

Potentially adaptive functional changes in cognitive processing for patients with multiple sclerosis and their acute modulation by rivastigmine

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Summary

One explanation for the weak relationship between neuropsychological deficits and conventional measures of disease burden in multiple sclerosis is that brain ‘plasticity’ allows adaptive reorganization of cognitive functions to limit impairment, despite injury. We have tested this hypothesis. Ten patients with multiple sclerosis and 11 healthy controls were studied using a functional MRI (fMRI) counting Stroop task. The two subject groups had comparable performances, but a predominantly left medial prefrontal region [Brodmann area (BA) 8/9/10] was more active during the task in patients than in controls (corrected $P < 0.001$), while a right frontal region (including BA 45 and the basal ganglia) was more active in controls than in patients (corrected $P = 0.004$). The magnitude of the differences correlated with the normalized brain parenchymal volume, a measure of disease

burden ($r = -0.72$, $P = 0.02$). We then tested the effects of acute administration of rivastigmine, a central cholinesterase inhibitor, on patterns of brain activation. In five out of five multiple sclerosis patients there was a relative normalization of the abnormal Stroop-associated brain activation, although no change in the patterns of brain activation was found in any of four healthy controls given the drug and tested in the same way. We suggest that recruitment of medial prefrontal cortex is a form of adaptive brain plasticity that compensates, in part, for relative deficits in processing related to the reduced right prefrontal cortex activity with multiple sclerosis. This functional plasticity is modulated by cholinergic agonism and must arise from potentially highly dynamic mechanisms such as the ‘unmasking’ of latent pathways.

Keywords: cerebral plasticity; cognition; fMRI; multiple sclerosis; neurophysiology

Abbreviations: AR = activation ratio; BA = Brodmann area; EDSS = Expanded Disability Status Scale; EPI = echo-planar imaging; fMRI = functional MRI; HADS = Hospital Anxiety and Depression Scale; NART = National Adult Reading Test; NBPV = normalized brain parenchymal volume; VF = verbal fluency

Introduction

Cognitive deficits occur frequently in patients with multiple sclerosis even early in the disease course (Rao *et al.*, 1991). These typically involve impairment of attention and executive functions, including decision making, error correction and suppression of pre-potent or habitual responses (Feinstein *et al.*, 1992). However, these deficits are not apparent in all patients and, like other clinical measures, do not correlate strongly with conventional MRI measures of cerebral disease burden (Rao *et al.*, 1989; Swirsky-Sacchetti *et al.*, 1992; Turchi and Sarter, 1997).

One possible reason for this is the adaptive reorganization of brain function to compensate for impairments of function in damaged cognitive networks (Muir *et al.*, 1992; Cifelli

et al., 2002). There are several precedents for this. Functional MRI (fMRI) studies of hand movement (Reddy *et al.*, 2000) and visual stimulation (Werring *et al.*, 2000) in patients with multiple sclerosis show enlarged brain networks. Studies using memory tasks have demonstrated that potentially adaptive cortical functional changes occur prior to clinical expression of (familial) Alzheimer’s disease (Bookheimer *et al.*, 2000; C.D.Smith *et al.*, 2002) or temporal lobe pathology (Dupont *et al.*, 2000).

Multiple mechanisms may be involved in such adaptive responses, but a significant contribution probably comes from changes in synaptic efficiency modulated by changes in local neurotransmitter levels. For example, short-term plasticity in

the sensorimotor system is associated with a local decrease in GABA (Levy *et al.*, 2002) and is impaired by increasing GABAergic tone (Butefisch *et al.*, 2000). The cholinergic system also may have effects relevant to brain recovery. Animal studies have demonstrated that acetylcholine release modulates activity in many neural pathways, including those involved in attention and executive functions (Everitt and Robbins, 1997). Some effects may be mediated by the amplification of responses to task-relevant stimuli (Everitt and Robbins, 1997; Turchi and Sarter, 1997; Sarter *et al.*, 1999; Himmelheber *et al.*, 2001). Prolonging the neuronal excitatory period could be useful in the treatment of multiple sclerosis in which functional impairment occurs both as a consequence of structural pathology (e.g. axonal loss; Trapp *et al.*, 1998; Evangelou *et al.*, 2000) and of reduced temporal coherence of neuronal firing as a consequence of demyelination (Smith and McDonald, 1999). Recent data suggesting beneficial effects of cholinesterase inhibition in the treatment of patients with diseases as varied as Alzheimer's disease, multi-infarct dementia and multiple sclerosis argues for very general clinical benefits (Freo *et al.*, 2002). Studies in healthy subjects suggest that cholinergic afferents may facilitate use-dependent plasticity (Sawaki *et al.*, 2002).

Here we wished to test first whether functional reorganization potentially could contribute to limiting cognitive deficits accompanying diffuse brain injury from multiple sclerosis. We chose to employ the counting Stroop task (Stroop, 1935; Bush *et al.*, 1998) as a probe. Subjects with frontal lobe damage perform poorly on the Stroop task (Perret, 1974; Vendrell *et al.*, 1995; Stuss *et al.*, 2001). We hypothesized that multiple sclerosis patients performing the task with accuracy and speed similar to healthy controls would recruit distinct or additional prefrontal cortical regions as an adaptive response to underlying brain injury and that, reflecting this, the extent of any abnormal prefrontal cortical recruitment would correlate with their disease burden.

We then wished to test whether any altered pattern of brain activity in patients was modulated acutely by cholinergic agonism. We chose to test for this using rivastigmine, a cholinesterase inhibitor, because it represents a form of clinically practical chronic treatment (Freo *et al.*, 2002). A recent study has also suggested that treatment with donepezil (a related acetylcholinesterase inhibitor) improves cognition and behaviour in patients with multiple sclerosis (Greene *et al.*, 2000).

Subjects and methods

Subjects

Study of the Stroop effect in multiple sclerosis patients and controls

Ten right-handed patients (seven women, three men; median age 42 years, range 31–54 years) with clinically definite multiple sclerosis (eight relapsing–remitting, two secondary progressive; median duration 10 years, range 5–21 years) according to the Poser criteria (Poser *et al.*, 1983) and

subjective complaints of poor concentration or memory were included in the study. Disability was assessed with the Kurtzke Expanded Disability Status Scale (EDSS) (median EDSS 2, range 0–6) (Kurtzke, 1983) at the time of the fMRI scanning by an experienced neurologist. None had experienced a relapse or treatment with steroids in the preceding two months. Eleven right-handed, age (median age 42 years, range 26–61 years) and sex (seven women, four men) matched healthy subjects also were studied as controls.

Rivastigmine study

Five of the patients (three women, two men; median age 42 years, range 39–51 years; median duration of disease 10 years, range 6–17 years; median EDSS 2.5, range 2–6) consented to participate in a trial testing the effects of rivastigmine on patterns of brain activation with the Stroop task. Four of the healthy subjects (three men, one woman; median age 37 years, range 26–51 years) also agreed to undergo the same test of rivastigmine effects. Each subject was studied on two separate days: once with administration of rivastigmine (3 mg orally) and once with administration of placebo 150 min before fMRI scanning. To minimize the side-effects of rivastigmine (which can cause nausea), all subjects also were administered 3 mg of domperidone orally once daily for 2 days before each fMRI scanning session, with an additional 3 mg at the same time that rivastigmine or placebo was taken on the day of fMRI scanning. The order of administration of rivastigmine or placebo was pseudo-randomized across trials to counterbalance the design. Neither the investigator nor the subjects knew whether placebo or rivastigmine was being administered. The image files also were coded so that the investigator was not aware of the agent administered in any study until the final stage of the data analysis. Subjects had been told that they could experience nausea and were asked to report any perceived effects of the agent administered.

Data from four of the patients and from two of the controls acquired during the placebo arm of the rivastigmine study were included in the initial analysis of the Stroop effect in multiple sclerosis patients and controls. These subjects were chosen as those who were administered placebo at their first visit so that their experience was otherwise comparable to that of the other subjects in the Stroop effect study.

Approval was obtained for this study from the Oxford Regional Ethics Committee (OxREC). Written informed consent was obtained from all the subjects prior to their participation in the study.

Neuropsychological battery

A brief neuropsychological battery was completed outside of the scanner before the imaging study to characterize the cognitive profile of subjects: (i) National Adult Reading Test (NART) (Nelson, 1991); (ii) phonemic and categorical verbal fluency tests (i.e. FAS/animals) (Majors and Meyers, 1991);

(iii) Rey Complex Figure (Majors and Meyers, 1991); (iv) Hopkins Verbal Learning Test—Revised (Warrington, 1984); (v) Symbol Digit Modality Test (Warrington, 1984); (vi) Digit Span (Wechsler) (Warrington, 1984); (vii) set I: Ravens Advanced Progressive Matrices (Warrington, 1984); and (viii) Letter Number Sequencing (Wechsler) (Warrington, 1984).

Raw data scores for each test were converted to Z scores by referring to normative data from the appropriate manuals or reference materials. A ‘FAS deficit’ was calculated by subtracting the FAS verbal fluency (VF) score obtained from a predicted ‘premorbid’ FAS score that can be derived from the NART (Crawford *et al.*, 1992) (a negative score representing an actual VF score below the predicted VF score). The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) also was administered.

Paradigm

The study used the counting Stroop task (Bush *et al.*, 1998). Subjects were presented with sets of between one and four words presented on a screen as a vertical list every 1.5 s. The words (balanced for across groups length) could be animal words (‘cat’, ‘dog’, ‘bird’ or ‘mouse’) (neutral trials) or number words (‘one’, ‘two’, ‘three’ or ‘four’) (interference trials). Eight 30-s neutral blocks alternated with eight 30-s interference blocks. A 30-s rest period was included at the start and at the end.

Stimulus presentation

The visual stimuli were generated using in-house software and projected onto a screen (In Focus LP1000; National Projector, Dallas, TX, USA) 2.5 m from the head of the patient. Subjects wore prism glasses to enable them to see the screen. The stimuli were printed in sans serif black font 3 cm in height. A four-button box was used by the subjects to indicate the number of words on the screen and to record reaction times.

The mean reaction time for each of the eight neutral and interference blocks and the magnitude of the Stroop effect (mean interference reaction time–mean neutral reaction time) were calculated for each neutral/interference block. Incorrect button-box responses were not included when calculating the reaction times. A mean Stroop effect was calculated across all eight of the paired neutral/interference blocks.

It was assumed initially that reaction times measured by the button press reflect speeds of cognitive processing. To test this in patients with multiple sclerosis, we compared performance on the manual and oral subtests of the Symbol Digit Modality Test. We found similar good correlations between the Z scores obtained with the manual and oral responses in both subject groups. We also did not observe any significant difference in the variance of the neutral reaction times between patients and controls (data not shown), further

validating use of button press reaction time as an estimate of relative cognitive processing speed for both groups.

Image acquisition

All scans were performed using a 3.0 Tesla whole body scanner with a Varian Inova console and a quadrature birdcage radiofrequency head coil. A 9-min echo-planar imaging (EPI) sequence was used to acquire the fMRI data [21 × 6 mm axial slices, echo time (TE) = 30 ms, repetition time (TR) = 3000 ms, field of view (FOV) = 256 × 256 mm, matrix = 64 × 64]. A T₁-weighted anatomical scan was acquired for each subject [64 × 2 mm axial slices, TR = 30 ms, inversion time (TI) = 500 ms, TE = 5 ms, flip angle = 15, FOV = 256 × 256 mm, matrix = 256 × 256]. A proton-density image also was acquired (spin echo, 30 × 4 mm axial slices, TE = 15.5 ms, TR = 3750 ms, FOV = 256 × 160 mm, matrix = 256 × 160). In one patient the latter could not be acquired due to technical difficulties.

Normalized brain parenchymal volume

Cross-sectional atrophy measures were performed using SIENAX (www.fmrib.ox.ac.uk/fsl) (S.M.Smith *et al.*, 2002) with the T₁-weighted anatomical images, which has a test–retest error of 0.5–1% (S.M.Smith *et al.*, 2002). The normalized brain volumes for the patients were adjusted for age using previously generated data from healthy controls to calculate the age-adjusted normalized brain parenchymal volume (NBPV).

Lesion segmentation

Lesion volume quantification was performed manually on the proton density images using DISPLAY (courtesy of Professor A. Evans, Montreal Neurological Institute) by an observer blinded to the clinical status of the patient. The mean (SD) percentage intra-rater lesion volume measurement variation was 4.1% (2.8%).

Image analysis

Analysis of the fMRI data was carried out using FMRI Expert Analysis Tool, version 4 (FEAT) (www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing steps were applied: motion correction using MCFLIRT (Jenkinson and Smith, 2001), spatial smoothing using a Gaussian kernel of full width half maximum (FWHM) 5 mm, mean-based intensity normalization of all volumes by a constant factor and high-pass filtering (Gaussian-weighted LSF straight line fitting, with sigma = 50.0 s). Statistical analysis was carried out using FMRIB’s Improved Linear Model (FILM) with local autocorrelation correction (Woolrich *et al.*, 2001). All probability values reported are corrected for multiple comparisons. The statistical images generated were related to

each the brain anatomy of each subject by registration with the individual T₁-weighted structural scan.

To identify the main effects of the Stroop task on brain activation, an analysis of the patient and control groups combined was performed (interference–neutral contrast). Two ‘between-group’ analyses were performed to determine whether there were differences in brain activations with the Stroop task (interference–neutral contrast) between the two groups: (i) patients–controls; and (ii) controls–patients. All group analyses were performed using a random-effects model, with *Z* (Gaussianized *T*) statistic images thresholded using clusters determined by $Z > 2.0$ and a (corrected) cluster significance of $P = 0.05$ (Worsley *et al.*, 1992; Friston *et al.*, 1994; Forman *et al.*, 1995). The high-resolution T₁-weighted images from the subjects were co-registered into standard space (Talairach and Tournoux, 1988) and averaged to produce a mean control and a mean patient structural image on which the thresholded *Z* statistic images were overlaid. This allowed assessment of activation areas in terms of anatomical landmarks (based on correspondence to structures in the Duvernoy atlas; Duvernoy, 1995) as well as reporting the Talairach co-ordinates of peak activations within each anatomically defined area (Talairach and Tournoux, 1988). The co-ordinates were transformed from the standard space of the Montreal Neurological Institute (MNI) standard brain to Talairach space using an automated estimator (www.mrc-cbu.cam.ac.uk/imaging).

Statistics

A multivariate analysis of variance (MANOVA) was used to determine the effect of group (patient or control) on the size of the Stroop effect and the Stroop error rate. A repeated measures ANOVA was used to determine whether there was an effect of time on the size of the Stroop effect. The Spearman’s correlation coefficient was used to relate change in signal intensity to behavioural or structural MRI indices. A corrected, two-tailed P value ≤ 0.05 was considered statistically significant. All statistics were performed using SPSS for Windows (version 9.0).

Results

Patients and controls had comparable performance in the counting Stroop task

Performance on the counting Stroop task was similar for the patients and healthy controls. The mean reaction times were only non-significantly longer for the patients (controls 677 ms, range 514–1138 ms, and patients 734 ms, range 515–1083 ms, for the neutral task, $P = 0.28$; controls 777 ms, range 583–1196 ms, and patients 852 ms, range 527–1167 ms, for the interference task, $P = 0.65$). The mean Stroop effect in the patient group was ~30% smaller than in the controls, but this difference was not statistically significant (controls, median 118 ms, range 56–272 ms; patients, median 78 ms, range 13–

Table 1 Areas of significant activation during the Stroop task (interference–neutral contrast) in a random-effects combined group analysis of patients and healthy controls

Anatomical region	Talairach co-ordinates of maximum <i>Z</i> score			Maximum <i>Z</i> score
	<i>x</i>	<i>y</i>	<i>z</i>	
Inferior frontal gyrus L	–40	16	8	4.9
Middle frontal gyrus L	–38	8	21	4.7
Intraparietal sulcus L	–25	–67	26	4.3
Inferior pre-central sulcus L	–40	–3	24	4.2
Inferior pre-central sulcus R	36	3	23	4.1
Cingulate sulcus L	–3	12	39	4.1
Superior parietal lobe L	–47	–42	36	4.1
Inferior frontal gyrus R	22	1	17	3.9
Inferior temporal gyrus L	–40	–32	–21	3.8
Anterior insula L	–24	24	10	3.8
Middle occipital lobe R	–10	–69	44	3.7
Middle frontal gyrus R	23	4	33	3.7
Superior frontal gyrus L	–13	8	51	3.6
Basal ganglia (caudate) L	–48	28	5	3.6
Superior frontal gyrus R	8	3	56	3.5
Supramarginal gyrus R	43	–46	38	3.5
Anterior insula R	33	6	–11	3.4
Intraparietal sulcus R	20	–62	35	3.3
Anterior cingulate gyrus R	6	22	22	3.3
Anterior cingulate gyrus L	–8	24	20	3.2

L = left; R = right.

151 ms, $P = 0.09$). There also were no clear differences in the error rates for the task between the patient and control groups (controls, median 2.0%, range 0.0–5.9%; patients, median 2.1%, range 1.3–12.8%, $P = 0.81$). There was no relationship between the size of the Stroop effect and either the age-corrected, NBPV, a measure of disease burden (Rudick *et al.*, 1999; S.M. Smith *et al.*, 2002), or the T₂-weighted MRI white matter lesion loads in the patients. A repeated measures ANOVA showed a reduction in the magnitude of the Stroop effect in individual trial blocks over the course of the experiment (Greenhouse-Geisser, $F = 3.62$, $P = 0.02$), but the reduction was not different between patients and controls (time/group interaction, $F = 1.02$, $P > 0.38$).

A distributed network of activation is associated with counting Stroop task performance

Results from patients and controls initially were combined in a random-effects group analysis to identify the main effect of the counting Stroop task (interference–neutral contrast). As described in previous reports (Bush *et al.*, 1998; Carter *et al.*, 1998), we found significant task-associated activations in brain regions including bifrontal, biparietal and anterior cingulate cortices (Table 1, Fig. 1). The maximum percentage signal intensity change (interference–neutral contrast) in these regions of interest correlated positively with the magnitude of the Stroop effect ($r = 0.49$, $P = 0.02$).

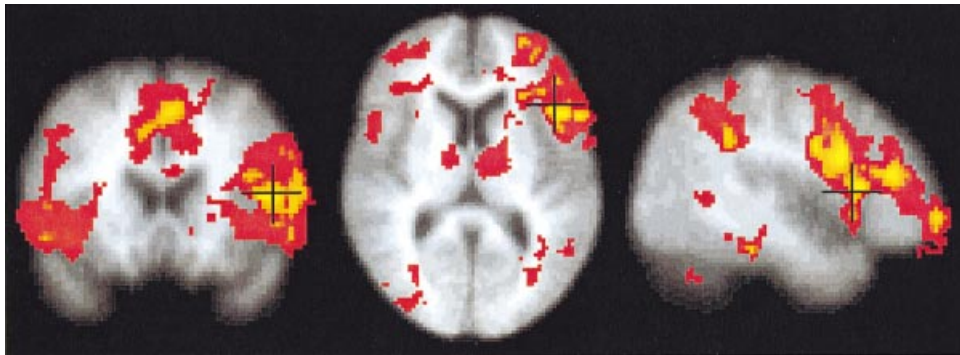


Fig. 1 Areas of significant activation during the Stroop task (interference–neutral contrast) in a random-effects combined group analysis of patients and healthy controls. Group random-effects Z maps are superimposed onto an average high resolution scan of all subjects. Cross hairs are situated at the local maximum Z score in the left inferior frontal gyrus. The anatomical locations and co-ordinates for the local activation maxima are shown in Table 1.

Table 2 Areas of significant activation during the Stroop task (interference–neutral contrast) in random-effects group contrasts between patients–controls and controls–patients

Anatomical region	Talairach co-ordinates of maximum Z score			Maximum Z score
	x	y	z	
Patients–controls				
Middle frontal gyrus	–20	12	36	3.5
L/superior frontal sulcus L				
Superior frontal gyrus L	–11	43	23	3.4
Superior frontal sulcus L	–24	24	47	3.2
Superior frontal gyrus R	6	39	42	2.4
Controls–patients				
Basal ganglia (caudate) R	20	12	14	4.1
Inferior frontal gyrus R (pars opercularis)	40	20	6	3.8
Putamen R	29	–1	–9	3.0

Patients showed greater predominantly left medial prefrontal activation than controls

There also were differences in the patterns of activation between the patient and healthy control groups. A random-effects contrast of the interference–neutral conditions for patients–controls identified a predominantly left medial frontal region corresponding to Brodmann area (BA) 8/9/10 with greater activity in the patients than controls (corrected $P < 0.001$, maximum Z score = 3.5, 1638 voxels) (Table 2, Fig. 2). The cluster defined at this threshold extended across several frontal lobe areas and included distinct maxima in the left middle frontal gyrus/superior frontal sulcus and in the left and right superior frontal gyri. The anatomical location of the peak Z score within this left frontal region for each patient was determined by reference to their individual T_1 -weighted structural image. The peak Z score was located in the left superior frontal sulcus in five patients, the left superior frontal

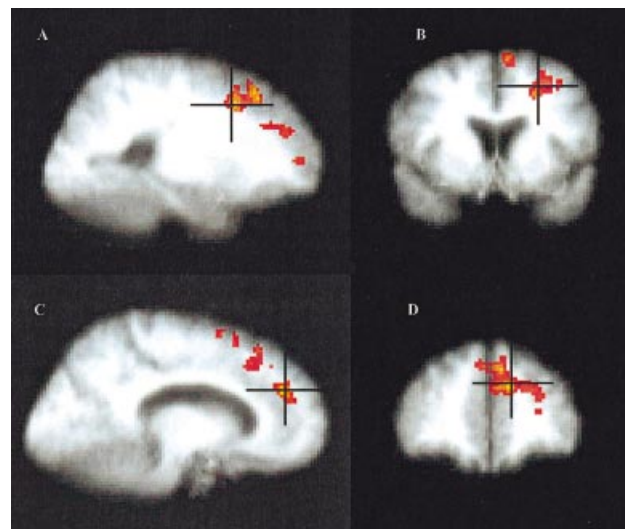


Fig. 2 A mixed-effects contrast of brain regions activated during the Stroop task (interference–neutral contrast) in patients–controls identified a significant cluster predominantly in the left frontal lobe. Within this cluster were distinct activation peaks in (A, B) the left middle frontal gyrus/left superior frontal sulcus (–20, 12, 36) and (C, D) the left superior frontal gyrus (–11, 43, 23). Group random-effects Z maps are superimposed onto average high-resolution scan from the ten patients. Cross hairs are situated at the local maximum Z score in each image.

gyrus in four patients and the left middle frontal gyrus in one patient.

The maximum percentage signal intensity changes for the left medial frontal activation cluster were significantly higher in the patients than for the controls (patients, median 0.71%, range 0.22–1.15%; controls, median 0.26%, range 0.20–0.39%, $P = 0.002$). The maximum signal intensity changes for this activation cluster were correlated ($r = 0.71$, $P = 0.02$) with the magnitude of the Stroop effect for the patients (Fig. 3). The maximum signal intensity changes in this region of interest showed no correlation with the magnitude of the Stroop effect for the controls.

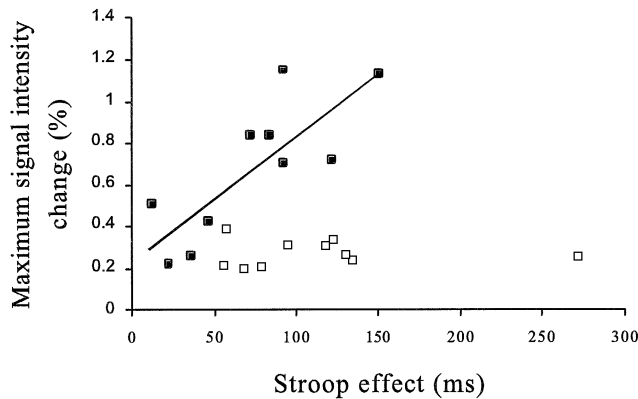


Fig. 3 Correlation between the size of the Stroop effect (ms) and the maximum percentage signal intensity change between the interference and the neutral conditions in the predominantly left frontal region (identified in the patient–control, random-effects group analysis) in patients (filled squares; $r = -0.71$, $P = 0.02$) and controls (open squares; $P > 0.05$).

To test whether this largely left medial prefrontal activation in the patients was a consequence of the (non-significantly) longer reaction time to the stimuli (as distinct from cognitive processing more specifically associated with the Stroop effect), we tested for a relationship between the maximum signal intensity change in this cluster region in the neutral–rest contrast and the mean neutral reaction time. No correlation was found ($r = 0.44$, $P = 0.20$).

Controls had greater right frontal activation than patients

A random-effects analysis contrasting controls–patients was performed for the interference–neutral contrast. A significant cluster (corrected $P = 0.004$, maximum Z score = 4.1, 1191 voxels) was found with distinguishable local activation maxima in the pars operculum of the right inferior frontal gyrus (BA 45) and in the right basal ganglia (Table 2, Fig. 4). The maximum percentage signal intensity changes for this right inferior frontal cluster were significantly higher in the healthy controls than in the patient group (controls, median 0.55%, range 0.26–1.09%; patients, median 0.19%, range 0.08–0.33%, $P < 0.001$). There was no correlation between the magnitude of the Stroop effect and the maximum signal intensity change (interference–neutral contrast) in this region of interest for either the controls or the patients.

Larger changes in brain activation relative to controls were found in patients with greater brain atrophy

For each patient, an activation ratio (AR) was calculated expressing the magnitude (mean signal intensity change) of the largely left medial prefrontal activation (unique to the patients) relative to activation in right frontal region and

(reduced in the patients). A low AR thus was characteristic of controls and higher AR values were characteristic of the patients. There was an inverse correlation between AR and the age-adjusted NBPV ($r = -0.72$, $P = 0.02$) for the patient group (Fig. 5). A similar relationship was not found for the controls. However, data from the patients did not show a significant relationship between the AR value and either the whole brain white matter lesion load ($r = 0.32$, $P = 0.41$) or the lesion load in the right frontal white matter ($r = 0.23$, $P > 0.55$).

The different patterns of activation in controls and patients observed during the interference–neutral contrast were not due to differences in ‘baseline’ signal intensity changes in the neutral task relative to rest

We tested whether the group activation differences for the interference–neutral contrast could have arisen from differences in relative brain activity during the neutral–rest contrast, i.e. whether the relative reduction of activity in the right hemisphere in the patient group during the interference–neutral task was due to a high ‘baseline’ (neutral–rest) activation. However, there was no significant difference between maximum signal changes for the patient or control groups in either the right inferior frontal or the predominantly left medial prefrontal regions of interest.

Stroop activation changes correlate with neuropsychological deficits in patients

A battery of neuropsychological tests was administered to both subject groups (see Subjects and methods). There was no significant difference in the frequency of anxiety or depressive symptoms between patients and healthy controls. There was a significant difference in neuropsychological test scores between patients only for phonemic VF (FAS) [patients, mean (SD) Z score -0.87 (1.03); controls, mean (SD) Z score 0.50 (1.45), $P = 0.05$; relative FAS deficit score for patients, mean (SD) -9.60 (8.33); FAS deficit for controls, mean (SD) 1.20 (14.98), $P = 0.04$]. The FAS deficit score correlated inversely ($r = -0.83$, $P < 0.001$) with AR for the patients, although there was no significant relationship between the FAS deficit and AR for the controls.

Rivastigmine normalized patterns of brain activation in patients during the counting Stroop task

To test for potential cholinergic modulation of the abnormal, disease-associated pattern of brain activation in the patients, rivastigmine effects were studied in five patients and in four healthy controls. Each subject was studied on two occasions



Fig. 4 A mixed-effects contrast of brain regions activated during the Stroop task (interference–neutral contrast) in controls–patients revealed a cluster extending over the opercular surface of right frontal lobe and right basal ganglia. Distinct activation maxima were found in the opercular surface of the right inferior frontal gyrus (38, 20, 6) and the right basal ganglia (20, 12, 14). Cross hairs are situated over the local maximum Z score in the right inferior frontal lobe.

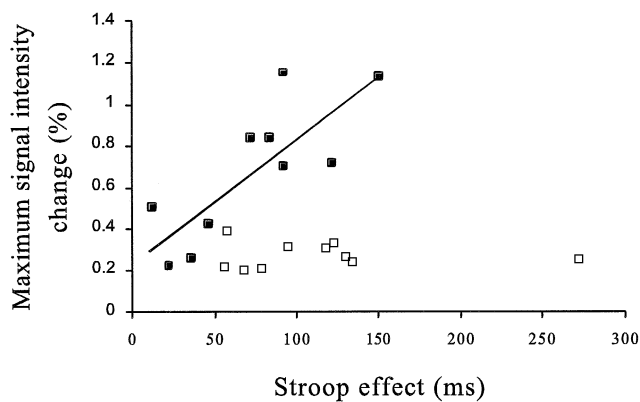


Fig. 5 Correlation between NBPV and the AR. A best-fit trend line is superimposed on the data points from the patients ($r = -0.72$, $P = 0.02$). No correlation was found for the controls. Filled squares, patients; open squares, controls.

and administered either oral rivastigmine or placebo 150 min before fMRI scanning in a double-blinded fashion.

Only mild adverse effects were reported. Two patients and two controls complained of feeling light-headed ~90 min after taking a rivastigmine tablet. One patient complained of feeling light-headed ~60 min after taking the placebo tablet.

There was a mean 56% lower maximum signal intensity change in the predominantly left medial prefrontal region of interest with the Stroop task after rivastigmine administration compared with placebo (relative signal intensities: median drug 0.36%, range 0.21–1.06%; median placebo 0.80%, range 0.72–1.21%) for the patients. This was associated with a mean 34% increase in maximum signal intensity in the right inferior frontal region of interest (relative signal intensities: median drug 0.32%, range 0.23–0.69%; median placebo 0.21%, range 0.17–0.86%) for the patients (Fig. 6). The AR was calculated from counting Stroop fMRI data for each patient both after being given rivastigmine or placebo. The median AR for the patients decreased by a mean 74% on rivastigmine relative to placebo (median AR drug 1.0, range 0.8–2.1; median AR placebo 3.9, range 2.5–8.9; Greenhouse–

Geisser, $F = 6.53$, $P = 0.05$). A decrease in AR with rivastigmine treatment was observed in five out of five of the patients.

To determine whether this effect was specific for the patient group, brain activity also was contrasted in four healthy controls receiving either placebo or rivastigmine. In contrast to the patients, there was no change in AR in any of the controls after rivastigmine administration (median AR drug 0.9, range 0.5–1.6; median AR placebo 1.1, range 0.4–1.6) (Fig. 6).

Comparison of results from patients or healthy controls who received no intervention with those who received placebo shows no effect of the placebo on AR.

The small size of the population in this pilot study prevented meaningful testing for behavioural responses to rivastigmine. However, no significant differences between accuracy or speed of responses in the rivastigmine and placebo trials could be defined (Greenhouse Geisser, $F = 0.37$, $P = 0.57$) for either patients or controls.

Discussion

Our first novel observation is that multiple sclerosis patients and age-matched, healthy controls activate distinct brain regions during the counting Stroop test, despite similar task performance. When contrasted with the healthy controls, the multiple sclerosis patients show greater activation primarily in the left middle frontal gyrus/left superior frontal sulcus and bilateral superior frontal gyrus (BA 8/9/10). When contrasted with the patients, the controls show greater activation in the right inferior frontal cortex (BA 45) and in the right basal ganglia. The patients did not show significant cognitive impairment. The recruitment of additional brain regions in the patients suggests that functional plasticity may contribute to maintaining this relatively normal cognitive behaviour. The extent of the differences in the patterns of brain activation observed in the multiple sclerosis patients (defined by the AR) is correlated with NBPV, a measure of total brain disease burden (Rudick *et al.*, 1999; S.M. Smith *et al.*, 2002).

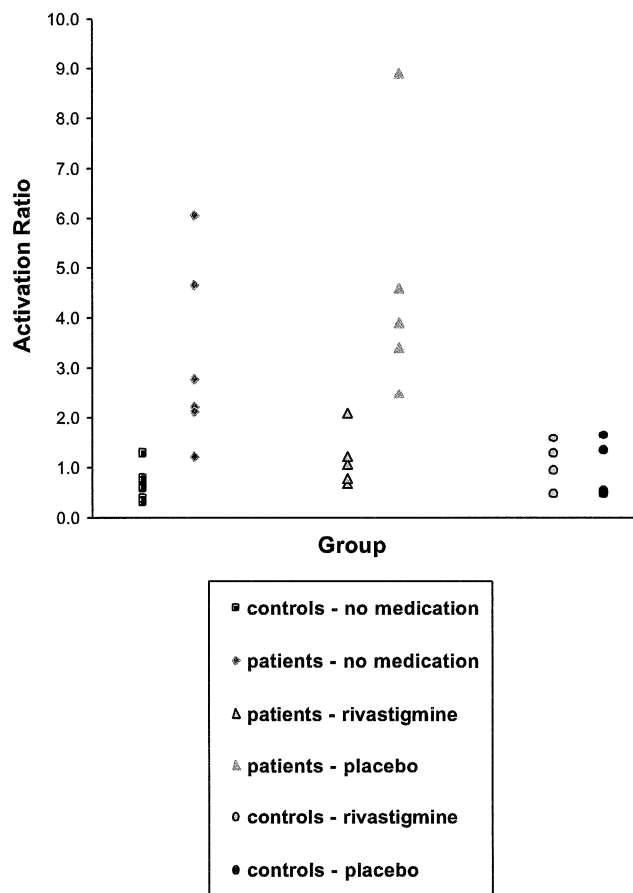


Fig. 6 A scatter plot showing AR values for individual subjects with no agent administered and after either placebo or rivastigmine administration. These data demonstrate show how the mean AR for patients is greater than for the healthy controls on placebo (or with no agent), but in the control range after rivastigmine administration. Decrease in AR with rivastigmine were found with five patients. However, no drug effect was seen in any of the healthy controls. These data also confirm that placebo treatment did not change the AR from that for subjects given no agent.

This suggests that the potentially adaptive functional changes are responses to disease-associated brain injury.

The functional relevance of the predominantly left medial frontal recruitment to the interference task for the patients was demonstrated by the significant relationship between the maximum signal change in this region of interest and the magnitude of the Stroop effect. There was no correlation in the relative signal intensity change in this region between the neutral–rest contrast and the neutral reaction time. Similar activations in the left middle and superior frontal gyri have been observed in healthy controls with other cognitive tasks requiring generation of an internal response, inhibition with selection of a response from among alternatives or self-monitoring while maintaining multiple contingencies on-line (Schlosser *et al.*, 1998; Leung *et al.*, 2000; Ruff *et al.*, 2001). We propose that the larger activation for patients in this region is related to the need for increased internal perform-

ance monitoring as the relative impairment of primary processing functionally relevant to task performance increases with greater disease burden.

Although not significant, there was a trend towards a reduction in the Stroop effect, despite previous reports of an increased Stroop effect in patients with multiple sclerosis (Pujol *et al.*, 2001; Vitkovitch *et al.*, 2002). This difference may reflect differences in the distribution of lesions in the brain for patients in the different studies. Patients with lesions predominantly in the right parietal lobe may have a reduced Stroop effect, for example (Pujol *et al.*, 2001).

Our second observation is that a single 3-mg dose of the cholinesterase inhibitor, rivastigmine (a drug that can enhance aspects of cognition in different neurodegenerative and vascular diseases; Freo *et al.*, 2002), led to normalization of the abnormal patterns of brain activation in the multiple sclerosis patients. This observation was consistent for all of the patients examined and not found for the healthy controls. This suggests that the functional changes in patients are modulated by cholinergic agonism and that they occur rapidly.

Right prefrontal cortex activity in the Stroop response is reduced in the patients

During the Stroop task, subjects must selectively attend to the task-relevant dimension of the stimulus while ignoring the stronger (and conflicting) task-irrelevant dimension. The prefrontal cortex is thought to play a critical role in this task by providing ‘top-down’ control to favour the processing of the task-relevant stimuli in the presence of more salient stimuli and to represent and maintain task demands needed for cognitive control (Miller *et al.*, 1998; Brass *et al.*, 2001). The right lateral prefrontal cortex specifically appears to mediate this behavioural inhibition (Miller and Cohen, 2001): fMRI activation in the right inferior frontal lobe and basal ganglia during the Stroop task has been observed consistently in previous studies of healthy subjects (Peterson *et al.*, 1999; Leung *et al.*, 2000). The ipsilateral basal ganglia shows strong connectivity to the prefrontal cortex and may process related functions in automating behaviour (Miller and Cohen, 2001) or in modulation of the motor output (Gehring and Knight, 2000).

Activation in this right prefrontal region is reduced in multiple sclerosis patients. As fMRI activation is related to local neuronal synaptic activity (Lauritzen, 2001; Logothetis, 2002), in the context of disease reduced activity likely results from the brain pathology. Consistent with this, fMRI activity was related to relative mean brain volume, which in this case is a measure of diffuse, irreversible pathology. The lack of correlation between activity changes and the alternative measure of disease burden provided by MRI lesion load is not surprising given the weak relation of this non-specific index of pathology to measures of functional impairment or disability and the relatively greater extent of the total injury burden found in the normal-appearing white matter (Miller *et al.*, 1998; Evangelou *et al.*, 2000). Specifically relevant pathology may involve functional ‘disconnection’ with

neuronal or axonal damage (Evangelou *et al.*, 2000; Cifelli *et al.*, 2002). Alternatively, demyelination could alter the summation of responses contributing to the blood oxygen level-dependent (BOLD) signal (i.e. change the relationship between time-averaged neuronal and haemodynamic responses by decreasing the temporal coherence of neuronal firing) (Smith and McDonald, 1999).

Distributed activation increases in the patients as an adaptive response to brain injury

We hypothesize that the abnormal recruitment of the predominantly left medial frontal brain regions observed in the patients is an adaptive response to the brain injury from multiple sclerosis. In principle, such an adaptive response may be mediated by altered synaptic efficiency, ‘unmasking’ of latent pathways (Sanes *et al.*, 1988; Jacobs and Donoghue 1991) or formation of new local connections (Li *et al.*, 1998). The acute modulation of this response by rivastigmine (see below) suggests that the latter is less likely. To our knowledge, this is the first time that potential functional reorganization potentially able to contribute to maintaining cognitive performance despite pathological changes has been reported with multiple sclerosis.

Action of rivastigmine in patients

The reduction in the AR in patients with rivastigmine administration was a result both of a decrease in the fMRI activation in the predominant left medial frontal region of interest and an increase in the fMRI activation in the right prefrontal region of interest. Acetylcholine-containing neurons project diffusely through the brain and modulate activity by increasing neuronal responsiveness to excitatory input (Mesulam *et al.*, 1986; McGaughy *et al.*, 2000). We propose that the primary effect of the drug-induced increase in acetylcholine is to facilitate brain processing associated with the right prefrontal activation. Adaptive responses in the predominantly left frontal cortex regions then decrease in consequence.

An earlier PET study (Furey *et al.*, 1997) examining the effects of physostigmine (an acetylcholinesterase inhibitor) on a visual working memory task in healthy control subjects demonstrated reduced task-associated activation in the right middle frontal gyrus, a region of the frontal cortex characteristically activated by this task. In this case, reduced functional activation was interpreted as reflecting improvements in task performance. A subsequent fMRI study using a cholinesterase inhibitor in patients with Alzheimer’s disease showed both increases and decreases in regionally specific, task-associated activations (Rombouts *et al.*, 2002). As they were accompanied by behavioural gains, the preferred interpretation was these changes reflected increases in activity in essential processing regions and decreases in activity in regions with adaptive responses.

We did not observe improvements in any of the behavioural outcome measures (e.g. a reduction in the size

of the Stroop effect with rivastigmine). The drug could alter cortical processing without changing performance, as has been observed in previous functional imaging studies (Kimberg *et al.*, 2001; Mattay *et al.*, 2002). However, the group of subjects studied was small and the power to detect a behavioural effect was low. An earlier, somewhat larger, study reported improvements in measures of cognitive function in multiple sclerosis patients treated with donepezil, an acetylcholinesterase inhibitor (Greene *et al.*, 2000).

Conclusions

Overall, our results show that patients and controls have significant differences in the regions of the prefrontal cortex activated during the counting Stroop task, despite showing similar Stroop effects behaviourally. The magnitude of the brain activation differences is strongly related to a global MRI measure of disease burden in the patients. The pattern of change suggests that cortical plasticity with recruitment of medial prefrontal cortex may adaptively compensate for functional impairment of in patients (Lee *et al.*, 2000). Defining factors contributing to this potential functional plasticity may be important for understanding the relationship between the disease burden in multiple sclerosis and neuropsychological consequences. We have identified one candidate factor by demonstration of effects of rivastigmine, which increases cholinergic agonism. The acute response to this drug also suggests that the plasticity characterized here may not demand structural reorganization, emphasizing the potential importance of ‘unmasking’ of latent pathways. Results suggest that cholinergic agonism could improve at least symptoms related to executive function and attention in multiple sclerosis patients. It is possible that this, in addition to possible effects on basal ganglia circuits (Chaudhuri and Behan, 2000), could also contribute to improvement of symptoms of fatigue.

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