Object Working Memory Performance Depends on Microstructure of the Frontal-Occipital Fasciculus

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Abstract

Re-entrant circuits involving communication between the frontal cortex and other brain areas have been hypothesized to be necessary for maintaining the sustained patterns of neural activity that represent information in working memory, but evidence has so far been indirect. If working memory maintenance indeed depends on such temporally precise and robust long-distance communication, then performance on a delayed recognition task should be highly dependent on the microstructural integrity of white-matter tracts connecting sensory areas with prefrontal cortex. This study explored the effect of variations in white-matter microstructure on working memory performance in two separate groups of participants: patients with multiple sclerosis and age- and sex-matched healthy adults. Functional magnetic resonance imaging was performed to reveal cortical regions involved in spatial and object working memory, which, in turn, were used to define specific frontal to extrastriate white-matter tracts of interest via diffusion tensor tractography. After factoring out variance due to age and the microstructure of a control tract (the corticospinal tract), the number of errors produced in the object working memory task was specifically related to the microstructure of the inferior frontal-occipital fasciculus. This result held for both groups, independently, providing a within-study replication with two different types of white-matter structural variability: multiple sclerosis–related damage and normal variation. The results demonstrate the importance of interactions between specific regions of the prefrontal cortex and sensory cortices for a nonspatial working memory task that preferentially activates those regions.

Key words: cognition; imaging, functional magnetic resonance imaging; multiple sclerosis; white matter; working memory

Introduction

Working memory is the ability to store and manipulate task-relevant information over short periods of time and is known to concurrently activate a widely distributed network of brain areas, including both the prefrontal cortex (PFC) and the posterior association cortices. Despite the importance of working memory for daily functioning and a plethora of research in this field, the specific neural mechanisms responsible for sustaining working memory-related activity in humans are still unclear.

Previous research in nonhuman primates has demonstrated that sustained activity in the PFC during the delay of a delayed-recognition task is particularly important for performance. Sustained activity is also observed in extrastriate sensory areas, but this activity can be disrupted by intervening irrelevant stimuli that do not necessarily affect performance (Kubota and Niki, 1971; Lara et al., 2009; Miller et al., 1996). However, cooling experiments in primates have demonstrated that inactivating the posterior cortices disturbs performance on a delayed-recognition task as much as cooling the PFC does (Fuster 2001). In monkeys, PFC areas demonstrating sustained activity during working memory delays are known to have direct reciprocal connections with extrastriate visual areas. These findings have led investigators to suggest a re-entrant circuit in which reverberating activity between the PFC and sensory areas serves as a mechanism for maintaining sustained patterns of neural activity (Fuster 2001). Alternatively, or in addition, re-entrant circuits may exist within the PFC, independent of sensory areas (Goldman-Rakic 1995). In either case, recent research on both sustained and oscillatory activity in local and long-range neural networks suggests that high-fidelity communication with excellent temporal precision is necessary for good working
memory performance (Düzel et al., 2010; Lee et al., 2005; Mehta 2005).

The general idea that rapid, high-fidelity communication is necessary among regions within the network activated during working memory tasks is supported by studies of individuals with multiple sclerosis (MS). This immune-mediated demyelinating disease of the central nervous system results in slowed transmission or loss of information along affected axons (Calabresi 2007; Smith and McDonald, 1999). Cognitive impairment is estimated to affect about half of all individuals with MS, with deficits in working memory and attention early in the disease course (Au Duong et al., 2005b; Bobholz and Rao, 2003; Janculjak et al., 1999; Parmenter et al., 2006; Santiago et al., 2007; Thornton and Raz, 1997), suggesting that these cognitive functions can be affected by even small amounts of MS damage. Previous research has suggested that the cognitive deficits observed in some individuals with MS are due to disruptions in communication between the PFC and other brain areas (Arnett et al., 1994; Au Duong et al., 2005a; Au Duong et al., 2005b; Dineen et al., 2009). However, because MS is a multifocal disease and previous studies focused on overall group differences between patients with MS and healthy controls, evidence for a specific and reliable relationship between individual white-matter pathways and a specific cognitive ability is lacking. Examining individual differences in lesion location and severity within the MS group is necessary for addressing this question. Furthermore, if working memory performance depends on long-range re-entrant circuits that demand rapid, high-quality communication between distant brain regions, then even normal variation in the structure of the relevant white-matter pathways could be expected to affect performance. Thus, in addition to examining differences in white-matter integrity across individuals with MS, this study also examined the relationship between working memory performance and individual differences in white-matter microstructure in healthy adults.

The study focused on specific pathways that could potentially provide communication between visual association cortices and PFC regions that are preferentially activated during performance of working memory tasks. Using both functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), this study examined specific portions of well-known, large white-matter bundles (such as the superior longitudinal fasciculus [SLF]) and the superior and inferior portions of the fronto-occipital fasciculus (FOF, IFO) (Catani et al., 2002; Makris et al., 2005; Mori et al., 2005; Philipp et al., 2009; Schmahmann and Pandya, 2007; Thomas et al., 2009) that appeared to connect regions preferentially activated by specific white-matter tasks and tested whether MS-related changes or normal structural variation in these tracts were related to an individual’s cognitive performance on those same tasks. The results demonstrate a specific dependence of object working memory performance on the microstructure of a portion of the IFO. These results were replicated in separate analyses for the MS and control groups, demonstrating that the conclusions are not specific to MS-related damage but generalize to small, normal variations in the structure of this long-range white-matter pathway. The results support the idea that object working memory depends on high-quality, rapid communication between the PFC and sensory regions.

Materials and Methods

Participants

Data were obtained for 19 women with relapsing-remitting MS and 14 age- and sex-matched healthy controls. Because of technical difficulties in collection of DTI images, two individuals with MS and three controls had to be excluded, leaving 17 individuals with MS (mean age = standard deviation, 39.2 ± 8.5 years; range, 24–55 years) and 11 control participants (mean age, 38.1 ± 7.993 years; range, 25–55 years). The ages of the two groups did not significantly differ according to t-tests (t(26) = 0.357; p = 0.724). All but two individuals with MS were receiving established treatment with standard disease-modifying medication (Avonex, Betaseron, Copaxone, or Rebif). The average Expanded Disability Status Scale (EDSS) score of the individuals with MS was 2 (range, 0–4). The average time since diagnosis was 82 mo (median, 78 mo; range, 4–192 mo).

All participants were otherwise in good health, with no history of traumatic brain injury. The study protocol was approved by the institutional review boards of the Johns Hopkins University and the Johns Hopkins Medical Institutions, Baltimore, Maryland. All participants provided written informed consent.

Materials

Stimuli for the memory tasks, drawn from a previous study in the authors’ lab (Sayala et al, 2006), were 12 male and 12 female faces cropped to remove hair and clothing. Control images were equated for luminance, contrast, and frequency content by using phase-scrambled images of the same faces. Practice was performed before scanning on a Mac PowerBook G4 laptop running SuperLab Pro software. An LCD projector located outside of the scanner room projected the stimuli onto a screen located inside the scanner. A mirror mounted on top of the head coil was used to view the stimuli. Responses consisted of right or left thumb presses of handheld button boxes connected via fiberoptic cable to a Cedrus RB-610 response box.

Task

Because spatial and nonspatial working memory have previously been shown to differentially depend on distinct neural systems (Mohr et al, 2006; Sala et al., 2003; Sala and Courtney 2007), participants performed two delayed-recognition tasks, one probing working memory for object identity and the other for locations (Fig. 1). Identical stimulus presentation was used for both tasks. Participants were given an instruction cue indicating whether the trial was an identity, location, or control (“nothing”) trial. A 3-second delay preceded stimulus presentation. Three sample items were then presented serially, for 1 second each, followed by a memory delay of 6.75, or 9 seconds. A test screen was then presented for 3 seconds. During the identity task, participants pressed one of two buttons to indicate whether the test face matched any one of the three sample faces for that trial, independent of the locations on the screen in which those faces were presented. During the location task, participants indicated whether the test face was in the same location as any of the three sample faces, independent of the identities of the faces. Instructions emphasized accuracy, and participants...
were given the full 3 seconds that the test stimulus was presented during which they could respond. This lack of emphasis on speed of processing ensured that performance would be primarily influenced by the maintenance processes hypothesized to depend on the prefrontal-to-sensory tracts. There was a jittered intertrial interval of 1.5, 3, or 4.5 seconds.

In control trials, the parameters were the same except participants were presented with the instruction “NOTHING” to indicate that they did not need to remember anything and the stimuli consisted of phase-scrambled images instead of faces. At test in the control trials participants pressed both buttons. There were eight working memory trials and eight control trials per scanning run and nine runs, resulting in 36 trials of each type of working memory task.

**Imaging protocol**

MRI was performed on a 3T Philips Gyroscan at the F.M. Kirby Research Center for Functional Brain Imaging. A multichannel SENSE (SENSitivity Encoding technique for fast acquisition) head coil was used to maximize sensitivity and minimize effects of noise and inhomogeneities (Jaer-ermann et al., 2004). Examinations consisted of a T1-weighted magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo (MP-RAGE) anatomic sequence (200 coronal slices, 1-mm thickness, 0-mm gap, 256×256 matrix, 256-mm field of view), and a T2*-weighted acquisition with an interleaved gradient echo sequence (echoplanar images: 27 axial slices, 3-mm thickness, 1-mm gap, 80×80 matrix, 240-mm field of view, 1500-ms repetition time [TR], 30-ms echo time [TE], 65° flip angle). DTI images were acquired using a multislice single-shot echo planar imaging spin-echo sequence with gradients in 32 directions and b=700 s/mm². We acquired one b=0 reference image for the 32-orientation DWIs, and the examination was repeated twice, resulting in two b=0 images. Sequence parameters were as follows: TR/TE, 5872/67 ms; acquired resolution, 2.2 mm isotropic; SENSE factor, 2.5; nominal slice thickness for all DTI scans, 2.2 mm, covering the whole brain in 60 slices (for individuals with MS numbers 1–12), or 70 slices (individuals with MS numbers 13–19); and Inferior-Superior field of view, 154 mm.

**fMRI analysis**

Analysis of Functional NeuroImages (AFNI) (Cox 1996) software was used for fMRI data analysis. Functional echo planar imaging data were phase-shifted by using Fourier transformation to correct for slice acquisition time and were motion-corrected by using three-dimensional volume registration. Multiple regression analysis was performed on the time series data at each voxel, for all voxels in the brain volume. Functional runs were concatenated such that a single reference baseline was used across all runs. Regressors of no interest included six regressors derived from the movement parameters and one accounting for linear drift within each run. There were event-related regressors for each component of each task (instructional cue, sample presentation, delay period, and test presentation), across all runs, convolved with a gamma function model of the hemodynamic response (rise time of 3 sec, delay time of 2 sec, and fall time of 5 sec). Scalar β weights for each of these regressors were converted into percentage signal change from the average baseline coefficient (composed of unmodeled time points across all runs combined) for each of the runs. Individual subject maps were then transformed into the Talairach coordinate system resampled to 3 mm³ and spatially smoothed by using a Gaussian kernel of 6 mm.

Functionally defined regions of interest for the DTI analysis were identified in a cross-subjects group analysis of areas that showed more activation for both working memory (identity and location) tasks combined compared to the control task during the delay period, collapsing across control and patient groups. We used the regions commonly activated for both object and spatial working memory relative to the control task, despite previous research indicating differential involvement of the dorsal areas for spatial working memory and ventral areas for nonspatial working memory, in order to have a nonbiased tract definition for subsequently identifying structure-function relationships.
FIG. 2. Functional magnetic resonance imaging activations comparing all working memory activity greater than delay activity. This contrast yielded a group of frontal and posterior regions of interest. The frontal regions of interest included the anterior middle frontal gyrus (blue), the junction of the inferior frontal sulcus with the precentral sulcus (green), and superior frontal sulcus (red). The posterior regions of interest included the fusiform gyrus (green), the intraparietal sulcus/superior parietal lobule region (red), and the temporal-occipital junction, which is roughly dorsal and posterior to the fusiform gyrus region shown here. The colors correspond to the relevant fiber tracts in Figure 3.

Tests of voxelwise significance for whole-brain analysis were held to a p value less than 0.01 (t-threshold of 2.85) and corrected for multiple comparisons via spatial extent of activation, holding each cluster of voxels to an experiment-wise p value less than 0.01. On the basis of a Monte Carlo simulation with 1000 iterations run via the AFNI software package on the union of all participants’ brain volumes (as classified by using the echo planar imaging signal intensity threshold), it was estimated that a 914-µL contiguous volume (65 voxels, each measuring 1.875 × 1.875 × 4 mm) would meet the p < 0.01 threshold.

Characterization of DTI regions of interest using fMRI activations and anatomy

The group fMRI activations, rather than the activations in individual participants, and a single probabilistic definition for locating tracts connecting these regions of activation across all participants were used so that the measures of white-matter structure were equivalent across all participants and thus could be appropriately compared. Furthermore, not all of the regions that were activated in the group analysis reached statistical threshold in all individual participants. Using individual-participant fMRI regions of activation could have resulted in the most damaged tracts (the ones in which signal transmission was severely disrupted, leading to a lack of fMRI activation) being missed and left out of the analysis. If one only measures fractional anisotropy (FA) within successfully traced fibers, the calculated average FA value for the entire tract will be artificially high. In addition, it was necessary to make sure that the same anatomic tract was identified in every participant. The Talairach spatial normalization process does not always successfully align individual participants’ sulcal anatomy. Thus, after the transformation of the group fMRI activations into an individual participant’s native DTI space, the regions of interest for tract tracing in that participant were adjusted by hand to be consistent with the anatomic location of these activations that had been found in numerous previous studies, according to the process described below.

The group fMRI regions of activation identified as described earlier were placed back into the brain space of each participant by using reverse transformation matrices and then aligned to that individual’s DTI images. Regions of interest for DTI tract tracing in that individual were then created by using those fMRI group activations, slightly modified according to the individual’s gyral and sulcal anatomy in accordance with the areas consistently activated for the same spatial and object working memory tasks in previous studies (Courtney et al., 1998; Sala et al., 2003; Sayala et al., 2006). The three frontal regions of interest resulting from this process corresponded in individual participants to 1) the posterior half of the superior frontal sulcus (SFS), including approximately 6 mm on either side along the sulcus; 2) the junction of the inferior frontal sulcus with the precentral sulcus (IFJ), including a centimeter anteriorly along the inferior frontal sulcus and 1 cm dorsally into the middle frontal gyrus; and 3) the middle frontal gyrus together with the inferior frontal sulcus and gyrus anterior and inferior to the IFJ region of interest. Three regions of interest were similarly defined in extrastriate cortices: the fusiform gyrus, the temporal-occipital junction, and the intraparietal sulcus (Fig. 2). The cortical spinal tract (CST) was traced in each participant by anatomically based manual drawing of region of interest drawing using that participant’s MP-RAGE image. Circular regions of interest were drawn in the horizontal plane at three locations: 1) around the spinal cord at the most inferior slice visible; 2) at the pons, where the tract changes to four bundles, and the most anterior two were selected (the cerebrospinal fasciculus); and 3) around the entire cerebral peduncle at the level of the most inferior extent of the thalamus. The fibers that were identified as passing through all three of these regions of interest were checked for correspondence to the known anatomy of the CST. This procedure enabled the successful identification of the CST in both hemispheres of all participants. Microstructure of the CST was used as a general measure of individual differences in white-matter structure that would not be expected to be directly related to cognitive performance.

DTI analysis and tractography

DTI images were motion-corrected by using CATNAP (Coregistration, Adjustment, and Tensor-solving—a Nicely Automated Program) (Landman et al., 2007) operating on a Matlab 7 platform using FSL FLIRT (FMRIB Linear Image Registration Tool) (Jenkinson et al., 2002). This program allowed for the adjustment of diffusion gradient directions and motion correction as well as computation of relevant tensor and derived quantities (including FA, mean diffusivity, color maps, and eigenvalues).

Tractography was performed by using DTI Studio (Jiang et al., 2006) with a fiber tracing threshold: FA greater than 0.13, turning angle less than 45°. Fibers passing through both a frontal and an extrastriate region of interest were traced, for all possible frontal-extrastriate pairs. Three portions of known white-matter bundles were identified...
connecting the regions of interest: a tract passing between SFS and intraparietal sulcus corresponding to a dorsal portion of the superior longitudinal fasciculus (dSLF), a tract passing between IFJ and fusiform gyrus corresponding to a ventral portion of the superior longitudinal fasciculus (vSLF), and another tract passing between middle frontal gyrus and temporal-occipital junction most likely corresponding to an inferior portion of the IFO (Fig. 3). All three of these frontal white-matter tracts were successfully reconstructed in at least one hemisphere in all control participants and in 14 of the 17 patients with MS.

**Probability maps**

DTI is susceptible to noise, partial volume effects, and convolution of multiple axonal structures with different orientations within a voxel. Furthermore, reliance entirely on tracts traced in individual participants would result in the exclusion of data from the most highly damaged parts of the tracts—fibers that are too damaged to be traced successfully. Therefore, probability maps were constructed to reduce these effects (Hua et al., 2008) and provide a method for standardizing the region of analysis for each tract across all participants. The probability map was based solely on data from control participants. Fibers traced in individual participants were normalized to a standard Talairach template. For each of the three tracts in each hemisphere, each voxel was assigned a probability of being in the tract of interest based on the number of participants who had a fiber successfully traced for that tract in that voxel. Thus, the probability map indicates the likelihood that a given voxel in an individual participant was actually in the tract of interest.

An FA profile for each tract, for each participant, was calculated as the average FA of all the voxels within each slice, positioned posteriorly to anteriorly along the tract, weighted by the probability that the voxel was in the tract of interest. Voxels with an FA value less than 0.25 were assumed to represent cerebral spinal fluid rather than white matter and were, therefore, excluded from the calculation of an individual’s average FA for each slice to prevent overestimating the amount of damage in that tract. An individual’s FA profile for a given tract was thus the weighted average FA value as a function of slice number along the posterior-anterior axis. An average normal FA profile for each tract was calculated by combining the FA profiles of all control participants.

To characterize the amount of MS-related damage to white-matter tracts, each patient’s FA profile was compared to the control mean profile (see Fig. 4 for the control mean profile, the profile of a patient with MS who had minimal damage to that tract, and a profile of a patient with MS who had a relatively large amount of damage). Normal inter-individual variation in the FA profiles of control participants was examined by comparing each control participant to the FA profile averaged across the profiles of all the remaining control participants. To quantify an individual participant’s tract integrity, the control mean profile was characterized as a function, which was used to fit each individual’s profile of each white-matter tract. This analysis involved performing a least-squares linear regression for each individual’s profile against the control mean profile (pairing each point along the tract in the individual and control profiles). Given that these profiles were already in common Talairach space, any remaining differences in tract length were treated by simply restricting the regression points to those for which a given participant had data.

**FIG. 3.** An individual’s fiber tracking results exhibiting the three white-matter tracts of interest. The red curve corresponds to a dorsal portion of the superior longitudinal fasciculus. The green tract corresponds to a ventral portion of the superior longitudinal fasciculus. The blue tract corresponds to a portion of the inferior frontal occipital fasciculus.

**FIG. 4.** An example of the fronto-occipital fasciculus fractional anisotropy profile. Location along the tract is indicated in millimeters (mm) relative to the anterior commissure (AC). The normal average curve is plotted as the black bold line. The dashed lines represent ±0.5 standard deviation from the mean. An individual with multiple sclerosis (MS) with a good curve fit is plotted in blue; the model fit is $R^2 = 0.967$ (residual $R^2 = 0.029$). An individual with MS with a bad curve fit is plotted in red; the model fit is $R^2 = 0.198$ (residual $R^2 = 0.802$).
of the general effects of age and overall white-matter structure, variables of interest were entered into a hierarchical regression. Working memory is not a function that is localizable to a single brain area or even a single brain network. The ability to sustain patterns of neural activity representing information in working memory is the property of many different brain networks, each preferentially representing different types of information (Courtney 2004; Sala and Courtney 2007). Thus, it was expected that each of the two working memory tasks would be dependent on different white-matter tracts connecting different parts of prefrontal and posterior cortices.

A study hypothesis was that ventral white-matter tracts (IFO and vSLF) connecting areas known to be preferentially activated for object working memory tasks would significantly correlate with performance on the object delayed-recognition task. Therefore, by using object delayed-recognition accuracy as the dependent variable, the following variables were entered into the hierarchical regression model in this order: age, CST damage, IFO damage, and vSLF damage. This model tested whether the ventral frontal tracts would contribute significantly to object task performance after the effects of the other variables were accounted for. To explore the specific contributions of the IFO versus the vSLF tracts, the order of the IFO and vSLF variables were flipped in a second hierarchical regression model. A third hierarchical regression model explored whether the dSLF tract was a significant contributor to performance accuracy after age and CST variance were accounted for. Hierarchical regressions were separately performed, with spatial delayed-recognition performance (percentage error) as the dependent variable. Because multiple comparisons were performed (three per dependent variable), a Bonferroni correction was used to control for the increase in family-wise errors. Thus, \( z = 0.05 \) corrected for multiple comparisons was used, which corresponds to an uncorrected \( z = 0.017 \).

Results

Behavioral results

Accuracy and reaction times for both participant groups are shown in Table 1. Both groups could adequately perform the working memory tasks, and both groups showed a large range of individual differences in performance. Independent sample \( t \)-tests revealed no significant differences in behavioral performance regarding accuracy between controls and individuals with MS on the object or spatial delayed-recognition tasks (\( t(26) = 0.552, p = 0.586; t(26) = 0.579, p = 0.567 \), respectively).

Table 1. Group Means and Standard Deviations for Object and Spatial Accuracy and Reaction Time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n=11)</th>
<th>Multiple sclerosis group (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Object accuracy (%)</td>
<td>77.00±11.82</td>
<td>73.86±16.24</td>
</tr>
<tr>
<td>Object reaction time (ms)*</td>
<td>1128.36±385.69</td>
<td>1450.14±271.92</td>
</tr>
<tr>
<td>Spatial accuracy (%)</td>
<td>78.41±15.52</td>
<td>75.00±14.98</td>
</tr>
<tr>
<td>Spatial reaction time (ms)</td>
<td>1097.45±334.69</td>
<td>1325.60±212.26</td>
</tr>
</tbody>
</table>

*\( p < 0.05 \).
White-matter microstructure results

MS group. For individuals with MS, reaction times for both object and spatial tasks were significantly correlated with the EDSS score ($p < 0.05$), a measure of MS disease severity primarily dependent on sensorimotor rather than cognitive symptoms. Reaction time was not significantly correlated with age, disease duration, or damage to the tracts measured here ($p > 0.05$). Because speed was not emphasized in the task instructions and because within-group reaction times did not correlate with measures of structural integrity in any of the tracts examined, the rest of the analyses were focused on performance accuracy. Object task accuracy, but not spatial task accuracy, was significantly correlated with damage to each of the three defined prefrontal white-matter tracts (Table 2).

To evaluate the specificity of the variables of interest on task performance, hierarchical regressions were performed separately for the object task and the spatial task (Table 3). It was predicted that damage to the vSLF and IFO would be significant contributors to object task accuracy because these are the tracts connecting the regions preferentially activated by that task, both in the current study and in earlier studies with the same tasks and stimuli (Courtney et al., 1998; Sala et al., 2003; Sayala et al., 2006). A hierarchical regression was performed with variables in this order: age, CST fit, vSLF fit, and IFO fit. The fit of this model was significant ($r(16) = 0.80; F(3, 13) = 7.84; p < 0.01$) and accounted for 56% of the variance in object task accuracy. After this variance was accounted for, adding the IFO variable to the model did not account for significantly more variance ($R^2$ change $= 0.074; F(1, 14) = 3.16; p = 0.101$).

### Table 2. Correlations of Task Performance for the Curve Fit Residual Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age</th>
<th>Disease duration</th>
<th>EDSS score</th>
<th>dSLF fit</th>
<th>vSLF fit</th>
<th>IFO fit</th>
<th>CST fit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple sclerosis group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Object Accuracy</td>
<td>-0.22</td>
<td>0.30</td>
<td>-0.37</td>
<td>0.48*</td>
<td>0.69**</td>
<td>0.55*</td>
<td>0.484*</td>
</tr>
<tr>
<td>Object reaction time</td>
<td>0.47</td>
<td>0.32</td>
<td>0.70**</td>
<td>0.07</td>
<td>0.12</td>
<td>-0.12</td>
<td>0.10</td>
</tr>
<tr>
<td>Spatial Accuracy</td>
<td>-0.02</td>
<td>-0.03</td>
<td>-0.06</td>
<td>0.13</td>
<td>0.25</td>
<td>0.18</td>
<td>0.132</td>
</tr>
<tr>
<td>Spatial reaction time</td>
<td>0.21</td>
<td>-0.13</td>
<td>0.60*</td>
<td>-0.08</td>
<td>-0.08</td>
<td>-0.34</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Object Accuracy</td>
<td>-0.591</td>
<td></td>
<td>0.11</td>
<td>-0.03</td>
<td>0.60*</td>
<td>0.527</td>
<td></td>
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<tr>
<td>Object reaction time</td>
<td>0.37</td>
<td></td>
<td>0.50</td>
<td>0.33</td>
<td>-0.20</td>
<td>-0.20</td>
<td></td>
</tr>
<tr>
<td>Spatial Accuracy</td>
<td>-0.165</td>
<td></td>
<td>0.03</td>
<td>-0.40</td>
<td>0.76**</td>
<td>0.329</td>
<td></td>
</tr>
<tr>
<td>Spatial reaction time</td>
<td>0.536</td>
<td></td>
<td>0.44</td>
<td>0.289</td>
<td>-0.30</td>
<td>-0.508</td>
<td></td>
</tr>
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</table>

*p $\leq 0.05$.

**p $\leq 0.01$.

CST, cortical spinal tract; dSLF, dorsal portion of the superior longitudinal fasciculus; EDSS, Expanded Disability Status Scale; IFO, fronto-occipital fasciculus; vSLF, ventral portion of the superior longitudinal fasciculus.

### Table 3. Object Accuracy (Percentage Correct) Ordered Regression for Multiple Sclerosis Group and Control Group

<table>
<thead>
<tr>
<th>Model (df)</th>
<th>$r$</th>
<th>Adjusted $R^2$</th>
<th>$F \Delta R^2$ (p value)</th>
<th>$F$ (Model)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple sclerosis group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, CST (2, 14)</td>
<td>0.55</td>
<td>0.18</td>
<td>4.68 (0.05)</td>
<td>2.81</td>
<td>0.09</td>
</tr>
<tr>
<td>Age, CST, vSLF (3, 13)</td>
<td>0.80</td>
<td>0.56</td>
<td>13.09 (&lt;0.01)</td>
<td>7.84</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, CST, vSLF, IFO (4, 12)</td>
<td>0.85</td>
<td>0.62</td>
<td>3.16 (0.10)</td>
<td>7.65</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, CST, IFO (3, 13)</td>
<td>0.83</td>
<td>0.61</td>
<td>16.38 (&lt;0.01)</td>
<td>9.39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, CST, IFO, vSLF (4, 12)</td>
<td>0.85</td>
<td>0.62</td>
<td>1.45 (0.25)</td>
<td>7.65</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, CST, dSLF (3, 13)</td>
<td>0.63</td>
<td>0.25</td>
<td>2.23 (0.15)</td>
<td>2.78</td>
<td>0.08</td>
</tr>
<tr>
<td>Age, CST, dSLF, IFO (4, 12)</td>
<td>0.764</td>
<td>0.445</td>
<td>4.559 (0.054)</td>
<td>4.206</td>
<td>0.023</td>
</tr>
<tr>
<td>Age, CST, dSLF, vSLF (4, 12)</td>
<td>0.784</td>
<td>0.486</td>
<td>5.885 (0.032)</td>
<td>4.783</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, CST (2, 8)</td>
<td>0.63</td>
<td>0.24</td>
<td>0.57 (0.47)</td>
<td>2.59</td>
<td>0.14</td>
</tr>
<tr>
<td>Age, CST, vSLF (3, 7)</td>
<td>0.64</td>
<td>0.16</td>
<td>0.19 (0.68)</td>
<td>1.63</td>
<td>0.27</td>
</tr>
<tr>
<td>Age, CST, vSLF, IFO (4, 6)</td>
<td>0.94</td>
<td>0.81</td>
<td>24.72 (&lt;0.01)</td>
<td>11.49</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, CST, IFO (3, 7)</td>
<td>0.92</td>
<td>0.78</td>
<td>20.38 (&lt;0.01)</td>
<td>12.70</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, CST, IFO, vSLF (4, 6)</td>
<td>0.94</td>
<td>0.81</td>
<td>2.06 (0.20)</td>
<td>11.49</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, CST, dSLF (3, 7)</td>
<td>0.66</td>
<td>0.20</td>
<td>0.57 (0.47)</td>
<td>1.83</td>
<td>0.23</td>
</tr>
<tr>
<td>Age, CST, dSLF, IFO (4, 6)</td>
<td>0.921</td>
<td>0.747</td>
<td>16.290 (0.007)</td>
<td>8.394</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The adjusted $R^2$ value reflects the overall adjusted $R^2$ for the listed model. The $F$ change and significance of the $F$ change reflects the change that the last variable contributes to the model. Model significance held at $\alpha = 0.05$ corrected for multiple comparisons, corresponding to an uncorrected $\alpha = 0.017$ (Bonferroni correction).

df, degrees of freedom.
A second hierarchical regression was performed reversing the order of the IFO fit and the vSLF fit. The fit of that model was significant \( (r(16) = 0.83; F(3,13) = 9.39; p = 0.001) \) and accounted for 61.1% of the variance in object task accuracy. After this variance was accounted for, the vSLF did not significantly add to the model \( (R^2 \text{ change} = 0.094; F(1, 14) = 1.45; p = 0.25) \). This particular pattern was probably due to the high correlation between IFO and vSLF values \( (r(16) = 0.672, p < 0.01) \), suggesting that one or both of these could be the major contributor.

To confirm that the dSLF was not a significant factor in object task accuracy, a third regression analysis was performed with variables in this order: age, CST fit, and dSLF fit. This model was not significant \( (r(16) = 0.63; F(3, 13) = 2.78; p = 0.08) \) and accounted for only 25% of the variance in object task accuracy. To verify the IFO and vSLF findings, two additional regressions were performed adding IFO fit and vSLF fit, respectively, to the nonsignificant model (age, CST fit, dSLF fit). If one or both of these variables contribute, that contribution should again be revealed in this model. In both cases, the model again reached (or nearly reached) significance \( (r(16) = 0.76, 0.78; F(4,12) = 4.21, 4.78; p = 0.002, 0.01, \) respectively), supporting the claim that the integrity of the IFO or the vSLF or both is a significant contributor to object task accuracy in individuals with MS, whereas damage to the dSLF does not account for any significant variance in object task accuracy above and beyond contributions from age and general disease severity.

To determine whether spatial task accuracy was related to the integrity of the fronto-posterior tracts in question, similar regression analyses were performed (Table 4). Previous research has suggested that parietal and dorsal PFC regions are preferentially involved in spatial working memory tasks (Mohr et al., 2006; Quintana and Fuster, 1993; Sala and Courtney, 2007; Wilson et al., 1993). Those results suggest that the integrity of the dSLF might be more related to spatial task accuracy than to object task accuracy. Therefore, a hierarchical regression analysis was performed with spatial task accuracy as the dependent variable and the order of the model as follows: age, CST fit, and dSLF fit. This model was not significant \( (r(16) = 0.51; F(3, 13) = 1.51; p = 0.259) \) and accounted for only 15% of the variance in spatial task accuracy.

To determine whether the vSLF or IFO accounted for a significant amount of variation in spatial task accuracy, two more hierarchical regressions were performed in the following orders: age, CST fit, and vSLF fit and age, CST fit, and IFO fit. Neither the vSLF nor the IFO accounted for a significant amount of variance when added to the model with age and CST (see Table 4 for details).

### Control group

In the control group, reaction time did not correlate with age, accuracy, or curve fit residual value for any tract. Object and spatial task accuracy were both significantly correlated only with the IFO tract. The same hierarchical regression analyses were performed for the controls as described earlier for the MS group (Table 3). First, object task accuracy was examined. With object task accuracy as the dependent variable, the first hierarchical regression model had the following variables in this order: age, CST fit, vSLF fit, and IFO fit. The model age, CST fit, and vSLF fit was not significant \( (r(10) = 0.64; F(3,7) = 1.63; p = .271) \) and accounted for only about 16% of the variance in object task accuracy. However, after this variance was accounted for the IFO fit contributed significantly to the model \( (F(1,6) = 24.72; p = 0.003) \). This model was significant \( (r(10) = 0.94; F(4,6) = 11.490; p = 0.006) \) and accounted for about 81% of the variance in object task accuracy.

The second hierarchical regression was performed with variables in this order: age, CST fit, IFO fit, and vSLF fit. The model age, CST fit, and IFO fit was significant \( (r(10) = 0.92; F(3,7) = 12.70; p = 0.003) \) and accounted for about 78% of the variation in object task accuracy. After age, CST fit, and IFO fit was accounted for, the vSLF did not significantly contribute to the model \( (R^2 \text{ change} = 0.40; F(1,6) = 2.063; p = 0.134) \);

### Table 4. Spatial Accuracy (Percentage Correct) Ordered Regression for Multiple Sclerosis Group and Control Group

<table>
<thead>
<tr>
<th>Model (df)</th>
<th>( r )</th>
<th>Adjusted ( R^2 )</th>
<th>( F \Delta R^2 ) (p value)</th>
<th>( F ) (Model)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple sclerosis group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, CST (2, 14)</td>
<td>0.51</td>
<td>-0.07</td>
<td>0.01 (0.93)</td>
<td>2.41</td>
<td>0.13</td>
</tr>
<tr>
<td>Age, CST, dSLF (3, 13)</td>
<td>0.51</td>
<td>0.15</td>
<td>4.81 (0.05)</td>
<td>1.51</td>
<td>0.26</td>
</tr>
<tr>
<td>Age, CST, vSLF (3, 13)</td>
<td>0.52</td>
<td>0.10</td>
<td>0.27 (0.62)</td>
<td>1.61</td>
<td>0.24</td>
</tr>
<tr>
<td>Age, CST, IFO (3, 13)</td>
<td>0.57</td>
<td>0.17</td>
<td>1.36 (0.26)</td>
<td>2.10</td>
<td>0.15</td>
</tr>
<tr>
<td>Age, CST, vSLF, IFO (4, 12)</td>
<td>0.58</td>
<td>0.12</td>
<td>1.29 (0.28)</td>
<td>1.56</td>
<td>0.25</td>
</tr>
<tr>
<td>Age, CST, IFO, vSLF (4, 12)</td>
<td>0.58</td>
<td>0.12</td>
<td>0.27 (0.61)</td>
<td>1.56</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, CST (2, 8)</td>
<td>0.27</td>
<td>-0.16</td>
<td>0.25 (0.55)</td>
<td>0.31</td>
<td>0.74</td>
</tr>
<tr>
<td>Age, CST, dSLF (3, 7)</td>
<td>0.27</td>
<td>-0.33</td>
<td>&lt; 0.01 (0.96)</td>
<td>0.18</td>
<td>0.91</td>
</tr>
<tr>
<td>Age, CST, vSLF (3, 7)</td>
<td>0.46</td>
<td>-0.13</td>
<td>1.22 (0.31)</td>
<td>0.62</td>
<td>0.63</td>
</tr>
<tr>
<td>Age, CST, vSLF, IFO (4, 6)</td>
<td>0.88</td>
<td>0.63</td>
<td>15.18 (&lt; 0.01)</td>
<td>5.19</td>
<td>0.04</td>
</tr>
<tr>
<td>Age, CST, IFO, vSLF (3, 7)</td>
<td>0.83</td>
<td>0.56</td>
<td>14.21 (&lt; 0.01)</td>
<td>5.28</td>
<td>0.03</td>
</tr>
<tr>
<td>Age, CST, IFO, vSLF (4, 6)</td>
<td>0.88</td>
<td>0.63</td>
<td>2.20 (0.12)</td>
<td>5.19</td>
<td>0.04</td>
</tr>
</tbody>
</table>

The adjusted \( R^2 \) value reflects the overall adjusted \( R^2 \) for the listed model. The \( F \) change and significance of the \( F \) change reflect the change that the last variable contributes to the model. Model significance held at \( z = 0.017 \) corrected for multiple comparisons, corresponding to an uncorrected \( z = 0.017 \) (Bonferroni correction).
63% of variance in spatial task accuracy. The model age, \( p = 0.20 \), is not highly intercorrelated (\( r(10) = -0.081; p = 0.81 \)). To be complete, a regression with Age, CST fit, and dSLF fit was done to verify that the dSLF was not contributing significantly. This regression was not significant and accounted for only 29% of the variance. Again, adding IFO to this model produced a significant increase in the variance accounted for and the model was significant (change in \( R^2 = 0.412; F(1,6) = 16.29; p = 0.007 \)).

Therefore, after age and variations in CST FA profile are accounted for, the fit of an individual’s IFO FA profile is the best predictor of object working memory performance in normal healthy adults. Given this result, the clearest interpretation is that the IFO was also the major contributor to object performance in the MS group and the vSLF only seemed to be contributing in that group because of its high correlation with the IFO.

Spatial task accuracy was examined (Table 4). With spatial task accuracy as the dependent measure, variables were entered into the first regression in this order: age, CST fit, and dSLF fit. This model accounted for only about 33% of the variance in spatial accuracy and was not significant (\( r(10) = 0.27; F(3,7) = 0.18; p = 0.906 \)). The second hierarchical regression included variables in this order: age, CST fit, vSLF fit, and IFO fit. This model was not significant (\( r(10) = 0.46; F(3,7) = 0.62; p = 0.626 \)). Variations in FA of the IFO tract did significantly contribute to the model of age, CST, and vSLF (\( R^2 \) change = 0.567; \( F(1, 6) = 15.18; p = 0.001 \)), but this model failed to reach significance after correcting for multiple comparisons (\( r(10) = 0.88; F(4,6) = 5.19; p = 0.037 \), accounting for about 63% of variance in spatial task accuracy. The model age, CST fit, and IFO fit was not significant (\( r(10) = 0.833; F(3,7) = 5.281; p = 0.032 \)) and accounted for about 56% of the variance in spatial task accuracy. Including vSLF did not add significantly to this model (\( R^2 \) change = 0.082; \( F(1, 6) = 2.20; p = 0.12 \)). Therefore, although variations in IFO FA are not significantly related to spatial task accuracy, there is a trend in this direction. Object task and spatial task accuracy were significantly correlated in controls (\( r(10) = 0.677; p = 0.02 \)). Therefore, it is unclear from the control group data whether the IFO has independent contributions to both the object and spatial tasks. This apparent contribution of the IFO to spatial working memory performance was not found in the MS group (Table 4), suggesting that IFO does not independently contribute to spatial working memory performance.

**Discussion**

This study sought to determine the specific influence of the microstructure of particular white-matter tracts on working memory task performance for object and spatial information. The results demonstrate a strong correlation between the microstructure of a specific frontal-to-extrastriate white-matter tract and accuracy measures for a delayed-recognition paradigm. Specifically, in the MS group, after factoring out variance due to age and general disease severity, microstructure of the vSLF or the IFO, or both, contributed to the number of errors produced in the object working memory task. Because of the high correlation between the vSLF and the IFO in the MS group, it was not possible to distinguish their contributions. However, the result for the IFO tract was replicated in the control group, which demonstrates that working memory performance depends not just on MS-related lesions within this particular tract that may severely disrupt transmission of sensory information to the PFC but even subtle, normal variability in the structure of this tract. This normal variability might not be expected to disrupt a single transmission of information, but it would be expected to affect processes that are highly sensitive to the temporal precision or signal-to-noise ratio of such information, such as synchronous, phase-locked oscillatory activity (Fuentemilla et al., 2010). These effects are specific in that neither MS damage nor normal variation in a different frontal tract, the dSLF, significantly affects object working memory performance in either subject group.

This study did not attempt to identify a cause for cognitive impairments that are commonly seen across individuals with MS, indicating the effects of the MS pathology in general. Instead this study focused on the high levels of inter-individual variability among patients with MS regarding the location and severity of white-matter lesions and the high variability in performance levels for particular cognitive tasks. Examining this variability enables the identification of specific relationships among these variables. Previous studies of the cognitive effects of frontal lobe lesions, both related and not related to MS, have shown mixed results (Arnett et al., 1994; Bobholz et al., 2006; Dineen et al., 2009; Mesaros et al., 2008; Morgen et al., 2006; Morgen et al., 2007; Owen et al., 1996; Sepulcre et al., 2008). The results of the current study, in conjunction with previous research, suggest that frontal lobe damage in general is neither necessary nor sufficient for poor performance on any particular cognitive task.

Instead, these results demonstrate that object working memory performance (in this simple delayed-recognition task) depends on tracts connecting specific parts of the ventral PFC to specific parts of occipitotemporal cortex but does not depend on a dorsal frontal-to-parietal tract. Moreover, the findings emphasize that damage at any point along these tracts that enable communication between frontal and posterior areas can limit the effectiveness of those prefrontal regions. Lesions in frontal lobe white-matter tracts not related to the cognitive tasks used to measure cognitive performance, or lesions that are in tracts that connect to frontal cortical regions but are not within the frontal lobe itself, would add noise to any attempt to identify correlations between cognitive performance and frontal lesion load.

Another potential explanation for the inconsistent results in previous research on cognitive dysfunction in MS is that complex cognitive tasks such as the Paced Auditory Serial Addition Test have traditionally been used. These tasks are useful clinically because they are very sensitive to detecting cognitive deficits, but they are not ideal for identifying specific structure-function relationships because they depend on many subprocesses, brain areas, and pathways. Although the results of previous studies (Bonzano et al., 2009; Dineen et al., 2009) have suggested that performance on complex cognitive tasks is impaired by MS-related damage to the structure of multiple white-matter pathways, including certain prefrontal pathways, none has had the specificity of the current study regarding the relationship of a particular pathway with a particular cognitive subprocess. Object working memory tasks in which performance is dependent on updating, manipulation, or other higher executive functions, might be dependent on dorsal regions and pathways (O’Hearn et al.,
2009; Roth et al., 2006), in addition to the ventral ones identified in the current study. This study used a simpler task, a delayed-recognition paradigm, which is known to consistently and preferentially activate a limited set of cortical regions. The results suggest that lesions to IFO significantly affect object working memory performance, presumably by disrupting communication between the brain areas preferentially involved in the task.

The specificity of the current results is consistent with previous research indicating the ability to sustain patterns of neural activity representing information in working memory is a property of many distributed neural systems, with different systems preferentially representing different types of information (Courtney et al., 2007). Performance on the working memory task for spatial locations was not correlated with damage in any of the tracts measured in the MS group, although there was a trend for a correlation with variations in the IFO tract for the control group. It is possible that the IFO is responsible for a general process involved in both object and spatial tasks, such as the tuning of representations in response to reward motivation (Kennerley and Wallis 2009). The lack of a relationship between spatial working memory performance and the SLF in the current study may simply be a lack of power because this pathway has been suggested in previous studies to be important for executively demanding tasks in general (Bonzano et al., 2009; Dineen et al., 2009) and specifically for spatial working memory tasks (Karlsgodt et al., 2010; Klingberg 2006).

One intriguing additional possibility regarding the lack of a pathway specifically relating to spatial working memory performance in the current study is the potential existence of multiple pathways that could be used to solve the spatial task. Spatial cognitive networks contain multiple representations of extrapersonal space, such as retinotopic, head-centered, body-centered, and allocentric (Colby and Goldberg, 1999; Maguire et al., 1998; O’Keefe et al., 1998). Preliminary analysis of the fMRI activations suggests there may be greater, potentially compensatory, activation during the spatial task than during the object task. Perhaps these results reflect greater flexibility for the spatial task than for the object task in switching to alternative neural systems when the ones typically used are damaged. White-matter pathways not examined here may contribute to this flexibility. Performance would be expected to be impaired only if both the primary and the compensatory systems are damaged. Further research will be required to explore the relationships among cognitive performance, integrity of primary white-matter tracts and others that might contribute to compensatory processes, and neural activity.

Because the analysis methods used here were novel and the number of participants was small, it will be important to confirm these results in future studies. However, the dependence of object working performance on IFO microstructure in the current study is particularly convincing because it was independently replicated in two different groups with different types of white-matter structure variability. The DTI measures in the MS group probably reflected both the premorbid normal variability seen in the control group and MS-related damage. MS-related damage leads to higher diffusion perpendicular to the tract (and therefore lower FA values); however, many other factors can also contribute to individual variations in FA (Mori and Zhang, 2006). This study quantified the amount of change in the DTI FA profile for an individual relative to the normal FA profile of the control group using a curve fit analysis. The range of FA variation was smaller in the controls than in the MS group, but the correlation with performance was very strong (Fig. 6).

Further study will be needed in a larger sample size to confirm these results and to fully understand the basis of this non–MS-related variability. As in previous studies demonstrating a relationship between normal white-matter microstructural variation and cognitive performance, the results in the control group are unlikely to be due to microscopic damage related to subclinical disease. The results were also independent of age, and the FA curve fit residuals appeared to be continuously distributed and not driven by a few individuals. Alternatively, these results might reflect axonal density that correlates with premorbid connectivity, possibly

**FIG 6.** Correlations between object accuracy and fronto-occipital fasciculus (IFO) integrity. Note that although IFO variability in the control group (right) is not as high as that in the multiple sclerosis (MS) group (left), a very strong correlation between IFO integrity and performance on the object working memory task is seen in both groups.
related to environmental variables such as education, or genetic factors in development. Indeed, long-term memory face recognition performance (Wilmer et al., 2009) and the functional organization of cortical areas involved in face processing (Polk et al., 2007) have both been shown in studies of twins to have a substantial genetic component.

In addition, congenital prosopagnosia, an impairment in face processing that has a familial component, has been shown to be associated with reductions in ventral occipito-temporal and IFO fiber tracts as identified with DTI (Thomas et al., 2009), and similar results have been found with age-related changes in the same tracts (Thomas et al., 2008). Thus, it is unlikely that these findings in the control group reflect damage to the tract per se. Rather, normal inter-individual variability in this tract appears to be a predictor of object white-matter performance. Similar results regarding correlations between normal variation in DTI measures of white-matter structure and cognitive performance have recently been found regarding the fornix and long-term memory recollection performance (Rudebeck et al., 2009).

Similar results have been found regarding normal variations in white-matter microstructure in frontoparietal white matter, including the SLF, and performance on spatial working memory and executive control tasks (Karlsodt et al., 2010; Klingberg 2006; Takeuchi et al., 2010). Although such premorbid factors are presumably independent of current or future disease status, they might leave the system more or less vulnerable to the effects of disease and thus have eventual clinical consequences. Understanding the neural bases of premorbid inter-individual variability in cognitive performance will increase the accuracy of cognitive impairment prognosis and lead to better individualized treatment decisions.

Conclusions

In conclusion, we have found a specific and reliable relationship between object working memory performance and both MS damage and normal variability localized to a particular white-matter tract that connects cortical areas preferentially activated by that task. Our results support the hypothesis that communication between posterior and prefrontal brain regions is necessary for successful working memory performance. The results support theories regarding the existence of a re-entrant circuit between prefrontal and posterior brain regions in which reverberating excitation between these two areas is necessary to sustain patterns of neural activity during working memory delay periods for successful working memory performance (Fuster et al., 1985; Fuster, 2001; Goldman-Rakic, 1995; Lee et al., 2005). Such a circuit would be more dependent on temporally precise, robust signal transmission than would the alternative model in which information merely needs to be transferred once from sensory to prefrontal areas. Even a small amount of demyelination, or even normal variation in tract effectiveness, could affect the ability of this circuit to reliably maintain a representation of the remembered information, as was found in this study.

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Author Disclosure Statement

No competing financial interests exist.

References


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