

A Study of Women Heterozygous for Colour Deficiencies

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Received 31 August 1992; in revised form 21 December 1992

We have examined the colour vision of 43 female subjects in the age range 30–59 yr of whom 31 were obligate carriers of various forms of colour deficiency and the rest were women who had no known colour-deficient relatives. In the case of all the carriers we established the phenotypes of their colour-deficient sons. As a group, carriers made significantly more errors on the Ishihara plates and showed enlarged matching ranges on the Nagel anomaloscope, but we could not replicate earlier reports of increased error scores on the Farnsworth–Munsell 100-Hue test or of systematic shifts in Rayleigh match mid-points. We did find that the colour matches of carriers of deuteranomaly were significantly displaced from those of normals in a ratio-matching task in which a mixture of 546 and 600 nm was matched with a mixture of 570 and 690 nm. Owing to X-chromosome inactivation, women who are heterozygous for anomalous trichromacy ought to have at least four types of cone in their retinæ and we ask whether this affords them an extra dimension of colour vision, by analogy to New World monkeys where heterozygous females gain trichromacy in a basically dichromatic species. Many carriers of anomalous trichromacy exhibited no evidence for tetrachromacy, in that they accepted large-field Rayleigh matches following a rod bleach and they were unable to set unique matches in our ratio-matching task. However, eight carriers of anomalous trichromacy—and no other subject—refused large-field Rayleigh matches; and we found one carrier of deuteranomaly who was apparently able to make unique matches in the ratio-matching task.

Colour vision Colour deficiency Anomalous trichromacy Genetics Heterozygote X-chromosome inactivation Tetrachromacy

INTRODUCTION

Approximately 15% of the human female population are carriers of X-linked colour deficiencies. As first suspected by Fleischer (1920), some heterozygotes have been found to exhibit mild abnormalities of colour matching and discrimination (Waalder, 1927; De Vries, 1948; Verriest, 1972) and very occasionally a mother who has both normal and colour-blind sons may herself exhibit frank colour blindness (Siemens, 1926, 1927; Kawakami, 1926). Most carriers of protan defects reveal themselves by reduced sensitivity to long wavelengths in flicker-photometric tests and other measures of relative luminosity (Schmidt, 1934; Walls & Mathews, 1952; Crone, 1959; Adam, 1969; Ikeda, Hukami & Urakubo, 1972; Yasuma, Tokuda & Ichikawa, 1984; Mollon, 1987; Swanson, 1991). Nevertheless, the majority of both protan and deutan heterozygotes are classified as normal by standard clinical tests of colour vision.

The fact that some women do exhibit a mild version of the deficiency exhibited more strongly by their colour-blind sons, is usually explained by X-chromosome inactivation (Lyon, 1961, 1972): early in embryonic development, one or other parental X-chromosome is randomly inactivated in any given cell and this inactivation is preserved in all descendants of that precursor cell. As a result of this process, the carriers are functionally hemizygous in all of their somatic cells: their retinæ are thought to consist of some cells that express the normal X-chromosome and some that express the X-chromosome that is abnormal at the colour-vision loci. There does exist psychophysical evidence that the carrier's retina consists of a mosaic of normal and defective patches (Born, Grützner & Hemminger, 1976; Grützner, Born & Hemminger, 1976; Cohn, Emmerich & Carlson, 1989). To explain the very rare cases of heterozygotes who are said to manifest full colour deficiency, such as the cases of Siemens (1926, 1927) and Kawakami (1926), we must suppose that by chance the same X-chromosome was inactivated in all, or almost all, the cone

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precursor cells (Thuline, Hodgkin, Fraser & Motulsky, 1969).*

We have so far considered heterozygotes as sharing a little in the disability of their sons, but there is the alternative possibility that some heterozygotes draw an advantage rather than a disadvantage from the mosaic character of their retina: carriers of anomalous trichromacy will have four types of cone in their retina—the three normal types and the additional anomalous type that their sons may inherit. Such women might be tetrachromatic, enjoying an extra dimension of colour discrimination.

This hypothesis gains plausibility from experiments on the colour vision of New World monkeys (Mollon, Bowmaker & Jacobs, 1984). In the case of the squirrel monkey, a basically dichromatic species, two-thirds of the females are heterozygous and gain trichromatic vision by expressing two of three possible alleles coding for pigments in the middle- to long-wave range of the spectrum. X-chromosome inactivation serves to segregate the alternative allelic products in different subsets of cones. The visual system of the heterozygous female is apparently plastic enough to take advantage of the presence of three classes of cone. For, in the laboratory, the heterozygous monkey is able to make discriminations in the red–green range that are impossible for all males and for homozygous females (Jacobs, 1984; Tovée, Bowmaker & Mollon, 1992). This advantage perhaps enables the heterozygote to judge better the ripeness of fruit, or to find fruit or conspecifics, in the dappled environment of the forest. Mollon (1987) and Mollon and Jordan (1988) proposed that such a heterozygous advantage might also exist in human carriers of anomalous trichromacy.

Two forms of tetrachromacy in human carriers for anomalous trichromacy should be distinguished according to the level to which the four signals remain independent:

First, consider the possibility that there are four different types of cone, but that their signals are processed by only three independent post-receptoral chan-

nels. We shall refer to this type of tetrachromacy as *weak tetrachromacy*, because only three independent signals are preserved by subsequent neural processing. Such a heterozygote would accept trichromatic colour matches, but would not exhibit the stability of matches under adaptation that is required by the three-pigment hypothesis (Brindley, 1957, 1960). Weak tetrachromacy of this kind has been shown by Nagy, MacLeod, Heynemann and Eisner (1981), who reported four probable heterozygotes whose trichromatic matches changed when the chromaticity of a background field was changed.

Second, consider the possibility of a female carrier who has four types of cone in her retina and who also has access at a cortical level to four independent transformations of these signals. We shall refer to this type of tetrachromacy as *strong tetrachromacy*. In a classical colour-matching task, the strong tetrachromat will need four variables to match all colours. The possibility of strong tetrachromacy was raised by De Vries (1948), before the existence of X-chromosome inactivation was known; but Nagy *et al.* (1981) suggest, in a footnote, that all their heterozygotes were trichromatic.

Not all previous studies have distinguished between types of carrier and phenotypes have often been inferred from reports of a history of colour deficiency within the family. However, we expect strong tetrachromacy only in carriers for anomalous trichromacy and therefore in the present study all heterozygotes were classified by examining their sons on the Nagel anomaloscope and other clinical tests. We report results for normal and heterozygous women on three types of test.

(1) *Clinical tests of colour vision.* There have been earlier reports that carriers exhibit shifts in Nagel match mid-points (Waalder, 1927; Wieland, 1933), enlarged Nagel matching ranges (Waalder, 1927), impaired discrimination of hue and saturation (Wieland, 1933; Pickford, 1944; Krill & Schneiderman, 1964; Verriest, 1972) and increased errors in reading the Ishihara plates (Waalder, 1927; Crone, 1959; Feig & Ropers, 1978). In the present study all subjects were tested on the Nagel anomaloscope, the Farnsworth–Munsell 100-Hue test and the Ishihara plates; and the results were analysed separately according to the phenotypes of their sons. In the case of the Nagel anomaloscope and the Farnsworth–Munsell 100-Hue test we obtained measurements separately for the two eyes of each subject. The comparison between eyes is a measure of the time of X-chromosome inactivation in embryonic development: if inactivation occurs relatively early, when there are only a few precursor cone cells, then we expect the retinal mosaic to be very coarse and hence a difference in the two eyes becomes more probable. In the extreme case one eye might be normal and the other colour-defective (Thuline *et al.*, 1969).

(2) *Large-field Rayleigh matches.* Rayleigh matches were measured under conditions known to yield good colour discrimination: the field was large (10 deg of visual angle) and the monochromatic standard and the red/green mixture field were temporally alternated (Nagy, 1980; Neitz & Jacobs, 1986). To avoid the

*True cases of fully manifesting heterozygotes are probably very rare indeed. Cases of colour-blind women with normal fathers (e.g. Kawakami, 1926; Waaler, 1927; Brunner, 1930) have been reported more often than cases of colour-blind women with normal sons. We prefer to place weight only on cases of the latter kind, where the principle of *pater semper incertus* does not apply, i.e. where an irregularity of parentage is unlikely. Jaeger (1972) echoed the scepticism of Schiötz (1922) in concluding "... there is no published case of manifest red–green defect in heterozygous women which could be accepted without any doubt". There are a series of reports of cases where only one of a pair of female monozygotic twins exhibited a colour deficiency. An early example is that described by Nettleship (1912): the apparently dichromatic twin shared her daltonism with her father but not with her mother, nor her twin sister nor any of her six brothers. Yokota, Shin, Kimura, Senoo, Seki and Tsubota (1990) have described a case of congenital deuteranomaly in one of monozygotic female triplets. But twins (and triplets) are probably a special case: there appears to be a mechanism that causes X-inactivation to be biased in opposite directions within a pair of twins (Jørgensen, Philip, Raskind, Matsushita, Christensen, Dreyer & Motulsky, 1992).

intrusion of rods in these large-field matches, a bleach was introduced before the measurements.

(3) *Ratio matches.* A ratio-matching task was designed to test specifically for strong tetrachromacy. We tested whether carriers of anomalous trichromacy make unique trichromatic matches in a colour sub-space where normal observers make dichromatic matches. Observers were asked to adjust a mixture of green and orange light (546 + 600 nm) and a mixture of yellow and red light (570 + 690 nm) to obtain a match. Since the primaries lie on the long-wave spectrum locus, where the S-cone excitation is virtually zero, a normal trichromat becomes a dichromat in this space. As is clear from the position of our four primaries in the CIE chromaticity diagram [see Fig. 1(a)], a normal trichromat should be able to make matches anywhere along the spectral line between 570 and 600 nm. The possible matching range is indicated by the square surrounding this part of the spectrum locus.

Consider now a carrier of anomalous trichromacy, who has an additional pigment in the middle- to long-wave region of the spectrum. Such an observer may become a trichromat in this spectral region. The exact form of her colour space is not known, but suppose that her long-wave spectrum locus were convex or concave as in Fig. 1(b). Since the four primaries no longer lie on a straight line, there will not be a range of acceptable match-points between 570 and 600 nm. Rather, the tetrachromat should make a unique match at one particular point in colour space (M) where the two mixing lines intersect.

In conventional colour-matching procedures, untrained subjects often have difficulties when asked to adjust each primary independently. We therefore gave subjects control over two ratios (546/600 and 570/690) and asked them to adjust the ratios so as to achieve a match of the two mixture fields in a temporal-substitution procedure.

METHODS

Subjects

The subjects were 43 women in the age range 30–59 yr. Of these, 12 were normal controls who had no knowledge of colour-blind relatives* and 31 were obligatory carriers who had at least one colour-deficient son. The sons were tested on a battery of standard clinical tests for red–green colour deficiencies. We were thus able to classify 20 deutan and 11 protan carriers. Table 1 shows the classification of subjects, the abbreviations used for the experimental groups and the number of subjects (n) within each group.

Clinical tests for red–green deficiencies

Subjects were asked to perform three standard clinical tests for red–green deficiencies. First, they read the Ishihara plates (10th edn) binocularly. Second, each eye was

*Note that there is always a small chance that a normal control is wrongly identified, since even a mother with several normal sons might in principle be a carrier who has not yet revealed herself.

TABLE 1. Classification of 43 subjects

Experimental group	Abbreviation	n
Normal trichromats	N	12
Carriers of simple deuteranomaly	cDA	7
Carriers of extreme deuranomaly	cEDA	4
Carriers of deuteranopia	cD	9
Carriers of protanomaly	cPA	7
Carriers of extreme protanomaly	cEPA	1
Carriers of protanopia	cP	3

Subjects were classified according their sons' performances on standard clinical tests for red–green deficiencies. Abbreviations for the experimental groups and numbers of subjects in each group are shown. The abbreviations are used throughout the text.

tested on the Nagel anomaloscope (Schmidt & Haensch; Model I), the matching range being taken as the difference between the highest and the lowest red/green ratio that the subject would accept after making her own brightness equations. Third, the Farnsworth–Munsell (FM)

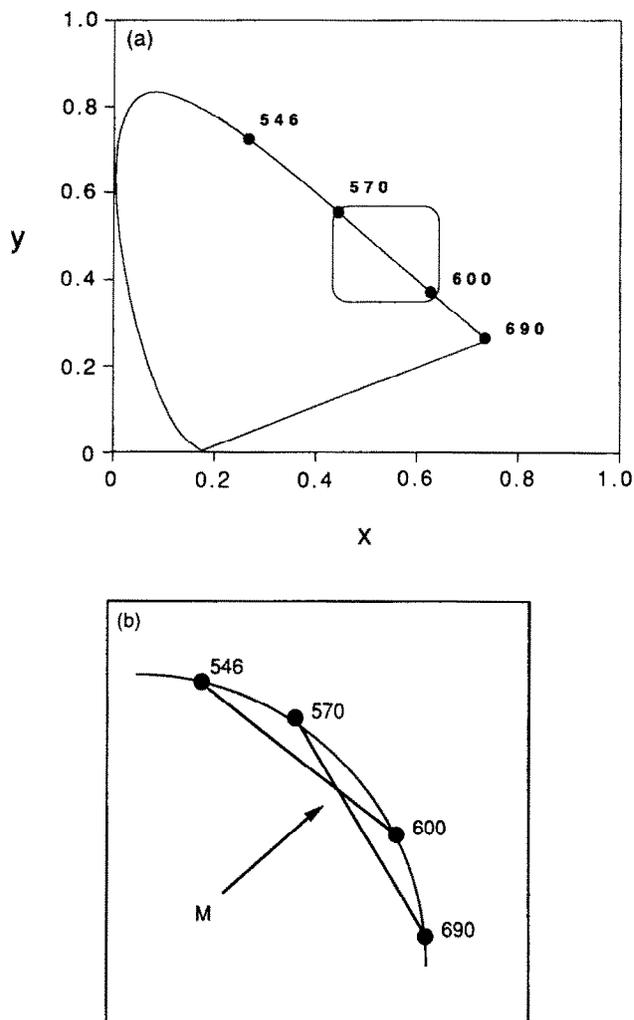


FIGURE 1. (a) CIE x,y-space. The primaries used for the ratio-matching task lie along a straight line. A normal trichromat should make matches all along the overlapping spectral region depicted by the square. (b) Hypothetical colour space of a tetrachromat. The spectrum locus in the middle- to long-wave region of the spectrum is represented as curved. M, the intercept of the two mixture lines, is the expected match-point for a tetrachromat asked to match a mixture of 570 and 690 nm to a mixture of 546 and 600 nm.

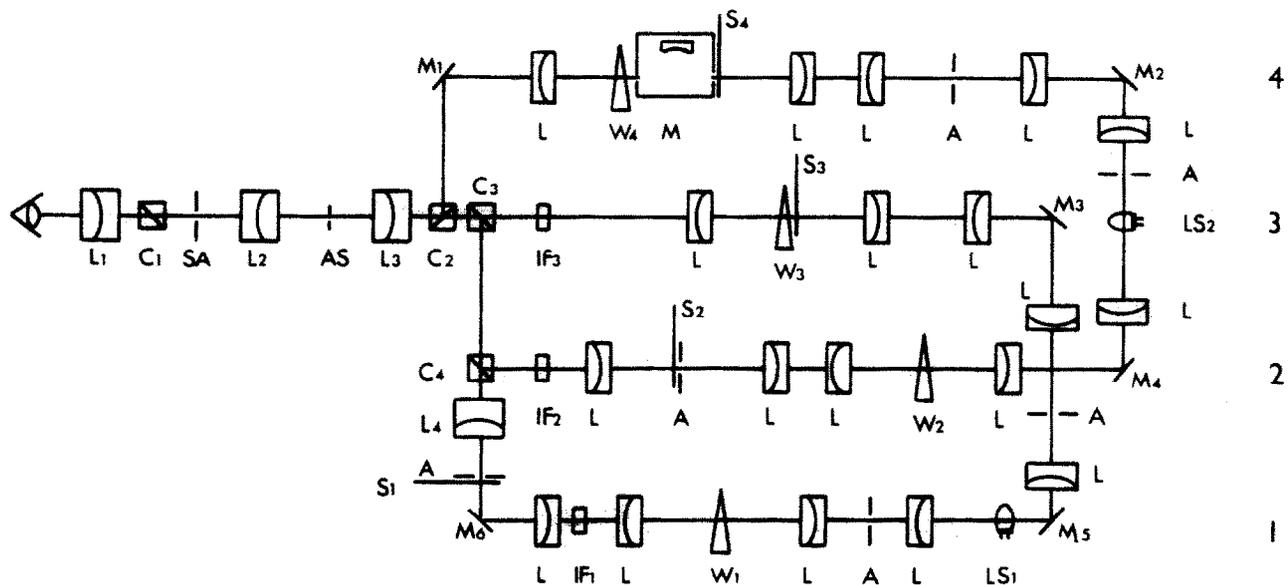


FIGURE 2. Schematic description of the four-channel Maxwellian-view system. The optical channels are numbered from bottom to top and provide primaries as follows: (1) 546 nm; (2) 600 nm; (3) 690 nm; (4) 570 nm. The following abbreviations are used: A, light baffle; AS, aperture stop; $C_{(1-4)}$, beam splitting cube; $IF_{(1-3)}$, interference filter; L, lens; $LS_{(1-2)}$, light source; M, monochromator; $M_{(1-6)}$, mirror; $S_{(1-4)}$, shutter; SA, stimulus aperture; $W_{(1-4)}$, neutral-density wedge.

100-Hue test was performed with each eye separately. The Ishihara plates and the FM 100-Hue test were done under Illuminant C at an illumination of about 125 lx, provided by a Macbeth easel lamp.

Large-field Rayleigh matches

The stimuli were shown in Maxwellian-view, using a four-channel, computer-controlled colorimeter with channel 4 blocked off (Fig. 2). In order to secure spatially uniform fields, the two light sources were ribbon-filament lamps. The red-green mixture (channels 1 and 3 in Fig. 2) was set to give 20 td retinal illumination; it was temporally alternated with the monochromatic standard (channel 2 in Fig. 2), each stimulus having a duration of 2 sec. The primaries were 546 and 690 nm for the red-green mixture field and 590 nm for the standard. The stimulus field was an annulus of 10.6 deg of visual angle, with the central 2.6 deg blocked off in order to minimize the effects of macular pigment and of foveal variation in receptor morphology. A small pin-hole in the centre of this black disk facilitated central fixation.

After a 2-min rod bleach,* the subjects were asked to fixate the dot in the black central disk of the stimulus. Leftward or rightward movement of a joystick allowed the subject to change the mixture field in the direction greener or redder respectively, while upward or downward movement increased or decreased the radiance of the 590 nm standard. The subjects were asked to make a perfect match, so that no residual differences could be

perceived. The test was repeated until five match-points were achieved. The test was carried out only on the subjects' dominant eye. Two normal subjects and one carrier for deuteranopia failed to participate in this part of the study.

A number of carriers (see below) reported that they were unable to obtain a perfect match at any red-green ratio. In these cases the subjects were asked to make as close a match as they could.

Ratio matches

The experiment was done on the four-channel colorimeter described earlier (Fig. 2). A field containing a mixture of monochromatic green and orange light (546 and 600 nm; channels 1 and 2 in Fig. 2) was alternated with a field containing a mixture of yellow and red light (570 and 690 nm; channels 3 and 4 in Fig. 2). The duration of each field was 2 sec. The stimulus configuration was the same as that described above for the large-field Rayleigh matches. Subjects were asked to fixate the dot in the black central disk of the stimulus.

The subject had control over the ratio of the mixture in each field. Rightward movement of the joystick increased the proportion of the long-wave component of whichever field was concurrently exposed and leftward movement decreased this proportion. The radiances of the primaries were controlled by four calibrated, 1 log unit, neutral-density wedges mounted on stepping motors; and the computer program referred to look-up tables in order to maintain the total troland value of each mixture field always at 100.

Subjects were asked to find colour matches between the two mixture fields and were encouraged to find different matches on different trials. The test was repeated until seven match-points were achieved. The test was carried

*The rod bleach was produced with an ancillary Maxwellian-view system giving approx. 50,000 td in a spectral band (Wratten 44) centred on 500 nm. The field subtended 12.5 deg of visual angle. Dark adaptation curves were measured for two observers and showed a cone plateau from the 3rd to the 11th minute after the bleach.

out only on the subject's dominant eye. One normal subject failed to participate in this part of the study.

RESULTS AND DISCUSSION

Clinical tests for red-green deficiencies

In the case of each test we first ask whether the carriers as a group, independently of their type, perform differently from the normal controls; and secondly we ask whether carriers of anomaly differ from carriers of dichromacy and whether protan carriers differ from deutan carriers. Not all studies reported in the literature have fully distinguished between carriers on the bases of their sons' phenotypes. The non-parametric Mann-Whitney and Kruskal-Wallis test statistics were used to analyse the data, because error scores on at least two of the clinical tests (Ishihara plates and Farnsworth-Munsell 100-Hue) cannot be normally distributed owing to ceiling effects.

Ishihara plates. Figure 3(a) shows the average number of plates misread by observers in each experimental group. A significantly larger error score was found for the carriers as a group compared to the normal controls ($U = 109, P < 0.01$). No significant differences were found between subgroups of carriers. The higher mean error score for carriers than for normals is compatible with earlier reports (Waalder, 1927; Crone, 1959; Feig & Ropers, 1978), but the absolute scores of our heterozygotes are low compared to those reported by Crone (1959) for an unspecified level of illumination: 10% of Crone's subjects made 8 errors with a maximum of 13, whereas our highest score was 6 (exhibited by one carrier of extreme deuteranomaly) and most of our heterozygotes made 3 or fewer errors.

It is interesting that 11 out of 30 heterozygotes (and only 1 out of 12 normal observers) misread the transformation plate No. 9 (a *post-hoc* test shows a significant difference between carriers and normal controls: $\chi^2 = 3.37, d.f. = 1, P < 0.05$). This plate is designed to reveal one number to the normal observer (74) and a different number (21) to the colour defective. The two alternative readings depend on the two fundamental sub-systems of human colour vision (Mollon & Jordan, 1988; Mollon, 1989).* For a normal observer the signal of the L/M sub-system is more salient so that she perceptually links the elements that have a common *greenness* and which, as a Gestalt, indicate the number 74 in plate No. 9. However, if the relative salience of the ancient sub-system is greater for heterozygotes than for normals, then we might expect their response to be determined by the *blueness* and *pinkness* that indicate the number 21 in plate No. 9. In fact, many of our carriers gave a hybrid response, 71: this may be a sign that the signals of the two sub-systems are more evenly balanced in the carriers than in the normals.

*The ancient sub-system compares the signal of the S-cones with some combination of the M- and L-cone signals and the phylogenetically younger sub-system of colour vision compares the signal of the M-cones with that of the L-cones.

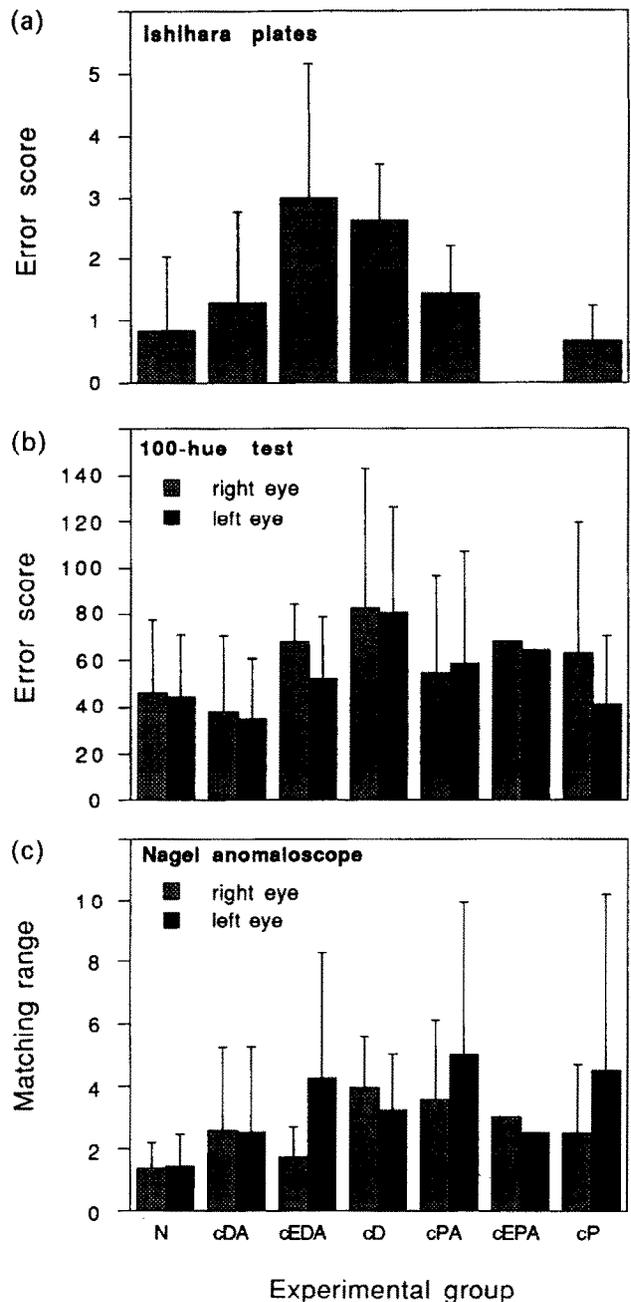


FIGURE 3. (a) The number of Ishihara plates misread by each experimental group. The error bars represent standard deviations. For identification of experimental groups see Table I. (b) Error scores on the Farnsworth-Munsell 100-Hue test for each experimental group. Shaded bars and solid bars represent the mean performance of right and left eyes respectively. The error bars represent standard deviations. (c) Matching ranges on the Nagel anomaloscope for right (shaded bars) and left eyes (solid bars) of different groups of observer.

Farnsworth-Munsell 100-Hue test. Hue discrimination was tested with the Farnsworth-Munsell 100-Hue test for each eye separately. In Fig. 3(b) the mean error scores for each experimental group are plotted for right and left eyes separately. Kruskal-Wallis tests showed that there was no significant variation in performance between groups of subjects for the right or for the left eye, nor for the absolute differences between eyes; and Mann-Whitney tests showed no difference between normals and heterozygotes.

We thus have no evidence for the claim of Verriest (1972) that heterozygotes as a group perform more poorly on the Farnsworth–Munsell test than do normal women. We note that most of our normals and carriers show lower error scores than the standard observer of the same sex and age (Verriest, 1963), even though the present tests were monocular rather than binocular. Our illumination was very similar in spectral composition and level to that used by Verriest (1963, 1972).

Our failure to find exaggerated differences in performance between the two eyes of heterozygotes (and indeed our failure to find any example of a heterozygote manifesting her son's phenotype unilaterally) argues that X-chromosome inactivation occurs at a late embryonic stage when a relatively large pool of cone precursor cells are present. This conclusion is compatible with that of Feig and Ropers (1978).

Nagel anomaloscope. The anomaloscope provides two measures: (1) matching ranges and (2) match mid-points. When normal controls ($n = 12$) and carriers ($n = 30$), independently of their genotypes, were compared, the matching ranges were found to be significantly greater for the heterozygotes for both right ($U = 96$, $P < 0.01$) and left eyes ($U = 99$, $P < 0.01$). Furthermore, the absolute differences in matching range between the two eyes of heterozygotes were found to be significantly larger than the absolute differences found between eyes of normal controls ($U = 121.5$, $P < 0.05$), a result that

is consistent with mosaicism but may only be secondary to the larger monocular ranges in heterozygotes. Since the matching range on the Nagel anomaloscope is conventionally taken as a measure of hue discrimination (Pokorny, Smith, Verriest & Pinckers, 1979), we find here the evidence for impaired discrimination in heterozygotes that we failed to find on the Farnsworth–Munsell test. However, when the heterozygotes were sub-divided according to their sons' phenotypes, no significant variation in matching ranges was found: carriers of anomalous trichromacy were not different from carriers of dichromacy and protan carriers were not different from deutan carriers. In Fig. 3(c) the mean Nagel matching ranges of each experimental group are plotted separately for right (shaded bars) and left eyes (solid bars). Match mid-points and matching ranges are shown in Fig. 4 for all individual subjects. It is clear that the matching ranges of carriers are generally enlarged compared to normal controls. This result is concordant with that of Pickford (1944) for 21 women who reported colour-blind blood relatives.

In the case of carriers of dichromacy the most straightforward explanation of the larger matching ranges would be that Lyonization produces an abnormal proportion of normal long-wave or middle-wave cones and that in consequence the number of chromatically-opponent midget ganglion cells is reduced. In the case of carriers for anomalous trichromacy the incidence of

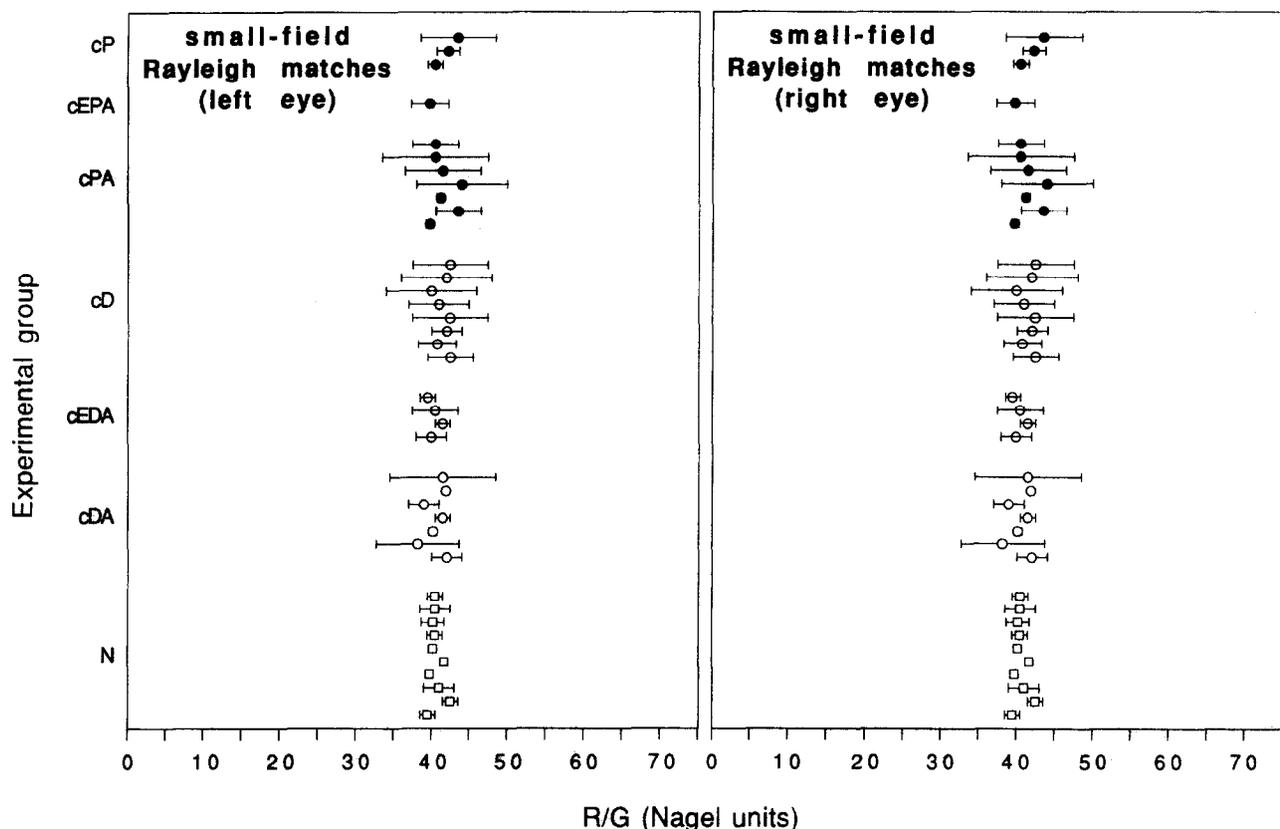


FIGURE 4. Nagel match mid-points and matching ranges are shown for left and right eyes of all individual subjects. The abscissa represents the red–green mixture settings in terms of Nagel units. The ordinate shows the classification of the subjects (see Table 1). Protan groups are shown with solid circles, deutan with open circles and normals with open squares. Subjects are sorted according to their code number, ascending upwards.

normal L/M units might also be reduced, but an alternative explanation would be that suggested by Mollon (1987): the heterozygote may be unable to make a precise match between the red-green mixture and the monochromatic orange because for her there is always a residual difference in appearance between the two fields. Suppose that our species were basically dichromatic, but there were a few female trichromats in our midst. The male majority would probably have invented a clinical colour-matching test in which a red and a blue light were mixed to match a white standard; and the occasional trichromat might well be diagnosed as *farbenschwach* when she was tested on such an anomaloscope.

The second measure obtained from the observer's Nagel settings is the mean red-green ratio chosen to match the yellow standard. Kruskal-Wallis tests showed no significant variation among groups in the match mid-points for either right or left eyes; nor was there a significant variation in the absolute differences between eyes. We thus find no evidence for the suggestion of a small displacement of the mean Rayleigh match toward red in the protan carriers and toward green in the deutan carriers (Verriest, 1972).

It is instructive to examine the provenance of the rule advanced by Verriest. Of his eight references, two (Krill & Schneiderman, 1964; Krill & Beutler, 1965) are not concerned with Rayleigh matches at all and the study by Pickford (1949) was performed with coloured papers of unknown spectral reflectance. Waaler (1927) claims only that some carriers of deuteranomaly show a slight deutan shift on the Nagel anomaloscope (model II); he explicitly denies any shift in protan carriers or in carriers for deuteranopia. Wieland (1933) reports a shift in the deutan direction for *all* sub-groups of carriers. Schmidt (1934, 1955) suggests that most carriers have matches within the normal range, but there is a tendency for protan carriers to give average settings on the protan side of the normal mean and for deutan carriers to give average settings on the deutan side. Most of the heterozygotes examined by Walls and Mathews (1952) had normal Rayleigh matches. Verriest does not cite the negative report of Wölfflin (1923).

Large-field Rayleigh matches

A Kruskal-Wallis test showed no significant difference between groups in the large-field match mid-points; and Mann-Whitney tests showed no difference between normals and heterozygotes or between deutan and protan carriers. Thus, we again find no evidence for systematic displacements of Rayleigh matches in heterozygotes. There was a positive correlation ($r = 0.73$) between the large-field Rayleigh matches and the small-field Rayleigh matches (done on the Nagel anomaloscope). In contrast to our finding of enlarged Nagel matching ranges in heterozygotes, we find no significant difference between normals and heterozygotes in large-field matches.

Eight out of 14 carriers of anomalous trichromacy (four cDA and four cPA) could not find a red-green mixture that satisfactorily matched the monochromatic yellow and were then asked to give the closest match

they could find. One carrier of deuteranomaly refused completely to press the button indicating a match. It is remarkable that no other subjects reported that they could not find an acceptable large-field match. A χ^2 test shows that the difference between carriers of anomalous trichromacy and all other subjects is significant ($\chi^2 = 19.81$, d.f. = 1, $P < 0.1$).

The reports of the match-refusers were instructive. If X-chromosome inactivation merely produced a coarse mosaic of normal and anomalous retina in the carriers of simple anomaly, then one might expect match-refusals to occur because the large field appeared blotchy, it being impossible to achieve a satisfactory match for all parts of the field. An appearance of this kind, however, is not what refusers reported. Rather they described a residual difference in hue between the two fields. Some examples of observers' comments are as follows: cDA2: *I want to be able to add more orange to the mixture, not red.* cPA2: *It is simply the wrong kind of orange.* cPA3: *It is the wrong kind of orange; it needs more yellow, it looks rather pink when I add more red.* cPA4: *If the joystick is just slightly off to the left-hand side, the mixture looks too green, but pushing it slightly more to the right makes it look pink and not orange.*

After a rod-bleach and at a retinal illuminance of 20 td, a trichromat might be expected to achieve a match between a monochromatic orange standard and a mixture of a red and a green primary. Those of our subjects without colour-deficient relatives and those who were mothers of dichromatic sons, did indeed behave as if they were dichromatic for this part of the spectrum locus. Those who refused the matches were drawn from exactly the group where we might expect to find tetrachromatic subjects—those women who are carriers of simple anomalous trichromacy. Alternative explanations of the match refusals (in terms of e.g. rod intrusion, S-cone intrusion, or missetting of the brightness control by the subject) would have to account for why the refusals were confined to the group of carriers of simple anomaly.

The match-refusals reported by some carriers of anomalous trichromacy provide preliminary evidence for tetrachromacy. This tetrachromacy would be of the strong form. The weak tetrachromat, who has four pigments but only three neural channels to process the incoming signals, ought to be able to make acceptable Rayleigh matches.

Ratio matches

In the ratio-matching task the subject was asked to find a combination of the two mixtures (546/600 and 570/690) that gave an acceptable match. The axes of Fig. 6 show the proportion of long-wave light in each mixture. In principle the subject might find a match anywhere within this two-dimensional space. Empirically the matches made by normal subjects lie along a straight line in the space, as expected and any individual subject is able to achieve matches at a range of positions (see Introduction).

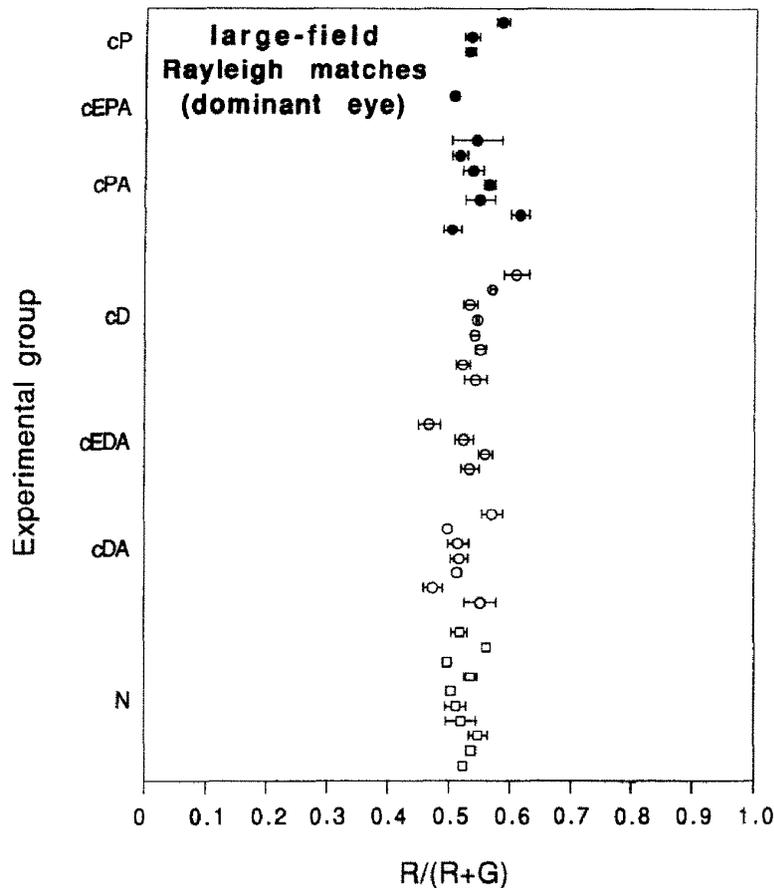


FIGURE 5. Individual large-field Rayleigh matches are shown. Each symbol represents the mean match-point of at least five settings. Standard deviations are included as bars. The abscissa is expressed in terms of $R/(R + G)$. Protan groups are shown with solid circles, deutan with open circles and normals with open squares. Subjects are sorted according to their code number, ascending upwards.

The ratio-matching data for heterozygotes were analysed in terms of two measures: (a) the displacement of match-points from the line describing the normal matches and (b) the range of match-points given by any individual subject.

Displacement of match-points from the normal regression line. In Fig. 6 we have fitted a linear regression line to the pooled match-points from all the normal subjects. The correlation coefficient of $r = 0.97$ indicates that most of the variance (within and between normal subjects) is accounted for by this regression line.

Individual match-points for the heterozygotes are illustrated for each experimental group in Fig. 7. Carriers for deutan defects are represented by the open circles on the left, carriers for protan defects are represented by the solid circles on the right. The regression line for the normals is included in each plot for comparison. An analysis of covariance (Snedecor & Cochran, 1967, Chap. 14) shows that the regression lines for carriers of protanopia and deuteranopia do not differ significantly from the regression line of the normals. The most interesting feature of Fig. 7 is that almost the entire group of cDA subjects made matches that fall below the normal regression line (upper left panel). The residual variance for the matches of these carriers differs significantly from the variance of the normal settings

($F = 11.92$, d.f. = 74, 45, $P < 0.01$). The difference between normals and carriers of deuteranomaly is still significant if we represent each subject by her mean deviation from the normal regression line ($F = 7.13$, d.f. = 10, 6, $P < 0.01$). In the case of the carriers of extreme deuteranomaly we found a significant difference in the slope of the regression line ($F = 16.7$, d.f. = 1, 95, $P < 0.01$). The residual variance of the settings of cPA subjects differed marginally from the normal variance ($F = 1.7$, d.f. = 74, 39, $P < 0.05$).

Although Schmidt's sign (a reduced sensitivity to long wavelength) allows most protan carriers to be identified (Schmidt, 1934) analogous measurements of spectral sensitivity (De Vries, 1948; Mollon, 1987) have not offered a reliable indicator of deutan carriers, whose spectral luminosity function differs little from normal. Our result for deuteranomalous carriers in the ratio-matching task (Fig. 7, upper left panel) suggests that this test might provide a reliable indicator of such women. The present primaries (546, 570, 600 and 690 nm) were chosen arbitrarily and it may prove possible to improve upon them for the purpose of identifying carriers.

Matching range. Figure 8 shows the individual matching ranges of all subjects, sorted according to their experimental groups. A Kruskal-Wallis test showed no

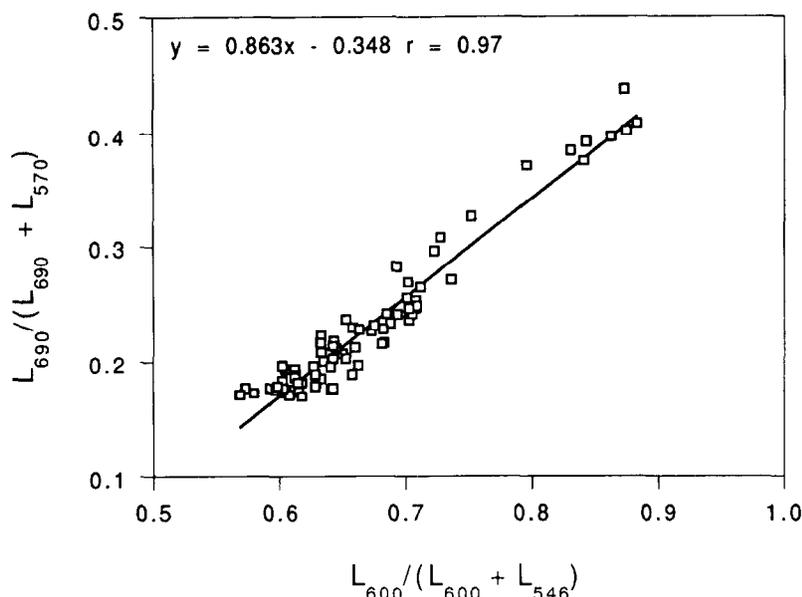


FIGURE 6. Results for normal subjects on the ratio-matching task. The ordinate represents the proportion of 690 nm light, expressed in luminance units, in the mixture of 690 and 570 nm and the abscissa represents the corresponding proportion of 600 nm light in the mixture of 600 and 546 nm. All individual matches pooled from all normal subjects are shown. Normal trichromats are expected to make matches that fall along a straight line in this space and the regression line shown does account for most of the variance.

systematic variation between groups ($H = 6.09$; $P < 0.1$); and inspection of the figure shows that most individual carriers exhibit matching ranges comparable to those of normals. In particular this is true for all carriers of protanomaly and most carriers of deuteranomaly—the two phenotypes where we had predicted tetrachromacy. Thus our main conclusion is that *most carriers of anomalous trichromacy show no evidence of strong tetrachromacy in the ratio-matching task*. In the spectral region that we have tested, these carriers behave like normal trichromats in that our four long-wave primaries lie effectively on a straight line in colour space and colour matches can be made in an extended region where the two mixtures (546 + 600 and 570 + 690) overlap.

Two of the carriers for deuteranomaly (cDA1 and cDA7) deserve special attention, in that theirs are the matches most distinct from the normal matching line. The matches of these two subjects are plotted individually in Fig. 9 and it can be seen that all the matches for the two women lie in the same small cluster in the ratio space. We can place little weight on the spread of settings of cDA1, who completed only three matches rather than the usual seven, but cDA7 is our one candidate tetrachromat. She behaves as if the long-wave spectrum locus is curved for her and that there is thus only one combination of the two mixtures (546 + 600 and 570 + 690) that gives an acceptable match.* Strictly,

*It is curious that cDA7 shows one of the largest ranges for small-field, Nagel matches (see Fig. 4) and the smallest range in the large-field ratio matching task (see Fig. 8). Just such a finding was predicted by Mollon (1987): a residual colour difference may handicap the tetrachromat at the Rayleigh match (see above). An alternative possibility is that the difference in matching ranges is associated with field size. In the large-field Rayleigh test (see above) cDA7 was not, and cDA1 was, an explicit match refuser.

of course, our data show only that cDA7 behaves as a trichromat in a spectral region where the normal observer behaves as a dichromat.

However, if cDA7 is indeed a tetrachromat, her tetrachromacy is not of the form we initially envisaged (see Introduction): her long-wave colour vision cannot depend on one channel that simply corresponds to the L/M channel of normal colour vision and a second that corresponds to the putative L/M' mechanism exhibited by the deuteranomalous son. If one of her channels were equivalent to a normal L/M channel, we should expect her match cluster to lie at a point on, or close to, the normal regression line. Just as a reduction dichromat is classically expected to accept the matches of a normal trichromat, so a normal trichromat would be expected to accept the unique match made by a tetrachromat in our ratio space.

The reader may ask whether cDA7 is constrained to match at a single point in the ratio space because she has an abnormal spectral luminosity function (our computer program held the two fields constant in td). We believe explanations of this type are unlikely, first because the temporal-substitution method is insensitive to small discrepancies in luminosity and second because the heterochromatic modulation sensitivity of both cDA7 and cDA1, as measured by the OSCAR test (Estévez, Spekrijse, Van Dalen & Verduyn Lunel, 1983), was found in an earlier study to lie near the middle of the distribution for normals (Mollon, 1987).

We have examined in detail the sons of the two carriers (cDA1, cDA7) whose settings are so distant from the normal regression line. The son of cDA1 had a matching range of 13–19 on the Nagel anomaloscope, while cDA7's son had a matching range of 22–30. The two subjects resembled each other in being noticeably

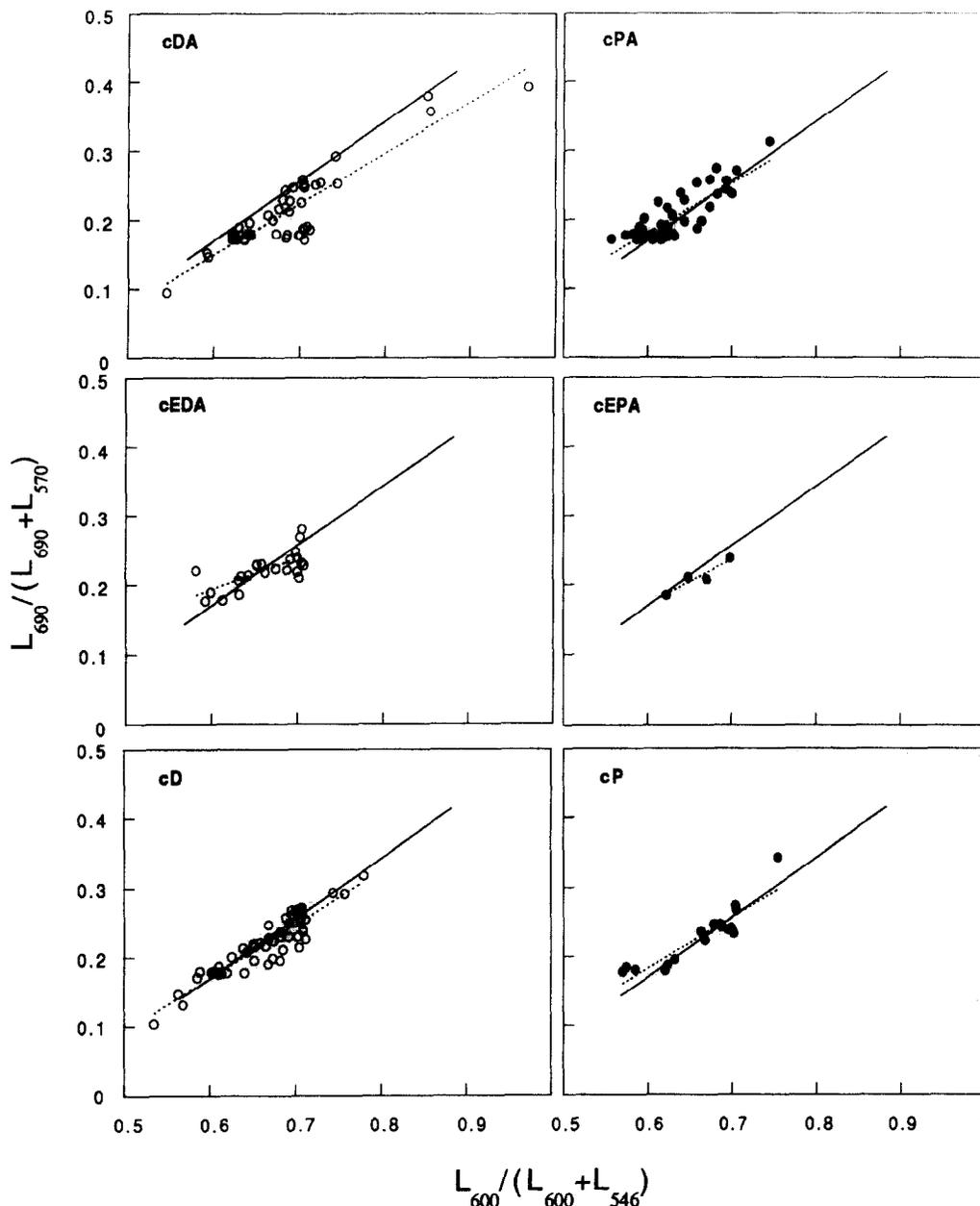


FIGURE 7. Results for different types of carrier on the ratio-matching task. Ordinates as for previous figure. The left hand panels show the results for deutan (○) and the righthand panels for protan (●) carriers. In each panel the solid line reproduces the regression line for normals (Fig. 6) and the dotted line represents the regression line for the carriers. Note in particular that the matches for carriers of deuteranomaly (cDA) lie systematically below the normal regression line.

finicky in their responses on the anomaloscope. DA1 had an error score of only 88 on the Farnsworth–Munsell 100-Hue test. DA7 had an error score of 236 on the Farnsworth–Munsell 100-Hue test, but made no errors on the City test (1st edn) and only minor transpositions on the D15. Figure 10 shows discrimination ellipses for these two subjects in the CIE chromaticity diagram. The latter data were obtained with the computer-controlled colour raster test described by Reffin, Astell and Mollon (1991), extended to probe 20 different directions of colour space. The extended version of the test was developed by Benedict Regan.

CONCLUSION

We have confirmed some of the classical beliefs about the colour vision of heterozygotes and failed to replicate others. Thus, we have found that carriers as a group exhibit significantly increased error scores on pseudoisochromatic plates and enlarged matching ranges on the Nagel anomaloscope. We have not been able to show systematic shifts in Rayleigh match mid-points nor increased error scores on the Farnsworth–Munsell 100-Hue test.

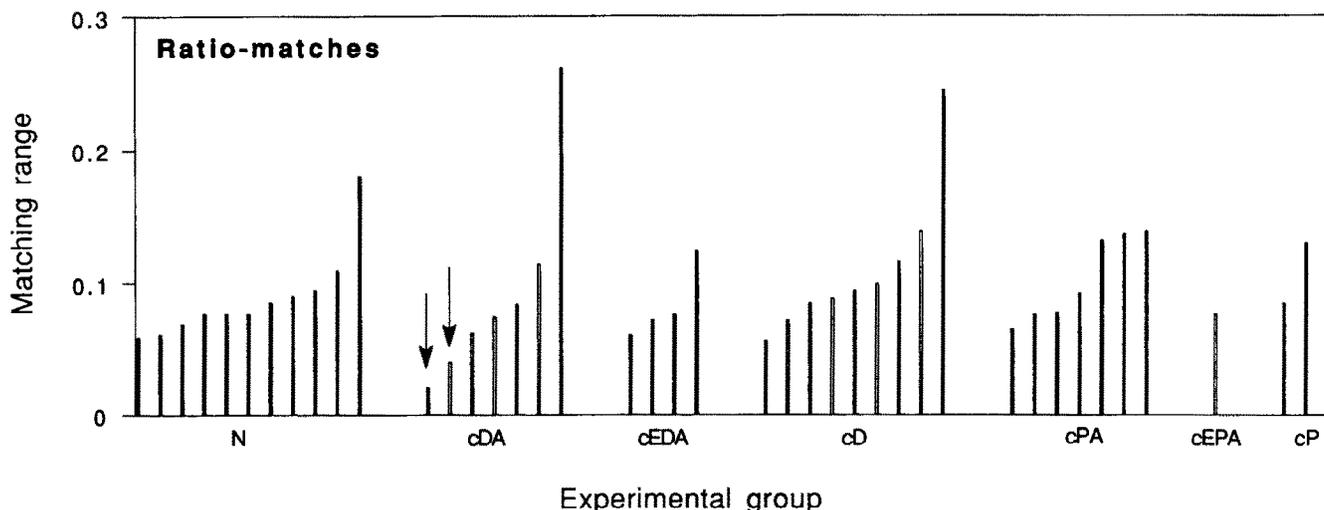


FIGURE 8. Individual matching ranges in the ratio-matching task. The matching ranges correspond to the absolute differences between the maximum and minimum values of the luminance ratio $L_{600}/(L_{600} + L_{546})$. The two subjects cDA1 and cDA7 are depicted by the arrows.

The existence of strong tetrachromacy

Our hypothesis that carriers of anomalous trichromacy may be tetrachromatic has received only limited support and it does not seem possible simply to translate the New World monkey model to our own species. Although several carriers of anomaly—and no other subject—rejected large-field Rayleigh matches, most carriers of anomaly do not find a unique match in our ratio-matching task and in this respect offer no evidence that they enjoy an extra dimension of discrimination in the particular long-wave spectral region that we have tested.

We did, however, find one woman (cDA7) who generated only a very restricted range of match-points in the ratio-matching task and who was the mother of a simple deuteranomalous son. This woman remains in play as a candidate tetrachromat in the strong sense. What are now required are full colour-matching functions for women of this phenotype. It also remains possible that a

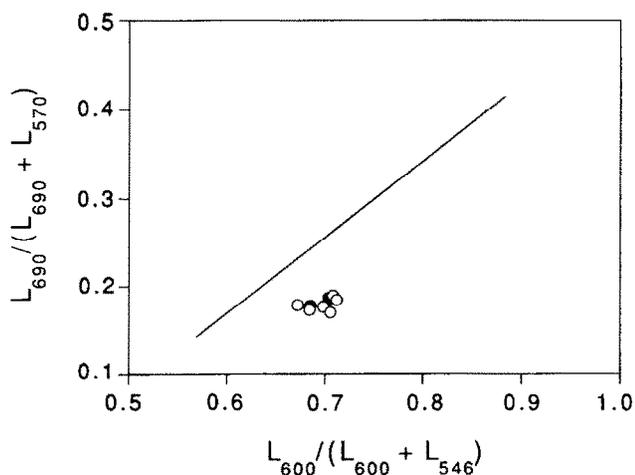


FIGURE 9. Matches set by two carriers of deuteranomaly [cDA1 (●) and cDA7 (○)]. The matches of these two observers show a large displacement from the normal regression line and form a tightly constrained cluster.

discrimination task, as opposed to a matching task, would reveal a higher proportion of tetrachromats (Cornsweet, 1970).

An obvious difficulty faces the hypothesis that some carriers of anomaly exhibit strong tetrachromacy: although Lyonization may ensure that there are four types of cone in the retina of a carrier of simple deuteranomaly, surely the visual system of such a woman would need the neural apparatus of an additional colour channel before she could make tetrachromatic discriminations? In fact, this difficulty may not be as great as it seems. Midget bipolar cells and midget ganglion cells in the primate retina commonly draw their centre input from a single long- or middle-wave cone. It is a matter of current debate whether the surround input is drawn from a single, antagonistic class of cone (Gouras, 1968; Reid & Shapley, 1992) or is drawn promiscuously and randomly from all cones in the local region (Shapley & Perry, 1986; Lennie, Haake & Williams, 1991). In either case, if a woman has three types of cone in the long-wave/middle-wave spectral region, she should have an additional type of chromatically-opponent midget ganglion cell. If the signals of these cells remain segregated throughout the parvocellular pathway, then to explain tetrachromacy we need only to suppose that the cortex can identify subsets of inputs that are correlated. It is commonly assumed today that the cortex exhibits just such a property (e.g. Linsker, 1990). Indeed if it is only a tiny minority of carriers of anomalous trichromacy who prove to be tetrachromatic, then the problem may be to explain why most are not. Within the limited sample of New World monkeys tested both behaviourally and by microspectrophotometry, no case has been found of a female who had three retinal cone types but was not trichromatic (Mollon *et al.*, 1984; Tovée *et al.*, 1992).

The nature of anomalous trichromacy

In the account of anomalous trichromacy advanced by Alpern and Moeller (1977) and Alpern (1987), the

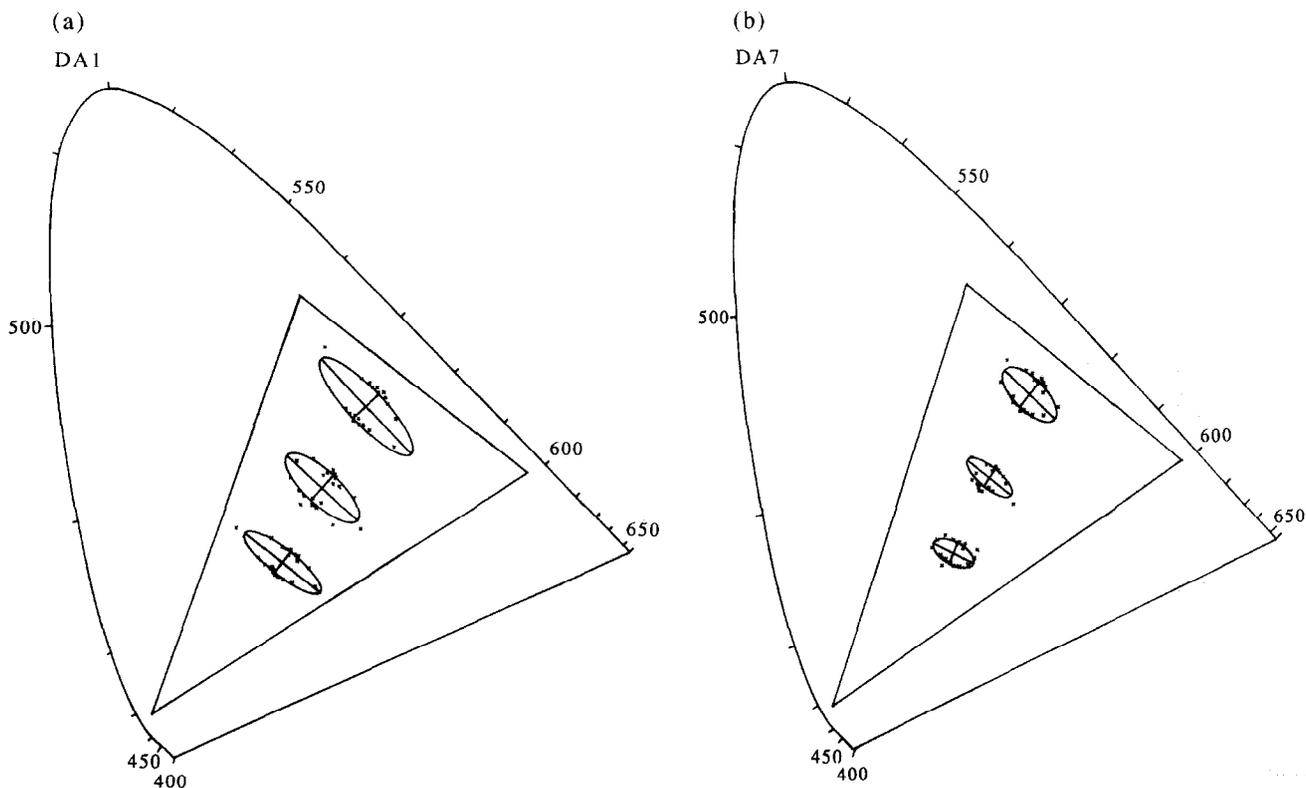


FIGURE 10. Discrimination ellipses of the deuteranomalous sons (DA1 and DA7) represented in the 1931 CIE chromaticity diagram. The triangle represents the limiting gamut of the colour monitor used for presenting the stimuli. The data points represent the thresholds measured for 20 directions for each of the three background chromaticities. The best-fitting ellipses are constrained in each case to be centred on the background chromaticity. For both of these sons the long axes of the ellipses have orientations very close to those of deuteranopic confusion lines.

residual red–green discrimination of the protanomalous observer is achieved by two forms of the normal middle-wave pigment and that of the deuteranomalous observer by two forms of the normal long-wave pigment. Neitz and Neitz (1992) and Neitz, Neitz and Jacobs (1992) have recently revived this hypothesis. However, they have additionally suggested that (a) two forms of the long-wave pigment and/or two forms of the middle-wave pigment may often be present in the normal male retina and (b) the alternative pigments are segregated in different cones. If these assumptions are correct, then the female carrier of deuteranomaly gains no special status through Lyonization and the inheritance of an anomalous gene. Many non-carrier women would also express two forms of the long-wave pigment, segregated in different outer segments. In so far as our results show that carriers of deuteranomaly do differ in their colour-matching behaviour, then we are left with an unresolved contradiction. One resolution would be to question assumptions (a) and (b) above. Another would be to suppose that the Alpern hypothesis is correct in so far as deuteranomalous pigments exhibit tyrosine at site 277 and threonine at site 285 [which would give them long-wave spectral sensitivities (Merbs & Nathans, 1992)]; but that the hypothesis is wrong in so far as the deuteranomalous pigment either carries a label that represents it as a middle-wave pigment to post-receptoral channels or is selectively expressed in cones that carry a middle-wave label. If we adopt this

explanation of why carriers of deuteranomaly differ from women who merely express two forms of erythro-labe, then we must follow Reid and Shapley (1992) in supposing that post-receptoral connections are specific and not random.

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Acknowledgements—This work was supported by MRC Grants G8807036N and G9113630N. We are grateful to B. Regan for providing Fig. 10 and to C.R. Cavonius, J. Moreland, M. Webster, P. Whittle and F. Viénot for comments and advice.