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# Eye Movement and Pupil Size Constriction Under Discomfort Glare

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Citation: Lin Y, Fotios S, Wei M, Liu Y, Guo W, Sun Y. Eye movement and pupil size constriction under discomfort glare. *Invest Ophthalmol Vis Sci.* 2015;56:1649-1656. DOI:10.1167/ iovs.14-15963 **PURPOSE.** Involuntary physiological responses offer an alternative means to psychophysical procedures for objectively evaluating discomfort glare. This study examined eye movement and pupil size responses to glare discomfort using new approaches to analysis: relative pupil size and speed of eye movement.

**M**ETHODS. Participants evaluated glare discomfort using the standard de Boer rating scale under various conditions manipulated to influence glare discomfort. Eye movement was recorded using an electro-oculogram (EOG), and pupil size was recorded using Tobii glasses. Ten young (mean age: 24.5 years old) and 10 senior (mean age: 61 years old) participants were recruited for this experiment.

**R**ESULTS. Subjective evaluation of glare discomfort was highly correlated with eye movement (multiple correlation coefficient  $[R^2]$  of >0.94, P < 0.001) and pupil constriction ( $R^2 = 0.38$ , P < 0.001). Severe glare discomfort increased the speed of eye movement and caused larger pupil constriction. Larger variations of eye movement were found among seniors.

Conclusions. The two physiological responses studied here to characterize discomfort glare under various lighting conditions had significant correlation with the subjective evaluation. The correlation between discomfort glare and physiological responses suggests an objective way to characterize and evaluate discomfort glare that may overcome the problems of conventional subjective evaluation. It also offers an explanation as to why long-term exposure to discomfort glare leads to visual fatigue and eyestrain.

Keywords: discomfort glare, eye movements, pupil constriction

**D** isability and discomfort are two commonly experienced forms of glare associated with conventional lighting,<sup>1</sup> experienced when exposed to a visual scene of extremely nonuniform illumination. Discomfort glare is the glare that causes discomfort without necessarily impairing the vision of objects; disability glare is that which impairs the vision of objects without necessarily causing discomfort.<sup>2</sup> Although disability glare, caused by scattered light forming a luminous veil over the retina, is reasonably well understood, there is insufficient understanding of the cause of discomfort glare.<sup>1</sup>

In numerous studies,<sup>3-12</sup> discomfort glare was measured using psychophysical procedures such as category rating, and from these data metrics have been developed to predict the degree of discomfort glare, including visual comfort probability,<sup>13</sup> discomfort glare rating, and unified glare rating.<sup>14</sup> Quantitative subjective measurements such as the category rating scales used to evaluate glare are prone to many forms of bias.<sup>15</sup> Involuntary physiological responses such as pupil dilation provide an alternative, objective evaluation of the discomfort glare and may help to understand the cause.

In two studies, pupil diameter was investigated alongside ratings of discomfort. Hopkinson<sup>16</sup> concluded there was no relationship between pupil diameter and the degree of discomfort from glare. In that experiment using a constant background luminance, the glare luminance was slowly increased to the point at which it was considered just perceptible, at which point pupil size was determined using flash photography. Following 5 minutes of adaptation, the glare luminance was increased to find the points at which glare was considered just acceptable, just uncomfortable, just intolerable. and definitely intolerable. Hopkinson<sup>16</sup> reported that pupil diameter varied "hardly at all," despite the variation in discomfort from just perceptible to definitely intolerable. However, this may be due to stimulus range bias<sup>15</sup> or to errors in the method of pupil size measurement rather than lack of relationship between discomfort glare and pupil size. Using a more precise methodology, Stringham et al.<sup>17</sup> examined discomfort glare under a limited range of conditions (two background luminances and one glare luminance), with discomfort evaluated using a 10-point scale (ranging from not noticeable glare to unbearable glare) and monitored pupil diameter using infra-red photography. They found that pupil diameter reduced as glare become more unbearable (correlation coefficient for bivariate analysis [r] = -0.429, P = 0.037): the smaller the pupil size, the higher the discomfort rating, which is somewhat paradoxical as less light is reaching the

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retina. To extend this background, we needed further confirmation of the change in pupil size with discomfort.

In previous studies, the parameter recorded was absolute pupil size.<sup>16,17</sup> However, absolute pupil size depends also on the luminous condition to which the eye is adapted.<sup>16</sup> In other words, pupil size may be jointly affected by background illumination condition and glare source. Investigating how the pupil constricts when it is exposed to glare in comparison to when it is adapted to background illumination may characterize discomfort glare more accurately.

A reaction to glare causing discomfort is a flinch response in the muscles surrounding the eye (i.e., squinting), and the intensity of the electrical activity in these muscles, the electromyography (EMG), can be measured easily.<sup>18</sup> Murray et al.<sup>18</sup> compared EMG and subjective responses (using a 10point scale similar to that by Stringham et al.<sup>17</sup>) for glare presenting an illuminance at the eye of between 20 and 6000 lux and concluded that the correlation between these measurements was significant (using coefficient of determination for bivariate analysis  $[R^2]$  of  $\geq 0.659$ , P < 0.001). Berman et al.<sup>19</sup> also used EMG as an objective measure but recorded the subjective response by using a horizontal line with key words (e.g., perceptible and intolerable) to identify points along the line, and concluded that there was significant between-subject variation in both measurements. Stringham et al.<sup>20</sup> investigated photophobia, which their definition suggests is a case of extreme (intolerable) discomfort glare, and found significant correlation (r = 0.98, P < 0.001) between subjective ratings of photophobia and EMG-derived thresholds from their two participants.

Electromyography records the electrical activity produced by skeletal muscles, which in glare studies are the extraocular muscles,18 and has uses including diagnosis of categories of disease to aid with the diagnosis of nerve injury and with other problems of the muscles or nerves.<sup>21</sup> Electrooculography (EOG) is an alternative measure of biopotential, measuring the corneoretinal standing potential that exists between the front and back of the eye to record eye movements. If the eye moves from its center position toward one of two electrodes (placed either above and below or to the left and right of the eye), this electrode sees the positive side of the retina, and the opposite electrode sees the negative side of the retina, resulting in a potential difference between the electrodes, which gives a measure of the eye's position. A main application of EOG is recording eye movement,<sup>21</sup> and it has been used in previous studies to investigate the relationship between evestrain and visual fatigue.<sup>22-25</sup> Thus, in the present study, we investigated the use of EOG as an alternative to EMG in measuring the involuntary vertical movement of the eyeball in response to discomfort glare and nystagmus.<sup>21</sup>

This article presents the results of experiments in which pupil size and eye movement responses to discomfort glare were measured under various lighting conditions and based on more human participants than in previous studies. This extends previous work by using EOG rather than EMG to record eye muscle movement and by considering pupil size following on-set of glare relative to its size when adapted to the background lighting rather than absolute size.

#### **METHODS**

#### **Participants**

Twenty Asian participants were recruited for this experiment. Ten were between 20 and 30 years of age (eight males and two females; mean  $\pm$  SD age = 24.5  $\pm$  1.6 years old) and 10 were

TABLE 1. Independent Variables Included in the Experiment

	Young, <i>n</i> = 10		Seniors, $n = 10$	
Independent Variable	No. of Levels Level		No. of Levels Levels	
CCT of glare source, K	2	3300	2	3300
		5700		5700
Vertical illuminance provided by	4	20	4	20
the glare source, $E_g$ : lx		50		50
		125		125
		300		300
Vertical illuminance provided by	3	0	3	0
ambient light, $E_b$ : lx		10		10
		200		200
Horizontal viewing angle, $\theta^{\circ}$	4	2	1	2
		4		
		8		
		16		

lx, lux.

between 55 and 65 years of age (three males and seven females;  $60.8 \pm 3.9$  years old). All participants were color normal as tested by using the Ishihara test and had normal visual acuity as tested by Snellen chart; none of them reported having any serious eye-related disease, and all had black irises. Only the young group wore Tobii eye-tracking glasses during the experiment. One reason for recruiting from two age groups was to explore differences in EOG and discomfort associated with changes in the macular pigment.<sup>26-30</sup>

#### Apparatus

The experiment was carried out in a room  $2 \times 2 \times 2$  m, in which the walls were painted white, with a reflectance of 90%. This is a similar situation to that used by Berman et al.<sup>31</sup> investigating visual perception in interior spaces. For tests with reduced luminances, the walls were covered by black felt with a reflectance of 10%. The participant sat facing the center of the rear wall, and 1.5 m from that wall. A fixation marker (cross mark) was located on the center of the rear wall at approximately the eye level of the seated participant.

Ambient lighting was provided by four ceiling recessed 8000 K light-emitting diode (LED) panels, with a surface area of  $600 \times 600$  mm. The output of these LED panels was adjusted by using pulse-width modulation. Glare was induced with a customized LED luminaire having a circular emitting surface and fitted to a horizontal track on the rear wall to allow movement in the horizontal plane. This glare source subtended an arc of  $10^{\circ}$  at the observer's eyes and was located  $10^{\circ}$  vertically above the fixation point.

#### **Independent Variables**

Four independent variables were included in this experiment: correlated color temperature (CCT) of glare source, vertical illuminance at the eye provided by the glare source  $(E_g)$ , vertical illuminance at the eye provided by ambient light  $(E_b)$ , and the horizontal viewing angle between the fixation mark and the glare source  $(\theta)$ . Past studies have demonstrated that each of these variables affects discomfort associated with exposure to bright light.<sup>12,20,32</sup>

Lin et al.<sup>12</sup> used subjective ratings to investigate how glare source luminance  $(L_g)$ , background luminance  $(L_b)$ , and the solid angle of the glare source subtended at the eye  $(\omega)$  and  $\theta$ affected discomfort, and from these data developed Equation 1 to predict the degree of discomfort.



**FIGURE 1.** Typical EOG response to the onset of glare. In this example, the glare source was switched on at 155.7 s. The frequency of the low cutoff filter of the EOG amplifier was 0.05 Hz; high cutoff filter was 100 Hz. Typical nystagmus has been found at approximately 4 Hz, <sup>34</sup> which was within the range measured by the equipment.

$$deBoer \, rating = 3.45 - \log\left(\frac{(L_g \times \omega)^{2.21}}{L_b^{1.02} \times \theta^{1.62}}\right). \tag{1}$$

Because the vertical illuminance at the eye provided by the glare source at a given position,  $E_g$ , is proportional to the product of  $L_g$  and  $\omega$ ,  $E_g$  was used in the current study to represent the combined effect of  $L_g$  and  $\omega$ . Also, the vertical illuminance at the eye provided by the background,  $E_b$ , is proportional to  $L_b$ ;  $E_b$  was used to represent  $L_b$ . Levels of each independent variable are listed in Table 1; full-factorial design resulted in 96 lighting conditions.

The 10 young participants experienced all 96 conditions. In order to reduce the experiment duration for the 10 senior participants, only one horizontal viewing angle (i.e., 2°) was included, and hence, each participant experienced only 24 conditions.

#### **Dependent Variables**

Three dependent variables were included in this experiment: vertical EOG, pupil size, and rating of discomfort glare using the de Boer scale.

Electro-oculography characterizes movement of the eye and was recorded at 10-ms intervals using a data acquisition system (MP 150; Biopac, Goleta, CA, USA). This system was synchronized with the DC driver controlling the output of the glare source so that EOG data were recorded synchronously with the on/off state of the glare source. Three electrodes were attached around one of the participant's eyes, with the positive electrode above the eye, the negative electrode below the eye, and the ground wire at the forehead. This enabled vertical movement of the eyeball to be recorded. When the eyeball moves downward, EOG becomes positive; when the eyeball moves upward, EOG becomes negative. For half of the participants, the electrodes were attached around the left eye and for half around the right eye.

Pilot studies were used to identify the different types of movement to enable the EOG values to be screened to capture those eye movements that were a response to the onset of glare and exclude movements such as looking away from the fixation point and normal blinks.<sup>33</sup> A total of 6.1% of the data was considered inappropriate measurement of movement due to glare and thus was discarded. A typical EOG response is shown in Figure 1. What this shows is that EOG activity takes place typically in the first 0.5 second and then returns to base



FIGURE 2. An example of pupil size recording. A: glare source switched on; B: point at which pupil responded; C: pupil reached minimum size; D: the glare source was switched off; E: the pupil began to increase in size; F: pupil size approached that of pre-onset.

level. Hence, we analyzed only the 50 EOG values within the first 0.5 second.

Electro-oculography recorded the movement of the eye.<sup>21</sup> In this study we used the average eyeball movement speed (*AEMS*) to characterize the physiological response to glare (Equation 2); the higher the *AEMS*, the faster the eye moved, as follows,

$$AEMS = \frac{\sum_{i=1}^{n-1} \frac{|V_{i+t} - V_i|}{T}}{50},$$
(2)

where V = EOG value at certain time (*mV*) and T = the sampling cycle interval (*s*).

Pupil size was measured at 20-ms intervals during the entire experiment using Tobii eye-tracking glasses, as were used in previous studies to measure pupil size.<sup>35-37</sup> Measurements of spectral transmittance confirmed that the glasses had only a small effect on the spectra of the two lamps used in the current study. For those test participants who wore the glasses, the light levels were adjusted to maintain the required illuminance at the eye (Table 1).

Figure 2 shows an example of the pupil size data recorded. Point A (Fig. 2) indicates the time when the glare source was turned on. It can be observed that the response of pupil size can be divided into four periods, as follows<sup>38</sup>: (1) the latent period from A to B, in which the pupil has not responded to illumination (usually approximately 300 ms); (2) the contraction period from B to C, in which the pupil has shrunk to its minimal size; (3) the stable period from C to E, which includes point D, the point at which the glare source was switched off (pupil size does not change significantly during this period); and (4) the recovery period from E to F, during which the pupil size gradually becomes larger.

Reduction of pupil size was characterized by relative pupil size (RPS), as defined by Equation 3,

$$RPS = \frac{P_s \frac{\sum_{i=1}^{10} P_{min}}{P_s}}{P_s},$$
(3)

where RPS = reduction of the participant under each lighting condition;  $P_s$  = the baseline pupil size of the each participant under each lighting condition, measured immediately before the glare source was turned on (Fig. 2, point A); and

$$\frac{\sum_{1}^{10} P_{min}}{10},$$

which yields the average of the 10 lowest values of pupil size recorded for each participant under each lighting condition during the stable period (Fig. 2, between points C and E).

Subjective evaluation of the degree of discomfort due to glare was obtained using the de Boer rating scale,<sup>5</sup> a 9-point scale widely used for glare evaluation<sup>6,9,11,12</sup> in which a rating of 1 represents unbearable glare and a rating of 9 represents just noticeable glare.

#### Procedure

At the start of each test session, the experimenter explained the procedure and gained informed consent to participate. The participant was seated in the test room, and the experimenter attached the electrodes around one of the participant's eyes and confirmed the success of the EOG data collection. The experimenter then switched on the overhead LED sources to provide the background illuminance according to the order determined before the experiment. A 10-minute period was allowed for adaptation to the background illumination. The experimenter then set the glare source to the first setting and asked the participant to fix his or her sight on the fixation point. After 3 seconds, the glare source was turned off and the participant was asked to rate the discomfort experienced using the de Boer scale. A 1-minute interval was allowed before moving to the next trial, allowing readaptation to the background illumination.

Trials with different background illuminances were carried out as separate blocks, within which combinations of illuminance and position of the glare source were presented in a random order. The blocks were carried out in an order that was counterbalanced between participants. Young participants carried out trials over 2 days, with 3300 K and 5700 K trials on separate days. Senior participants completed evaluation of the 24 light settings in 1 day. Presentation order of the two levels of CCT was counterbalanced between participants.

The experimental protocol was approved by the Institutional Review Board of Fudan University.

#### **RESULTS AND ANALYSIS**

#### de Boer Ratings

The subjective evaluations of discomfort due to glare are shown in Figures 3 and 4 for the young and senior participants, respectively. For the young group, Figure 3c shows the variance ( $\pm$ SE) for a sample of conditions, this variance was similar under all conditions. First, these show that the test stimuli provided a wide range of glare conditions according to the de Boer rating scale. Second, they illustrate the expected trends that discomfort glare is rated to be higher with lower background illuminance, higher glare source illuminance, and lower eccentricity.<sup>12</sup>

Repeated-measures analysis of variance (ANOVA) was used to test the effect of the independent variables on de Boer ratings (Table 2). This suggests that background illuminance, glare source illuminance, and the interaction between these two variables are significant effects for both age groups and that viewing angle is a significant effect for the young age group. The data do not suggest that CCT is a significant effect.

#### Average Eyeball Movement Speed

Repeated measures ANOVA was used to test the effect of the independent variables on AEMS (Table 3). Because the young and senior participants did not experience identical conditions, data from the two groups were analyzed separately. This suggests that background illuminance, glare source illuminance, and the interaction of these two variables are significant effects for both age groups and that viewing angle is a significant effect for the young age group. Data do not suggest that CCT had a significant effect. This pattern is identical to that found for de Boer ratings of discomfort: both measurements of discomfort responded in a similar way to changes in lighting.

Figure 5 shows average AEMS plotted against de Boer ratings for two groups of participants. For conditions providing a lower level of glare (i.e., de Boer ratings of >5) the change in AEMS between steps of the de Boer scale are relatively small, but for conditions providing a higher level of glare (i.e., de Boer ratings of  $\leq$ 5) then AEMS changes more rapidly, and this increases more rapidly for senior than for young participants. Larger variance can be observed among the senior participants than the young participants.



FIGURE 3. Mean de Boer rating evaluated by the young participants under each lighting condition. Note different line types in (a) and (b) represent different viewing positions of the glare source: *solid lines* are  $2^\circ$ , *dotted lines* are  $4^\circ$ , *dashed lines* are  $8^\circ$ , and *long-dashed lines* are  $16^\circ$ . (a) The conditions with a 3300 K glare source; (b) the conditions with a 5700 K source; (c) the conditions with a 3300 K source and  $2^\circ$ viewing position, shown with standard *error bars*.

#### **Relative Pupil Size**

Analysis using repeated-measures ANOVA suggested that background illuminance, glare source illuminance, and viewing angle are significant effects (Table 4). The data do not suggest that CCT is a significant effect, nor do they suggest the

 TABLE 2.
 Significant Effects Found in Subjective Ratings of Discomfort (de Boer Rating)

Independent Variable	Age Group	F Value	df	P Value
Background illuminance, $E_b$	Young	46.88	2	< 0.001
	Senior	7.74	2	0.004
Glare source illuminance, $E_g$	Young	115.81	3	< 0.001
0	Senior	3.41	3	0.032
Viewing angle, $\theta^{\circ}$	Young	33.60	3	< 0.001
Interaction: $E_b \times E_g$	Young	2.82	6	0.024
	Senior	33.91	6	< 0.001





**FIGURE 4.** Mean de Boer rating evaluated by the senior participants under each lighting condition, shown with the standard error. (a) The conditions with a 3300 K glare source; (b) the conditions with a 5700 K glare source.

interaction of background illuminance and glare source illuminance to be significant. As shown in Figure 6, RPS is correlated ( $R^2 = 0.38$ , P < 0.001) with de Boer rating, with a correlation coefficient of -0.61. In other words, when the glare source provided more discomfort, the pupil became smaller in comparison to that just before presentation of the glare stimulus.

#### DISCUSSION

This experiment confirmed involuntary physiological responses to visual conditions causing discomfort, pupil constriction, and movement of the muscles surrounding the eye. It was found that these responses were correlated with subjective evaluation of discomfort under various lighting conditions.

Lin et al.<sup>12</sup> characterized discomfort glare using luminance to characterize the effects provided by the background and glare source (Equation 1) and found a high degree of correlation with de Boer ratings ( $R^2 = 0.93$ ). In the current study, illuminance was recorded rather than luminance. However, this should have a linear correlation to the luminance used by Lin et al.,<sup>12</sup> as  $E_g \propto (L_g \times \omega)$  and  $E_b \propto L_b$ . Equation 4 is

TABLE 3. Sig	nificant	Effects	Found	in	AEMS
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Independent Variable	Age Group	F Value	df	P Value
Background illuminance, $E_b$	Young	16.75	2	< 0.001
	Senior	4.71	2	0.023
Glare source illuminance, $E_{g}$	Young	18.45	3	< 0.001
0	Senior	9.91	3	< 0.001
Viewing angle, $\theta^{\circ}$	Young	3.16	3	0.041
Interaction: $E_b \times E_g$	Young	2.78	6	0.020
	Senior	4.71	6	< 0.001



FIGURE 5. Relationship between average AEMS and de Boer rating for two groups of participants, shown with the standard error.



FIGURE 6. Relationship between RPS and de Boer rating.

thus a transformation of Equation 1, using illuminance rather than luminance, with the constant established as the best fit with the combined results of the young and senior participants and with the background illuminance set to 0.188 in those trials when it was zero. Figures 7 and 8 show the mean de Boer ratings given by the participants plotted against ratings predicted using Equation 4 for the parameters defined in Table 1. There is significant correlation between the measured and predicted values for the young ( $R^2 = 0.96$ , P < 0.001) and senior ( $R^2 = 0.88$ , P < 0.001) groups.

$$de Boer Rating = 7.09 - \log_{10} \left( \frac{E_g^{2.21}}{E_b^{1.02} \times \theta^{1.62}} \right)$$
(4)

Using ANOVA to analyze the results did not suggest the effect of CCT was significant for either subjective (de Boer ratings) or involuntary (pupil size, EOG) responses. Lin et al.<sup>12</sup> also concluded that CCT was not a significant factor. This is of interest because the subjective impression of glare may be related to the impression of brightness, and it is known that lighting of different spectral power distribution (SPD) can appear significantly different in brightness,<sup>39</sup> and glare is essentially the result of differences in brightness. One explanation for this conflict is that CCT is not a sufficiently precise metric for variations in SPD, as it is an attempt to

describe a complex SPD with a single number; different SPDs can have identical CCT values. A second explanation is that the effect of SPD on brightness is subtle compared with that of the extreme variations in luminance that cause glare, as can be seen in the results of Boyce and Cuttle.<sup>40</sup> Including metameric stimuli with different spectral composition and stimuli with extreme luminance levels can be used in the future to investigate the relationship between CCT and discomfort glare.

A large variation in perceptual responses among seniors is not unexpected<sup>41</sup> and may be associated with stray light or scattering,<sup>30,42-45</sup> as previous studies identified the fact that seniors suffered more from stray light and that the response to stray light varies a lot among persons.<sup>46</sup> Density of the macular pigment decreases with age,<sup>1,44,46</sup> and previous studies suggest this results in greater visual discomfort.<sup>17,47</sup> Variations in macular pigment density may thus explain the variance found between seniors. In the current study, the senior test

TABLE 4. Significant Effects Found in RPS

Independent Variable	Age Group	F Value	df	P Value
Background illuminance, $E_b$	Young	61.77	2	0.001
Glare source illuminance, $E_g$	Young	9.53	3	0.011
Viewing angle, $\theta^{\circ}$	Young	8.52	3	0.031



FIGURE 7. Mean de Boer ratings of discomfort glare by young test participants (20-30 years of age) plotted against glare predictions by using the model of Lin et al.<sup>12</sup> shown with standard errors.

participants did not report serious eye disease, but this was not assessed through eye examination. The underlying cause of the difference between senior and young people and between seniors merits investigation in future studies.

The correlation found between physiological responses (AEMS and PSR) and subjective responses (de Boer rating) offers an explanation as to why long-term exposure to discomfort glare may lead to visual fatigue and eyestrain.<sup>1,48</sup> The link was demonstrated by Chi and Lin<sup>22</sup> who found significant correlation between visual fatigue and velocity of eye movement.

Furthermore, we took the pupil size constriction caused by background illumination into account and investigated pupil size constriction caused by glare source in comparison to the pupil size when the eyes were adapted to the background illumination rather than solely pupil size. After the eyes are adapted to the background illumination, the exposure to glare will cause the pupil to constrict further. The glare source is affecting the trigeminal nerve, together with the dilator and constrictor muscles. Pupil constriction is expected to compromise the discomfort glare and to reduce the amount of light entering the eye. The current study furthers our understanding that both background illumination and glare source will lead pupil constriction.

Correlation between relative pupil size and discomfort identified here (r = -0.61, P < 0.001) is higher than that in a previous study using absolute pupil size (r = -0.429, P = 0.037).<sup>17</sup> Similarly, the correlation between AEMS characterized by EOG and discomfort rating ( $R^2$  of >0.94, P < 0.001) is also higher than that in a previous study using EMG ( $R^2$  of  $\geq 0.659$ , P < 0.001).<sup>18</sup> This suggests that the two alternative psychological responses proposed here, RPS and AEMS characterized by EOG, provide better correlation with subjective discomfort than absolute pupil size and EMG, measurements used in previous work.

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**FIGURE 8.** Mean de Boer ratings of discomfort glare by senior test participants (55-65 years of age) plotted against glare predictions by using the model of Lin et al.<sup>12</sup> shown with standard errors.

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