Clinical Investigative Study

The Uncinate Fasciculus as a Predictor of Conversion from Amnestic Mild Cognitive Impairment to Alzheimer Disease

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A B S T R A C T

BACKGROUND AND PURPOSE

Amnestic mild cognitive impairment (aMCI) is associated with the risk of Alzheimer's disease (AD). Although diffusion tensor imaging (DTI)-based fractional anisotropy (FA) analyses have been used to evaluate white matter changes in patients with AD, it remains unknown how FA values change during the conversion of aMCI to AD. This study aimed to elucidate the prediction of conversion to AD and cognitive decline by FA values in uncinate fasciculus (UF) in aMCI patients.

METHODS

Twenty-two aMCI patients were evaluated for their UF FA values by a tractography-based method with DTI and cognitive performance by neuropsychological testing at baseline and after a 3-year follow-up. Patients were divided into 2 groups after 3 years: 14 aMCI-stable (aMCI-aMCI) and 8 AD-conversion (aMCI-AD).

RESULTS

At baseline, FA values in the right UF were significantly lower in the aMCI-AD group than in the aMCI-aMCI group. These values also showed significant correlations with the neuropsychological scores after a 3-year follow-up. The area under the curve of the receiver operation characteristic curves for predicting conversion to AD was .813.

CONCLUSION

These results suggested that FA values in the right UF might be an effective predictor of conversion of aMCI to AD.

Introduction

Mild cognitive impairment (MCI) has been described as an intermediate clinical condition that is thought to be a transitional stage between normal aging and Alzheimer's disease (AD).[1] MCI is classified into 2 subtypes: amnestic MCI (aMCI) and nonamnestic MCI.[1] Because patients with aMCI have a high risk of developing AD with a conversion rate of 10-15% per year,[2] aMCI is considered a clinical state that may be critical for the detection of early-stage AD and the prediction of conversion to AD. Biological markers, which are used as predictors of the conversion of aMCI to AD, contribute to diagnostic accuracy and add prognostic value.

Several recent studies have elucidated the detection of AD with structural and functional neuroimaging techniques. A voxel-based morphometry (VBM) magnetic resonance imaging (MRI) study has shown that the gray matter (GM) density in the posterior association cortex is significantly decreased in patients with AD compared with healthy controls.[3] Longitudinal MRI studies have shown that the volumes of other brain areas, such as the hippocampus, entorhinal cortex, and temporal lobe, are decreased more in patients with AD than in those with MCI.[4] VBM is a promising technique for evaluating brain atrophy/damage related to conversion to AD, but it remains difficult to predict conversion only by GM atrophy. Therefore, some recent studies have focused on white matter (WM) atrophy as an alternative detector of early-stage AD.

WM changes can be evaluated noninvasively by diffusion tensor imaging (DTI).[5] DTI is a technique used to investigate WM microstructure based on water diffusion. DTI-derived parameters, such as fractional anisotropy (FA), can be used to evaluate the integrity of fiber tracts. Several investigations conducted with DTI have reported decreased FA values of the temporal and frontal WM in patients with MCI.[6] In the conversion of healthy subjects to AD, changes in FA values have been observed in the frontal, parietal, and subcortical WM regions.[7]

Apart from the frontal and temporal WM, another WM region that may be potentially affected in MCI and AD is the uncinate fasciculus (UF).[8] UF is a WM tract connecting

the anterior part of the temporal lobe with the frontal lobe and is associated with episodic memory.[9] Although region of interest (ROI)- or voxel-based analyses are common methods because they are relatively easy to perform, ROI- and voxel-based analyses can include various unnecessary fibers.[10] Therefore, Taoka et al have used a tractography-based method with DTI to avoid the contamination of fibers other than UF; they have indicated that FA values in UF are significantly lower in patients with AD than in healthy controls.[11] Our previous study used a tractography-based method and reported that FA values in the left UF were significantly lower in patients with aMCI than in healthy controls.[12] However, it is still unclear how FA values in UF change in patients with aMCI during conversion to AD. The aim of this study was to evaluate the temporal changes in FA values in UF in aMCI patients with or without conversion to AD by a tractography-based method using DTI.

Methods
Patients

Twenty-two patients with aMCI ware recruited from Kyoto University Hospital. After a 3-year follow-up, 8 patients were diagnosed with AD (aMCI-AD), and 14 patients remained in aMCI (aMCI-aMCI). The diagnosis of aMCI was made on the basis of the Mayo Clinic Alzheimer's Disease Research Center's following criteria[1]: (1) Memory complaints by patient or informant; (2) objective memory impairment, presenting as a logical memory (immediate memory) score on the Wechsler Memory Scale-revised (WMS-R) <1.5 standard deviations (SD) below the mean of the normative data of a large sample of Japanese patients (WMS-R, Japanese version), or, specifically, a raw score of ≤ 13;[12] (3) A clinical dementia rating (CDR) score of .5;[13] (4) Preserved activities of daily living;[14] (5) Normal general cognitive function; Mini-Mental State Examination (MMSE) score of ≥ 24;[15] and (6) Not meeting the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD.[16] We used these criteria as described in our previous study.[12] In addition, the diagnosis of AD was made on the basis of the NINCDS-ADRDA criteria as follows: (1) MMSE score of <24; (2) a WMS-R logical memory score of <13, and (3) a CDR score of ≥ 1. At baseline and the 3-year follow-up, all patients were evaluated by MRI scans, the AD assessment scale (ADAS), MMSE, and the logical memory subscales of WMS-R for episodic memory. The follow-up neuropsychological tests were completed at an average of $2.96 \pm .31$ years after baseline tests.

This study was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine (E 479), and written informed consent was obtained from all subjects.

MRI Acquisition and DTI

MRI scans were performed using a 3.0-T MR scanner (Trio; Siemens AG, Erlangen, Germany) in Kyoto University Hospital. Single-shot spin-echo echo-planar sequences were used to record DTI data. Three-dimensional magnetization-prepared rapid gradient echo sequences were used to obtain the structural MRI data. The imaging parameters for DTI were echo time, 79 ms; repetition time, 5,200 ms; 128×128 matrix; field of view, 220 mm $\times$ 220 mm; 40 continuous axial slices of 3.0 mm thickness; 12 noncollinear axis motion probing gradient; and b = 700 seconds/mm^2. The acquisition time that was applied per dataset was 100 seconds. Trials were repeated 5 times to enhance the signal-to-noise ratio.

The tensor calculations and fiber tractography were performed by DTIStudio, version 2.4.[17] Because the eddy-current-related geometric distortions between images obtained in each motion-probing gradient direction can be low, postprocessing distortion corrections were not applied in this study, as described in a previous study.[12] We obtained 3 eigenvalues and 3 eigenvectors from calculations of diffusion tensor and calculated FA images.[5]

For the fiber tractography, we used the means of the continuous tracking method that were derived from the fiber assignments.[18] On the basis of our previous study, the criteria of termination of tracking were a FA value <.18 and a turning angle of 2 consecutive vectors >70°.[12] In this study, we defined 2 ROIs to visualize UF in accordance with the method by Taoka et al[11] and Fujie et al.[12] The first ROI was set in the anterior temporal lobe WM on the axial slice below the temporal stem (Fig 1A). The second ROI was set in the frontal lobe WM on the coronal slice near the tip of the frontal horn of the lateral ventricle (Fig 1B). Finally, the mean FA and the number of fibers within UF were measured. Because visualization of UF varies considerably in its anterior portion, 10 consecutive coronal slices from the most posterior portion were used in the study as described in a previous study[12] (Fig 1E).

Statistical Analysis

The demographic and neuropsychological data were compared between the aMCI-aMCI and aMCI-AD groups by unpaired 2-tailed t-tests (age and the scores on the neuropsychological tests at baseline and the 3-year follow-up) and Pearson's s tests (gender). The FA values and number of fibers in UF were analyzed by a 2-way mixed model analysis of variance (ANOVA) with the groups as a between-group factor, the year as a within-group factor. The correlations between FA values at baseline and the scores on the neuropsychological tests at the 3-year follow-up were analyzed by the Spearman's rank correlation method. Differences were considered significant if P-values were <.05. To assess the discrimination of the aMCI-AD group and the aMCI-aMCI group, the receiver operating characteristic (ROC) curves, the area under the curve (AUC), and the 95% confidence intervals (CI) were also calculated.

Results
Patient Characteristics

Table 1 illustrates the demographic and basic neuropsychological data for the study participants. At baseline, there were no significant differences between the aMCI-AD and aMCI-aMCI groups in age and MMSE, ADAS, and WMS-R logical memory scores. However, the aMCI-AD group exhibited significantly lower MMSE scores ($P < .001$), lower WMS-R logical memory scores ($P < .01$), and higher ADAS scores ($P < .001$) than the aMCI-aMCI group at the 3-year follow-up. In the
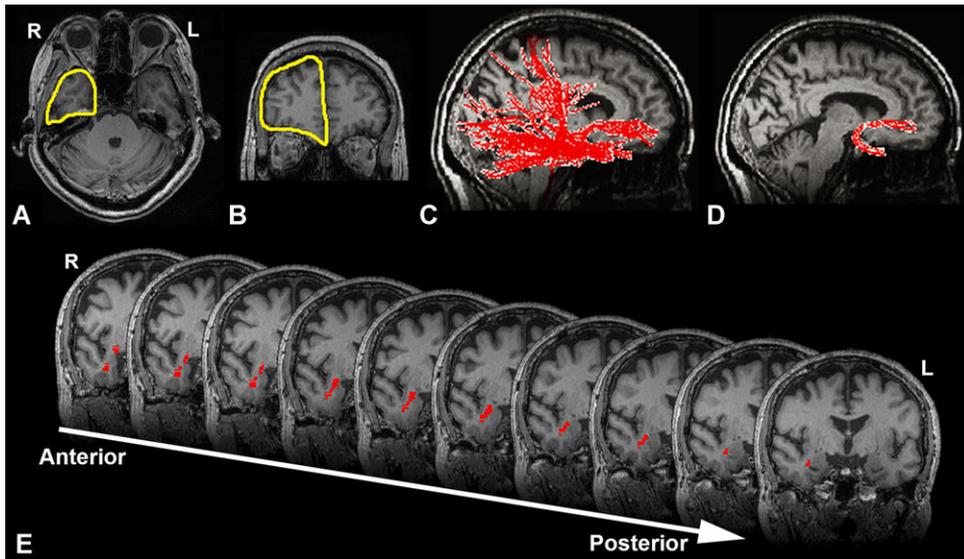
Fig 1. (A) An axial slice of the first ROI that was placed in the anterior temporal lobe. (B) A coronal slice of the second ROI that was placed in the frontal lobe. (C) Tractography that was generated by the first ROI and superimposed on structural MRI. (D) Tractography of the UF that was generated by these 2 ROIs. (E) Ten consecutive coronal slices from the most posterior portion that were used to calculate the FA values in UF.

Table 1. Demographic and Neuropsychological Data of the aMCI-aMCI and aMCI-AD Groups

	aMCI-aMCI	aMCI-AD
Number of subjects	14	8
Gender (male/female)	4/10	1/7
Baseline		
Age, years	70.9 (4.4)	71.8 (5.3)
MMSE score	27.2 (2.2)	25.3 (1.8)
ADAS score	8.1 (3.9)	9.6 (2.6)
WMS-R logical memory	7.2 (3.0)	4.0 (4.3)
Follow-up at 3 years		
Age, years	73.9 (4.8)	75.0 (5.2)
MMSE score	27.6 (2.3)[**]	20.8 (2.5)[**]
ADAS score	7.3 (6.2)[**]	15.2 (5.6)[**]
WMS-R logical memory	14.1 (9.2)[*]	5.8 (4.9)[*]

AD = Alzheimer's disease; ADAS = Alzheimer's disease assessment scale; aMCI = amnestic mild cognitive impairment; MMSE = mini-mental state examination; WMS-R = Wechsler memory scale-revised.
Values are shown as mean (standard deviation).
[*]$P < .01$ between the aMCI-aMCI and aMCI-AD groups;
[**] $P < .001$ between the aMCI-aMCI and aMCI-AD groups.

aMCI-AD group, MMSE scores at the 3-year follow-up were significantly lower than those at baseline ($P < .01$), whereas the aMCI-aMCI group showed no significant changes in MMSE or WMS-R logical memory scores ($P = .56$).

Group Comparisons of FA Values in UF

For FA values in the right UF, ANOVA indicated significant main effects of group [$F(1,20) = 16.8$, $P < .001$] and year [$F(1,20) = 15.5$, $P < .001$] (Fig 2A). The interaction between group and year was not significant [$F(1,20) = .008$, $P = .92$]. For FA values in the left UF, the main effect of group [$F(1,20) = 3.3$, $P = .082$] or year [$F(1,20) = 2.7$, $P = .11$] was not significant, and the interaction between the group and year was not

significant [$F(1,20) = .6$, $P = .45$]. The numbers of fibers in the right UF were 438.1 ± 278.5 (mean $\pm$ SD) and 297.4 ± 221.6 at baseline in the aMCI-aMCI group and the aMCI-AD group, respectively, and 370.3 ± 290.1 and 270.8 ± 143.6 at the 3-year follow-up in the aMCI-aMCI group and the aMCI-AD group, respectively. The numbers of fibers in the left UF were 335.5 ± 242.9 and 183.9 ± 90.1 at baseline in the aMCI-aMCI group and the aMCI-AD group, respectively, and 398.4 ± 232.7 and 280.9 ± 167.4 at the 3-year follow-up in the aMCI-aMCI group and the aMCI-AD group, respectively. ANOVA indicated no significant main effects of group [right fibers: $F(1,20) = 3.6$, $P = .062$; left fibers: $F(1,20) = 2.9$, $P = .097$] or year [right fibers: $F(1,20) = 1.0$, $P = .33$; left fibers: $F(1,20) = 1.9$, $P = .18$] and no interaction between group and year [right fibers: $F(1,20) = .4$, $P = .522$; left fibers: $F(1,20) = .2$, $P = .645$].

Figure panels 2B–D show scatter plots of the FA values in the right UF at baseline and the MMSE, ADAS, and WMS-R logical memory scores at the 3-year follow-up. All neuropsychological data at the 3-year follow-up were significantly correlated with FA values in the right UF at baseline (MMSE: $r = .58$, $P < .01$; ADAS: $r = -.53$, $P < .05$; WMS-R logical memory: $r = .48$, $P < .05$).

ROC Analysis

Figure 3 shows ROC curves for the 2 predictive models (FA values in the right UF and left UF at baseline, respectively) for the aMCI-AD and aMCI-aMCI groups. The AUC for FA values in the right UF was .813 (95% CI, .634-.991), whereas AUC for FA values in the left UF was .598 (95% CI, .338-.858).

Discussion

In this study, we showed for the first time that measuring WM abnormalities in UF is a potential indicator of the conversion of aMCI to AD. In addition, it also revealed the possible
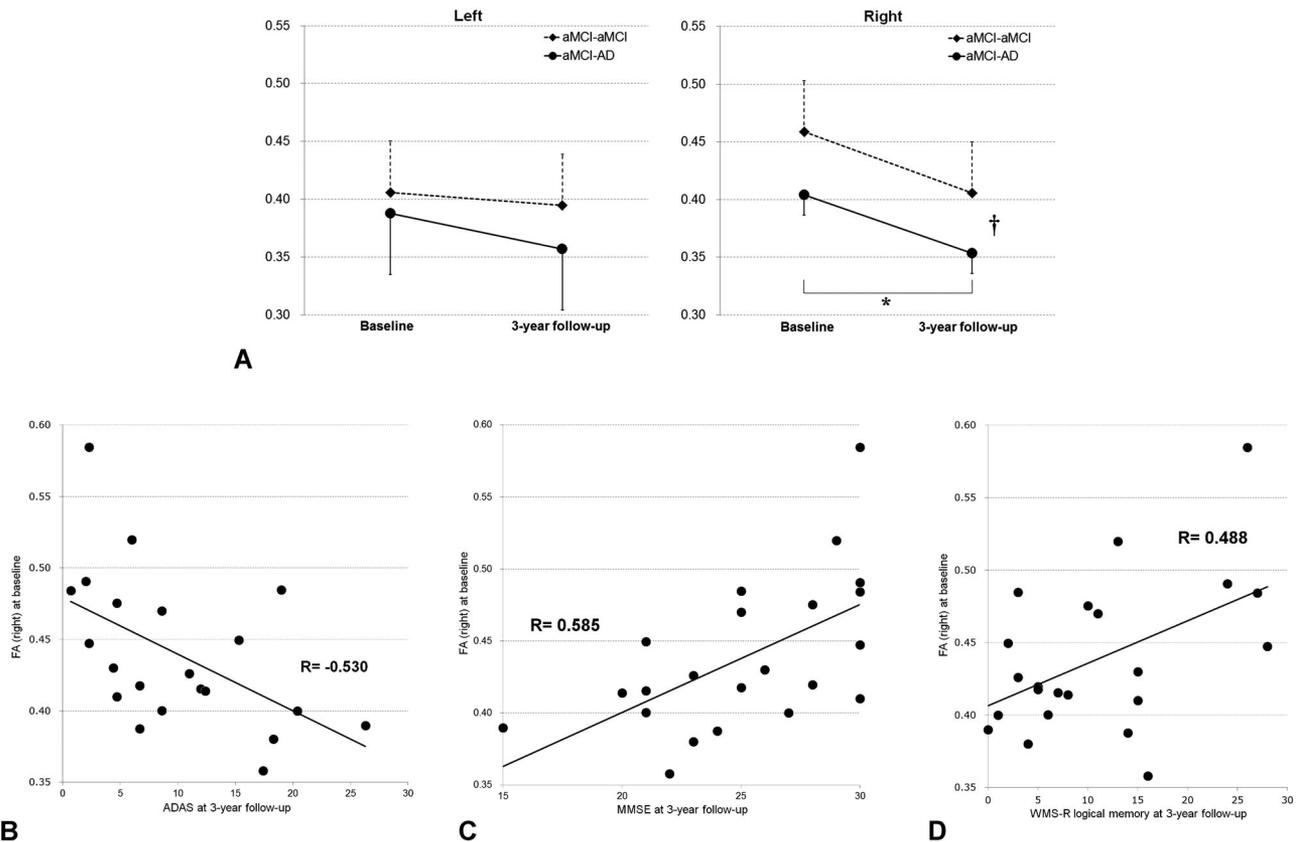
Fig 2. (A) Temporal changes in the FA values in the left and right UF in the aMCI-aMCI and aMCI-AD groups. Values are presented as mean ± SD; *P < .001, significant main effect (time) with ANOVA; †P < .001, significant main effect (group) with ANOVA. (B-D) Scatter plots illustrating the relationship between FA values in the right UF and scores on the ADAS (B), the MMSE (C), and logical memory scores of the WMS-R (D) at the 3-year follow-up examination.

association of UF pathology with AD conversion in patients with aMCI with memory impairment. Here, we discuss our results point by point.

Decrease in FA Values in the Right UF at Baseline

In this study, we showed that FA values in the right UF were significantly lower in the aMCI-AD group than in the aMCI-aMCI group. On the other hand, our previous study found that FA values in the left UF were significantly lower in the aMCI group than in the normal control group.[12] FA values in the left UF in the aMCI group in this study were consistent with those reported in our previous study.[12] Therefore, FA values in the left UF may be related to the conversion of a normal state to aMCI, and FA values in the right UF may predict the conversion of aMCI to AD.

A number of studies have indicated a loss of volume in several regions of the right GM and a decrease in FA values in the right WM in patients with AD. Kim et al have reported a reduction in GM volume in the right inferior frontal gyrus in patients with AD compared with healthy controls.[19] In addition, the FA values in the right frontal and temporal WM have been found to be significantly lower in patients with AD than in healthy controls.[20] Significant reductions in the FA values in patients with AD have also been observed in the right temporal WM extending to the parahippocampal gyrus and the poste-

rior corpus callosum in a voxel-based meta-analysis.[21] These previous studies have provided some evidence that the conversion to AD is related to decreased FA values on the right side. In this study, we found that FA values in the right UF were decreased, even at the aMCI stage. Our results were consistent with the findings of other tractography-based studies that have shown decreased FA values in UF in patients with AD.[8,11] However, our findings suggested that the decreased FA values in the right UF might be a more prominent factor in the patients undergoing the conversion of aMCI to AD. Further prospective studies with larger sample size are needed to verify these hypotheses.

The differences in the numbers of fibers or FA values in UF were not significantly different by unpaired 2-tailed *t*-tests between female and male at baseline or after a 3-year follow-up in this study. A recent study has shown that the number of fibers in the right UF was significantly higher only in male subjects with conduct disorder and there is a significantly difference in the FA values in the bilateral UF between female and male with conduct disorder.[22] Further studies with larger sample size are needed to investigate gender effects on the UF in aMCI. In addition, subjects with the apolipoprotein E (APOE) ε3/ε4 genotype, which is a well-known risk factor of AD, had a significant effect on the FA values in UF after adjusting age-11 IQ and vascular disease history.[23] Although the patients were not
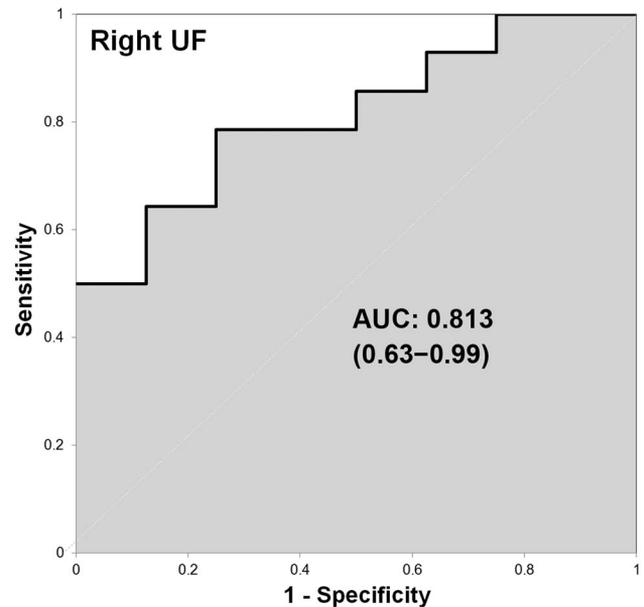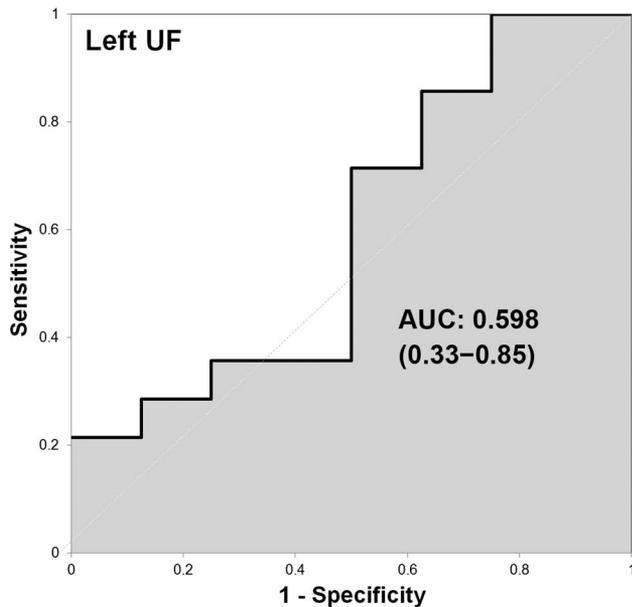
Fig 3. ROC curves with the AUC and the 95% CI values that were obtained from FA values in the left and the right UF at baseline for predicting a conversion to AD.

checked for APOE status in the study, subgroup analyses using APOE genotype might highlight the difference in FA values in UF between the aMCI-AD and aMCI-aMCI groups.

Association between FA Values in the Right UF and Memory Impairment

We demonstrated that the lower FA values in the right UF at baseline were significantly correlated with the scores on MMSE, ADAS, and WMS-R logical memory cognitive tests at the 3-year follow-up. The UF is a ventral fiber bundle that connects the orbital cortex with the amygdala and hippocampal gyrus,[24] and plays an important role in the formation and retrieval of memory and cognition. In functional MRI studies, the degree of cognitive decline has been predicted by hippocampal activation in patients with MCI.[25] Moreover, a VBM study has revealed significant atrophy of the right hippocampus-amygdala region and the right superior temporal gyrus in patients with MCI compared with healthy controls.[26] Our results are in line with these previous studies, and indicate that decrease of WM integrity in the right UF can be a predictor of future cognitive decline.

FA Values as a Predictor of Conversion to AD

Because early prediction of the conversion of aMCI to AD is a major topic of clinical research, it is important to identify effective indices for this prediction. In a previous study, AUC, which has been shown to be a key factor in the prediction of the conversion to AD, of FA values was .71-.94 in the corpus callosum, body of fornix, and cingulum within a time frame of 1-1.5 years.[27] In this study on UF, AUC of FA values in the right UF was .813, whereas the same in the left UF was .598. Thus, FA values in the right UF might be a better predictor of the conversion to AD than those in the left.

Limitations

The main limitation of this study was the relatively small number of patients (22 patients). In spite of the small group, however, statistically significant differences were found in FA values in UF between the aMCI-AD and aMCI-aMCI groups. Another limitation was that we have not investigated here fiber tracts other than UF. Other fiber tracts might also be important in the conversion of aMCI to AD.

Conclusions

This study showed that FA values in the right UF in aMCI who converted to AD was decreased compared with those who did not convert. Moreover, we found correlations between several measures of cognitive performance and FA values in UF at baseline. To the best of our knowledge, this is the first study to report a specific relationship between FA values in the right UF and conversion from aMCI to AD as well as their cognitive performances. These findings suggest that decreased FA values in the right UF might be an effective predictor of conversion of aMCI to AD.

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