VARIABILITY OF VISUAL THRESHOLD IN MULTIPLE SCLEROSIS

EFFECT OF BACKGROUND LUMINANCE ON FREQUENCY OF SEEING

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INTRODUCTION

A VISUAL threshold is the minimum luminous intensity of a light stimulus necessary for its perception. It is one of the simplest and most fundamental properties of visual function and one which depends on the integrity of the visual system from cornea to cortex. In clinical practice visual thresholds may be measured by static perimetry with a Goldmann or Tübinger perimeter. The intensity of the light stimulus is increased until it is perceived by the subject, this intensity value being taken as the threshold. Repeated testing of the same point by this method produces a normal variability of within 0.3 to 0.4 log units of light intensity (Ellenberger, 1974).

It is hardly surprising that visual thresholds are sometimes elevated in multiple sclerosis (MS), a disease in which the visual pathway is frequently affected. Raised thresholds have been reported by Burde and Gallin (1975) in the affected eyes of patients with previous retrobulbar neuritis. Harms (1976) not only found raised thresholds in patients with recovering retrobulbar neuritis, but also noted excessive scattering of thresholds on repeated testing at the same point.

We too have found retinal sites in patients with MS at which threshold shows increased variability, but have noticed that this variability seems to be most marked when the patients are examined at high background luminance levels. In order to elucidate this, we have quantified threshold variability and determined how it is affected by background luminance in MS patients and control subjects.

SUBJECTS

Five patients with multiple sclerosis (MS), in whom abnormally variable visual thresholds had been noted, were selected for study. Three patients had clinically definite MS and two had probable MS, according to the diagnostic criteria of

Rose, Ellison, Myers and Tourtellotte (1976). None of the eyes tested had ever had visual symptoms but all had subclinical optic neuropathy as evidenced by nerve-fibre bundle defects on tangent screen examination of the visual fields (V. H. Patterson and J. R. Heron, in preparation). Optic discs were all judged to be normal. Further details are given in Table 1.

Five subjects without evidence of MS acted as controls. Four were members of hospital staff and the other was a patient with a radial nerve palsy. All but two were unaware of the purpose of the experiment. They showed a similar distribution of age, sex and refractive error as the patients. Informed consent was obtained from all subjects.

TABLE 1. DETAILS OF PATIENTS

Case	Sex	Age (yrs)	Classification	Clinical manifestations	Duration (yrs)
1	M	32	Clinically definite	Optic neuritis. Relapsing and remitting paraparesis.	8
2	M	41	Clinically definite	Progressive paraparesis. Subclinical optic neuropathy.	7
3	M	26	Clinically definite	Relapsing and remitting cerebellar and spinal signs. Subclinical optic neuropathy.	3
4	F	24	Probable	Recurrent ataxia. Subclinical optic neuropathy.	5
5	M	28	Probable	Lhermitte's sign. Persistent visual symptoms with signs.	1

PROCEDURE

Subjects sat in a chair with a firm headrest and viewed a circular white screen of diameter 0.6 m at a distance of 1.6 m through an adjustable eyepiece. Spectacles were worn if appropriate and the eye not being tested was occluded. An artificial pupil was not used. Subjects fixated a small target at the centre of the screen. The screen was illuminated by two pairs of 100 W incandescent lamps powered by a stabilized d.c. supply which at 250 V gave a uniform screen luminance of 3.0 log cd m^{-2}. Neutral density filters of 1.0 and 2.0 log units could be placed in front of the subject's eye to give apparent screen luminances of 2.0 and 1.0 log cd m^{-2}, respectively. For zero background luminance the screen was covered with black material, and the subject fixated the centre of an array of four small white lights. The stimulus flash was provided by a red light-emitting diode (LED) of peak emission wavelength 635 nm (type MV 5752), the time course and intensity of which was controlled by suitable electronics. The LED subtended 11 minutes of arc at the subject's eye. Flash duration was fixed at 20 ms, and flash intensity was controlled by the experimenter. In preliminary measurements on patients, retinal sites in each quadrant at 5 deg eccentricity and about 45 deg inclination from the horizontal meridian were examined at a background luminance of 3.0 log cd m^{-2} to determine the site at which visual threshold seemed most variable. This was then selected for further study. Similar measurements in normal subjects had not shown any difference in variability between different retinal quadrants. Each subject was tested in two sessions of about one hour each, which were usually held on successive days. In the first session the subject was tested at a background luminance of 3.0 log

cd m^{-2} and then, after dark-adaptation for 30 minutes, tested at zero background luminance. In the second session, the subject was dark-adapted for 20 minutes and then tested at background luminances, first of 1.0 log cd m^{-2}, and then of 2.0 log cd m^{-2}. The order in which the background luminances were presented was found not to be critical since similar results were obtained when the order was changed. Fixation was not specifically monitored, but all the patients had consistently identified the blind spots on visual field testing, and none had nystagmus.

A frequency-of-seeing curve was constructed for each subject at each background luminance as follows. An approximate threshold value for the stimulus flash was determined by a method of limits (Engen, 1971). Ten consecutive intensity settings at 0.1 log-unit intervals were then selected with the approximate threshold value in the middle of the range, and flashes of these intensities were presented to the subject in a random order. The subject controlled the onset of the flash by means of a push-button switch and indicated after each presentation whether or not he had seen the flash. After a rest period of 30 seconds, the ten flashes were presented in a different order, and this procedure was repeated until each flash of a given intensity had been presented 10 times. The sequence of presentations of the flashes was predetermined and was balanced for order and residual (carry-over) effects (Finney, 1960). The frequency-of-seeing at each stimulus intensity was then calculated, and a frequency-of-seeing curve was constructed.

We used the classical method of constructing a frequency-of-seeing curve in preference to a two-interval forced-choice technique (Tanner and Swets, 1954; Nachmias, 1972), after carrying out preliminary experiments in which both methods were used. The results obtained by the two methods were similar but the two-interval forced-choice technique was more time-consuming because of the number of blank presentations involved, and subjects preferred the conditions of the classical method.

STATISTICS

The frequency-of-seeing curves were analysed by computer probit analysis (Finney, 1952). This procedure assumes that the sigmoid nature of the frequency-of-seeing curve is determined by an underlying normal distribution; the mean of this distribution is the intensity ΔI_{50} at which a stimulus is seen 50 per cent of the time, and the standard deviation σ of the distribution corresponds to the variability in seeing. This assumption of underlying normality is not intended here to have any theoretical significance (Blackwell, 1963); it is used merely as a means of quantifying the frequency-of-seeing data. The mean values of ΔI_{50} and σ for the patient group were compared with those for the control group using Student's t test.

In order to determine whether fatigue effects (Sunga and Enoch, 1970) occurred over the course of the experiment or within the groups of ten presentations, we computed the number of positive responses for each group and for each position within the groups at the two highest background luminances. Correlation coefficients and regression lines for the trends in these numbers were obtained in all subjects, and their significance calculated using a t test.

RESULTS

Computer-fitted frequency-of-seeing curves from a representative patient and control are shown in fig. 1. In the control subject the slope of the curve is substantially the same at all background luminances although there is a small increase with the introduction of the background. In the patient, however, there is a striking progressive decrease in slope with increasing background luminance.
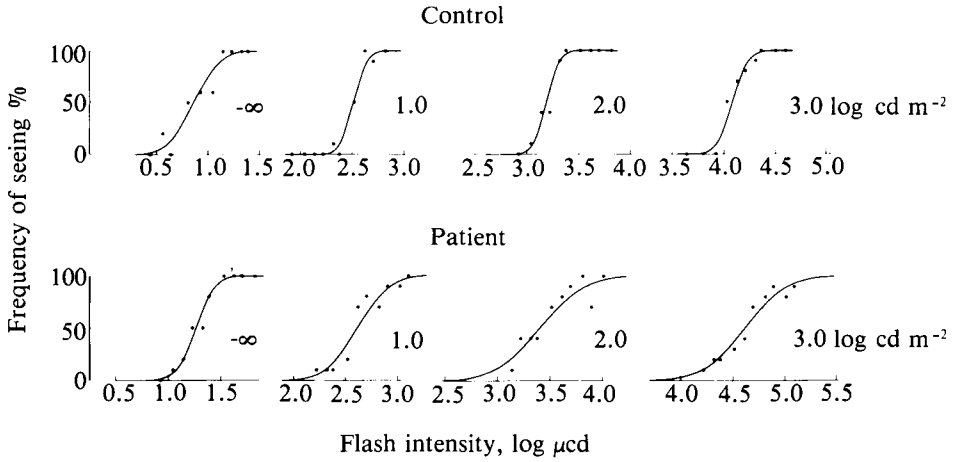
FIG. 1. Frequency-of-seeing curves for a representative patient and control. Each data point is derived from ten trials and the smooth curves are fitted by computer probit analysis. The background luminance for each curve is indicated.
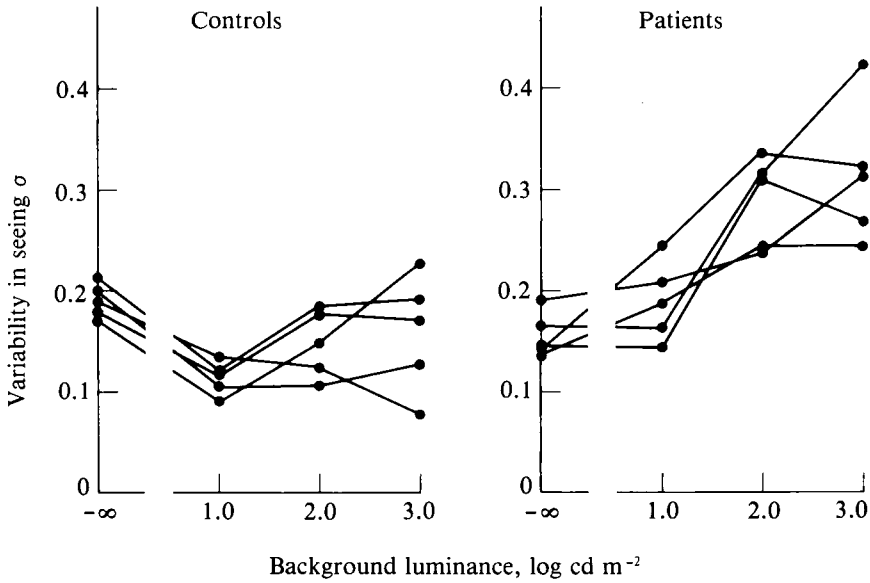
FIG. 2. Variability in seeing obtained by probit analysis plotted against background luminance for individual patients and controls.

When the data are subjected to probit analysis and the variability in seeing σ is plotted against background luminance, significant general differences between the patient and control groups are seen (fig. 2). First, variability for the patient group is slightly less than that of the control group at zero background luminance ($t = 2.74$, df $= 8$, $P < 0.05$), but is significantly greater at 1.0 log cd m^{-2} ($t = 4.01$, df $= 8$, $P < 0.01$), 2.0 log cd m^{-2} ($t = 5.06$, df $= 8$, $P < 0.001$) and 3.0 log cd m^{-2} ($t = 3.86$, df $= 8$, $P < 0.01$), there being no overlap between the two groups at these three non-zero luminances.

Secondly, when variability at zero background luminance and at 3.0 log cd m^{-2} is compared in each group, there is no significant difference for the control group ($t = 1.20$, df $= 8$, $P > 0.2$) but a highly significant difference for the patient group ($t = 4.84$, df $= 8$, $P < 0.01$). Thirdly, the initial fall in variability between zero background and 1.0 log cd m^{2}, shown by the control group ($t = 7.35$, df $= 8$, $P < 0.001$) is not shown by the patient group ($t = 1.63$, df $= 8$, $P > 0.1$).

The 50 per cent seeing intensities ΔI_{50} for the two groups differ significantly only at the highest background level, 3.0 log cd m^{-2} ($t = 3.22$, df $= 8$, $P < 0.05$). A significant fatigue effect was found in only 3 of the 20 measurements in the patients and in only 2 of the 20 measurements in the controls.

DISCUSSION

Our findings concerning variability of seeing in the control subjects are in close agreement with those of Mueller (1951). Using a foveal stimulus he found no change in threshold variability (as measured by the reciprocal of the slope of the frequency-of-seeing curve) at most levels of background luminance, and he noted a rise in variability at very low light levels, an effect also reported by Blackwell (1963).

Our results in the MS patients differ in several respects from those in the control subjects. First, they confirm and quantify the abnormal variability reported by Harms (1976) and secondly, they show that abnormal variability may occur in conjunction with a normal threshold value (as determined by the 50 per cent seeing intensity). This suggests that in MS, threshold variability is a more sensitive indicator of visual pathway damage than the usual measure of mean threshold. The most important finding, however, is that variability in seeing increases with background luminance in the MS patients. Such an effect would be explained if the transmission of visual signals were subjected to a *fluctuating* source of interference which increased with the luminance of the background field; a constant source of interference at each luminance level would produce only a change in the 50 per cent seeing intensity, with no change in the variability of seeing.

It should be stressed that this luminance-dependent variability cannot be ascribed to a fatigue effect of the type reported by Sunga and Enoch (1970) in patients with optic neuritis. At a background luminance of 2.0 log cd m^{-2}, where the difference in threshold variability between patients and controls was most

significant, none of the patients showed a fatigue effect either over the course of the experiment or within the groups of ten presentations.

Since there is no firm evidence for the existence of a retinal effect in MS, the likely site for the occurrence of the fluctuating interference is the demyelinated visual pathway. Two possible physiological mechanisms underlying the variable effect reported here are intermittent conduction block and cross-excitation between affected nerve fibres. In the normal vertebrate visual system, the form of the response of a retinal ganglion cell, in terms of its firing rate as a function of time, varies with the intensity of both the stimulus flash and the adapting background (Stone and Fabian, 1968; Enroth-Cugell and Pinto, 1972a, b; Enroth-Cugell and Shapley, 1973). In particular, the impulse frequency of the initial or final components of the response increases with adaptation level. The capacity of a nerve to transmit high frequency impulses is known to be impaired by demyelination (McDonald and Sears, 1970), and intermittent conduction block has been shown to occur at frequencies which are sufficiently low that they overlap with those occurring in the response of the fibre to natural stimulation (Rasminsky and Sears, 1972). Increased variability in seeing with increase in background luminance could therefore arise as a direct consequence of the increasing vulnerability of the stimulus response signal to intermittent conduction block at the site of a demyelinating lesion.

In addition to intermittent conduction block, we also suggest the possible relevance of interference with signal transmission by cross-excitation between nerve fibres at the demyelinating lesion. Osterman and Westerberg (1975) have postulated that ephaptic transmission between adjacent sensory and motor fibres underlies various paroxysmal phenomena in MS, such as tonic seizures, spinal sensory motor seizures, paroxysmal dysarthria and ataxia, and Lhermitte's sign. Although there is no direct evidence for such side-to-side transmission in man, there is evidence for cross-excitation in congenitally dysmyelinated roots in the dystrophic mouse (Huizar, Kuno and Miyata, 1975; Rasminsky, 1978).

If side-to-side transmission were to occur between nerve fibres in the visual pathway, then interference could arise between fibres signalling the response to the stimulus flash and fibres carrying information concerning background luminance (Barlow and Levick, 1969; Stone and Fukuda, 1974). As activity in the latter fibres increases with the luminance level, interference with signal transmission would also increase. The fluctuating nature of this proposed interference could originate either in the 'luminance' fibres or in the side-to-side transmission process.

If abnormal threshold variability of the kind reported here were present at many retinal sites in a patient's eye, it would be expected to produce a disturbance of everyday vision in bright lights but not in dim ones. One of our patients volunteered this symptom and found that his vision in strong sunlight was much improved by tinted spectacles. We have observed this effect previously in a number of our patients with demyelinating optic neuropathy and McDonald (1977) considers that approximately half the patients with acute optic neuritis notice that

they see more clearly in a dimly lit environment than in bright sunlight. In 1926, Percival mentioned obscuration of vision in bright lights as a symptom of acute retrobulbar neuritis and also commented that patients with chronic retrobulbar neuritis saw better in dim light. Lillie (1934) reported a similar symptom in chronic optic neuritis and more recently, Perkin and Rose (1976) in a review of Uhthoff's syndrome, noted increased illumination as a cause of transient visual blurring in some patients with optic neuritis and MS.

Increased variability in seeing may also explain a phenomenon found on tangent screen examination of the visual field in some patients with MS for whom the test object appears to flicker on and off in some areas of the visual field (Frisén and Hoyt, 1974). This occurs most commonly between 10 and 25 degrees eccentricity where, because the test object is normally not greatly above threshold, any increase in threshold variability would result in the object being seen intermittently, that is, appearing to flicker on and off.

SUMMARY

Visual thresholds were measured at four different background luminance levels in patients with multiple sclerosis (MS) and in control subjects by means of frequency-of-seeing curves. Results were examined by probit analysis and measures of threshold and threshold variability were obtained. Comparison of patient and control groups showed that the patient's threshold was significantly raised only at the highest background luminance level, but that threshold variability was greater at all three non-zero background luminance levels tested. In addition, threshold variability increased with background luminance in the MS patients but not in the control subjects. Possible underlying pathophysiological mechanisms are discussed, and it is suggested that this luminance-dependent variability in visual threshold shown by patients with multiple sclerosis may be due to intermittent conduction block or ephaptic transmission occurring within the demyelinated visual pathway.

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