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Optic neuritis
Differential losses of luminance and chromatic function near a scotoma

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Summary
Visual sensitivity to achromatic and chromatic stimulus flashes was determined at sites just inside, on the boundary and just outside scotomata in 11 patients with recovered optic neuritis. The colour of the flashes and the size of the steady background on which they appeared were such that detection was more likely to be mediated by either the large-diameter, magnocellular fibres or the small-diameter, parvocellular fibres of the anterior visual pathway. The spacing of the test sites ranged from 0.5° to 4° visual angle, depending on the shape and location of the scotomata. The greatest differences in sensitivity were between sites just inside and just outside the scotomata and in response to achromatic stimuli more likely to involve the magnocellular fibres. This effect may be due to the size of magnocellular fibres or to their relatively smaller numbers.

Key words: optic neuritis; demyelination; luminance and chromatic thresholds; scotomata; magnocellular; parvocellular

Introduction
Optic neuritis refers ordinarily to an acute, commonly self-limiting syndrome, characterized clinically by the rapid failure of visual acuity and colour vision in association with a central scotoma and periocular pain. Pathologically it is associated with the finding of demyelination of the optic nerve. During the recovery period, the visual field defect shrinks in size, often leaving a small central or paracentral scotoma or enlarged blind spot (Perkin and Rose, 1979; Honan *et al.*, 1990) or arcuate scotomata (Patterson and Heron, 1980). In addition to these scotomata, significant subclinical deficits may be revealed by psychophysical or evoked-potential methods (*see*, for example, reviews in Hess and Plant, 1986; Foster, 1991; and by McDonald and Barnes, 1992), the nature of the losses reflecting the distribution and severity of the lesions in the optic nerve and tract and more central visual pathways.

The experimental investigation of the relationship between changes in visual function and demyelination has been complicated by the variability (Patterson *et al.*, 1980) and patchiness of the losses over the visual field (Galvin *et al.*, 1976; Honan *et al.*, 1990). The size and location of the stimulus may be critical: large-field stimuli may give diluted responses, representing activity of both affected and unaffected nerve fibres, and small well-localized stimuli may give responses which, although representing more specific effects on fibre activity, may confound variations in the severity of demyelination with natural variations in the distributions of fibre densities and of fibre diameters over

the retina. In one area of the retina, however, a more controlled approach to exploring the effects of demyelination may be possible; namely, in the region of a scotoma. A small stimulus placed just outside the scotoma, then on its boundary and then just inside the scotoma (as illustrated in Fig. 1) will selectively involve nerve fibres that are progressively more affected by demyelination, over a region of the retina where in the normal eye there would be little variation—depending on eccentricity—in the distributions of fibre densities and fibre diameters.

The anterior visual pathway can be divided anatomically and functionally into the magnocellular and parvocellular pathways (Hubel and Livingstone, 1987; Livingstone and Hubel, 1987*a,b*; Lee and Stromeyer, 1989; Merigan and Maunsell, 1990; Schiller *et al.*, 1990; Kolb, 1991; Merigan *et al.*, 1991; *see also* Russell *et al.*, 1991). The magnocellular pathway, which involves ~10% of the total number of optic-nerve fibres (Silveira and Perry, 1991), arises from large retinal ganglion cells (M-cells) with large, radiate, dendritic trees and projects via thick axons to the magnocellular layers of the dorsal lateral geniculate nucleus (LGN). The parvocellular pathway, which involves ~80% of the total number of optic-nerve fibres (the remaining 10% projecting to mid-brain structures), arises from small retinal ganglion cells (P-cells) with small, bushy, dendritic trees and projects via thin optic-nerve fibres to the parvocellular layers of the dorsal LGN. The magnocellular and parvocellular pathways also differ in their responses to time-varying stimuli, such as flicker or movement, but the general effects of demyelination on temporal responsiveness (Mason *et al.*, 1982; Plant and Hess, 1985; Snelgar *et al.*, 1985; Edgar *et al.*, 1990) may make the interpretation of selective effects difficult.

The magnocellular pathway has been assumed to subserve detection of luminance or achromatic stimuli of low-to-medium spatial frequency. The parvocellular pathway has been assumed to subserve detection of chromatic stimuli of low-to-medium spatial frequency and achromatic stimuli of high spatial frequency (Merigan and Maunsell, 1990; Merigan *et al.*, 1991); this pathway thus performs a 'double duty' (Ingling and Martinez-Uriegas, 1983, 1985; Merigan *et al.*, 1991), transmitting colour information under one condition and luminance information under another. Nevertheless, there is an overlap of function of the two pathways, and cortically the division is not completely maintained (Ferrera *et al.*, 1992).

In this study a technique was used for investigation of luminance and chromatic function in which a small (1° visual angle) circular stimulus flash of yellow or red light was presented on a steady yellow background field, which by edge-masking, controlled the effective sharpness of the stimulus boundary, and thereby its effective spatial-frequency spectrum (Foster *et al.*, 1985; Snelgar *et al.*, 1987). Although the spatial-frequency spectrum of such a stimulus is broader than a sine-wave grating stimulus of several degrees visual angle (e.g. Mullen, 1985; Mullen and Plant, 1986; Plant and Hess, 1987), it is the spatial extent and localization of the stimulus in relation to a scotoma that is particularly important here. The efficacy of the technique is considered later.

The boundary of the scotoma was first carefully mapped in each patient with recovered optic neuritis. Visual sensitivity to each of the stimuli was then measured just inside the scotoma, on its boundary and then just outside the scotoma. The greatest differences in sensitivity were found between sites just inside and just outside the scotoma and in response to achromatic stimuli that were effectively 'edgeless' (of medium-to-low spatial frequency), a result which suggests that, in the region of an optic-nerve lesion, demyelination may have a preferential effect on the large-diameter axons of the magnocellular pathway.

Methods

Subjects

Eleven patients were investigated, eight female and three male, with age range 24–39 years. Each had had an attack of optic neuritis in at least one eye, but no patient was in an acute phase of the disease at the time of testing (at least 6 weeks since the last optic neuritis attack) and none had nystagmus. Patients were classified according to the criteria of McDonald and Halliday (1977), with isolated optic neuritis accepted as an additional diagnostic category. Clinical details are given in Table 1. One eye only of each patient was tested, and patients wore their own spectacles, if necessary.

The research followed the tenets of the Declaration of Helsinki concerning human subjects. Informed consent was obtained from each patient after the nature and consequences of the study were explained. The research was approved by the Local Ethical Committee.

Stimuli and apparatus

Sensitivity to the stimulus light flash was measured by its increment threshold, i.e. the luminance of the flash when it was just detectable. Increment thresholds were obtained for three stimulus conditions: (a) a circular red flash of 1° angular subtense, presented on a coextensive, steady, yellow background; (b) a circular yellow flash of 1° angular subtense presented on the same coextensive, steady background; (c) a circular yellow flash of 1° angular subtense presented on a larger, concentric, yellow background of 5° angular subtense. The duration of the flash was 200 ms and the luminance of the background was fixed at 2 log cd/m^2 ($\log_{10}$ units throughout). The peak-emission wavelength of the red light was 640 nm, and of the yellow light 584 nm. All the stimuli were presented in the centre of a large, steady, rectangular, 'conditioning' field, 40° W×24° H, luminance 1 cd/m^2, which maintained a constant state of retinal adaptation.

A purpose-built perimeter system with moveable clusters of light-emitting diodes (Marl, UK) driven by a digital-electronics system under the control of a laboratory computer (Edgar *et al.*, 1990) produced the stimuli. Viewing was

Table 1 *Summary of clinical data*

Case	Age (years)	Sex	Snellen acuity	Near vision acuity	Colour vision*	Classification	Scotoma	Centre of test site† (degrees)
1	39	F	6/60	>N45	N/D	Clinically definite	Absolute central	3.5, 0.0
2	34	F	6/12	N12	N	Clinically definite	Absolute arcuate	20.0, 193.0
3	32	M	6/9	N9	N	Clinically definite	Relative central	11.0, 0.0
4	33	F	6/6	N4.5	N	Clinically definite	Absolute paracentral	1.0, 180.0
5	34	F	6/36	N18	N	Clinically definite	Absolute hemianopia	5.0, 20.0
6	34	M	6/5	N4.5	N	Clinically definite	Relative arcuate	10.0, 0.0
7	24	F	6/12	N8	N	Clinically definite	Relative hemianopia	5.0, 105.0
8	27	F	6/5	N4.5	N	Clinically definite	Relative arcuate	12.0, 90.0
9	29	M	6/9	N4.5	M	Early probable	Relative hemianopia	8.0, 90.0
10	24	F	6/4	N5	N	Early probable	Absolute arcuate	12.0, 90.0
11	27	F	6/24	N4.5	N	Optic neuritis	Absolute caeco-paracentral	15.0, 240.0

*Colour vision: N = normal; D = deuteranope; M = mixed deuteranope and protanope; †eccentricity from fovea, azimuth anticlockwise from horizontal.

monocular, and the eye not being tested was occluded. Head position was stabilized with an adjustable headrest. A small, red, light-emitting diode provided a fixation target. Measurements were made in an otherwise darkened room.

On the basis of the studies previously cited (*see also* Foster, 1981; Foster and Snelgar, 1983; Nacer *et al.*, 1989), it was assumed that the red flash on the coextensive yellow background defined an effectively edgeless (low-to-medium spatial-frequency) chromatic stimulus, detection of which was more likely to be mediated by the parvocellular pathway; the yellow flash on the coextensive yellow background defined an effectively edgeless (low-to-medium spatial-frequency) achromatic stimulus, detection of which was more likely to be mediated by the magnocellular pathway; and the yellow flash on the larger yellow background defined a sharp-edged (high spatial-frequency) achromatic stimulus, detection of which was more likely to be mediated by the parvocellular pathway. These assumptions refer only to biases in the expected distributions of responses; no stimulus was assumed to be exclusive to a particular pathway.

Preliminary visual assessment

For each patient, measurements were made of far visual acuity (Snellen Chart), near visual acuity (Faculty of Ophthalmologists Near Vision Test Type) and colour vision (The City University Test; Fletcher, 1980). The extent and location of the scotomata in one eye of each patient were determined by a plot of the visual field on a Bjerrum screen viewed at a distance of 2 m. The mean luminance of the screen was 0.5 log cd/m^2. The more affected eye was chosen for investigation except in one patient who could only perceive light in the more affected eye. Three different stimulus discs were used for plotting (Patterson and Heron, 1980): a 5 mm white disc, of luminance 2.1 log cd/m^2, to demarcate the blind spot and to determine a luminance isopter; a 2 mm white disc, also of luminance 2.1 log cd/m^2, to determine a second luminance isopter; and a two-sided red-and-green 5 mm disc, of luminance 1.8 log cd/m^2 (red) and 1.7 log cd/m^2 (green), to determine a chromatic isopter.

Scotomata were classified by position (central, paracentral, arcuate or hemianopia) and by severity (relative or absolute). The term 'relative' was used for scotomata in which visual sensitivity was impaired to the extent that the patient complained of 'dull vision' or 'fading'. The term 'absolute' was used for scotomata in which visual sensitivity was impaired to such an extent that the patient complained of areas of blindness and was unable to detect the stimuli used in the Bjerrum-screen mapping. Results are summarized in Table 1. Notice that absolute and relative scotomata were defined only with respect to the mapping stimuli; as is shown later, sufficiently intense stimulus flashes could be detected when placed close to the boundary of the scotomata.

Perimetric increment thresholds

Increment thresholds were determined at three sites near a scotoma according to the Bjerrum-screen measurements: just inside (site 1), at the boundary (site 2), and just outside (site 3) (Fig. 1).

The three sites were positioned radially or tangentially (with respect to the visual field) depending on their distance from the fovea and the shape of the scotoma. Their spacing was guided by the luminance and chromatic isopters: site 2 was positioned on the 5 mm luminance isopter, site 3 between the 2 mm luminance isopter and the more-distant chromatic isopter (except when the scotoma was central), and site 1 an equal distance on the other side of the 5 mm luminance isopter. (It was not assumed that function at site 3 just outside the scotoma was necessarily normal.) For example, for patient 3, the sites were on the horizontal meridian (azimuth 0°) with eccentricities of 9°, 11° and 13°; and, for patient 4, the sites all had constant eccentricity (1°) and azimuths of 150°,

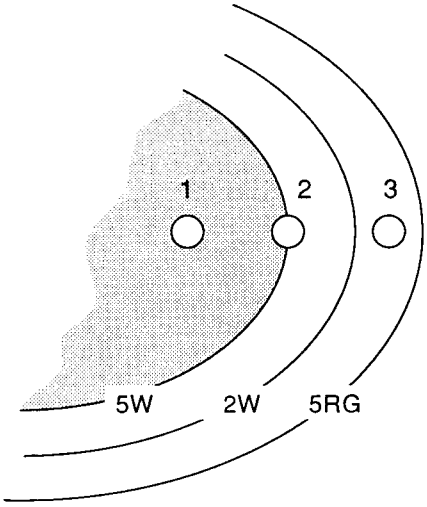

Fig. 1 Illustration of the positions of three stimulus test sites (1) just inside the scotoma (shaded region), (2) on the boundary, (3) just outside the scotoma, in relation to the luminance and chromatic isopters: 5W, 5 mm white; 2W, 2 mm white; 5RG, 5 mm red–green. The separation of the test sites ranged from 0.5° to 4° visual angle, depending on the shape and location of the scotoma (*see* Table 1).

180° and 210°. The separations of the test sites ranged from 0.5° to 4° visual angle, depending partly on eccentricity.

Since the stimuli were located in relation to the three perimetric isopters, the test sites were appropriately matched to the structure of the scotoma, independent of whether it had a sharply defined boundary or whether it was uniform.

The patient sat in a chair of adjustable height and placed the eye to be tested against the eye-cup of the viewing system. Because of the angular eccentricity of the stimuli, an artificial pupil was not used. The patient fixated the fixation target and initiated each trial by pressing a push-button switch connected to the computer. Patients were capable of maintaining good fixation, for in addition to none having nystagmus, each was able to demarcate the blind spot in the original Bjerrum-screen testing; moreover, as is shown later, significant differences in stimulus sensitivity were obtained at the three sites, a result which would have been impossible with poor fixation.

A modified sequential-testing procedure (PEST) (Taylor and Creelman, 1967; Hall, 1981) was used to obtain increment thresholds for each of the three stimulus conditions (a)–(c) at each of the three sites (*see under* Stimuli and apparatus). The site inside the scotoma was tested first, then the site on the boundary and then the site outside the scotoma. There were 30 stimulus trials (with five empty 'catch' trials randomly interleaved) for each condition: in each trial the patient reported (forced-choice) whether the stimulus was seen. The luminance of the stimulus was determined by the PEST procedure, which produced a spread of testing levels sufficient to define a sigmoidal 'frequency-of-seeing' curve, the analysis of a result which is described shortly.

Each patient was familiarized with the testing procedure in a sequence of practice trials at the beginning of the experimental session. To offset the possibility of fatigue, a short (5 s) break was given half-way through each set of 35 trials, and a longer break (of at least 2 min) at the end of the 35 trials. The temperature of the patient and of the room were recorded at the beginning and end of the testing session to control for temperature-dependent variations in visual function (Davis, 1966; Namerow, 1971).

Data analysis

A computer-based technique was used to analyse the raw data. A cumulative Gaussian curve was fitted to each set of frequency-of-seeing data by a maximum-likelihood procedure (Foster and Bischof, 1991). Increment threshold was defined as the luminance value of the stimulus flash that corresponded to 50% seeing. The standard deviation of this threshold value was estimated by a bootstrap technique (Foster and Bischof, 1991). Differences in mean thresholds at each site were assessed statistically with paired t tests.

Results

For each patient, differences in thresholds for sites inside and outside the scotoma (sites 1 and 3) and for sites on the boundary and outside the scotoma (sites 2 and 3) were obtained for each of the three stimulus conditions governing spatial and chromatic responses: (a) a red flash on a coextensive yellow background; (b) a yellow flash on a coextensive yellow background; (c) a yellow flash on a larger, concentric, yellow background.

Over the patient group as a whole, these threshold differences were statistically distributed not significantly different from normal for each of the various conditions ($\chi^2 = 39$, d.f. $= 30$, $P > 0.1$); the means of the differences and their standard errors are shown in the bar graph of Fig. 2 for each pair of sites and stimulus condition.

Thresholds on the boundary and inside the scotoma were, on average, higher than those outside the scotoma in all three stimulus conditions. Except in two conditions, however, none of the elevations in threshold reached significance ($t \leqslant 1.3$, d.f. $\geqslant 10$, $P > 0.1$). The exceptions were in the elevation in threshold inside the scotoma compared with the threshold outside for the yellow flash on the large background (difference 0.10 log unit; $t = 2$, d.f. $= 11$, $P < 0.05$), and for the yellow flash on the coextensive background (difference 0.24 log unit; $t = 3.1$, d.f. $= 10$, $P < 0.01$). The variation in this elevation with eccentricity of the test site did not reach significance ($t = 1.9$, d.f. $= 8$, $P > 0.05$).

Discussion

Early investigations of the specificity of luminance and chromatic losses in demyelinating disease produced apparently conflicting findings: greater luminance losses than chromatic losses (Zisman *et al.*, 1978; Alvarez *et al.*, 1982);

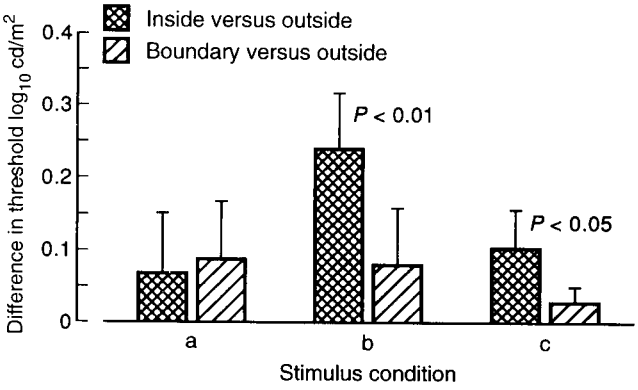

Fig. 2 Mean differences in threshold for detection of a 200 ms flash of light presented at sites (1) just inside, (2) on the boundary and (3) just outside a scotoma (*see* Fig. 1) in 11 patients with recovered optic neuritis. The three stimulus conditions were (a) a red flash presented on a coextensive yellow background; (b) a yellow flash presented on a coextensive yellow background; (c) a yellow flash presented on a larger, concentric, yellow background. The luminance of the background was 2 log cd/m^2. The vertical bars show 1 SEM.

approximately equal luminance and chromatic losses (Foster *et al.*, 1985); and greater chromatic losses than luminance losses (Fallowfield and Krauskopf, 1984; Mullen and Plant, 1986). The reasons for the disparities have been reviewed elsewhere (Foster, 1986; Plant, 1991), and subsequent studies (Travis and Thompson, 1989; Dain *et al.*, 1990; Grigsby *et al.*, 1991; Russell *et al.*, 1991) were more in agreement, and consistent with the suggestion (Foster *et al.*, 1985) that losses of luminance and chromatic function were on average equal, at least in the central fovea.

It has been proposed that the fibres of the optic nerve subserving the foveal region are more susceptible to metabolic disturbances, because of their smaller diameters and denser packing (Potts *et al.*, 1972; Ogden, 1984; Reese and Ho, 1988; Naito, 1989; Jonas *et al.*, 1990), although this group of axons has no definitive border (Reese and Ho, 1988; Naito, 1989; Plant and Perry, 1990). Post-mortem histological investigation (Gartner, 1953) of the optic nerves of patients with optic neuropathy in multiple sclerosis has shown that the atrophied areas included large portions of the foveal outflow bundle, although they were not confined to it. These small-diameter fibres would predominantly subserve both luminance and chromatic function in the central fovea. Hence, independent of the detailed spatial-frequency spectrum of the stimulus, luminance and chromatic sensitivities should, on average, be affected similarly. In contrast, the greater range in the diameters of fibres arising from more peripheral regions of the retina (Potts *et al.*, 1972; Ogden, 1984; Reese and Ho, 1988; Jonas *et al.*, 1990) might make the detection of any selective effects of demyelination more easy there (Foster *et al.*, 1985; Plant, 1991).

In the present study, the regions of the scotomata investigated were indeed mainly extrafoveal. The results of the measurements of luminance and chromatic function at sites just inside, on the boundary and just outside the scotomata showed the largest differences in sensitivity between the inside and outside sites for achromatic stimuli that were effectively edgeless (of medium-to-low spatial frequency). Smaller differences in sensitivity–all but one not statistically significant–were found between the inside and outside sites and between the boundary and outside sites for achromatic stimuli with sharp edges (of high spatial frequency) and chromatic stimuli that were effectively edgeless (of low-to-medium spatial frequency). On the basis of the data summarized earlier, this result appears to suggest that demyelination may have a greater effect on the large-diameter axons of the magnocellular pathway than on the small-diameter axons of the parvocellular pathway. There is, however, an alternative explanation of the largest differences in sensitivity being associated with effectively edgeless achromatic stimuli. These stimuli are the only ones that involved no change in spatial-frequency content and no change in colour with respect to the coextensive steady yellow background. It might be argued, therefore, that they were more difficult to detect, particularly if vision was impaired. But any variations in detectability due to stimulus condition were offset by the calculation of *differences* in sensitivity (or threshold) between the sites for each condition. Moreover, the effectively edgeless achromatic stimulus still involved a change with respect to the steady yellow background; namely, in low-to-medium spatial-frequency content.

If there is a preferential effect of demyelination on the large-diameter fibres of the magnocellular pathway, its cause is unclear. Fibre diameter is a possible factor, but the evidence is complicated. An animal model of demyelination based on the Semliki Forest Virus (SFV) in the mouse (Fleming *et al.*, 1982; Tansey *et al.*, 1985) led to the proposal that small- rather than large-diameter fibres are more affected by the disease process. The distributions of fibres in the optic nerve are, however, different in the mouse and human. In SFV-infected mice, demyelination was found to predominantly affect the small-diameter fibres at the periphery of the optic-nerve trunk, where there were large blood-vessels (Tansey *et al.*, 1985); in the monkey, large-diameter fibres are more common around the circumference than towards the centre, at all points along the optic nerve except immediately behind the eye (Reese and Ho, 1988; Naito, 1989).

Evidence for the vulnerability of large-diameter fibres has been found in some other conditions affecting the anterior visual pathway. In glaucoma, there appear to be preferential losses of large-diameter axons in the human (Quigley *et al.*, 1988; Silverman *et al.*, 1990) and monkey (Quigley *et al.*, 1987) optic nerve, although there has been a suggestion that these losses may involve both P and M pathways (Smith *et al.*, 1993). Pressure block has also been found to affect preferentially large-diameter fibres in the optic nerve of the cat (Burke *et al.*, 1986), but pressure due to a subchiasmal

tumour in the macaque monkey was shown to affect small-diameter fibres (Reese and Cowey, 1989).

Another possible cause of a preferential effect of demyelination on magnocellular fibres may be related simply to absolute fibre number. The proportion of M-ganglion cells varies from ~10% of the total to 15–20% in the more peripheral nasal retina (Silveira and Perry, 1991). Given that demyelination can affect large portions of the optic nerve (Ulrich and Groebke-Lorenz, 1983), a substantial loss of conducting fibres could, by chance alone, reduce the number of magnocellular fibres to a level below that necessary for reliable signal transmission from an affected region of the retina.

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