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# Multi-task functional MRI in multiple sclerosis patients without clinical disability

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## Abstract

While the majority of individuals with multiple sclerosis (MS) develop significant clinical disability, a subset experiences a disease course with minimal impairment even in the presence of significant apparent tissue damage on magnetic resonance imaging (MRI). Functional magnetic resonance imaging (fMRI) in MS patients with low disability suggests that increased use of the cognitive control system may limit the clinical manifestation of the disease. The current fMRI studies tested the hypothesis that nondisabled MS patients show increased recruitment of cognitive control regions while performing sensory, motor and cognitive tasks. Twenty two patients with relapsing-remitting MS and an Expanded Disability Status Scale (EDSS) score of ≤ 1.5 and 23 matched healthy controls were recruited. Subjects underwent fMRI while observing flashing checkerboards, performing right or left hand movements, or executing the 2-back working memory task. Compared to control subjects, patients demonstrated increased activation of the right dorsolateral prefrontal cortex and anterior cingulate cortex during the performance of the working memory task. This pattern of functional recruitment also was observed during the performance of non-dominant hand movements. These results support the mounting evidence of increased functional recruitment of cognitive control regions in the working memory system of MS patients with low disability and provide new evidence for the role of increased cognitive control recruitment in the motor system.

### Keywords

Anterior cingulate cortex; cognitive control; cortical reorganization; dorsolateral prefrontal cortex; functional magnetic resonance imaging; multiple sclerosis



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## 1. INTRODUTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that commonly results in visual and motor dysfunction as well as cognitive impairment in 40 to 70% of patients (Chiaravalloti and DeLuca, 2008). While the majority of individuals afflicted with MS accumulate clinical disability throughout their lifetime, approximately one-quarter of them experiences a course with minimal or no detectable disability (Ramsaransing et al., 2001) even in the presence of significant lesion load on MRI (Strasser-Fuchs et al., 2008). The brain mechanisms that protect these patients from developing clinical disability are currently unknown.

Studies using functional MRI (fMRI), the major technique for non-invasive detection of cortical activity, have identified aberrant brain activation in MS patients in response to tasks. These patterns of altered activation appear to reduce the clinical manifestations of the disease (Pantano et al., 2006; Pelletier et al., 2009). The initial wave of fMRI studies in MS investigated right hand movements and suggested that increased functional recruitment of ipsilateral motor regions allowed preservation and recovery of function (Lee et al., 2000; Reddy et al., 2000a, 2000b), and that the extent of this recruitment is related to disease burden (Pantano et al. 2002a; Reddy et al., 2002; Rocca et al., 2002a) and disability (Reddy et al., 2002; Rocca et al., 2005). Greater areas of activation have also been observed during working memory studies (Audoin et al., 2003, 2008; Mainero et al. 2004; Staffen et al., 2002; Sweet et al., 2004) and greater recruitment was detected in patients with better cognitive function as well as those with more severe tissue damage (Mainero et al. 2004). Other studies describe no differences (Meyn et al., 2010) while others reported decreased activation (Cader et al., 2006; Wishart et al., 2004). The difficulty in controlling for performance differences and disability levels may have contributed to this variability in findings.

Our current knowledge gained from motor and cognitive fMRI studies in MS is summarized by the recently proposed MS disease progression hypothesis by Schoonheim et al. (2010), which suggests that initial structural damage causes brain hyperactivation, which results in low disability and cognitive preservation, but after this hyperactivation peaks, progressive cognitive impairment and disability ensue. While this hypothesis elegantly describes the general mechanism of altered brain activation observed in MS patients, it also illustrates the lack of specific mechanisms that may prevent development of disability in patients, especially in patients who follow a milder course. A recent meta-analysis of 33 functional imaging studies suggests that altered patterns of brain activation during working memory tasks may represent increased use of the cognitive control system (Hillary, 2008). Across several clinical populations including MS, there was a consistent recruitment of cognitive control regions, including the dorsolateral prefrontal cortex (DLPFC) and, to a lesser extent, the ventrolateral prefrontal cortex and anterior cingulate cortex (ACC) (Audoin et al., 2003; Bobholz et al., 2006; McAllister et al., 1999; Perlstein et al., 2003; Sweet et al., 2004). It has been proposed that increased use of the cognitive control system may be a mechanism to allow patients to cope with increasing cognitive demands and accommodate disease-related neural dysfunction (Au Duong et al., 2005; Audoin et al., 2008; Hillary et al., 2006, 2008).

Given this evidence, we investigated whether increases in activation of the cognitive control system is also observed in MS patients with very minimal or no neurological findings and without clinical disability as assessed by the Expanded Disability Status Scale (EDSS). Specifically, we hypothesized that these patients would show increased recruitment of cognitive control regions across sensory, motor and cognitive tasks. To address this question, we measured blood-oxygen level dependent (BOLD) signal changes using fMRI in patients with relapsing-remitting MS (RRMS) with no detectable clinical disability while

they observed flashing checkerboards, performed right and left hand movements, or executed the N-back working memory task. From a clinical standpoint, identifying patterns of brain activation that may be protective against developing disability, which is the ultimate goal of therapy, may be exploited as potential targets for clinical intervention and customization of patient treatment, improved accuracy of disease prognosis and better understanding of disability progression in MS.

## 2. MATERIALS AND METHODS

### 2.1 Subjects

Twenty two patients with clinically definite MS (Polman et al., 2011) were recruited from the MS Clinic of The University of Texas Medical School at Houston. Inclusion criteria were: relapsing-remitting course of disease, absence of neurological abnormal signs in the upper limbs, and an EDSS score of ≤ 1.5. A detailed clinical neurological examination and EDSS scoring was performed by an experienced neurologist (JSW) within less than one month prior to imaging, except for one patient who was scanned two months later. All patients were in remission from the time of the clinical examination until the imaging session. Upper limb function was assessed with the Nine Hole Peg Test. The Edinburgh Handedness Inventory (Oldfield, 1971) was administered to control for hand dominance during motor tasks. The control group consisted of 23 age-matched healthy volunteers with no history of psychiatric or neurological disorders and normal MRI. Both groups had at least 13 years of education. The study was approved by the local Institutional Review Board and all subjects provided a written informed consent. Demographic, clinical characteristics and behavioral performance of the subjects are presented in Table 1.

### 2.2 MRI data acquisition

Subjects underwent one MRI session lasting approximately 60 min on a 3.0 T Philips Intera system with a Quasar gradient system (maximum gradient amplitude 80 mT/m, slew rate 200 T/m/s) and an 8-channel head coil (Philips Medical Systems, Best, Netherlands). The structural MRIs included a 3D high-resolution T1-weighted magnetization prepared rapid acquisition of gradient echo (MPRAGE) sequence (TE 3.7 ms, TR 8.1 ms, 1.0 mm isotropic resolution and FOV of 256 mm × 256 mm × 170 mm), a 3D T2-weighted sequence (TE 362.9 ms, TR 2500 ms), a fluid-attenuated inversion recovery (FLAIR) sequence (TE 337.16 ms, TR 8000 ms). The image geometry for both T2-weighted and FLAIR is identical to that of the MPRAGE.

Functional MRI data included two sessions of T2*-weighted echo planar imaging (EPI; TE 30 ms, TR 2015 ms, 3.0 mm × 33 slices, matrix 80 × 80, FOV of 220 mm × 220 mm, 90° flip angle) while subjects performed motor, visual or cognitive tasks. Presentation of the tasks was conducted using a block design in which periods of an activating condition alternated with periods of a control condition with sessions lasting between 4 to 6 min. To improve the spatial coverage of the occipital cortex, TR and the number of slices for the visual sessions were increased to 2177 ms and 36 slices, respectively.

### 2.3 fMRI stimuli and design

Stimuli for each task were programmed using the E-Prime software (Psychology Software Tools, Pennsylvania, USA) and presented using Eloquence functional imaging system (Invivo Corporation, Florida, USA) through an LCD screen built into the head coil. Responses to the tasks were recorded using a keypad. Subjects were trained beforehand for accurate performance using a mock scanner. The paradigms were presented in the following order: cognitive, visual, and motor. The visual task involved alternating between the observation of minimal visual stimulation and periods of substantial bilateral visual

stimulation. During the control periods, subjects observed a black screen displaying a flashing red crosshair in the middle of the screen. The activating periods involved the display of full field radial checkerboard flashing at 8 Hz (Drobyshevsky et al., 2006; Schneider et al., 1993) with a flashing red crosshair in the middle of the screen. Subjects were instructed to focus on the red crosshair at all times. In order to confirm that subjects were looking at the screen, they were instructed to press a key at the beginning of the flashing checkerboards. Two sessions of 12 blocks (6 control, 6 activation) were included and 96 EPI volumes were acquired per session.

The motor task consisted of blocks of rest alternated with blocks of flexion and extension of the last four fingers of the right or left hand and was based on prior fMRI motor studies in MS (Pantano et al., 2002b; Rocca et al., 2002a). Subjects were visually cued with the words “REST”, “RIGHT” or “LEFT”. Hand side was alternated after each rest period. Two sessions of 21 blocks (11 control, 10 activation) were included and 168 EPI volumes acquired per session. Subjects were trained to self-pace movements at 1 Hz and correct execution of the task and mirror movements were monitored via video cameras.

To identify cortical areas involved in working memory, the widely used N-back task was implemented (Drobyshevsky et al., 2006; Owen et al., 2005). This paradigm was chosen over other common ones such as the Paced Auditory Serial Addition Task (PASAT) because it allowed precise automated acquisition of response reaction time. During the control condition (0-back), subjects were instructed to respond with their index finger (positive response) to a sequence of 10 red letters shown one at a time if presented with the letter X, and with their middle finger (negative response) otherwise. For the activating condition (2-back), subjects were shown a series of 10 yellow letters one at a time and were instructed to provide a positive response if the current letter was the same as that presented two letters previously and a negative response otherwise. Each letter was displayed for 1 sec and the inter-stimulus interval lasted for 2 sec. Stimuli to distracter ratio was 1:5. Two sessions of 15 blocks (8 control, 7 activation) were included and 150 EPI volumes acquired per session. Reaction time and percent of correct responses (accuracy) were recorded for both conditions. Subjects with an accuracy of < 50% for the positive trials during the 2-back condition were excluded from the analysis.

### 2.4 fMRI processing and analysis

Preprocessing and analysis of the fMRI data was conducted using the Statistical Parametric Mapping 8 (SPM8) software (Wellcome Trust Centre for Neuroimaging, University College London, UK) implemented in Matlab (Mathworks, Massachusetts, USA). Volumes with significant artifacts were identified using the ArtRepair toolbox (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm) based on scan-to-scan motion (>1 mm/TR) and outliers relative to the global mean signal (> 5 sd from global mean). Images with artifacts were repaired by interpolation from the nearest unaffected volumes. Images then underwent intra-subject linear motion correction to reduce head motion effects. Subjects with head motion greater than 3.0 mm in translation or 3.0° in rotation were eliminated from the analysis of the corresponding task. Functional-structural coregistration of fMRI and MPRAGE data was performed to improve spatial localization of activity. Each subject’s MPRAGE was then normalized to the coordinates of the Montreal Neurological Institute (MNI) template (Collins et al., 1995; Mazziotta et al., 2001) and the resulting transformation was applied to the fMRI data. Subsequently, fMRI data underwent resampling to a 2 mm isotropic resolution, spatial smoothing with an 8 mm full-width-at-half-maximum isotropic Gaussian kernel and temporal filtering with a high pass filter (t = 128 sec).

Statistical analysis was performed using a two-level stage random-effect analysis. At the first level, significant signal changes due to the effect of interest (i.e. flashing checkerboards, hand flexion-extension, 2-back condition) versus baseline condition for each subject were assessed with *t* statistical parametric maps (*t* maps). Individual *t* maps were then used in a second-level analysis to assess differences in brain activation at the group level between MS patients and control subjects. A cluster-defining threshold of $p = 0.01$ and cluster p values after correction for multiple comparisons using Random Field Theory (Adler, 1981) to control for family wise error (FWE) rate of less than 0.05 (Friston et al., 1996) were used in all analyses reported in this manuscript.

### 2.5 T2 lesion load (T2LL) determination

Lesion segmentation was based on a multi-spectral segmentation technique that used the 3D T1- and T2-weighted and FLAIR images using the procedure described by Datta et al. 2011 (manuscript submitted). Briefly, T1-weighted and FLAIR images were co-aligned with T2-weighted images for each subject using a rigid body registration technique. Intracranial brain masks including cerebrospinal fluid were extracted from T2 images by exploiting the fat-sat technique and applying image histogram-based thresholds followed by the application of region connectivity and region labeling algorithms (Datta and Narayana 2011). The skull-stripped images were further processed for intensity inhomogeneity correction and noise filtration.

False lesion classifications were minimized by masking the lesion class with white matter masks obtained from the co-aligned brain template and were delineated using fuzzy connectivity (Sajja et al., 2006). Deep gray matter structures are generally poorly segmented. Therefore accurate classification of these structures was realized using the method described elsewhere (Tao et al., 2009). Finally, lesions on segmented results were validated by an expert.

The relationship between BOLD signal changes and extent of tissue damage in the patient group was examined using T2LL as a covariate of interest during a within-group analysis of all the conditions of interest. Significant clusters of correlation were evaluated with the aforementioned criteria.

## 3. RESULTS

### 3.1 Quality control measures: handedness, head motion and task performance

Two patients were excluded from all the analyses due to severe head motion and poor performance during the 2-back paradigm. Two additional left-handed patients (Oldfield, 1971) were excluded from the analysis of the motor paradigm. Two controls were excluded from all analyses due to motion artifacts. Two additional controls did not perform the visual task and two others were excluded from the analysis of the 2-back paradigm due to poor performance. The final analysis consisted of 20 patients and 19 controls for the visual and 2-back paradigm, and 18 patients and 21 controls for the motor paradigm.

Groups did not differ in mean age, or time to complete the Nine Hole Peg test when using their right or left hand (Table 1). No mirror movements were noted during hand movements while performing the motor tasks. Performance on the 2-back paradigm, measured as accuracy and reaction time, did not differ between the patient group and healthy controls in either the control trial or the working memory trials (Table 1).

### 3.2 fMRI within-group analysis

Comparison of the observation of flashing checkerboards to a black screen in a within-group analysis resulted in extensive activation of the occipital cortex in both groups (Fig 1a). Analyses of right and left flexion-extension hand movements compared to rest resulted in extensive activation of contralateral primary motor regions and minimal activation of ipsilateral motor regions in both groups (Fig 1b, 1c). During the performance of the 2-back condition as compared to the 0-back condition, both groups activated a network of frontoparietal and midline structures associated with working memory tasks (Fig 1d) (Owen et al., 2005).

### 3.3 fMRI between-group analysis

A two-sample comparison of patients versus controls identified clusters of greater activation in patients during the right hand, left hand and 2-back conditions while none were identified during the visual task. Controls failed to show greater activation compared to patients during any of the conditions. The coordinates of the maximum voxel t value, its approximate anatomical location, number of voxels, percent whole brain BOLD, p value, and center of mass are shown for each significant cluster in Table 2. The following sections provide a more complete description of the anatomical location of each cluster.

**3.3.1 Right hand movements—**Group comparison of subjects while performing right hand movements identified one cluster of significantly greater activation in patients (Fig 2a). Regions in this cluster involved right precentral gyrus (BA4) and postcentral gyrus (BA5), left superior parietal gyrus (BA7), bilateral supplementary motor areas (SMA) (BA6), middle cingulate cortex (BA31), and precuneus (BA5 and 7).

**3.3.2 Left hand movements—**For the left hand condition, two clusters were found in which patients showed greater activation than controls (Fig 2b). The main regions inside these clusters included right superior and middle frontal gyri (BA9 and 10) within the DLPFC (BA 9 and 46), right insula (BA 13), and bilateral middle and anterior cingulate cortices (BA 24 and 32). Other regions included right inferior frontal gyrus pars triangularis and pars opercularis, SMA, putamen, caudate and superior temporal gyrus.

**3.3.3 Working memory task—**During the performance of the 2-back condition as compared to the 0-back condition, patients showed greater activation than controls in one cluster (Fig 2c). Regions in this cluster primarily included right superior and middle frontal gyri (BA 9, 10 and 46), and middle and anterior cingulate cortices (BA32). Other regions included right inferior frontal gyrus pars orbitalis (BA11), opercularis, and triangularis.

**3.3.4 Correlation between fMRI and T2LL—**During the performance of the right hand movements activation of the right precentral gyrus, postcentral gyrus, supramarginal gyrus, temporal superior gyrus, right Rolandic operculum, and insula significantly increase with increasing T2LL (Fig 3a). Increasing activation during the performance of left hand movements were associated with increasing T2LL in the right precentral gyrus, postcentral gyrus, supramarginal gyrus, inferior and superior parietal lobules and the caudate nucleus (Fig 3b). No significant relationships were identified between the patterns of activation during the performance of the visual or N-back task and T2LL.

## 4. DISCUSSION

The current studies provide the first fMRI characterization of recruitment of cognitive control regions across multiple tasks in the subset of MS patients who have lesions but do not have clinical disability. Our results in these patients demonstrate increased activation of

the right DLPFC and ACC during the performance of a demanding working memory task. Moreover, this pattern of functional recruitment also was observed during the performance of non-dominant hand movements. These results support the mounting evidence for increased functional recruitment of cognitive control brain regions in the working memory system of MS patients with low disability (Au Duong et al., 2005; Audoin et al., 2008; Hillary et al., 2006; Sweet et al., 2004, 2008) and provide new evidence for its role in the motor system.

The approach taken in these studies addresses many of the issues contributing to the inconsistent findings observed in fMRI studies in MS. Brain activation was investigated in a homogeneous MS patient group based on disability because as prior studies have shown, functional recruitment patterns in MS patients vary by disability (Rocca et al., 2005). Patients with accuracy and reaction times similar to those of healthy controls were used to limit between-group differences in behavioral performance. This is important because it is challenging to interpret increased brain activation as adaptive in patients whose performance is not comparable to that of controls. While performance measures were not controlled in early fMRI studies (Hillary et al., 2003; Penner et al., 2003; Staffen et al., 2002), others have only control for equivalent accuracy but not reaction time (Forn et al., 2006; Sweet et al., 2006) which results in the comparison of patient and control groups that may differ in information processing speed. This is nontrivial since decreased processing speed is the most common cognitive deficit and the primary cause of information processing impairments in MS patients (DeLuca et al., 2004). Finally, the same group of patients and controls was used across the different studies. This reduces the variability from interindividual differences in brain activation and allows probing for brain mechanisms that may be common across functional domains. To date, most fMRI studies in MS patients have investigated brain activation in only a single functional neurological system (e.g. motor or working memory system), and hence functional recruitment has been interpreted as it pertains to one particular functional system (e.g. motor cortical reorganization).

## 4.1 Motor tasks

Patterns of activation consistent with motor execution and planning were observed in our patients and controls during the performance of right and left hand movements (Loubinoux et al., 2001). Group comparison during right hand movements showed that patients increased activation of the ipsilateral primary motor cortex (BA4) as well as bilateral activation of regions associated with the sensorimotor network (BA5–7, 31). Consistent with our findings, similar fMRI motor studies in MS patients with low disability have reported increased activation of bilateral sensorimotor regions during right hand movements (Giorgio et al., 2010; Pantano et al., 2002a, Rocca et al. 2005). While increased ipsilateral motor cortex activation in patients compared to controls may represent an adaptive mechanism, recent evidence suggests that it is also related to reduced task-associated deactivation (Manson et al. 2008) and loss of transcallosal inhibitory fibers (Lenzi et al. 2007). An increase in activation of regions outside of the classical motor network has also been described during right hand movements, which was not observed in this study. However, the patients in these studies had greater disability (Wang et al., 2007) or were in the progressive stage of the disease (Rocca et al., 2002b).

Interestingly, when patients performed the same motor task with the non-dominant hand, additional areas not typically activated in simple motor tasks, including the bilateral ACC and the right DLPFC, were recruited. These findings may be related to increased cognitive effort that patients may require for performing non-dominant hand movements. While most motor fMRI studies in MS have involved right hand movements, a recent fMRI study by Rico et al. (2010) examined bilateral movements in patients with clinically isolated

syndrome suggestive of the first clinical manifestation of MS (CIS) with low disability and devoid of corticospinal dysfunction. Consistent with our findings, these authors found increased activation of the ACC when patients performed non-dominant hand movements but not with dominant hand movements. These findings suggest that non-dominant hand movements result in recruitment of brain networks involved in cognitive control in patients with MS and minimal or no disability.

### 4.2 Cognitive task

Performance of the 2-back condition in both groups activated brain regions associated with working memory tasks (Owen et al., 2005). However, between-group comparison identified increased activation in patients mainly involving the right DLPFC and right ACC. Increased activation of these regions in MS patients with low disability has been described across different fMRI working memory studies (Audoin et al., 2008; Bobholz et al., 2006; Sweet et al., 2004), and consistent with our findings, several investigators have noted increased DLPFC activation primarily involving the right hemisphere (Hillary et al., 2006). For instance, a recent longitudinal fMRI study of a group of patients with CIS and low disability identified increased levels of activation in the right DLPFC and ACC in patients who improved their scores in the PASAT over 1 year relative to patients who did not (Audoin et al., 2008). These authors concluded that recruitment of adaptive cognitive control processes may limit the cognitive dysfunction associated with MS. In another fMRI study of patients with CIS, investigators observed an enhancement in the effective connectivity between right DLPFC to right ACC when patients performed the PASAT (Au Duong et al., 2005). The authors interpreted these changes as an adaptive mechanism related to cognitive control enhancement.

Posterior parietal regions which are associated with visual short term memory storage (Todd and Marois, 2004; Xu and Chun, 2006), have also been reported to show increased activation in MS patients performing working memory tasks (Penner et al., 2003; Wishart et al., 2004). Group differences in these regions were not observed in this study or that by Sweet et al. (2004) who investigated brain activation in patients with MS and low disability during 2-back task performance. This finding may be related to preservation of short term memory storage. Importantly, the patients studied by Sweet et al. (2004), similar to the ones in the current study, had normal information processing speeds as reflected by their normal reaction times.

### 4.3 Visual task

As expected, the performance of the visual task resulted in extensive activation of the occipital cortex in both groups, which is consistent with previous fMRI studies in healthy subjects using similar paradigms (Drobyshevsky et al., 2006; Schneider et al., 1993). However, between-group comparison yielded no group differences in our studies. This is somewhat different from the altered patterns of cortical activity reported by Rombouts et al. (1998) in a group of RRMS patients with unilateral optic neuritis. These authors reported reduced visual cortex activation upon monocular stimulation of the affected and unaffected eyes. They observed a trend of greater activation in recovered patients upon stimulation of both the affected and unaffected eyes. Similar findings have been reported by other investigators (Werring et al., 2000). A possible explanation for these discrepant results is that none of our patients had a recent episode of optic neuritis.

### 4.4 Correlation between fMRI and T2LL

Consistent with previous studies in patients with MS and low disability, we found a positive relationship between brain activation during the performance of the motor tasks and tissue injury in several regions of the motor network (Giorgio et al. 2010; Pantano 2002a; Ricco et

al. 2010). This relationship was not observed with the visual or the working memory tasks. In contrast to our results, other investigators reported a relationship between lesion load and increased brain activation during working memory tasks in MS patients with mild disability and varying levels of cognitive performance (Bobholz et al., 2006; Mainero et al. 2004). A possible explanation for this discrepancy is that the spatial location of the lesions may have a more dominant effect on the activation than the absolute lesion load. Unfortunately in these studies we have not performed this analysis. Overall, we suggest from these findings that the relationship between T2LL in nondisabled MS patients and fMRI activation in cognitive and visual networks is more complex than in motor system (Loitfelder et al. 2011).

### 4.5 Increased Cognitive Control in MS

The aim of the current investigation was to test if nondisabled MS patients show increased recruitment of cognitive control regions across visual, motor and working memory tasks. The current findings support in part our hypothesis and indicate that these patients recruit the right DLPFC and ACC while performing working memory tasks and non-dominant hand movements. These two regions are key elements of the neural architecture of the cognitive control system, which involves maintaining mental states representing goals and the means to accomplish them (Miller and Cohen, 2001) and require processes such as planning, attention and working memory. The DLPFC is involved in multiple executive processes including monitoring, manipulation and integration of multiple pieces of information (Petrides, 2000; Rypma and D Esposito, 1999; Tanji and Hoshi, 2008). While the ACC has also been implicated in multiple high-order cognitive processes, it has gained particular attention for its involvement in conflict monitoring (Botnivik et al., 1999; Egner and Hirsch, 2005; Kerns et al., 2004). This evidence led to an influential model of cognitive control in which the role of the ACC is to identify the occurrence of conflictive information and to signal the DLPFC to resolve such conflict (Botvinick et al., 2001; Carter et al., 2007). Other investigators propose that the primary role of the ACC is not conflict monitoring but rather a function in response selection, estimation of reward uncertainty and direct implementation of actions needed to resolve conflict (Mansouri et al., 2009; Roelofs et al., 2006). Moreover, recent evidence suggests that the identification of conflict is recognized by the DLPFC, with a subsequent behavioral adjustment accomplished by the interaction of the DLPFC and ACC (Morishima et al., 2010).

Although we lack an accepted model for the dynamic interaction of the DLPFC and ACC to allow individuals with intact neural networks cope with conflicting and demanding cognitive situations, it is clear that they are essential for cognitive control. In cases involving damaged neural pathways such as seen in patients with MS, higher levels of cognitive control, and therefore DLPFC and ACC recruitment, may be required at lower cognitive load thresholds (Hillary et al., 2006). If increased cognitive control allows patients to cope with increasing cognitive demands, usage of this brain mechanism should not only be limited to the working memory system but should function across any situation that demands greater cognitive effort. Current findings support this idea and provide novel evidence for increased recruitment of cognitive control when patients perform mildly demanding motor tasks.

Another important finding of the current study is the lateralization of functional recruitment to the right DLPFC during both the working memory and motor tasks. Interestingly, preferential recruitment of the right DLPFC has also been described in fMRI working memory studies in MS, as previously mentioned, as well as other clinical populations, including victims of traumatic brain injury (McAllister et al., 1999; Perlstein et al., 2003) and patients with major depression (Fitzgerald et al., 2008). Moreover, several investigators have observed a relationship of increasing right DLPFC recruitment with increasing task demand in working memory studies in healthy adults (D Esposito et al., 1999; Mostofsky et al., 2003; Rypma et al., 2002). These studies suggest that right DLPFC recruitment during

working memory tasks may represent a general response to cerebral challenge (Hillary et al., 2006). Consistent with this idea, we observed increased right DLPFC activation when patients performed the more cognitively demanding tasks including the working memory task and non-dominant hand movements, while only minimal recruitment occurred during dominant hand movements and no involvement during the visual task.

### 4.6 Conclusion

In conclusion, our findings support the growing evidence that increased activation of cognitive control brain regions, particularly in the right hemisphere, may be an important mechanism allowing patients with MS to accommodate to the neural disruption caused by this disease. Moreover, the current study shows the usefulness of testing the same group of patients during multiple tasks to identify adaptive brain mechanisms that may be sustained across different functional domains. Future clinical interventions may focus to increase cognitive control in MS patients. Current advances in imaging technology may allow monitoring efficiency of cognitive control recruitment while patients undergo rehabilitation and provide feedback to increase use of cognitive control. Evaluation of cognitive control recruitment may allow identification of patients at higher risk for developing cognitive and clinical deficits. Finally, this knowledge opens a window to the possibility of enhancing cognitive control through emerging therapeutic interventions such as repetitive transcranial magnetic stimulation, which has provided encouraging results in MS (Koch et al., 2008) and other neurologic diseases (Padberg and George 2009; Ridding et al., 2007).

### 4.7 Limitations

While our study is an important step towards better understanding the role of cognitive control recruitment in nondisabled MS patients, it is not without its limitations. First, as with most previous fMRI studies in MS, the cross-sectional nature of our investigation and the small number of subjects limit the generalization of our results. Nonetheless, the homogeneity of the patients included in this study makes this group reasonably representative. Longitudinal studies with larger homogenous patient groups testing multiple functional domains should provide better understanding of brain mechanisms that may be protective for the developing neurological disability in MS.

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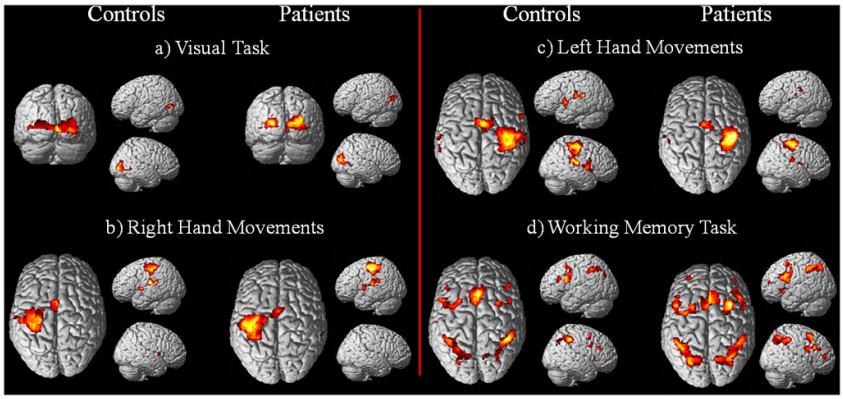


**Figure 1.**

Cortical activation patterns in MS patients with no clinical disability and control subjects during the (a) visual task, (b) right hand movements, (c) left hand movements and (d) performance of the 2-back task (one sample t-test, $p < 0.05$ FWE-corrected at voxel and cluster level). Images are in neurological convention (left is left).

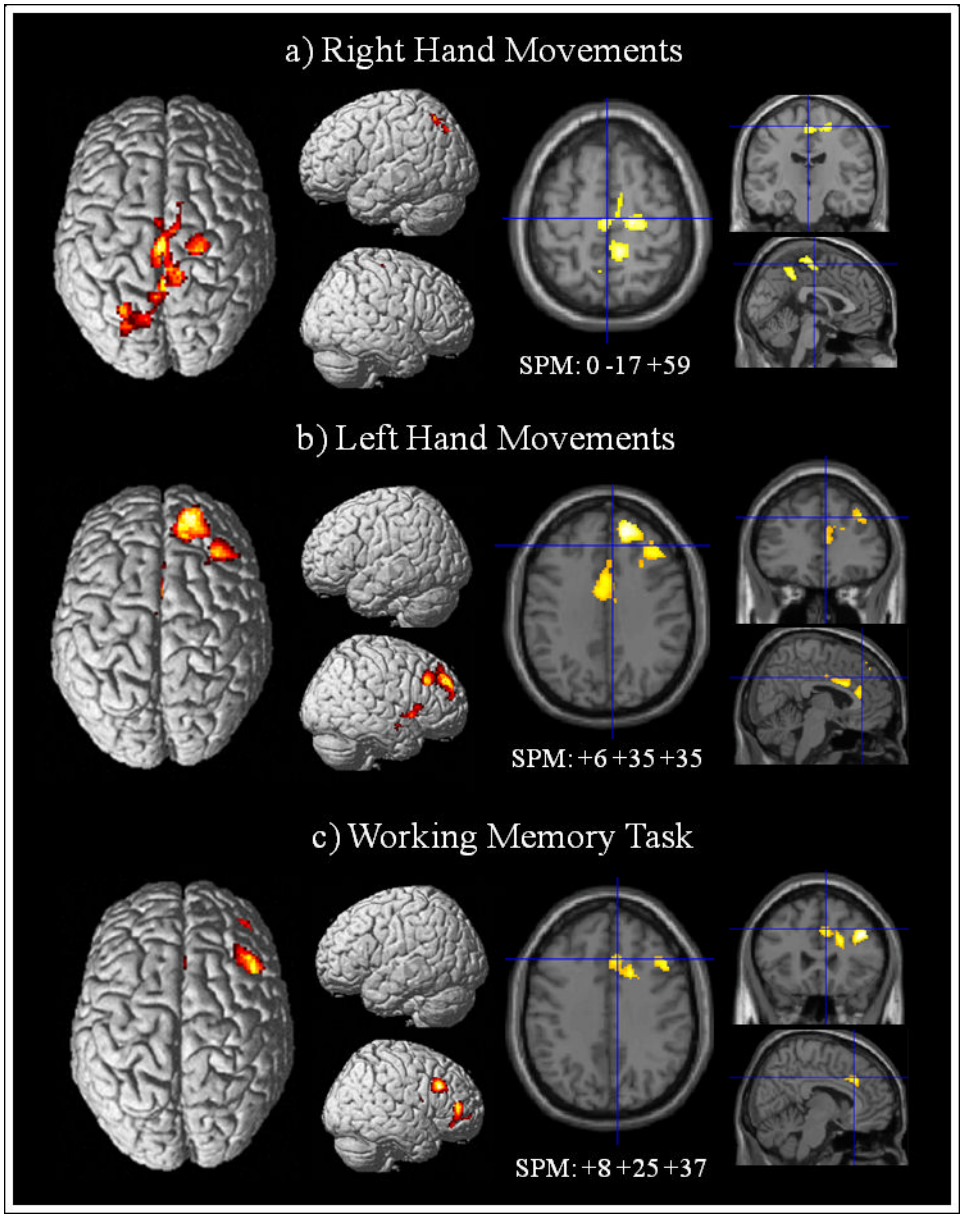


**Figure 2.**
Areas of increased brain activation in MS patients with no clinical disability relative to controls during (a) right hand movements, (b) left hand movements and (c) performance of the 2-back task (two sample t-test, $p < 0.05$ FWE-corrected at cluster level). Images are in neurological convention (left is left).

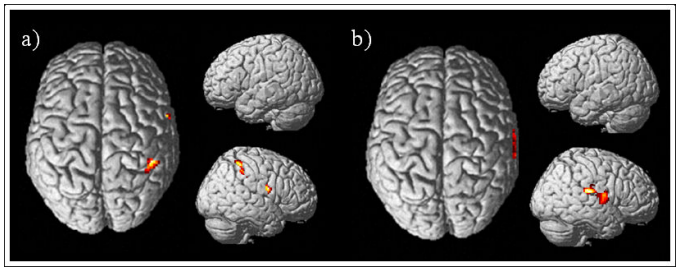


**Figure 3.**
Areas of activation that positively correlated with T2 lesion load in MS patients with no clinical disability during the performance of (a) right hand movements and (b) left hand movements ($p < 0.05$ FWE-corrected at cluster level). Images are in neurological convention (left is left).

**Table 1**

Demographics, clinical data and task performance.

| | Patients | Controls | p* |
|---|---|---|---|
| Total (females/males) | 20/3 | 21/7 | |
| Age, mean +/− SD | 41.8 +/− 9.9 | 38.1 +/− 12.5 | 0.31 |
| Duration since diagnosis, mean +/− SD | 7.4 +/− 6.7 | n/a | |
| Duration since first symptoms, mean +/− SD | 10.2 +/− 7.4 | n/a | |
| EDSS, median (range) | 0 (0–1.5) | n/a | |
| T2 lesion load, mean +/− SD (ml) | 12.8 +/− 15.9 | n/a | |
| Time to complete Nine Hole Peg Test | | | |
| Meant time right hand +/− SD (sec) | 18.8 +/− 2 | 17.9 +/− 1.6 | 0.14 |
| Meant time left hand +/− SD (sec) | 19.1 +/− 2 | 18.8 +/− 2.5 | 0.68 |
| N-back 0-back condition performance | | | |
| Mean accuracy +/− SD (% correct) | 95.8 +/− 2 | 94.6 +/− 6 | 0.42 |
| Mean reaction Time +/− SD (sec) | 0.55 +/− 0.07 | 0.55 +/− 0.07 | 0.94 |
| N-back 2-back condition performance | | | |
| Mean accuracy +/− SD (% correct) | 87.3 +/− 4 | 87 +/− 6 | 0.86 |
| Mean reaction Time +/− SD (sec) | 0.77 +/− 0.10 | 0.77 +/− 0.20 | 0.88 |

* p values are for an unpaired two-sample student's *t*-test. Demographic and clinical data is shown for all subjects. Performance data for the Nine Hole Peg Test and for the N-back task is displayed only for the subjects included in the motor and N-back fMRI analyses, respectively.

**Table 2**

Random effects comparison of activations during the visual paradigm, right and left hand movements and 2-back task between MS patients (MS) and control subjects (CS).

| Condition | Comparison | Cluster label(center of mass) | Corrected cluster p | Mean difference across all voxels in cluster(± 90% CI) [% whole brain BOLD] | Voxels in cluster | Maximal voxel T | X Y Z | Location |
|---|---|---|---|---|---|---|---|---|
| VISUAL | MS > CS | | < 0.05 | | | | | No significant clusters |
| | CS > MS | | < 0.05 | | | | | No significant clusters |
| RIGHT | MS > CS | 1 (3,−38,54) | 0.005 | 0.531 (0.242) | 1616 | 3.76 | 8 −41 57 | R precuneus (BA5) |
| | | | | | | 3.67 | 18 −21 59 | R precentral g (BA4) |
| | | | | | | 3.33 | −4 −27 67 | L supplementary motor area (BA6) |
| | CS > MS | | | | | | | No significant clusters |
| LEFT | MS > CS | 1 (9,28,32) | 0.002 | 0.400 (0.165) | 1687 | 4.69 | 16 47 33 | R superior frontal g (BA9) |
| | | | | | | 3.79 | 20 55 19 | R superior frontal g (BA10) |
| | | | | | | 3.69 | 2 11 29 | R middle cingulate g (BA24) |
| | | 2 (34,18,10) | 0.011 | 0.446 (0.192) | 1248 | 4.69 | 28 17 19 | R insula (BA13) |
| | | | | | | 3.89 | 44 −5 −17 | R superior temporal g |
| | | | | | | 3.83 | 24 21 13 | R caudate |
| | CS > MS | | < 0.05 | | | | | No significant clusters |
| 2-BACK | MS > CS | 1 (28, 30, 18) | 0.001 | 0.453 (0.133) | 1893 | 4.61 | 40 23 31 | R middle frontal g (BA9) |
| | | | | | | 4.53 | 20 43 11 | R anterior cingulate g (BA32) |
| | | | | | | 4.32 | 36 45 7 | R middle frontal g (BA10) |
| | CS > MS | | < 0.05 | | | | | No significant clusters |

p values are corrected with FWE adjustment for multiple comparisons at cluster level. Within each significant cluster, the three maximal voxel t values that are greater than 8 mm apart and their approximate anatomical location are shown. Coordinates are in MNI space (mm). BA = approximate Brodmann area, g = gyrus, L = left, R = right.