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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Submitted: December 1, 2017
Accepted: February 7, 2018
Citation: Zivcevska M, Lei S, Blakeman A, Goltz HC, Wong AMF. A novel visual psychometric test for light-induced discomfort, and to measure the effects of viewing condition and stimulus wavelength.

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/m²) or blue (1.4, 7.1, 14.3, 28.6, 42.9, 57.1, 71.4 cd/m²) randomized light intensities (1 s each) in four blocks. Constant white-light stimuli (3 cd/m², 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.22,23,25 Furthermore, the action spec-
Novel Psychophysical Light-Induced Discomfort Test

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: 655 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/m²) 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/m²) or blue (1.4, 7.1, 14.3, 28.6, 42.9, 57.1, 71.4 cd/m²) light were presented and interspersed with dim white light (5 cd/m², 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.

Consistent with previous reports in visually normal observers,20,22,25 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
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.\(^5\) (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.\(^5\) 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.

**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 (\(\bar{x} = 45.43, \sigma = 13.59 \) cd/m\(^2\)) than red light stimulation (\(\bar{x} = 121.75, \sigma = 93.58 \) 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\(_{\text{blue}} \& \text{binocular} = 34.72\% \) versus CV\(_{\text{red}} \& \text{monocular} = 74.74\%\) and monocular (CV\(_{\text{blue}} \& \text{monocular} = 31.30\% \) versus CV\(_{\text{red}} \& \text{monocular} = 76.88\%\) 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\(^2\); \(t_{(10)} = 3.15, P < 0.01, d = 1.08\). 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; \(t_{(10)} = 2.18, P = 0.06, d = 0.66\)).
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.\textsuperscript{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 broadband light\textsuperscript{2,27–29,36–38,40,43} or variable-wavelength stimulation\textsuperscript{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.\textsuperscript{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\textsuperscript{20,22,23} and clinical populations,\textsuperscript{21} and correlates with the peak spectral sensitivity of melanopsin.\textsuperscript{6} Our results are also consistent with studies that show alleviation of photophobia symptoms when patients with migraine\textsuperscript{25} and benign essential blepharospasm\textsuperscript{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).
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.45

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.52 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.

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

**References**


Previous psychophysical studies2,21–25,28,29,35,36–40,42–44 have not used pharmacological mydriasis. Wirtschafter and Bourassa27 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 other confounders in the experimental setting. Stimulus-dependent pupillary responses39,50 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,49 prolonged testing time may lead to artifacts as a result of changes in emotional state,17,48 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 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.


