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The Enhanced S Cone Syndrome: An Analysis of Receptoral and Post-receptoral Changes

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The purpose of the study was to test the hypothesis that the retinae of patients with enhanced S cone syndrome (ESCS) have more S cones than the normal retina and these cones have replaced some of the L and M cones. Standard and spectral full-field electroretinograms, measurements of L, M, and S cone system sensitivities and S cone acuity were obtained from three patients with ESCS. The results were qualitatively consistent with the presence of more S cones and more S cone ganglion cells. To test this hypothesis further, a model of the receptoral and post-receptoral components of the S cone system was used in conjunction with psychophysical measurements of S cone system sensitivity under flashed and steady-state adaptation conditions. Within the context of the model, the data were consistent with an increase in the number of S cones and S − (L + M) ganglion cells and with a decrease in the total L + M cone input to each S − (L + M) ganglion cell. Copyright © 1996 Elsevier Science Ltd.

a-wave S cone S cone system Retinal disease Psychophysics

INTRODUCTION

Retinal diseases often lead to preferential loss of sensitivity to short-wavelength lights. There is, however, an inherited retinal degenerative disease that is characterized by increased sensitivity of the short-wavelength-sensitive (S) cone system. This disease, the enhanced S cone syndrome (ESCS), is associated with nightblindness, cystoid maculopathy and unusual electroretinograms (ERG) which are similar in waveform for both dark and light-adapted conditions (Jacobson *et al.*, 1990; Marmor *et al.*, 1990; Jacobson *et al.*, 1991). In fact the negative component (*a*-wave) of the ERG can be as large or larger than the normal dark-adapted rod *a*-wave, even in the presence of a background field (Gouras *et al.*, 1985; Fishman & Peachey, 1989; Jacobson *et al.*, 1990; Marmor *et al.*, 1990; Jacobson *et al.*, 1991; Kellner *et al.*, 1993). Spectral ERGs indicate that these large responses are mainly S cone driven (Jacobson *et al.*, 1990, 1991; Roman & Jacobson, 1991). In addition S cone system sensitivity, as measured by psychophysical tests, is markedly increased, particularly in peripheral retinal areas whereas L and M cone system and rod system sensitivities are severely decreased (Jacobson *et al.*, 1990; Kellner *et al.*, 1993).

Various explanations ranging from changes in receptoral to post-receptoral mechanisms have been suggested for the unusual ERG and psychophysical findings. For example, increased S cone system sensitivity has been attributed to:

1. An increase in the number of S cone photoreceptors compared to the normal;
2. Rod photoreceptors containing an opsin similar to S cone opsin;
3. Alterations in post-receptoral retinal mechanisms, i.e., alterations at the S − (L + M) opponent site.

A recent study by Hood *et al.* (1995) provides support for an explanation based on the presence of an increased number of S cones in the retinae of patients with ESCS. In that study, high intensity flashes were used to record ERGs from three patients with ESCS and the *a*-wave responses were shown to be described by a cone model of phototransduction (Hood & Birch, 1995). The three patients had characteristically large *a*-waves in response to blue and white flashes, which were driven almost entirely by receptors containing S cone pigment and the waveforms were quantitatively consistent with cone rather than rod responses. Based on these findings, it was suggested that the retinae of patients with ESCS have

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many more S cones than normal and that these cones have replaced some of the normal L and M cones and many of the rods.

The purpose of the present study was to use psychophysical techniques to analyze receptoral and post-receptoral changes in the S cone systems of patients with ESCS. The techniques included measurements of L, M, and S cone system sensitivities using the two-color increment threshold technique, and measurements of S cone acuity. The results of these measurements were qualitatively consistent with an increase in the number of S cone photoreceptors and ganglion cells. An increase in the number of photoreceptors and ganglion cells has implications for changes in sensitivity at the receptoral and post-receptoral levels of the S cone system. These sensitivities were measured for normal and ESCS observers by stimulation of either the S cone input or the L + M input to the opponent stage of the S cone system. The data were compared within the context of a quantitative model of the S cone system (Zaidi *et al.*, 1992).

METHODS

Subjects

Three patients with ESCS participated in the study. They were diagnosed as having ESCS based on clinical, psychophysical and ERG criteria (Jacobson *et al.*, 1990, 1991; Marmor *et al.*, 1990). The patients had steady central fixation on visuscopy and areas of increased S cone system sensitivity within 10 deg of the fovea. Patient 1 (P1) is a 23-yr-old man from a family with no other known affected members. He complained of long-standing night vision disturbances. Visual acuity in the tested eye (right eye) was 20/20. Color vision as tested with the Farnsworth–Munsell (FM) 100-hue test was normal. Goldmann kinetic visual fields were full with the V-4e target and showed a relative scotoma in the inferonasal mid-peripheral field with the I-4e target. Ophthalmoscopy revealed a few yellow flecks and rare pigment clumps in the mid-periphery. Patient 2 (P2) is a 17-yr-old girl from a family with no other known affected members but with parental consanguinity. She complained of disturbances of night vision and visual acuity. Best corrected visual acuity in the right eye was 20/60. Color vision testing revealed a slight deficit in hue discrimination (square root 100-hue error score 12.96). Goldmann kinetic visual fields were full with the V-4e target. With the I-4e target there was a central island of function separated from a peripheral island by a mid-peripheral relative scotoma. Cystic changes in the macula and pigment epithelial disturbances in the mid-periphery were observed on ophthalmoscopy. Selected ERG data for P2 were presented in a previous study [Patient 2 in Hood *et al.* (1995)]. Patient 3 (P3) is a 28-yr-old woman with a younger sibling who complained of night blindness but who had no other proven affected family members. Visual acuity in the left eye (tested eye) was 20/25. Color vision as tested with the FM 100-hue test was normal. Goldmann visual fields were full with the V-4e and were limited to the central 10 deg with the I-4e. Ophthalmoscopy revealed pigment epithelial abnormalities around the arcades and clumped pigment in the superior retina.

Nine normally sighted subjects (mean age = 23 yr; SD = 3.4 yr; range = 17–30 yr) also participated in the study. All subjects gave informed consent after a full explanation of the procedures was given.

Electroretinography and static threshold perimetry

Standard and spectral full field ERGs were performed using techniques previously described by Jacobson *et al.* (1990, 1991), Roman and Jacobson (1991), and by Hood *et al.* (1995). Static threshold perimetry was performed with monochromatic test stimuli (diameter 103′) at 75 loci across the visual field using a modified automated perimeter. Two-color dark-adapted perimetry was performed with 500 and 650 nm stimuli, and S cone perimetry with a 440 nm stimulus on a "yellow" adapting background [for details see Jacobson *et al.* (1990, 1991)].

L, M, and S cone system sensitivities: Two-color increment thresholds

The sensitivities of the L, M, and S cone systems were measured in a retinal area 6 deg superior to the fovea using a two-color increment threshold technique. Light stimulation was provided by a two-channel Maxwellian view system and monochromatic light was provided by interference filters with half bandwidths of *ca* 6 nm. For details on apparatus and procedure see Greenstein *et al.* (1989, 1990), and Greenstein and Hood (1992). To assess S cone system sensitivity increment thresholds were obtained for a 440 nm test light (1.25 deg in diameter and 200 msec in duration) superimposed on a series of 14 deg steady 600 nm adapting fields of increasing retinal illuminance (from 1.8 to 3.9 log td). Test spectral sensitivities to 440, 480, 500, 540 and 580 nm lights were obtained in the presence of the 600 nm adapting field at 3.9 log td to confirm the mechanisms mediating detection. To assess L and M cone system sensitivities, increment thresholds for a 660 nm (1.25 deg in diameter and 10 msec in duration) and then for a 540 nm test light (1.25 deg, 200 msec in duration) were obtained on a series of 600 nm adapting fields of increasing retinal illuminance (from −0.17 to 3.9 log td). After 10 min of dark adaptation, subjects adapted to each adapting field for at least 2 min before the test light was presented. Thresholds were obtained using a modified method of limits procedure.

S cone grating acuity

S cone acuity was measured using a technique described by Wilson *et al.* (1988) and by Swanson (1989). Achromatic square wave gratings were generated on the screen of a Macintosh computer. Light from the computer screen was reflected off a front surface mirror, through a blue filter (Balzar DTB500) then reflected off a dichroic beam splitter (Balzar DVB480). The beam splitter was used to superimpose the blue and black test

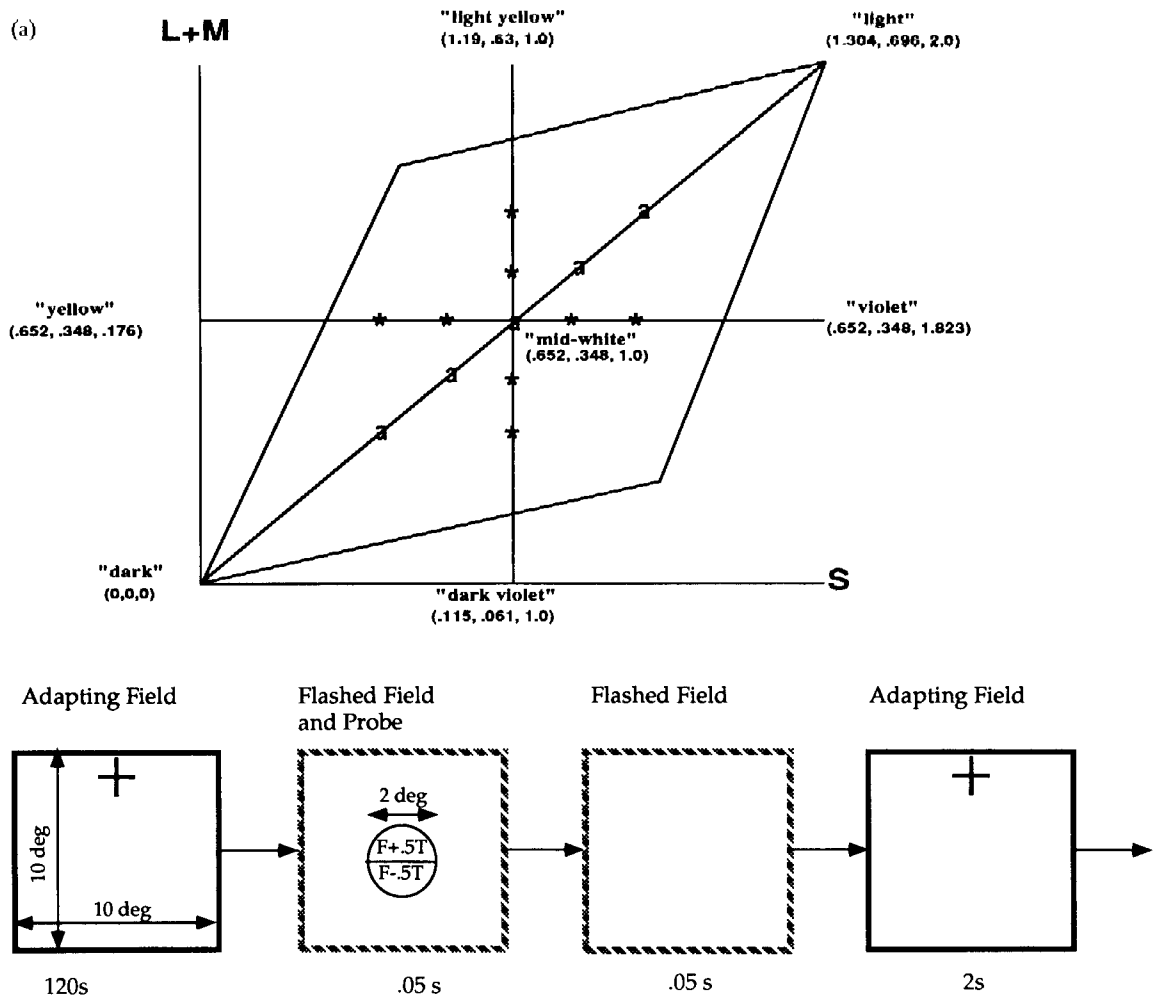


FIGURE 1. (a) schematic of the color plane defined by the S and L + M axes. The ordered triplets were obtained by transforming the CIE (1931) coordinates to Smith-Pokorny (1975) fundamentals. The light at *W* is metameric to equal-energy white with a luminance defined to be 1 unit, where 1 unit is equal to 28 cd/m^2. The quadrilateral boundary encloses lights that could be generated by the equipment. The letters "a" represent the set of adapting lights for the steady-state condition. The asterisks represent the flashed fields that were used as judgement points for the probe-flash paradigm. (b) spatial and temporal paradigm for the post-receptoral S cone system sensitivity measurements.

gratings on a "yellow" background (Tiffen 16). The gratings were viewed through a 3 mm artificial pupil and subjects were optically corrected for chromatic aberration. The gratings consisted of five equally spaced bars oriented either vertically or horizontally, and were presented to a retinal area 6 deg superior to the fovea. A two-interval forced-choice technique was used to measure acuity for the blue square wave gratings superimposed on a series of yellow adapting fields of increasing luminance. The subject had to indicate which 750 msec interval contained the vertically oriented grating. Psychometric functions were obtained using four grating spatial frequencies at each adapting field. The threshold (defined as 75% correct) was estimated by fitting a Quick (1974) function to the data using a maximum likelihood estimate.

S cone system sensitivity: Probe-flash thresholds

In this part of the study the responses of the S cone system were assessed using a modified version of the probe-flash and steady-state threshold techniques previously described by Zaidi *et al.* (1992) and Greenstein *et al.* (1992). The stimuli were displayed on a Barco 7651 color monitor with a refresh rate of 100 non-interlaced frames/sec. Images were generated using a Cambridge Research Systems Video Stimulus Generator (CRS VSG2/2). The mean luminance of the display was 28 cd/m^2. All stimulus presentation and data collection were computer controlled. The stimuli were varied along theoretically defined lines and were restricted to the color plane defined by the S and L + M color axes that is shown in Fig. 1. Lights are represented in the figure by (L,M,S) cone excitations which were obtained by transforming the CIE (1931) coordinates for each light to Smith-Pokorny fundamentals (Smith & Pokorny, 1975). The light at *W* ("mid-white") is metameric to equal energy white with a luminance defined to be 1, where one unit of luminance is specified as being equal to 28 cd/m^2. Three

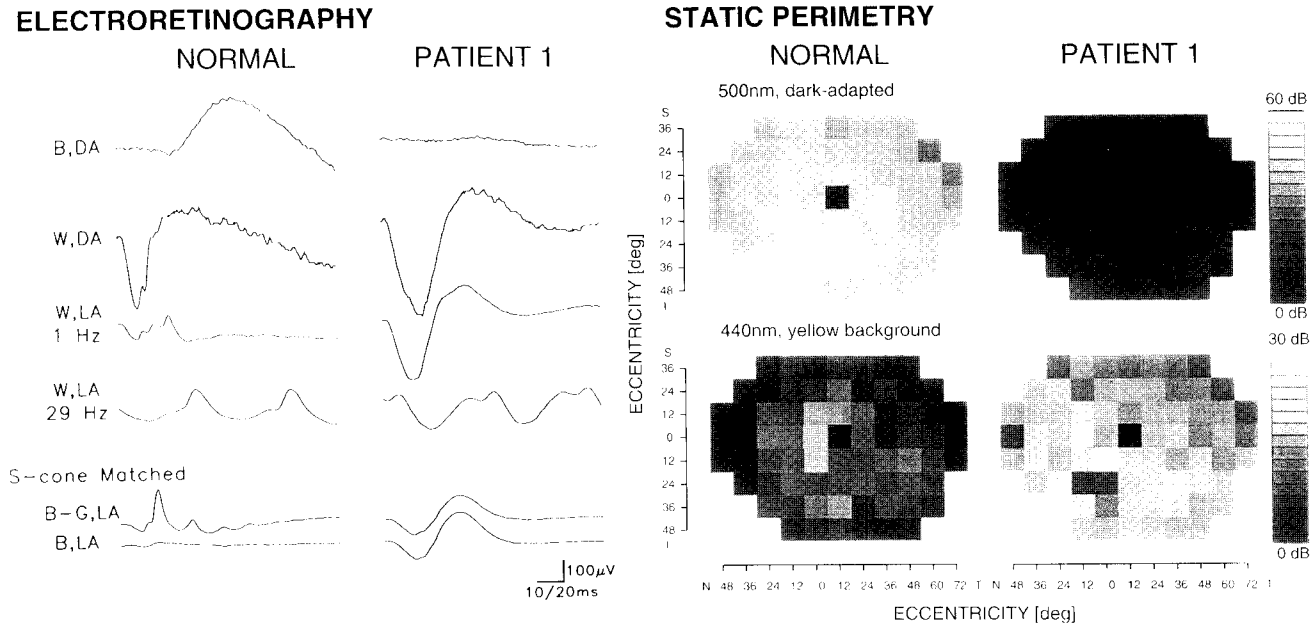


FIGURE 2. ERGs (left) and static threshold perimetry (right) in a normal subject and ESCS patient 1 (P1). Left, the blue flash, dark-adapted (B,DA), elicits a rod *b*-wave in the normal subject but no measurable response in P1. The normal response to the white flash, dark-adapted (W,DA), is a mixed cone and rod ERG with *a*- and *b*-wave components; on a steady white background of 30 cd/m^2 (W, LA, 1 Hz), the response is from the cone system. To both of these stimuli, P1 shows the same large negative waveform. White flicker at 29 Hz (W, LA, 29 Hz) produces a response with reduced amplitude and delayed timing in P1 compared to the normal. S cone matched blue (B,LA) and blue–green (BG,YB) stimuli on a white background produce small and unequal responses in the normal but large equal waveforms in P1. The horizontal calibration is 20 msec for all ERG records except the 29 Hz flicker, which is 10 msec; the vertical calibration is 100 μV. Right, gray scale maps of dark-adapted thresholds measured with a 500 nm stimulus (above) and S cone thresholds with a 440 nm stimulus on a yellow background (below) in a normal subject and P1. S cone thresholds are normal at the central and mid-peripheral loci tested and supernormal (by about 1 log unit) in the peripheral field.

types of stimuli were used; ΔS, Δ(L + M) lights and achromatic lights. ΔS stimuli refer to lights that vary parallel to the S cone axis shown in Fig. 1 and produce changes exclusively in S cone input; without perturbing L and M cone excitations. Δ(L + M) stimuli refer to lights that vary along the L + M axis, and produce proportional increases or decreases in L and M cone excitation while S cone excitation remains constant. Steady achromatic lights varying in luminance along the diagonal "light" "dark" axis result in a proportional increase or decrease in excitation of all three cone types.

For the S cone system we assume that the outputs of S cone photoreceptors are opposed by the outputs of the sum of the L and M cone photoreceptors. To ensure that we were measuring the sensitivity of an observer's S cone system with the probe-flash paradigm we used ΔS probes. The function of various components of the S cone system was assessed by using:

1. Flashes that affect sensitivity at the receptoral and opponent stage (ΔS lights);
2. Flashes that affect measurements only at the opponent stage (Δ(L + M) lights); and
3. Lights that affect sensitivity only at the receptoral stage (steady achromatic lights).

The spatial and temporal paradigm for the probe-flash technique is shown in the lower panel of Fig. 1. The 2 deg, 50 msec test light or probe was presented to a retinal area 6 deg superior to the fovea. It consisted of two halves of a disk, one half at $F + 0.5T$ and the other at $F - 0.5T$, where T was the test amplitude along the S cone axis (color line) and F was the flashed field. Probe thresholds were obtained in the presence of a series of flashed fields which were either pure S cone increments or decrements along the S cone axis passing through W or pure L + M increments or decrements along the L + M axis. Steady state thresholds were measured on achromatic backgrounds of increasing luminance. In Fig. 1 (a) the points labeled "a" along the "light" "dark" axis represent the set of adapting lights used for the steady state threshold technique and the asterisks along the S cone and the L + M axes represent the flashed fields used for the probe-flash technique. After adapting for 2 min to each steady adapting field, thresholds were obtained to the 2 deg, 50 msec test light. For this part of the procedure, one half of the disk was at $W + 0.5T$ and the other at $W - 0.5T$. For both techniques the division of the disk was randomly presented as either horizontal or vertical and the subject had to make a forced choice as to the orientation. A double random staircase was used to find the value of T at which the subject could discriminate between either $F + 0.5T$ and $F - 0.5T$ or $W + 0.5T$ and

$W - 0.5T$ with a probability of 0.71. Threshold was calculated as the mean of eight transitions.

RESULTS AND DISCUSSION

Electroretinography and static threshold perimetry

Standard ERGs for P1 and a normal subject are shown in Fig. 2 (left panel). The dim blue flash elicits a "rod" *b*-wave in the normal but no measurable response in P1. Rod responses to dim blue light flashes in the dark-adapted state were also not measurable for the other two patients. The bright white flash in the dark-adapted state elicits a mixed cone and rod ERG with *a*- and *b*-wave components in the normal; for the light-adapted state a smaller, faster cone response is elicited. For P1 bright white flashes elicit large amplitude responses that are similar in waveform appearance for both the dark- and light-adapted states. Similar responses were elicited for P2 and P3. The waveforms were not like those of normal rod, mixed cone and rod, or cone ERGs. Flicker ERGs were reduced in amplitude and delayed in timing for all three patients.

Spectral ERGs indicated that the large waveforms in the patients were S cone driven. As shown in Fig. 2, S cone matched blue and blue–green light stimuli on a white background produce small and unequal responses in the normal subject but similar large amplitude waveforms in P1; this finding was also present in P2 and P3.

Figure 2 (right panel) illustrates the results of dark-adapted perimetry and S cone perimetry in P1 compared to the normal subject. Dark-adapted rod system thresholds for P1 are increased by at least 3.0 log units. S cone perimetry for P1 shows "supernormal" (lower than normal) thresholds at some central field loci (not shown) and throughout the far peripheral field. In the mid-periphery, thresholds are within the normal limits. For P2 and P3, rod system thresholds were elevated and S cone system thresholds were "supernormal" at some central field loci and throughout the far peripheral field. For all three patients L/M cone thresholds were abnormal and elevated by about 1 log unit.

This pattern of electrophysiological and psychophysical results is consistent with those previously reported for patients with ESCS (Jacobson *et al.*, 1990, 1991; Marmor *et al.*, 1990; Roman & Jacobson, 1991).

L, M and S cone system sensitivity

L, M and S cone increment threshold data for the three patients were compared to mean increment threshold data for nine normals. The differences in L, M and S cone threshold values compared to the mean threshold values for normals are shown in Fig. 3. L and M cone system thresholds are higher by 0.8 and 0.5 log units, respectively, for P1, by 0.85 and 0.70 log unit for P2 and by 1.0 and 0.6 log unit for P3. S cone system thresholds are lower by 0.6 log unit for P1, 0.15 log unit for P2 and 0.3 log unit for P3. These results obtained at a superior retinal area on a Maxwellian view system, are in agreement with L/M and S cone perimetry findings on the three patients. Figure 4 provides additional evidence for increased S cone system sensitivity. Increment threshold data for patients are compared to mean thresholds for normals over a range of adapting backgrounds. Thresholds for P1 and P3 are lower than normal. For P2, thresholds are slightly lower at the higher levels of adaptation. For both patients and normal subjects, the level of adapting illuminance has very little effect on threshold values; thresholds increase by approximately 0.3 log unit over a 2.0 log unit range. Spectral sensitivity data obtained for the patients in the presence of the 600 nm adapting field at 3.87 log td [see Fig. 4 (b)] show that detection of the 440 and 480 nm test lights in this superior retinal area is mediated by receptors with S cone pigment, and that S cone system sensitivity is increased for P1 and P3. The data for the patients also show that detection of the 580 nm test light does not appear to be mediated by receptors with M cone pigment.

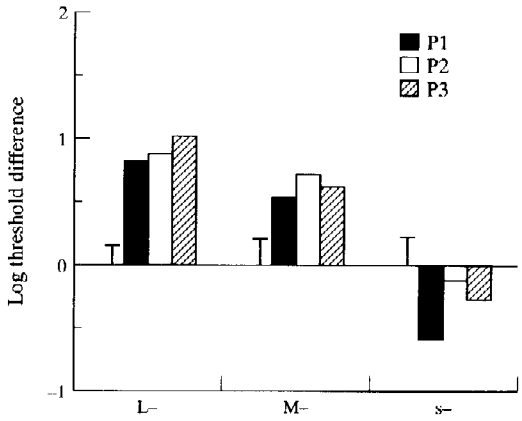


FIGURE 3. Log threshold differences for the L, M and S cone systems for P1 (solid bar), P2 (open bar), and P3 (hatched bar) compared to mean data for nine normals (represented by zero). The error bars represent +1 SD for the normals. L, M and S cone system thresholds were measured at −0.17, 2.5, and 3.9 log td, respectively, in a retinal area 6 deg superior to the fovea.

S cone grating acuity

The psychophysical data obtained at a retinal area 6 deg superior to the fovea (i.e., increased L and M cone system thresholds and decreased S cone system thresholds) are qualitatively consistent with the ERG data. However, decreased thresholds do not necessarily reflect increased numbers of S cone receptors. The decrease in thresholds for example, could also be due to increased quantal efficiency in each individual photoreceptor. Measurement of S cone acuity provides a means for testing whether there are increased numbers of functioning receptors.

S cone acuity was measured at the same retinal location. Grating acuity data for the three patients as a function of increasing luminance of the "yellow" background are compared to averaged acuity data for

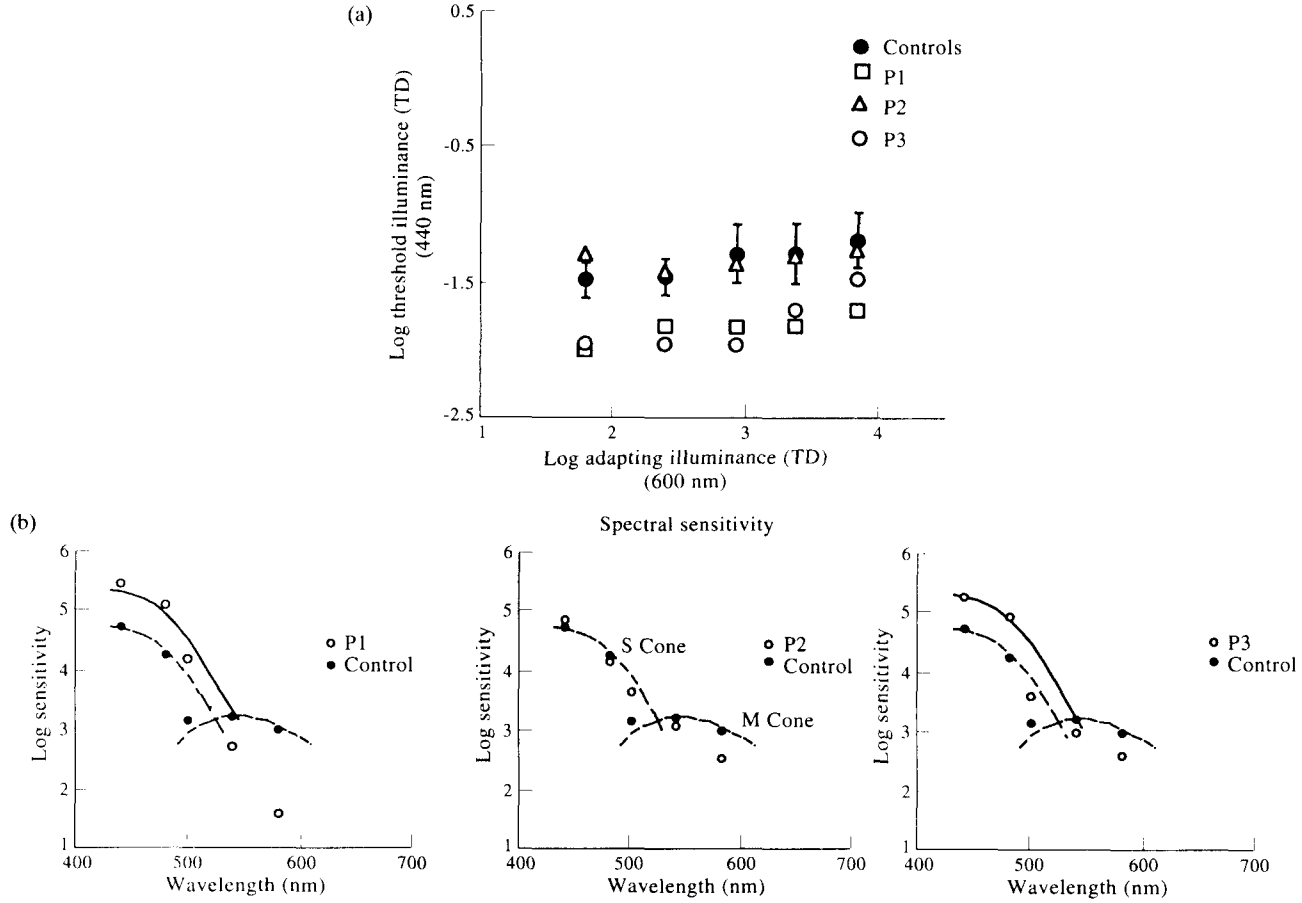


FIGURE 4. (a) Increment threshold data for P1, P2, and P3 (open symbols) compared to mean threshold data for nine normals (±1 SD). (b) Spectral sensitivity data for five test wavelengths obtained at 3.9 log td for the three patients (○) and for a control subject (●).

eight normal subjects in Fig. 5. For normal subjects grating acuity gradually decreases with increasing luminance of the "yellow" adapting background. As the luminance of the "yellow" background is increased relative to the test grating, the effective contrast for the L and M cones is decreased while the effective contrast for the S cones remains relatively unaffected. A plateau is reached at *ca* 4.0 log td, it is in this region that grating resolution is mediated by the S cones. S cone acuity for the eight normals is 3.7 c/deg. For the patients, there is little or no change in acuity as a function of adaptation level and S cone acuities are increased compared to the normal. The implications are that grating resolution for the patients is mediated by S cones over a 3.5 log unit range. S cone acuity for P1 is 10.76 c/deg, 7.2 c/deg for P2, and 6.53 c/deg for P3.

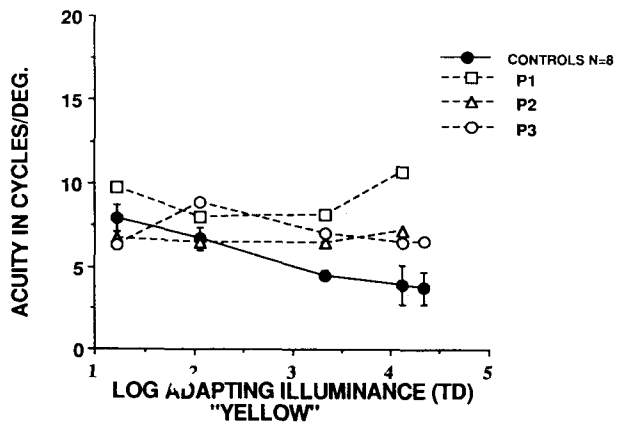


FIGURE 5. S cone acuity as a function of adaptation level for P1, P2, and P3 (open symbols) compared to mean acuity data for eight normals (●). The error bars represent ±1 SD.

The results of the S cone acuity study are qualitatively consistent with finer spatial sampling by the S cone system. To achieve these levels of S cone acuities the implications are that these patients with ESCS have relatively more S cones and that there are more S cone ganglion cells driven by S cones in the affected retinal areas. However, this hypothesis, that there are more S cones and more S − (L + M) ganglion cells, will yield specific predictions only when tested within the framework of a model of the S cone system. The model we use was proposed by Zaidi *et al.* (1992). It provides a good description of psychophysically elicited responses of the S cone system of normal observers under different

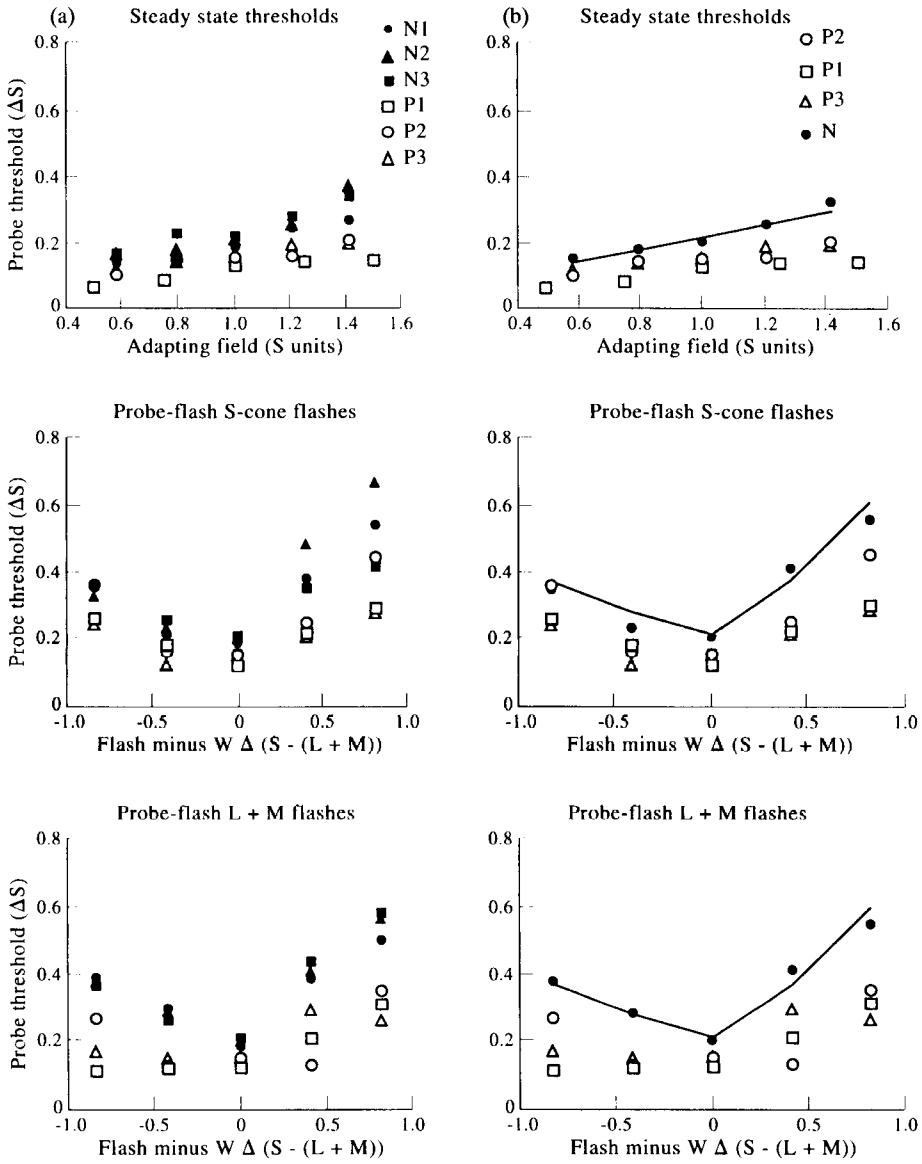
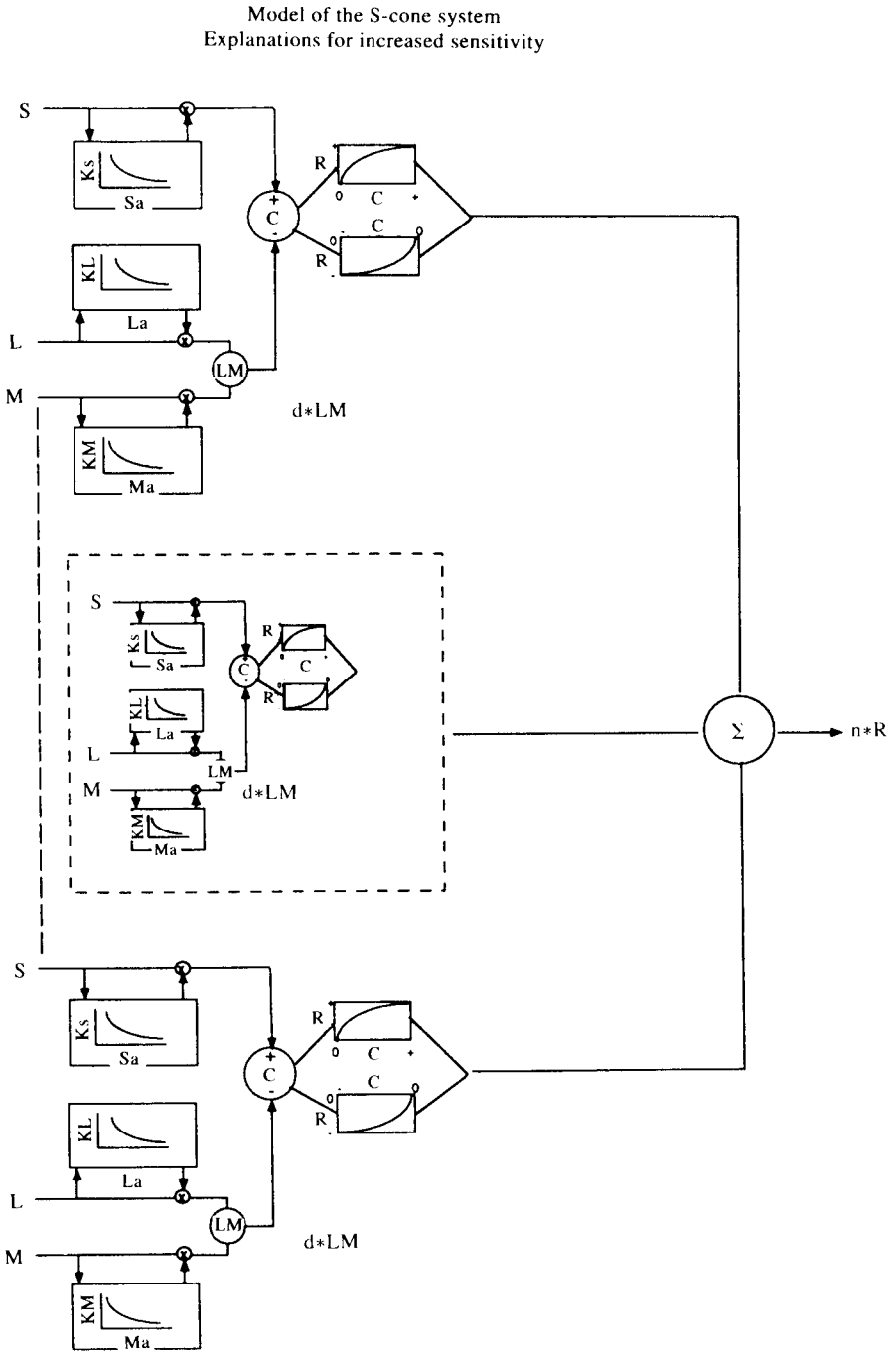


FIGURE 6. (a) Upper panel, difference thresholds as a function of steady-state ('no flash') adaptation levels for three normal observers (solid symbols) and for P1, P2, and P3 (open symbols). Center panel, difference thresholds as a function of S cone flashes for three normal observers (solid symbols) and for P1, P2, and P3 (open symbols). Lower panel, difference thresholds as a function of L + M flashes. (b) The solid curves in the upper, center, and lower panels represent the fit of the model of the S cone system to the median data for the normals.

adaptation conditions. In order to test the hypothesis within the context of the model, measures of post-receptoral S cone system sensitivity under steady state and flashed field adaptation conditions are needed. We used probe-flash and steady-state threshold techniques to obtain these measures from the patients and from normal subjects.

Receptoral and post-receptoral S cone system sensitivities

Measurements. Figure 6 shows the results obtained using the steady-state and probe-flash threshold techniques. Thresholds for detecting differences between pure S cone increments and decrements on steady achromatic backgrounds of increasing luminance are shown in the upper left hand panel. Thresholds for three normal subjects (solid symbols) are compared to thresholds for the three patients (open symbols). For normal subjects, probe thresholds increase with an increase in S + L + M excitation. Compared to the data for normals, probe thresholds for the three patients are lower for all adapting levels (adapting levels are expressed in terms of S cone units). Probe-flash data for three normal subjects (solid symbols) and for the three patients (open symbols) are shown in the center and lower panels. Probe thresholds are plotted as a function of the flashed level of excitation of the S cone system i.e., the difference between the color of the flash and the "white" adapting background. Both S



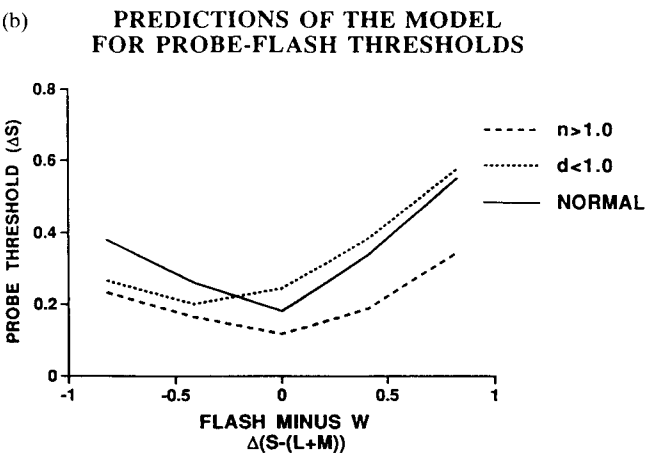


FIGURE 7. (a) A model of the S cone system with adaptive and static mechanisms. The S, M, and L cones act as linear transducers. The signals from the L and M cones are summed to make the LM signal. The opponent signal (C) is the difference between the S and the sum of the L and M cone signals.There are multiplicative gain controls on the pre-opponent branches.The post-opponent response, R, is a compressive function of the magnitude of the instantaneous opponent signal, C. n is defined as the number of S − (L + M) ganglion cells in the patient divided by the number for the average normal observer. A change in the total L + M input to each S − (L + M) ganglion cell is represented by d, a multiplicative constant. For the patients $d < 1.0$. (b) Probe-flash curves predicted from the model for changes in n and d.

cone and L + M flashes are expressed in S − (L + M) units. The zero points on the flash axes represent the "no flash" or steady-state condition i.e. probe thresholds obtained on a steady "white" background. For normals, probe thresholds are lowest at the zero point and increase with increasing distance from the steady-state adapting point. A "V" shaped pattern of results can be seen for S cone flashes (center panel) and for L + M flashes (lower panel). Thresholds are slightly higher for S cone flashes which are S cone increments. For the patients, probe thresholds are decreased compared to the normal, the "V" shaped pattern is shallower, and for both flash conditions there is a shift in the minimum in the probe-flash curves from the zero point or "no-flash" condition towards negative Δ(S − (L + M)) values i.e. "light yellow" or "yellow" flashes.

Model. To test whether the decreased thresholds found for the patients under these conditions could be explained by an increase in the number of S cones combined with an increase in the number of S − (L + M) ganglion cells we assumed a model of the S cone system [see Fig. 7(A)]. The following is a summary of the main features of the model which is described in detail in Zaidi *et al.* (1992) and Greenstein *et al.* (1992). Light is absorbed at the first stage by the L, M and S cones which act as linear transducers. The spectral sensitivities of these cones correspond to the Smith and Pokorny fundamentals (Smith & Pokorny, 1975). The signals from the L and M cones are summed into a LM signal. The difference between the S cone and LM signals is the opponent chromatic signal (C) at the opponent stage. Based on the results of detailed measurements on normal observers, it is assumed that in any state of adaptation, sensitivity is limited by invariant compressive response functions (R) at the opponent stage, and that sensitivity is altered only by pre-opponent S, L and M adaptation processes that set the gain as a function of the time-integrated signal of each receptor. Consequently, using the current spatio-temporal paradigm, the gain mechansims are affected only by changes in steady adapting lights; they are not affected by the briefly flashed lights. The post-opponent response R is a compressive function of the magnitude of the instantaneous opponent signal C.

$$\text{If } C > 0 \; R = p_\phi[1 - e^{-\phi C}] \tag{1}$$

$$\text{If } C < 0 \; R = p_\nu[1 - e^{-\nu C}] \tag{2}$$

where p_ϕ, p_ν, ϕ, and ν are parameters whose values can be estimated from the probe-flash data for normal observers shown in Fig. 6. The parameters p_ϕ, p_ν, are derived from the increment and decrement probe threshold values obtained on a steady "white" background i.e. at the zero point on the flash axes. The values for the parameters ϕ, and ν can be estimated by obtaining best fitting curves to the limbs of the "V" shaped probe-threshold function for S cone flashes [see Zaidi *et al.* (1992) for details]. In the model, the gain of the S, L, and M pre-opponent branches is given by κ_S, κ_L, and κ_M. These have values equal to 1.0 in the dark-adapted state and < 1.0 with light adaptation according to the following equations:

$$\kappa_S = \frac{\kappa}{\kappa + S_a/S_w} \tag{3}$$

$$\kappa_L = \frac{\kappa}{\kappa + L_a/L_w} \tag{4}$$

$$\kappa_M = \frac{\kappa}{\kappa + M_a/M_w} \tag{5}$$

where S_a, L_a, M_a are the responses of the S, L, and M cones, respectively, to the steady adapting light a. It is assumed that the parameter κ is identical for the S, L, and M pre-opponent branches. The value of κ can be estimated from the steady-state adaptation data shown in the upper panel of Fig. 6. The model therefore has five free parameters all of which can be estimated from the probe-flash and steady-state data.

The values of the five parameters were estimated from the median data for normals. The fits of the model to the steady-state and probe-flash data can be seen in Fig. 6(b). Given the values of the parameters estimated from the data for normal subjects, we used the model to test specific hypotheses about changes in the S cone system by comparing predicted probe-flash curves against the probe-flash data for the patients. Based on the two-color increment threshold and S cone acuity results, we assume that increased S cone system sensitivity in ESCS is due to an increase in the number of S cones, and that some of these S cones feed into an increased number of S − (L + M) ganglion cells. In the model [Fig. 7(A)], this is represented by n, which is defined as the ratio of the number of S − (L + M) ganglion cells in the patient to the number in the average normal observer; i.e. $n > 1.0$ represents an increased number of S − (L + M) ganglion cells which increases the total response R of the S cone system by the factor n. If the criterion response is assumed to be equal for patients and normals, then an increased total response leads to greater sensitivity. The predicted probe-flash curve derived from the model when $n > 1.0$ is shown as the dashed curve in Fig. 7(b). The solid curve is the curve for normals. The predicted probe-flash curve is shifted down compared to the normal curve and it is flatter than the normal. An increase in the number of S cones and in the number of S − (L + M) ganglion cells is sufficient to explain the flattening of the probe-flash curves, the increase in S cone system sensitivity, the ERG findings, and the increase in S cone acuity.

One problem that remains is that the predicted probe-flash curve still has a minimum at the zero point, i.e. probe threshold values are lowest for the "no-flash" or steady-state condition. For the patients, the probe-flash curves show a shift in the minimum because probe thresholds are as low or lower for "light yellow" and "yellow" flashes as they are for the zero point. This is more noticeable for L + M flashes. To account for this we assume that there is a decrease in the number of L and M cones in these patients, with no change in individual cones, but with a decrease in the total L + M input to each

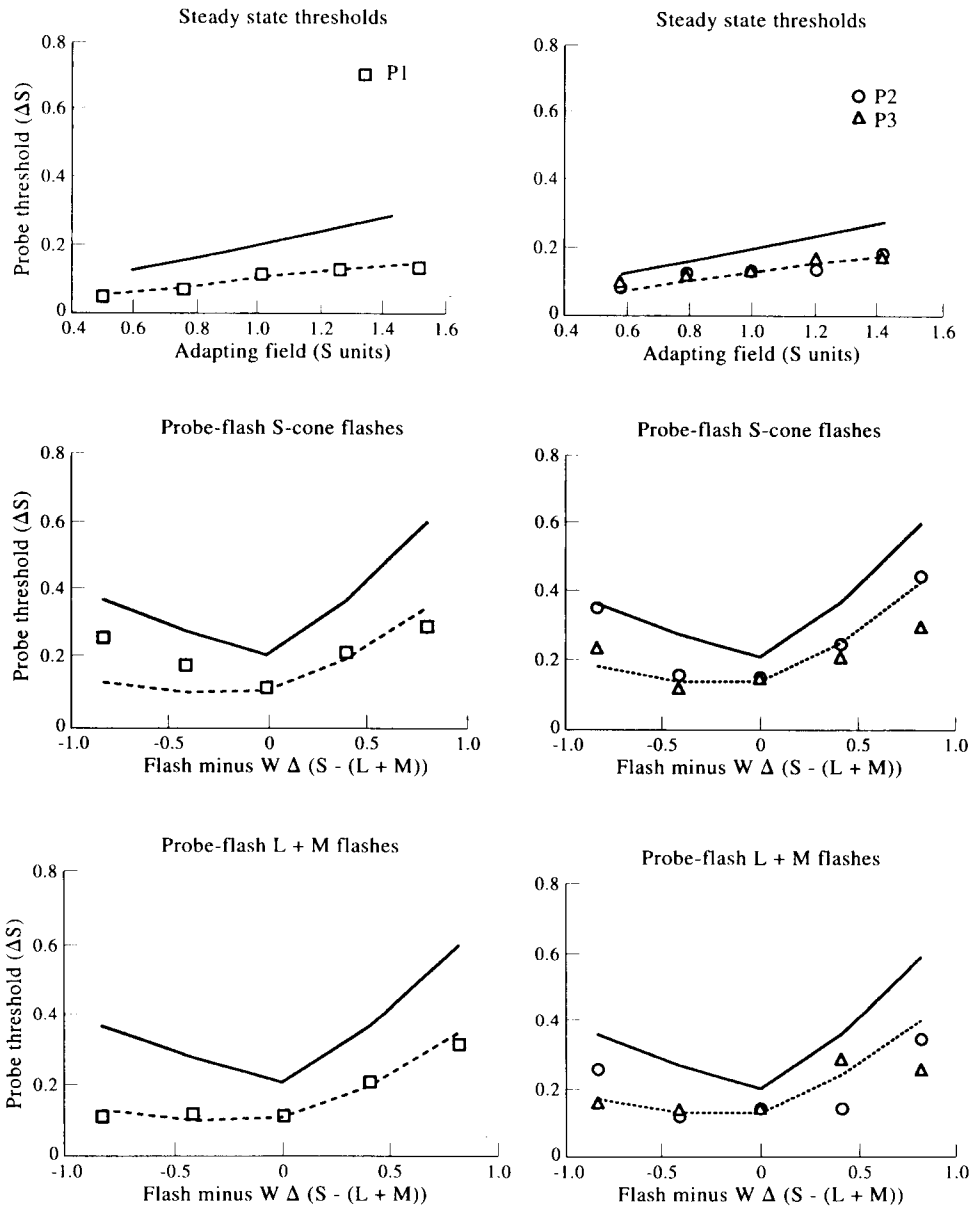


FIGURE 8. The fits of the model to the steady-state adaptation and probe-flash data for P1 (squares), P2 (circles), and P3 (triangles), with $n = 2.2$, $d = 0.9$ for P1; $n = 1.65$, $d = 0.99$ for P2; and $n = 1.8$, $d = 0.96$ for P3.

S − (L + M) ganglion cell. This is a reasonable assumption, given our electrophysiological and psychophysical findings of decreased L and M cone system sensitivities. In the model this assumption is represented by the multiplicative factor $d < 1.0$. A decrease in the L + M input results in an imbalance at the opponent site and the predicted probe-flash curve shows a shift in the minimum [see dotted curve in Fig. 7(b)]. The fits of the model to the steady-state and probe-flash data for P1, P2, and P3 are shown in Fig. 8. To account for the data, we need to assume an increase in the number of S cones, an increase in the number of S − (L + M) ganglion cells and a decrease in the total L + M input to each S − (L + M) ganglion cell. These assumptions are reasonable given the prevailing physiological picture of the S − (L + M) ganglion cells. Dacey (1994) and Dacey and Lee (1994) have shown that each S cone ganglion cell center is fed by one or a very small number of S cones, whereas the surround is fed by a diffuse combination of L and M cones. (Note: an increase in the S cone input to the opponent site will also result in an imbalance of the system, and the probe flash-curves will be altered in the same manner as if the L + M output were scaled by $d < 1.0$).

GENERAL DISCUSSION

The results of the psychophysical tests showing increased S cone system sensitivities and acuities, and decreased L and M cone system sensitivities in the affected retinal areas are consistent with an increase in

the number of S cones and a decrease in the number of L and M cones. In addition, the increase in S cone acuity implies that these patients also have an increased number of S − (L + M) ganglion cells. The shift in the minimum in the probe-flash curves is consistent with a decrease in the total L + M input to each S − (L + M) ganglion cell.

Since retinal diseases are generally thought to lead to deficits in cone pathway function rather than enhancements, it is important to demonstrate that the results of our study cannot be explained simply by a decreased number of L and M cones and a normal complement of S cones. Recently, Pokorny and Smith (1994, 1995) suggested that estimates of S cone sensitivity may be biased by disease processes affecting the L and M cone types. For the conditions where measures of S cone sensitivity fall in the pi-1 region of the threshold vs retinal illuminance (TVR) function, a decrease in L and M cone sensitivity could result in an overestimation of S cone sensitivity measurements. In this region the sensitivity of the pi 1 mechanism is presumed to be regulated by a post-receptoral opponent channel influenced by L and M cone activity (Pugh & Mollon, 1979). If the retina of a patient with ESCS contains the normal complement of S cones but a decreased number of L and M cones, this could affect our measurements of S cone sensitivity. In terms of the TVR functions, the decrease in L and M cones would result in a decrease in the effective illuminance of the steady adaptation level, i.e. measurements of S cone system function would be obtained at effectively lower L and M cone excitation levels compared to the normal, S cone thresholds for the patients would be equivalent to lower S cone thresholds for normals, sensitivities would appear to be "supernormal" and S cone acuities to be increased. This type of explanation, however, cannot account for the probe-flash threshold results. For the patients, probe thresholds were decreased compared to the normal, and the probe-flash curves were flatter. In a study of the effects of adaptation on the differential sensitivity of the S cone color system, Zaidi *et al.* (1992), found that a decrease in the steady luminance level resulted in a steepening not a flattening of the probe-flash curves. In addition for the range of stimuli used in the probe-flash experiment S cone thresholds were constant across L and M adaptation levels. The electrophysiological findings are also not consistent with an explanation based on the presence of a normal number of S cones. All three patients had the characteristic ERGs of ESCS with large amplitude *a*-wave responses. It has been shown that these *a*-wave responses are driven almost entirely by the S cones. The electrophysiological results are consistent with a large increase in the number of S cones, up to 75 times the normal number of S cones (based on the maximum *a*-wave response of 600 μV for P1 compared to the estimated normal S cone signal of *ca* 8 μV) and a decrease in the number of L and M cones (Hood *et al.*, 1995). Our psychophysical results are consistent with the presence of more S cones, more S − (L + M) ganglion cells and a decrease in the total L + M input to each S − (L + M) ganglion cell. Our results are not, however, consistent with the presence of large numbers of S cones feeding into large numbers of S − (L + M) ganglion cells. Part of the discrepancy could be due to the problems of comparing psychophysically obtained threshold responses from one area of the retina to electrophysiologically obtained supra-threshold responses from the entire retina. It is also possible that not all the S cones feed into S − (L + M) ganglion cells, or alternatively that the receptive field centers of some of the S − (L + M) ganglion cells receive input from an increased number of S cones. This increased input would also be consistent with the shift in the minimum of the probe-flash curves.

It has been suggested that ESCS may be due to abnormal retinal development; specifically there may be an alteration in the differentiation of cone subtypes (Hood *et al.*, 1995). Studies following the expression of S and M cones in developing rodent retinas, for example, have shown that most of the early maturing S cones change their phenotype to become M cones (Szel *et al.*, 1994). If S cones did not undergo transformation, this could result in a reduced complement of L and M cones and an increased complement of S cones. An increase in S cones could in turn influence the development of more proximal S cone circuitry. Such an abnormal developmental sequence could lead to the type of findings in ESCS patients. With increasing understanding of photoreceptor development in monkey and man (Wikler & Rakic, 1994; Hendrickson *et al.*, 1994) we will gain further insight into the exact mechanism leading to ESCS.

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