Callosal Degeneration Topographically Correlated With Cognitive Function in Amnesic Mild Cognitive Impairment and Alzheimer's Disease Dementia

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Abstract: Degeneration of the corpus callosum (CC) is evident in the pathogenesis of Alzheimer's disease (AD). However, the correlation of microstructural damage in the CC on the cognitive performance of patients with amnesic mild cognitive impairment (aMCI) and AD dementia is undetermined. We enrolled 26 normal controls, 24 patients with AD dementia, and 40 single-domain aMCI patients with at least grade 1 hippocampal atrophy and isolated memory impairment. Diffusion tensor imaging (DTI) with fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (DA), and radial diffusivity (DR) were measured. The entire CC was parcellated based on fiber trajectories to specific cortical Brodmann areas using a probabilistic tractography method. The relationship between the DTI measures in the subregions of the CC and cognitive performance was examined. Although the callosal degeneration in the patients with aMCI was less extended than in the patients with AD dementia, degeneration was already exhibited in several subregions of the CC at the aMCI stage. Scores of various neuropsychological tests were correlated to the severity of microstructural changes in the subregional CC connecting to functionally corresponding cortical regions. Our results confirm that CC

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degeneration is noticeable as early as the aMCI stage of AD and the disconnection of the CC subregional fibers to the corresponding Brodmann areas has an apparent impact on the related cognitive performance. *Hum Brain Mapp* 35:1529–1543, 2014. © 2013 Wiley Periodicals, Inc.

Key words: corpus callosum; diffusion tensor imaging; Brodmann area; probabilistic tractography; neuroimaging

INTRODUCTION

Evidence has suggested that callosal degeneration is common in patients with Alzheimer's disease (AD) dementia [Chaim et al., 2007; Teipel et al., 2002; Tomaiuolo et al., 2007]. However, little is known about how early the microstructure changes of the corpus callosum (CC) start in the pathogenesis of AD. [Di Paola et al., 2010c]. Callosal degeneration was not a consistent finding in past studies that investigated patients with amnesic mild cognitive impairment (aMCI) [Di Paola et al., 2010a; Di Paola et al., 2010b; Ukmar et al., 2008; Wang and Su, 2006].

Although most CC fibers carry homotopic links between the two hemispheres, numerous heterotopic fibers in the CC connect to different cortical areas [Clarke and Zaidel, 1994; Witelson, 1989]. The CC topographically exhibits functional specialization of the callosal subregions connecting to various cortical lobes [de Lacoste et al., 1985]. The genu of the CC connects the orbitofrontal and frontal cortices, whereas the body and the splenium connect the temporal, parietal, and occipital regions [Abe et al., 2004]. Damage to different portions of the CC fibers may contribute to distinctive behavioral and cognitive symptoms.

Despite the importance of accurately determining the callosal subregions connecting to distinct cortical areas, there are no obvious anatomical landmarks to define clearly how to sub-divide the CC [Chao et al., 2009; Hofer and Frahm, 2006]. Various methods have been proposed to sub-divide the CC into several geometric partitions, and most previous studies have equally sub-divided the CC at the midsagittal plane by vertical lines [Weis et al., 1993; Witelson, 1989] or angular sectors [Hampel et al., 1998]. The main disadvantage of these methods was that either the fiber compositions or the fiber connections were not reflected in the subregions.

Diffusion tensor imaging (DTI) is a noninvasive technique that detects the water molecular diffusion in the local microstructure at a given voxel to provide information about the white matter fiber pathways in the human brain [Basser et al., 2000; Mori and van Zijl, 2002]. Parcelation of the CC based on the connectivity profile to the specific cortical areas by tractography of diffusion imaging technique has been applied in several studies [Chao et al., 2009; Hofer and Frahm, 2006; Park et al., 2008; Zarei et al., 2006]. When using this type of technique, striking differences were found from Witelson's classification in the anterior and mid-body parts of the CC [Hofer and Frahm, 2006]. Furthermore, inter-individual variations were evi-

dent in the white-matter fiber connections [Catani et al., 2005; Scholz et al., 2009]. Sub-dividing the CC using DTI to track the destination of fibers in each subject may provide a more accurate anatomical division of the CC.

Knowledge of the relationship between the region-specific CC microstructural alterations and cognitive performance in patients with AD dementia and aMCI remains limited. Using tractography, white matter (WM) destruction in the splenium of the CC and posterior cingulum has consistently been noted in patients with AD dementia [Kiuchi et al., 2009; Pievani et al., 2010; Taoka et al., 2006; Xie et al., 2005; Yasmin et al., 2008; Zhang et al., 2009]. However, only few DTI tractography studies have included patients with aMCI [Kiuchi et al., 2009; Pievani et al., 2010] and the results have been inconsistent. None of these studies sub-divides the CC using the probabilistic topography approach to investigate the correlation between cognitive performance and the CC subregional changes in aMCI and AD dementia.

In this study, the integrity of the CC was measured by four diffusivity indices: mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (DR) and axial diffusivity (DA). The MD (average diffusion coefficient, $[(\lambda_1 + \lambda_2 + \lambda_3)/3]$) is recognized as being an index of the alteration of microstructures in the brain (Basser et al., 1994). DA is the diffusion coefficient along the direction of maximal "apparent" diffusion (principle diffusion component, λ_1). The second and third eigenvalues in the DTI can be averaged and expressed as DR (transverse diffusion component, $[(\lambda_2 + \lambda_3)/2]$). The relative ratio of axial to radial diffusivities is known as FA and indicates the integrity of white matter fibers [Basser, 1995; Basser and Pierpaoli, 1996]. We measured all these 4 diffusivity indices to comprehensively explore the different types of diffusion changes in the CC.

We estimated the probabilistic topography of the CC by anatomical cytoarchitectural parcellation and the CC was divided into seven subregions according to the projections to the specific cortical Brodmann areas (BA). Regional callosal degeneration in patients with aMCI and AD dementia was examined. Subregional CC changes and their association with cognitive performance in patients with aMCI and AD dementia were investigated.

METHODS

Participants

The participant group was composed of 26 normal elderly control (NC) (male/female: 15/11, age = 73.8 ± 6.7

TABLE I. Demographic and clinical characteristics among normal controls, amnesic mild cognition impairment, and Alzheimer disease groups

Demographic variables	NC (<i>n</i> = 26)	aMCI (<i>n</i> = 40)	AD dementia (<i>n</i> = 24)	<i>F</i> or <i>X</i> ² value	<i>P</i> value
Age (years)	73.8 ± 6.7	76.4 ± 7.6	78.3 ± 5.7	2.638	0.077
Sex (male/female)	15/11	25/15	13/11	0.451	0.798
Education (years)	13.3 ± 3.5	12.1 ± 3.4	11.2 ± 3.7	2.380	0.099
Handedness (left/right)	1/25	2/38	0/24	0.338	0.845
MTA score	0.6 ± 0.6	2.1 ± 0.6	2.8 ± 0.8	82.203	<0.001
Bilateral hippo. volume	7.2 ± 0.8	6.6 ± 0.9	6.0 ± 1.0	10.098	<0.001
GM(cm ³)	565.2 ± 48.5	561.0 ± 47.1	519.7 ± 47.5	7.226	0.001
WM(cm ³)	475.7 ± 63.9	477.2 ± 47.7	457.1 ± 45.9	1.214	0.302
TIV(cm ³)	1330.5 ± 131.2	1356.6 ± 110.9	1307.7 ± 122.8	1.277	0.284
MMSE	28.8 ± 0.4	27.3 ± 0.3	21.0 ± 0.4 ^b	108.034	<0.001
CVVLT recall	7.9 ± 0.4	5.6 ± 0.3 ^a	1.4 ± 0.4 ^{b,c}	76.331	<0.001
CFT copy	16.0 ± 0.5	15.4 ± 0.3	14.3 ± 0.4 ^b	4.571	0.014
CFT recall	11.1 ± 0.8	7.5 ± 0.6 ^a	1.5 ± 0.8 ^{b,c}	36.144	<0.001
Verbal fluency test	17.4 ± 0.9	15.3 ± 0.6	12.1 ± 0.9 ^{b,c}	8.806	<0.001
BNT	28.3 ± 0.6	26.5 ± 0.4	23.6 ± 0.6 ^{b,c}	18.238	<0.001
TMT-B lines	13.4 ± 0.7	12.6 ± 0.5	8.5 ± 0.7 ^{b,c}	14.032	<0.001
Stroop test	35.7 ± 2.6	29.6 ± 1.8	20.8 ± 2.4 ^{b,c}	8.374	<0.001

Data are presented as mean ± standard deviation. Boldfaced *P*-value indicate significant differences (*P* < 0.05) in appropriate statistical tests. Hippocampal volumes were normalized to total intracranial volume [(volume of bilateral hippocampi in cm³/TIV in cm³)×1,000]. Results of a post-hoc ANCOVA test in different neuropsychological tests were corrected for multiple comparisons using Tukey's correction (adjusted for age, sex, and education).

NC, normal control; aMCI, amnesic mild cognition impairment; AD, Alzheimer's disease; MTA, medial temporal atrophy; hippo., hippocampus; GM, grey matter; WM, white matter; TIV, total intracranial volume; MMSE, Mini-Mental Screening Examination; CVVLT, Chinese version of the Verbal Learning Test; CFT, Complex Figure Test; BNT, Boston Naming Test; TMT-B lines, Trail-making Test Part B lines completed in 120 s.

^a*P* < .05 in post-hoc comparison with NC and aMCI.

^b*P* < 0.05 in post-hoc comparison with NC and AD.

^c*P* < 0.05 in post-hoc comparison with aMCI and AD.

years), 40 patients with aMCI (male/female: 25/15, age = 76.4 ± 7.6 years), and 24 patients with AD dementia (male/female: 13/11, age = 78.3 ± 5.7 years). A summary of the demographics and clinical information of the participants is listed in Table I. All participants and guardians of patients with AD dementia provided written informed consent before participating in this study. This study was approved by the Local Ethics Committee of Human Research in Taipei Veterans General Hospital Taiwan.

Every subject was interviewed by the neurologist (Dr. Wang) to obtain an extensive clinical history and neuropsychological evaluation. Laboratory and MR examinations were used to rule out other major neuropathologies such as tumors, strokes, severe white matter disease, or inflammation, but not to diagnose dementia. All subjects had no history of major brain trauma, brain tumor, stroke, epilepsy, alcoholism, major psychiatric illness, and other systemic diseases that affect cognitive function. The NC subjects were volunteers. All NC subjects were free of neurological disease and had no cognitive complaints.

To minimize the effect of severe white matter change in the image processing, an experienced radiologist (Dr. Linng) screened all MRI images for abnormal visible alterations of white matter (WM). Only subjects with mild or without white matter hyperintensities (WMH) in T2

weighted images [Scheltens et al., 1993] were recruited for this study.

Clinical Assessments

The Mini-Mental State Examination (MMSE) [Folstein et al., 1975] was administered to assess the global cognitive function for all participants. The function of daily living and the severity of dementia was assessed by the Clinical Dementia Rating (CDR) scale [Hughes et al., 1982]. To obtain the performance of different cognitive domains, the Chinese version Verbal Learning Test (CVVLT; 9 items, 4 trials, and 10-min delayed recall) [Chang et al., 2010], the modified Rey-Osterrieth Complex Figure Test (CFT) [Boxer et al., 2003], the categorical (animals) Verbal Fluency Test (VFT), the 30-item Boston Naming Test (BNT) [Cheung et al., 2004], the Stroop test, and the modified Trail-Making Test, Part B (TMT-B) [Kramer et al., 2003] were performed.

Patients with AD dementia were diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [McKhann et al., 1984]. All patients with AD dementia

included in this study had mild AD dementia with a CDR score of 1. All patients with aMCI fulfilled the Petersen criteria [Petersen et al., 1999]: (1) memory complaints, preferably corroborated by an informant; (2) objective memory impairment (verbal memory test, CVVLT ≤ 5 , below 1.5 SD of norm data) [Chang et al., 2010]; (3) normal general cognitive function (MMSE ≥ 24); (4) intact daily living activities; and (5) dementia criteria not met. Only patients with aMCI and isolated memory impairment and without neuropsychological evidence of dysfunction in other cognitive domains were recruited into the aMCI group for this study.

Data Acquisition

The MRI data of all participants were acquired on a 1.5T MR system (Excite II; GE Medical Systems, Milwaukee, WI) with an eight-channel coil at Taipei Veterans General Hospital in Taiwan. To minimize the artifact caused by motion during the scan, each participant's head was immobilized with cushions inside the coil. All of the images were acquired parallel to the anterior commissure-posterior commissure line. Whole brain high-resolution T1 weighted structural images were acquired using an axial three-dimensional fluid-attenuated inversion-recovery fast spoiled gradient recalled echo (3D FLAIR-FSPGR) sequence (TR/TE/TI = 8.548/1.836/400 ms; flip angle = 15°; 124 slices; NEX = 1; matrix size = 256 × 256; field of view = 260 × 260 mm²; slice thickness = 1.5 mm; voxel size = 1.02 × 1.02 × 1.5 mm³). Furthermore, whole brain diffusion weighted images were acquired using single shot spin-echo echo-planar imaging (EPI) sequence (TR/TE = 17,000/67.8 ms; 70 axial slices; NEX = 6; matrix size = 128 × 128 without zero padding; slice thickness = 2.2 mm without gapping; field of view = 260 × 260 mm²; voxel size = 2.03 × 2.03 × 2.2 mm³). The diffusion images gradient encoding schemes included thirteen noncollinear directions with *b*-value 900 s/mm² and a nondiffusion weighted image volume according to the minimal energy arrangement of electron distribution (<http://www2.research.att.com/~njas/electrons/dim3>). To assess the severity of the WMH in each participant, additional fast spin echo T2 weighted (TR/TE = 3,700/109 ms; 48 slices; NEX = 2; matrix size = 256 × 256; field of view = 240 × 240 mm²; slice thickness = 3 mm; voxel size = 0.47 × 0.47 × 3.0 mm³) and FLAIR T2 weighted (TR/TE/TI = 9,000/122/2,250 ms; 48 slices; NEX = 1; matrix size = 256 × 256; field of view = 240 × 240 mm²; slice thickness = 3 mm; voxel size = 0.47 × 0.47 × 3.0 mm³) structural images were also acquired. The total scanning time of the above protocol was ~45 min for each participant.

Data Preprocessing

All data were preprocessed using FSL v4.1.7 (Functional Magnetic Resonance Imaging of the Brain Software

Library; <http://www.fmrib.ox.ac.uk/fsl>). Each diffusion weighted image was registered to the nondiffusion weighted image by the affine registration approach that was implemented in FMRIB's Linear Image Registration Tool v5.5 (FLIRT; part of FSL) to minimize image distortions by eddy currents and reduce the artifacts caused by simple subject motion. Notably, subject motion induced the alteration of diffusion orientation. In this study, each gradient direction of the diffusion weighted images was reoriented with a corresponding transformation matrix that described the rotation parameters of subject motion [Leemans and Jones, 2009]. For further accuracy of cross-modality image registration, the non-diffusion weighted image, and corresponding T1 images of each participant were skull striped using the Brain Extraction Tool v2.1 (BET; part of FSL) to remove non-brain tissues and background noise from the images [Smith, 2002].

Data Analysis

Standard space identification and cross modality image registration

The Montreal Neurological Institute (MNI) space was used to serve as the standard template space for group comparison in this study. For each participant, the transformation matrix for registering DTI dataset from native space to MNI space was determined by a two-stage registration approach [Jenkinson and Smith, 2001]. The first stage transformation matrix was determined by registering the nondiffusion weighted image to a high-resolution T1 image with a 6 degree of freedom (DOF) affine registration approach and the second stage transformation matrix was determined by taking the structural T1 image to the MNI T1 standard template with a nonlinear registration approach. FMRIB's Linear Image Registration Tool v5.5 (FLIRT, part of FSL) and FMRIB's Non-linear Image Registration Tool v1.0 (FNIRT, part of FSL) were used in the linear and non-linear registration procedures. To avoid possible artifacts due to interpolation of image registration multiple times, these two transformation matrices were concatenated into a final transformation matrix to transform the images from the native diffusion space to the standard space. The inversed final transformation matrix was also calculated.

DTI analysis

After preprocessing the image and calculating the transformation matrix, the diffusion tensor model was fitted in each voxel using FMRIB's Diffusion Toolbox v2.0 (FDT; part of FSL), which provided a voxel-wise calculation of FA, MD ($(\lambda_1 + \lambda_2 + \lambda_3)/3$), DA (principle diffusion component, λ_1) and DR (transverse diffusion component, $(\lambda_2 + \lambda_3)/2$) values. All these diffusion indices inherently registered to the diffusion weighted images were spatially normalized into the MNI standard space using the

Figure 1.

Three dimensional surface reconstruction of the entire corpus callosum, cortical masks and global topography of corpus callosum. (a) The three-dimensional surface reconstruction of the entire corpus callosum which the primary volume of interest in current study. (b) BAs were reassigned to seven cortical target masks including frontal cortex (red, including BA8, BA9, BA10, BA11, BA44, BA45, BA46, and BA47), premotor and supplementary motor area [SMA] cortex (orange, including BA6), primary motor cortex (yellow, including BA4), primary sensory cortex (green, including BA1, BA2, BA3, and BA5), parietal cor-

tex (dark blue, including BA7, BA39, and BA40), occipital cortex (violet, including BA17, BA18, and BA19), and temporal cortex (light blue, including BA20, BA21, BA22, BA37, BA38, BA41, and BA42). (c) The global topography of the single subject's CC was constructed using connectivity-based parcellation approach with hard segmentation method in sagittal view (along with x-axis). The color of each CC subdivision corresponded to its connection profile of different cortical areas. BAs, Brodmann areas; CC, corpus callosum. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

two-stage registration approach mentioned above. The final voxel size of the images was 2 cubic mm.

Parcellation of the CC

A probabilistic tractography was performed to parcellate the entire three-dimensional human CC into different subregions based on connection profiles according to previous detailed literature [Behrens et al., 2003a,b]. The probability distribution function (PDF) of the principal fiber direction was estimated in each voxel using a Bayesian approach by sampling techniques for crossing fibers (BEDPOSTX; part of FSL). After modeling the local diffusion signal in each voxel, the probability distribution of global connectivity between a pair of seed and target regions was also estimated using repeated sampling 5,000 times at each voxel in the seed region with a curvature threshold of 0.2 and a step length of 0.5 mm. A spatial probability distribution of the fiber pathway from the seed to the target region was calculated. The seed mask for the entire three-dimensional CC for each participant was derived from the atlas based on the diffusion tensor maps obtained from 81 normal subjects acquired under the initiative of the International Consor-

tium of Brain Mapping (ICBM-DTI-81 atlas) [Mori et al., 2008]. We combined the genu, body, and splenium labels from this atlas into a single mask of CC. This ICBM-DTI-81 atlas is available in FSL atlas tool (<http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#wm>).

Figure 1 illustrates the volumes of interest of the entire three-dimensional CC detected in the current study. To determine the target masks of the fiber tractography, the template image for Brodmann areas [Brodmann, 1909] provided by MRICroN (MRICroN, software by C. Rorden; <http://www.cabiatl.com/mricro/mricron/index.html>) was used to parcellate the whole cerebral cortex into seven cortical supra-regions (frontal, premotor and supplementary motor, primary motor, primary sensory, parietal, occipital, and temporal cortices). The seven cortical supra-regions and the resulting seven subregions of the CC are also presented in Fig. 1. The definition of the seven cortical supra-regions was followed by the previous human CC parcellation study [Chao et al., 2009]. A detailed definition of the seven cortical supra-regions is listed in Supporting Information Table I. After probabilistic tracking, the number of samples that passed through each cortical target region was recorded and a probability of the connection from the seed region to

each cortical region was calculated as a proportion of the total number of samples (5000 samples). Hard segmentation of the entire three-dimensional CC was performed by the classification of the seed region according to the highest probability of connection to the corresponding cortical target regions. All tractography and hard segmentation were performed in the native space of the subject dataset and the resulting maps were warped into MNI space using the previous two-stage registration approach. All results were visually checked by an experienced radiologist to ensure the success of the whole registration procedure and fiber tractography.

Visual Rating of Hippocampal Atrophy

All of the T1 images were acquired parallel to the anterior commissure-posterior commissure line. The medial temporal lobe atrophy (MTA) was rated on the coronal T1-weighted images in their native space by a 5-point visual rating scale based on the height of the hippocampal formation, the width of the temporal horn, and the width of the choroid fissure [Scheltens et al., 1992]. Grade 0 indicates no MTA and Grade 4 indicates the most severe atrophy. All images were rated by a neurologist (Dr. Wang), who was blind to the subjects' clinical information when rating the severity of MTA. The intra-rater reliabilities coefficient for 20 randomly selected hippocampi was $\kappa = 0.91$. MTA scores of the left and right hippocampi were averaged to present the MTA grade of a subject [Visser et al., 2002].

Volumetric Analysis of Brain MRIs

The hippocampal volumes were normalized to the total intracranial volume (TIV) [(volume of bilateral hippocampi in cm^3 /TIV in cm^3) $\times$ 1,000] to adjust for individual differences in brain size. The TIV was calculated as the summation of grey matter, white matter, and CSF volumes in the native space using Gaser's VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) with statistical parametric mapping (SPM8, Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and implemented in Matlab r2010a (MathWorks, Natick, Massachusetts). Volume estimation of bilateral hippocampi was performed using FMRIB's Integrated Registration and Segmentation Tool v1.2 (FIRST, part of FSL). All the tissue segmentation results were also checked by an experienced radiologist.

Statistical Analysis

Clinical and volumetric data

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software package (version 17 for Windows®, SPSS Inc. Chicago, IL). Descriptive statistics of demographic, neuropsychological and vol-

umetric data are presented as mean $\pm$ standard deviations. The threshold for statistical significance was set as a P -value less than 0.05. The Chi-square test and analysis of variance (ANOVA) were applied to compare the categorical and continuous demographic variables among the groups. A univariate analysis of covariance (ANCOVA) model with age, sex, and years of education as covariates was used to investigate the differences in the scores of the neuropsychological tests among the three groups. Post-hoc tests with Tukey's correction were performed for multiple comparisons.

Global and subregional diffusivity indices of corpus callosum

The statistical comparison of the different diffusivity indices of the entire three-dimensional CC was twofold. Both the global (diffusivity indices of the entire three-dimensional CC) and the subregional (diffusivity indices of the seven subregions of the entire three-dimensional CC) characteristics were compared among the three groups. The Shapiro-Wilk test was used to examine the data distribution of global and subregional DTI-related indices of the entire three-dimensional CC revealed that the global and regional DTI-related indices satisfied the parametric assumption. Subsequently ANCOVA model with the age, sex, and years of education of each participant as covariates was used to investigate the differences in the global and regional diffusivity indices among the three groups. Post-hoc tests with Tukey's correction were performed for multiple comparisons.

Correlation between neuropsychological performance, global and subregional diffusivity indices of CC

Pearson partial correlation with the age, sex, and years of education as covariates was used to investigate the possible relationship between the neuropsychological test scores and the DTI-related indices for the whole CC and the subregional areas.

RESULTS

Subject Characteristics

Table I lists the demographics and clinical information of the participants. The three study groups did not differ by age ($F = 2.638$, $P = 0.077$, ANOVA), gender distribution (Chi-square = 0.451, $P = 0.798$) and education years ($F = 2.380$, $P = 0.099$, ANOVA). As expected, the patients with AD dementia performed significantly worse than the NC and aMCI patients in all the neuropsychological tests. ($P = 0.014$ for CFT copy and $P < 0.001$ for other tests, ANOVA). The cognitive performance of the patients with aMCI was between that of the NC and the patients with AD dementia, but a statistically significant difference

between the aMCI and NC subjects was only present in the scores of the verbal and visual memory tests.

MTA Scores, Hippocampal, and Brain Volumes

The three diagnostic groups were compared with their MTA scores, TIV, adjusted hippocampal, GM, and WM volumes. As demonstrated in Table I, there were group differences in the MTA scores, hippocampal volumes, and GM volumes. Subjects with AD dementia had the highest MTA scores (indicating greater atrophy), followed by the aMCI patients, and then the patients with AD dementia. The NC subjects had the largest bilateral hippocampal volumes, followed by the MCI group, and the patients with AD dementia had the smallest bilateral hippocampal volumes.

The majority (96.2%) of the NC subjects had MTA scores ≤ 1 . All of the aMCI patients had MTA scores ≥ 1 and most of them (87.5%) had MTA scores ≥ 2 . The patients with AD dementia all had MTA scores ≥ 2 . If a cut-off MTA score of 2 or greater is considered as evidence of hippocampal atrophy [de Leon et al., 1993], all of our AD dementia patients and the majority of our aMCI patients fulfilled the National Institute on Aging and the Alzheimer's Association (NIA-AA) recommended criteria for AD dementia [McKhann et al., 2011] and MCI due to AD [Albert et al., 2011] with intermediate evidence of the AD pathophysiological process.

Group Comparison of the Four DTI Indices in the Entire CC

The aMCI group had intermediate values of FA, MD, DR, and DA measures over the entire CC between the NC and AD dementia groups (Table II and Fig. 2). Significant group differences (aMCI vs. NC, AD dementia vs. NC, and AD dementia vs. aMCI) were noted in all of the four DTI indices.

Group Comparison of Four DTI Indices in Subregions of CC

Compared with the NC subjects, the patients with AD dementia exhibited significant changes in almost all of the subregions of the CC except the primary motor, primary sensory, and occipital subregions. However, only some of the subregions of the CC presented changes in the comparison of the aMCI and the NC groups. Furthermore, the CC degeneration detected by different diffusivity indices (MD, DR, DA and FA) presented changes in different CC subregions in the comparisons between the aMCI and the AD dementia or the NC groups (Fig. 2). The mean values of the subregional DTI indices in the NC, aMCI, and AD dementia groups are presented in Table II and the results are summarized below.

AD dementia vs. NC groups

Compared with the NC subjects, the patients with AD dementia presented lower FA, higher MD, higher DA, and higher DR in the frontal CC subregions. In the parietal subregion, patients with AD dementia revealed higher MD and higher DR. Higher MD, higher DA, and higher DR were found in the temporal CC subregions in the AD dementia than in the NC group. The AD dementia group had lower FA and higher DR in the premotor/SMA subregion than the NC group. There were no between-group differences in the primary motor, primary sensory, and occipital subregions.

aMCI vs. NC groups

Compared with the NC subjects, the patients with aMCI revealed lower FA, higher MD, and higher DR were presented in the frontal CC subregion. In the parietal CC subregion, the aMCI group showed higher MD than the NC group. Higher MD and higher DA were exhibited in the temporal CC subregion of the aMCI group. Lower FA and higher DR in the premotor/SMA CC subregion were noted in the aMCI subjects than in the NC subjects. There were no between-group differences in the primary motor, primary sensory, and occipital CC subregions.

AD dementia vs. aMCI groups

Compared with the subjects with aMCI, the patients with AD dementia revealed lower FA, higher MD, higher DA, and higher DR in the frontal subregion. In the parietal and temporal CC subregions, the AD dementia group had higher DR than the aMCI group. There were no between-group differences in the primary motor, primary sensory, premotor/SMA, and occipital CC subregions.

Correlation Between the Neuropsychological Performance and MD Diffusivity Index in the Subregions of CC

The correlations between the scores of the neuropsychological tests in all subjects and the DTI-related indices of the whole CC and subregional areas were examined using the Pearson partial correlation analysis. Because MD is the diffusivity measure the revealed the most prominent microstructural changes over the CC in the present study, we demonstrate the correlation coefficients of the neuropsychological tests and MD in the whole CC and subregions in Fig. 3. The relationship between the neuropsychological tests and other DTI-related indices (FA, DR, and DA) in the supplementary material is presented in Supporting Information Table II.

Almost all the scores of the neuropsychological tests were inversely correlated with the MD value for the entire CC. The performance in different cognitive domains was correlated to distinct subregional fibers in the CC. The

TABLE II. Mean values of DTI indices in different subregions of corpus callosum in normal controls, amnesic mild cognition impairment, and Alzheimer's disease groups

CC subdivision	Whole	Frontal	Premotor/SM/A	Primary Motor	Primary Sensory	Parietal	Temporal	Occipital
FA								
NC	0.54 ± 0.03	0.54 ± 0.04	0.50 ± 0.05	0.47 ± 0.05	0.50 ± 0.06	0.45 ± 0.05	0.57 ± 0.04	0.59 ± 0.03
aMCI	0.52 ± 0.03 ^a	0.51 ± 0.03 ^a	0.47 ± 0.04 ^a	0.44 ± 0.05	0.46 ± 0.07	0.45 ± 0.06	0.56 ± 0.04	0.57 ± 0.04
AD	0.50 ± 0.03 ^b	0.49 ± 0.04 ^{b,c}	0.45 ± 0.04 ^b	0.42 ± 0.07	0.46 ± 0.09	0.42 ± 0.07	0.54 ± 0.04	0.56 ± 0.04
F value	5.731	9.736	5.272	1.744	1.779	2.267	1.693	1.826
p value	0.005	<0.001	0.007	0.181	0.175	0.110	0.190	0.167
MD								
NC	924.81 ± 52.19	894.46 ± 63.05	872.69 ± 61.64	941.04 ± 75.37	865.35 ± 54.38	806.65 ± 47.47	1099.42 ± 73.57	907.08 ± 69.58
aMCI	968.30 ± 49.95 ^a	928.35 ± 56.91 ^a	910.65 ± 69.72	964.42 ± 151.14	906.50 ± 102.90	850.38 ± 66.92 ^a	1146.53 ± 78.51 ^a	961.03 ± 89.26
AD	1012.13 ± 48.51 ^{b,c}	997.50 ± 56.38 ^{b,c}	924.42 ± 69.64	984.33 ± 119.05	912.42 ± 106.79	867.50 ± 81.07 ^b	1184.08 ± 82.23 ^b	976.08 ± 77.37
F value	14.622	15.620	2.298	1.196	1.541	3.717	5.237	2.810
p value	<0.001	<0.001	0.107	0.307	0.220	0.028	0.007	0.066
DR								
NC	631.00 ± 61.06	607.46 ± 69.34	624.00 ± 71.19	692.19 ± 85.75	601.96 ± 54.60	596.12 ± 58.62	749.81 ± 83.41	581.15 ± 76.58
aMCI	678.70 ± 56.40 ^a	651.20 ± 62.14 ^a	669.58 ± 69.09 ^a	765.13 ± 103.56	658.33 ± 97.97	633.18 ± 76.21	791.65 ± 80.53	633.67 ± 96.76
AD	723.96 ± 59.48 ^{b,c}	724.58 ± 65.36 ^{b,c}	690.25 ± 73.92 ^b	743.13 ± 126.47	670.38 ± 106.74	667.88 ± 97.03 ^{b,c}	834.88 ± 91.89 ^{b,c}	653.67 ± 92.51
F value	11.586	15.510	3.659	1.856	2.393	3.730	4.270	2.297
p value	<0.001	<0.001	0.030	0.163	0.098	0.028	0.017	0.107
DA								
NC	1512.23 ± 44.26	1468.42 ± 59.03	1369.81 ± 73.16	1438.54 ± 99.52	1391.77 ± 127.24	1227.85 ± 71.95	1798.54 ± 75.36	1558.69 ± 65.99
aMCI	1547.60 ± 52.10 ^a	1482.28 ± 65.59	1392.68 ± 92.16	1462.40 ± 176.62	1383.00 ± 163.39	1284.80 ± 97.43	1856.38 ± 106.11 ^a	1615.50 ± 88.45
AD	1588.04 ± 36.89 ^{b,c}	1543.13 ± 61.44 ^{b,c}	1392.42 ± 77.28	1407.08 ± 233.29	1396.17 ± 200.39	1266.46 ± 103.33	1882.50 ± 89.18 ^b	1621.17 ± 62.59
F value	12.815	7.998	0.245	0.715	0.101	2.028	4.316	2.980
p value	<0.001	0.007	0.784	0.492	0.904	0.138	0.016	0.056

ANCOVA analyses were applied to estimate statistical differences among the three study groups (adjusted for age, sex, and education). Boldfaced *P*-value indicates significant differences ($P < 0.05$) in ANCOVA test. Results of post-hoc ANCOVA test were corrected for multiple comparisons using LSD correction. The unit of the diffusivity values (MD, DA, and DR) is 10^{-6} mm²/s. The DTI indices are demonstrated as means/standard deviation. CC, corpus callosum; FA, fractional anisotropy; MD, mean diffusivity; DR, radial diffusivity; DA, axial diffusivity; NC, normal control; aMCI, amnesic mild cognition impairment; AD, Alzheimer disease.

^a $P < 0.05$ in post-hoc comparison with NC and aMCI.

^b $P < 0.05$ in post-hoc comparison with NC and AD.

^c $P < 0.05$ in post-hoc comparison with aMCI and AD.

Figure 2.

Bar charts of different diffusivity indices of frontal, premotor/ SMA, primary motor, primary sensory, temporal, parietal, occipital subregions of corpus callosum, and entire corpus callosum in the normal controls, amnesic mild cognitive impairment and Alzheimer's disease groups. Significant differences after Tukey's correction of post-hoc ANCOVA test are marked with asterisks

($P < 0.05$). The unit of the diffusivity values (MD, DA, and DR) is $10^{-6} \text{ mm}^2/\text{s}$. CC, corpus callosum; FA, fractional anisotropy; MD, mean diffusivity; DR, radial diffusivity; DA, axial diffusivity; NC, normal control; aMCI, amnesic mild cognition impairment; AD, Alzheimer disease. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 3.

Partial correlation coefficient between mean diffusivity (MD) values of corpus callosum and neuropsychological tests. The Pearson partial correlation was estimated with age, sex, and former education years as the confounding covariates. The grids in black meant there were no correlation between the subregions and the neuropsychological tests (i.e., P value more than 0.05); the white grid indicated P value less than 0.05, the light gray grid indicated P value less than 0.01, and the dark gray indicated the

corrected- P value less than 0.05 after Bonferroni correction. Abbreviation of neuropsychological test; MMSE, Mini-Mental Screening Examination; CVVLT, Chinese version of the Verbal Learning Test; CFT, Complex Figure Test; BNT, Boston Naming Test; TMT-B, Trail-making Test Part B. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

lower MMSE scores were correlated with higher MD values in the frontal subregion of the CC. The verbal memory measured by delayed recall in the CVVLT and the visual memory measured by delayed recall in the CFT were negatively correlated with MD changes in the frontal, temporal subregions of the CC. Delayed recall in the CFT was negatively correlated with MD change in the primary sensory subregions of the CC.

Visuoperceptual ability (scores of the copy part of CFT) was negatively correlated with MD change in the frontal and parietal subregions of the CC. The BNT and the Stroop test were negatively correlated with MD changes in the frontal, parietal, temporal, and occipital subregions. The BNT scores were negatively correlated with MD changes in the premotor/SMA subregion. Categorical VFT scores were negatively correlated with MD changes in the frontal, premotor/SMA subregions of the

CC. Lines completed within 120 seconds in the modified TMT-B were not correlated with any callosal subregions.

DISCUSSION

All of our AD patients and the majority of our aMCI patients respectively fulfilled the NIA-AA recommended criteria for AD dementia and MCI due to AD with intermediate evidence of the AD pathophysiological process. Therefore, most of them were proposed to have aMCI or dementia with AD pathology.

We parcellated the entire three-dimensional CC according to cortical trajectories to specific BAs. BAs atlas is a cytoarchitectonic map based on the differences in cell layers [Brodmann, 1909] and has been widely used as a reference map in functional brain research. In this study,

the entire three-dimensional CC was parcellated according to individual cortical trajectories to different BAs that accurately sub-divided the entire three-dimensional CC into functional subgroups. The main findings of this study were: (i) callosal degeneration had extensively developed over several of the subregions of the CC at the aMCI stage; (ii) the scores of the neuropsychological tests were correlated to the alterations in the subregional CC fibers connected to the corresponding cortical functional areas.

Alternations of the CC Microstructure in Patients With aMCI and AD Dementia

Previous evidence illustrates that CC atrophy is primarily located in the genu, isthmus, and splenium subregions of the CC in patients with AD dementia [Chaim et al., 2007; Di Paola et al., 2010c; Teipel et al., 2002; Tomaiuolo et al., 2007]. Our study showed that the most significant callosal degeneration in patients with aMCI and AD dementia was over the frontal, parietal, and temporal subregions. These subregions are located over the genu and splenium portions of the CC.

Our results demonstrate that primary motor, primary sensory, and occipital CC subregions did not reveal significant changes in patients with aMCI and AD dementia. Occipital involvement is not prominent in mild AD dementia [Frisoni et al., 2002]. The primary motor and primary sensory cortices are supposed to be the last involved region in the pathology of AD [Arendt et al., 1998; Brun and Gustafson, 1976]. The primary motor and sensory subregions are mainly located at the posterior mid-body of the CC [Chao et al., 2009]. The degeneration of the mid-body of the CC has been suggested to be typically spared in patients with AD dementia [Di Paola et al., 2010c].

Although most of the previous research proposes that callosal degeneration generally occurs in patients with AD dementia, if callosal degeneration can be detected in patients with aMCI is inconsistent [Damoiseaux et al., 2009; Di Paola et al., 2010a; Fellgiebel et al., 2004; Ukmar et al., 2008; Wang and Su, 2006; Wang et al., 2009]. Although we only enrolled patients with aMCI and isolated memory impairment in the present study, WM microstructure changes in the several subregions of the CC were revealed in our aMCI patients.

Patterns of Callosal Degeneration in aMCI

The separation of the diffusivities into axial (DA) and radial (DR) components has been validated as being a specific measure in longitudinal and transverse diffusion directions [Song et al., 2003]. Changes in DA indicate axonal damage in the fibers; in contrast, alteration in DR supports demyelination with the disruption of myelin integrity [Song et al., 2005]. Although both MD and FA were altered in most of the subregions of the CC in the patients with AD dementia and aMCI in our study, the

changes in DR and DA demonstrated a more complex pattern.

Neuroanatomical studies have shown that the CC presents a peculiar myelination pattern with small diameter fibers located anteriorly and larger fibers located more posteriorly [Aboitiz, 1992; Aboitiz and Montiel, 2003]. Wallerian degeneration principally affects the posterior portion of the CC, but the myelin breakdown process involves the anterior portions of the CC in patients with AD dementia [Di Paola et al., 2010a]. We have comparably demonstrated patients with aMCI exhibited increases of DA (indicating axonal damage) in the temporal subregion, but increases of DR (indicating myelin degradation) mainly in the frontal and premotor/SMA subregions of the CC. As the disease progresses to the AD dementia stage, both the axonal damage and myelin degradation spread to the anterior and posterior portions of the CC.

Correlation of the CC Subregions and Cognitive Function in aMCI and AD Dementia

The microstructural alteration of these different functional bundles in the CC may contribute to the cognitive change associated with corresponding BAs. Some previous studies reported that the cognitive functions of AD dementia were associated with some parts of the CC [Black et al., 2000; Chaim et al., 2007; Tomaiuolo et al., 2007]. However, none of them identified the connection between these CC portions and the corresponding cortices. We have effectively demonstrated that the performance in neuropsychological tests was correlated with the CC subregions connected to the characteristic cerebral functional areas.

The MMSE score has been reported to be associated with atrophy over the isthmus [Black et al., 2000; Lyoo et al., 1997], splenium [Lyoo et al., 1997], and anterior portion [Chaim et al., 2007; Janowsky et al., 1996; Kaufer et al., 1997] of the CC in patients with AD dementia. This study identified the MMSE score to be correlated with the frontal subregion of the CC, and this finding is in agreement with the findings of functional imaging studies. The MMSE decline in patients with AD dementia has been associated with reduced perfusion in frontal and parieto-temporal regions [Hanyu et al., 2010; Lampl et al., 2003].

The delayed recall scores of CVVLT and CFT in our subjects were correlated to the frontal and temporal subregions of the CC. The memory tasks are accomplished by a complicated process of encoding, storage, and retrieval. In the functional MRI study with verbal short-term memory tasks, the patients with AD dementia showed less activation in the middle frontal, the inferior frontal, and the transverse temporal gyri than healthy aging [Peters et al., 2009]. Accordingly, we found that delayed recall in the verbal memory test scores were not only correlated with the temporal subregion but were also associated with the changes in the frontal subregion of the CC.

Drawing or copying a figure needs to integrate the abilities of visuoperception, spatial organization, and judgment of location. Coping with more complex figures requires active additional associated cortical areas to accomplish the tasks [Forster et al., 2010]. In accordance with the findings in the functional imaging study, our study revealed that the scores of CFT copy not only correlated to the changes in the parietal but also the frontal subregions.

The BNT is primarily designed to assess the confrontation naming ability; however, this test measures the naming ability from line drawings. Consequently, not only language, but also the visuoperceptual function, contributed to the performance of BNT. The ability to name an object spontaneously or after phonemic cues was associated with the metabolism of bilateral inferior temporal, bilateral inferior frontal, right superior frontal, and left occipital regions in patients with AD dementia [Melrose et al., 2009]. The BNT scores of our subjects were correlated with changes in frontal, premotor/SMA, temporal, parietal, and occipital subregions of the CC.

We found that the frontal and premotor/SMA subregions were correlated with the scores of the categorical VFT. The VFT assesses the language and executive function in patients with AD dementia [Binetti et al., 1996]. The frontal atrophy [Fama et al., 2000] and prefrontal hypoperfusion [Kitabayashi et al., 2001] have been reported to be associated with semantic verbal fluency in patients with AD dementia. The premotor/SMA cortex was essential to control the planning and reaction time of motor movement and cognitive processing [Nakayama et al., 2008; Schubotz and von Cramon, 2002]. In our study, the premotor/SMA subregion of the CC that is specifically associated with the tests regarding the processing speed was a critical issue, such as the VFT.

The Stroop test is a complex task that integrates multiple potential sources of relevant information (e.g., word, ink color, and speech output). In agreement with another functional MRI study (Banich et al., 2000), we demonstrate that several CC subregions, including frontal, parietal, temporal, and occipital were associated with the Stroop test.

LIMITATIONS

Our study has some limitations, the first of which is that all of the recruited patients with aMCI had single-domain aMCI. The pathological changes in these early patients with aMCI may be not as severe as multi-domain aMCI. Using a less-affected group may reduce the probability of finding WM changes in early stage AD. However, subjects with multi-domain aMCI may not be good candidates for investigating the early changes during the pathogenesis of AD. Amnesia may not be the first symptom of the multi-domain aMCI subjects and many of them may progress to dementias other than AD [Nordlund et al., 2010; Stephan et al., 2012]. Secondly, we only provided indirect evidence

of the relationship between the integrity of the CC microstructure and cognition performance in our study groups due to the cross-sectional nature of the study design. The prospective trajectory of the CC network changes would provide more direct information regarding the temporal correlation between cognitive decline and the corresponding connecting CC fibers.

CONCLUSIONS

To the best of our knowledge, this is the first study that divides the entire three-dimensional CC according to cortical trajectories to specific BAs to investigate the relationship between the CC subregions and cognitive function in patients with aMCI and AD dementia. Through this method, we demonstrated that callosal degeneration is evident in patients with aMCI and AD dementia. Furthermore, we proved the association of changes between subregional CC and cognitive performance. Future prospective investigations should elucidate the temporal correlation between cognitive decline and the corresponding subregional degeneration of CC in patients with aMCI and AD dementia.

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