
Abnormalities of chromatic and luminance critical flicker frequency in multiple sclerosis

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Critical flicker frequency (CFF) was measured for stimuli varying in chromaticity only and in luminance only for patients with multiple sclerosis (MS) and for matched normal controls. The two CFF measurements showed different underlying linear interdependencies for the two groups, consistent with a greater loss of temporal luminance function than of temporal chromatic function in MS patients. These results are discussed in relation to the pathophysiology of demyelinated nerve fibers. It is suggested that demyelination affects all types of nerve fiber unselectively; in particular, no support is found for the notion of a special vulnerability of fibers carrying time-varying chromatic information. (INVEST OPHTHALMOL VIS SCI 23:246-252, 1982.)

Key words: critical flicker frequency, color vision, multiple sclerosis, optic neuritis

Impairment of visual function, due either to optic neuritis (ON) or to subclinical demyelination in the optic nerve, is common in multiple sclerosis (MS).^{1, 2} Psychophysical measurements of temporal visual function in

patients with MS have shown increased latencies, impaired double-flash resolution, reduced critical flicker frequency (CFF), and an increased temporal variability of luminance threshold.³⁻⁹ In patients with MS, abnormalities of color vision may also occur. These abnormalities include general and specific losses of color discrimination and a desaturation in color appearance.¹⁰⁻¹⁴ Differential losses in chromatic and luminance function in ON have also been reported.¹⁵ Some authors^{15, 16} suggest that such effects might be caused by selective damage of optic nerve fibers differing in diameter and function.

In view of the frequent impairment of temporal and chromatic visual function in patients with MS, it might be conjectured that there is a special vulnerability of nerve fibers carrying time-varying chromatic information to damage by demyelination. We investigated temporal chromatic function in MS patients by measuring CFF for stimuli varying in chromaticity only and for stimuli varying in luminance only; a special loss of

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temporal chromatic function would, it was reasoned, be revealed by a reduction of chromatic CFF relative to luminance CFF. For comparison, we made the same measurements in a group of normal control subjects matched for age, sex, and visual acuity to the patient group.

Methods

Stimuli and apparatus. The principal experiment was concerned with the measurement of chromatic and luminance CFFs. The stimuli were presented by means of a modified visual perimeter. This consisted of a square matt white screen subtending 20 by 20 deg at the subject's eye. The screen was illuminated by four incandescent lamps powered by a stabilized DC supply, which provided a constant uniform white background field of luminance of 290 cd/m² and color temperature of 2800° K.

Within this field, the test stimulus was produced by means of two light-emitting diodes (LEDs), one green (Monsanto MV5252, peak-emission wavelength 560 nm) and the other red (Monsanto MV5752, peak-emission wavelength 630 nm). The light from the LEDs was combined using a fiber-optic Y guide and was presented through a small glass diffusing plate at the center of the perimeter screen. This arrangement provided an unstructured, 10 min arc diameter circular test field, which appeared dark before and after presentation of the flickering stimulus. The intensities and time courses of the LED lights were controlled by suitable electronics. (The stimulus configuration used here is not critical; further experiments in which the flickering test stimulus was superimposed on a spatially uniform background field have given identical results to those presented here. The size of test field, although small, is sufficient to involve the pathways subserving chromatic function.¹⁹)

Red-green rather than blue-yellow chromatic CFF was measured because of the abnormalities in temporal response associated with the short-wavelength-sensitive mechanism.¹⁷ (This point is relevant to the method of generating the time-varying luminance stimuli described below.)

This apparatus produced two spatially coincident trains of square-wave temporal flicker. The individual intensities, temporal frequency, and the phase relationship of the red- and green-flicker trains could be independently controlled. The two flicker trains were presented either in antiphase or in phase, as illustrated in Fig. 1, *a* and *b*, respec-

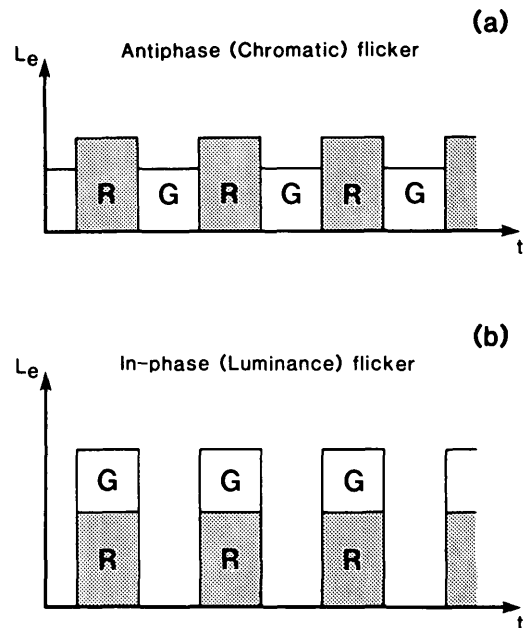


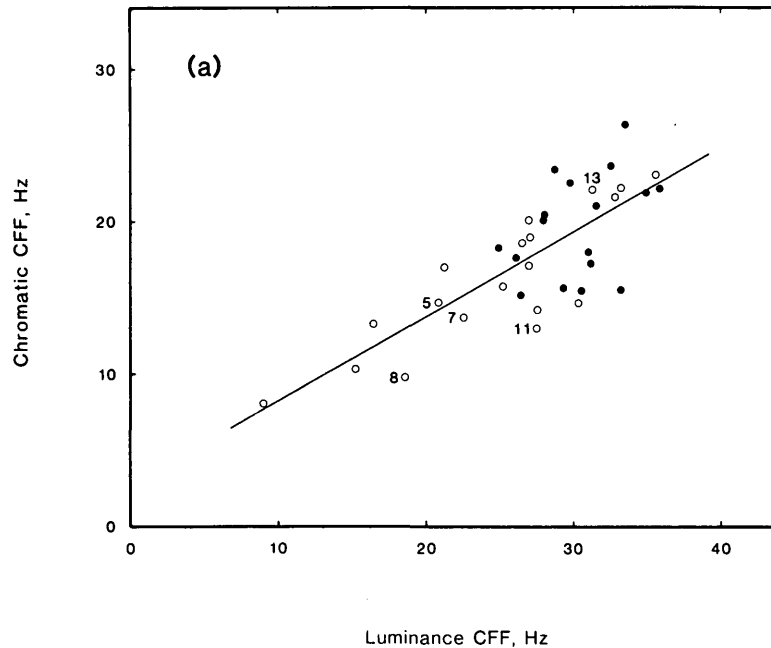
Fig. 1. Red (R) and green (G) LED intensities (L_e) plotted against time (t) for (a) antiphase (chromatic) and (b) in-phase (luminance) flicker (see text).

tively. The red-green antiphase condition (Fig. 1, *a*) produced the chromatic flicker stimulus when the red- and green-LED intensities were suitably adjusted to minimize luminance changes. This condition was achieved by each subject performing a heterochromatic flicker match¹⁸ as detailed below. The green-LED intensity remained constant throughout all of the measurements, with a luminance of 60 cd/m². The in-phase condition (Fig. 1, *b*) produced the luminance flicker stimulus, the red- and green-LED intensities having been fixed as above.

The chromatic flicker stimulus and the luminance flicker stimulus were thus equated for time-averaged wavelength and time-averaged luminance. The duration of each flicker stimulus presentation was set at 3 sec and was initiated by the subject using a push-button switch.

The subject viewed the stimulus screen through an eyepiece at a distance of 1.7 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.

To test static red-green color matching function, Rayleigh matches were made with a conventional three-channel Maxwellian-view optical system,¹⁹ with spectral composition of the chan-



Figs. 2a and 2b. Chromatic CFF plotted against luminance CFF. The straight lines are least-squares linear fits to the data.

Fig. 2a. CFF plot for MS patients. *Open circles*, Eyes previously classified as abnormal. Numerals alongside symbols indicate results from particular patients referred to in the text.

nels determined by interference filters (bandwidths all less than or equal to 8 nm). Matches were made between a central 2 deg disc, a mixture of red (651 nm) and green (539 nm) lights, and an annular surround consisting of a monochromatic yellow (576 nm) of fixed intensity, $8.75 \log \text{quanta sec}^{-1} \text{deg}^{-2}$, equivalent to 120 cd/m^2 (identical to the maximum luminance of the stimuli used in the luminance CFF determinations). The intensities of the red and green lights could be adjusted with compensated neutral-density wedges. The subject viewed the stimuli through a 2 mm diameter artificial pupil. Head stabilization was by means of a chin rest.

Procedure. At the beginning of the first experimental session, subjects' near vision, Snellen acuity, and color discrimination were assessed by printed charts and the City University color vision test.^{20, 21}

In the principal experiment to determine chromatic and luminance CFFs, the procedure was as follows: For each eye studied, the intensity of the red LED was first set so that its luminance was equal to that of the fixed-intensity green LED. To achieve this, the red- and green-flicker trains were set in the antiphase condition (Fig. 1, a) and the

flicker frequency and the red-LED intensity were alternately adjusted until a frequency was found for which the subject perceived flicker for all red-LED intensities except for a small range of intermediate values. At this flicker frequency the red-LED intensity was varied in a systematic up-down staircase manner, and the subject was required to indicate (forced-choice) at each intensity whether or not flicker was seen. The mean of those red-LED intensities where the subject saw no flicker was taken as the value of red-LED intensity that was equal in luminance to the fixed-intensity green LED. (A deliberate mismatch in the intensities from this luminance-equating procedure of the order of their standard deviation was found not to affect the value of chromatic CFF obtained.)

After this luminance-equating procedure, chromatic and luminance CFFs were determined by a method of limits. Each of the two CFFs was derived from a block of six ascending and descending series of varying flicker frequencies. These series were centered on frequency values previously determined in short practice series with coarser frequency increments. In each trial the experimenter cued the subject, who then fixated the center of the field and pressed a button that started the 3 sec

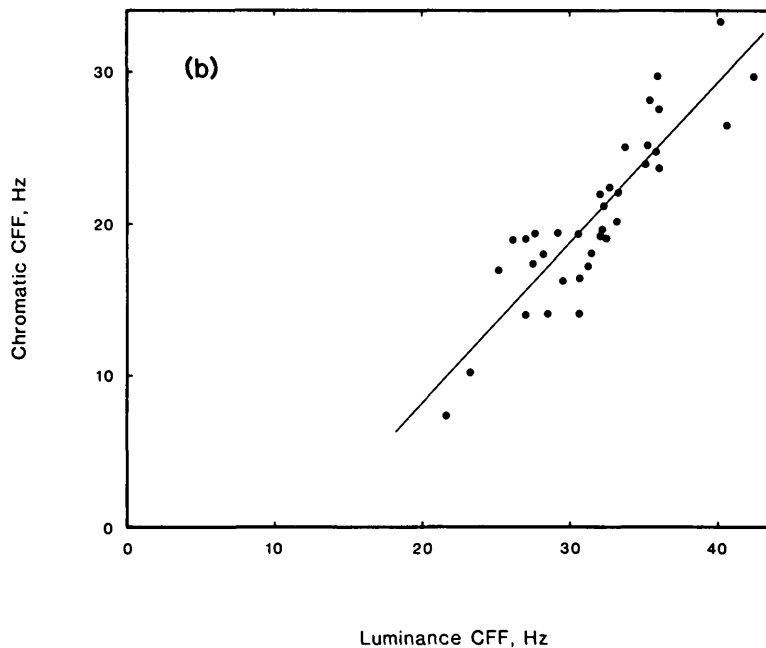


Fig. 2b. CFF plot for normal control subjects.

(chromatic or luminance) flicker stimulus presentation at the fovea. The subject indicated (forced-choice) whether or not flicker was seen. Repeat trials were allowed only when the subject failed to see the stimulus because of inappropriate fixation or blinking. However, such trials were rare.

The order of measuring chromatic and luminance CFFs in each eye was randomized over subjects. For each patient and matched normal the order of the two CFF measurements was the same. Each subject was tested in a single session lasting about 1.5 hr.

Some patients with low chromatic CFFs had their static color matching and discrimination ability further evaluated in auxiliary experiments in which they made a standard Rayleigh match (see previous section) and performed a Farnsworth-Munsell 100-hue²² discrimination test. To determine the Rayleigh match with the Maxwellian-view system, the experimenter adjusted the intensities of the red and green lights forming the central spot until the subject reported that the spot matched in color its yellow annular surround. This procedure was repeated six times and a mean value of the logarithm of the red-green intensity ratio was calculated.

For comparison, these auxiliary experiments were also performed with a group of normal subjects.

Subjects. Twenty patients and 20 normal controls participated in this study. Patients with MS were classified²³ as follows: 11 clinically definite, two progressive probable, two early probable, one progressive possible, and two suspected. The distribution of demyelinating lesions within the central nervous system was as follows: 15 spinal, 10 optic nerve, two brainstem, and one cerebellar. Additionally, two patients had had optic neuritis only. In the patient group, four eyes were excluded because of poor acuity or complete loss of vision. Thirty-six eyes were therefore studied, 19 of which had records of previous visual disturbance, including optic neuritis and deficiencies of color vision (see Results). All the patients' eyes included in the study had Snellen acuities equal to or better than 6/12 and near vision equal to or better than N5. No patients reported difficulty in fixation and none had nystagmus. Of these patients only two gave abnormal responses to the City University color vision test. These were patient 8 (left eye), with 30% protan and 30% deutan errors, and patient 13 (right eye), with 40% tritan errors (see Results).

Twenty normal controls were matched with the patient group for age and sex. From this normal control group 36 eyes matched to those of the patient group were tested. The normal control group all had normal color vision and covered a range

Table I. Pearson product moment correlation coefficients (magnitudes) for chromatic and luminance CFFs with age, Snellen acuity, and the red intensity required in the heterochromatic flicker match

	Age	Snellen acuity	Red intensity
Patients			
Chromatic CFF	0.09	0.47*	0.23
Luminance CFF	0.06	0.48*	0.36*
Normals			
Chromatic CFF	0.80**	0.42*	0.07
Luminance CFF	0.81**	0.32*	0.01

Statistical significance: * $p < 0.05$; ** $p < 0.001$.

Table II. Results of auxiliary experiments to test static color matching and discrimination (see text)

Subject	Color match (log red/green ratio, mean \pm S.D.)	100-hue test (error score)
Normal eye	1.4428 \pm 0.0723	41
Patient 5 (right eye)	1.4693 \pm 0.0355	109
Patient 7 (right eye)	1.5835 \pm 0.0924	156
Patient 11 (right eye)	1.5244 \pm 0.0920	138

of visual acuity similar to that of the patient group.

Subjects in both groups were unpracticed in performing psychophysical tests and were unaware of the aims of the study. Informed consent was obtained from all subjects.

Data analysis. Values for chromatic and luminance CFFs were computed from the raw data for each eye by means of probit analysis.²⁴ The underlying normal distribution assumed by probit analysis is not intended to have any theoretical significance here.

Results

Plots of chromatic CFF against luminance CFF are shown in Fig. 2a for the patient group and in Fig. 2b for the normal control group. For the patient group, results for eyes previously classified as clinically abnormal are indicated by the open circles. Numerals next to some symbols indicate particular patients referred to in the text.

There is an evident linear relationship underlying chromatic CFF and luminance CFF for both patients and normal controls. The

straight lines in both figures are least-squares regression lines of chromatic CFF on luminance CFF; correlation coefficients (in all cases Pearson product moment) are 0.78 and 0.89 for the patient and normal groups, respectively.

The main difference between the patient and normal data is in the gradients of the underlying linear relationships. The gradient of the regression line for the patient data is 0.555, and that for the normal control data is 1.063. The difference in these two gradients is statistically highly significant ($p < 0.001$).

Table I shows the correlation coefficients for regressions of chromatic and luminance CFFs on age, Snellen acuity, and the red intensity required in the heterochromatic flicker color match. In this table, the most striking correlations occur in the normal control group for chromatic CFF with age and for luminance CFF with age (both CFFs decreasing with age). The magnitudes of these correlation coefficients are greater than or equal to 0.80 and each is highly significant ($p < 0.001$). In contrast, in the patient group the same correlations are not significantly different from zero.

For both the patient group and the normal control group, correlations of chromatic CFF with Snellen acuity and luminance CFF with Snellen acuity reach significance ($p < 0.05$) but each have correlation coefficients of magnitude not more than 0.48. Correlation between the CFFs and the red intensity required in the heterochromatic flicker match is greater for the patient group, reaching significance for luminance CFF, but again the correlation coefficient (0.36) has small magnitude.

Table II shows results of the auxiliary experiments carried out with selected ambulatory patients (Nos. 5, 7, and 11; see Fig. 2a) with low chromatic CFFs. In the Rayleigh matches, normal values for red-green ratio and standard deviation are the means for three normal control subjects. In producing the match, these patients required slightly more red than did normal controls, although the difference of the patients' red-green ratio from the normal ratio is significant ($p < 0.05$).

only for patient 7. Poorer discrimination may be suggested as a greater-than-normal variability in these matches for patients 7 and 11.

In the Farnsworth-Munsell 100-hue test, patients 5, 7, and 11 showed a general reduction of color discrimination, the worst score being 156 (patient 7). (Mean score for three normal subjects under the same experimental conditions was 41.) None of these patients exhibited a significant lobe, characteristic of the common inherited-type deficiencies, in these reduced-discrimination responses.

Discussion

The patient and normal control group both show strong positive linear correlations between chromatic CFF and luminance CFF. Although chromatic CFF is well known to be lower than luminance CFF,^{25, 26} we are not aware of previous reports of the underlying linear interdependence of these measures over different eyes.

Other studies in normal subjects have shown correlation of luminance CFF with age.²⁷⁻²⁹ Our results confirm this observation and additionally extend it to the case of chromatic CFF. For patients the correlation of both chromatic and luminance CFFs with age is apparently suppressed. This might be interpreted as an effect of demyelination on temporal aspects of chromatic and luminance information processing that acts randomly, independent of age. Other factors such as variations in visual acuity and reduced red sensitivity (see Table I) are clearly insufficient to explain the observed interdependence of the two CFF measures. (Separate correlations of acuity with age were 0.04 for patients and 0.36 for normal controls.)

It might be suggested that the difference between the patient and normal control groups for chromatic and luminance CFF interdependence resulted from static color vision deficiencies in the patient group. In this case we might expect the gradient of the chromatic CFF against luminance CFF data from the patient group to be *greater* than unity (or at least greater than the normal con-

trol group gradient), since chromatic CFF would be preferentially lowered in affected eyes. This is not the case and our results exhibit the opposite gradient change. An explanation of the present data in terms of static color deficiencies thus appears unjustified.

The suggestion was put forward earlier in this article that nerve fibers carrying time-varying chromatic information might be particularly vulnerable to the effects of demyelination. The evidence presented here provides no support for this conjecture. Indeed, as has been observed, there appears to be a greater loss of temporal luminance processing capacity than temporal chromatic processing capacity in the patient group. This outcome may be explained, however, without recourse to the notion of a special susceptibility of certain classes of nerve fiber to demyelination. For example, from studies on demyelinated nerves^{30, 31} it is known that demyelination blocks or impairs the transmission of nerve impulses at high repetition rates and can also give rise to an intermittent conduction block. These effects almost certainly underlie the psychophysically observed reduction in temporal responsiveness measured by double-flash resolution and luminance CFF. In this respect, the effect of demyelination may be compared to the action of a low-pass filter. Because in normal subjects luminance CFF is greater than chromatic CFF, the preferential reduction in luminance CFF observed in patients would then be a natural consequence of the attenuating action of this filter at high temporal frequencies, *independent* of the type of information being carried and class of fiber subserving transmission.

It may be noted that this hypothesized low-pass filter should be different in characteristics from that describing the effects of age on the visual pathway, otherwise the gradients of luminance CFF vs. chromatic CFF for patients and normal controls shown in Fig. 2 would presumably be the same.

In summary, it appears that the effect of demyelination is a reduction of chromatic CFF and luminance CFF, with the latter most strongly affected. This result is consis-

tent with there being a general loss of high-frequency function in affected nerve fibers. In particular, no support is offered for the notion that fibers carrying time-varying chromatic information are specially vulnerable to damage by demyelination.

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