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Cortical recruitment during selective attention in multiple sclerosis: An fMRI investigation of individual differences

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ABSTRACT

Recent studies with multiple sclerosis (MS) participants have provided evidence for cortical reorganization. Greater recruitment of task-related areas and additional brain regions are thought to play an adaptive role in the performance of cognitive tasks. In this study, we compared cortical circuitry recruited by MS patients and controls during a selective attention task that requires both focusing attention on task-relevant information and ignoring or inhibiting task-irrelevant information. Despite comparable behavioral performance, MS patients demonstrated increased neural recruitment of task-related areas along with additional activation of the prefrontal cortices. However, this additional activation was associated with poor behavioral performance, thereby providing evidence against compensatory brain reorganization. Future studies specifically investigating the nature of additional activation seen in MS patients in a wider variety of cognitive tasks would provide insight into the specific cognitive decline in MS.

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1. Introduction

Multiple sclerosis is a disease of the central nervous system that affects the integrity of white and gray matter (Bermel, Innus, Toja, & Bakshi, 2003; Prinster et al., 2006) resulting in a variety of psychopathological symptoms, one of which is cognitive deficits (Bobholz & Rao, 2003; Calabrese, 2006). Historically, clinicians have underestimated the prevalence of MS-related cognitive decline, but studies in the last two decades have focused on investigating the specific cognitive deficits that are associated with MS (Calabrese, 2006; Rao, Leo, Bermadin, & Unverzagt, 1991). Neuropsychological studies report that nearly 40–65% of patients diagnosed with MS exhibit impaired functioning in one or more cognitive domains (Rao et al., 1991). Deficits have been found in domains of memory, attention, executive functioning and visuospatial processing, with most prominent impairments reported in areas of working memory and information processing speed (Amato, Zipoli, & Portaccio, 2006; Rao et al., 1991).

Based on advances in brain imaging techniques, such as functional magnetic resonance imaging (fMRI), evidence indicates that MS patients exhibit altered patterns of cerebral activation during performance of different cognitive tasks (Audoin et al., 2003; Mainero, Caramia, Pozzilli, Pisani, & Pestalozza, 2004; Staffen et al., 2002). Such studies have consistently reported greater magnitude of activation in the MS population as opposed to healthy controls during tasks of working memory (such as the Paced Auditory Serial Addition Test or the PASAT) and motor organization (such as object manipulation). Audoin et al. (2003) compared brain activation patterns of patients with clinically isolated syndrome suggestive of multiple sclerosis (CISSMS) to that of healthy controls during performance on the PASAT. Despite similar behavioral performance for the two groups, the study reported greater activation of the bilateral prefrontal cortices (BA 45/46) and the right cerebellum in those with CISSMS. The additional activation in these regions was hypothesized to reflect compensatory mechanisms that were used by patients to counter the cognitive decline associated with the disease. The existence of such cortical plasticity in MS is encouraging as it can have potential implications for intervention studies aimed at reducing these cognitive deficits (Prakash et al., 2007). Though an interpretation of cortical plasticity based on the finding

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of increased activation in prefrontal areas is a plausible one, it is important to determine the role played by this additional activation within the MS-cohort (Hillary, Genova, Chiaravalloti, Rypma, & DeLuca, 2006) to better understand the variability in cognitive deficits within the MS population.

Given that both neuropsychological (Heaton, Nelson, Thompson, Burks, & Franklin, 1985; Rao et al., 1991) and neuroimaging studies (Chiaravalloti et al., 2005; Penner, Rausch, Kappos, Opwis, & Radu, 2003) suggest significant intra-cohort variability in cognitive task performance in the MS population, an investigation of the relationship between additional activation and behavioral performance is critical to our understanding of the nature of cognitive decline in MS (Chiaravalloti et al., 2005; Hillary et al., 2003, 2006). Using tasks of working memory, Chiaravalloti et al. (2005) and Hillary et al. (2003) reported additional recruitment of the right prefrontal cortices in those with MS. Interestingly, in both studies the authors reported a negative correlation between task performance and percent signal change in the right prefrontal cortical areas, thereby suggesting that the greater recruitment of cortical areas seen in MS may not necessarily be facilitative of task performance. The negative association between task performance and right DLPFC activation reported by Chiaravalloti et al. (2005) and Hillary et al. (2003) in their work with MS patients is consistent with findings of similar studies involving TBI patients and HIV patients (see Hillary et al., 2006, for a review).

The fact that working memory task performance is negatively correlated with additional activation in the right DPLFC in MS patients provides an opportunity firstly to explore the functional significance of this additional activation in MS patients and secondly to examine whether the negative relationship between task performance and greater activation is generalizable to other cognitive tasks. In this study, we investigated the relationship between cortical recruitment and differences in cognitive performance within the MS group on a task of selective attention, namely the modified version of the Eriksen flanker task (Botvinick, Nystrom, Fissel, Carter, & Cohen, 1999; Colcombe, Kramer, Erickson, & Scalf, 2005). The studies reported above (Chiaravalloti et al., 2005; Hillary et al., 2003) focused primarily on tasks of working memory, whereas this study is the first to investigate the relationship between behavioral performance on a task of selective attention and associated cortical recruitment within the MS-cohort. Further, the flanker task is a well-characterized paradigm in terms of mechanisms, behavioral and neuroimaging findings and to our knowledge none of the previous studies focusing on altered patterns of brain activations associated with tasks of attentional processes have specifically addressed the issue of functional significance of additional cortical activation in the MS group.

Given that the flanker task solely reflects the operation of processes of selective attention with minimal working memory load (Colcombe et al., 2005; Rouder & King, 2003), we hypothesized that MS patients might perform similarly to controls. We also predicted, based on the extant literature on MS and cognition, that MS patients would show greater activation of brain regions necessary for the performance of the selective attention task, particularly in the more difficult incongruent condition. In addition, we were also interested in examining the association between behavioral performance on the flanker task and concomitant changes in cortical recruitment. There are thus two possible results that can be obtained based on this intra-group analysis. First, if the additional activation is compensatory, aiding in the performance of the selective attention task, we would expect that the additional activation be correlated negatively with reaction time data. In other words we would expect that the better performing MS patients (i.e. those with faster response times, especially in the more difficult incongruent condition) would show greater activation as compared to poor-performing MS patients. On the other hand, if there were a positive correlation between behavioral performance (reaction time) and additional activation, it would reflect an overall reduction in the neural efficiency of patients with MS.

2. Methods

2.1. Participants

Twenty-four females diagnosed with definite relapsing-remitting MS (Poser et al., 1983) with a mean Expanded Disability Status Score (EDSS; Kurtzke, 1983) of 2.61 (S.D. = 1.76), and 15 age- and education-matched healthy female controls were recruited for the current study. Mean age-and education of MS participants was 45.86 and 15.54 years, respectively. Mean age of healthy controls was 44.74 and 15.8 years, respectively. Participants were recruited by advertising in the local newspapers and using the database maintained by one of the authors of the study. The mean disease duration for MS participants was 8.02 (5.07) years. All participants were screened for any contraindications for participating in an MR environment. MS patients were excluded from the study if they met any one of the following criteria: a score below 51 on the Modified Mini-Mental State Examination (mMMSE, highest score = 57; Stern, Sano, Paulsen, & Mayeux, 1987), lack of consent from their primary physician. Further, during the initial screening, participants were also given a health history questionnaire in which questions were asked about history of different psychiatric disorders, neurological disorders other than MS, head injury and substance abuse or dependence. Participants were excluded from the study if they reported any history of psychiatric disorders other than depression. Two of the 24 participants were currently on anti-depressants but none of the participants met DSM-IVTR diagnosis of a mood disorder. None of the participants endorsed any items related to head injury or other neurological disorders. The visual acuity of all participants was screened, with corrective lenses provided in order to achieve visual acuity of at least 20/30. The University of Illinois Institutional Review Board approved the study, and all participants provided informed consent.

2.2. Neuropsychological assessment

The cognitive status of participants was established using a battery of neuropsychological tests. The test battery included the K-BIT (verbal), a test of verbal intelligence; a computerized version of the Wisconsin Card Sort Test (WCST), a test of set-shifting and Rao's Brief Repeatable Battery (BRB) of neuropsychological tests. The BRB includes five subtests: the Selective Reminding Test (SRT), a measure of verbal learning and delayed recall of a 12 paired word list; the Spatial Recall Test which measures visuo-spatial learning and delayed recall; the Symbol Digit Modalities Test (SDMT), which is a measure of sustained attention, working memory, and information processing speed and the Word List Generation (WLG), a verbal fluency test and the Paced Auditory Serial Addition Test (PASAT), a test of sustained attention, working memory and information processing speed.

2.3. Neurocognitive task and fMRI parameters

In order to investigate the patterns of fMRI activation in MS patients and controls, we employed a modified version of the Eriksen flanker task (Botvinick et al., 1999; Colcombe et al., 2005). Participants were given a four-button response pad and were asked to respond to the direction of the central arrow in an array of five arrows. For half of the trials, the direction of the central arrow was congruent to the direction of the target arrows (see Fig. 1). During the other half of the trials, the direction of the target arrow was incongruent with the direction of the central arrow. Participants were asked to depress the left innermost key on the four-button response pad if the central arrow pointed left and were asked to depress the right innermost key if the central arrow pointed to the right.

A total of 100 stimuli (25 of each type) were presented to each participant for a period of 1.5 s per trial with a 3 s response window. A fixation cross was presented to the participants during the inter-stimulus interval (ISI), which was used as a baseline to compare activation across different conditions. The range of ISI's was from 2 to 10 s with a mean of 5 s. Each stimulus type was first-order counterbalanced across the entire run, which lasted for 7 min. Stimulus sequence and timing were generated with optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq; see also Dale, 1999; Dale, Greve, & Burock, 1999). Participants were scanned in a 3T Siemens Allegra head-only scanner with a fast echo-planar imaging (EPI) sequence protocol (28 horizontal slices; TR = 1500 ms; TE = 25 ms; ascending slice acquisition; 80° flip angle; 4 mm isotropic thickness). High-resolution structural images were also collected for each participant using a spoiled gradient sequence (256 mm × 256 mm FOV; 1.3 mm thick slices, with a 1.3 mm × 1.3 mm in-plane resolution) for spatial registration.

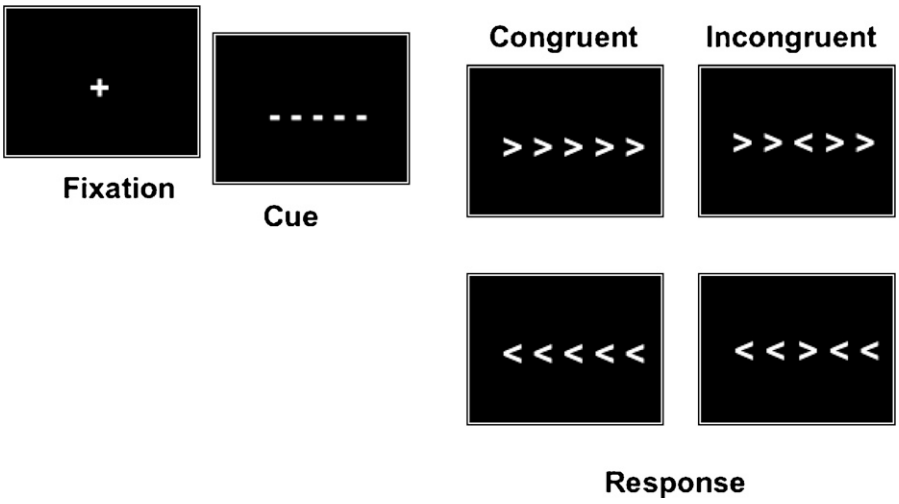

Fig. 1. A graphic representation of the Eriksen flanker task used in the study.

2.4. Data analysis

Behavioral data (reaction time and accuracy) were analyzed using a repeated measures analysis of variance with condition (congruent, incongruent) as a within-subjects factor and group (MS, healthy controls) as a between-subjects factor. We then carried out planned comparisons using paired *t*-tests across the two groups to investigate differences between the experimental conditions. We performed the Kolmogorov–Smirnov test for normality on our RT data and obtained a *p*-value of 0.200, thereby suggesting there was no difference between the distribution of the RT data and a normal one. All behavioral data were analyzed using SPSS 11.0.3 for Mac.

The neuroimaging data were analyzed using a statistical parametric approach using FSL Version 3.2 (http://www.fmrib.ox.ac.uk/fsl) and FEAT (fMRI Expert Analysis Tool) Version 5.43. The 220 images that were collected while the participants performed the task, were slice-time corrected, motion corrected using a rigid-body algorithm in MCFLIRT (Jenkinson, 2003), and temporally smoothed with a Gaussian low pass (1.5 s cut-off) and high pass (100 s cut-off) filter. Spatial smoothing was done with a 8 mm (Full Width at Half Maximum: FWHM) three-dimensional Gaussian kernel. Following this, all high-resolution T1-weighted images were skull stripped using a robust deformable brain extraction technique (BET) (Smith et al., 2002). These skull-stripped images for each participant were spatially registered using a 12-parameter affine transformation to a study-specific template in stereotaxic space that was specifically created for the study in order to avoid potential biases due to structural differences between participants. This was done by: (a) warping each participant's high-resolution scan to MNI space, (b) creating an average of these registered images and (c) spatially smoothing the average image with a 10 mm (FWHM) Gaussian kernel. This study-specific template was subsequently used for spatial registration of the fMRI data.

Correct trials for each participant were modeled in FILM (FMRIB's Improved Linear Model) using a double gamma function with temporal derivatives. In addition, six motion correction parameters and error trials were treated as covariates of no interest within this first-level analysis. This resulted in voxel-wise parameter estimates for each participant that represented the fit of the model with the underlying time series. The parameter estimate maps and variance maps for the incongruent trials (v/s baseline), congruent trials (v/s baseline) and the contrast of incongruent > congruent for each participant were then forwarded to a whole-head second level analysis whereby inter-participant variability was treated as a random variable. Mixed-effects analysis was performed using FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004) to locate regions of cortex that were significantly active for the MS group, controls, MS > controls and the controls > MS contrast. Results from the final whole-head analysis resulted in *Z* statistic images that were thresholded using clusters determined by a voxel-wise threshold of $z > 2.33$ ($p < 0.01$) and a corrected cluster-wise threshold of $p < 0.05$ (Forman et al., 1995; Friston, Jezzard, & Turner, 1994; Worsley, Evans, Marrett, & Neelin, 1992). The regions that survived this threshold in the MS > controls for the incongruent > congruent contrast were used as *a priori* ROIs by drawing a 8 mm sphere around each of the peak voxels within each cluster. The average percent signal change from these regions was then extracted and examined in order to investigate the association between behavioral performance and activation within the MS cohort. Specifically reaction time data for the incongruent trials was correlated with percent signal change by calculating partial correlations in each of the ROIs while controlling for age, education and duration of illness. All images were rendered in Mri3DX Version 5.

3. Results

3.1. Neuropsychological results

Neuropsychological data were analyzed by a series of independent *t*-tests (see Table 1). We found a significant difference between MS patients and controls on three neuropsychological measures of the Brief Repeatable Battery: Symbol Digit Modalities Test ($t = -4.43$, $p < 0.001$); Paced Auditory Serial Addition Test ($t = -2.14$, $p < 0.03$) and Word List Generation Test ($t = -3.02$, $p < 0.005$). The two groups did not differ with respect to the mMMSE or the K-BIT

Table 1
Demographic and neuropsychological data for all participants

	Controls	MS patients	Significance	Cohen's *d*
Total	15.00	24.00		
Age (years)	44.71 (8.37)	44.81 (7.07)	0.88	
EDSS	N/A	2.61 (1.76)		
mMMSE	55.80 (1.52)	54.92 (1.79)	0.67	0.11
K-BIT	110.00 (9.5)	107.07 (8.78)	0.70	0.07
Brief repeatable battery				
Selective Reminding Test	46.93 (13.46)	40.87 (10.75)	0.12	0.11
Spatial Reminding Test	24.86 (7.89)	23.37 (6.28)	0.51	0.04
Symbol Digit Modalities Test	**61.2** (**11.55**)	**45.08** (**10.71**)	**0.00**	**0.33**
Paced Auditory Serial Addition Test	**49.66** (**8.65**)	**42.54** (**10.84**)	**0.03**	**0.16**
Word List Generation Test	**11.08** (**2.81**)	**8.86** (**1.81**)	**0.01**	**0.22**

Standard error is given in parenthesis *p*-values significant at 0.05 or less are in bold.

Table 2
Reaction time and accuracy data for all participants

	Congruent	Incongruent
Controls		
Reaction time	605.15 (18.19)	688.17 (23.42)
Error rates	2.0 (1.33)	2.9 (1.52)
MS patients		
Reaction time	644.39 (21.53)	725.26 (23.48)
Error rates	4.9 (2.33)	5.1 (1.97)

Standard error is represented in parentheses.

(verbal) suggesting that in this study the two groups performed similarly on measures of generalized cognitive functioning and crystallized intelligence.

3.2. Behavioral results

3.2.1. Response times

Response times and error rates were recorded while all participants performed the flanker task in the scanner. For response time analyses, only RT's for correct trials were included. The results from the repeated measures analysis of variance with condition (congruent, incongruent) as a within subjects factor and group (MS patients, controls) as a between subjects factor revealed a main effect of condition ($F(1,38) = 25.43$, $p < 0.001$). We did not find a main effect of group ($F(1,38) = 1.44$, $p = 0.24$). The interaction of Group × Condition was not significant ($F(1,38) = 0.01$, $p = 0.90$). Both MS patients and controls were slower in responding to the incongruent condition than the congruent condition (Table 2).

3.2.2. Accuracy

Similar to the RT data, error rates were analyzed using a repeated measures ANOVA. Neither the main effect of condition ($F(1,38) = 1.52$, $p = 0.23$) nor group ($F(1,38) = 0.77$, $p = 0.38$) was significant. The interaction of Group × Condition was also not significant ($F(1,38) = 0.51$, $p = 0.48$).

3.3. Neuroimaging results

MS patients and controls activated a number of regions in the frontal, parietal, temporal and occipital cortices during performance on the incongruent condition of the flanker task (see Table 3 and Fig. 2 for significant activations in the two groups). A direct comparison between MS patients and healthy controls during the incongruent trials indicated that the MS group displayed greater activation of the right prefrontal cortex compared to healthy controls. We also compared patterns of activation between MS patients and healthy controls on the incongruent > congruent contrast and found that MS patients demonstrated greater activation of the bilateral inferior frontal gyri during the incongruent > congruent contrast. Again the control > MS contrast did not result any significant activations.

3.3.1. Correlations with reaction time data

The whole-head analyses reported above suggests that MS patients show greater activation of task-related regions and recruit additional regions of cortex while responding to the Eriksen flanker task. We assessed the specific role of the greater activation demonstrated by the MS group by conducting correlational analyses between performance and brain activity. Specifically, we constructed a 8 mm sphere around the peak voxel for each of the clusters reported to be active in MS patients relative to healthy controls (MS > controls contrast) during the incongruent > congruent contrast (Fig. 3). We then extracted percent signal change for each of the clusters and correlated these with the reaction time data of the incongruent condition for all MS participants. Using partial correlations (pr), we removed the variance associated with age, education and duration of illness and found significant correlation between reaction time data and percent signal change for the right inferior frontal gyrus (rt. IFG). Interestingly, we found a positive correlation between activation in this region and RT data ($pr = 0.52$, $p < 0.01$) suggesting that greater activation in this region was associated with poor behavioral performance on the task.

4. Discussion

Consistent with previous studies (Chiaravalloti et al., 2005; Hillary et al., 2003; Mainero et al., 2004), we found additional cortical activation in MS patients as opposed to healthy controls during performance on the Eriksen flanker task. This study provides additional novel evidence of significantly greater activation of the right prefrontal cortices in MS patients in a selective attention task. Furthermore, this activation was associated with poor behavioral performance. These results are consistent with a number of other studies done with MS patients (Chiaravalloti et al., 2005; Hillary et al., 2003), TBI patients (Christodoulou et al., 2001) and HIV patients (Chang et al., 2001; Ernst, Chang, Jovicich, Ames, & Arnold, 2002). Furthermore, these results indicate that greater recruitment of the neural circuitry might not always be beneficial to task performance (Hillary et al., 2006) and may in fact reflect a reduction in the neural efficiency of the system as a whole, which eventually interferes with cognitive performance, in the present case the ability to selectively attend to task-relevant information in the visual environment and ignore task-irrelevant and misleading information.

Though neural inefficiency is a plausible interpretation, another potentially plausible interpretation of the role of the right PFC in neurologically impaired populations as suggested by Hillary et al. (2006) is that the recruitment of the right PFC is directly proportional to the level of the difficulty of the task. These authors suggested that the right PFC, which is recruited by healthy controls in response to increases in task load is recruited by patients at lower task demands, suggesting a lower threshold of right PFC recruitment in such individuals. This interpretation provided by Hillary et al. (2006) was based on their review of studies of verbal WM tasks. In this study, we employed a non-verbal task of selective attention with no WM component and found results similar to that reported in Hillary et al. (2006) suggesting that the right DLPFC activation increases during periods of cerebral challenge. Additional studies specifically manipulating the levels of inhibitory demands in MS patients would further help to examine the functional specificity of the PFC.

Previous studies examining the relationship between behavioral performance and increased cortical activation have primarily examined verbal WM tasks (Chiaravalloti et al., 2005; Hillary et al., 2003; Mainero et al., 2004). Our results based on a non-verbal selective attention task are consistent with some studies (Chiaravalloti et al., 2005; Hillary et al., 2003), but stand in contrast with other neuroimaging studies investigating the altered patterns of cerebral activation in multiple sclerosis (Staffen et al., 2002; Mainero et al., 2004). Greater activation of task-related areas by MS patients has been taken as evidence for neural plasticity; adaptive mechanisms exhibited by those with MS to compensate for the neural decline associated with the disease. For example, Mainero et al. (2004), using the Paced Auditory Serial Addition Task (PASAT), compared differences in activation patterns between MS patients and healthy controls. They also divided the participants on the basis of behavioral performance on the PASAT task, and compared cortical recruitment across the two groups. The results indicated that

Table 3
Cortical regions recruited by MS patients and healthy controls in response to the Eriksen flanker task

Anatomical region	Control				Multiple sclerosis patients			
	Max *z*-score	Tal. co-ordinates			Max *z*-score	Tal. co-ordinates		
		X	*Y*	*Z*		*X*	*Y*	*Z*
Frontal								
L. anterior cingulate	2.84	−1	19	28				
R. anterior cingulate	2.78	1	18	28				
L. inferior frontal gyrus	4.39	−58	5	33	4.55	−63	5	21
R. inferior frontal gyrus					5.93	51	7	34
L. medial frontal gyrus	3.15	−3	−1	52	4.39	−1	−1	63
R. medial frontal gyrus	2.9	1	−1	52	4.68	1	−1	65
L. middle frontal gyrus	4.53	−41	−3	60	4.48	−36	−7	63
R. middle frontal gyrus	3.86	31	−9	65	5.83	51	7	−4
R. posterior cingulate	3.45	27	−73	10	3.64	27	−73	10
L. superior frontal gyrus	2.91	−4	3	52	4.31	−1	1	63
R. superior frontal gyrus	2.6	1	3	52	4.5	1	1	63
Temporal								
L. inferior temporal gyrus	6.05	−47	−67	−7	6.51	−45	−71	−7
R. inferior temporal gyrus	7.02	45	−67	−7	6.79	45	−67	−5
L. middle temporal gyrus	5.92	−49	−65	0	6.2	−47	−65	0
R. middle temporal gyrus	6.38	45	−63	−4	6.54	45	−63	−4
L. superior temporal gyrus	5.26	−46	−27	16	5.58	−53	7	−4
R. superior temporal gyrus	2.74	41	−53	7	4.36	45	11	−7
Parietal								
L. inferior parietal lobule	5.88	−57	−33	50	5.27	−57	−31	50
R. inferior parietal lobule	5.01	49	−29	48	4.62	41	−41	58
L. superior parietal lobule	5	−27	−61	48	5.02	−17	−65	63
R. superior parietal lobule	4.51	23	−69	50	4.63	27	−57	60
L. supramarginal gyrus	4.86	−43	−39	38	4.85	−39	−39	38
R. supramarginal gyrus	3.3	41	−39	38	3.57	41	−39	37
Occipital								
L. fusiform gyrus	6.8	−21	−91	−18	6.63	−21	−91	−18
R. fusiform gyrus	6.94	39	−73	−18	7.13	43	−65	−18
L. inferior occipital gyrus	6.87	−21	−91	−15	6.93	−23	−91	−15
R. inferior occipital gyrus	7.26	39	−69	−11	7.08	39	−69	−11
L. lingual gyrus	6.79	−21	−91	−11	6.63	−21	−91	−11
R. lingual gyrus	6.29	21	−89	0	6.52	33	−71	−13
L. middle occipital gyrus	6.99	−33	−91	−1	7.09	−33	−91	−4
R. middle occipital gyrus	7.38	39	−71	−15	7.25	39	−71	−15
L. superior occipital gyrus	3.62	−33	−75	23	4.71	−29	−91	19
R. superior occipital gyrus	4.37	29	−83	23	4.56	31	−85	19
Subcortical								
L. claustrum	4.56	−29	−1	11	3.34	−34	−1	−5
R. claustrum	3.14	31	−5	11	3.2	35	−1	3
L. caudate	2.86	−14	−1	15	2.73	−14	−1	15
R. caudate	3.86	13	−1	15	3.55	13	−11	19
L. insula	5.71	−52	−21	16	4.84	−48	−27	15
R. insula	2.91	33	−5	11	4.36	45	10	−7
L. lentiform nucleus	4.8	−27	−1	7	3.67	−17	−11	−1
R. lentiform nucleus	4.55	25	−17	−4	3.47	11	−1	−1
L. parahippocampal gyrus	4.15	−22	−31	−4	3.17	−30	−3	−13
R. parahippocampal gyrus	4.34	35	−31	−24	3.96	31	−45	−15
L. thalamus	5.18	−13	−17	0	3.82	−15	−15	0
R. thalamus	4.58	11	−17	3	4.13	11	−13	4
Cerebellum								
L. cerebellar lingual	3.06	−10	−47	−19	2.92	−10	−47	−19
R. cerebellar lingual	3.18	5	−49	−21	3.35	9	−47	−19

the cortical regions recruited by the MS patients exceeded that of the controls both in terms of magnitude of activation as well as in the extent of activity. Further, they reported that within the MS group, patients whose performance matched that of healthy controls showed greater activation than patients who performed worse. The authors argued that increases in activation accompanied with comparable behavioral performance reflected a compensatory reorganization to eliminate the behavioral consequences of neuropathology (Zarahn, Rakitin, Abela, Flynn, & Stern, 2007). However, using a selective attention task with minimal working memory demands, we found that increases in activation were associated with poor behavioral performance within the MS group, reflecting a reduction in the neural efficiency of the brain system as a whole (Zarahn, Rakitin, Abela, Flynn, & Stern, 2007).

Taken together, these results suggest that the previously reported finding of increased activation observed in MS, should not be taken to imply universal compensatory reorganization of the brain processes. One possible explanation of these discrepant findings could be that the additional activation was beneficial to performance on the PASAT because of the higher working memory load of the task. PASAT, a measure of sustained attention, working memory and information processing speed has been extensively

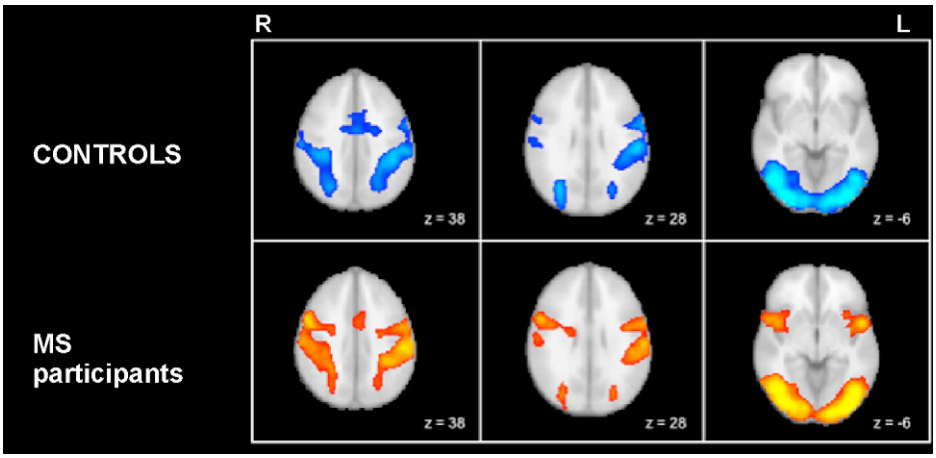

Fig. 2. Cortical regions that were activated by study participants in response to the incongruent condition of the Eriksen flanker task. All images are in radiological orientation (R = L, L = R) and are thresholded at a voxel-wise threshold of $z > 2.33$ and a corrected cluster-wise threshold of $p < 0.05$.

studied with this population (Audoin et al., 2003; Chiaravalloti et al., 2005; Prakash et al., 2007) and is a core measure of the Multiple Sclerosis Functional Composite Scale (MSFC). Behavioral and neuroimaging studies have suggested that the PASAT task places heavy demands on verbal working memory processes (Audoin et al., 2003; Fisk & Archibald, 2001) resulting in compromised behavioral performance. During performance on this task, participants are presented with a series of digits either auditorily or visually. They are asked to vocalize the result of addition of the currently presented digit to the digit presented previously. Interference arising from the previous vocalization is a source of conflict, requiring participants to exert greater effort to perform the task to overcome the competition or conflict presented by the task (Prakash et al., 2007). The PASAT task, thus requires participants to inhibit interference arising from the previous addition and engage working memory processes in order to perform the new addition (Audoin et al., 2005; Lazeron, Rombouts, Sonneville, Barkhof, & Scheltens, 2003). Recruitment of additional brain regions such as the right frontal regions, as seen in PASAT studies (Audoin et al., 2003; Chiaravalloti et al., 2005; Mainero et al., 2004) has also been reported to assist performance of other verbal working memory tasks in healthy individuals (Rypma and D'Esposito, 1999).

The Eriksen flanker task, on the other hand, is a selective attention task (Botvinick et al., 1999; Eriksen & Eriksen, 1974; Rouder

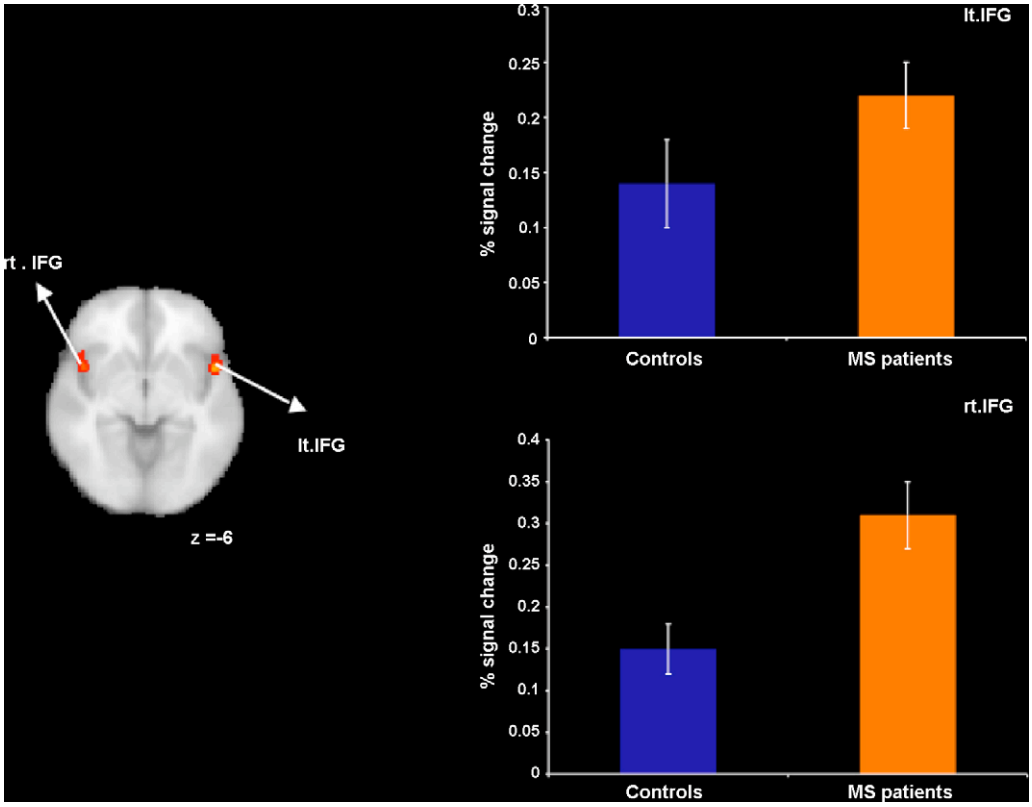

Fig. 3. Regions of frontal cortex that were significantly active in the MS > controls contrast. All images are in radiological orientation (R = L, L = R) and are thresholded at a voxel-wise threshold of $z > 2.33$ and a corrected cluster-wise threshold of $p < 0.05$.

& King, 2003) with relatively low working memory demands. Instead this task involves the ability to precisely focus spatial attention in order to avoid processing of the flanking distractors (Lavie, 2005). Poor behavioral performance associated with greater recruitment of neural circuitry during performance on our task might be explained by the load theory of selective attention and cognitive control (Lavie, 1995, 2005; Lavie, Hirst, De Fockert, & Viding, 2004). Relatively easy perceptual tasks (such as the one employed in the current study), require few attentional resources, thereby freeing up resources to not only process the target item but also the distracter items. This in turn results in significantly greater interference from the distracter arrows producing a greater compatibility effect, and compromising behavioral performance. Greater cortical recruitment of the right MFG/IFG during the Eriksen flanker task might thus reflect an inability to selectively process the target arrow producing larger response competition.

There is a potential limitation to our study. We used individual differences in cognitive performance to understand the functional significance of increased cortical activation in MS patients. Though we did control for several demographic variables (age, education, and disability status) in our examination of the relationship between performance and brain activation of the MS patients there may be other factors that may have an impact on MS-related cognitive impairment. Future studies using a within-subject design and specifically manipulating the level of task demands within each subject may provide additional information on the role of different cortical areas.

In summary, the results of the current study are consistent with observations from previous neuroimaging studies of MS, in terms of increased activation during performance of cognitive tasks in this group. However, our data suggests that recruitment of additional brain regions by MS patients does not always have a positive compensatory effect on task performance. Additional studies specifically manipulating the level of conflict between a target and distracters as well as working memory load would be useful to further explicate the manner in which MS patients deal with different types of perceptual and cognitive challenges as well as the brain regions that support their performance.

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