

# Ocular Topical Anesthesia Does Not Attenuate Light-Induced Discomfort Using Blue and Red Light Stimuli

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Submitted: May 14, 2018

Accepted: August 22, 2018

Citation: Lei S, Zivcevska M, Goltz HC, Chen X, Wong AMF Ocular topical anesthesia does not attenuate light-induced discomfort using blue and red light stimuli. *Invest Ophthalmol Vis Sci.* 2018;59:4714–4719. <https://doi.org/10.1167/iovs.18-24797>

**PURPOSE.** To investigate whether melanopsin-containing ophthalmic trigeminal ganglion cells provide significant input to mediate light-induced discomfort. This is done by studying the effect of ocular topical anesthesia on light-induced discomfort threshold to blue light and red light stimuli using a psychophysical approach.

**METHOD.** Ten visually normal participants completed the experiment consisting of two trials: an anesthesia trial in which light stimuli were presented to both eyes following 0.5% proparacaine eye drops administration, and a placebo trial in which normal saline drops were used. In each trial, a randomized series of 280 blue and red light flashes were presented over seven intensity steps with 20 repetitions for each color and light intensity. Participants were instructed to report whether they perceived each stimulus as either “uncomfortably bright” or “not uncomfortably bright” by pressing a button. The proportion of “uncomfortable” responses was pooled to generate individual psychometric functions, from which 50% discomfort thresholds (defined as the light intensity at which the individuals perceived the stimulus to be uncomfortably bright/unpleasant 50% of the time) were calculated.

**RESULTS.** When blue light was presented, there was no significant difference in the light-induced discomfort thresholds between anesthesia and placebo trials ( $P = 0.44$ ). Similarly, when red light was used, no significant difference in threshold values was found between the anesthesia and placebo trials ( $P = 0.28$ ).

**CONCLUSIONS.** Ocular topical anesthesia does not alter the light-induced discomfort thresholds to either blue or red light, suggesting that the melanopsin-containing ophthalmic trigeminal ganglion cells provide little or no significant input in mediating light-induced discomfort under normal physiologic conditions.

**Keywords:** light-induced discomfort, photophobia, psychophysical test, melanopsin, topical anesthesia

The term “photophobia” (or “light sensitivity”) was broadly defined as a sensory state in which light causes or exacerbates discomfort in the eye or head. It can be further divided into two main categories: light aversion, unpleasant light exposure causing avoidance reaction without overt pain; and photo-oculodysnia, light-induced pain or exacerbation of pain in the eye.<sup>1</sup> Commonly seen in a wide spectrum of neurologic and ophthalmic disorders, including migraine, traumatic brain injury, corneal abrasion, keratitis, and uveitis,<sup>2</sup> photophobia is clinically important and yet its underlying neural mechanism is still poorly understood.

It is generally believed that photophobia is a result of photosensory input superimposed on the trigeminal nociceptive pathway.<sup>1</sup> There is a growing body of literature<sup>1,3-9</sup> suggesting that melanopsin, a blue light sensing photopigment (peak absorption wavelength = 478 nm<sup>10</sup>) that was found in the intrinsically photosensitive retinal ganglion cells (ipRGCs), may play a major role in transducing photosensory input for photophobia. IpRGCs are effectively a third class of retinal photoreceptor that gives rise to a range of visual and nonvisual photo responses including the pupillary light reflex and

circadian photo-entrainment.<sup>10-12</sup> Recently, a few mechanisms have been proposed that connect the ipRGC pathway to the trigeminal nociceptive pathway.<sup>5-9</sup> Most interestingly, melanopsin has also been found outside of the retina in a small subset of ophthalmic trigeminal ganglion cells (TGCs) in both mice and humans.<sup>3,4</sup> These cells have been localized predominantly in the ophthalmic (V1) area of the trigeminal ganglia.<sup>4</sup> Based on cellular morphology, melanopsin TGC fibers appear to be nociceptive C type fibers and/or mechanoreceptor A $\delta$  type fibers.<sup>13</sup> In mice, melanopsin mRNA expression has been found in trigeminal nerve fibers innervating corneal tissue.<sup>3</sup> The expression of melanopsin in human cornea has not yet been confirmed; however, it is a well-known feature that melanopsin-positive ganglion cells have diffused melanopsin expression over cell bodies, dendrites, and axons.<sup>14-16</sup> The presence of melanopsin-positive sensory neurons in the V1 area of trigeminal ganglia in humans suggests the possibility that melanopsin-positive trigeminal fibers may also be found in ocular tissues that receive trigeminal sensory innervation, including the conjunctival and cornea.



TABLE. Melanopic Illuminance of Chromatic Light Stimuli (Melanopic Lux)

<b>Blue light (cd/m<sup>2</sup>)</b>	<b>1.4</b>	<b>7.1</b>	<b>14.3</b>	<b>28.6</b>	<b>42.9</b>	<b>57.1</b>	<b>71.4</b>
Melanopic illuminance (melanopic lux)	13.27	67.31	135.56	271.13	406.69	541.31	676.87
<b>Red light (cd/m<sup>2</sup>)</b>	<b>1.5</b>	<b>19.1</b>	<b>38.2</b>	<b>57.3</b>	<b>76.3</b>	<b>152.7</b>	<b>305.3</b>
Melanopic illuminance (melanopic lux)	<0.01	0.04	0.08	0.11	0.15	0.31	0.61

The existence of melanopsin-containing trigeminal ganglion cells and nerve fibers provides a plausible mechanism for photophobia. Matynia et al.<sup>4</sup> found that melanopsin-containing TGCs are indeed photosensitive, supporting the hypothesis that melanopsin photoactivity can directly activate trigeminal nociceptive sensation. However, conflicting evidence has also emerged. Delwig et al.<sup>3</sup> demonstrated melanopsin expression in trigeminal nerve fibers in cornea of mice, yet they found no light-evoked activation of melanopsin-containing trigeminal nerve fibers in the cornea using electrophysiology recording and calcium imaging,<sup>3</sup> arguing against the role of melanopsin-containing ophthalmic TGCs in mediating photophobia. Collectively, the recent discovery of melanopsin expression in a subset of ophthalmic trigeminal ganglion cells raises an intriguing question as to whether these cells contribute to photophobia.

To provide in vivo evidence regarding the contribution of melanopsin-containing ophthalmic TGCs on photosensitivity, we investigated the effect of topical ophthalmic anesthesia on light-induced discomfort threshold in visually normal humans using a recently established psychometric test<sup>17</sup> during blue and red light stimulation. Previous studies have shown that melanopsin is expressed in the trigeminal fibers within the cornea, conjunctiva, iris, and ciliary body.<sup>1,3,4</sup> Among all ocular tissues that are innervated by trigeminal nerves, the cornea has the highest density of nociceptive sensors and it appears to be the primary destination of melanopsin-positive trigeminal fibers.<sup>18,19</sup> Therefore, topical administration of 0.5% proparacaine eye drops (a sodium channel blocker that is commonly used as topical anesthetic for intraocular pressure measurement,<sup>20</sup> and ocular surgeries such as phacoemulsification<sup>21</sup>) should significantly reduce the melanopsin-driven photoactivity within the trigeminal nociceptive pathway by blocking the voltage-gated sodium channels in the cell membrane responsible for propagation of depolarizing action potential. We hypothesize that if melanopsin-containing ophthalmic TGCs exhibit intrinsic photosensitivity significant enough to cause light-induced discomfort, topical anesthesia will: significantly increase the light-induced discomfort threshold to melanopsin-activating blue light by blocking the conjunctival and corneal trigeminal fiber action potential propagation, and have no effect on the light-induced discomfort threshold to melanopsin-silent red light. In contrast, if melanopsin-containing ophthalmic TGCs do not contribute significantly to light-induced discomfort, topical anesthesia will have no effect on the light-induced discomfort threshold to either blue or red light stimulation.

## METHODS

### Participants

Ten visually normal participants were included in this study (four female; mean age: 27.8 years of age; range, 22–60 years). All participants underwent ocular assessments by an ophthalmologist, including examinations of visual acuity (ETDRS), refractive error, color vision (Mollon-Reffin Minimal Color Vision Test), ocular motility, slit-lamp, and dilated fundus exam. Informed consent was collected from each participant. This

study was approved by the Research Board at The Hospital for Sick Children, Toronto, Canada. All study protocols adhered to the tenets of the Declaration of Helsinki.

### Experimental Conditions and Procedures

This experiment was a double-masked study, conducted on 2 separate days (at similar times during the day), testing the effect of 0.5% proparacaine (Alcon, Fort Worth, TX, USA), a topical anesthetic drop, on light-induced discomfort, relative to a placebo drop (balanced salt solution). The two drops were stored in identical bottles, labeled as drop A and drop B. During the first visit, participants received either drop A or drop B. During the second visit, the other drop was administered. The drop order was randomized across participants.

At the start of both visits, participants received bilateral application of 2.5% phenylephrine (Minims, Bausch & Lomb, Laval Quebec, Canada) to dilate the pupils. Dilating drops were used to control for pupillary size variability, which may affect the number of photons reaching the retina and thus the perceptual threshold across trials. About 40 to 60 minutes following the instillation of the dilating drops (or after complete dilation has been reached), either anesthetic (anesthesia trials) or placebo drops (placebo trials) were administered. Participants were then instructed to rest their head on a chinrest in front of a full-field Ganzfeld stimulator (Espion V5 system with the ColorDome LED full-field stimulator; Diagnosys LLC, Lowell, MA, USA) and look at an LED fixation point in the middle of the dome. The experiment was done in a quiet, darkened room. Participants received an initial 10-second presentation of dim white light (3 cd/m<sup>2</sup>) at the onset of each trial to ensure consistent light adaptation levels. The experiment comprised four 6-minute blocks. Each block included seven randomized light intensities of either blue light (peak wavelength: 470 nm, full width at half maximum: 31 nm, at seven intensities: 1.4, 7.1, 14.3, 28.6, 42.9, 57.1, 71.4 cd/m<sup>2</sup>) or red light (peak wavelength: 635 nm, full width at half maximum: 22 nm, at seven intensities: 1.5, 19.1, 38.2, 57.3, 76.3, 152.7, 305.3 cd/m<sup>2</sup>). The blue light was chosen to stimulate melanopsin activation while the red light was to serve as melanopsin-silent stimuli that induced very little melanopsin activities. Based on the spectral sensitivity of melanopsin, we calculated melanopic illuminance for both chromatic conditions across all intensity steps by using the method proposed by Lucas et al.,<sup>22</sup> and the values are reported in the Table.

Each light level was presented 10 times/block, 1-second duration, interspersed with 4-second intervals of dim white light (3 cd/m<sup>2</sup>) in between the color stimuli. The interstimulus white light presentation was included to give participants a break in between flashes, and to minimize sequential effects. The order of color stimuli presented was randomized across participants. Participants were instructed to assess each light intensity by pressing one of two buttons. If they perceived the light to be “uncomfortably bright/unpleasant,” they were required to press a button on their left. If they perceived the light to be “not uncomfortably bright/unpleasant,” they were required to press a button on their right. Between the same

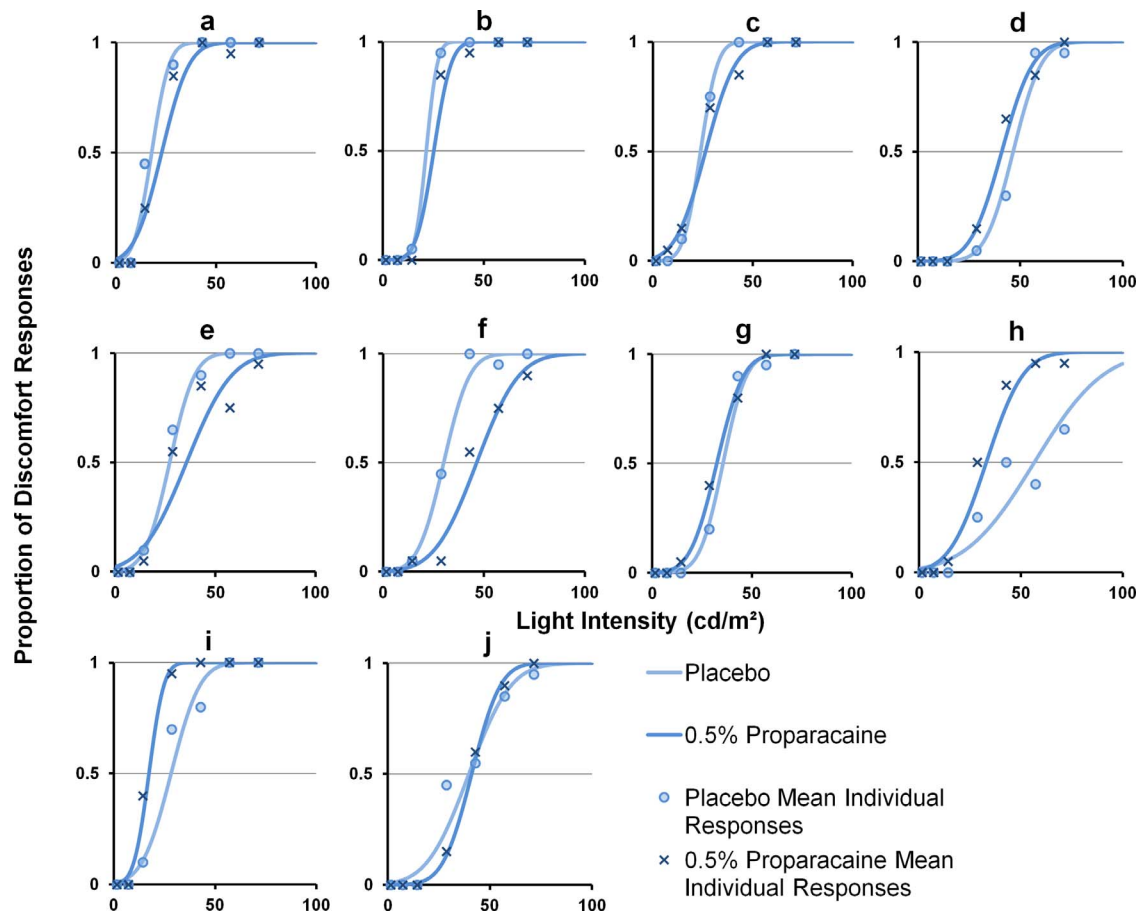


FIGURE 1. Proportion of discomfort responses of 10 visually-normal participants during blue light stimulation at various light intensity levels (1.4, 7.1, 14.3, 28.6, 42.9, 57.1, 71.4  $\text{cd}/\text{m}^2$ ) following administration of 0.5% proparacaine and placebo drops.

color blocks (i.e., blue following blue or red following red), participants were allotted a 1-minute break, and between red and blue blocks, participants were given a 5-minute break. The total experiment took 1.5 hours to complete (including dilation waiting time) for each day.

### Data Processing and Analysis

A custom-written script (MATLAB; MathWorks, Inc., Natick, MA, USA) was used to analyze button press responses for all participants. Each button press generated a “1” for perception of uncomfortably bright/unpleasant stimuli and a “0” for not uncomfortably bright/unpleasant perceptual experience. At each light intensity, the proportion of “1” responses were pooled together, and a cumulative normal distribution function was fit to the data points. Twenty random initial starting points were used for the curve fit to prevent the optimization from getting “stuck” at a local minimum, and the lowest fit error was used. Minimizing the negative log sum of the probability density function (for both observed and predicted values from the fitting function) allowed us to find the best values. From each individual psychometric function generated, the perceived discomfort threshold was found. This threshold was defined as the light intensity at which individuals perceived the stimulus to be uncomfortably bright/unpleasant 50% of the time.

Statistical analyses were performed on the discomfort threshold values using statistical software (SPSS 22.0; IBM Corporation, Armonk, NY, USA). Data distributions were inspected for normality with the Shapiro-Wilk test, where

50% discomfort thresholds were found to be normally distributed across all groups. Discomfort thresholds under the same light condition were compared between the anesthetic and placebo trials. Discomfort thresholds were also compared in the same drop trials between blue and red light stimuli conditions. The difference in discomfort thresholds between different testing conditions were compared by four one-tailed, paired sample *t*-tests with Bonferroni correction to adjust for multiple comparisons. A value of  $P < 0.0125$  was considered statistically significant.

### RESULTS

Psychometric response functions of each individual subject in the anesthetic and placebo trials are shown in Figure 1 during blue light stimulation and in Figure 2 during red light stimulation. When blue light was presented, there was no significant difference in light-induced discomfort thresholds between the anesthetic ( $\bar{x} = 32.07$ ,  $\sigma = 9.20$   $\text{cd}/\text{m}^2$ ) and placebo trials ( $\bar{x} = 32.65$ ,  $\sigma = 12.06$   $\text{cd}/\text{m}^2$ ;  $t_{(9)} = 0.17$ ,  $P = 0.44$ ,  $d = 0.05$ ; Figs. 3, 4A). Similarly, when red light was used, no significant difference in discomfort threshold values was found between anesthetic ( $\bar{x} = 106.67$ ,  $\sigma = 67.95$   $\text{cd}/\text{m}^2$ ) and placebo trials ( $\bar{x} = 109.48$ ,  $\sigma = 72.83$   $\text{cd}/\text{m}^2$ ;  $t_{(9)} = 0.28$ ,  $P = 0.39$ ,  $d = 0.09$ ; Figs. 3, 4B).

To determine if there is a color specific difference, we also compared the light-induced discomfort thresholds for the same drop condition, between the two different wavelengths of light. Blue light induced significantly greater discomfort (lower

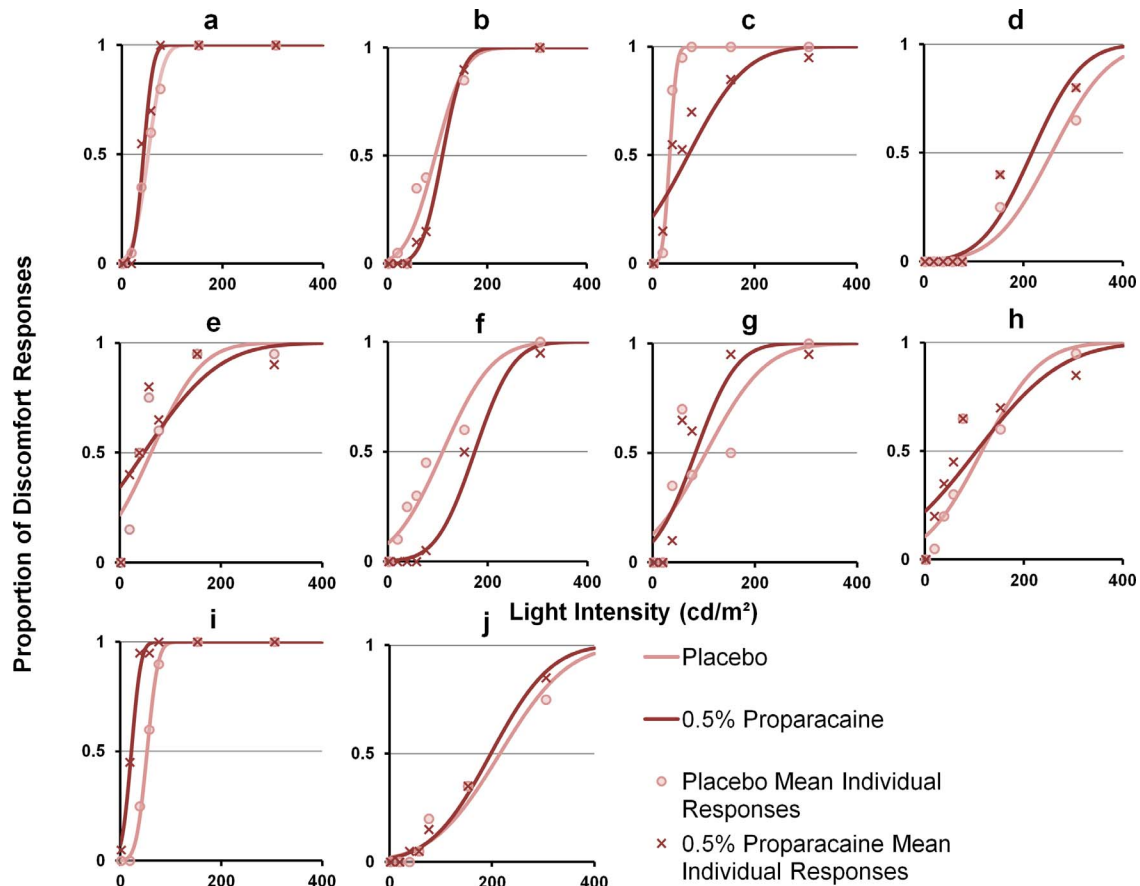


FIGURE 2. Proportion of discomfort responses of 10 visually-normal participants during red light stimulation at various light intensity levels (1.5, 19.1, 38.2, 57.3, 76.3, 152.7, 305.3 cd/m<sup>2</sup>) following administration of 0.5% proparacaine and placebo drops.

threshold) than red light in both anesthetic trials (for blue light:  $\bar{x} = 32.07$ ,  $\sigma = 9.20$  cd/m<sup>2</sup>, for red light:  $\bar{x} = 106.67$ ,  $\sigma = 67.95$  cd/m<sup>2</sup>;  $t_{(9)} = 3.89$ ,  $P = 0.002$ ,  $d = 1.23$ ) and Placebo Trials (for blue light:  $\bar{x} = 32.65$ ,  $\sigma = 12.06$  cd/m<sup>2</sup>, for red light:  $\bar{x} = 109.48$ ,  $\sigma = 72.83$  cd/m<sup>2</sup>;  $t_{(9)} = 3.70$ ,  $P = 0.0025$ ,  $d = 1.16$ ).

Responses showed considerably greater variability for red light stimuli (Figs. 3, 4). To compare the variability across the two light stimuli, the inter-subject coefficients of variation (CV) for the discomfort thresholds were calculated. The CVs of discomfort thresholds generated under blue light stimulation

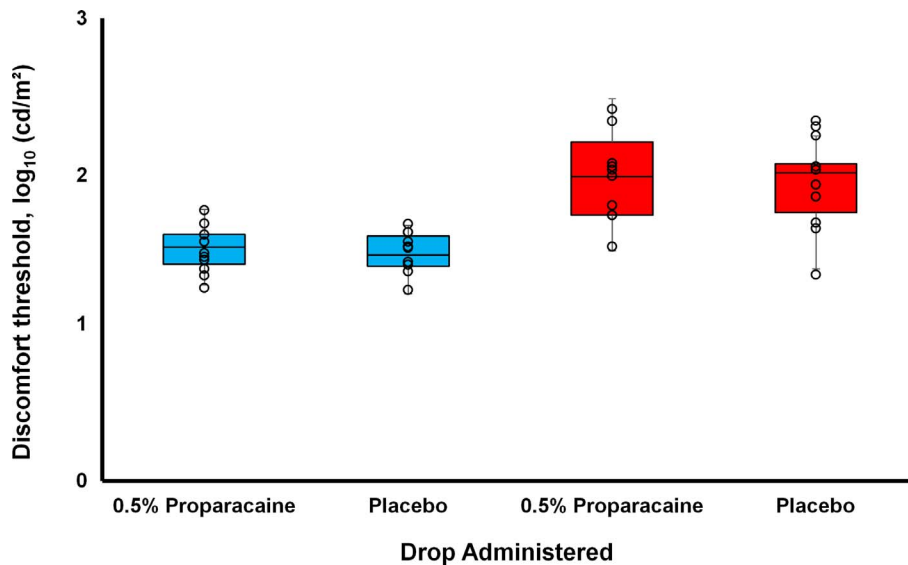


FIGURE 3. Discomfort thresholds generated from individual psychometric fitting for 10 visually normal participants during anesthetic (0.5% proparacaine) and placebo trials for both blue and red light conditions. Individual values are plotted and represented as circles in the figure. The data are shown in log<sub>10</sub> units.



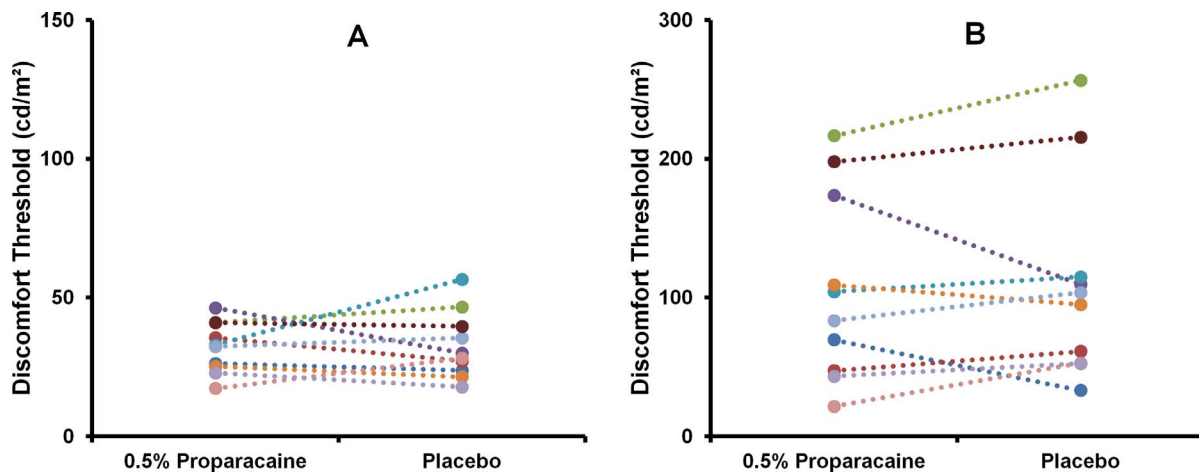


FIGURE 4. The relation of the individual discomfort threshold values between anesthetic (0.5% proparacaine) and placebo trials using (A) blue light stimuli and (B) red light stimuli.

(anesthetic trials = 28.70%, placebo trials = 36.93%) were lower than those under red light stimulation (anesthetic trials = 67.95%, placebo trials = 72.83%) irrespective of the drop administered, suggesting that blue light is a more effective stimulus for inducing light discomfort.

## DISCUSSION

The main goal of current study is to investigate whether the melanopsin-containing ophthalmic TGCs contribute to light-induced discomfort in visually normal participants. We hypothesized that if trigeminal nerve fibers on ocular surface (conjunctiva and cornea) provide melanopsin-dependent photosensitive light sensory input, the administration of topical anesthesia will attenuate light-induced discomfort to melanopsin-activating blue light by blocking the signal transduction of melanopsin-containing ganglion fibers on the ocular surface. Our results showed that blue light induced significantly greater discomfort than red light across the anesthesia and placebo trials, consistent with characteristics of a melanopsin-mediated photoactivity. However, and importantly, ocular anesthesia did not produce any attenuating effect on light-induced discomfort under blue (or red) light stimulation. These results indicate that melanopsin-containing ophthalmic TGCs do not provide significant nociceptive light sensory input that is great enough to cause discomfort under normal physiologic condition.

A plausible explanation for the lack of attenuating effect of topical anesthesia on light-induced discomfort in our experiment is that the melanopsin-containing trigeminal nerve fibers are not pain sensors; therefore, the melanopsin-mediated photoactivity of these fibers do not cause discomfort or pain. Considering the fact the melanopsin-mediated photoactivity gives rise to a wide range of visual and nonvisual biologic photo responses (e.g., circadian rhythm),<sup>10,11,15,23–26</sup> we can further speculate a few other possibilities regarding the functions of melanopsin in TGCs. First, in one of our previous studies,<sup>27</sup> we demonstrated that light-induced tear production is mediated by melanopsin photoactivity. It appears that the light-induced tearing is mainly mediated by ipRGCs in the retina<sup>27</sup>; however, we cannot rule out the possibility that the melanopsin-containing ophthalmic TGCs are also involved in mediating the light-induced tear production via a local loop that is independent of nociceptive perception. Second, Sikka et al.<sup>28</sup> demonstrated melanopsin expression in the aorta and tail vessels of rats. They showed that melanopsin photoactivity

elicited vessel relaxation in surgically isolated ex vivo aorta ring and evoked vessel constriction in the tail of rats. In the eye, choroidal blood flow is regulated by melanopsin-driven photoactivity of ipRGCs.<sup>8,29</sup> It is possible that the melanopsin-containing TGCs may similarly play a role in regulating blood flow to the ocular surface or the anterior part of the eyeball. Third, it has been shown that melanopsin can effectively function as a temperature sensing protein rather than a light-sensing photopigment in *Drosophila* larvae.<sup>30</sup> In the initial study by Matynia et al.<sup>4</sup> on melanopsin-containing TGCs, they demonstrated intrinsic photosensitivity of these cells using whole cell patch clamp and calcium imaging. However, in a subsequent study by Delwig et al.,<sup>3</sup> they were unable to record photo responses using similar technique. Delwig et al.<sup>3</sup> proposed that melanopsin might serve other sensory function in the cornea, in a similar way whereby melanopsin functions as a temperature sensor in *Drosophila* photoreceptor. Given the above conflicting findings regarding the intrinsic photosensitivity of melanopsin-containing TGC, the lack of an attenuating effect of ocular topical anesthesia on light-induced discomfort in our study is in keeping with the notion that melanopsin-containing ophthalmic TGCs may not be intrinsically photosensitive and may serve other functions.

Our study was conducted on a group of visually healthy participants without pathologic photophobic disorder; therefore, the findings of the current study do not rule out the possibility that melanopsin-containing ophthalmic TGCs may play a role in photophobia under pathologic conditions. In the study by Matynia et al.,<sup>4</sup> after demonstrating the intrinsic photosensitivity of melanopsin-positive trigeminal fibers, they further demonstrated that optic nerve transection (a procedure that cut off retinal photosensory input, leaving the melanopsin-containing trigeminal ganglion cells as the only alternative photosensory input to the brain) completely diminished the avoidance reaction to light in normal mice. However, if these mice were pretreated with nitroglycerin to induce a migraine model, avoidance reaction to light was present even after optic nerve transection, suggesting that the reaction to trigeminal melanopsin sensory input was boosted by nitroglycerin. Amini et al.<sup>31</sup> reported a case of a 68-year-old woman with invasive pituitary adenoma who underwent multiple resections and radiation therapy. The patient had no light perception nor any pupillary reaction to light in either eye, yet she was severely photophobic. Loh et al.<sup>32</sup> reported a patient with progressive optic nerve glioma requiring bony orbital decompression, optic nerve transection, and tumor resection. Postoperatively,

the patient developed ocular ischemia, eye pain, and severe photophobia. The authors of the above-mentioned studies speculated that under extreme pathologic conditions, trigeminal pathway may become an alternative route to carry photo signal for photophobia. However, it is worth noting that the animal study by Matynia et al.<sup>4</sup> may not represent human conditions and that the clinical cases of photophobia in patients with optic nerve transection are exceedingly rare (there was no direct evidence that their optic nerves were indeed completely transected). Therefore, the intrinsic photosensitivity of melanopsin-containing TGCs causing photophobia in pathologic conditions remains a speculation at this point of time.

In summary, the lack of attenuating effect of topical anesthesia on light-induced discomfort during blue and red light stimulation in visually healthy participants suggest that melanopsin-containing ophthalmic TGCs have little or no significant photosensory input to light-induced discomfort in normal physiological conditions. Whether or not the melanopsin-containing ophthalmic TGCs are indeed intrinsically photosensitive, and whether these cells contribute to photophobia in pathological conditions warrant further investigation.

### Acknowledgments

Supported by the Canada Foundation for Innovation, John and Melinda Thompson Endowment Fund for Vision Neuroscience, and the Department of Ophthalmology and Vision Sciences at The Hospital for Sick Children.

Disclosure: **S. Lei**, None; **M. Zivcevska**, None; **H.C. Goltz**, None; **X. Chen**, None; **A.M.F. Wong**, None

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