New Objective Methods for Understanding the Cause and Treatment of Photosensitivity

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FINANCIAL DISCLOSURE

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- Funding from Department of Defense; TATRC
- Funding from VA Rehabilitation Research and Development
- Novartis steering committee OCTiMS
- Acorda steering committee visual symptoms
- Zeiss Meditec consultant for perimetry and OCT

Poll Question 1

Which is your main role at the VA?

- 1) Ophthalmologist
- 2) Optometrist
- 3) Neurologist
- 4) Primary Care Physician or Physician's Assistant
- 5) Occupational/Physical Therapist
- 6) Social Worker
- 7) Research Scientist

Poll Question 2

How many new patients with photosensitivity do you see per year?

- 1) 1-5 patients
- 2) 6-10 patients
- 3) 11-20 patients
- 4) >20 patients

Photosensitivity

- Associated with acute uveitis
- Common in retinal dystrophies
- Can occur following meningitis
- A major symptom in some brain tumors
- More common in patients with migraine
- Common after TBI (59% report it)
- Psychogenic component?

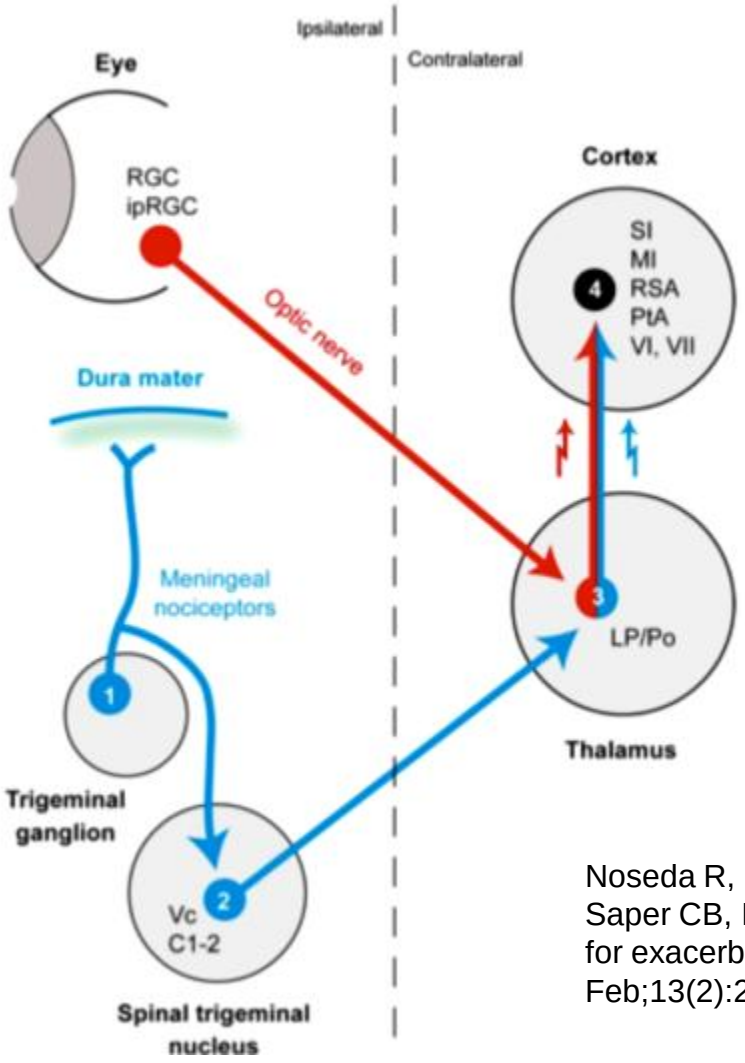
nature neuroscience

A neural mechanism for exacerbation of headache by light

Rodrigo Noseda[1], Vanessa Kainz[1], Moshe Jakubowski[1], Joshua J Gooley[2], Clifford B Saper[2,3], Kathleen Digre[4] & Rami Burstein[1,3]

The perception of migraine headache, which is mediated by nociceptive signals transmitted from the cranial dura mater to the brain, is uniquely exacerbated by exposure to light. We found that exacerbation of migraine headache by light is prevalent among blind individuals who maintain non–image-forming photoregulation in the face of massive rod/cone degeneration. Using single-unit recording and neural tract tracing in the rat, we identified dura-sensitive neurons in the posterior thalamus whose activity was distinctly modulated by light and whose axons projected extensively across layers I–V of somatosensory, visual and associative cortices. The cell bodies and dendrites of such dura/light-sensitive neurons were apposed by axons originating from retinal ganglion cells (RGCs), predominantly from intrinsically photosensitive RGCs, the principle conduit of non–image-forming photoregulation. We propose that photoregulation of migraine headache is exerted by a non–image-forming retinal pathway that modulates the activity of dura-sensitive thalamocortical neurons.

Noseda R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, Burstein R. A neural mechanism for exacerbation of headache by light. Nat Neurosci. Feb;13(2):239-45. 2010



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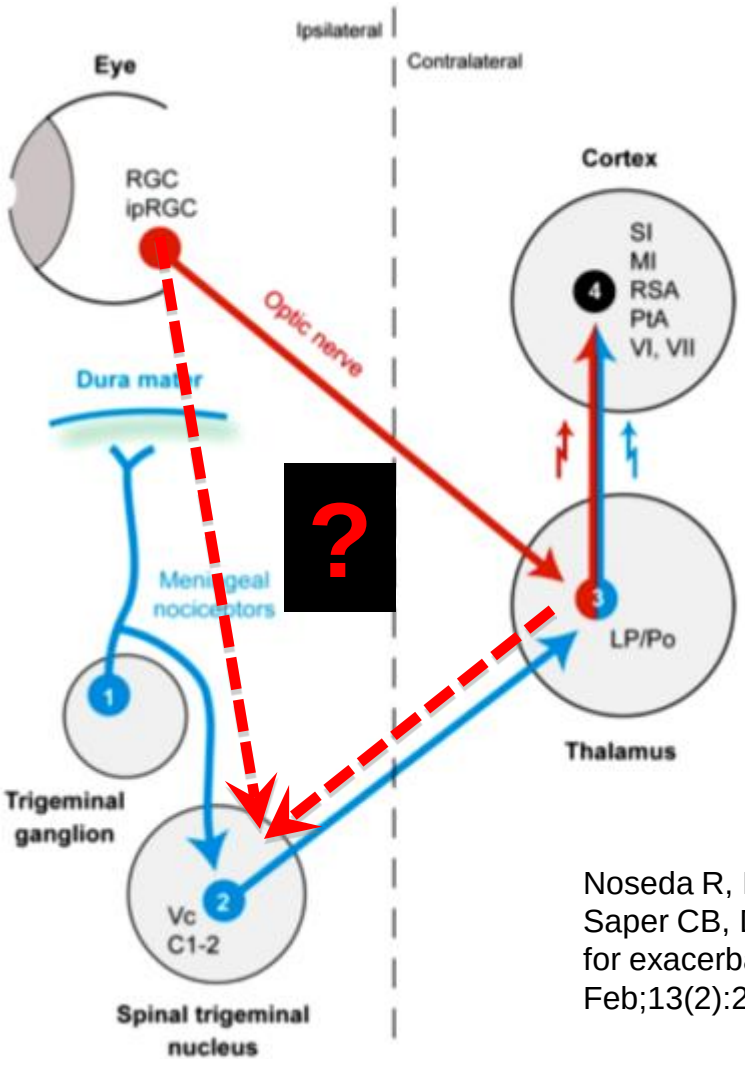

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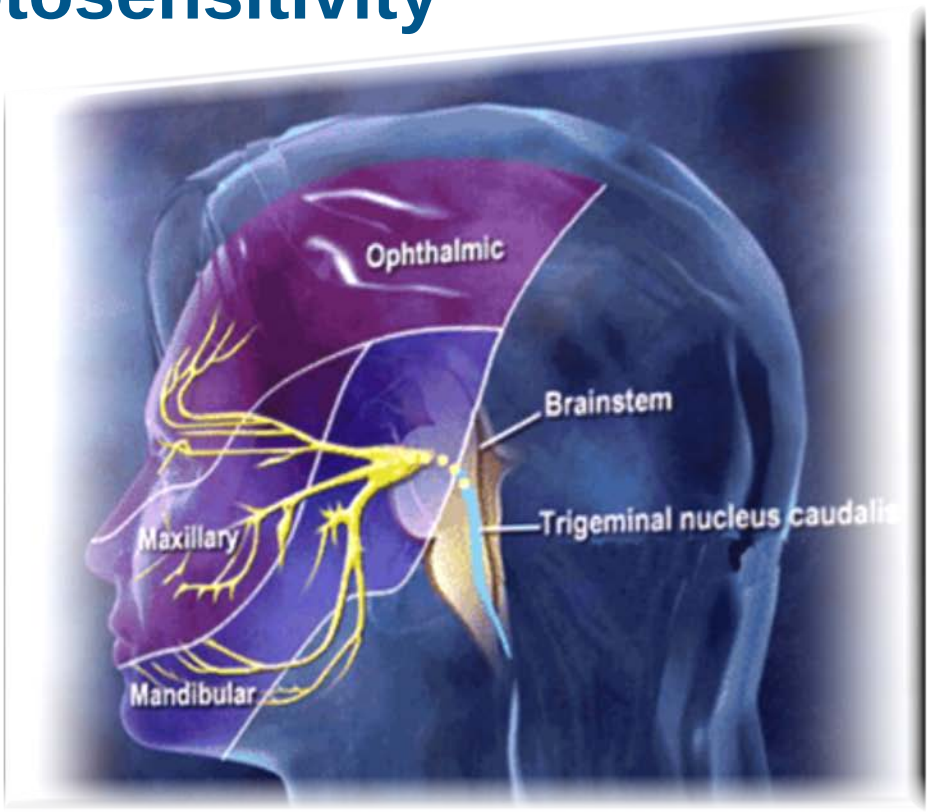
CGRP, Migraine and Photosensitivity

Calcitonin Gene-Related Peptide (CGRP) modulates trigeminal activity in the eye and brain

1. CGRP levels reported elevated in migraine
2. Injection of CGRP induces headache and photophobia
3. CGRP receptor antagonist



Light-Induced Trigeminal Sensitization without Central Visual Pathways: Another Mechanism for Photophobia

Sarah Dolgonos,[1] *Haripriya Ayyala,*[2,3] *and Craig Evinger*[2,3,4]

Purpose. The authors investigated whether trigeminal sensitization occurs in response to bright light with the retina disconnected from the rest of the central nervous system by optic nerve section.

Methods. In urethane-anesthetized rats, trigeminal reflex blinks were evoked with air puff stimuli directed at the cornea in darkness and at three different light intensities. After normative data were collected, the optic nerve was lesioned and the rats were retested. In an alert rat, reflex blinks were evoked by stimulation of the supraorbital branch of the trigeminal nerve in the dark and in the light.

Results. A 9.1×10^3 $\mu W/cm^2$ and a 15.1×10^3 $\mu W/cm^2$ light significantly enhanced the magnitude of reflex blinks relative to blinks evoked by the same trigeminal stimulus when the rats were in the dark. In addition, rats exhibited a significant increase in spontaneous blinking in the light relative to the blink rate in darkness. After lesioning of the optic nerve, the 15.1×10^3 $\mu W/cm^2$ light still significantly increased the magnitude of trigeminal reflex blinks.

Conclusions. Bright lights increase trigeminal reflex blink amplitude and the rate of spontaneous blinking in rodents. Light can modify trigeminal activity without involving the central visual system. (*Invest Ophthalmol Vis Sci.* 2011;52:7852–7858) DOI: 10.1167/iovs.11-7604

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Bright light activates a trigeminal nociceptive pathway

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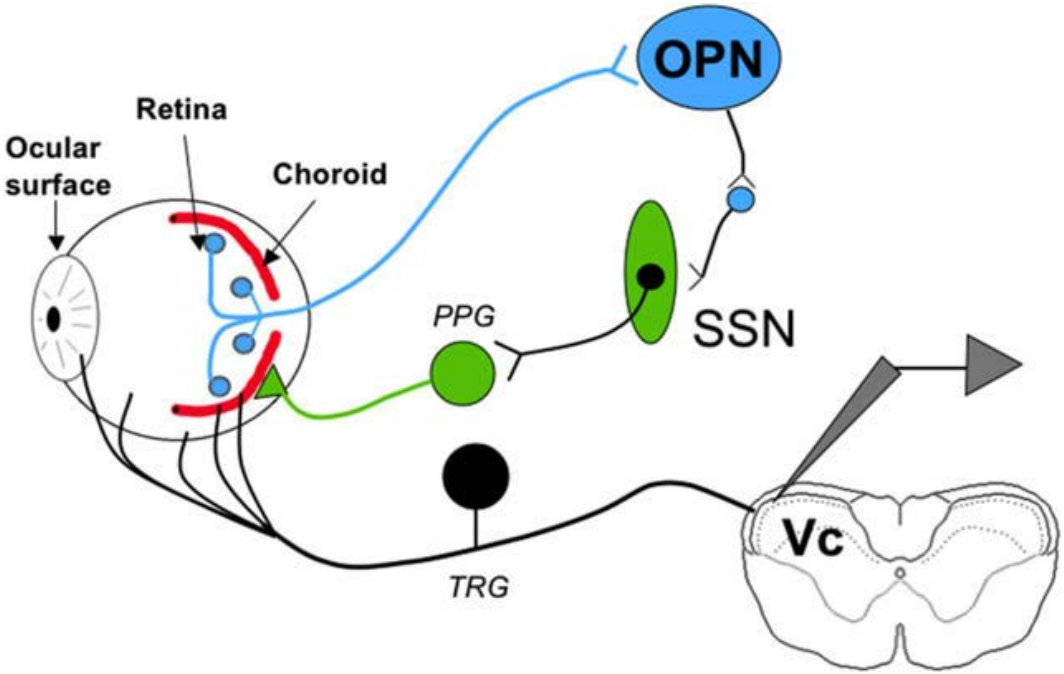
abstract

Bright light can cause ocular discomfort and/or pain; however, the mechanism linking luminance to trigeminal nerve activity is not known. In this study we identify a novel reflex circuit necessary for bright light to excite nociceptive neurons in superficial laminae of trigeminal subnucleus caudalis (Vc/C1). Vc/C1 neurons encoded light intensity and displayed a long delay (>10 s) for activation. Microinjection of lidocaine into the eye or trigeminal root ganglion (TRG) inhibited light responses completely, whereas topical application onto the ocular surface had no effect. These findings indicated that light-evoked Vc/C1 activity was mediated by an intraocular mechanism and transmission through the TRG. Disrupting local vasomotor activity by intraocular microinjection of the vasoconstrictive agents, norepinephrine or phenylephrine, blocked light-evoked neural activity, whereas ocular surface or intra-TRG microinjection of norepinephrine had no effect. Pupillary muscle activity did not contribute since light-evoked responses were not altered by atropine. Microinjection of lidocaine into the superior salivatory nucleus diminished light-evoked Vc/C1 activity and lacrimation suggesting that increased parasympathetic outflow was critical for light-evoked responses. The reflex circuit also required input through accessory visual pathways since both Vc/C1 activity and lacrimation were prevented by local blockade of the olivary pretectal nucleus. These findings support the hypothesis that bright light activates trigeminal nerve activity through an intraocular mechanism driven by a luminance-responsive circuit and increased parasympathetic outflow to the eye.



erygopalatine ganglion; TRG, trigeminal root ganglion.

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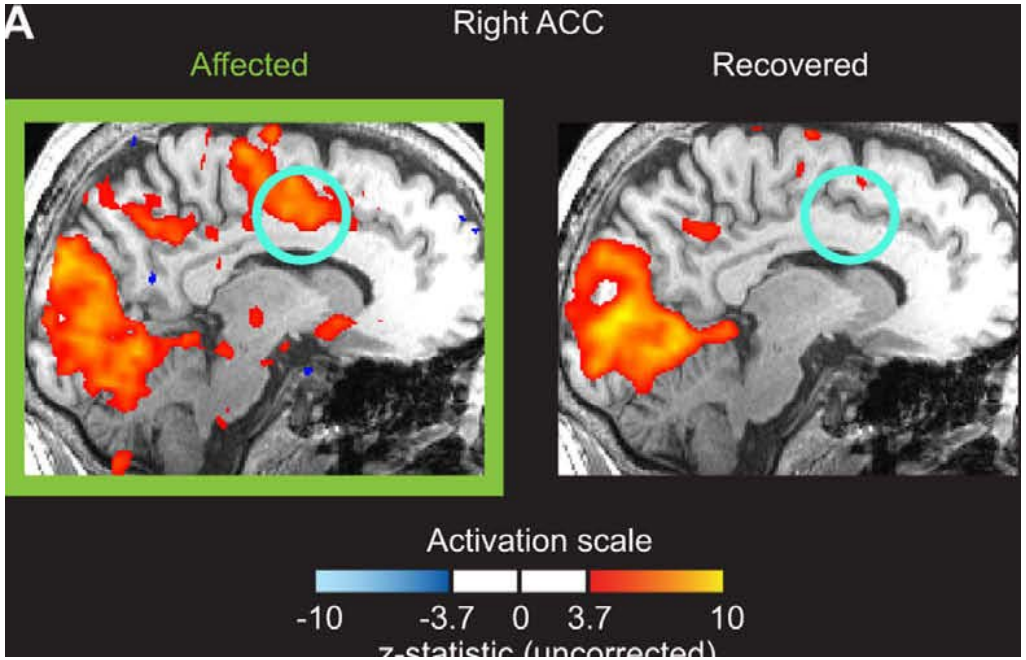
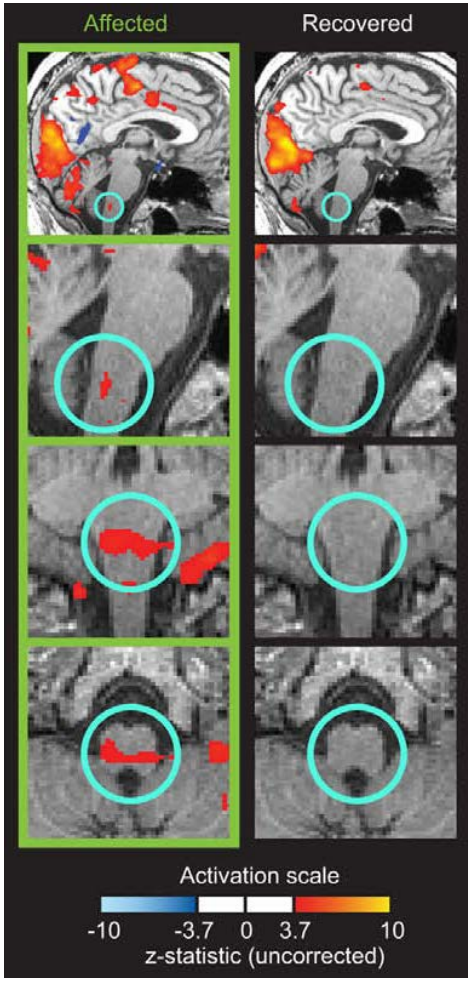
Clinical note

An fMRI case report of photophobia: Activation of the trigeminal nociceptive pathway

E.A. Moulton *, L. Becerra, D. Borsook

Mclean Hospital, PAIN Group, Brain Imaging Center, 115 Mill Street, Belmont, USA





Neuroscience 160 (2009) 858–864

BRIGHT LIGHT PRODUCES Fos-POSITIVE NEURONS IN CAUDAL TRIGEMINAL BRAINSTEM

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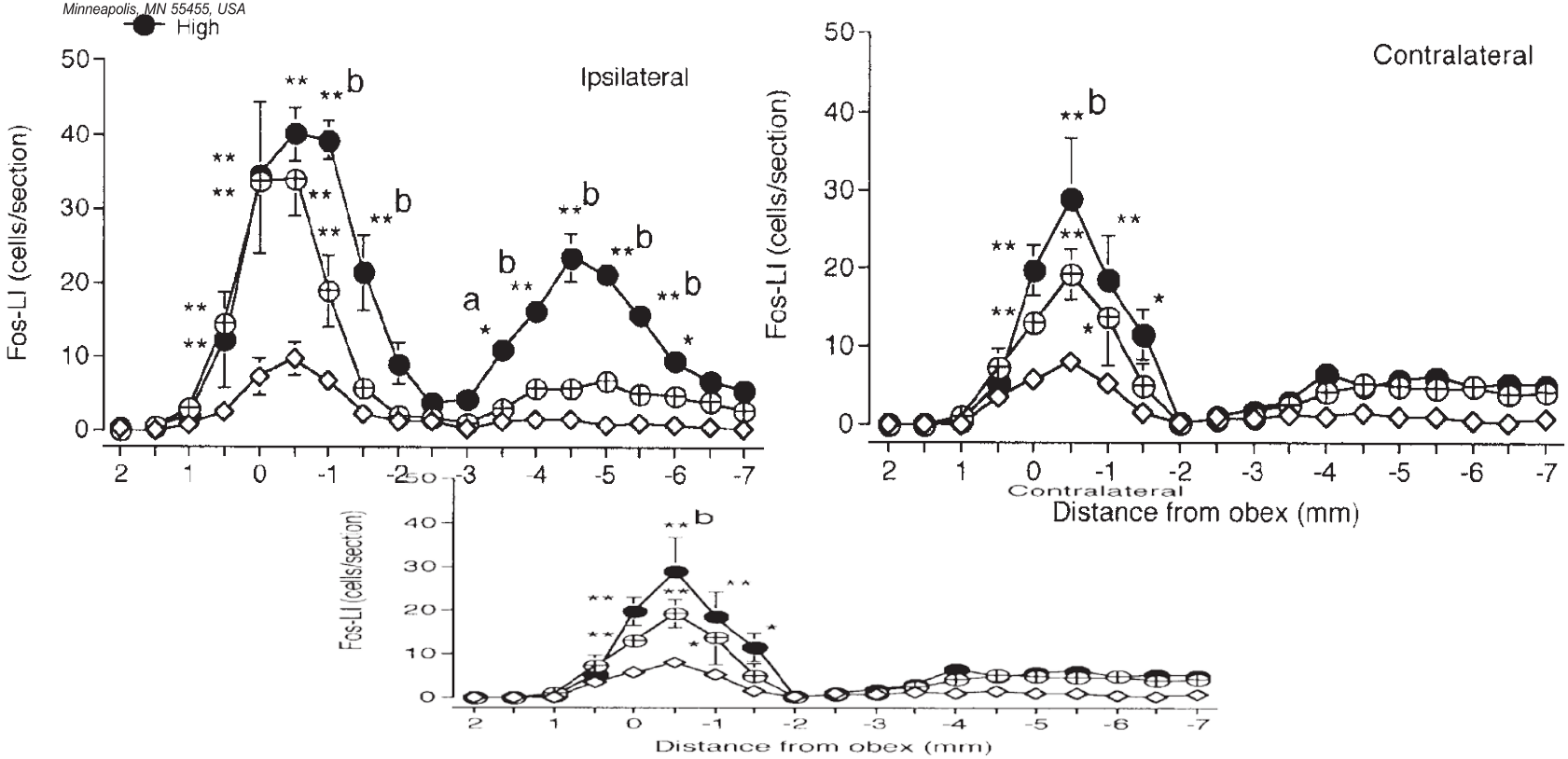
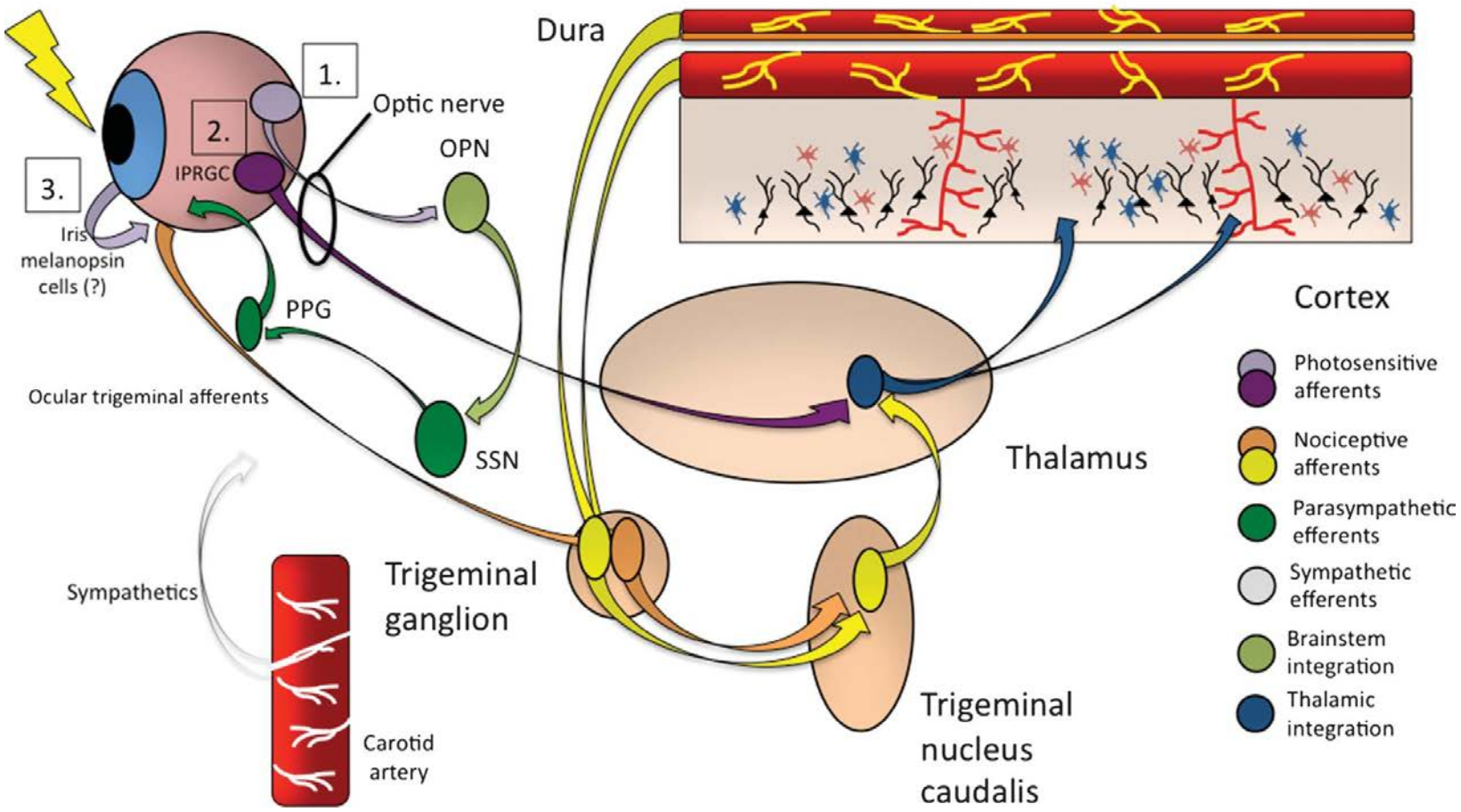


Photophobia Circuit



State-of-Art Reviews, Section Editors: Grant T. Liu, MD and Randy H. Kardon, MD, PhD
Journal of Neuro-Ophthalmology, 2012;32:68-81, Shedding Light on Photophobia
Kathleen B. Digre, MD and K.C. Brennan, MD

The Photo-Blink Reflex

- Protects the eye after a bright flash[1-4]

1.Mukuno K et al.. Jpn J Ophthalmol. 27(1):261-70. 1983.
2.Malin JP. Elektroenzephalogr Elektromyogr Verwandte Geb. Sep;13(3):101-7. German. 1982.
3.Yasuhara M, Naito H.. Int J Neurosci. Jul;17(1):23-31. 1982.
4.Ozaki T.. Nippon Seirigaku Zasshi. 38(1):15-6. Japanese. 1976.
5.Noseda R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, Burstein R. A neural mechanism for exacerbation of headache by light. Nat Neurosci. Feb;13(2):239-45. 2010

The Photo-Blink Reflex

- Protects the eye after a bright flash[1-4]
- Melanopsin containing retinal ganglion cells may mediate the afferent arm of this reflex through projections to the thalamus and trigeminal nucleus[5] and may explain the paradoxical photosensitivity in patients blinded by photoreceptor loss[5]

1. Mukuno K et al.. Jpn J Ophthalmol. 27(1):261-70. 1983.
2. Malin JP. Elektroenzephalogr Elektromyogr Verwandte Geb. Sep;13(3):101-7. German. 1982.
3. Yasuhara M, Naito H.. Int J Neurosci. Jul;17(1):23-31. 1982.
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5. Noseda R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, Burstein R. A neural mechanism for exacerbation of headache by light. Nat Neurosci. Feb;13(2):239-45. 2010

Poll Question 3

Of the patients you see with photosensitivity, which cause best characterizes the majority?

- 1) thought to be caused by Traumatic Brain Injury
- 2) thought to be a manifestation of migraine (can be during or between headaches)
- 3) related to ocular cause (e.g. uveitis, ocular trauma)
- 4) related to other brain disorder (e.g. post meningitis, tumor)

Poll Question 4

Of the patients you see with photosensitivity, which of the two choices best characterizes their light sensitivity?

- 1) everything seems too bright, but headache is not a major component of the symptom.
- 2) light causes headache or makes their headaches worse, but visually, the light does not seem brighter than normal

Photosensitivity Hypothesis

- Abnormal sensitivity of the trigeminal nerve and its recipient sensory brainstem nucleus
- A trigeminal brainstem reflex mediated by light would be exagerated in photosensitivity

Methods

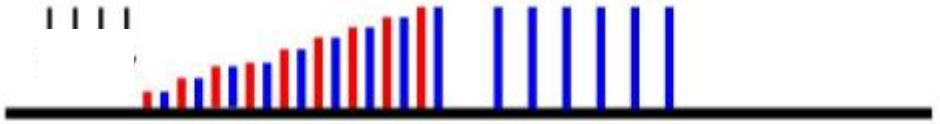
- 15 normal subjects and 12 patients with photosensitivity were tested using red (640nm) and blue (485nm) Ganzfeld light, one second in duration over a 6 log unit range of intensity (0.5 log unit steps).

- Time-stamped, computerized recording of the pupil, orbicularis and procerus muscle EMG, skin conductance and heart rate were measured simultaneously.

Methods

Light exposure

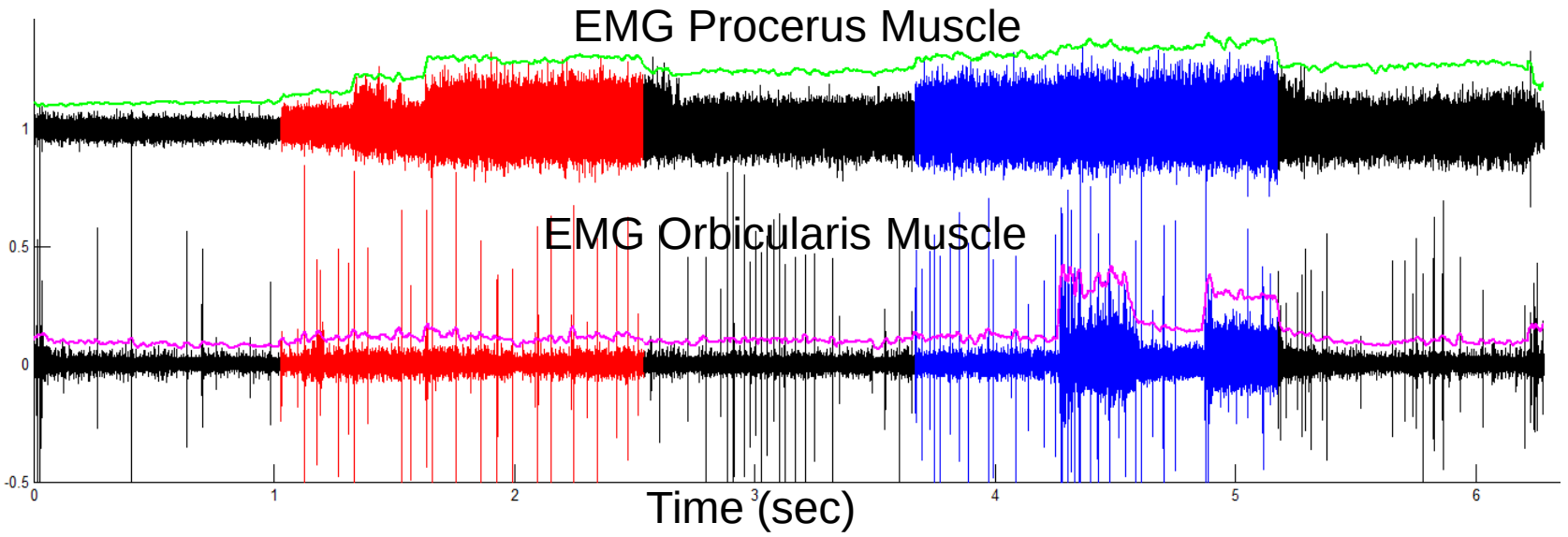
Electromyography



Dark adapted baseline | Red/Blue alternating 1 second flashes | 10 seconds max blue 30 seconds dark | Recovery time points

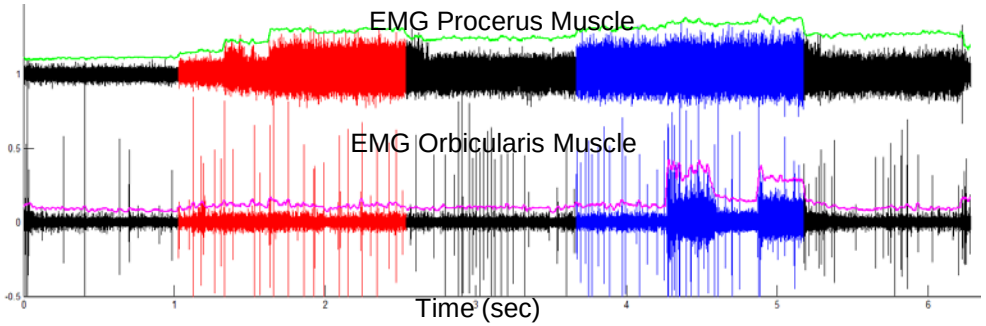
Pre-Stimulus | Stimulus | Post-Stimulus

Photic-EMG Induced by Red and Blue Light



One second in duration, over 6 log unit range of intensity (0.5 log unit steps)

Photic-EMG Induced by Red & Blue Light (cont.)



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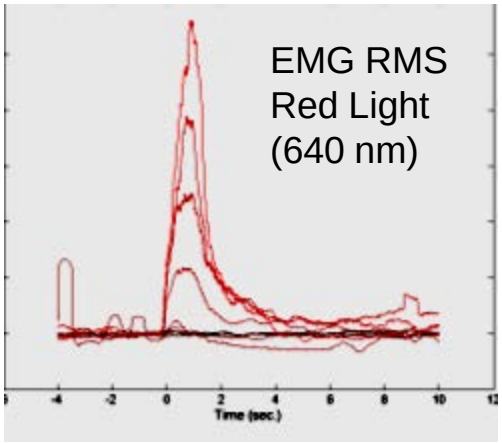
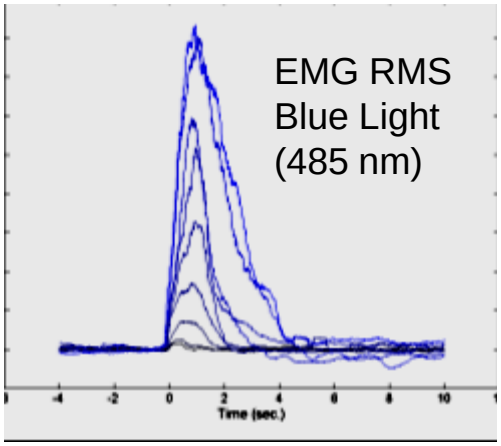
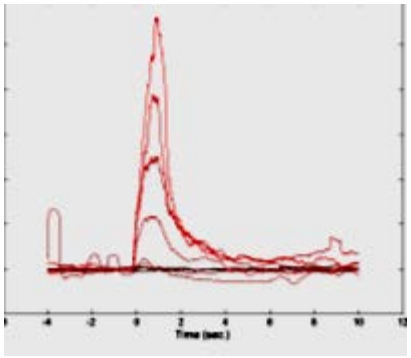


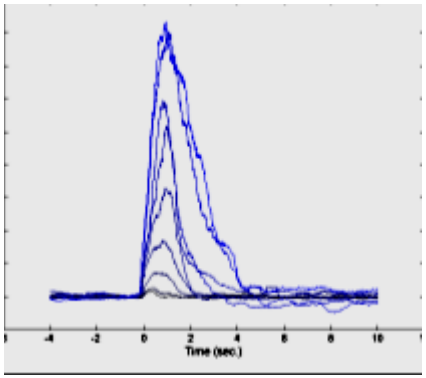


Pieter Poolman, Randy Kardon

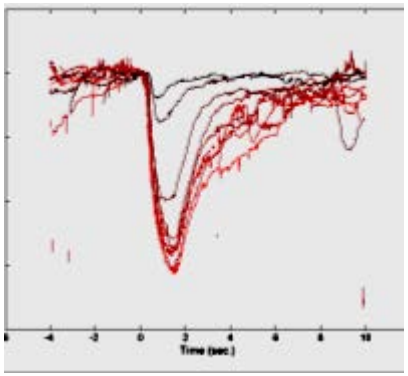
EMG and Pupil Responses to Different Red and Blue Light Intensities



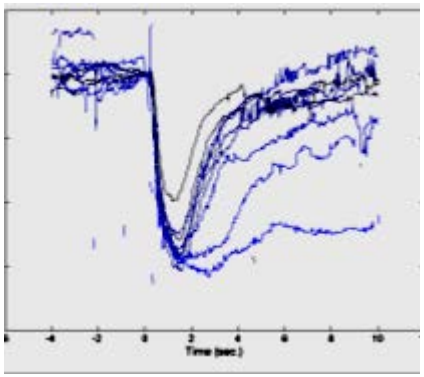
EMG RMS
Red Light



EMG RMS
Blue Light



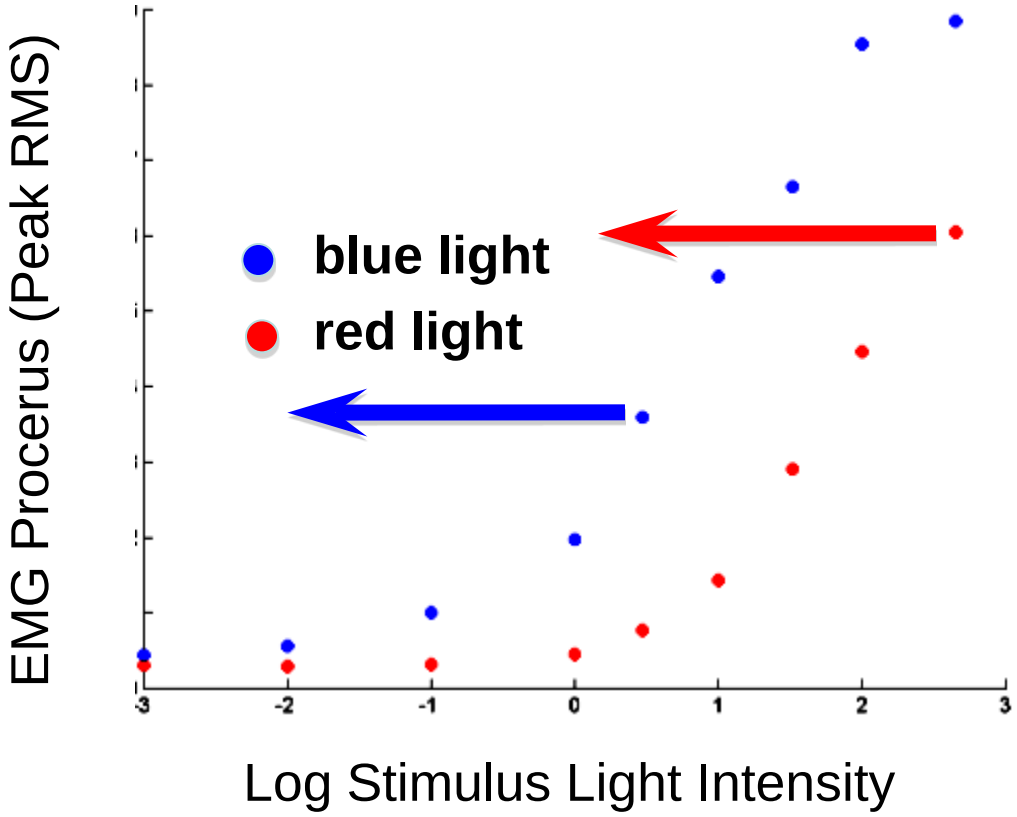
Pupil Size
Red Light



Pupil Size
Blue Light

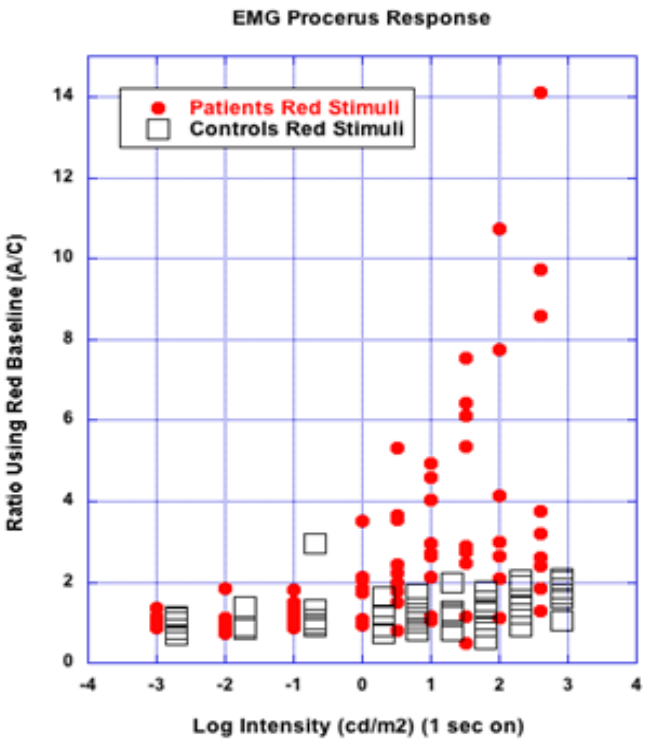
Photic-EMG Response Function

Does it Shift in Photophobia and in Migraine?

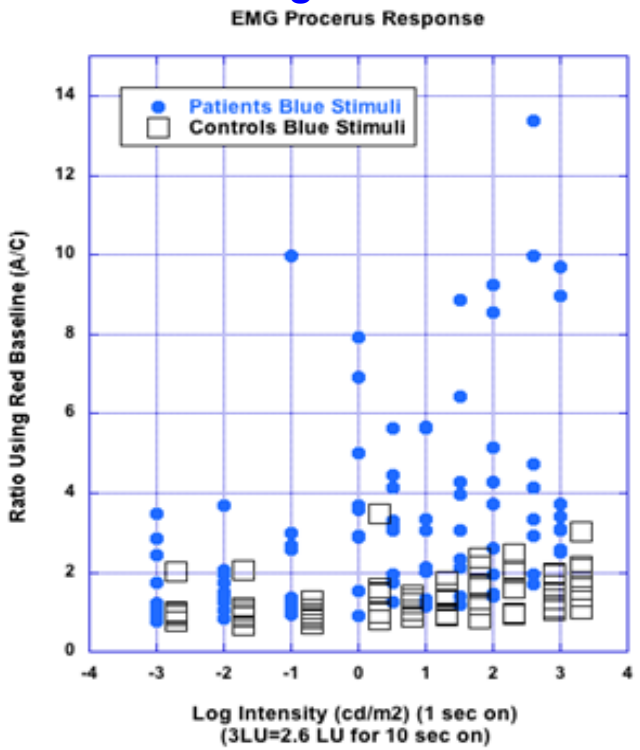


Exaggerated EMG Responses in Patients with Photosensitivity

Red Light Stimuli

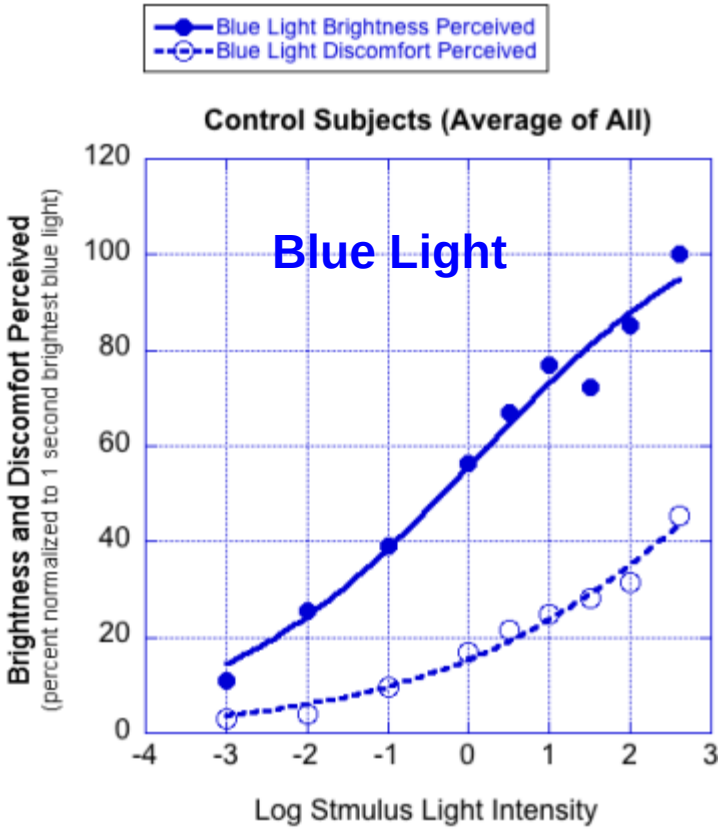


Blue Light Stimuli



Pieter Poolman, Susan Anderson

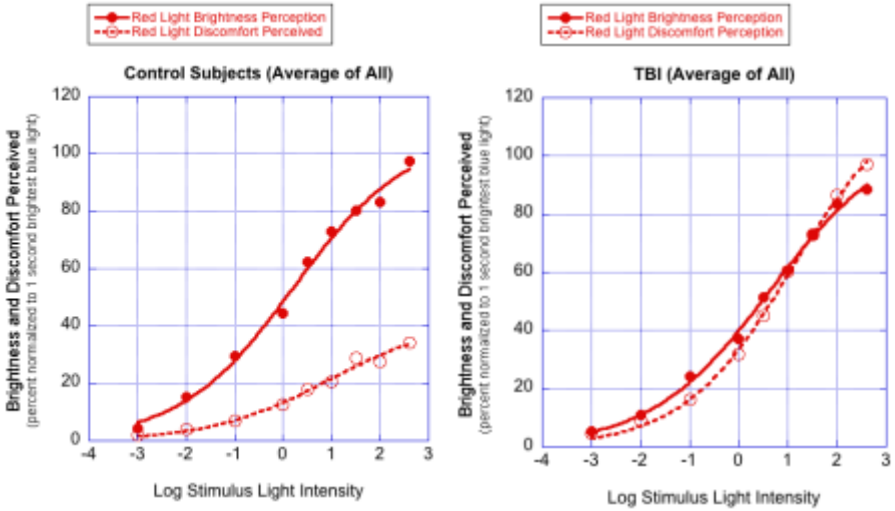
Brightness Sense vs Discomfort Magnitude of Estimation



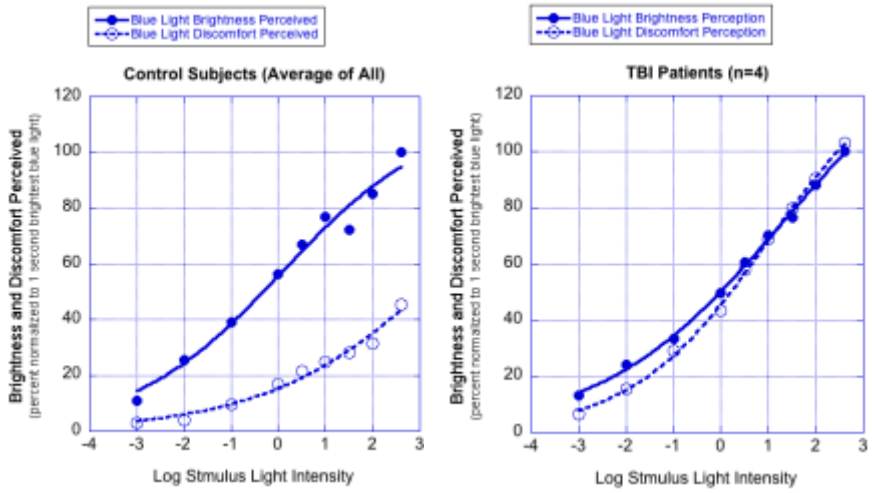
Brightness Sense vs Discomfort

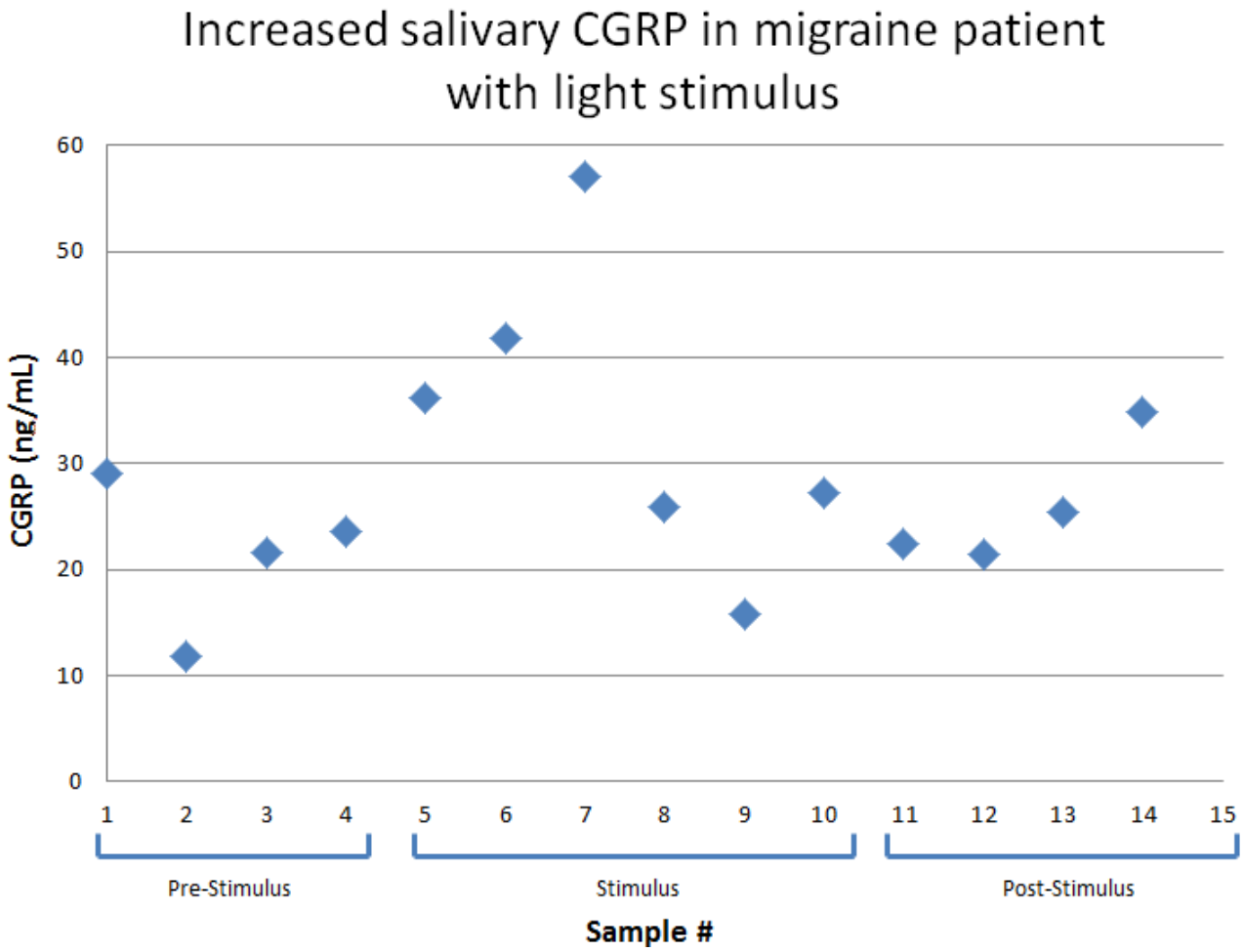
Normal vs TBI Patients

Red Light

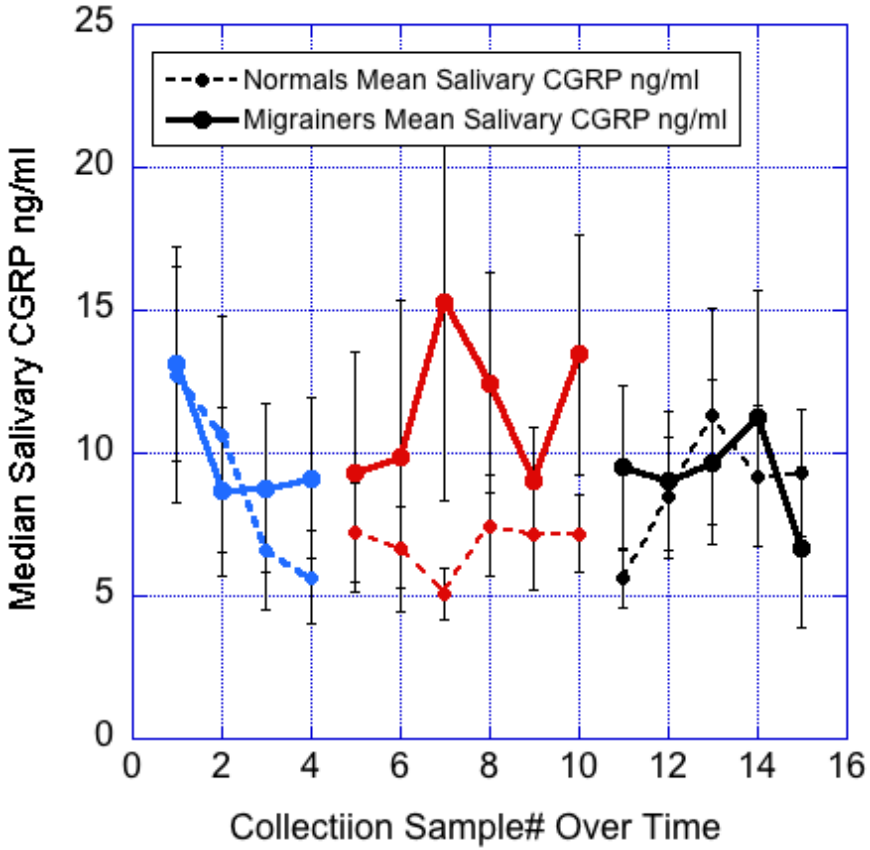


Blue Light

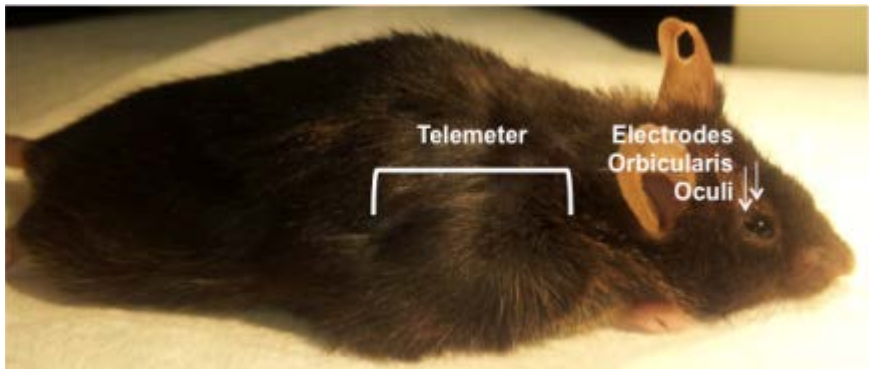


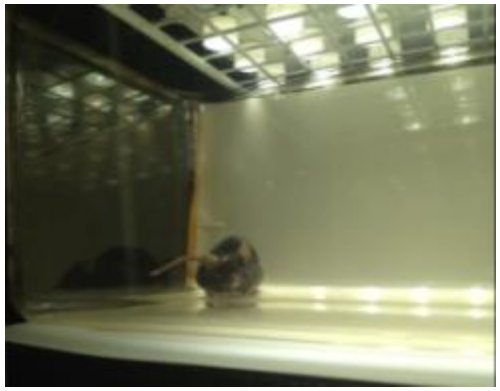

Increased salivary CGRP in migraine patient with light stimulus
CGRP (ng/mL)
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Pre-Stimulus
Stimulus
Post-Stimulus
Sample #

Salivary Calcitonin Gene Related Peptide (CGRP) Responses to Light

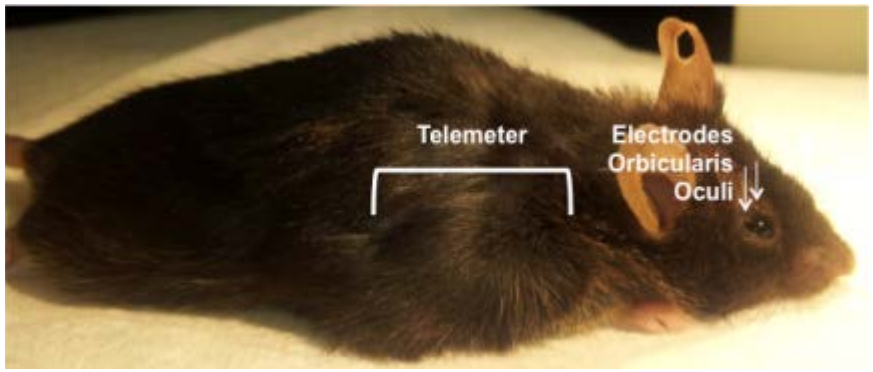


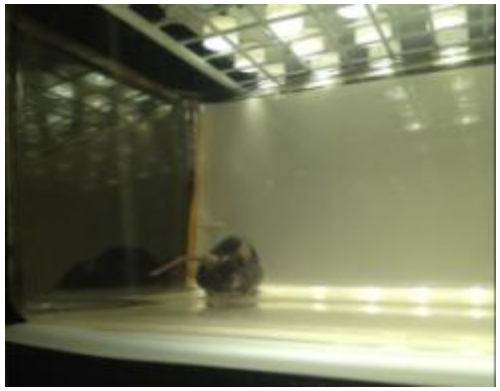
Photic-induced Orbicularis Oculi EMG Responses to Light and CGRP in Awake Mice



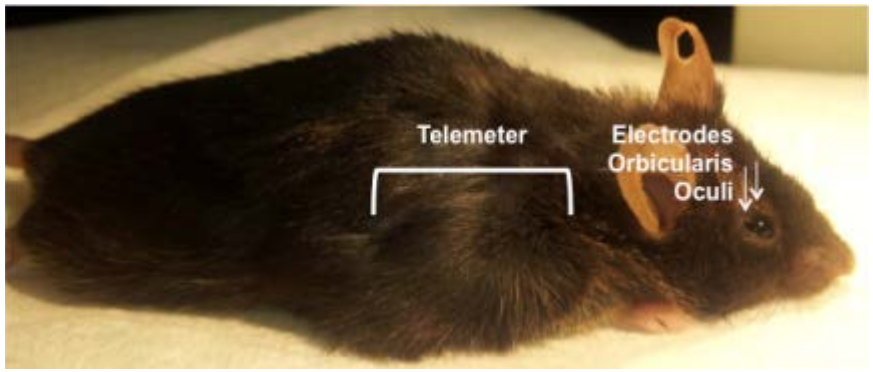


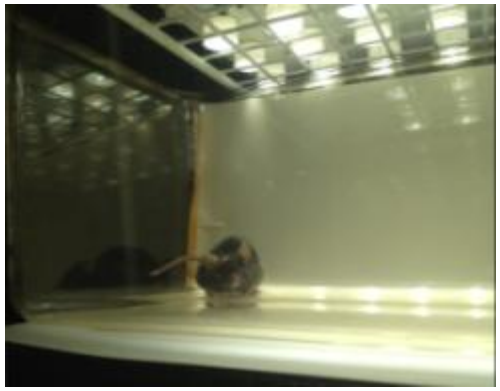
Photic-induced Orbicularis Oculi EMG Responses to Light and CGRP in Awake Mice



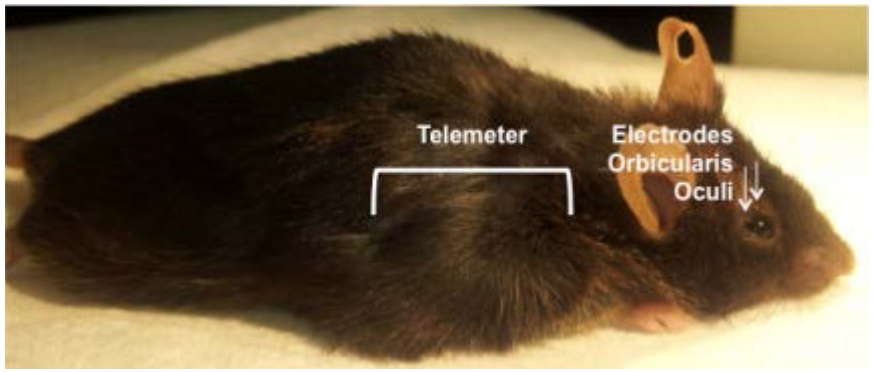


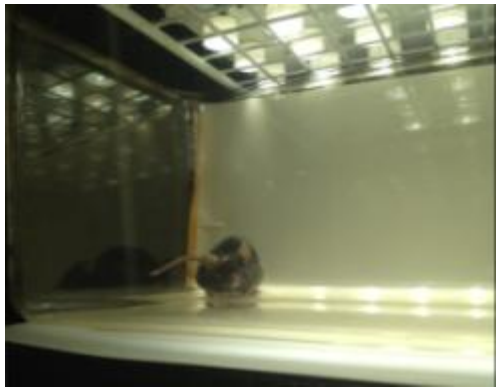
Photic-induced Orbicularis Oculi EMG Responses to Light and CGRP in Awake Mice

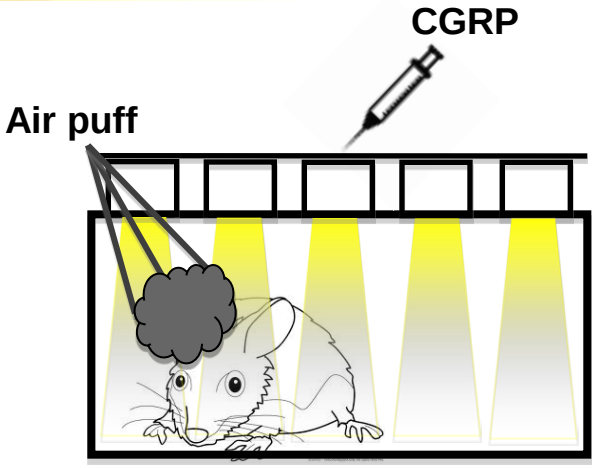




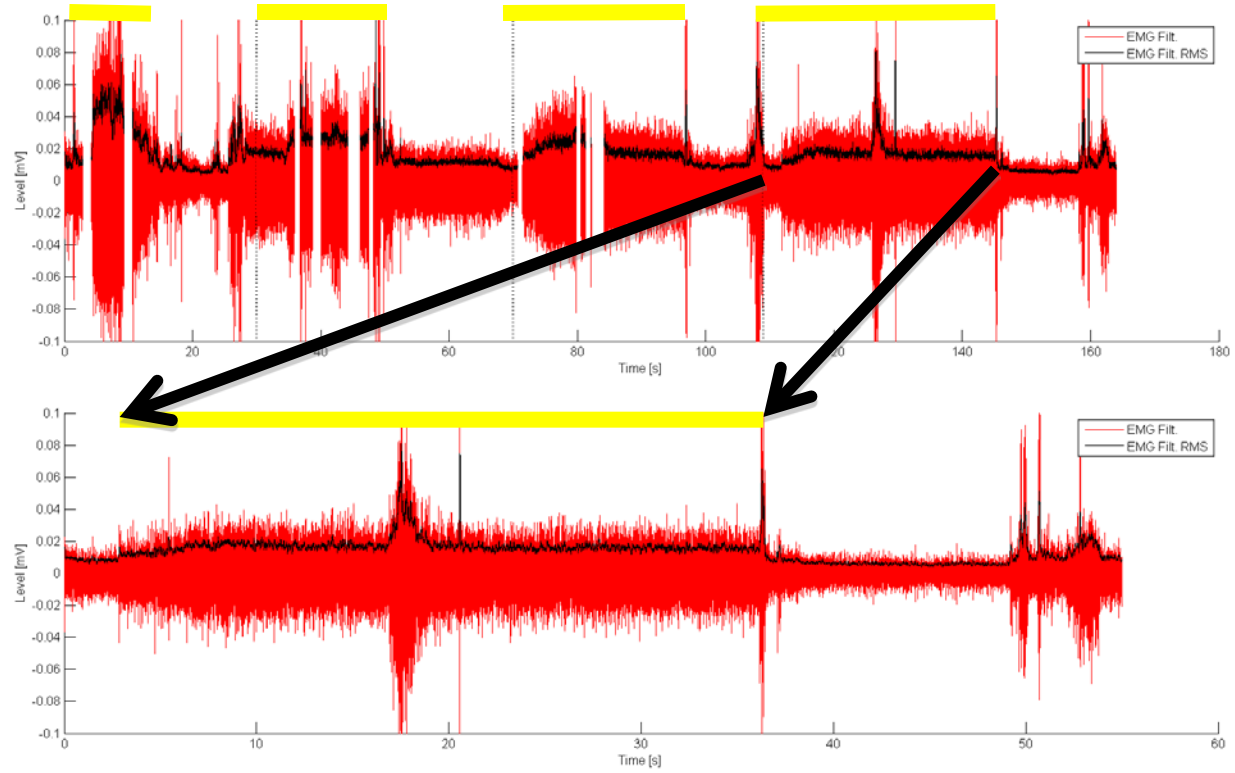
Photic-induced Orbicularis Oculi EMG Responses to Light and CGRP in Awake Mice



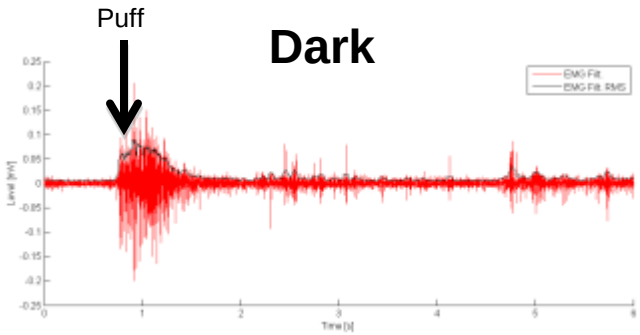


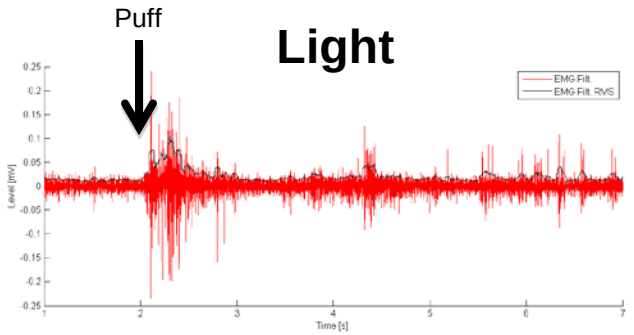


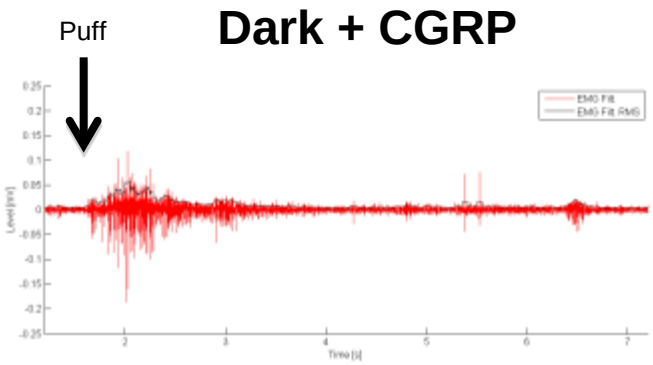
Exposure To Bright Light Increase Orbicularis Oculi EMG Activity in Chronically Implanted Mice

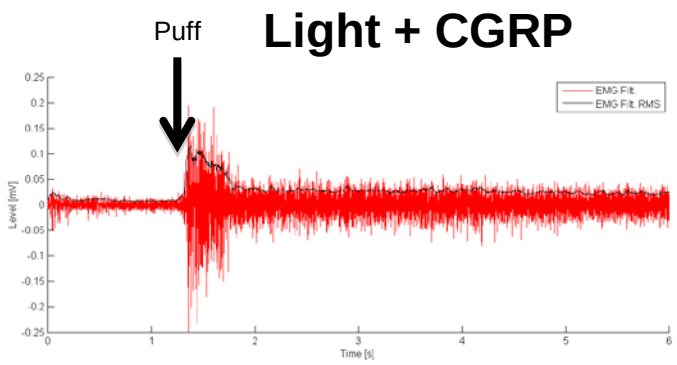


Air Puff Induced Blink Reflex:
Accentuation by Light and CGRP

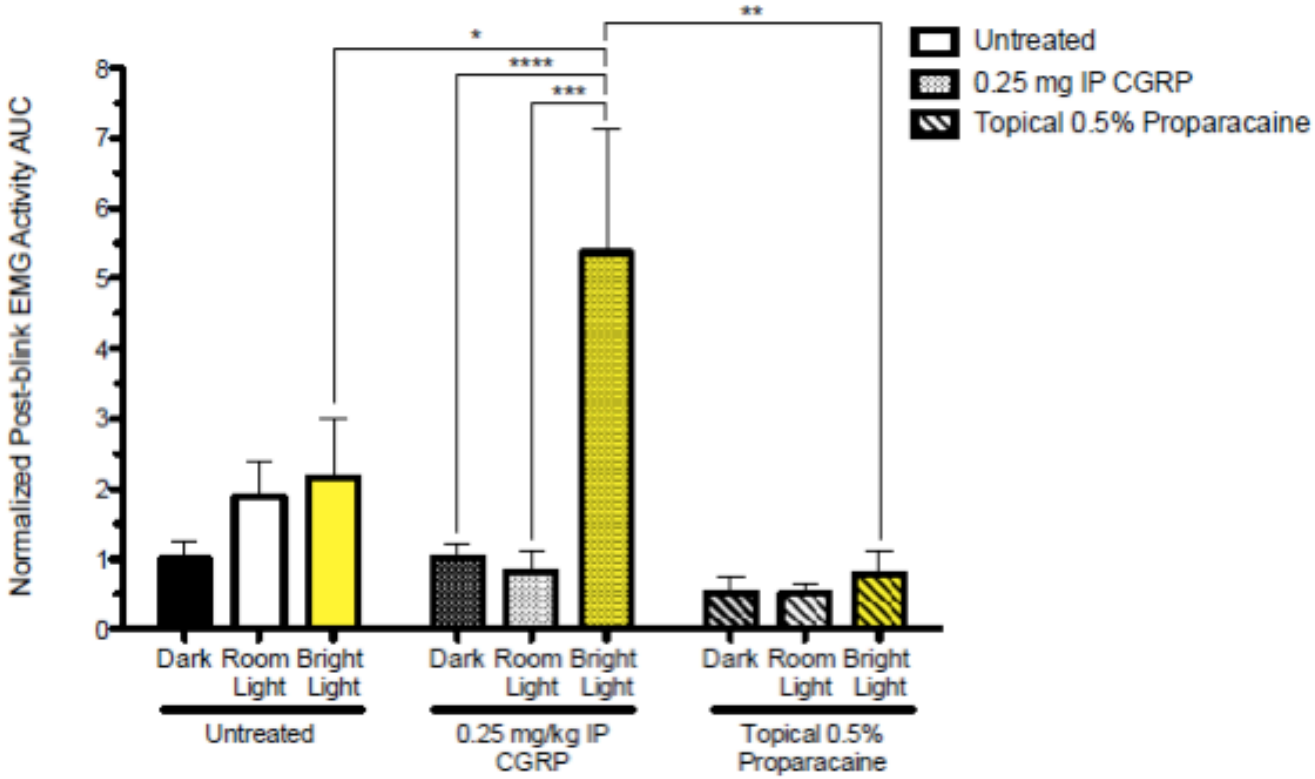




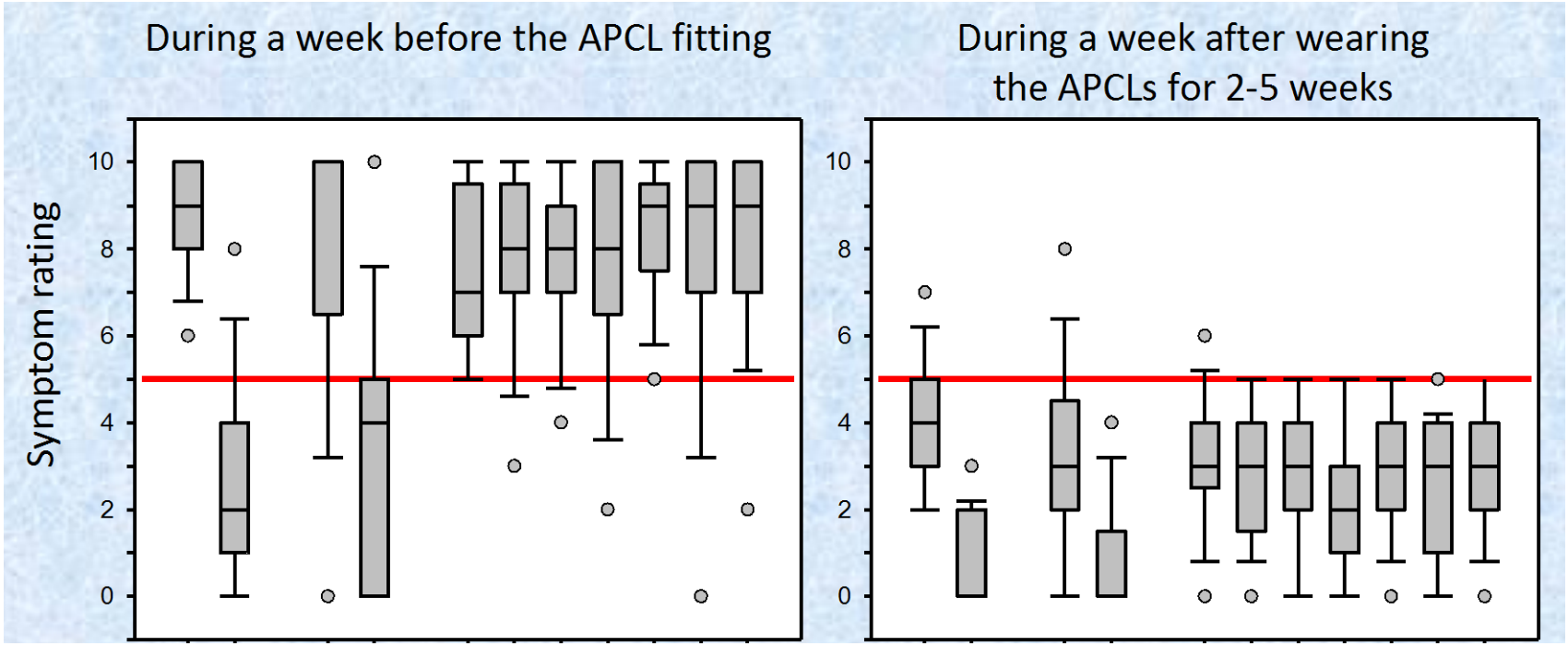




Air Puff Induced Blink Reflex:
Accentuation by Light and CGRP



Controlling Photophobia and Light-Induced Headache:
The Use of Artificial Pupil Contact Lenses



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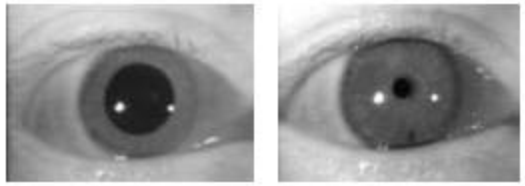
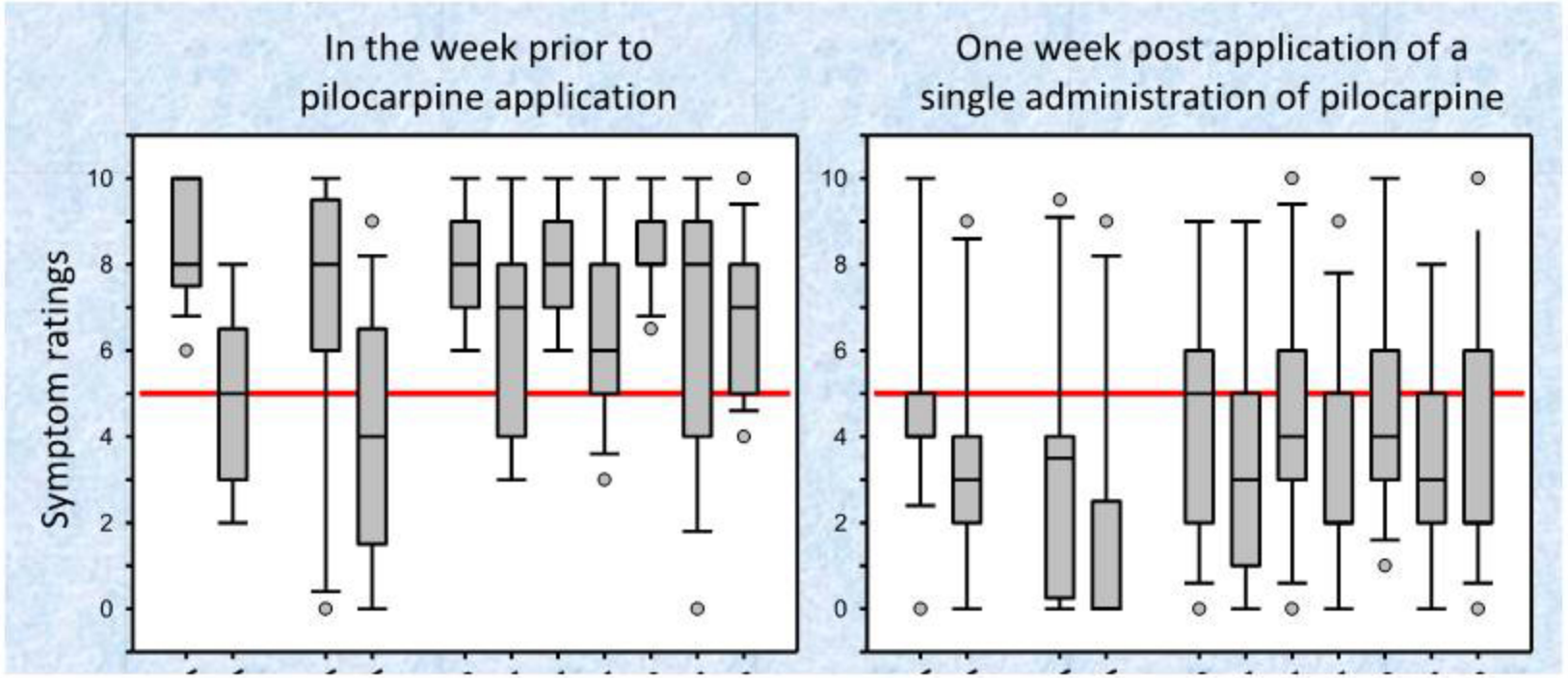


Photophobia and Light-Induced Headache:
Novel Long-Term Effects of Pilocarpine



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Poll Question 5

Which treatment do patients feel is most helpful?

- 1) dark sunglasses
- 2) orange colored sunglasses
- 3) blue colored sunglasses
- 4) contact lenses with artificial pupils
- 5) miotic eye drops
- 6) medications used to treat migraine
- 7) nothing seems to help significantly

Conclusions

- Physiological evidence is provided in humans that photic-EMG responses are exaggerated in photosensitive patients
- The photic-blink reflex may be mediated by melanopsin containing retinal ganglion cells (MCGs)
- MGCs likely provide input to the trigeminal sensory nucleus, which stimulates the facial nucleus, as evidenced by EMG responses of orbicularis and procerus muscles
- CGRP may mediate excessive trigeminal sensory activation
- Treatment Options: CGRP antagonists, blue blocking lenses, occlusive contact lenses, pilocarpine

Thank You!

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Iowa City VA Center of Excellence for the Prevention and Treatment of Visual Loss Website:

http://www.vision.research.va.gov/