Published in final edited form as:

J Neuroimaging. 2012 October ; 22(4): 365–374. doi:10.1111/j.1552-6569.2011.00633.x.

The fornix sign: a potential sign for Alzheimer's disease based on diffusion tensor imaging

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Abstract

BACKGROUND—We investigated a simple imaging sign for Alzheimer's disease (AD), using diffusion tensor imaging (DTI). We hypothesized that a reduction in fractional anisotropy (FA) in the fornix could be utilized as an imaging sign.

METHODS—Twenty-three patients with AD, 24 patients with amnesic mild cognitive impairment (aMCI), and 25 control participants (NC) underwent DTI at baseline and one year later. The diagnosis was re-evaluated one year and three years after the initial scan. A color-scaled FA map was used to visually identify the FA reduction (“fornix sign”). We investigated whether the fornix sign could differentiate AD from NC, and could predict progression from aMCI to AD or NC to aMCI. We also quantified FA of the fornix to validate the fornix sign.

RESULTS—The fornix sign was identical to the *lack* of any voxels with an FA > 0.52 within the fornix. The fornix sign differentiated AD from NC with specificity of 1.0 and sensitivity of 0.56. It predicted conversion from NC to aMCI with specificity of 1.0 and sensitivity of 0.67, and from aMCI to AD with specificity of 0.94 and sensitivity of 0.83.

CONCLUSIONS—The fornix sign is a promising predictive imaging sign of AD.

Keywords

fornix sign; fractional anisotropy; diffusion tensor imaging; Alzheimer's disease; mild cognitive impairment

Introduction

Diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI) technique that evaluates the translational motion of water molecules, has been extensively applied to investigate white matter alterations in Alzheimer's disease (AD). In addition to a conventional region-of-interest (ROI) analysis [1-13], voxel-based or multivariate analyses of the whole brain have also been used to evaluate regional abnormalities in DTI-derived

parameters, such as anisotropy and diffusivities [14-18]. These studies have identified AD-specific abnormalities in the limbic fibers, the fronto-occipital fasciculi, the inferior longitudinal fasciculi, and the forceps major, even in early-symptomatic patients or asymptomatic participants at risk for AD [19-26]. These robust and consistent findings of abnormal diffusivity measures suggest that DTI could provide useful information for the routine clinical diagnosis of AD patients. However, the image quantification procedure, which requires time-consuming and precise ROI placement, is not practical for the daily clinical routine. As an alternative approach, automated voxel-based analyses have been postulated, but they often require multiple pre-processing steps with costly human intervention to ensure accurate image normalization.

In this study, we tested whether a reduction in fractional anisotropy (FA) of the fornix would be visually identifiable in AD patients. Scanners with DTI capability are becoming widely available and FA maps are now easily accessible in scanners and off-line viewing software. FA reduction in the fornix is a robust and consistent finding in AD that has been demonstrated with manual ROI-based analysis [12, 13] and normalization-based whole brain analysis [15, 20, 21, 27]. This reduction most likely reflects pathological alterations of the fornix itself, as well as the partial volume effects caused by atrophy. Among other areas with reported FA reductions in AD, the fornix is especially attractive as a location for an imaging marker because the body of the fornix is readily identifiable (no other confounding fibers are adjacent to the body of the fornix), and located adjacent to the lateral ventricle, with minimal B0 susceptibility distortions. We investigated whether we could visually observe reduced FA in the fornix with high inter- and intra- reader reliability, and termed this the fornix sign, as it is apparent on visual inspection. Based on the multiple-reader visual examination results, the sensitivity and specificity to differentiate AD from cognitively normal control participants (NC) were measured. In addition, we investigated whether reduced FA can predict conversion from NC to amnesic mild cognitive impairment (aMCI), and from aMCI to AD. Quantification of the FA, based on ROI analyses of the fornix and the whole brain, was also performed to validate the fornix sign.

Methods

Subjects

We used data from a study of well-characterized individuals, conducted by the Johns Hopkins Alzheimer's Disease Research Center (ADRC). Written, informed consent was obtained in accordance with an oversight of the Johns Hopkins Institutional Review Board and using guidelines endorsed by the Alzheimer's Association [28]. Initial findings were reported previously [12], including demographic, health, and clinical features. Briefly, 25 AD patients (mean age, 75.6) who met NINCDS/ADRDA criteria for AD [29] and who had a Clinical Dementia Rating (CDR) of 1; 25 aMCI patients (mean age, 75.8) who met criteria for amnesic aMCI [30] and who had a CDR=0.5; and 25 NC participants (mean age, 74.3) who were cognitively normal and had a CDR=0, were included. Two AD and one aMCI patients were excluded from the analysis because they could not complete the baseline and follow-up DTI scanning. Therefore, DTI from 23 AD patients, 24 aMCI patients and 25 normal participants were used for the analysis. During three years of follow-up, six aMCI patients had converted to AD and three NC participants had converted to aMCI. Clinical measures, including the mini-mental state examination (MMSE), the Logical Memory Story A from the Wechsler Memory Scale (WMS), the California Verbal Learning Test (CVLT), the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), and the Geriatric Depression Scale (GDS), were also assessed at the time of the scans. Participant clinical characteristics and the use of "anti-dementia" medications are summarized in Table 1.

Image acquisition and processing

Participants were imaged twice using the same methods, at baseline and approximately one year later. The only exception was an aMCI patient who underwent a follow-up scan three months later (Fig. 3, #14) and did not have a one-year scan available. MRI was acquired on a 3T scanner (Philips Medical Systems, Best, The Netherlands). Single-shot echo-planar imaging sequences with sensitivity encoding and a parallel imaging factor of 2.0 [31] were used. The imaging matrix was 96×96 , with a field of view of 212×212 mm, zero-filled to 256×256 mm. Transverse sections of 2.2 mm thickness were acquired parallel to the anterior commissure-posterior commissure line. A total of 50 - 60 sections covered the entire hemisphere and brainstem without gaps. Diffusion weighting was encoded along 30 independent orientations [32], and the b-value was 700 s/mm^2 . Five additional images with minimal diffusion weighting ($b = 33 \text{ mm}^2/\text{sec}$) (b0 images) were also acquired. The scanning time per dataset was approximately four minutes. The raw diffusion-weighted images (DWIs) were first co-registered to one of the b0 images and corrected for participant motion and eddy current distortion, using a 12-parameter affine transformation of the Automated Image Registration (AIR) [33], with subsequent b0 distortion correction using large deformation diffeomorphic metric mapping [34]. The six elements of the diffusion tensor were calculated for each pixel with multivariate linear fitting using DtiStudio (H. Jiang and S. Mori, Johns Hopkins University, Kennedy Krieger Institute, lbam.med.jhmi.edu or www.MriStudio.org) [35, 36]. Fractional anisotropy (FA) [37] was calculated from the tensor field, and visualized using an NIH color-scale implemented in MRICron (<http://www.cabiatl.com/mricro/mricron/index.html>). The color was scaled from purple (FA = 0.1) to red (FA = 0.8) and shown in black (FA < 0.1 and FA > 0.8). The FA maps from the initial visit (baseline scans) were used for the primary analysis to determine the diagnostic value, and the follow-up scans were used to determine the reproducibility of the initial findings.

Identification of the “fornix sign”

FA reduction in the body of the fornix was identified by the color-scaled FA map. Using this color-scale, the normal fornix is usually visualized as an orange string-like structure (Fig. 1A). We defined the “fornix sign” as the lack of a yellow to red area in the fornix, which means the lack of any area with an FA of approximately > 0.5 . This criterion was based on our previous publication [12] indicating the reduction of FA below 0.5 in the AD population. After instruction, which took approximately three minutes, a radiologist (S.Y.) and a lab technician (J.H.), both blinded to the diagnosis, read all 144 FA maps (72 participants with two time points) to identify the fornix sign. The order of the FA maps was pseudo-randomized. The instruction was performed as follows, with visual instruction using Fig. 1. “First, identify the c-shaped corpus callosum in the mid-sagittal plane. The fornix is a string like structure bellow the corpus callosum (visually indicate the fornix). Then, scroll the sagittal images for several slices bilaterally, and observe the entire fornix. The sign is negative if you find red or yellow area inside the fornix. The sign is positive if you cannot find red or yellow area inside the fornix, or if you cannot find the fornix.” The FA maps were presented on a monitor screen (Dell 2790W Flat Panel 27 inch Monitor) with a resolution of 1920×1200 pixels, and the image size (sagittal plane) was approximately 4×6 cm for each slice.

Inter- and intra- reader agreement, and the reproducibility one year after the baseline scan

The two readers repeated the image reading of the baseline scans twice, with a three-month interval in between readings. Observed % agreement and a Cohen's kappa coefficient (beyond chance agreement) were used to evaluate inter- and intra- reader agreements, and the reproducibility of the fornix sign. Inter-reader agreement was estimated by comparing the results from each reader, based on the first reading. Intra-reader agreements were estimated comparing results from the first reading and a reading three months later for both

readers. The reproducibility of the fornix sign was estimated between baseline scans and follow-up scans, which were performed approximately one year after the baseline scans. For the reproducibility analysis, the results from the initial reading were used, and the fornix sign was judged as “present” only if both readers stated it was “present.”

ROI analyses—Three-dimensional ROIs were manually drawn on the body of the fornix and the whole brain. The inferior edge of the body of the fornix was defined as one axial slice above the upper edge of the anterior commissure, and the posterior edge was defined as one coronal slice anterior to the junction of two crura of the fornix. The whole brain was defined as an area including the brain parenchyma and the ventricles, located above the axial slice, including the lower edge of the cerebellum. The software MriStudio/RoiEditor (www.MriStudio.org or mri.kennedykrieger.org) was used to draw the ROIs, and to measure the mean FA value (mean-FA) and the maximum FA value (max-FA) inside the ROIs. The receiver operating characteristic (ROC) curves were drawn based on the mean-FA and max-FA of each ROI to investigate whether the FA values could classify AD and NC. In addition, we investigated the correlation between measured FA values and the cognitive-psychiatric scores (MMSE, WMS, CVLT, ADAS-cog, and GDS). Spearman's rank correlation coefficient was used to evaluate the correlations, and the p value was calculated without correction for multiple comparisons.

To investigate scan-rescan reproducibility of the FA of the fornix, ten sets of images from ten NC participants were used. The first and second scans were performed on different days. The second scan was acquired and processed using exactly the same method as the first scan, and an ROI was placed on the fornix, as well, to measure the mean-FA. The Bland-Altman analysis [38, 39] was used to calculate whether the differences between the repeated scans were significantly different from 0 (analysis of the 95% Confidence Interval for the difference), as well as to assess whether a particular difference was outside the expected range (limit-of-agreement statistic). In addition, the normalized difference between two scans was calculated to assess the relative magnitude of variability over two scans.

SPSS 19 (IBM Corporation, New York, U.S.A.) was used for the statistical analyses, except for the non-parametric pair-wise comparison between the areas under ROC curves and the Bland-Altman analysis, for which MedCalc 11.5.1 (MedCalc Software, Mariakerke, Belgium) was used.

Results

The fornix sign: the inter- and intra- reader agreement, and reproducibility

The time required to read one FA map was under 30 seconds for both readers. The inter-reader agreement at baseline was 0.98% (141/144) (Cohen's kappa = 0.95). The readers disagreed on only three out of 144 FA maps (Fig. 2, #21; Fig. 3, #19; Fig. 4, #6). The intra-reader agreement comparing the first and second reading of the baseline scans was 100% for both readers (Cohen's kappa = 1.0). In Fig. 2, images from 25 NC (22 NC-stables and three NC-converters) are shown. The observed % agreement of the fornix sign between baseline and follow-up scans (approximately one year after the baseline scans) was 88% (Cohen's kappa = 0.52). In the baseline FA maps, the fornix sign was seen in two NC participants, both of whom later converted to aMCI. One normal participant without the fornix sign converted to aMCI over the follow-up [Fig. 2, #23]. Images from the 24 aMCI patients are shown Fig. 3. The observed % agreement of the fornix sign between baseline and follow-up scans was 92% (Cohen's kappa = 0.78). The fornix sign was seen in five aMCI patients. All of these converted to AD over the follow-up. One aMCI patient, who later converted to AD, did not demonstrate the fornix sign at baseline FA map, but FA was reduced during the first follow-up period [Fig. 3, #16]. Images from 23 AD patients are shown in Fig. 4. The

observed % agreement of the fornix sign between baseline and follow-up scans was 70% (Cohen's kappa coefficient = 0.39). Thirteen AD patients demonstrated the fornix sign. Four AD patients (Fig. 4, #5, 7, 8 and 9) did not demonstrate the fornix sign at the baseline scan, but had a fornix sign at the one-year follow-up scan. On the other hand, four AD patients with the fornix sign at the initial scan (Fig. 4, #11-14) did not have the fornix sign a year later.

Based on baseline FA maps from 22 NC participants who did not convert to aMCI within three years and 23 AD patients, the performance of the fornix sign for AD diagnosis was evaluated. The fornix sign was judged as “present” only if both readers rated it as “present.” The specificity was 1.0, the sensitivity was 0.56, the positive predictive value (PPV) was 1.0, the negative predictive value (NPV) was 0.68 and the likelihood ratio positive (LRP) was more than 56 (calculated by use of 0.99 as the specificity). The ability of the fornix sign to predict conversion of NC participants to aMCI within three years was: specificity (1.0); sensitivity (0.67); PPV (1.0); NPV (0.96); and LRP (> 67: calculated by use of 0.99 as the specificity). The ability to predict conversion of aMCI patients to AD within three years was: specificity (0.94); sensitivity (0.83); PPV (0.83); NPV (0.94); and LRP (14).

ROI-based analysis

The mean and the standard deviation (SD) of the sets of max-FA and mean-FA, and the result of the statistical analyses, are summarized in Table 2. A significant difference in the fornix was found among the three groups (one-way ANOVA). The max-FA and the mean-FA of the AD were significantly lower than that of the aMCI and NC groups, although there was no difference between aMCI and NC (Tukey's post-hoc test). As expected, the fornix sign represented the decreased max-FA of the fornix, and the FA threshold between “exists” and “absent” was 0.52 (Fig. 5). In contrast, for the whole brain FA values (max-FA and mean-FA), there was no significant difference among the three groups (one-way ANOVA).

The ROC curves were drawn based on the ROI-based FA measurements and the diagnostic criteria (Fig. 6). Measurements from 23 AD patients and 22 NC participants were used for the analysis (three NC participants who later converted to aMCI were excluded from the analysis). The AUCs of the FA values (mean-FA and max-FA) of the fornix were greater than that of the whole brain, with good sensitivity and specificity (Table 3).

Correlation between measured FA values and cognitive scores

There were significant correlations between measured FA values (mean- and max- FA) of the fornix and cognitive scores, as summarized in Table 4. Among these scores, the correlation coefficient was highest with the memory tasks (WMS delayed recall and CVLT). No correlation was found between measured FA values of the fornix and a depression scale (GDS).

Scan-rescan reproducibility

The mean mean-FA of the fornix was 0.345 (scan 1) and 0.344 (scan 2). The difference between two scans was small (range = 0.0001 – 0.0154), and the mean normalized difference was 0.43% (range = 0.03 – 4.67%). The Bland-Altman analysis indicated that there was no significant difference between the two scans (95% Confidence interval of the difference was -2.14E-03 – 5.26E-03 and the limit-of-agreement statistic was -8.59E-03 – 1.17E-02).

Discussion

Currently, the standard clinical criteria for the diagnosis of AD only uses MRI measures to rule out other pathologies that cause dementia (e.g., ischemia, hemorrhage, tumor, or hydrocephalus). For these purposes, conventional anatomical MRI, including T1-, T2-weighted images and fluid attenuated inversion recovery images, are commonly used. DTI is usually not a part of the routine imaging protocol in daily clinical practice since its diagnostic significance is still uncertain, even though many research studies have identified AD-related anatomical features revealed by DTI. The difficulty in applying the research findings to clinical practice is that these research studies are based on image quantification and subsequent statistical analysis, while routine image-based diagnosis is almost exclusively performed by qualitative visual inspection. For example, numerous publications link AD to hippocampal volume loss (reviewed in [40]). Although the correlation is certain, hippocampus atrophy is rarely quantified in daily diagnosis because of the time-consuming nature of accurate hippocampal volume measurements. If DTI is to provide clinically useful information for AD diagnosis, such information has to be visually appreciable. The fornix sign introduced here is an attempt to define image signs characteristic of AD using DTI. Although the sensitivity was limited, the specificity and LRP differentiating AD from NC were high for this study group. Notably, the ability to predict, in this small sample, conversion from NC to aMCI, and from aMCI to AD, was strong, especially among normal controls. These findings indicate that the fornix sign is a promising imaging biomarker of AD, especially in early disease phases. The reproducibility of the fornix sign one year after the initial scan was generally high. However, the “absent” to “present” conversion of the fornix sign was seen in three NC participants, two aMCI patients, and four AD patients, and the “present” to “absent” conversion of the fornix sign was seen in four AD patients. The bases of these changes are unclear at this point and require further investigation.

The fornix sign was validated by the quantitative 3D-ROI-based FA measurement of the fornix and the whole brain. The FA of the fornix was significantly reduced in AD compared to that in aMCI and AD. Since we could not find any statistical difference in the FA of the whole brain among the AD, aMCI, and NC groups, the observed FA reduction in the fornix was not the result of a global (whole brain) FA reduction, but rather, a structure-specific change. In addition, the FA of the fornix correlated with cognitive scores, but not depression. Further, there was a tendency toward stronger correlation with memory scales (CVLT and WMS delayed recall) than the more general cognitive scales (ADAS-cog and MMSE). This can be explained by the functional role of the fornix, which is involved in recognition memory [41]. The FA threshold that we qualitatively judged as “present” or “absent” for the fornix sign was the lack of any voxels with an FA greater than 0.52. Both inter- and intra- reader agreements for the fornix sign were substantially high, which indicated that human visual capability is sensitive enough to recognize this FA threshold, assisted by color scaling. The high inter-reader agreement between a neuroradiologist and a lab technician suggests that extensive training is not required to read the fornix sign. With research tools and time to draw manual 3D-ROIs, the mean FA of the fornix may provide better classification than the qualitative fornix sign, since the sensitivity (0.70), specificity (0.91), and the LRP (7.65) of the mean-FA was good in this study population. We assume that the fornix sign, which requires less than 30 sec to judge as “present” or “absent,” is suitable for clinical situations without image quantification tools.

We would like to emphasize that the fornix sign we have described is a preliminary observation, because this analysis was based on a small number of highly selected participants, which included only three NC to aMCI converters and six aMCI to AD converters. The AD patients were clinically diagnosed and pathological confirmation was not available. Whether the three NC participants who converted to aMCI will further convert

to AD in the future is also unclear. DTI, in general, is prone to several sources of artifacts, including subject motion and instrument imperfections, such as eddy current, which can lead to inaccurate results at a rate higher than that for conventional anatomical MRI. Although scan-rescan reproducibility of the FA of the fornix was high in this study using a single research scanner, the reproducibility might be lower in clinical scanners. It is known that the FA value may vary according to the voxel size. Therefore, whether we could observe the fornix sign in the FA maps with different voxel sizes is unknown. To be established as a truly useful image sign of AD, further efforts that include the identification of appropriate scan parameters and cross-scanner calibrations, as well as investigations of the fornix sign in other types of dementia, are essential.

Acknowledgments

The authors thank Dr. Shoko Yoshida and Mr. Johnny Hsu for reading FA maps and Ms. Mary McAllister for help with manuscript editing.

Funding sources: KO was funded by the NIH (R21AG033774) and the Johns Hopkins Alzheimer's Disease Research Center (P50AG005146 from NIH). SM was funded by NIH (P41 RR015241, R01NS058299 and R01AG20012). MM was funded by the NIH (R21NS060271). The images acquired from Alzheimer's patients, mild cognitive impairment patients, and age-matched controls were supported by a methods development grant from Glaxo-Smith-Kline, awarded to MA and CGL. CGL has received grant support from the following organizations: NIMH, NIA, Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, Glaxo-Smith-Kline, Eisai, Pfizer, Astra-Zeneca, Lilly, Ortho-McNeil, Bristol-Myers, and Novartis. CGL has served as a consultant/advisor for Astra-Zeneca, Glaxo-Smith-Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, and Genentech. CGL has received honorarium or travel support from Pfizer, Forest, Glaxo-Smith-Kline, and Health Monitor.

Abbreviations

AD	Alzheimer's disease
aMCI	amnesic mild cognitive impairment
DTI	diffusion tensor imaging
FA	fractional anisotropy
ROI	region of interest
ROC	receiver operating characteristic
AUC	area under receiver operating characteristic curve

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Figure 1.

Example of the fornix sign. The axial (left), coronal (middle), and sagittal (right) slices of the color-scaled FA map are shown with the magnified view of the fornix (yellow rectangle). A: FA map of a cognitively normal 80-year-old woman without a fornix sign. The core part of the fornix appears yellow to red (FA 0.5 – 0.8). B: FA map of an 80-year-old woman with Alzheimer's disease with the fornix sign. The fornix appears green (FA < 0.5). FA, fractional anisotropy.

Figure 2.

Color-scaled FA maps from 25 cognitively normal elderly participants. Sagittal and axial magnified views of the body of the fornix are shown (baseline image, left), and compared with the FA maps of one year later (follow-up image, right). Color scale is the same as that used in Fig. 1. The age of the participants at the baseline scan are shown in the second column to the left, with the participants' identification number (#) in the leftmost column. Participants with an identification number marked by a red square developed aMCI one year after the baseline scan, and those with an identification number marked by a green square developed aMCI within three years after the baseline scan. The images with the fornix sign (both readers judged the fornix sign as "present") are marked by a yellow rectangle, and the images with an "equivocal" fornix sign (the images with a split decision by the readers) are marked by a pink rectangle.

Figure 3.

Color-scaled FA maps from 24 aMCI patients. Sagittal and axial magnified views of the body of the fornix are shown (baseline image, left), and compared with the FA maps of one year later (follow-up image, right). Color scale is the same as that used in Figs. 1 and 2. The ages of the participants at the baseline scan are shown in the second to the left column, with the participants' identification number (#) in the leftmost column. Participants with an identification number marked by a red square developed AD one year after the baseline scan, and those with an identification number marked by a green square developed AD within three years after the baseline scan. The images with the fornix sign (both readers judged the fornix sign as "present") are marked by a yellow rectangle, and the images with an "equivocal" fornix sign (the images with a split decision by the readers) are marked by a pink rectangle.

Figure 4.

Color-scaled FA maps from 23 AD patients. Sagittal and axial magnified views of the body of the fornix are shown (baseline image, left), and compared with the FA maps of one year later (follow-up image, right). Color scale is the same as that used in Figs. 1 - 3. The ages of the participants at the baseline scan are shown in the second left column, with the participants' identification number (#) in the leftmost column. The images with the fornix sign (both readers judged the fornix sign as "present") are marked by a yellow rectangle, and the images with an "equivocal" fornix sign (the images with a split decision by the readers) are marked by a pink rectangle.

Figure 5.

Scattergrams of the mean-FA and max-FA of the fornix. Points with an “absent” fornix sign are shown on the left side, and points with a “present” fornix sign are shown on the right side. Blue circles: cognitively normal control participants (NC); blue triangles: NC who later converted to amnesic mild cognitive impairment (aMCI); yellow circles: aMCI stable for three years; yellow triangles: aMCI who converted to Alzheimer's disease (AD); red circles: AD.

Figure 6.

ROC curves drawn from FA values measured by three-dimensional region-of-interest analyses. Blue line: mean-FA of the fornix; green line: max-FA of the fornix; yellow line: mean-FA of the whole brain; red line: max-FA of the whole brain.

Table 1

Demographic and cognitive characteristics of the participants

Baseline diagnosis	NC	aMCI	AD
Number	25	24	23
Age at baseline	74 (7.1)	75 (5.2)	75 (6.9)
Conversion (1st year)	1 to aMCI	3 to AD	N/A
Conversion (1 - 3 years)	2 to aMCI	3 to AD	N/A
Antidementia drugs at baseline	0/25	3/24	21/24
Antidementia drugs at one year	0/25	5/24	22/24
MMSE baseline	29 (1.3)	27 (2.1)	22 (2.9)
MMSE at one year	29 (1.0)	27 (2.7)	19 (4.9)
ADAS-cog baseline	10 (2.0)	12 (5.0)	19 (5.9)
ADAS-cog at one year	9.9 (1.9)	11 (2.4)	23 (9.9)
WMS immediate recall baseline	13 (3.4)	8.3 (3.1)	3.7 (3.7)
WMS immediate recall at one year	15 (2.9)	8.8 (5.2)	2.0 (2.6)
WMS delayed recall baseline	12 (4.1)	6.0 (4.1)	1.0 (2.0)
WMS delayed recall at one year	14 (3.3)	7.4 (5.2)	0.78 (2.1)
CVLT total correct trials baseline	53 (11)	34 (13)	18 (7.7)
CVLT total correct trials at one year	55 (11)	36 (13)	16 (5.9)
CVLT short delay free recall baseline	10 (2.0)	5.2 (3.7)	1.2 (1.4)
CVLT short delay free recall at one year	11 (3.4)	5.7 (4.5)	0.62 (0.97)
CVLT long delay free recall baseline	11 (3.1)	5.3 (3.9)	0.61 (1.2)
CVLT long delay free recall at one year	12 (2.9)	5.9 (4.4)	0.38 (1.2)
GDS baseline	0.84 (1.3)	1.39 (1.2)	2.0 (2.0)
GDS at one year	1.6 (2.5)	1.2 (1.0)	2.4 (2.5)

For the age at baseline and cognitive scores, the mean and the standard deviation are listed. The second scan was performed approximately one year after the baseline scan. Antidementia indicates the number of patients using cholinesterase inhibitors, memantine, or both. Abbreviations: NC = cognitively normal participants; aMCI = amnesic mild cognitive impairment; AD = Alzheimer's disease; N/A = not applicable; MMSE = Mini-mental State Examination; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; WMS = Wechsler Memory Scale; CVLT = California Verbal Learning Test; GDS=15-item Geriatric Depression Scale.

Table 2

Results of the FA quantification based on 3D-ROI

	NC		aMCI		AD		* (p-value)	NC vs. aMCI (p-value)		post hoc test (Tukey)		aMCI vs. AD (p-value)
	mean (SD)		mean (SD)		mean (SD)			NC vs. AD (p-value)		NC vs. AD (p-value)		
fornix	max-FA	0.672 (0.121)	0.644 (0.146)	0.524 (0.154)			0.001	0.778		0.002		0.013
	mean-FA	0.339 (0.020)	0.335 (0.026)	0.304 (0.052)			0.002	0.893		0.003		0.011
whole brain	max-FA	0.990 (0.058)	0.987 (0.014)	0.984 (0.115)			0.201					
	mean-FA	0.186 (0.099)	0.189 (0.012)	0.180 (0.022)			0.132					

Abbreviations: NC = cognitively normal participants; aMCI = amnesic mild cognitive impairment; AD = Alzheimer's disease

* Comparison among NC, aMCI and AD; one-way ANOVA

Table 3

Results of the receiver operating characteristic curve analyses

Predictor		AUC [95% CI]	Optimal cut-off	Sensitivity	Specificity	PPV	NPV	LRP
formix	lower max-FA	0.798 (0.671, 0.926) [*]	< 0.625	0.762	0.781	0.750	0.762	2.87
formix	lower mean-FA	0.818 (0.692, 0.945) [#]	< 0.326	0.700	0.909	0.889	0.741	7.65
whole brain	lower max-FA	0.615 (0.442, 0.787)	< 0.988	0.591	0.773	0.722	0.654	2.60
whole brain	lower mean-FA	0.543 (0.330, 0.717)	< 0.188	0.682	0.586	0.556	0.708	1.65

Abbreviations: AUC = area under the receiver operating characteristic curve; PPV = positive predictive value; NPV = negative predictive value; LRP = positive likelihood ratio

^{*} AUC greater than that of whole brain mean-FA, $p = 0.02$ [#] AUC greater than that of whole brain mean-FA, $p = 0.01$

Table 4

Correlation between FA measurements of the fornix and functional scores

	max-FA correlation coefficient *	P-	mean-FA correlation coefficient *	P-
MMSE	0.353	0.002	0.335	0.004
ADAS-cog	-0.364	0.002	-0.353	0.002
WMS immediate recall	0.302	0.01	0.327	0.005
WMS delayed recall	0.388	0.001	0.436	1.31E-04
CVLT total correct trials	0.426	2.67E-04	0.463	6.20E-05
CVLT short delay free recall	0.388	0.001	0.447	1.18E-04
CVLT long delay free recall	0.373	2.00E-03	0.414	4.05E-04
GDS	0.104	0.389	0.068	0.574

Abbreviations: MMSE = mini-mental state examination; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; WMS = Wechsler Memory Scale; CVLT = California Verbal Learning Test; GDS = Geriatric Depression Scale

* Spearman's rank correlation coefficient