A Novel Visual Psychometric Test for Light-Induced Discomfort Using Red and Blue Light Stimuli Under Binocular and Monocular Viewing Conditions

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Purpose. To develop an objective psychophysical method to quantify light-induced visual discomfort, and to measure the effects of viewing condition and stimulus wavelength.

Methods. Eleven visually normal subjects participated in the study. Their pupils were dilated (2.5% phenylephrine) before the experiment. A Ganzfeld system presented either red (1.5, 19.1, 38.2, 57.3, 76.3, 152.7, 305.3 cd/m^2) or blue (1.4, 7.1, 14.3, 28.6, 42.9, 57.1, 71.4 cd/m^2) randomized light intensities (1 s each) in four blocks. Constant white-light stimuli (3 cd/m^2, 4 s duration) were interleaved with the chromatic trials. Participants reported each stimulus as either "uncomfortably bright" or "not uncomfortably bright." The experiment was done binocularly and monocularly in separate sessions, and the order of color/viewing condition sequence was randomized across participants. The proportion of "uncomfortable" responses was used to generate individual psychometric functions, from which 50% discomfort thresholds were calculated.

Results. Light-induced discomfort was higher under blue compared with red light stimulation, both during binocular ($t_{(10)} = 3.58$, $P < 0.01$) and monocular viewing ($t_{(10)} = 3.15$, $P = 0.01$). There was also a significant difference in discomfort between viewing conditions, with binocular viewing inducing more discomfort than monocular viewing for blue ($P < 0.001$), but not for red light stimulation.

Conclusions. The light-induced discomfort characteristics reported here are consistent with features of the melanopsin-containing intrinsically photosensitive retinal ganglion cell light irradiance pathway, which may mediate photophobia, a prominent feature in many clinical disorders. This is the first psychometric assessment designed around melanopsin spectral properties that can be customized further to assess photophobia in different clinical populations.

Keywords: melanopsin, photophobia, light-induced discomfort, psychophysical test

Photophobia is a sensory state of light-induced ocular or cranial discomfort, and/or subsequent tearing and squinting.[1] A common symptom of several neurological and ophthalmic disorders, including migraine, traumatic brain injury, blepharospasm, and dry eye, photophobia can lead to severe impairment in everyday life.[1–3] Visually normal individuals also experience a similar phenomenon when stepping into a brightly lit environment, especially after being in a dark room for a period of time. Because photophobia may present heterogeneously both in visually normal and diverse clinical populations,[4,5] adopting a "one-size-fits-all" definition is likely oversimplifying a complex phenomenon, the underlying mechanisms of which remain poorly understood and require further investigation. In this study, we use the term "visual discomfort" to refer to light sensitivity experienced by the visually normal population, and "photophobia" to describe light sensitivity associated with pathology.

Recent literature shows that in addition to mediating unconscious nonvisual photoresponses, such as circadian rhythm entrainment and the pupillary light reflex,[6–8] the melanopsin-containing intrinsically photosensitive retinal ganglion cell (ipRGC) light irradiance pathway plays a critical role in transducing light information into a painful percept.[1,9–16] This is supported by several lines of evidence. First, animal studies report light-aversive behaviors in neonatal rodents before rod/cone development, but an absence of these behaviors in melanopsin knockout mice.[17,18] Second, ipRGC photoactivity has a higher activation threshold and unique photon-tracking ability that allows continuous coding of ambient light irradiance levels without fatigue.[19] The ipRGC pathway is therefore best positioned to code potentially irritating or damaging high-irradiance light stimuli. Third, short-wavelength blue light has been reported to induce the most visual discomfort,[20–23] whereas blue-filtering lenses have been reported to reduce the symptom in patients with photophobia.[2,24,25] Furthermore, the action spec-

trum for visual discomfort and that for ipRGCs (~480 nm, blue light)[6,8] are remarkably similar.[23] Fourth, ipRGCs project directly to pain centers in the posterior thalamus where afferent retinal inputs converge with the trigeminal nociceptive pathway.[9,10] Collectively, there is accumulating evidence showing that the ipRGC pathway is the primary transducer of photophobia.[14] In addition, binocular viewing has been reported to induce greater visual discomfort following broad-spectrum light than monocular viewing conditions.[26–29] Interestingly, greater melanopsin response is evident when a larger retinal area is stimulated,[30,31] suggesting that greater melanopsin activity also may be seen when both eyes are stimulated simultaneously. Together, this suggests that photophobia may be a perceptually summated phenomenon mediated by the melanopsin response.

Currently available diagnostic tools for photophobia are largely restricted to self-reports and questionnaires.[1,32] Because these are subjective evaluations, they are limited by many factors, including patients' mood, general state of health, and language and/or culture differences, and thus may have reduced generalizability and applicability across populations. An objective assessment tool for photophobia is important not just for diagnosis, but also to monitor changes over time and evaluate treatment efficacy. Several efforts have been made toward the development of objective techniques using involuntary light-induced behavioral responses, such as squinting[22,33] and lacrimation,[15] as markers for photophobia. These physiologic behavioral indices, however, can be invasive, are often not closely aligned with the clinical complaint of photophobia, and may not be useful in quantifying light sensitivity for individuals with aberrant blink responses (e.g., as seen in benign essential blepharospasm) and aberrant lacrimal responses (e.g., as seen in dry eye syndrome).[14] Interestingly, Stringham and colleagues[22] reported a high correlation between psychophysical rating scales and physiologic blinking electromyography (EMG) paradigms, suggesting that psychophysical measures can be used reliably to assess photophobia thresholds.[34] Objective psychophysical assessments[35] may thus be better suited to capture the perceptual experience of visual discomfort. However, past psychophysical studies have largely predated the discovery of the melanopsin system and thus did not account for its properties in their methodological design.[21,27–29,36–40] For example, retinal response features differ with stimulus wavelength,[41] and given the photon-counting feature of the ipRGC system (namely a sustained pupillary constriction that persists after stimulus offset[6]), a preexposure bias likely exists, particularly in studies that evaluate chromatic responses separately.[21,42] In addition, variable pupil diameter across trials may have altered the proportion of photons that reach the retina, thus two different light intensities may have elicited a similar perceptual experience and biased the discomfort thresholds generated. More recent studies have adapted earlier psychophysical protocols and are faced with similar challenges.[2,22,23,33,34,42–44]

As a first step in quantifying pathological photophobia, we developed a psychophysical tool to quantify light-induced discomfort in visually normal participants. By incorporating the latest information on the ipRGC pathway characteristics, we examined the effects of stimulus wavelength (blue versus red light) and viewing condition (monocular versus binocular) on light-induced discomfort. To control for pupillary size variability, which may affect the number of photons reaching the retina and thus the perceptual threshold, we dilated participants' pupils pharmacologically before the experiments. Based on the spectral properties of melanopsin, we hypothesized that visually normal participants will experience the greatest light-induced discomfort under blue light stimuli and binocular viewing conditions.

Methods

Participants

Eleven visually normal subjects (five females; mean age 25 years; range 22–31 years) participated in this study. Participants were examined by an ophthalmologist, including tests for visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] Chart), refractive error, color vision (Mollon-Reffin Minimal Color Vision Test), ocular motility, slit-lamp, and dilated fundus examinations. Informed consent was obtained from each participant. None of the participants had any history of visual disorders, photophobia, or migraine. The study was approved by the Research Ethics Board at The Hospital for Sick Children, Toronto, Canada. All study protocols adhered to the guidelines of the Declaration of Helsinki.

Experimental Conditions and Procedure

The experiment was conducted on two separate days to minimize adaptation. Light-induced discomfort was evaluated under two viewing conditions: monocular and binocular. Under monocular viewing conditions, one eye was occluded with an eye patch. Both the order of viewing condition and eye patching were randomized across participants and conducted at approximately the same time of day for each subject.

Phenylephrine 2.5% dilating eye drops (Minims; Bausch & Lomb, Laval, Quebec, Canada) were instilled bilaterally 40 to 60 minutes (or until fully dilated) before starting the experiment in both testing sessions. This was to ensure consistent retinal stimulation both within and across trials. Once both eyes were dilated, participants were seated in a quiet darkened room, in front of a Ganzfeld stimulator (Espion V5 system with the ColorDome light-emitting diode [LED] full-field stimulator; Diagnosys LLC, Lowell, MA, USA) with their head supported on a chin rest. Blue (peak wavelength: 470 nm, full width at half maximum: 31 nm) and red (peak wavelength: 635 nm, full width at half maximum: 22 nm) light stimuli were used. The light stimuli were separated into four monochromatic blocks of equal duration and the order of color presentation was randomized. To prevent fatigue and cross-color effects, participants were given a 1-minute break between same-colored light blocks (red-red or blue-blue) and a 5-minute break between red and blue light blocks.

We used the psychophysical method of constant stimuli to assess the perceptual response because it allows full sampling of the psychometric function from which 50% thresholds can be calculated directly (see below). At the start of each block, 10 seconds of dim white light (3 cd/m^2) was presented by the Ganzfeld system as preexposure to standardize initial light-adaptation levels across participants and to reduce potential rod contribution. At 15 seconds after block onset, seven different light intensities (1-second duration each) of either red (1.5, 19.1, 38.2, 57.3, 76.3, 152.7, 305.3 cd/m^2) or blue (1.4, 7.1, 14.3, 28.6, 42.9, 57.1, 71.4 cd/m^2) light were presented and interspersed with dim white light (3 cd/m^2, 4-second duration) between the chromatic trials (to serve as break periods and to prevent dark adaptation). To make the test more easily tolerated, we also reduced stimulus duration by 50%, while increasing the break period by 50% relative to previous psychophysical experimental designs.[28,29,40]

Consistent with previous reports in visually normal observers,[20,22,23] our pilot analysis showed that participants were less sensitive to red light stimulation; therefore, the chosen intensities were higher under red light conditions. This allowed us to generate visual sensitivity data that could be fitted reliably with a psychometric function, sampling the full range from 0 to 1 in the proportion of responses, and thus

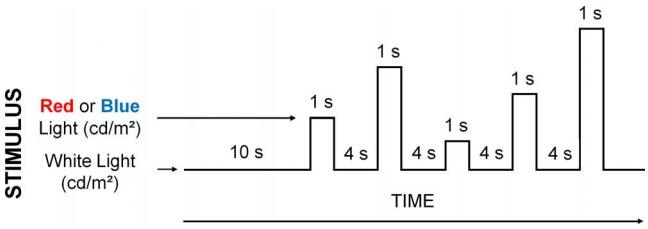

FIGURE 1. Stimulation paradigm (randomized method of constant stimuli) for the visual discomfort assessment. Each monochromatic block presented 1 second of either red (1.5, 19.1, 38.2, 57.3, 76.3, 152.7, 305.3 cd/m^2) or blue (1.4, 7.1, 14.3, 28.6, 42.9, 57.1, 71.4 cd/m^2) randomized light stimuli. To minimize adaptation and give participants a break, 4 seconds of dim white light (3 cd/m^2) was interleaved with the chromatic stimuli. Participants were given a 1-minute break between same-colored blocks (red-red or blue-blue) and a 5-minute break following red-blue blocks. After each light stimulus, participants were asked to report their perception of the light intensity by pressing one of two buttons.

capture the full light-sensitivity function for each light-stimulus condition. Each participant received a different randomized sequence of light intensities for each block to reduce potential habituation and anticipatory errors[35] (see Fig. 1 for more information). In total, each light-intensity level was presented 20 times per testing session. Participants indicated whether they experienced discomfort following the presentation of the light stimuli. If participants felt that the stimulus was "uncomfortably bright/unpleasant," they were instructed to press a button on their left. If they felt that the light was "not uncomfortably bright/unpleasant," they were instructed to press a button on their right (see Fig. 2 for more information). Stimulus presentation was controlled by supplying text files containing stimulus timing, wavelength, and intensity commands to the proprietary Espion software. The Espion system produced a digital transistor-transistor logic (TTL) output at stimulus onset that was read by a second computer. This second computer recorded the button-press responses using custom button-press hardware and software via the parallel port of the computer.

Data Processing and Analysis

The button-press responses were analyzed offline with a custom-written script (MatLab; MathWorks, Inc., Natick, MA, USA). The responses were binary: "1" for uncomfortably bright/unpleasant or "0" for no discomfort. The proportion of uncomfortably bright responses was collected for each light intensity and collectively were fit with a cumulative normal distribution function with two parameters: the mean (bias) and the standard deviation (slope). To ensure that the optimization did not get trapped at a local minimum, the fitting was performed using 20 random initial starting points (from 0–150 cd/m^2), and the fit with the smallest error was used. The best-fit values were found by minimizing the negative log sum of the probability density function for the observed values and the predicted values from the fitting function.[45] The perceived discomfort threshold was defined as the interpolated stimulus intensity at which the chromatic light stimulus was deemed to be uncomfortably bright/unpleasant 50% of the time (bias) from the individually fitted psychometric functions. The data were visually inspected on an individual basis to ensure data quality and the goodness of fit of the psychometric curves generated. For discomfort thresholds, smaller values represented greater light sensitivity.

Statistical analyses were performed on the 50% threshold values using SPSS 22.0 (IBM Corporation, Armonk, NY, USA). The differences in discomfort thresholds between the viewing conditions were compared using four two-tailed paired sample *t*-tests. Bonferroni correction was used to compensate for multiple comparisons and, accordingly, a value of $P < 0.0125$ was considered statistically significant.

RESULTS

The individual psychometric curves used to calculate the 50% light discomfort thresholds for all 11 visually normal participants are shown in Figure 3. These data were found to be normally distributed (Shapiro-Wilk test, $P > 0.05$) across all conditions (monocular blue, monocular red, binocular blue, and binocular red), justifying the use of paired samples *t*-tests for comparisons. Figure 4 shows the mean threshold values in response to binocular and monocular viewing conditions for the two chromatic stimuli. Qualitatively, both figures show more consistent responses under blue light stimulation, for both monocular and binocular viewing.

Influence of Wavelength on Light Sensitivity

To determine if there was a wavelength-specific effect, we compared the discomfort thresholds between blue and red stimuli separately for binocular and monocular viewing conditions. For binocular viewing, light sensitivity was higher (lower discomfort threshold) under blue light stimulation ($\bar{x} = 30.59$, $\sigma = 10.62$ cd/m^2) as compared with red light stimulation ($\bar{x} = 106.68$, $\sigma = 79.74$ cd/m^2); a statistically significant increase of 76.10 cd/m^2 (95% confidence interval [CI] 28.68–123.52 cd/m^2; $t_{(10)} = 3.58$, $P < 0.01$, $d = 1.08$). The same pattern was observed under monocular conditions. Light sensitivity was higher (lower discomfort threshold) under blue light stimulation ($\bar{x} = 43.43$, $\sigma = 13.59$ cd/m^2) than red light stimulation ($\bar{x} = 121.73$, $\sigma = 93.58$ cd/m^2); a statistically significant increase of 78.29 cd/m^2 (95% CI 22.87–133.71 cd/m^2; $t_{(10)} = 3.15$, $P = 0.01$, $d = 0.95$).

Figure 4 shows considerably greater variability for responses generated in response to red light stimulation. To inspect the variability across the two stimulus wavelengths, the intersubject coefficients of variation (CV) for the discomfort thresholds were compared. The CV was lower under blue light stimulation than during red light stimulation for both binocular ($CV_{blue\ \&\ binocular} = 34.72\%$ versus $CV_{red\ \&\ binocular} = 74.74\%$) and monocular ($CV_{blue\ \&\ monocular} = 31.30\%$ versus $CV_{red\ \&\ monocular} = 76.88\%$) viewing conditions, suggesting that blue light is a more effective stimulus for inducing visual discomfort consistently in visually normal participants.

Influence of Viewing Condition on Light Discomfort

Viewing condition (binocular versus monocular viewing) had an effect on light sensitivity for blue, but not red light. For blue light stimulation, light sensitivity was higher (lower discomfort threshold) for binocular viewing ($\bar{x} = 30.59$, $\sigma = 10.62$ cd/m^2) than monocular viewing ($\bar{x} = 43.43$, $\sigma = 13.59$ cd/m^2) conditions; a statistically significant increase of 12.85 cd/m^2 (95% CI 7.70–18.00 cd/m^2; $t_{(10)} = 5.6$, $P < 0.001$, $d = 1.68$). In contrast, during red light stimulation, light sensitivity did not differ statistically for binocular ($\bar{x} = 106.68$, $\sigma = 79.74$ cd/m^2) and monocular viewing ($\bar{x} = 121.73$, $\sigma = 93.58$ cd/m^2) with a difference of 15.04 cd/m^2 (95% CI –0.37 to 30.44; $t_{(10)} = 2.18$, $P = 0.06$, $d = 0.66$).

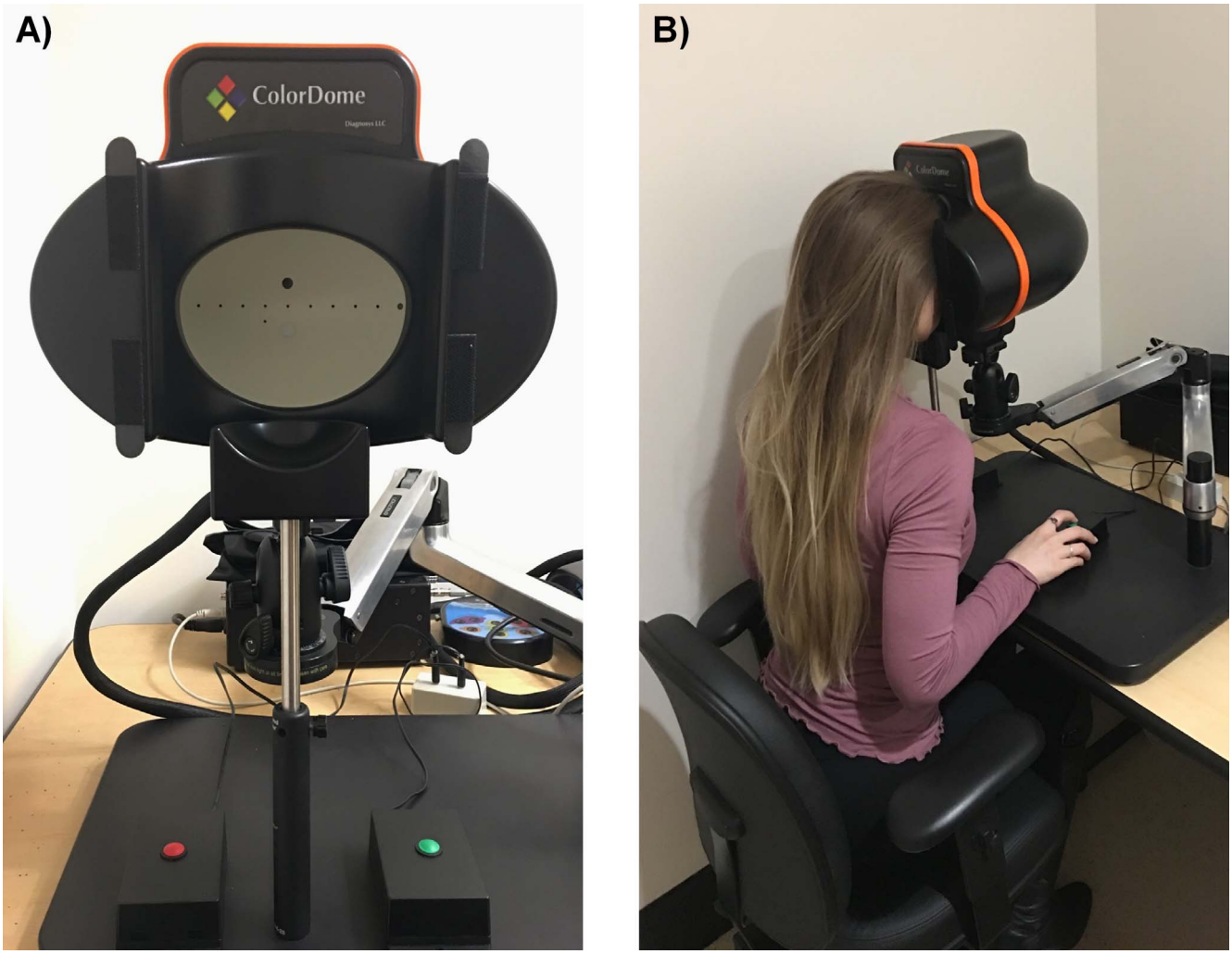

FIGURE 2. (A) ColorDome Stimulator with an LED fixation target and two press buttons used to evaluate the light stimuli. (B) In each trial, light perception was reported by pressing the button on the left if the light stimulus was "uncomfortably bright/unpleasant," and the button on the right if the light stimulus was "not uncomfortably bright/unpleasant."

DISCUSSION

The mechanisms underlying photophobia have been investigated intensely over recent years, with considerable evidence suggesting that the melanopsin-mediated ipRGC pathway is involved in transduction of photophobia signals.[1,9–16] Clinically, however, there are no objective assessment tools to quantify this perceptual phenomenon, particularly in the context of currently known properties of the melanopsin pathway. We have designed a psychophysical assessment tool to measure light-induced discomfort using a commercially available Ganzfeld stimulator and a basic button press apparatus. By using a randomized presentation of melanopsin-active blue light stimulation and melanopsin-silent red light stimulation, the involvement of the melanopsin-containing ipRGC pathway in light-induced discomfort is quantified.

The first major finding of this study is that blue light induced greater light sensitivity (lower discomfort threshold) than red light stimulation for both binocular and monocular viewing conditions. Past psychophysical studies have largely used the method of ascending limits to evaluate light sensitivity in both normal and clinical populations, using either broad-spectrum light[2,27–29,36–38,40,43] or variable-wavelength stimulation[21–23,33,34,42] presented incrementally in a stepwise fashion until visual discomfort was reported. Their paradigms were limited by potentially significant levels of habituation, which may lead to overestimation of the actual absolute threshold value, as well as anticipation errors, which may result in underestimation of the actual absolute threshold value.[35] In this study, we used the method of constant stimuli and a randomized sequence of blue and red light intensities to reduce potential habituation and anticipatory errors. Our finding is consistent with previous reports indicating that short-wavelength blue light generates more perceptual discomfort in comparison with long or medium wavelengths of light in visually normal[20,22,23] and clinical populations,[21] and correlates with the peak spectral sensitivity of melanopsin.[6] Our results are also consistent with studies that show alleviation of photophobia symptoms when patients with migraine[25] and benign essential blepharospasm[2,24] were fitted with tinted lenses that filter out blue light.

A second major finding from the current study is that under binocular viewing conditions, there was significantly greater light-induced discomfort for blue light than for red light stimuli. Given that the melanopsin irradiance pathway is a photon-tracking system that continually detects light in the environ-

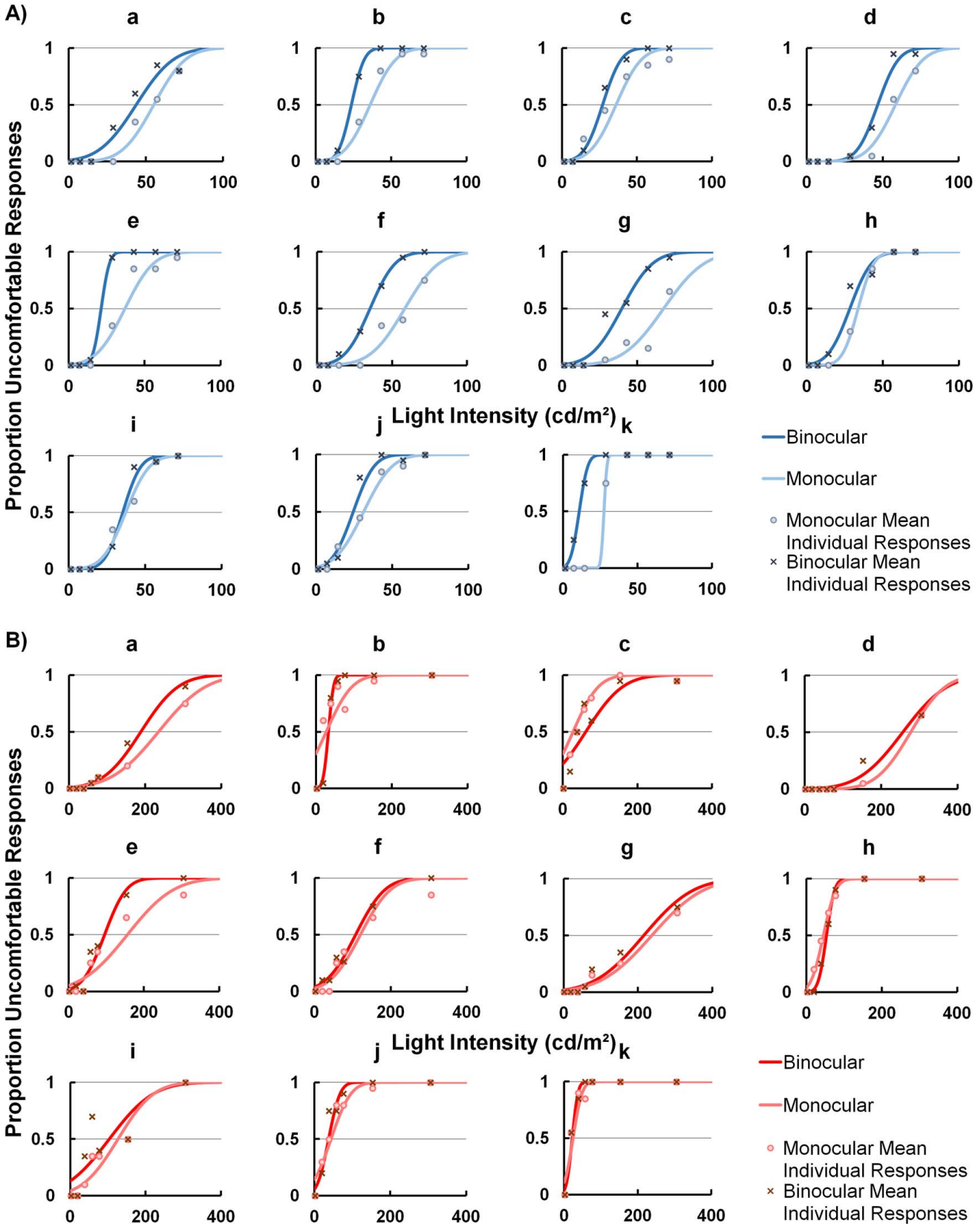

FIGURE 3. Proportion of "visually uncomfortable" responses in relation to each individual light intensity presented under both blue (**A**) and red (**B**) light stimulation for 11 visually normal participants (**a**–**k**). The relation between the monocular and binocular viewing conditions is represented by the difference between those two curves. A leftward shift in the psychometric function represents greater light sensitivity. The discomfort threshold for each individual participant was defined by interpolating light intensity at which the participant found the stimulus to be uncomfortably bright/unpleasant 50% of the time, which was used for statistical analysis. Overall, there is a leftward shift in the binocular condition for blue light only, indicating an increase in light sensitivity (lower discomfort threshold).

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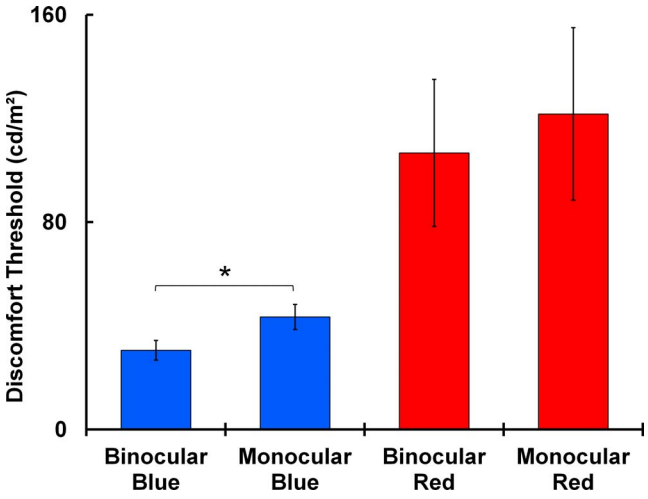

FIGURE 4. Mean discomfort thresholds generated from individual psychometric fits for 11 visually normal participants under blue light stimulation and red light stimulation, for both binocular and monocular viewing conditions. Lower values represent greater light sensitivity. *Error bars* represent 95% confidence intervals. *Asterisk* indicates statistical significance ($P < 0.0125$).

ment,[19] with activity proportional to the retinal area stimulated,[30,31] it is not surprising that melanopsin-active blue light stimuli would induce greater perceptual discomfort than melanopsin-silent red light stimuli. Nevertheless, one recent study reported no significant difference in light-induced perceptual discomfort between monocular and binocular viewing conditions in visually normal observers.[44] We speculate that the discrepancy between their finding[44] and ours may be due to inadequate retinal stimulation, particularly in the context of the melanopsin system. Although Verriotto and colleagues[44] used an improved methodological design whereby stimuli were presented in a staircase fashion, thus limiting habituation and anticipation errors, an LED panel positioned 50 cm from the eye was used to present white-light stimuli. This light source is not ideal because (1) it is not optimized for melanopsin activation (which is selectively sensitive to bright blue light), and (2) it does not fully stimulate the entire retinal field; the distance of the light source from the eye may have led to stimulus intensity loss and scatter, and given the mostly even distribution of ipRGCs across the human retina,[19] much of the periphery may have not been stimulated. Other photophobia studies that predated the discovery of melanopsin have reported greater light sensitivity (lower threshold) under binocular viewing conditions following broad-spectrum light presentation in both normal and clinical populations.[26–29] Our study is the first to demonstrate a wavelength-dependent perceptual difference in binocular versus monocular light-induced discomfort.

We found that the psychometric response curves computed following red light stimulation show shallower slopes for both viewing conditions and greater intersubject variability in discomfort thresholds relative to responses generated under blue light stimulation. This suggests that blue light may be a more effective and potentially clinically relevant stimulus for producing light-induced discomfort. Collectively, our findings further support the involvement of the melanopsin pathway in the perception of light sensitivity, and represent an initial step in evaluating the utility of this assessment tool for clinical populations.

Previous psychophysical studies[2,21–23,28,29,33,34,36–40,42–44] have not used pharmacological mydriasis. Wirtschafter and Bourassa[27] investigated the effect of dilation on discomfort thresholds in a small subset of their participants (6 of 76 participants), but this experimental manipulation was not applied to their entire sample of participants. Stimulus-dependent pupillary responses[19,30] can alter the baseline pupil diameter, and thus may alter the retinal stimulation both within and between trials. In this way, two identical light intensities may elicit a different perceptual response, based on their sequential testing order and the preceding intensity level. Increasing the time interval between light exposures is perhaps another way to standardize pupil diameter across trials, but it will increase the total testing time significantly, rendering the approach less patient-friendly. In addition, because pupil diameter is a physiological marker of autonomic system activity,[46] prolonged testing time may lead to artifacts as a result of changes in emotional state,[47,48] lapses in attention,[49] and mental fatigue.[50] Instillation of dilation drops inherently makes participants more light sensitive, but this is necessary to control for other confounders in the experimental setting. Our study is the first to use mydriasis in the experimental design to control for variation in retinal stimulation both within and between test trials and thus offers a less biased perceptual evaluation of each light stimulus.

The ability of our assessment tool to quantify light-induced discomfort in the context of the melanopsin system is of considerable utility and may be of significant clinical relevance. In addition to its objectivity, our protocol is highly customizable. It can be scaled to fit the perceptual dynamic range of the population of interest (e.g., stimulus intensity, duration, wavelength, and retinal area stimulated can be altered easily), and has the potential to generate a photophobia gradient, which can be used to identify clinical versus subclinical populations and stratify photophobia based on etiology. This might be useful for the population of migraineurs, because preliminary results suggest subgroup differences in photophobia severity between probable, episodic, and chronic migraineurs.[43]

In summary, our study adds further support that light-induced discomfort in visually normal observers is an ipRGC-mediated phenomenon. We have designed a novel assessment tool as the first step toward developing a photophobia biomarker that may hold promise in refining diagnosis and revealing subgroup differences in clinical populations. This tool also may offer a way to assess photophobia treatments over time, including the efficacy of tinted lenses (e.g., FL-41) and botulinum neurotoxin in mitigating light sensitivity.[32] Future studies are needed to compare our objective psychophysical measures with existing photophobia assessment protocols to determine whether our test is better able to capture the perceptual response.

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References

1. Digre KB, Brennan KC. Shedding light on photophobia. *J Neuroophthalmol*. 2012;32:68–81.
2. Adams WH, Digre KB, Patel BC, Anderson RL, Warner JE, Katz BJ. The evaluation of light sensitivity in benign essential blepharospasm. *Am J Ophthalmol*. 2006;142:82–87.e8.

3. Llop SM, Frandsen JE, Digre KB, et al. Increased prevalence of depression and anxiety in patients with migraine and interictal photophobia. *J Headache Pain* 2016;17:34.
4. Ahn AH, Brennan K. Unanswered questions in headache: so what is photophobia, anyway? *Headache*. 2013;53:1673–1674.
5. Noseda R. Unanswered questions in headache: so what is photophobia, anyway? *Headache*. 2013;53:1679–1680.
6. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science*. 2002;295:1070–1073.
7. Hattar S, Liao H-W, Takao M, Berson DM, Yau K-W. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science*. 2002;295:1065–1070.
8. Gamlin PD, McDougal DH, Pokorny J, Smith VC, Yau K-W, Dacey DM. Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells. *Vision Res*. 2007;47:946–954.
9. Noseda R, Kainz V, Jakubowski M, et al. A neural mechanism for exacerbation of headache by light. *Nat Neurosci*. 2010;13:239–245.
10. Noseda R, Constandil L, Bourgeais L, Chalus M, Villanueva L. Changes of meningeal excitability mediated by corticotrigeminal networks: a link for the endogenous modulation of migraine pain. *J Neurosci*. 2010;30:14420–14429.
11. Okamoto K, Tashiro A, Chang Z, Bereiter DA. Bright light activates a trigeminal nociceptive pathway. *Pain*. 2010;149:235–242.
12. Noseda R, Burstein R. Advances in understanding the mechanisms of migraine-type photophobia. *Curr Opin Neurol*. 2011;24:197–202.
13. Okamoto K, Tashiro A, Thompson R, Nishida Y, Bereiter DA. Trigeminal interpolaris/caudalis transition neurons mediate reflex lacrimation evoked by bright light in the rat. *Eur J Neurosci*. 2012;36:3492–3499.
14. Katz BJ, Digre KB. Diagnosis, pathophysiology, and treatment of photophobia. *Surv Ophthalmol*. 2016;61:466–477.
15. Lei S, Goltz HC, Chen X, Zivcevska M, Wong AM. The relation between light-induced lacrimation and the melanopsin-driven postillumination pupil response light-induced lacrimation and PIPR. *Invest Ophthalmol Vis Sci*. 2017;58:1449–1454.
16. Ksendzovsky A, Pomeraniec IJ, Zaghloul KA, Provencio JJ, Provencio I. Clinical implications of the melanopsin-based non–image-forming visual system. *Neurology*. 2017;88:1282–1290.
17. Johnson J, Wu V, Donovan M, et al. Melanopsin-dependent light avoidance in neonatal mice. *Proc Natl Acad Sci U S A*. 2010;107:17374–17378.
18. Delwig A, Logan AM, Copenhagen DR, Ahn AH. Light evokes melanopsin-dependent vocalization and neural activation associated with aversive experience in neonatal mice. *PLoS One*. 2012;7:e43787.
19. Dacey DM, Liao H-W, Peterson BB, et al. Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature*. 2005;433:749–754.
20. Flannagan MJ, Sivak M, Ensing M, Simmons C. Effect of wavelength on discomfort glare from monochromatic sources. In: *Tech Rep UMTRI-89-30*. Ann Arbor, Michigan: University of Michigan Transportantion Research Institute; 1989:1–20.
21. Main A, Vlachonikolis I, Dowson A. The wavelength of light causing photophobia in migraine and tension-type headache between attacks. *Headache*. 2000;40:194–199.
22. Stringham JM, Fuld K, Wenzel AJ. Action spectrum for photophobia. *J Opt Soc Am A Opt Image Sci Vis*. 2003;20:1852–1858.
23. Stringham JM, Snodderly DM. Enhancing performance while avoiding damage: a contribution of macular pigment. *Invest Ophthalmol Vis Sci*. 2013;54:6298–6306.
24. Blackburn MK, Lamb RD, Digre KB, et al. FL-41 tint improves blink frequency, light sensitivity, and functional limitations in patients with benign essential blepharospasm. *Ophthalmology*. 2009;116:997–1001.
25. Hoggan RN, Subhash A, Blair S, et al. Thin-film optical notch filter spectacle coatings for the treatment of migraine and photophobia. *J Clin Neurosci*. 2016;28:71–76.
26. Siegwart K. Zur Frage nach dem Vorkommen und dem Wesen des Blendungsschmerzes. *Schweiz Med Wochenschr*. 1920;50:1165–1169.
27. Wirtschafter JD, Bourassa CM. Binocular facilitation of discomfort with high luminances. *Arch Ophthalmol*. 1966;75:683–688.
28. Vanagaite J, Pareja J, Støren O, White L, Sanc T, Stovner L. Light-induced discomfort and pain in migraine. *Cephalalgia*. 1997;17:733–741.
29. Vanagaite Vingen J, Stovner L. Photophobia and phonophobia in tension-type and cervicogenic headache. *Cephalalgia*. 1998;18:313–318.
30. Lei S, Goltz HC, Chandrakumar M, Wong AM. Full-field chromatic pupillometry for the assessment of the postillumination pupil response driven by melanopsin-containing retinal ganglion cells. *Invest Ophthalmol Vis Sci*. 2014;55:4496–4503.
31. Lei S, Goltz HC, Chandrakumar M, Wong AM. Test–retest reliability of hemifield, central-field, and full-field chromatic pupillometry for assessing the function of melanopsin-containing retinal ganglion cells. *Invest Ophthalmol Vis Sci*. 2015;56:1267–1273.
32. Wu Y, Hallett M. Photophobia in neurologic disorders. *Transl Neurodegener*. 2017;6:26.
33. Stringham JM, Fuld K, Wenzel AJ. Spatial properties of photophobia. *Invest Ophthalmol Vis Sci*. 2004;45:3838–3848.
34. Wenzel AJ, Fuld K, Stringham JM, Curran-Celentano J. Macular pigment optical density and photophobia light threshold. *Vision Res*. 2006;46:4615–4622.
35. Grondin S. Psychophysics. In: *Psychology of Perception*. Cham, Switzerland: Springer; 2016:1–15.
36. Drummond PD, Woodhouse A. Painful stimulation of the forehead increases photophobia in migraine sufferers. *Cephalalgia*. 1993;13:321–324.
37. Woodhouse A, Drummond PD. Mechanisms of increased sensitivity to noise and light in migraine headache. *Cephalalgia*. 1993;13:417–421.
38. Main A, Dowson A, Gross M. Photophobia and phonophobia in migraineurs between attacks. *Headache*. 1997;37:492–495.
39. Drummond PD. Photophobia and autonomic responses to facial pain in migraine. *Brain*. 1997;120:1857–1864.
40. Kowacs P, Piovesan E, Werneck L, et al. Influence of intense light stimulation on trigeminal and cervical pain perception thresholds. *Cephalalgia*. 2001;21:184–188.
41. Lobato-Rincón L-L, del Carmen Cabanillas-Campos M, Bonnin-Arias C, Chamorro-Gutiérrez E, Murciano-Cespedosa A, Roda CS-R. Pupillary behavior in relation to wavelength and age. *Front in Hum Neurosci*. 2014;8:221.
42. Noseda R, Bernstein CA, Nir R-R, et al. Migraine photophobia originating in cone-driven retinal pathways. *Brain*. 2016;139:1971–1986.
43. Cortez MM, Rea NA, Hunter LA, Digre KB, Brennan K. Altered pupillary light response scales with disease severity in migrainous photophobia. *Cephalalgia*. 2016;37:801–811.
44. Verriotto JD, Gonzalez A, Aguilar MC, et al. New methods for quantification of visual photosensitivity threshold and symptoms. *Trans Vis Sci Tech*. 2017;6(4):18.

Investigative Ophthalmology & Visual Science

45. Lu Z-L, Dosher B. Data analysis and modeling. In: *Visual Psychophysics: From Laboratory to Theory*. Cambridge, MA: The MIT Press; 2014:301–349.
46. Beatty J, Lucero-Wagoner B. The pupillary system. In: Cacioppo JT, Tassinary LG, Berntson GG, eds. *Handbook of Psychophysiology*. Cambridge, MA: Cambridge University Press; 2000:142–162.
47. Partala T, Surakka V. Pupil size variation as an indication of affective processing. *Int J Hum Comput Stud*. 2003;59:185–198.
48. Bradley MM, Miccoli L, Escrig MA, Lang PJ. The pupil as a measure of emotional arousal and autonomic activation. *Psychophysiology*. 2008;45:602–607.
49. Unsworth N, Robison MK. Pupillary correlates of lapses of sustained attention. *Cogn Affect Behav Neurosci*. 2016;16:601–615.
50. Hopstaken JF, Linden D, Bakker AB, Kompier MA. A multifaceted investigation of the link between mental fatigue and task disengagement. *Psychophysiology*. 2015;52:305–315.

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