Color discrimination in carriers of color deficiency

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Abstract

Carriers of X-linked color vision deficiencies have previously been reported to exhibit mild abnormalities of color matching and discrimination. In a sample of 55 carriers of protan and deutan deficiencies and 55 age-matched normal controls, we measured chromatic discrimination along a red-green axis. We found that discrimination was impaired in the case of carriers of deutan deficiencies (which affect the middle-wave-sensitive cones of the retina), but was normal in the case of carriers of protan deficiencies (which affect the long-wave-sensitive cones). We argue that this result can be explained by the difference in the relative numbers of middle- and long-wave cones in heterozygous retinae: the imbalance of the two cone types is predicted to be much greater in the case of the deutan heterozygote than in the case of the protan heterozygote. In future studies it will be necessary to consider separately the two types of heterozygote.
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1. Introduction

Approximately 15% of women are carriers of X-linked deficiencies of color vision. Are such conditions truly recessive, so that the color vision of carriers is indistinguishable from that of normal control subjects? Or do the carriers share a little in the disability of their sons and exhibit poorer discrimination of colors than do other women (Wieland, 1933)? Or alternatively, just as carriers of sickle cell anemia are resistant to malaria (Allison, 1954), do carriers of color deficiency enjoy a heterozygous advantage, perhaps gaining tetrachromatic vision (Jordan & Mollon, 1993)?

There is evidence for both the second and the third of these possibilities, and they are not incompatible, since the number of dimensions of color vision is distinct from the fineness of discrimination along a given dimension. We here examine the recurrent claim that discrimination is impaired in some carriers of color deficiency (Feig & Ropers, 1978;

Pickford, 1944; Wieland, 1933), and we argue that carriers of deficiencies of the long-wave-sensitive cones (*protan* carriers) must be considered separately from carriers of deficiencies of the middle-wave-sensitive cones (*deutan* carriers).

The photopigments of the long-wave-sensitive (L) cones and the middle-wave-sensitive (M) cones are encoded by a small array of genes on the q arm of the X-chromosome (Nathans, Piantanida, Eddy, Shows, & Hogness, 1986a; Nathans, Thomas, & Hogness, 1986b). To understand why a difference between protan and deutan carriers might be expected, it is necessary to consider two independent and stochastic events that influence the ratio of L and M cones in the retina of a female subject (Fig. 1).

First, random X-chromosome inactivation determines which X-chromosome will be expressed in a given cone cell (Lyon, 2002; Teplitz, 1965). A second stochastic event later determines which type of photopigment gene (L or M) is actually expressed by the favored X-chromosome: this latter event is thought to be the probabilistic binding of an upstream locus control region to the promoter region of one of the genes in the array (Hayashi, Motulsky, & Deeb, 1999; Wang et al., 1999). See Fig. 1.

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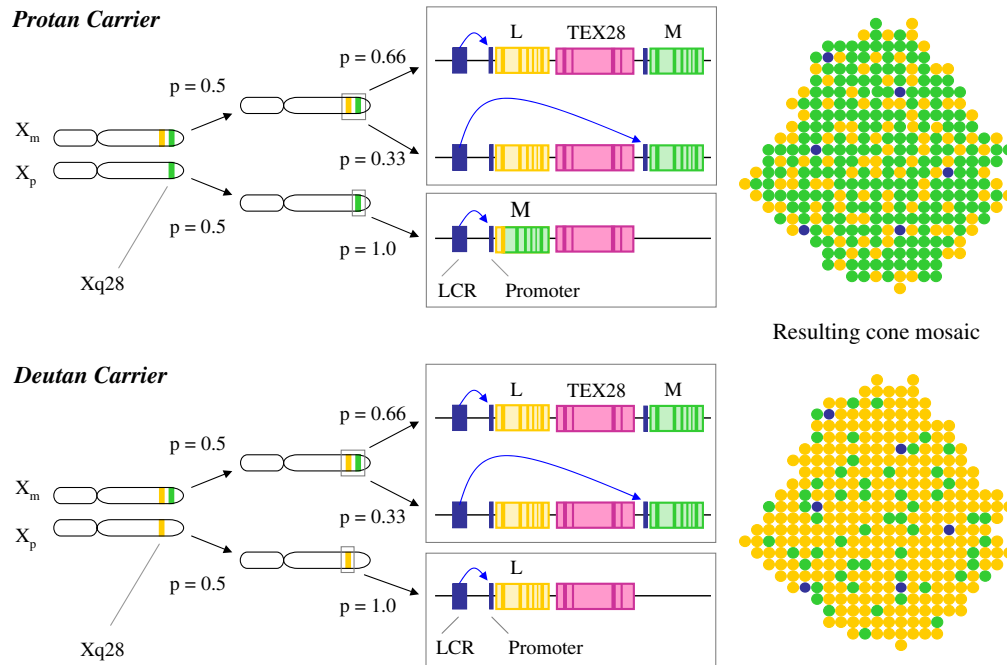   *E-mail address:* gabriele.jordan@ncl.ac.uk (G. Jordan).

Fig. 1. The two successive, stochastic events that determine the relative numbers of L and M cones in the retina of a carrier of colour deficiency. The first event determines which X-chromosome is active within a given cell. The second event—the binding of a locus control region to the promoter region of one of the photopigment genes—determines which gene is expressed by the active X-chromosome. The upper panel shows the case of a carrier of protanopia and the lower panel shows the case of a carrier of deuteranopia. To the left in each panel are represented the carrier's maternal and paternal X-chromosomes, with the genes for L (orange strip) and M (green strip) photopigments indicated near the tip of the q arm. In the middle is represented the array of photopigment genes at Xq28. Exons are indicated by darker bars within each gene. The Locus Control Region and the promoter regions are indicated in blue. TEX28 is an independent gene, expressed in the testis. To the right is shown in each panel the retinal mosaic that would result if the two stochastic events have the probabilities shown in the figure. For our illustration we have used the simplest form of defect, where the defective X-chromosome carries only a single photopigment gene. In the case of a protanomalous subject, a second gene may be present that also encodes an M-typecone photopigment, and in the case of a deuteranomalous subject, a second gene may be present that also encodes an L-type cone photopigment (Hayashi et al., 1999; Nathans et al., 1986a): What is important is that a 'protan' chromosome does not express any photopigments with peak sensitivities in the region of the normal L pigment and that a 'deutan' chromosome does not express any photopigments with peak sensitivities in the region of the normal M pigment.

The binding of the locus control region to the promoter region appears to be biased in favor of the gene for the L photopigment: in normal subjects, the average ratio of L to M cones is close to 2:1 (Bowmaker, Parry, & Mollon, 2003; Carroll, McMahon, Neitz, & Neitz, 2000; Cicerone & Nerger, 1989; Kremers et al., 2000), although considerable variation between individuals has been reported (Roorda, Metha, Lennie, & Williams, 2001; Rushton & Baker, 1964). A consequence of this bias is that a carrier of a deutan deficiency (Fig. 1, lower panel) will have a particularly high disproportion of L to M cones in her retina. Whether she is a carrier of deuteranopia or of deuteranomaly, one of her X-chromosomes lacks an (expressed) gene for an M-cone photopigment (Alpern & Moeller, 1977; Hayashi et al., 2001; Mollon, 1997; Wang et al., 1999) and this X-chromosome will be active, on average, in half of her retinal cones. All such cones (unless they are of the rare short-wave-sensitive type) must thus be obligatory L cones. If her normal X-chromosome leads to expression of L and M genes in the usual ratio of 2:1, then her overall L:M cone ratio has an expected value of 5:1. Her predicted foveal array is depicted to the right in the lower panel of Fig. 1.

Consider, in contrast, a carrier of a protan deficiency (upper panel of Fig. 1). One of her X-chromosomes lacks a gene for an L-cone photopigment. On average, this X-chromosome will be active in half her (non-shortwave) cones and so all these cones will be obligatory M cones. However, half her cones will express her normal X-chromosome, and here she gains from the normal bias towards expression of the L pigment. Her expected L:M cone ratio will be 1:2, a value that is much closer to unity than is the ratio expected for deutan carriers and indeed is no more unbalanced than the 2:1 ratio of the normal observer. Her predicted foveal array is depicted to the right in the upper panel of Fig. 1.

We hypothesized that the extreme L:M cone ratios present in deutan but not in protan carriers would impair color discrimination. The retinae of deutan carriers will contain large clumps of cones of the long-wave type, and a midget ganglion cell that drew centre and surround inputs from such a region could not exhibit L/M chromatic opponency. One current view is that cone ratios may be quite extreme, without impairment of color discrimination (Miyahara, Pokorny, Smith, Baron, & Baron, 1998; Williams & Hofer, 2004). On the other hand, Gunther and Dobkins (2002) used heterochromatic flicker photometry to estimate cone ratios

in a sample of subjects (including some self-reported heterozygotes). They reported that "…a significant relationship was observed between L:M cone ratio and chromatic contrast sensitivity, wherein subjects possessing the most symmetrical L:M cone ratios (i.e., near 1:1) appear to possess the relatively greatest chromatic contrast sensitivity."

According to the latter view, color discrimination would be predicted to be poorer in carriers of deutan deficiencies than in protan carriers. To test this hypothesis empirically, we have examined chromatic discrimination for square-wave red-green gratings of 2 cycles per degree. Our stimulus—a square-wave grating of intermediate spatial frequency with just visible edges between half-periods—resembles the stimulus that Hilz and Cavonius (1970) found optimal for chromatic discrimination.

When testing color discrimination in heterozygotes it is especially important to eliminate the possibility that subjects use luminance cues. Sensation luminance (Kaiser, 1988), which represents the spectral luminous efficiency function of the individual eye, is thought to depend on a summed signal from L and M cones (Lennie, Pokorny, & Smith, 1993). So the very fact that carriers have unusual cone ratios means that they do not share the spectral sensitivity of the standard observer. We took two precautions against the use of luminosity cues. First, we obtained luminance matches for each individual subject under the same conditions as for the color discrimination task. Second, we introduced additional random luminance noise into the final display.

2. Methods

2.1. Subjects

Our panel of volunteers comprised 55 carriers of color deficiency and 55 control subjects, all within the age range 35–60 years. Each of the 55 carriers had at least one color-deficient son, whose phenotype had been explicitly established with an Oculus anomaloscope. The panel contained 9 carriers of protanopia, 10 of protanomaly, 8 of deuteranopia and 28 of deuteranomaly. There were 30 female controls and 25 male controls. The protan, deutan and control groups did not differ significantly in age ($F[2] = 0.95$, $p = 0.39$): the average values and standard deviations were 47.57 yrs (5.82), 47.75 yrs (5.32) and 46.01 yrs (7.13), respectively. All subjects were naïve as to the aim of the experiment and all had normal color vision according to the standard criteria for the Ishihara Plates.

2.2. Stimuli

For both the initial equation of sensation luminance and for the measurement of chromatic discrimination, the stimuli were horizontal square-wave gratings of 2 cycles per degree (see Figs. 2 and 4). The gratings were displayed on a Sony Trinitron monitor (GDM-F500R) under control of a graphics board that allowed 15 bits resolution per gun (VSG2/5, Cambridge Research Systems). Calibrations were made with an OptiCAL photometer (Cambridge Research Systems) and a PR650 spectroradiometer (Photoresearch).

To eliminate the possibility of cues from chromatic aberration, we restricted the spectral range of our stimuli to medium and long wavelengths by turning off the blue gun of the monitor and placing a yellow filter (Ilford 111) in front of the screen. In addition, we separated the individual half-periods of the display by thin black lines of one pixel width (Kim & Mollon, 2002).
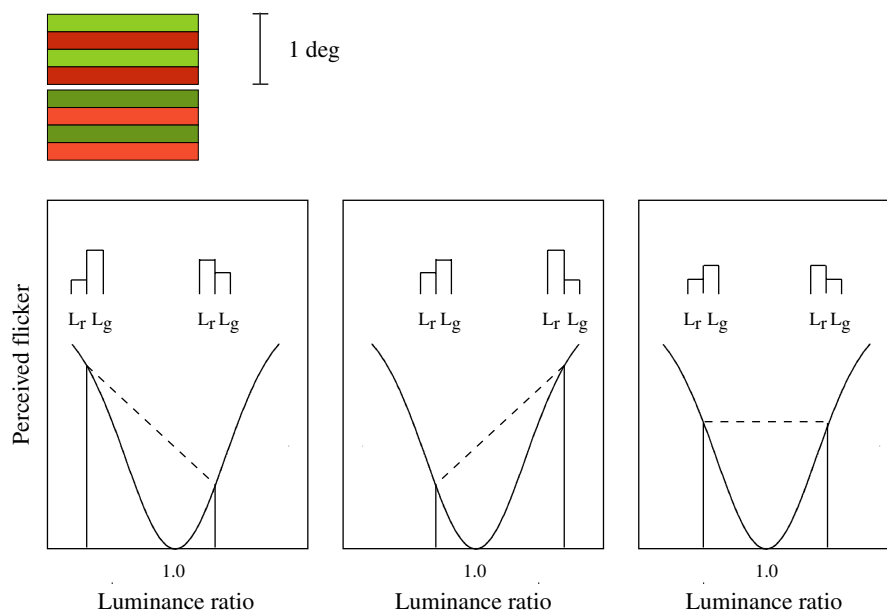

Fig. 2. The Webster–Mollon method of establishing equal 'sensation luminance' (Kaiser, 1988) for the red and green phosphors of the monitor. The observer views a field divided into upper and lower halves, as illustrated above. Each half-field contains two cycles of a red-green square-wave grating flickering in counter-phase at 25 Hz. The relative luminances of the red and green bars in the two half-fields are different, but are yoked so that the Michelson luminance contrast in one half-field always differs by 0.09 from that in the other. The leftmost panel shows a situation where the two contrasts are not centred on the subject's point of equality of luminance: in the part of the screen where the luminance of the red stimulus is lower, the effective contrast is greater for the subject than in the other half-field (where the red bars are of higher luminance)—and accordingly the subject perceives the flicker to be more salient in the former half-field. The middle panel shows the situation where the luminance ratios are mis-set in the opposite direction: now the flicker is more salient for the subject in the half-field where the red bars of higher luminance. The rightmost panel shows the situation that is sought by the computer program: here the effective luminance contrast is equal and opposite in the two half-fields and the subject is equally likely to report one field or the other as more salient in its flicker.

2.3. Procedure

2.3.1. Luminance matching

Luminance equations of the red and green phosphors of the display were obtained for individual subjects by the method of Webster and Mollon (1993). The stimulus display was divided into two half-fields each containing 2 cycles of a red-green grating (Fig. 2). Alternate half-periods were illuminated exclusively by the red phosphor of the monitor or exclusively by the green phosphor. The grating flickered in counter-phase at 25 Hz. The relative luminances of the red and green components were different in the upper and lower half-fields and the subject's task was to indicate which field appeared to flicker more strongly. Untrained subjects find this judgment much easier than the adjustments required in conventional flicker photometry. The Michelson luminance contrast in one half-field always differed by 0.09 from that in the other, luminance contrast being defined as: $(L_r - L_g)/(L_r + L_g)$ where L_r is the luminance of the red phosphor and L_g is the luminance of the green phosphor. Thus a positive contrast value indicated that the red phosphor was more luminous, and a negative contrast value, that the green phosphor was more luminous. The half-field with the higher contrast was randomly assigned to the upper or the lower region of the display.

On the basis of the subject's responses, the contrasts of the two half-fields were covaried in steps of 0.015 using two randomly interleaved staircases. So, for each staircase, on successive trials the two contrasts might, for example, change from +0.045, −0.045 to +0.03, −0.06, to +0.015, −0.075. The objective average luminance of both half-fields was kept constant at 12.0 cd m⁻². Each subject completed two experimental runs. The averages of the last 10 of 15 reversals for each staircase from each run were used to estimate the pair of contrast values at which the subject chose each half-field equally often. As the mean luminances of the red and green bars are equated for the subject at this point, the magnitude of the contrast can be used to calculate sensation luminance.

2.3.2. Chromatic discrimination

For each subject, the luminance equations obtained in the preliminary task were used to set the mean luminance in the color discrimination task. Discrimination was tested for variation on the *l*-axis of the MacLeod–Boynton chromaticity diagram (MacLeod & Boynton, 1979), i.e., the axis that represents the ratio of excitation of the L and M cones of the standard observer. Thresholds were measured by a two-alternative forced-choice method. The sequence of an individual trial is shown in Fig. 4a. In one of two intervals, a small red-green modulation was introduced and the subject had to indicate with a button press which of these contained the red-green grating. The depth of the red-green modulation was increased or decreased according to the subject's accuracy in identifying the interval containing the chromatic modulation. Auditory signals indicated the stimulus intervals. In the absence of modulation, the grating had a MacLeod–Boynton chromaticity (MacLeod & Boynton, 1979) of *l, s* = 0.7000, 0.0002 and the chromatic modulation was centred on this chromaticity. The luminance of each half-cycle of the grating was randomly selected from nine values in the range ±10% of the value required to maintain equal sensation luminance.

Each subject completed four blocks of trials, each containing two, randomly interleaved, staircases. The staircases followed a 1-up/3-down rule and terminated after nine reversals. Data from the first block were treated as practice. Data from blocks 2–4 (about 250 trials) were combined to reconstruct psychometric functions. For each *l* modulation visited by the staircases, the overall percentage correct was calculated. A four-parameter weighted sigmoid was then fitted to the plot of percent correct vs depth of modulation, and detection threshold was defined as the depth of the *l* modulation needed to sustain 75% correct.

3. Results and discussion

3.1. Individual differences in sensation luminance

Fig. 3 shows the average values of sensation luminance (Kaiser, 1988) for different groups of observers. The
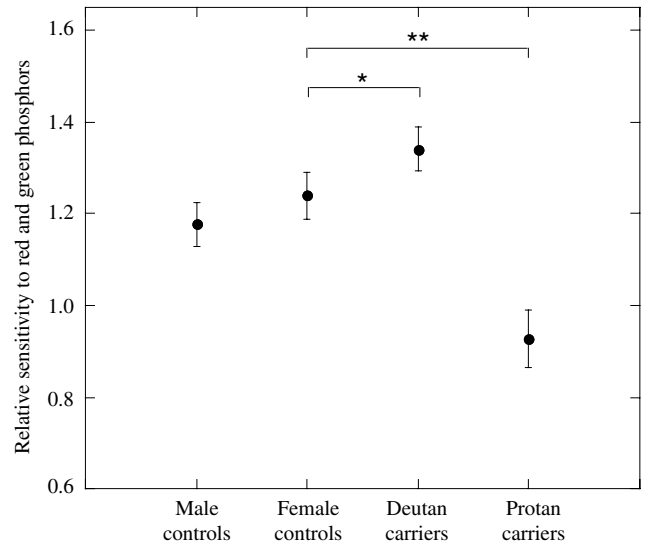

Fig. 3. Relative luminous efficiency of the red and green phosphors for different subject groups. The ordinate values represent the subjective luminance ratio of the red to the green phosphor when the phosphors are of equal objective luminance for the Judd (1951) standard observer (Smith & Pokorny, 1996). Error bars: ±2 SEM.

ordinate values represent the subjective luminance ratio of the red to the green phosphor when the phosphors are of equal objective luminance for the Judd (1951) standard observer (Smith & Pokorny, 1996). An ANOVA shows a highly significant difference between groups of subjects ($F[3, 106] = 39.71$, $p < 0.001$) and Bonferroni t tests indicate that protan and deutan carriers differ significantly from each other and in both cases differ significantly from each control group ($p < 0.001$ in all cases except for deutan carriers vs. female controls, where $p = 0.018$).

These results illustrate the importance of making individual luminance equations when studying heterozygotes. The protan carriers are substantially less sensitive to red light than are normal controls, a characteristic known as Schmidt's sign (Schmidt, 1934). Conversely, the deutan carriers, though overlapping with the normal male and female samples, are significantly more sensitive to red light (Crone, 1959; Jordan & Mollon, 1997). Note that the two groups of carriers—so clearly separated by this task—were classified purely on the basis of color matches made by their sons on the anomaloscope.

3.2. Chromatic discrimination in carriers

Fig. 4b shows measurements of chromatic discrimination for carriers and controls. Thresholds are expressed in terms of modulation of the *l*-axis in the MacLeod–Boynton chromaticity diagram. An ANOVA shows a significant effect of subject group ($F[3, 106] = 4.806$, $p = 0.004$). Bonferroni t tests indicate that deutan carriers differ significantly from male controls ($p = 0.042$) and from female controls ($p = 0.004$): they need more red/green contrast to detect the chromatic modulation of the grating. Protan carriers do not differ significantly from either control group. The

a

Background   Interval 1   Background   Interval 2   Background
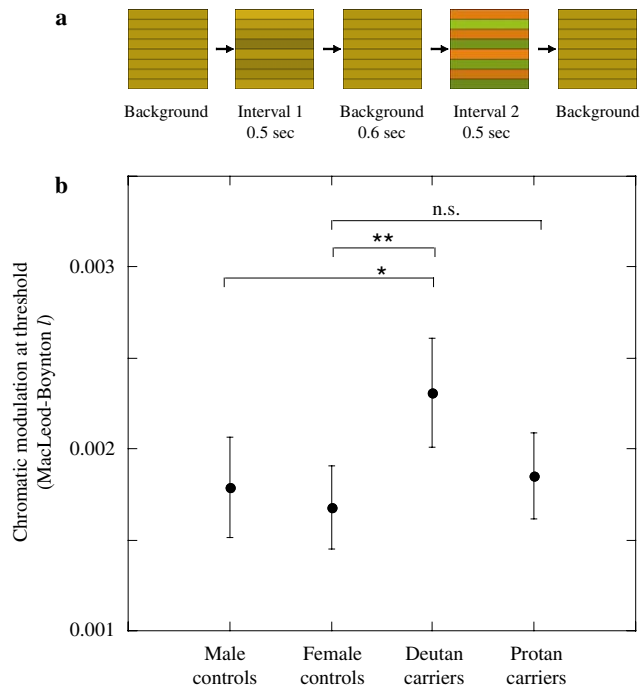   0.5 sec   0.6 sec   0.5 sec

b

Fig. 4. (a) Sequence of a single trial in the chromatic discrimination task. The background grating is uniform in both luminance and chromaticity. In one or other test interval it is modulated only in luminance and in the critical interval it is modulated in both luminance and chromaticity. (b) Thresholds for detecting the presence of a red-green chromatic modulation. Thresholds are expressed as the modulation of l in the MacLeod-Boynton chromaticity diagram. Error bars: ± 2 SEM. Deutan carriers differ significantly from male controls ($p = 0.042$) and from female controls ($p = 0.004$), but protan carriers do not differ significantly from either control group.

difference between protan and deutan carriers failed to reach significance when a Bonferroni correction was applied ($p = 0.174$). Significant differences were not found between carriers of protanopia and protanomaly or between deuteranopia and deuteranomaly. We would expect our group of female controls to contain a small number of unrevealed heterozygotes, but their presence would serve only to attenuate the group differences that are found.

Thus our results suggest a revision of the long-held view that carriers of color deficiency themselves exhibit impaired chromatic discrimination. Carriers of protan deficiencies do not differ significantly from male or female controls, but deutan carriers, as a group, are significantly worse. Verriest in 1972 similarly found that only deutan carriers were impaired on a clinical test of color discrimination, but he attributed the good performance of his protan carriers to the use of luminance cues (Verriest, 1972). In our experiment, luminance cues were explicitly not available to the subjects.

We propose that deutan carriers, as a group, have poorer color discrimination than controls because random X-chromosome inactivation leads to an extreme ratio of L to M cones in their retinae. Carriers of protan deficiencies, on the other hand, have an average ratio closer to unity, so their chromatic discrimination is just as good as that of controls.

Although our deutan carriers differed significantly from controls, we should not want to suggest that their color vision is *pathologically* impaired. Quite extreme ratios of L and M cones may be compatible with clinically normal color vision (Miyahara et al., 1998). Nevertheless, our results support the claim of Gunther and Dobkins (2002) that the relative numbers of L and M cones determine the fineness of human red-green color discrimination.

Even before random X-inactivation was understood, De Vries (1948) proposed that carriers of anomalous trichromacy might be tetrachromatic, and this possibility has often been discussed (e.g., Jordan & Mollon, 1993; Nagy, MacLeod, Heyneman, & Eisner, 1981). Our present results suggest not an enhancement but an impairment in the color discrimination of carriers of deuteranomaly, but we emphasize that this result does not bear one way or the other on the issue of tetrachromacy: the number of dimensions of color vision is independent of the precision of discrimination along any one of those dimensions. It might well be, for example, that the deuteranomalous signal—obtained by differencing two types of long-wave cone—is most salient in those heterozygotes who have few M cones and for whom the normal L/M signal is weak. The existence of tetrachromatic women still awaits a formal experimental demonstration.

3.3. Absence of sex differences in normal controls

Our results for normal controls bear upon the entrenched belief that women enjoy better color discrimination than do men. Already forty years ago, that claim was widespread in social psychological texts and Reynolds (1966) was led to identify it as a scientific fiction. There are, in fact, rather few systematic studies of sex differences in chromatic discrimination and their results are not coherent. Nichols (1884) mixed small quantities of colored pigment with white powder and asked his subjects—31 males and 23 females—to sort the mixtures by hue and by saturation. In the case of red and yellow pigments (red lead and chromate of lead), the average man could detect much lower dilutions than could the average woman, although women were somewhat more sensitive than men in detecting ultramarine; and for all colors tested, the women were more accurate in ordering the vials by saturation. Henmon (1910) asked subjects to place in order a series of red and orange papers that varied in hue: in the case of adults he found a small advantage for women, while in the case of children, there was no difference between the sexes. From his own tests, Pickford (1951) concluded 'apart from the colour blind and anomalous subjects, men are just as good judges of all colours as women'. Verriest, Vandevyvere, and Vanderdonck (1962), administering the 100-hue test to 248 men and 232 women of varying age, found no overall difference between men and women, but an analysis of variance showed a significant interaction of sex and age, females in the age range 15–24 being superior to males of that age group. Verriest et al. suggested, however, that the screening

test used (the H-R-R) may not have eliminated all anomalous observers from their male sample.

Our own test stimulus—a square-wave grating of 2 cycles per deg—was one chosen for optimal color discrimination, and our task required a forced-choice judgment. Under these conditions, there proved to be no significant difference in average threshold between our age-matched male and female controls. Thus, if known heterozygotes for color deficiency are removed from the female population and if the explicitly color deficient are removed from both the male and the female populations, then there appears to be no sex difference in the ability to discriminate on the L/M axis of color space. Women may well be more expert in the use of color names (Dubois, 1939; Nowaczyk, 1982) and they may have different color preferences (Ling, Robinson, & Hurlbert, 2004), but these differences may reflect interest or culture rather than a difference in the delicacy of discrimination.

Acknowledgments

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