# Evaluation of bilateral cingulum with tractography in patients with Alzheimer's disease

Sheng Xie,[1,CA] Jiang Xi Xiao,[1] Yin Hua Wang,[2] Hong Kun Wu,[1] Gao Lang Gong[3] and Xue Xiang Jiang[1]

[1]Departments of Radiology; [2]Neurology, Peking University First Hospital, Beijing 100034; [3]National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100080, P.R. China

[CA]Corresponding Author: ouyangxu2004@vip.sina.com

Received 9 June 2005; accepted 12 June 2005

A fiber-tracking algorithm was used to extract fractional anisotropy of bilateral cingulum bundles in patients with probable Alzheimer's disease and normal aging controls. In addition, their hippocampal volumes were measured manually. Relative to normal controls, Alzheimer's disease patients showed a significant reduction of fractional anisotropy and hippocampal volumes. Significant correlation was observed between fractional anisotropy values and volumes of hippocampi and mini-mental state examination scores. This study suggests that lower anisotropy of cingulum bundles is associated with cognitive dysfunction and atrophy of the limbic system. *NeuroReport* 16:1275–1278 © 2005 Lippincott Williams & Wilkins.

**Key words**: Alzheimer's disease; Cingulum bundle; Diffusion tensor imaging

## INTRODUCTION

Alzheimer's disease (AD) is one of the most severe and cognitively devastating chronic, degenerative diseases encountered in the older population. In addition to medial temporal lobe atrophy, involvement of the posterior cingulate cortex in preclinical AD was found recently [1–3]. The cingulum bundle is the most prominent tract of the limbic lobe, which connects the limbic lobe with the neocortex. Many studies have suggested that some functions of the cingulate gyrus depended on the integrity of its connections with other parts of the neuronal network [4]; therefore, the cingulum bundle, which serves to connect the cingulate cortex with other regions, would be important in the maintenance of the processing of cognitive functions. Although white matter damage in AD was studied in some works by using diffusion tensor imaging [5,6], no study explored the characteristics of the cingulum bundles and their relationships with volumes of hippocampi in AD.

In this paper, we applied a fiber-based scheme to extract the anisotropy of the cingulum in groups of patients with AD and normal elderly controls. At the same time, hippocampal morphometric measurement was performed. Then, a comparison of fractional anisotropy (FA) was conducted between the two groups and their correlation with hippocampal volumes and mini-mental state examination (MMSE) scores was identified.

## MATERIALS AND METHODS

***Patients:*** Twenty patients with AD (12 men, 8 women; age range, 62–83 years; mean age, 72.3 years) were recruited in this study. The diagnosis of probable AD was established according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria. Their MMSE scores ranged from 10 to 24, mean $19 \pm 4$. According to the neuropsychological scales, 11 patients were classified as having mild Alzheimer's disease and nine patients with moderate severity. Twenty normal elderly volunteers (11 men, 9 women; age range, 60–81 years; mean age, 70.4 years) were recruited from the local community as controls. Controls were defined as individuals who did not have active neurological or psychological conditions, had no cognitive complaints, had no severe systemic disease, and were not taking any psychoactive medicines in doses that would affect cognition. Their MMSE scores were all above 27. They were matched with the patients for education and age. All patients were right-handed. Informed consent for participation was obtained from every patient. The human subjects committee at the Peking University approved all the protocols used in this study.

***Magnetic resonance data acquisition:*** All magnetic resonance imaging was performed on a 1.5 T magnetic resonance scanner (GE signa 1.5 T Twinspeed, Milwaukee). Diffusion tensor imaging was acquired with a single-shot echo planar imaging sequence in alignment with anterior–posterior commissure plane. The diffusion-sensitizing gradients were applied along 13 noncollinear directions with $b$-value 1000 s/mm$^2$, together with an acquisition without diffusion weighting ($b$=0). Thirty contiguous axial slices were acquired with 4 mm thickness and no gap. The acquisition parameters were as follows: TR 10 000 ms; TE 80 ms; matrix $128 \times 128$; FOV $24 \times 24$ cm; number of excitations 2. In addition, a high-resolution T1-weighted

volume magnetic resonance imaging scan was obtained for each patient, which covered the whole brain with slice thickness 1.8 mm and pixel size $0.9 \times 0.9\,mm^2$, using the spoiled gradient recalled acquisition sequence (TR 11.3 ms, TE 4.2 ms, TI 400 ms, FA 15°, FOV $24 \times 24$ cm, matrix $256 \times 256$). After an automatic interpolation in the $Z$ direction, the voxel size became $0.9 \times 0.9 \times 0.9\,mm^3$ each.

***Anisotropy measurement of cingulum:*** With specific seed region definition as shown in Fig. 1, the cingulum bundles were reconstructed using the tractography algorithm proposed by Lazar *et al.* [7]. For the traced cingulum bundles, each point holds FA as its characteristics. The values of FA of each reconstructed cingulum bundle were extracted and averaged. Because cingulum bundles are greatly dispersed in the most anterior and posterior portions, and will induce unreliable measurement, only the part of the tract dorsal to the body of corpus callosum was analyzed. The full details of algorithm and parameter have been previously published [8].

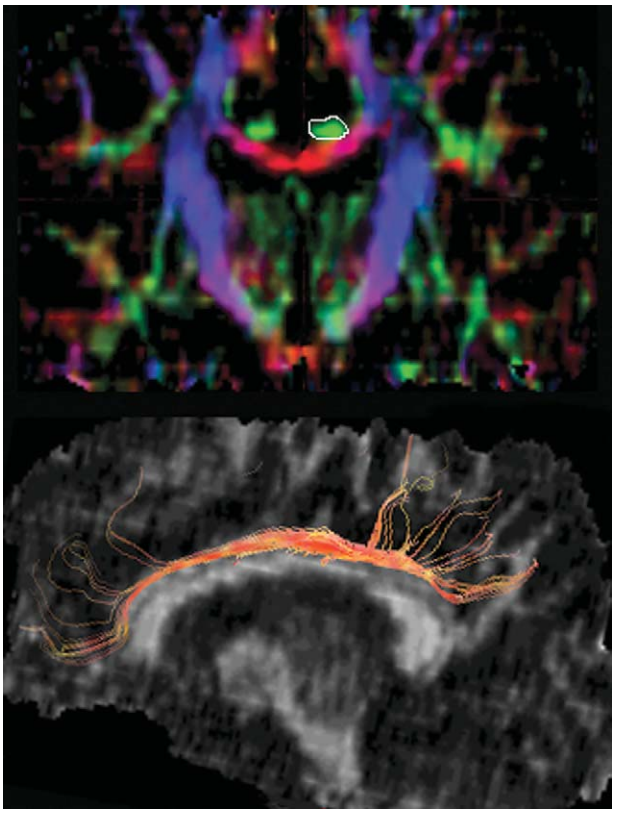

**Fig. 1.** Top: the coronal color-encoded tensor image in a patient. The left cingulum was outlined to be the seed region for reconstruction. Bottom: the reconstructed fibers of the left cingulum were shown in the sagittal fractional anisotropy map.

***Morphometric measurement of hippocampi:*** Coronal T1-weighted images with 3 mm thickness and no gap were reconstructed from high-resolution three-dimensional T1-weighted images. The slices were positioned to run parallel to a line that joins the posterior commissure and the obex. The volumes of bilateral hippocampi were measured manually by tracing the boundaries of the hippocampus from the head to the tail [9]. Apart from this, the intracranial volume was estimated by summing the product of slice thickness and the area of the inner table of the skull on successive sagittal images [9]. All image processing steps in every patient were performed by the same research associate who was blinded to all clinical information (age, sex, clinical course) to insure that the volumetric data was unbiased.

***Statistical analysis:*** The student $t$-test was used to assess the difference in hippocampal volumes and FA values between AD patients and normal controls. Correlation of FA values of bilateral cingulum bundles with volumes of hippocampi and MMSE scores was tested using the partial correlation method.

## RESULTS

The hippocampal volume measurements of each patient were normalized for interpatient variation in head size by dividing hippocampal volume by the total intracranial volume of that particular patient. For data display purposes, the volumes were presented as (hippocampal volume/intracranial volume) $\times 1000$. The hippocampal volumes and normalized hippocampal volumes of AD patients and normal controls are shown in Table 1. Significant differences were observed for bilateral hippocampal volumes between the AD group and control group. The results in this study are all presented as means $\pm$ SD.

The FA values were $0.34 \pm 0.08$ in AD patients and $0.42 \pm 0.05$ in controls for the left cingulum, while they were $0.34 \pm 0.07$ in AD patients and $0.41 \pm 0.05$ in normal elderly people for the right cingulum. The Student $t$-test revealed a significant group difference ($p < 0.01$).

After controlling for age, FA values of bilateral cingulum bundles were significantly correlated with normalized hippocampal volumes. ($r=0.45$ for correlation of the left cingulum with the left hippocampus, $p < 0.01$; $r=0.50$ for correlation of the right cingulum with the right

**Table 1.** Hippocampal volumes and normalized hippocampal volumes of Alzheimer's disease (AD) patients and normal controls.

| Measures | AD group | Control group | $t$ value | df | $p$ value |
|---|---|---|---|---|---|
| Left hippocampal volume ($mm^3$) | 2114 ± 576 | 2718 ± 433 | −3.75 | 38 | 0.001 |
| Right hippocampal volume ($mm^3$) | 2175 ± 580 | 2897 ± 455 | −4.39 | 38 | 0.000 |
| Normalized left hippocampal volume | 1.46 ± 0.40 | 1.89 ± 0.29 | −3.91 | 38 | 0.000 |
| Normalized right hippocampal volume | 1.50 ± 0.41 | 2.01 ± 0.32 | −4.37 | 38 | 0.000 |
| FA of left cingulum | 0.34 ± 0.08 | 0.42 ± 0.05 | −3.73 | 38 | 0.001 |
| FA of right cingulum | 0.34 ± 0.07 | 0.41 ± 0.05 | −3.57 | 38 | 0.001 |

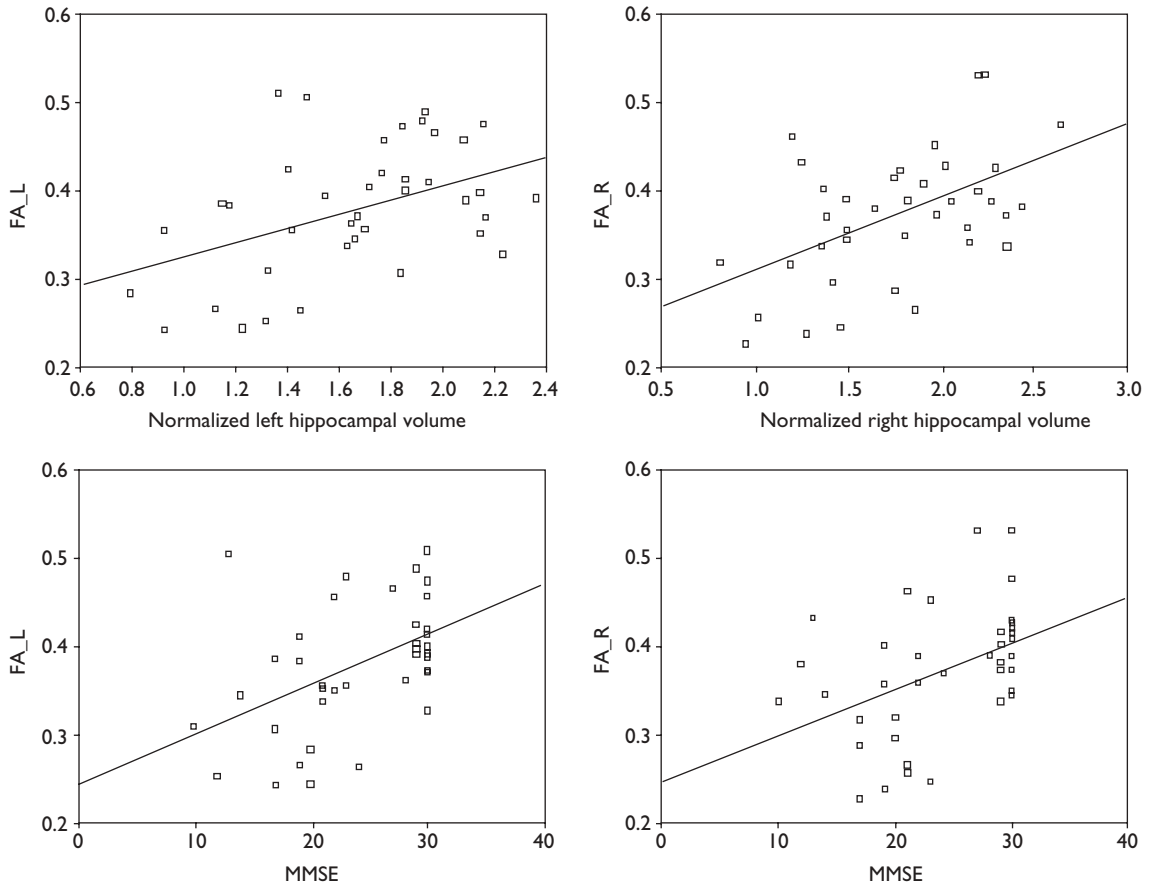


**Fig. 2.** Top: scatterplots of fractional anisotropy (FA) values of the cingulum with respect to normalized hippocampal volumes ($n$=40). Bottom: scatterplots of FA values of the cingulum with respect to mini-mental state examination (MMSE) scores ($n$=40).

hippocampus, $p<0.01$). After controlling for age and education period, FA values of bilateral cingulum bundles were significantly correlated with MMSE scores. ($r$=0.49 for correlation of the left cingulum with MMSE, $p<0.01$; $r$=0.45 for correlation of the right cingulum with MMSE, $p<0.01$) (see Fig. 2).

## DISCUSSION

Now it is widely accepted that measures of the temporal cortices, including the amygdala, hippocampus, and inferior temporal lobes, along with the anterior cingulate cortex, could serve as the most useful structures to help clinicians differentiate AD from healthy normal aging [10]. Consistent with previous imaging studies [11,12], significant volumetric reduction of hippocampi was observed in patients with AD in our study.

The cingulum contains fibers that arise from the cingulate cortex, and projects to the entorhinal cortex along with fibers from other neocortical areas. The entorhinal cortex is a major site of convergence of cortical inputs to the hippocampal formation. Therefore, the integrity of the cingulum bundle is important for the maintenance of cognitive function. Chetelat *et al.* [13] reported that the posterior cingulate gyrus may undergo atrophy even in preclinical AD. As an indicator of its function above the cortex, the cingulum may show signs of degenerative changes in AD. Some previous works studied white matter in the cingulate gyrus by using diffusion tensor, and discovered some index may reflect progression of AD-related pathological changes [5,6]. However, those studies were all based on the measurement of regions of interest. Considering the long distance the cingulum travel, we applied the fiber-tracking algorithm to extract the FA values of the fiber tract. The main advantage of this method is that it can assess a continuous part of the cingulum instead of measuring FA in a local region. The FA values of AD patients were significantly decreased relative to normal controls in our study, which reflected a loss of anisotropy in cingulum bundles.

Diffusion tensor imaging is a relatively new technique that can provide information about the random displacement of water molecules in the brain tissue. Loss of tissue organization would cause a decrease in anisotropy; diffusion tensor is thus a meaningful measure of fiber tract organization [14,15]. Usage of additional diffusion tensor imaging may even detect subtle regional alterations of hippocampal structure in schizophrenics [16]. Although AD is generally considered to affect gray matter, histological studies show pathological changes, such as the loss of axons and oligodendrocytes together with reactive astrocytosis in the white matter. In a serial study

of Bronge [17], the work characterized pathological changes in the white matter not visible on conventional magnetic resonance imaging. They also claimed that white matter changes in a specific location might impair cognitive functions that rely on those specific pathways. In the light of the previous studies of the pathologic white matter conditions in AD, the finding of decreased anisotropy of bilateral cingulum bundles in patients with AD is in agreement with rarefaction of axons and myelin and can be explained on the basis of anterograde Wallerian degeneration.

Apart from comparison of anisotropy in AD patients with those of normal elderly controls, we analyzed the correlation between anisotropy of cingulum bundles and volumes of hippocampi and MMSE. Moderate significant correlation was found between them. It indicated that the degeneration of fibers in cingulum bundles is related to a decline of cognitive function in the AD patients. Similarly, the relationship between anisotropy of cingulum bundles and volumes of hippocampi might reflect the impact of atrophy of limbic lobes on the integrity of cingulum bundles. However, 20 patients with AD in this study is a relative small sample; thus, a profound study with more cases is needed to elucidate the effect of cingulum degeneration in the progress of AD.

The limitations of this study came from the fiber-tracking algorithm. First, seed regions were placed manually, and their size would affect tractography in the aspect of the thickness of the traced bundle, which would have an impact on the measurement of FA values sequentially. Second, thresholds for FA and limits for angulation changes would also have an effect on the results of tractography.

## CONCLUSION

Diffusion tensor imaging reveals lower anisotropy of bilateral cingulum bundles in AD. Lower anisotropy of bilateral cingulum bundles is associated with atrophy of hippocampi and cognitive dysfunction. It may indicate secondary degenerative changes of fiber tracts resulting from atrophy of limbic lobes.

## REFERENCES


1. Baron JC, Chetelat G, Desgranges B *et al*. *In vivo* mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. *Neuroimage* 2001; **14**:298–309.
2. Fox NC, Crum WR, Scahill RI *et al*. Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images. *Lancet* 2001; **358**:201–205.
3. Thompson PM, Mega MS, Woods RP *et al*. Cortical change in Alzheimer's disease detected with a disease-specific population-based brain atlas. *Cereb Cortex* 2001; **11**:1–16.
4. Cohen RA, Kaplan RF, Moser DJ *et al*. Impairments of attention after cingulotomy. *Neurology* 1999; **53**:819–824.
5. Yoshiura Takashi, Mihara Futoshi, Ogomori Koji *et al*. Diffusion tensor in posterior cingulate gyrus: correlation with cognitive decline in Alzheimer's disease. *Neuroreport* 2002; **13**:2299–2302.
6. Rose SE, Chen F, Chalk JB *et al*. Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. *J Neurol Neurosurg Psychiatry* 2000; **69**: 528–530.
7. Lazar M, Weinstein DM, Tsuruda JS *et al*. White matter tractography using diffusion tensor deflection. *Hum Brain Mapp* 2003; **18**:306–321.
8. Gong GL, Jiang TZ, Zhu CZ *et al*. Asymmetry analysis of cingulum based on scale-invariant parameterization by diffusion tensor imaging. *Hum Brain Mapp* 2005; **24**:92–98.
9. Jack CR Jr, Petersen RC, Xu YC *et al*. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology* 1999; **52**:1397–1403.
10. Poulin P, Zakzanis KK. *In vivo* neuroanatomy of Alzheimer's disease: evidence from structural and functional brain imaging. *Brain Cogn* 2002; **49**:220–225.
11. Pennanen C, Kivipelto M, Tuomainen S *et al*. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiol Aging* 2004; **25**:303–310.
12. Wolf H, Grunwald M, Kruggel F *et al*. Hippocampal volume discriminates between normal cognition; questionable and mild dementia in the elderly. *Neurobiol Aging* 2001; **22**:177–186.
13. Chetelat G, Desgranges B, De La Sayette V *et al*. Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. *Neuroreport* 2002; **13**:1939–1943.
14. Beaulieu C. The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR Biomed* 2002; **15**:435–455.
15. Pierpaoli C, Jezzard P, Basser PJ *et al*. Diffusion tensor MR imaging of the human brain. *Radiology* 1996; **201**:637–648.
16. Kalus P, Buri C, Slotboom J *et al*. Volumetry and diffusion tensor imaging of hippocampal subregions in schizophrenia. *Neuroreport* 2004; **15**: 867–871.
17. Bronge L. Magnetic resonance imaging in dementia. A study of brain white matter changes. *Acta Radiol Suppl* 2002; **428**:1–32.