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THE COLOR APPEARANCE OF STIMULI DETECTED VIA SHORT-WAVELENGTH-SENSITIVE CONES: COMPARISONS WITH VISUAL ADAPTATION AND VISUAL FIELD DATA FOR PERI- OR POST-MENOPAUSAL WOMEN UNDER 70 YEARS OF AGE

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Abstract

Dynamics of foveal light adaptation for vision mediated via short-wavelength-sensitive (SWS) cones were compared for two groups of healthy amenorrheic (peri- or post-menopausal) women not using hormonal medication. Each subject was assigned to a group based on the color name – "lavender" (~2/3 of all subjects) or "white" (~1/3 of all subjects) – chosen in a forced-response paradigm to best describe a threshold-level 440-nm test presented on a larger 3.6 log td 580-nm background that had been viewed for ~5 minutes. During the first 20–30 seconds after this 3.6 log td background abruptly replaced a much dimmer background, the threshold elevations (relative to the steady-state levels measured at ~5 minutes) were significantly greater for the lavender-naming subjects than for the white-naming subjects. However, exponential rates of recovery were indistinguishable for the two groups. A viable interpretation is that the gain of the visual response at background onset is greater for lavender-naming subjects than for white-naming subjects at or distal to a site where responses from middle-wavelength-sensitive and long-wavelength-sensitive (MWS and LWS) cones oppose responses from SWS cones. In addition, the color names derived from foveal testing were related systematically to extrafoveal sensitivities measured with Short Wavelength Automated Perimetry (SWAP), in a manner suggesting that response gain and/or response speed may be greater for lavender-naming subjects in the direction of increased SWS response also. Evidence from other subject populations suggests that the choice of color name and the dynamics of visual response each can be affected by alterations (particularly reductions) of estrogen synthesis and response.

Keywords

adaptation; clinical; color; perception; S cone

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INTRODUCTION

The most common way to effectively isolate responses mediated via short-wavelength-sensitive (SWS) cones is to present a short-wavelength test pedestal (typically about 440 nm) on a yellow background adapting field (typically about 580 nm) that preferentially depresses the sensitivity of responses mediated via middle- and long-wavelength-sensitive (MWS and LWS) cones. Under these conditions, the test stimulus may be perceived as containing reddish and/or bluish components (Cicerone, Krantz & Larimer, 1975, Hurvich, 1981), consistent with the more general understanding that signals from SWS cones are capable of contributing to redness and blueness (Kaiser & Boynton, 1996). However, the color appearance of even simple stimulus combinations depends on many factors – low level visual adaptation (Chichilinsky & Wandell, 1995; Hillis & Brainard, 2005) plus higher order effects (Monnier & Shevell, 2004; Webster, Malkoc, Bilson & Webster, 2002) – that typically are investigated psychophysically using small numbers of dedicated in-house laboratory personnel or students, who are likely to be young adults. Studies using larger populations can complement these mechanistic studies by helping to discern systematic individual differences, which may become more apparent as people age.

Color naming responses of older adults of both genders were recorded in each of two separate population studies that presented 440-nm test stimuli on 580-nm background stimuli for subjects who were elderly (Eisner, 1993) or middle-aged (Eisner, Samples, Campbell & Cioffi, 1995). Whereas almost all men in both age ranges reported that “lavender” described the color appearance of a 440-nm/580-nm test/background stimulus combination better than did either “white” or “blue” at the threshold for detecting the test stimulus, about a third (33%) of the women in each age range reported that “white” best described the color appearance. (The allowable choices of color names were provided in a 3-alternative forced-response paradigm devised on the basis of descriptions offered by subjects tested previously.) The dependence of color naming on gender suggested that hormonal differences might be responsible for the color naming differences. This suggestion led Eisner & Incognito (2006) to assess the color-naming responses of middle-aged women who used the drug tamoxifen, a selective estrogen receptor modulator (SERM) that for decades has been used as adjuvant therapy to prevent recurrence of early-stage hormone-receptor-positive breast cancer. Tamoxifen acts as an estrogen-receptor antagonist in some tissues (including the breast) but as an estrogen-receptor agonist in other tissues (Lonard & Smith, 2002), with any effects on retinal estrogen receptors (Munaut, Lambert, Noel, Frankenne, Deprez, Foidart & Rakic, 2001) still uncertain. As a group, tamoxifen users were significantly more likely to be white-namers than were age-matched female control subjects not using any hormonal medication (Eisner & Incognito, 2006). Furthermore, women using tamoxifen for > 2 years were significantly more likely than women using tamoxifen for ≤ 2 years to be white-namers. These two sets of results were consistent with the broad hypothesis that estrogenic responses affect color appearance.

In addition to assessing color appearance at threshold, Eisner & Incognito (2006) also assessed color appearance at a suprathreshold test illuminance. Raising the test stimulus above threshold caused some changes in the color-naming responses, with the overall proportion of white-naming subjects increasing. Interestingly, the greatest background-induced threshold elevations (as assessed in the steady-state) among tamoxifen users occurred mostly among subjects who described the suprathreshold test stimulus as “lavender”. This result led Eisner & Incognito (2006) to hypothesize that alterations in the gain and/or timing of responses at a low level in a spectrally opponent SWS cone pathway affected color naming. This hypothesis led to the present study, which provides new means for assessing whether and how women’s choices of color name are related to the gain and/or timing of visual response, particularly for women not using tamoxifen. The data are analyzed in the context of the classic (Pugh & Mollon, 1979) 2-site model of SWS-cone-mediated response, which may be regarded as a model of

retinal (low level) response and adaptation. This analytical model was developed to account for a diverse set of psychophysical phenomena, and its incorporation of a spectrally opponent site provides a means for interpreting the changes of SWS- cone-mediated sensitivity occurring over the several minutes following the onset of adapting background fields that do not appreciably stimulate SWS cones. Although Pugh and Mollon (1979) used the perceptually based term “blue/yellow” to denote the spectrally opponent pathway responsible for mediating SWS cone responses, we will instead use the more physiologically based term “S – (L+M)” to denote this pathway (Sun, Smithson, Zaidi & Lee, 2006), bearing in mind that the signals from the different classes of cones need not combine linearly (Giulianini & Eskew, 2007).

Most of the data for this paper were obtained from peri- or post-menopausal women not using any hormonally acting medications and with no histories of adjuvant endocrine therapy for breast cancer. However, to further evaluate the role of estrogenic response (or more specifically of changes in estrogenic response), additional data are reported briefly for women using the aromatase inhibitor (AI) anastrozole (Arimidex®). AIs block estrogen synthesis almost completely in post-menopausal women (Geisler & Lonning, 2005), and they are replacing tamoxifen as the gold-standard adjuvant therapy for early-stage breast cancer in post-menopausal women (Lonning, 2007). Anastrozole was the first AI to receive FDA-approval (in 2002) for this purpose, and it remains the AI used most often. Because AIs reduce all estrogenic effects, whereas SERMS do not, there are distinct advantages to investigating effects of AIs.

As stated at the top of this Introduction, the most common way to effectively isolate responses mediated via SWS cones is to present a short-wavelength test pedestal on a yellow background. Although this approach is used often in experimental laboratories, its most widespread use is clinical, in the form of Short Wavelength Automated Perimetry (SWAP) (Racette & Sample, 2003). Thus, an additional aim of this study was to determine whether color naming is related to SWAP visual field results, and to use this determination to provide further insight into the visual processes underlying the choice of color name. The data were analyzed in the context of a model (Eisner, Toomey, Incognito, O’Malley & Samples, 2006) that dissected the various factors determining SWAP sensitivities for peri-or post menopausal women under 70 years of age and not using any hormonal medication. Since two of the factors in the model were derived from foveal data, a further aim of the present study was to extend our knowledge of relations between foveal and extrafoveal vision.

METHODS

Because the subject populations and individual testing procedures all have been detailed previously, this Methods section highlights the most essential information. Readers are referred to previous papers, cited throughout the Methods section, for additional details.

Subjects

The analyses for this paper were based mainly on data obtained from healthy amenorrheic (peri-or post-menopausal) women 40–69 years old and not using any hormonally acting medications, such as hormone replacement. Some additional data are reported from post-menopausal women 40–69 years old and using 1 mg anastrozole daily (the standard dose) for at least 4 months following successful primary treatment for early-stage breast cancer. None of these women was using any other hormonal medication, and no subjects in either group had previously used any endocrine medication, such as tamoxifen, as adjuvant therapy for breast cancer. Because most analyses for this paper were used for assessing relations between color naming and visual threshold entirely *within* the first group of subjects, this group henceforth is referred to as the “no-hormonal-medication” group rather than as a control group. Amenorrhea was denoted by the absence of menses for 6 months.

All subjects passed a stringent set of criteria for excellent ocular health, which included 20/20 visual acuity or better in one eye and no worse than 20/25 in the other. In addition, all subjects made no more than one minor (i.e., transposition) error in either eye and no major errors on the D-15 test as performed under standard illuminant C, which is the light provided by Macbeth Easel Lamp illumination (no longer manufactured). No subjects had diabetes. These and additional eligibility criteria have been described previously (Eisner, Toomey, Falardeau, Samples & Vetto, 2007; Eisner et al., 2006).

Color naming and dynamic threshold data were obtained for 41 subjects in the no-hormonal-medication group and for 29 subjects in the anastrozole group. The mean ages were 57.3 (SD=6.0) years and 56.4 (SD=6.4) years, respectively. Because SWAP visual field data were not obtained at the outset of the study, SWAP data were obtained for only 29 subjects in the no-hormonal-medication group; the mean age was 57.3 (SD= 5.3) years. Recruitment of anastrozole users began later, after SWAP testing had been incorporated into the protocol. For subjects in the anastrozole group, the mean duration of use was 16.1 (SD= 9.8) months [but reduced to 14.7 (SD=6.9) months after recalculation without the data from one subject having a duration of use = 53 months.]

Subjects were unpaid volunteers. Means of recruitment have been described previously (Eisner & Incognito, 2006). All subjects gave written informed consent prior to enrolling in the study and after explanation of the nature and possible consequences of the study.

Procedures

Instrumentation—All data other than visual field data were obtained using a Maxwellian View apparatus with an eyeguard/chinrest assembly. This device has been used for many population studies (including all the visual function studies from this laboratory that are cited for this paper), and its optics have been described in detail (Eisner, 1986). Visual field data were obtained using a Humphrey Field Analyzer II model 750i instrument (Carl Zeiss Meditec, Dublin, CA).

Stimuli – Maxwellian View testing—All background stimuli for Maxwellian View testing were 11° diameter disks. Subjects were instructed to fixate the center of these disks; thus all testing was foveal. Fixation was aided by a set of diagonal crosshairs with a 4° central gap. Test stimuli were 3° diameter disks that were centered inside the background crosshairs and square-wave modulated (100% contrast, 50% duty cycle) at 1.5 Hz. Thus, the test stimulus on- and off-intervals each were 333 msec. The test stimulus alternation was continuous.

Stimuli – Visual Field testing—Full Threshold SWAP visual fields were administered using a 24-2 test pattern with size V [1.72° diameter] spots. White-on white visual fields were administered using a Swedish Interactive Threshold Algorithm (SITA Standard) with size III [0.43° diameter] spots. These and all other testing procedures and stimulus parameters were conventional. Thus, the background luminance level for SWAP was 100 cd/m^2, the background luminance level for whiteon-white perimetry was 10 cd/m^2, and all test stimulus durations were 200 msec. Additional details are provided by Eisner et al. (2006). Full Threshold SWAP uses a staircase methodology to measure threshold, and SITA Standard uses a staircase/maximum-likelihood hybrid (Turpin, McKendrick, Johnson & Vingrys, 2003).

Choice of test eye—For each subject, one eye was designated as the test eye, and all Maxwellian View data and visual field data were obtained for this eye only. All test eyes had 20/20 or better visual acuity, after modest optical correction if necessary. The criteria for selecting the test eye have been described previously (Eisner et al., 2006).

Maxwellian-View threshold measurements—Increment-threshold measurements were obtained for a series of test/background stimulus combinations under steady-state adaptation conditions, and also as a function of time after onset of the final background (580 nm, 3.6 log td).

Thresholds were obtained using a method of ascending limits, in which the subject signaled when the test stimulus first became visible. For steady-state adaptation conditions, the incremental step size was 0.06 log unit, and four separate threshold measurements were obtained for each test/background stimulus combination (e.g., for a 440-nm test on a 580-nm background). The mean of these four measurements was computed, and these means provide the steady-state threshold values reported in this paper. For thresholds measured as a function of time, the step size was 0.10 log unit, and threshold settings typically were obtained at a rate of about one measurement every 8–10 seconds. Only a single set of these dynamic measurements was obtained for each subject.

Steady-state thresholds were measured for each of three different 580-nm background fields – 2.0 log td, 1.6 log td, and 3.6 log td, in this order – using test wavelengths and adaptation periods described previously (Eisner et al., 2006). SWS-cone-mediated thresholds were measured at 440 nm, with verification of SWS-cone isolation at 440 nm being made by comparing 440-nm thresholds with 490-nm thresholds (Eisner et al., 1995).

Thresholds were measured dynamically as a function of time only for 440-nm test stimuli presented during the first 3 minutes after abruptly raising the illuminance of the 580-nm background from 1.6 to 3.6 log td. Threshold values at 10-second intervals (at 20 sec, 30 sec, … 180 sec) were computed by linearly interpolating the settings made in real time. Because the ratio of MWS to LWS cone sensitivity is virtually identical at 440 and 490 nm (Stockman, MacLeod & Johnson, 1993) and because macular pigment densities are nearly equal at these two wavelengths (Sharpe, Stockman, Knau & Jagle, 1998), isolation of SWS cone-mediated response at 490 nm ensures an additional 1.3 log units of isolation at 440 nm, where SWS cone sensitivity is higher but MWS and LWS cone sensitivities are lower. Thus, isolation of SWS cone-mediated response at 490 nm in the steady state ensures that the dynamic 440-nm thresholds are detected via SWS cones whenever the threshold elevation relative to the steady-state does not exceed 1.3 log units (Eisner et al., 1995). Verification of SWS-cone isolation at 490 nm was made by comparing thresholds for 490 and 510 nm.

Maxwellian-View color naming procedures—Immediately after the final threshold setting was made for the 440-nm test stimulus on the 3.6 log td 580-nm background and before this setting was changed, subjects were asked, “If you had to choose, which of the following 3 colors best describes the test light: blue, lavender, or white?” After each subject gave her response, the test-stimulus illuminance was raised 0.2 log units, and the same question was asked again.

Visual-field threshold measurements – dividing the field into concentric regions —As is standard, the SWAP and white-on-white visual field sensitivities, respectively, were age-corrected at each locus, and expressed in terms (called the “total deviation” (Eisner et al., 2006, Heijl & Patella, 2002)) of their departure from the respective age-corrected population norms. Total deviations are expressed in decibel (dB) units, with 1 dB = 0.1 log unit. For analysis purposes, the visual field data were subdivided into 4 concentric rings representing progressively greater distances from fixation. For the innermost ring (ring 1), sensitivities were averaged from the 4 visual field loci positioned at 4.2° from fixation along the diagonals passing though the center of the visual field. Rings 2, 3 and 4 had mean eccentricities of 10.9°, 16.8°, and 21.5°, respectively. Complete definitions are provided by Eisner et al. (2006). Following Eisner et al (2006), effects of eccentricity on visual field data are evaluated in the present paper

by differencing visual field sensitivities between rings 2 and 3 to compute an "eccentricity factor".

Statistical Analyses

All p-values are based on 2-tailed tests. Comparisons of central tendency were made using Mann-Whitney U tests. All statistical analyses were conduced using SYSTAT 11.0 (San Jose, CA).

RESULTS

Data and analyses from within the no-hormonal-medication group – dynamics of visual adaptation

Threshold elevations (440-nm test stimuli) following onset of the 3.6 log td 580-nm background were computed as a function of time relative to the 440-nm steady-state thresholds measured ~5 minutes after background onset. Figure 1 graphs the threshold elevations at 20 seconds post-onset vs. age. At 20 seconds, data were available for all but 2 subjects and SWS-cone-mediated response could be confirmed to be isolated for almost all subjects (and probably was isolated for all subjects). The data are coded according to each subject's threshold-level color naming response (○ white, ● lavender, and ∗ blue). Only 1 subject called the stimulus "blue", consistent with previous results (Eisner, 1993;Eisner et al., 1995;Eisner & Incognito, 2006).

Among white- and lavender-naming subjects, the degree of threshold elevation at 20 seconds was significantly greater for the lavender-naming subjects ($p = .009$). The corresponding difference was significant at 30 seconds also ($p = .046$), but not thereafter. The difference of medians between groups was 0.38 log units at 20 seconds, and 0.24 log units at 30 seconds. We also assessed the rise in threshold from the baseline SWS-cone-mediated sensitivity level measured earlier after (a) ~3 minutes, and (b) ~5 minutes of viewing a 1.6 log td 580 nm background (Eisner et al., 2006). The between-group difference of medians at 20 seconds was (a) 0.30 log units ($p = .009$), and (b) 0.28 log units ($p = .065$), respectively. The baseline sensitivities of the white- vs. lavender-naming subjects were themselves indistinguishable.

Based on earlier work (Eisner et al., 1995), we expected ~3 minutes to be required for most subjects' sensitivities to asymptote after onset of a 3.6 log td, 580-nm adapting background field. The median threshold elevations (in log units) computed from individuals' steady-state thresholds measured ~5 minutes after onset of the 3.6 log td background are plotted at 10-second intervals from 20–180 seconds separately for white-naming and lavender-naming subjects in Fig. 2. The expectation was borne out, but the lavender-naming subjects appeared to approach asymptotic levels later than did the white-naming subjects, as the threshold elevations appeared to be greater for the lavender–naming subjects for most of the 3-minute period. Medians rather than means were used to represent central tendencies because medians are more immune to distortion by outliers and are more likely to resemble the response of a representative subject, and because determinations of medians (as distinguished from the median values themselves) are unaffected by transformations from one scale of units to another (see next paragraph).

To describe the rates of threshold recovery for each of the two groups, each group's median threshold elevations first were converted to linear units, since SWS-cone-mediated response at or after the site of "S – (L+M)" spectral opponency may be compressed little enough so as to remain linear over the assessed portion of its operating range (Shapiro, Beere & Zaidi, 2003). The results of this conversion are shown in Fig. 3 (left), with the ordinate representing the factor by which threshold is elevated relative to the final thresholds measured much later, ~5 minutes after background onset. The superimposed exponential curves were derived by

transforming the data in Fig. 3 (left) so as to convert a function of the form $y=1+Kexp(-t/t_0)$ to a straight line having a slope equal to the inverse negative time constant $(-1/t_0)$ of the exponential. This allowed the parameters of the superimposed exponential curve to be calculated using linear regression. The transformation function was $f(y) = \ln(y-1) = \ln K - t/t_0$. The results of this transformation are shown in Fig. 3 (right).

Because each group's data from ~30–100 seconds were well described by parallel straight lines (not added to the graph in Fig. 3 [right]), we may deduce that the exponential time constants of recovery over this period were indistinguishable for the two groups. These time constants were t_0 = 35.0 seconds for the lavender-naming subjects and t_0 = 35.7 seconds for the white-naming subjects. These time constants and K values (all computed based on the data from 30 to 100 sec) were used for generating the exponential curves in Fig. 3 (left). The noise in the transformed data corresponding to low threshold elevations (above 100 seconds) is expected, since the logarithmic transformation will amplify small differences from steady-state levels as the corresponding exponential function begins to asymptote. At 20 seconds, the threshold elevation for each group appeared to exceed that ascribable solely to an exponential rate of recovery (see Fig. 3 [left]), perhaps indicating a non-negligible degree of response compression lasting for as long as 20 seconds after background onset. Regardless, if the initial response to the background caused by LWS and MWS cone input to the L+M arm of the "S − (L+M)" spectrally opponent site were greater for the lavender-naming subjects than for the white-naming subjects, the similarity of the exponential rates of threshold change would explain why the threshold elevations appeared to remain higher for the lavender-naming subjects for several minutes. At ~5 minutes after background onset, when the color names were elicited, the sensitivities at 440 nm could be not be distinguished statistically between groups (p = .41 for the color-naming factor in an analysis of covariance with age as the covariate).

Data and analyses from within the no-hormonal-medication group – visual fields

For reasons stated at the end of the Introduction, we also compared color-naming results with SWAP visual field results. Following Eisner et al (2006), these comparisons featured the difference in sensitivities (strictly speaking, the difference in total deviations, see Methods) between SWAP and white-on-white visual fields. This strategy helps to eliminate effects of factors that influence visual field tests generally. There were two main sets of results.

First, at the eccentricity nearest to the fovea (4.2°), the difference in sensitivities between SWAP and white-on-white visual fields was significantly greater for lavender-naming subjects than for white-naming subjects (p = .022). This result appeared to depend mainly on effects occurring for the SWAP fields themselves.

Second, the effect of retinal eccentricity on visual-field sensitivities also was related to subjects' color naming data. The effect of eccentricity was quantified using the same "eccentricity factor" defined by Eisner et al (2006) based on visual field data from rings 2 and 3, which contain eccentricities ranging from ~9° to ~17° from fixation. We found that the SWAP/white-on-white sensitivity difference decreased with eccentricity significantly more for white-naming subjects than for lavender-naming subjects (p = .025). In fact, SWAP sensitivities increased relative to white on-white sensitivities for the majority of lavender-naming subjects. This can be seen in Figure 4, which graphs the eccentricity factor vs. the SWAP/white-on-white sensitivity difference measured at 4.2°. (The ordinate is oriented so that larger *reductions* of SWAP sensitivity with eccentricity are represented in the *downward* direction.) The effect of eccentricity depended mainly on effects occurring for the SWAP fields themselves.

Data and analyses from within the no-hormonal-medication group – changes of color name from threshold to suprathreshold

All the results described thus far were based on subjects' threshold-level color-naming responses. Six subjects in the no-hormonal-medication group (5 subjects with visual field data) switched their choice of color name from "lavender" to "white" when the test stimulus illuminance was raised 0.2 log units, but only one subject switched from "white" to "lavender". These results together provide evidence that subjects' "white" responses at threshold did not result from response uncertainty. The results described next show more specifically how changes in subjects' choices of color name may be related systematically to psychophysical and clinical threshold measurements. The results also indicate that the use of color naming to distinguish groups of subjects must take into account the proximity of the test stimulus to threshold.

Because of the small numbers of subjects switching their responses from threshold to suprathreshold, there was little statistical power for evaluating functional relations concerning changes in color naming. Nevertheless, when the dynamics-of-adaptation data (Fig. 1) were reassessed after restriction to the pool of subjects who called the suprathreshold stimulus "white", women who switched color name (i.e., who had called the stimulus "lavender" at threshold) were found to have significantly greater threshold elevations at 20 seconds than women who did not switch ($p = .039$). In addition, when the visual-field data (Fig. 4) were reassessed for these two subgroups, women who switched color name were found to have significantly greater SWAP/white-on-white sensitivity differences at 4.2° than women who did not switch ($p = .018$). For the results in Fig. 4 concerning eccentricity, $p = .066$. The corresponding between-group analyses (switchers vs. non-switchers) restricted to the pool of subjects who called the threshold-level stimulus "lavender" were suggestive but inconclusive.

Data and analyses involving anastrozole users

In contrast to the results from the tamoxifen users (Eisner & Incognito, 2006) there did not appear to be any effect of the duration of medication use on color naming, although if such an effect existed, it might have been missed since only 3 anastrozole users had been using their medication for more than 2 years. There was a significant effect of age, with the white-naming anastrozole users (mean age = 53.7 years, n=15) being significantly younger ($p = .027$) than the lavender-naming anastrozole users (mean age = 59.4 years, n=14). Given that estrogen levels of post-menopausal women normally continue to decrease with advancing age (Labrie, Luu-The, Labrie & Simard, 2001), this result suggests that the processes underlying the choice of color name may depend on the magnitude of the sudden reduction in estrogen synthesis caused by AI use rather than solely on a low estrogen level itself.

Overall, the threshold elevations at 20 seconds were significantly less ($p = .018$) for the anastrozole users than for women in the no-hormonal-medication group. This result depended largely or entirely on the data from lavender-naming subjects, for whom the difference was highly significant ($p = .009$). Among the anastrozole users themselves, the threshold elevations at 20 seconds after onset of the 3.6 log td background differed little or not at all between white- and lavender-naming anastrozole users. Nor did any of the visual field results described in the second portion of this Results section approach significance when the corresponding analyses were conducted for anastrozole users. The reasons for the negative results are not yet known, but the assembly of negative and positive results suggests that the ability of estrogen (or conversely, estrogen depletion) to affect vision is not limited to a single anatomic site or physiologic effect.

DISCUSSION

Since at least the late 1930s (Stiles, 1939), scientists and then later also clinicians have presented short wavelength test stimuli (e.g., ~440 nm) on longer wavelength adapting stimuli (e.g., ~580 nm) in order to isolate responses mediated by SWS cones at visual threshold. However, color appearance information is recorded and analyzed in this context only rarely. The results of this study show that foveal color naming responses at threshold contain important information that can be used for advancing the understanding of the dynamics of visual response and adaptation. Furthermore, the same foveal color naming responses are related systematically to extrafoveal SWAP visual field data obtained using separate equipment and with different threshold methodologies for women not using any hormonally acting medication. Since obtaining color names requires little extra methodological effort, the results reported for this and a previous study (Eisner & Incognito, 2006) suggest that subjects' (or patients') color naming responses be elicited routinely when 2-color threshold methodologies are used for isolating the responses of SWS cone pathways.

The remainder of this Discussion is divided into two parts. The first discusses mechanistic considerations pertaining expressly to the results from women not using any hormonally acting medication, such as hormone replacement or endocrine therapy for breast cancer. The second discusses some of the evidence indicating that changes in estrogenic response affect visual function.

Visual mechanisms

The rates of recovery of SWS-cone-mediated sensitivity following onset of a moderately bright (3.6 log td) middle-wavelength (580 nm) background can be assessed in the framework of the classic model developed by Pugh & Mollon (1979) to account for sensitivities to test increments detected via SWS cones through a spectrally opponent "S – (L+M)" pathway. We found that the threshold elevations for the first 20–30 seconds after background onset (compared to steady-state levels measured subsequently) were significantly greater for lavender-naming subjects than for white-naming subjects, and that furthermore, the exponential time constants of recovery thereafter (in linear rather than logarithmic units) were indistinguishable for these two groups. These results can be explained by postulating (a) that the initial response in the "L +M" direction to onset of a 580 nm background tends to be greater for lavender-naming subjects than for white-naming subjects, but that (b) the restoring force responsible for returning the response of the "S – (L+M)" pathway towards its equilibrium proceeds with the same first-order kinetics for each subject group.

Pugh and Mollon (1979) distinguished models in which the polarized spectrally opponent signal fed forward onto itself from models in which the polarized spectrally opponent signal fed back onto itself. Because the feedback model but not the feed forward model "predicts that observers with the greater magnitude transients should have faster recovery rates", the results in the present paper favor application of the feed forward model. Thus, given the absence of any compelling evidence for a between-group difference in asymptotic sensitivity levels, the model suggests that a salient response difference between the two color-naming groups occurred at or distal to the site of "S – (L+M)" spectral opponency most responsible for limiting the dynamics of "S – (L+M)" adaptation, perhaps at the small bistratified ganglion cells or even at the outer plexiform layer (Dacey, 2000). That is, the data plausibly can be interpreted to mean that the onset of a 580-nm background induces an "L+M" retinal response that tends to be greater for lavender-naming subjects than for white-naming subjects. This "L+M" response may be specific for an "S – (L+M)" pathway, but this is not known. In any case, since the dynamics of recovery for each color-naming group was well described by a single exponential function after ~20 seconds, it is likely that detection of the 440-nm test pedestals

at threshold was mediated through all or most of recovery via a single pathway, which most likely was the same ON-pathway (McLellan & Eskew, 2000) for each color-naming group.

If the magnitude of the spectrally opponent response in the "L+M" direction to the onset of a 580-nm stimulus differs between subjects, the timing of the visual response must differ too. In the simplest case, if the response gain to onset of the 580-nm background stimulus were greater for lavender-naming subjects than for white-naming subjects, and if the response difference between the two groups were of scale only, then the speed of the response would necessarily be greater for the lavender-naming subjects. It is important to consider whether between-group differences in response gain or speed occur for stimuli that directly stimulate SWS cones.

Since steady-state foveal thresholds differed little or not all between the white- and lavender-naming subjects, our data do not provide evidence for a difference in the gain of responses mediated via SWS cones, although an effect of gain could have been negated or obscured by other factors. In contrast, the parafoveal SWAP sensitivities of the two groups did differ, being lower for the white-naming subjects after age-correction when compared with white-on-white visual fields. In addition, the color naming responses of the two groups differed at the fovea, by definition. These two sets of results are jointly consistent with the single possibility that the temporal response properties of white-naming subjects are relatively sluggish. Since the foveal test stimulus durations were 333 msec but the SWAP stimulus durations were only 200 msec, any subject for whom the temporal integration periods for SWS-cone mediated vision exceeded 200 msec would be selectively disadvantaged on SWAP visual field testing, especially if the temporal integration periods for achromatic white-on-white fields remained below 200 msec (Smith, Bowen & Pokorny, 1984). Moreover, because the ability of a flashed test stimulus to alter the color appearance of a steady background may be diminished when transient responses are reduced (Davies, Faivre & Werner, 1983), a sluggish response to the 440-nm test stimulus might cause the 440-nm/580-nm test/background stimulus combination to be perceived as less lavender (i.e., less bluish and/or less reddish), and hence closer to white. These considerations lead to the testable hypothesis that the temporal integration periods of white-naming subjects are longer than those of lavender-naming subjects, particularly for stimulus combinations causing isolation of SWS-cone-mediated response.

Estrogen and visual function

The bulk of the evidence suggests that estrogenic response affects the color naming of short-wavelength test stimuli presented on 580-nm backgrounds. Eisner (1993) and Eisner et al. (1995) showed that women were much more likely than men to be white-namers, Eisner & Incognito (2006) showed that almost all breast cancer survivors using the SERM tamoxifen for more than 2 years were white-namers (and tended to have low SWAP sensitivities in the peripheral visual field [Eisner et al, 2004]), and the results in the present paper show that white-naming breast cancer survivors who use anastrozole are significantly younger than lavender-naming anastrozole users. A parsimonious way of relating all these results is to postulate that substantial chronic *alterations* of estrogen function impact color naming. Unlike men, women have a clearly demarcated age-related reduction of estrogen synthesis, with the result that post-menopausal women typically have lower circulating levels of estrogen than do age-matched men (Vermeulen, Kaufman, Goemaere & van Pottelberg, 2002; Simpson, 2003). In addition, the body's response to tamoxifen is known to change in multiple ways over a period of several years as resistance develops (Lewis & Jordan, 2005). Considerations in the preceding portion of the Discussion suggest that changes in estrogenic response are capable of affecting visual response gain and/or speed, at least within the pathways responsible for setting SWS-cone-mediated sensitivity. The data from the anastrozole users suggest more specifically that sufficiently profound or abrupt *reductions* of estrogen synthesis can affect visual function, perhaps by causing some types of visual responses to become relatively sluggish. The ability

of estrogen to maintain or bolster neural response transmission and speed represents an active area of neuroscientific investigation (Hu, Cai, Wu & Yang, 2007; Jelks, Wylie, Floyd, McAllister & Wise, 2007), and studies of the human visual system may provide tractable *in vivo* means for assessing effects of estrogen depletion (or estrogen supplementation) on neural response more generally.

Although the dynamics of visual adaptation differed significantly between the anastrozole group and the no-hormonal-medication group when the two groups were compared in toto, the between-group differences became more pronounced when the comparisons were restricted to lavender-naming subjects only. Conversely, the relation between color naming and the dynamics of adaptation that was apparent for the no-hormonal-medication group was either absent or masked for the anastrozole group. These several observations provide further reason for investigating relations between visual response and estrogenic response as directly as possible without relying on classifications subject to the various complexities of color naming.

Testing women across their own menstrual cycles provides another means of assessing effects of hormonal change, bearing in mind that estrogen levels of reproductive-age women stay low for only days at a time and that progesterone and other hormones also cycle (Speroff, Glass & Kase, 1999). Eisner, Burke, and Toomey (2004), who tested several women daily across successive menstrual cycles, reported that one woman exhibited large (reaching 1 log unit) cyclic visual adaptation changes occurring in phase with her menstrual cycle, with the greatest background-induced sensitivity reduction occurring premenstrually and with the least occurring near ovulation, when estrogen levels are highest and progesterone levels have only begun to rise. Moreover effects of visual adaptation ceased to vary cyclically after initiation of oral contraceptive use that involved manipulation of estrogen (and progesterone) levels. The effects of the menstrual cycle on visual adaptation were most evident for sensitivities mediated via SWS cones, but the adaptation properties of other visual pathways appeared to be affected to a lesser degree and with a different time course. The results from this subject suggest that effects of estrogenic change in older women might not be limited to SWS cone pathways. Several other studies have found that 2-pulse resolution is better near ovulation than it is premenstrually (Friedman & Meares, 1978, Wong & Tong, 1974), consistent with the possibility that exposure to estrogen can enhance response gain and/or response speed.

Both types of estrogen receptor (ERα and ERβ) are present within the human retina (Munaut et al., 2001), but although there is direct electroretinographic evidence for hormonal effects on human visual response (Brule, Lavoie, Casanova, Lachapelle & Hebert, 2007), the roles of estrogen receptors for visual processing remain unknown. The results of this study provide additional reason and direction for investigating these roles.

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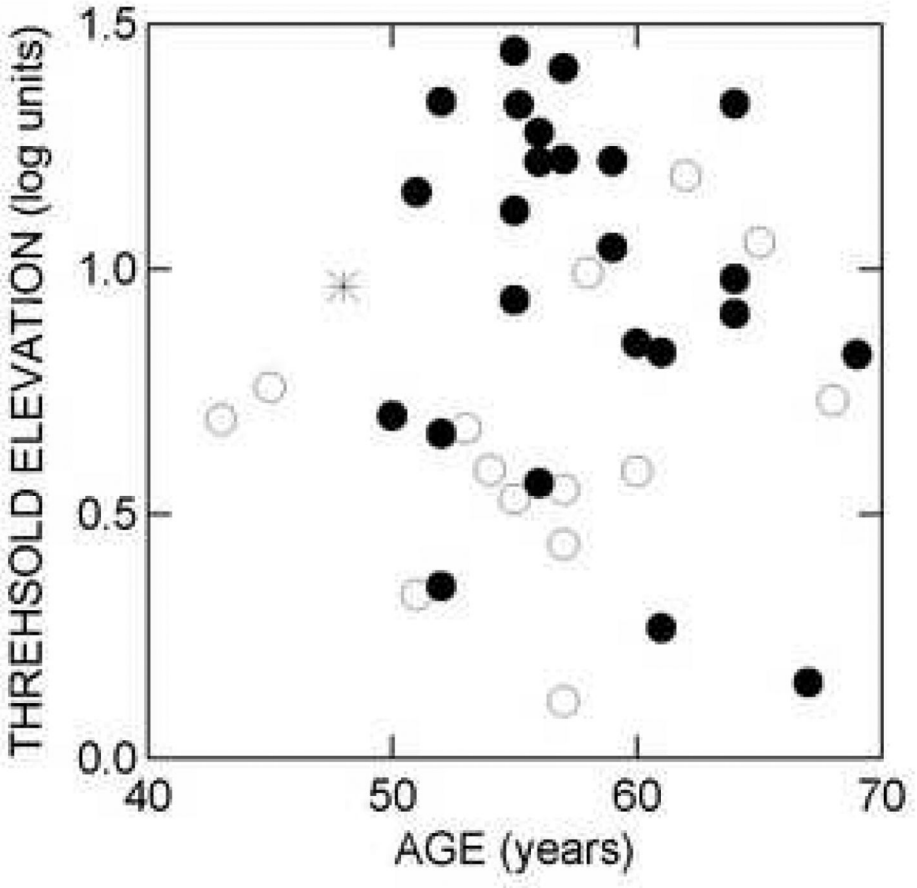

Figure 1.
Threshold elevations (log units) at 20 sec (interpolated values) after onset of the 3.6 log td, 580-nm adapting background field. Filled circles (●) represent subjects who chose "lavender" to best describe the threshold-level 440-nm test stimulus, unfilled circles (○) represent subjects who chose "white", and the asterisk (*) represents the subject who chose "blue". Threshold elevations are computed relative to the final asymptotic thresholds, measured ~5 minutes after background onset.

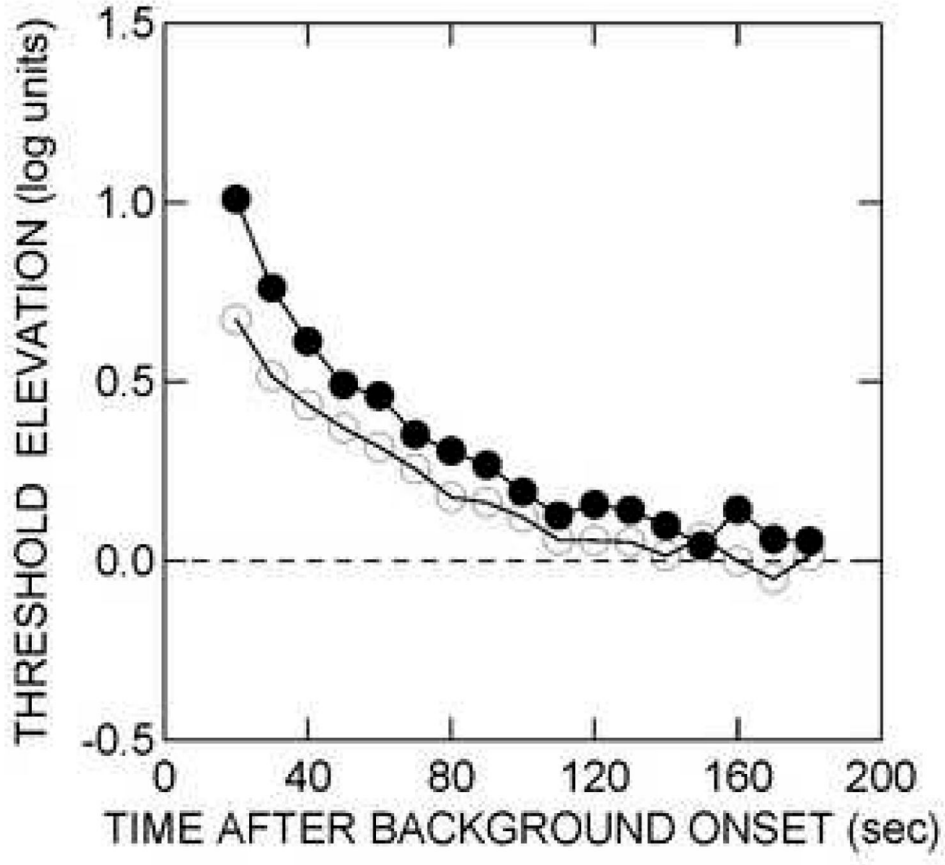

Figure 2.
Threshold elevations (log units) as a function of time at 10-second interpolated intervals after onset of the 3.6 log td, 580-nm adapting background field. Filled circles (●) represent the median values from "lavender-naming" subjects, and unfilled circles (○) represent the median values from "white-naming" subjects. The horizontal dashed line corresponds to no threshold elevation. Connecting lines have no theoretical significance. The between-group differences were significant ($p < .05$) at 20 and 30 seconds. Other details as in Fig. 1

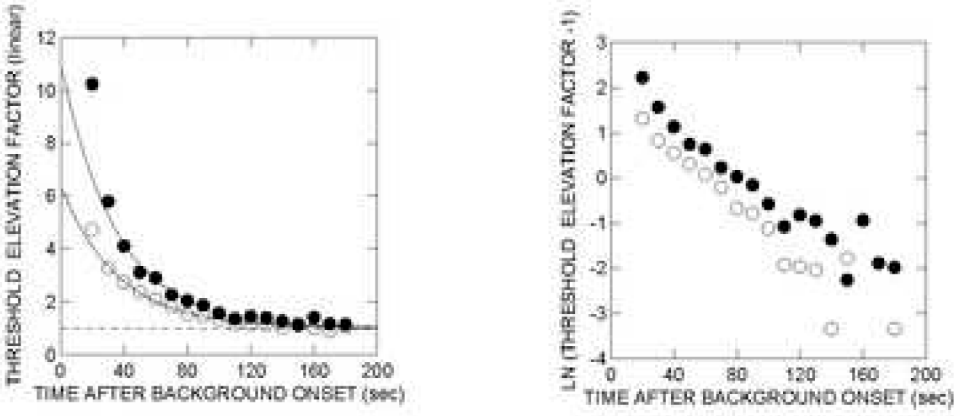

Figure 3.

Figure 3 (left). Threshold elevation factor (linear units, converted from the data in Fig. 2) plotted as a function of time after onset of the 3.6 log td, 580-nm adapting background field. Horizontal dashed line (threshold elevation factor = 1) corresponds to no threshold elevation. The superimposed exponential curves are calculated based on the data from 30–100 sec, as described in the text and using the equation also provided in the legend to Fig. 3 (right). For reference, the interquartile range of threshold elevation factors at 20 sec spanned values of 5.9 to 17.9 for lavender-naming subjects; thus this range contains the value of the exponential curve at 20 sec. For white–naming subjects, the corresponding range spanned values of 3.4 to 5.7. Same symbols as Fig. 2.

Figure 3 (right). Data from Fig. 3 (left) transformed so as to convert an exponential curve of the form $y=1+K\exp(-t/t_0)$ to a straight line having a slope equal to the inverse negative time constant ($-1/t_0$) of the exponential curve. The transformation function was $f(y) = \ln(y-1) = \ln K - t/t_0$. Same symbols as Fig. 2. For lavender-naming subjects, t_0 =35.0 and K=10.1; for white-naming subjects, t_0 =35.7 and K=5.62.

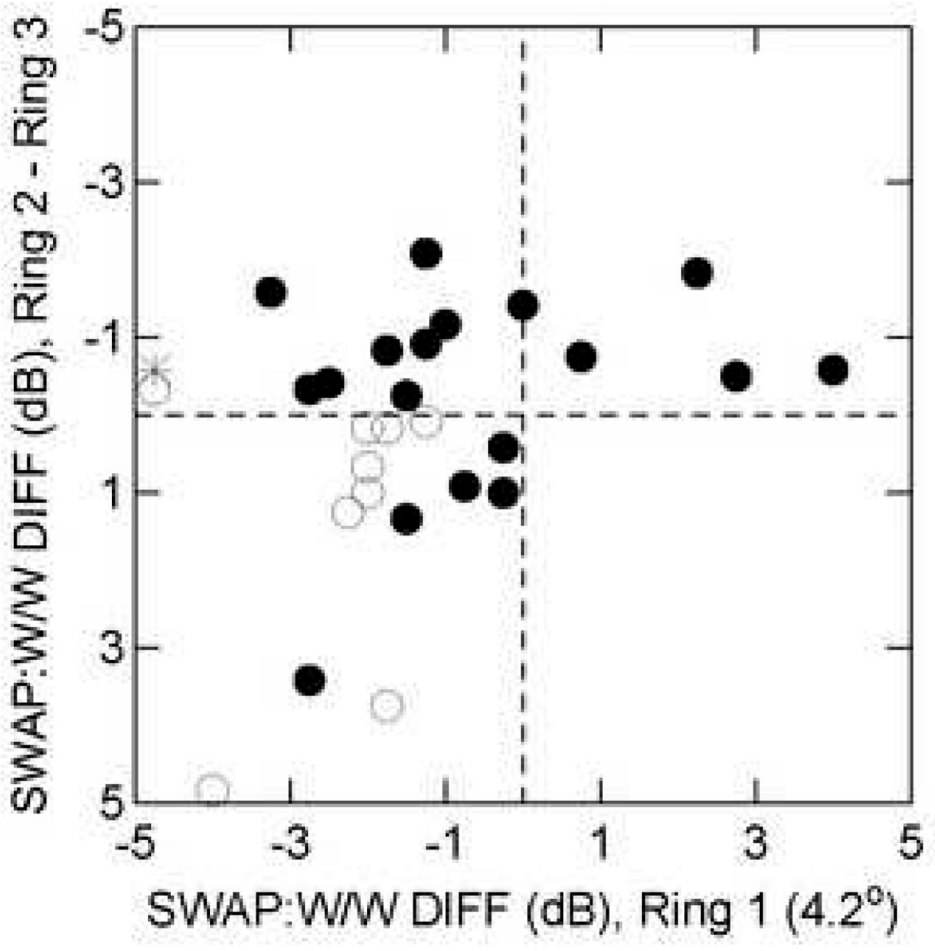

Figure 4.
Data represent differences (in dB units) between Full Threshold SWAP and SITA Standard white-on-white visual field "total deviations". The abscissa represents each subject's total deviation difference averaged across the 4 points in the innermost portion of the visual field, at 4.2° (ring 1, see Methods). The ordinate represents the each subject's total deviation difference (SWAP – white-on-white) averaged across ring 2 minus the corresponding value for ring 3. (This difference of differences is the "eccentricity factor", see Methods, also Eisner et al. (2006)). The ordinate is oriented so that larger reductions of SWAP sensitivity with eccentricity are represented in the downward direction. Same symbols as Fig. 1.