

Functional brain reorganization for hand movement in patients with multiple sclerosis: defining distinct effects of injury and disability

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Summary

Previous work has demonstrated potentially adaptive cortical plasticity that increases with brain injury in patients with multiple sclerosis. However, animal studies showing use-dependent changes in motor cortex organization suggest that functional changes also may occur in response to disability. We therefore wished to test whether brain injury and disability lead to distinguishable patterns of activation with hand movement in patients with multiple sclerosis. By employing a passive as well as an active movement task, we also wished to test whether these changes were independent of voluntary recruitment and thus more likely to reflect true functional reorganization. Fourteen patients [Extended Disability Status Score (EDSS) 0–7.5] with relapsing–remitting multiple sclerosis were selected on the basis of pathology load and hand functional impairment for three study groups: group 1, low diffuse central brain injury (DCBI) as assessed from relative N-acetylaspartate concentration (a marker of axonal integrity) and normal hand function ($n = 6$); group 2, greater DCBI and normal hand function ($n = 4$); and group 3, greater DCBI and impaired hand function ($n = 4$). Functional MRI (fMRI) was used to map brain activation with a four-finger and both one-finger passive and active flexion–extension movement tasks for the three groups. Considering all the patients, we found increased activity in ipsilateral premotor and ipsilateral motor cortex (IMC) and in the ipsilateral inferior parietal lobule

with increasing global disability (as assessed from the EDSS score). These changes appear to define true functional reorganization, as fMRI activations in IMC ($r = 0.87$, $P < 0.001$) and in the contralateral motor cortex ($r = 0.67$, $P < 0.007$) were highly correlated between active and passive single finger movements. We attempted to disambiguate any distinct effects of disability and brain injury by direct contrasts between patients differing predominantly in one or the other. To make these contrasts as powerful as possible, we used impairment of finger tapping as a measure of disability specific to the hand tested. A direct contrast of patients matched for DCBI, but differing in hand disability (group 3 – group 2) showed greater bilateral primary and secondary somatosensory cortex activation with greater disability alone. A contrast matched for hand disability, but differing in DCBI (group 2 – group 1) showed a different pattern of changes with relative ipsilateral premotor cortex and bilateral supplementary motor area activity. We conclude that the pattern of brain activity with finger movements changes both with increasing DCBI and with hand disability in patients with multiple sclerosis, and that these changes are distinct. Those related directly to disability may reflect responses to altered patterns of use. As injury- and disability-related activation changes are found even with passive finger movements, they may reflect true brain reorganization.

Keywords: fMRI; multiple sclerosis; brain; disability; recovery

Abbreviations: BICCR = brain to intra-cranial capacity ratio; CMC = contralateral motor cortex; Cr = creatine; DCBI = diffuse central brain injury; EDSS = Extended Disability Status Score; fMRI = functional MRI; IMC = ipsilateral motor cortex; LI = laterality index; MRS = magnetic resonance spectroscopy; NAA = N-acetylaspartate; ROI = region of interest; SMA = supplementary motor area

Introduction

In the early stages of multiple sclerosis, there can be good functional recovery from relapses but, even then, myelin and axonal injury are only incompletely reversible (De Stefano *et al.*, 1995, 1997; Scolding, 1999). Adaptive reorganization by activation of parallel pathways, local synaptic reorganization or expansion of functional cortex may additionally compensate for injury. This occurs after brain injury from stroke, for example, in both animal models and in humans (Weiller *et al.*, 1992; Cramer *et al.*, 1999; Nelles *et al.*, 1999; Marshall *et al.*, 2000; Dijkhuizen *et al.*, 2001; Pineiro *et al.*, 2001). Previously, we provided evidence for such phenomena in patients with multiple sclerosis in whom measures of motor cortex reorganization for movement control correlate with disease burden (e.g. as measured by T₂ lesion load) or axon injury [measured by decreases in N-acetylaspartate (NAA)] (Lee *et al.*, 2000; Reddy *et al.*, 2000a, b). These cortical functional changes evolve dynamically: this is consistent with the notion that they may provide an early mechanism to facilitate clinical recovery before reversible axonal injury is repaired (Reddy *et al.*, 2000b).

There likely is a complex interaction between disability and functional activation in the brain. Traditional imaging approaches to multiple sclerosis have concentrated on directly relating structural measures of pathological change (Riahi *et al.*, 1998; Pineiro *et al.*, 2000) to disability. Functional MRI (fMRI) studies such as those cited above suggest that functional changes may account in part for the limited relationship between brain pathology and disability. However, repeated limb movements also dynamically alter motor cortex excitability or threshold and the localization or extent of representations (Butefisch *et al.*, 2000; Ziemann *et al.*, 2001). An altered pattern of limb use after brain injury can lead to changes in brain activity with movement (Pascual-Leone *et al.*, 1994; Taub *et al.*, 1999; Liepert *et al.*, 2000). Limiting independent movement of individual digits leads to fusion of cortical sensory representations of the digit (Clark *et al.*, 1988). Thus, while there may be a general relationship between pathological injury and new patterns of brain activation, disability itself may further modify these patterns.

Testing this hypothesis fully in humans is difficult. General confounds to interpretation of differences in patterns of brain activity between healthy controls and patients come from performance differences. This may be less problematic when mildly impaired patients are studied (Reddy *et al.*, 2000a), but restricting the study population in this way limits the range of injury responses that can be investigated. Use of a passive task to allow meaningful comparisons between controls and patients has been proposed (Weiller *et al.*, 1996; Nelles *et al.*, 1999). This approach has recently been validated for at least one example of pathology (Reddy *et al.*, 2001). There are strong reciprocal projections between motor and related sensory cortex; thus, patterns of brain activation which reflect local field potentials from presynaptic activity primarily (Mathiesen *et al.*, 1998; Logothetis *et al.*, 2001),

even with entirely passive movements, may define those brain regions involved in active voluntary movements.

Responses to a passive task also may allow the conceptually important distinction between adaptive reorganization and compensation to be made in studies of brain injury (Robertson and Murre, 1999). Reorganization implies a longer lasting change in synaptic strengths or connections in response to injury, and would be expected to alter patterns of brain activation for both active and passive tasks. This could involve recruitment of novel pathways or changes in the way pathways customarily engaged are recruited. In contrast, compensation occurs when an altered strategy is used so that the task is performed in a different way. Compensation mechanisms for motor action should not alter activation patterns induced by passive movement of the limb.

Here we describe a series of fMRI experiments designed to better understand the significance of altered patterns of brain activation with finger movements in patients with multiple sclerosis. The load of pathology in both the brain and cervical spinal cord in each patient was characterized by structural and spectroscopic MRI. A first experiment was to use a general approach to identify regions of the brain that show changes in activity correlated with increasing global disability, as assessed from the Extended Disability Status Score (EDSS). We compared responses to both active and passive finger movement tasks to test whether activation changes reflect adaptive reorganization or compensation. We then tried to identify patients with similar injury load but different degrees of hand disability to test whether factors related to impairment or disability make independent contributions to determining patterns of brain activity associated with movement in multiple sclerosis. As the EDSS is less sensitive to functional impairment of the upper limb, we assessed hand disability from the maximum rate of finger tapping to maximize the power of the contrasts here.

Methods

Patients

All subjects were right-handed. Eight healthy controls from hospital and research staff were studied for spectroscopy and finger tapping rates. Relapsing–remitting or relapsing–progressive multiple sclerosis patients (Table 1) were selected according to four criteria: (i) degree of disability specific to the hand as assessed from the maximum finger tapping rate (Rooney *et al.*, 1998); (ii) central brain NAA/creatine (Cr) levels within or below two standard deviations from normal (mean \pm 1 SD = 3.1 \pm 0.2); and (iii) absence of symptoms or signs of sensory impairment in the upper limbs (Table 1).

Six relapsing–remitting patients were selected as group 1 with normal, control range maximum hand tapping rates (>4 Hz), NAA/Cr > 2.7. Four relapsing–progressive patients were selected for group 2 with normal maximum four-finger tapping rates and central brain NAA/Cr < 2.7. Four relapsing–progressive patients were selected for group 3 with reduced

Table 1 Description of disability in patients and measures of load of pathology

Patient	EDSS	Maximum finger tapping rate (Hz)	NAA/Cr	Normalized cerebral volume (BICCR)	Axonal equivalents	Cervical cord area (mm ²)
Group 1						
1	1	6.8	3.08	0.841	2.59	73.1
2	1.5	4.7	2.96	0.878	2.60	65.6
3	1.5	5.2	3.00	NA	NA	80.5
4	0	4.7	3.32	0.926	3.07	95.2
5	1	5.6	3.14	0.871	2.73	84.3
6	0	4.3	2.83	0.910	2.58	71.1
Mean/median	1	5.2	3.06	0.885	2.71	77.1
SD		0.9	0.17	0.033	0.21	11.5
Group 2						
7	4	6.3	2.59	0.844	2.19	NA
8	4	4.8	2.34	0.883	2.07	64.9
9	6	5.3	2.47	0.851	2.10	71.4
10	5.5	3.9	2.49	0.842	2.10	63.3
Mean/median	5.0	5.1	2.47	0.855	2.12	66.5
SD		1.0	0.10	0.019	0.05	4.3
Group 3						
11	2.5	3.4	2.59	0.838	2.17	68.7
12	6	2.7	2.58	0.832	2.15	55.0
13	7.5	2.6	2.24	0.841	1.88	62.9
14	6	3.5	2.69	0.825	2.22	71.8
Mean/median	6	3.1	2.53	0.834	2.11	64.6
SD		0.5	0.30	0.071	0.15	7.4

The patients were divided into three groups based on relative right hand functional impairment (maximum finger tapping rate) or pathology load (central brain NAA/Cr). Additional pathology measures of BICCR and cervical spinal cord area, as well as the derived measure of 'axonal equivalents' are shown. The median (rather than the mean) is given for EDSS. NA = data not available.

maximum four-finger tapping rates and central brain NAA/Cr < 2.7. There was no significant difference between the diffuse central brain injury (DCBI) assessed by NAA/Cr for groups 2 and 3 (Table 1).

In a secondary test, we also used measures of normalized brain to intra-cranial capacity ratio (BICCR) (Collins *et al.*, 2002) and spinal cord cross-sectional area (Narayanan *et al.*, 2000) at the C2 level to confirm that the burden of pathology did not differ significantly between patients in groups 2 and 3 (Table 1). None of the patients had evidence for, or a history of, clinically-evident sensory impairment of the limb tested.

Hand movement task for fMRI

The first fMRI task was a simple four-fingered flexion-extension of the right hand at the metacarpal-phalangeal joints alternating with rest. This was done at 75% of each patient's maximum rate, measured as the mean of values averaged between two trials of 10 s each. The second task involved flexion-extension of the metacarpal-phalangeal joint of the third (middle) finger at 50% of each individual's maximum rate either actively or passively, alternating with rest. The finger was splinted at the proximal and distal interphalangeal joints. The splint was attached to the upper surface

of the finger and, in the active task, the subjects moved their finger through a fixed angle (approximately 30°). In the passive task, the finger was raised and lowered the same distance by the experimenter holding the end of the splint. Cutaneous stimulation was, therefore, similar between the two tasks. The experimenter stood just outside of the magnet bore and was able to observe the arm and hand easily during all movements. Subjects were instructed not to aid the passive movements in any way.

For both tasks, subjects were trained outside the scanner. Surface EMG (high filter 10 k; low filter 20 k; gain adjusted for peak-to-peak baseline amplitude typically under 10% of the maximum signal response seen with movement) was performed at this time with an electrode placed over the mid-belly of the extensor digitorum longus muscle to ensure that the passive task could be performed by each subject without detectable muscle activity.

Structural MRI

Conventional proton MRI and magnetic resonance spectroscopy (MRS) examinations of the brain were performed during the same scanning session using a Philips Gyroscan ACS II (Philips, Best, The Netherlands) at 1.5 T. Normalized

BICCR was measured from dual echo MRI images [TR (repetition time)/TE1 (echo time 1)/TE2 (echo time 2) = 2075/32/90 ms, 256 × 256 matrix, 250 mm FOV (field of vision), slice thickness 3 mm] using a fully automated method measuring the BICCR (Collins *et al.*, 2002). Briefly, the method relies on a Bayesian tissue classification in standard brain space, from which the parenchyma volume is computed as a fraction of the total intracranial volume. Spinal cord atrophy was measured from T₁-weighted images (TR = 27 ms, TE = 7.5 ms, 256 × 256 matrix, 150 mm FOV, 20° flip angle). Twenty-five transverse slices (0.6 mm × 0.6 mm × 1 mm) were acquired perpendicular to the cord. This small volume dataset was resampled to align it more precisely perpendicular to the cord. The cord was segmented according to signal intensity and the cross-sectional area at C2 measured from the calibrated total cord voxel count at this level (Narayanan *et al.*, 2000).

MRS

Anatomical images were used to select a 20 mm thick volume of interest centred on the corpus callosum and measuring 90 mm × 90 mm in the axial plane. Acquisition of spectroscopic images and post-processing of the raw data were performed as previously described (De Stefano *et al.*, 1998). Values for the NAA/Cr ratio were calculated individually for each voxel and then averaged across the entire acquisition volume to calculate the average in each subject. Lesions were segmented manually using Display software developed in-house (Dr D. Macdonald, Brain Imaging Centre, Montreal Neurological Institute, Canada).

Central brain NAA/Cr measurements reflect an effective axonal 'density'. The total loss of axonal volume in the multiple sclerosis patients is best estimated by a combined measure accounting both for decreased axonal density and volume (Evangelou *et al.*, 2000). The relative total axonal injury in the patients therefore was estimated as 'axonal equivalents' (Matthews *et al.*, 1998), a unit-less index calculated as the product of the BICCR and the central brain NAA/Cr ratio.

fMRI

Data were acquired using a 1.5T Siemens Magnetom Vision (Siemens, Erlangen, Germany) [gradient echo EPI (echo-planar imaging), TR = 4 s, TE = 47 ms, FOV 320 × 320 mm, 64 × 64 matrix, slice thickness 6 mm]. For the four-finger tapping task, movement was alternated with rest in an 'ABAB' block design. The single digit active movement task was alternated with rest or passive movement in an 'ABAC' block design. Two trials were performed for movements of each hand during each experimental session.

For the analysis, data from the two trials with each hand were concatenated. Image processing and statistical analysis for individual brain analyses were carried out using FEAT (www.fmrib.ox.ac.uk/fsl), an analysis package developed in

Oxford using basic functionalities of MEDx 3.0 (Sensor Systems, Inc., Maryland, USA). Activation maps were calculated using Student's unpaired *t*-test, and cluster detection was performed on all voxels above $Z = 6.0$ to determine clusters significantly activated ($P < 0.01$) (Forman *et al.*, 1995; Poline *et al.*, 1997). The EPI was registered to the high resolution structural image and the resulting transform applied to the activation map, which was then overlaid on a high resolution T₁ structural image for neuroanatomical correlation of the activations.

Analysis of group activation behaviour was carried out using an extension of FEAT statistics after transformation of the activation images into a standard brain space. This involved using a linear model at the second level (i.e. after primary statistical comparison between the task versus rest conditions) for a random effects analysis (Holmes and Friston, 1996). Data for the second level were the parameter estimates (equivalent to the voxel-by-voxel percentage signal change for the task) from the first level analyses for each subject with the EDSS for each subject as the regressor. This second level linear model was fitted separately at each voxel assuming a 'white' noise model. The resulting Z (Gaussianized T/F) statistical images were thresholded to generate activation clusters determined by $Z > 2.3$ with a significance threshold of $P = 0.01$ (Worsley *et al.*, 1992; Holmes and Friston, 1996; Poline *et al.*, 1997).

The motor cortex was defined on the structural image using anatomical landmarks to allow quantitative assessment of the extent of activation. Three regions of interest (ROIs) were defined and registered with the Z -statistical functional images; significantly activated voxels within each were counted. The primary motor cortex included the volume bounded by the interhemispheric fissure medially, the central sulcus posteriorly, the pre-central sulcus anteriorly, and the sylvian fissure laterally. The premotor area included the middle frontal gyrus posterior to the anterior commissure. The supplementary motor area (SMA) was defined to include the superior frontal gyrus posterior to the anterior commissure and anterior to the primary motor cortex. The term 'motor cortex' is used to include both the primary motor cortex and the premotor cortex either ipsilateral or contralateral to the hand moved. A motor activation laterality index (LI) was calculated as $(C - I)/(C + I)$ where C is the number of significantly activated voxels in the contralateral motor cortex (CMC) and I is the number of significantly activated pixels in the ipsilateral motor cortex (IMC).

Statistics for multiple comparisons were performed using an ANOVA (analysis of variance) with Tukey's *post hoc* test as implemented in SPSS v.7.0 (www.spss.com). Correlations were tested with Spearman's test. Values are given as mean ± 1SD.

Results

The right-handed patients had either relapsing–remitting ($n = 6$) or relapsing–progressive ($n = 8$) multiple sclerosis

(Table 1). None had suffered a recent relapse. None had sensory symptoms or signs in the arms or hands. No mirror movements were noted during finger tapping for any of the patients. The BICCR and effective 'axonal equivalents' were reduced in both groups 2 ($P < 0.001$) and 3 ($P = 0.001$) relative to group 1, but were similar in groups 2 and 3. Relative disability specific to the dominant (right) hand was assessed from the maximum rate of finger tapping. Group 1 did not show a significant reduction relative to healthy controls ($n = 8$) in either maximum finger tapping rates ($4.5 \text{ Hz} \pm 0.6 \text{ Hz}$) or in central brain NAA/Cr (3.26 ± 0.16). The maximum finger tapping rate was lower for group 3 than either group 1 ($P = 0.005$) or group 2 ($P = 0.01$), but there was no difference between rates for groups 1 and 2. No significant differences in cervical cord cross-sectional areas at the C2 level were found between the patient groups.

Brain activation changes correlating with increasing disability

Patterns of brain activation with four-finger extension–flexion movements were as described previously (Reddy *et al.*, 2000a). The most significant activations were in the contralateral primary sensorimotor ($x = -38$, $y = -19$, $z = 66$; $Z_{\text{max}} = 22.8$) cortex, the SMA ($x = -4$, $y = -11$, $z = 54$; $Z_{\text{max}} = 13.8$), the ipsilateral post-central gyri ($x = 58$, $y = -32$, $z = 44$; $Z_{\text{max}} = 4.9$), anterior pre-central gyri ($x = 37$, $y = 0$, $z = 44$; $Z_{\text{max}} = 5.0$) and bilateral secondary somatosensory cortex (superior temporal gyri) (coordinates given as ipsilateral or contralateral, respectively, with respect to the hand moved: $x = 52$ or $x = -52$, $y = -27$ or $y = -29$, $z = 16$ or $z = 16$; $Z_{\text{max}} = 9.2$ or $Z_{\text{max}} = 9.1$).

Our previous fMRI studies of multiple sclerosis concentrated on analysis of relative activation in motor cortex because analysis of multiple ROIs across individual subjects suggested that these areas showed the largest disease-associated changes (Lee *et al.*, 2000; Reddy *et al.*, 2000a). To test this conclusion more directly, we used disability (EDSS) as an explanatory variable in a random effects analysis across the patients in the current study (Fig. 1). The most significant changes correlated with disability were again found in ipsilateral dorsal premotor (middle/superior frontal gyrus) ($x = 22$, $y = -17$, $z = 52$; $Z_{\text{max}} = 4.0$) and primary motor (precentral gyrus) cortex ($x = 40$, $y = -15$, $z = 52$; $Z_{\text{max}} = 4.0$), as well as the inferior parietal cortex ($x = 36$, $y = -53$, $z = 48$; $Z_{\text{max}} = 4.0$) (Table 2). Activation was found in the SMA ($x = 12$, $y = -20$, $z = 52$; $Z_{\text{max}} = 2.9$).

Both brain injury and impairment of hand function may contribute to altered patterns of brain activation

A weakness of this test for the possible role of disability in determining patterns of functional activation is that disability and DCBI are, in general, strongly correlated. To test for

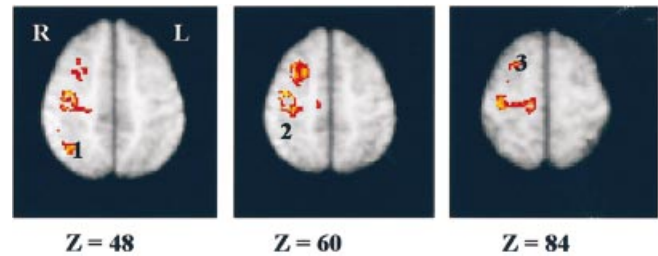


Fig. 1 Random effects group analysis showing regions of statistically significant activation change for (dominant) right hand movement with increasing disability (EDSS). The most significant changes are in the ipsilateral premotor and primary sensorimotor cortex, with additional changes in parietal cortex (intraparietal sulcus) and in the ipsilateral SMA. Clusters are thresholded for a corrected significance of $P = 0.01$ with Z-coordinates in standard space shown below the corresponding image. Regions: 1, inferior parietal cortex; 2, precentral gyrus (ipsilateral primary motor cortex); 3, superior/middle frontal gyrus (ipsilateral premotor cortex). Right (R) and left (L) hemispheres are marked.

Table 2 ROI analysis for the four-finger extension task

Patient	CMC	IMC	SMA	LI
Group 1				
1	25	0	5	1.00
2	43	3	31	0.87
3	25	0	14	1.00
4	14	0	2	1.00
5	49	13	68	0.58
6	59	1	21	0.97
Mean	36	3	24	0.90
SD	17	5	24	0.17
Group 2				
7	17	3	35	0.70
8	23	2	12	0.84
9	60	23	69	0.45
10	26	7	4	0.58
Mean	32	9	30	0.64
SD	19	10	29	0.17
Group 3				
11	107	56	19	0.31
12	36	11	9	0.53
13	35	13	17	0.46
14	30	14	53	0.36
Mean	52	24	25	0.42
SD	37	22	19	0.10

Numbers of significantly activated voxels or relative motor cortex LI are given below as mean values \pm SD.

specific relationships between patterns of brain activation and either DCBI or disability, we tested contrasts between groups of patients chosen to differ in only one of these two variables. As the EDSS score does not provide a good index of hand disability, we used the maximum rate of finger tapping as a measure of disability specific to the hand studied by fMRI.

First, we investigated the effects of differences in DCBI. A direct contrast (group 2 – group 1) of patients without significant hand disability who had either normal (group 1) or reduced NAA/Cr and 'axonal equivalents' (group 2) showed

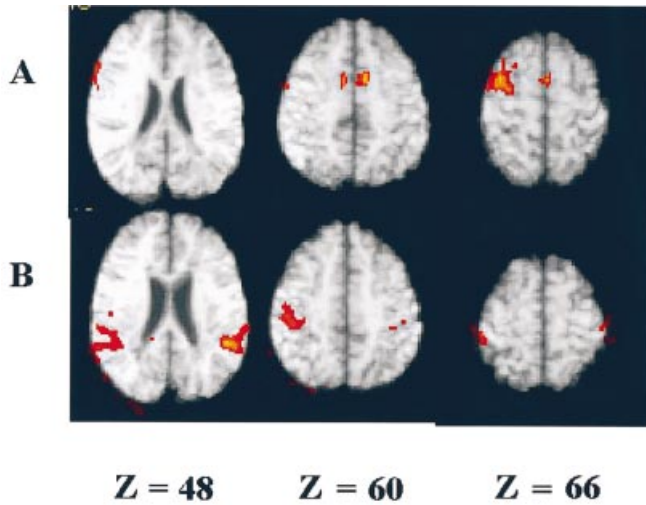


Fig. 2 Random effects group analysis of pairwise comparisons to test for increases in brain activation with: (A) greater diffuse cerebral brain injury (assessed by the relative central brain NAA/Cr) with no apparent functional impairment of the limb tested from contrast of group 2 versus group 1; and (B) greater limb functional impairment with similar diffuse cerebral brain injury in contrast of group 3 versus group 2. Note that distinct maps of change are defined for the two contrasts suggesting potentially independent contributions to cortical activation changes from brain injury and functional impairment or disability. Both maps are thresholded at $P = 0.01$ (corrected) with Z-coordinates in standard space shown below the corresponding image.

a significant activation increase in the ipsilateral premotor cortex (middle frontal gyrus) ($x = 36, y = 1, z = 60; Z_{\max} = 5.8$) and SMA bilaterally (coordinates given as ipsilateral or contralateral, respectively, to the hand moved: $x = 8$ or $-10, y = 4$ or $6, z = 48$ or $z = 52; Z_{\max} = 5.0$ or $Z_{\max} = 5.7$) with increased DCBI (Fig. 2A).

From measurement of the extent of activation in anatomically-defined ROIs including the CMC and the IMC, the motor cortex activation LI was found to be lower for group 2 than for group 1 ($P < 0.04$) (Table 2). A modest correlation between NAA/Cr and LI was found over the whole group ($r = -0.49, P = 0.03$).

To test whether hand disability itself (or factors determining it other than the central brain NAA/Cr measured) may alter patterns of cortical activation associated with hand movement, a direct contrast was performed between patients with similar DCBI, but either with (group 3) or without (group 2) a significant reduction in maximum finger tapping rate (Fig. 2B). A random effects analysis (group 3 – group 2) demonstrated a pattern different from that found with increased DCBI, showing greater bilateral primary (post-central gyrus) ($x = 46$ or $x = -46, y = -24$ or $y = -28, z = 40$ or $z = 54; Z_{\max} = 7.0$ or $Z_{\max} = 5.1$) and secondary somatosensory (superior temporal gyrus) cortex ($x = 62$ or $x = -50, y = -44$ or $y = -46, z = 20$ or $z = 20; Z_{\max} = 5.1$ or $Z_{\max} = 8.9$) with greater hand disability assessed in this way.

Consistent with the failure to identify activation changes in motor cortex using the extent of activation in a volume of interest defined by the IMC, there was only a trend ($P < 0.06$) for increased activation (associated with decreased LI) with greater hand disability over the whole group. Nonetheless it was group 3, which had the greatest hand disability and DCBI, that showed the lowest LI ($P < 0.01$ relative to group 1).

Altered patterns of activation change may reflect functional reorganization

A specific concern with this and previous studies demonstrating changes in functional activation with movement after injury was that the changes may reflect compensation rather than adaptation. To distinguish between these, we tested the patients with fMRI during both an active and a passive middle finger tapping task.

The passive task was, by design, performed in exactly the same way by all the subjects. We confirmed for each subject that the passive task could be performed with finger flexor and extensor muscles maintained at rest by direct observation during the passive movement task and by surface EMG performed during a training session preceding scanning (data not shown). There was no muscle contraction detectable by either method in the limb tested with passive movement during scanning.

As with the four-finger flexion–extension movement, all patients showed activation in both ipsi- and contralateral sensorimotor and premotor cortex and in the contralateral SMA for both the active and passive tasks (Table 3). Quantitative measures of relative extents of activation were made using large, anatomically-defined ROIs including both the IMC and CMC and the SMA (Table 2). The extents of activation were compared between the active and passive tasks for each ROI. There were good correlations between the extents of active and passive activation in the IMC ($r = 0.82, P = 0.001$) and CMC ($r = 0.67, P = 0.007$), but not in the SMA. LI values calculated for the active and passive tasks were highly correlated ($r = 0.93, P < 0.001$) (Fig. 3). The relative hemispheric lateralization of motor cortex activation with active movement has been shown previously to be sensitive to changes with multiple sclerosis (Lee *et al.*, 2000; Reddy *et al.*, 2000a, b) and other predominantly white matter disease (Reddy *et al.*, 2002). Here we found similar strong correlations between patient group membership (groups 1, 2 or 3) and LI for both the active ($r = -0.93, P < 0.001$) and passive ($r = -0.90, P < 0.001$) tasks, demonstrating a progressively decreasing LI as both injury load and hand disability increase (Fig. 4). Together, these results are consistent with the hypothesis that activation changes in the patients reflect true functional reorganization of motor pathways, independent of any altered patterns of volitional recruitment.

Table 3 ROI analysis for one-finger active or passive movements

Patient	CMC		IMC		SMA		LI	
	Active	Passive	Active	Passive	Active	Passive	Active	Passive
Group 1								
1	28	9	2	1	1	0	0.87	0.80
2	16	13	0	1	1	8	1.00	0.86
3	15	28	0	4	12	22	1.00	0.75
4	10	5	0	0	30	7	1.00	1.00
5	74	82	14	10	64	39	0.68	0.78
6	29	23	3	4	15	12	0.81	0.70
Mean	29	27	3	3	21	15	0.89	0.82
SD	23	28	5	4	24	14	0.13	0.11
Group 2								
7	11	8	3	2	14	23	0.57	0.60
8	23	21	6	4	44	4	0.59	0.68
9	50	31	14	5	65	42	0.56	0.72
10	34	31	11	13	16	5	0.51	0.41
Mean	30	35	9	6	35	19	0.56	0.60
SD	17	24	5	5	24	18	0.03	0.14
Group 3								
11	96	37	31	12	62	8	0.51	0.51
12	22	20	8	11	3	33	0.47	0.29
13	14	17	7	8	12	4	0.33	0.36
14	28	18	9	8	37	30	0.51	0.38
Mean	40	23	14	10	29	19	0.46	0.39
SD	38	9	12	2	27	15	0.09	0.09

The middle finger of the dominant hand was extended or flexed at 50% of each individual's maximum rate. Mean values are given \pm 1 SD for numbers of significantly activated voxels (in CMC, IMC or SMA) or the motor cortex LI.

Discussion

In previous work, we showed that patients with multiple sclerosis have altered patterns of brain activation that change progressively with increasing disease burden (Lee *et al.*, 2000; Reddy *et al.*, 2000a). However, as disease burden and disability are correlated (Arnold and Matthews, 2002) and changes in brain activation patterns may be expected from altered chronic limb use associated with disability (Pascual-Leone *et al.*, 1994; Taub *et al.*, 1999; Liepert *et al.*, 2000), we wished to test whether disability has an independent role in determining altered patterns of brain activation in multiple sclerosis. We also wished to resolve a fundamental ambiguity in interpretation of these functional imaging changes by determining whether the altered patterns of brain activation found in the patients were independent of voluntary recruitment and thus likely to reflect true functional reorganization of motor pathways.

Significant activation was found in both primary motor and premotor cortex when a global measure of disability (EDSS) was used as the explanatory variable for movement-related changes across all of the patients. This suggested a relationship between increasing disability and changes in patterns of brain activation. The IMC contributes projections to the corticospinal tract (Tanji *et al.*, 1988), a potential mechanism by which this activation could contribute to

limiting functional impairment with corticospinal tract injury. As reported earlier, the reduced LI with greater DCBI demonstrates that the increase in IMC activity in multiple sclerosis patients is relatively larger than any change in CMC activation. Ipsilateral inferior parietal lobule activation was also found to increase with greater disability. Greater parietal activation has been identified previously in patients with hemiparesis after stroke (Nelles *et al.*, 1999; Marshall *et al.*, 2000). This activation change may be related to the role the parietal cortex plays in control of movement, particularly with respect to an external reference frame.

However, this approach to identifying an independent role for disability in determining patterns of brain responses for hand movement after brain injury from multiple sclerosis is limited both by the underlying general correlation between disability and brain injury measures and the fact that the EDSS provides a poor measure of upper limb disability. We therefore attempted to assess hand disability more specifically using the maximum hand tapping rate. Then, to better test whether brain injury and hand disability might make independent contributions to patterns of brain activation with hand movements, specific contrasts between the patient groups chosen to be relatively homogeneous for differences in hand disability or brain injury load were performed. The contrast between group 2 and group 1 isolated effects of brain

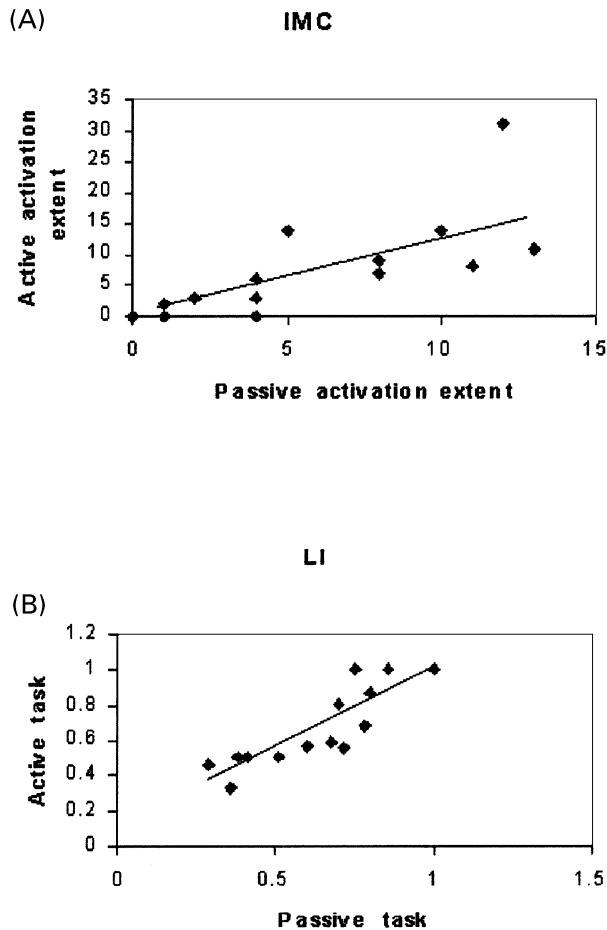


Fig. 3 The volumes of activation correlated highly for active and passive movements of (A) the third digit in the IMC ($r = 0.82$, $P = 0.001$) and (B) LI ($r = 0.93$, $P < 0.001$). This observation provides further evidence that the altered patterns of activation found reflect true functional reorganization of the motor cortex rather than, e.g. simply effort-dependent differences in voluntary recruitment.

injury by using only patients without demonstrable functional impairments of hand movements. This extends our earlier observations showing that ipsilateral motor cortex and SMA activity during finger movement increase with either greater lesion load (Lee *et al.*, 2000) or lower central brain NAA/Cr (Reddy *et al.*, 2000a). LI was confirmed to be a sensitive measure of these changes.

The contrast between group 3 and group 2 was the complementary attempt to isolate independent effects of hand disability, as these two groups were relatively well-matched for measures of brain injury from multiple sclerosis (central brain NAA/Cr, normalized brain atrophy and cervical cord cross-sectional area), but differed in maximum finger tapping rates. The significant activation differences found in the primary and secondary somatosensory cortices were distinct from those identified in the contrast based on injury burden. Increased somatosensory cortex activation may reflect greater attention to somatosensory feedback (Johansen-Berg *et al.*,

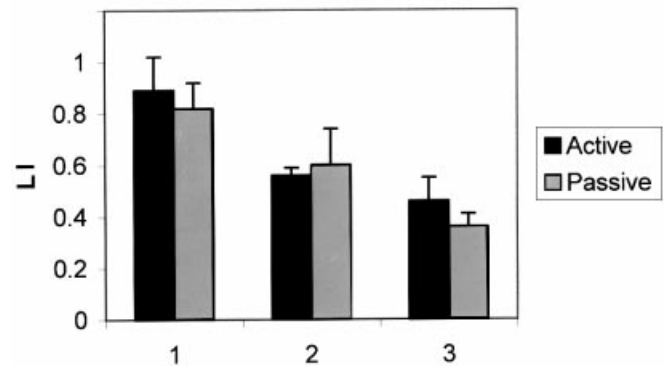


Fig. 4 Progressively decreasing relative hemispheric motor cortex LI with both active (filled bars) and passive (textured bars) finger movements. One standard deviation is marked for each bar.

2000) for movements with the relatively disabled hand. It is important to emphasize that these changes were found in patients without clinically evident sensory impairment of the affected limb.

The results together support the hypothesis that both functional impairment or disability and cerebral injury burden contribute to changes in the patterns of movement-associated brain activation. The demonstration that functional changes with increasing brain injury and disability are different and involve predominantly motor and sensory cortex, respectively, suggests that interacting, but distinguishable networks contribute to a highly distributed cortical response to white matter injury from multiple sclerosis. We speculate that chronic changes in limb use may account for these apparently independent effects of disability on brain functional activation.

The need for rigorous patient selection with respect to multiple criteria limited the size of this study, but other results are also consistent with this hypothesis. We have recently demonstrated, for example, that movement-related brain activation patterns change with reduction of disability after stroke (Johansen-Berg *et al.*, 2002a). In this case, the injury load remains constant in the patients (chosen to be >6 months post-stroke), while disability alone changes. The independent effects of disability on patterns of brain activation potentially offer insights into brain mechanisms responsible for disability limitation and an objective, neurobiologically-based marker of outcome for therapeutic trials.

A fundamental question raised during the interpretation of the current and similar studies is whether the changes (particularly in patterns of IMC activation) found in patients with multiple sclerosis reflect adaptive reorganization (implying longer term changes in synaptic efficiencies or connections responsible for controlling the action) rather than merely compensation (implying use of an alternative action strategy for the task) (Robertson and Murre, 1999). This question was tested by comparing the results from the active and passive finger movement tasks. Previous work has demonstrated that activation during active and passive hand

movement is similar in localization and extent of activation in healthy controls, and that pathologically altered patterns of cortical activation with movement can be defined using a passive task (Weiller *et al.*, 1992; Reddy *et al.*, 2001). Here we found similar increases in IMC activation extent and decreases in LI with greater disability or injury in the multiple sclerosis patients with passive and active movements. This implies that these changes do not depend on the pattern of voluntary activation, i.e. that they are performance-independent and likely to be a consequence either of changes in synaptic connections or of their efficiency. Increased activation in IMC in this multiple sclerosis patient population may, therefore, reflect true functional reorganization of the motor cortex.

It was noted incidentally in our study that there was no correlation between the extents of SMA activation in the active and passive tasks. Activation changes measured by blood oxygenation level-dependent (BOLD) fMRI [and the related physiological measures of cerebral blood flow (CBF) or fluoro-2-deoxyglucose (FDG) uptake] appear to be largely a consequence of increased metabolic activity in or around synapses, rather than neuronal firing rates (Mathiesen *et al.*, 1998; Logothetis *et al.*, 2001). The activation pattern thus primarily reflects the pattern of synaptic activity. A similar extent of activation between active and passive tasks in the primary cortex may be a consequence of the rich network of reciprocal connections between primary motor and proprioceptive afferents. Less direct correspondence might be anticipated in the SMA, as it receives less direct or dense somatosensory input (Dum and Strick, 1992; Strick *et al.*, 1998).

There are a number of methodological issues concerning the fMRI to consider in interpreting our results. The rate at which subjects performed the task was normalized to their individual maximum hand tapping rate. We attempted to match task difficulty between patients and controls in this way, as previous work has shown decreases in motor cortex activation lateralization with increasing difficulty, but not with rate (H. Johansen-Berg and P. M. Matthews, unpublished data). The slower mean finger tapping for group 3 could not itself account for differences defined in the contrast with group 2, because decreases in movement rate are associated consistently with a lower (rather than greater) activation extent.

A second issue concerns the definition of activation extent. We used the absolute number of activated voxels as a measure of relative activation. This is a function of the statistical threshold chosen. Use of $Z > 6.0$ ($P < 0.0003$) allowed relevant activation to be identified in both patients and controls while suppressing artefactual 'activation' (e.g. from subject motion). In separate studies, we have shown that detection of relative changes in LI is relatively insensitive to the precise Z -threshold chosen (H. Johansen-Berg, R. Pineiro and P. M. Matthews, unpublished data). In the present case, both patients and controls were highly co-operative and the absolute activation magnitude was similar between the two

groups, thus justifying use of a single threshold level in the comparisons. Finally, the number of subjects studied was small in this exploratory study. Further work is needed to confirm the relationships identified. The failure to identify activations in specific comparisons has little power to rule out contributions.

Changes in NAA (the primary index of disease burden) provide a relative measure of axonal injury or loss (Bjartmar *et al.*, 2000). While a recent cell culture study was interpreted as offering evidence that, under some conditions, oligodendroglial cells may express NAA (Bhakoo and Pearce, 2000), immunohistochemical localization shows that only neurones and their processes have significant amounts of NAA *in vivo* (Koller *et al.*, 1984; Moffett *et al.*, 1991).

In this study, we used changes in the central brain NAA/Cr ratio to estimate axonal density changes. The ratio was used in preference to an 'absolute' quantitation to limit the lengths of the examination and to maximize sensitivity to change by use of an intrinsically normalized measure. Previous studies have suggested that normal-appearing white matter Cr changes little in multiple sclerosis, so that any decreases in the NAA/Cr ratio are primarily a measure of loss in NAA (Sarchielli *et al.*, 1999). Acquiring data from a large central volume rather than localizing specifically to a region of the descending corticospinal tract subserving hand movement is unlikely to have introduced substantial variance. Previous work has also shown that NAA measures in the central brain correlate well with clinical progression (De Stefano *et al.*, 1997, 1998, 2001). NAA decreases with multiple sclerosis are diffuse in the white matter (Narayanan *et al.*, 1997) and vary only modestly across the brain (Pelletier *et al.*, 2001). The groups studied here also did not show consistent or significant differences between cervical spinal cord cross-sectional area, an index of spinal lesion load (Losseff *et al.*, 1996).

Do activation pattern changes in these multiple sclerosis patients (particularly the increased IMC activation) reflect functional reorganization or are the activation changes merely a reflection of the brain pathology? There is evidence that, despite stable behaviour, the increased IMC activation normalizes over time after an acute relapse, as expected if it is an adaptive response to limit disability (Reddy *et al.*, 2000b). Finding changes in patients with brain injury who are without clinically apparent functional impairments of a limb is also consistent with this (Reddy *et al.*, 2000a). Increased IMC activity has been found in patients who make good recovery from other types of brain injury, including stroke, as expected if common functional mechanisms operate in the different pathological contexts (Weiller *et al.*, 1992). In our recent study of post-stroke patients undergoing an intensive two-week period of motor rehabilitation, there was a strong correlation between improvements in limb muscle power and ipsilateral premotor activity (Johansen-Berg *et al.*, 2002a). This suggested a functional relevance for the changes rather than that they simply reflected pathology. More direct evidence comes from the demonstration that interference with cued finger tapping following transcranial magnetic

stimulation of the IMC increases in direct proportion to the relative extent of IMC fMRI activation in patients post-stroke (Johansen-Berg *et al.*, 2002b). Our demonstration here of similar relative changes between patients and healthy controls with active and passive tasks adds to the accumulating evidence that these changes represent true adaptive 'plasticity' after brain injury.

However, while such work suggests that adaptive plasticity could reduce functional impairment, it is clear from the clinical progression in our relapsing–progressive patients that this capacity is limited. Our observations confirm that changes continue even after impairment develops. Previously, this was interpreted in the context of evolving pathology (Reddy *et al.*, 2000b), but the current work suggests the need to also consider the effects of behavioural changes consequent to injury. This conclusion is not surprising if the mechanisms responsible for this functional reorganization are the same or similar to those involved in experience-dependent plasticity in the healthy brain (Pascual-Leone *et al.*, 1994). Enhancing any beneficial effects of this cortical adaptive plasticity, therefore, should be considered as a potential target for therapy in the progressive, as well as the relapsing phase of the disease. This provides a neurobiological rationale for use of rehabilitation therapy in multiple sclerosis, as well as suggesting the need for increased attention to potential pharmacological methods for modulating brain plasticity (Garraghty *et al.*, 1991; Jacobs and Donoghue, 1991; Hess *et al.*, 1994; Goldstein, 1997; Pariente *et al.*, 2001).

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