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Working memory deficits are common in Multiple Sclerosis (MS) and have been identified behaviorally in numerous studies. Despite recent advance in functional magnetic resonance imaging (fMRI), few published studies have examined cerebral activations associated with working memory dysfunction in MS. The present study examines brain activation patterns during performance of aworking memory task in individuals with clinically definite MS, compared to healthy controls (HC). fMRI was performed using a 1.5 Tesla GE scanner during a modified Paced Auditory Serial Addition Test (mPASAT). Participants were 6 individuals with MS with working memory impairment as evidenced on neuropsychological testing, 5 individuals with MS without working memory impairment, and 5 HC. Groups were demographically equivalent. Data were analyzed using Statistical Parametric Mapping (SPM99) software, with a stringent significance level (alpha < .005, voxel extent ≥ 8). Both MS groups and the HC group were able to perform the task, with comparable performance in terms of numbers of correct responses. Activation patterns within the HC and MS not-impaired groups were noted in similar brain regions, consistent with published observations in healthy samples. That is, activations were lateralized to the left hemisphere, involving predominantly frontal regions. In contrast, the MS impaired group showed greater right frontal and right parietal lobe activation, when compared with the HC group. Thus, it appears that working memory dysfunction in MS is associated with altered patterns of cerebral activation that are related to the presence of cognitive impairment, and not solely a function of MS.

Multiple Sclerosis (MS) is a progressive disease of the central nervous system (CNS) characterized by the production of widespread lesions, or plaques, in the brain and spinal cord. These plaques involve the myelin sheath of the CNS, which is vital to the normal transmission of neural impulses (Rumrill, Kaleta, & Battersby, 1996). As a result of the

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widespread and largely unpredictable nature of these plaques, MS results in a broad symptom array, including motor, cognitive and neuropsychiatric problems (Brassington & Marsh, 1998), with high variability in symptom presentation between individuals (Gordon, Lewis, & Wong, 1994). In addition, cognitive deficits may occur independently of physical disability, thereby complicating their identification (Cobble, 1992). This wide variability in observed symptoms and disease course creates a significant obstacle in understanding the disease process and identifying effective treatments.

Recent research indicates that cognitive dysfunction may be evident in 40–60% of individuals with MS (Rao, Leo, Bernardin, & Unverzagt, 1991), with particular problems noted in working memory (Demaree, DeLuca, Gaudino, & Diamond, 1999). For example, Demaree and colleagues (1999) showed that individuals with MS performed significantly worse than age and education matched healthy controls on the Paced Auditory Serial Addition Test (PASAT), a finding documented by other researchers as well (Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994; Grigsby, Busenbark, Kravcisin, Kennedy, & Taylor, 1994). Thus, for those individuals with MS with cognitive dysfunction, working memory appears to present significant difficulties, also potentially affecting other realms of cognitive functioning.

Previous research has shown that individuals with MS with cognitive impairment are impaired in the specific cognitive domains theorized by Baddeley (1986) to comprise working memory. In this model, working memory is theorized to be comprised of a central executive and two “slave” systems, the phonological loop and the visuospatial sketchpad. The two slave systems are theorized to be responsible for the maintenance of information in working memory, while the central executive system is thought to be responsible for the manipulation of the information within working memory. In their investigations of the phonological loop in MS, both Rao et al. (1993) and Litvan Grafman, Vendrell, & Martinez, 1988 noted a phonological loop deficit in individuals with MS, which compromised their articulatory rehearsal abilities. D’Esposito et al. (1996), on the other hand, investigated the impact of MS on another aspect of working memory, the central executive, concluding that persons with MS are impaired with regard to the central executive functioning. Together, these data suggest that individuals with MS are impaired in both the central executive and phonological loop components of working memory.

Functional neuroimaging has been applied to the study of working memory in healthy individuals in an attempt to identify the neural substrates involved in such tasks. Results of such studies have shown brain activation in a number of regions during a working memory task, specifically the prefrontal and premotor regions of the frontal lobes (e.g., involving the middle frontal gyrus and inferior frontal gyrus; Belger et al., 1998; Braver et al., 1997; Courtney, Ungerleider, Kell, & Haxby, 1997; Crosson et al., 1999; Grossman et al., 1994), and the parietal lobes (Braver et al., 1997; McAllister et al., 1999; Paulesu, Frith, & Frackowiak, 1993). Although less common, activation has also been seen in temporal regions (Paulesu et al., 1993; Salmon et al., 1996; Seidman et al., 1998). The results of these studies provide clear patterns of activation in healthy individuals, to which activations in neurological populations can be compared.

In recent years there has been an increase in the number of studies attempting to relate lesion location and lesion burden (as derived from neuroimaging) to cognitive dysfunction (as derived from neuropsychological testing) in MS. Multiple researchers have noted a measurement of total lesion area in individuals MS to be a useful predictor of cognitive test performance (Rao, et al., 1989; Swirsky-Sacchetti, et al., 1992). Swirsky-Sacchetti and colleagues (1992) additionally noted that lesions in the frontal regions were the most significant predictors of impairment on nearly 50% of the cognitive tasks administered. Regional MRI studies have shown that the greatest representation of lesion volume in subjects with MS is in the frontal regions, consistently observable over the course of 4 years in the same subject sample (Sperling et al., 2001). Furthermore, a relationship has been noted between total, frontal, and parietal lesion burden and cognitive performance on tasks assessing working memory and new learning (Sperling et al., 2001).

The functional basis of cognitive impairment in MS has been examined by numerous researchers utilizing Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT). PET studies have shown widespread reduction in glucose metabolism in an MS sample on tasks designed to measure frontal lobe functions (Paulesu et al., 1996). Other studies have found decreasing frontal (Bakshi, Miletich, Kinkel, Emmet, & Kinkel, 1998; Blinkenberg, Jensen, Holm, Paulson, & Sorensen, 1999; Roelcke et al., 1997) and parietal (Blinkenberg et al., 1999) cortical cerebral metabolism with advancing MS over a period of two years. In addition, significant correlations have been noted between the regional rate of glucose metabolism and measures of total lesion area and cognitive dysfunction (Blinkenberg et al., 2000). SPECT studies in MS have shown similar findings, with significant reductions in regional cerebral blood flow (rCBF) noted in the frontal lobes (Lycke, Wikkelso, Bergh, Jacobsson, & Anderson, 1993; Paulesu et al., 1996) and in the left temporal lobe (Paulesu et al., 1996) in MS patients.

In contrast to PET and SPECT, fMRI has had limited use in the MS population. To our knowledge, there are only a handful of published studies using fMRI in MS. fMRI has thus far been used to study optic neuritis (Rombouts et al., 1998; Werring et al., 2000), motor organization (Reddy et al., 2000a, 2000b; Rocca, Falini et al., 2002; Rocca Matthews et al., 2002), fatigue (Filippi et al., 2002) and working memory (Staffen et al., 2002) in MS. The majority of these studies examine the cerebral organization of motor—but not *cognitive*—functions. Reddy and colleagues (2000b) presented a longitudinal case of a patient with a relapse of MS, suggesting a relationship between the extent of brain pathology and the cortical organization of movement in this patient. Lee et al. (2000) verified these results within a larger, cross-sectional study, noting altered patterns of cortical activation for motor tasks, suggesting cortical changes in proportion to lesion burden. In another study, Reddy et al. (2000a) utilized magnetic resonance spectroscopic imaging (MRS) and fMRI to test the cortical response to normal motor functions (i.e., simple hand movements) in 9 MS subjects, as compared with 8 healthy control subjects. Results indicated activation of the ipsilateral sensorimotor cortex to increase five times that of normal controls, suggesting compensatory cortical adaptive responses in the presence of MS. Rocca, and colleagues (2002) reported similar findings. On a simple motor task, their MS sample showed increased activation in contralateral primary sensorimotor cortex, bilateral supplementary motor area, bilateral cingulate motor area, contralateral ascending bank of the sylvian fissure and contralateral intraparietal sulcus. In a second study, Rocca, Matthews, and colleagues (2002) noted individuals with MS tend to show increased activation of brain regions involved in motor planning and motor execution, as well as several multimodal cortical regions in the temporal, parietal, and occipital lobes. Finally, Filippi and colleagues investigated the relationship between brain and cervical lesions and fMRI activations associated with small hand movements. Results indicated that primary progressive multiple sclerosis patients showed greater bilateral activation in the superior temporal gyrus, greater ipsilateral activation in the middle frontal gyrus, and greater contralateral activation in the insula/claustrum when compared with healthy controls. In addition, the authors noted moderate to strong correlations between cortical activation during the fMRI task and the severity of structural changes (Filippi et al., 2002b).

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In addition to these motor studies, an additional fMRI study in MS examined the relationship between measurements of fatigue and patterns of cerebral activation in an MS sample (Filippi et al., 2002a). These authors noted significant differences in cerebral activation for a simple right hand motor task between healthy participants and individuals with MS (with and without fatigue). Most notably, individuals with MS showed greater activations in the contralateral primary somatomotor cortex, the contralateral ascending limb of the Sylvian fissure, the contralateral intraparietal sulcus, the contralateral supplementary motor area, and the ipsilateral and contralateral cingulate motor area. In addition, MS participants with reported fatigue showed more significant activation of the contralateral cingulate motor area (Filippi et al., 2002a). Together, these studies indicate that the MS group shows patterns of cerebral activation on motor tasks that are distinct from those observed in healthy samples, with more activation of regions contralateral to those typically responsible for a given motor activity.

The only published fMRI investigation focusing on cognitive functioning in MS examined the cerebral representation of Working Memory, utilizing the Paced Visual Serial Addition Test (PVSAT), a visual modification of the Paced Auditory Serial Addition Test (Staffen et al., 2002). Participants were 21 individuals with MS and 21 healthy control subjects. Results indicated different activation patterns for the MS participants as compared with the healthy control subjects. Healthy individuals demonstrated activation in the frontal part of the right gyrus cinguli, whereas the main activation in the MS group was noted at the right hemispheric frontal cortex and the left hemisphere Brodman's area 39 (Staffen et al., 2002).

FMRI has been used minimally to study cognition, particularly working memory, in multiple neurological populations in addition to MS. One previous study from our laboratory examined working memory in a moderate to severe traumatic brain injury (TBI) sample using fMRI (Christodoulou et al., 2001). The brain regions activated (i.e., middle frontal gyrus and middle temporal gyrus) among moderate and severe TBI subjects were similar to those identified in the literature with healthy individuals. However, activations in the TBI group during the verbal working memory task appeared somewhat more dispersed throughout brain regions other than middle frontal and temporal gyri, and were significantly more lateralized to the right cerebral hemisphere in comparison to healthy controls. In another study, McAllister and colleagues (1999) also examined working memory using fMRI with persons within one month of a mild TBI. The mild TBI subjects in that study did not demonstrate behavioral impairment on a verbal working memory task, but they did demonstrate more lateralized cerebral activation, displaying a right lateralized increase in activation (particularly right prefrontal and right parietal) in response to increased verbal working memory load. A further investigation by the same group (McAllister et al., 2001) noted that a further increase in processing load (beyond what was done in the 1999 study) resulted in increased activation in the healthy control participants. However, in the right frontal and parietal regions of the mild TBI participants, less of an increase in activation was noted in response to increased cognitive load. This finding highlights the possibility that perhaps the TBI participants are reaching their maximum activation levels on tasks of less difficulty than healthy control participants. Taken together, the results of these studies suggest that CNS compromise significantly alters the functional cerebral substrates of working memory. This finding of altered cerebral functioning in the presence of neurological compromise raises questions regarding the cerebral representations of working memory in other neurological populations in which working memory is known to be deficient.

The present study examines cerebral activation during a working memory task in MS, a population in which working memory dysfunction is a major cognitive symptom. Individuals with MS often present with deficits in working memory abilities observed behaviorally, which may be associated with altered patterns of cerebral activation on fMRI investigation (Staffen et al., 2002). Cognitive impairment among individuals with MS have been examined frequently using radioligand-based imaging techniques such as PET and SPECT, but fMRI holds a number of advantages over other forms of functional neuroimaging (Kollias, Valavanis, Golay, Bosiger, & McKinnon, 1996; Papanicolaou, Moore, Deutsch, Levin, & Eisenberg, 1988) and leaders in the field of neuropsychological rehabilitation have specifically recommended its use in neurological rehabilitation (Crosson et al., 1999; Stein, 2000).

Given the importance of working memory abilities in other, higher level cognitive abilities (Johnson, 1992), as well as the prevalence of these deficits in MS, we examined working memory functioning in MS at both a behavioral level and a functional neuroanatomical level. This study utilizes fMRI technology to examine the cerebral activation associated with a modification of a common working memory task in an MS population. Based on the fMRI studies of working memory in TBI, we hypothesized that individuals with MS with working memory impairment would show greater right hemisphere activation, most notable in the frontal and parietal lobes, than healthy control participants on the mPASAT, a test requiring working memory. In addition, we hypothesized that MS subjects without working memory impairment would not be significantly different from healthy control subjects in terms of patterns and magnitude of cerebral activation.

Method

Participants

Participants were recruited via advertisements at local support groups and MS Centers. In addition, participants from previous MS studies were contacted by phone and invited to participate in the current study. Eleven individuals with clinically definite MS were included in the study, 6 with a documented impairment in working memory and 5 with no impairment in working memory. Participants also included 5 healthy individuals. Impairment in working memory was defined as performance on the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977), falling two or more standard deviations below the mean of healthy controls in published normative data. Thus, by definition, there was a significant difference noted between the groups on the PASAT, with the MS impaired group ($M = 76.67$, $SD = 8.04$, range 67–84) performing significantly below the MS not impaired group ($M = 115.00$, $SD = 12.86$, range 96–131) and the HC group ($M = 133.80$, $SD = 22.23$, range 100–150) ($F(2,13) = 20.69$, $p < .001$).

Subjects were excluded if they were over the age of 55, reported a history of chronic medical disorders (other than MS), alcohol or drug abuse, bipolar disorder, psychotic disorder, schizophrenia, or head injury resulting in loss of consciousness. All subjects were at least one-month post-exacerbation and/or steroid treatment. Based on medical record review, 9 subjects had a relapsing-remitting course and 2 subjects had a secondary-progressive course. The duration of MS from diagnosis to the current evaluation ranged from 2–32 months, with a mean (±SD) of 14.09 (±9.95) months. There was a wide range in degree of physical disease severity, as measured by the Ambulation Index (Range: 0–6; $\text{Mean} = 1.75 \pm 1.91$). The impaired and not impaired MS groups did not differ in terms of either duration since diagnosis or the Ambulation Index (Table 1). In addition, no significant differences were noted between the two MS groups in terms of disease subtype, with 100% of the MS not impaired group and 67% of the MS impaired group having a

Table 1

Disease Characteristics for all MS Subjects by Group (MS impaired MS not impaired)

	MS Impaired Mean(SD) $n = 6$	MS Not Impaired Mean(SD) $n = 5$	*p*
Ambulation index	2.33 (1.9)	2.8 (1.9)	ns
Duration since diagnosis	10 (7.0)	19 (11.5)	ns
Lesion load: Right frontal lobe	42.75 (51.47)	78.5 (27.91)	ns
Lesion load: Left frontal lobe	42.58 (50.45)	64.13 (28.31)	ns
Lesion load: Right parietal lobe	15.42 (16.08)	13.75 (12.67)	ns
Lesion load: Left parietal lobe	17.92 (21.59)	20.63 (9.44)	ns
Lesion load: Right temporal lobe	9.25 (9.83)	12.63 (9.52)	ns
Lesion load: Left temporal lobe	50.8 (7.54)	12 (10.07)	ns

relapsing-remitting disease course. The two groups also did not demonstrate any significant differences in terms of lesion load (Table 1). Structural MRI images were taken at the time of testing and examined by a board certified neuroradiologist who was blind to group membership. Quantifications of lesion load were calculated from his measurements of the lesions (see below for details). This variable served as a covariate in later analyses.

There were no significant differences between the groups in terms of age, education, gender, or estimated premorbid intellectual abilities (Table 2). All participants were right handed. The three groups were also similar in terms of total scores on the Beck Depression Inventory and the State Trait Anxiety Inventory—State Anxiety scale both before and after undergoing the fMRI procedures (Table 2). All participants provided informed consent, as approved by the institutional review boards of both UMDNJ-New Jersey Medical School and Kessler Medical Rehabilitation Research and Education Corporation (KMRREC).

Procedure

Potential study participants were prescreened for study participation according to the above criteria. If an individual met study criteria, an initial appointment was scheduled for the neuropsychological evaluation. Within one week following the neuropsychological evaluation, participants underwent fMRI procedures.

Neuropsychological Testing Procedures

The neuropsychological assessment was conducted in one session, completed within 2 hours. Cognitive realms assessed included attention and concentration (WAIS-R Digit Span; Wechsler, 1981), Working Memory (WAIS-III Letter-Number Sequencing; Wechsler, 1997), Paced Auditory Serial Addition Test (PASAT, Gronwall, 1977), N-Back (McAllister et al., 1999), and overall intellectual ability (WAIS-R Vocabulary and Block Design; Wechsler, 1981).

fMRI Behavioral Tasks

Prior to undergoing fMRI procedures, the participant was oriented to the behavioral tasks to be presented within the scanner. These tasks consisted of a Modified Paced Auditory

Table 2

Demographic Characteristics and Cognitive Performance for all Subjects by Group (MS impaired, MS not impaired, healthy control)

	MS Impaired Mean(SD) $n = 6$	MS Not Impaired Mean(SD) $n = 5$	Healthy Control Mean(SD) $n = 5$	p
Age (years)	45 (7.1)	50.6 (3.2)	41.2 (11.1)	ns
Education (years)	15.67 (.8)	15 (2.0)	14.8 (2.4)	ns
Percent female	50%	80%	40%	ns
WAIS-R Vocabulary Scaled Score	11.3 (2.9)	12.6 (3.4)	11.2 (1.9)	ns
WAIS-R Block Design Scaled Score	8.17 (1.5)	9.4 (1.1)	9.8 (1.5)	ns
Beck Depression Inventory	12.17 (10.7)	6.80 (5.5)	2.6 (2.8)	ns
State Trait Anxiety Inventory – State Anxiety before fMRI	40 (13.5)	30.8 (10.8)	26.2 (6.9)	ns
State Trait Anxiety Inventory – State Anxiety after fMRI	32.83 (7.0)	28.2 (9.4)	27.2 (6.7)	ns
PASAT: Total correct	76.67 (8.04)	115.00 (12.86)	133.80 (22.23)	$P < .001$

Serial Attention Test (mPASAT) and Auditory Monitoring (the control task). The mPASAT, which has been used in previous studies (Christodoulou et al., 2001), is a challenging task with verbal working memory demands, significantly tapping the central executive working memory system. In the mPASAT subjects are presented with a series of numbers, ranging from one to nine, at the rate of one number every two seconds. Subjects are instructed to silently add each number to the number they hear immediately before it, and to press the response button (instead of answering aloud) only when the sum of the last two numbers is 10. This modification to the standard PASAT procedure was designed to limit head movement artifacts associated with verbal output during image acquisition. Total number of correct responses served as the behavioral independent variable. The Auditory Monitoring task involves the presentation of individual single-digit numbers. The subject is instructed to respond by a simple button-press when the number "7" is presented. The mPASAT and Auditory Monitoring were administered in a fixed sequence that consists of four sets of alternating 32-second blocks. Prior to the administration of the two tasks, there was one 32-second baseline period in which no stimuli were presented. In examining cerebral activation during the mPASAT, the activations during Auditory Monitoring and the initial 32 second baseline period were digitally subtracted from the activations of the experimental tasks (i.e., mPASAT) to control for cognitive processes not of interest in the current study (e.g., attention, reading numbers, simple motor responding).

Functional Imaging Procedure

All neuroimaging was performed on a General Electric Signa Horizon Echo-Speed 1.5 Tesla MR scanner. Prior to functional imaging, sagittal T1-weighted localizer images were obtained, followed by whole brain axial T1-weighted conventional spin-echo images for anatomic overlays (TR = 450, TE = 14, contiguous 5 mm, 256 x 256 matrix, FOV = 24, NEX = 1), yielding an in-plane resolution of 0.94 mm^2.

Functional imaging consisted of multislice gradient echo images that were acquired with echoplanar imaging (EPI) methods (TE [echo time] = 60 ms; TR [repetition time] = 4000 ms; FOV [field of view] = 24 cm; flip angle = 90; slice thickness = 5 mm contiguous). This yielded a 64 x 64 matrix with an in-plane resolution of 3.75 mm^2. A total of 28 images in the axial plane were acquired, providing coverage of the entire brain.

Prior to scanning, the task was practiced with the study participant outside the scanner. During scanning, subjects performed the working memory and control tasks while lying supine in the scanner. Foam cushioning and tape were utilized to immobilize the head within the coil in order to minimize motion degradation. Auditory stimuli were presented to subjects through MRI compatible headphones designed in our laboratory. Sound volume was adjusted so that each participant could adequately hear the stimuli. Study participants were provided with a response key for "yes/no" response.

Analyzing Images

Functional MRI data were initially analyzed on a voxel-by-voxel basis with a general linear model approach, using statistical parametric mapping (SPM99) software. The first three images were eliminated from analyses to control for saturation effects and in order to remove subvoxel motion-related signal change. All raw scan data (72 images) underwent spatial realignment using the SPM99 six-parameter model to remove minor (subvoxel) motion-related signal change. The realigned EPI images were then coregistered to the participant's T1 anatomical image and resliced. Following coregistration, the participant's T1 anatomical was matched to the SPM99 T1 template (standardized T1 from the Montreal Neurological Institute, MNI) using a 12-parameter affine approach. Thus, normalization of the coregistered EPIs was based upon the linear and nonlinear normalization parameters for the T1 template in SPM99 and the study participant's T1. Bilinear interpolation was used during the normalization procedure. Normalized scans were then spatial smoothed to 8 X 8 X 10 mm and, consistent with prior working memory research, SPM maps were thresholded to an alpha level of .005 with a cluster size (k) of 8 (Duara et al., 1992; Minoshima et al., 1993).

All data points for each significant cluster were then calculated. This method allowed us to access every X, Y, and Z coordinate comprising the clusters identified by SPM99. An exhaustive list of such coordinates was submitted to the Talairach Daemon (TD), a high-speed database server for querying and retrieving data about human brain structure over the Internet (Duara et al., 1992), to determine the location of each X, Y, and Z coordinate. The coordinate system used by SPM99 is from the Montreal Neurologic Institute (MNI) and MNI coordinates do not map exactly to the TD coordinate system. Therefore, prior to submission to the TD, all coordinates were adjusted based upon three separate calculations for the X, Y, and Z axes to more accurately represent the TD coordinate system. Such an adjustment method is consistent with previous fMRI research (Rorden & Brett, 2000). A positive z-value resulted in the following calculations: $X = (0.99^* X)$, $Y = [(0.9688 * Y) + (0.46^* Z)]$ and $Z = [(-0.0485^* Y) + (0.939^* Z)]$. Similarly, a negative z-value resulted in a slightly different calculation: $X = (0.99^* X)$, $Y = [(0.9688^* Y) + (0.42^* Z)]$, and $Z = [(-0.0485^* Y) + (0.839^* Z)]$.

Defining Brain Regions

Given the nature of the working memory paradigm used in this study, the cerebral cortex was of primary interest for data analysis. Therefore, analyses were focused on the left and right frontal, parietal, temporal and occipital cortices. Activation listed by the TD as cortical white matter was included in the analyses. Areas of activation listed by the TD nonspecifically as gray matter or white matter (e.g., nonspecific area of corpus callosum, sub-gyral white matter) were not included in the analyses.

Calculation of Gross Lesion Burden

To examine the extent to which the location and extent of lesions affected fMRI patterns of activation, we conducted a quantitative, clinical analysis of lesion burden for each participant. A clinical quantitative technique was chosen due to the fact that this type of approach is utilized with MS patients in their clinical care and such data would therefore be available to a treating clinician when discussing cognition with a patient.

Gross measurements of lesion burden were obtained via visual inspection of each participant's T2 weighted and FLAIR images by a board-certified neuroradiologist (AJK). During review, the neuroradiologist remained blind to subject group. Lesions were identified, and the size of each lesion was measured to the nearest millimeter. Lesions were then grouped by anatomical region to allow the examination of the lesion location data in relationship to the activation data obtained via fMRI procedures. Within the anatomic region of interest (e.g., Frontal Lobe), lesions were grouped by size (e.g., 5mm or less, 6–10 mm, 10+ mm) and weighted. The weighting procedure involved multiplying the number of lesions in each category by the approximate size of that category (i.e., the number of lesions 6–10 mm in diameter was multiplied by 7.5). A total lesion burden in that area of interest (e.g., Frontal Lobe) was then obtained by adding the weighted totals for all three categories. There were no significant differences between the MS impaired group and the MS not impaired group in terms of the lesion burden for any specific brain region.

While the procedure utilized in the current study was clinical in nature, it is important to note that the lesions were quantified by size, number and location by a board certified neuroradiologist, allowing a quantitative measurement of lesion burden to be obtained. Although this method of measuring lesion burden does provide a quantification of lesions along with their location, it can be improved upon with the more advanced volumetric analyses currently applied in neuroimaging research, such as Voxel Based Morphometry (Ashburner & Friston, 2001). Therefore, the results of this study that relate specifically to lesion burden should be viewed as preliminary in nature. That being said however, the method of lesion quantification utilized in the current study is likely the only one available to the majority of neurologists and neuroradiologists evaluating individuals with MS on a clinical basis and it is therefore more clinically applicable.

Data analysis

Each subject provided two mean images, one from the mPASAT condition and another that combined control (Auditory Monitoring) and baseline activation. Neuroanatomical regions activated on the control/baseline image were subtracted from regions activated by the working memory task (the mPASAT) to obtain only the cerebral activation associated with more complex working memory functions (i.e. central executive system), controlling for attention, concentration, motor response, and auditory processing of numerical information. Multiple t-tests were used to identify neuroanatomical regions of significant activation in each individual. Individual activations on the working memory task were then submitted to the neuroanatomical atlas of Talairach and Tournoux, as described previously (Deshpande, Millis, Reeder, Fuerst, & Ricker, 1996).

Once individual regions of activation were identified, voxels were grouped according to region. Additional analyses were then performed to evaluate differences between the MS group with working memory impairment, the MS group without working memory impairment, and the healthy control group in terms of the location and extent of activation on a working memory task, as well as the relationship between activation patterns and neuropsychological test performance. These analyses were accomplished through the use of nonparametric, Mann-Whitney U tests and Pearson product-moment correlations. The use of parametric, independent sample t-tests allowed the computation of effect sizes (Hedges *G*) in order to quantify the magnitude of group differences.

The study analyses focused on examining the a priori hypotheses regarding differences in brain activation between the two MS groups and the healthy control group. Given the highly specific nature of these hypotheses, Mann-Whitney U tests and independent sample t-tests were used addressing two specific contrasts: 1) the healthy control group versus the MS not impaired group, and 2) the healthy control group versus the MS impaired group. In addition, the working memory focus of the study led us to examine specific regions within the cerebral hemispheres thought to underlie cognitive functions. As such, the activation in the primary sensory areas of the frontal and parietal lobes were not included in the analysis. Specifically, we restricted our examination of the data to activation in only those areas of the parietal lobe believed to subserve cognitive functions, thus eliminating the post-central gyrus due to the fact that the postcentral gyrus is known to be primarily responsible for the detection of sensory experience. All other parietal lobe regions were maintained. A similar procedure was used in regard to frontal lobe activation. Activations in the precentral gyrus were not included in the analyses due to the fact that this region is known to subserve motor functions. The frontal lobe activations were composed of activations in the inferior frontal gyrus, the middle frontal gyrus, and the superior frontal gyrus.

Results

Working Memory Performance

Independent sample t-tests revealed no significant differences between the healthy control group and the MS impaired group in terms of performance on the behavioral tasks administered during the fMRI protocol. This was true of the mPASAT, working memory task (Figure 1a), as well as the Auditory Monitoring, control task(Figure 1b).

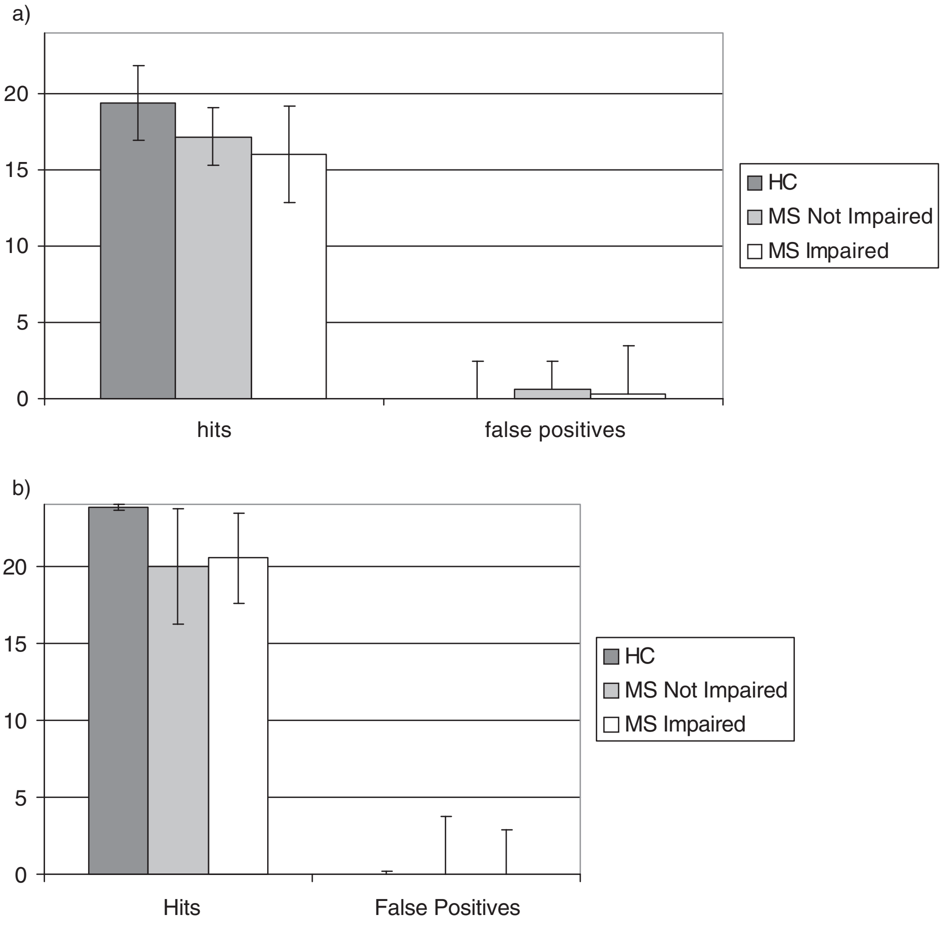

Figure 1. a) Behavioral performance on the mPASAT* within the fMRI by group; b) Behavioral performance on auditory monitoring* within the fMRI by group (*maximum possible correct = 24).

Working Memory Cerebral Activations

Independent samples t-tests revealed no significant difference between the healthy control group and either the MS impaired group or the MS not impaired group in terms of activation within any of the lobes in the left hemisphere. This result remained when examining the data nonparametrically.

When comparing the healthy control group to the MS impaired group in the amount of activation in the right parietal lobe cognitive regions, there was a significant difference between the groups ($t(9) = 2.27$, $p < .05$, Mann-Whitney $U = 4$, $p < .05$), with the MS impaired group showing significantly greater activation in the right Parietal Lobe than the healthy control group (Figure 2; Figure 3). This analysis revealed a large effect size (Hedges$G = 1.26$). In contrast, there was no significant difference in level of cerebral activation of the right parietal lobe cognitive regions between the MS not impaired group and the healthy control group ($t(8) = .48$, $p = .65$, Mann-Whitney $U = 9$, $p = .47$).

When examining differences between the groups (MS impaired vs. healthy control) in terms of the number of voxels activated in the cognitive regions of the right frontal lobe, a statistically significant effect was not observed ($t(9) = .81$, $p = .44$, Mann-Whitney $U = 12$, $p = .66$). We did however, observe a moderate effect size (Hedges$G = 0.45$), indicating that although our analysis does not reach statistical significance, group differences likely exist. However, the power to detect may be limited by the sample size (Figure 2; Figure 4). There was no significant difference in levels of cerebral activation of the cognitive regions of the right frontal lobe between the MS not impaired group and the healthy control group ($t(8) = .41$, $p = .69$, Mann-Whitney $U = 12$, $p = .917$). There were also no significant differences between the healthy control group and either the MS impaired group or MS not impaired group in terms of amount of activation in the right occipital or temporal lobes.

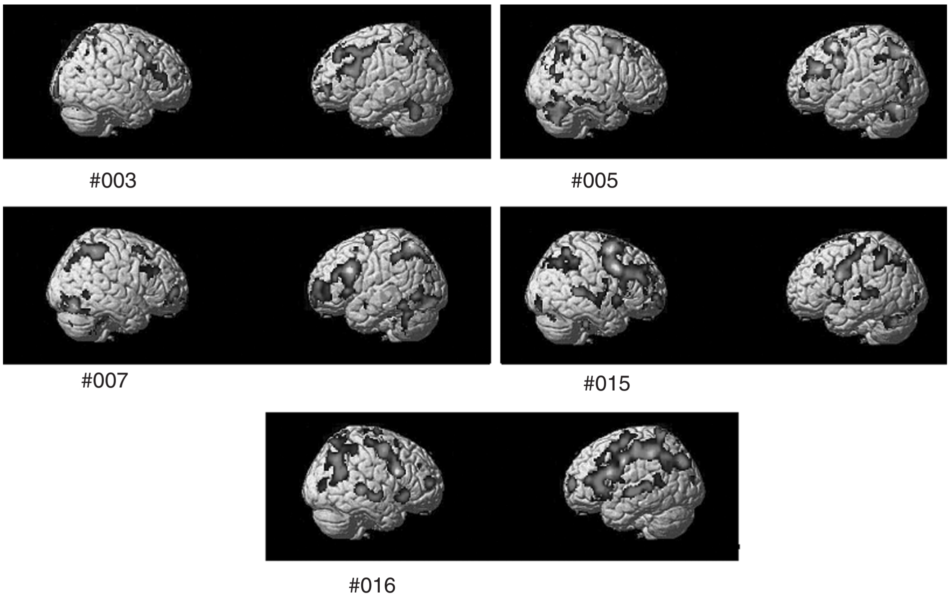

Figure 2a. SPM surface renderings for healthy control participants ($N = 5$).

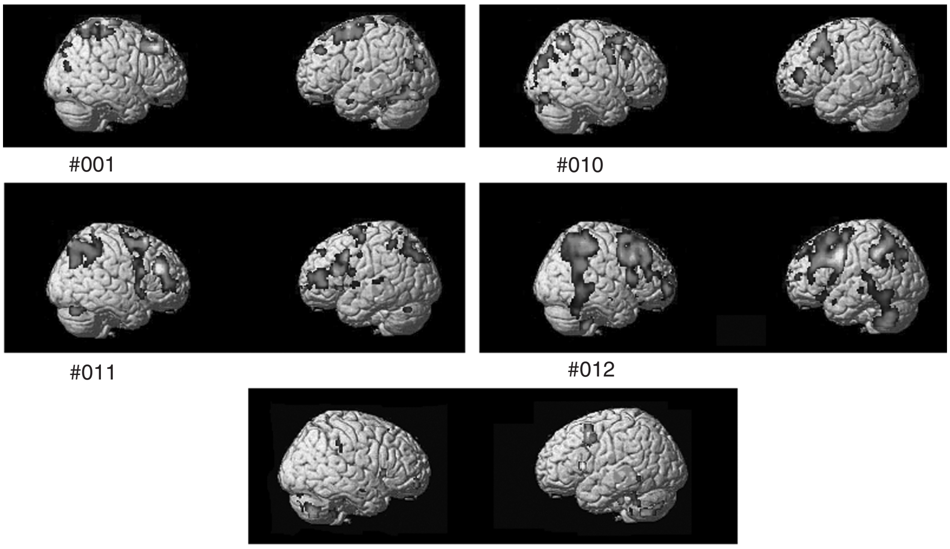

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Figure 2b. SPM surface renderings for MS Not Impaired participants (*N* = 5).

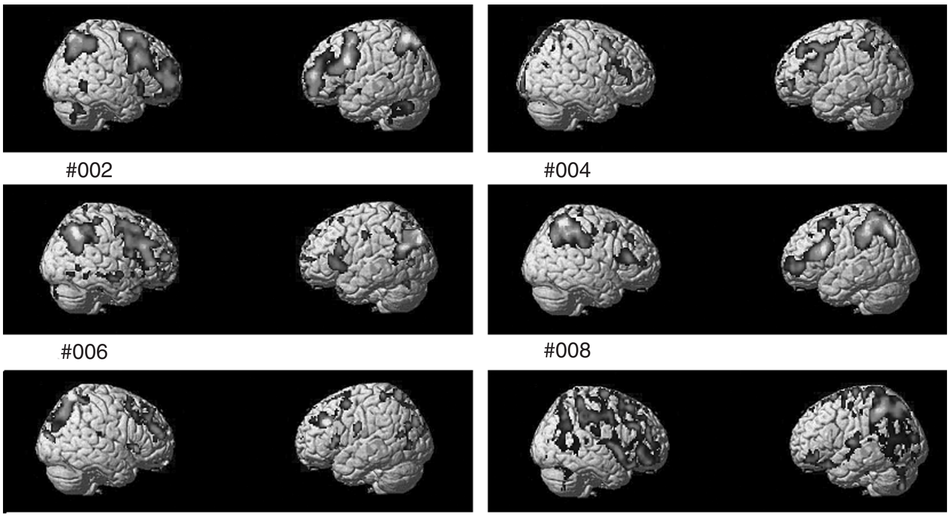

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Figure 2c. SPM surface renderings for MS Impaired participants (*N*=6).

The Relationship Between Working Memory Performance and Cerebral Activation

To examine differences between the MS impaired group and the healthy control group in terms of neuropsychological test performance, conducted outside the scanner, independent sample t-tests were performed. Results indicated significant differences between the MS impaired group ($M = 76.67$, $SD = 8.04$) and both the MS not impaired group ($M = 115$, $SD = 12.86$) and the healthy control group ($M = 133.8$, $SD = 22.23$) in terms of performance

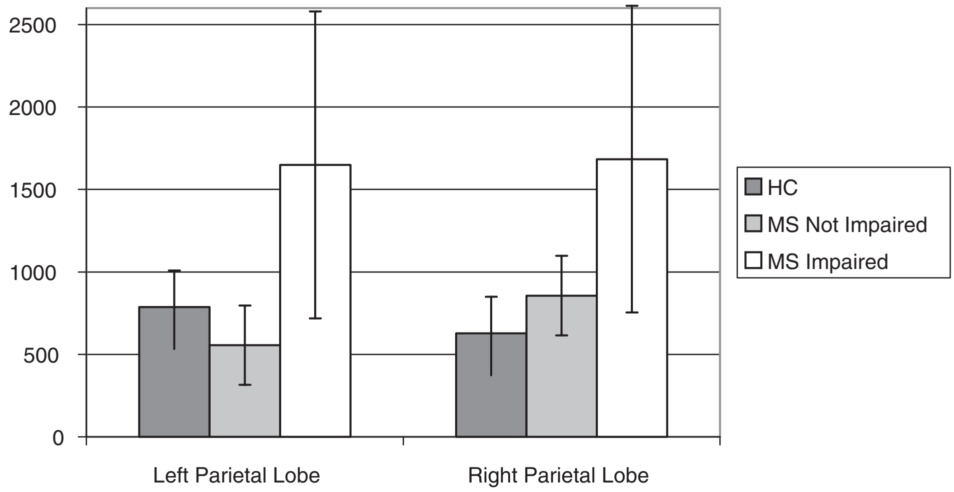

Figure 3. Number of activated voxels in the cognitive regions of the parietal lobes by group.

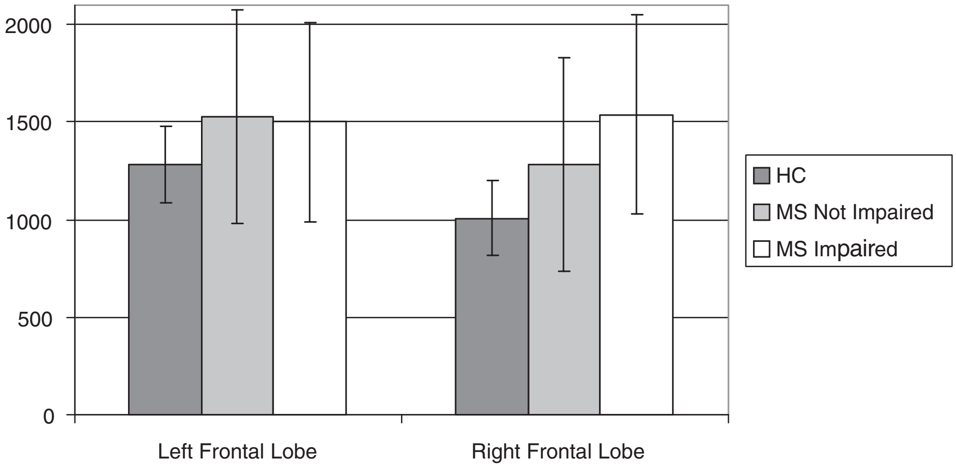

Figure 4. Number of activated voxels in the cognitive regions of the frontal lobes by group.

on the PASAT, with the MS impaired group obtaining significantly lower scores than both groups (F(2,13) = 20.69, $p < .001$). This finding was expected based on the fact that PASAT performance was used to define the groups. There were no other significant differences between groups in reference to neuropsychological test performance.

Pearson Product Moment correlations were performed on all subjects to examine the relationship between the amount of intra-scanner activation in various brain regions and performance on working memory tasks administered during the extra-scanner neuropsychological evaluation. Results indicated a significant positive relationship between activation in the left ventrolateral frontal lobe and performance on WAIS-R Digit Span Backward, with greater activation being associated with better performance. The opposite pattern was noted with regard to activation in the cognitive regions of the right parietal

Table 3
Correlation Between Amount of Cerebral Activation in Frontal and Parietal Regions and Neuropsychological Test Performance

	Digits Backward	WAIS-III Letter-Number	PASAT Trial 3	PASAT Trial 4
Right Dorso-lateral frontal	.11	.19	−.48	−.42
Right Ventromedial frontal	.41	.20	−.26	−.27
Right frontal cognitive	.20	.21	−.46	−.39
Right parietal cognitive	.25	−.10	−.52*	−.33
Left Dorso-lateral frontal	.37	.37	−.10	−.12
Left Ventro-medial frontal	.61*	.22	.04	.01
Left frontal cognitive	.46	.34	−.05	−.07
Left Parietal cognitive	.27	−.20	−.27	−.24

*$p < .05$.

lobe and PASAT performance. That is, increased activation in the right parietal lobe seems to be associated with poorer performance on trial 3 of the PASAT (Table 3).

The Impact of Gross Lesion Burden

To examine the potential impact of white matter plaques on fMRI activation, an analysis of gross lesion burden and fMRI activation was conducted. Non-parametric analysis of lesion burden data revealed no significant differences between the MS impaired and the MS not impaired groups in terms of the location and extent of lesion load. Pearson product moment correlations across all subjects revealed no relationship between the location and extent of lesions and patterns of fMRI activation on the mPASAT. However this finding should be interpreted cautiously due to the fact that the procedures used to quantify lesion burden were relatively gross, involving visual inspection of the T2 by a neuroradiologist.

Discussion

As noted, working memory deficits are not universal within the MS population. The results of the present study show altered patterns of cerebral activation in MS as compared with healthy control subjects, a finding consistent with the only other fMRI study in the literature of working memory in MS (Staffen et al., 2002). However, the present findings represent the first fMRI study to demonstrate that there are differences in the cerebral substrates of working memory that are specific to the presence and absence of cognitive impairment, and not simply associated with MS more generally. When MS subjects are divided into those experiencing an impairment in working memory functions and those without such difficulties, the MS group with working memory impairment showed patterns of cerebral activation that were significantly different from a healthy control sample. However, no significant differences were noted between the MS group without working memory impairment and the healthy control sample. Therefore, the distinction between the two MS groups is not only observable behaviorally, but also holds true at the level of the cerebral substrate. Because MS is a disease that results in heterogeneity of clinical presentations, it may be important to better characterize the nature and incidence of the behavioral deficits within each sample. Without this consideration, the magnitude of a subgroup's cognitive deficits or the efficacy of treatment effects may be masked.

In contrast to the control group, the MS impaired group showed significantly greater activation in the right parietal lobe than healthy controls. The critical role of the parietal lobes during working memory operations have been clearly demonstrated (Jonides et al., 1998; Smith & Jonides, 1998). In addition, damage to the left parietal lobe has long been associated with acalculia, or an inability to perform computational operations, such as those required by the PASAT (see Lezak, 1995 for a complete review). Therefore activation within the left parietal lobe is expected due to the calculation demands of the task, and this was in fact observed in the all subjects in the present study. However, the increase in the right parietal lobe activation when performing this manipulation is not the norm, and was only observed in the MS subjects with cognitive impairment, perhaps due to a need for additional resources in this clinical group to sufficiently perform this cognitive function. A similar phenomenon was observed when examining the cognitive regions of the right frontal lobe. That is, subjects with working memory impairment showed greater activation than healthy controls in the right frontal lobe during cognitive tasks. This is quite intriguing given that prior published research has demonstrated that the mPASAT is a task which predominantly requires left frontal lobe involvement in healthy individuals (Christodoulou et al., 2001). While left frontal lobe activation remains comparable between the two groups, the MS impaired group appears to require the additional utilization of resources within the contralateral hemisphere. The moderate trend (i.e., effect size) noted in the frontal lobe comparison, suggests that with an increased number of subjects, this trend would most likely achieve statistical significance. Q4

There are a number of possible explanations for the finding of increased right parietal and right frontal activation in the MS impaired group. The first may involve task load or task difficulty. Specifically, increased task difficulty may require additional cerebral resources to effectively complete the task. This relationship has been demonstrated in studies of healthy individuals in which an increase in verbal working memory load has resulted in increased right frontal activation (Manoach et al., 1997; Rypma & D'Esposito, 1999), as well as in a TBI population (Christodoulou et al., 2001). It is possible that the altered cerebral activation observed in the present study is a "normal" response to a difficult working memory task and this task was simply much more difficult for the MS impaired group than the other two groups. That is, despite equivalent behavioral performance, the task may still have been more "difficult" for the MS impaired subjects, requiring more resources to achieve this equivalent performance. Thus, titration of the task in order to control for task difficulty could result in similar activation patterns for each of these groups. Future research should focus on ways to address this hypothesis.

A second potential explanation for the pattern of cerebral activation observed in the MS impaired group may be the result of the need for the additional resources in the right hemisphere. In a clinical population, such as MS, compromised brain tissue could result in reduced efficiency in information processing, leading to the recruitment of additional resources in the right hemisphere. This effect is not unique to MS, having been seen in the TBI population (Christodoulou et al., 2001) and aging (Cabeza et al., 1997; Reuter-Lorenz et al., 2000) and therefore may be a more generalized result of cerebral damage, rather than a specific concomitant of MS.

A similar but more specific explanation could invoke the nature of the neuropathology in MS. MS is a degenerative disease of the central nervous system largely affecting the integrity of white matter. Such degradation of white matter may interfere with, or least slow down, the transfer of information. Some models of information processing identify the right hemisphere as holding a vital role in the initial processing of novel information (e.g., Goldberg & Costa, 1981). According to this model, when an individual encounters a new task, this initial experience with the task is more difficult due to its novelty, with the result that early processing occurs predominantly within the right hemisphere. However, according to this model, increased task efficiency with repeated practice results in a transfer in the processing of this information to the left hemisphere. That is, novel information is initially processed in the right hemisphere and meaning, and/or action, may be assigned to that information following transfer to the left hemisphere (Goldberg, Podell, & Lovell, 1994; Seger, Desmond, Glover, & Gabrieli, 2000). According to this model, one would expect that processing of the mPASAT task would begin in the right hemisphere due to novelty. But with additional trials, processing would transfer to the left hemisphere due to the fact that participants are becoming familiar with the task. Given the difficulty with white matter transmission in MS (Evangelou et al., 2000; Pelletier et al., 2001), this information transfer from the right to the left hemisphere may be disrupted by demyelization. However, for this model to explain the data in the present study, the novelty would somehow need to be maintained in MS participants with cognitive impairment and not in MS subjects without working memory problems. Future studies would be required to specifically demonstrate this functional dissociaition before this explanation could be supported. For instance, future investigations may utilize an event-related paradigm, possibly combined with electrophysiological methods, to evaluate the timing and potential disruption of this transfer of information, thus examining this hypothesis more specifically.

A final possible explanation for the results, and that which has been used to explain similar findings in fMRI studies of motor functioning in MS (Reddy et al., 2000a) and cognitive functioning in MS (Staffen et al., 2002), emphasizes the differential activation patterns between the MS subjects and healthy controls. Specifically, the right parietal and frontal regions are noted to be activated during the mPASAT in the healthy control group and the MS not impaired group, but to a much lesser extent than in the MS impaired group. In addition, as stated previously, right hemisphere regions are noted to be activated in healthy subjects on tasks of increasing complexity (Manoach et al., 1997; Rypma & D'Esposito, 1999). The possibility has therefore been proposed that an altered pattern of cerebral activation in the motor representation in MS subjects represents an "unmasking" of existing motor pathways (Reddy et al., 2000a). The same may be true of working memory pathways. As stated by Staffen and colleagues (2001), the altered cerebral representation of working memory functions in MS may be compensatory in nature. That is, this altered pattern of cerebral activation on the mPASAT may be the result of an "unmasking" of working memory pathways in response to disease related, or cognition related factors.

It is interesting to note that while the MS Impaired and Not Impaired groups were defined on the basis of differences in performance on the PASAT, administered during a neuropsychological evaluation, the two groups did not perform significantly different on the mPASAT, the task that was administered during the fMRI procedure. In evaluating potential reasons for this finding, differences between these two tasks must be taken into account. The mPASAT was created as a modification of the standard PASAT in which no verbal output is required. That is, subjects are required to press a button if the last two numbers they hear add to 10. This is much less difficult than the standard PASAT, in which the subject must add each number to the number presented immediately before it and call out the total, over 4 progressively faster trials. Given that MS subjects who have a working memory impairment do not appear to be impaired behaviorally on simpler working memory tasks, such as WAIS-III Letter-Number Sequencing (Wechsler, 1997) or Digit Span backwards (Wechsler, 1997), it is not surprising that such individuals would not be Q5 impaired on a simpler version of the PASAT. However, it is interesting to note that despite intact behavioral performance on the mPASAT, subjects in the MS impaired group did show alterations in patterns of cerebral activation associated with this working memory task. Future research should therefore examine this altered pattern of cerebral activation in both simple working memory tasks administered in the scanner and more complex working memory tasks administered in the scanner.

In addition to noting differences in activation patterns for the different groups, results also indicated significant relationships between patterns of cerebral activation and performance on neuropsychological tests. Poorer performance on a verbal working memory task (PASAT) was associated with increased activation in the right parietal lobe. In contrast, better performance on Digit Span backward, another working memory task, was associated with increased activation in the left ventromedial frontal lobe. These findings potentially indicate that greater cerebral activation in regions known to be responsible for a cognitive function may be associated with increased performance of that function. Alternatively, increased cerebral activation of regions not typically responsible for mediating a function may be associated with poorer performance. However, it remains undetermined if these changes are secondary to brain reorganization, functional adaptation to injury, or are simply a “normal” response to greater task load.

A substantial amount of additional research is necessary to fully understand the implications of the results of the present study. Such research may seek to clarify the many issues raised in the present study. For instance, it will be necessary to more clearly examine the issue of lateralization of activation in MS, particularly in those individuals with impairment in working memory. The present results may be a unique function of the paradigm employed (i.e., it may have required a disproportionate amount of left hemisphere processing), thus additional paradigms that use tasks known to specifically activate the right hemisphere would be useful. It will also be of interest to examine working memory across the range of clinical presentations of MS, with varying subtypes and ranges of severity, in a much larger study. However, the increased right hemisphere activation observed in the MS impaired group in the present study has been observed in other populations such as the elderly (Cabeza et al., 1997; Reuter-Lorenz et al., 2000), individuals with HIV (Chang et al., 2001), alcoholism (Pfefferbaum et al., 2001), and TBI (Christodoulou et al., 2001; McAllister et al., 1999). These similarities across populations suggest that this recruitment may be a more general phenomenon, not specific to MS. Future research should also vary the task parameters in order to tease apart the potential interaction between task difficulty, cognitive load, and lateralization of cerebral activations.

While providing valuable information regarding the cerebral activation associated with working memory performance in MS, the current study does suffer from some methodological limitations that restrict the conclusions that can be drawn. First, the sample size in the current study was small, thus limiting the power of our statistical tests. It is therefore important that the findings be replicated with larger samples. Related to sample size is the fact that the groups studied were not ideal in terms of their demographic composition. Although not significant, there was a difference between the groups in terms of their gender, age, and duration of diagnosis, factors which could have potentially affected the results. In addition, to further delineate changes in activation patterns due to the central executive from changes due to the phonological loop, future studies should include a task that specifically taxes the phonological loop as well as a central executive task such as the mPASAT. This type of methodology would then begin to address the source of the observed working memory deficit. Finally, the present study was limited in the methodology employed to analyze the extent and location of lesions and its relation with fMRI activation patterns. Future studies should utilize more state-of-the-art methodology, such as Magnetic Resonance Spectroscopy (e.g., Foong et al., 1999; Pan, Krupp, Elkins & Coyle, 2001) or Magnetic Transfer Imaging (e.g., Dousset et al., 1992; Filippi, 1999; Rovaris, Horsfield, Filippi, 1999; van Waesberghe & Barkhof, 1999) to specifically examine how lesions in the brain may affect cerebral activation patterns on fMRI in participants with MS.

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