Abnormalities of cerebral perfusion in multiple sclerosis

W Rashid, L M Parkes, G T Ingle, D T Chard, A T Toosy, D R Altmann, M R Symms, P S Tofts, A J Thompson, D H Miller

Background: Measuring perfusion provides a potential indication of metabolic activity in brain tissue. Studies in multiple sclerosis (MS) have identified areas of decreased perfusion in grey matter (GM) and white matter (WM), but the pattern in clinical subgroups is unclear.

Objectives: This study investigated perfusion changes in differing MS clinical subgroups on or off β-interferon therapy using a non-invasive MRI technique (continuous arterial spin labelling) to investigate whether different clinical MS subtypes displayed perfusion changes and whether this could give a further insight into the pathological mechanisms involved.

Methods: Sixty patients (21 relapsing remitting, 14 secondary progressive, 12 primary progressive, 13 benign) and 34 healthy controls were compared. Statistical parametric mapping (SPM ‘99) was used to investigate regional variations in perfusion in both GM and WM. Global WM perfusion was derived by segmenting WM from images using T1 relaxation times.

Results: Regions of lower perfusion in predominantly GM were observed in the primary and secondary progressive cohorts, particularly in the thalamus. Increased WM perfusion was seen in relapsing remitting and secondary progressive cohorts.

Conclusions: Low GM perfusion could reflect decreased metabolism secondary to neuronal and axonal loss or dysfunction with a predilection for progressive forms of MS. Increased WM perfusion may indicate increased metabolic activity possibly due to increased cellularity and inflammation. Improved methodology and longitudinal studies may enable further investigation of regional and temporal changes, and their relationship with physical and cognitive impairment.

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system in which breakdown of myelin is thought to be due to immune mediated inflammation. In addition to demyelination, axonal loss has emerged as a prominent neuropathological feature, especially in chronic lesions. In vivo MRI studies have revealed a reduction in the volume of whole brain, grey matter (GM), and white matter (WM), which is also consistent with neuroaxonal loss. Furthermore, there is a reduction in the concentration of N-acetyl aspartate, an amino acid that is contained almost exclusively in neurones and axons in the adult central nervous system in normal appearing WM and GM, which is more pronounced in patients with progressive forms of MS and irreversible disability. Consequently, it has been suggested that axonal loss is a key substrate for irreversible disability in MS.

Cerebral perfusion is a fundamental biological function which, at least under normal conditions, is coupled with parenchymal metabolism. In addition to cerebrovascular diseases, altered perfusion occurs in a variety of other diseases of the central nervous system. For example, in Alzheimer’s disease, frontotemporal dementia, vascular dementia, and dementia with Lewy bodies, decreases in regional cerebral perfusion and blood volume have been reported and are consistent with decreased metabolic activity secondary to neurodegeneration. The potential therefore exists for measurement of perfusion to provide an indication of the extent of neuronal and axonal loss or dysfunction in patients with MS.

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) have previously investigated cerebral perfusion in MS and have generally shown significant decreases in blood flow in areas of cortical GM and WM. Little work has been performed to investigate perfusion abnormalities in all the clinical subgroups of MS. In this present work, we estimated cerebral perfusion using continuous arterial spin labelling (CASL), an arterial spin labelling (ASL) technique that continuously labels arterial water in a proximal inversion plane. Image acquisition occurs in a distal area after a delay time to allow a high proportion of the labelled water to reach the sampling section. This method has the advantage of a higher signal to noise ratio compared with other ASL techniques. We obtained absolute measurements of perfusion in 60 MS subjects and 34 healthy volunteers in order to investigate: (a) the potential of a non-invasive in vivo method to detect cerebral perfusion abnormalities in MS and (b) regional patterns of perfusion abnormality in both GM and WM and in clinical MS subgroups. We hypothesised that decreased perfusion would, in reflecting neuronal and axonal loss, be associated with progressive and disabling forms of MS.

METHODS

Subjects

Using previously defined criteria, 60 subjects (mean age 48.1 years, range 17–69, median EDSS 4; 21 male, 39 female) from four different subgroups of clinically definite MS (21 relapsing remitting, 14 secondary progressive, 13 benign and 12 primary progressive) were compared with 34 healthy controls (mean age 40.7 years, range 20–67; 15 male, 19 female). In addition, the relapsing remitting cohort was subdivided into those who were on β-interferon (n = 11; median treatment 1.6 years (range 0.15–2.05)) and those not.

Abbreviations: ASL, arterial spin labelling; CASL, continuous arterial spin labelling; EPI, echo planar imaging; FOV, field of view; GM, grey matter; MS, multiple sclerosis; MSFC, MS Functional Composite; PD, proton density; PET, positron emission tomography; SPECT, single photon emission computed tomography; SPM, statistical parametric mapping; TE, echo time; TR, repetition time; WM, white matter
(n = 10) (table 1). No subject had a previous history of any other significant central nervous or systemic autoimmune conditions. Because of the potential effect on cerebral perfusion, subjects with a history of cerebrovascular disease, psychomotor depression, illicit drug use, poorly controlled hypertension, or ongoing medication with an immunosuppressant other than β-interferon were also excluded. Subjects were scanned at least 30 days after a relapse or steroid treatment.

All MS subjects underwent a neurological examination to evaluate their EDSS19 and MS Functional Composite (MSFC) scores.20 The latter is a combined objective measure of upper and lower limb function and cognition. Written informed consent was obtained from all subjects and the study had approval by the ethics committee of the National Hospital for Neurology and Neurosurgery.

Magnetic resonance imaging protocol
All scans were acquired on a Sigma 5.6 1.5 T system (General Electric, Milwaukee, USA). A CASL pulse sequence using gradient echo planar imaging (EPI) was performed.24 The scanning parameters were: labelling duration 1.73 seconds, post-labelling delay 0.75 seconds, repetition time (TR) 4000 ms, echo time (TE) 34 ms, 45 averages, 64 x 64 matrix, 240 x 240 mm field of view (FOV), eight 6 mm thick slices with a 3 mm inter-slice gap covering a volume, with the axis aligned to the infracallosal line and extending inferiorly from just above the tentorium to the superior margin of the centrum semiovale. The slices were acquired in an interleaved, ascending order and the in plane resolution was 3.75 x 3.75 x 6 mm³. The labelling plane was positioned 4 cm inferior to the most caudal imaging slice. Double inversion labelling (with identical scanning parameters) was used for the control sequence, as this has no net effect on arterial water longitudinal magnetisation, but matches the magnetisation transfer effects in the labelled image. Control and labelled image collection was interleaved. The entire perfusion scan for each subject took 6 minutes, with a further 3 minutes required for the acquisition of a T₁ map using a 3 point inversion recovery technique in order to exactly match the distortions of the perfusion images (inversion time = 1 second and 1.6 seconds, and one measure without inversion to calculate M₀ (the equilibrium tissue magnetisation), TR 7.2 seconds).

All MS subjects had conventional spin echo proton density (PD) and T₂ weighted images (TR 3000 ms, TE 15/90 ms, matrix size 256 x 256; FOV 240 x 240 mm; 46 contiguous slices of 3 mm thickness) acquired prior to the CASL sequence. A two dimensional T₁ weighted protocol (TR 620 ms, TE 20 ms, matrix size 256 x 256; 46 contiguous slices of 3 mm thickness) was also acquired. Total scanning time was about 35 minutes.

Quantitative perfusion maps were calculated from the CASL images and T₁ map using a two compartment methodology described elsewhere.26 The model assumed the following parameters: inversion efficiency 0.7; T₁ of blood 1.4 s; arrival time from the labelling plane to the imaging slab, 0.32–0.83 s (increasing with slice distance, assuming a linear path, with a blood velocity of 14 cm/s); permeability surface area product (PS) /blood water content (Vbw) = 1.5/0.05 = 30/minute.

Image processing
Perfusion image spatial pre-processing
To allow regional quantification in WM and GM, the quantitative perfusion maps were spatially pre-processed using statistical parametric mapping (SPM ‘99, Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). The perfusion images were spatially normalised into a standardised space defined by the EPI template (Montreal Neurological Institute) and subsequently smoothed with a 12 mm full width half maximum kernel. Extracerebral contributions were minimised using a whole brain mask and absolute lower limit perfusion threshold of 5 ml/min/100 ml.

Global evaluation of white matter perfusion
In house software21 was used to register the T₁ map to the perfusion images. Segmentation of the perfusion maps was achieved using T₁ values derived from previous studies.22–24 (500–800 ms for WM). This narrow limit was chosen to ensure high specificity for WM selection. Quantitative WM perfusion values for each slice were then averaged and weighted for the number of voxels to give an average WM perfusion value (ml/min/100 ml) for each subject. GM perfusion values were not used for this study because the T₁ segmentation could not reliably avoid WM lesion contamination owing to similarities between GM and focal lesion T₁ relaxation times.27

Lesion quantification
All images were displayed on a Sun workstation (Sun Microsystems, Mountain View, CA, USA) using the Dispimage display software package (Plummer, Department of Medical Physics, University College Hospitals NHS Trust, London, UK). Lesions were outlined using a semi-automated contouring technique28 on the PD weighted images. T₁ weighted images were used to identify hypointense WM lesions using the same threshold method. These lesion segmentations were used to calculate brain T₁ and T₂ lesion loads.

Statistical analysis
For all statistical models employed, p < 0.05 was considered significant and in the analysers of perfusion maps all p values were corrected for multiple comparisons. Individual MS subgroups were compared with all controls, with the potential effect of any age difference between the groups included and accounted for in each model.

Table 1 Entry stratification of all recruited subjects

<table>
<thead>
<tr>
<th>MS subtype</th>
<th>n</th>
<th>M</th>
<th>F</th>
<th>Mean age (range), years</th>
<th>Median EDSS (range)</th>
<th>Median disease duration (range), years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>34</td>
<td>15</td>
<td>19</td>
<td>40.7 (20–67)</td>
<td>0</td>
<td>16 (1–40)</td>
</tr>
<tr>
<td>All MS groups</td>
<td>60</td>
<td>21</td>
<td>39</td>
<td>48.1 (17–69)</td>
<td>4.0 (0–8.5)</td>
<td>10 (1–31)</td>
</tr>
<tr>
<td>Relapsing remitting</td>
<td>21</td>
<td>8</td>
<td>13</td>
<td>38.9 (17–59)</td>
<td>2.5 (0–6.5)</td>
<td>7 (2–31)</td>
</tr>
<tr>
<td>No treatment</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>37.9 (17–55)</td>
<td>3.0 (0–6)</td>
<td>10 (1–17)</td>
</tr>
<tr>
<td>On β-interferon</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>39.8 (27–59)</td>
<td>2.5 (1–6.5)</td>
<td>18 (7–40)</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>14</td>
<td>3</td>
<td>11</td>
<td>51.2 (30–68)</td>
<td>6.0 (2–8)</td>
<td>16 (8–34)</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>12</td>
<td>5</td>
<td>7</td>
<td>55.7 (40–69)</td>
<td>6.5 (3.5–8.5)</td>
<td>24 (20–36)</td>
</tr>
<tr>
<td>Benign</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>52.6 (40–60)</td>
<td>2.5 (1–3)</td>
<td>24 (20–36)</td>
</tr>
</tbody>
</table>
Statistical parametric mapping analysis of perfusion maps

SPM employs a general linear model with Gaussian field theory to make statistical inferences about regional effects from the normalised SPM perfusion maps. The statistical model included age, gender, and disease status as covariates of interest to correct for any differences between control and patient groups. The subjects were included as random effects, with each subject contributing one pre-processed perfusion image. The design matrix also included the global mean intensities as confounders, which ensured that the results reflected regionally specific differences in perfusion. Following model estimation, "T contrasts" were specified to test the statistical significance of particular linear combinations of parameter estimates. Voxelwise significance was determined by using Gaussian random field theory and the resulting statistical maps (SPM13 maps) were corrected for multiple comparisons over the whole perfusion volume. Contrasts were specified to compare the control group with MS subgroups and different MS subgroups with each other. In order to avoid reporting areas of doubtful physiological relevance, only local maxima coordinates with a voxel cluster >50 were used.

White matter perfusion values using T1 segmentation

A further multiple linear regression model was created to evaluate WM perfusion values derived from T1 segmentation values. In the model, WM perfusion was the dependent variable, while gender and disease subgroup were included as categorical variables, and age as a continuous covariate to assess absolute disease effects allowing for age and gender.

Correlations between perfusion measures and clinical measures

To quantify the associations between perfusion and clinical status, models included age and gender as before, along with either MSFC as a continuous covariate or dichotomised EDSS values (mild 0–3, moderate or severe 3.5) as a categorical variable.

RESULTS

Statistical parametric mapping based perfusion analysis

Smoothed, normalised perfusion maps were generated for 33 controls and 59 MS subjects. Maps from one control and one secondary progressive subject were not included owing to inadequate normalisation to the EPI template. The most prominent abnormalities were seen in primary and secondary progressive subgroups, where subjects exhibited regions of reduced perfusion that involved both cortical and deep GM structures and adjacent WM areas (table 2, fig 1) compared with controls. Smaller regions of decreased perfusion were seen in patients with benign disease, and no areas of reduced perfusion were seen in the relapsing remitting group.

Compared with controls, there was one small region of increased perfusion (69 voxels, p = 0.001) in the secondary progressive group in right frontal subcortical WM, and another small area of increased perfusion (78 voxels, p = 0.003) in 10 relapsing remitting patients not receiving β-interferon in a predominantly WM region adjacent to the left precentral and superior temporal gyrus.

White matter perfusion results using segmentation based on T1 value range

Absolute WM perfusion values were compared in the subjects. Some WM lesions had T1 relaxation values of above 800 ms, and the resulting WM masks will have excluded such lesions. Table 3 lists the results using this technique.

The mean values in healthy subjects compare well with other studies. A significant increase in WM perfusion was observed when all MS subjects were compared with controls (p = 0.007). In the subgroup analysis, a significant WM perfusion increase was also seen in the pooled relapsing remitting cohort (p = 0.03) and secondary progressive subjects (p = 0.02) when compared with controls. The relapsing remitting group not on β-interferon showed a significant increase in perfusion (p = 0.04) whilst statistical significance was not reached in those on β-interferon (p = 0.14). There was weak evidence for increased WM perfusion in the benign MS group (p = 0.08), when compared with controls. No WM perfusion differences were detected between primary progressive subjects and controls. There were no statistically significant differences seen when comparing any of the MS subtypes directly.

Correlations between perfusion measures and MRI lesion load or clinical measures

In the SPM analysis there was no evidence of a correlation between perfusion measures and either lesion load or clinical outcomes. However in the T1 segmented WM perfusion analysis, there was evidence that correlations between PD lesion volumes and WM perfusion differed between MS subtypes (p = 0.03), with a suggestion that WM perfusion may be increasing more with PD lesion volume in the secondary progressive group than in other subtypes. There were no other significant correlations.

DISCUSSION

Previous studies of cerebral perfusion in MS have used PET or SPECT and have revealed areas of decreased perfusion in GM and WM. Exogenous contrast MR methods have been

<table>
<thead>
<tr>
<th>Table 2</th>
<th>SPM analysis: regions of hypoperfusion (voxel clusters with significance of patient groups compared with controls) in the combined multiple sclerosis cohort and clinical subgroups of multiple sclerosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td>All MS</td>
</tr>
<tr>
<td>Deep grey matter and adjacent white matter</td>
<td>50% GM;</td>
</tr>
<tr>
<td>R and L thalamus, caudate and extranuclear areas</td>
<td>2399; p &lt; 0.001</td>
</tr>
<tr>
<td>Cortical grey matter and adjacent white matter</td>
<td>66% GM;</td>
</tr>
<tr>
<td>R and L middle frontal and precentral and postcentral gyri and inferior parietal areas</td>
<td>1450; p &lt; 0.001</td>
</tr>
<tr>
<td>R and L superior frontal and medial gyrus</td>
<td>1049; p &lt; 0.001</td>
</tr>
<tr>
<td>R and L precuneus and cingulate gyri</td>
<td>390; NS</td>
</tr>
<tr>
<td>R and L paracentral lobule</td>
<td>259; NS</td>
</tr>
<tr>
<td>L superior parietal lobe and subcortical areas</td>
<td>185; NS</td>
</tr>
</tbody>
</table>

No regions of hypoperfusion were detected in the relapsing remitting subgroup. MS, multiple sclerosis; SP, secondary progressive; PP, primary progressive; B, benign; GM, grey matter; WM, white matter; R, right; L, left.

Percentages of grey and white matter for each subgroup are derived from the total number of clusters in these regions as determined using the Montreal Neurological Institute brain template.
used to evaluate cerebral blood volume in MS lesions with the largest of the studies showing, in 25 patients, an increase in cerebral blood volume in enhancing lesions and a decrease in T1 weighted hypointense lesions. The present study is the first to quantify cerebral perfusion in MS using a non-invasive method. The main findings in this study were a reduction of perfusion of GM structures, especially deep GM, and an increase in perfusion in WM.

**Decreased grey matter perfusion**

Using SPM, there was a large number of regions with lower perfusion located in both cortical and deep GM and adjacent WM regions. Neuronal and axonal dysfunction and loss in GM, with a corresponding reduction in local metabolic activity, may be the most likely causes of decreased GM perfusion. These findings are generally concordant with previous perfusion studies. Another possible explanation for non-homogeneity of perfusion could be a ‘steal phenomenon’ occurring in the local vascular network as a result of the redistribution of perfusion caused by abnormalities of brain activity in other regions. Additional, more localised, perfusion studies are required to investigate this further.

The primary progressive subjects exhibited the largest areas of reduced perfusion (table 2, fig 1), consistent with axonal loss being a prominent neuropathological feature in this subgroup. Secondary progressive subjects also revealed substantial areas of reduced perfusion (table 2), which is again consistent with neuroaxonal loss or dysfunction observed using other putative MR markers of axonal integrity at this stage of disease. The analysis of data derived from subjects with benign MS showed only limited areas of decreased perfusion (table 2), which could reflect a generally less severe underlying pathology, mirroring the clinical phenotype. No regions of reduced perfusion were seen in the relapsing remitting group, which could be consistent with this subgroup having less neuroaxonal damage.

The evidence for hypoperfusion in MS patients relative to controls was apparent in both cortex and deep GM, and was especially striking in the thalamus and caudate nuclei. A recent MR study in MS has reported a decrease in thalamic volume and N-acetyl aspartate. Furthermore, evaluations of glucose uptake in MS using PET have revealed areas of low metabolic function in the thalamus. The decreased thalamic perfusion observed in our pooled MS cohort is consistent with neuronal loss or dysfunction in this structure. The decreased perfusion in cortex and deep GM structures may also be indicative of disconnection between cortical regions and subcortical relay systems due to demyelination. The observation of decreased perfusion in the primary and secondary progressive subgroups of MS suggests that this non-invasive imaging measure has the potential to investigate the adverse effects of neuroaxonal damage on brain metabolism in MS. In addition, as PET metabolic studies suggest a possible correlation between areas of low function and cognitive or memory disturbance, ASL may provide a potentially useful non-invasive evaluation into these symptoms in MS.

**Increased white matter perfusion**

Global assessment, using segmented T1 maps, revealed raised perfusion in MS WM compared with controls. Raised perfusion was evident only in relapsing remitting and secondary progressive subgroups, and in relapsing remitting subjects it was only apparent in those not being treated with β-interferon; these subgroup findings in global WM were supported by observations of small regions of increased WM perfusion using SPM.

The increase in WM perfusion may reflect higher metabolic activity due to an increase in cell number and activity in normal appearing WM or WM lesions (both normal appearing WM and lesions with a T1 relaxation time of less than 800 ms were included in the globally segmented WM). In normal appearing WM in MS, such features include astrocyte proliferation. In lesions, especially if of recent onset, inflammatory features including perivascular cuffs of lymphocytes and macrophage infiltrates may be prominent. Further evidence of the potential role of inflammation in WM in MS is provided by PET studies (using benzodiazepine agonists as a microglial marker) that show increased activity in gadolinium enhancing lesions and in normal appearing WM of subjects with greater disease progression. In addition, further emphasising that perfusion may increase in areas of active inflammation in MS, a recent gadolinium bolus study demonstrated an increase in cerebral blood flow in areas of WM just before the area transformed into a gadolinium enhancing lesion.

Although gadolinium enhanced scans were not obtained to investigate the presence of inflammatory lesions, it is known from previous studies that such lesions occur more often in relapsing remitting and secondary progressive MS than in primary progressive and benign MS, and are less common in patients receiving β-interferon. Our observation with the relapsing remitting subgroup not treated with β-interferon should, however, be interpreted cautiously, as there were only 10 subjects in this cohort and the increase was only marginally significant.

The analysis of WM perfusion using SPM suggests a complex pattern of regional perfusion. Although small foci of increased perfusion were observed in relapsing remitting and secondary progressive subgroups, areas of decreased perfusion were also seen, especially adjacent to the areas of decreased deep GM perfusion observed in patients with primary progressive or secondary progressive MS. Axonal loss has been described in WM lesions and normal appearing WM, and if extensive, might be expected to result in...
regions with decreased metabolic activity and hence perfusion.

Methodological considerations

ASL relies upon a reduction in the tissue signal intensity associated with the passage of magnetically labelled blood through capillaries. Relative signal loss allows the quantification of perfusion. A new two compartment model was used to quantify perfusion. It includes a correction for the selective permeability of the blood brain barrier, producing a technique with greater physiological accuracy, as previous assumptions of free permeability of the capillary wall to water lead to an overestimation of perfusion, particularly in the WM where the loss of label (due to $T_1$ relaxation) is approximately twice as fast as in blood. In addition, ASL is potentially more accurate in MS than using a gadolinium bolus technique, as the latter assumes that the label remains intravascular, and as such, perfusion values may be affected by blood–brain barrier breakdown, which is known to occur in MS.

With CASL and two compartment modelling, an increase in blood–brain barrier permeability to water in MS compared with controls could result in a small underestimation of perfusion, which could contribute to some of the perfusion reductions noted, but not the white matter increases. However, simulations of the two compartment model show that even relatively large changes in the permeability constant result in minimal changes to the perfusion measurements. Additionally, it would be difficult to model exactly for permeability differences between MS subjects and controls as this would vary not only between MS subgroups but also within subgroups, as it could be influenced by the individual variability of inflammatory activity. Furthermore, disease related effects on $T_1$ relaxation values should not cause any significant error as these are measured and included in the calculation. A delay time between arterial water inversion and image acquisition is used to allow a high proportion of the tagged blood to reach its final tissue destination thereby minimising the contribution from blood transported in larger non-perfusing vessels. It is theoretically possible that a specific effect on the blood $T_1$ relaxation time due to MS may significantly alter the measured perfusion result. However, there is a paucity of evidence to suggest that MS has such an effect, hence, this technique offers a potentially more accurate evaluation of perfusion in MS than previous approaches.

Further improvements, however, would be beneficial, particularly regarding improved focal lesion segmentation on the perfusion maps. The acquisition of a $T_2$ weighted sequence that is fully registered with the perfusion images would be desirable in this respect. An increased number of signal averages to improve the signal to noise ratio would improve resolution but at the cost of increased scan time, and hence increase any potential subject motion artefact. Therefore, the optimal CASL sequence should balance these two competing influences. Image acquisition must be achieved within the time frame of the $T_2$ relaxation time of blood, necessitating high speed echoplanar imaging acquisition with relatively low resolution and limited brain coverage. Higher field strength scanners would increase the $T_2$ relaxation time and signal to noise ratio, although specific absorption rate limitations may occur above 1.5 T.

CONCLUSIONS

This study of patients with MS has revealed reduced perfusion, especially in the WM, compared with controls. This was most apparent in the primary and secondary progressive subgroups. The decreases affected both cortical and deep GM structures, and are consistent with decreased neuronal metabolic activity or neuronal loss. Elevated perfusion was seen in WM in relapsing remitting and secondary progressive MS, possibly reflecting an increase in cell number and metabolic activity. Further investigation of the longitudinal changes in perfusion, and possible correlations with cognitive dysfunction and the effects of therapeutic interventions, particularly using methodological improvements such as higher field scanning, may provide further insights.

ACKNOWLEDGEMENTS

We thank D Alsop for the use of his CASL sequence, the Multiple Sclerosis Society of Great Britain and Northern Ireland for their continuing support of the NMR Research Unit (including W Rashid), the Brain Research Trust UK for support of L M Parkes, the Wellcome Trust for support of G T Ingle and M R Symms, Schering AG for support of D T Chard and The Mrs F B Laurence Trust and The Barnwood House Trust for support of A T Toosy. We are grateful to all the people who kindly agreed to take part in this study.

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Competing interests: none declared

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J Neurol Neurosurg Psychiatry 2004 75: 1288-1293
doi: 10.1136/jnnp.2003.026021

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