Visual problems after concussion and the fragile receptor hypothesis

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There are Many Visual Complaints After Concussion

- Visual task induced eye pain or headache
- Sensitivity to visual motion
- Photophobia
- Blur
- Losing place when reading
- Having to re-read for content
- Fatigue with Reading
- Discomfort on computer screens
- Discomfort under fluorescent lights
- Sleep disturbance?

- Kapoor N. & Ciuffreda K.J. Vision disturbances after traumatic brain injury. *Curr Treat Options Neurol* (2002) 4: 271
- Cockerham et al. Eye and visual function in traumatic brain injury. *J Rehabil Res Dev* 2009;46(6):811-8Greewald et al. Visual impairments in the first year after traumatic brain injury. *Brain Inj.* 2012;26(11):1338-1359.
- Capó-Aponte et al. Visual dysfunction and symptoms during the subacute stage of blast-induced mild traumatic brain injury. *Mil Med*. 2012;177(7):804-813.
- Armstrong RA. Visual problems associated with traumatic brain injury. *Clin Exp Optom*. 2018;101(6):716-726.
- Spiegel et al. First- and second-order contrast sensitivity functions reveal disrupted visual processing following mild traumatic brain injury. *Vision Res*. 2016;122:43-50.

I have many patients with concussion who like blue tinted lenses

- Some arrive wearing the tint
- Others had observed this as well
- Trial set available (Chadwick optical)
- Allow them to choose, most will choose blue over other color tints reporting improved comfort
- Contrary to optical logic (blue light scatters more)

In examining these patients I found many with poor convergence eye movements after concussion.

Readily observed with near point of convergence test

Many others have reported this as well

- Ciuffreda et. al.. Occurrence of oculomotor dysfunctions in acquired brain injury: a retrospective analysis. *Optometry*. 2007;78(4):155-161.
- Raghuram, Aparna et al. Postconcussion: Receded Near Point of Convergence is not Diagnostic of Convergence Insufficiency, American Journal of Ophthalmology, Volume 206, 235 - 244

Convergence Eye Movements

- Co-contraction of medial recti to keep both fovea pointed on the near target

- Symptoms are blur or instability of vision, double vision only if severely impaired.

DuPrey et al 2017, Am J Sport Med

- 50% of athletes showed reduced near point of convergence
- When controlling for potential confounding variables
- 12.3x odd of prolonged >28 days recovery
- May be a predictor of poor outcomes

DuPrey, et al. (2017). "Convergence Insufficiency Identifies Athletes at Risk of Prolonged Recovery From Sport-Related Concussion." Am J Sports Med **45**(10): 2388-2393.

Many causes of poor convergence

- Uncorrected Refractive Error
- Accommodative Dysfunction (insufficiency, infacility)
- Primary Convergence Insufficiency
- Fatigue
- Vestibular Dysfunction
- Low Vision

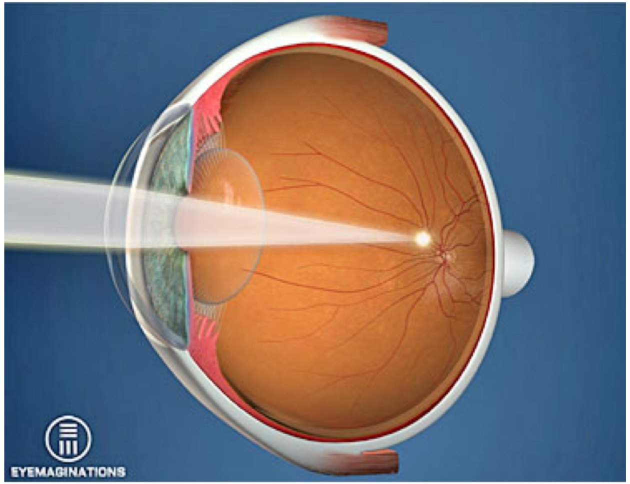
When looking closer I started to notice nearly all also had accommodative dysfunction

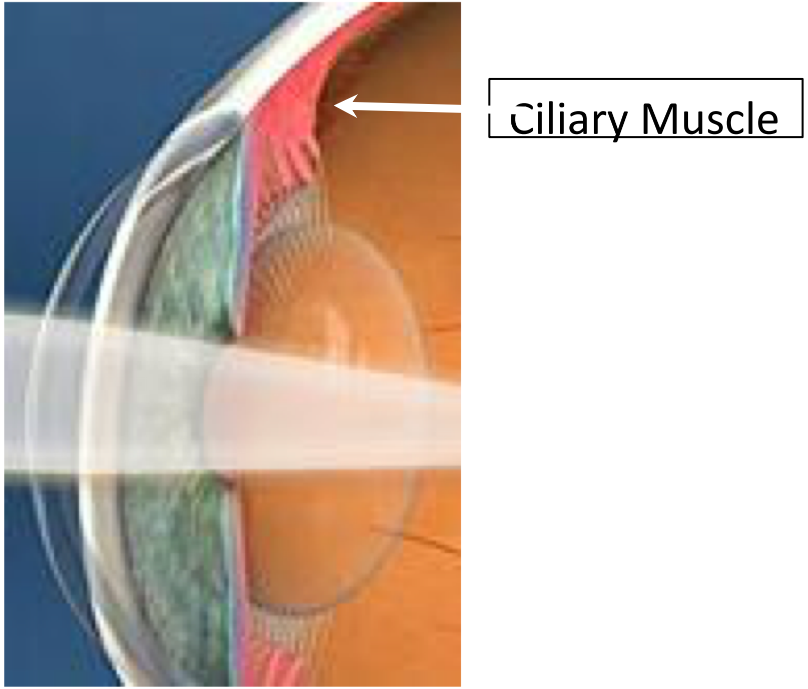
- Requires special testing equipment

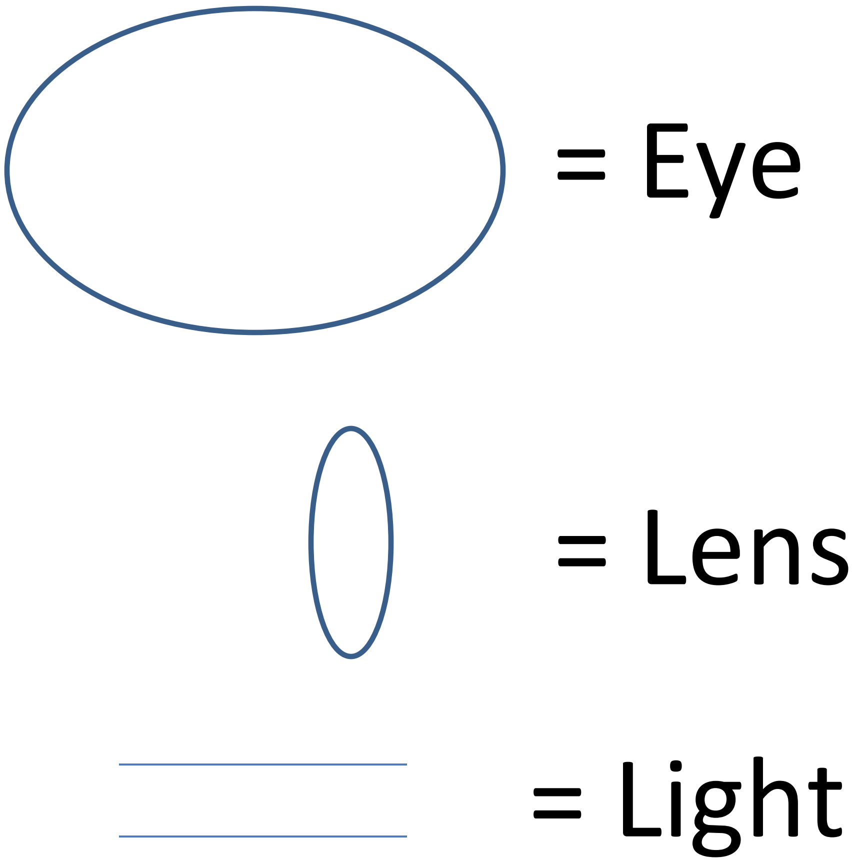
- Also not an isolated observation

- Marran et al. Accommodative insufficiency is the primary source of symptoms in children diagnosed with convergence insufficiency. Optom Vis Sci. 2006;83(5):281-289.
- al-Qurainy IA. Convergence insufficiency and failure of accommodation following midfacial trauma. British Journal of Oral and Maxillofacial Surgery 1995;33:71-75.
- Suchoff et al. The occurrence of ocular and visual dysfunctions in an acquired brain-injured patient sample. J Am Optom Assoc 1999;70:301-308.
- Ciuffreda et. al.. Occurrence of oculomotor dysfunctions in acquired brain injury: a retrospective analysis. Optometry. 2007;78(4):155-161

What is Accommodation?



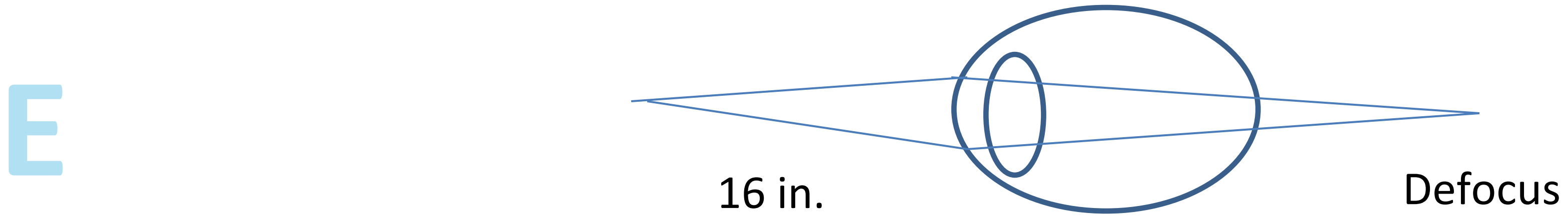



= Eye
= Lens
= Light

An eye is considered to be refractively perfect (ammetropia) if when viewing at distance the ciliary muscle is relaxed and the eye is in focus.

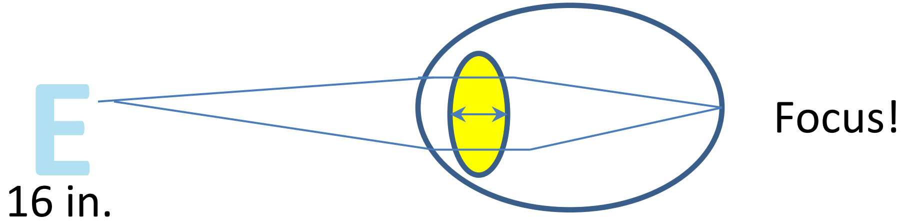
“Perfect eye”

Even a Perfect Eye Needs More Power for Near Object



"Perfect eye"

Extra power is provided by ocular accommodation
Ciliary muscle contracts, lens changes shape



Crystalline Lens “Accommodates”

Accommodation Pathway

Light ->

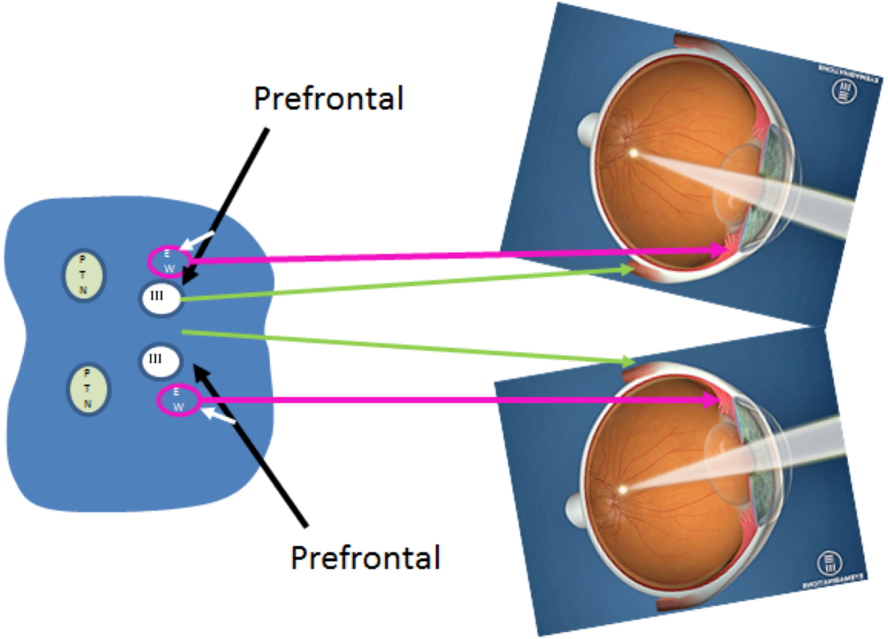
Photoreceptor -> RGC -> Optic Nerve ->

Thalamus -> Optic Radiations -> Occ Cortex

-> prefrontal cortex -> internal capsule

oculomotor nucleus -> Convergence

E. Westfal (parasym) -> ciliary ganglion < spincter pupillae & ciliary muscle



Accommodation, the Autofocus system

- Driven by defocus
- One type of defocus is chromatic
- Longitudinal Chromatic Aberration

To understand chromatic “blur” need to review what is “white light”

Made of visible spectrum ~400 to 800nm

Blue = short wavelength
Green = medium wavelength
Red = long wavelength

Blue Bends More

- Short wavelengths are refracted more in an optical media

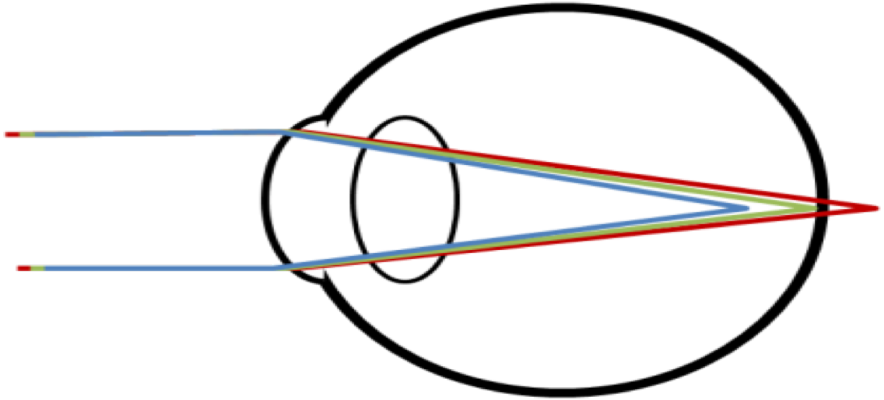
- Results in blue focusing in front of green and red rays on retina

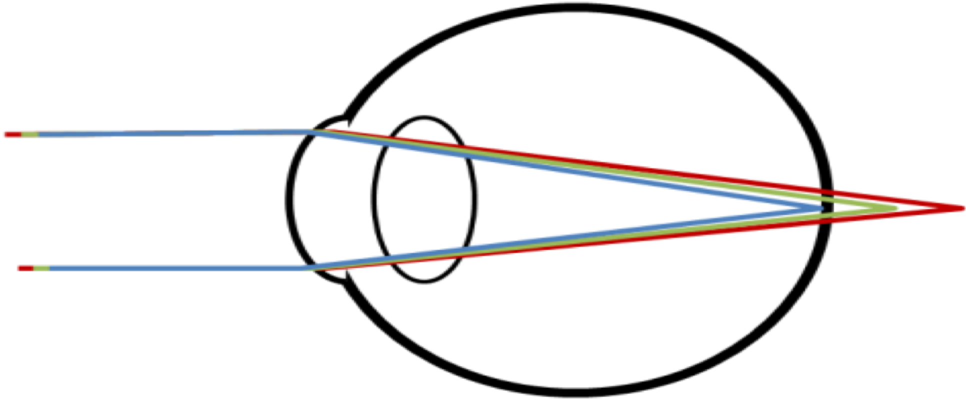
- Provides feedback to accommodative system for focus adjustment

- Eye tries to keep middle wavelengths focused

The eye has 3 main cone photoreceptor types

- Red (long), green (middle), blue (short)
- Increase in contrast to blue receptors signals need for increase in accommodation





We are not talking about color perception

- Chromatic cues for accommodation use the visual system’s sensors for sensing color to determine direction of blur

- It is not color vision itself - uses same machinery

- Subtle deficits in chromatic system unlikely detectable on common color discrimination screening tests

- Patient unlikely to notice change in color vision - Similar to other eye diseases which cause subtle color deficits

Poor Accommodation Can Be Seen As Poor Convergence Eye Movements

- Eyes must converge and accommodate together for near viewing
- Eyes must diverge and relax accommodation to shift from near to distance viewing
- Inability to accurately relax accommodation or convergence could cause distance vision problems as well

Convergence insufficiency (CI) is more widely discussed due to a recent randomized control trial (CITT trial) that offer evidence for efficacy of treatment with vision therapy

Scheiman M. A Randomized Clinical Trial of Treatments for Convergence Insufficiency in Children. *Archives of Ophthalmology*. 2005;123(1):14.

Accommodative dysfunction (**AD) may be the cause of most symptomatic cases of CI**

Marran et al. Accommodative insufficiency is the primary source of symptoms in children diagnosed with convergence insufficiency. Optom Vis Sci. 2006;83(5):281-289.

It is my clinical experience that AD is present in nearly all the cases of poor convergence found after concussion

Developing a hypothesis

Wondered if selective injury to one of the cone systems could cause accommodative dysfunction

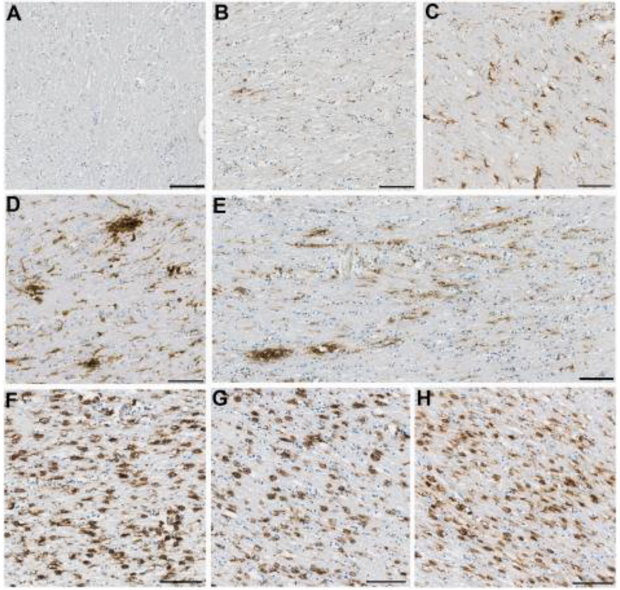
Wondered if the reason many concussion patients like to wear blue tinted lenses could be related

Connected with Dr. Panorgias who will explain his expertise, the hypothesis and preliminary results

Evidence of Retinal Damage

There is an acute inflammatory response in the brain post-TBI. (microglia, astrocytes etc).

Evidence also exists for prolonged inflammatory processes past the acute phase of TBI.



non-TBI

4-weeks post-TBI

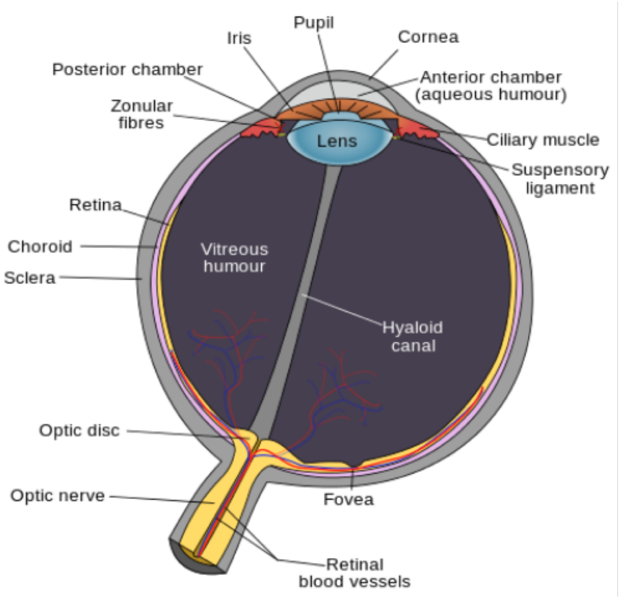
4y, 8m, and 16 y post-TBI

Johnson, V. E., et al. (2013). Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain : a journal of neurology*, *136*(Pt 1), 28–42. doi:10.1093/brain/aws322

Evidence of Retinal Damage

The retina, part of the CNS, is accessible for imaging *in vivo* both in animals and humans.

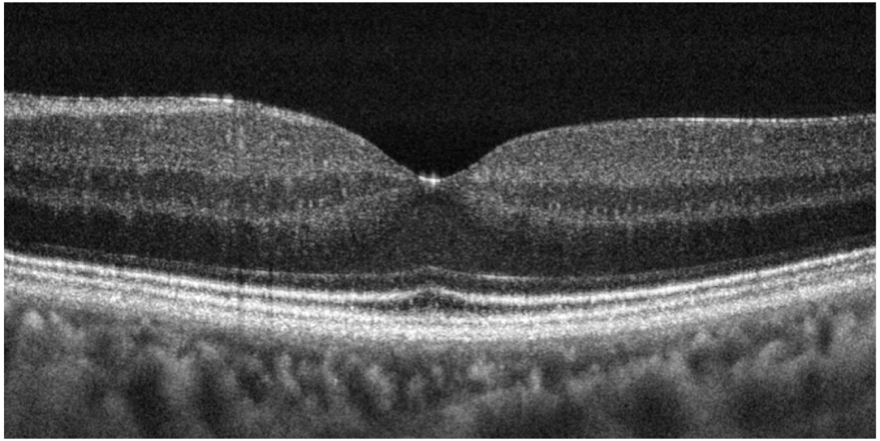
Imaging studies have shown microglia activation at the retina in an impact concussion mouse model of TBI.



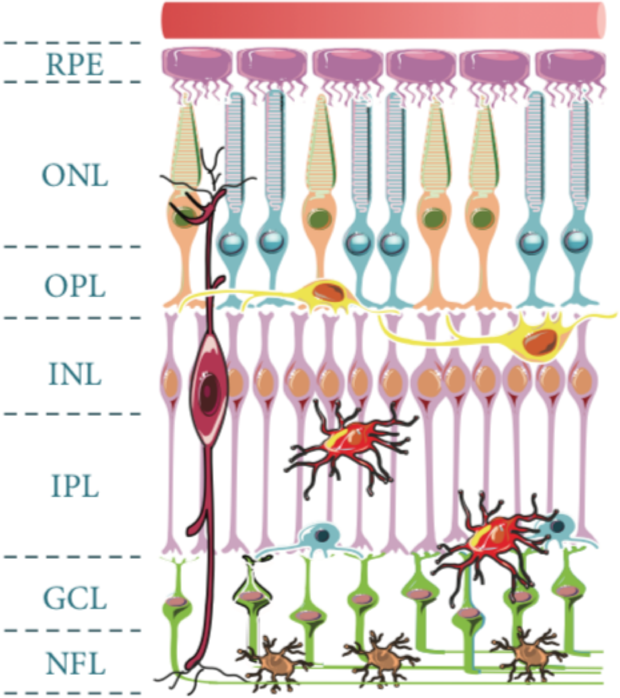
- Lee E Goldstein, et al. In Vivo Retinal Imaging of Post-Traumatic Neuroinflammation and Sequelae in Impact Concussion and Blast Exposure Mouse Models. *Invest. Ophthalmol. Vis. Sci.* 2018;59(9):5512.
- Lee E Goldstein, et al. Retina microglial activation and functional deficits in an impact concussion mouse model.of traumatic brain injury (TBI).. *Invest. Ophthalmol. Vis. Sci.* 2019;60(9):4408.
- James D Akula, et al. Changes in Retinal Function and Glial Reaction in an Impact Concussion Mouse Model. *Invest. Ophthalmol. Vis. Sci.* 2017;58(8):4282.
- Lee E Goldstein, et al. Retinal microgliosis, functional sequelae, and traumatic brain injury (TBI) in an impact concussion mouse model.. *Invest. Ophthalmol. Vis. Sci.* 2017;58(8):1761.

Evidence of Retinal Damage

Optical Coherence Tomography



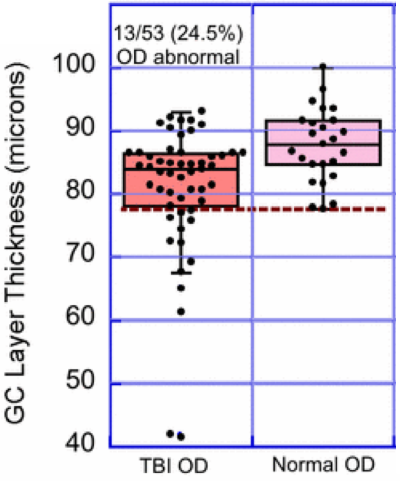
A cross-section of the retina *in vivo*



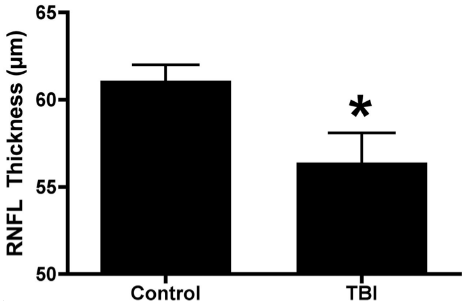
Madeira, M. H.et al. (2015) Contribution of microglia-mediated neuroinflammation to retinal degenerative diseases. *Mediators of inflammation*, *2015*, 673090. doi:10.1155/2015/673090

Evidence of Retinal Damage

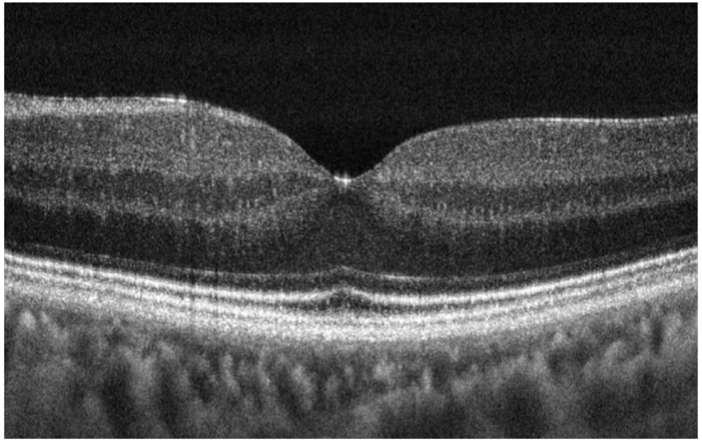
Humans



Mouse model



Optical Coherence Tomography



Retinal Ganglion cells

Bipolar cells

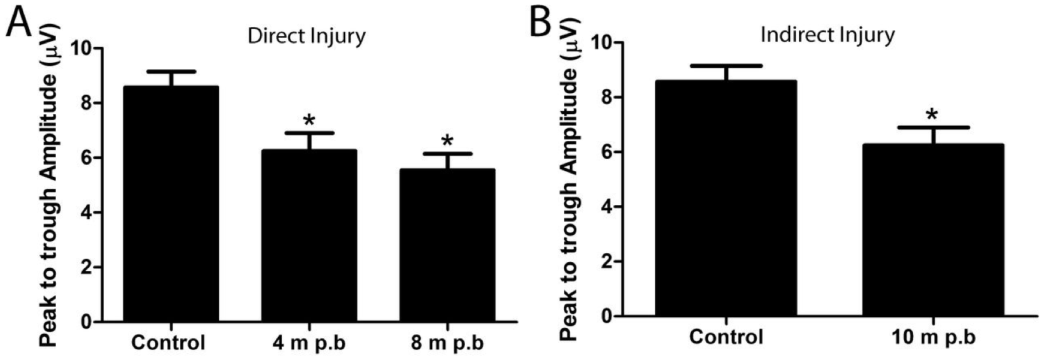
Photoreceptors

- Randy Kardon et al. Prevalence of Structural Abnormalities of the Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Layer Complex (GCLC) by OCT in Veterans with Traumatic Brain Injury (TBI). *Invest. Ophthalmol. Vis. Sci.* 2013;54(15):2360.
- Kabhilan Mohan et al. Retinal Ganglion Cell Damage in an Experimental Rodent Model of Blast-Mediated Traumatic Brain Injury. *Invest. Ophthalmol. Vis. Sci.* 2013;54(5):3440-3450. doi: 10.1167/iovs.12-11522.

Evidence of Retinal Damage

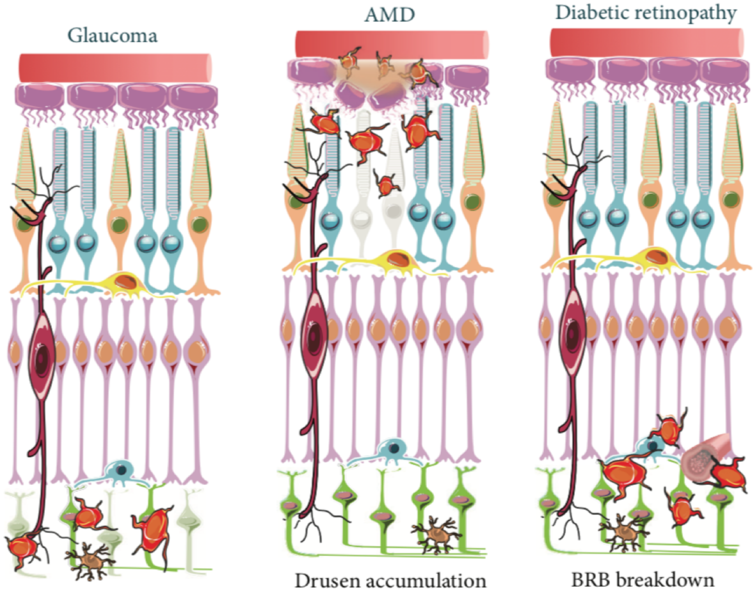
Apart from structural damage of the retina there are also functional changes.

Retinal Electrophysiology



- Roa Al-Abdalla et al. The photopic negative response in mild traumatic brain injury. *Invest. Ophthalmol. Vis. Sci.* 2017;58(8):4281.
- Laura Dutca et al. Time-dependent changes in spontaneous and light-evoked retinal ganglion cell activity in a mouse model of blast-induced traumatic brain injury. *Invest. Ophthalmol. Vis. Sci.* 2014;55(13):2383.
- Kabhilan Mohan,et al. Retinal Ganglion Cell Damage in an Experimental Rodent Model of Blast-Mediated Traumatic Brain Injury. *Invest. Ophthalmol. Vis. Sci.* 2013;54(5):3440-3450. doi: 10.1167/iovs.12-11522.

Evidence of Retinal Damage



Neurodegeneration of RGCs
Activated microglia in GCL

Drusen accumulation
Accumulation of microglia in subretinal space

BRB breakdown
Perivascular microglia activation

Madeira, M. H.et al. (2015) Contribution of microglia-mediated neuroinflammation to retinal degenerative diseases. *Mediators of inflammation*, *2015*, 673090. doi:10.1155/2015/673090

One of the earlier vision changes due to these diseases is the change in perceiving colors, especially blue-yellows.

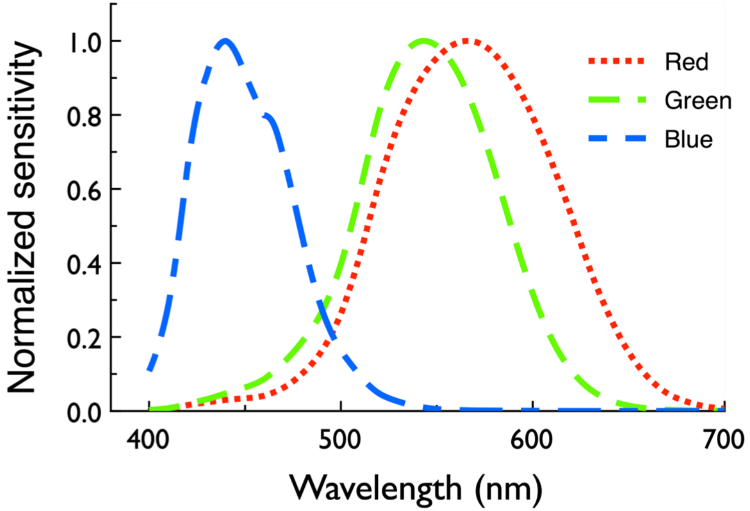
The blue cones are phylogenetically different than the red and green cones and found to be more susceptible to oxidative stress, and various eye and systemic diseases.

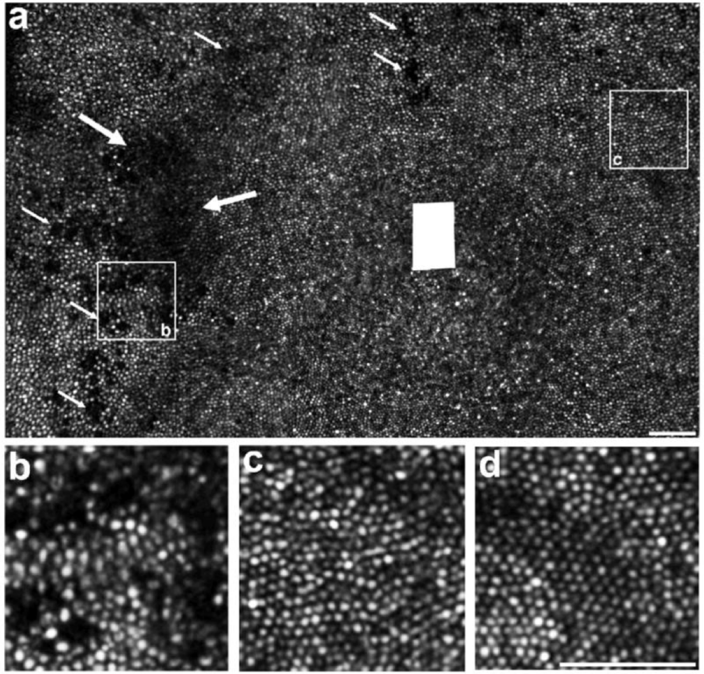
Hood et al. termed the blue cones as the fragile receptor.

- Hood et al. Blue (S) cone pathway vulnerability: a test of a fragile receptor hypothesis. *Appl Opt*. 1988;27(6):1025-1029.
- Cho et al. Selective loss of S-cones in diabetic retinopathy. *Arch Ophthalmol*. 2000;118(10):1393-1400.
- Zwas et al. Spectral Sensitivity Measurements in Early Diabetic Retinopathy. *Ophthalmic Res*. 1980;12(2):87-96.

Evidence of Retinal Damage

Vision is mediated by three cone photoreceptors (red, green and blue).





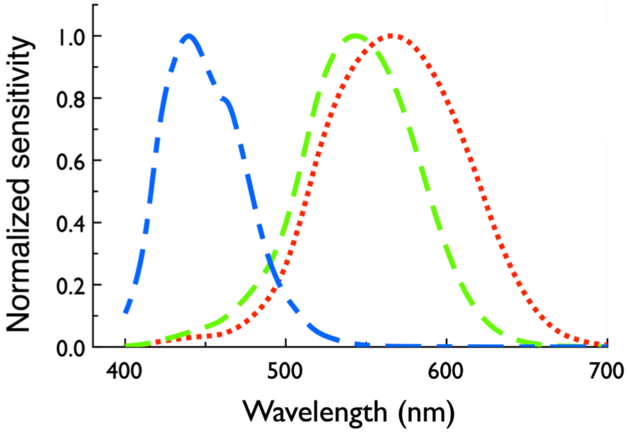
Stepien et al. Subclinical photoreceptor disruption in response to severe head trauma. *Arch Ophthalmol*. 2012;130(3):400-402.

Evidence of Retinal Damage

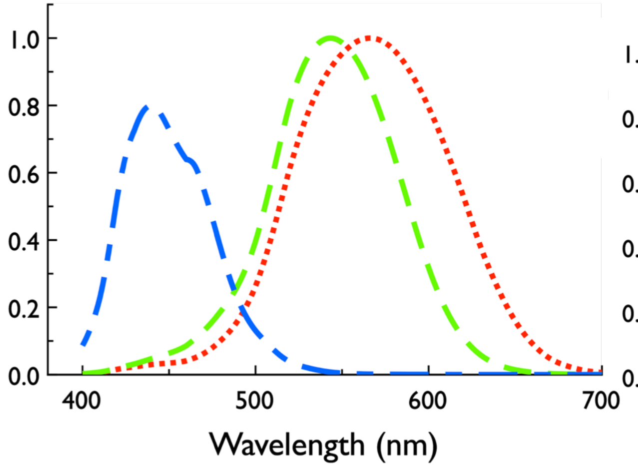
It is being observed in clinic that blue filters improve some of the visual problems that TBI patients experience.

How does this link with our hypothesis that the blue cones are differentially affected in patients with TBI?

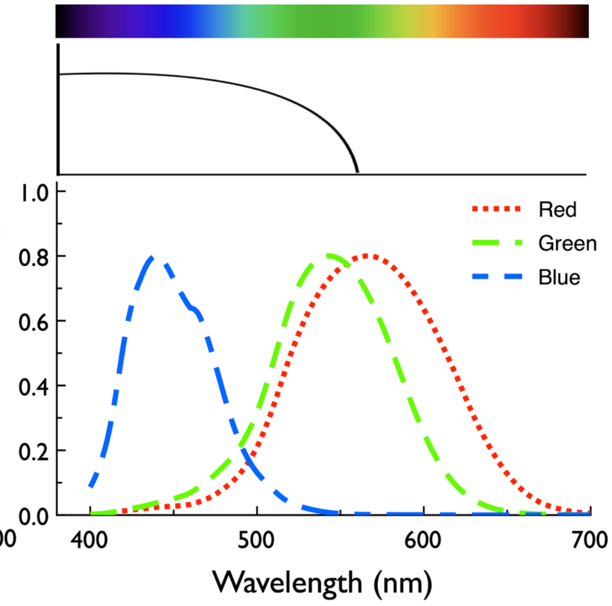
Evidence of Retinal Damage



Non-TBI



TBI



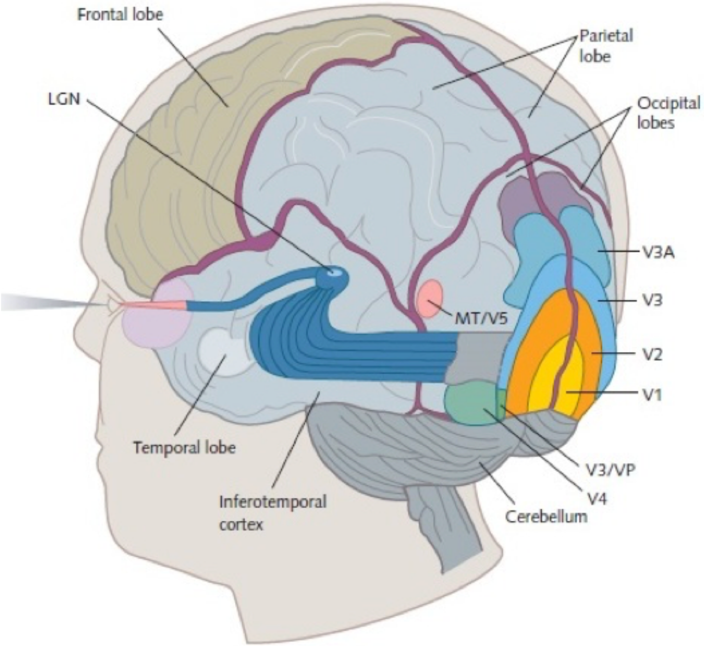
TBI w/ blue filters

Methods

TBI can affect any part of the visual system, from the retina, to the striate and extra-striate cortex.

Electrophysiological and psychophysical approaches allow us to dissect the visual pathway.

- Photoreceptors
- Retinal Ganglion cells
- Primary visual cortex (V1)



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Very Preliminary Results

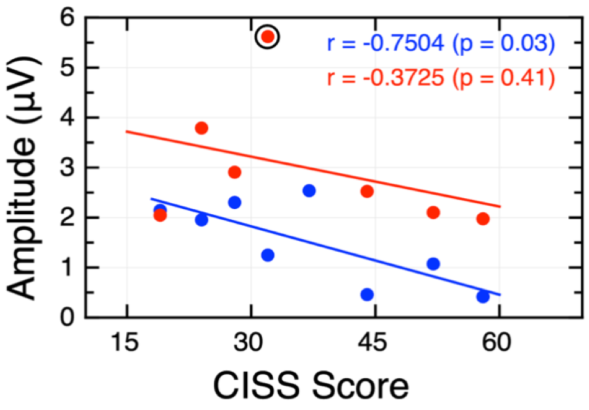
• Documentation of a history of mTBI or concussion of at minimum Grade I (confusion for less than 30 minutes)

• Best corrected visual acuity of at least 20/25 in one eye.

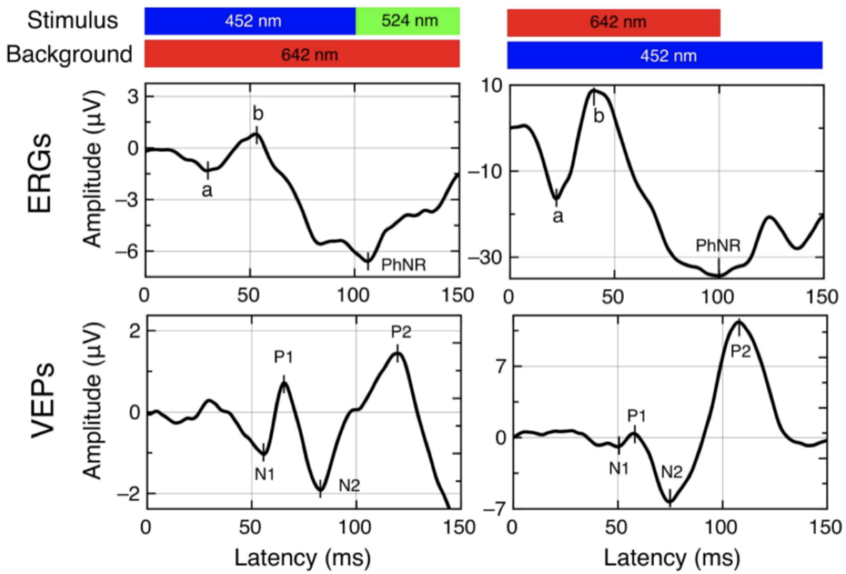
• Age between 18 and 50 years.

• Diagnosis of one accommodation or convergence problem.

A preliminary study on a small cohort of mTBI subjects showed a reduction in the amplitude of the visual evoked potential amplitude for a blue-yellow stimulus with increasing severity of convergence insufficiency.



Future Study

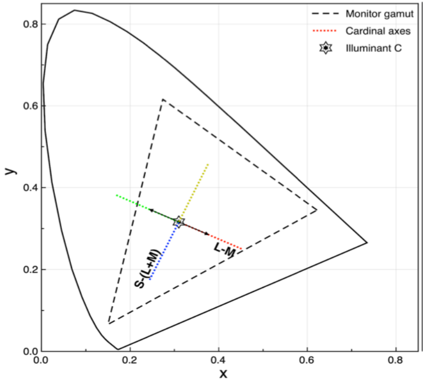


Retinal activity as measured with cone-specific electroretinograms.

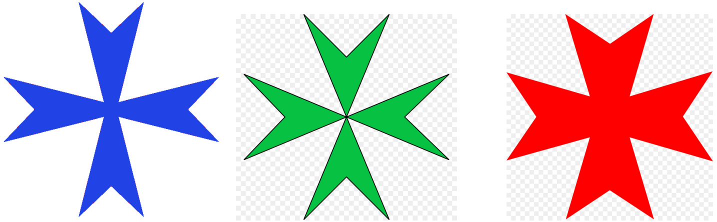
- A-wave (photoreceptors)
- B-wave (bipolar cells)
- PhNR (ganglion cells)

Primary visual cortex activity as measured with visual evoked potentials.

Future Study



Chromatic sensitivity of the visual pathways using Bayesian methods for clinical applications.



Cone specific lab-based accommodative responses.

Thank You.