Nonselective Losses in Foveal Chromatic and Luminance Sensitivity in Multiple Sclerosis

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A psychophysical technique involving simple increment threshold measurements was used to determine foveal chromatic and luminance sensitivity in patients with multiple sclerosis (MS) and in matched normal controls. The patient group showed substantial and nonselective losses in chromatic and luminance sensitivity relative to the normal control group, and these losses were significantly correlated with each other over individual patients. It is suggested that impairment of foveal visual function due to demyelination is not more specific to fibers carrying chromatic information than to fibers carrying luminance information.
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Visual function is frequently abnormal in demyelinating disease. In multiple sclerosis (MS) and recovered optic neuritis patients may variously exhibit raised luminance threshold,[1] and increased variability in luminance threshold[2]; impaired temporal function, including increased perceptual latency,[3,4] increased interval for two-flash resolution,[5–7] and decreased critical flicker frequency (CFF) for stimuli varying in luminance only,[8–11] and in chromaticity only[11]; and reduced spatial acuity[12,13] and reduced sensitivity for medium spatial frequencies.[14,15] Deficiencies in color vision also occur often in MS, being revealed in desaturation in color appearance,[16,17] in losses in color discrimination,[18–21] and in abnormal color matching under special conditions of stimulus presentation.[22] Acquired color deficiencies have been classified (see Pokorny et al[23] for review) with reference to opponent-process theories[24–28] of color vision. According to traditional opponent-process theories, color information is processed, postreceptorally, by two parallel systems. One system, the achromatic, nonopponent system, transmits cone signals combined with the same sign and typically signals information such as luminance. The other system, the chromatic, opponent-color system comprising a "red–green" and a "blue–yellow" channel, transmits cone signals combined with different signs and typically signals information such as hue. Color-vision deficiencies in MS have most frequently been reported as being of an acquired red–green type.[18,19,21,22] It should perhaps be emphasized that the detailed representation of postreceptoral color processing is more complex than the simple description above might suggest,[29–32] which fact is relevant to some of the studies discussed here. A number of different notations for various postreceptoral channels have also been employed.[29–32]

Some clinical and psychophysical data[17,33–35] have suggested that in demyelinating diseases, losses in chromatic function may be selective, or relatively more severe than losses in luminance function. Other psychophysical data[36,37] have, however, indicated that losses in luminance function may be more profound. One difficulty in determining whether there is a greater loss in chromatic function than in luminance function involves establishing comparable measures of the two functions, and, in particular, which aspects of luminance function are being tested. Zisman et al[36] and Alvarez et al[37,38] measured detection thresholds for a sharp-edged, 1-deg spectral test flash presented on a large, bright (1000-Td) white background. Following King-Smith and Carden,[39] it was argued that in the normal visual system, when the flash was presented at a rate of 1 Hz, the thresholds obtained were, except for a region of the spectrum around 580 nm, characteristic of the chromatic system; when the stimulus was presented at a rate of 25 Hz, the thresholds obtained

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were characteristic of the luminance system. Selectivity of the stimuli thus depended on the differential temporal response characteristics assumed for the chromatic and luminance systems. For patients with retrobulbar neuritis (RBN), there were changes in shape of the 1-Hz spectral sensitivity curve commensurate with a loss in red–green opponent-color function and in sensitivity of the short-wavelength-sensitive color mechanism. There were also threshold elevations relative to normal-control values of 0.4–0.6 log unit for the 1-Hz stimuli at long wavelengths (compare Verriest and Uvijls[40]) and more than 1 log unit for the 25-Hz stimuli. This was taken[36–38] to imply that losses for the luminance system were more severe than losses for the chromatic system. As noted above, however, losses in high-frequency–flicker response may be quite general, and it is not certain from the data of Zisman et al[36] and Alvarez et al[37,38] whether greater losses in luminance sensitivity would be expected to persist at low temporal frequencies.

Fallowfield and Krauskopf,[33] using a color television system, measured saturation or excitation–purity thresholds by determining thresholds for the detection of changes in color from "white" in a sharp-edged 2-deg circular field on zero background. The time course of the flash was "raised cosine" of 2.2-sec duration. During the course of these changes, luminance was held constant according to previous measurements involving flicker photometry. Fallowfield and Krauskopf[33] also measured conventional luminance increment thresholds by determining thresholds for the detection of an increase in luminance from the central white. By this procedure, it was found that, on average, excitation–purity thresholds in patients with MS or recovered optic neuritis were higher than those in normal controls by about 0.4 log unit, whereas the conventional luminance thresholds were higher by about 0.2 log unit. It was concluded[33] that impairment was more severe for chromatic discrimination than for luminance discrimination, and that the disease process may selectively attack those fibers that carry chromatic information.

Mullen and Plant,[34,35] also using a cathode-ray-tube display system, measured contrast thresholds for low-spatial-frequency (1 cycle · deg^{-1}), long-, and medium-wavelength sine wave gratings presented in spatial antiphase. The contrasts of the two gratings were linked together electronically so that they were always equal to each other, although their individual mean luminances could differ. Measurements were made for various ratios of the mean luminances of the gratings, preserving a constant mean luminance of the full display. The composite stimuli were presented sinusoidally phase-reversed at 0.5 Hz. Field size was 6.5 deg. Both red–green and blue–yellow gratings were used. Threshold modulation depths for "chromatic" and "luminance" conditions of the grating mixtures, corresponding respectively to approximately equal ratios of the grating luminances (eg, 55% red, 45% green) and to extreme ratios of the grating luminances (eg, 100% red, 0% green), were determined in each eye of patients who had had recent episodes of optic neuritis and who showed marked asymmetries in residual losses between the two eyes. The ratio of chromatic and luminance sensitivities for the less affected eye was plotted against the ratio for the more affected eye. The asymmetric form of the plot was concluded to imply a greater color deficit than luminance deficit in patients. No differences in these effects were detected for red–green and blue–yellow function,[34,35] in contrast to the findings by Fallowfield and Krauskopf.[33]

A different approach was adopted here to the isolation and testing of chromatic and luminance sensitivities in patients with MS. All measurements were of simple intensity thresholds for detection of a small stimulus flash. Stimuli were presented centrally in the visual field and subtended 15 min arc, which was apparently sufficiently large to involve the processes subserving chromatic function.[41] The technique was based, in part, on previous work on chromatic processes in normal subjects.[41,42] This showed that if threshold measurements were made with a spectral stimulus of small-to-medium size (0.15–1.0 deg), of moderate duration (typically 200 msec), presented on a steady spatially coincident white or monochromatic background (auxiliary field), then detection of the test flash was determined almost exclusively by the chromatic system, whether measurements were made of test spectral sensitivity, or of field spectral sensitivity in the manner of Stiles.[43]

Evidence for this assertion has been reviewed in detail elsewhere.[41,42] In brief, it has been suggested[41] that high-spatial-frequency adaption or contour masking occurred where the boundaries of test and auxiliary fields coincided. This resulted in the suppression of the spatial transient that would normally be responded to by the luminance system, which, under most conditions, is traditionally assumed to have greater high-spatial-frequency sensitivity than the chromatic system (for discussion, see references 31, 41, 42, 44). It was also assumed that a large white adapting field preferentially depressed sensitivity of the luminance system.[45] When such a background was made spatially coincident with the test field, isolation of the chromatic system from the luminance system was improved further over the large-background configuration used by Zisman et al[36] and Alvarez et al[37,38] by 0.35–0.5 log unit.[42] The dependence of this isolation on the relative sizes of test and auxiliary fields has been discussed elsewhere.[41]

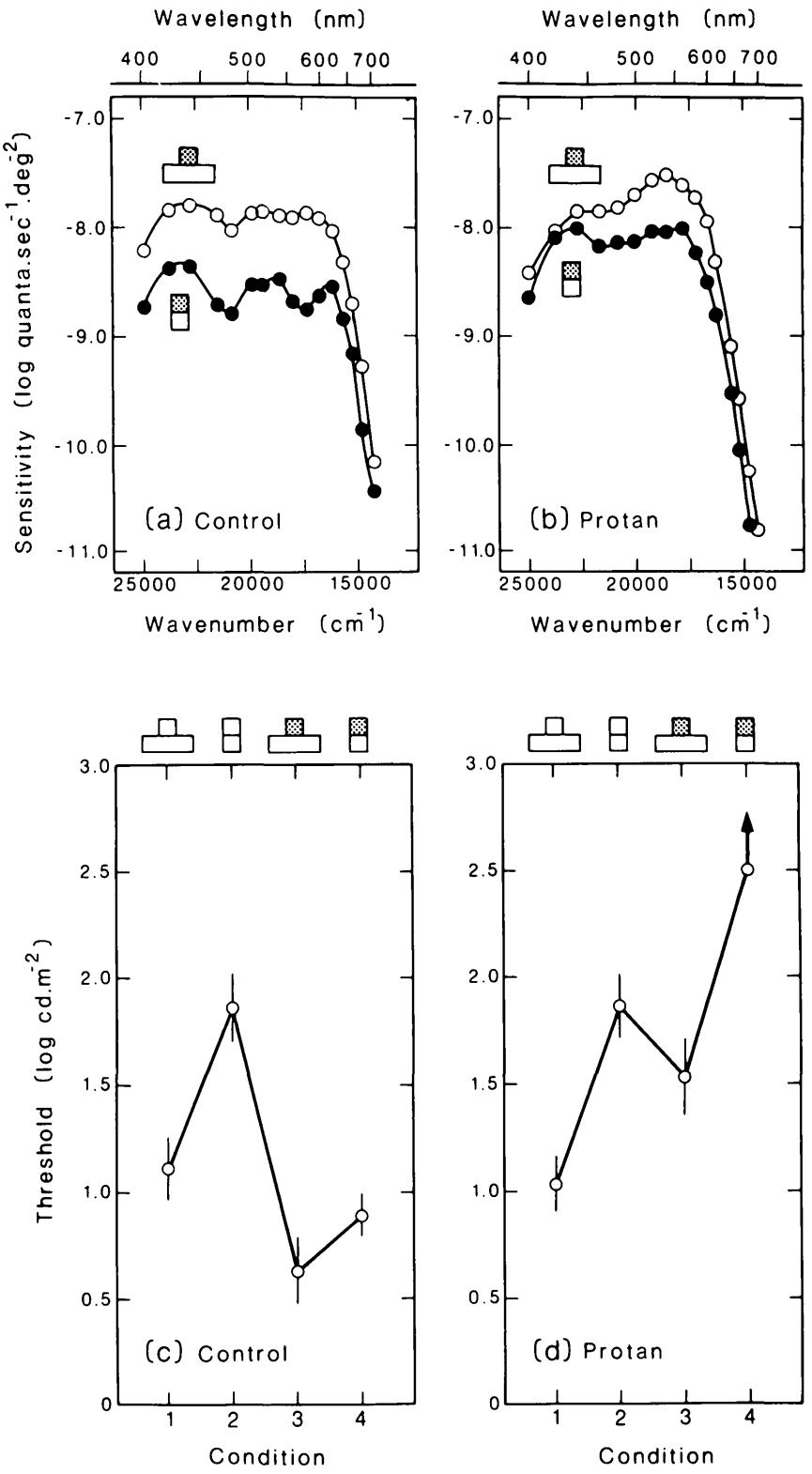

Fig. 1. **a** and **b**, Test spectral sensitivities obtained on a large (10-deg) white auxiliary field (unfilled circles) and on a small (1-deg) white auxiliary field spatially coincident with the test field (filled circles). Log reciprocal threshold intensity of the test flash is plotted against wavenumber of the test flash. The white auxiliary field had color temperature 3400K and gave a retinal illuminance of 1000 Td. Each point is the mean of six readings and the vertical bars show ±1 SEM where this is sufficiently large. **c** and **d**, Separate measurements of threshold for a 0.15-deg test flash presented under four stimulus conditions: (1) white flash on a large white auxiliary field, (2) white flash on a spatially coincident white auxiliary field, (3) red flash on a large white auxiliary field, and (4) red flash on a spatially coincident white auxiliary field. The white auxiliary field had color temperature 3400K and gave a retinal illuminance of approximately 2000 Td. The vertical bars show the variabilities associated with the thresholds. For further details see text. The data in **a** and **c** are for a color-normal subject; in **b** and **d** for a protanopic subject (threshold for the latter in condition 4, part **d** of the figure, exceeded the maximum available flash intensity).

The data presented in Figure 1 illustrate the effectiveness of the technique. Figure 1a shows test spectral sensitivity obtained on two different-sized auxiliary fields for a subject with normal color vision (score for the Farnsworth-Munsell 100-hue test was 16). The test flash subtended 1 deg and threshold was determined on a concentric white auxiliary field of subtense 10 deg (unfilled circles) and 1 deg (filled circles). Retinal illuminance was 1000 Td (for further details, see Foster and Snelgar[42]). The differences in the shapes of the

curves at medium-to-long wavelengths are marked, the peak in sensitivity at approximately 620 nm, and the trough at approximately 570 nm being characteristic of opponent-color function.[39,42] The difference in sensitivities on the large auxiliary field and spatially coincident auxiliary field was more than 0.35 log unit greater at 577 nm than at 620 nm; consistent, in particular, with the hypothesis that detection of a 570–580-nm flash on a large auxiliary field (but not necessarily on a spatially coincident auxiliary field) is determined by the luminance system, whereas detection of a 620-nm flash on a spatially coincident auxiliary field is determined by the chromatic system, in particular by the red–green channel. For subjects with inherited color deficiencies, test spectral sensitivity is modified.[40,46–48] Figure 1b shows, for the same two auxiliary fields as in Fig. 1a, data for a protanopic subject (classified by Pickford-Nicolson anomaloscope and Farnsworth-Munsell 100-hue test; score on the latter was 151 and the plot classically polarized). As expected,[40,46–48] the peak at approximately 620 nm was absent for the test flash presented on the coincident auxiliary field (filled circles), and the difference in sensitivity on the large auxiliary field and spatially coincident auxiliary field was the same at 582 and 615 nm. Similar results were obtained for a deutan subject.

This technique was adapted to the present clinical study in the following way. The stimulus flash was either of long wavelength (appearing red) or white and was presented on a steady white auxiliary field, which was either spatially coincident with the test field or five times larger. Retinal illuminance associated with the auxiliary field was approximately 2000 Td. It was assumed that, when the test flash was of long wavelength and presented on the spatially coincident auxiliary field, detection would be determined principally by the chromatic system, specifically by the "red–green" channel (see also Dain and King-Smith[49]); conversely, when the test flash was white and presented on the large auxiliary field, detection would be determined principally by the luminance system (the white flash would clearly serve in this condition at least as well as the monochromatic yellow flash used in the test spectral sensitivity measurements of Figures 1a, b; see also Smith et al[50]). The other two stimulus conditions (red test flash on the large auxiliary field, and white test flash on the spatially coincident auxiliary field) were included to provide controls on the effectiveness of this procedure.

Illustrations of these threshold measures, determined as detailed below, are shown in Figures 1c and 1d for the two subjects whose test spectral sensitivities are shown in Figures 1a and 1b, respectively. Notice that thresholds for the white test flash presented on the large auxiliary field and spatially coincident auxiliary field, conditions 1 and 2 in the figure, were almost identical for the normal and protanopic subject; whereas for the red test flash on the large auxiliary field, condition 3, threshold for the protanope was 0.9 log unit greater than for the normal, and this threshold difference rose to more than 1.6 log unit when the auxiliary field was made coincident with the test field, condition 4 in the figure. A loss in sensitivity at long wavelengths for the protanope is characteristic, but more importantly here, is the result that when the auxiliary field was made coincident with the test field, a much greater loss in long-wavelength sensitivity was revealed for the protanope than for the normal, presumably a consequence of attempting to force detection through severely spectrally modified or absent red–green opponent-color pathways (compare references 25, 40, 46–48, 49).

Determinations of these intensity thresholds for each of the four stimulus conditions were made in a group of patients with MS or recovered optic neuropathy (ON), and in a group of normal control subjects matched for age and sex to the patient group. One eye only of each subject was tested. Variabilities of thresholds were also determined since these have been found in other conditions[2] to be raised in some patients with MS. Although subjects' color vision was assessed, subjects were not preselected according to their performances in these tests.

Materials and Methods

Stimuli and Apparatus

Stimuli were presented by means of a modified visual perimeter. To control the overall state of retinal adaptation of the subject, a circular white background, color temperature 2600 K, luminance 35 $cd \cdot m^{-2}$, and angular subtense 24 deg at the eye, was present continuously for all measurements.

The test stimulus was circular, of angular subtense 15 min arc, and of duration 200 msec. The steady white auxiliary field was also circular, of angular subtense 15 min arc or 75 min arc, luminance 160 $cd \cdot m^{-2}$ (approximately 2000 Td under the given conditions of adaptation), and color temperature 3400 K. The stimuli were all concentric. Small differences in the nominal sizes given above for test and auxiliary fields (not more than 1 min arc) and differences in retinal images due to ocular chromatic differences in magnification were not important in determining the efficacy of the procedure.[41]

The test stimulus was produced by a tungsten–halogen lamp run from a regulated dc power supply. Fibre-optic guides were used to channel long-wavelength or white light to the stimulus field. (Heat-reflecting filters, [Calflex Balzers, Liechtenstein] were interposed between the lamp and the fiber optics.) Spectral content

Table 1. Details of patients

Patient	*Age (yr)*	*Sex*	*Duration disease (yr) since first attack*	*Symptoms*	*Previous optic neuropathy (no. attacks)*	*Clinical diagnosis*
1	51	F	6	Spinal ON	2	Clinically Definite MS
2	31	M	9	Spinal ON	2	Clinically Definite MS
3	41	M	5	ON	2	ON
4	48	M	0.5	ON	1	ON
5	38	F	6	ON	1	ON
6	26	F	0.7	Spinal ON	1	Early Probable
7	46	F	3	ON	3	ON
8	34	F	10	Spinal ON	3	Clinically Definite
9	44	F	8	Spinal ON	1	Clinically Definite

ON: optic neuropathy; MS: multiple sclerosis.

of the long-wavelength test stimulus was controlled by a long-pass gelatin filter which gave maximum intensity in situ at 640 nm, with half-height cuton wavelength 607 nm; when weighted by the standard relative spectral luminous efficiency function, intensity was maximum at 615 nm. Unfiltered light (over 400–700 nm) was used to provide the white test stimulus, which had color temperature approximately 4000 K. The intensity of the light in each channel could be varied by the experimenter with rotary neutral-density wedges. An electromagnetic shutter controlled the duration of the test stimulus.

The subject viewed the stimulus field through an eyepiece at a distance of 1.2 m. Spectacles were worn if appropriate, and the eye not being tested was occluded. An artificial pupil was not used. Head position was stabilized with a contoured headrest. The subject controlled the start of a stimulus presentation with a push-button box.

Procedure

Initial assessments of subjects' Snellen acuity, near vision, and color vision were carried out with Snellen Standard Test Type, Faculty of Ophthalmologists' Test Type, and The City University color vision test.[51] The last test was used for classification purposes only.

The four stimulus conditions were the same as in the preliminary experiments described in the Introduction: condition 1, white test flash on the large auxiliary field; condition 2, white test flash on the spatially coincident auxiliary field; condition 3, red test flash on the large auxiliary field; and condition 4, red test flash on the spatially coincident auxiliary field. Measurements of threshold intensity for each stimulus condition were made using a method of constant stimuli in which the subject indicated after each presentation whether the test flash was seen. First, an approximate value of threshold was determined by a method of limits. Then, sequences of 10 consecutive stimulus settings, spaced at approximately 0.1-log unit intervals and centered about the approximate threshold value, were presented to the subject five times in all, according to a randomized block design that minimized order and carryover effects within and across sessions. Each threshold value for each subject was thus based on 50 trials.

Subjects

Nine patients and nine normal controls participated in this study. Patients were classified according to the criteria of McDonald and Halliday.[52] Details are given in Table 1. The mean age of the patients was 40 yr. There were six female patients and three male patients. None had nystagmus, and no patient reported difficulty in fixation. None had central scotomata at the time of carrying out the measurements. All patients had experienced at least one attack of ON during the course of their disease, but none showed evidence of an active ON at the time of examination and investigation.

Of the nine patients' eyes included in this study, eight patients had Snellen acuities equal to or better than 6/9 and near vision equal to or better than N14; one patient had Snellen acuity 6/12 and near vision N24. Five patients were classified as abnormal on The City University color vision test. Two gave some tritan-type errors and three could not perform the test. Nine normal controls were matched with the patient group for age and sex. All controls had normal color vision on The City University test and covered a range of visual acuities similar to that of the patient group. All subjects were unpractised in performing psychophysical tests and were unaware of the purpose of the study.

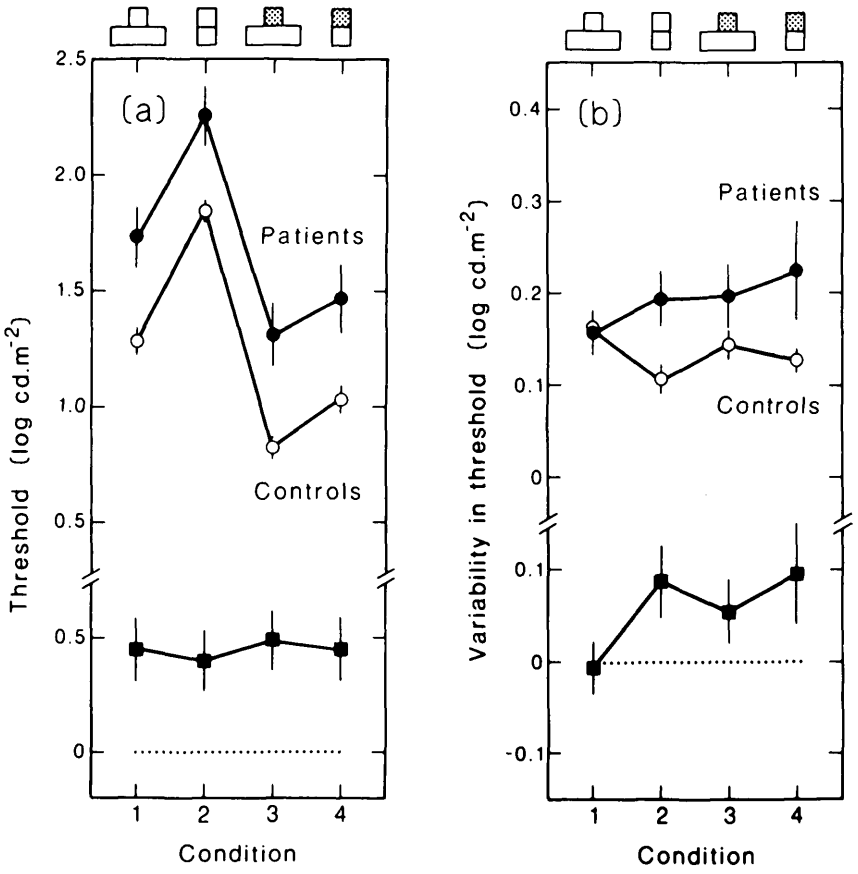

Fig 2. Test-flash threshold for stimuli selective for luminance and chromatic function. **a**, Mean thresholds and **b**, mean variabilities in threshold for patients (filled circles) and normal controls (unfilled circles) are shown for four stimulus conditions: (1) white flash on a large white auxiliary field, (2) white flash on a spatially coincident white auxiliary field, (3) red flash on a large white auxiliary field, and (4) red flash on a spatially coincident white auxiliary field. Mean differences in thresholds and in threshold variabilities for paired patients and normal controls are shown in the lower sections of **a** and **b**, respectively (filled squares). Vertical bars show ±1 SEM.

Informed consent was obtained from all subjects prior to undertaking the study.

Data Analysis

Probit analysis[53] was used to compute the 50% seeing level defining threshold and a standard deviation that corresponded to the variability associated with that level.[2] The underlying normal distribution assumed by probit analysis was not intended to have any theoretical significance here. The effects of the four stimulus conditions on threshold for patients and normal controls were analyzed by analysis of variance and by planned comparisons.

Results

In Fig. 2a, the two graphs in the upper section show mean thresholds for patients (filled circles) and normal controls (unfilled circles) for each of the four stimulus conditions illustrated in the figure and described in the Materials and Methods section. Mean differences in thresholds for paired patient and normal controls are shown in the lower section of Fig. 2a. In Fig. 2b, the two graphs in the upper section show mean variabilities in threshold for patients (filled circles) and normal controls (unfilled circles) for each of the four stimulus conditions, and the lower section shows mean differences in variabilities for paired patients and normal controls. The vertical bars show ±1 SEM. Thresholds and variabilities are expressed in log cd · cm^{-2} rather than in radiometric units, to permit comparison with previously published data. Table 2 shows data for individual patients and normal controls.

Thresholds

The effects of stimulus condition on thresholds for patients and normal controls (Fig. 2a) were similar to those illustrated in the preliminary data of Fig. 1c. The most obvious effect was that of spectral content of the test flash. Thresholds for the white test flash (averaged over conditions 1 and 2) were greater than those for the red test flash (averaged over conditions 3 and 4) by 0.61 log unit for the patient group and 0.64 log unit for the normal control group (Fig. 2a, upper section). These values did not differ significantly from each other ($z = 0.41$, $P > 0.5$), and were each highly significantly different from zero [$t(8) \geq 7.2$, $P < 0.001$ for both, two-tailed tests].

The effect of auxiliary-field size depended strongly on spectral content of the test flash. Thus, for the white test flash, when auxiliary-field diameter was reduced from 75 min arc to 15 min arc so that the auxiliary

field was spatially coincident with the test field (condition 1 to 2), there was a pronounced increase in test-flash threshold of 0.52 log unit for the patient group and 0.57 log unit for the normal control group. These elevations did not differ significantly from each other ($z = 0.47$, $P > 0.5$), and each was highly significantly different from zero [respectively, $t(8) = 5.8$, $P < 0.001$, and $t(8) = 12.1$, $P < 0.001$, two-tailed tests for both]. In contrast, for the red test flash, when auxiliary-field diameter was reduced so that it was spatially coincident with the test field (condition 3 to 4), there was only a small increase in test-flash threshold of 0.17 log unit for the patient group and 0.21 log unit for the normal control group. The first was not significantly different from zero [$t(8) = 1.8$, $P > 0.1$, two-tailed test], although the second was significantly different from zero [$t(8) = 3.7$, $P < 0.01$, two-tailed test].

As shown in the lower section of Fig. 2a, there was a substantial and highly significant loss in sensitivity by patients relative to normal controls of 0.45 log unit on average [$t(35) = 6.8$, $P < 0.001$, two-tailed test]. This loss of sensitivity did not vary significantly with spectral content of the test flash or auxiliary-field size [$t(8) \leq 0.6$, $P > 0.5$, two-tailed test]. In particular, there was no significant difference between the loss in sensitivity in condition 1, preferential for luminance function, and the loss in sensitivity in condition 4, preferential for chromatic function [$t(8) = 0.1$, $P > 0.5$, two-tailed test].

Threshold values for individual patients and normal controls are given in Table 2. For patients, thresholds were significantly correlated for condition 1 and condition 4, the Pearson product moment correlation coefficient r being 0.74 ($P < 0.05$). Thus, abnormally high luminance thresholds in individual patients were generally associated with abnormally high chromatic thresholds. For the normal control group, however, thresholds were not significantly correlated for conditions 1 and 4, where r was 0.21 ($P > 0.2$). Thus, small, normal variations in luminance threshold were not associated with small, normal variations in chromatic threshold.

Variability of Thresholds

Overall, there was significantly greater threshold variability for patients than for normal controls [$t(35) = 2.8$, $P < 0.01$, two-tailed test, see Figure 2b, upper section), although, for condition 1, presumably selective for luminance function, variabilities for patients and normal controls were indistinguishable [$t(8) = 0.0$, $P > 0.5$, two-tailed test, compare Patterson et al[2]].

For the normal control group, threshold variability was slightly greater (0.04 log unit) with the large auxiliary field (averaged over conditions 1 and 3, Fig. 2b, upper section, unfilled circles) than with the small auxiliary field (averaged over conditions 2 and 4, Fig. 2b, upper section, unfilled circles) [$t(8) = 2.7$, $P < 0.05$, two-tailed test]. This difference may have been a consequence of marginally poorer fixation with the large auxiliary field. Such a fixation artifact appeared not to be important for the patient group (Fig. 2b, filled circles). There were no other significant effects of spectral content of the test flash or auxiliary-field size, and no significant interaction between the two for either patient or normal control group [$t(8) \leq 1.5$, $P \geq 0.1$ in all cases]. Threshold-variability values for individual patients and normal controls are given in parentheses in Table 2. For patients, there was no significant correlation between threshold variability and threshold in any of the conditions except condition 2 ($r = 0.65$, $P < 0.05$), and, for normal controls, there was no significant correlation in any of the conditions ($r \leq 0.48$, $P > 0.1$).

Table 2. Detection thresholds with variabilities in parentheses for test flashes (white or red, 200 msec duration, 15 min-arc diameter) on white auxiliary fields (large, 75 min-arc diameter, or small, 15 min-arc diameter)

	White test flash		*Red test flash*	
	Large auxiliary (condition 1)	*Small auxiliary (condition 2)*	*Large auxiliary (condition 3)*	*Small auxiliary (condition 4)*
Patient				
1	1.69 (0.12)	2.13 (0.20)	1.11 (0.17)	1.49 (0.28)
2	1.90 (0.21)	2.21 (0.15)	1.54 (0.24)	1.61 (0.29)
3	2.18 (0.09)	3.07 (0.38)	1.46 (0.30)	1.83 (0.05)
4	1.19 (0.28)	1.98 (0.19)	1.12 (0.11)	1.23 (0.25)
5	1.87 (0.11)	2.39 (0.13)	1.63 (0.21)	2.29 (0.04)
6	2.31 (0.18)	2.30 (0.09)	2.05 (0.09)	1.68 (0.23)
7	1.87 (0.16)	2.55 (0.31)	1.39 (0.38)	1.44 (0.58)
8	1.30 (0.17)	1.96 (0.10)	0.75 (0.08)	0.91 (0.08)
9	1.29 (0.09)	1.72 (0.20)	0.70 (0.20)	0.82 (0.22)
Normal				
1	1.14 (0.16)	1.92 (0.15)	0.88 (0.10)	1.21 (0.08)
2	1.14 (0.11)	1.86 (0.07)	0.79 (0.09)	1.10 (0.13)
3	1.15 (0.23)	1.80 (0.08)	0.63 (0.20)	0.89 (0.12)
4	1.34 (0.18)	1.96 (0.14)	0.88 (0.21)	0.73 (0.14)
5	1.21 (0.15)	1.73 (0.13)	0.76 (0.18)	1.14 (0.13)
6	1.53 (0.10)	2.00 (0.15)	1.05 (0.08)	1.07 (0.06)
7	1.48 (0.15)	1.94 (0.03)	0.92 (0.13)	1.14 (0.17)
8	1.48 (0.25)	1.81 (0.12)	0.94 (0.16)	1.14 (0.17)
9	1.08 (0.13)	1.66 (0.09)	0.53 (0.16)	0.84 (0.17)

All values in log cd · m^{-2}. Threshold was defined by the 50% level in each probit fit; variability was defined by the standard deviation of the normal distribution assumed to underlie the fit.[53]

Discussion

Nonselective Losses in Chromatic and Luminance Function

The principal outcome of this study was that patients with MS or stable ON showed substantial reductions in luminance and chromatic sensitivities and that these reductions were, on average, equal. This result was ap-

parently not attributable to some failure in the effectiveness of the auxiliary-field technique to select chromatic channels in patients. Evidence for the general effectiveness of the auxiliary-field technique in normal subjects has already been cited.[41,42] Its applicability within the present paradigm, based on considerations of spectral sensitivity, white-light threshold, and auxiliary-field size for the control normal and congenitally color-defective subjects, has been discussed in the Introduction, and confirmatory analysis of the effects of spectral content of the test flash and auxiliary-field size for patients and normal controls has been given in the Results section. For both patients and normal controls, the luminance and chromatic systems were apparently correctly selected by the various combinations of test-flash spectral content and auxiliary-field geometry. In particular, condition 1, white flash on the large auxiliary field, was selective for luminance function, and condition 4, red flash on the spatially coincident auxiliary field, was selective for chromatic function (Fig. 2).

The present results showing large and nonselective foveal losses in chromatic and luminance sensitivity in patients appeared not to be an artifact of pooling thresholds over patients and over normal controls. Abnormal elevations in threshold for luminance and chromatic function in the patient group did not occur independently of each other in individuals. The correlation data for the patient group showed that high chromatic thresholds were associated with high luminance thresholds, presumably resulting from the common effects of demyelination. Moreover, high chromatic thresholds were found associated with high Farnsworth-Munsell 100-hue scores. For example, for patient 6, an abnormally high chromatic threshold, 0.61 log unit greater than the matched control value in condition 4, was associated with an abnormally high luminance threshold, 0.78 log unit greater than the matched control value in condition 1, and with an abnormally high 100-hue score of 492. For patient 8, a normal chromatic threshold, 0.23 log unit below the matched control value in condition 4, was associated with a normal luminance threshold, 0.18 log unit below the matched control value in condition 1, and with a close-to-normal 100-hue score of 68. Correlation between chromatic and luminance thresholds did not occur in normal controls, suggesting that normal variations in these functions were determined by unrelated and independent processes (this situation contrasts with that found in normal controls for covariation of chromatic and luminance CFFs, attributed to a general age-related loss in flicker sensitivity[11]).

The absence of selective chromatic dysfunction was also apparently not attributable to reduced visual acuity in the patient group which might have lead to inefficient isolation of chromatic pathways. Snellen acuity was not seriously below that of the normal control group, and the control threshold measurements (condition 3, red test flash on the large auxiliary field, and condition 2, white test flash on the spatially coincident auxiliary field) (Fig. 2a) showed that the differential effects of auxiliary-field geometry on test-flash threshold were precisely the same for patients and for controls. In separate exploratory measurements, the technique has also been used successfully with an albino subject who had reduced acuity and nystagmus (R. S. Snelgar and D. H. Foster, unpublished observations).

The present results differ from some earlier-cited findings. Alvarez and King-Smith[38] drew attention to the seemingly conflicting implications of: (1) their own earlier data[36,37] suggesting that the luminance system was more affected by demyelination than the chromatic system, (2) preliminary data from the present study suggesting the general equality of effects, and (3) data reported by Fallowfield and Krauskopf[33] suggesting that the chromatic system was more affected that the luminance system. Alvarez and King-Smith[38] proposed that there might be two distinct types or stages in retrobulbar neuritis. Although both would involve moderate to severe impairment of the color-opponent system, only one would involve a conduction block for fast flicker. This explanation, which is not incompatible with the notion[29,31] of two distinct "achromatic" channels, the one sensitive to high spatial frequencies, the other sensitive to high temporal frequencies, may account for some of the differential effects found in patients for luminance sensitivity determined with flashed or slowly varying stimuli as used here and elsewhere[33-35] and with flickering stimuli.[36,37] Other factors relating to methodology may also have been important. In the paradigm used by Fallowfield and Krauskopf,[33] the removal of luminance differences in the chromatic modulation experiments was confirmed by flicker photometry with normal subjects, a procedure which, as has been noted elsewhere,[35] may not have been appropriate with patients. Luminance sensitivity was also apparently measured relative to normal values on the equivalent of the usual log-luminance scale, whereas chromatic discrimination was measured relative to normal values on the equivalent of a log-saturation or log-excitation-purity scale. It might be reasoned that the scales were not strictly comparable or equally sensitive to equal losses in the underlying visual functions: in general, there is a nonequivalence in that luminance values may be unbounded whereas excitation-purity values have a maximum value of unity. Data obtained by Smith et al[50] have, however, suggested that empirically correct comparisons can be made between the two scales. This complication does not apply to the luminance and chromatic contrast thresholds determined by Mullen and Plant.[34,35] These were defined

on a common scale as members of a continuum of values describing modulation sensitivity over different ratios of the mean luminances of the component gratings.

The disparate outcomes of these various studies may also have been determined, in part at least, by the different populations of patients selected for study, and by the different sizes of stimulus field used to assess visual function.

Fiber Diameter Spectra

The present data suggesting large and nonselective losses in chromatic and luminance sensitivity in the central fovea of patients with MS are compatible with data from at least one animal model of demyelinating disease and with postmortem data from patients with MS. Morphologic studies[54-56] of fibers in the optic nerve of mice infected with Semliki Forest virus have revealed a preferential effect of demyelination for small-diameter fibers. In man, macular fibers are characterized by high density and small diameter, although exceptions have been observed.[57] The greater concentration of these fibers may make them particularly vulnerable to metabolic disturbances associated with demyelinating lesions, and, because of their small diameter, they may also be more susceptible to conduction block. Postmortem histologic investigation[58] of the optic nerves of patients with MS has shown that the atrophied areas included large portions of the papillomacular bundle, although they were not confined to it and often included peripheral fibers. Given that these small-diameter fibers predominantly subserve both chromatic and luminance function in the central fovea (more specific assumptions have been made,[29,31,32] but see Zrenner[48]), it might be anticipated that for sufficiently small (15 min arc in the present study), centrally presented, flashed stimuli, luminance and chromatic sensitivities would, on average, be affected equally. For luminance function measured with high-frequency-flicker stimuli,[36,37] a disproportionately greater impairment in sensitivity might also be anticipated, resulting from a generalized loss in temporal performance in affected pathways.[5-11] As in the present study, it is possible[48,59] that with a 1-deg test field Zisman et al[36] and Alvarez et al[37] tested luminance and chromatic functions that were mediated by the same types of fiber.

Outside the fovea, the proportion of small-diameter fibers appears to decrease,[57] and the effects of demyelination on those fibers there might be conjectured to be less severe. If so, there would be less reduction in detection performance at the edges of a large sharp-edged stimulus flash, where the luminance system might normally have more sensitivity, than at the center, where the chromatic system might normally have more sensitivity. Such a hypothesis was offered by Fallowfield and Krauskopf[33] to explain their data suggesting preferential losses in chromatic function. Whether there would be sufficient variation in fiber-diameter spectra over the central 2 deg of the retina investigated in their study is not at present certain. Greater potential for variation in fiber-diameter spectra would certainly have been offered by the 6.5-deg field used by Mullen and Plant.[34,35] It may be relevant, however, that perimetric spectral and white-light sensitivity data reported by Verriest and Uvijls[46] did not show substantial diminution in opponent-color function relative to luminance function until stimulus eccentricities exceeded 6 deg.

Variability

Harms[1] noted the abnormal luminance threshold in patients with recovering RBN. Patterson et al[2] quantified this variability using procedures similar to those used here. They[2] showed that for selected MS patients, variability in luminance threshold increased markedly with background luminance; whereas, for normal controls, luminance-threshold variability remained substantially constant with background luminance. Two possible causes proposed by Patterson et al[2] for this abnormal variability in MS patients were based on ephaptic transmission[60] and intermittent conduction block.[61] Drugs which block potassium channels have been shown[62] to reduce abnormal variability in some patients.

The present data did not reveal a significant relationship between threshold variability and threshold for patients, except for the white flash on the coincident auxiliary field (condition 2, Figs. 2a, 2b). This condition was associated with the highest thresholds (Fig. 2a), which fact is consistent with the findings by Patterson et al.[2] There was an increase in threshold variability for patients relative to normals in all conditions except condition 1 (Fig. 2b, lower section), the only condition likely to have involved detection of the sharp edges of the stimulus flash. This suggests the possibility of spatial-frequency selectivity for abnormal variability. In conditions 2, 3, and 4 (Fig. 2b), only the medium-to-low spatial frequency content of the stimulus flash should have elicited a response (in conditions 2 and 4 because of the coincident auxiliary field, and in condition 3, and 4 also, because of the spectral content of the stimulus). A spatial-frequency-selective threshold variability does not conflict with previous results on variability[2] and would extend other findings on the existence of spatial-frequency-selective losses in luminance sensitivity with grating stimuli.[14,15]

We conclude that in patients with MS and recovered ON, there may be substantial losses in foveal chromatic

and luminance sensitivity but these losses appear generally nonselective. This result, obtained by means of a simple threshold detection paradigm allowing the presentation of small, well-localized stimuli, is compatible with previous observations,[11] indicating that there is no selective impairment of fibers carrying time-varying chromatic and time-varying luminance information from the central fovea. It is also compatible, at a different level, with findings[63] showing nonspecific losses in rod- and cone-mediated function in patients with MS. We suggest that, although there may be variations in impairment across foveal fibers carrying different types of visual information, these variations are essentially random across fibers. In particular, when losses in chromatic and luminance sensitivity are determined by similar measures made over small central regions of the field, no evidence emerges for chromatic pathways being more vulnerable to damage than luminance pathways.

Key words: color vision, chromatic sensitivity, luminance sensitivity, optic neuropathy, multiple sclerosis

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