Clinical Investigative Study

Use of Diffusion Tensor Imaging for Evaluating Changes in the Microstructural Integrity of White Matter Over 3 Years in Patients with Amnesic-Type Mild Cognitive Impairment Converting to Alzheimer’s Disease

Jian-Liang Fu, PhD, Yu Liu, MS, Yu-Mei Li, MS, Cheng Chang, MS, Wen-Bin Li, PhD

From the Department of Neurology, Shanghai Jiaotong University Affiliated Sixth People’s Hospital, Shanghai 200233, P. R. China (J-LF, Y-ML); Department of Emergency, Shanghai Eighth People’s Hospital, Shanghai 200235, P. R. China (YL); and Department of Radiology, Shanghai Jiaotong University Affiliated Sixth People’s Hospital, Shanghai 200233, P. R. China (CC, W-BL).

Keywords: Alzheimer’s disease, mild cognitive impairment, diffusion tensor imaging, fractional anisotropy, apparent diffusion coefficient.

Acceptance: Received November 18, 2012, and in revised form July 2, 2013. Accepted for publication July 3, 2013.

Correspondence: Address correspondence to Jian-Liang Fu, Department of Neurology, Shanghai Jiaotong University Affiliated Sixth People’s Hospital, 600 Yi Shan Road, Shanghai 200233, P. R. China. E-mail: fujianliang@163.com.

These authors contributed equally to this work (J-LF, YL, Y-ML, CC).

J Neuroimaging 2014;24:343-348. DOI: 10.1111/jon.12061

ABSTRACT

BACKGROUND AND PURPOSE
Patients with amnestic mild cognitive impairment (aMCI) are at risk of developing Alzheimer’s disease (AD). It is therefore important to identify biomarkers of conversion to AD. This study examined whether the integrity of white matter can predict this conversion.

METHODS
Magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) and neuropsychological features of aMCI subjects (n = 41) were compared with normal controls (n = 20) for 12-36 months.

RESULTS
Compared to controls, 22 aMCI subjects had lower fractional anisotropy (FA) values in the cingulate fasciculus (CF) at baseline, and 19 of those converted to AD during follow-up. Only two of the other 19 aMCI patients converted to AD. Compared to baseline, AD converters showed lower FA values in the anterior frontal lobe, temporal lobe, hippocampus, inferior fronto-occipital fascicles, corpus callosum genu and CF, and higher apparent diffusion coefficient values in the temporal lobe and hippocampus.

CONCLUSIONS
Those aMCI subjects with lower than normal FA values in the CF were more likely to convert to AD. The connectivity of the hippocampus and cingulate bundles may be affected in the early stage of AD. Impairment of white matter and fiber bundles was more severe at the AD stage than the aMCI stage.

Introduction
Alzheimer’s disease (AD) is the most common cause of dementia, and the amnestic type of mild cognitive impairment (aMCI) represents a transitional stage between normal aging and early dementia.1 Subjects with aMCI are at higher risk of developing AD. It is therefore important to identify predictive biomarkers of conversion to AD. Compared to cerebral spinal fluid (CSF) markers,2 a noninvasive imaging marker is more appealing for the screening of aMCI patients to establish those at greater risk of conversion to AD.

Diffusion tensor imaging (DTI) is a form of magnetic resonance imaging (MRI) that combines diffusion-weighted pulse sequences with tensor mathematics to measure molecular diffusion in three dimensions. White matter tracking using DTI enables the noninvasive tracking of neuronal fiber bundles based on diffusion anisotropy of the water molecules in white matter.3 Two complementary parameters obtained from DTI measurements are apparent diffusion coefficient (ADC) and fractional anisotropy (FA), which are influenced by changes in the tissue microenvironment and provide quantitative measures of directionally averaged diffusion. These parameters can be used to assess the degradation of white matter and fiber tracts in the brain, and have therefore been applied to the study of a variety of neurodegenerative disorders. The integrity of the white

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
In addition, a small number of DTI studies have shown microscopic white matter changes in patients with mild cognitive impairment (MCI).\(^4\) In the current longitudinal study, the microstructural damage (estimated by DTI) and the DTI indexes of microstructural damage were compared in patients at the aMCI and AD stage, using a group of healthy elderly volunteers as normal controls (NCs). The study aimed to test whether the integrity of the white matter fiber tracts in aMCI patients can predict conversion to AD.

### Materials and Methods

#### Subjects

Forty-one patients diagnosed with aMCI were consecutively recruited from a memory impairment clinic (Department of Neurology, Shanghai Sixth People’s Hospital, which is affiliated with Shanghai Jiao Tong University) between June 2008 and June 2010. Twenty healthy NCs, who were rigorously matched with patients in terms of age, gender and education, were recruited from the same geographical area. For all participants, the clinical assessment consisted of the following: (1) a medical, psychiatric and neurological history; (2) a list of current medications; and (3) a physical and neurological examination. The neuropsychological examination included the mini-mental state examination (MMSE),\(^14\) the Montreal Cognitive Assessment (MoCA),\(^15\) the clinical dementia rating (CDR)\(^16\) and the modified Hachinski ischemic scale (HIS).\(^17\) Patient histories were collected from reliable individuals with knowledge of the patient, who were usually relatives. The demographic and clinical data of participants are listed in Table 1. There were no significant differences between the two NC and aMCI groups in terms of age, education, and gender.

### Table 1. Demographic and Neuropsychological Data

| Characteristics | NC group (n = 20) | aMCI group (n = 41) | P value (MWU) | NC group (n = 18) | aMCI nonconverters (n = 20) | aMCI converters (n = 21) | P value (MWU) |
|-----------------|------------------|------------------|---------------|------------------|--------------------------|--------------------------|---------------|
| Gender [M/F]    | 10/10            | 20/21            | NS            | 10/8             | 9/11                     | 11/10                    | NS            |
| Age (years)     | 71.00 ± 5.33     | 70.57 ± 6.32     | NS            | 73.43 ± 4.72     | 74.60 ± 6.12             | 73.35 ± 5.21             | NS            |
| Education (years) | 13.90 ± 2.88     | 12.64 ± 2.04     | NS            | 13.38 ± 2.51     | 13.15 ± 2.74             | 12.52 ± 3.34             | NS            |
| MMSE            | 29.65 ± .49      | 24.68 ± 1.14\(^4\) | .036          | 28.91 ± .87      | 23.54 ± 1.56             | 17.78 ± 3.56\(^**\)      | .025          |
| MoCA            | 28.45 ± .94      | 21.25 ± 1.09\(^6\) | .043          | 22.87 ± .98      | 20.45 ± 2.73             | 12.43 ± 3.82\(^**\)      | .033          |
| CDR             | 0                | .5               | -             | 0                | .5                       | 1                        | -             |

Values represent counts or means ± SD. MWU = Mann-Whitney U-test, which was used here because the neuropsychological data were not normally distributed. *A statistical difference between the NC group and aMCI group, P < .05; **A statistical difference between the aMCI nonconverter group and aMCI converters group, P < .05. NS = not significant; MMSE = Mini-Mental Status Examination; MoCA = Montreal Cognitive Assessment; CDR = Clinical dementia rating. \(^6\)Two healthy controls converted to AD.

A number of recent studies have examined different predictors of conversion from MCI to AD using neuropsychological tests, MRI, or CSF biomarkers.\(^1,0,9,10\) In the current longitudinal study, aMCI patients can predict conversion to AD.

#### Clinical follow-up

All patients were clinically followed for periods of 1-3 years after their baseline MRI and DTI scan. Over this follow-up period, there was either no change in their diagnosis (nonconverters) or their symptoms and clinical performance declined to the extent that they fulfilled the criteria for AD (converters). The criteria for AD were: (1) diagnostic evidence of probable AD consistent with the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria;\(^19\) and (2) MMSE score of ≤23, MoCA score of ≤14, CDR score >1 or HIS score <.4.

#### MR image acquisition

None of the subjects had any metal implants in the body or any other contraindication to MRI. All 41 participants underwent the same imaging protocol using a 3.0 Tesla Allegra MR scanner (3.0T Achieva, Philips Medical System, Best, The Netherlands) with an eight-channel phased array head coil. This protocol included whole-brain T1-weighted imaging (T1WI), diffusion-weighted scanning, and standard clinical sequences (T2, fluid-attenuated inversion recovery [FLAIR]). Patients with small cognition; (3) normal activities of daily living; (4) nondemented; and (5) MMSE score between 24 and 27, and MoCA score between 15 and 24, or a CDR score of .5. Exclusion criteria were as follows: age > 80 years, a history of overt depression or other psychiatric diseases; significant cerebrovascular disease; a modified HIS score of ≥4; or a lack of any daily living activity.

As part of an ongoing study, neuropsychological assessments were performed four times over the course of a year: at 0, 3, 6 and 12 months. For NCs and nonconverters, MRI scans were investigated twice: at the start of the study and at the end of follow-up period. An additional MRI scan was performed on aMCI converters, after the AD diagnosis had been made. The median number of months between the initial diagnosis of aMCI and the subsequent diagnosis of AD in converters was 21.00 (interquartile range p25-p75 values = 12.00-27.00).

The study procedures were undertaken according to the guidelines of the hospital research ethics committee. All participants signed written informed consent forms.

#### MR image acquisition

None of the subjects had any metal implants in the body or any other contraindication to MRI. All 41 participants underwent the same imaging protocol using a 3.0 Tesla Allegra MR scanner (3.0T Achieva, Philips Medical System, Best, The Netherlands) with an eight-channel phased array head coil. This protocol included whole-brain T1-weighted imaging (T1WI), diffusion-weighted scanning, and standard clinical sequences (T2, fluid-attenuated inversion recovery [FLAIR]). Patients with small...
vessel disease show high-signal intensity on T2-weighted imaging (T2WI) representative of ischemic cell damage, which makes it difficult to differentiate AD from vascular dementia. Therefore, those subjects with white matter alterations on T2WI were excluded.

The MR parameters were as follows: flip angle 90°; slice thickness 6mm; axial T1 WI turbo spin-echo (TSE) (repetition time [TR]/ echo time [TE] 2000/20 ms, field of view [FOV] 220 × 220 mm, matrix = 512 × 512); axial T2-weighted TSE (TR/TE 3,000/80 ms, FOV = 256 × 256 mm, matrix 512 × 512); sagittal T1W TSE (TR/TE 2000/20 ms, FOV 230×220 mm, matrix 296×200); coronal T2WI TSE (TR/TE 3000/80 ms, FOV 250×190 mm, matrix 436×300); and axial FLAIR (TR/TE 11,000/120 ms, inversion time 2800 ms, FOV = 220 × 220 mm, matrix = 512 × 512).

Single-shot spin echo-echo planar imaging (SE-EPI) was used in DTI. Scan layers were aligned parallel to the anterior/posterior line with the following settings: TR/TE 6518/60 ms, FOV = 256 mm × 256 mm, slice thickness 2 mm, matrix 256×256, sensitivity encoding (SENSE) factor = 2, 15 nonlinear directions, b-value of 0 and 800 s/mm² respectively. To increase the signal-to-noise ratio, scanning was repeated three times (total scanning time = 4 min 13 s).

The various association tracts were identified based on standard atlases. Post-processing FiberTrak software (Philips Medical System) was used to measure FA and ADC values in different layers of B0 map and color-coded map of the axial and coronal images. In the color-coded maps, red represents left and right, green represents before and after, and blue represents top and bottom. Regions of interest (ROIs) of 15-25 pixels were placed into the following white matter regions: the prefrontal lobe, temporal lobe, parietal lobe, occipital lobe, hippocampus (Fig. 1). For most regions, we used the ROI designations described by Fellgiebel et al. (Fig. 2). These ROIs included: the inferior fronto-occipital fascicles (IFOF), genu and splenium of the corpus callosum (GCC, SCC), superior longitudinal fasciculus II (SLF-II), and the cingulate fasciculus (CF). The size of the ROIs was dependent on the anatomical region studied. The nonmidline regions were measured on both sides. The rater, an experienced neuroradiologist who was blinded to the clinical diagnosis of all the participants, defined the placements of ROIs for FA and ADC measurements.

Statistical analyses

Data were analyzed using the Statistical Package for Social Sciences (SPSS for Windows, Version 15.0, SPSS, Chicago, Illinois,
USA). A Mann-Whitney test was used, as the neuropsychological data were not normally distributed. A Student’s t-test for nonpaired data was used to compare FA and ADC values of the white matter in each region within each group (at the start of the study and after follow-up). For all the analyses, a value of \( P < .05 \) was considered statistically significant.

**Results**

**Neuropsychological data**

Healthy controls displayed levels of cognitive performance within the normal range, both at baseline and at follow up (Table 1). Compared to the control group, the aMCI group showed lower scores for the MMSE and MoCA. At the start of the study, the aMCI group had an average MMSE score of 24.68. In addition, 22 of the 41 aMCI patients (53.60%) had lower FA values in the CF at the baseline than the mean value determined in the controls. During the 12 to 36-month follow-up, 19 of these 22 (86.36%) clinically converted to AD. However, only two of the other 19 (10.53%) aMCI patients (with normal FA values in the CF) converted to AD. Compared to MCI nonconverters, the aMCI converters showed lower scores for the MMSE and MoCA. Two of the 20 healthy volunteers (10%) converted to AD, with an average MMSE score of 17.78 (\( P < .01 \)).

**ROI-based measures**

We measured the FA and ADC at different locations of white matter using ROI-based analysis. There were no significant differences between groups in the symmetric regions. At baseline, the FA values of the CF were significantly decreased in aMCI patients compared to the normal aging control. Compared to aMCI nonconverters, aMCI converters had lower FA values in the anterior frontal lobe, temporal lobe, hippocampus, IFOF, GCC and CF. With regards to ADC values, there were no significant differences between groups for various regions at the baseline. During the 12- to 36-month follow-up period, aMCI converters showed higher ADC values than aMCI nonconverters in the temporal lobe and hippocampus (\( P < .05 \); Tables 2 and 3).

**Discussion**

In addition to clinical features and neuropsychological assessments, neuroimaging studies play an important role in the early diagnosis of aMCI and AD. In this longitudinal study, DTI data from aMCI patients were examined in order to detect the white matter abnormalities between AD converters and nonconverters. Two main findings were noted. First, compared to aging controls, disturbances were found in cingulum fibers in aMCI patients. Second, compared to aMCI nonconverters, widespread regions of the brain were found to have a lower FA values in aMCI converters. In addition, increased ADC values were found in the temporal lobe and hippocampus of aMCI converters. Overall, the findings of this investigation indicate that microstructural damage of multiple association fiber tracts may occur at different times in the course of AD thus may be differentially sensitive.

In line with previous studies,\(^3,23–28\) reduced FA values were found in the cingulum fibers of aMCI patients. However, most of these studies indicated that DTI of the posterior cingulate region was able to discriminate MCI from cognitively normal individuals, but our results showed no differences between groups in the symmetric regions. The discrepancy between these finding and the results of the current study might be due to differences in the study group or technical differences. The cingulum fibers, which connect the hippocampus and the posterior of the cingulum bundle, are related to the pathological process of AD. Abnormal FA in the cingulum bundle reflects the greater susceptibility of the cortical cognitive system, which is related to impairment of the cholinergic conductional pathway. It has been suggested that the basal forebrain cholinergic system is associated with learning and memory, and is the first region

### Table 2. FA Values of Selected White Matter Areas Across Different Groups

| Region      | Baseline NC group | Baseline aMCI group | Nonpaired t-test NC group vs. aMCI group | Follow-up NC group | Follow-up aMCI group | Nonpaired t-test Nonconverters vs. converters |
|-------------|-------------------|---------------------|-----------------------------------------|--------------------|----------------------|-----------------------------------------------|
| Prefrontal | .446 ± .018       | .463 ± .019         | NS                                      | .438 ± .021        | .444 ± .023          | .321 ± .017**                                 |
| Temporal    | .390 ± .017       | .398 ± .016         | NS                                      | .388 ± .019        | .385 ± .027          | .287 ± .015**                                 |
| Parietal    | .458 ± .021       | .446 ± .020         | NS                                      | .461 ± .020        | .456 ± .023          | .455 ± .022                                   |
| Occipital   | .409 ± .021       | .416 ± .018         | NS                                      | .411 ± .018        | .412 ± .010          | .415 ± .021                                   |
| Hippocampus | .416 ± .025       | .424 ± .027         | NS                                      | .421 ± .021        | .417 ± .022          | .334 ± .018**                                 |
| IFOF        | .575 ± .008       | .551 ± .011         | NS                                      | .571 ± .013        | .566 ± .011          | .423 ± .012**                                 |
| GCC         | .732 ± .015       | .736 ± .021         | NS                                      | .729 ± .012        | .725 ± .016          | .654 ± .016**                                 |
| SCC         | .769 ± .008       | .771 ± .012         | NS                                      | .771 ± .009        | .776 ± .012          | .764 ± .011                                   |
| SLFII       | .614 ± .008       | .634 ± .009         | NS                                      | .627 ± .010        | .634 ± .011          | .632 ± .009                                   |
| CF          | .626 ± .006       | .598 ± .023*        | .029                                    | .611 ± .008        | .614 ± .021          | .543 ± .011**                                 |

Values are represented as means ± SD. NC = normal controls; aMCI = amnestic mild cognitive impairment; AD = Alzheimer’s disease; IFOF = inferior fronto-occipital fascicles; GCC = corpus callosum genu; SCC = corpus callosum splenum; SLF = superior longitudinal fasciculus; CF = cingulate fasciculus.

Differences of the measurement data were compared using the \( t \)-test and data among groups were processed with the nonpaired \( t \)-test according to the analysis of variance homogeneity. *A statistical difference between the NC group and aMCI group, \( P < .05 \); **A statistical difference between aMCI nonconverters group and aMCI converters group, \( P < .05 \); NS = not significant.
to be impaired in aMCI patients. Nineteen of the 22 (86.36%) aMCI patients with lower FA values clinically converted to a diagnosis of AD during the follow-up period. Thus, abnormal FA observed in the cingulum may be a sensitive parameter by which to predict the conversion from aMCI to AD.

Compared to aMCI nonconverters, aMCI converters had reduced FA in multiple areas. The decrease of prefrontal lobe and temporal lobe white matter anisotropy may be due to early temporal-to-frontal disconnections. The IFOF represent the only direct connection between the occipital and frontal lobes, and the CF is adjacent to the parahippocampal cortex and provides connections to prefrontal cortical areas.29 Those changes indicate that there is regional specificity to the degradation of axon integrity and loss of cortical connections. Alternative explanations include small vessel alterations, demyelination of axonal structures, loss of axonal structure and possibly gliosis, which reduce directional diffusion and may contribute to reduced FA.3,29 The above results are in line with some other studies8,29 and suggest that the progression of AD initially implicates the medial temporal structures (the entorhinal cortex and hippocampus), followed by the temporal cortex, then the posterior parietal lobe, and finally the different levels of the frontal lobe of the cerebral cortex are involved.

In the current study, aMCI converters showed increased ADC values in the temporal lobe and hippocampus compared with aMCI nonconverters. This may indicate that involvement of the hippocampus and temporal lobe occurs early on during the pathological progression of AD. ADC is derived from diffusion-weighted MR images and describes the basic diffusion properties of the tissue. The pathological disruption of cell membranes, and the loss of myelin (affecting axonal processes), reduces the restrictions on the movement of water, and therefore the diffusivity expressed as the ADC would be expected to increase.31,32

In order to eliminate subjective errors, an experienced neuroradiologist who was blind to the clinical diagnosis of all participants defined ROIs following strict criteria. However, our study had some limitations. First, we used anisotropic voxels in the DTI, which might have caused a bias in the calculation of FA. Second, the fact that patients with T2 hyperintensities were excluded may have introduced some bias into the results. Third, the sample size of the study was small, and future studies should use larger groups of patients.

In summary, DTI could (in addition to traditional imaging and neuropsychological testing), serve as a sensitive technique for the early detection of white matter changes in aMCI and AD patients. Moreover, depending on which parts of the white matter and fiber tracts are involved, DTI scans may provide a sensitive index of the likelihood of clinical conversion to AD for aMCI patients.

Acknowledgment
This work was supported by a grant from the Cross Research Fund of Medical & Engineering of Shanghai jiaotong University [YG2012MS12].

### References
1. Petersen RC, Negash S. Mild cognitive impairment: an overview. *CNS Spectr* 2008;13:45-53.
2. Heister D, Brewer JB, Magda S, et al. Predicting MCI outcome with clinically available MRI and CSF biomarkers. *Neurology* 2011;77:1619-1628.
3. Fellgiebel A, Muller MJ, Wille P, et al. Color-coded diffusion-tensor-imaging of posterior cingulate fiber tracts in mild cognitive impairment. *Neurobiol Aging* 2005;26:1193-1198.
4. Cherubini A, Peran P, Spoletoni I, et al. Combined volumetry and DTI in subcortical structures of mild cognitive impairment and Alzheimer’s disease patients. *J Alzheimer’s Disease* 2010;19:1273-1282.
5. Mielke MM, Kozauer NA, ChanK CG, et al. Regionally-specific diffusion tensor imaging in mild cognitive impairment and Alzheimer’s disease. *Neuroimage* 2009;46:47-55.
6. Oishi K, Mielke MM, Albert M, et al. The fornix sign: a potential sign for Alzheimer’s disease based on diffusion tensor imaging. *J Neuromaging* 2012;22(4):365-374.

### Table 3. ADC Values of Selected White Matter Areas Across Different Groups

| Region            | Baseline | Nonpaired t-test | Follow-up |
|-------------------|----------|------------------|-----------|
|                   | NC group | aMCI group       | NC group  | aMCI group | NC group  |
|                   | (n = 20) | (n = 41)         | vs. aMCI group | (n = 18) | aMCI nonconverters | aMCI converters | NC group aMCI converters | Nonpaired t-test converters |
| Prefrontal lobe   | .457 ± .015 | .461 ± .012     | NS        | .438 ± .021 | .466 ± .019 | .460 ± .012 | NS |
| Temporal lobe     | .433 ± .009 | .439 ± .009     | NS        | .388 ± .019 | .442 ± .014 | .543 ± .011 | .035 |
| Parietal lobe     | .451 ± .009 | .460 ± .011     | NS        | .461 ± .020 | .448 ± .012 | .458 ± .011 | NS |
| Occipital lobe    | .425 ± .010 | .439 ± .013     | NS        | .411 ± .018 | .430 ± .009 | .443 ± .018 | NS |
| Hippocampus       | .445 ± .015 | .455 ± .021     | NS        | .421 ± .021 | .457 ± .021 | .642 ± .017 | .026 |
| IFOF              | .444 ± .006 | .452 ± .014     | NS        | .571 ± .013 | .447 ± .022 | .454 ± .018 | NS |
| GCC               | .452 ± .008 | .458 ± .021     | NS        | .729 ± .012 | .454 ± .009 | .449 ± .022 | NS |
| SCC               | .453 ± .010 | .454 ± .017     | NS        | .771 ± .009 | .453 ± .016 | .450 ± .015 | NS |
| SLF               | .451 ± .008 | .458 ± .013     | NS        | .627 ± .010 | .460 ± .011 | .458 ± .019 | NS |
| CF                | .452 ± .008 | .455 ± .010     | NS        | .611 ± .008 | .457 ± .012 | .458 ± .011 | NS |

Values are represented as means ± SD. NC = normal controls; aMCI = amnestic mild cognitive impairment; AD = Alzheimer’s disease; IFOF = inferior fronto-occipital fascicles; GCC = corpus callosum genu; SCC = corpus callosum splenium; SLF = superior longitudinal fasciculus; CF = cingulate fasciculus.

Differences of the measurement data were compared using the *t*-test and data among groups were processed with the nonpaired *t*-test according to the analysis of variance homogeneity. *A statistical difference between the aMCI nonconverters group and aMCI converters group, P < .05; NS = not significant.*
7. Medina D, DeToledo-Morrell L, Urresta F, et al. White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. *Neurobiol Aging* 2006;27:663-672.
8. Shim YS, Yoon Bora, Shona YM, et al. Difference of the hippocampal and white matter microalterations in MCI patients according to the severity of subcortical vascular changes: neuropsychological correlates of diffusion tensor imaging. *Clin Neurol Neurosurg* 2008;110:552-561.
9. Bruggen T, Steljes B, Thomann PA, et al. Do Alzheimer-specific microstructural changes in mild cognitive impairment predict conversion? *Psychiatry Res* 2012;203:184-193.
10. Huang J, Auchus AP. Diffusion tensor imaging of normal appearing white matter and its correlation with cognitive functioning in mild cognitive impairment and Alzheimer’s disease. *Ann NY Acad Sci* 2007;1097:259-264.
11. Buerger K, Uspenskaya O, Hartmann O, et al. Prediction of Alzheimer’s disease using midregional proadrenomedullin and midregional proatrial natriuretic peptide: a retrospective analysis of 134 patients with mild cognitive impairment. *J Clin Psychiatry* 2011;72:556-563.
12. McEvoy LK, Holland D, Hagler DJ Jr, et al. Mild cognitive impairment: baseline and longitudinal structural MR imaging measures improve predictive prognosis. *Radiology* 2011;259:834-843.
13. Modrego PJ, Fayed N, Sarasa M. Magnetic resonance spectroscopy in the prediction of early conversion from amnestic mild cognitive impairment to dementia: a prospective cohort study. *BMJ Open* 2011;1:e000007.
14. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
15. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53(4):695-699.
16. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43:2412-2414.
17. Rosen WG, Terry RD, Fuld PA, et al. Pathological verification of ischemic score in differentiation of dementia. *Ann Neurol* 1980;7:486-488.
18. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256:183-194.
19. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer’s disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease. *Neurology* 1984;34:939-944.
20. Kim SH, Park JS, Ahn HJ, et al. Voxel-based analysis of diffusion tensor imaging in patients with subcortical vascular cognitive impairment: correlates with cognitive and motor deficits. *J Neuroimaging* 2011;21(4):317-324.
21. Lee SK, Kim DI, Kim J, et al. Diffusion-tensor MR imaging and fiber tractography: a new method of describing aberrant fiber connections in developmental CNS anomalies. *Radiographics* 2003;23(1):53-65.
22. Mori S, Crain BJ, Chacko VP, et al. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann Neurol* 1999;45:263-269.
23. Fellgiebel A, Schermuly I, Gerhard A, et al. Functional relevant loss of long association fibre tracts integrity in early Alzheimers disease. *Neuropsychologia* 2008;46:1698-1706.
24. Zhang Y, Schiff N, Jahng GH, et al. Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. *Neurology* 2007;68:13-19.
25. Chua TC, Wen W, Chen X, et al. Diffusion tensor imaging of the posterior cingulate is a useful biomarker of mild cognitive impairment. *Am J Geriatr Psychiatry* 2009;17(7):602-613.
26. Huang H, Fan X, Weiner M, et al. Distinctive disruption patterns of white matter tracts in Alzheimer’s disease with full diffusion tensor characterization. *Neurobiol Aging* 2012;33(9):2029-2024.
27. Alves GS, O’Dwyer L, Jurcoane A, et al. Different patterns of white matter degeneration using multiple diffusion indices and volumetric data in mild cognitive impairment and Alzheimer patients. *PLoS One* 2012;7(12):e52859.
28. Zhuang L, Sachdev PS, Trollor JN, et al. Microstructural white matter changes in cognitively normal individuals at risk of amnestic MCI. *Neurology* 2012;79:748-754.
29. Bai F, Zhang Z, Watson DR, et al. Abnormal integrity of association fiber tracts in amnestic mild cognitive impairment. *J Neurol Sci* 2009;278:102-106.
30. Canu E, McLaren DG, Fitzgerald ME, et al. Mapping the structural brain changes in Alzheimer’s disease: the independent contribution of two imaging modalities. *J Alzheimers Dis* 2011;26:263-274.
31. Kantarci K, Jack CR, Xu YC, et al. Regional diffusivity of water in mild cognitive impairment and Alzheimer disease. *Radiology* 2001;219:101-107.
32. Zhang B, Zhang JG, Zhao H, et al. Evaluation of apparent diffusion coefficient mappings in amnestic mild cognitive impairment using an image analysis software brain search. *Acta Radiol* 2011;52:1147-1154.