42. Sons and mothers: classification of colour-deficient and heterozygous subjects by counterphase modulation photometry

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Abstract

In the OSCAR test of Estévez *et al.* (1983) red and green lights are modulated in counterphase and the subject is asked to adjust their relative depths of modulation so as to minimize flicker. In a population consisting of normal mothers and carriers of colour deficiency (classified by their sons' performance on the Nagel anomaloscope), the OSCAR settings of the mothers were strongly correlated with those of their sons. Protan and deutan carriers formed discrete populations; and many individual carriers of protan deficiencies could be distinguished from normals with confidence. Protan and deutan sons were distinguished from each other with complete reliability, but some deutan sons, and most deutan carriers, fell within the distribution of normal settings.

Introduction

Can carriers of colour deficiency be identified psychophysically? Since 1920 it has been suspected that red–green colour deficiencies are not always completely recessive and that some carriers may reveal themselves by abnormalities of colour vision (Fleischer, 1920; Schiötz, 1920; Waaler, 1927). In fact, abnormalities of spectral matching or of colour discrimination are rather rare in heterozygotes (Jordan and Mollon, 1993). More diagnostic have been tests of increment threshold or spectral sensitivity. Thus protan carriers exhibit depressed sensitivity to long wavelengths (a condition known as Schmidt's sign; Schmidt, 1934, 1955; Walls and Mathews, 1952; Crone, 1959; Ikeda *et al.*, 1972; Swanson, 1991). An analogous loss of middle wavelength sensitivity has been reported in deutan carriers (de Vries, 1948; Crone, 1959; Adam, 1969) and has been named de Vries' sign, although this phenomenon has been more difficult to demonstrate than Schmidt's sign.

Such manifestations of the carrier state have been explained by the phenomenon of X-chromosome inactivation: although a woman inherits two X-chromosomes, a random process determines which of the two is expressed in

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any individual cell of her body (Lyon, 1972). The retinal mosaic of the heterozygote is thought to contain a subset of cones that express the abnormal chromosome which her colour-deficient son inherits.

Estévez *et al.* (1983) introduced a rapid measure of relative luminosity, called the OSCAR test (**O**bjective **S**creening of **C**olour **A**nomalies and **R**eductions). Since earlier reports suggest that carriers of colour deficiency reveal themselves rather readily in measurements of this kind, we have been prompted to ask whether the OSCAR test is clinically useful for identifying heterozygotes.

The test presents to the observer a mixture of two flickering lights, one a nearly monochromatic red light of 650 nm and one a relatively broad-band green light of dominant wavelength 560 nm. The two sources are light-emitting diodes and their outputs are mixed within a solid perspex rod. One end of the rod is slightly roughened to give a diffusing surface; and this end is viewed by the subject. The two component lights are alternated in counterphase at approximately 16 Hz (Fig. 1). A single control knob allows the subject to increase the depth of modulation of one component while concurrently decreasing the depth of modulation of the other component. The subject is asked to adjust the knob until the flicker is minimally visible. The advantage of this counterphase modulation photometry over flicker photometry is that the time-averaged luminance and chromaticity of the stimulus remain constant as the adjustment is made.

Materials and methods

Subjects

The 144 subjects comprised 43 carriers of X-linked colour deficiencies and their colour-deficient sons, and 25 colour normal mothers and their sons. In some cases, more than one son was tested from a given family. Most carriers had already participated in an earlier study of the colour vision of heterozygotes (Jordan and Mollon, 1993). All subjects were naive as to the aim of the experiment and were paid a small sum for their participation.

OSCAR test

The subject held the OSCAR test in two hands while operating the knob with his or her right hand. The stimulus field subtended approximately 0.7° at the eye. The dominant wavelength was approximately 594 nm and the luminance was 15 cd/m^2. Between successive settings the control knob was offset by the experimenter, alternately to one or other end of its range. Subjects made five settings binocularly. The OSCAR test is known to be sensitive to the lighting conditions (Birch, 1993): all the present subjects were tested in the presence of a low level of Illuminant C (Macbeth easel lamp) giving approximately 3 lux in an otherwise dark room. The version of the test we used was manufactured commercially by Medilog (The Netherlands).

Nagel anomaloscope

The Rayleigh match was measured with the Nagel anomaloscope (model I) for the dominant eye of each subject. The procedure was as follows: the experimenter set the red–green mixture and the subject adjusted the luminance of the monochromatic yellow to equate the fields in brightness. After this was done, the subject looked at a white piece of paper illuminated by Illuminant C to neutralize his or her adaptation and then rated the goodness of the match. The procedure was repeated until both ends of the matching range were securely determined.

Results

The main panel of Figure 2 plots the OSCAR settings of sons against the settings of their mothers. The ordinates represent the arbitrary scale units of the OSCAR test, normalized so that the mean setting of our population of normal mothers and sons is zero. Projected to the left of the main panel is the histogram of settings of individual sons; and projected below the main panel is the

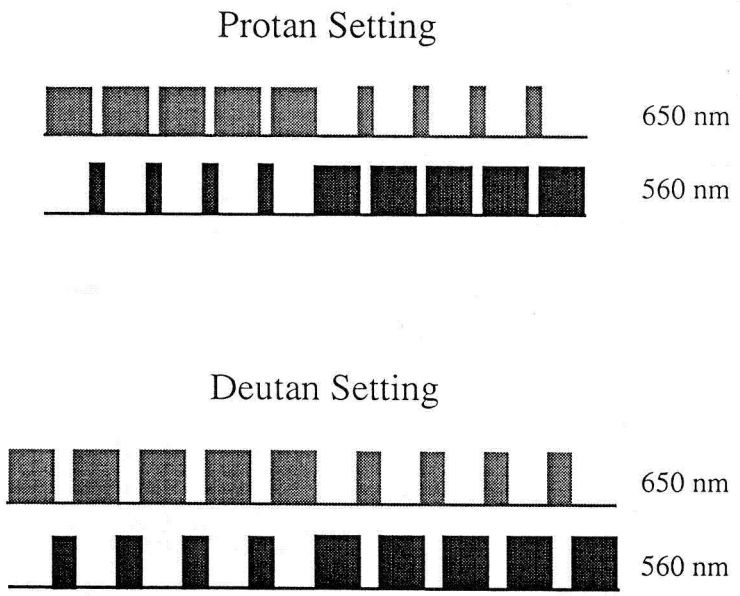

Fig. 1. In the OSCAR test the red and the green components of the stimulus are modulated in counterphase at 16 Hz. The depth of modulation is controlled not by varying the LED current (which would change the spectral output of an individual LED) but by turning the lamps fully on and off at a much higher frequency and varying the proportion of time the lamp is on during the two phases of each cycle. Thus the diagram shows schematically the high-frequency modulation during the opposite phases of just one period of the 16 Hz stimulus.

histogram of settings of mothers.

From the histogram for sons, it is seen that counterphase modulation photometry achieves a complete separation of subjects defined as protan and deutan by the Nagel anomaloscope. Moreover, all the protan subjects lie outside the distribution of colour-normal subjects. However, there is significant overlap between the normal and the deutan sons. In judging this overlap, and the similar overlap in Figure 1 of Cavonius and Kammann (1984), it is important to remember that normal individuals are about 15 times more common in the population than are deutans and thus, to obtain likelihood ratios for clinical use,

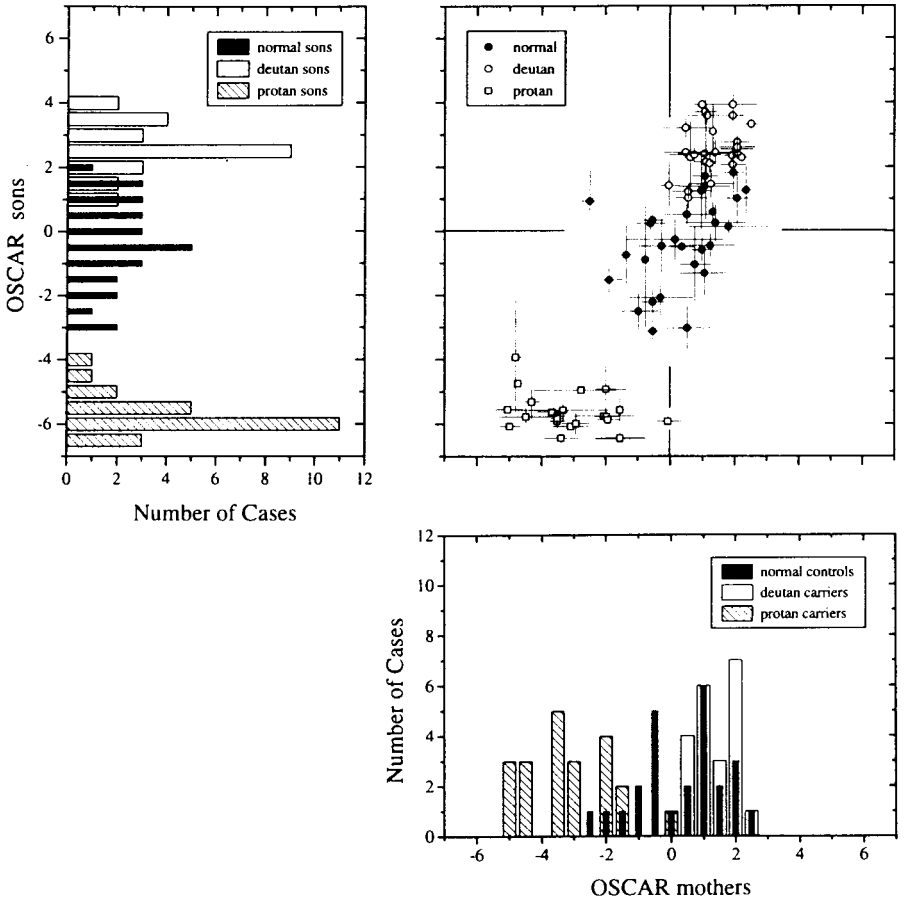

Fig. 2. The upper right panel shows the relationship between the settings of mothers and sons on the OSCAR test. Note the clear difference between settings of deutan and protan carriers. The distributions of settings for sons and those for the mothers are projected on to the two subsidiary histograms. The cell centred on 0.0 in the histogram for mothers represents one normal, one protan heterozygote and one deutan heterozygote.

we must increase the relative height of the colour-normal distribution so that areas of the normal and deutan distributions are in the ratio 15:1; 'colour-normal' thus becomes the more likely diagnosis over a significant fraction of the range occupied in the histogram by deutan settings.

The main panel of Figure 2 exhibits a strong overall correlation ($R = 0.85$, $p < 0.001$) between the minimum-flicker settings of mothers and sons. As can be seen in the lower histogram, this rapid clinical test achieves an almost complete separation of protan and deutan carriers. There is overlap between the control mothers and the two types of carrier, especially the deutan carriers. Nevertheless, many protan carriers exhibit Schmidt's sign, in that they are less sensitive to long wavelengths than are any of the normals. None of our population of protan carriers exhibited a setting as extreme as the most extreme protan sons, but some carriers are as extreme as some of the protanopic sons.

The OSCAR test did not distinguish between dichromatic and anomalous sons, nor between the corresponding subsets of mothers. A moderate but significant correlation between OSCAR and anomaloscope settings was found for normal sons ($R = -0.62$; $p = 0.003$), but not for normal mothers ($R = -0.15$; $p = 0.44$).

Discussion

Counterphase modulation photometry as a test for colour blindness

We confirm the judgement of others (Cavonius and Kammann, 1984; Zisman *et al.*, 1987; Verriest and Uvijls, 1987) that the OSCAR test is not ideal as a screening test for colour blindness. Its failure to distinguish some deutans from normal individuals reflects a difficulty that has classically faced tests that depend on the measurement of spectral luminosity (Crone, 1959; Adam, 1969); Nevertheless, the OSCAR test has a role in clinical diagnosis. We found, as did Cavonius and Kammann (1984) and Verriest and Uvijls (1987), that the test was completely reliable in distinguishing deutans from protans, a discrimination that is only poorly made by pseudoisochromatic plates (Walls, 1959; Frey, 1958). If a patient has failed a plate test, the OSCAR test offers an economical means to classify him or her as protan or deutan. But to distinguish protanomalous subjects from protanopes, and deuteranomalous from deuteranopes, it will still be necessary to turn to the anomaloscope.

Counterphase modulation photometry and the heterozygote

The OSCAR test has a role to play in the examination of carriers of colour deficiency. As groups, the protan and deutan heterozygotes are statistically quite distinct from each other and from the putatively homozygous women. A subgroup of heterozygotes can be individually identified with some confidence using the OSCAR test: these are the protan carriers who make a very negative

Table 1. The relationship between OSCAR settings and the probability that a woman is a protan carrier rather than a normal.

OSCAR	–6.0	–5.5	–5.0	–4.5	–4.0	–3.5	–3.0	–2.5	–2.0
$p_{(protan)}$	1.0	1.0	0.99	0.97	0.91	0.77	0.53	0.28	0.14

setting. If we take Verriest's (1972) estimates of the relative frequencies of normal mothers and protan carriers (84/3.7) and if we fit normal distributions to our OSCAR settings for normal mothers and for protan carriers, then we can calculate that 'protan heterozygote' becomes the more likely diagnosis when the OSCAR reading is less than –3.0 and becomes almost certain for readings of –4 or less. Table 1 shows the calculated probabilities over a range of OSCAR settings. Our estimates are conservative because statistically our sample of 'homozygous' mothers ought to contain one or more heterozygotes who have not yet revealed themselves by bearing a colour-deficient boy. It would be desirable to have data for a larger sample of colour-normal women, each of whom had several sons, none of whom are colour blind.

Theory of counterphase modulation photometry

To understand why deutan and protan heterozygotes perform differently on the OSCAR test, we must consider what is happening when a subject sets the instrument to minimum flicker. Only in the case of the dichromat is there a straightforward basis for the setting. Such a subject can find a setting that completely abolishes flicker. In the case of, say, a protanope, this is thought to be the setting at which an increment in the 650 nm light gives an increase in the quantum catch of the middle wavelength cones that is exactly balanced by a decrement in the quantum catch from the 560 nm light (see Estévez *et al.*, 1983). This setting corresponds closely to the setting that Rushton called the 'isolept' when discussing the exchange-threshold method of isolating individual classes of receptor (Rushton *et al.*, 1973).

We do not know the exact basis on which a trichromat finds a setting of minimum flicker. A setting that corresponds to the isolept for his long wavelength cones will not correspond to the isolept for his middle wavelength cones, and vice versa. Perhaps he has independent access to the two cone signals and compromises between their isolepts, finding an intermediate setting where the counterphase modulations of the two separate cone signals are both equally small (Mollon, 1987); or perhaps, as more commonly assumed, there is a post-receptoral channel (the 'luminance' channel) that combines signals from the long and middle wavelength cones, so that decrements in one signal cancel increments in the other (Ingling and Tsou, 1985). The first possibility might be called the compromise hypothesis and the second the cancellation hypothesis. It is empirically difficult to distinguish psychophysically between compromise and

addition; for both hypotheses require a setting intermediate between the two isolepts. In either case, we should expect the OSCAR setting to be easier and more precise for an anomalous trichromat than for a normal observer. In anomalous trichromacy the spectral sensitivities of the long and middle wavelength cones are thought to be closer together than normal; the two isolept settings would, therefore, also be close and an intermediate setting would not modulate strongly the signal of either class of cone.

How are we to explain the different settings of protan and deutan heterozygotes? Consider a carrier for protanopia. Owing to X-chromosome inactivation, we may suppose that a subset of her cones expresses the X-chromosome that her protan sons inherit. In consequence, an increased proportion of cones in her retina will contain a middle wavelength-sensitive pigment. Since the total strength of the signal from a given class of cones is likely to depend on their numerosity, our protan carrier should require more modulation of the red LED to compensate a given modulation of the green LED. In terms of the compromise hypothesis, her abnormal setting is necessary to keep the absolute modulation of the middle wavelength cone signal small and equal to that of the long wavelength signal. In terms of the cancellation hypothesis, the shift is necessary because a larger decrement in the signal of individual long wavelength cones is needed to cancel a given increment in the middle wavelength signal. In the case of a carrier of protanomaly, the argument must be somewhat less certain since the nature of anomalous trichromacy remains unsettled. However, most accounts of protanomaly suppose that the protanomalous trichromat depends for his residual red–green discrimination either on two normal middle wavelength pigments with different spectral sensitivities or on the combination of a normal middle wavelength pigment and an anomalous pigment that occupies a spectral position close to that of the middle wavelength pigment(s). Whichever hypothesis one prefers, a heterozygote for protanomaly will effectively end up with an excess of cones that contain pigment(s) with their peak sensitivity in the middle wavelength region; and the signal of these cones will dominate flicker photometric settings. *Mutatis mutandis*, the same arguments can be applied to carriers of deuteranopia and deuteranomaly.

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