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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.