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OPTIC NEURITIS: VARIATIONS IN TEMPORAL MODULATION SENSITIVITY WITH RETINAL ECCENTRICITY

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SUMMARY

Temporal modulation sensitivity functions were measured centrally and at eccentricities of 2.5°, 5° and 10° in the temporal visual field of 12 patients with recovered optic neuritis and in a group of matched normal controls. A circular, spatially uniform stimulus of 1° angular subtense was presented with sinusoidal modulation at 5, 8, 14 and 23 Hz. The general pattern of results in patients was a loss of sensitivity relative to normal controls at all temporal frequencies at 0° and 2.5° eccentricity, with rather greater losses occurring at the medium-to-lower temporal frequencies. At 5° eccentricity, the losses were confined to medium temporal frequencies only, and at 10° eccentricity there was no significant loss at any temporal frequency. These findings may be explained by a greater vulnerability of optic nerve fibres of small diameter to the effects of demyelinating disease.

INTRODUCTION

Demyelination of nerve fibres leads to delayed transmission of nerve impulses, an increased refractory period, and the possibility of conduction block if demyelination is sufficiently severe (Halliday and McDonald, 1977). As a consequence, an impairment of temporal visual function is frequently evident in multiple sclerosis (MS) and recovered optic neuritis (ON).

A traditional method of assessing altered temporal response function is by measurement of the critical flicker frequency (CFF), which is often lowered in MS patients (Titcombe and Willison, 1961; Daley *et al.*, 1979; Mason *et al.*, 1982). The disadvantage of this method is that it assesses sensitivity at a single high temporal frequency. A more comprehensive approach is to measure the full de Lange attenuation characteristic (de Lange, 1952, 1958). This method employs a stimulus whose luminance varies sinusoidally with time, but rather than the temporal frequency being adjusted to threshold so that flicker is just detectable, as in CFF determinations, the frequency is held constant and

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the modulation depth is adjusted to threshold. Modulation depth is specified in terms of the time-varying luminance L as $(L_{max}-L_{min})/(L_{max}+L_{min})$. The threshold may be defined as the modulation depth at which flicker is detected in a certain proportion (e.g., 50%) of trials. Threshold measurements are made at a number of temporal frequencies to yield the attenuation characteristic, a direct temporal analogue of the contrast sensitivity function used to assess spatial vision.

It has been commonly assumed that the overall spatial response of the visual system may be determined by a collection of discrete 'channels', each channel sensitive to a narrow band of spatial frequencies (Pantle and Sekuler, 1968; Blakemore and Campbell, 1969). Similarly, it has been suggested (Kulikowski and Tolhurst, 1973; Watson and Robson, 1981; Hess and Plant, 1985) that the temporal response of the visual system may be determined by a collection of temporal channels, the relative activities of which depend on the spatial frequency of the stimulus. Hess and Plant (1985) proposed that, at medium-to-high spatial frequencies, two channels mediated the overall response, one being low-pass for temporal frequency and the other band-pass, whereas at low spatial frequencies there was a third channel that was high-pass for temporal frequency.

Plant and Hess (1985), using sinusoidal gratings of fixed spatial frequency, examined the effect of ON and MS on the de Lange attenuation characteristic and, although a number of different patterns of loss were evident, the most common was one consistent with a greater loss of function of the low-temporal-frequency (low-pass) channel. Medjbeur and Tulunay-Keesey (1985), in a related investigation, studied the effect of temporal modulation on the contrast sensitivity function in patients with ON or MS. From their results they suggested that two temporal-frequency channels determined the overall temporal response and that it was the lower temporal frequency ('sustained') channel that was more affected in ON and MS.

One of the consequences of using sinewave gratings is that they involve extended areas of the retina and therefore may not reveal highly localized variations in performance that are associated with patchy demyelination of the optic nerve. Another important factor is the possible association between the effects of demyelination and the diameters of optic nerve fibres (discussed in more detail later). There is a natural variation in fibre diameter with increasing retinal eccentricity, the highest concentration of small diameter fibres serving the macula (Potts *et al.*, 1972; Sanchez *et al.*, 1986). Any losses associated with a particular range of fibre diameters may be less evident with the use of a large stimulus such as a sinewave grating. In the present investigation a small (1° angular subtense), spatially uniform, circular (spot) stimulus was used to measure de Lange attenuation characteristics at the central fovea and at three increasingly eccentric sites in the temporal visual field of 12 patients with previous ON. For comparison, the same sites were tested in a group of 8 matched normal controls. Although the spot stimulus used was, in spatial-frequency terms, broad band, its small spatial size made possible a test of the relationship between temporal modulation sensitivity loss and retinal location in recovered ON.

METHODS

Subjects

Twelve patients were investigated (1 male, 11 females). All had previous ON and, in some cases, evidence of demyelination elsewhere in the central nervous system. None were in an acute phase of the disease at the time of testing and none had nystagmus. Patients were classified according to the criteria of McDonald and Halliday (1977), with isolated ON accepted as an additional diagnostic category. Clinical details are given in Table 1. Eight healthy subjects (1 male, 7 females) with a similar age range to the patients acted as normal controls. No control subject had an acuity worse than Snellen 6/9. Two of the controls were experienced psychophysical observers; the remainder were experimentally naive. Subjects wore their own spectacles (or, if necessary, trial lenses were substituted). Informed consent was obtained from each patient and control subject.

Stimuli and apparatus

The stimulus consisted of a temporally sinusoidally modulated, spatially uniform, yellow circular field, of 1° angular subtense with a contiguous, steady, uniform annular surround (5° outer diameter) matched in colour and luminance to the time-averaged (d.c.) stimulus (a configuration that has been shown to maximize sensitivity to achromatic flicker; Wisowaty, 1981). The luminance of the time-averaged stimulus and surround was 2.0 $\log_{10}$ cd·m^{-2}, peak-emission wavelength 584 nm. Stimulus duration was 2 s with, at the beginning and end of the stimulus interval, an additional 0.5 s ramp-up and ramp-down of modulation depth. The stimuli were generated within a special-purpose perimeter system. The combined output from 2 identical light-emitting diodes (LEDs) (Marl BP200 UBA 12H CW) under the control of a digital electronics system was used to produce the stimulus, with 8 other LEDs (Marl BP200 FUA 12H CW), identical apart from lens configuration, used to produce the surround field. A high-frequency pulse train was used to drive the stimulus LEDs (minimum frequency 800 Hz). Sinusoidal modulation of the pulse density produced the apparent sinusoidal amplitude modulation of the stimulus luminance. The whole system was under the control of a laboratory microcomputer. Harmonic distortion in the stimulus was assessed with a Brüel and Kjaer frequency analyser; the amplitude of harmonics of frequencies up to 500 Hz was found to be more than 50 dB below the amplitude of the fundamental.

The stimulus and surround were presented on a large steady background field (40° W×24° H) of luminance 1.0 log cd·m^{-2}, which maintained a constant state of retinal adaptation. Stimuli were viewed monocularly and stimulus presentation was initiated by the subject using a push-button box connected to the computer.

TABLE 1. SUMMARY OF CLINICAL DATA*

Case	Age (yrs)	Sex	Snellen acuity	Near vision acuity	Optic disc pallor	Visual field	Classification	Duration (yrs)	No. of attacks	Optic neuritis	Lesions at other sites
1	38	F	6/6	N5	+	+	Clinically definite	6	5	+	Spinal cord, brainstem
2	30	F	6/12	N5	+	+	Clinically definite	4	4	+	Brainstem
3	43	F	6/18	N9	+	+	Clinically definite	5	5	+	Brainstem, spinal cord
4	36	F	6/9	N4.5	+	+	Early probable	0.6	2	+	Brainstem
5	39	F	6/9	N5	+	+	Optic neuritis	1.4	1	+	
6	39	F	6/6	N4.5	+	+	Optic neuritis	6	1	+	
7	37	F	6/9	N5	+	+	Clinically definite	2	2	+	Spinal cord
8	39	F	6/6	N4.5	−	−	Clinically definite	6	2	+	Spinal cord
9	40	M	6/5	N5	−	+	Clinically definite	11	9	+	Brainstem, spinal cord
10	35	F	6/12	N5	+	+	Clinically definite	11	4	+	Brainstem
11	30	F	6/6	N4.5	+	−	Optic neuritis	0.7	1	+	
12	37	F	6/5	N4.5	−	−	Optic neuritis	0.8	1	+	

* Optic disc pallor, the presence of scotomata in the visual field, and optic neuritis are indicated by + in the appropriate columns.

Procedure

Measurements were made at 4 retinal sites (central, 2.5°, 5° and 10° eccentricity in the temporal visual field), with 4 temporal frequencies being tested at each site (5, 8, 14 and 23 Hz). For each participant in this study it was possible to record modulation thresholds at all these sites and frequencies.

The subject sat in a chair of adjustable height and placed his or her eye against the rubber eye-cup of the viewing system. An artificial pupil was not used. The subject fixated the stimulus for central presentation or an off-axis red (LED) fixation target for eccentric presentation. At each site, measurements were made in ascending order of temporal frequency. There were 30 stimulus trials (with 5 empty 'catch' trials randomly interleaved) at each frequency, and in each trial the subject reported (forced-choice) whether or not the stimulus was seen to flicker. The level of the stimulus modulation depth in each trial was determined by a modified PEST routine (Taylor and Creelman, 1967; Hall, 1981) that produced a spread of levels sufficient to define a sigmoidal 'frequency-of-seeing' curve. There was a short (5 s) break after 15 trials and a break of at least 2 min between each new frequency setting. The 4 sites were tested in separate counterbalanced sessions over 2 days, with 0° and 5° (in that order) examined on the first day, and 10° and 2.5° (also in that order) examined on the second day.

Visual fields for each subject were plotted using a 2 m Bjerrum screen.

Data analysis

A computer-based technique (Foster, 1986*a*) was used to analyse the data. A cumulative Gaussian curve was fitted to each set of frequency-of-seeing data by a maximum-likelihood procedure. Threshold was defined as the value of modulation depth corresponding to 50% detection. The SD of this threshold was estimated by a bootstrap technique (Foster and Bischof, 1987). Because there were significant deviations from normality in the distribution of patient thresholds, a conservative nonparametric approach was adopted to the analysis. Mann-Whitney U tests were used to assess the significance of differences in threshold between normal and patient groups and the significance of the trend in these differences over temporal frequency and eccentricity. In all cases, two-tailed tests were used to make comparisons.

RESULTS

Fig. 1 shows, at each eccentricity, threshold modulation depth as a function of temporal frequency. Thresholds for patients are plotted as individual data points and for normal controls as group means connected by solid lines, with the hatched area indicating ± 2 SD.

The results of the analysis of the difference between the patient and control groups at each frequency and eccentricity are shown in Table 2. At 0° and 2.5° eccentricity there was a significant difference in temporal modulation sensitivity between the patient and control groups at all frequencies, with rather greater losses occurring at the medium-to-lower temporal frequencies. At 5° eccentricity, the losses occurred at medium temporal frequencies only, and at 10° eccentricity there was no significant loss at any temporal frequency. A nonparametric test of the eccentricity dependence of the losses, evaluated over all temporal frequencies, showed a significant linear trend in the improvement with eccentricity ($z = -2.30$, $P < 0.02$, two-tailed test).

Measurement of visual fields revealed scotomata within the test region in only 3 patients. Case 2 had a central scotoma extending to 10° eccentricity and Case 5 had a relative central scotoma, also extending to 10° eccentricity. Case 4 had a relative paracentral scotoma extending from 2.5° to 10° eccentricity. Temporal-modulation sensitivity losses for these patients were as follows. Case 2 showed significant losses over all frequencies

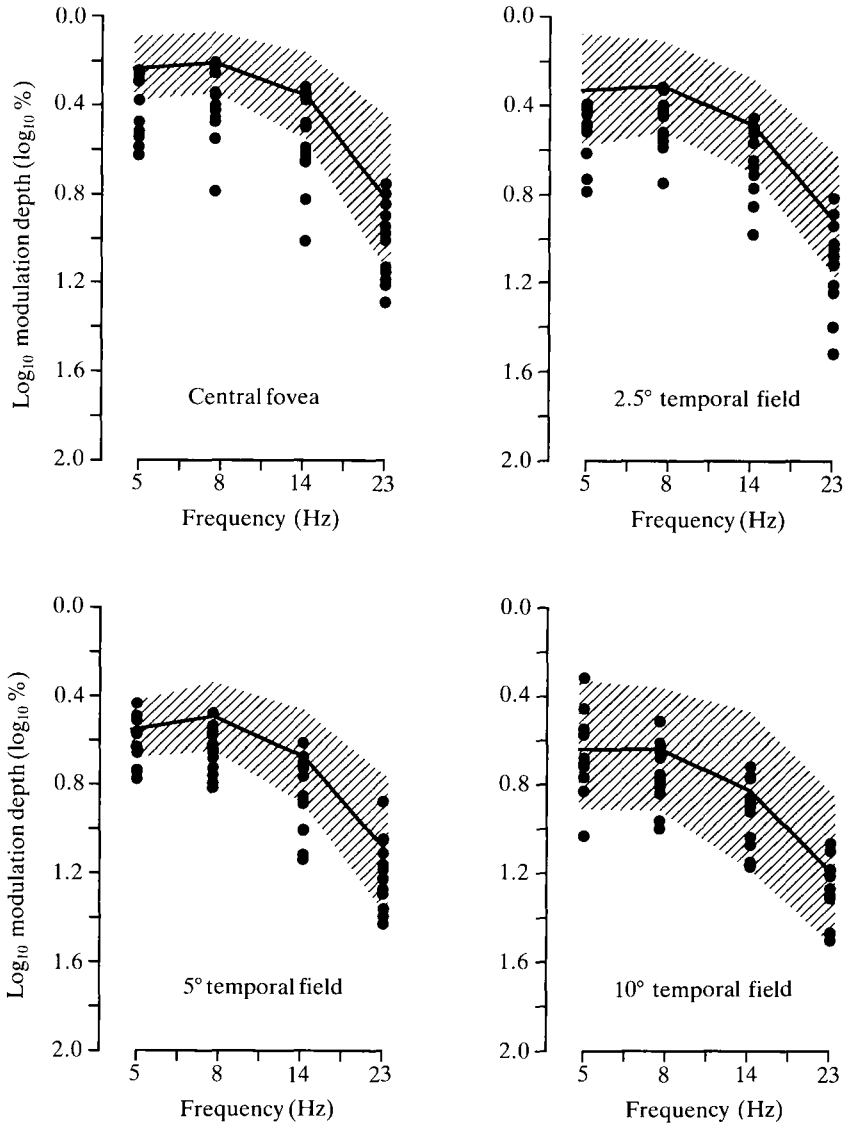

FIG. 1. Modulation sensitivity as a function of temporal frequency (de Lange attenuation characteristic) at 4 retinal eccentricities for patients with previous optic neuritis and for normal controls. Data points represent individual values for patients and the solid lines connect means for the control group, with ±2 SD shown by the hatched areas.

at 0°, but with increasing eccentricity these losses diminished, more rapidly at medium-to-high frequencies. Case 4 showed significant losses over all frequencies at both 0° and 2.5° eccentricities, and these losses also decreased with eccentricity. For Case 5, losses were confined to medium and high frequencies (8−23 Hz) and, at the higher frequencies, these losses also decreased with eccentricity.

TABLE 2. SUMMARY OF SIGNIFICANT DIFFERENCES IN MODULATION SENSITIVITY BETWEEN THE PATIENT AND CONTROL GROUPS AS A FUNCTION OF STIMULUS ECCENTRICITY AND TEMPORAL FREQUENCY

		Frequency (Hz)			
		5	*8*	*14*	*23*
Retinal eccentricity	0°	++	++	+	+
	2.5°	+++	+++	+	+
	5°	−	+++	+	−
	10°	−	−	−	−

(− = n.s., + = $P < 0.05$, ++ = $P < 0.02$, +++ = $P < 0.01$, two-tailed tests)

DISCUSSION

The results of this investigation clearly indicate systematic variations in the pattern of temporal-modulation sensitivity loss with retinal location in recovered optic neuritis. There was a general loss relative to normal controls at all temporal frequencies at 0° and 2.5° eccentricity, a loss restricted to medium temporal frequencies at 5° eccentricity, and no loss at any frequency at 10° eccentricity. These effects are compatible with the results of some animal models of demyelinating disease. Morphological studies (Tansey *et al.*, 1985) of fibres in the optic nerves of mice infected with Semliki Forest virus have suggested that smaller diameter fibres were more likely to be affected by demyelination. Because the average diameter of fibres is greater outside the fovea (Potts *et al.*, 1972; Sanchez *et al.*, 1986) and because these fibres are certainly capable of transmitting signals at higher temporal frequencies (Cleland and Levick, 1974; de Monasterio, 1978), the relative preservation in patients of high temporal-frequency modulation sensitivity at intermediate eccentricities (2.5° − 5°) and the preservation of sensitivity at all frequencies at larger eccentricities could be due to conduction by these less affected fibres.

A loss of function of small diameter fibres is consistent with the results of a study by Trauzettel-Klosinski and Aulhorn (1987) in which patients made brightness matches of a steady field to a flickering test field. The reduction in brightness at medium (5 − 15 Hz) temporal frequencies was concluded to be the result of selective damage to X-type fibres. It is not necessary to suppose that a particular temporal frequency channel, or fibre of a particular type, or particular retinal area is directly and preferentially affected in ON and MS (Foster *et al.*, 1985), merely that conduction along small diameter nerve fibres is, because of their physical characteristics, more vulnerable to disruption by demyelinating lesions.

Although a particular psychophysical channel may not be directly affected in ON and MS, a psychophysical channel that was low pass (Plant and Hess, 1985; Medjbeur and Tulunay-Keesey, 1985), and that depended upon impulse transmission along small diameter fibres, might exhibit altered temporal modulation sensitivity. This alteration could result (1) from a decrease in the overall sensitivity of the channel as a consequence of conduction block reducing the number of active fibres serving a given area of the retina, and (2) from a change in the shape of the temporal response characteristics, which

could become increasingly low-pass as transmission of high frequency impulses was impaired. The effect of the second mechanism would be to modify the overall attenuation characteristic so that there was a loss in sensitivity at medium temporal frequencies, as was found in this study. Given the general increase in fibre diameter with increase in retinal eccentricity, the effect of demyelination would be greatest in the fovea where, it seems likely, the responses of all psychophysical channels are mediated by smaller diameter fibres (Potts *et al.*, 1972; Perry *et al.*, 1984; Sanchez *et al.*, 1986; Cowey *et al.*, 1989). In this region, losses in temporal modulation sensitivity should extend over a greater range of temporal frequencies, as was also found here.

Classically, localized visual sensitivity loss has been assessed by kinetic perimetry. Visual field measurements of patients during acute ON showed central scotomata to be present in the large majority of cases (Nettleship, 1884; Hyllested and Møller, 1961). In recovered ON, however, the proportion of patients with central scotomata is reduced. Perkin and Rose (1979) found that one-third of patients with recovered ON had evidence of a central scotoma, whereas Patterson and Heron (1980) in a study of 54 patients with MS or recovered ON found the commonest visual field defect to be an arcuate scotoma.

A number of studies have used different techniques to examine the variation of temporal responsiveness with retinal eccentricity in patients with ON and MS. These studies include those of Miles (1951) who measured the variation of CFF over the visual field, Galvin *et al.* (1976) who measured two-flash resolution and relative perceptual latency, and Brussell *et al.* (1981/82) who used a multiflash campimetry technique (altering the duty-cycle of a light flickering at 5 Hz until flicker could just be detected) to measure temporal resolution. A common finding in these studies was of 'islands' of poorer performance in the visual fields of patients, although these islands were not necessarily correlated over different temporal functions (Galvin *et al.*, 1976; Snelgar *et al.*, 1985), or with obvious retinal structures. It does not follow that these patchy losses need be directly related to more systematic losses in temporal modulation sensitivity with retinal eccentricity. In ON, demyelination may affect the full thickness of the nerve (Ulrich and Groebke-Lorenz, 1983) but, because of the topography of plaques (Fog, 1965), the length over which demyelination affects transmission will vary over the nerve section. The only data in the present study bearing on a possible relationship between field losses and eccentricity-dependent changes in temporal modulation sensitivity come from the 3 patients who had field defects within the test region. Two had scotomata extending from the fovea to 10° eccentricity and the third had a paracentral scotoma extending from 2.5° to 10° eccentricity. Each of these 3 patients showed losses in modulation sensitivity that diminished with eccentricity, most rapidly at medium-to-high temporal frequencies.

If, as suggested, the results of the present investigation may be attributed to a greater effect of demyelination on small diameter fibres, then it might be expected that patients with ON and MS would show losses of spatial contrast sensitivity that also diminished with eccentricity. Contrast sensitivity determined with high spatial-frequency gratings, thus assessing acuity, should be most affected. Plant and Hess (1987) used circular patches

of sinewave gratings (2.5° in diameter) counterphase sinusoidally modulated at 8 Hz to measure threshold contrast sensitivity at a number of eccentricities, up to 7.5°, within the central visual field of patients with recovered ON. For medium-to-low spatial frequencies, they found no variation in sensitivity, relative to control subjects, over this region of the field. When spatial-frequency performance was extrapolated, however, to yield estimated acuity losses, they found that at the largest eccentricities there was a significant reduction in the impairment. A factor contributing to the absence of eccentricity-dependent losses at lower spatial frequencies may have been the choice of temporal frequency of modulation. In the present measurements, the threshold deficit was found to vary most rapidly with eccentricity at the lowest temporal frequency of 5 Hz.

An effect of demyelination related to fibre size may also have implications for variations in colour vision in ON and MS. There is evidence that chromatic function is mediated by smaller diameter fibres that project to the parvocellular layers of the lateral geniculate nucleus (Perry *et al.*, 1984; Livingstone and Hubel, 1987). If smaller diameter fibres are more affected by demyelination, then colour vision losses should be greatest in the fovea and should diminish with eccentricity, a prediction which is consistent with common reports in ON of a central or relative central scotoma with an associated loss in colour perception (Gunn, 1897; Burde and Gallin, 1975; Glaser, 1976). Whether losses in chromatic sensitivity are observed to be greater than losses in luminance sensitivity depends on a number of factors. With small (0.25°) centrally located stimulus fields, chromatic losses have been found to be indistinguishable from luminance losses (Foster *et al.*, 1985), both systems there presumably being subserved by fibres with similar small diameters (*see* Travis and Thompson, 1989, for related arguments). With medium-to-large stimulus fields (2°−6.5°), where there is more scope for variation in fibre diameter spectra and the possibility of obtaining responses at lower spatial frequencies, greater losses in chromatic sensitivity have been recorded (Fallowfield and Krauskopf, 1984; Mullen and Plant, 1986). Discussion of some of the technical issues has been given in Foster (1986*b*) and Plant (1990).

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Erratum

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VISUAL LOSS IN MULTIPLE SCLEROSIS AND ITS RELATION TO PREVIOUS OPTIC NEURITIS, DISEASE DURATION AND CLINICAL CLASSIFICATION

by W. P. HONAN, J. R. HERON, D. H. FOSTER, G. K. EDGAR, M. O. SCASE *and* M. F. COLLINS

Two lines of text were inadvertently omitted at proof correction stage at the bottom of the first page of the above article. The publishers regret any inconvenience caused. The missing lines are printed below:

proportion of cases: one series (Matthews *et al.*, 1977) reported abnormal VEPs in 5% of suspected MS cases. Duration of disease may be an important factor in this category.