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Regionally-Specific Diffusion Tensor Imaging in Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

Background—Diffusion tensor imaging (DTI) studies have shown significant cross-sectional differences among normal controls (Bozzali et al., 2002), mild cognitive impairment (Robbins et al.) and Alzheimer's disease (AD) patients in several fiber tracts in the brain, but longitudinal assessment is needed.

Methods—We studied 75 participants (25 NC, 25 amnesic MCI, and 25 mild AD) at baseline and 3 months later, with both imaging and clinical evaluations. Fractional anisotropy (Bozzali et al., 2002) was analyzed in regions of interest (ROIs) in: (1) fornix, (2) cingulum bundle, (3) splenium, and (4) cerebral peduncles. Clinical data included assessments of clinical severity and cognitive function. Cross-sectional and longitudinal differences in FA, within each ROI, were analyzed with generalized estimating equations (GEE).

Results—Cross-sectionally, AD patients had lower FA than NC ($p < 0.05$) at baseline and 3 months in the fornix and anterior portion of the cingulum bundle. Compared to MCI, AD cases had lower FA ($p < 0.05$) in these regions and the splenium at 0 and 3 months. Both the fornix and anterior cingulum correlated across all clinical cognitive scores; lower FA in these ROIs corresponded to worse performance. Over the course of 3 months, when the subjects were clinically stable, the ROIs were also largely stable.

Conclusions—Using DTI, findings indicate FA is decreased in specific fiber tracts among groups of subjects that vary along the spectrum from normal to AD, and that this measure is stable over short periods of time. The fornix is a predominant outflow tract of the hippocampus and may be an important indicator of AD progression.

Introduction

Diffusion tensor imaging (DTI), a relatively new magnetic resonance imaging procedure, was developed to examine the integrity of white matter fiber bundles in the nervous system (Basser and Jones, 2002; Beaulieu et al., 1996; Mori et al., 1999) by measuring fractional anisotropy (FA) (Bozzali et al., 2002) and mean diffusivity. It can be used to assess the degradation of

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white matter tracts in the brain, and has therefore been applied to the study of a variety of neurodegenerative disorders, such as Alzheimer's disease (AD).

Using DTI, a number of studies have reported reduced FA and/or increased mean diffusivity in patients with established AD, compared to normal controls (Bozzali et al., 2002), within the splenium of the corpus callosum (Bozzali et al., 2002; Duan et al., 2006; Naggara et al., 2006; Rose et al., 2000; Sydykova et al., 2007) and the cingulum bundle (Cho et al., 2008; Ding et al., 2008; Fellgiebel et al., 2005; Fellgiebel et al., 2008; Takahashi et al., 2002; Zhang et al., 2007). DTI studies of white matter integrity within several cortical regions have also shown differences between patients with AD and controls (Bozzali et al., 2002; Choi et al., 2005; Fellgiebel et al., 2004; Medina et al., 2006; Naggara et al., 2006; Stahl et al., 2007; Takahashi et al., 2002).

A small number of studies have also used DTI to assess subjects with mild cognitive impairment (MCI) (Petersen, 2004; Petersen et al., 1999). Individuals with amnesic MCI have an increased risk of progressing to AD (Petersen and Morris, 2005), and recent studies indicate that the majority of amnesic MCI cases have AD pathology in their brains on autopsy (Bennett et al., 2005; Jicha et al., 2006). The DTI studies have demonstrated reduced FA and/or increased mean diffusivity in MCI cases relative to NC in the cingulum bundle (Zhang et al., 2007) and the splenium of the corpus callosum (Cho et al., 2008; Stahl et al., 2007). Differences in white matter integrity from selected cortical regions has also been reported in MCI cases compared to controls (Fellgiebel et al., 2004; Huang and Auchus, 2007; Stahl et al., 2007).

These findings suggest that FA in the cingulum bundle and splenium may be useful for assessing the evolution of disease as AD progresses. This is particularly important because of the continuing need to identify biological measures that can accurately assess the early progression of ongoing pathological change and, therefore, speed drug development for both prodromal and established AD. However, longitudinal DTI studies are necessary to understand the reliability of these measures over time, and their relation to change in clinical status, in order to determine whether DTI measures may be useful biomarkers of AD.

As part of an ongoing longitudinal study examining the utility of DTI as a biomarker of AD progression, the aims of the present analyses were to: (1) examine cross-sectional differences in FA, among a group of cognitively NC, and subjects with amnesic MCI and AD; (2) to examine the short-term stability of these measures between baseline and 3 months; and (3) to examine the relationship between FA in the regions of interest and assessments of cognitive status in the subjects. Regions of interest included ones that have been used in previous DTI studies of AD and MCI cases, specifically the corpus callosum and the cingulum bundle. A measure of the fornix was also included as one previous study that looked at asymptomatic individuals with a dominant genetic mutation for AD reported abnormalities in this region (Ringman et al., 2007). We hypothesized that there would be reductions in FA for the fornix, cingulum and splenium in AD compared to MCI and controls and that FA in these regions would remain stable over the 3-month follow-up.

Methods

Subjects

Participants were primarily recruited from two sources: the Johns Hopkins Alzheimer's Disease Research Center and memory clinics associated with Johns Hopkins Hospital. Three groups of subjects were recruited: (1) Normal Controls (Bozzali et al., 2002): subjects who were cognitively normal and had a Clinical Dementia Rating (CDR) of 0 (Hughes et al., 1982; Morris, 1993); (2) Mild Cognitive Impairment (Robbins et al.): subjects who were non-demented but had mild memory problems, had a CDR=0.5, and met criteria for amnesic MCI,

single or multiple domains impaired (Petersen, 2004); (3) Alzheimer's disease (AD): subjects who had mild AD, had a CDR=1, and met NINCDS/ADRDA criteria for AD (McKhann et al., 1984).

Subjects were excluded from enrollment if they were under the age of 55, had a history of a neurological disease other than AD or a history of major psychiatric illness. Subjects were required to have an informant who could provide information about their daily function.

All subjects provided informed consent prior to the initiation of the study in accordance with the requirements of the Johns Hopkins Institutional Review Board. Consent procedures followed the guidelines endorsed by the Alzheimer's Association for participation of cognitively impaired individuals (Alzheimer's Association, 2004). Eighty participants met the initial inclusion criteria and were consented. However, four were not able to tolerate the MRI and one was found to be too impaired based on the baseline neuropsychological examination, leaving a total of 75 participants: 25 NC, 25 MCI, and 25 AD.

Study Design and Assessments

As part of an ongoing study, participants are evaluated four times over the course of a year: at 0, 3, 6 and 12 months. Each visit includes a clinical assessment, a neuropsychological examination, and an MRI scan. Blood specimens are also obtained for later analysis. The present report describes the findings from the first two visits. The clinical assessment consisted of: (1) a medical, psychiatric and neurologic history; (2) a medication inventory; (3) a physical and neurological examination; and (4) a psychiatric examination consisting of the Geriatric Depression Scale (Yesavage et al., 1982) and the Neuropsychiatric Inventory (Cummings et al., 1994). The degree of clinical severity of each subject was evaluated by a semi-structured interview (Hughes et al., 1982; Morris, 1993). This interview generates both an overall CDR rating and a measure known as the CDR Sum of Boxes (CDR-SB). The neuropsychological battery consisted of eight tests and included: (1) two tests of global cognitive function: the Mini-Mental State Exam (Folstein et al., 1975) and the Alzheimer's Disease Assessment Scale – cognitive portion (ADAS-Cog) (Mohs et al., 1997); (2) three tests of episodic memory: the California Verbal Learning Test (CVLT) (Delis et al., 1988), the Logical Memory Story A from the Wechsler Memory Scale (WMS), (Wechsler, 1988), and the Paired Associate Learning test from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins et al., 1994), (3) one test of executive function: the Trail Making Test (TMT) (Reitan, 1958), and (4) two tests of language: the total score on the Controlled Word Association test for category and letter fluency (Benton and Hamsher, 1976), and the Graded Naming Test from the CANTAB (Robbins et al., 1994).

MRI Acquisition

MRI images were acquired on a 3.0 Tesla (3T) scanner (Philips Medical Systems, Best, The Netherlands) at the F.M. Kirby Research Center for Functional Brain Imaging at the Kennedy Krieger Institute. At each scanning session, a Magnetization Prepared Rapid Gradient Recalled Echo (MPRAGE) scan and a DTI scan was acquired. The MPRAGE scan was conducted according to the protocol of the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Jack et al., 2008). The current report will focus on the DTI imaging only.

DTI images were acquired using a SENSE head coil on the 3T scanner, equipped with Dual Quasar gradients (up to 80 mT/m). For acquisition, an eight-element arrayed RF coil, converted to six-channel to be compatible with the six-channel receiver, was used. For DTI acquisitions, a single-shot spin echo - echo planar sequence (SE-EPI) was used, with diffusion gradients applied in 32 non-collinear directions and $b = 700 \text{ s/mm}^2$. Five additional reference images with least diffusion weighting ($b = 33 \text{ s/mm}^2$) were also acquired. Fifty-sixty axial slices were

acquired to cover the entire hemisphere and the cerebellum, parallel to the AC-PC line. The field of view, the size of the acquisition matrix, and the slice thickness were 212×212 mm/ $96 \times 96/2.2$ mm. Other imaging parameters were: TR > 7,000 ms and TE = 80 ms; and SENSE reduction factor = 2.5. To improve the signal-to-noise ratio, two datasets were acquired, leading to a total acquisition time of 7 minutes. It should be noted that the 'real' brain orientation inside the scanner does not affect the oblique slice because the gradient table is dynamically rotated on the oblique slice angles in such a manner that the "X gradient" is always X (right-left) of the image.

DTI Data Processing

The DTI datasets were transferred to a personal computer running a Windows platform and were processed using DtiStudio (mri.kennedykrieger.org or www.DtiStudio.org) (Jiang et al., 2006). Images were first realigned by affine transformation using Automatic Image Registration (Woods et al., 1998), in order to remove any potential small bulk motion and Eddy-current distortion. The six elements of the diffusion tensor were calculated for each pixel using multivariant linear fitting. After diagonalization, three eigenvalues and eigenvectors were obtained. For the anisotropy map, fractional anisotropy (Bozzali et al., 2002) was used (Pierpaoli and Basser, 1996). The eigenvector (v1) associated with the largest eigenvalue was used as an indicator for fiber orientation. A 24-bit color-coded orientation map was created by assigning red, green, and blue channels to the x (right-left), y (anterior-posterior), and z (superior-inferior) components of the v1 and its intensity was modulated by FA.

DTI Regions of Interest

Protocols were developed to identify specific fiber tracts and to manually delineate eight regions of interest (ROI) within the fiber tracts using the in-house software MriStudio/RoiEditor (www.MriStudio.org or mri.kennedykrieger.org).

The selection of the eight ROIs was accomplished by using both the DTI color maps and the FA images generated by the software. The appropriate slice on which the ROI was identified was chosen by using both the color maps and anatomical landmarks from the FA maps, for consistent slice identification. The ROIs were then drawn manually, using standardized guidelines based on location, color, and size.

The eight ROIs from four fiber tracts were identified as follows (Fig. 1): 1) fornix: the body of the fornix drawn in two adjacent axial slices (FX1 and FX2) using the ventral midbrain and splenium of the corpus callosum as anatomic landmarks; 2) cingulum bundle: inferior cingulum (CG1) at the same axial slice as the cerebral peduncles; the posterior portion of the cingulum bundle (CG2 and CG3) on the same axial slices as the body of the fornix; the anterior portion of the cingulum bundle (CG4) identified in a coronal slice at the level of the anterior commissure; 3) splenium: the mid-sagittal slice of the splenium (Kalus et al.), identified as the enlarged, caudal-most region of the corpus callosum; and 4) cerebral peduncles: the cerebral peduncles (CP) identified on an axial slice just inferior to the decussation of the superior cerebellar peduncles (the latter region was included as a 'control' region, since no changes in this region were anticipated).

The inter-rater reliability of the protocol described above was assessed by having two independent operators (MMM, NAK) manually draw the eight ROIs on the same set of 10 DTI scans. The intra-class correlation of the ROIs ranged from 0.82–0.95, with a mean of 0.87. The same two raters completed the ROI analysis on all of the subjects in the present study, blind to the diagnosis.

With the exception of the splenium and fornix, all ROIs were drawn on both the right and left hemispheres. When longitudinal data were analyzed, slices were chosen by comparing subsequent images to previously analyzed scans from the same subject and choosing the slice that most closely corresponded to that chosen at the previous visit.

Statistical Analysis

The demographic and health-related characteristics were examined across diagnostic groups using Fischer's Exact Test for dichotomous variables and ANOVA for continuous variables with t-tests for pairwise comparisons when there was a significant ($p < 0.05$) group difference. Generalized Estimating Equations (GEE) (Zeger et al., 1988) were used to analyze the baseline and 3-month longitudinal measurements. For group (NC, MCI, AD) comparisons of the DTI measures and the clinical and cognitive measures, Wald tests of regression coefficients were used. Longitudinal data techniques are adopted here in order to handle correlation for repeated data measured from the same subject. In the GEE analysis, an exchangeable working correlation structure was used to handle correlated measurements within subjects. Robust variance estimates were included because they guarantee that the inferences are valid in a large sample, even where the assumptions on the working correlation structure are misspecified. Covariates for analyses incorporating the DTI measures included baseline age and the number of voxels in the ROI. Covariates for analyses incorporating the clinical and cognitive measures included baseline age and years of education. Partial correlation coefficients were used to examine the correlation between the DTI ROIs and cognitive test scores, adjusting for baseline age, years of education, and number of voxels in each ROI. All the techniques used in the GEE analysis are under a semiparametric model and do not require normality assumptions in measurements. Since some of the DTI measures were obtained from both the right and left hemispheres (i.e., CG and CP), each side was initially examined separately. As there was little difference in the results, the FA of the two sides were averaged for the analyses presented here. The *a priori* p-value was set at $p < 0.05$. All analyses were conducted using STATA Version 10.0 (StataCorp, College Station, TX).

Results

Subject Characteristics

The baseline demographic, health and clinical characteristics of the subjects (Table 1) were compared across diagnostic groups using Fisher's Exact test for categorical variables and ANOVAs for continuous variables (with t-tests for pairwise comparison when $p < 0.05$). There were no demographic differences between the groups with regards to age, sex, race, and education. In addition, the prevalence of vascular factors such as hypertension, hypercholesterolemia, and heart attack, did not differ between the groups. As expected, the AD group was more likely to be taking a dementia medication and had markedly lower scores across neuropsychological tests compared to MCI and NC ($p < 0.001$). The MCI group also had significantly ($p < 0.05$) worse mean scores compared to the NC groups for the CDR, MMSE, CVLT immediate and delayed recall and Wechsler Story A- immediate and delayed recall. At baseline, there were 2 AD participants whose DTI data could not be processed. At 3 months, 1 MCI withdrew, 1 AD withdrew, and 1 additional AD participant had data that could not be processed. Those with missing DTI data at baseline were not the same as those with missing data at 3 months. Thus, all participants were included in cross-sectional analyses when data were available. Longitudinal analyses consisted of 25 NC, 24 MCI, and 21 AD.

Baseline Group Differences in FA for the Eight ROIs

Using GEE methods and calculating the cross-sectional associations, there were three ROIs that differed at baseline between the AD and NC groups, controlling for age and number of voxels. Compared to NC, AD subjects had lower mean FA in FX1 (0.444 vs. 0.512, $p = 0.008$),

FX2 (0.430 vs. 0.499, $p=0.026$), and CG4 (0.409 vs. 0.439, $p=0.031$). Compared to the MCI subjects, the AD cases also had lower mean FA at baseline for FX1 (0.444 vs. 0.503, $p=0.025$), FX2 (0.430 vs. 0.476, $p=0.026$), CG4 (0.409 vs. 0.443, $p=0.031$), as well as for SP (0.606 vs. 0.632, $p=0.042$) (see Table 2 & Fig. 2).

There were no cross-sectional differences in mean FA between the NC and MCI group. However, the MCI group varied substantially in degree of impairment. We therefore divided the group on the basis of clinical severity, based on the CDR-SB, as has been done previously (Daly et al., 2000). One subgroup (MCI1) consisted of 12 individuals with CDR-SB of 0.5–1.0; the other subgroup (MCI2) consisted of 13 individuals with a CDR-SB of 1.5–3.5). There were significant differences in FX2 at baseline between the MCI-2 subgroup and the NC (0.445 vs. 0.499, $p<0.001$). There was also a significant difference for FX1 between MCI-1 and the normal controls (0.536 vs. 0.512 $p = 0.02$) (Table 3).

DTI FA Changes Between Baseline and Three Months

An assessment of differential change in FA between baseline and 3 months showed that almost all of the ROIs were stable over the three-month interval (Table 4). The three ROIs that were significantly different between the NC and AD cases at baseline (FX1, FX2 and CG4) were also similarly lower in the AD vs. NC group at 3 months, with the exception of FX1, which did not reach significance at the $p = 0.05$ level (0.466 vs. 0.515, $p=0.093$). The AD cases also continued to have lower mean FA compared to the MCI cases for FX1, FX2, CG4, and SP at 3 months. Likewise, the significant difference between the NC group and MCI2 subgroup for FX2 was also present at 3 months (Table 3). The difference between the NC group and the MCI1 subgroup for FX1 was, however, not maintained at 3 months. The only region that showed a significant decline between baseline and 3 months was the CG4 region, for the comparison of the NC vs MCI group ($b = -0.027$, $p=0.026$).

Neuropsychological Changes Between Baseline and Three Months

The clinical diagnosis of all participants between baseline and 3 months remained the same. Differences in the neuropsychological test scores at baseline and 3 months are presented in Table 5. As at baseline, there were significant cross-sectional group differences ($p<0.05$) for all neuropsychological tests at 3 months. In longitudinal analyses the AD group, compared to the NC group, performed worse on the MMSE, CVLT long-delay free recall, and Wechsler Memory Scale Immediate and Delayed Recall (Table 5, $p<0.05$). However, this difference was due to a better performance in the NC group between 0–3 months, likely due to a practice effect, rather than a worsening in performance for the AD group. There were no differences between the NC and MCI groups over time.

Correlations between DTI and Neuropsychological Performance

Correlations between the DTI measures and the clinical and cognitive scores were examined among the patient groups (i.e. MCI and AD) in order to better interpret disease progression. The FX1, FX2 and CG4 were correlated across all of the cognitive measures at baseline (Table 6), with lower FA in these ROIs corresponding to worse performance, after controlling for age, education and number of voxels. The SP was inversely correlated with the clinical measures [CDR-Rating ($r = -0.263$, $p=0.081$) and CDR-Sum of Boxes ($r = -0.321$, $p=0.032$), but not with any of the cognitive measures.

Discussion

The present findings demonstrate significant cross-sectional differences in fiber tract integrity (as measured by FA) including 1) for AD vs. NC: reduced FA in the fornix and the anterior portion of the cingulum bundle; 2) for AD vs. MCI: reduced FA in the fornix, the anterior

portion of the cingulum, and the splenium; and 3) for MCI vs. NC: Cross-sectional differences for the fornix, but only among the most impaired subgroup of MCI cases (i.e. MCI2 vs. NC). Over a 3-month interval, during which the subjects were clinically stable, only one region showed a significant decrease in FA, the anterior portion of the cingulum bundle. This decrease was observed only for the MCI group relative to the NC group. Lastly, there were strong cross-sectional correlations between the fornix and anterior portion of the cingulum bundle and all neuropsychological tests.

The primary finding of the study pertains to the importance of differences in fiber integrity in the fornix among NC, MCI cases and AD patients. The only other previous study with comparable findings evaluated presymptomatic PS1 mutation carriers vs. non-carriers (Ringman et al., 2007). Thus, these data extend that finding to an older age range, and in particular to individuals with amnesic MCI as well as late onset AD. The strength of this finding is emphasized by the fact that the FA values in the fornix were strongly correlated with all of the cognitive measures (e.g., CVLT), as well as with measures of disease severity (e.g., CDR-SB). These results are also consistent with the known neurobiology of AD since the fornix is a predominant outflow tract of the hippocampus. It has been hypothesized that the intracortical (e.g. limbic) projecting fibers are preferentially affected early in the course of AD while extracortical fiber tracts are relatively preserved (Braak and Braak, 1996; Hyman et al., 1984; Teipel et al., 2007), and the present findings further support this theory.

As noted above, there were no differences in FA across ROIs for the MCI vs. NC group. Due to the variability in the MCI group, participants were subgrouped based on their CDR-SB, as has been done previously (Daly et al., 2000). With these subgroups, there were differences only in the fornix for MCI-1 vs. AD and MCI-2 vs. NC. These findings further support the fornix being an early marker of disease progression. Future studies will determine if this region is a sensitive indicator of disease progression over time.

DTI studies of MCI and AD patients have varied greatly in ROIs examined. Recent cross-sectional studies have reported white matter abnormalities in the temporal lobes (Fellgiebel et al., 2004; Head et al., 2004; Kalus et al., 2006; Takahashi et al., 2002; Xie et al., 2006) and other posterior lobe regions (Fellgiebel et al., 2004; Head et al., 2004; Takahashi et al., 2002), posterior corpus callosum (Takahashi et al., 2002), left centrum semiovale (Fellgiebel et al., 2004), and both the anterior (Takahashi et al., 2002) and posterior (Ding et al., 2008; Takahashi et al., 2002; Zhang et al., 2007) cingulum. While we did not directly examine many of these ROIs, our results generally agree in locality because our strongest findings were with the fornix. Interestingly, while previous studies with similarly drawn ROIs in the cingulum reported significant group differences in the posterior portion of the cingulum, (Ding et al., 2008; Zhang et al., 2007) we found group differences in the anterior portion. One other study reported a similar finding with lower mean FA in this region for AD patients compared to NC (Takahashi et al., 2002), but another study did not find a difference between groups (Cho et al., 2008). Head et al. (Head et al., 2004) reported age-associated changes in white matter exhibited a roughly anterior to posterior gradient while dementia status was characterized more by posterior changes. There were no mean age differences between our diagnostic groups so the age-associated findings can not explain our current results. Given our strong findings in the anterior portion of the cingulum, additional studies are warranted

The vast majority of ROIs were stable across the 3-month follow-up. This was expected as patients were clinically stable over this short interval and suggests that changes in FA in these regions may be useful as markers of disease severity. However, we did observe a significant reduction in FA over the 3-month interval for the anterior cingulate region in the MCI group relative to the controls. Whether this change is an indicator or predictor of future clinical progression, or resulting from error and an unreliable measurement, will be further investigated

with additional follow-up of these participants. If this finding is replicated, it would be an important indicator of disease progression and therefore a potential biomarker for clinical trials.

The present study has several advantages including a larger sample size relative to other DTI studies, a well-characterized group of subjects and multiple measures of cognition as well as disease severity. Moreover, it is the first to examine short term longitudinal change in DTI measures among normals, MCI cases and AD patients. One potential limitation of the study is the fact that we did not analyze other measures of white matter or gray matter to determine their relationship to the present findings (apart from an assessment of vascular risks). Moreover, the presence of white matter hyperintensities (WMH) was not considered in the exclusion criteria. While the prevalence of vascular factors including hypertension, hypercholesterolemia, angina and myocardial infarction, did not vary by group, there still is a possibility that the presence of WMH could partially confound the DTI findings. Another potential limitation is that CSF suppression was not used in the acquisition of the images, which raises the possibility that partial voluming is, at least in part, related to the group differences in regions near the ventricles (e.g., the fornix). Future studies can address this issue.

In conclusion, we found cross-sectional differences in FA between AD and NC for the fornix and anterior cingulate. Compared to the MCI group, the AD group also had lower FA levels in the fornix, anterior cingulate, and splenium. Importantly, while most ROIs were stable over the 3-month follow-up, during which there was no diagnostic change, the FA of the anterior cingulate did significantly decrease in the MCI group relative to the NC group, suggesting that this marker could be a sensitive, early indicator of AD progression. Since these subjects were re-evaluated at both 6 and 12 months we hope to further pursue whether, in fact, this ROI continues to change with disease severity and whether change in other ROIs may also be important predictors of AD progression. Additional analyses will also provide valuable information about the importance of DTI regional measures for characterizing brain changes over a time interval useful for clinical trials.

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Fig 1.
Illustration of the diffusion tensor imaging regions of interest: A) Fornix 1 (FX1) and Cingulum bundle 2 (CG2); B) Fornix 2 (FX2) and Cingulum 3 (CG3); C) Cingulum 4 (CG4); D) Splenium (Kalus et al.); E) Cerebral Peduncles (CP) and Cingulum 1 (CG1)

Fig. 2.
Comparison of diffusion tensor imaging regions of interest among groups at baseline (v1) and 3 months (v2). NC = Normal Control; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease. Lines with p-values indicate significant ($p < 0.05$) group differences.

Table 1
Baseline demographic, health and neuropsychological characteristics by diagnostic group.

	NC n=25 Mean(SD)/n(%)	MCI n=25 Mean(SD)/n(%)	AD n=25 Mean(SD)/n(%)	F	p-value
<i>Demographics</i>					
Age	74.3 (7.1)	75.6 (5.3)	75.6 (7.0)	0.25	0.779
Female	14 (56.0%)	7 (28.0%)	7 (28.0%)		0.081
Caucasian vs. Other	24 (96.0%)	23 (92.0%)	18 (72.0%)		0.066
Education	16.2 (2.6)	15.7 (3.0)	14.4 (3.9)	1.24	0.295
<i>Health Characteristics</i>					
Current Hypertension	14 (56.0%)	12 (48.0%)	13 (52.0%)		0.957
Current Hypercholesterolemia	9 (36.0%)	13 (52.0%)	16 (64.0%)		0.160
Current or History of Angina	1 (4.0%)	2 (8.0%)	3 (12.0%)		0.866
Current or History of Atrial Fibrillation	1 (4.0%)	3 (12.0%)	3 (12.0%)		0.687
History of Heart Attack	0	3 (12.0%)	1 (4.0%)		0.315
Current Diabetes	2 (8.0%)	3 (12.0%)	4 (16.0%)		0.903
Geriatric Depression Scale (15-item)	0.8 (1.3)	1.5 (1.3)	2.0 (2.0)	2.69	0.075
Current Dementia Medication	0	4 (16.0%)	23 (92.0%)		0.005
<i>Clinical Characteristics</i>					
CDR Rating	0.01(0.1)	0.5 (0.1)	1.1 (0.4)	118.09	<0.001
CDR Sum of Boxes	0.01(0.1)	1.4 (0.8)	5.8 (2.4)	109.54	<0.001
MMSE	28.8 (1.2)	26.6 (2.1)	22.4 (3.1)	51.69	<0.001
ADAS-Cog	10.4 (2.2)	12.6 (5.1)	18.3 (5.9)	17.99	<0.001
CVLT-total immed recall	54.0 (11.6)	34.3 (12.4)	17.7 (7.9)	71.49	<0.001
CVLT-long delay	10.6 (3.2)	5.2 (3.8)	0.8 (1.5)	64.93	<0.001
Wechsler Story A - Immed	12.9 (2.9)	8.3 (3.0)	3.8 (3.8)	49.08	<0.001
Wechsler Story A - delay	11.1 (3.7)	6.1 (4.1)	1.1 (2.1)	54.14	<0.001
Trail Making Test, Part A	35.5 (13.9)	43.2 (13.8)	80.2 (38.4)	23.07	<0.001
Trail Making Test, Part B	83.6 (34.9)	129.5 (75.3)	248.4 (79.8)	40.91	<0.001
PAL Total Stages	4.5 (1.3)	3.8 (0.7)	2.2 (1.7)	21.85	<0.001
PAL Total Trials	12.4 (2.7)	15.1 (2.9)	25.5 (9.9)	31.23	<0.001

NC=Normal Control; MCI=Mild Cognitive Impairment; AD=Alzheimer's Disease

ANOVA for continuous variables; Fischer's Exact Test for Dichotomous Variables

Table 2
Cross-sectional comparison of fractional anisotropy (FA) by diagnostic group at baseline and the 3-month follow-up.

ROI		NC mean (SE)	MCI mean (SE)	AD mean (SE)	NC vs. MCI p-value	NC vs. AD p-value	MCI vs. AD p-value
CP:	Visit 1	0.610 (0.008)	0.625 (0.007)	0.612 (0.007)	0.277	0.969	0.287
	Visit 2	0.606 (0.008)	0.615 (0.008)	0.623 (0.009)	0.654	0.293	0.536
CG1:	Visit 1	0.414 (0.008)	0.406 (0.008)	0.397 (0.006)	0.467	0.116	0.442
	Visit 2	0.406 (0.006)	0.407 (0.007)	0.396 (0.007)	0.845	0.416	0.344
CG2:	Visit 1	0.444 (0.008)	0.447 (0.011)	0.449 (0.009)	0.688	0.801	0.913
	Visit 2	0.452 (0.008)	0.446 (0.009)	0.442 (0.009)	0.428	0.657	0.746
CG3:	Visit 1	0.456 (0.008)	0.468 (0.007)	0.455 (0.010)	0.443	0.887	0.384
	Visit 2	0.455 (0.007)	0.456 (0.007)	0.451 (0.009)	0.901	0.821	0.742
CG4:	Visit 1	0.439 (0.007)	0.443 (0.008)	0.409 (0.011)	0.401	0.031	0.007
	Visit 2	0.446 (0.007)	0.428 (0.010)	0.411 (0.010)	0.153	0.010	0.292
FX1:	Visit 1	0.512 (0.011)	0.503 (0.015)	0.444 (0.019)	0.798	0.008	0.025
	Visit 2	0.515 (0.010)	0.489 (0.017)	0.466 (0.022)	0.265	0.093	0.489
FX2:	Visit 1	0.499 (0.009)	0.478 (0.012)	0.430 (0.018)	0.184	0.001	0.026
	Visit 2	0.495 (0.012)	0.462 (0.013)	0.438 (0.017)	0.095	0.012	0.313
SP:	Visit 1	0.636 (0.010)	0.632 (0.008)	0.606 (0.009)	0.882	0.069	0.042
	Visit 2	0.630 (0.007)	0.624 (0.010)	0.604 (0.010)	0.643	0.073	0.142

MCI Subanalysis: Cross-sectional comparison of fractional anisotropy (FA) by diagnostic group at baseline and the 3-month follow-up.

Table 3

ROI		NC mean (SE)	MCI-1 mean (SE)	MCI-2 mean(SE)	AD mean (SE)	MCI-1 vs. NC p- value	MCI-2 vs. NC p- value	MCI-1 vs. AD p- value	MCI-2 vs. AD p- value
CP:	Visit 1	0.612 (0.009)	0.632 (0.012)	0.619 (0.011)	0.613 (0.009)	0.148	0.571	0.186	0.655
	Visit 2	0.603 (0.009)	0.611 (0.012)	0.619 (0.012)	0.621 (0.009)	0.488	0.271	0.613	0.913
CG1:	Visit 1	0.410 (0.007)	0.397 (0.011)	0.414 (0.010)	0.398 (0.008)	0.290	0.535	0.850	0.135
	Visit 2	0.412 (0.007)	0.406 (0.011)	0.407 (0.010)	0.397 (0.008)	0.602	0.943	0.666	0.378
CG2:	Visit 1	0.444 (0.009)	0.438 (0.013)	0.455 (0.013)	0.437 (0.010)	0.628	0.506	0.977	0.261
	Visit 2	0.451 (0.009)	0.433 (0.013)	0.451 (0.013)	0.442 (0.010)	0.223	0.897	0.468	0.541
CG3:	Visit 1	0.456 (0.008)	0.457 (0.012)	0.475 (0.011)	0.454 (0.008)	0.955	0.187	0.899	0.133
	Visit 2	0.454 (0.008)	0.450 (0.012)	0.462 (0.011)	0.452 (0.008)	0.764	0.522	0.817	0.482
CG4:	Visit 1	0.439 (0.009)	0.460 (0.013)	0.428 (0.013)	0.409 (0.009)	0.218	0.823	0.003	0.119
	Visit 2	0.446 (0.009)	0.443 (0.013)	0.415 (0.013)	0.410 (0.009)	0.529	0.158	0.155	0.511
FX1:	Visit 1	0.512 (0.016)	0.536 (0.024)	0.476 (0.023)	0.443 (0.017)	0.455	0.334	0.170	0.142
	Visit 2	0.518 (0.016)	0.510 (0.024)	0.470 (0.023)	0.454 (0.017)	0.722	0.153	0.084	0.484
FX2:	Visit 1	0.499 (0.014)	0.513 (0.021)	0.453 (0.020)	0.429 (0.015)	0.597	0.059	0.001	0.343
	Visit 2	0.498 (0.014)	0.491 (0.021)	0.433 (0.020)	0.450 (0.015)	0.952	0.011	0.094	0.425
SP:	Visit 1	0.636 (0.009)	0.607 (0.009)	0.636 (0.013)	0.628 (0.012)	0.924	0.896	0.146	0.137
	Visit 2	0.630 (0.009)	0.604 (0.009)	0.626 (0.013)	0.622 (0.013)	0.700	0.851	0.316	0.221

NC=normal control; MCI=mild cognitive impairment; AD=Alzheimer's Disease

MCI-1: CDR-SB?1.0; MCI-2: CDR-SB?1.5

Comparisons of group differences are assessed by Wald test of GEE regression coefficients for linear models adjusting for baseline age and number of voxels in the ROI for DTI measures.

Table 4
Comparison of mean change in fractional anisotropy (FA) between 0 and 3 months for MCI and AD groups compared to NC.

ROI	MCI vs. NC		AD vs. NC	
	coeff (SE)	p-value	coeff (SE)	p-value
CP	-0.006 (0.009)	0.483	0.013 (0.011)	0.260
CG1	0.010 (0.011)	0.361	0.009 (0.010)	0.376
CG2	-0.015 (0.014)	0.287	-0.009 (0.014)	0.539
CG3	-0.007 (0.013)	0.573	-0.001 (0.011)	0.951
CG4	-0.027 (0.012)	0.029	-0.005 (0.014)	0.732
FX1	-0.018 (0.013)	0.191	0.018 (0.017)	0.292
FX2	-0.006 (0.016)	0.698	-0.029 (0.017)	0.086
SP	-0.003 (0.010)	0.777	0.004 (0.012)	0.754

Analyses control for baseline age and area of ROI (# of pixels)

Table 5
Cross-sectional Neuropsychological test scores and mean change between 0 and 3 months by diagnostic group

Cross-sectional Mean Scores				Mean Group Change Between 0 and 3 Months			
	NC mean (SE)	MCI mean (SE)	AD mean (SE)	MCI vs. NC		AD vs. NC	
				coeff (SE)	p-value	coeff (SE)	p-value
<i>CDR Rating</i>							
Visit 1	0.02 (0.02)	0.48 (0.02)	1.06 (0.07)	-0.062 (0.053)	0.243	0.022 (0.069)	0.753
Visit 2	0.02 (0.02)	0.42 (0.04)	1.08 (0.09)				
<i>CDR Sum of Boxes</i>							
Visit 1	0.02 (0.08)	1.40 (0.16)	5.80 (0.44)	-0.168 (0.163)	0.304	0.069 (0.269)	0.797
Visit 2	0.04 (0.09)	1.25 (0.15)	5.89 (0.46)				
<i>MMSE</i>							
Visit 1	28.84 (0.23)	26.64 (0.40)	22.40 (0.61)	-0.356 (0.511)	0.486	-1.400 (0.525)	0.008
Visit 2	29.20 (0.25)	21.36 (0.49)	21.36 (0.49)				
<i>ADAS-Cog</i>							
Visit 1	10.35 (0.49)	12.56 (0.98)	18.44 (1.17)	0.312 (1.189)	0.792	1.148 (0.946)	0.225
Visit 2	10.32 (0.38)	12.85 (0.73)	19.57 (1.29)				
<i>CVLT-total immed recall</i>							
Visit 1	54.04 (2.17)	34.05 (2.31)	17.68 (1.61)	-2.534 (2.068)	0.220	-2.717 (1.868)	0.146
Visit 2	56.19 (2.04)	33.67 (2.09)	17.12 (1.39)				
<i>CVLT-long delay</i>							
Visit 1	10.61 (0.65)	5.13 (0.71)	0.80 (0.35)	-0.611 (0.692)	0.378	-1.113 (0.532)	0.037
Visit 2	11.43 (0.66)	5.34 (0.77)	0.51 (0.31)				
<i>Wechsler Story A - Immed</i>							
Visit 1	12.88 (0.51)	8.32 (0.58)	3.76 (0.75)	-1.216 (0.821)	0.139	-2.426 (0.659)	<0.001
Visit 2	14.56 (0.58)	8.78 (0.70)	3.01 (0.57)				
<i>Wechsler Story A - delay</i>							
Visit 1	11.12 (0.68)	6.08 (0.75)	1.12 (0.43)	-1.278 (0.803)	0.112	-2.155 (0.670)	0.001
Visit 2	13.28 (0.62)	6.96 (0.70)	1.13 (0.54)				
<i>Trail Making Test, Part A</i>							
Visit 1	35.52 (2.71)	43.24 (2.48)	80.24 (7.40)	2.034 (2.408)	0.398	1.278 (4.953)	0.796
Visit 2	36.24 (2.71)	45.99 (2.89)	82.24 (7.41)				
<i>Trail Making Test, Part B</i>							

	Cross-sectional Mean Scores			Mean Group Change Between 0 and 3 Months			
	NC mean (SE)	MCI mean (SE)	AD mean (SE)	MCI vs. NC		AD vs. NC	
				coeff (SE)	p-value	coeff (SE)	p-value
Visit 1	83.56 (6.94)	129.52 (15.54)	248.4 (15.54)	-11.548 (15.291)	0.450	-6.546 (8.038)	0.415
Visit 2	93.20 (9.75)	127.61 (13.61)	251.49 (15.33)				
PAL Total Stages							
Visit 1	4.48 (0.24)	3.76 (0.14)	2.16 (0.33)	-0.263 (0.314)	0.402	-0.577 (0.370)	0.119
Visit 2	4.56 (0.16)	3.58 (0.17)	1.66 (0.27)				
PAL Total Trials							
Visit 1	12.44 (0.52)	15.12 (0.55)	25.48 (1.92)	1.254 (0.820)	0.126	-1.387 (2.059)	0.501
Visit 2	12.36 (0.56)	16.29 (0.75)	24.01 (1.02)				

Table 6
Baseline correlation between DTI and cognitive tests among the MCI and AD groups.

ROI	ADAS-Cog Total Score		MMSE		CDR-Rating		CDR-Sum of Boxes		CVLT-total Immediate Recall		CVLT-Long Delay Free Recall	
	Corr	p-value	Corr	p-value	Corr	p-value	Corr	p-value	Corr	p-value	Corr	p-value
CP	-0.126	0.415	0.053	0.727	-0.287	0.056	-0.292	0.052	0.206	0.180	0.267	0.080
CG1	-0.221	0.150	0.350	0.018	-0.235	0.121	-0.190	0.211	0.246	0.107	0.145	0.348
CG2	-0.113	0.465	0.048	0.753	-0.164	0.282	-0.055	0.717	0.023	0.881	0.011	0.944
CG3	-0.032	0.839	0.061	0.689	-0.268	0.076	-0.206	0.175	-0.006	0.967	0.084	0.589
CG4	-0.367	0.014	0.434	0.003	-0.427	0.003	-0.446	0.002	0.462	0.002	0.451	0.002
FX1	-0.271	0.076	0.259	0.085	-0.410	0.005	-0.450	0.002	0.401	0.007	0.469	0.001
FX2	-0.262	0.086	0.348	0.019	-0.507	<0.001	-0.571	<0.001	0.413	0.005	0.504	<0.001
SP	-0.216	0.159	0.131	0.392	-0.263	0.081	-0.321	0.032	0.099	0.522	0.094	0.543

ROI	Wechsler Immediate		Wechsler Delayed		Trail Making Test - Part A		Trail Making Test - Part B		PAL Total Stages		PAL Total Trials	
	Corr	p-value	Corr	p-value	Corr	p-value	Corr	p-value	Corr	p-value	Corr	p-value
CP	0.145	0.342	0.193	0.205	-0.180	0.237	-0.154	0.311	0.136	0.374	-0.296	0.048
CG1	0.232	0.126	0.046	0.765	-0.221	0.144	-0.100	0.512	0.264	0.079	-0.149	0.328
CG2	0.002	0.988	-0.050	0.743	0.055	0.718	-0.015	0.921	0.123	0.420	-0.091	0.552
CG3	0.013	0.930	0.045	0.772	0.195	0.199	0.073	0.632	0.147	0.334	-0.151	0.323
CG4	0.333	0.026	0.347	0.020	-0.235	0.120	-0.343	0.021	0.471	0.001	-0.461	0.001
FX1	0.160	0.293	0.226	0.135	-0.149	0.328	-0.230	0.129	0.264	0.079	-0.150	0.326
FX2	0.215	0.155	0.344	0.021	-0.131	0.393	-0.282	0.060	0.315	0.035	-0.185	0.224
SP	0.052	0.733	0.112	0.465	-0.166	0.276	-0.152	0.318	-0.062	0.684	-0.062	0.684

All analyses control for baseline age, education, and area of the ROI

Bolded values indicate significance at the p<0.05 level.