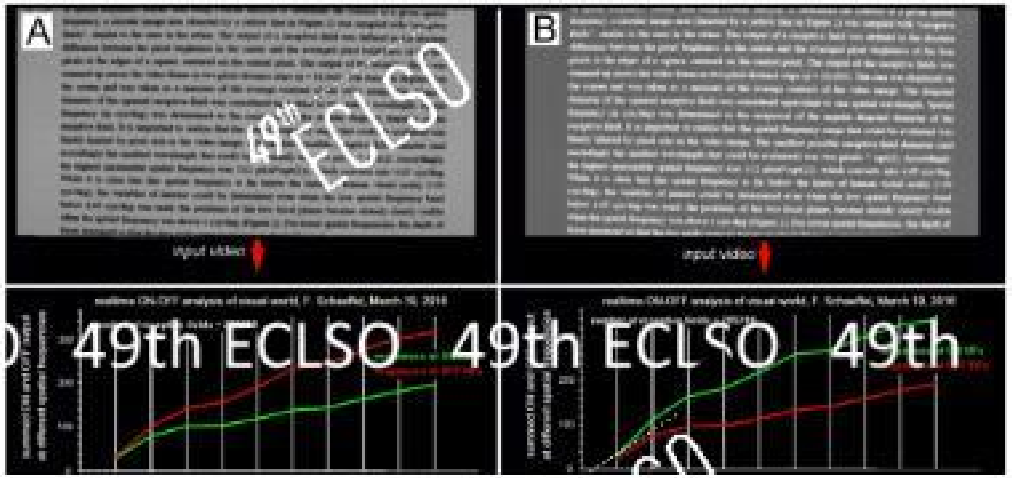
July 2016

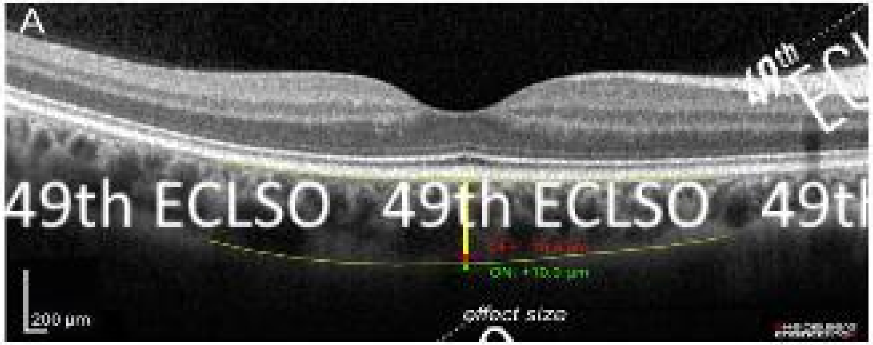
We had previously found that

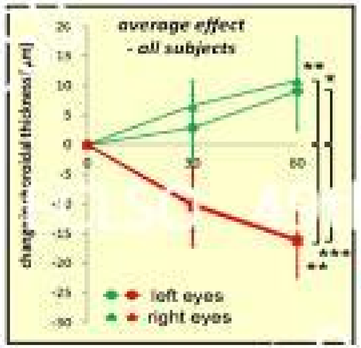
matched brightness

reading dark text on bright background overstimulates OFF pathways + makes the choroid thinner

reading bright text on dark background overstimulates ON pathways + makes the choroid thicker

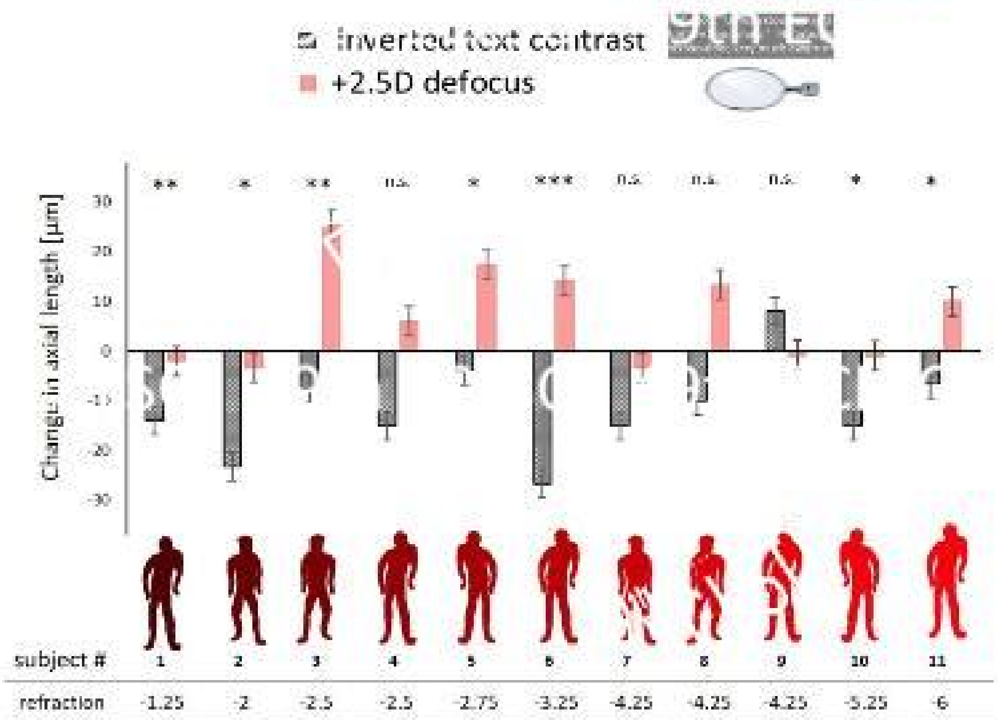




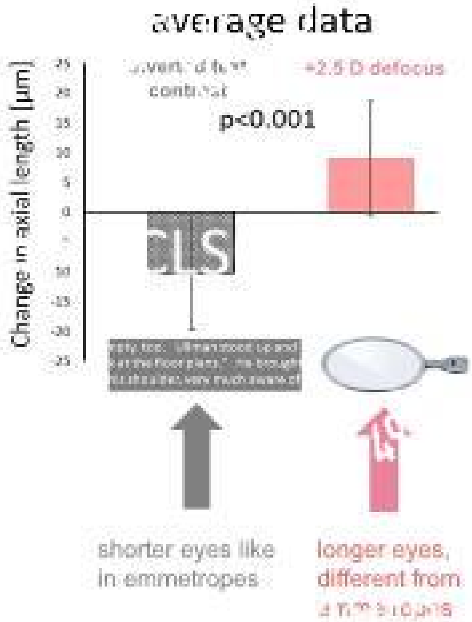


and this worked: the myopic retina triggers choroidal thickening as in emmetropes – the biochemical cascade is intact !

Myopic subjects



Yes! – also myopic subjects could still develop temporarily shorter eyes when they read text with inverted contrast



Swiatczak and Schaeffel (2022) "Transient eye shortening during reading text with inverted contrast: effects of letter size and refractive error" Transl Vis Sci Technol.11(4):17.

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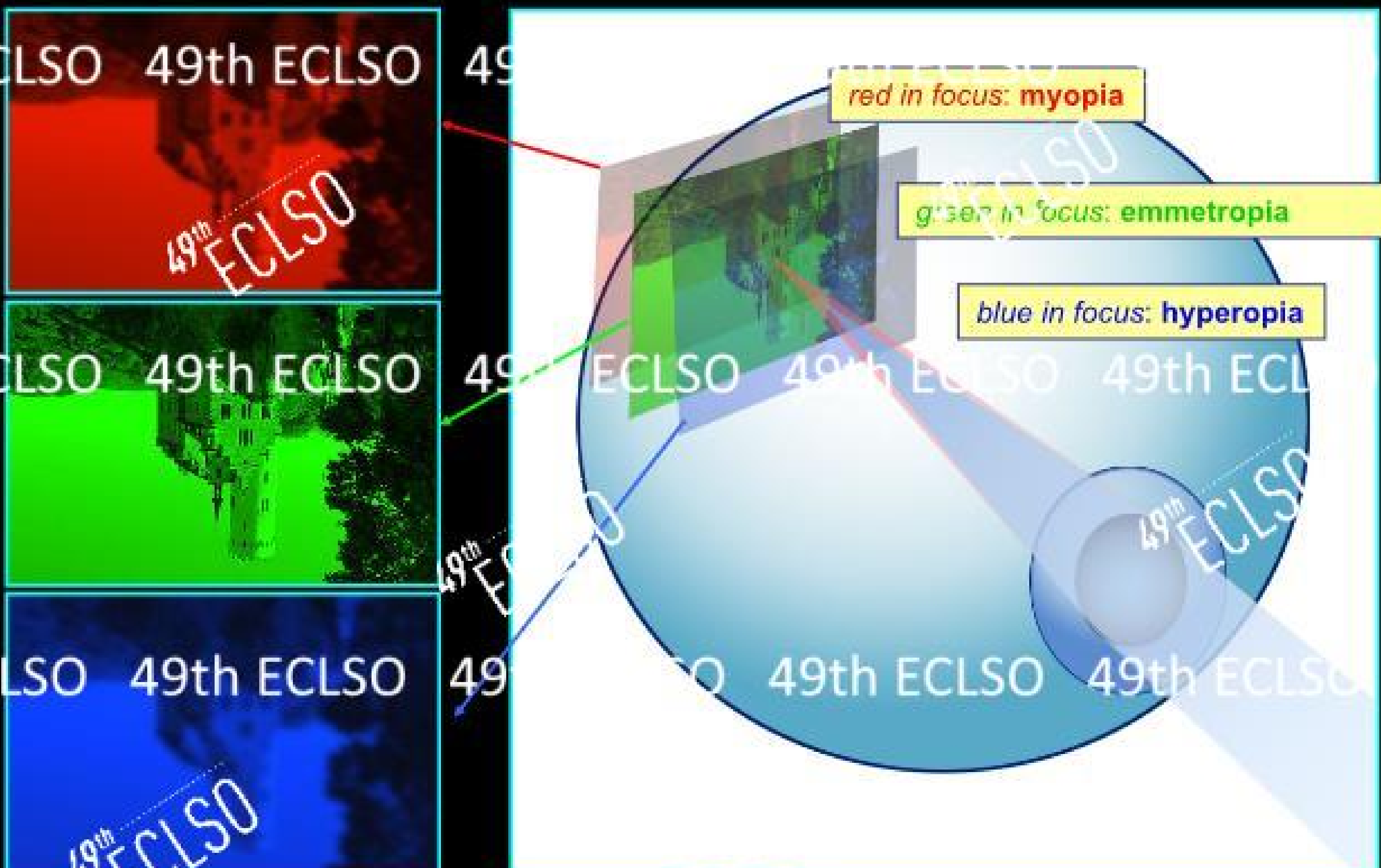
How could the retina detect positive defocus ? – chromatic aberration would be great



… also suggests a role of chromatic cues in emmetropization: less myopia in color-blind people

Clinical and Epidemiologic Research

Association Between Color Vision Deficiency and Myopia in Chinese Children Over a Five-Year Period

Capital Medical University, Beijing, China

Citation: 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):2. https://doi.org/10.1167/iovs.63.2.2

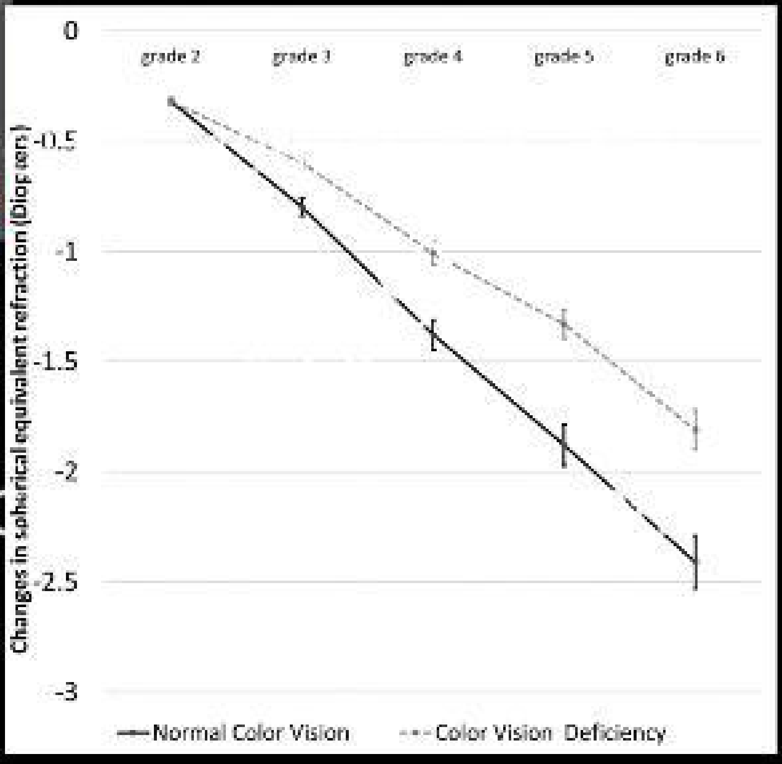
A total of 2549 grade 1 students (aged 7.1 ± 0.4 years) from 11 primary schools were enrolled and followed up for five years.

The prevalence of color vision deficiency was 1.68%, with 2.81% in boys and 0.15% in girls. Color-deficient cases consisted of 91.6% deutan and 8.3% protan. Over the five years, the cumulative incidence of myopia was 35.4% (17/48) in the color-vision deficiency group, which was lower than the 56.7% (1017/1794) in the color normal group ($P = 0.004$). Over the five-year study period, the change in spherical equivalent refraction in the color vision–deficiency group (−1.81 D) was also significantly lower than that in the color normal group (−2.41 D) ($P = 0.0$[illegible]2).

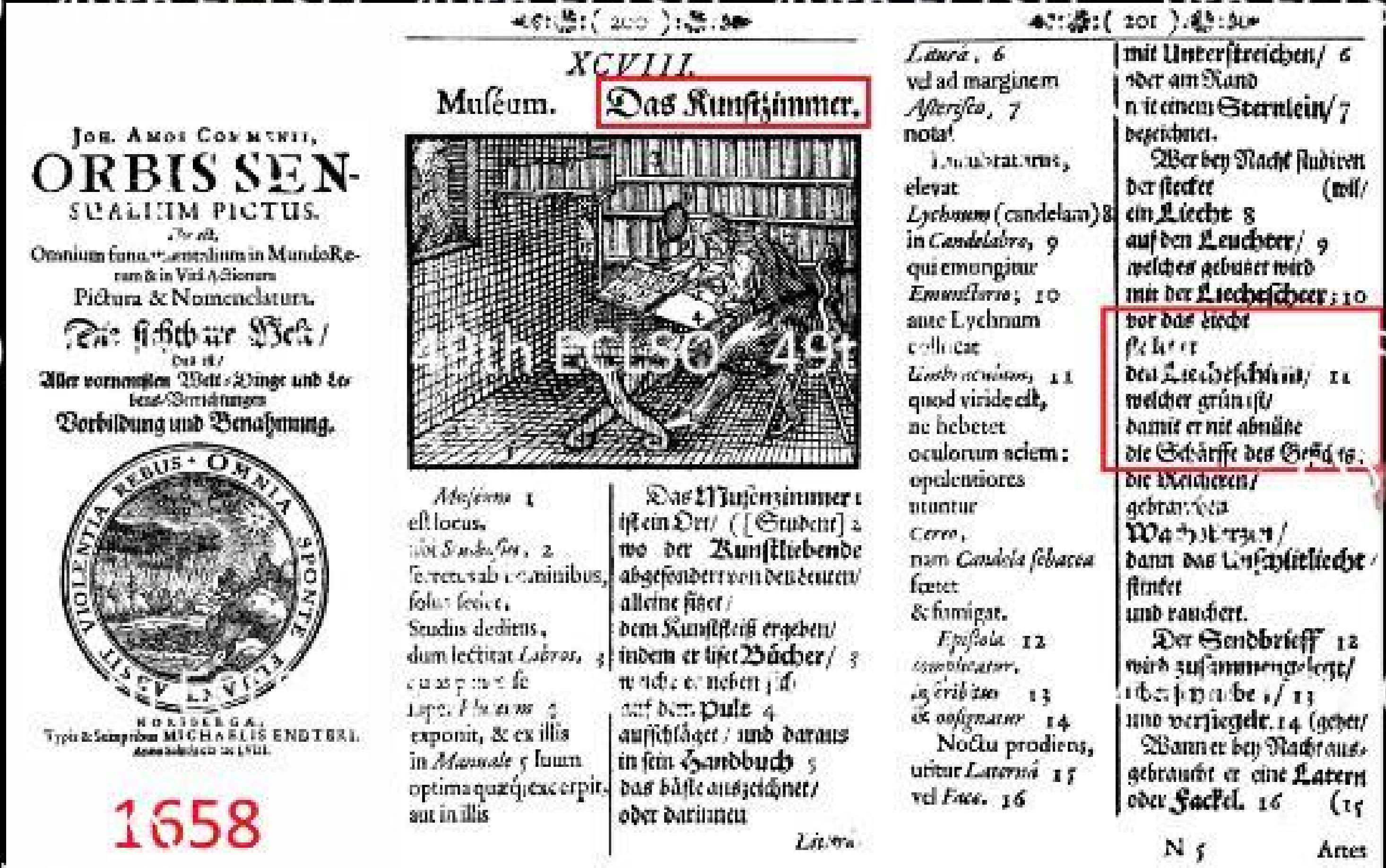
color-deficient individuals are less susceptible to myopia onset and development.

protanopia

deuteranopia

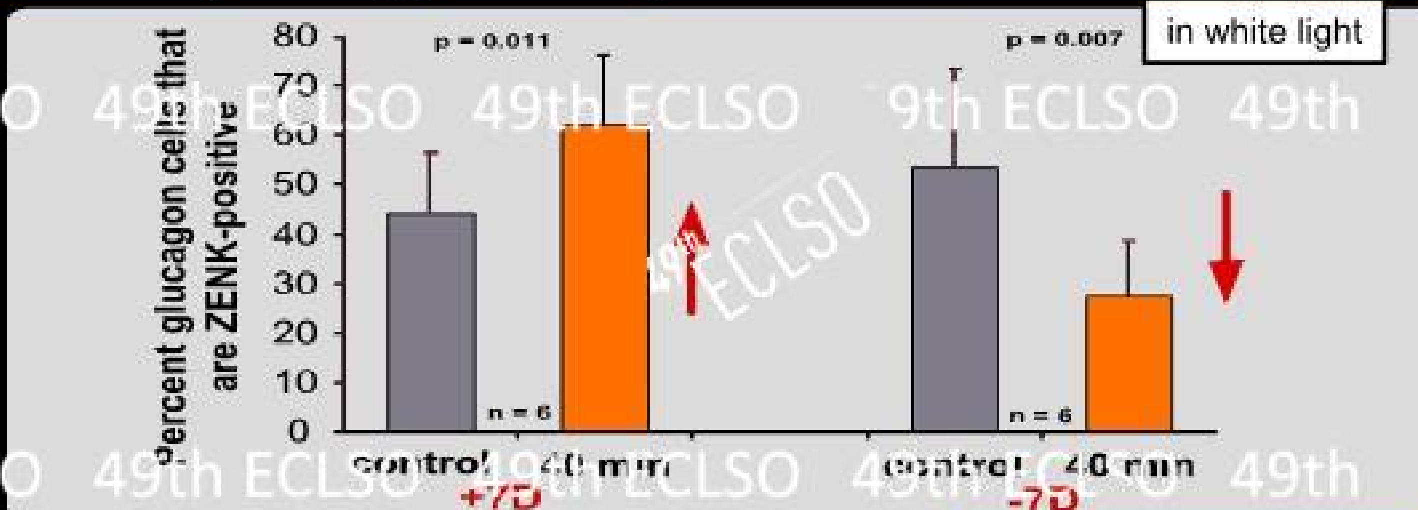


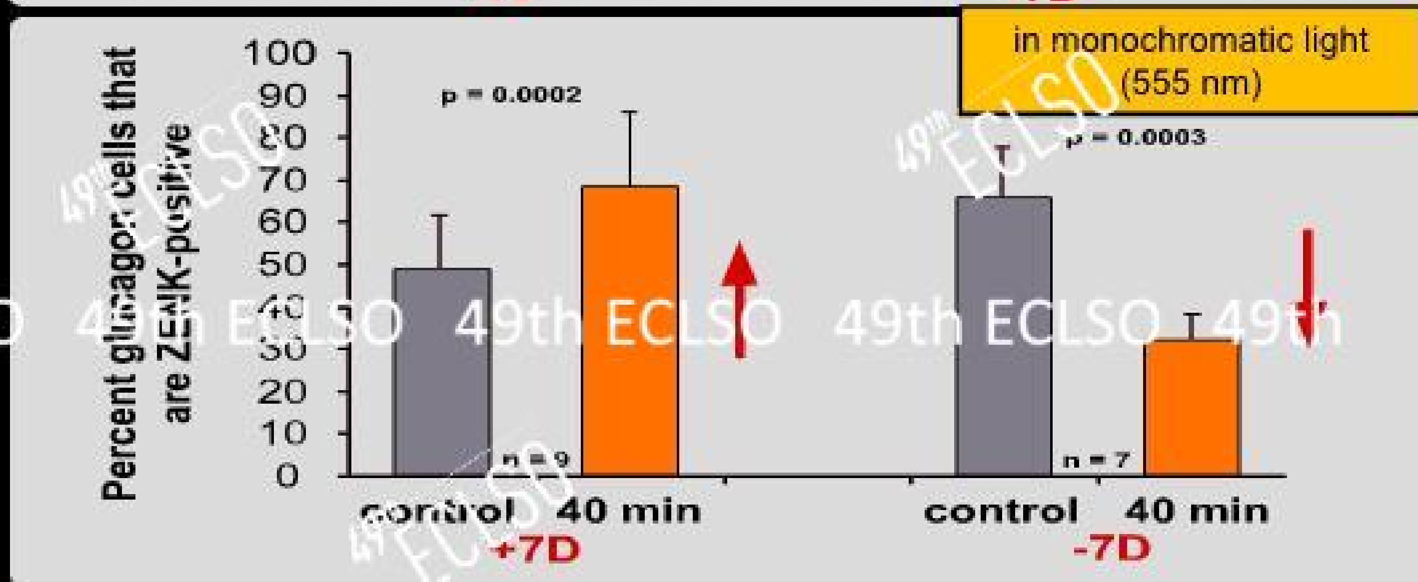
already 1658, it was postulated that book writers should use a green lamp to “prevent loss of visual acuity”

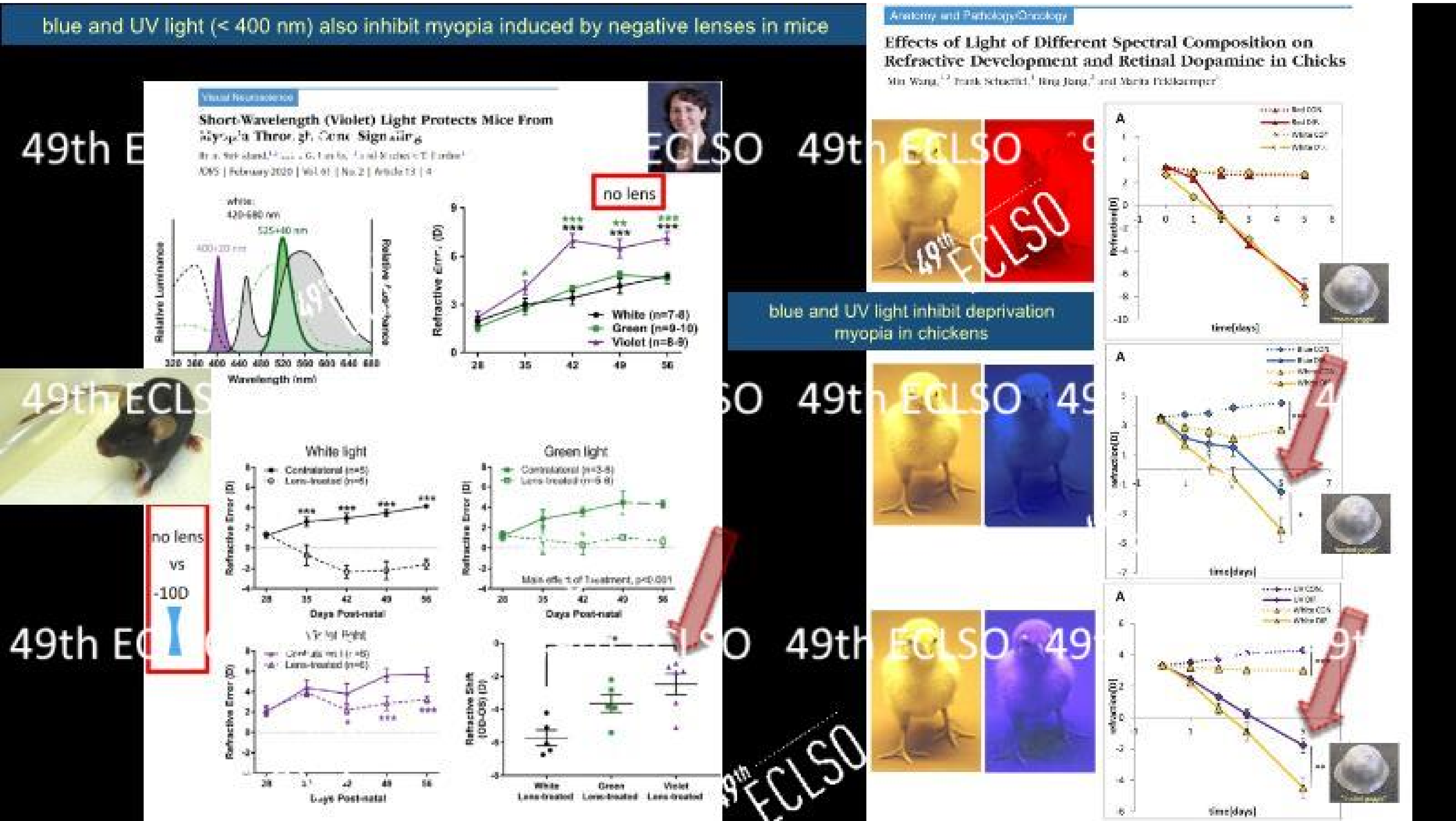


found Klaus-Peter Schaeffel, Bärschwil, CH both myopia and hyperopia can be induced with positive and negative lenses also in **monochromatic light** and ZENK responds in a sign-of-defocus dependent way, just as in white light

retinal glucagon amacrine cells "know" in a few minutes the sign of defocus: expression of the ZENK protein (2002,1999)





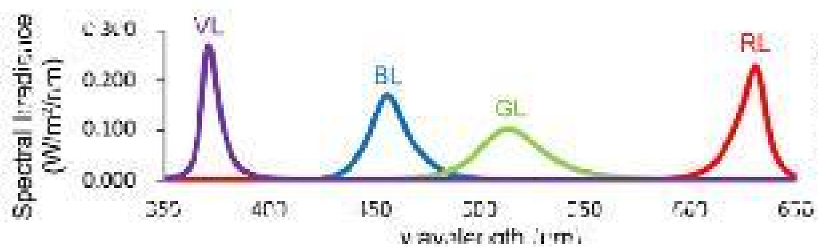

blue and UV light (< 400 nm) also inhibit myopia induced by negative lenses in mice
Visual Neuroscience
Short-Wavelength (Violet) Light Protects Mice From Myopia Through Cone Signaling
IOVS | February 2020 | Vol. 61 | No. 2 | Article 13
no lens
white:
420-680 nm
525±40 nm
400±20 nm
Relative Luminance
Wavelength (nm)
Refractive Error (D)
White (n=7-8)
Green (n=9-10)
Violet (n=8-9)
White light
Contralateral (n=5)
Lens-treated (n=6)
Days Post-natal
Green light
Main effect of Treatment, p<0.001
Refractive Shift (OD-OS) (D)
White Lens-treated
Green Lens-treated
Violet Lens-treated
no lens
vs
-10D
Anatomy and Pathology/Oncology
Effects of Light of Different Spectral Composition on Refractive Development and Retinal Dopamine in Chicks
blue and UV light inhibit deprivation myopia in chickens
time(days)
49th ECLSO

In mice, "violet" light (370 nm) inhibits myopia induced by negative lenses

Violet light suppresses lens-induced myopia via neuropsin (OPN5) in mice

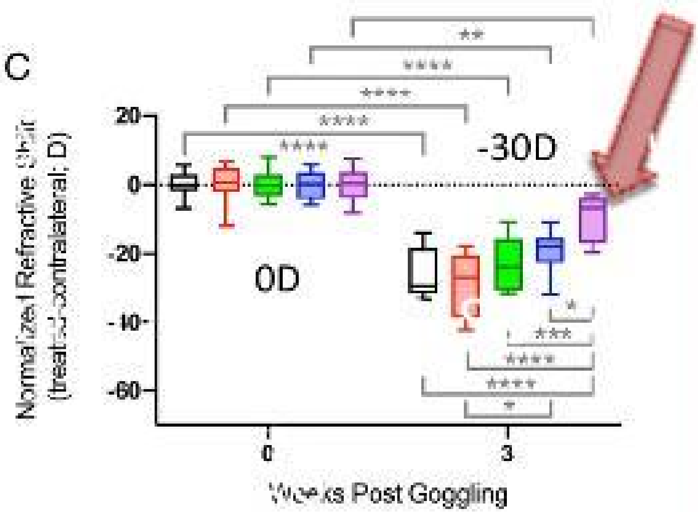
Xiaoyan Jiang, Machelle T. Pardue, Kiwako Mori, Shin-ichi Ikeda, Hidemasa Torii, Shane D'Souza, Richard A. Lang, Toshihide Kurihara, and Kazuo Tsubota

PNAS 2021 Vol. 118 No. 22 e2018840118 https://doi.org/10.1073/pnas.2018840118

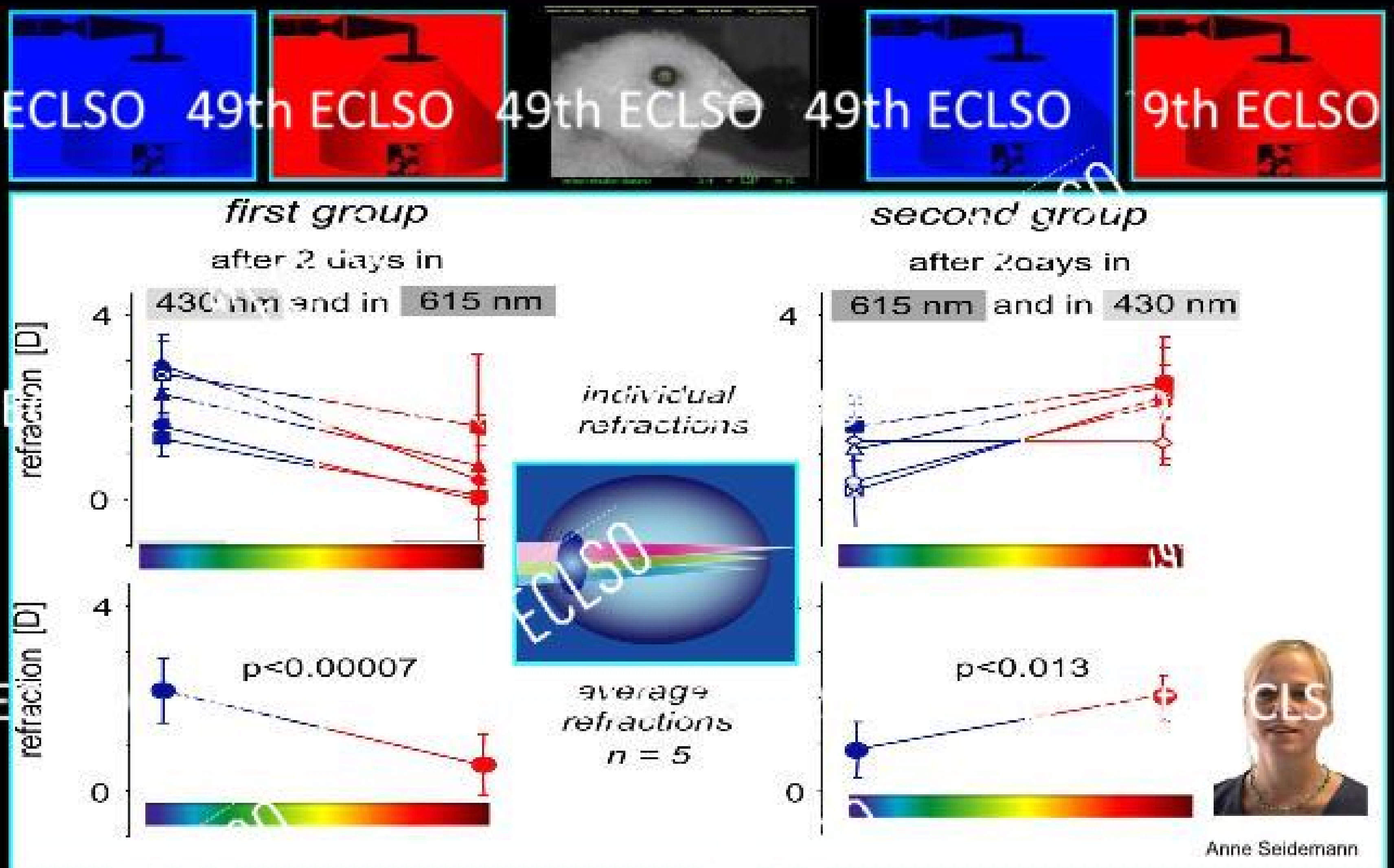


was added to white background light every evening 5-8 p.m.

0D -30D



red or blue – chicken eyes grow towards the different focal planes if nothing else is available



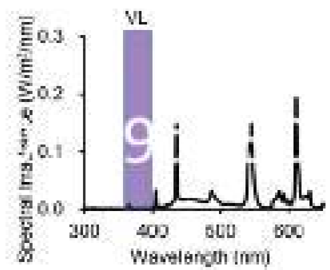
Seidemann A, Schaeffel F (2002). Vision Res. 42(21):2409-2417 inhibition of myopia by violet light also in humans? Torii et al (2018)

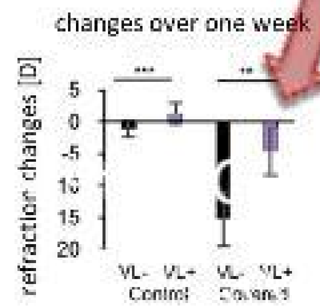

EBioMedicine
ELSEVIER

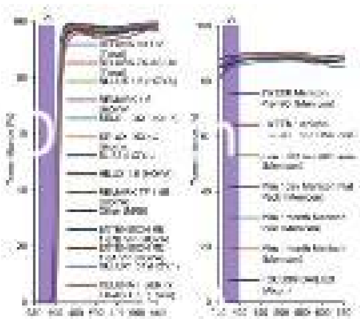
Research Paper

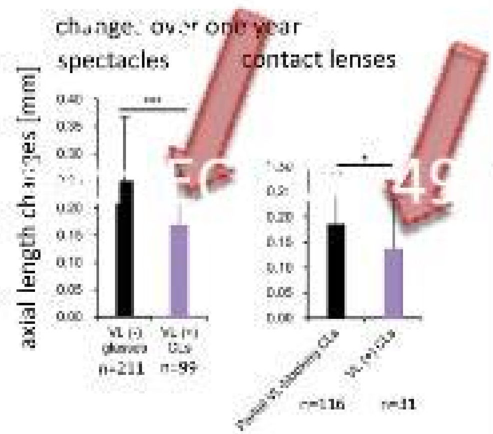
Violet Light Exposure Can Be a Preventive Strategy Against Myopia Progression

Hidemasa Torii, Toshihide Kurihara, Yuko Seko, Kazuno Negishi, Kazuhiko Ohnuma, Takaaki Inaba, Motoko Kawashima, Xiaoyan Jiang, Shinichiro Kondo, Maki Miyauchi, Yukihiro Miwa, Yusaku Katada, Kiwako Mori, Keiichi Kato, Kazuo Tsubota, Hiroshi Goto, Mayumi Oda, Megumi Hatori, Kazuo Tsubota









spectacles and contact lenses with higher transmission of violet light can also inhibit myopia in humans?

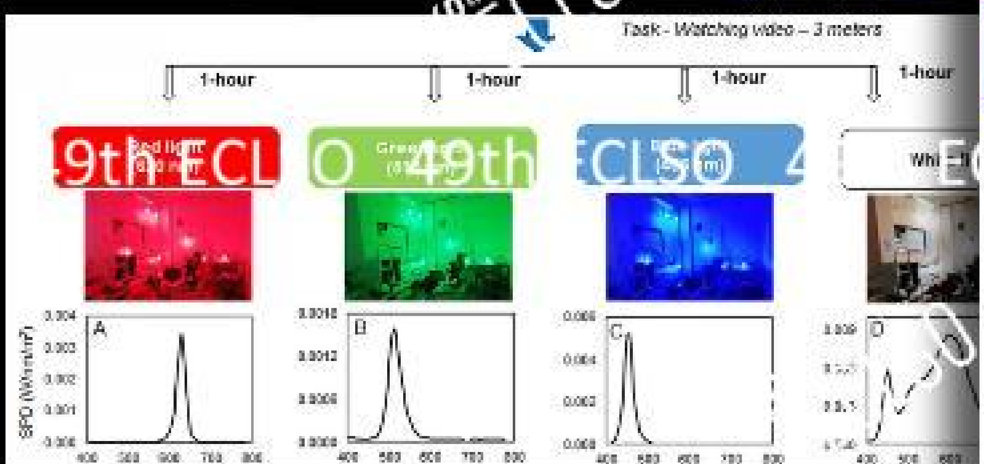
young subjects (20-32 years) develop shorter eyes in **blue** light (due to thickening of the choroid)
and longer eyes in narrow-band **red** and **green** light in one hour (due to thinning of the choroid)

Visual Neuroscience

Short-Term Exposure to Blue Light Shows an Inhibitory Effect on Axial Elongation in Human Eyes Independent of Defocus

Swapnil Thakur, Rohit Dhakal, and Pavan K. Verkicharla
Myopia Research Lab – Prof. Brien Holden Eye Research Centre, L V Prasad Eye Institute,
Brien Holden Institute of Optometry and Vision Sciences, L V Prasad Eye Institute, Hyderabad

Citation: Thakur S, Dhakal R, Verkicharla PK. Short-term exposure to blue light shows an inhibitory effect on axial elongation in human eyes independent of defocus. *Invest Ophthalmol Vis Sci.* 2021;62(15):22.
https://doi.org/10.1167/iovs.62.15.22



axial length

choroidal thickness

Combined Effect of Chromatic and Optical Defocus on Ocular Biometry | IOVS | December 2021 | Vol. 62 | No. 15 | Article 22 | 5

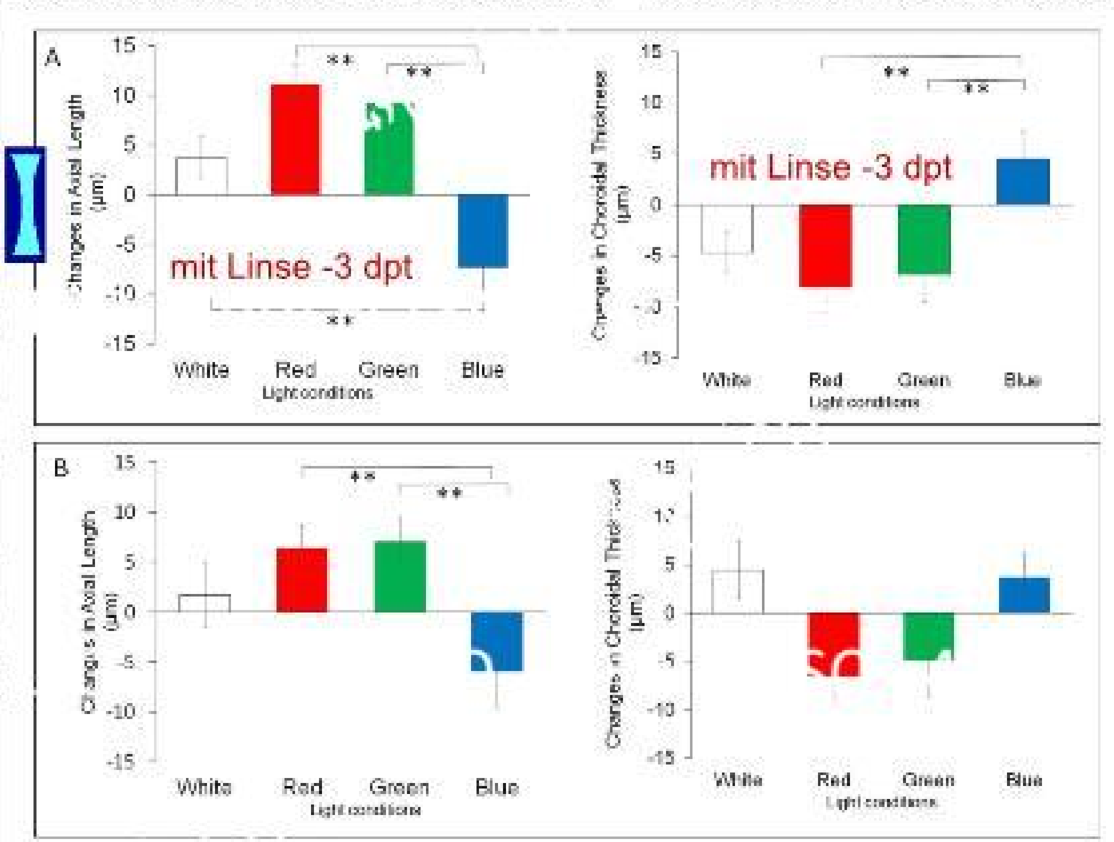
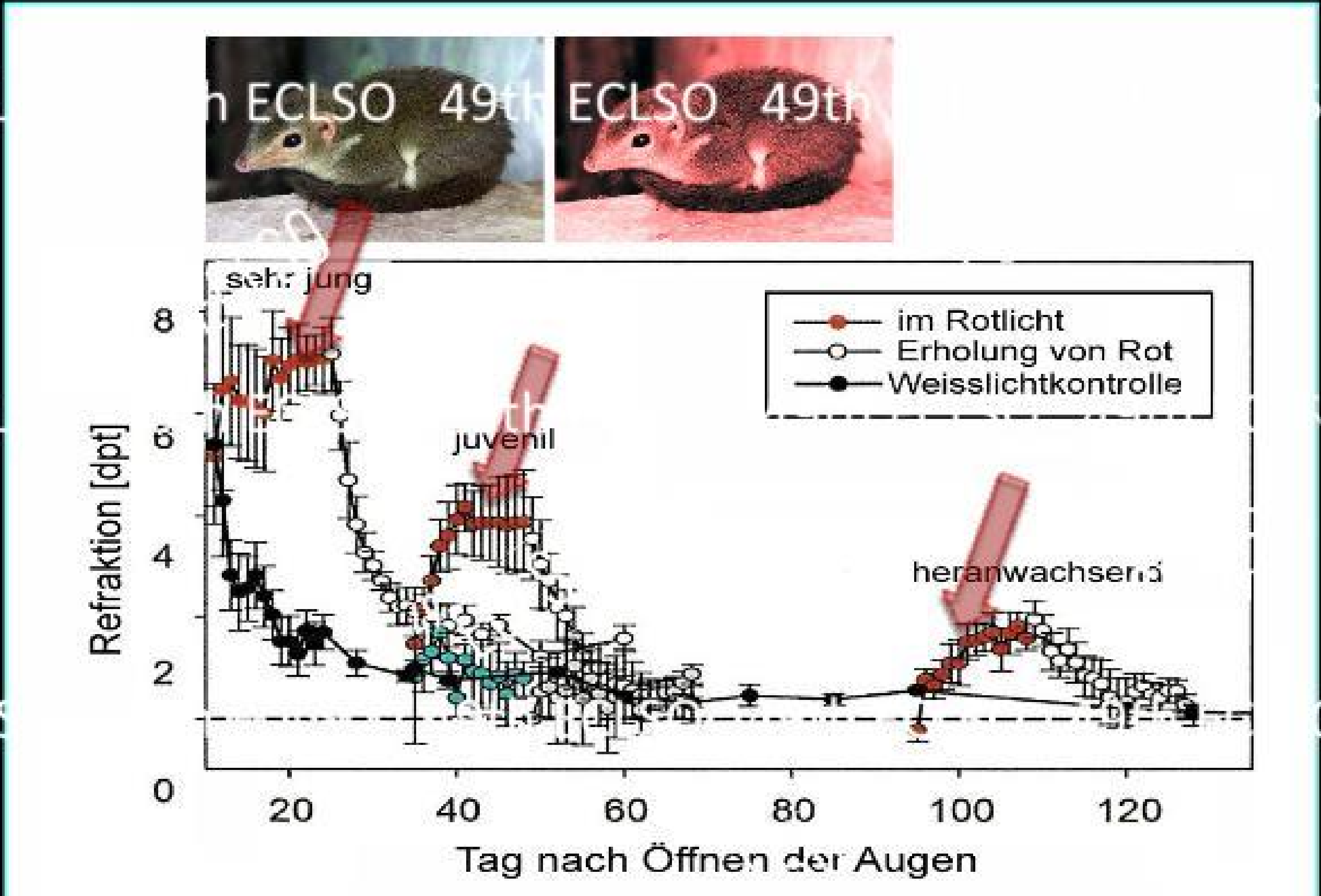


FIGURE 3. Changes in axial length and choroidal thickness in the defocused eye (top panel) and non-defocused eye (bottom panel) after 1 hour of light exposure. Error bar indicates standard error of mean (SEM). ** Indicates P value < 0.05.

but -- red light makes eyes hyperopic in tree shrews!

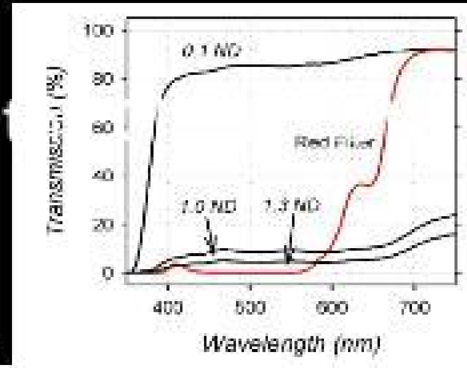


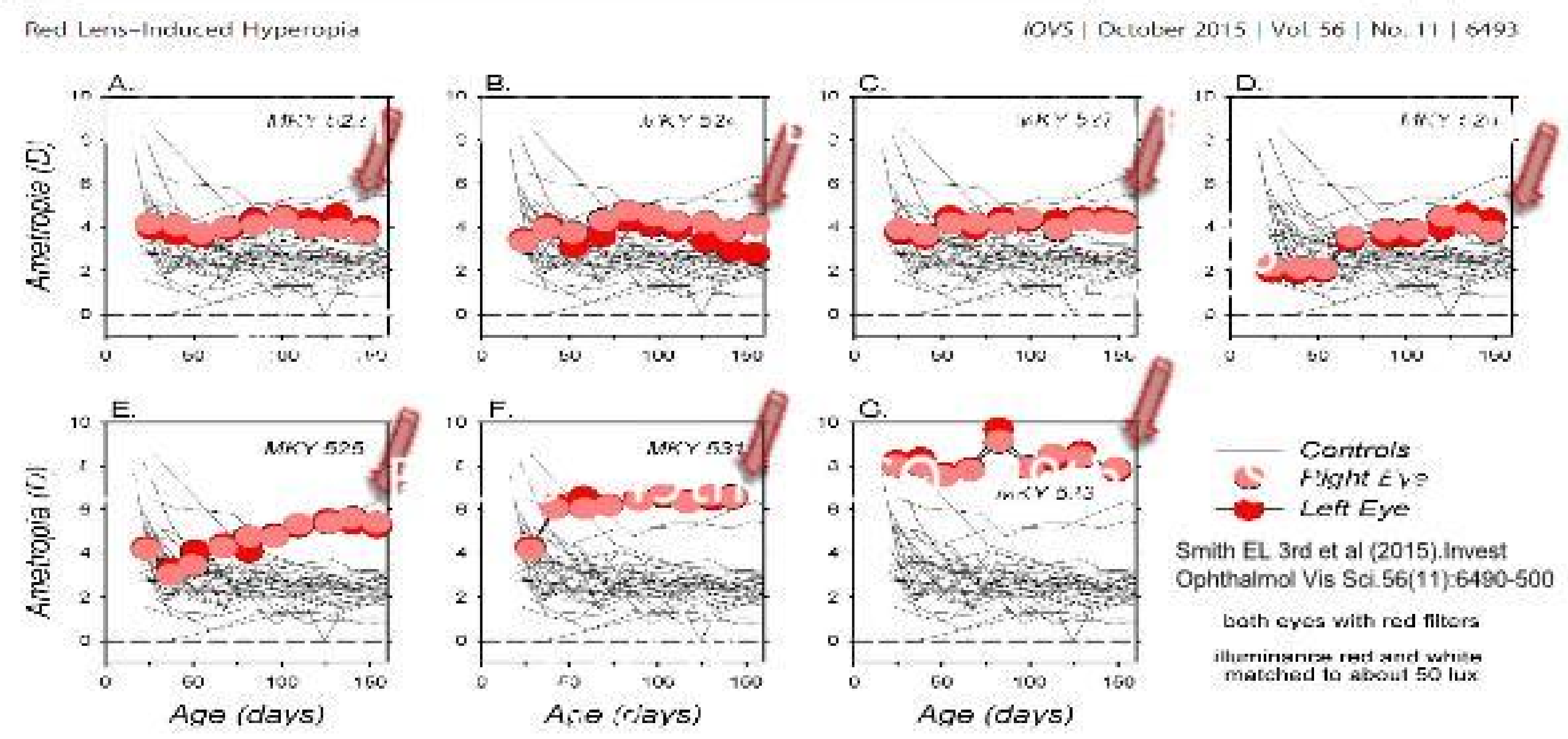
also rhesus monkeys become more hyperopic in red light

Visual Psychophysics and Physiological Optics

Effects of Long-Wavelength Lighting on Refractive Development in Infant Rhesus Monkeys

Earl L. Smith III,[1,2] Li-Fang Hung,[1,2] Baskar Arumugam,[1,2] Brien A. Holden,[2] Maureen Neitz,[3] and Jay Neitz[3]





Smith EL 3rd et al (2015).Invest Ophthalmol Vis Sci.56(11):6490-500

both eyes with red filters

illuminance red and white matched to about 50 lux

... strategies with unknown mechanisms: exposing children to low power red laser light


Research Square

Low-intensity, Long-wavelength Red Light Slows the Progression of Myopia in Children: an Eastern China-based Cohort

Lei Zhou
Ningbo Eye Hospital
Chao Xing
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Wei Dang
Ningbo Eye Hospital
Chaoqun Hua
Ningbo Eye Hospital
Liyang Tong
Ningbo Eye Hospital

Research Article

Posted Date: June 25th, 2021

myopia progression over 9 month:

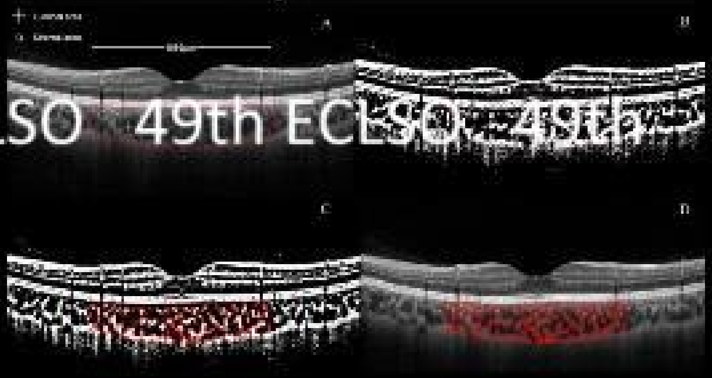
without laser therapy: from -3.09 D to – 2.87 D (n = 105)

with laser therapy: from -3.03 D to – 3.57 D (n = 56)

All the children wore spectacles and underwent repeated 650-nm, low-intensity, single-wavelength red light treatment twice a day for three minutes each time.

Issues:

- 0.4 mW at 635-650 nm – is almost nothing
- experiments in monkeys at 630 nm, 274 lux, about x 40,000 brighter
- no clear information about light delivery
- company not accessible (from europe?)



blue light tended to cause more myopia in monkeys and had no effect on deprivation myopia

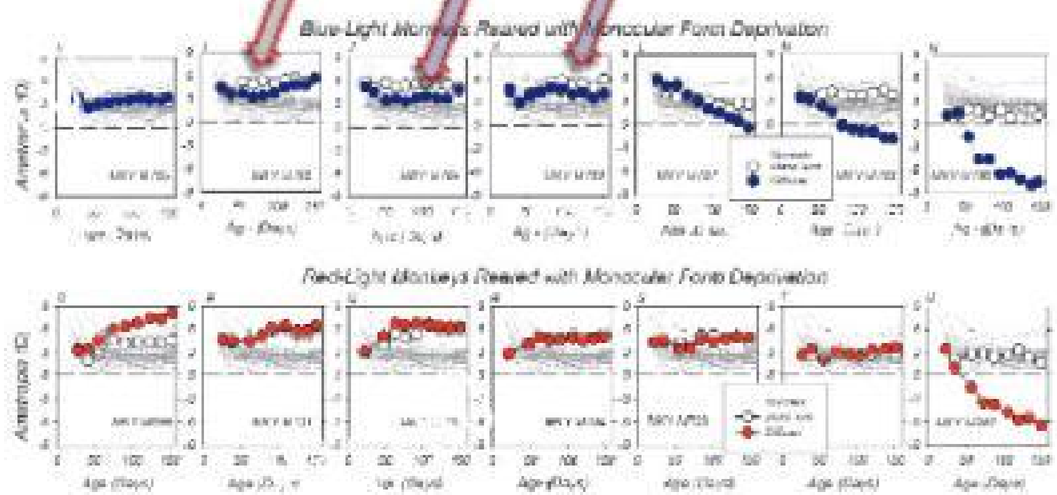
UNIVERSITY of HOUSTON
COLLEGE of OPTOMETRY

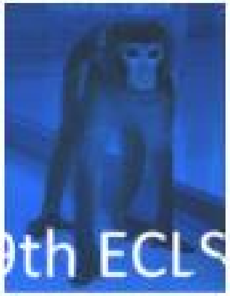
BHVI

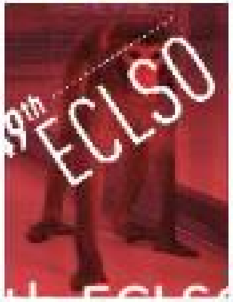
Effects of narrowband, short-wavelength ambient lighting on form-deprivation myopia in infant rhesus monkeys

Li-Fang Hung, Krista M. Beach, Zhihui She, Lisa A. Ostrin, Earl L. Smith III

ARVO 2021
(schlechte Auflösung da Poster nur online)







SUMMARY

3. Compared with typical white ambient lighting, narrowband, short-wavelength lighting neither enhanced nor inhibited either the incidence or degree of form deprivation myopia in infant monkeys, which is in contrast to our previous observations that narrowband, long-wavelength lighting inhibited FDM.

∑ but there is a complex pattern of emmetropization in narrow-band light

effects of narrow-band light on emmetropization

Smith et al IOVS 2014

emmetropization breaks down - more variability

NEW - humans
IOVS 2022, Thakur et al
also blue makes eyes shorter

hyperopia (!)

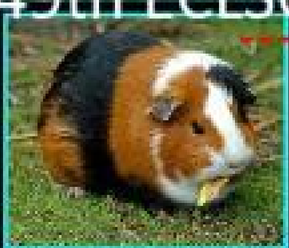
red light at 650 nm used to inhibit myopia in children in China

near UV — 400 nm — 500 nm — 600 nm

emmetropization breaks down! — *hyperopia (!)* — *hyperopia (!)*

chickens and guinea pigs respond as expected from chromatic aberration

hyperopia — *hyperopia* — ***OK*** — ***OK*** — *myopia*



hyperopia — ***OK*** — *myopia*

for application in children, only broadband spectra are feasable and may provide different results

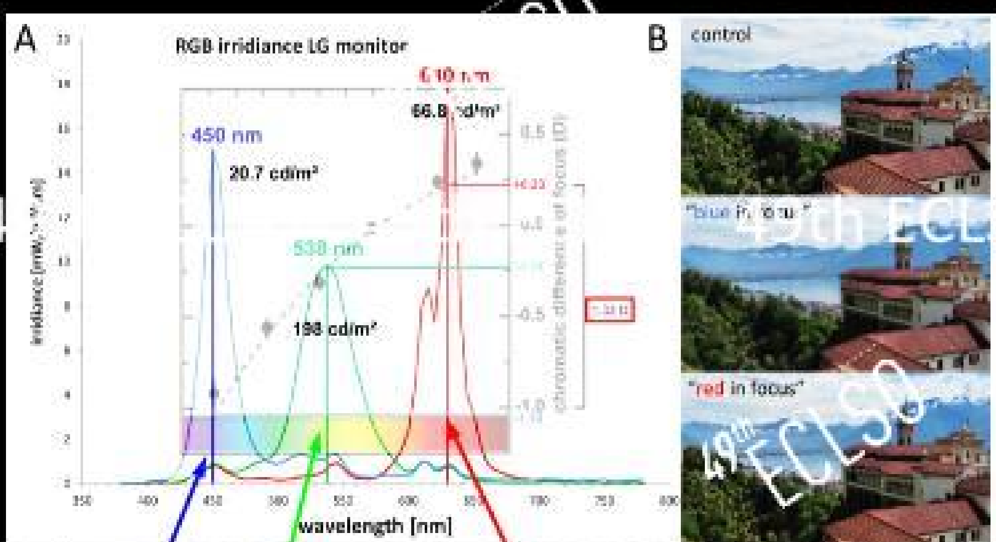
the role of chromatic cues in emmetropization is confusing … but note:

the retina may compare image contrast in the red and blue

How can we find out? We can simulate longitudinal chromatic aberration in the movies (**"LCA"**)

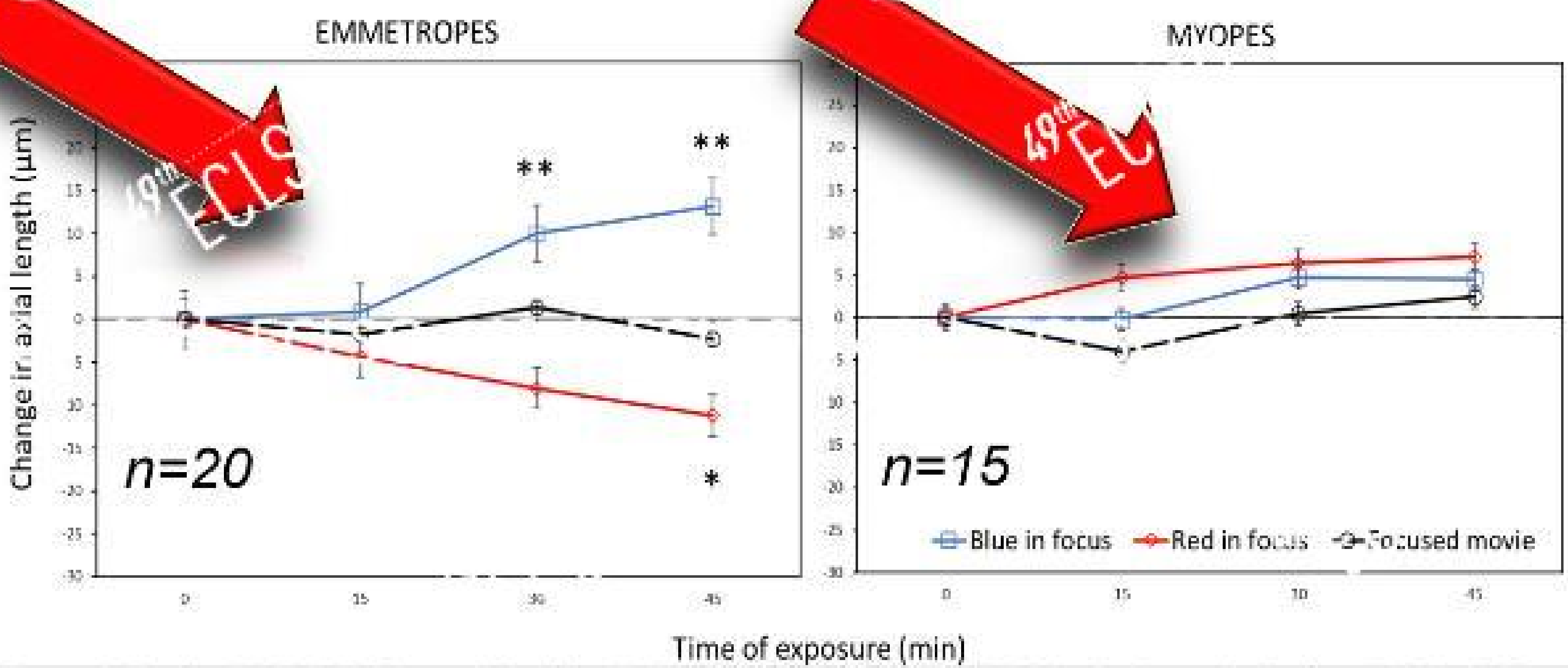
if blue is in focus, the eye is too short → the retina should tell that the eye should grow

if red is in focus, the eye is too long → the retina should tell that the eye is too long ... and inhibit myopia



movie with either blue or red channel in focus

Results from 35 subjects (unpublished):

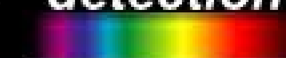


This is it !! Emmetropic eyes respond to LCA exactly as expected – but myopic eyes no longer respond to LCA

... "2" mechanisms of emmetropization (hypothesis Swiatczak/Schaeffel)

(everything works in the low spatial frequency range (< 10 cyc/deg) and without accommodation, and both mechanisms act at the same time)

and LCA detection



Inhibitory retinal signal deficient in the myopic eye

retina

- low pass WITHOUT PLUS DEFOCUS
- slow response, prolonged exposure needed
- atropine, pirenzepine, dopamine, NO, bright light

- low pass WITH PLUS DEFOCUS
- fast response, short exposure time sufficient
- NOT atropine, pirenzepine, dopamine, NO, bright light

... have different genetic networks with little overlap

choroid

- inhibited by ON stimuli and short duty cycles > 5 Hz
- OFF stimulus inhibited

- bi-directional signals ZENK/Egr1, RA, BMP2, ...

- default growth, low energy, choroidal thinning — oxygen ↓
- inhibition has high energy consumption, choroidal thickening — oxygen ↑

sclera

scleral fibroblasts

Conclusions

The emmetropic retina generates a perfect control signal to keep the eye emmetropic.

The myopic retina looses the ability to generate a growth inhibiting signal since it responds less to positive defocus and to chromatic defocus – which is used by the emmetropic eye to detect positive defocus.

These results explain why myopia does not inhibit itself and why it does not respond to undercorrection as hoped.

But what happens in the myopic retina at the point when it stops inhibiting eye growth?