Correlation of MRI lesions with visual psychophysical deficit in secondary progressive multiple sclerosis

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Summary
The aim of this work was, first, to clarify the nature of the relationship between the sensory deficit in the demyelinated visual pathway and morphological changes revealed by MRI and, secondly, to test whether there was a preferential effect of demyelination for either the magnocellular or parvocellular pathway in established multiple sclerosis. Twenty-four patients with secondary progressive multiple sclerosis were studied psycho-physically and by MRI of the optic nerve and brain. MRI was performed with a Phillips (0.5T) scanner. Visual pathway MRI lesion load was evaluated independently using the total optic nerve lesion length and lesion area seen on STIR (short inversion time inversion recovery) images of the optic nerve and the total post-chiasmal lesion area on T1-, T2- and proton-density-weighted images of the brain. Psychophysical tests determined 75%-seeing thresholds for horizontal gratings consisting of isoluminant red and green sinusoids of the same spatial frequency combined out-of-phase for preferential stimulation of the parvocellular system and in-phase for preferential stimulation of the magnocellular system. It was found that, in this group of patients, visual psychophysical loss was significantly correlated with lesion area seen on proton density MRI sequences of the post-chiasmal visual pathway, and that the parvocellular pathway was more affected than the magnocellular pathway, especially at lower spatial frequencies.

Keywords: multiple sclerosis; MRI; visual psychophysics; magnocellular/parvocellular; chromatic

Abbreviations: EDSS = Kurtzke Expanded Disability Status Score; FOV = field of view; PEST = parameter estimation by sequential testing; STIR = short inversion time inversion recovery

Introduction
The visual pathway is one of the most commonly affected sites in multiple sclerosis (McDonald and Barnes, 1992). A spectrum of pathology exists, ranging from acute optic neuritis with relatively sudden loss of vision to subtle subclinical disturbance evident only on neurophysiological or psychophysical testing. The relationship between functional disturbance of the visual system and structural abnormality in established multiple sclerosis is unclear.

At present, MRI is the optimum technique for the identification of multifocal white matter lesions in the brain in multiple sclerosis in vivo (Young et al., 1981; Ormerod et al., 1987; Miller, 1997). Such lesions are thought to represent plaques of inflammation, demyelination, oedema or gliosis (Ormerod et al., 1986, 1987; Hawkins et al., 1990). Additionally, MRI has been used in optic neuritis and multiple sclerosis to identify abnormalities in the optic nerve (Miller et al., 1988; Barkhof et al., 1991; Youl et al., 1991; Davies et al., 1998) and post-chiasmal visual pathway (Hornabrook et al., 1992; Plant et al., 1992).

Involvement of the visual system in multiple sclerosis was...
noted as early as 1890 by Uhthoff and subsequently in large case series (Poser et al., 1979; Perkin and Rose, 1979). Abnormality of the visual evoked response (Halliday et al., 1973) and histological study of the optic nerve and post-chiasmal pathway (Ulrich and Groebke-Lorenz, 1983) have also identified visual pathway pathology. Studies in acute optic neuritis using STIR (short inversion time inversion recovery) images with gadolinium-DTPA enhancement have suggested that blood–brain barrier breakdown associated with inflammation is the predominant cause of functional deficit (Youl et al., 1991). Treatment with steroids did not appear to influence visual outcome or lesion length measured on optic nerve STIR images (Beck and Cleary, 1993; Kapoor et al., 1998).

Visual psychophysics offers an established, sensitive approach to detecting and measuring disturbance in the different modalities of vision, the results of which may be interpreted in terms of the underlying anatomy and physiology. Anatomical studies show a division of the anterior human visual system into magnocellular and parvocellular pathways (Shapley, 1990). The magnocellular pathway contains ~10% of optic nerve fibres (Silveira and Perry, 1991) and is involved in the detection of achromatic stimuli of low-to-medium spatial frequency. The parvocellular pathway contains ~80% of optic nerve fibres and is involved in the detection of chromatic stimuli of low-to-medium spatial frequency and achromatic stimuli of high spatial frequency (Ingling et al., 1983; Merigan et al., 1991). The parvocellular pathway is thought to provide the substrate for opponent signals from red- and green-sensitive cones. [A third pathway, the koniocellular pathway (Casagrande, 1994), may provide the substrate for signals from blue-sensitive cones.] The temporal responses of the magnocellular and parvocellular pathways differ: the magnocellular pathway is more sensitive at high temporal frequencies and the parvocellular pathway at low temporal frequencies. The difference in temporal response may, however, be partly confounded by the general effects of demyelination, in that if demyelination acts simply as a low-pass filter, then all high-frequency responses will be attenuated independently of fibre type (Mason et al., 1982; Plant and Hess, 1985; Snelgar et al., 1985; Herbst et al., 1997; Vleugels et al., 1998). Although initially well defined, there are conflicting reports as to whether the pathways remain segregated cortically (DeYoe and Van Essen, 1988; Maunsell et al., 1990, 1999; Baizer et al., 1991; Regan et al., 1991; Ferrera et al., 1992; Nealey and Maunsell, 1994).

MRI is currently used as a putative surrogate marker of pathophysiological change in multiple sclerosis. A recent study in established multiple sclerosis has shown a correlation between optic nerve lesion load on MRI and abnormality of the visual evoked potential (Davies et al., 1998). Morphological change in the visual pathway on MRI may thus prove useful in interpreting other measures of visual dysfunction. Twenty-four patients with secondary progressive multiple sclerosis were therefore studied by visual psychophysics and by MRI of the optic nerve and brain to compare functional deficit with structural abnormality in the visual system.

Methods

Patients and controls

The study was approved by the ethical committee of the North Staffordshire Hospital and informed consent was obtained from all subjects. Patients included in the study had clinically definite secondary progressive multiple sclerosis of at least 2 years duration as defined by the Poser criteria (Poser et al., 1983). Patients were aged 18–55 years and had a Kurtzke Expanded Disability Status Score (EDSS) of 2.5–6.0 and no past history of serious eye disease or diabetes mellitus. There was no history of steroid treatment or other immunotherapy in the 2 months before the study. The study included seven male and 17 female patients with a mean age of 40.5 years (range 24–53 years), mean disease duration of 11 years (range 3–24 years) and a mean Kurtzke EDSS score of 5.0. Five patients (eight eyes) had a previous history of acute unilateral optic neuritis in the course of their illness. The mean duration since the last attack of optic neuritis was 11.9 years (range 4–23 years). Twenty-three healthy age- and sex-matched volunteers were also studied to provide a control population for visual psychophysics.

Ophthalmic examination

Snellen acuity was obtained for each eye at 6 m in standard lighting. Visual fields were obtained for each eye in all patients by clinical confrontation and centrally using a Bjerrum screen. Colour vision was tested monocularly with Ishihara pseudoisochromatic plates, and pupil reactions were also tested. Full slit-lamp examination was performed to exclude corneal, lenticular and media opacities. The fundus was examined using direct and indirect fundoscopy.

Snellen acuity was 6/9 or better in 45 out of 48 eyes (93%), and it was 6/9 or better in the eight eyes with previous acute optic neuritis. Visual field testing demonstrated small arcuate scotomata in 16 out of 48 eyes (33%) in a pattern that has been described previously (Patterson and Heron, 1980). Scotomata were all outside the central 15° of central vision. Only two out of these 16 eyes had a previous history of acute optic neuritis. Colour vision was mildly impaired in seven out of 48 eyes (15%; 3–4 Ishihara plates incorrect out of 21); moderately impaired in two out of 48 eyes (4%; 5–10 plates incorrect out of 21) and severely impaired in one eye (>10 plates incorrect). Colour vision was abnormal in five out of eight eyes with previous optic neuritis. A relative afferent pupillary defect was not seen in any of the 48 eyes and optic disc pallor was apparent in only four out of 48 eyes.

MRI and visual pathway lesion analysis

A Phillips 0.5 Tesla Gyroscan was used for all imaging. The patient’s head was positioned comfortably in a head holder
to minimize movement. A sagittal pilot scan was performed (TR 300–500 ms, 128 matrix excitation) with the inter-hemispheric fissure used as the initial landmark. Positioning of the patient was corrected for ear-to-shoulder tilt in the coronal sections and right-to-left rotation on axial sections. Optic nerve imaging used a coronal STIR sequence (IR 1400/140/25) to identify lesions within the optic nerve. The STIR sequence consisted of 12 contiguous 4 mm slices with a 1 mm interslice gap, a field of view (FOV) of 20 cm, with two acquisitions, obtained sequentially anterior to posterior from the optic nerve papilla to the optic chiasm.

Imaging of the post-chiasmal pathway used axial T1-weighted (SE 550/10), conventional T2-weighted (SE 2760/80) and proton-density-weighted (SE 2760/20) brain images to show the post-chiasmal pathway from the optic tract anteriorly to the visual cortex posteriorly. These images were obtained as contiguous axial 5 mm slices with an interslice gap of 0.5 mm and FOV of 23 cm. Two acquisitions were used for the T1-weighted sequences and one acquisition for the variable echo sequences. The post chiasmal pathway was identified by a neuroradiologist (N.H.) on relevant axial brain images for each sequence using recognized landmarks (Miller, 1982) and subsequently divided anatomically into the optic tracts, the lateral geniculate nuclei, the optic radiations and the projections to the primary visual cortex.

Subsequently, a neuroradiologist (N.H.) and MRI research fellow (M.B.D.) independently identified lesions within the visual pathway on MRI unaware of the patient’s identity and history. Lesions involving the optic nerve or post-chiasmal pathway on MRI were only scored when agreed by both assessors and were marked on hardcopy before quantitative analysis.

Involvement of the optic nerve on coronal STIR images was defined as an abnormal focal area of high signal originating within the optic nerve (Fig. 1). Quantitative analysis of optic nerve involvement on STIR involved measurement of total optic nerve lesion area (total area of optic nerve high signal abnormality measured on coronal images). A computer-assisted manual outlining package was used (by M.B.D.) to outline the area of abnormal signal in each involved optic nerve on coronal images. These areas were then summed to give the total lesion area within that optic nerve. It was assumed that the high signal abnormality on STIR sequences was due to involved optic nerve rather than to cerebrospinal fluid in the optic nerve sheath. A small interslice gap was used and it was assumed that abnormality on adjacent slices traversed the interslice gap.

Because of limited image resolution, it was difficult to identify chiasmal lesions clearly on coronal optic nerve STIR images and on axial brain images, and, therefore, chiasmal involvement could not be assessed accurately in this study. Involvement of the post-chiasmal pathway on MRI was defined on axial images as discrete areas of hypointensity on T1-weighted images and discrete areas of high signal on T2-weighted and proton-density-weighted images identified within the optic tract, the lateral geniculate nucleus, the optic radiations and the projections to the visual cortex (Fig. 2). A computer-assisted manual outlining package was used as before (by M.B.D.) to identify lesions within the post-chiasmal pathway on each sequence. Their areas were calculated and then summed to give the total post-chiasmal pathway lesion area.

The intra-operator reproducibility of optic nerve STIR and post-chiasmal quantitative area measurement was assessed as part of the study. A single observer performed the initial analysis of the whole patient cohort (M.B.D.) and the same observer subsequently quantified the lesion area in 10 randomly selected patients more than a year later. Statistical analysis of intra-observer reproducibility was calculated using a previously described methodology (Filippi et al., 1995).

**Psychophysics**

A visual stimulus in the form of a sinusoidal grating was presented on a 20 inch monitor (Sony, Japan; Trinitron). The stimulus was created with a raster-graphics generator (Cambridge Research Systems, UK; VSG, version 2/2, with Psycho software version 4.3), controlled by a laboratory computer. The grating appeared within a circular window of 8° visual angle, which produced at least four visible cycles of the coarsest gratings (0.25 cycles/degree). A graded annular diffuser placed over the stimulus region reduced any potential edge effects of the circular window. A black fixation cross of 0.5° visual angle was placed at the centre of the screen. Mean luminance of the screen was 20 cd/m². Stimuli were viewed monocularly at a distance of 82 cm. All photometric calibrations were performed at the viewing position.

The psychophysical tests produced 75%-seeing thresholds for the visual stimulus.
for contrast sensitivity by means of an adaptive routine (parameter estimation by sequential testing, PEST; Taylor and Creelman, 1967) for left and right eyes examined in random order. The horizontal, sinusoidally modulated gratings had spatial frequencies of 0.25, 1.0 and 4.0 cycles/degree. Although this was not an investigation into temporal responsiveness, the gratings were made to drift slowly upwards in order to minimize the effects of local spatial adaptation to the stimuli. Each grating moved at the same low speed of 0.4 degrees/s (so that if there were a cue to inadvertent eye tracking it would be the same for each condition). The corresponding temporal frequencies of the gratings (0.1, 0.4 and 1.6 cycles/s, respectively) were about an order of magnitude below those at which any temporal

Fig. 2 Discrete lesions in the right optic radiation and right occipital region in the postchiasmal visual pathway shown as (A) high signal lesion on T2-weighted brain MRI and corresponding (B) low signal hypointensity (‘T1 hole’) on T1-weighted MRI, and (C) hyperintensity on proton-density-weighted MRI.
effects of demyelination might be expected to occur. Subjects gazed steadily at the fixation target during stimulus presentation. To provide a starting point for the PEST routine, an initial approximate threshold was obtained for each grating by a method of adjustment. Stimulus duration was 1.0 s with a 0.3 s rise, 0.4 s plateau and 0.3 s fall. The luminances of the red and green components in the isoluminant gratings were estimated by a method for non-flickering stimuli similar to that described by Mullen (Mullen, 1985). Thus gratings of all three spatial frequencies were shown three times, comprising mixtures: 25% red / 75% green; 50% red / 50% green; and 75% red / 25% green. The resulting nine possible stimuli were presented in random order to each eye. A simple quadratic formula was used to compute the optimum red/green mixture for isoluminance at each spatial frequency.

The PEST routines were then started. The red and green components were presented 180° out-of-phase (giving the appearance of alternating red and green bands, effectively high chromatic modulation with no luminance modulation) for preferential stimulation of the parvocellular system; and in-phase (giving the appearance of bright yellow bars alternating with dark yellow bars, effectively high luminance modulation with no chromatic modulation) for preferential stimulation of the magnocellular system. These six conditions were presented in a random order for each eye tested. The whole series of measurements required 60–75 min depending on the patient’s speed in learning the task and need for rest. Data were analysed offline to yield a contrast threshold and standard deviation estimated by a bootstrap procedure (Foster and Bischof, 1991) for each spatial frequency and phase arrangement of red and green gratings. Weighted mean thresholds were calculated for each spatial frequency and phase arrangement for patients and controls.

Psychophysical data were sorted into two groups (left and right eyes) to avoid introducing spurious correlations from the eyes of the same patient (Glynn and Rosner, 1992).

**Psychophysical–MRI correlation**

Psychophysical data were combined to give a mean magnocellular threshold and a mean parvocellular threshold for each eye. The mean total optic nerve lesion length and the mean total post-chiasmal lesion area were calculated for patients with normal and with abnormal psychophysical thresholds. Robust Pearson product–moment correlation coefficients (trim value 0.05) were calculated with percentiles estimated by the bias-corrected and adjusted (BCa) bootstrap method (Efron and Tibshirani, 1993). Where comparisons were made involving multiple measures, Bonferroni corrections were applied to reported P-values.

**Results**

**MRI**

**Optic nerve (coronal STIR images)**

Nineteen out of 24 patients (79%) had abnormal optic nerve STIR images with 28 out of 48 optic nerves (58%) studied showing intrinsic high signal abnormality. Nine patients (38%) had bilateral optic nerve lesions. The mean total optic nerve lesion area was 7.43 mm² (range 0–31.7 mm²) for the right eye and 7.88 mm² (range 0–37.1 mm²) for the left eye.

**Post-chiasmal visual pathway (axial T₁-, T₂- and proton-density-weighted images)**

Fifteen out of 24 patients (63%) had T₁ hypointensities into that described by Mullen (Mullen, 1985) for post-chiasmal pathway lesions, with bilateral lesions in 83% of these patients. The mean total lesion area was 33.5 mm² with range 0–136 mm². Twenty out of 24 patients (83%) had post-chiasmal pathway lesions, with bilateral lesions in 83% of these patients. The mean total lesion area was 181.8 mm² (range 0–1634 mm²). Twenty-one out of 24 patients (88%) had post-chiasmal pathway lesions, with bilateral lesions in 88% of these patients. The mean lesion area was 278.7 mm² (range 0–2660 mm²). There was no significant difference in the quantitative post-chiasmal MRI lesion area in patients with and without a past history of optic neuritis for any sequence.

The reproducibility of quantitative lesion area analysis on STIR, T₁-, T₂- and proton-density-weighted images produced median intra-observer agreement values of 97% (range 76–100%), 90% (range 56–97%), 88% (range 28–98%) and 85% (range 4–99%), respectively using a manual outlining technique.

**Psychophysical thresholds**

The normal range for psychophysical thresholds was taken as the weighted means for control subjects ±2 weighted standard errors of the weighted mean. As a preliminary test, mean weighted thresholds were compared for patients with and without a past history of optic neuritis. There was no significant difference and all patients were included in the study.

Every eye had at least one threshold higher than the normal range. In 14 patients (58%), all six psychophysical thresholds were higher than the normal range in both eyes. There were more abnormal thresholds for the parvocellular pathway than for the magnocellular pathway (right eyes P < 0.05; left eyes P < 0.01). Figure 3 shows weighted mean thresholds for patients and normal controls for stimuli preferential for parvocellular (Fig. 3A) and magnocellular (Fig. 3B) pathways. In terms of the proportional increase in thresholds for patients with respect to those for normal controls, the deficit was greater for the parvocellular pathway than for the magnocellular pathway, particularly at lower spatial frequency (see Table 1). There was a significant correlation in psychophysical loss between the two eyes (r = 0.83, P < 0.01).

**The relationship between MRI lesion load and psychophysical thresholds**

The mean total lesion area on all post-chiasmal MRI sequences of the visual pathway was greater in patients...
with secondary progressive multiple sclerosis and in normal control subjects. Stimuli preferential for (A) parvocellular and (B) magnocellular pathways. Data for 24 patients and 23 controls. Filled squares = patient’s right eye; filled circles = patient’s left eye; open diamonds = normal controls.

Table 1 Loss in contrast sensitivity for patients in comparison with normal controls

<table>
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<tr>
<th>Spatial frequency (cycles/degree)</th>
<th>Percentage increase in threshold</th>
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<tr>
<td></td>
<td>Parvocellular pathway</td>
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<tr>
<td></td>
<td>Right eye</td>
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<tr>
<td>0.25</td>
<td>96.74</td>
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<tr>
<td>1.0</td>
<td>92.66</td>
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<td>4.0</td>
<td>65.73</td>
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Percentage increase in psychophysical contrast thresholds in each eye for stimuli preferential for parvocellular and magnocellular pathways. Data for 24 patients and 23 controls.

Discussion

A quantitative analysis of the relationship between functional deficit and structural abnormality in established multiple sclerosis has not been reported previously. This study has revealed a strong correlation between visual psychophysical deficit and total post-chiasmal lesion area on proton density-weighted MRI, suggesting that morphological change in the post-chiasmal pathway has functional consequences. There was no reliable correlation between psychophysical deficit and lesion area on T1- or T2-weighted post-chiasmal MRI or for optic nerve STIR images.

Conventional MRIs are not specific for a particular type of histopathological lesion and any one MRI lesion may be heterogeneous. It is possible that proton-density images, by reflecting both an intracellular excess of water (inflammatory cells and gliosis) and expansion of the extracellular space (tissue oedema and water occupying the space created by loss of myelin and axons), are more representative of the range of pathologies affecting conduction of nerve impulses.

In comparison, T2-weighted images are more sensitive to extracellular water and therefore vasogenic oedema, demyelination or axonal loss, and may bias against a linear relationship with cumulative lesion load (Barnes et al., 1987). However, neither sequence is specific pathologically, and it is still not possible to distinguish on proton-density-weighted images the main pathological substrates of the deficit in multiple sclerosis, namely demyelination and axonal loss. These considerations are necessarily speculative, and it may be simply that total lesion extent is the dominant factor. For example, T1-hypointensities seen on T1-weighted imaging have been shown to indicate tissue disruption and axonal loss and to correlate significantly with clinical disability when compared with conventional imaging (van Walderveen et al., 1995, 1998). The close-to-zero correlation between psychophysical deficit and the area of post-chiasmal T1-hypointensity may here reflect the fact that the area of lesion T1-hypointensity in the visual pathway was small and therefore probably involved only a small proportion of the fibres in the posterior visual pathways. The strong correlation between post-chiasmal proton-density-weighted MRI abnormality and psychophysical deficit could also be due to the extent of the pathology being measured more sensitively.
with proton-density-weighted images than with T2- or T1-weighted images, albeit with limited specificity. A recent study evaluating several MRI parameters also showed a strong correlation between lesion load on proton-density-weighted MRI and disability (Grimaud et al., 1999), supporting the notion that proton-density-weighted images may be better than other commonly used sequences in measuring the extent of functionally important pathology. Compared with T2-weighted imaging, proton-density-weighted sequences improve identification of multiple sclerosis lesions within the post-chiasmal visual pathway especially in the periventricular areas where lesions commonly affect the optic radiations.

This study used STIR imaging, which has now been superseded by fat-suppressed fast spin-echo sequences for better identification of lesions within the optic nerve and chiasm (Gass et al., 1996). Lesion identification in the optic chiasm proved difficult here with the STIR sequence and possibly underestimated any contribution of the optic nerve to the psychophysical deficit. Nevertheless, the data suggest that a clinical attack of optic neuritis is not a prerequisite for the development of optic nerve lesions on STIR images.

There have been previous studies of the effects of multiple sclerosis and optic neuritis on the parvocellular and magnocellular visual pathways, with conflicting results. Several studies have suggested that luminance or magnocellular function was the more affected in optic neuritis and multiple sclerosis (Zisman et al., 1978; Regan et al., 1991; Phillips et al., 1994), whereas others have suggested that chromatic or parvocellular function was the more affected (Fallowfield and Krauskopf, 1984; Mullen and Plant, 1986; Wall, 1990; Porciatti and Sartucci, 1996). A further group of studies has found luminance and chromatic function to be affected unselectively (Mason et al., 1982; Foster et al., 1983, 1985; Travis and Thompson, 1989; Dain et al., 1990; Russell et al., 1991; Schiller et al., 1991; Vleugels et al., 1998). A recent smaller study of 14 patients

![Fig. 4 Mean total post-chiasmal lesion area (mm²) on MRI in patients with abnormal and with normal psychophysical thresholds. Data for 24 patients.](image)

<table>
<thead>
<tr>
<th>MRI lesion area</th>
<th>Parvocellular pathway</th>
<th>Magnocellular pathway</th>
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<tr>
<td></td>
<td>Right eye</td>
<td>Left eye</td>
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<tr>
<td></td>
<td>r</td>
<td>P-value</td>
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<tr>
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<td>NS</td>
</tr>
<tr>
<td>T1</td>
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<tr>
<td>T2</td>
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<td>NS</td>
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<tr>
<td>Proton density</td>
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<td>&lt;0.01</td>
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Thresholds were obtained for stimuli preferential for parvocellular and magnocellular pathways. Pearson product–moment correlation coefficients (r) are shown with P-values after Bonferroni correction for multiple comparisons (‘NS’ indicates P > 0.3). Data for 24 patients.
with multiple sclerosis, all with a history of optic neuritis, indicated a similar higher vulnerability of the parvocellular pathway (Porciatti and Sartucci, 1996). In that study, chromatic and luminance function was assessed with visual psychophysics, and measurement of visual evoked potentials and pattern electroretinograms. The results of the present larger study, predominantly in patients without a past history of optic neuritis, are in accordance with these findings and further quantify the visual loss. It is possible that the parvocellular pathway is involved preferentially in established multiple sclerosis because parvocellular axons are smaller than magnocellular axons, and may, therefore, be more susceptible to the effects of mechanical or metabolic insult. The issue is complex, however, and the relative magnitudes of observed losses in luminance and chromatic function may depend on several factors including the size and position of the visual stimuli, their temporal characteristics, the luminance level at which the test takes place and the particular method used for determining isoluminance. Thus, small-field stimuli may show more specific responses from affected fibres but lead to difficulties in interpretation as the variation in the effect of demyelination may be confounded with the normal variation in fibre distribution within the retina (Plant and Hess, 1987). These and related problems in assessing the visual psychophysical deficit in optic neuritis and multiple sclerosis have been reviewed (Foster, 1986; Plant, 1991).

To summarize, the principal results of this study of established multiple sclerosis are, first, that there appears to be a strong correlation between quantitative area measurement on proton-density-weighted MRI and the functional deficit assessed psychophysically and, secondly, that the parvocellular pathway seems more affected than the magnocellular pathway, especially at lower spatial frequencies.

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References


