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White Matter Integrity and Episodic Memory Performance in Mild Cognitive Impairment: A Diffusion Tensor Imaging Study

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Abstract

White matter (WM) integrity in the medial temporal lobes and episodic memory performance was examined in patients with mild cognitive impairment (MCI) and age-matched cognitively intact controls. Material specific associations between WM in the left versus right hemisphere and verbal versus visual memory performance were examined as well. Fourteen right-handed amnestic MCI patients underwent diffusion tensor imaging (DTI) and received verbal (words, story) and visual (designs) memory tests. Delayed verbal memory was significantly correlated with loss of WM integrity in the medial temporal lobe. This finding was associated with both the left and right temporal regions. Immediate visual memory performance was significantly correlated with the loss of WM integrity in the left temporal region. The results indicate that WM integrity in the medial temporal lobe is associated with objective memory functioning in MCI. However, strong material specific relationships were not observed, possibly reflecting diverse encoding strategies used by participants such as imagery of verbal material and verbal encoding of designs.

Keywords

Mild Cognitive Impairment; Memory; Diffusion Tensor; White Matter; Magnetic Resonance Imaging

Loss of white matter (WM) integrity is a radiologic and histopathologic feature of Alzheimer's disease (AD) and has been increasingly recognized as important to the pathogenesis and progression of disease symptoms in these patients (Bracco et al., 2005; Englund, 1998; Haglund and Englund, 2002; Tian et al., 2004). White matter pathways include projection fibers that transmit sensory and motor information to and from the cortex, commissural fibers that act via the corpus callosum to allow communication between the cerebral hemispheres, and association fibers that connect cortical areas. Destruction of these myelinated tracts can disrupt communication between cortical structures and functional connectivity of those structures despite normal cortical and subcortical grey matter (Filley, 1998). It has been proposed that disturbances of WM structure may produce disconnections of cortical regions and result in age-related cognitive declines (O'Sullivan et al., 2001). Mild cognitive impairment (MCI) is often a precursor to dementias such as AD, with rates of progression estimated between 12-15% a year (Kelly and Petersen, 2007; Petersen et al., 2001, Petersen, 2003). As such, it is possible

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that WM changes could serve as a marker for an early neurodegenerative process in MCI patients who have not yet transitioned to AD (Kantarci et al., 2005).

While conventional magnetic resonance imaging (MRI) may not be able to study WM structure in detail, especially subtle microscopic interruptions, a number of investigations have applied diffusion tensor imaging (DTI) to examine loss of WM integrity in AD and MCI patients. Using specially designed gradient schemes in the diffusion weighted MRI method, DTI is capable of measuringdirectionally restricted water diffusion in brain tissue. Microscopic changes through processes such as axonal loss and demyelination alter the intact WM fiber bundle and lead to a reduction of directionally restricted water diffusion as indicated by the fractional anisotropy (FA) index, while there is a corresponding increase in random diffusion as measured by the apparent diffusion coefficient (ADC) index. WM microstructural damage has been demonstrated even in patients with mild AD who have normal appearing WM on conventional MR images (Bozzali et al., 2001, 2002; Choi et al., 2005; Head, 2004; Naggara et al., 2006; Rose et al., 2000; Takahashi et al., 2002). Recent DTI studies in MCI patients have also demonstrated WM changes, especially in the medial temporal lobes (Fellgiebel et al., 2004, 2005; Huang and Auchus, 2007; Medina et al., 2006; Stahl et al., 2007; Zhang et al., 2007).

While loss of WM integrity is becoming recognized as a potential marker for an early neurodegenerative process, less is known about the clinical significance of this finding with respect to cognitive deficits. The establishment of a relationship is critical for validating the importance of observed WM tract disruptions on cognitive functioning. In previous reports, the majority of DTI studies in MCI or AD patients have correlated indices of WM disruption with global cognitive measures such as the Mini-Mental State Examination (MMSE) (Bozalli et al., 2002; Head et al., 2004; Rose et al., 2000; Takahashi et al., 2002). Exceptions are papers by Fellgiebel et al. (2005) and Huang and Auchus (2007). Fellgiebel and colleagues found that delayed verbal memory of words was significantly correlated with fractional anisotropy and mean diffusivity measures in the posterior cingulate of a combined sample of MCI and AD patients and normal controls. Separate correlations within each group were not reported. Huang and Auchus performed DTI on 4 AD patients, 8 MCI patients, and 6 normal controls and correlated the imaging findings with results on the MMSE, CERAD Neuropsychological Battery, and Trailmaking. It was found that temporal diffusivity was significantly correlated with verbal memory performance (word list recall) and that frontal diffusion measurements were significantly correlated with verbal memory (word list recall) and visuomotor processing speed (Trails A). However, this study combined the AD and MCI patients into one group since there were no differences in their DTI measurements. Thus, it is not clear whether the WM and cognitive relationships were specific for MCI patients. In addition, no study to our knowledge has yet examined whether hemispheric laterality findings exist for verbal versus visual cognitive measures.

In the current study, we examined associations between measures of verbal and visual episodic memory and WM integrity in medial temporal lobe regions. Memory is of particular interest in studies of MCI due to its being a risk factor for progression to AD (Fleisher et al., 2007). It was hypothesized that poorer performance on memory measures would be correlated with greater loss of WM integrity in the temporal lobe. We also examined whether material specific deficits were observed. Studies of right handed patients who have undergone surgery, for example, for intractable epilepsy, as well as research in healthy right handed individuals reveal that the left temporal lobe is specialized for verbal material such as words and stories, whereas the right temporal lobe is specialized for visuospatial material such as geometric figures and faces (Milner, 1972; Weber et al., 2007a, b). In the present study which examined right handed MCI patients, it was hypothesized that verbal memory performance would be associated with left hemisphere temporal lobe WM integrity, whereas visual memory would be associated with right hemisphere temporal lobe WM integrity. For comparison purposes, we examined possible

relationships between the memory measures and frontal lobe WM integrity in order to determine whether the associations were specific to the temporal region or whether they were the result of loss of WM integrity in general. Finally, we also investigated if similar relationships between DTI indices and memory performance in the patients were observed in a group of community residing normal controls as a gauge of whether any observed relationships were specific to MCI.

Method

Participants

Study participants were recruited from the Memory Assessment Clinics of the Wesley Woods Center on Aging and from the Emory Alzheimer's Disease Research Center. The study was approved by the Emory University Institutional Review Board, and signed informed consent was obtained from all participants and their representatives. Uniform evaluations included screening for other types of dementia or for coexisting conditions that could affect cognition. Participants did not have histories or findings suggestive of stroke as determined by a review of their medical records and a neurologic exam.

The final sample included 14 right handed (Oldfield, 1971) patients (mean age=71.5 years, SD=8.2; mean education=15.2, SD=3.0 years) who were diagnosed with amnestic MCI by experienced neurologists (A.L., J.L.) using criteria of Petersen (2001) including a subjective cognitive complaint (corroborated by an informant), cognitive impairment in memory (≥ -1.5 SDs below the performance of age and education controls), normal general cognitive functioning, and preserved instrumental activities of daily living. Nine cognitively intact community residing volunteers were recruited as a comparison group (mean age=71.1 years, SD=7.4; mean education=17.0, SD=2.1).

There were no significant differences in age, education, or the distribution of gender ($p>.05$) between patient and control groups. MMSE scores were significantly lower in the patient group (mean=26.6 points, SD=2.1) compared to the controls (mean=29.7, SD=0.5, $p<.001$). As part of their clinical workup, cognitive domains in addition to memory were evaluated involving attention, language, visuospatial performance, and executive functioning (see Table 1). Attention was assessed by the maximum number of digits forward (Wechsler, 1987) and the number of seconds needed to sequence numbers using a pencil (Trails A) (U.S. Army Individual Test Battery, 1944). Language was examined via the 30 item Boston Naming Test (Kaplan, Goodglass, and Weintraub, 1983) and timed phonemic fluency (Benton, Hamsher, and Sivan, 1983). Visuospatial performance was evaluated by having participants determine the angular orientation of lines on a 15 item Judgment of Line Orientation Test (Benton, Hamsher, Varney, and Spreen, 1983). Finally, executive functioning was measured via the Clock Drawing Task (Freedman et al., 1994) and Trails B (U.S. Army Individual Test Battery, 1944). There were no significant differences between the MCI patients and normal controls on any measure with the exception of a near significant difference in naming ability ($p=.05$). Instrumental Activities of Daily Living (IADLs) were assessed via the Lawton and Brody (1969) questionnaire. Informants were asked to rate their significant other's independence in using the telephone, shopping for items, preparing a meal, performing housekeeping duties and the laundry, traveling by car or public transportation, taking medications, and handling finances. Inspection of the individual items revealed that none of the patients were unable to perform or required significant assistance in any of these activities.

Vascular comorbidities, which in themselves can contribute to WM changes, were comparably represented between the groups (Patients/Controls: Hypertension=64%/89%; Non-Insulin Dependent, Diet Controlled Diabetes=0%/11%; Cardiac Disease=21%/22%; Hypercholesterolemia=57%/56%).

Procedure

Evaluation of memory and MRI brain scans were performed within one month of each other in 11 patients. The remaining three patients underwent both procedures less than five months apart.

Cognitive Evaluations—Verbal memory was assessed using the CERAD Word List (Morris et al., 1989) which required participants to recall 10 words over three trials, followed by short-delay recall. Story A of Logical Memory (Wechsler, 1987) was also administered during which participants recalled a story both immediately after hearing it and then after 30 minutes. The dependent variables included the number of words or story units recalled. Visual memory was evaluated by having participants learn and recall the patterns and locations of six designs both immediately and after 30 minutes (Brief Visuospatial Memory Test-Revised) (Benedict, 1997). The dependent variable included the number of total points for correct reproduction and placement of the designs.

Magnetic Resonance Imaging—DTI and structural MRI were performed on a 3T whole body scanner (Phillips Intera, Philips Medical Systems, Best, The Netherlands). For high-resolution anatomic brain scans for evaluating possible abnormalities and for identifying regions of interest (ROIs) for DTI data analysis, 3D T1-weighted multi-plane gradient echo (MPGR) with TR/TE=45/15 ms and T2 weighted fast spin-echo imaging with TR/TE=4900/110 ms were collected using the parallel imaging acquisition. All T1 weighted and T2 weighted imaging was performed in the axial direction with 60 slices, 2 mm thickness and no gap at the same slice location. The same field of view (FOV) of 240 mm, matrix of 256×256 was used, giving an in-plane resolution of 0.94 mm. For DTI, images were recorded in the axial direction with the same FOV and slice location used in the structural MRI to align co-plane with structural images. Sixty slices with 2 mm thickness were used without gap. Directional sensitized diffusion weighting single-shot spin echo echo-planar imaging (EPI) sequence with16 gradient directions was used with imaging parameters: TR/TE=9800/74 ms, *b*-values of 0 or 1,000 s/ mm^2 using the b=0 image as a reference. DT images were collected with matrix of 128×128 but reconstructed to 256×256. Parallel imaging was used with an acceleration factor of 2.

Image Analysis

All images were examined by the study radiologist (L.W.) for possible abnormalities. Participants included in the sample did not exhibit white matter hyperintensity in T2 weighted images. The image analyses were carried out independently by investigators (H.M., C.N., L.W.) who were blinded to the clinical diagnoses. DTI data were analyzed using the FSL program (FMRIB Center, University of Oxford, UK). After Motion and Eddy corrections were made, diffusion tensor eigenvalues (λ_1, λ_2, λ_3) and eigenvectors (ε_1, ε_2, ε_3) were calculated for each voxel, and the average diffusion coefficient (ADC) and FA maps were generated. FA and ADC measurements were obtained for the whole brain and specific areas using region of interest (ROI) analyses. These analyses were carried out for each subject. Using the ROI drawing tools provided by the FSL program, ROIs were drawn from the b=0 images then transferred to FA maps. High resolution three dimensional (3D) T1 weighted images were also used as anatomic references to determine the frontal lobe and temporal lobe structures. High resolution T1 images were helpful in validating ROIs in the proper anatomic regions in some subjects when they were difficult to identify using the b=0 image. Motion related misalignment betweenT1 weighted structural imaging and DTI was examined using the realignment routine implemented in the SPM program (SPM2, Wellcome Department of Cognitive Neurology). If the motion related displacement from two sets of images exceeded 0.5 mm, we chose not to use T1 weighted structural images, but rather to use b=0 images from DTI. In this study, ROIs were selected based on the procedure used by Huang and Auchus (2007) in light of their

findings of significant relationships between memory and the temporal region. ROIs were typically a rectangular shape as shown in Figure 1 A and 1B. Using a rectangular ROI is preferable because it usually contains the entire voxel volume and does not require any interpolation and estimation procedures that may be needed in other ROI shapes. The ROIs were measured in both the right and the left hemispheres from the WM areas of the inferior frontal gyrus (IFG) and the medial frontal gyrus (mFG) in the frontal lobe; and from WM areas of the superior temporal gyrus and medial temporal gyrus (mTG) in the temporal lobe. FA was measured beginning at the mammillary bodies and continuing on the next 4 slices for a total of 5 slices as determined on the structural and b=0 image. The frontal WM ROI was placed on a slice that included the entire section of the lateral ventricle. The most anterior slice was at the rostral point of the cingulated sulcus and continued on the next 4 slices for a total of 5 slices. The examples of ROIs are shown in Figure 1A and 1B. FA and ADC values of each ROI from each subject were measured and then averaged within the group. Reliability of the FA measurements across different readers was evaluated by randomly selecting four research participants and obtaining the standard deviations of FA values of the ROIs from the same anatomic regions by three independent readers. To calculate the whole brain white matter FA and ADC, WM of each brain was segmented from a set of 3D T1 weighted gradient echo images using the segmentation routine provided by the SPM program to obtain a WM mask without normalizing the images. This mask was used as the ROI and superimposed on the FA or ADC maps as shown in Figure 1C and 1D to obtain the averaged values of these measurements. One limitation of using the WM mask generated from T1 images is that distortions of DT images, typically in regions where there is tissue-air interface, may affect the accurate co-registration of DTI and T1 images, therefore introducing FA measurement errors.

Results

Neuropsychological Performance of MCI Patients

Table 2 shows the performance of the MCI patients on the memory measures as compared to the controls. As seen, the patients performed significantly poorer than the controls on the verbal and visual measures.

DTI Indices

Table 3 shows the FA and ADC measures for patients and controls. FA and ADC measurements yielded <10% standard deviations in the ROIs of four subjects independently selected by three different readers. For example, an averaged FA of 0.333 with a standard deviation of 0.019 from the ROIs in the frontal area and an averaged FA of 0.390 with a standard deviation of 0.03 from the ROIs in the temporal area were obtained from three readers.

Significant differences were observed between the groups in average FA and ADC in the medial temporal area. In addition, there were significant differences in FA in the left and right medial temporal regions, and in ADC in the left medial temporal region. FA and ADC measures are also shown for the prefrontal region and the whole brain. Frontal and whole brain FA and ADC were not statistically different between the groups.

Correlations between DTI Indices and Memory Performance

Averaged Left and Right Hemisphere WM—Pearson Product Moment Correlation coefficients were calculated between memory measures and the averaged temporal, frontal, and whole brain WM indices in the patients (Table 4). Lower average medial temporal lobe ADC, indicative of greater WM integrity, was associated with significantly better delayed verbal recall of words and the story, as well as better savings of the words that were initially learned. Trends in the hypothesized direction were observed for lower temporal ADC to be associated with better savings of the story and total recall of designs. In addition, higher whole

brain FA and lower whole brain ADC, both indicative of greater WM integrity, were significantly correlated with better performance in delayed word recall and savings. Visual memory was not significantly associated with averaged FA and ADC whole brain measures. Moreover, the averaged prefrontal FA and ADC measures were not significantly associated with either verbal or visual memory.

For comparison purposes, correlations between the WM indices and memory performance were examined in the controls (Table 4). Higher average medial temporal lobe FA, indicative of greater WM integrity, was associated with significantly better delayed recall of words, with a trend as well for higher immediate total recall of the words. Against expectation, however, lower values of medial temporal lobe FA were associated with worse savings on the visual memory task. Medial temporal ADC values were not significantly correlated with memory performance. Similar to the patients, none of the prefrontal DTI indices were significantly related to memory functioning. Lower whole brain ADC, indicative of greater WM integrity, was significantly associated with better savings of the story.

Material Specific Hemispheric Analyses—Pearson Product Moment Correlation coefficients were calculated for the patients between the WM indices in the left and right medial temporal and prefrontal regions and the memory measures (Table 5). Lower left hemisphere medial temporal ADC, reflective of greater WM integrity, was significantly correlated with better word list savings, delayed story recall, and immediate visual memory. Lower right hemisphere medial temporal ADC was also significantly associated with better word list savings. For the prefrontal indices, there was a significant association, in the opposite direction, between higher right hemisphere ADC and better total word recall.

Correlations between the WM indices and memory measures in the controls revealed that higher left hemisphere FA, reflective of greater WM integrity, was significantly associated with better delayed word recall. Other significant material specific correlations were not observed between left and right hemisphere indices and verbal versus visual memory performance.

Discussion

The majority of DTI research in AD and MCI patients examining relationships between WM disease and cognitive functioning has used global indices such as the MMSE which screens a number of diverse areas including memory, attention, and language. These studies have had negative (Takahashi et al., 2002; Naggara et al., 2006; Stahl et al., 2007), positive (Bozalli et al., 2002; Head et al., 2004; Rose et al., 2000), and mixed (Yoshiura et al., 2002) results in being able to demonstrate significant correlations between the MMSE score and WM indices. The current findings extend those of Fellgiebel et al. (2005) and Huang and Auchus (2007) by demonstrating cognitive-anatomic correlations using detailed memory measures in a group comprised of MCI patients alone. Our results indicate that WM integrity in the medial temporal lobes is associated with objective memory performance in amnestic MCI patients. Specifically, we found that the loss of medial temporal lobe WM integrity was associated with poorer delayed recall of words and stories, with a trend observed as well for poorer recall of designs. In contrast, average frontal lobe WM integrity was not significantly associated with memory performance, and whole brain WM integrity was associated with word list recall only. The strongest relationships were observed between temporal WM and delayed recall and savings, as opposed to immediate recall. Delayed recall has been found to be a good predictor of conversion to AD (Fleisher et al., 2007). Moreover, baseline measures of hippocampal ADC are predictive of eventual conversion from MCI to AD (Kantarci et al., 2005).

It is tempting to attribute the associations between memory performance and DTI findings to neurodegeneration in the MCI patients, but this conclusion is not warranted at the present time. The specificity and sensitivity of these findings to MCI cannot be established given the results in the controls for a significant association between temporal lobe FA and delayed word recall, as well as the trend for temporal lobe FA to be associated as well with total word recall. Future studies should test the predictive value of associations between WM changes and memory in MCI patients versus other control groups.

While both temporal ADC and FA values differed between MCI patients and normal controls, significant correlations between the memory measures and DTI indices were observed only for temporal ADC but not for FA in the patients. There is precedent in the literature for finding dissociations between these two indices. Kantarci et al. (2001) reported that hippocampal ADC, but not the FA index, was significantly different in MCI patients compared to normal controls. Fellgiebel and colleagues (2004) noted that mean diffusivity, but not FA values, were significantly different in the left centrum semiovale, the left and right temporal, and the left hippocampal regions of MCI patients versus normal controls. A dissociation of the DTI indices with respect to cognitive functioning has also been observed by Yoshiura et al. (2002) who found that scores on the MMSE were significantly correlated with mean diffusivity but not FA in patients with Alzheimer's disease. It has been proposed that expansion of the extracellular environment due to cell loss is associated with an increase in diffusivity and that this index is especially sensitive to early pathological changes, more so than FA (Yoshiura et al., 2002). It is intriguing to speculate that this may account, in part, for the significant correlations of memory performance with ADC observed in our study for patients but not for controls.

We did not find compelling evidence for a material specific relationship between type of memory test (verbal versus visual) and hemispheric localization in either the patients or the controls. Loss of WM integrity in the right medial temporal region was also related to poor recall and savings of words, whereas left medial temporal lobe WM loss was associated with poorer recall of designs. The lack of a strong relationship between left versus right temporal lobe WM integrity and the type of to-be-learned information may reflect a number of factors including the nature of the materials themselves and the strategies adopted by the patients. For example, the mixed hemispheric laterality findings for verbal material could be due to the possibility that participants visually encoded some words or the story. In addition, the BVMT-R includes geometric figures which can be named by participants (e.g., a circle intersecting with a diamond; a box with smaller box inside). Thus, participants may adopt a verbal strategy to remember the pictures. Support for this idea comes from an fMRI study by Golby and colleagues (2001) who demonstrated that differences in the verbalizability of visual material had different effects on activation of the right or left medial temporal lobe. The encoding of abstract patterns activated the right medial temporal lobe, whereas material which could also be verbally encoded such as faces and scenes activated both the left and the right medial temporal lobe. Future studies might use low imagery verbal material or a visual test with a lower likelihood of being verbally encoded such as the Nonverbal Selective Reminding Test (NVSR) which requires the recall of the location of dots. The NVSR has been found to be a good discriminator of left versus right temporal lobe epilepsy (Plenger et al., 1995), and thus may be able to detect WM microstructural damage in the nondominant hemisphere.

In summary, the results of this study indicate that loss of WM integrity in the medial temporal lobe is associated with objective memory performance. Limitations of this study include the relatively small sample size and the cross-sectional nature. Increasing the sample size will also improve the reliability of FA and ADC measurements since our analyses were performed on a subject by subject basis using individually placed ROIs, resulting in potential variations from different image readers. In addition, while we were able to demonstrate a comparable frequency of vascular comorbidities such as hypertension and hypercholesterolemia in our patients and

the cognitively intact participants, we did not ascertain their severity and control. Since vascular comorbidities are themselves associated with white matter changes, it is important to determine the extent to which these risk factors could be contributing to DTI findings in studies of neurodegeneration. Finally, while the white matter ratings were performed independently of knowledge concerning diagnosis (MCI versus Control) and the memory scores, future studies should employ a wider range of memory measures including those not used in the diagnosis of MCI. Longitudinal investigations of WM changes over time will also add to our understanding of their impact on functional outcome.

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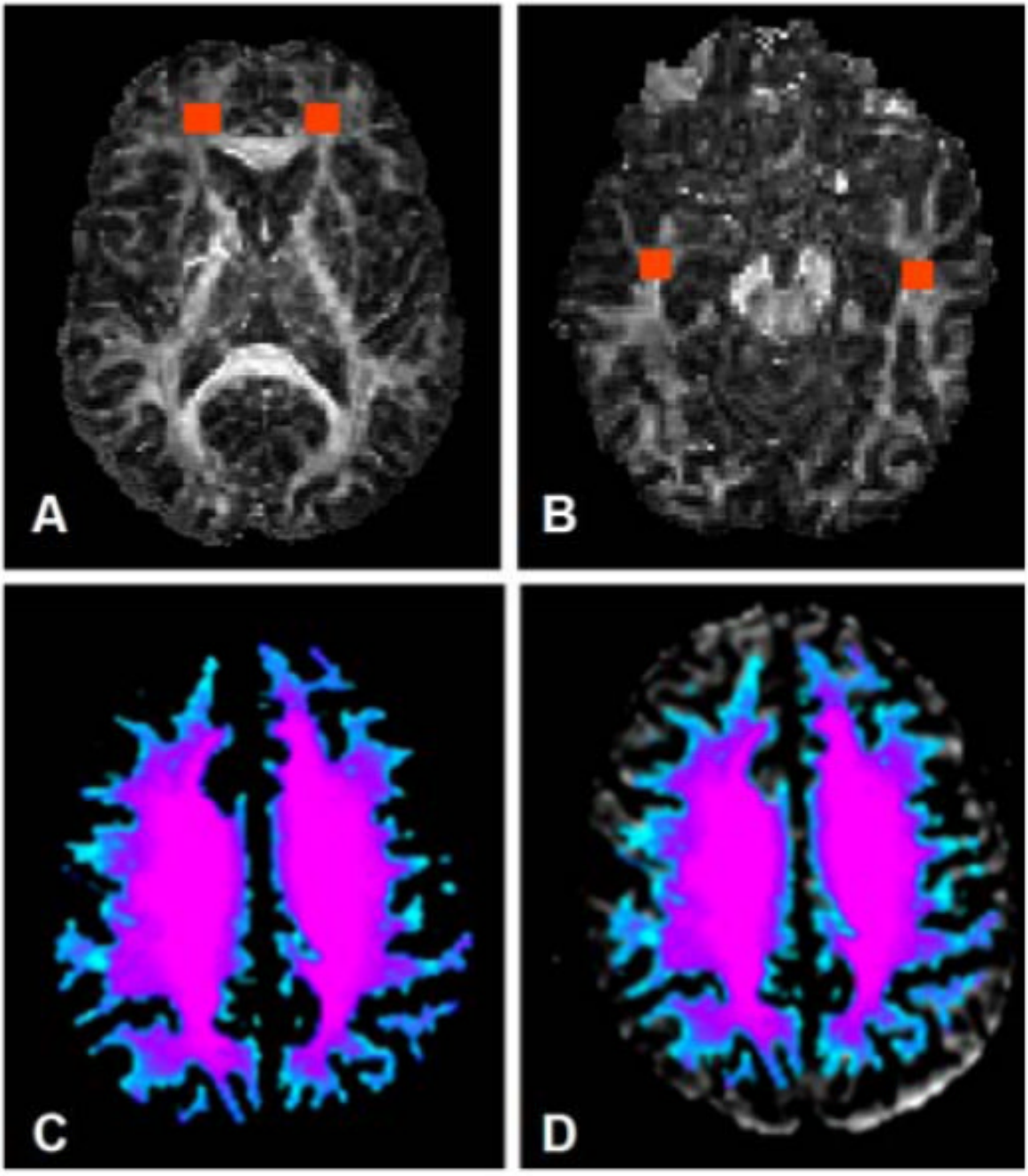

Figure 1.
Examples of regions of interest (ROI) placed in prefrontal (A) and temporal (B) areas of the FA map obtained from DTI of a subject. Whole brain FA can be calculated from the regions in a white matter mask (colored) obtained from the segmentation of 3D T1 weighted image (C) that can be overlaid on the FA map of the same subject (D).

Table 1

Non-Memory Performance of MCI Patients and Controls

	MCI Patients	Controls	p Value
Attention			
Digit Span Forward			
# Digits	6.7 (0.7)	6.7 (0.7)	.88
Trails A			
# Seconds	39.1 (13.2)	39.9 (12.8)	.90
Language			
Boston Naming Test			
# Correct/30	24.5 (3.5)	27.4 (2.6)	.05
Letter Fluency (FAS)			
# Words	37.9 (11.1)	40.3 (9.4)	.61
Visuospatial Performance			
Judgment of Line Orientation			
# Correct/15	20.8 (8.2)	22.0 (5.6)	.72
Executive Functioning			
Clock Drawing			
# Points/13	11.7 (1.2)	11.8 (1.4)	.91
Trails B			
# Seconds	131.7 (80.2)	105.9 (45.9)	.39

Table 2

Memory Performance of MCI Patients and Controls

	MCI Patients	Controls	p Value
Verbal Memory			
CERAD Word List			
Total Recall			
# Words (30 possible)	15.4 (3.5)	22.9 (3.3)	.001
Delayed Recall			
# Words (10 possible)	3.1 (2.0)	7.3 (1.8)	.001
% Savings (Delay/Trial 3)	53.3 (35.2)	86.4 (13.0)	.03
Logical Memory-Story A			
Immediate Recall			
# Points (25 possible)	7.2 (3.6)	14.8 (2.9)	.001
Delayed Recall			
# Points (25 possible)	4.1 (4.3)	12.9 (3.1)	.001
% Savings			
(Delay/Immediate)	50.1 (42.7)	85.2 (12.3)	.01
Visual Memory			
Brief Visuospatial Memory Test-Revised			
Total Recall			
# Points (36 possible)	6.9 (6.0)	19.7 (7.3)	.001
Delayed Recall			
# Points (12 possible)	2.2 (3.2)	9.1 (2.4)	.001
% Savings (Trial 3/Delay)	38.6 (50.5)	103.6 (18.7)	.002

Table 3

DTI Indices in MCI Patients and Controls[1]

	MCI (N=14)	Controls (N=9)	P value
Temporal Region:			
Average FA	.28 (.06)	.34 (.06)	**.01**
Left Hemisphere	.27 (.07)	.34 (.07)	**.04**
Right Hemisphere	.28 (.06)	.34 (.07)	**.04**
Average ADC	928.0 (80.6)	861.3 (30.9)	**.03**
Left Hemisphere	927.4 (77.9)	858.3 (43.3)	**.02**
Right Hemisphere	928.7 (112.2)	864.2 (45.2)	.12
Prefrontal Region:			
Average FA	.30 (.03)	.29 (.03)	.49
Left Hemisphere	.30 (.03)	.29 (.02)	.35
Right Hemisphere	.29 (.05)	.28 (.04)	.66
Average ADC	885.4 (78.0)	859.5 (58.0)	.40
Left Hemisphere	873.1 (82.1)	863.0 (69.0)	.75
Right Hemisphere	897.6 (97.9)	856.4 (55.3)	.27
Whole Brain:			
FA	.26 (.03)	.26 (.02)	.77
ADC	1223.1 (113.1)	1139.3 (106.6)	.09

[1] FA=Fractional Anisotrophy; ADC=Apparent Diffusion Coefficient. Higher values of FA and lower values of ADC signify greater WM integrity.

Table 4

Correlations Among Memory Scores and DTI Indices in MCI Patients and Controls[1]

N=14 for CERAD and Logical Memory, N=11 for BVMT-R for MCI; N=9 for Controls	CERAD Total Word Recall	CERAD Delayed Recall	CERAD Savings	Logical Memory Immediate	Logical Memory Delayed	Logical Memory Savings	BVMT Total Recall	BVMT Delayed Recall	BVMT Savings
Temporal FA									
MCI	.17	−.39	.15	.34	.21	.03	−.18	.08	.15
Controls	.60+	**.77** *	.55	−.44	−.41	−.14	.21	−.03	**−.67** *
Temporal ADC									
MCI	−.06	**−.56** *	**−.66** **	−.39	**−.60** *	−.50+	−.51+	−.39	−.30
Controls	.15	−.11	−.09	.27	.12	−.14	.11	.25	.37
Frontal FA									
MCI	−.22	−.04	.29	.28	.33	.32	.10	.36	.20
Controls	.18	.27	.16	.14	.33	.47	.31	.24	−.12
Frontal ADC									
MCI	.44	−.03	−.21	−.24	−.33	−.19	−.22	−.31	−.08
Controls	−.40	−.26	−.02	.00	.16	.17	−.19	−.05	.31
Whole Brain FA									
MCI	.12	**.66** **	**.73** **	.17	.14	.13	.04	−.08	−.01
Controls	.12	−.01	−.44	−.57	−.28	13	−.29	−.21	−.05
Whole Brain ADC									
MCI	.04	**−.66** **	**−.84** **	−.06	−.34	−.40	−.36	−.31	−.28
Controls	−.57	−.45	.14	−.07	−.47	**−.76** *	−.09	−.34	−.23

[1] BVMT-R=Brief Visuospatial Memory Test-Revised; FA=Fractional Anisotrophy; ADC=Apparent Diffusion Coefficient

* p<.05

** p<.01

+ p<.10

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Table 5

Correlations Among Memory Scores and Left versus Right Hemisphere DTI Indices in MCI Patients and Controls[1]

N=14 for CERAD and Logical Memory, N=11 for BVMT-R for MCI; N=9 for Controls	CERAD Total Word Recall	CERAD Delayed Recall	CERAD Savings	Logical Memory Immediate	Logical Memory Delayed	Logical Memory Savings	BVMT Total Recall	BVMT Delayed Recall	BVMT Savings
Temporal FA									
Left Hemisphere									
MCI	.13	.29	.13	.26	.08	−.14	−.26	−.26	−.11
Controls	.46	**.77** *	.63+	−.12	−.05	.12	.20	.10	−.43
Right Hemisphere									
MCI	.17	.13	.13	.34	.30	.23	−.04	.44	.40
Controls	.50	.44	.22	−.59+	−.62+	−.36	.13	−.16	−.63+
Temporal ADC									
Left Hemisphere									
MCI	−.19	−.40	**−.57** *	−.35	**−.56** *	−.49+	**−.77** **	−.37	−.23
Controls	−.19	−.21	.14	.23	−.02	−.34	.20	−.01	−.03
Right Hemisphere									
MCI	.04	−.52+	**−.56** *	−.32	−.47+	−.38	−.19	−.29	−.26
Controls	.39	.05	−.26	.15	.19	.13	−.04	.35	.53
Frontal FA									
Left Hemisphere									
MCI	.08	.33	.37	.30	.37	.23	.01	.40	.26
Controls	.16	.16	.10	−.34	.03	.44	.43	.38	−.09
Right Hemisphere									
MCI	−.34	−.13	.19	.21	.24	.30	.14	.25	.12
Controls	.17	.27	.16	.30	.40	.43	.24	.17	−.11
Frontal ADC									
Left Hemisphere									
MCI	.14	−.14	−.26	−.16	−.43	−.38	−.55+	−.43	−.18

N=14 for CERAD and Logical Memory, N=11 for BVMT-R for MCI; N=9 for Controls	CERAD Total Word Recall	CERAD Delayed Recall	CERAD Savings	Logical Memory Immediate	Logical Memory Delayed	Logical Memory Savings	BVMT Total Recall	BVMT Delayed Recall	BVMT Savings
Controls	−.26	−.13	.16	−.06	.13	.19	.09	.24	.30
Right Hemisphere									
MCI	**.59** *	.07	−.12	−.25	−.17	.02	−.11	−.13	.02
Controls	.−.51	−.38	−.25	.08	.18	.11	−.51	−.39	.28

[1]BVMT-R=Brief Visuospatial Memory Test-Revised; FA=Fractional Anisotrophy; ADC=Apparent Diffusion Coefficient

*p<.05

**p<.01

+p<.