Enhancing Performance While Avoiding Damage: A Contribution of Macular Pigment

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Submitted: May 6, 2013
Accepted: August 13, 2013

Citation: Stringham JM, Snodderly DM. Enhancing performance while avoiding damage: a contribution of macular pigment. *Invest Ophthalmol Vis Sci*. 2013;54:6298–6306. DOI:10.1167/iovs.13-12365

Purpose. To compare action spectra for visual discomfort in the fovea and the parafovea and to determine the effect of macular pigment (MP).

Methods. Visual discomfort thresholds to lights from 440 to 600 nm were obtained for six young (<35 y), visually normal subjects with a wide range of MP densities (0.10–0.71 at 30′ eccentricity). Foveal and parafoveal conditions were assessed. Discomfort thresholds were also obtained for xenon-white light (partially absorbed by MP), and a broadband yellow (outside the absorption band of MP). MP was measured psychophysically using heterochromatic flicker photometry (HFP).

Results. For the parafovea, discomfort sensitivity (1/threshold) increased sharply with decreasing wavelength for all subjects. Commensurate with a subject's MP level, MP significantly reduced visual discomfort to short wavelengths (including xenon-white light) for central viewing.

Conclusions. MP simultaneously reduces visual discomfort and protects from light damage at short wavelengths. As a result, MP increases the range of safe and comfortable light levels. Because higher light levels enable improved visual sensitivity for fine detail, these findings indicate that the spectral absorption properties and spatial distribution of MP combine to protect the retina while enhancing visual performance. The action spectrum for visual discomfort closely matches the risk for acute light damage to the retinal pigment epithelium, and it is consistent with a major influence from the intrinsically photosensitive retinal ganglion cells containing melanopsin. We suggest that MP interacts with nonimage-forming retinal input to achieve the dual outcomes of visual discomfort reduction and protection from light damage.

Keywords: photophobia, light damage, visual acuity, carotenoids, xanthophylls, melanopsin, visual discomfort

Visual discomfort elicited by light is a very common experience that usually occurs at transitions from relatively low to high light levels. These transitions can be of the temporal variety (e.g., leaving a dark movie theater on a sunny day) or the spatial variety (e.g., performing a visual search when the background illumination is very high). Unfortunately, ophthalmic patients experience visual discomfort at light levels that most people would consider moderate and comfortable (e.g., normal room lighting). This condition is commonly referred to as photophobia, and is associated with ocular or central pathology such as corneal abrasion, iritis,[1] trigeminal neuralgia,[2] and, frequently, migraine headache (both episodic[3] and interictal[4]). Despite the fact that visual discomfort appears to result from a basic pain-signaling mechanism, the underlying neurophysiological processes are not well understood. Because there are no pain receptors in the retina,[5] the sensation of discomfort or pain is probably derived from the trigeminal nerves, which signal oral and facial pain. These nerves innervate the dilator and constrictor muscles of the irides,[6] and it has been demonstrated that intact trigeminal nerves are necessary to experience photophobia.[5] Moreover, visual discomfort is heavily dependent on adaptation level: the more dark-adapted a person is, the lower the light-induced discomfort threshold.[7] The finding that the pupillary light reflex exhibits adaptation that is roughly commensurate with retinal adaptation[8] led to proposals for the iris's pain-signaling role in visual discomfort. Hopkinson[9] postulated that upon reaching the discomfort threshold, the pupil response was affected by simultaneous antagonistic sympathetic/parasympathetic nervous system activation, which would cause the pupil to fluctuate between constriction and dilation (pupillary hippus). However, when this hypothesis was tested (nearly 40 years later), it was found that subjective reports of discomfort and pupillary hippus were not consistently associated.[10]

An alternative mechanism for the genesis of visual discomfort was recently proposed by Okamoto et al.[11] They recorded light-evoked responses from nociceptive neurons in a trigeminal subnucleus in the brainstem of albino rats. These neurons were activated by bright light and their activation depended on light responses being relayed through the olivary pretectal nucleus (OPN). The OPN is part of a pupillary control circuit that receives its light-driven input from the intrinsically photosensitive retinal ganglion cells (ipRGCs) containing melanopsin.[12–14] Because the nociceptive brainstem neurons are activated even when pupillary constriction is blocked by atropine, it appears that the ipRGC-driven OPN response may

trigger the pain pathway at the same time it serves as a motor command to the iris. Thus, the iris may be serving as an indicator of the strength of neural activation, rather than as the source of the nociceptive input.

Two lines of evidence suggest that the discomfort associated with viewing intense lights serves the function of biological protection.[15,16] First, Stringham et al.[15] found that discomfort increases with decreasing wavelength, so that photophobia occurs more readily for lights that have greater potential to inflict acute photic damage. Indeed, short-wavelength (blue) light has been shown to be nearly 100 times more effective than long-wavelength (red) light at producing acute threshold lesions in the rhesus monkey retinal pigment epithelium.[17] Secondly, photophobia occurs with approximately half as much light directed onto the fovea as compared with the parafovea (the discomfort decreases linearly with eccentricity[16]). This finding suggests that photophobia is a behavioral mechanism that is biased to protect the foveal region of the retina, which is most crucial to visual performance.

Another way in which the fovea is preferentially treated is the selective deposition of the dietary carotenoids, lutein (L) and zeaxanthin (Z), as macular pigment (MP).[18,19] MP is yellow in color and absorbs short-wavelength (blue) light,[19] thereby affording protection from acute light damage.[20] Moreover, L and Z are excellent quenchers of photosensitizers and singlet oxygen, which confers protection against oxidative stress to the tissue.[21] The concentration of MP is highest in the center of the fovea, and characteristically decreases to an asymptote at approximately 5 to 8° eccentricity.[22–24] MP levels vary widely among individuals, ranging from 0 to ~1.5 log optical density at the foveal center.[23] For individuals with relatively high amounts of MP, it has been shown that under central-viewing conditions, MP greatly attenuates photophobia for short-wavelength lights.[15,16,25]

A specific characterization of the effect of different levels of MP on the action spectrum for visual discomfort formed the basis of the motivation for our study. This kind of investigation would allow for determination of response dynamics involved in visual discomfort versus MP level (e.g., linear versus logarithmic) and, depending on the shape of the action spectrum, could reveal neurophysiological mechanisms underlying visual discomfort.

Methods

Subjects

Five males (aged 21, 24, 25, 26, and 33 years) and one female (aged 34 years) served as subjects for this study. Each subject maintained visual acuity of 20/25 or better, and none of the subjects required optical correction. Normal color vision was ensured via use of Ishihara's pseudoisochromatic test plates. Three of the subjects had dark-brown irides, one light brown, and two medium blue. None of the subjects had a history of visual pathology. All experimental procedures adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study. This study was approved by the Medical College of Georgia's Human Assurance Committee.

Apparatus, Visual Discomfort Experiment

A three-channel standard Maxwellian view system with a 1000 W xenon arc lamp was used. In one channel, a xenon-white, 20° diameter, mesopic-level (0.1 cd/m^2) background field served to maintain subjects' adaptation level prior to presentation of the test stimulus. The second channel was used to present a 10′ red fixation point. The third channel provided the test stimulus, an 8° disc of either monochromatic (wavelengths of 440, 460, 480, 500, 530, and 600 nm) or broadband (xenon-white or yellow) lights. Light from the optical system was rendered monochromatic by the use of interference filters (Edmund Optics, Barrington, NJ). The yellow-appearing stimulus was created by passing xenon-white light through a broadband filter (Corning 3-67) transmitting only long (>520 nm) wavelengths. The transmission characteristics of this filter were measured using a spectral radiometer (CS-2000; LightSpex, Chapel Hill, NC). Integrating the transmission values between 410 and 640 nm, we found that only 0.007% of the total luminance was below 520 nm. Because macular pigment absorbs light from approximately 400 nm to 530 nm, use of this filter for producing visual discomfort precluded effects from macular pigment absorption. Neutral-density filters and a neutral-density wedge were used to adjust the intensity of the test stimulus. The diameter of the xenon arc image conjugated with the pupil was 1.50 mm. Energy levels that induced visual discomfort were measured after each session with a radiometer (model S-371; Graseby Optronics, Orlando, FL).

In previous studies of visual discomfort, we used a quasi-physiological method to determine thresholds.[15,16] A criterion squinting response, detected by recording the electromyogram (EMG) served as the operational definition of threshold visual discomfort. During these studies, we recorded subjects' ratings of visual discomfort, and found that these subjective judgments were strongly correlated with the EMG-based thresholds (r = 0.97). Because of this finding, and because visual discomfort is by definition a response based on the subjective interpretation of discomfort, we used subjects' judgments of visual discomfort to determine thresholds for this study. Wenzel et al.[25] have also successfully used such a method to determine thresholds for visual discomfort. To ensure consistent, reliable data, subjects underwent extensive training, which consisted of a 1-hour practice session in which the experimental procedure (see the Procedure section that follows) was conducted. The primary goal of this practice session was to ensure that subjects were able to differentiate the experience of visual discomfort from dazzling or other brightness-related phenomena, such as the well-known photic startle response.[27]

Procedure

There were two conditions for this experiment: central and parafoveal viewing. For the central viewing condition, the dimly lit red fixation point remained in the center of the background field during the approximately 10-minute adaptation period. Once it was determined that the subject could detect the on/off flash of the mesopic-level background field, the background was left on, and the subject was instructed to view the fixation point for 1 minute. The 8° test stimulus, of predetermined spectral composition (see Apparatus section), was then presented for 5 seconds. See Figure 1 (top) for a schematic representation of the central viewing stimulus arrangement, and its relationship to an approximately exponential spatial profile of MP. The order of presentation of the stimulus wavelengths was randomized. A criterion visual discomfort threshold was indicated by a subject's rating of "10" on a scale from 1 (comfortable to view) to 10 (cannot view directly without much discomfort or squinting of the eyes). The method of ascending limits was used, in which a relatively low-intensity light (determined in the practice session for each subject) was gradually increased until the visual discomfort threshold was reached. The light intensity

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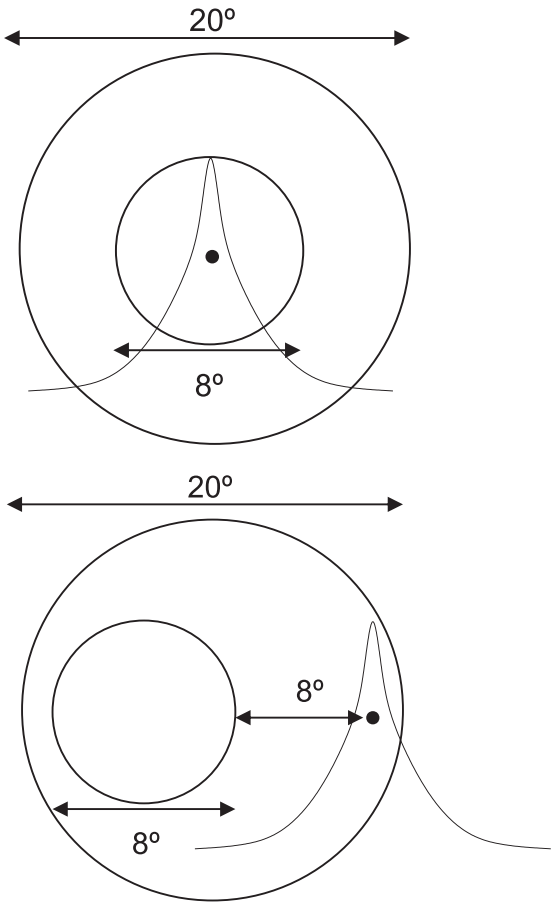

FIGURE 1. *Top*: Stimulus arrangement for central viewing condition. *Smaller circle* denotes the test stimulus, *larger circle*, the background. *Black dot* is the fixation point. Peaked distribution schematically represents a common MP spatial distribution. *Bottom*: Eccentric (parafoveal) viewing conditions.

was increased in steps of 0.1 log units separated by periods of dark adaptation. Before the second and subsequent trials, the subject dark-adapted for approximately 10 minutes and was then instructed to view the mesopic-level background. The background was flashed on and off by the experimenter and the subject was asked if a residual afterimage from the previous trial was present. The perception of an afterimage necessitated additional dark adaptation in order to reach the mesopic threshold. At the point when no afterimage was present, the procedure, as described above, continued. The reader is referred to Stringham et al.[16] and Wenzel et al.[25] for more thorough treatments of the procedure for obtaining thresholds for visual discomfort.

The procedure for the parafoveal-viewing condition was identical to the foveal viewing condition in every way except for the location of the fixation point and the test stimulus: The fixation point was located 8° to the right of the center of the background field, and the center of the 8° test stimulus was located 4° to the left of the center of the background field (see Fig. 1, bottom). This stimulus arrangement allowed for the test stimulus to be imaged onto the temporal retina, outside the spatial extent of measurable MP density.

To ensure a subject's stable alignment with the optical system, a dental impression bite bar and forehead stabilizers were used. A pupil alignment procedure was performed to confirm that the light from the optical system was in focus in the plane of the subject's pupil and passing through the center of the subject's pupil. Each experimental session, in which a subject completed one condition (either central or parafoveal viewing), lasted approximately 1.5 hours. Each subject completed two central-viewing and two eccentric-viewing visual discomfort action spectra.

Measurement of Spatial Profiles of MP

A device slightly modified from the one described by Wooten et al.[28] was used to obtain spatial distribution profiles of MP optical density (MPOD). This device was designed to use heterochromatic flicker photometry (HFP) for measurements of MPOD (for a detailed treatment of the method of HFP, see Snodderly and Hammond[29]). A 460-nm light (maximally absorbed by MP) was alternated in square-wave counterphase with a 550-nm light (not absorbed by MP). The task involved minimizing or nulling the perceived flicker in the test stimulus. To do this, the subject adjusted the radiance of the 460-nm light relative to the 550-nm light. The radiance of the 460-nm null flicker settings were compared with null flicker settings made for a retinal locus known to have little or no MPOD (7° eccentricity). The log difference in these settings yields a measure of MPOD at the test locus. To determine values for MPOD near the foveal center, subjects viewed centrally one of two stimuli, 40′ or 60′ in diameter. It has been shown that HFP thresholds are dominated by the values at edges of the test fields used.[24] This conclusion has been questioned,[30] but recent data confirm that the "edge effect" dominates when the flicker frequency is carefully tuned to the observer's optimal sensitivity.[31] Thus, in our study, the derived MPOD values correspond to the retinal loci at the edges of the test stimulus. For example, using a 60′ diameter test stimulus that is centrally fixated provides an estimate of MPOD at 30′ (the radius of the test field) retinal eccentricity. To obtain MPOD values for retinal eccentricities beyond 30′, we used centrally fixated, 20′-thick annuli (radii of 1° and 1.75°), and fixation points placed at the desired angular distance from the nearest edge of a 2° flickering disc. Because we wished to obtain detailed spatial profiles of MPOD, the subjects performed the flicker-nulling task at several retinal loci (20′, 30′, 1°, 1.75°, 3°, and 7°) along the temporal retinal meridian. Two MPOD profiles were obtained for each subject, with six measurements taken at each locus for each profile. The order of testing retinal loci was counterbalanced with respect to session to control for potential order effects. The averaged profiles were compared with the data obtained in the visual discomfort experiment to determine the relationship between visual discomfort and MP.

Measurement of Lens Density

The Maxwellian-view optical system described above was used to obtain measures of lens optical density at wavelengths of 410 nm and 440 nm, with the reference wavelength at 560 nm. Subjects were initially aligned to the optical system, then dark-adapted for 40 minutes prior to threshold determinations. Subjects were instructed to view a 10′ red fixation point, which was 12° temporal to the test stimulus. The test stimulus was a 5° disc of 410-, 440-, or 560-nm light. The test stimulus was flashed every 5 seconds, with an exposure time of 500 ms. The intensity of the test stimulus was adjusted in 0.10 log steps by the experimenter via a neutral density wedge, and the subject signaled the experimenter with an electronic buzzer if s(he) detected the flash of light. Based on the percentage of visibility at the various test stimulus intensities, psychometric functions were generated for each subject; the intensity associated with the 70% point on the ogive curve was defined as a threshold. Lens optical density was calculated by subtracting the subjects' thresholds from the corresponding

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Table. Individual Subject Data for Age, MPOD at 30′ Locus, and Lens Optical Density

Subject	Age, y	MPOD, 460 nm	Lens Optical Density	
			410 nm	440 nm
VH	25	0.10	0.96	0.46
JW	23	0.22	0.77	0.38
VR	23	0.39	0.99	0.45
NF	22	0.52	0.69	0.31
MS	35	0.64	1.06	0.54
JS	34	0.71	1.01	0.50

rhodopsin extinction coefficients determined by Wald and Brown,[32] using 560 nm (a wavelength that is not appreciably absorbed by the crystalline lens) as the normalizing wavelength at which the lens is assumed to be transparent. This method assumes that the ocular media density is dominated by the crystalline lens.[33]

Results

The Table presents each subject's age, lens density at 410 nm and 440 nm, and MPOD at the 30′ locus. We statistically analyzed the visual discomfort–attenuating effect of MPOD at each eccentricity as well as an integrated MPOD measure, and found significant effects for all measures of MP except for the 5° locus, where MPOD values are low. The standard 30′ measure of MPOD explained the greatest proportion of variance in our visual discomfort thresholds and it was used for all further analyses.

Action Spectra—Relation to Light Damage

The central and parafoveal action spectra for visual discomfort, with sensitivity referred to the cornea, are presented in Figure 2. For all subjects except VH (the subject with the lowest density of MP), the central-viewing condition (top panel) produced functions with a pronounced "notch" in sensitivity centered at 460 nm, the peak of the MP absorbance spectrum. The curves are shifted on the vertical axis to equate them at 600 nm so that the effect of MP is separated from individual differences in overall sensitivity. In a monotonic fashion, subjects' discomfort sensitivity to short-wavelength light decreased with increased MP density. Subject VH, who had the lowest MP density (0.10 MPOD), exhibited a very shallow notch, whereas subject JS, who had the highest MPOD of all subjects (0.71), had the deepest notch. Subject JS was shown to tolerate over 1.0 log unit more energy at 460 nm than subject VH did. For the parafoveal-viewing condition where MP had minimal density (bottom panel), subjects showed a monotonic increase in sensitivity with decreasing wavelength and no notch. Here the curves are plotted on an absolute basis so that individual differences in sensitivity are preserved.

In addition to absorption by MP, these curves reflect the influence of lens absorption. To account for absorption by the lens, subjects' individual lens density curves were calculated by fitting a first-order decreasing exponential function to the empirical data obtained at 410 nm, 440 nm, and 560 nm. Lens absorption values for wavelengths corresponding to those used in the visual discomfort experiments were then determined by interpolation. The action spectra corrected for lens density can be seen in Figure 3. Because the lens more strongly absorbs short- relative to long-wavelength light, when the lens is accounted for, the action spectrum increases most strongly in the short-wavelength region of the action spectra. When this correction is made, the shape of the action spectrum for visual discomfort closely matches the action spectrum for acute light damage to the retinal pigment epithelium determined for rhesus monkeys by Ham et al.,[17] which was also corrected for ocular media absorption.

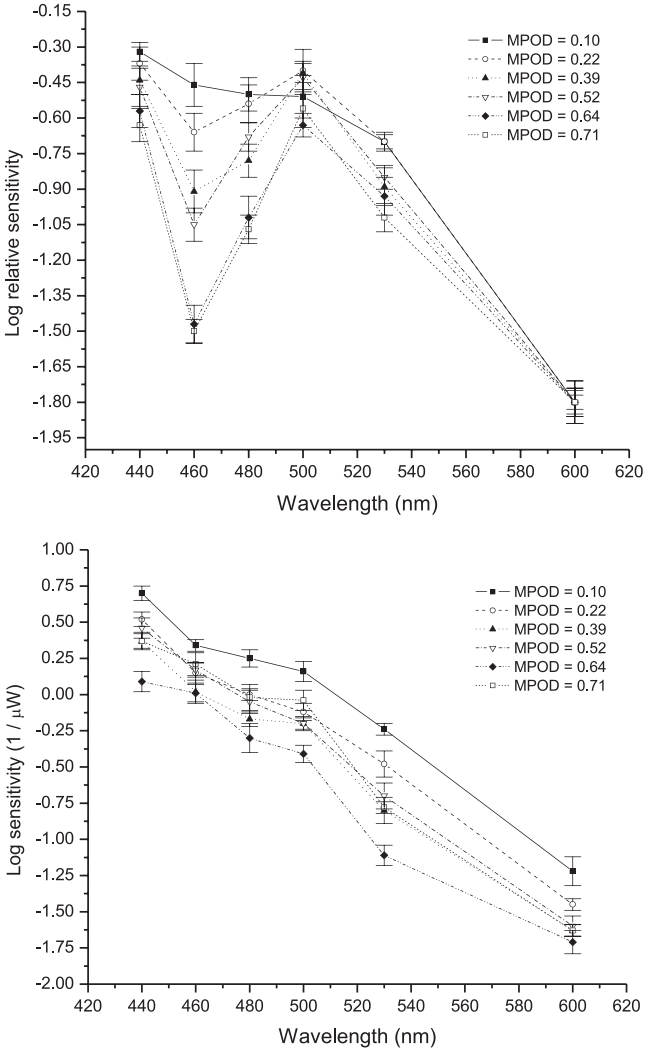

Figure 2. *Top*: Log relative visual discomfort action spectra for central viewing for the six subjects. Functions are shifted on the vertical axis to equate at 600 nm. MPOD values of individual subjects for the 30′ locus are noted in the key. *Bottom*: Visual discomfort action spectra for eccentric viewing (parafovea), plotted in absolute terms (no adjustments). *Error bars* are ±1 SD from the mean.

Difference Spectra—Effect of MP

To more thoroughly investigate the possibility that MP was responsible for the decrease in sensitivity in the short-wavelength region of the central action spectrum, we examined the central/parafoveal difference spectrum (Fig. 4). To determine the specific contribution of MP, corrections were made for each subject's central/parafoveal visual discomfort sensitivity difference. This value was obtained at a wavelength that is not absorbed by MP (530 nm), and it was consistently near 0.3 log units (parafovea less sensitive than fovea). The shapes of the resulting functions are quite similar to the absorption spectrum of MP, which suggests that the attenuation of visual discomfort for the central viewing condition is nearly entirely accounted for by MP absorption. Indeed, upon

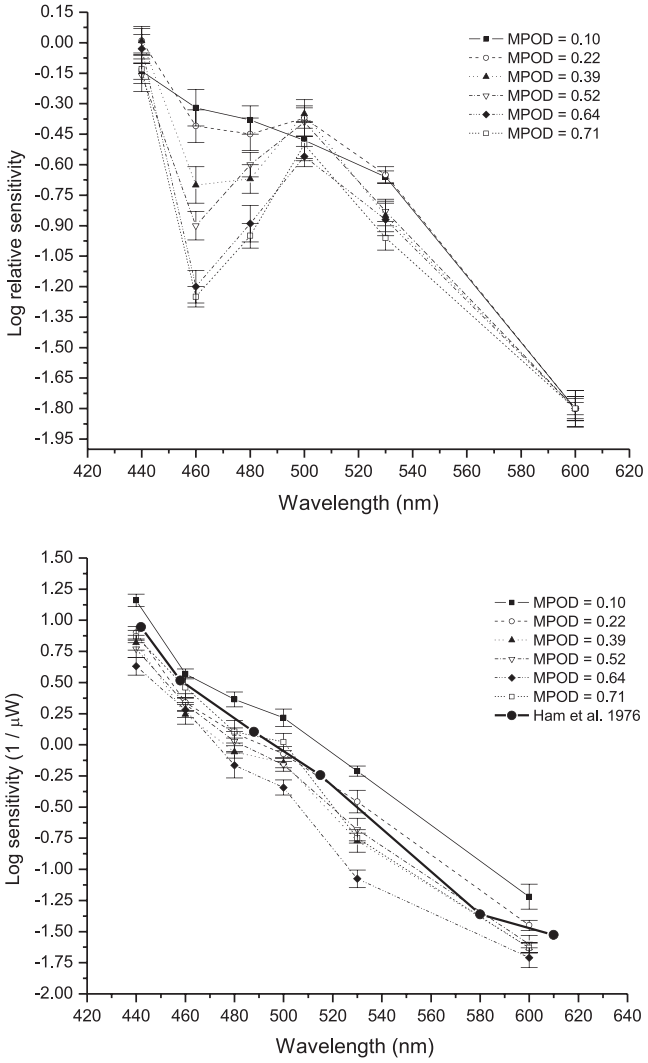

Figure 3. Same as Figure 2, except functions have been corrected for absorption by the crystalline lens (see text for details). *Top*: Lens-corrected log relative visual discomfort action spectra for central viewing for the six subjects. Functions are shifted on the vertical axis to equate at 600 nm. MPOD values of individual subjects for the 30′ locus are noted in the key. *Bottom*: Lens-corrected log relative visual discomfort action spectra for eccentric viewing (parafovea). *Error bars* are ±1 SD from the mean. Ham et al.[17] threshold retinal damage function least-squares fit to subject data, plotted for comparison.

analyzing statistically the differences in sensitivity as a function of wavelength, 460 nm (the wavelength of peak MP absorption) exhibited the largest reduction in visual discomfort sensitivity, compared with wavelengths not absorbed by MP (e.g., 530 nm [$P < 0.001$] and 600 nm [$P < 0.001$]). By contrast, although strongly absorbed by MP, 480 nm deviated from 530 nm ($P = 0.012$) and 600 nm ($P = 0.010$) somewhat less strongly. An interesting feature of the difference spectra that can be seen in Figure 4 is that the size of the difference is larger than would be expected from a simple subtraction of MPOD from the parafoveal spectrum.

The results from the xenon-white versus yellow light experiment are shown in Figure 5. As was found previously[16] for lights not absorbed by MP, approximately twice the amount of light was required in the parafovea, compared with the fovea, to induce visual discomfort (see lower set of lines in Fig. 5). For xenon-white light, however, subjects with high MP were able to tolerate greater amounts of light in the fovea

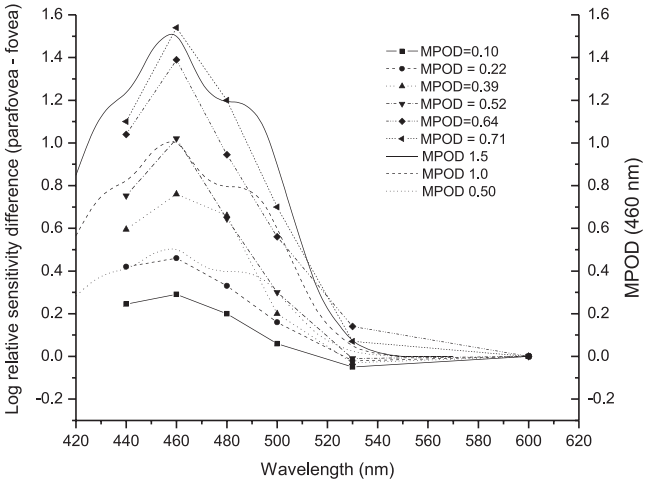

Figure 4. Fovea/parafovea visual discomfort difference spectra for each subject, compared with MP absorption spectrum at peak values of 0.50, 1.0, and 1.50 optical density. All functions normalized to 0 at 600 nm. Individual subject MPOD values for the 30′ locus are noted in the legend.

relative to the parafovea, and the increased thresholds for visual discomfort were strongly related to MP level (see upper set of lines in Fig. 5).

To examine the effect of MP on absolute sensitivity for visual discomfort, subjects' threshold energy levels for centrally viewed xenon-white light were plotted against their MP levels (Fig. 6). The relationship was highly statistically significant ($r = 0.997$, $P < 0.0001$). The slope of the best-fitting line through the data was 0.96, which means that for our stimulus conditions, increases in 0.1 log units MP yield approximately 0.1-log unit decreases in visual discomfort to xenon-white light. Further examination of this point is presented in Figure 7, where the magnitude of the peaks in the difference spectra and individual subjects' 8° spatially averaged MP values are shown to correlate significantly ($r = 0.992$; $P < 0.001$). Figure 8 shows how MPOD at 30′ retinal eccentricity relates to the radiance required to produce visual discomfort. The correlation was found to be significant ($r = 0.982$; $P < 0.001$), and slope of the best-fit line was shown to be 2.08. The slope suggests that the optical density of MP measured at 30′ can simply be doubled to obtain a measure of effective discomfort attenuation, for central viewing of 460-nm light.

Discussion

Visual Discomfort, MP, and Retinal Protection

The findings of the present study support the idea that MP attenuates visual discomfort for centrally viewed lights that contain short-wavelength energy. The effect of visual discomfort attenuation is illustrated graphically for monochromatic light in Figure 2 (top panel) and for broadband, xenon-white light in Figures 5 and 6. Given that the fovea/parafovea difference spectra for all of the subjects yield functions that closely follow the MP absorption spectrum, we are confident that the mechanism underlying the reduction in photophobia for short-wavelength light is dominated by MP. Additional evidence to support this claim is the nearly perfect correlation (Fig. 7) found between the magnitude of the peaks in the difference spectra and individual subjects' 8° spatially averaged MP values. Figure 7 also suggests that the attenuation of

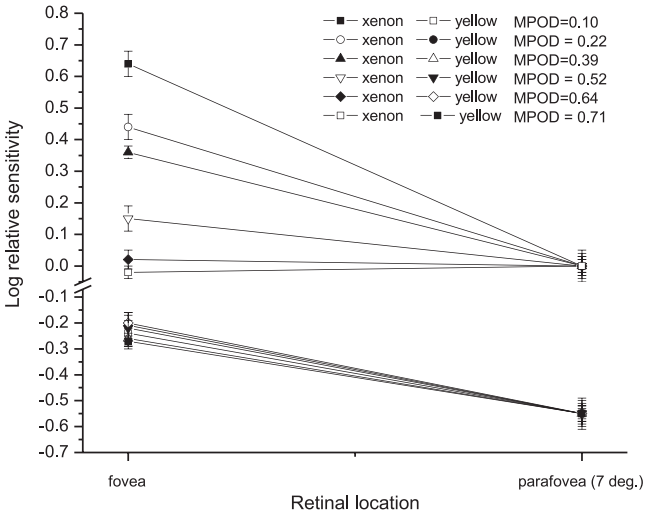

Figure 5. Log relative foveal and parafoveal visual discomfort sensitivities for xenon-white versus yellow light. For clarity, lines between corresponding pairs of points have been plotted, and within each condition, values for each subject have been shifted vertically to equate them at the parafovea. Individual subject MPOD values for the 30′ locus are noted in the legend.

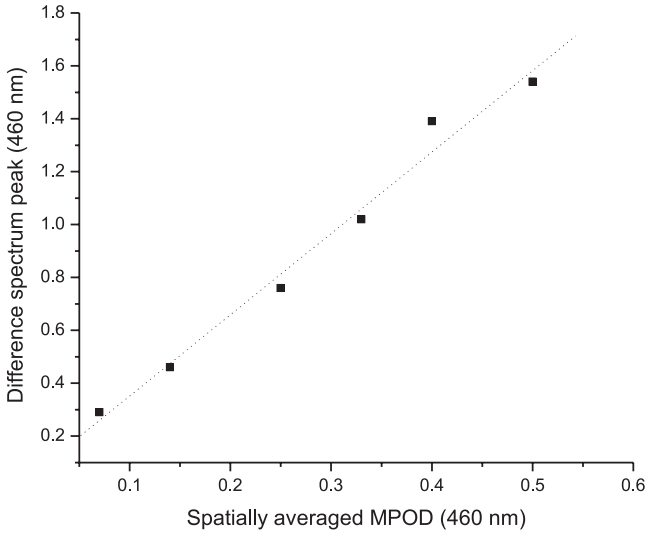

Figure 7. Peak of visual discomfort difference spectra (parafovea minus fovea), at 460 nm, for each subject, plotted against each subject's averaged MPOD (460 nm) over the 8° stimulus area. *Dotted line* is least-squares linear fit to data: $y = 3.08x + 0.04$; $r = 0.992$, $P < 0.001$.

discomfort afforded by MP is much higher than if MP acted as an optical filter with summation over a spatially uniform retinal sensitivity distribution. The slope of the best-fitting line shown in Figure 7 is 3.08, which indicates that the attenuation of visual discomfort is over three times that predicted by spatially averaging MP. This result is consistent with the idea that retinal sensitivity to discomfort is greatest at the foveal center (where MP is also densest) and it declines with eccentricity. As a result of this central enhancement effect, even someone with a very low total amount of MP may be afforded an appreciable reduction in visual discomfort by the small peak at the center. In terms of a practical way to predict MP's reduction in visual discomfort, Figure 8 shows how a common measure of MP (the 30′ locus) relates to the radiance required to produce discomfort. The slope of the best-fit line in this case is 2.08,

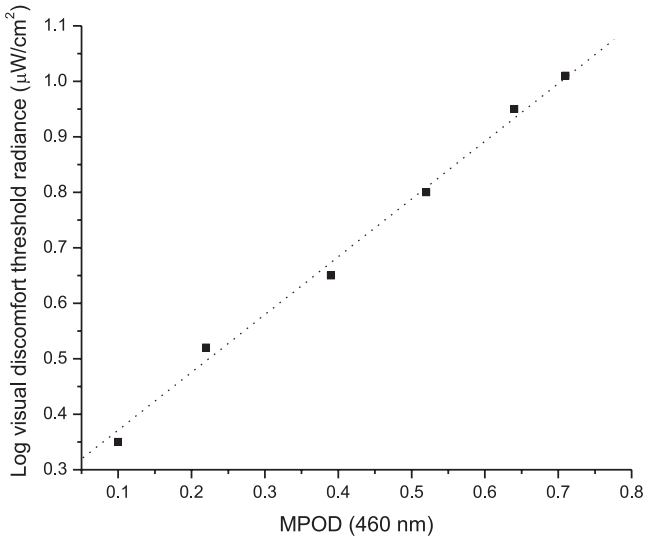

Figure 6. Radiance necessary to elicit visual discomfort with centrally viewed xenon-white light, plotted as a function of subjects' MPOD values (30′ locus). *Dotted line* is least-squares linear fit to data: $y = 0.96x - 0.257$. $r = 0.997$, $P < 0.001$.

which suggests that the optical density of MP measured at 30′ can simply be doubled to obtain a measure of effective discomfort attenuation, for central viewing 460-nm light.

In terms of protection from light damage, it appears that, based on the close correspondence between the action spectrum for visual discomfort and the action spectrum for acute light damage to the retinal pigment epithelium determined by Ham et al.[17] (see Fig. 3), visual discomfort is a behavioral mechanism to prevent damage to the eye.

Implications for Visual Performance

Our results indicate that MP can increase visual performance by increasing the range of comfortable visual operation. For example, visual acuity is strongly dependent on luminance,[34] and by reducing visual discomfort and glare caused by intense light, MP could make tolerable a state of light adaptation where visual acuity is very good. Indeed, results from both cross-sectional[26,35] and longitudinal[36] studies of MP and visual performance in glare support this idea. In terms of temporal vision, Kelly[37] showed that the temporal contrast sensitivity function shifts to higher temporal frequencies with higher retinal adaptation, and that less than 1% contrast is needed to detect flicker for these frequencies. This indicates that, like spatial visual performance, temporal visual performance improves with higher light adaptation. Additionally, Hammond and Wooten[38] found that critical flicker fusion thresholds were significantly positively associated with MPOD. So even at moderate photopic adaptation levels, those with higher MPOD appear to maintain higher temporal visual performance. Moreover, being a short-wave filter, MP does not absorb appreciably in the middle wavelength region (500–600 nm) and therefore does not itself (except perhaps in cases of extremely high MP) markedly reduce luminance. In summary, MP may facilitate visual performance in both moderate and high light, visual environments.

The results of the present study are consistent with the findings of Wenzel et al.,[25] who found a dose-response relationship in which higher levels of MPOD resulted in higher short-wave: long-wave discomfort threshold ratios for centrally viewed lights. Given that MP levels are highly modifiable via

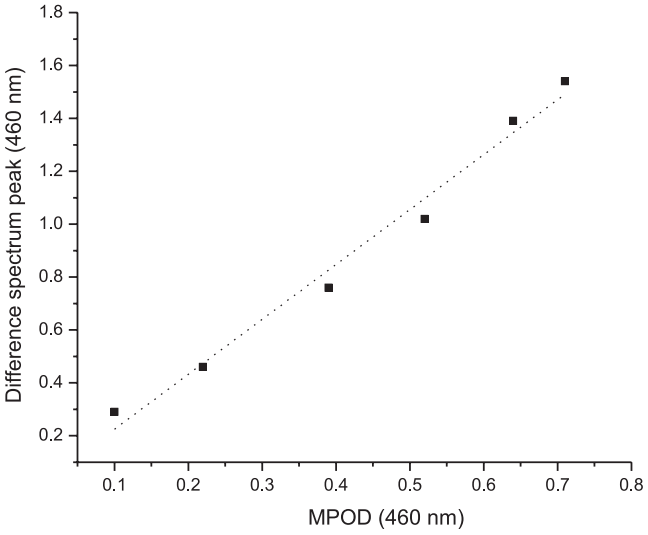

Figure 8. Peak of visual discomfort difference spectrum (parafovea minus fovea), at 460 nm, for each subject, plotted against each subject's MPOD value (30′ locus). *Dotted line* is least-squares linear fit to data: $y = 2.08x + 0.017$; $r = 0.992$, $P < 0.001$.

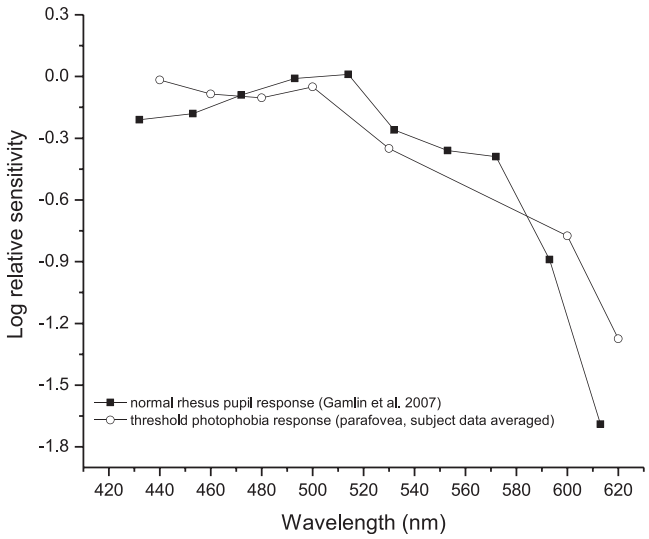

Figure 9. Least-squares fit between subjects' averaged parafoveal visual discomfort action spectrum (*open circles*) and the action spectrum for rhesus monkey pupil constriction (*filled squares*). An estimate of a 620-nm value for visual discomfort was added to the graph based on results of an earlier study by Stringham et al.[15] The estimate assumed that the difference between the 600 and 620 nm thresholds would be the same in this study as in the earlier study. This is a reasonable assumption because these wavelengths would not be affected by individual differences in MP, and one of the subjects participated in both studies. Furthermore, this subject's thresholds in the parafovea were near the mean of the group. Sensitivity plotted on a quantal basis.

diet or supplementation,[39,40] the findings presented in this study suggest that visual discomfort can be reduced by increasing MP. Indeed, Wenzel et al.[25] showed in four subjects that increases in MPOD, via lutein supplementation, increased the discomfort threshold for a broadband short-wave light relative to a broadband long-wave light. Based on our results presented in Figure 5, increasing MP at the 30′ locus by 0.3 log units would result in a roughly 0.29-log unit (i.e., nearly twice the intensity) increase in the intensity of broadband white (e.g., solar) light necessary to produce visual discomfort. Moreover, an increase in MP may allow patients who experience discomfort in moderate lighting to comfortably tolerate these kinds of lighting conditions.

Although the effects characterized in this investigation appear to be consistent with optical filtering and spatial summation, ecologically speaking, there are many other factors to consider. By using Maxwellian view in the present study, what we have gained in experimental control is offset somewhat by what we have lost in ecological validity. However, Stringham et al.[26] presented their 26 subjects with intense light stimuli in free view, which allowed the action of the iris to modulate the amount of light reaching the retina. They found a similar, significant (albeit somewhat weaker than the present study) effect for MP in reducing visual discomfort: Their strength of association between MP and visual discomfort rating was –0.602 ($P = 0.002$).

Candidate Physiological Mechanism

To understand the factors governing visual discomfort more fully requires determination of the neurophysiological mechanisms that mediate it. As noted in the introduction, the trigeminal pain pathway, receiving input from the ipRGCs, appears to be the most likely candidate. To examine the plausibility of this idea, we sought an appropriate comparison between our action spectrum for visual discomfort and the action spectrum for the ipRGCs. For that purpose, Figure 9 compares the action spectrum for pupillary constriction of rhesus monkeys at high irradiances[14] with our human subjects' averaged visual discomfort action spectrum in the parafovea (a value at 620 nm has been added as described in the legend). There is good evidence that the ipRGCs contain melanopsin and control pupil constriction,[12–14] so we can take the pupil measurements as a proxy for direct measurement of the ipRGC neural responses. The overall similarity of the two action spectra is consistent with a major influence of the ipRGCs on visual discomfort, although the discomfort spectrum appears to be broader.

Because ipRGCs receive input not only from melanopsin, but also from rods and cones (reviewed by Fu et al.[41]), their spectral response is very dependent on stimulus conditions, namely visual adaptation. Given these considerations (and possible species differences), we cannot decide whether additional mechanisms are involved or if there is just a different balance in the multiple inputs to the ipRGCs. Nevertheless, there are several ways in which the stimulus conditions in the two experiments are sufficiently compatible that the comparison is useful. First, both experiments used large stimuli: 8° diameter in our case and 36° diameter for the monkey experiments. Second, the stimuli were of long duration: 5 seconds in our case and 10 seconds for the monkeys. Third, the response outlasted the duration of the stimulus, with visual discomfort lingering after stimulus offset and pupillary constriction also continuing after stimulus offset.

A potential objection is that we are comparing our parafoveal action spectrum with the pupil action spectrum that includes illumination of the fovea. Why does the pupil action spectrum not show a notch corresponding to the macular pigment? There are two reasons for this outcome: First, the pupil data were collected with an extremely large (36° diameter) stimulus that would include spatial summation primarily from the parafovea where there is little MP.[22] Second, rhesus monkeys usually have relatively little macular pigment compared with humans (Snodderly, unpublished observations, 2002), so its effect would be small. It is plausible, therefore, that our data are consistent with the proposal that ipRGCs are providing an important input to a risk-avoidance system to

protect the eye. This proposal is also consistent with recent experimental results demonstrating that the ipRGCs can elicit avoidance behavior in neonatal mice.[42,43]

Perhaps the most urgent potential benefit from MP is a reduction in risk for developing AMD,[44] the leading cause of blindness in people aged 65 years and older in developed countries.[45] One could question whether the accumulation of lutein and zeaxanthin in the foveal region of the retina evolved to protect against AMD, because AMD occurs so long after reproduction and the maturation of offspring. For protection from AMD to be a selective pressure, one would have to assume a mechanism like kin selection drawing on the potential benefits of an extended family. Instead, protection against AMD may be secondary to more immediate functions like the ones considered here—protecting against acute retinal damage,[17,20] and improving visual performance by reducing discomfort from bright light.

Acknowledgments

We thank David Berson for helpful discussions of the intrinsically photosensitive retinal ganglion cells.

Supported by the Gustavus and Louise Pfeiffer Research Foundation, Fight for Sight, Research to Prevent Blindness America (PD04042), and NSF IOS 0843354.

Disclosure: **J.M. Stringham**, None; **D.M. Snodderly**, None

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