

# Side and handedness effects on the cingulum from diffusion tensor imaging

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In order to explore the microstructure of bilateral cingulum bundles associated with side and handedness, fractional anisotropy was extracted from diffusion tensor imaging. Distinguished from the conventional region of interest-based method, a fiber-based analysis method called scale-invariant parameterization method was employed to ascertain the anisotropy along the cingulum bundle in 31 normal right-handers and 14 normal left-handers. The statistical results showed a remarkable left-greater-than-right

asymmetry pattern of anisotropy in most segments of cingulum bundles except the most posterior segment, for both right-handers and left-handers. Interestingly, higher anisotropy of the right-hander than the left-hander was found in the bilateral cingulum bundles. No significant handedness-by-side interaction was obtained in the present study, however. *NeuroReport* 16:1701–1705 © 2005 Lippincott Williams & Wilkins.

**Keywords:** cingulum, diffusion tensor imaging, handedness, side

## Introduction

Previous neuroimaging studies have demonstrated that the cingulate cortex was involved in many higher-level cognitive functions [1,2]. Some studies have suggested that the function of the cingulate gyrus might depend on the connections with other parts of the neuronal network [3]. Evidence from schizophrenia studies has also shown that some symptoms and cognitive dysfunction in patients may be partly explained by the disconnections between the cingulate cortex and other regions [4]. The cingulum bundle, which connects the cingulate cortex with other regions, however, has rarely been studied. It is not surprising because there is no clear boundary between the cingulum bundle and its adjacent white matter tracts on the conventional structural magnetic resonance imaging (e.g. T1-weighted and T2-weighted) in which the cingulum cannot be extracted clearly and quantified.

As a relatively new technique, diffusion tensor imaging (DTI) can provide information about the random displacement of water molecules in the brain tissue. On the basis of this information, some scalar indices such as fractional anisotropy (FA) have been proposed to characterize the diffusion anisotropic extent and indicate the directional similarity of the diffusion [5]. A higher anisotropy index may reflect higher density, or directional coherence, of the fiber tracts, whereas lower anisotropy indicates less coherence of directionality and more random movement of water in all directions measured [6]. Some new findings have been reported in the studies of brain development, normal aging,

brain asymmetry and neurological and psychiatric diseases using aforementioned indices from DTI [7,8].

So far, there have been a few DTI studies in which the cingulum was investigated. The alteration of cingulum anisotropy asymmetry between controls and schizophrenic patients has been reported on the basis of the region of interest (ROI) method [9,10]. Alternatively, we previously proposed a novel fiber-based scheme called scale-invariant parameterization of the cingulum [11], to analyze the characteristics of the cingulum in normal right-handers. The existing studies have consistently found a left-greater-than-right asymmetry pattern in the right-handers. Also, the morphologic asymmetry related to gender has been found in the anterior cingulate cortex [12]. All these studies, however, were confined to right-handers without considering the left-handers. More recently, some research has emerged to probe the relationship between anisotropy and handedness [13]. These DTI studies suggest that it would be significant to ascertain the relationship of the cingulum microstructure with the handedness and side. Therefore, we recruited a group of healthy right-handers and a group of healthy left-handers to examine this issue.

## Materials and methods

### Study participants

Two groups participated in this study. The first group consisted of 31 healthy right-handed participants (20 men, 11 women, aged 20–40 years, mean age=25.6 years, SD=3.6)

who had been studied in previous work [11]. The second group consisted of 14 healthy left-handed participants (nine men, five women, aged 20–40 years, mean age=24.2 years, SD=3.7). Another six right-handed participants and one left-handed participant were also scanned, but not included in the final analysis for reasons that will be described in the Results section. No significant difference in age was observed between the two groups. All volunteers were recruited by local advertisement and informed consents were obtained after a complete description of the study. All procedures were approved by the local Institutional Review Boards.

Handedness direction and degree were assessed according to a self-report questionnaire. The assessment was completed by Li's Handedness Inventory [14], which was designed for the Chinese in view of the significant differences in language, living and habits associated with the handedness between the Chinese and foreigners. The inventory consists of 10 items: (1) Writing, (2) Chopstick, (3) Throwing, (4) Toothbrush, (5) Scissors, (6) Striking a match, (7) Threading a needle (thread), (8) Holding a hammer, (9) Holding a racket and (10) Toweling a face. Each item was given an answer ('only right', 'only left' or 'right or left') for hand preference. A laterality quotient (LQ) was assigned to each participant according to the following formula:  $LQ = (R - L) \times 100 / (R + L)$ , where  $R$  and  $L$  are the total scores of the questions answered in 'only right' and 'only left', respectively. The answers, 'only right' or 'only left', receive 10 points for each question, while 'right or left' receives 0 points for each question. The LQ ranges from -100 for extreme left-handedness to +100 for extreme right-handedness. The handedness degree for both right-handed and left-handed participants therefore can be quantified by the absolute value of the LQ.

### Image acquisition

All magnetic resonance imaging was performed on a 1.5-T magnetic resonance scanner (GE Signa, Milwaukee, Wisconsin, USA; 1.5 T Twinspeed), which was equipped with shielded magnetic field gradients of up to 40 mT/m. A standard head coil was used for radio frequency transmission and reception of the nuclear magnetic resonance signal. Head motion was minimized with restraining foam pads offered by the manufacturer.

Diffusion weighted images were acquired with a single-shot echo planar imaging sequence in alignment with the anterior-posterior commissure plane. The diffusion sensitizing gradients were applied along 25 non-collinear directions with  $b$ -value = 1000 s/mm<sup>2</sup>, together with an acquisition without diffusion weighting ( $b$ -value = 0). Totally, 12 slices were gathered with the most caudal slice passing through the genu of corpus callosum to cover as many cingulum bundles as possible. The acquisition parameters were as follows: time of repetition (TR) = 4000 ms; time of echo (TE) = 80 ms; matrix = 128 × 128; field of view (FOV) = 24 × 24 cm; number of excitations (NEX) = 3; slice thickness = 3 mm without gap. Moreover, a high-resolution three-dimensional T1-weighted image (TR = 11.3 ms, TE = 4.2 ms, FOV = 24 × 24 mm, matrix = 128 × 128, slice thickness = 2.4 mm, NEX = 2) was also obtained.

### Quantification of fractional anisotropy along the cingulum

The fiber-based method with scale-invariant parameterization [11] was employed to extract the FA values along the

cingulum and establish the correspondence of the cingulum across participants. It can be briefly summarized as follows. (1) Diffusion tensor matrix was calculated on a pixel-by-pixel basis. (2) Tractography algorithm proposed by Lazar *et al.* [15] was used to reconstruct the cingulum bundles with specific seed regions definition. (3) A common polar coordinate system was established. All cingulum fibers were then mapped into this standardized coordinate frame and parameterized by arc-angle. (4) For each arc-angle, FA values of the unilateral cingulum fibers were averaged as the typical FA. All algorithm parameters and ROI definition of this method were similar to those in [11]. More detail can be found in this reference.

### Statistical analysis and correlation with the handedness degree

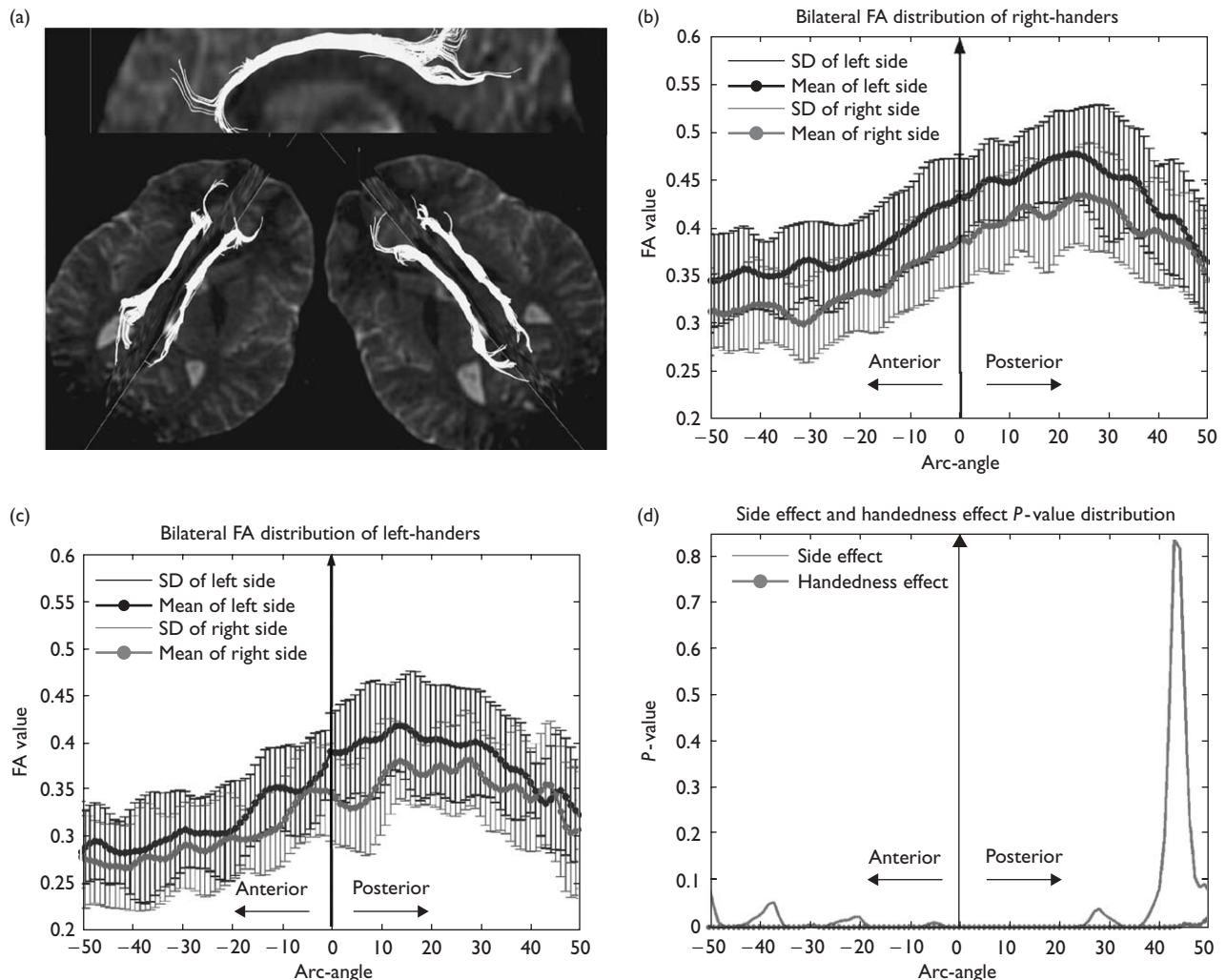
For each arc-angle, FA values in each side of male and female participants were compared using a *t*-test, but no significant difference was found for both right-handed and left-handed participants. Therefore, the sex factor was excluded from the following analysis. Repeated-measures analysis of variance (ANOVA), with handedness (right-handed, left-handed) as a between-participants factor and side (left, right) as a repeated-measures factor, was then used to test for differences of FA values. In addition, considering the significant difference in the degree of handedness in left-handers, we correlated the FA with the LQ of left-handers to explore their relationship.

### Results

The left-handed participants showed significant variability between participants in the degree of handedness (LQ range -80 to -13, mean -58.1), whereas all the right-handed participants in this study showed extreme right-handedness (LQ range 90–100, mean 94.5).

The current analysis was concentrated on the part of the cingulum bundle dorsal to the corpus callosum because the most anterior and posterior portions of the cingulum bundles are greatly dispersed, which would prohibit reliable measurement of FA. Here, the sampling interval ( $\theta$ ) is 1°, and the range of arc-angle was from -50° for the extreme anterior to 50° for the extreme posterior. Note that the reconstructed cingulum bundles in the other six right-handed participants and one left-handed participant were not long enough to cover the arc-angle range (-50° to 50°) and thus these participants were excluded in the final analysis.

The reconstruction of the left and right cingulum bundles in one participant is illustrated in Fig. 1. The FA value distribution along the bilateral cingulum bundles, as a function of arc-angle, was obtained for each participant. Repeated-measures ANOVA was carried out using SPSS 11.5 (SPSS Inc., Chicago, Illinois, USA) for each arc-angle. Figure 1 shows the mean and standard deviations of the FA distribution for right-handed and left-handed participants in both sides, respectively. The *P*-value distributions corresponding to side and handedness effect are plotted. The results showed no contiguous (>5°) significant differences in handedness-by-side interaction, which suggests no significant difference in any segment of the cingulum. Therefore, the corresponding *P*-value distribution was not plotted. The *P*-value distributions revealed significant side difference [ $F(1,43) > 4.07, P < 0.05$ ] in most segments of the



**Fig. 1** The reconstruction of cingulum bundles and statistical analysis using repeated-measures ANOVA. (a) The traced cingulum of one participant; (b) the averaged fractional anisotropy (FA) and SD distribution in a right-hander, black and grey denote left side and right side, respectively; (c) the averaged FA and SD distribution in a left-hander, black and grey denote left side and right side, respectively; (d) significance of repeated-measures ANOVA by side and handedness effect, respectively. For horizontal axis, left to right represents anterior to posterior.

cingulum bundles ( $-50^{\circ}$  to  $40^{\circ}$ ) except in the most posterior portion of the cingulum ( $40^{\circ}$ – $50^{\circ}$ ), as well as significant handedness difference [ $F(1,43) > 4.07$ ,  $P < 0.05$ ] in all segments of the cingulum bundles ( $-50^{\circ}$  to  $50^{\circ}$ ) (lower right of Fig. 1). Also, Fig. 1 shows a decrease in FA value from the middle of the cingulum to anterior and posterior approximately. No significant correlation between FA and degree of handedness (i.e. LQ) was found along the cingulum (data was not shown).

## Discussion

In this paper, the diffusion anisotropy was explored to ascertain the cingulum microstructure related to side and handedness. A significant left-greater-than-right asymmetry pattern was observed in most segments of the cingulum bundles except the most posterior segment, for both right-handers and left-handers. Interestingly, the results also showed significant differences between left-handers and right-handers in the bilateral cingulum, whereas neither

handedness-by-side interaction nor significant correlation with the degree of handedness along the cingulum was found. Such results were obtained by statistical analysis of the FA values, which were extracted from the scale-invariant parameterization of the cingulum [11]. Note that our results were not corrected for multiple comparisons.

The anisotropic diffusion in the white matter might be affected by myelination, axonal thickness, amount of parallel organization of axons or a combination of these three factors [6]. The exact microscopic pictures that cause the anisotropic water diffusion, however, remain unclear. As one of the most popular indices describing the anisotropic extent, FA has been applied to many studies to evaluate the directionality and the integrity of white matter tracts in normal controls and patients [16,17].

## Related to side

Previous study of brain asymmetry mainly focused on the structure and function of the gray matter [18]. Recently,

some asymmetry studies of the white matter from DTI were emerging. In normal controls, a left-greater-than-right asymmetry pattern of the diffusion anisotropy has been observed in the subinsular white matter [19] and arcuate fasciculus [20], whereas a right-greater-than-left pattern has been found in the anterior limb of the internal capsule [21].

The cingulum has also been investigated using DTI. The higher anisotropy in the left cingulum was reported in normal right-handers on the basis of the manual ROI drawing method. Alternatively, we analyzed the anisotropy along the cingulum bundles on the basis of the scale-invariant parameterization method. Our finding of the left-greater-than-right asymmetry pattern [11] along the cingulum was consistent with those of Kubicki *et al.* [9] and Sun *et al.* [10], who further found the reduction of such asymmetry pattern in schizophrenia. In the present study, we also found the same left-greater-than-right asymmetry pattern in left-handers, but found no handedness-by-side interaction. The observed left-greater-than-right asymmetry along the cingulum in both right-handers and left-handers may reflect a higher density, or directional similarity, of fibers in the left cingulum, and may indicate the asymmetry of adjacent structure and the lateralization of the function in the limbic system.

#### Related to handedness

Handedness is naturally expected to result from the asymmetry in the motor system. Also, the morphological difference of the motor cortex has been observed to be related to handedness [22,23]. Interestingly, the hand preference also showed a strong association with language dominance [24]. Recent DTI studies have attempted to probe the relationship between anisotropy and handedness. Buchel *et al.* [20] found the anisotropy difference related to handedness in the white matter of the precentral gyrus. Westerhausen *et al.* [13] found significant alterations of the anisotropy in the human corpus callosum with respect to handedness, whereas Peled *et al.* [21] failed to demonstrate any handedness-dependent asymmetry of anisotropy in the whole brain.

To our knowledge, no study has focused on the cingulum associated with handedness. The works by Kubicki *et al.* [9] and Sun *et al.* [10] mentioned above employed only right-handed participants. The studies of Peled *et al.* [21] and Buchel *et al.* [20] were focused on the whole brain and revealed no significant difference of the cingulum anisotropy depending on handedness. Therefore, we recruited a left-hander group to probe this issue for the cingulum. Interestingly, significant difference of anisotropy between left-handers and right-handers along the bilateral cingulum was found, while no asymmetry difference associated with handedness and no significant correlation with the degree of handedness along the cingulum was found in the present study. The discrepancy between the results of the present study and those obtained by Peled *et al.* [21] and Buchel *et al.* [20] might be explained by a different handedness classification, different ROI placement or different sample size.

Although FA difference related to side and handedness was observed along the cingulum in the present study, the interpretation of these results requires some caution. For

example, the sample size in the present study is relatively small, especially for left-handers. For this reason, the sex factor has not been analyzed deeply and was excluded in the repeated-measures ANOVA. Apart from this, the present study assessed handedness by Li's inventory designed especially for the Chinese, which would produce some difference in the evaluation of the degree of handedness with some other inventory.

#### Conclusion

The aim of the current study was to explore the side and handedness effects on the microstructure of the bilateral cingulum, which is the most prominent white matter tract in the limbic system. On the basis of a novel analysis method specific to the cingulum, a remarkable left-greater-than-right asymmetry pattern of anisotropy was observed in most segments of the cingulum bundles except the most posterior segment, which strongly supports previous neuroimaging findings of the cingulum. Moreover, higher anisotropy of the right-hander than the left-hander was also found along the bilateral cingulum bundles, whereas no significant handedness-by-side interaction was obtained in the present study.

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