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An Investigation of Working Memory Rehearsal in Multiple Sclerosis Using fMRI

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ABSTRACT

The present study examined patterns of cerebral activation during a working memory (WM) rehearsal task in individuals diagnosed with multiple sclerosis (MS) and in healthy adults. BOLD functional magnetic resonance imaging (fMRI) was performed using a 1.5 T GE scanner to assess activation during a WM task adapted from the Sternberg paradigm (Sternberg, 1969). Participants included 8 individuals diagnosed with MS, and 5 healthy controls (HCs) matched for age and education. Task difficulty was manipulated by increasing the length of time that strings of letters were to be rehearsed. Findings revealed increased right prefrontal cortex activation and increased right temporal lobe activation in individuals diagnosed with MS compared to HCs. The potential explanations for increased right hemisphere activation in persons with MS are discussed.

AN fMRI INVESTIGATION OF WM REHEARSAL IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is the most common non-traumatic neurological disease affecting younger adults (Rao, 1990). Over the last 20 years it has become well established that cognitive deficits are common in MS, occurring in 50–65% of the population (Peyser, Rao, LaRocca, & Kaplan, 1990). Deficits have been observed in the areas of attention and concentration, executive control, working memory (WM), and episodic memory. In fact, WM deficits in MS have been observed across disease course (e.g., relapsing-remiting vs. progressive; Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994; Grigsby, Busenbark, Kravcisin, Kennedy, & Taylor, 1994) and may account for a substantial portion of the general cognitive dysfunction observed in MS (DeLuca, Barbieri-Berger, & Johnson, 1994; Demaree, DeLuca, Gaudino, & Diamond, 1999; Diamond, DeLuca, Kim, & Kelley, 1997; Litvan et al., 1988).

The construct of "WM" essentially encompasses a cognitive system that simultaneously but temporarily stores, processes, and manipulates information (Baddeley, 1986, 1992). In Baddeley's model, the construct of WM comprises at least three major components: a central executive and two "slave systems" (Baddeley, 1986). The central executive is conceptualized as an attentional supervisory system that controls, coordinates and manipulates information processing. The central executive is subserved by two "slave systems," referred to as the *phonological loop* and the *visuospatial sketchpad*. These slave systems provide for the temporary storage and

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maintenance of auditory and visual information, respectively.

In MS, some behavioral studies have suggested dysfunction in the phonological loop, specifically with rehearsal of information (Diamond et al., 1997; Rao et al., 1993; Ruchkin et al., 1994), and other examiners have focused on compromise within the central executive (D'Esposito et al., 1996). Additional behavioral and functional neuroimaging research is needed to delineate the specific mechanism(s) causing WM compromise in MS.

Structural neuroimaging techniques have received extensive application in studies of MS and measures quantifying lesion load have shown positive correlation with degree of cognitive deficit (Arnett et al., 1994; Comi et al., 1995; Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989). Moreover, advanced MR techniques such as magnetic transfer imaging and magnetic resonance spectroscopy have been used to measure the relationship between white matter damage and general cognitive performance (Filippi, 2001; Foong et al., 1999; Pan, Krupp, Elkins, & Coyle, 2001; Rovaris et al., 1998). Alternatively, brain function in MS has been examined with positron emission tomography, where investigators have examined differences in cerebral metabolism between HCs and individuals with MS during tasks of cognition (Blinkenberg et al., 1996, 2000; Paulesu et al., 1996). To date, application of fMRI in MS has focused on examination of primary motor, sensory, and visual systems (Filippi, Rocca, Colombo, et al., 2002; Filippi, Rocca, Falini, et al., 2002; Gareau et al., 1999; Reddy, Narayanan, Arnoutelis, et al., 2000b; Reddy, Narayanan, Matthews, et al., 2000; Rocca et al., 2002) and the application of fMRI to examine *cognitive* performance in MS has only just begun (Staffen et al., 2002).

Over the past decade, much has been learned about the functional cerebral organization of WM in healthy individuals through the use of functional neuroimaging techniques such as positron emission tomography and functional MRI (for review see Cabeza & Nyberg, 2000). Among the most consistent findings across a variety of WM studies involving either verbal or visuospatial stimuli are activation of the prefrontal and premotor regions of the frontal lobes and particularly the middle or inferior frontal gyrus (Braver et al., 1997; Cohen et al., 1994; Cohen, Perlstein, & Braver, 1997; Rypma & D'Esposito, 1999; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). Parietal and temporal lobe activations have also been reported, albeit less frequently (Braver et al., 1997; Salmon et al., 1996; Seidman et al., 1998).

Because recent literature suggests that individuals with MS exhibit deficits in their ability to hold information within the WM buffer (Diamond et al., 1997; Rao, 1990), the current study was designed to specifically examine rehearsal (or maintenance) within WM. Three separate fMRI studies of individuals with traumatic brain injury (TBI) examined WM, and, specifically, central executive functioning, revealing increased right hemisphere activation (Christodoulou et al., 2001; McAllister et al., 1999, 2001). More specifically, Christodoulou et al. (2001) noted increased right prefrontal cortex activation. Staffen et al. (2002) also noted increased right prefrontal cortex activation on a task of mental arithmetic in a group of individuals with clinically definite MS. These convergent data suggest a role of the right prefrontal cortex to compensate for deficits on tests of WM functioning that require an important central executive role. What has not been determined is if right prefrontal cortex recruitment would be evident during a task not engaging the central executive, but demanding only WM rehearsal (or the phonological loop). In the current study, we hypothesized that a task of WM rehearsal would result in increased right prefrontal cortex activation in individuals with MS compared to healthy adults. We also hypothesized that neuropsychological functioning on tests measuring WM would be significantly correlated with the degree of right prefrontal cortex recruitment.

METHOD

Participants

The participants were 8 individuals with clinically definite MS based upon criteria proposed by Poser et al. (1983) and 5 healthy adults. All participants were

between the ages of 18 and 55 with a mean age of 47.8 ($SD = 4.8$) for individuals with MS and 40.6 ($SD = 11.1$) for healthy adults. The mean number of years of education (14.8, $SD = 1.2$ and 15.4, $SD = 2.1$, respectively) and the ratio of women to men (5/8 or 62% female and 3/5 or 60% female, respectively) were also comparable between groups. All participants were right-hand dominant. 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). Participants diagnosed with MS were recruited through advertisements in local chapters of the National Multiple Sclerosis Society, primarily within northern New Jersey. 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 prior head injury resulting in hospitalization. All subjects were at least one-month postexacerbation and/or steroid treatment. Pregnant women were also excluded from the study. Given the nature of the instructions, task demands, and English-speaking standardization of psychometric tests used in the study (i.e., WAIS-III Digit Span, Vocabulary), participants were required to have English as a primary language. Consecutive respondents to advertising who fulfilled the study criteria were entered into the study and paid $50 for their involvement. For this sample of individuals with MS, 75% (6/8) had a relapsing-remitting course to their disease and 25% (2/8) displayed a progressive disease. All participants were properly screened for any prior surgical history indicating the presence of metal objects or electronic devices within the body using the existing screening protocol established in the Department of Radiology at UMDNJ-NJMS.

Cognitive Testing Procedures

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. This evaluation lasted approximately 1–2 h and consisted of a battery of standardized tests commonly used to examine cognitive difficulties associated with MS (DeLuca et al., 1994). These tests assessed the areas of attention and concentration (WAIS–R Digit Span; Wechsler, 1981), working memory and processing speed and efficiency (WAIS-III Letter-Number Sequencing, Wechsler, 1997; Paced Auditory Serial Addition Test, PASAT, Gronwall, 1977; *N*-Back, McAllister et al., 1999), overall intellectual ability (WAIS–R Vocabulary; Wechsler, 1981); verbal fluency (Animal Naming), problem solving (WCST) and sequencing (Trails B) were administered. Finally, due to the high incidence of depressive symptoms associated with MS (Feinstein, 2000), the Beck Depression Inventory (BDI) was administered to measure mood and physical symptomatology. Within 1 week following the neuropsychological evaluation, participants underwent the fMRI procedures. The results of these cognitive and emotional assessment measures were then correlated with the functional and structural imaging results in order to determine the relationship between brain activation patterns and neuropsychological status.

Cognitive Task Used During fMRI Acquisition

The present study employed a modification of the Sternberg paradigm (MSP). The Sternberg paradigm is a well-established WM paradigm that combines differential encoding and rehearsal demands. In the context of WM theory, the MSP places demands on the phonological loop, one of the slave systems in Baddeley's model (Baddeley, 1986). In this paradigm the study participant is required to listen to a short string of letters and, following a delay, when presented with a single letter as the "target," determine if the target was included within the stimulus string. Two separate experimental manipulations occur. First, the stimulus string varies in length between two and five letters (i.e., low or high load). Second, the delay between the stimulus string and the target is set at 4 or 12 s (i.e., short or long delay). When the target stimulus is heard, the participant is required to respond via button press if the letter presented as the target stimulus was included in the previously presented stimulus string. If the target was not included in the initial stimulus string, the participant should not respond. Figure 1 illustrates the timing and nature of this auditory paradigm. The MSP requires: (1) auditory perception of the numbers; (2) attention; (3) rehearsal/maintenance within WM; (4) motor response. Importantly, the short and long delays contained an identical number of target responses and alternations between short and long stimulus strings.

Given the primary interest in this study on maintenance/rehearsal deficits in MS, data analysis focused on the effect of delay on brain activation, with the main effect of "delay" being the difference in brain activation between the long and short delay periods. Thus, the results of subtracting the activation associated with the short delay period from the activation associated with the long delay represent the demands of holding information within the WM buffer for this additional time period. Participants received task instructions and engaged in three practice trials before entering the MRI environment. This paradigm was administered in a counterbalanced sequence that consisted of 32 sets of alternating 24-s blocks. Prior

Stimulus string	Delay	Target	Response
AH	4 sec. or 12 sec.	H	Yes
YUBNP	4 sec. or 12 sec.	T	No
5 sec.		1 sec.	

Fig. 1. The timing and nature of the modified Sternberg paradigm employed in this study. Participants were exposed to a stimulus string of either 2 or 5 letters in length. All stimuli were perceived aurally, followed by a delay period of 4 or 12 s. Following the delay, participants were provided a single target letter and they were required to respond via button press if the target was included in the stimulus string.

to the administration of the 13-min paradigm, participants were allowed to acclimate to the fMRI environment during a 32-s baseline period where they were not required to perform any cognitive operations.

Functional Imaging Procedure

All neuroimaging was performed on a General Electric Signa Horizon Echo-speed (1.5 T) MR scanner. Prior to functional imaging, sagital T1-weighted localizer images were obtained, followed by whole brain axial T1-weighted conventional spin-echo images for anatomic overlays (TR [repetition time] = 450, TE [echo time] = 14, contiguous 5 mm, 256 × 256 matrix, FOV [field of view] = 24, NEX = 1), with 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 = 60 ms; TR = 4000 ms; FOV = 24 cm; flip angle = 90; slice thickness = 5 mm contiguous). This yielded a 64 × 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.

During scanning, participants performed the cognitive tasks while positioned supine in the scanner and to minimize motion degradation, foam cushioning and tape were utilized to immobilize the head. Auditory stimuli were presented to participants 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.

Image Analysis

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 volumes were eliminated from analyses to control for saturation effects and in order to remove subvoxel motion-related signal change and all EPI data (192 images) were aligned to the first image during spatial realignment. 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 and normalized scans were then spatially smoothed to 8 × 8 × 10 mm. SPM maps were thresholded to an alpha level of 0.001 with a cluster level of 5. Based on prior application of fMRI to clinical samples (Billingsley, McAndrews, Crawley, & Mikulis, 2001), individual voxels were extracted and summed to give a total voxel count as the dependent variable.

Through the use of code adapted for this study, every data point for each cluster listed in the SPM99 was calculated. That is, with this method of inquiry, we were able to access every x, y, and z coordinate comprising the clusters for each area of activation and not just the three most statistically significant coordinates listed by the SPM99 program. This method of analysis was critical in order to calculate the location and extent of each cluster of active voxels.

In order to determine the location of each x, y, and z coordinate, submission of an exhaustive list of coordinates to the Talairach Daemon (TD) was necessary. The TD is a high-speed database server for querying and retrieving data about human brain structure over the Internet (Lancaster et al., 2000). Prior to submission to the TD, all coordinates were transformed from the Montreal Neurologic Institute (MNI) coordinate system (which is the default coordinate system in SPM99) to the Talaraich coordinate system (Brett et al., 2002). For these adjustments, when the z value was positive the following adjustments were made: $x = (0.99x)$, $y = [(0.9688y) + (0.46z)]$ and $z = [(-0.0485y) + (0.939z)]$. In addition,

when the z value was negative the following adjustments were made: $x = (0.99x)$, $y = [(0.9688y) + (0.42z)]$, and $z = [(-0.0485y) + (0.839z)]$. By submitting every data point to the TD, we have reduced the probability of including spurious activations that cannot be linked to a specific brain site, therefore, diminishing the effects of analyzing activations that may be related to large vessel effects detected by the gradient echo sequence.

Defining Brain Regions

The brain regions of primary interest included the four lobes and the cingulate gyrus. Whole brain analyses were conducted first for the left and right hemispheres, and then the four lobes bilaterally. In addition, activation listed by the TD as cortical white matter was included in the analyses. For example, "left frontal lobe" activation included any activations listed as "left frontal" and "left frontal white matter" by the TD. The same was true for the remainder of the cortical lobes and cingulate gyrus for both right and left hemispheres. Areas of activation listed by the TD nonspecifically as gray matter or white matter of no particular location (e.g., unspecified areas of corpus callosum, sub-gyral white matter) were not included in the analyses. Thus, a very small number of supra-threshold voxels, that could not be assigned a specific brain location, were eliminated from analyses investigating the differential activation patterns in the left and right hemisphere and left and right frontal lobe.

For analysis of voxel counts, the frontal lobes were divided by hemisphere (i.e., right vs. left) and by location (e.g., ventral, dorsal). Analysis of frontal activation included five regions: anterior cingulate, right dorsolateral frontal, right ventrolateral frontal, left dorsolateral frontal, and left ventrolateral. Due to the overlap of Brodmann's areas across the ventrolateral and dorsolateral cortices (as well as the variability in Brodmann's areas across individuals), the ventrolateral frontal cortex (VLFC) was defined as any area listed by the TD as "inferior frontal" activation. These predefined areas included Brodmann's areas (or portions of Brodmann's areas) 9, 13, 32, 44, 45, 46, and 47. Similarly, the dorsolateral frontal cortex (DLFC) was defined as any area listed by the TD as "middle frontal," "medial frontal" or "superior frontal" activation. This included Brodmann's areas (or portions of Brodmann's areas) 6, 8, 9, 10, 11, 32, and 46.

Structural Imaging

In order to determine if white matter plaques associated with MS would influence fMRI activation patterns, a gross measure of lesion load was determined through the use of structural imaging. Thus, for a measure of gross lesion load in this MS sample, T2 weighted and FLAIR images were acquired at the time of the functional scanning and examined by a board certified neuroradiologist (AJK) who was not informed a priori regarding group membership. Based upon both the T2 and FLAIR images, lesions were grouped according to size across three categories: (1) less than 5 mm was a score of 2.5; (2) 6–10 mm was a score of 7.5; (3) greater than 10 mm was a score of 12.5. This procedure was adapted from previously used methodology examining gross lesion load in a group of individuals with chronic fatigue syndrome (Lange et al., 2001). Lesions were categorized for peripheral/subcortical (e.g., corona radiata) and for periventricular white matter areas. In addition, white matter changes were noted if present in the basal ganglia and the midbrain structures and in the fourth ventrical, the pons, and the cerebellum. Thus, based upon hyperintensities in the structural images, the neuroradiologist measured the size of each lesion for both healthy adults and individuals diagnosed with MS and a score was determined for each brain area (e.g., right frontal lobe, left frontal lobe, right temporal lobe, etc.). The great majority of lesions were demonstrated on both T2 weighted and FLAIR images. However, on the few occasions that one scan demonstrated a lesion consistent with MS and the second scan was less conclusive (but did not contradict a potential lesion), the lesion was included in the analysis as an MS lesion.

Data Analysis of Brain Activation

Because of the small sample size, between-group differences were determined through the use of nonparametric statistical analysis. This eliminated the likelihood that one individual with an inordinately large voxel count could artificially drive the statistical analysis (i.e., comparison of means). Therefore, differences in brain activation between healthy adults and individuals with MS were determined by calculating the total number of active voxels in predefined regions and applying nonparametric statistics (e.g., Mann–Whitney test) to determine between-group differences. Initially, the total activation for right and left hemisphere were compared between groups, followed by between-group comparisons for each of the cortical lobes. Thus, between-group comparisons were conducted for the left and right frontal, left and right temporal, left and right parietal, and left and right occipital lobes.

Pearson correlations were employed to determine the relationship between brain activation, neuropsychological functioning, and gross lesion load. To examine the relationship between cognitive functioning and brain activation irrespective of brain disease, all 13 participants were included in the correlation between neuropsychological scores and areas of brain activation. Similarly, correlational analyses conducted between areas of brain activation and gross lesion load included all 13 participants.

RESULTS

MS and Healthy Adults and Brain Activation

Figure 2 provides the activation maps for all 13 study participants. Comparison of the two groups for the total number of active voxels in the left and right hemisphere revealed significantly greater right hemisphere activation in individuals diagnosed with MS compared to healthy adults, $z(1) = -2.05$, $p = .040$. In contrast, no significant difference between groups

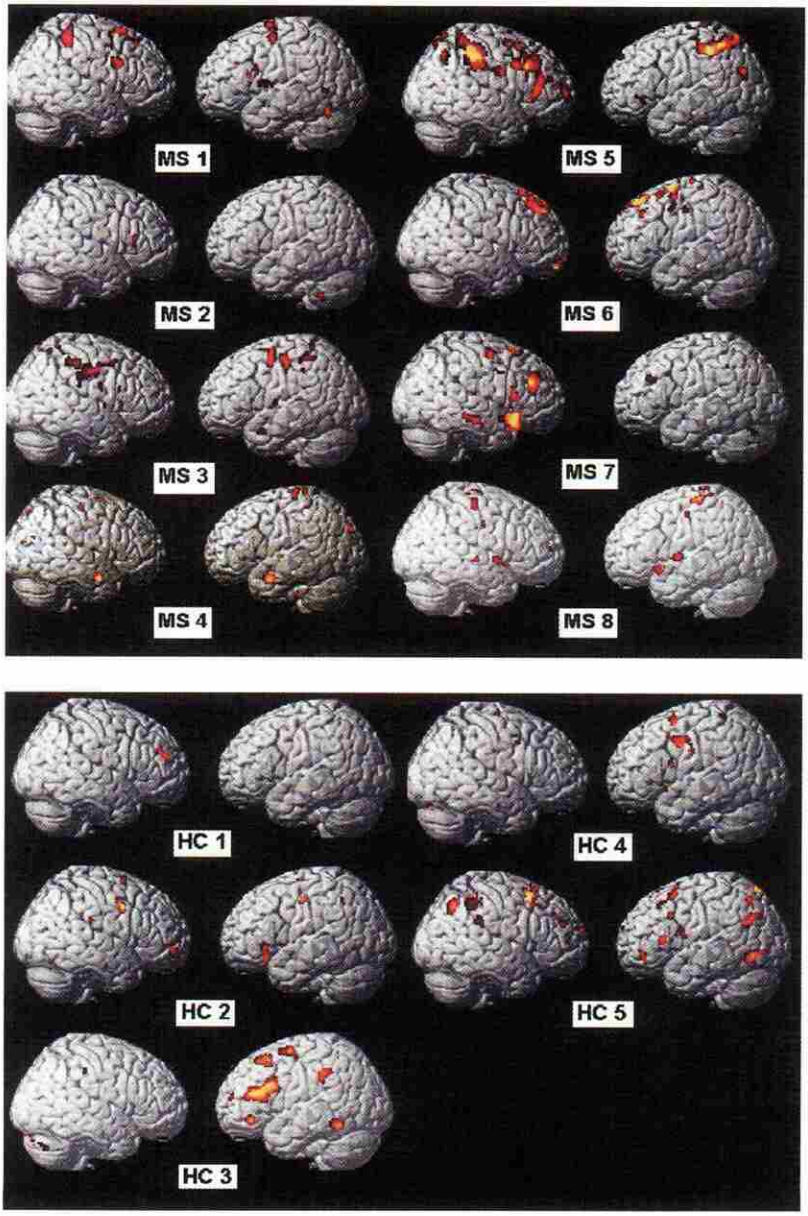

Fig. 2. Activation maps displaying areas of activation for lateral/surface areas of the left and right hemispheres for the 13 study participants.

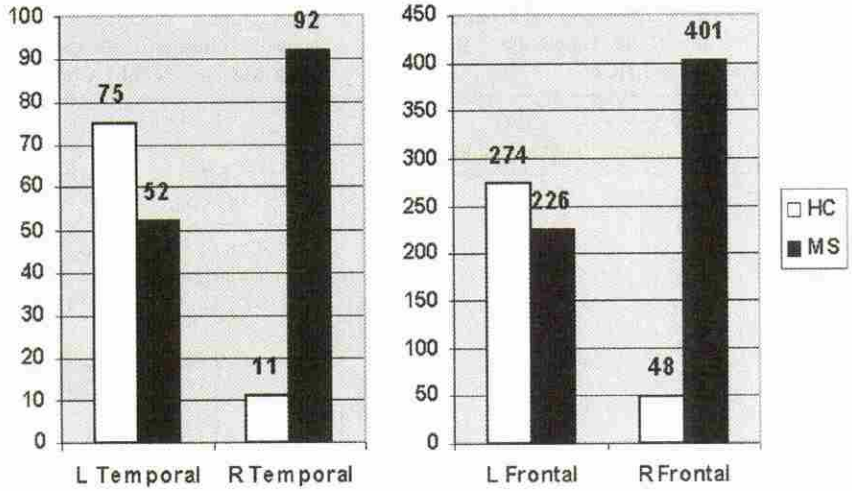

Fig. 3. The average number of active voxels in the left and right frontal and temporal lobes across both groups. For left and right frontal activation only those areas defined as DLFC and VLFC were included and for the temporal lobe all areas of activation were included.

was observed for total left hemisphere activation, $z(1) = -0.293$, $p = .770$. Based upon the between-group differences observed in the right hemisphere, nonparametric statistics were used to determine the areas of activation within the right hemisphere accounting for these differences. Analyses revealed significantly greater right prefrontal cortex activation (defined as the right DLFC and VLFC; $z(1) = -2.05$, $p = .040$) and significantly greater right temporal lobe activation, $z(1) = -2.20$, $p = .027$, in individuals diagnosed with MS when compared to healthy adults. Figure 3 shows the mean voxel count in prefrontal areas and temporal lobes for HCs and individuals diagnosed with MS and Table 1 provides voxel counts for the inferior, middle and superior frontal gyri in all 13 participants. Between-group comparisons for the right parietal, $z(1) = -1.00$, $p = .317$, and right occipital lobe, $z(1) = -0.462$, $p = .644$, revealed no significant between-group differences. As expected, there were no significant between-group differences for the left prefrontal cortex, $z(1) = -0.073$, $p = 0.942$, the left temporal lobe, $z(1) = -0.520$, $p = .603$, the left parietal lobe, $z(1) = -0.147$, $p = 0.883$, and the left occipital lobe, $z(1) = 0.00$, $p = 1.00$.

Neuropsychological Status and Brain Activation

Between-Group Comparison

Table 2 summarizes the performances on measures of neuropsychological functioning for both groups. Nonparametric comparison revealed significant between-group differences on the behavioral task within the scanner, the MSP. Individuals diagnosed with MS scored significantly worse than healthy participants, $z(1) = -2.10$, $p = .035$. Between-group differences in the same direction were also noted for the PASAT, $z(1) = -2.78$, $p = .005$.

Correlational Analysis

Because of the between-group differences in activation for frontal and temporal lobes, correlational analyses between brain activation and neuropsychological results were focused in these areas. The results of correlational analysis between frontal and temporal lobe activation and neuropsychological testing is provided in Table 3. When considering all study participants ($n = 13$), performance on the MSP was significantly correlated with right temporal lobe activation ($r = -.655$, $p = .02$) and its correlation with right prefrontal cortex activation approached

Table 1. Voxel Counts for DLFC (SFG and MFG) and VLFC (IFG) for the Right Hemisphere in Individuals With MS and HCs.

	IFG (voxel count)	MFG (voxel count)	SFG (voxel count)
Left hemisphere			
HC1	(0)	(0)	(0)
HC2	(109)	(131)	(0)
HC3	(338)	(444)	(136)
HC4	(25)	(69)	(20)
HC5	(12)	(82)	(3)
MS1	(0)	(116)	(94)
MS2	(0)	(0)	(0)
MS3	(0)	(412)	(83)
MS4	(0)	(1)	(0)
MS5	78	(74)	(41)
MS6	(0)	(243)	(379)
MS7	(5)	(38)	(7)
MS8	(21)	(56)	(0)
Right hemisphere			
HC1	(0)	(39)	(5)
HC2	(0)	(59)	(30)
HC3	(0)	(32)	(0)
HC4	(0)	(20)	(12)
HC5	(2)	(35)	(5)
MS1	(0)	(84)	(113)
MS2	23	(0)	(0)
MS3	15	(135)	(19)
MS4	(0)	(18)	(0)
MS5	258	(794)	(151)
MS6	(0)	(86)	(344)
MS7	389	(333)	(180)
MS8	(0)	(87)	(3)

Table 2. Demographic Variables and Performance on Neuropsychological Measures for Individuals With MS and Healthy Controls (HCs).

	Mean (*SE*)		
	MS ($n = 8$)	HCs ($n = 5$)	
Age	47.8 (1.7)	40.6 (4.9)	*ns*
Education	14.8 (0.44)	15.4 (0.97)	*ns*
PASAT (total)	94.2 (8.7)	142.2 (5.2)	$p < .05$*
LNS	11 (0.46)	12.2 (0.73)	$p < .10$**
WCST (errors)	26.2 (5.2)	24.2 (8.1)	*ns*
Trails B	29.7 (3.2)	33.6 (6.5)	*ns*
1-Back and 2-Back	12.2 (0.70)	13.0 (0.316)	*ns*
Digits Forward	8.0 (0.56)	8.8 (1.0)	*ns*
Digits Backward	6.3 (0.62)	8.2 (1.3)	$p < .10$**
MSP	27.8 (0.59)	30.0 (0.632)	$p < .05$*
Vocabulary	52.5 (3.3)	51.8 (4.7)	*ns*
Animal Naming	18.8 (1.6)	23.2 (1.0)	$p < .10$**
CFL	35.3 (4.1)	35.8 (2.7)	*ns*
BDI	9.37 (2.5)	2.4 (1.1)	$p < .10$**

*Significant at $p < .05$.
**Approached significance at $p < .10$.

significance ($r = -.563$, $p = .057$). Tests of WM outside the scanner were negatively correlated with both right prefrontal and temporal lobe activation, but not left frontal and temporal lobes (see Table 3). Finally, the correlation between right frontal activation and BDI scores approached significance ($r = .550$, $p = .052$). In contrast, correlational analyses revealed no significant relationship between left frontal lobe or left temporal lobe activation and any test of cognitive performance or the BDI.

Lesion Burden and Brain Activation

In order to determine if the location of white matter lesions and/or the total gross lesion burden were related to brain activation as measured by fMRI, correlational analysis were conducted. As can be seen in Table 3, correlational analyses revealed no significant relationship between right hemisphere gross lesion burden or left hemisphere gross lesion burden and right or left frontal or temporal lobe activation. Examination of the total lesion burden for the left and for the right hemispheres in individuals with MS revealed that two individuals exhibited equal burden across hemispheres, three individuals had slightly greater left hemisphere lesion burden, and three individuals had slightly greater right hemisphere lesion burden. When considering the entire sample, lesion burden scores ranged from 0 to 50 for total gross lesion burden, from 0 to 31 for left hemisphere and from 0 to 29 for right hemisphere. Considering everyone in the sample, the average total left hemisphere gross lesion load was 12.3 ($SE = 3.1$, $n = 13$) and the total

Table 3. Results of Correlational Analyses Between Frontal and Temporal Activation and Performance on Measures of Cognition and Measures of Gross Lesion Load.

	Right frontal activation[a]	Left frontal activation[a]	Right temporal activation	Left temporal activation
MSP	$r = -.563$ $p = .057$ $n = 12$	$r = .399$ $p = .199$ $n = 12$	$r = -.655$ $p = .021$ $n = 12$	$r = .318$ $p = .314$ $n = 12$
PASAT	$r = -.496$ $p = .085$ $n = 13$	$r = .144$ $p = .639$ $n = 13$	$r = -.281$ $p = .353$ $n = 13$	$r = .231$ $p = .447$ $n = 13$
Digits Backward	$r = -.205$ $p = .502$ $n = 13$	$r = .107$ $p = .727$ $n = 13$	$r = -.382$ $p = .197$ $n = 13$	$r = .282$ $p = .350$ $n = 13$
Letter Number Sequencing	$r = -.242$ $p = .425$ $n = 13$	$r = -.110$ $p = .722$ $n = 13$	$r = -.376$ $p = .206$ $n = 13$	$r = .381$ $p = .199$ $n = 13$
N-Back (total)	$r = -.169$ $p = .582$ $n = 13$	$r = .103$ $p = .739$ $n = 13$	$r = -.041$ $p = .895$ $n = 13$	$r = .256$ $p = .398$ $n = 13$
BDI	$r = .550$ $p = .052$ $n = 13$	$r = .105$ $p = .733$ $n = 13$	$r = .218$ $p = .475$ $n = 13$	$r = .067$ $p = .828$ $n = 13$
Lesion burden left	$r = -.012$ $p = .968$ $n = 13$	$r = -.290$ $p = .336$ $n = 13$	$r = .453$ $p = .120$ $n = 13$	$r = -.084$ $p = .784$ $n = 13$
Lesion burden right	$r = -.05$ $p = .870$ $n = 13$	$r = -.188$ $p = .539$ $n = 13$	$r = .373$ $p = .209$ $n = 13$	$r = -.083$ $p = .787$ $n = 13$

Note. [a]Does not include primary motor cortices.

right hemisphere gross lesion burden was 12.9 ($SE = 3.3$, $n = 13$).

DISCUSSION

To our knowledge, the present study is the first fMRI investigation of WM *rehearsal* in MS. The results showed that while performing the WM rehearsal task, individuals with MS exhibited greater right hemisphere activation compared to healthy adults. Further, this increased activation was disproportionately represented in the right frontal and right temporal lobes. While HCs exhibited primarily left VLFC and DLFC and temporal lobe activation (consistent with a prior examination specifically examining WM rehearsal in healthy adults, Ranganath & D'Esposito, 2001), individuals with MS exhibited bilateral prefrontal and temporal lobe activation (see Table 1). The greatest right frontal lobe activation in MS occurred within the dorsolateral prefrontal cortex (defined as the middle and superior frontal gyri).

Tests of WM functioning administered both inside and outside the scanner were negatively correlated with extent of right prefrontal cortex activation. Similarly, performance on the MSP within the scanner maintained a significant negative correlation with the degree of right temporal lobe activation (see Table 3). In contrast, no test of

WM, within or outside the scanner, maintained significant correlation with left hemisphere activation. The current data indicate that there is a relationship between increased right prefrontal cortex and right temporal lobe activation and poor performance on tasks of WM. While not all participants with MS showed increased right hemisphere activation relative to HCs, in cases where minimal right hemisphere recruitment was observed, the behavioral performance was comparable to that of HCs (e.g., MS1 and MS3). Thus, the current data indicate that there is an important interaction between performance on the MSP and the degree of right hemisphere recruitment in persons with MS.

Potential Explanations for Study Findings

The current findings are consistent with what has been observed thus far in studies using fMRI to examine MS. For example, relative to controls, significantly increased ipsilateral activation has been observed on tasks of motor functioning in participants with MS (Filippi, Rocca, Colombo et al., 2002; Reddy, Narayanan, Arnoutelis, et al., 2000) and, more recently, increased contralateral activation (right hemisphere) has been observed on tasks of attention and WM among MS subjects (Staffen et al., 2002). These alterations in brain activation observed in MS have been interpreted as compensatory in nature by these authors. There are several potential explanations for the altered functional cerebral activation observed in this study and they are discussed below.

Task Novelty and a Functional Disconnection

Earlier models of information processing (e.g., Goldberg & Costa, 1981; Goldberg, Podell, & Lovell, 1994) have emphasized the primacy of the right hemisphere in the initial processing of novel information and, in particular, the integration of intermodal information. According to these investigators, the right hemisphere is responsible for early processing of novel stimuli and the left hemisphere is responsible for the manipulation of information that has already been associated into routines or actions. Thus, as the individual becomes more efficient with the task, there is a right to left shift in primary processing. In a clinical population, such as MS, reduced efficiency with cognitive tasks due to compromised brain status, and, potentially, slower integration of information may result in right hemisphere predominance. To test this hypothesis, future investigation would benefit from an event-related paradigm or the use of network analysis (for review, see McIntosh & Gonzalez-Lima, 1994) to assess the timing and potential disruption of this right-to-left transfer of information.

Brain Reorganization

A second potential explanation for the current data is that the observed right hemisphere recruitment is representative of changes in the cerebral substrate resulting from demeylination and/or axonal disruption. From this perspective, observed differences in the hemodynamic response in individuals with MS may be due to alterations at the synapse, to the restructuring of existing neural networks, or even to recruitment of adjacent and auxiliary brain regions to help compromised brain regions (Buonomano & Merzenich, 1998; Thickbroom, Byrnes, Archer, Nagarajan, & Mastaglia, 2001; Waxman, 1988). According to these explanations, the brain is actively adapting to neurologic illness resulting in systemic changes in brain functioning and the recruitment and/or reorganization of areas of the right hemisphere. Thus, the increased right prefrontal and temporal activation observed in the current study may be due to some combination of these factors resulting in functional adaptation. While the current study was not designed to address this issue specifically, determinations could be made in the future through the use of serial scanning with a homogenous sample in regards to age at the time of disease onset and time since diagnosis. This would allow investigators to track changes in brain activation over the disease duration.

Task Demand and Right Hemisphere Recruitment

The influence of task demand on brain activation may also help to explain the current findings. Some studies of *healthy* individuals have elicited right prefrontal cortex activation by increasing the amount of information to be maintained (Manoach et al., 1997; Rypma & D'Esposito,

1999). In the current study individuals diagnosed with MS performed significantly worse than healthy adults on the MSP during scanning, which indicates that this task may have been more demanding for them. Also, in the current study, there was a significant negative correlation between MSP performance and increased right hemisphere activation. Thus, the right hemisphere recruitment in the current study may be similar to what has been observed in healthy adults by Rypma and D'Esposito (1999) when the task demand is increased.

Related to the issue of increased demand and right hemisphere recruitment are the prior findings in other populations supporting a relationship between diminished cerebral resources and increased right DLPFC activation. As noted, this pattern of increased activation in the right hemisphere has been observed in persons with mild, moderate and severe TBI on a task of WM (Christodoulou et al., 2001; McAllister et al., 1999, 2001). In fact, the data presented by Christodoulou et al. (2001) specifically showed increased activation in the right dorsolateral prefrontal cortex during a modified PASAT task. Additionally, increased right hemisphere activation in parts of the prefrontal cortex during WM tasks has been noted in cases of individuals diagnosed with HIV (Chang et al., 2001). Still further, investigations in normal aging have indicated that hemispheric asymmetry traditionally observed during some cognitive tasks (i.e., left frontal activation > right frontal activation during verbal encoding) was reduced in the elderly and the observed increased right hemisphere activation has been interpreted as compensatory in nature (Cabeza et al., 1997; Reuter-Lorenz et al., 2000). As seen in Figure 3, this reduction in lateralization of frontal activation is evident in the current study of individuals diagnosed with MS. That is, the paradigm used in the current study elicits greater left hemisphere involvement for healthy adults and greater right hemisphere involvement for individuals with MS. Thus, the current findings are consistent with previous literature regarding WM; recruitment of right prefrontal cortex appears to be a generic response to diminished brain resources and this finding is consistent across populations.

BDI Scores, Lesion Load, and Brain Activation

It should be noted that in the current study, there was a near significant relationship noted between BDI scores and increased right frontal activation. Individuals with MS in this study had higher BDI scores compared to healthy adults, but the mean BDI score in the MS group was only 9.7, which falls within the normal range and is comparable to other examinations of nondepressed patients with MS (Arnett et al., 1999). It may be the case that these slightly elevated BDI scores are related to physical symptomatology secondary to disease progression and/or severity and not necessarily disordered mood. For these reasons, it is unlikely that depressed mood can account for the observed differences in right frontal and right temporal lobe activation between healthy adults and individuals with MS.

While neither quantitative measurement of the lesion extent nor specific contributions to cognitive dysfunction caused by certain lesion constellations were focuses of this study, it was important to consider the gross distribution of the lesions present in this sample. Importantly, correlational analysis revealed no relationship between total gross lesion load and frontal and temporal lobe activation.

CONCLUSION

In sum, during a demanding task of WM maintenance, individuals with MS exhibit greater right hemisphere activation compared to healthy adults. This right hemisphere recruitment results in diminished asymmetry typically observed in a verbally mediated WM task such as the one employed in this study. What remains undetermined is if this increased right prefrontal and temporal activation represents more permanent brain reorganization, functional adaptation to injury, response to greater task difficulty, or some combination of these factors.

While this preliminary investigation represents an important first step in using fMRI to examine WM rehearsal in individuals with MS, it is not without its limitations. First, the sample size remains small which precludes group comparisons of brain activation patterns (i.e., random effects

analysis) and examination of the subgroups that exist in individuals diagnosed with MS. As noted, based upon behavioral data, it is apparent that several individuals diagnosed with MS are not experiencing significant cognitive dysfunction, which could attenuate between-group differences in both the observed behavioral data and the neuroimaging results. Future studies need to replicate and extend the current findings by using a larger sample size and examining individuals with MS with more severe cognitive impairment. Second, future investigation should employ a parametric design to tease apart the interaction between task demands and recruitment of additional brain regions. By controlling for the demand of the WM task, investigators may begin to draw more definitive conclusions regarding the nature of the altered brain activation patterns observed in MS. Finally, the current investigation used only a gross measure of lesion burden. Future investigations would benefit from the use of more advanced methods for detecting white matter pathology such as diffusion imaging, transfer imaging, or MR spectroscopy.

Certainly, a substantial amount of additional research is necessary before the implications of this work can be realized. For example, it will be important to examine WM across the range of clinical presentations of MS and at different time points in the disease course. Eventually, it will also be important to determine how the cerebral representation of WM processes relate to functional status and how, in turn, these information can be used to develop improved clinical interventions.

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