Disruption of Limbic White Matter Pathways in Mild Cognitive Impairment and Alzheimer's Disease: A DTI/FDG-PET Study

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Abstract: *Background:* Alzheimer's disease (AD) and mild cognitive impairment (MCI) affect the limbic system, causing medial temporal lobe (MTL) atrophy and posterior cingulate cortex (PCC) hypometabolism. Additionally, diffusion tensor imaging (DTI) studies have demonstrated that MCI and AD involve alterations in cerebral white matter (WM) integrity. *Objectives:* To test if (1) patients with MCI and AD exhibit decreases in the integrity of limbic WM pathways; (2) disconnection between PCC and MTL, manifested as disruption of the cingulum bundle, contributes to PCC hypometabolism during incipient AD. *Methods:* We measured fractional anisotropy (FA) and volume of the fornix and cingulum using DTI in 23 individuals with MCI, 21 with mild-to-moderate AD, and 16 normal control (NC) subjects. We also measured PCC metabolism using ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) in AD and MCI patients. *Results:* Fornix FA and volume were reduced in MCI and AD to a similar extent. Descending cingulum FA was reduced in AD while volume was reduced in MCI and even more so in AD. Both FA and volume of the fornix and descending cingulum reliably discriminated between NC and AD. Fornix FA and descending cingulum volume also reliably discriminated between NC and MCI. Only descending cingulum volume reliably discriminated between MCI and AD. In the combined MCI-AD cohort, PCC metabolism directly correlated with both FA and volume of the descending cingulum. *Conclusions:* Disruption of limbic WM pathways is evident during both MCI and AD. Disconnection of the PCC from MTL at the cingulum bundle contributes to PCC hypometabolism during incipient AD. *Hum Brain Mapp* 33:1792–1802, 2012. © 2011 Wiley Periodicals, Inc.

Key words: Alzheimer's disease; mild cognitive impairment; diffusion tensor imaging; FDG-PET; fornix; cingulum bundle; posterior cingulate
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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia among older adults and traditionally conceptualized as a disease of brain gray matter, with particular involvement of the medial temporal lobe (MTL), temporoparietal cortex, and posterior cingulate cortex (PCC). However, studies with diffusion tensor imaging (DTI), an MRI technique that assesses microstructural organization of white matter (WM) based on measurements of water diffusion, have demonstrated that AD also involves alterations in WM integrity. Patients with probable AD have a reduction in the integrity of WM tracts connecting regions of association cortex, such as the splenium of the corpus callosum, superior longitudinal fasciculus, and cingulum bundle, while integrity of the pyramidal tracts (e.g., posterior limb of the internal capsule) is generally preserved [Bozzali et al., 2002; Fellgiebel et al., 2008; Rose et al., 2000]. The likely pathogenic mechanism of these WM changes in AD is Wallerian degeneration of fiber tracts due to neuronal loss in cortical associative areas affected by AD pathology [Bozzali et al., 2002; Braak and Braak, 1996].

DTI has also been extended to study older adults with mild cognitive impairment (MCI), who have an increased risk of developing dementia relative to their healthy counterparts. Fellgiebel et al. [2005] showed that fractional anisotropy (FA), a measure of WM integrity, differed significantly between controls and both MCI and AD patients in regions affected by AD neurodegeneration. They also showed that performance of the MCI-AD group on the delayed verbal recall test was correlated with posterior cingulum bundle FA. Other studies have shown that FA of cingulum fibers are significantly reduced in MCI, and even more so in AD [Choo et al., 2008; Liu et al., 2009; Zhang et al., 2007]. DTI studies of limbic WM in MCI and AD show some discrepancy, however. Kiuchi et al. [2009], using DTI tractography, found decreased FA in the posterior cingulate fasciculus of MCI patients (relative to normal controls) but no difference between MCI and AD groups. In contrast, Mielke et al. [2009], utilizing a region-of-interest (ROI) technique, found FA differences between MCI and AD subjects in a different region of the cingulum and the fornix but no differences between NC and MCI groups in these areas. In general, studies examining limbic FA in the three subject groups (normal controls, MCI and AD) have not been able to demonstrate a three-way distinction; either the normal or MCI groups differed from ADs, but not from each other, or MCI and AD reveal similar changes in FA, different from the controls.

In addition to FA alone, some recent studies have employed multimodal MRI to obtain simultaneous measures of FA and volume. The most common way to do this has been with an ROI-based assessment of FA combined with voxel-based morphometry, as was employed by Walhovd et al. [2009]. This study showed that higher diagnostic accuracy was achieved when multiple methods and ROIs were combined, though morphometry showed the best diagnostic

(predictive) sensitivity. In our study, as in some others [Mielke et al., 2009; Thomas et al., 2008; Zhang et al., 2007], a tract-based approach is used to obtain the volumetric information as well as the mean FA of that volume.

WM degeneration has been proposed as a mechanism for the well-documented functional deficit of the PCC observed on ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) scans, a finding often present during early stages of AD in parallel with MTL atrophy [Minoshima et al., 1997]. This hippocampal-neocortical "disconnection" hypothesis posits that PCC hypometabolism occurring during incipient AD may be due to a distant effect of neuronal dysfunction in the MTL via disconnection at the cingulum bundle, an idea first put forth in the early 1990s [Jobst et al., 1992] with more recent imaging support from FDG-PET [Nestor et al., 2003] and combined FDG-PET/MRI studies [Chételat et al., 2008; Meguro et al., 2001; Villain et al., 2008]. Consistent with this hypothesis, Zhou et al. [2008] used DTI and fMRI to show that there is decreased structural connectivity from both the PCC and hippocampus to the whole brain as well as a reduction in functional connectivity between these two regions in MCI and AD. Few studies, however, have tested the "disconnection" hypothesis directly.

The present study was designed to (1) address the discrepancies from prior DTI studies of limbic WM in MCI and AD; and (2) directly test the "disconnection" hypothesis of PCC hypometabolism via a combined structural-functional approach. Specifically, we hypothesized that patients with both MCI and AD should exhibit decreases in the integrity of limbic WM pathways, reflective of the neuronal dysfunction and atrophy in the MTL. We used DTI to investigate changes in FA and volume of the fornix and cingulum on a continuum from normal aging to MCI to AD. We also investigated the relationship between integrity of the cingulum bundle and PCC hypometabolism with combined DTI and FDG-PET.

METHODS

Participants

MCI and AD subjects were recruited from the Cognitive Disorders Clinic at Michigan State University between 2005 and 2007. Healthy senior participants were recruited from a database of individuals who volunteered to participate in response to fliers and paid advertisements in the

TABLE I. Subject demographic information and MMSE scores

	NC	MCI	AD
Age	65.9 (8.5)	70.8 (7.9)	71.6 (10.6)
Gender (M/F)	6/10	12/11	6/15
Education (years)	16.0 (3.3)	15.6 (3.2)	14.3 (3.3)
MMSE score	29.5 (0.7)	26.8 (2.5)	22.0 (4.5)

Lansing, Michigan community. They were selected based on demographics in order to match the MCI and AD subjects for age, gender, and educational attainment. The final group consisted of 23 patients with MCI, 21 patients with mild to moderate probable AD and 16 normal controls (NC). Table I shows demographic information and Mini Mental State Examination (MMSE) scores [Folstein et al., 1975] for the three subject groups.

Patients from the Cognitive Disorders Clinic underwent a standardized assessment for dementia. Based on results of this evaluation, all patients were classified according to NINCDS-ADRDA criteria for the clinical diagnosis of probable AD [McKhann et al., 1984; Tierney et al., 1988], and Petersen's modified criteria for the diagnosis of MCI [Petersen, 2004]. Exclusion criteria included a history of loss of consciousness for >10 minutes, stroke, psychosis, bipolar disorder, alcoholism, or substance abuse. For healthy seniors, any neurologic disease was considered exclusionary; for MCI and AD subjects, neurologic comorbidities were exclusionary. For all subjects, a history of depression was acceptable only if the condition was currently in remission, with or without medication. Medications, including cholinesterase inhibitors, were permitted. All subjects or their authorized legal guardians provided written informed consent. The procedures in the present study were approved by the Michigan State University Committee on Research Involving Human Subjects.

Image Acquisition

All subjects underwent DTI scans. FDG-PET scans were administered only to MCI and AD patients, for whom the imaging was justified on clinical grounds, but not normal control subjects to avoid unnecessary exposure to the radioactive tracer. Imaging was conducted according to the following protocol.

DTI

General Electric Signa Excite 3 Tesla scanner was used for data acquisition. For each scan (scan time = 4 min 50 s), 40 axial slices were collected using a spin echo EPI pulse sequence with TE = 69.3 ms, TR = 10,000 ms, in-plane resolution = 3 mm, slice thickness = 3 mm, interslice gap = 0 mm, 240 mm FOV (80 × 80 matrix), and NEX = 4. Diffusion encoding was accomplished in six non-collinear directions with b-value of 1,000 s mm⁻². DTI images were interpolated on the scanner to a voxel size of 0.9375 × 0.9375 × 3 mm³.

FDG-PET

General Electric Discovery STE scanner was used for data acquisition. Images were acquired following 10 mCi injection of FDG-PET and 30-minutes uptake time using 3D acquisition over 9 min in three 3-minutes dynamic frames. CT attenuation correction was used.

Data Processing

DTI

After transferring raw DTI data to a separate computer workstation, they were interpolated to an isotropic voxel size of 1.5 mm³ using tools from the FMRIB Software Library [Smith et al., 2004]; during this step, DTI data were also converted from the native DICOM format to ANALYZE format. Data were further processed using MRI Studio (www.mristudio.org) [Jiang et al., 2006] to calculate whole-brain diffusion tensor and FA maps for subsequent fiber tracking. The 3D reconstructions of the fornix, cingulum bundle, its associated parietal projection fibers, and posterior limb of the internal capsule (a control region) were accomplished by using computational tractography algorithms implemented in MRI Studio. For each tract, multiple 2D region of interest (ROI) "seeds," selected based on *a priori* knowledge of tract anatomy, were placed on DTI maps created within MRI Studio (Fig. 1a-c); an FA "colormap," indicating fiber orientation, aided in the placement of ROI seeds. Fibers were then tracked voxel-by-voxel along the primary eigenvector (i.e., vector of the largest eigenvalue), constrained by the ROI seeds. An FA threshold of ≥0.2 and curvature threshold of ≥60° were used to further constrain the course of fiber tracts in the brain. Some post-hoc "pruning" of tracts was necessary in order to remove extraneous fibers if they were determined to be inconsistent with known tract anatomy. Figure 1d shows 3D reconstructions of the fornix, cingulum, and internal capsule from a representative subject. A neurologist checked the tractography results for each subject. Fiber tracts and FA maps were subsequently re-oriented into standard orientation relative to the AC-PC and horizontal transverse axes of an anatomical template via affine transformation. These re-oriented fiber tracts and FA maps were then exported in a binary format for further analysis in MATLAB (MathWorks, Natick, MA), which was used to "crop" specific tract ROIs based on a standardized set of anatomical landmarks (Fig. 1d).

The landmark boundaries for each ROI, identified on the non-diffusion weighted DTI image for each subject, were as follows: The fornix body was defined as that portion of the tract posterior to the fornix columns and anterior to the crura. The cingulum bundle was divided into three portions: superior cingulum was defined as that portion of the tract posterior to the genu and anterior to the splenium of corpus callosum; descending cingulum was defined as that portion of the tract below superior aspect of the fornix body and above inferior aspect of the temporal horn; parietal projection fibers were defined as that portion of the tract above superior aspect of the fornix body and posterior to the descending cingulum. Posterior limb of the internal capsule was defined as that portion of the tract below superior aspect of the fornix body and above superior aspect of the midbrain as well as posterior to the genu and anterior to the splenium of corpus callosum. Then, average FA and volume were computed for each ROI, as measures of tract integrity, for subsequent statistical

Figure 1. (legend on page 1796).

Figure 2. (legend on page 1796).

TABLE II. Means and standard deviations of tract FA and volume

Region	NC	MCI	AD	F (2,57)
FA				
Fornix	0.31 (0.02)	0.28 (0.01)	0.28 (0.02)	12.2**
Superior cingulum	0.40 (0.02)	0.39 (0.02)	0.38 (0.03)	n.s.
Parietal projection fibers	0.35 (0.01)	0.34 (0.02)	0.33 (0.02)	n.s.
Descending cingulum	0.36 (0.02)	0.34 (0.02)	0.33 (0.02)	7.3*
Internal capsule	0.51 (0.04)	0.50 (0.04)	0.49 (0.03)	n.s.
Volume (ml)				
Fornix	1.8 (0.5)	1.3 (0.5)	1.1 (0.5)	8.5*
Superior cingulum	3.4 (0.7)	3.3 (0.8)	3.2 (0.8)	n.s.
Parietal projection fibers	2.0 (0.8)	1.7 (0.9)	1.1 (0.6)	7.2*
Descending cingulum	4.6 (0.8)	3.5 (0.8)	2.7 (0.8)	25.3**
Internal capsule	7.0 (1.4)	7.3 (2.3)	6.7 (1.8)	n.s.

F-statistic for group ANOVA shown (Bonferroni-corrected *P*-values: **P* < 0.05; ***P* < 0.01; n.s., not significant).

analysis. Certain steps of the processing stream were performed manually (seed placement, post-hoc pruning of fibers, and definition of ROI boundaries) by an operator, who was blinded to subjects' diagnostic group.

FDG-PET

FDG-PET data were analyzed using an automated voxel-based approach involving the 3D stereotactic surface projection technique [Minoshima et al., 1995], as implemented within Cortex ID software (GE Healthcare). Subject images were first reconstructed using a filter back-projection method (matrix 128², FOV 30 cm²) to match the resolution of the program's age-matched normal subject database. Then pons-normalized Z-scores (representing standardized glucose metabolism) were computed for posterior cingulate, medial parietal, parietal association, temporal association, and visual cortices for each subject relative to the age-matched, normal subject database. These regions of interest were defined using a PET atlas based on a stereotactic localization technique, as developed by Minoshima et al. [1994]. Figure 2 shows representative MCI and AD subjects analyzed with the above method.

Statistical Analysis

SPSS Statistics (version 17; IBM, Chicago, IL) was used for statistical analysis. Univariate analysis of variance (ANOVA) and post-hoc *t* tests were used to assess the effect of group on tract FA and volume and PET Z-scores. Receiver operating characteristic (ROC) analysis was used to determine the discriminative power of different DTI measurements. Pearson (bivariate) correlations were used to assess the relationship between tract FA/volume and PET Z-scores as well as the relationship between DTI/PET measurements and MMSE performance. All *P*-values were adjusted for multiple comparisons using Bonferroni correction.

RESULTS

Demographic Information

Age, gender composition, and years of education (Table I) did not significantly differ among the three groups. As expected, MMSE scores (Table I) differed among the three groups [$F(2,54) = 27.9$, $P < 0.001$], with NC exhibiting greater MMSE scores than both MCI ($P < 0.001$) and AD

Figure 1.

DTI tractography. ROI seeds (white solid lines) displayed on FA color maps as used for tracking the fornix (A), internal capsule (B), and cingulum (C). The 3D reconstructions of the cingulum bundle (D, top), fornix (D, bottom), and internal capsule (D,

middle) from a representative normal control subject are shown overlaid on T1-weighted sagittal MRI, with specific tract ROIs that were defined for quantitative analysis marked (dotted white line; see text for details).

Figure 2.

FDG-PET Z-score map of cortical metabolism in representative subjects with MCI and early AD. Data were analyzed using an automated voxel-based approach involving the 3D stereotactic surface projection technique [Minoshima et al., 1994, 1995]. Pons-normalized Z-scores were computed for each MCI and AD patient relative to the age-matched normal subject database. In the MCI subject's scan, spatial clustering of Z-scores can be seen in posterior cingulate and medial parietal cortices. In the

AD subject's scan, there are higher Z-scores, indicating more significant relative FDG hypometabolism in the posterior cingulate and medial parietal cortex and a larger spatial extent with involvement of temporoparietal associative cortex and to a lesser degree dorsolateral frontal association cortex with sparing of primary sensorimotor and visual cortices. Images show right lateral (top) and right medial (bottom) views of the brain.

($P < 0.001$) and MCI exhibiting greater MMSE scores than AD ($P < 0.01$).

DTI Data

FA and volume

Table II shows the means and standard deviations of tract FA and volume for NC, MCI, and AD groups as well as ANOVA results. Figure 3 shows example fiber tracts (fornix and descending cingulum) from the three groups. Although DTI measurements differed between hemispheres for some regions, this lateralization was independent of group membership, and we therefore combined data across both hemispheres in our analysis.

Fornix

FA differed across groups, with NC exhibiting greater FA than both MCI ($P = 0.001$) and AD ($P < 0.001$); however, FA did not differ between MCI and AD. Similarly, volume differed across groups, with NC exhibiting greater volume than both MCI ($P = 0.02$) and AD ($P < 0.001$); however, volume did not differ between MCI and AD.

Descending cingulum

FA differed across groups, with NC exhibiting greater FA than AD ($P = 0.001$); however, MCI did not differ in this regard from NC or AD. Volume also differed across groups, with NC exhibiting greater volume than both MCI and AD (both $P < 0.001$) and MCI exhibiting greater volume than AD ($P = 0.004$).

Parietal projection fibers

FA did not differ across groups but volume did, with NC exhibiting greater volume than AD ($P = 0.001$). MCI did not differ in this regard from NC or AD.

Superior cingulum and internal capsule (control)

Neither FA nor volume of these structures differed across groups.

Age as a covariate

Because of the 5-year mean age difference between NC and MCI/AD groups, we re-analyzed FA and volume data with age as a covariate, and the results above did not change.

ROC analysis

Table III shows the area under the curve (AUC), a statistic indicating the discriminative power, for tract FA and volume measurements. Both the FA and volume of fornix, parietal projection fibers and descending cingulum discriminated between NC and AD groups with moderately

TABLE III. ROC analysis statistics

Region	NC vs. AD	NC vs. MCI	MCI vs. AD
FA			
Fornix	0.86*	0.84*	0.56
Superior cingulum	0.67	0.60	0.59
Parietal projection fibers	0.80*	0.73	0.56
Descending cingulum	0.81*	0.62	0.69
Volume			
Fornix	0.86*	0.73	0.66
Superior cingulum	0.58	0.57	0.52
Parietal projection fibers	0.82*	0.66	0.69
Descending cingulum	0.96*	0.79*	0.79*

Area under the curve (AUC) as a measure of discriminative power (Bonferroni-corrected P -values: * $P < 0.05$). Asymptotic P -values for the ROC curve were computed based on an assumption that the AUC distribution is nonparametric and the null hypothesis that $AUC = 0.5$.

high power (AUC range: 0.80–0.96, all $P < 0.05$). FA of the fornix and volume of the descending cingulum also reliably discriminated between NC and MCI groups (all $P < 0.05$). Only descending cingulum volume reliably discriminated between MCI and AD groups ($P < 0.05$).

FDG-PET Data

Table IV shows the means and standard deviations of PET Z-scores for MCI and AD groups. Although Z-scores differed between hemispheres for some regions, this lateralization was independent of group membership, and we combined data across both hemispheres in our analysis. Relative to a database of normal control subjects, the MCI-AD cohort exhibited decreased Z-scores in parietal, temporal, and posterior cingulate cortices (all $P < 0.01$) but not visual cortex (control region). The AD group had lower Z-scores than the MCI group in parietal and temporal association cortices and medial parietal cortex (all $P < 0.05$, uncorrected), but these effects did not survive after correcting for multiple comparisons. The AD group showed lower Z-scores than the MCI group when parietal, temporal, and posterior cingulate ROIs were averaged together ($t(41) = 2.4$, $P < 0.05$).

TABLE IV. Means and standard deviations of FDG-PET Z-scores

Region	MCI	AD
Parietal association	−1.0 (0.8)*	−2.0 (1.6)*
Temporal association	−1.1 (0.6)*	−1.8 (1.3)*
Posterior cingulate	−1.4 (0.5)*	−1.7 (0.8)*
Medial parietal	−1.1 (0.7)*	−1.8 (1.3)*
Visual	0.0 (0.9)	−0.5 (1.3)

Z-scores represent standardized glucose metabolism relative to the normal subject database (Bonferroni-corrected P -values: * $P < 0.01$).

TABLE V. Relationship between descending cingulum integrity and regional metabolism

Regional PET Z-scores	Descending cingulum	
	FA	Volume
Parietal association	0.11	0.17
Temporal association	0.20	0.15
Posterior cingulate	0.35*	0.35*
Medial parietal	0.15	0.23

Pearson correlation coefficients are shown, indicating strength of the relationship between descending cingulum FA/volume and regional PET Z-scores for the posterior cingulate, parietal, and temporal cortices (Bonferroni-corrected P -values: * $P < 0.05$).

Correlation with DTI

We examined the relationship between posterior cingulate hypometabolism (a feature seen early in the course of AD) and integrity of superior and descending cingulum (major input and output pathways of the posterior cingulate). Pearson correlations (see Fig. 4) across the combined MCI-AD cohort revealed that posterior cingulate PET Z-scores (i.e., metabolism) correlated with both FA and volume of the descending cingulum (both $r = 0.35$, $P < 0.05$) but not with that of the superior cingulum. To further examine the specificity of this structure–function relationship, we asked whether descending cingulum FA and volume correlated with PET Z-scores of any other closely associated regions involved in AD. As shown in Table V, descending cingulum integrity (FA and volume) selectively correlated with posterior cingulate Z-scores and not that of the medial parietal, parietal association, or temporal association cortices.

DTI and PET Correlation With MMSE Performance

For regional measures of tract integrity and metabolism that exhibited differences across groups, we tested their association with MMSE performance. Specifically, MMSE scores correlated with fornix FA ($r = 0.42$, $P < 0.01$) and volume ($r = 0.45$, $P < 0.01$), descending cingulum FA ($r = 0.45$, $P < 0.01$) and volume ($r = 0.52$, $P < 0.01$), parietal projection volume ($r = 0.48$, $P < 0.01$) as well as posterior cingulate ($r = 0.38$, $P = 0.06$), parietal association ($r = 0.43$, $P < 0.05$), temporal association ($r = 0.50$, $P < 0.01$) and medial parietal ($r = 0.41$, $P < 0.05$) PET Z-scores. Figure 5 shows scatter plots for some of these relationships. We also asked to what extent PCC metabolism and descending cingulum integrity independently predicted MMSE performance. Partial correlation analysis revealed that the relationship between MMSE scores and descending cingulum FA ($r = 0.37$, $P < 0.05$) and volume ($r = 0.45$, $P < 0.01$) remained significant after controlling for PCC metabolism. In contrast, the relationship between MMSE scores and PCC metabolism was not statisti-

cally significant ($r = 0.23$, $P = 0.2$) after controlling for descending cingulum FA and volume, even when using a more liberal α -level of 0.1.

DISCUSSION

The results of this study suggest that fornix integrity declines during the transition from normal aging to MCI. In contrast, descending cingulum integrity declines during both the transition from normal aging to MCI and the transition from MCI to AD. The posterior limb of the internal capsule, which is part of the motor system, did not show significant changes in its integrity across the normal-to-AD continuum. Similarly, the superior cingulum, which is also part of the limbic system but less intimately associated with the MTL memory system, was also unaffected. Thus, our results indicate that white matter degeneration shows selectivity during early-to-moderate stages of AD, affecting pathways which mediate memory function (i.e., fornix and descending cingulum) more prominently than pathways related to non-memory function (e.g., superior cingulum and internal capsule). This is consistent with previous findings that intracortical (e.g., limbic) projecting fibers are affected preferentially early in the course of AD, at a point in time when extracortical fiber tracts are still relatively preserved [Braak and Braak, 1996; Teipel et al., 2007]. Furthermore, our ROC analysis indicates that the integrity of fornix and descending cingulum (measured as FA and/or volume) can reliably distinguish among NC, MCI, and AD groups. Our findings are consistent with other recent DTI studies that have reported declines in fornix and cingulum FA in both MCI and AD patients [Kiu-chi et al., 2009; Liu et al., 2009; Mielke et al., 2009; Teipel et al., 2007; Xie et al., 2005; Zhang et al., 2007].

Our DTI findings are consistent with the idea that degeneration of the fornix and cingulum bundle, which serve as major input and output pathways of the hippocampal formation [Duvernoy, 1998], likely occurs secondary to progressive hippocampal damage in MCI and AD. Furthermore, the observed decline in fornix and cingulum integrity on a continuum from normal-to-MCI-to-AD was further corroborated by significant positive relationships between fornix/cingulum integrity and MMSE scores, as a surrogate of disease severity.

Although we found differences in PET metabolism between the combined MCI/AD cohort and the normal subject database, we did not see robust differences between individual patient groups. We believe that this is related to the heterogeneity of our MCI sample, which included amnesic and non-amnesic MCI individuals, as well as those with multi-domain deficits. We deliberately sought to include all MCI subtypes both because it better reflects the actual patient population with this condition, and because it is far from clear in the existing literature whether these subtypes represent different underlying etiologies.

Figure 3. (legend on page 1800).

Figure 4. (legend on page 1800).

Figure 5. (legend on page 1800).

Results from the DTI-PET correlation analysis indicate that PCC hypometabolism is, at least in part, related to descending cingulum integrity in the combined MCI/AD cohort (see Fig. 4). In our study, this structure–function relationship exhibited anatomical specificity (as opposed to being a global effect) given that such a relationship was absent for the superior cingulum and parietotemporal regions (Table V). This finding lends support to the hippocampal-neocortical “disconnection” hypothesis of PCC hypometabolism in early AD, which posits that PCC hypometabolism may be due to a distant effect of neuronal dysfunction in the MTL via disconnection at the cingulum bundle [Chételat et al., 2008; Jobst et al., 1992; Meguro et al., 2001; Nestor et al., 2003].

Nevertheless, the structure–function relationship between descending cingulum and PCC was modest in the present study, accounting for ~12% of the variance ($r = 0.35$). This implies that there may be other concurrent mechanisms contributing to PCC hypometabolism, independent of its connection to the MTL via the cingulum bundle. Local damage (i.e., neuronal dysfunction and/or atrophy) in the PCC serves as one such alternate mechanism for causing PCC hypometabolism [Baron et al., 2001; Chételat et al., 2002, 2009]. Damage in the PCC may result, for instance, from local β -amyloid accumulation that reaches critical levels during early stages of AD, as measured by PET imaging [Buckner et al., 2005; Sperling et al., 2009]. Interestingly, we found that descending cingulum integrity predicted MMSE performance independently of PCC metabolism but not vice-versa. This suggests that the association between cognitive decline (as measured by MMSE performance) and PCC dysfunction in our study was secondary to disruption of the descending cingulum, consistent with the “disconnection” hypothesis.

To our knowledge, few studies have tested the disconnection hypothesis directly by correlating measurements of the cingulum bundle with either structural or functional properties of the PCC. Villain et al. [2008, 2010] used voxel-based morphometric analysis of volumetric MRI data and FDG-PET to show that hippocampal atrophy was related to cingulum bundle atrophy, which itself was associated with PCC hypometabolism in MCI and early AD patients. Our findings complement those of Villain et al. by providing DTI-based evidence for the disconnection hypothesis. Similar to our study, Choo et al. [2008] also investigated the disconnection hypothesis using DTI in MCI and AD patients, but they used volumetric MRI to assess structural damage in the PCC. They found associations among atrophy of MTL structures, cingulum FA, and PCC atrophy. In contrast to the purely structural imaging approach used by Choo et al., we provide evidence for the disconnection hypothesis using a structural–functional approach correlating DTI with FDG-PET, which is widely used in the clinical setting for differential diagnosis of AD.

Limitations

DTI data were acquired without suppression of the CSF signal, which can contribute to partial volume effects, particularly in WM adjacent to ventricular spaces [Concha et al., 2005]. This limitation, coupled with a relatively limited six gradient direction and 3 mm² in-plane resolution acquisitions likely contributed to our inability to map the crura of the fornix, thereby restricting our analysis of the fornix to the fornix body. Future studies will proceed with improved technical acquisition parameters as well as CSF signal suppression in order to improve the signal-to-noise ratio of limbic DTI data. Another limitation of the present

Figure 3.

Examples of fornix and descending cingulum fiber tracts. Fornix body (fxb) is shown in red and right descending cingulum bundle (cgb) in green for three representative subjects, one from each of the groups (NC, MCI, AD). B0 DTI image is shown in the background (midsagittal slice at the level of fornix body and parasagittal slice at the level of the descending cingulum).

Figure 4.

Posterior cingulate hypometabolism is associated with descending cingulum integrity. Scatter plots show correlations between posterior cingulate PET Z-scores and descending cingulum FA (**A**) and volume (**B**) in the MCI-AD cohort. Both $r = 0.35$, $P < 0.05$ (Bonferroni-corrected). Fit lines are shown. Group centroids are shown separately for MCI (blue diamonds) and AD (green stars) subjects.

Figure 5.

MMSE performance is associated with limbic tract integrity and cortical metabolism. Scatter plots show correlations between MMSE scores and descending cingulum volume (**A**; $r = 0.52$, $P < 0.01$), fornix FA (**B**; $r = 0.42$, $P < 0.01$) and temporal associa-

tion cortex PET Z-scores (**C**; $r = 0.50$, $P < 0.01$) in the MCI-AD cohort. Fit lines and Bonferroni-corrected P -values are shown. Group centroids are shown separately for NC (red circles), MCI (blue diamonds) and AD (green stars) subjects.

study is its cross-sectional, case-control design, which limits the generalizability of findings and interpretation regarding causal mechanisms. Follow-up longitudinal studies can help confirm our findings. Finally, we chose to limit this analysis to limbic tracts that are directly related to the hippocampal formation and posterior cingulate gyrus, but an analysis that included a more extensive array of structures from the Papez circuit might have yielded additional results. Although the lack of PET data in normal control subjects could be viewed as a potential limitation, the Cortex ID program uses an age-matched (in 5 year increments) normal subject database to generate Z-scores, and thereby “builds in” a control population, albeit not one with local population demographics.

CONCLUSION

In conclusion, our results indicate that disruption of limbic white matter pathways occurs during MCI as well as in early-to-moderate AD in a selective manner. This disruption occurs in a graded manner, with more severely affected individuals having a greater degree of fornix and descending cingulum damage. In addition, our results provide support for the disconnection hypothesis as a mechanism contributing to PCC hypometabolism during incipient AD; this is evidenced by an anatomically specific structural-functional relationship between PCC and descending cingulum.

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