The Link Between Head Injury, Photophobia and Pupillary Function

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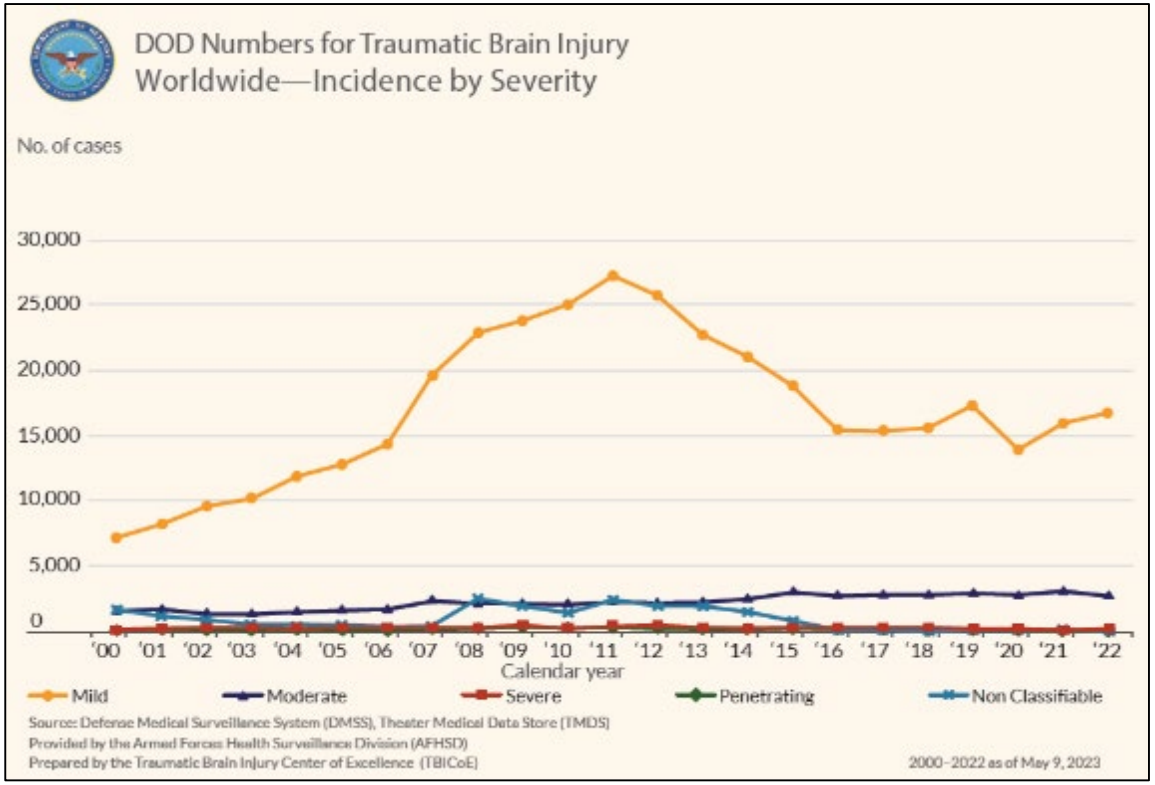
- Estimated 69 million people world-wide sustain a TBI per year.
- The overall incidence of TBI per 100,000 people was greatest in North America (1299 cases, 95% CI 650-1947).
- Increased public attention over last 15 years perhaps due to prevalence in sports and military



Dewan et al. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2018 130(4):1080-1097.

- Important to note that designation of ‘mild’ relates to deficits occurring at time of injury
  - Loss of consciousness < 30 min and amnesia < 24 h

- It does NOT indicate the severity of persistent impairments!

- In fact, many mTBI individuals have cognitive, emotional, behavioral and physical impairments that affects quality of life and that can persist for many months or years

- Visual system often chronically impacted

- Below, prevalence of some visual symptoms in military members with blast vs non-blast mTBI on deployment
  - acute (<45 d) and chronic (>1 y)

	BLAST		NON-BLAST	
	Acute	Chronic	Acute	Chronic
Blurry near vision	57%	64%	74%	79%
Eye strain	56%	53%	54%	62%
Reading issue	43%	36%	60%	75%
Visual field defect	25%	17%	26%	15%
Light sensitivity	43%	36%	42%	45%

Capo-Aponte et al. 2017, OVS

- The high prevalence of visual symptoms not unique to adults or veterans; BV disorders also common in children with acute mTBI

- In a study on 34 adolescents (age 9 to 17) with acute sports-related mild TBI, we found vast majority (79.4%) had clinically significant binocular vision disorder

Concussion Group		n
(+) Vision Disorder	79.4%	27
(-) Vision Disorder	20.6%	7
Type of Disorder		
Vergence Disorder	77.8%	21
Accommodative Disorder	48.1%	13
Oculomotor Disorder	40.7%	11
Multiple Disorders	48.1%	13

Peiffer, MacDonald, Duerson, Mitchell, Hartwick, McDaniel, *Clinical Pediatrics*. 2020;59(11):961-969.

		Never	(Not Very Often) Infrequently	Sometimes	Fairly Often	Always
1.	Do your eyes feel tired when reading or doing close work?					
2.	Do your eyes feel uncomfortable when reading or doing close work?					
3.	Do you have headaches when reading or doing close work?					
4.	Do you feel sleepy when reading or doing close work?					
5.	Do you lose concentration when reading or doing close work?					
6.	Do you have trouble remembering what you have read?					
7.	Do you have double vision when reading or doing close work?					
8.	Do you see the words move, jump, swim or appear to float on the page when reading or doing close work?					
9.	Do you feel like you read slowly?					
10.	Do your eyes ever hurt when reading or doing close work?					
11.	Do your eyes ever feel sore when reading or doing close work?					
12.	Do you feel a "pulling" feeling around your eyes when reading or doing close work?					
13.	Do you notice the words blurring or coming in and out of focus when reading or doing close work?					
14.	Do you lose your place while reading or doing close work?					
15.	Do you have to re-read the same line of words when reading?					

Convergence Insufficiency Symptom Survey-V15.

Validity of CISS tested in Ophthalmic Physiol Opt. 2004 Sep;24(5):384-90.

- 23 of the 27 SRC group with BV dysfunction uncovered during the optometric exam scored 13 or more on CISS
  - Cutoff of 13 had 85% sensitivity, 100% specificity

- Thus, we found that BV disorders were very prevalent in acute SRC and that the CISS could be used as a rapid screening tool for trainers/sports physicians to identify cases of SRC with significant BV issues

- Furthermore, we found that those with SRC and BV disorders scored significantly worse on a neurocognitive test (CogState) commonly used to concussion screen

Peiffer, MacDonald, Duerson, Mitchell, Hartwick, McDaniel, AAO 2018

- In terms of TBI-related visual symptoms…
  - Accommodation dysfunction
  - Oculomotor deficits (vergence/version)
  - Reading difficulties
  - Visual field defects
  - Photosensitivity

- There are pretty well-established guidelines for clinically assessing the first 4 of these (and treating some of them)

- But there is no standard evidence-based assessment protocol or treatment for photosensitivity

- “A sensory state in which light causes discomfort in the eye or head; it may also cause an avoidance reaction without overt pain”
  (Digre & Brennan, *J Neuro-Ophthalmol* 2012)

- What is known about the neural circuitry that underlies this condition?

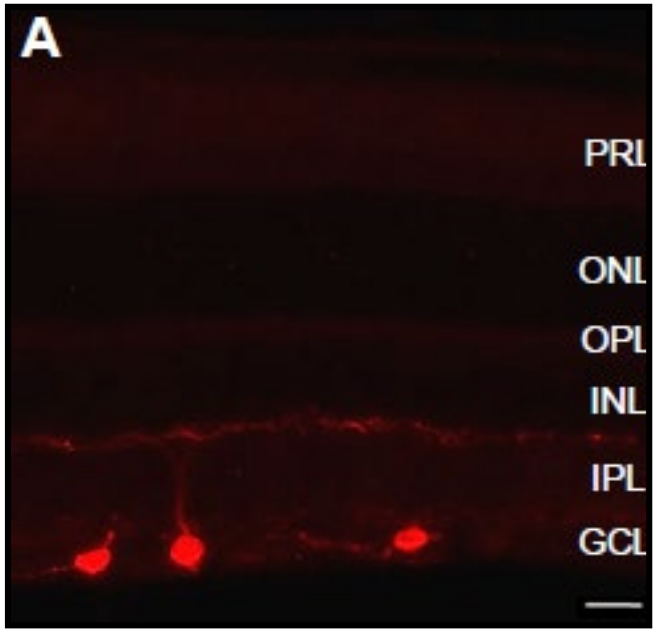
Role for Eyes, but not Rods/Cones?

- Noseda et al (*Nature Neurosci* 2010) reported on a series of visually blind patients who suffered regular migraines
- Light exposure made the migraines worse in many of the patients with outer retinal disease
- No light effect in patients who had had their eyes enucleated
- Consistent with hypothesis that photoreceptors in inner retina were mediating light's effect

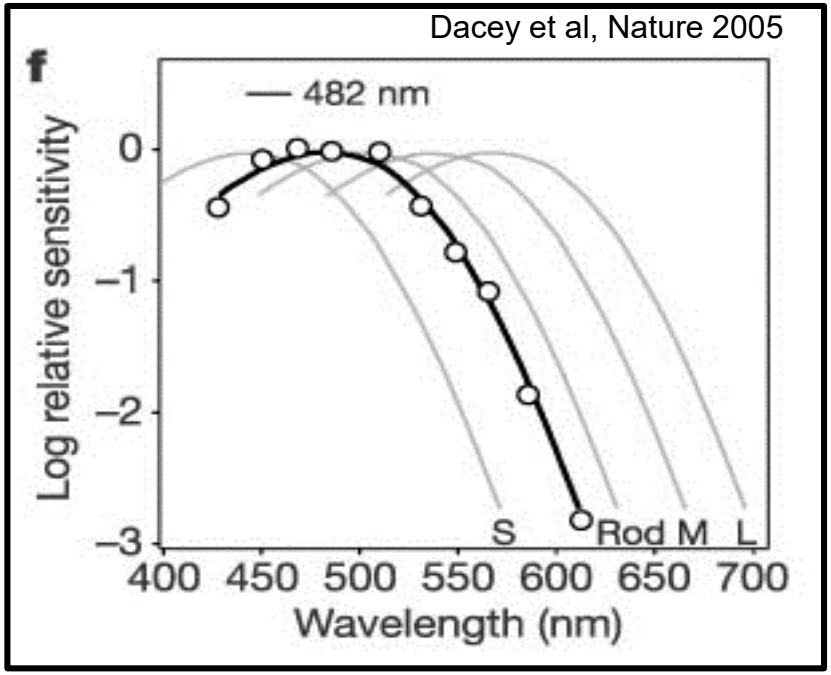
- Mammals (including humans!) have a photopigment in a small population of ganglion cells in the inner retina

- Melanopsin photopigment has peak spectral sensitivity at ~480 nm light

Sodhi & Hartwick, J Physiol 2014

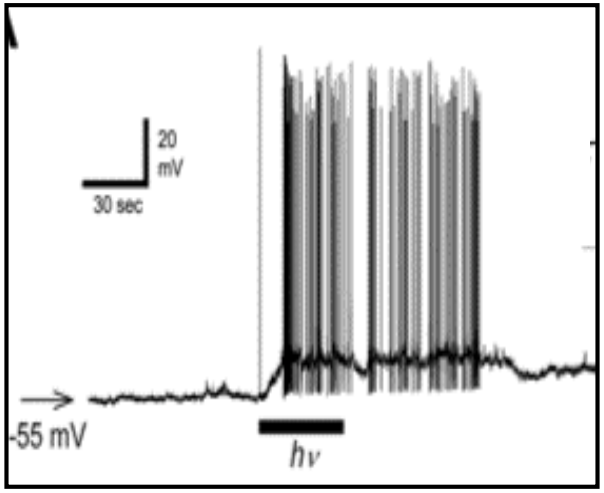


Dacey et al, Nature 2005



- Due to expression of melanopsin, these intrinsically photosensitive RGCs (ipRGCs) can capture light and convert this energy into an electrical signal
  - Berson et al Science 2002; Hattar et al Science 2002

Hartwick *et al*, J Neurosci 2007

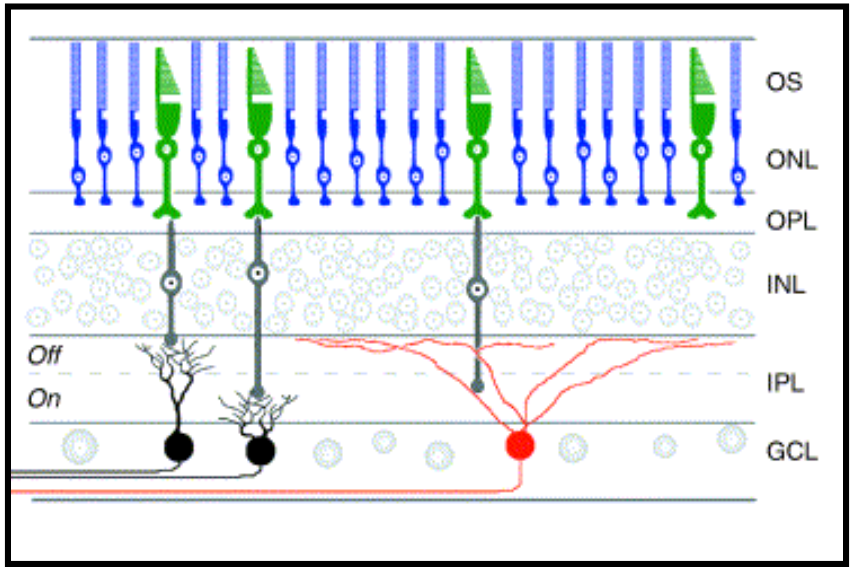


Patch-clamp recording of light-evoked action potential firing in cultured rat ipRGC isolated through antibody-mediated immunopanning

Intrinsically Photosensitive ipRGCs

- ipRGCs involved in irradiance detection
  - signal info about ambient light levels to brain

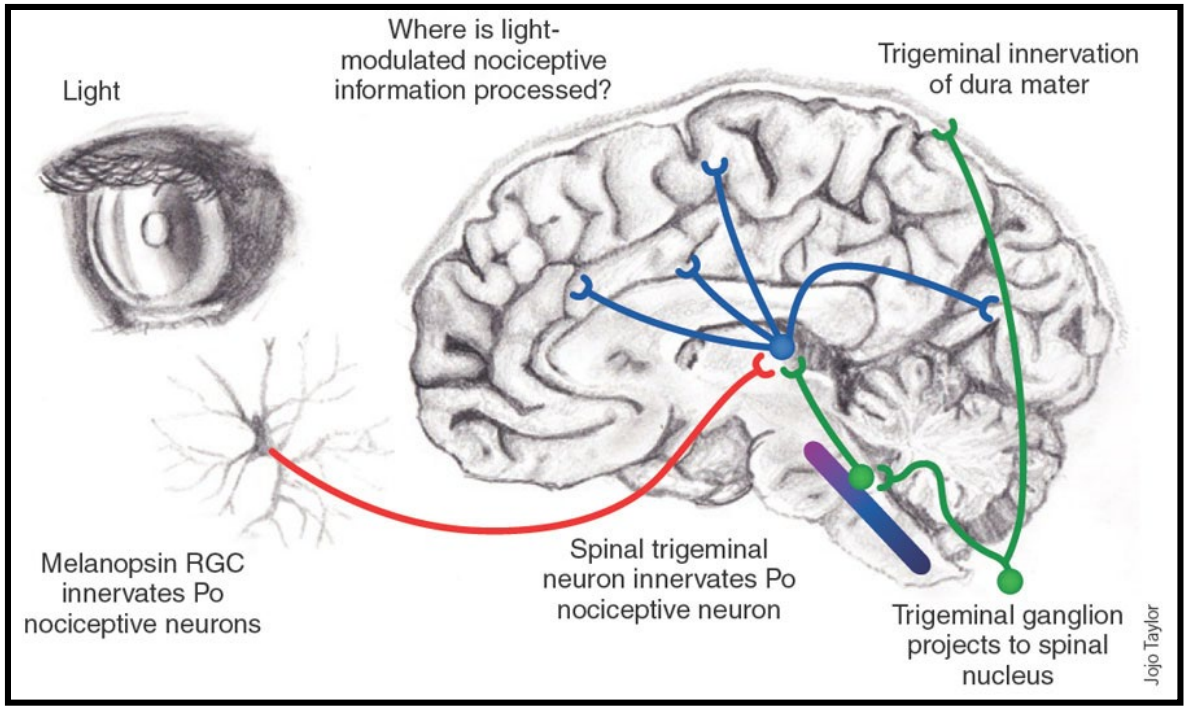
- ipRGCs play a key role in mediating light's effect on a variety of functions:
  - Circadian rhythm synchronization
  - Pupil constriction
  - Suppression of melatonin release from pineal (sleep/wake)



ipRGCs & Photophobia: Anatomical Evidence

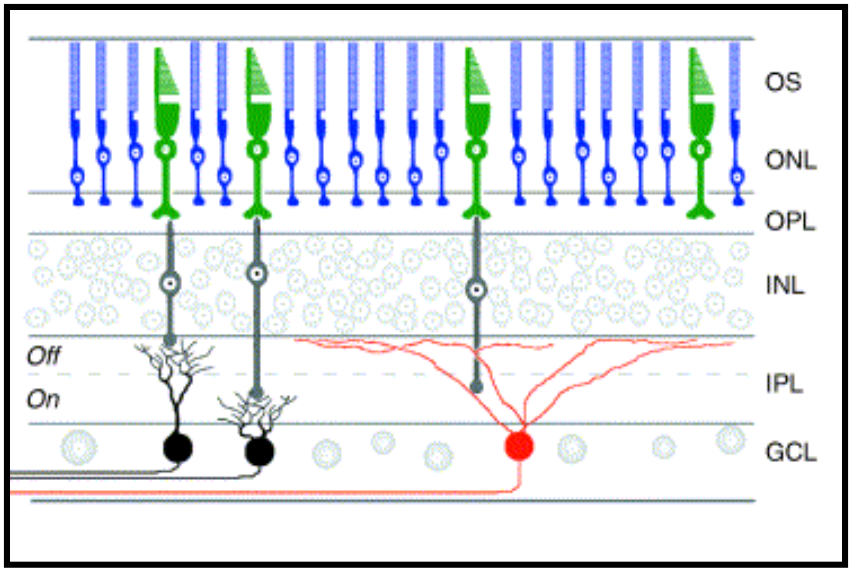
- As mentioned, clinical evidence indicated migraine-associated photophobia mediated by inner retina

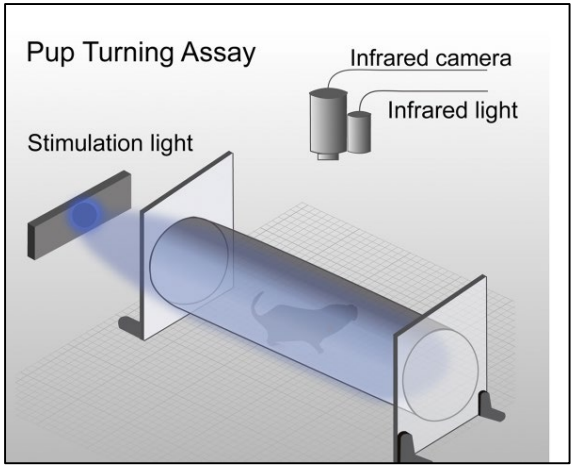
- In same paper (Noseda et al. 2010), tracing studies in rats showed that some ipRGCs project to pain centers in the thalamus



ipRGCs & Photophobia: Rodent Behavioral Evidence

- During first week of rodent life, ipRGCs are functional while rod/cone-driven signaling is not
- Neonatal rodents will exhibit light avoidance behavior (freeze, turn away from light)
- In mice w/o melanopsin, light avoidance behavior is lacking

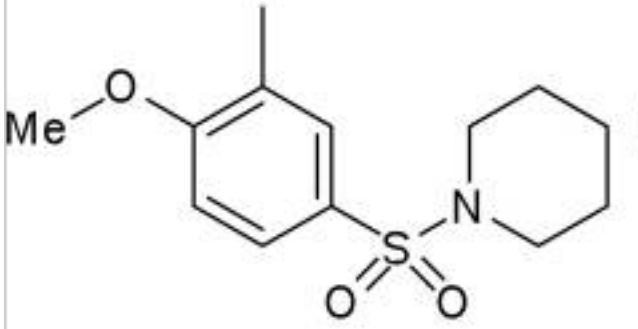




Johnson et al, PNAS 2010

An intriguing aspect of a potential link between ipRGCs and photophobia is it presents a therapeutic target

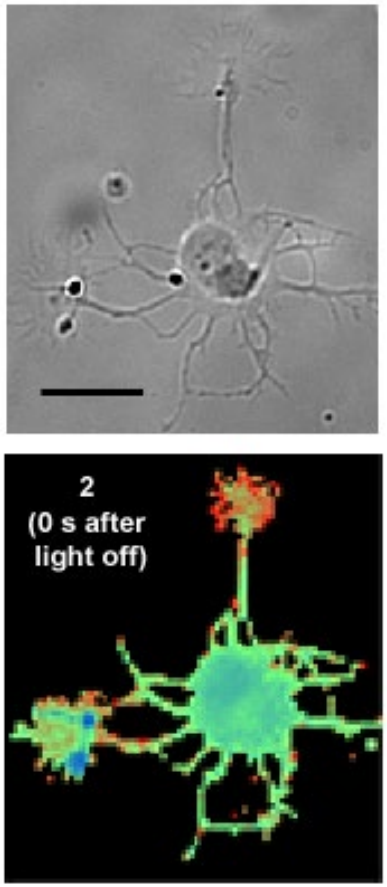
In a screen of 80,000 drug compounds Lundbeck Research identified a few that bound to melanopsin, presumably displacing its interaction with its chromophore



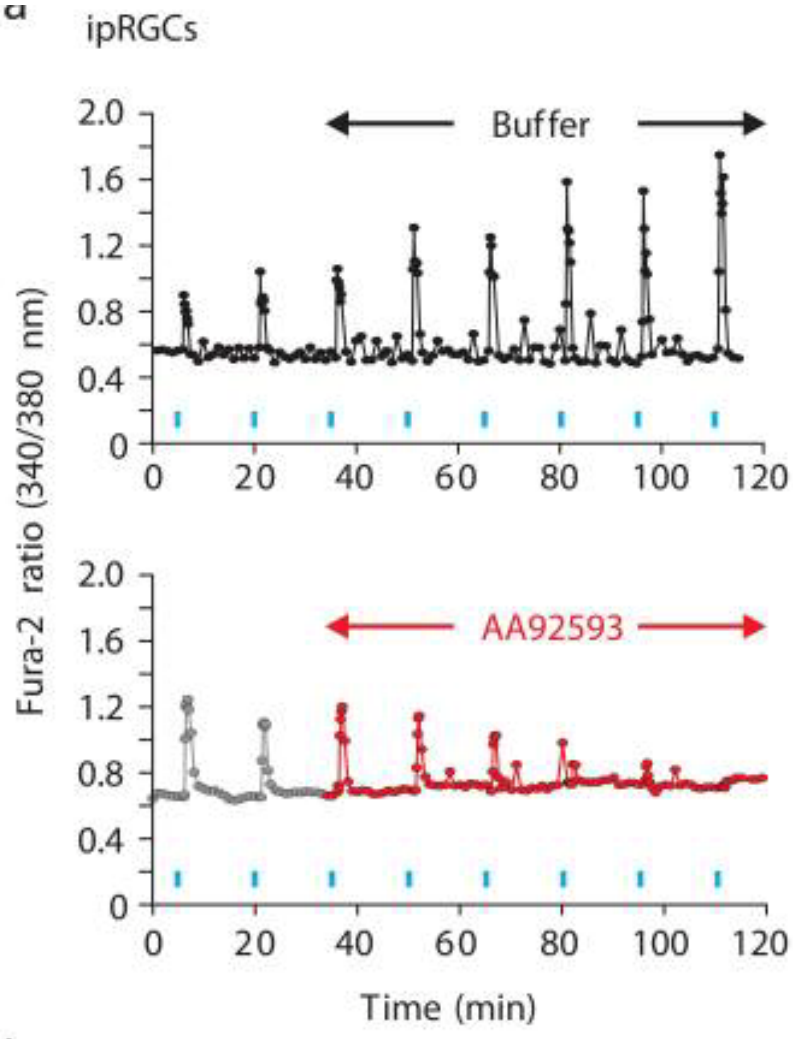
AA92593

This represented a potential pharmaceutical "melanopsin antagonist" which we used to determine whether it altered light avoidance behavior in rodents

Pharmacological ipRGC Inhibition



Hartwick *et al*, J Neurosci 2007

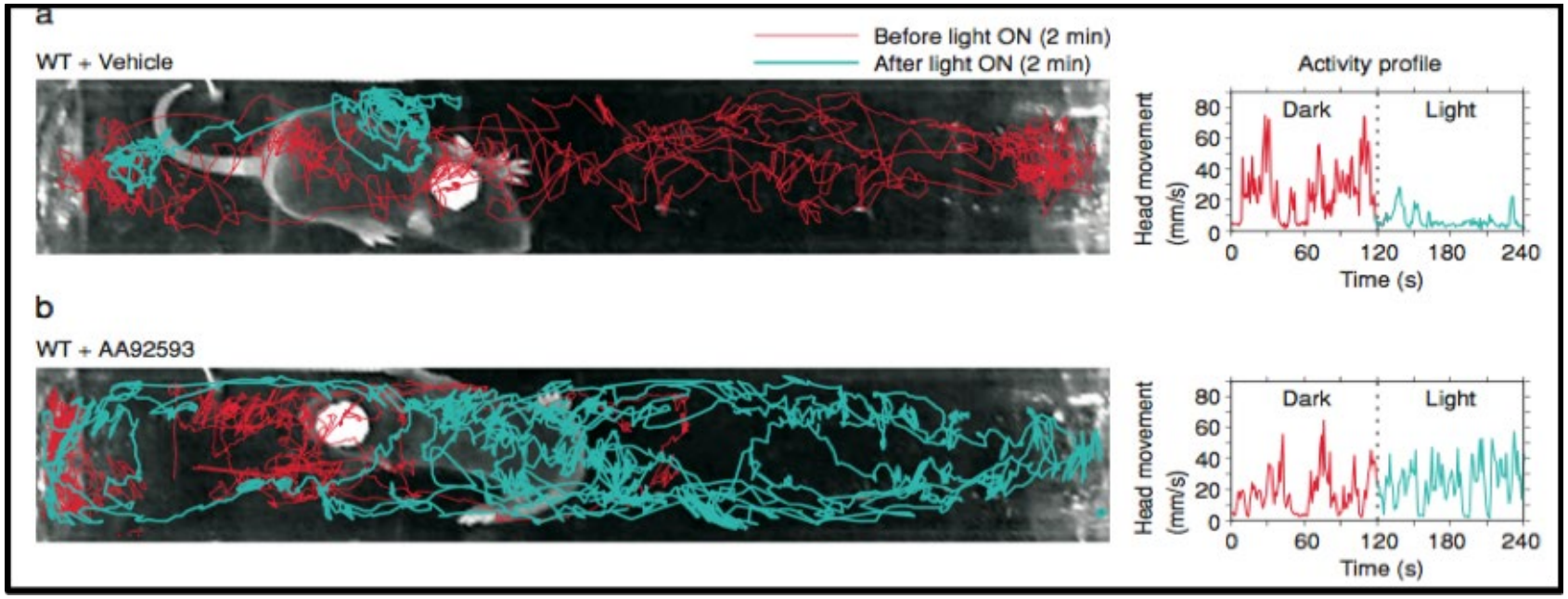


Jones et al. 2013, *Nature Chemical Biology*

Movie here

Jones et al. 2013, *Nature Chemical Biology*

- Light aversion is absent in mice injected with opsinamide (AA92593, pharma-developed melanopsin antagonist)



- Represents a potential pharmacological approach to target ipRGCs

Rationale for Optical Tints in Photophobia?

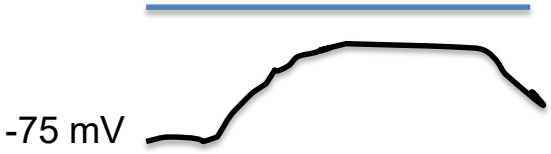
- Role for ipRGCs in photophobia meshes well with current clinical use of blue-blocking lenses
- Case reports or small-scale studies have reported that orange- (e.g. CPF 527) or rose (e.g. FL-41) tinted lenses can be useful as a symptomatic remedy
- No randomized trials; reports mostly anecdotal

- This early evidence, obtained from studies on rodents and migraine patients with outer retinal disease, bolstered link between ipRGCs and photophobia
- What about mTBI-associated photophobia?
- We tested the theory that ipRGCs are ‘hypersensitive’ to light in individuals with TBI-related photophobia
- We assessed ipRGC function through pupil testing
  - Hypothesis was ipRGC-mediated component of pupil response would be more robust in this population

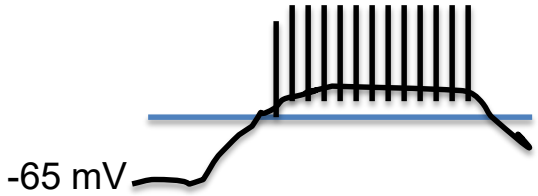
"Hypersensitive" ipRGC Hypothesis

- Intrinsic light responses in ipRGCs need relatively bright light (due to low photon capture rate by melanopsin)

- Following TBI, it has been posited that neurons can become "leaky", increased cation influx results in subsequent depolarization of the neuronal membrane potential (McAllister 2011).

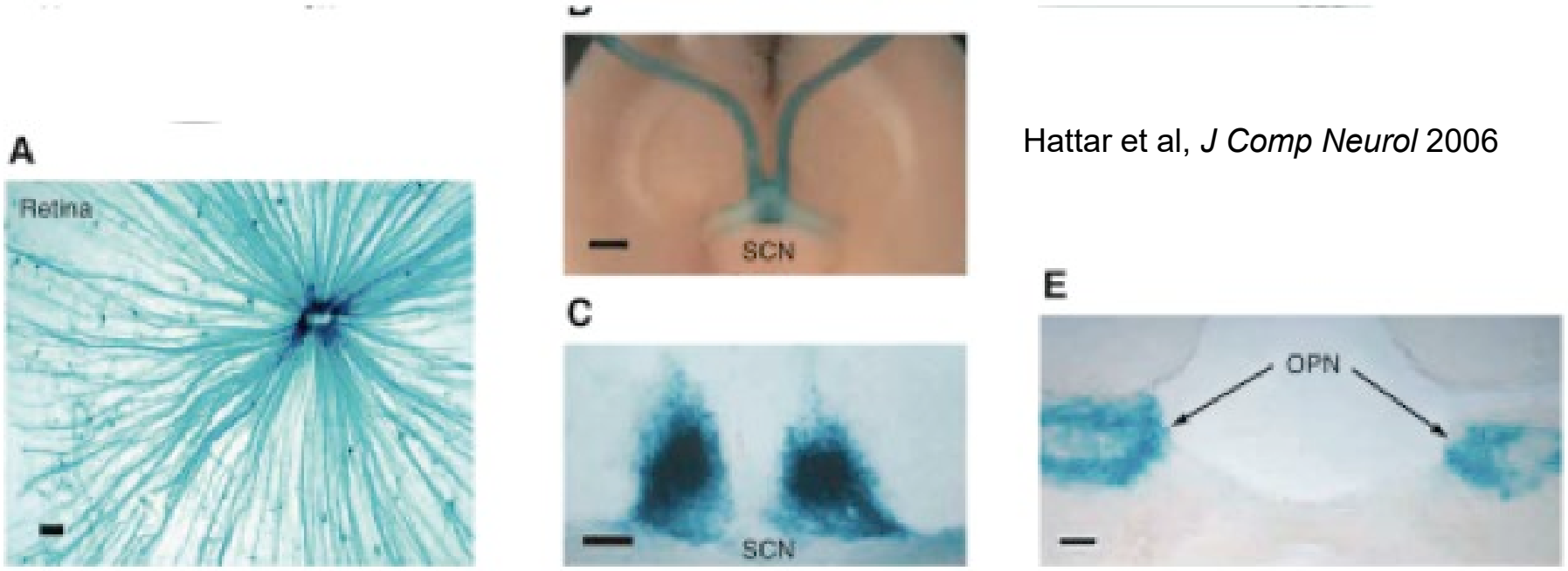


Example of a light that is too dim to cause ipRGC spiking



If injured ipRGC is depolarized, same light causes ipRGC spiking – signals reach brain including thalamic pain centers

ipRGCs Project Heavily to Non-Visual Areas



Hattar et al, *J Comp Neurol* 2006

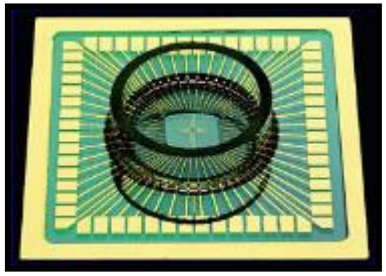
SCN – involved in circadian rhythm regulation

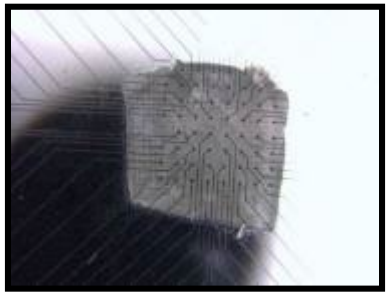
OPN – involved in pupillary light reflex

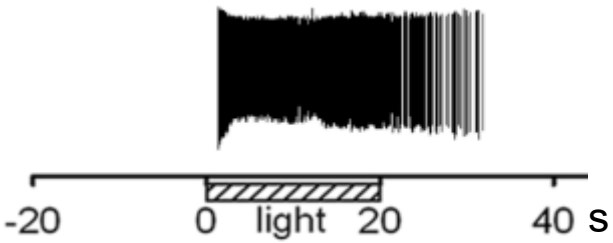
ipRGCs project to OPN pretectum and contribute to pupillary light reflex *in vivo*

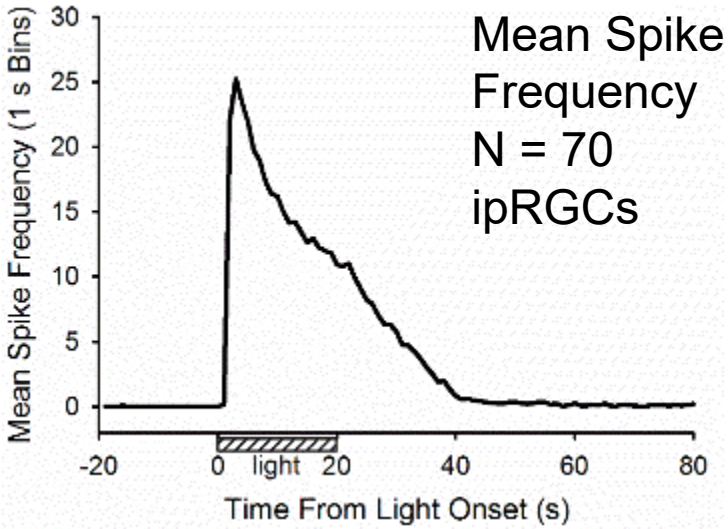
ipRGCs Respond Sluggishly to Light

- ipRGCs exhibit prolonged light responses that persists post-light offset – spiking gradually slows until stopping







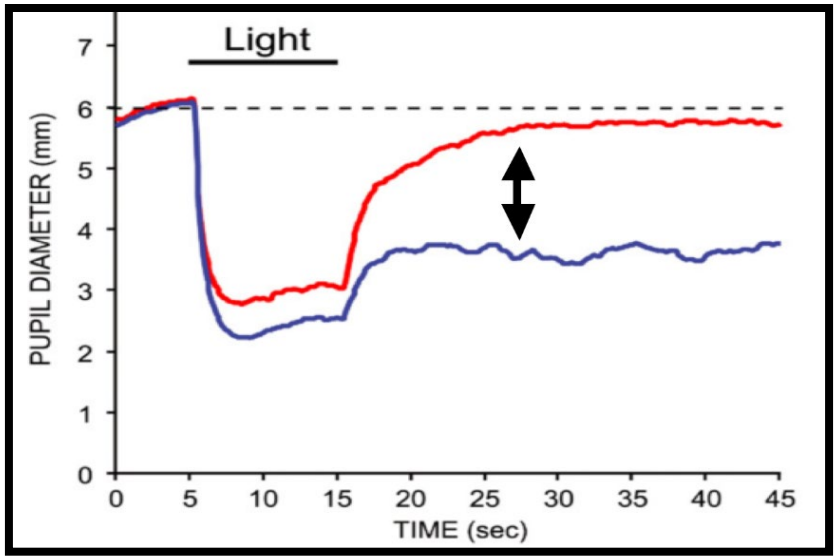


Sodhi & Hartwick, 2014

ipRGC Contribution to Human Pupil Responses

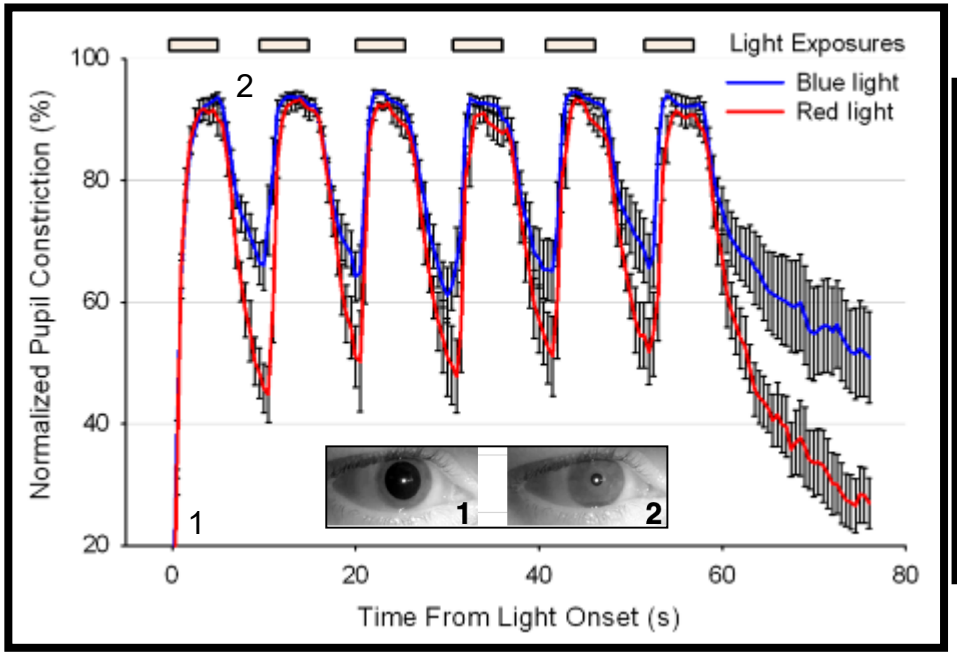
- In humans, pupil-redilation is longer with blue light stimulation versus red light stimulation – consistent with contribution from sluggish ipRGCs to blue light response

- By blocking rod/cone signaling pharmacologically, Gamlin et al. (2007) showed post-illumination pupil response (PIPR) in primates is melanopsin-mediated

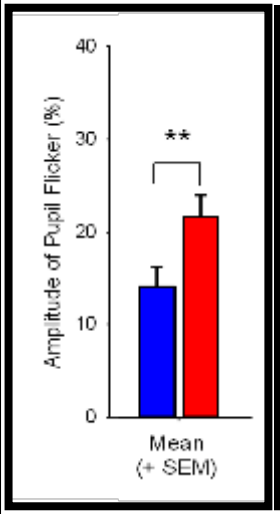


Pupil Responses to Red light, Blue Light…

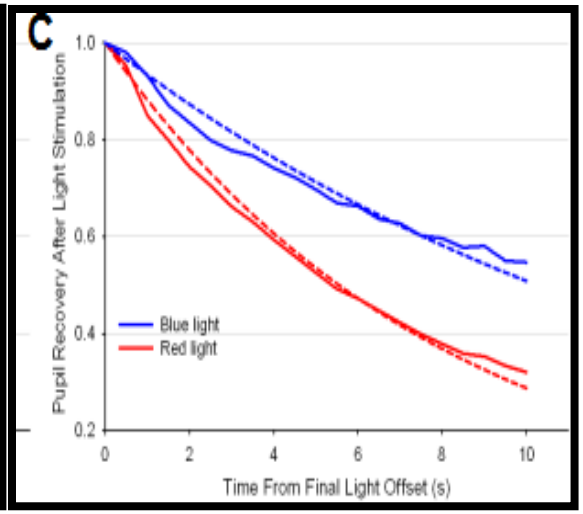
- Example below uses slow (0.1 Hz) flashing red and blue lights to look at ipRGC contributions to pupil light responses in humans



Red $7x10^{14}$; Blue $1x10^{14}$ phots/s/cm^2



Fourier Analysis



Pupil re-dilation can be fit by decay equation:
$y = e^{-bx}$

n = 19; age range = 23 to 27, 42% female

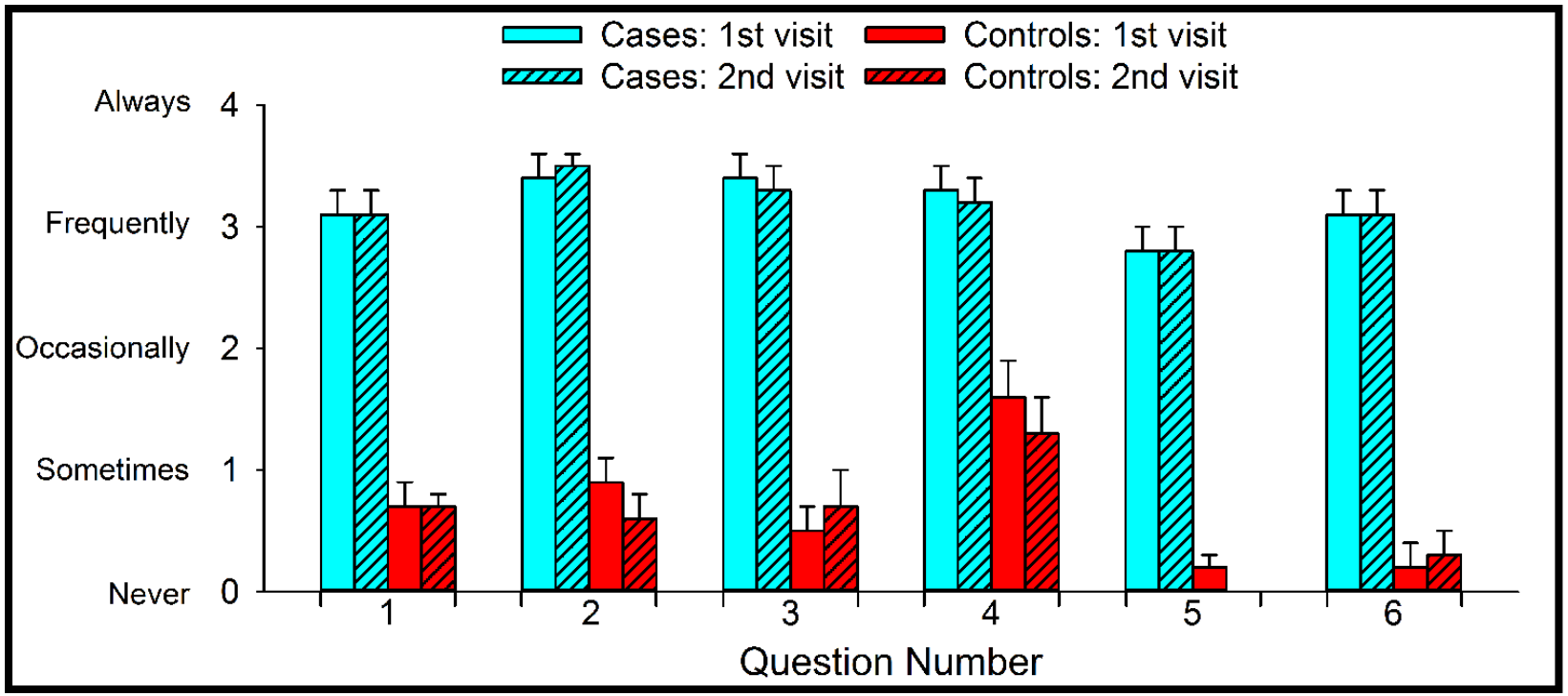
Phil Yuhas

Head Injury-Associated Photosensitivity and Pupillary Function (HIPP) Study

- Subjects were >18 years old
  - Had previous head injury occurring >6 months prior
  - Had not lost consciousness for more than 30 min (mild TBI)
  - Found lights more bothersome since injury
  - 24 case and 12 control subjects completed 2 sessions in study

  - Of 24 case subjects
    - 10 = strike/blow to the head
    - 6 = fall
    - 5 = motor vehicle accident
    - 1 = assault
    - 1 = athletic injury
    - 1 = blast injury

Survey: Light Aversion



1. I find indoor lighting levels in public places to be uncomfortably bright
2. I find indoor *fluorescent* lighting to be bothersome
3. I try to avoid light at home (e.g. close curtains, turn down lights)
4. I find outdoor light (sunlight) to be uncomfortably bright
5. My light sensitivity interferes with my daily activities
6. Light causes me to have prolonged discomfort (e.g. headaches) even after light exposure stops

Example Study Participant Experience

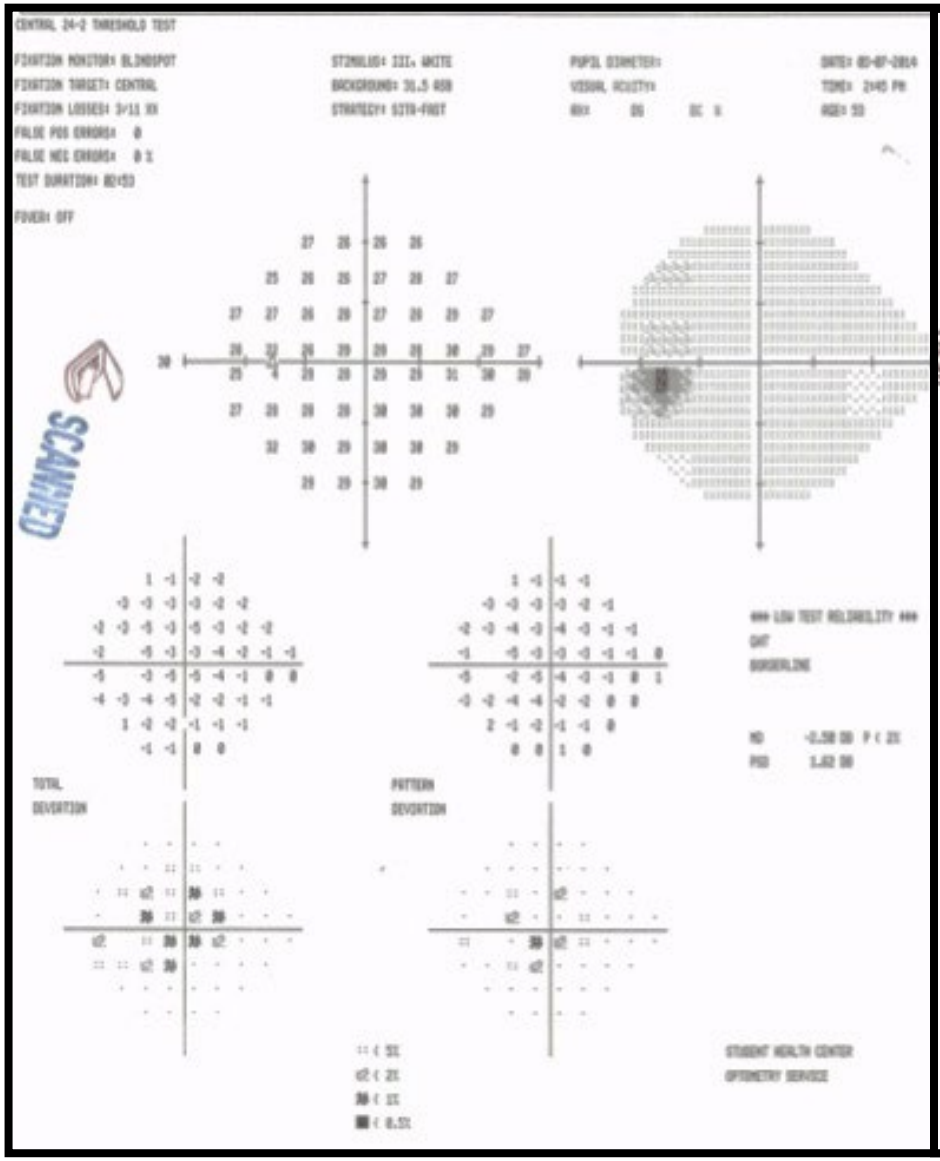
- 49 year-old Caucasian, male physician
  - Reports that "something is wrong with his retinas" despite repeated clinical exams that find nothing

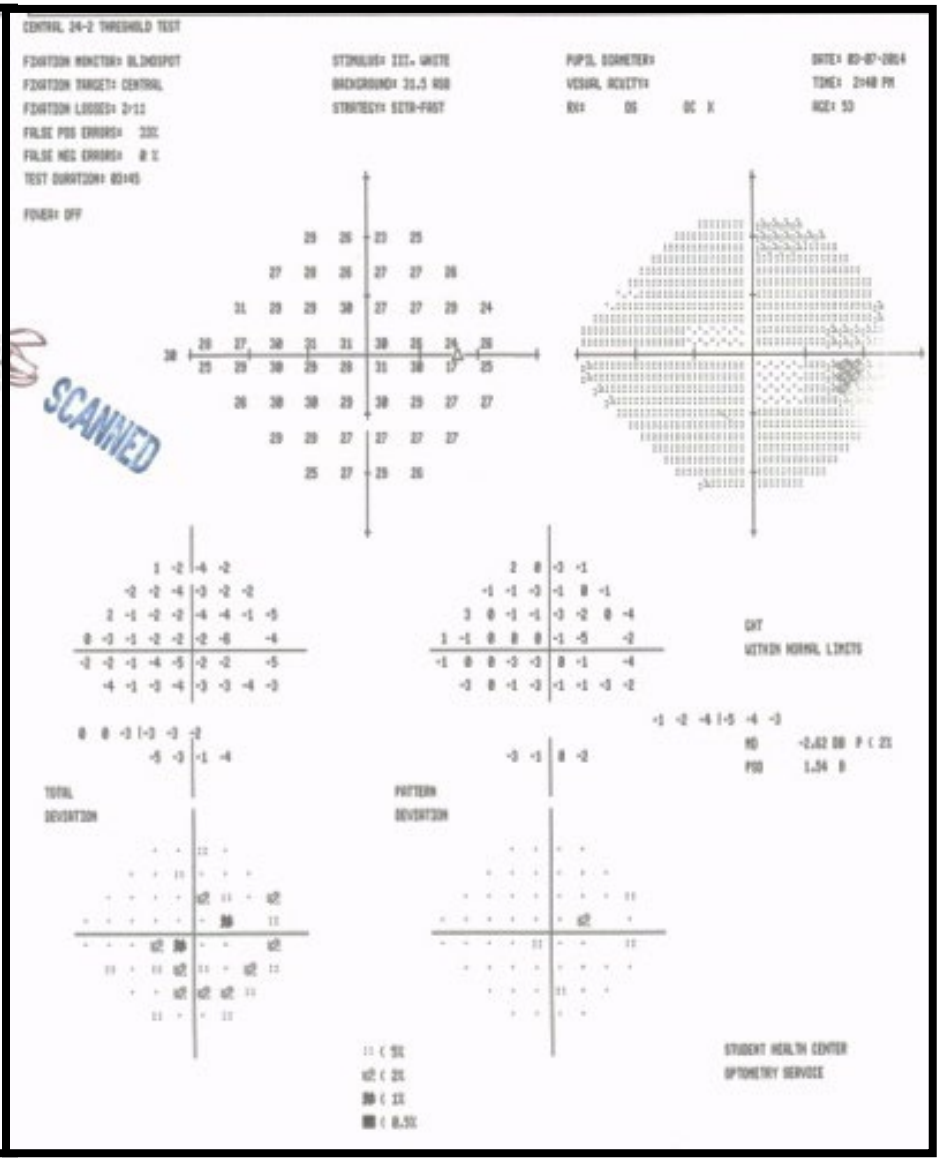
- History of ~5 mTBI – last one 4.5 years ago due to MVA

- Since MVA, he has found lights extremely bothersome

- OD: +0.25 -1.75 x 90 20/20
  OS: +0.50 -1.75 x 90 20/20 Add: +1.75 20/20

- Binocular vision testing and ocular health assessment unremarkable (including OCT)


CENTRAL 24-2 THRESHOLD TEST
SCANNED
TOTAL DEVIATION
PATTERN DEVIATION
STUDENT HEALTH CENTER
OPTOMETRY SERVICE

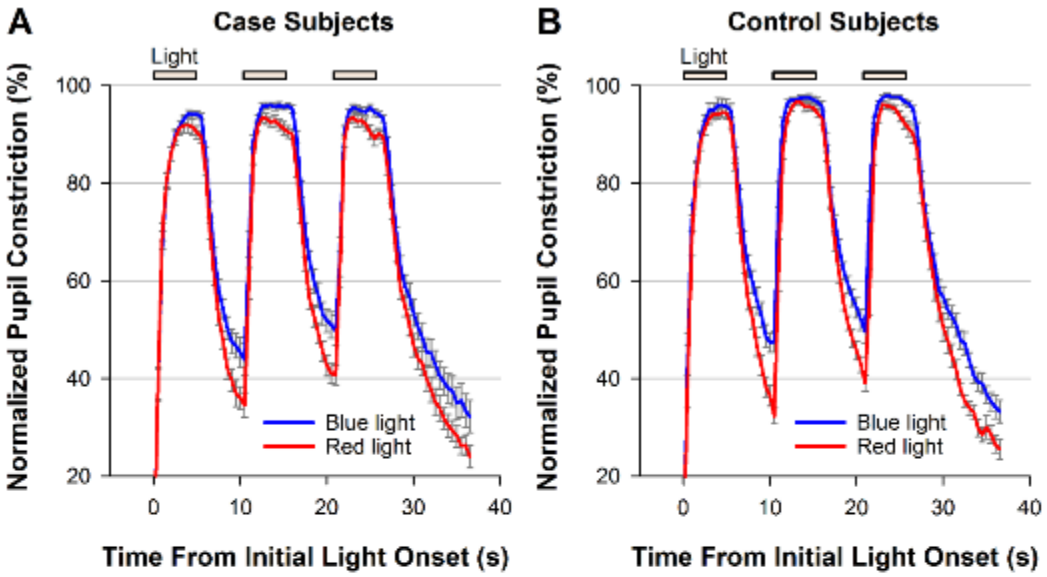

CENTRAL 24-2 THRESHOLD TEST
SCANNED
TOTAL DEVIATION
PATTERN DEVIATION
STUDENT HEALTH CENTER
OPTOMETRY SERVICE

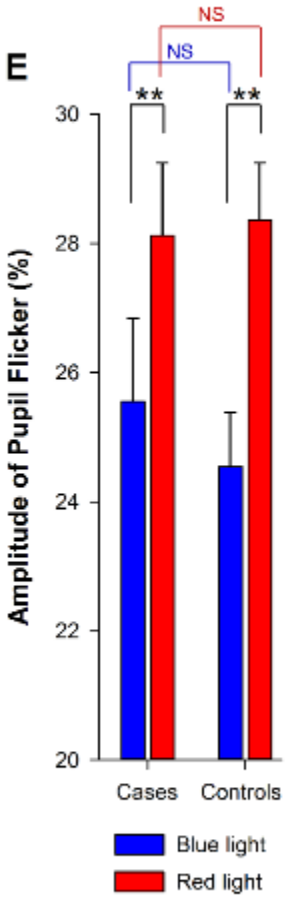
- Email exchange with study participant:

- “Today, killer migraine and lots of photophobia for the bright sunlight even coming into the house. This confounds me and this conundrum of weird symptoms that follow a ‘nonstructural’ injury from a concussion is frustrating. What is causing this?”

Pupil Responses in HIPP Study

Yuhas et al. 2017, *Optometry & Vision Science*



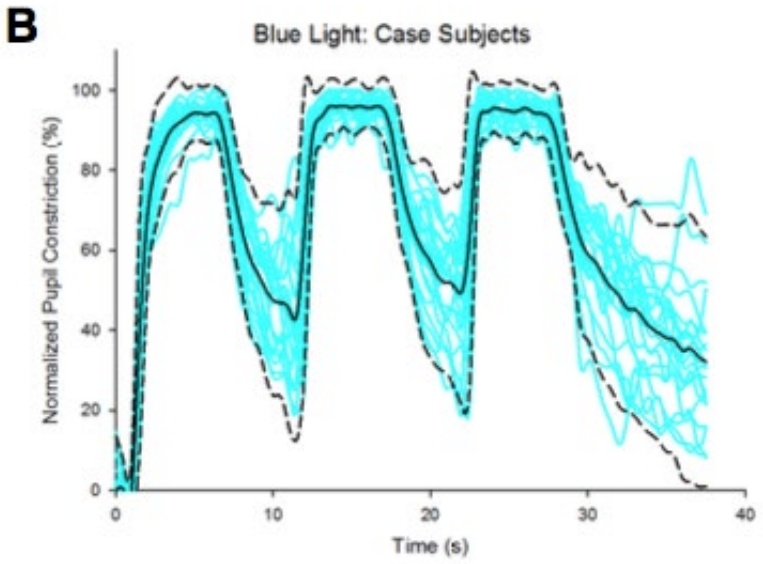


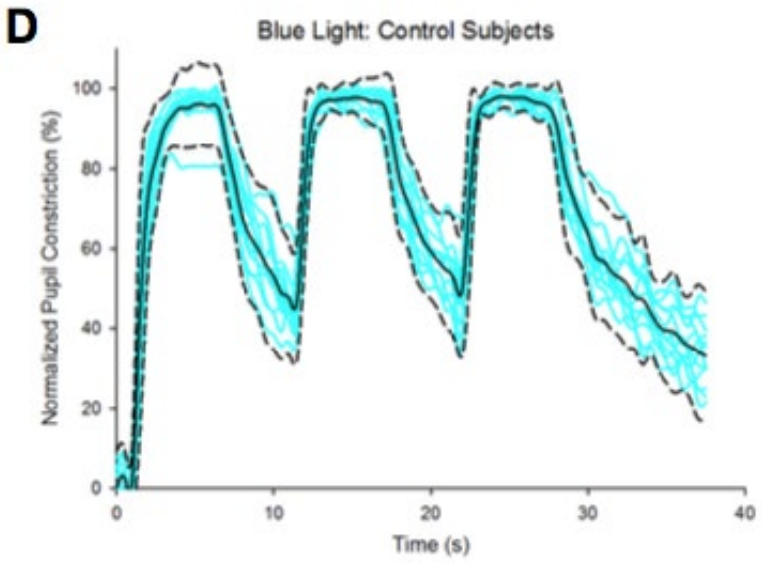
Light stimuli

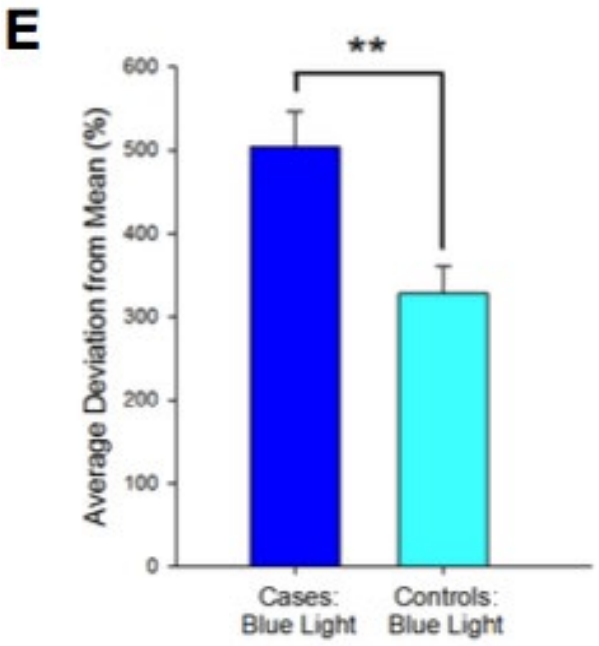
Red: $7x10^{13}$;
Blue: $1x10^{13}$
phots/s/cm^2

No difference in responses between subject groups
n = 24 cases
n = 12 controls

Pupil Responses in HIPP Study







Increased variablility in the pupil responses in the case group

Heterogeneous group?

Yuhas et al. 2017, *Optometry & Vision Science*

Effects of mTBI on RGC Light Adaptation

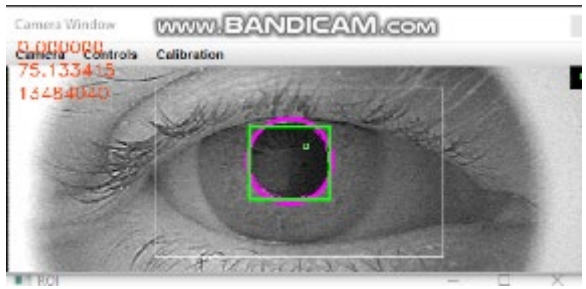
- Currently, we (collaboration with Suresh Viswanathan at SUNY), are further studying RGC and ipRGC light adaptation in individuals with mTBI-associated photophobia

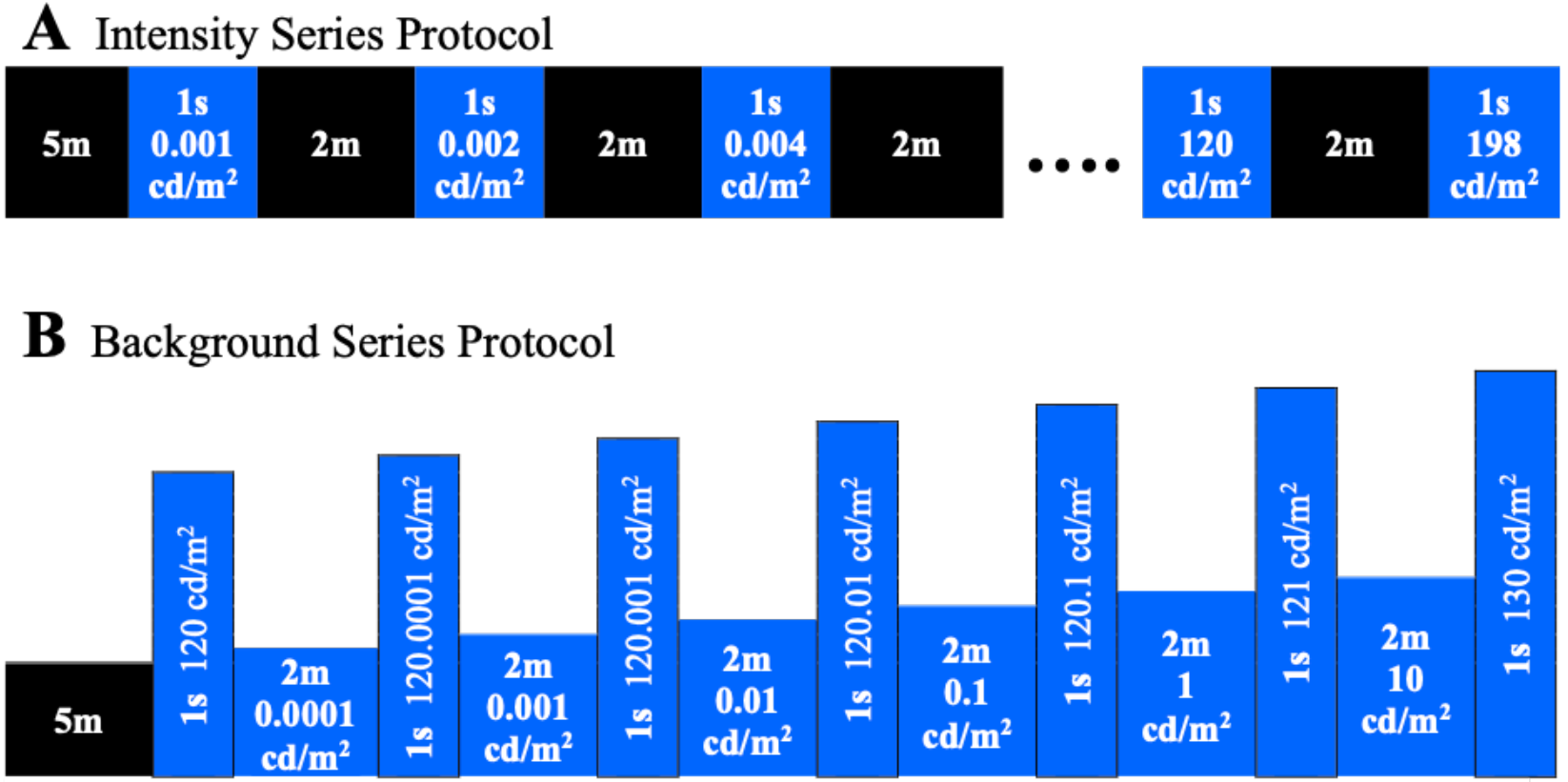
- A variety of protocols have been tested that utilize multiple irradiances, during and following adaptation to different background light levels

- Both ERGs and pupil responses measured during these protocols

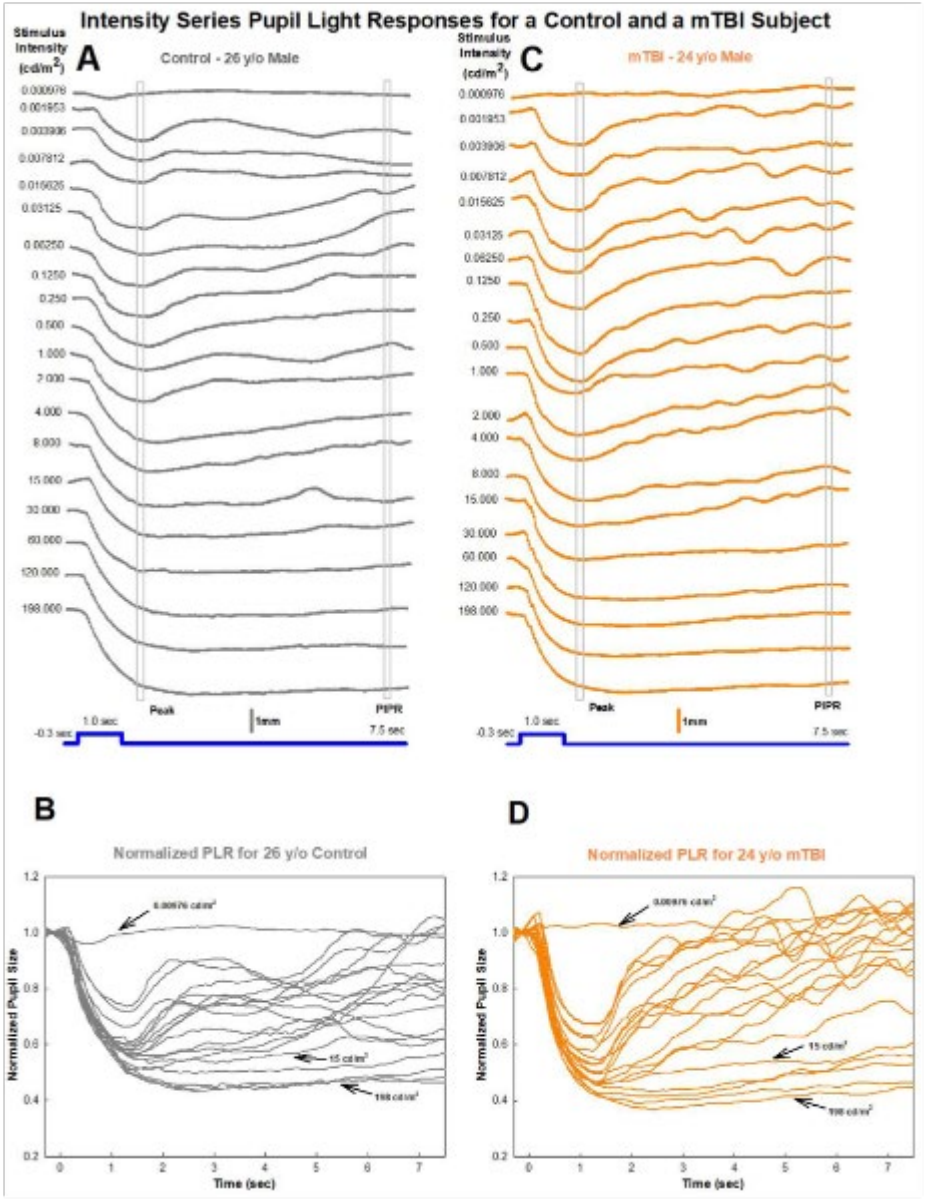
ERGs and RGC Adaptation

Jeff Farmer, Diagnosys LLC

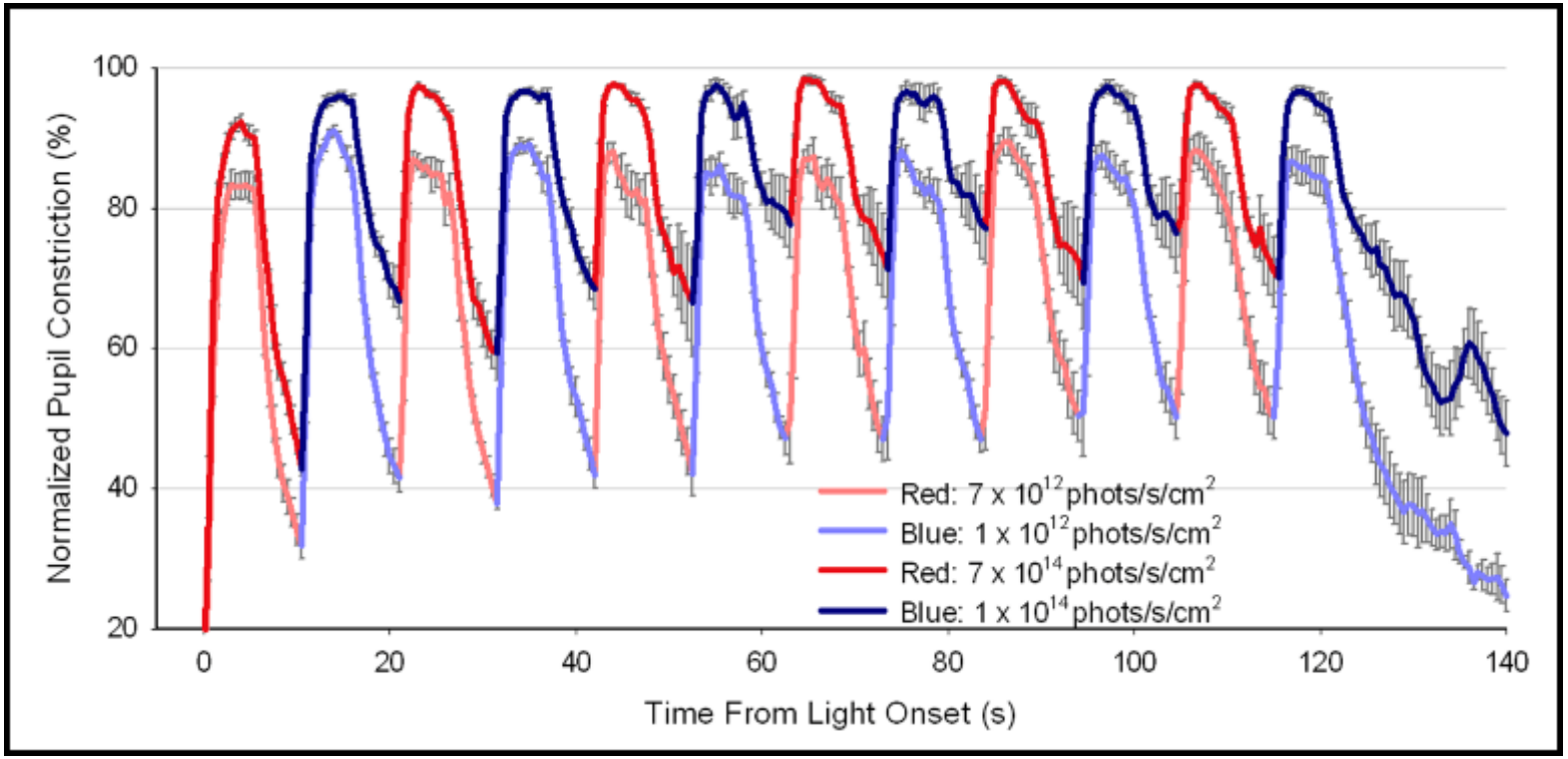



A Intensity Series Protocol
5m
1s 0.001 cd/m²
2m
1s 0.002 cd/m²
2m
1s 0.004 cd/m²
2m
....
1s 120 cd/m²
2m
1s 198 cd/m²
B Background Series Protocol
5m
1s 120 cd/m²
2m 0.0001 cd/m²
1s 120.0001 cd/m²
2m 0.001 cd/m²
1s 120.001 cd/m²
2m 0.01 cd/m²
1s 120.01 cd/m²
2m 0.1 cd/m²
1s 120.1 cd/m²
2m 1 cd/m²
1s 121 cd/m²
2m 10 cd/m²
1s 130 cd/m²

Pupil Responses and Light Adaptation

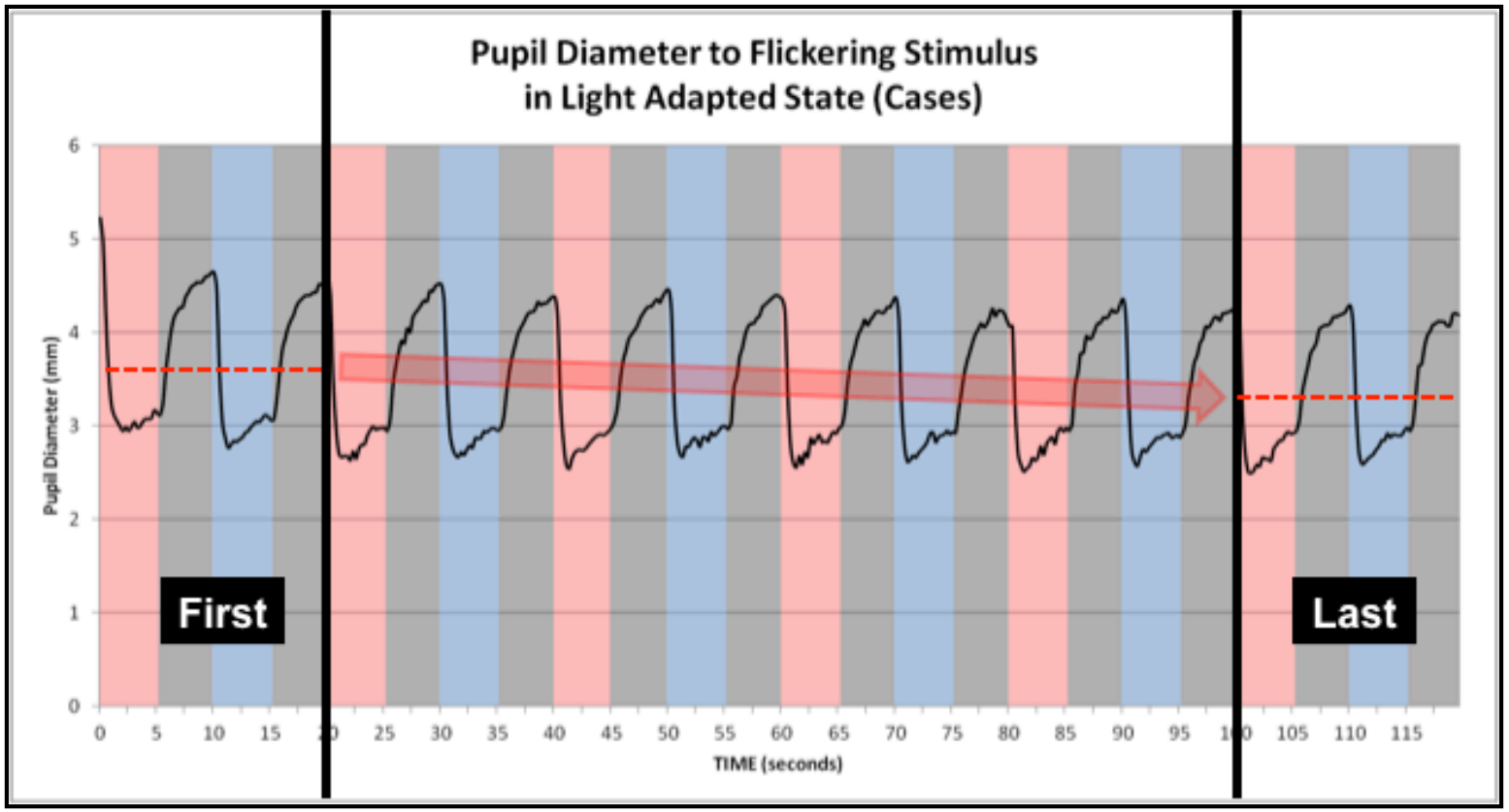


- We've found that pupil responses to red light change, when red and blue light pulses are alternated
  - The prior blue light stimuli 'potentiates' the responses to red light



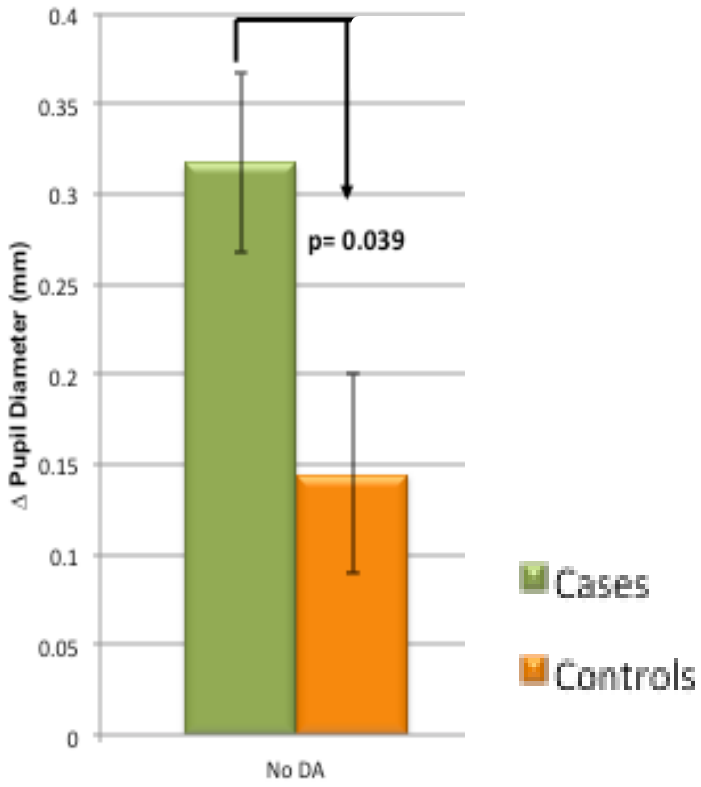
Photopotentiation of Pupil Responses

- Not clear the mechanism for this photopotentiation, but we've looked at the increased pupil constriction that occurs following repeated stimulation with red/blue alternating stimuli



Photopotentiation of Pupil Responses

- Photosensitive TBI subjects showed enhanced pupil constriction at end of 2 minute testing protocol
- Relatively simple pupil test may have promise in assessing these subjects
- Evidence for inability for ipRGCs to adapt to repeated light challenge?



Treatment for Photophobia?

- Does this data have clinical implications for the treatment of TBI-associated photosensitivity?
- Not yet….

- But, anecdotally, I can report that the subjects seem to benefit from short-wavelength blocking lenses
- 71% of the subjects chose prescription orange tinted (CPF 527 glasses) over $65 reimbursement

- Feedback from the subjects on the glasses have been extremely positive

HIPP Subject quote from email:

“Things are so clear and I'm just surprised. I just don't understand how I'm not complaining or squinting. I don't understand but I'm thrilled right now. My kids don't get it bc they cant see a difference to them, things just look orange. But things look so clear and the sun is super bright and I'm not whining about being dizzy bc of the light. THANK YOU, THANK YOU!!! Just wish I could understand how these are working...”

- Strong placebo effect? We need carefully designed, masked studies that evaluate efficacy of tinted lenses

Summary

- Accumulating evidence that ipRGCs are involved in aspects of photophobia, but direct involvement in TBI-associated photophobia not established
  - Why would ipRGCs be more vulnerable to trauma?
- Our data suggests that ipRGCs don't simply become 'hypersensitive' to light after mTBI
- Instead, our data suggests that there may be a deficit in their ability to adapt to repeated or changing light exposure (altered gain control)
- Increased baseline pupil size may also be associated

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