

New Methods for Quantification of Visual Photosensitivity Threshold and Symptoms

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Purpose: Visual photosensitivity is a common symptom difficult to measure and diagnose, and is found in many ocular and neurological disorders. We developed two novel reproducible quantitative assessments of visual photosensitivity.

Methods: We designed and built the ocular photosensitivity analyzer (OPA), an automated instrument to determine light intensity visual photosensitivity threshold (VPT), and developed the Visual Light Sensitivity Questionnaire-8 (VLSQ-8), an eight-question survey to assess the presence and severity of photosensitivity symptoms. We evaluated the test-retest variability and obtained normative values of these two approaches in 35 healthy normal subjects, distributed evenly over five age groups from eight to 60 years. Each subject underwent two test sessions, each with VLSQ-8, eye examination, and OPA, four weeks apart, between April 2015 and June 2016.

Results: Log-transformed VPTs (\log_{10} lux) and VLSQ-8 results were highly reproducible between the two sessions (VPT intraclass correlation coefficient [ICC] = 0.86; 95% confidence interval [CI] = 0.71–0.93; binocular testing, VLSQ-items ICC range = 0.53–0.87). No consistent significant differences in VPTs were found with monocular ($P = 0.053$, session 1) or binocular ($P = 0.26$) testing. Subjects in age group >30 to 40 years had significantly higher VPTs than those in other age groups ($P \leq 0.011$) except the >40 to 50 years age group ($P = 0.11$). Photosensitivity symptoms assessed by the VLSQ-8 generally were low and highly reproducible with $\geq 88\%$ of responses between the 2 sessions being within one category of each other.

Conclusions: Our results provide reliability data and normative results toward validation of two novel approaches to quantify visual photosensitivity and provide support for their potential use in ocular and neurologic conditions as well as in clinical trials.

Translational Relevance: The new quantitative photosensitivity approaches are potential measures to characterize disease severity, monitor disease progression, and evaluate treatment efficacy.

Introduction

In normal subjects, visual photosensitivity is a physiologic protective mechanism to avoid potentially damaging high intense light (e.g., sunlight). While normal subjects have relatively high tolerance to bright light, visual photosensitivity is increased in many conditions, including ocular disorders, such as ocular albinism and benign essential blepharospasm, and neurological disorders, such as migraines and traumatic brain injuries.^{1,2} The

pathophysiologic basis of increased visual photosensitivity is incompletely understood and treatment often is difficult. Afferent light inputs arise from the rod, cone, and melanopsin photoreceptors in the retina,^{3–5} and light stimulation may lead to pain from stimulation of the trigeminal nerve.^{6–8} Associated features of visual photosensitivity may include light-induced glare or dazzle, involuntary blinking, squeezing or closure of the eyelid, and discomfort or pain in the eyes or head.²

For conditions where visual photosensitivity is a prominent feature, quantitative measures of visual

photosensitivity are important to characterize the stage or severity of the disease, monitor disease progression, and evaluate efficacy of a treatment.^{2,9} Achromatopsia gene therapy clinical trials are good examples where visual photosensitivity quantitation is useful. Achromatopsia patients have markedly reduced visual acuity and severe visual photosensitivity. Reliable and accurate methods to quantitate visual photosensitivity thresholds and symptoms could serve as outcome measures to assess the efficacy of the gene therapy.

Previous studies suggest visual photosensitivity threshold variation among healthy persons with no significant correlation between threshold and age.¹ Binocular viewing generally lowers the visual photosensitivity threshold compared to monocular viewing.^{1,10} With respect to assessment of visual photosensitivity symptoms, one or more mostly “yes” or “no,” photosensitivity questions are included as part of disease-specific questionnaires targeting patients with migraines, dry eye, blepharospasm, or adult attention-deficit/hyperactivity disorder; some of which are nonvalidated.^{1,11–17} Our goal was to create and design a questionnaire dedicated to the assessment of the presence and severity of visual light sensitivity (VLS) symptoms that can be applied broadly.

Given the lack of sensitive, objective measures available to assess visual photosensitivity, we aimed to develop a quantitative assessment of visual photosensitivity by building the Ocular Photosensitivity Analyzer (OPA), an automated instrument to determine the light intensity visual photosensitivity threshold (VPT), and designed a questionnaire consisting of eight questions to assess the presence and severity of visual photosensitivity symptoms. In this study, we evaluated the test–retest variability and obtained normative values of these two novel approaches by applying them to a group of normal healthy subjects of different ages.

Methods

Subjects

Study participants consisted of 35 healthy subjects with seven subjects in each of the following age groups: 8 to 20, 21 to 30, 31 to 40, 41 to 50, and 51 to 60 years. The study was approved by the institutional review board and carried out in accordance to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects. Inclusion criteria were a

corrected visual acuity of 20/25 or better and normal undilated fundoscopic examination in each eye. Exclusion criteria were a history of migraine, chronic medication use, and presence of any ocular condition (other than refractive error) or systemic condition with potential ocular manifestations (e.g., diabetes, autoimmune conditions). Self-reported race and ethnicity consistent with the United States Bureau of Census was collected (Table 1). Skin and hair colors were graded based on previous reports.^{18,19}

Procedures

To assess test–retest reliability, the subjects underwent two sessions performed 4 weeks apart; all procedures were performed without pupillary dilation for each session. For each subject, the two sessions were performed at approximately the same time of day. During each session, the Visual Light Sensitivity Questionnaire-8 (VLSQ-8, Fig. 1) was first administered to each subject before any visual testing to avoid any effect of visual testing on the responses to the VLSQ-8. To evaluate the possible relationship of photosensitivity to headaches, the Headache Impact Test-6 (HIT-6), a validated questionnaire composed of 6 questions to evaluate the presence and impact of headaches on normal daily activities, then was administered.²⁰ This was followed by a slit-lamp examination including undilated 90 diopter (D) lens funduscopy. The visual photosensitivity threshold test then was performed 20 minutes later in the dedicated OPA room.

Assessment of Visual Photosensitivity Light Threshold: OPA

The OPA is an automated noncontact instrument designed and built at our institution to quantitate VPT (Aguilar MC, et al. *IOVS*. 2014;55:ARVO E-Abstract 4108). The OPA produces light stimuli with a bi-cupola array panel configured with 210 light-emitting diodes (LEDs) focused at 50 cm (Fig. 2a), with a power regulator controlled via computer (Fig. 2b). The device’s light intensity is calibrated using an optometer (X1 Gigahertz-Optik, Inc., Newburyport, MA) positioned at the patient’s eye distance and can output light stimuli ranging from 0.1 to 32,000 lux. The OPA meets the requirements for optical radiation safety defined in the International Organization for Standardization, ISO 15004-2 for light hazard protection for ophthalmic instruments.

During testing, a background lighting of 10 lux was used. The instrument was controlled by a touch-

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Visual Light Sensitivity Questionnaire-8 (VLSQ-8)

This questionnaire is designed to detect visual sensitivity to light. Please circle one answer for each question. Choose the response that best describes your situation. Answer all of the questions as if you are wearing your regular glasses or contact lenses. Take as much time as needed to answer each question. All your answers are confidential.

- 1) In the past month, how often did you have visual light sensitivity outdoors during daylight?

Never	Rarely	Sometimes	Often	Always
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- 2) In the past month, how often did you have a sense of glare in your eyes?

Never	Rarely	Sometimes	Often	Always
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- 3) In the past month, how often did you have visual light sensitivity from flickering lights or bright colors?

Never	Rarely	Sometimes	Often	Always
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- 4) Please rate the severity of the worst visual light sensitivity you experienced in the past month.

None		Moderate		Severe
1	2	3	4	5

- 5) When you have sensitivity to light, do you also experience headache?

Never	Rarely	Sometimes	Often	Always
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- 6) When you have sensitivity to light, how often is your vision blurry?

Never	Rarely	Sometimes	Often	Always
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- 7) How often does sensitivity to light limit your ability to read, watch TV, or use the computer?

Never	Rarely	Sometimes	Often	Always
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- 8) In the past month, how often did you need to wear dark glasses on cloudy days or indoors?

Never	Rarely	Sometimes	Often	Always
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Figure 1. VLSQ-8. An eight-question survey carefully developed to quantitatively assess visual photosensitivity symptoms.

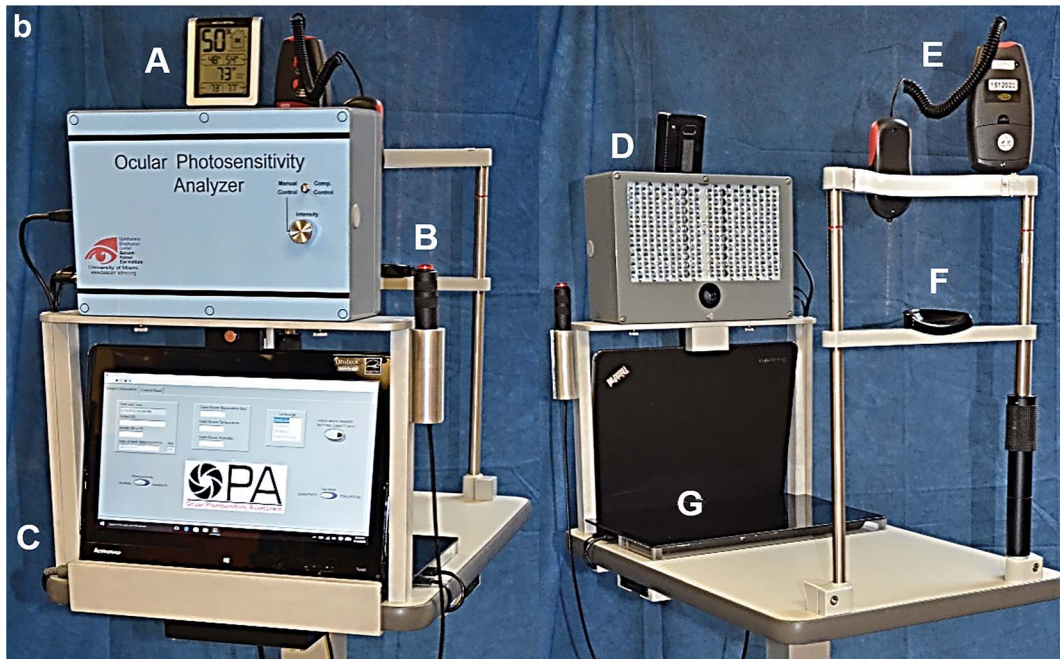
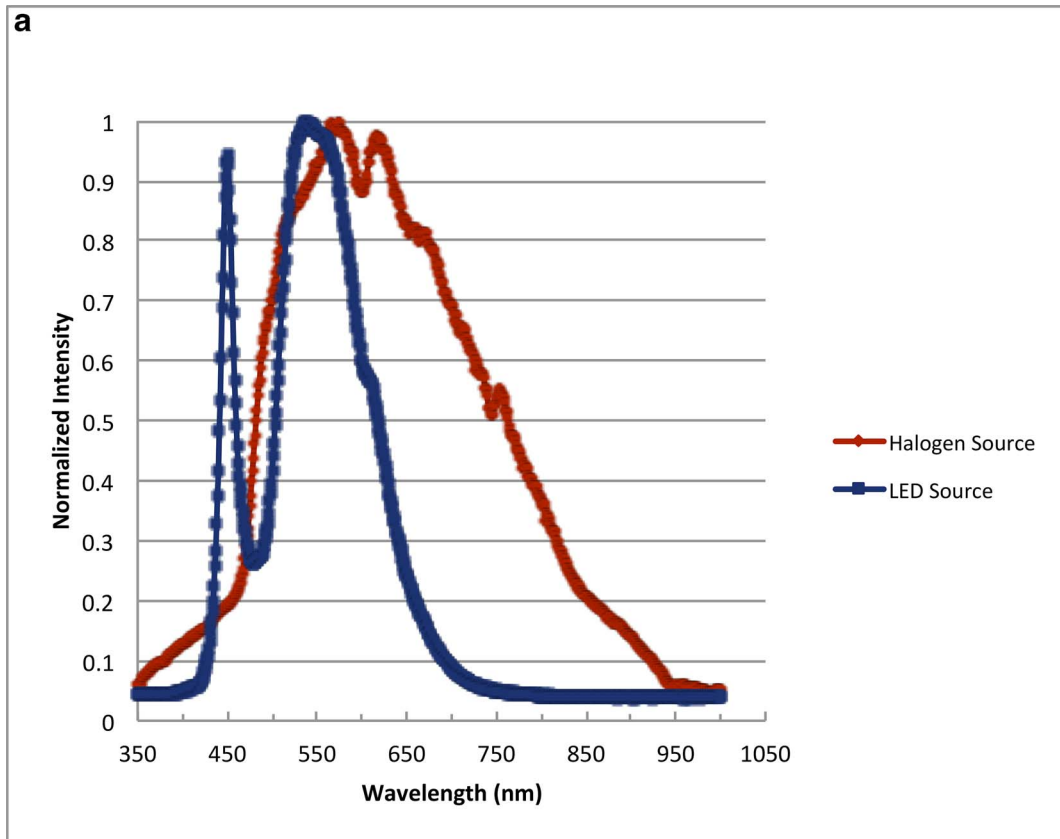


Figure 2. (a) Normalized emission spectrum of the LED array of the OPA compared to the tungsten halogen source with heat filters used by Vanagaite et al.,¹ both measured using a spectrometer (SM442-USB; Spectral Products, Inc., Putnam, CT) and a fiberoptic probe (F-OS-0400-H-1, Newport Co., Irvine, CA). (b) OPA mounted on a motorized table. (A) Humidity and temperature meter. (B) Hand-held push button, (C) Touch-based computer graphical user interface. (D) Concave LED array panel (light source) with central blinking fixation LED and infrared camera. (E) Lux meter, (F) Headrest and adjustable chinrest. (G) Laptop computer. Distance LED panel to patient eyes is 50 cm.

based computer graphical user interface (National Instruments, Austin, TX) designed to record high resolution infrared video (50 fps), record light intensity data, track the interval between stimuli, record subject responses, and calculate the light intensity for subsequent stimuli (Fig. 2).

The seated subject was positioned in front of the light panel with the head supported by a chin and forehead support frame, and the subject was asked to fixate on a blinking light located at the center of the panel; the operator then adjusted the patient's chin side-wise and the chinrest up/down until both eyes were aligned to the monitor horizontal line; thus, assuring both eyes received the same light stimulus. During the entire test, the subject was instructed by the automated computer-generated voice in the preferred language of English, Spanish, French, or Portuguese. At the beginning of the test, a carefully written script was read by the computer-generated voice to each subject to ensure every subject was given the same instructions. The computer voice then performed the test and instructed the subject to indicate when the light stimulus was uncomfortable by pressing a hand-held button connected to the computer. The total instrument light range could be divided into 100 steps (enhanced testing mode) or 25 steps (normal testing mode) depending on the severity of the subject's photophobia with a fixed stimulus duration of 2 seconds and a 4-second interstimulus rest period. All participants reported in this study were healthy normal subjects and were tested using the normal testing mode. The enhanced test mode was developed to increase sensitivity for future testing of patients with conditions with increased photosensitivity and low VPT. For normal subjects, the first light intensity level was 1.5 lux. After each light stimulus and dependent on subject's response, each succeeding stimulus intensity was adjusted using the Garcia-Perez staircase technique,²¹ which used unequal ascending and descending steps. A response reversal occurred when the subject responded positively to a light intensity that caused photosensitivity discomfort and did not respond to the following dimmer light stimulus. The test was completed after 10 response reversals, and the VPT measurement was calculated from the mean of 10 response reversals (Figs. 3, 4). Integrated into the testing protocol were reliability indices that used catch trials to gauge performance reliability (Fig. 4). Response consistency scores were calculated by repeating previously administered light stimuli every third stimulus to assess the subject's response agreement to the

response of the previous stimulus. Positive and negative inconsistency indices allowed tracking catch trial accuracy.

During each session, one monocular VPT for each eye and one binocular VPT were measured without pupillary dilation and without correct spectacle or contact lenses. Six different test sequences resulted from monocular (OD = right eye, OS = left eye) and binocular (OU = both eyes) testing: OD/OS/OU, OD/OU/OS, OS/OD/OU, OS/OU/OD, OU/OD/OS, OU/OS/OD. The specific test sequence used during each specific session was pseudo-randomly predetermined by applying this order of test sequence. The subject was allowed 10 minutes of light adaption before and in between each test with ambient lighting of 120 lux.

Assessment of Photosensitivity Symptoms: VLSQ-8

The VLSQ-8 was created and designed to be dedicated to the assessment of the presence and severity of VLS symptoms. The VLSQ-8 was developed by the following process. First, we reviewed existing literature to recognize the multiple factors pertinent to detection of photosensitivity symptoms.^{12,13,20,22} This was followed by discussions of focus groups consisting of ophthalmologists, biostatisticians, and patients with photosensitivity. Drafts of the questionnaire then underwent several rounds of field testing, focus group discussion, and questionnaire revision. Multiple drafts were pilot tested and revised based on comments of the tested subjects, persons who administered the questionnaire, and the focus group. We aimed to develop the VLSQ-8 at a reasonable reading level but at the same time be responsive to the feedbacks we received from the pilot testing. The reading level of the VLSQ-8 using the Lexile Framework for Reading, a scientific approach to measuring reading ability and the text demand of reading materials, showed an overall approximate reading grade level of grade 10 for the entire questionnaire (Lexile measure 1010L) with reading grade levels ranging from grades 8 to 11 for each question (Question 1, 1080L; Question 2, 850L; Question 3, 1100L; Question 4, 1100L; Question 5, 730L; Question 6, 830L; Question 7, 1120L; Question 8, 1100L).²³

Of the eight VLSQ-8 questions, Questions 1 to 3 were designed to assess the frequency of photosensitivity. Question 4 was designed to gauge the severity of photosensitivity. Questions 5 and 6 evaluated

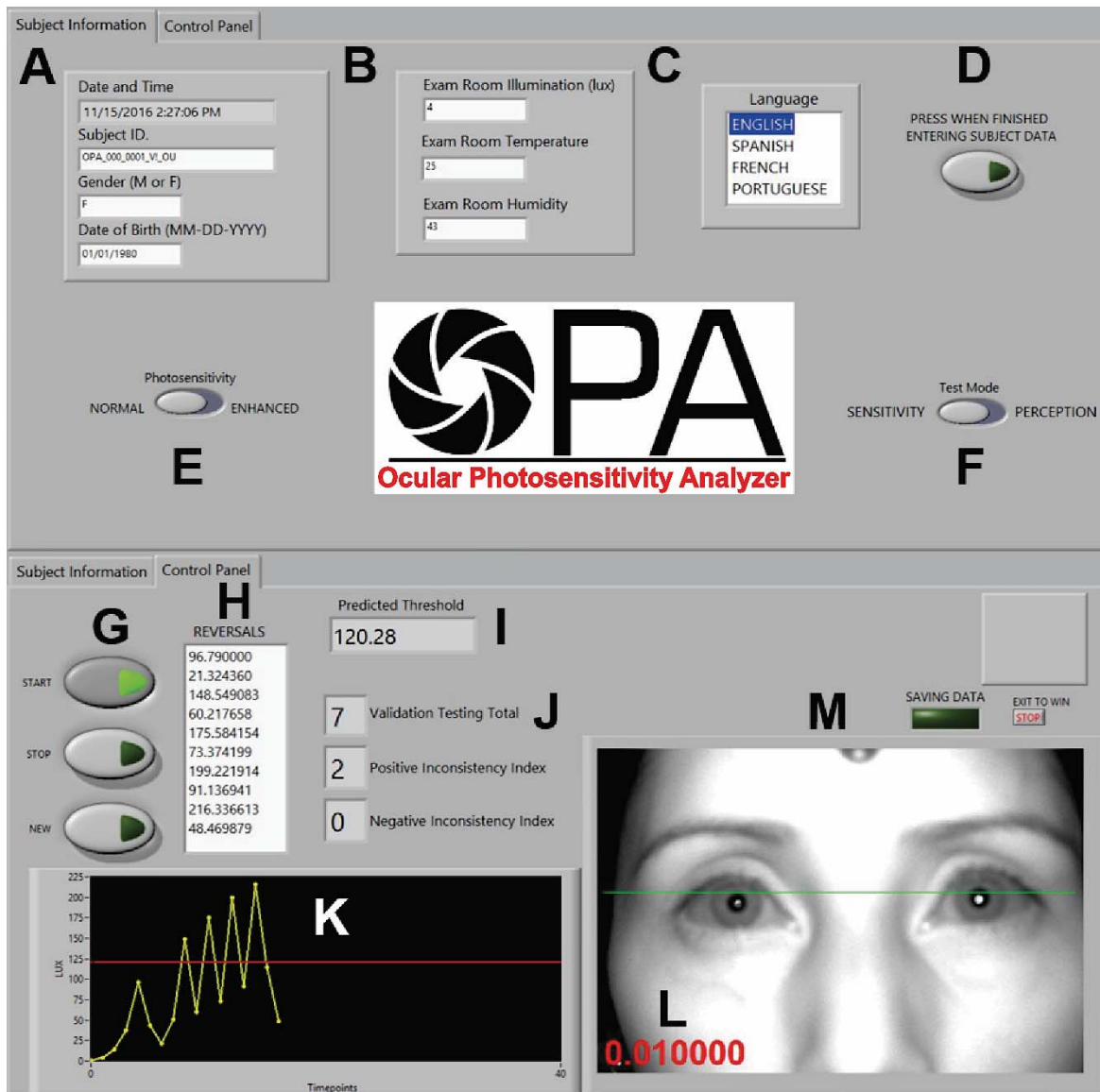


Figure 3. OPA touch-based computer graphical user interface, testing and control panels: (A) Subject information. (B) Room parameters. (C) Instruction language. (D) Save button. (E) Photosensitivity mode: normal or enhanced. (F) Testing mode: sensitivity or perception. (G) Control button: start, stop, and new. (H) Recorded reversals. (I) Predicted threshold. (J) Reliability indices. (K) Data graph with reversals and mean indicator. (L) Illumination intensity (Lux), and (M) live video recording frame with *horizontal line* to align patient eyes using chin rest.

related photosensitivity symptoms, such as headache and blurry vision. Questions 7 determined the effect of photosensitivity on reading, television use, and computer use. Question 8 assessed the use of sunglasses on cloudy days and indoors.

The study subjects were instructed to answer the VLSQ-8 questions as if they were wearing usual correction (i.e., glasses or contact lenses, if any) and to choose one answer for each question. No time limit for answering the VLSQ-8 was imposed. The VLSQ-8 is copyrighted by the University of Miami.

Log Transformation of VPT Measurements

Table 2 displays descriptive statistics of the lux photosensitivity thresholds obtained in the test and retest sessions. As expected, because photosensitivity bears a logarithmic relation to light intensity,²⁴ the distributions were highly skewed and non-Gaussian (all monocular/binocular combinations different from Gaussian by Kolmogorov-Smirnov; $P < 0.001$). Therefore, we log-transformed thresholds that produced symmetric distributions not different from

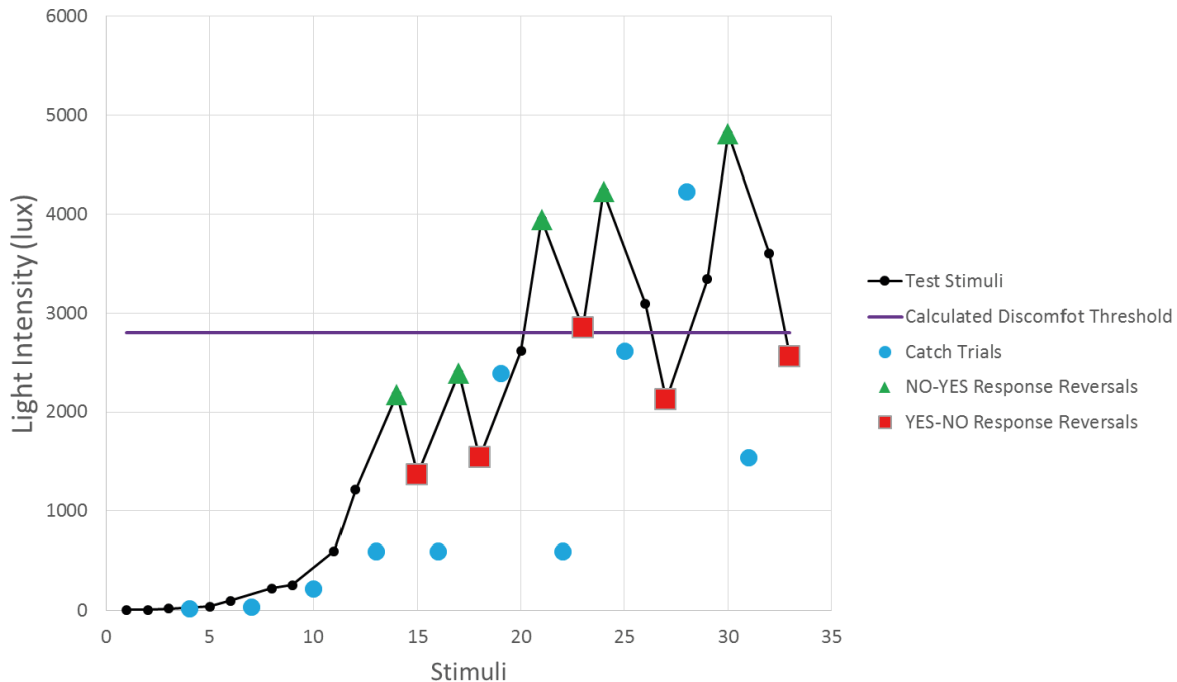


Figure 4. Example of a data graph from a normal subject of the VPT from the OPA. The VPT measurement was calculated from the mean of 10 response reversals. Integrated into the testing protocol were reliability indices that used catch trials that repeat the previously administered light stimuli every third stimulus to measure the subject's response agreement to the response of the previous stimulus. Positive and negative inconsistency indices allowed tracking catch trial accuracy.

Gaussian (all $P \geq 0.085$, Table 2, Fig. 5). All analyses of the thresholds henceforth were performed on the \log_{10} lux thresholds.

Statistical Analysis

Values were expressed as means \pm standard deviation (SD) and logarithmic transformation. Data were analyzed with fixed effects and linear mixed models.²⁵ The intraclass correlation coefficient (ICC) was used to quantify the correlation between the two eyes of subjects during a single testing session and as a gauge of test–retest reproducibility for subjects measured in two different sessions. Briefly, the ICC differs from the familiar Pearson correlation coefficient in that it is used when there is no division of variables into, say, dependent versus independent but, rather, when one wishes to assess the agreement of measurements of the same variable made within a class, for example within a participant. The ICC ranges from 0 to 1, with 0 indicating no correlation between the measurements within participants and 1 indicating perfect correlation within participants. Commonly accepted ranges for ICCs are <0.4 , poor agreement; 0.4 to 0.75, fair to good agreement; >0.75 , excellent agreement.²⁶ A P value of <0.05 was considered significant.

Results

Of the 35 healthy subjects (mean age, 34.5 [SD = 14.6] years; range, 9–59 years), 12 (34%) were male and 23 (66%) were female (Table 1). As planned, 7 subjects were recruited for each of the 5 age groups. The subjects were recruited between April 2015 and June 2016 and 25 subjects completed the follow-up testing at 4 weeks. Of 10 subjects who did not return for the second visit, 6 were 8 to 20 years old, while 4 were aged 41, 42, 44, and 59 years.

VPT Intrasessional Reliability: Monocular and Binocular Differences, Test Order Effects

Mean test duration for the VPT from the automated OPA was 11.4 ± 4 minutes for all subjects (adults 11.7 ± 4 and children 8.5 ± 1.3 minutes).

Intrasessional reliability was assessed using monocular and binocular measurements of the same patients measured on the same day (session 1, $n = 35$; session 2, $n = 25$). For data from each session, we compared measurements made on right, left, and both eyes. In the first session there was a borderline significant difference by laterality ($P = 0.053$, Greenhouse-Geisser corrected repeated measures analysis of

Table 1. VPT Measurements (\log_{10} lux, OPA) by Sex, Race, Ethnicity, Skin Color, Hair Color, Session 1 Mean (SD) \log_{10} lux photosensitivity

Characteristic	N (%)	OD	OS	OU
Sex				
Female	23 (66)	2.27 (0.76)	2.26 (0.8)	2.16 (0.75)
Male	12 (34)	2.31 (1.0)	2.36 (0.92)	2.11 (0.88)
<i>P</i> value		0.89 <i>t</i> -test	0.74 <i>t</i> -test	0.86 <i>t</i> -test
Ethnicity				
Hispanic	23 (66)	2.25 (0.79)	2.32 (0.85)	2.07 (0.78)
Not Hispanic	12 (34)	2.35 (0.96)	2.25 (0.84)	2.28 (0.81)
<i>P</i> value		0.74 <i>t</i> -test	0.83 <i>t</i> -test	0.45 <i>t</i> -test
Race				
White	27 (77)	2.31 (0.88)	2.29 (0.84)	2.14 (0.8)
Black	4 (11)	2.00 (0.64)	2.25 (0.89)	2.06 (0.97)
Asian	4 (11)	2.43 (0.83)	2.40 (0.96)	2.21 (0.71)
<i>P</i> value		0.76 ANOVA	0.97 ANOVA	0.96 ANOVA
Skin Color				
White	13 (37)	2.09 (0.93)	1.98 (0.90)	1.97 (0.87)
Light brown	15 (43)	2.37 (0.88)	2.47 (0.98)	2.21 (0.85)
Medium brown	6 (17)	2.67 (0.67)	2.65 (0.74)	2.4 (0.69)
Black	1 (3)	1.13 (0)	1.56 (0)	1.3 (0)
<i>P</i> value		0.28 ANOVA	0.23 ANOVA	0.54 ANOVA
Hair Color				
Black	12 (34)	2.38 (0.81)	2.34 (0.81)	2.18 (0.76)
Brown	19 (54)	2.20 (0.87)	2.31 (0.93)	2.11 (0.79)
Blond	4 (11)	2.4 (0.96)	2.10 (0.48)	2.15 (1.05)
<i>P</i> value		0.81 ANOVA	0.88 ANOVA	0.97 ANOVA

Table 2. Monocular and Binocular VPT Measurements (OPA)

	Session 1			Session 2		
	OD	OS	OU	OD	OS	OU
VPT measurements (lux)						
N	35	35	35	25	25	25
Mean	836.0	854.1	523.2	656.4	918.9	579.5
SD	1257.8	1315.6	798.1	1099.8	1776.0	988.9
Median (lux)	170.0	171.1	106.0	116.9	101.1	113.1
Minimum (lux)	12.1	13.4	8.4	4.7	3.9	4.7
Maximum (lux)	3848.5	5899.8	2929.6	4185.1	6916.6	3409.4
VPT measurements (\log_{10} lux)						
N	35	35	35	25	25	25
Mean	2.28	2.30	2.14	2.14	2.19	2.10
SD	0.84	0.83	0.78	0.84	0.89	0.83
Median log(lux)	2.23	2.23	2.03	2.07	2.00	2.05
Minimum log(lux)	1.08	1.13	0.92	0.67	0.59	0.67
Maximum log(lux)	3.59	3.77	3.47	3.62	3.84	3.53

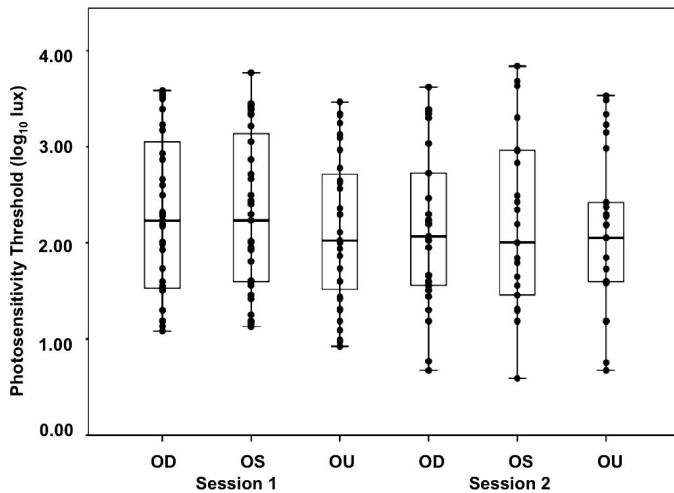


Figure 5. Visual photosensitivity thresholds (in \log_{10} lux scale) obtained with the OPA and plotted for eye or eyes tested (OD, OS, OU). All analyses of session/eye combinations were not different from Gaussian by Kolmogorov-Smirnov (all $P \geq 0.085$).

variance [ANOVA]) owing to lower average thresholds in the binocular measurements (Table 2, Fig. 5). However, this was not confirmed in data from the second session ($P = 0.264$, Greenhouse-Geisser corrected repeated measures ANOVA) and did not achieve conventional statistical significance. Further, there were no systematic differences between any of the three measurements made in the two sessions (all $P > 0.34$, paired t -test), indicating no learning effect, and both eye thresholds were similar to right and left eye thresholds in the second session (Table 2).

The average interocular photosensitivity threshold differences (right minus left eyes) were small, -0.01 (SD = 0.44), in session 1 and -0.05 (SD = 0.35) in session 2; however, there was a substantial range in interocular threshold differences (session 1, -1.16 , 1.00). Therefore, we assessed the correlation between eyes with the ICC. The ICCs for sessions 1 and 2 were 0.863 and 0.921, respectively, indicating excellent correlation.²⁵

Since the order of monocular and binocular test (OD/OS/OU) was assigned randomly to each subject, we were able to examine order effects by comparing the interocular threshold differences of subjects assigned to OD followed by OS ($n = 12$, session 1; $n = 10$, session 2) to those assigned to OS followed by OD ($n = 10$, session 1; $n = 8$, session 2). In session 1, interocular threshold differences for OD first thresholds averaged -0.13 (SD = 0.41) which did not differ significantly ($P = 0.33$) from those with OS first, average 0.08 (SD = 0.58). Similarly in session 2, interocular threshold differences for OD first thresh-

olds averaged -0.14 (SD = 0.40) which did not differ significantly ($P = 0.25$) from those with OS first, average 0.08 (SD = 0.45).

Intratesting reliability was good. For a test session, the mean number of catch trials was 7.4 ± 2.0 . Overall mean percent correct catch trial accuracy was ($79.1\% \pm 15\%$) with borderline significant difference between incorrect positive (1.029 ± 1.0) and negative (0.6 ± 0.88) catch trial responses ($P = 0.096$, paired t -test).

Intersessional Interocular Reliability

Intersessional reliability was assessed using monocular and binocular measurements of the same patients who attended both sessions ($n = 25$). Given six subjects in the age group 8 to 20 years did not return for session 2, the results are from adults only. \log_{10} lux threshold measurements showed excellent test-retest reproducibility from sessions 1 to 2 with ICCs of 0.845, 0.815, and 0.857 for OD, OS, and OU measurements, respectively.

VPT and Demographic Characteristics

None of the demographic characteristics appearing in Table 1 (sex, ethnicity, race, skin color, hair color) was associated with the VPTs (all $P > 0.2$). However, our ability to identify correlations is limited by the size and composition of our sample. For example, most participants had dark iris pigmentation and not all iris colors in the classification system were readily available in our patient population.¹⁴ Therefore, a correlation of iris colors to light sensitivity was not found as it has been shown in other studies.^{27,28}

Neither sex ($P > 0.7$) nor ethnicity ($P > 0.4$) nor race ($P > 0.75$), categorical variables that we studied, had significant associations with VPT. No substantial or significant Pearson correlations were observed between continuous variables and VPT either (r from 0.09–0.11, all $P > 0.5$) or eye color (r from -0.14 –0.06, all $P > 0.4$). However, comparison of photosensitivity by decades of age (all $n = 7$) found a nonlinear difference in average VPTs (Fig. 6, $P = 0.017$, binocular session 1, 1-way ANOVA). Specifically, the >30 to 40 age group was less light sensitive than all age groups except age group >40 to 50 ($P = 0.11$). None of the other four groups was different from any of the others (post hoc Least Significant Difference tests).

Photosensitivity Symptoms: VLSQ-8

Given there is no standard scoring algorithm for this newly developed questionnaire, we assessed

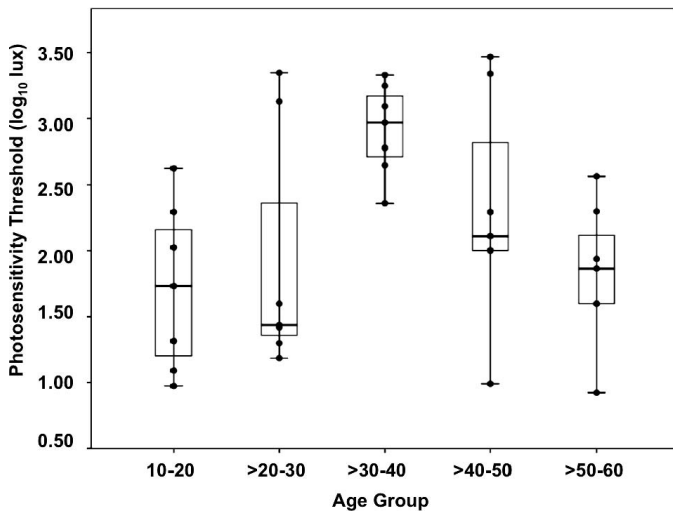


Figure 6. Differences in VPT ($\log_{10}\text{lux}$) by age groups. Subjects in the age group >30 to 40 years had significantly higher photosensitivity thresholds than those in the other age groups ($P \leq 0.011$) except the >40 to 50 age group ($P = 0.11$).

trends for each question. Each question was recoded to never = 1, rarely = 2, sometimes = 3, often = 4, and always = 5. Tables 3 and 4 summarize the VLSQ-8 results for sessions 1 and 2. The VLSQ-8 results indicated photosensitivity symptoms generally were low among the normal subjects with responses rarely being higher than 3. The VLSQ-items showed good to excellent reproducibility (ICC range = 0.53–0.87, Table 3), and $\geq 88\%$ of responses between the 2 sessions being within one category of each other.

There was no correlation of age with VLSQ (all $|r| < 0.3$, all $P > 0.13$). When the VLSQ results in the children were compared to those in the adults, there were no significant differences for each VLSQ question except for question 8 (“In the past month, how often did you need to wear dark glasses on cloudy days or indoors?”), where adults had significantly higher scores than children ($P = 0.019$). We suspect this may be because children are not in the habit of wearing sunglasses.

Correlation of Visual Photosensitivity Threshold and VLSQ-8

Pearson correlations between VPT and the VLSQ-8 items ranged from $r = 0.16$ ($P = 0.16$, question 8 related to wearing dark glasses) to $r = 0.65$ ($P < 0.001$, question 5, related to headache). Session 2 showed more statistically significant relationships. Session 2 did not include the children, which may account for the higher correlations.

Discussion

The results of our study indicated that the VPT from the automated OPA and the VLSQ-8 evaluation of photosensitivity symptoms are reproducible, quantitative measures that assess different aspects of photosensitivity. The VPT from the OPA is a subjective functional measure of visual photosensitivity. The VLSQ-8 is a survey to assess photosen-

Table 3. VLSQ-8 Results

Question	VLSQ-8 Brief Description	Response (%)					Mean	Median	SD	Agreement between Sessions		ICC
		Never	Rarely	Sometimes	Often	Always				Response within One Category	Exact %	
1	Outdoors daylight	15 (43)	6 (17)	11 (31)	2 (6)	1 (3)	2.1	2.0	1.1	44	88	0.62
2	Glare	20 (57)	7 (20)	4 (11)	3 (9)	1 (3)	1.8	1.0	1.1	72	92	0.80
3	Flickering lights	22 (63)	7 (20)	3 (9)	3 (9)	0 (0)	1.6	1.0	1.0	64	96	0.74
4	Severity	15 (43)	6 (17)	11 (31)	3 (9)	0 (0)	2.1	2.0	1.1	56	88	0.65
5	Headache	23 (66)	4 (11)	5 (14)	2 (6)	1 (3)	1.7	1.0	1.1	68	96	0.80
6	Vision blurry	23 (66)	6 (17)	3 (9)	1 (3)	2 (6)	1.7	1.0	1.1	76	92	0.64
7	Limitations	22 (63)	6 (17)	5 (14)	2 (6)	0 (0)	1.6	1.0	0.9	80	100	0.87
8	Dark glasses	29 (83)	1 (3)	2 (6)	2 (6)	1 (3)	1.4	1.0	1.0	72	88	0.53

Table 4. Mean (SD) of Binocular VPT (mean log₁₀lux [SD]), OPA and VLSQ-8 Questionnaire

VLSQ Question	Answers, 1, never to 5, always					Linear Nonpar P value
	1	2	3	4	5	
VLSQ-8 Responses Session 1						
1	2.16 (0.69) <i>n</i> = 15	2.05 (0.93) <i>n</i> = 6	2.38 (0.83) <i>n</i> = 11	1.14 (0.22) <i>n</i> = 2	1.6 (0) <i>n</i> = 1	0.52 0.64
2	2.44 (0.7) <i>n</i> = 20	1.57 (0.5) <i>n</i> = 7	1.68 (0.75) <i>n</i> = 4	2.48 (0.94) <i>n</i> = 3	0.99 (0) <i>n</i> = 1	0.052 0.027
3	2.29 (0.74) <i>n</i> = 22	1.7 (0.77) <i>n</i> = 7	2.66 (0.8) <i>n</i> = 3	1.55 (0.72) <i>n</i> = 3	<i>n</i> = 0	0.23 0.21
4	2.29 (0.74) <i>n</i> = 15	2.31 (0.65) <i>n</i> = 6	1.94 (0.92) <i>n</i> = 11	1.78 (0.79) <i>n</i> = 3	<i>n</i> = 0	0.19 0.18
5	2.33 (0.74) <i>n</i> = 23	2.23 (0.45) <i>n</i> = 4	1.37 (0.28) <i>n</i> = 5	2.23 (1.75) <i>n</i> = 2	1.09 (0) <i>n</i> = 1	0.026 0.032
6	2.2 (0.76) <i>n</i> = 23	2.02 (0.58) <i>n</i> = 6	1.67 (1.23) <i>n</i> = 3	3.47 (0) <i>n</i> = 1	1.84 (0.74) <i>n</i> = 2	0.70 0.56
7	2.21 (0.78) <i>n</i> = 22	1.98 (0.84) <i>n</i> = 6	1.93 (0.65) <i>n</i> = 5	2.39 (1.52) <i>n</i> = 2	<i>n</i> = 0	0.73 0.66
8	2.19 (0.77) <i>n</i> = 29	1.42 (0) <i>n</i> = 1	1.29 (0.43) <i>n</i> = 2	2.53 (1.32) <i>n</i> = 2	2.36 (0) <i>n</i> = 1	0.86 0.58
VLSQ-8 Responses Session 2						
1	2.29 (0.88) <i>n</i> = 8	2.26 (0.71) <i>n</i> = 10	1.7 (1.28) <i>n</i> = 3	1.63 (0.68) <i>n</i> = 4	<i>n</i> = 0	0.13 0.20
2	2.3 (0.77) <i>n</i> = 14	2.07 (0.69) <i>n</i> = 6	1.7 (1.28) <i>n</i> = 3	1.36 (0.98) <i>n</i> = 2	<i>n</i> = 0	0.078 0.084
3	2.16 (0.75) <i>n</i> = 13	2.33 (0.82) <i>n</i> = 9	1.4 (0.92) <i>n</i> = 2	<i>n</i> = 0	0.67 (0) <i>n</i> = 1	0.094 0.38
4	2.24 (0.8) <i>n</i> = 10	2.44 (0.55) <i>n</i> = 6	1.66 (0.81) <i>n</i> = 7	3.15 (0) <i>n</i> = 1	0.67 (0) <i>n</i> = 1	0.14 0.18
5	2.51 (0.84) <i>n</i> = 11	2.00 (0.59) <i>n</i> = 9	1.41 (0.78) <i>n</i> = 3	2.05 (0) <i>n</i> = 1	0.67 (0) <i>n</i> = 1	0.007 0.011
6	2.39 (0.8) <i>n</i> = 13	2.1 (0.66) <i>n</i> = 8	0.87 (0.27) <i>n</i> = 3	2.05 (0) <i>n</i> = 1	<i>n</i> = 0	0.027 0.029
7	2.31 (0.77) <i>n</i> = 17	1.64 (0.41) <i>n</i> = 4	1.53 (1.41) <i>n</i> = 3	2.05 (0) <i>n</i> = 1	<i>n</i> = 0	0.13 0.068
8	2.37 (0.79) <i>n</i> = 17	1.51 (0.72) <i>n</i> = 3	1.66 (0.5) <i>n</i> = 3	1.36 (0.98) <i>n</i> = 2	<i>n</i> = 0	0.026 0.018

Bold face indicates some of the cell means that do not fit a trend.

sitivity symptoms and, like all survey measures, is influenced by interindividual physiologic, perceptive, and cognitive differences. Our findings supported the potential use of these two approaches, particularly longitudinally, to characterize disease severity, monitor disease progression, and evaluate treatment efficacy.

Test–retest analyses of the two test sessions, 1 month apart, showed high reproducibility for the VPT and VLSQ-8 among our normal subjects of

different age groups. The VLSQ-8 was administered first during each testing session to prevent any impact of the eye examination or the OPA testing on the results of the VLSQ-8. The VPT obtained using OPA and the VLSQ-8 were completed by our normal subjects without difficulty and as expected, the VPTs generally were high indicating good light tolerance and the VLSQ-8 showed generally low photosensitivity symptoms.

To avoid the influence of examiner bias, the OPA

is a fully automated instrument providing uniform standard instructions through a computer-generated voice available in different languages throughout the entire OPA test. The OPA not only calculates the VPT but also provides an index of intratesting reliability through the use of catch trials that revealed good intratesting reliability among our normal subjects. Log-transformed VPTs (\log_{10} lux) was needed to produce symmetric VPT distributions not different from Gaussian, because photosensitivity bears a logarithmic relation to light intensity.²⁴ No significant differences in VPTs were found with monocular or binocular testing, and the order of the monocular and binocular testing had no significant effect on the VPTs. Subjects in the age group >30 to 40 years were more tolerant to light and had significantly higher VPTs than did the subjects in the 8 to 20 ($P = 0.003$), >20 to 30s ($P = 0.011$), >50 to 60 ($P = 0.006$), but not >40 to 50 ($P = 0.11$) age groups. The physiologic basis of this finding is unclear, although this finding would not affect longitudinal intraindividual use of VPT. Previous studies have suggested visual photosensitivity threshold variation among healthy persons with no significant correlation between threshold and age,¹ and found binocular viewing generally lowers the VPT compared to monocular viewing.^{1,10} The differences between our results and those of previous studies are likely related to considerable differences in methodology, including the use of fully automated versus manual testing, as well as differences in study population. Of interest, there was a borderline significant difference by laterality ($P = 0.053$, Greenhouse-Geisser corrected repeated measures ANOVA) for session 1 owing to lower average thresholds in binocular measurements of both eye (Table 2), but session 2 also showed no significant differences in VPTs with monocular or binocular testing.

The VPT as a functional test and the VLSQ-8 as a symptom questionnaire assessed different aspects of photosensitivity. In the current study, only few subjects in this group of normal persons reported 3 or higher levels of photosensitivity symptoms (sometimes = 3, often = 4, always = 5) in the VLSQ-8, which limited the range for correlation with the VPTs. Correlation between VPT and the VLSQ-8 is assessed best in patient population with a wide range of photophobia. Pearson correlations between VPT and the VLSQ-8 items ranged from $r = 0.16$ ($P = 0.16$, question 8 related to wearing dark glasses) to $r = 0.65$ ($P < 0.001$, question 5, related to headache).

Approximately 15% of the variability in the VPT measurements was explained by the responses to Question 5 in the first session and approximately 27% in the second session.

Although patients with a history of migraine were excluded, we included the HIT-6 questionnaire to confirm our normal subjects had a low rate of headache given a high rate could confound the data. As expected, the HIT-6 scores of our normal subjects were low (mean 46.3, SD 7.8, range 36–64). Of interest, Question 5 of the VLSQ-8 is related to headache and had a high correlation of $r = 0.65$ ($P < 0.001$) with the HIT-6 score.

Limitations of this study included the subjects in the youngest age group 8 to 20 years did not return for retest (Session 2) due to lack of time and interest in completing the follow-up visit. Thus, the test and test–retest analysis was not available for this age group. The young subjects had no difficulties in completing the VPT test and the VLSQ-8, but more data are needed to determine the validity of the results in children. The participants reflected the racial and ethnic population in our locale, and most have dark irises, which prevented an adequate analysis with respect to factors, such as iris color. While data from our sample size are helpful to establish test re–test reliability, further studies to include a larger number of persons in each age category and across with other racial and ethnic makeup would be helpful to further the establishment of normative data.

Taken together, our findings provided reliability data and normative results that are essential toward validation of these two novel approaches to quantify visual photosensitivity and are necessary before applying these measures to ocular and neurologic conditions where photosensitivity is an important feature. Given photosensitivity is a subjective symptom difficult to measure and diagnose,²⁹ these new approaches will likely improve detection and quantitation of photosensitivity and support the potential use of these two approaches as quantitative measures in research studies such as clinical trials.

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