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ORIGINAL ARTICLE

Full diffusion characterization implicates regionally disparate neuropathology in Mild Cognitive Impairment

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Abstract Diffusion tensor imaging (DTI) is used to detect tissue pathology. In Alzheimer's disease (AD) research, DTI has been used to elucidate differences in disease stages and to track progression over time and clinical severity. Many of these studies have identified the fornix as particularly vulnerable in the early stages of pathology associated with memory decline in prodromal AD. Emerging research suggests principal tensor components, axial (DA) and radial (DR) diffusivity, are more sensitive to underlying tissue pathology than are mean diffusivity (MD) and fractional anisotropy (FA). Given the established regionally specific tissue decline in MCI, we examined components of the full diffusion tensor (MD, FA, DR, and DA) for sensitivity to regional pathology associated with specific memory deficits in 18 individuals with MCI. We investigated multiple regions of interest, including fornix, temporal stem, and control regions for association with severity of impairment on multiple memory measures, including a type of neuropsychological task shown to be particularly sensitive to early memory decline in MCI. Better paired associate learning was selectively associated with lower DA ($\beta = -0.663$, $p = 0.003$), but not with DR, MD, or FA of the temporal stems. Conversely, better paired associate learning was associated with lower DR ($\beta = -0.523$, $p = 0.026$), higher FA ($\beta = 0.498$, $p = 0.036$), and lower MD ($\beta = -0.513$, $p = 0.030$), but not DA in the fornix. No association was found for control regions, or for control cognitive measures. These findings suggest disparate pathology of temporal stems and fornix white matter in association with early memory impairment in MCI. Further, they highlight the methodological importance of evaluating the full tensor, rather than only summative metrics in research using DTI.

Keywords Mild Cognitive Impairment · Alzheimer's disease · Associative learning · Diffusion tensor imaging · Fornix · Radial diffusivity

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Background

Diffusion tensor imaging (DTI) is increasingly becoming common in evaluation of in vivo white matter (WM) integrity and the rapid increase in its use has yielded important neuropathological information. As applied to Mild Cognitive Impairment (MCI), a clinical condition representing increased risk for Alzheimer's disease (AD), DTI has revealed early and progressive loss of integrity of WM that is temporally antecedent to overt clinical evaluation (Braskie et al. 2011; Gold et al. 2010; Oishi et al. 2012).

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The majority of DTI studies in MCI and AD populations have utilized summative metrics of diffusivity, fractional anisotropy (FA), and mean diffusivity (MD). Such studies have demonstrated loss of integrity of temporal lobes (Balthazar et al. 2009) and more extensive damage in AD relative to MCI (Balthazar et al. 2009; Duara et al. 2008). Decreased integrity of the splenium (posterior region) of the corpus callosum (PCC) also has been observed in MCI (Wang et al. 2009) and AD (Balthazar et al. 2009; Chen et al. 2009). Regions that appear to be spared in MCI and AD, or to become involved only very late in the disease process are the primary sensory and motor cortices (Whitwell et al. 2008; Yakushev et al. 2008) and corresponding corticospinal tracts (Kiuchi et al. 2009) as well as the cerebellum (Yakushev et al. 2008). Attention has been paid relatively recently to fiber tracts of the limbic system, specifically the fornix, in research related to MCI and AD pathogenesis. As summarized in Table 1, neuroimaging studies have found reduced integrity (increased MD, DR, DA, and decreased FA) of the fornix to be associated with progressive loss of integrity in MCI and/or AD (Acosta-Cabronero et al. 2010; Copenhaver et al. 2006; Huang et al. 2012; Mielke et al. 2009; Oishi et al. 2012; Wang et al. 2012; Sexton et al. 2010) and in pre-clinical familial AD (Gold et al. 2010), providing compelling evidence for involvement of fornix WM in the early cognitive decline seen in MCI.

While studies employing summative metrics (mean diffusivity and fractional anisotropy) are useful in characterizing the in vivo profile of neurodegeneration associated with MCI and AD pathology, emerging evidence suggests that component analysis of the diffusion tensor parallel to (axial or DA) and perpendicular to (radial or DR) the principal diffusion direction provides additional insight into underlying pathology. These measures are reflective of neuronal and myelin dysfunction, respectively (Kim et al. 2006; Kinoshita et al. 1999; Schmierer et al. 2008; Song et al. 2002, 2003). While MD and FA describe the size and shape of a diffusion ellipsoid, DA describes the diffusivity along the long axis of the ellipsoid, and DR describes the diffusivity along the short axes, a mean of the two radial vectors (Fig. 1b). As such, these measures provide a more specific description of diffusivity and may give a more accurate picture of the pathology present in a given tissue. Myelin abnormalities in mice lacking myelin basic protein are associated with increased DR in the absence of neuronal dysfunction and DA effects (Song et al. 2002). DA is selectively independent of myelin content (Schmierer et al. 2008) and lower DA has been associated with neuronal dysfunction (Kinoshita et al. 1999), strongly implicating diffusivity along the long axis to be impacted by neuronal, as opposed to myelin pathology.

Neuropsychological tests of episodic memory are noted to be particularly sensitive to identifying cognitive deficits in individuals with MCI who ultimately progress to AD diagnosis (Albert et al. 2011). Verbal list learning and verbal associative learning measures, both of which probe episodic memory, have been shown to be sensitive to cognitive decline in AD (Fowler et al. 1995, 2002). However, there is evidence that the cognitive demands of these tasks are distinct and that they elicit different activity in structures of the medial temporal lobes. Associative learning depends critically upon the hippocampi and parahippocampal structures to a much greater extent than list learning or priming of semantically related word pairs (Chua et al. 2007; Petrella et al. 2007; Staresina and Davachi 2006; Weintrob et al. 2007; Weniger et al. 2004). Notably, reduced hippocampal activity during associative learning has been found in AD patients (Sperling et al. 2003), which is consistent with the involvement of medial temporal lobe structures in mediating associative learning, and the recognized atrophy of these structures in AD pathobiology. Together, these findings reinforce the sensitivity of associative learning tests to the neuropathology observed in MCI and AD, and this sensitivity makes such tasks well suited for identification of individuals at increased risk of progressive neurodegeneration.

While clinical classification of individuals with MCI provides a means for identifying those at an increased risk for progression, not all persons with MCI progress to AD (Mitchell and Shiri-Feshki 2009). The joint use of neuroimaging and clinical evaluation, therefore, may lead to better prediction of progression to AD. Motivated by emerging evidence of fornix, and established temporal lobe involvement in MCI and early AD pathogenesis, we sought to identify the sensitivity of summative (FA, MD) and component (DA, DR) metrics in detecting possible underlying tissue pathology in these and other ROIs in individuals with MCI. Based on the number of DTI studies which have identified the fornix as uniquely associated with both early MCI pathology relative to age-matched controls and associated with cognitive decline in MCI (Table 1), we focused on identifying the regional white matter profiles associated with specific memory decrements in a cohort of MCI subjects. Specifically, we evaluated these metrics in each ROI with respect to their association with a paired associate learning task expected to be particularly sensitive to the early functional decline in MCI and AD, as well as other commonly used clinical measures of memory performance. We hypothesized that component measures would provide more specific evaluation of tissue diffusivity than summative metrics, relative to specific neurocognitive performance in individuals with MCI. The ultimate aim of this work is to inform research

Table 1 Summary literature review of DTI-based studies in AD or MCI finding specific effects in the fornix

Groups	*N*	DTI measure (s)	Study design	Fornix-specific findings	Citation
AD, C	38	FA, MD, DA, DR	Cross-sectional	AD relative to control: ↑MD, ↓FA, ↑DA, ↑DR	Acosta-Cabronero et al. 2010
AD, MCI, C	53	FA, MD, DA, DR	Cross-sectional	AD relative to control: ↑MD, ↓FA; non-specific ↑DA, ↑DR	Agosta et al. 2011
AD, MCI, C	61	FA, MD, DA, DR	Cross-sectional	AD relative to control: ↑MD, ↓FA, ↑DR	Huang et al. 2012
AD, MCI, C	75	FA	Longitudinal at 3 months	AD relative to MCI at baseline: ↓FA AD relative to MCI at 3 mo: no difference in FA correlated to clinical cognitive scores; fornix FA selectively unstable over 3 months	Mielke et al. 2009
AD, MCI, C	72	FA	Longitudinal at 1, 3 years	AD relative to MCI: ↓FA; FA predicted conversion from C to MCI and from MCI to AD	Oishi et al. 2012
AD, MCI, C	59	FA, MD, DA, DR	Cross-sectional	AD relative to control: ↑MD in all regions *except* fornix and IFF; ↓FA in fornix only; ↑DA in all regions *except* fornix and cingulum; ↑DR in fornix and ILF only	Pievani et al. 2010
AD, MCI, C	23	FA, MD, DA, DR	Cross-sectional	DR, DA, FA, MD in fornix associated with episodic memory performance	Sexton et al. 2010
Preclinical, presympomatic genetic risk (PS1 or APP) carriers versus non-carriers	35	FA	Cross-sectional	Carriers relative to non-carriers: ↓FA in preclinical and presymptomatic groups; FA predictive of mutation status	Ringman et al. 2007
Presympomatic genetic risk (CLU) carriers versus non-carriers	398	FA	Cross-sectional	Carriers relative to non-carriers: ↓FA	Braskie et al. 2011
Presymptomatic genetic risk (family history and APOE4 status) versus low risk (neither)	57	FA, MD, DA, DR	Cross-sectional	Carriers relative to non-carriers: ↓FA, no specific findings for DR, DA.	Gold et al. 2010

IFF inferior fronto-occipital fasciculus, *ILF* inferior longitudinal fasciculus, *AD* Alzheimer's disease, *C* control, *FA* fractional anisortropy, *MD* mean diffusivity, *DR* radial diffusivity, *DA* axial diffusivity

into a biomarker of progressive MCI, and ultimately of very early AD status, with the long-term goal of guiding early intervention.

Methods

Participants

Study procedures were approved by the Medical Institutional Review Board of the University of Cincinnati and written informed consent was obtained from all study participants. Participants were recruited from the greater Cincinnati/Northern Kentucky region with print advertising. Screening of prospective participants included a number of instruments. The Academic and Medical History Questionnaire (Busch et al. 2005) provided a means of gathering self-reported information on academic achievement, medical history, medication, supplement, and substance use. Exclusionary conditions included diabetes, liver or kidney disease, substance abuse disorder, diagnosis of a psychiatric or neurological condition which could impact cognitive performance or neural integrity, current use of medications that might affect clinical measures (e.g., benzodiazepines), or individuals with contraindication to high-field MRI (e.g., metallic objects in body, claustrophobia). Our data were acquired on a 4 Tesla dedicated research scanner, and standard clinical images, such as those obtained with FLAIR sequence, were not acquired. We, therefore, cannot comment on the clinical (radiologic) profile of our participants.

Enrolled participants met diagnostic criteria for MCI as determined by the Clinical Dementia Rating (CDR) (Morris 1993), which assesses six domains of functioning; memory, orientation, judgment/problem solving, community affairs, hobbies, and personal care. CDR assessment

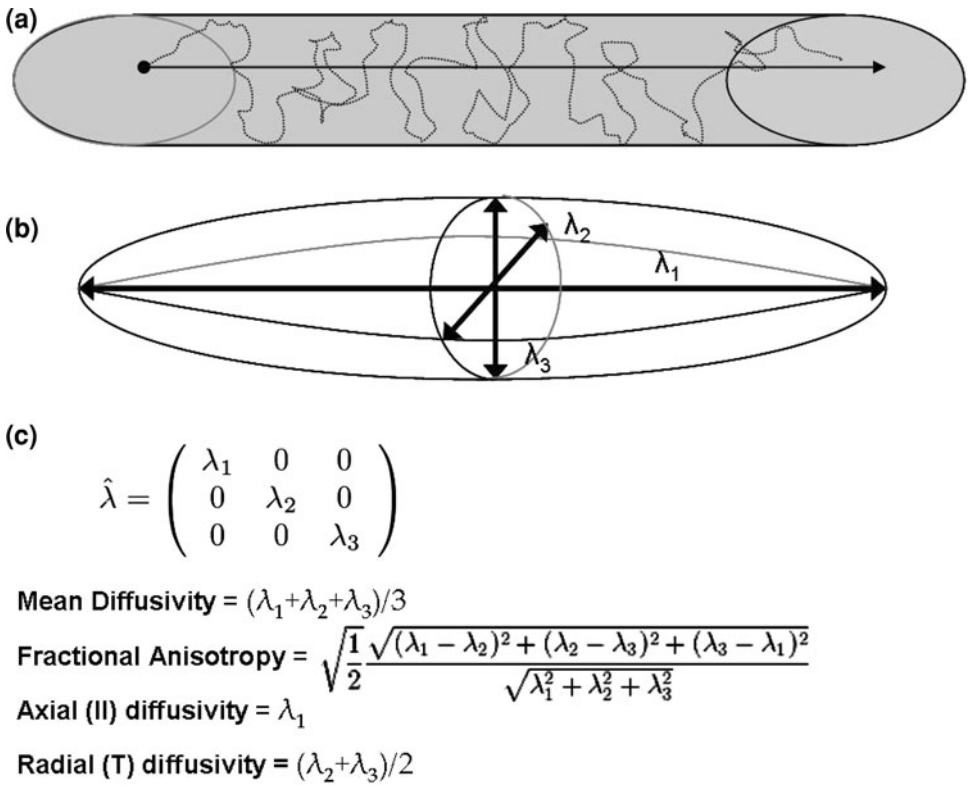

Fig. 1 Diffusion tensor imaging. When bound by micro- or macro-anatomic features, water particles move anisotropicaly, with a net (vector) direction along the long axis of a fiber bundle (**a**). Characterization of diffusivity in this context is described by the principal vector directions of an ellipse (**b**, **c**). Deconvolution and subsequent computation of vectors allows isolation of multiple characteristic indices, including mean diffusivity, which is the average of the three principal vector directions, fractional anisotropy, which describes the directionality of movement, and axial and radial diffusivity, which describe the diffusivity along the long and short axes, respectively

was determined with the use of a structured clinical examination that includes information obtained from an informant about the prospective participant. All enrolled participants were classified as having memory decline but not dementia (CDR global score equal to 0.5). We did not specifically distinguish amnestic (aMCI) versus multi-domain MCI in this study. However, all of our enrolled subjects meet the criteria for aMCI as they were classified as having MCI based on a predominant memory decline, as determined by the CDR and objective memory testing, showed relative preservation of overall cognitive ability and capability for independent functioning, and their memory decline was corroborated by an informant. These are in keeping with the criteria outlined in the diagnostic criteria for aMCI (Petersen 2004). This is of particular relevance, as individuals with chiefly memory complaints have a greater propensity to progressive decline than are those with multi-domain or non-memory-domain MCI (Petersen et al. 1999). Further, prospective participants were screened using a brief measure of general intellectual function, the Montreal Cognitive Assessment (MoCA), as corroborative evidence of MCI status (>26) (Nasreddine et al. 2005). To avoid possible confound of memory performance by mood, the full 30-item version of the Geriatric Depression Scale (Yesavage 1988), was administered and individuals with scores indicative of a possible depressive disorder (>16) were excluded from the study and referred for evaluation and treatment.

Neurocognitive testing

Tests of episodic memory which have been demonstrated to identify age-related memory decline were principal neurocognitive assessments. The Verbal Paired Associate Learning Test (V-PAL) has been used in non-clinical standardization studies (Krikorian 1996) in clinical research across the lifespan (Krikorian 2006) and in intervention studies with MCI participants (Krikorian et al. 2010). The task consists of four learning/testing trials in which participants are asked to learn ten word pairs including five semantically related, or easy associates (e.g., "north–south"), and five semantically unrelated, or hard associates (e.g., "village-copy"). Exposure to the easy associates involves priming existing semantic relationships to facilitate their recall, while learning the semantically unrelated hard associates requires new learning. We also administered The California Verbal Learning Test-II (CVLT-II) (Delis et al. 2000), a list learning task consisting of presentation of 16 common words over five learning and testing trials. The total number of words recalled during the five trials served as the outcome measure for the CVLT and this score paralleled the V-PAL cumulative learning scores.

Magnetic resonance imaging data

Brain imaging data were acquired within a few hours of the cognitive testing. All imaging was performed at the

University of Cincinnati Center for Imaging Research (CIR) using a 4.0 Tesla Varian Unity INOVA whole body MRI/MRS system (Varian Inc., Palo Alto, CA). Padding was inserted around each participant's head to minimize movement. A high-resolution, T1-weighted 3-D brain scan was obtained using a modified driven equilibrium Fourier transform sequence (TMD = 1.1 s, TR = 13 ms, TE = 6 ms, FOV = 25.6 × 19.2 × 19.2 cm, matrix 256 × 192 × 96 pixels, flip angle = 20°) (Lee et al. 1995). Diffusion-weighted spin-echo echo planar-images were acquired using a 30-direction diffusion-encoding scheme with six non-diffusion-weighted (B0) images (Jones et al. 1999). A mid-sagittal localizer scan was obtained to place 30 slices that extend from the inferior cerebellum to encompass the entire brain (TR = 10 s, TE = 96.2 ms, slice thickness = 4 mm, FOV = 25.6 cm × 25.6 cm, flip angle = 90 °, slice orientation = axial, matrix size = 64 × 64, maximum *b* value = 1,000.65). A multi-echo reference scan was obtained and used for reduction of Nyquist ghosting and geometric distortion correction (Schmithorst et al. 2001).

Raw scanner data were reconstructed and converted to AFNI (Analysis of Functional NeuroImages: Cox 1996) format using in-house software developed in Interactive Data Language. DTI data were co-registered using scanner coordinates to the high-resolution anatomical scan, visually inspected for accurate co-registration and manually aligned if necessary. Images were motion corrected with a twelve-parameter rigid body transformation and mutual information cost function (Cox and Jesmanowicz 1999). Anisotropy measures were calculated in AFNI via the 3dDWItoDT and 3dDTeig programs.

Regions of interest (ROIs)

A region of interest (ROI) approach was applied because it does not require data to be normalized to a standard space, which may require spatial warping of original data (Friston 1995). For a visual representation of ROI placement, see Fig. 2. Given the small size of the fornix, the warping and resampling process might significantly alter the voxel-wise representation of the fornix. Given its small size and proximity to the ventricular system, the fornix was manually traced for each participant using an established protocol providing specific guidelines on defining the posterior boundary (Copenhaver et al. 2006; Rametti et al. 2009). Briefly, the tract was defined from the anterior commissure to "the point where the crus of the fornix can be seen in its entirety, extending inferior-laterally to connect with the hippocampus" (Rametti et al. 2009). To further specify the fornix region and to exclude voxel contamination from CSF, the high-resolution T1-weighted anatomical data was segmented using MATLAB and SPM5 Unified Segmentation (Friston 1995) software (Wellcome Department of Cognitive Neurology, UK) to classify brain tissue into gray matter, white matter, or CSF compartments. The CSF segmentation results were then used to exclude voxels containing greater than 20 % CSF in each individual's fornix mask (Hetherington et al. 2001). This resulted in possible CSF contamination in the fornix of less than 2 % for all individual datasets. The fornix, particularly when very near to the hippocampal formation (HF), runs close to the stria terminalis, which contains fibers running from multiple regions to the amygdala. The manual tracing methods employed here avoid this region, because tracing does not include to the region that would likely include stria terminalis fibers. This also reduces concern over errant inclusion of gray matter of the hippocampus in the fornix ROI. Mean anisotropy for each region were computed and analyzed, so participant-to-participant variation in ROI volume would not confound analysis.

Positive and negative control ROIs of 4 mm radius spheres were placed in ten additional regions. Negative control regions were placed in tracts serving regions known through independent studies to be spared in MCI and early AD (Kiuchi et al. 2009; Whitwell et al. 2008; Yakushev et al. 2008). This set of regions included the sensorimotor

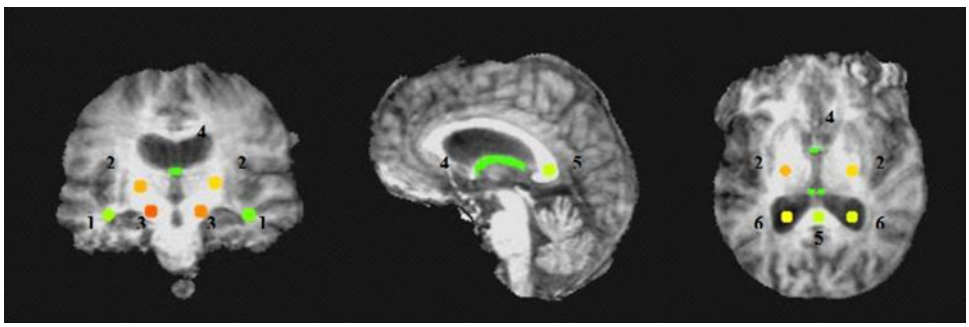

Fig. 2 Regions of interest (ROIs). Manual tracing of the fornix was performed due to its small size and proximity to the ventricles. This and placement of additional 4 mm spherical ROIs was done via a high resolution anatomical scan. Visible in this representative sample are; (1) bilateral temporal stems (TS), (2) bilateral posterior limb of the internal capsule (PLIC), (3) bilateral crus cerebri (CRUS), (4) fornix, (5) splenium of the corpus callosum (PCC), and (6) bilateral lateral ventricle (VENT)

tracts, sampled bilaterally in the posterior limb of the internal capsule (PLIC) and the crus cerebri (CRUS). PLIC ROIs were placed lateral to the thalamus and medial to the lateral globus pallidus and putamen. CRUS regions were placed in the medial third of the crus cerebri (through which the corticospinal tracts run) at the axial level of the inferior boundary of the superior colliculus. The CRUS sphere was placed at the edge of the midbrain to avoid inclusion of the substantia nigra. Additional negative control regions were placed medial to the branching points of the middle cerebellar peduncles (PED), anterior to the anterior border of the fourth ventricle, in a slice in which the superior cerebellar peduncle was visible in the coronal view.

Putative positive control regions included white matter of the temporal stems (TS) given their established involvement in the early stages of MCI and AD, as was discussed. ROI placement in the TS was based on methods previously described (Kier et al. 2004). We used established anatomical landmarks described as "the level of the amygdala anteriorly to the level of the lateral geniculate body posteriorly" (Taoka et al. 2005) with preferential placement in the more anterior segment to avoid the optic radiations.

While there is evidence that the splenium of the corpus callosum is also compromised in MCI and AD (Chen et al. 2009), we considered it as an additional investigative region given the incomplete evidence of its involvement in AD pathobiology and the complexity of its connections. As part of the large commissural fibers in the corpus callosum, the splenium supplies inter-hemisphere connections between the temporal and occipital lobes, the most dorsal of which sweeps lateral to the striatum to meet the dorsal and lateral temporal lobes and the occipital lobes. We placed this ROI in the most posterior portion (PCC) as observed in the mid-sagittal slice.

Absolute positive control ROIs were placed in each of the lateral ventricles (VENT). These regions will have the lowest FA in the brain and the highest MD, per DTI theory, given the absence of fibers in this region and unrestricted space through which water can easily diffuse in all directions. All ROIs were placed by a single rater blind to neurocognitive test performance. To determine reliability of our tracing, ten participant datasets were randomly sampled and traced by a second rater. Pearson correlations of FA and MD values between the two raters showed significant similarity between tracers ($\beta = 0.820$, $p = 0.004$ (two-tail) and $\beta = 0.718$, $p = 0.019$, respectively).

Statistical approach

Lateralized differences of bilateral homologue ROIs (TS, VENT, PLIC, CRUS, PED) were evaluated with paired samples t tests. No significant difference in MD or FA was observed between homologue regions, and bilateral ROIs were collapsed for subsequent analyses. For DR, no significant difference was observed between homologue regions so bilateral ROIs were collapsed for DR. The PLIC were statistically different ($p = 0.03$) for DA, so all but PLIC DA were collapsed for subsequent analyses. Comparisons of ROIs across anatomical regions were made using paired t tests with Bonferroni correction for multiple comparisons. Correlations of DA and DR with neurocognitive and demographic variables were derived from simple, separate linear regression analyses. Effects of age were explored as a possible confounding variable. Statistical analyses were performed in SPSS (SPSS, 2001).

Results

Imaging data were acquired from 19 participants, and one dataset was excluded due to poor data quality (excessive distortion). The final sample included 18 participants (13 female, 13 Caucasian, 5 African American) with mean age of 73 years (SD 5.5 years) and mean years of education of 14.4 (SD 2.4 years). MoCA scores were in the range expected for MCI participants (mean 23.1, SD 2.0). Although we were sensitive to the possible confound of depressive symptoms in the cognitive performance of our subjects, the depressive symptoms of this study sample were low (mean 4.9, SD 2.9), mitigating our concern over this possible confound. Relative to participants ($N = 20$) of similar age (mean 72.1 years) and education (mean 15.5 years) with age-associated memory decline in a separate study (although at time of publication without neuroimaging data), participants' hard associate cumulative score on the V-PAL was much lower (10.3, SD 4.7 vs. 5.9, SD 4.8 out of 20 possible points). Performance on the CVLT-II Cumulative Learning was below average for female (41 vs. T score 49) and male (42 vs. T score 56) participants.

ROI comparisons

All mention of significance across ROIs is $p < 0.007$ Bonferroni corrected for multiple comparisons. Figure 3 contains graphical representations of mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (DR), and axial diffusivity (DA) values by region. The ventricles (positive control regions) had significantly lower FA and higher MD, DR, and DA than all tracts, indicating reliability of the method.

Fornix and other ROIs

The fornix had significantly lower FA and higher MD, DR, and DA than all regions, including negative control regions of sensorimotor tracts (CRUS, PLIC, and PED) and TS.

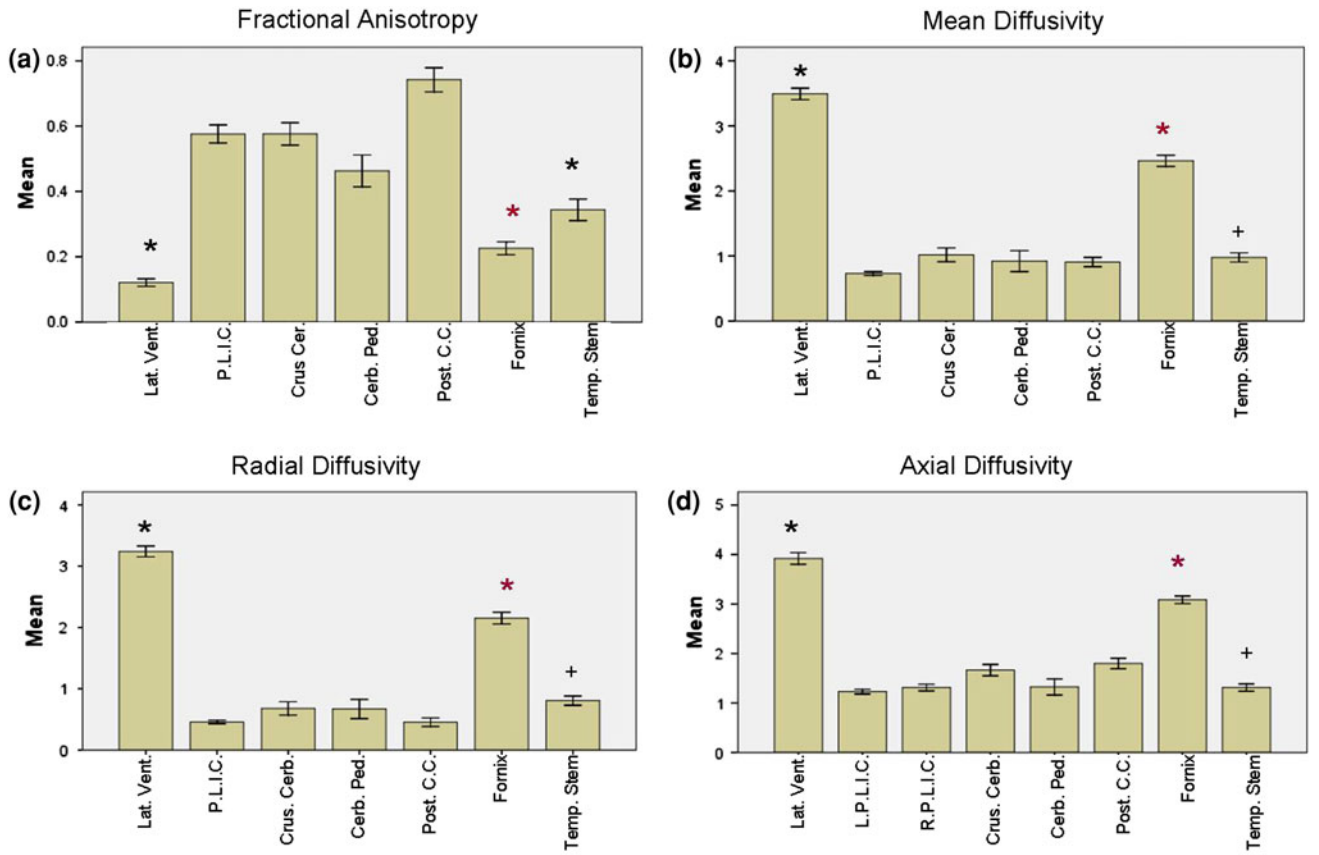

Fig. 3 Relationship between ROI diffusivity. Ventricles had lower FA (**a**), and higher MD (**b**), DR (**c**) and DA (**d**) than all WM ROIs, showing reliability of methods. Fornix had lower FA (**a**), and higher MD (**b**), DR (**c**), and DA (**d**), than all other WM ROIs, including the TS, regions known to be early and severely affected in MCI. TS had mixed relationships to control (sensorimotor) tracts; lower FA (**a**) but not higher MD, DR, or DA than all sensorimotor tracts, as indicated by *plus symbol*. For specific relationships, see text. *$p < 0.007$, paired t tests Bonferroni corrected for multiple comparisons. *Error lines* ± SE 2

Temporal stem (TS) and other regions

TS diffusivity demonstrated a mixed relationship to the sensorimotor and cerebellar tracts, such that TS FA was lower than that observed for the PLIC and CRUS, but not the PED, and TS MD was higher than all white matter tracts except the PLIC. TS had significantly lower DA than CRUS, but not PLIC or PED, and significantly higher DR than PLIC but not CRUS or PED.

Posterior corpus callosum (PCC) and other regions

PCC FA was higher than the TS, but MD was not dissimilar to the TS. The PCC had significantly lower DA and DR than the fornix and VENT and significantly higher DR and lower DA than the TS. Mixed relationships between PCC and sensorimotor regions were found; the PCC had significantly higher DA than the PLIC and PED, but not CRUS. DR of the PCC was significantly lower than CRUS but not PLIC or PED.

Evaluation of regions of interest (ROIs) with neuropsychological data

The relationships between neuropsychological tests and diffusivity in ROIs demonstrated the functional significance to the above findings. Standardized β coefficients are reported. In looking only at summative metrics (fractional anisotropy [FA] and mean diffusivity [MD]), we found evidence of specific fornix involvement in paired associate learning. Among demographic and neuropsychological variables evaluated, including multiple memory measures (CDR, MoCA, V-PAL, CVLT-II cumulative learning), only age (FA $\beta = -0.577$, $p = 0.012$, MD $\beta = 0.677$, $p = 0.002$) and V-PAL performance (FA $\beta = 0.498$, $p = 0.036$, MD $\beta = -0.513$, $p = 0.030$) were significantly associated with fornix MD or FA. As the integrity of the participants' fornix declined, i.e. as FA decreased and MD increased, so did performance on this task (Table 2, columns 1–4). These associations remained significant even after controlling for the effects of age via Pearson partial correlation analyses (FA

$r = -0.412$, $p = 0.050$, MD $r = 0.434$ $p = 0.041$, 1-tail). While there was an association found between fornix and PCC MD and performance on the easy associates of the V-PAL (Table 2), these relationships were no longer significant after controlling for the effects of age. There was no significant relationship between TS FA or MD and performance on the V-PAL hard items, nor for the easy items on the V-PAL or CVLT-II cumulative learning, nor was there any association between MD or FA of CRUS (control) regions and any of these memory measures (Table 2).

In evaluation of component measures (DR, DA) we found disparate relationships between fornix and TS, a profile which was different than observed for MD and FA. Better learning on the V-PAL hard associates was associated with low fornix DR ($\beta = -0.523$, $p = 0.026$) but not fornix DA (Table 2, columns 5–8). Conversely, better performance on the V-PAL hard associates was associated with lower TS DA ($\beta = -0.663$, $p = 0.003$), but not with TS DR. These relationships remained significant in Pearson partial correlations controlling for the effect of age (fornix DR $r = -0.451$, $p = 0.035$, TS DA $r = -0.632$ $p = 0.003$, 1-tail). No significant relationship was found between V-PAL hard associate performance and DA or DR in the PCC or the CRUS. Relationships between easy items on the V-PAL were significant for DA of the fornix ($\beta = -0.523$, $p = 0.026$) and DR of the PCC ($\beta = -0.479$, $p = 0.044$) only, although in Pearson partial correlation analyses, these relationships were no longer significant after controlling for the effects of age. No significant association was found between fornix, TS, PCC, or CRUS diffusivity (DA or DR) and the cumulative learning performance on the CVLT-II (Table 2).

After controlling for the effects of age in these data, the diffusion profile of the fornix and TS showed inverse relationships to paired associate learning, specifically. Fornix MD, FA, and DR, but not DA, are associated with V-PAL performance, while TS DA, but not MD, FA, or DR was associated with new learning (Table 2; Fig. 4).

Discussion

Spurred by existing evidence of the role of afferent and efferent tracts of the HF, specifically the fornix, in MCI and AD pathobiology (Table 1), we investigated the sensitivity of the full diffusion tensor in these and control ROIs to specific memory decrements known to be associated with MCI. We evaluated diffusivity in these regions and performance on a neurocognitive measure known (1) to be sensitive to early decline in AD and MCI, (2) to recruit integrated parahippocamal activity, and (3) to require new learning. We employed the most commonly used metrics of DTI methodology, mean diffusivity (MD), and fractional anisotropy (FA), which describe the magnitude and directionality, respectively, of diffusivity in the tissue, as well as component measures, radial and axial diffusivity (DR and DA), which describe the diffusivity across and along the principal diffusion direction, respectively.

Our findings of increased DR and MD, and decreased FA in the fornix relative to other ROIs in individuals with MCI (Fig. 3) are consistent with those of other studies which also found similar diffusivity profiles to reflect ongoing structural degradation with progressing disease status (Acosta-Cabronero et al. 2010; Copenhaver et al. 2006; Huang et al. 2012; Mielke et al. 2009; Oishi et al. 2012; Wang et al. 2012; Sexton et al. 2010). In addition, our findings suggest that (1) in the MCI brain, memory decrements are associated with disparate pathology in the fornix and temporal stem and (2) these effects are only evident in evaluation of the complete diffusion tensor.

These data highlight the utility of investigating the full diffusion tensor, including DR and DA, in studies employing DTI methods. As can be seen in Fig. 4, had our methods employed only summative diffusion metrics (MD, FA), we would have found associations between paired associative learning performance (a proxy for medial temporal lobe malfunction) and fornix diffusivity, but not TS diffusivity. These data would have implicated fornix pathology and explicitly excluded TS pathology in the specific memory decrements observed in MCI. However, in employing DR and DA in our analyses, rather than excluding TS white matter in a proposed mechanism, we found evidence of (1) significant involvement of the TS and (2) disparate diffusion profile of TS and fornix in MCI. Specifically, tensor component analyses revealed a relationship between V-PAL performance and MD, FA, and DR, but not MD (Fig. 4 a, b, c, d), a diffusion profile consistent with myelin pathology (Beaulieu, 2002; Song et al. 2002, 2003), while the inverse was found for TS (Fig. 4 e, f, g, h), consistent with neuronal pathology (Kinoshita et al. 1999).

Together, these data raise intriguing questions about the mechanism(s) underlying our observations. Specifically, are changes in white matter, especially the fornix, which is of particular interest, primary or secondary in AD pathology? Specifically, is there a principal pathology of cortical (cell body) regions, resulting in Wallerian-like degeneration of tracts serving the area, or does loss of input to target structures (from the loss of integrity of white matter serving the regions) lead to atrophy of the target regions? Or, perhaps there are multiple biological processes co-occurring in the MCI brain that independently target myelin and neurons that synergistically contribute to the diffusivity profile in our and other datasets (reduced FA, increased MD, and increased DR). While DTI is an indirect measure of pathology, our data are consistent with the following, which suggest possible pathological mechanisms.

Table 2 Correlation of diffusivity and selected learning measures

	MD		FA		DA		DR	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*
V-PAL HT								
Fornix	*−0.513*	*0.030*	*0.498*	*0.036*	−0.389	0.110	*−0.523*	*0.026*
TS	0.363	0.138	−0.341	0.166	*−0.663*	*0.003*	−0.227	0.365
PCC	−0.382	0.117	0.498	0.035	−0.430	0.075	−0.357	0.146
CRUS	0.320	1.351	−0.113	0.655	0.192	0.446	0.232	0.354
V-PAL ET								
Fornix	−0.468	0.050	0.151	0.551	−0.523	0.026	−0.41	0.091
TS	−0.098	0.700	−0.363	0.139	−0.338	0.170	0.012	0.964
PCC	−0.495	0.037	0.457	0.057	−0.431	0.074	−0.479	0.044
CRUS	−0.243	0.332	0.342	0.165	−0.210	0.404	−0.298	0.230
CVLT-II cumulative								
Fornix	−0.102	0.687	0.161	0.524	−0.063	0.805	−0.110	0.663
TS	0.165	0.513	−0.420	0.083	−0.057	0.822	0.255	0.307
PCC	0.209	0.406	0.154	0.543	0.402	0.098	0.010	0.967
CRUS	0.165	0.513	−0.093	0.714	0.169	0.502	0.144	0.568

Investigation of only summative metrics (FA, MD) suggests fornix diffusivity to be selectively associated with new paired associate learning, while TS white matter is not implicated. Further investigation, using component measures (DR, DA) suggests disparate pathology in the fornix and TS may underlie new learning performance, selectively. Of all associations, when controlling for the effects of age, only fornix and TS diffusivity remained significantly correlated (italicized values)

V-PAL Verbal Paired Associates Test, *ET* total of easy items learned, *HT* total of hard items learned, *CVLT* California Verbal Learning Test, *TS* temporal stems, *PCC* posterior region of the corpus callosum, *CRUS* crus cerebri

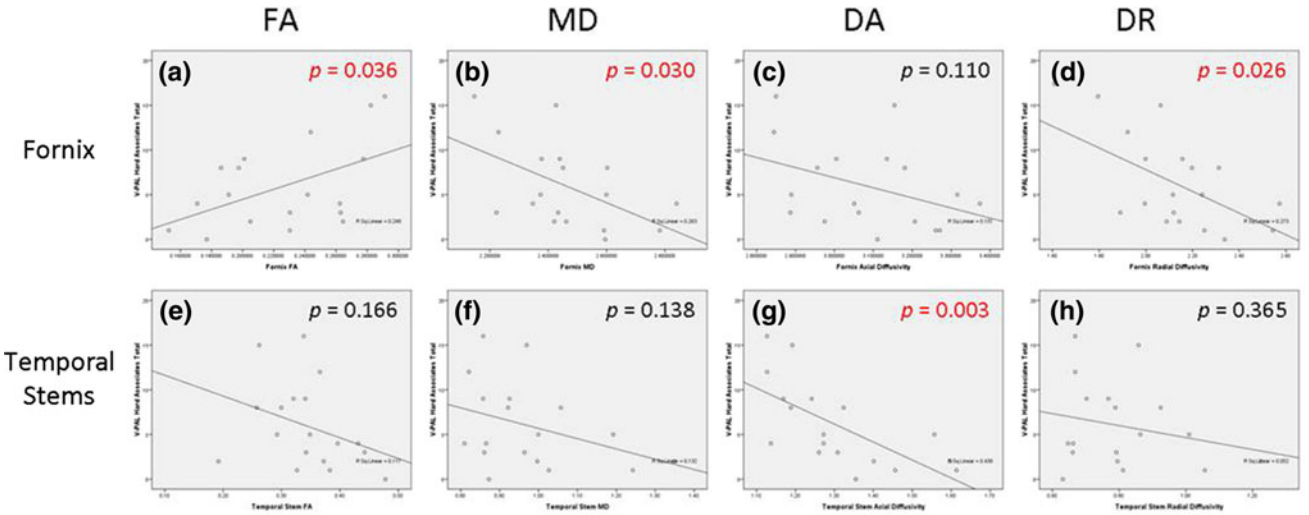

Fig. 4 Correlation of new learning and diffusion metrics of temporal stem and fornix white matter. Although in looking only at mean diffusivity (*MD*) and fractional anisotropy (*FA*), metrics typically used in DTI analysis, suggests involvement only of fornix white matter in new learning, further investigation into component vectors suggests a more intricate relationship. Here, we see that V-PAL performance is associated with low DR (**d**), high *FA* (**a**), and low *MD* (**b**) but not with *DA* (**c**) in the fornix. Conversely, *DA* of the TS is highly correlated to VPAL performance (**g**), while *DR*, *FA*, and *MD* are not (**e**, **f**, **h**). This disparate diffusion profile implicates myelin and neuronal pathology in these regions, respectively

Fornix white matter

Our findings of specific effects of new learning and fornix white matter contribute to a rapidly growing body of recent studies that implicate fornix deterioration in AD and MCI pathology (Acosta-Cabronero et al. 2010; Huang et al. 2012; Mielke et al. 2009; Oishi et al. 2012; Sexton et al. 2010; Braskie et al. 2011; Gold et al. 2010) and link

specific effects of fornix integrity to new learning (Buckley et al. 2008).

Further, our findings of significant correlations of FA, MD, and DR, but not DA with new learning in individuals with MCI, provides a unique perspective on the potential pathological mechanism in the fornix, particularly when contrasted to TS findings. Given that both FA and MD were significantly correlated, as well as DR but not DA, the significant effect of DR appears to be driving the relationship between FA or MD and performance on the V-PAL (see equation, Fig. 1). That is, it is the increased diffusivity across the fiber tracts (DR) that carries most of the effect found for the summative metrics (FA and MD). Recently published works, which include AD and control comparisons, found similar relationships between the fornix and multiple measures of diffusivity. DR differences were found specifically in the fornix in disease states, but not healthy (Huang et al. 2012; Sexton et al. 2010). These studies, in addition to findings of increased DR without concomitant DA changes reflecting myelin-specific abnormalities (Beaulieu 2002; Song et al. 2002, 2003), support the interpretation that our data reflect myelin pathology in the fornix.

A myelin-centric model would suggest that degradation of the medial temporal lobe structures is secondary to degradation of the fornix following loss of structural connectivity and subsequent retrograde degeneration of the soma in the hippocampal formation. A related scenario would be that myelin surrounding the efferent fibers of the hippocampus traveling in the fornix is affected, leading to degeneration of cells originating in the mammillary nuclei and/or septal area. Myelin facilitates neuronal signaling by increasing the conduction velocity of neurons, and compromised fidelity of neocortical signals into the hippocampus would have implications in multiple cognitive processes, including associative learning. Both afferent and efferent functions of the fibers within the fornix contribute to memory performance and reduced fidelity of either function is likely to contribute to the deficits observed in early AD memory performance.

Several observations support a myelin-centric hypothesis. The neuropathological progression of AD lesions is roughly reverse of the developmental myelination pattern (Braak and Braak 1996). Further, a diffusion profile consistent with myelin breakdown is found in individuals with increased genetic risk of AD (Braskie et al. 2011; Gold et al. 2010) and genetic risk factors for late-onset AD code for gene products which are closely tied to lipid transport, particularly cholesterol, a principal membrane component of myelin. In fact, there is a compelling argument of a myelin model of AD, in which canonical AD pathological factors (Aβ and tau) are presented as by-products of homeostatic myelin repair processes (see Bartzokis, 2009, for review).

Temporal stem white matter

The relationship between TS white matter integrity and paired associate learning indicated that as memory performance decreased, DA increased but not FA, MD, or DR in the TS (Fig. 4 e, f, g, h). While there is less empirical evidence of the relationship between DA and AD neuropathology, this finding is consistent with pathological mechanisms involving tau. Tau is found predominately in the axons of intact neurons and is thought to stabilize microtubules and regulate axonal transport (Ittner and Gotz 2011). Under pathological conditions, however, microtubule destabilization is thought to occur, and tau is re-localized in the somatodendritic regions of the neuron (Ittner and Gotz 2011). Axonal swelling can result from a number of pathological conditions, including instances of impaired axonal transport (Yagishita 1978). Such swelling of the axons could increase diffusivity, and if myelin remains intact, DR would not increase to the extent as does DA, because of the hydrophobic nature of myelin blocking diffusion across the short axes. Researchers have found increased DA but unchanged MD or DR in tandem with marked decrease of microtubules and moderate decrease of neurofilaments in the axons myelinated optic nerves in methylmercury treated mice (Kinoshita et al. 1999). In this context, the increased DA, without concomitant association of DR, MD, or FA with impaired learning supports a model of axonal swelling, decreased microtubules, and decreased neurofilaments but stable myelin in the TS white matter.

The implication of neuronal (in contrast to myelin) dysfunction is that such pathology of the TS is antecedent to myelin disruption and that functional loss is, principally, the effect of lost neuronal cell function. This is in keeping with canonical AD pathology, in which TS pathology is observed first and most severely. Accordingly, cortical atrophy of the hippocampus and subsequently of the surrounding medial temporal lobe structures would lead to degeneration of the tract.

Given the substantial evidence of early myelin dysfunction and of neuronal pathology of the temporal lobes in MCI and AD, our data are in agreement with the notion that neuropathology of MCI and AD is heterogeneous. The unique value of these data is the in vivo evidence of loss of integrity and associations with specific neuropsychometric measures, which may enhance the early identification of individuals at risk of progressive neurodegeneration and inform future research. In order to identify the progressive profile of these findings, and to contribute to work identifying a biomarker of very early, progressive neurodegeneration in MCI, it will be important to track the progression of fornix integrity over time and clinical changes in a group of individuals with MCI, particularly in light of data

showing that the fornix, specifically, is unstable over a 3-month period in progressing MCI (Mielke et al. 2009).

Our data suggest early loss of structural connectivity within the medial temporal lobe, as indicated by selective association between new learning deficits and TS DA. Further, white matter pathology (perhaps myelin loss) of the fiber tracts serving these structures, specifically the fornix, is associated with poorer new learning performance. These interpretations are consistent with "disconnection syndrome" (Geshwind 1965), wherein functionally related neuroanatomical areas fail to maintain task utility because of the loss of sufficient structural connectivity. The central posit to this conceptualization is that interconnectivity, specifically as pertains to the hippocampus, parahippocampus, and the fiber tracts serving them, is critical in memory function. The functional implication of this disconnection would be, then, the cognitive deficits associated with early AD pathology. This idea is rapidly gaining recognition in AD and MCI literature (Acosta-Cabronero et al. 2010; Gold et al. 2010; Wang et al. 2012). Our data contribute to this growing body of research supporting the role of specific white matter pathology in the early AD brain.

As part of a longer study scan session, we chose a slice thickness that would allow us to obtain diffusion data across the whole brain, while limiting the amount of time participants spent in the scanner. This sampling parameter was deemed sufficiently large, given (1) existing literature citing average cross-sectional fornix diameter is larger than our sampling (mean 16.4 mm^2) (Ringman et al. 2007) and (2) additional methodological procedures performed to define gray matter/white matter/CSF boundaries. Specifically, in addition to manually tracing the fornix boundaries in each subject dataset, we used published methods to define the posterior boundary (gray/white matter intersection) and further isolated the white matter from CSF using additional masking based on tissue segmentation techniques, as was discussed in the "Methods" section. It is possible that partial volume effects could be present in our data, given the anatomical nature of the fornix being surrounded by CSF. However, concomitant findings of specific memory impairment only in isolated regions strongly reinforce the idea that these findings have pathological significance.

Conclusions

We found that investigation of component diffusion values provides more comprehensive evaluation of possible tissue pathology in DTI studies. Further, we found performance on a task of new learning, specific to the early cognitive decline in MCI, to be disparately associated with TS and fornix diffusivity profiles. These findings replicate and extend previous work suggesting a unique role of the fornix in early MCI pathology and provide new evidence of the relationships among loss of integrity in the temporal stem and the fornix in association with a particular deficit of memory function in MCI. Such data may inform targeted studies of the identification of individuals at risk of progressive decline into AD, with the long-term goal of informing research into prevention or early intervention. From a methodological perspective, these findings also highlight the importance of evaluating multiple measures from the diffusion tensor in DTI data analysis.

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