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## Uncinate Fasciculus Abnormalities in Recent Onset Schizophrenia and Affective Psychosis: A Diffusion Tensor Imaging Study

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### Abstract

Two of the most frequently investigated regions in diffusion tensor imaging studies in chronic schizophrenia are the uncinate fasciculus (UF) and cingulum bundle (CB). The purpose of the present study was to determine whether UF and CB white matter integrity were altered at the early stage of illness and specific to schizophrenia. Fifteen schizophrenia subjects and 15 affective psychosis within 4 years of first hospitalization (12 patients with schizophrenia and 12 patients with affective psychosis during their first hospitalization), and 15 psychiatrically healthy controls underwent line-scan diffusion tensor imaging. Fractional anisotropy (FA) and mean diffusivity ( $D_m$ ) were used to quantify water diffusion, and cross-sectional area was defined with a directional threshold method. Bilaterally reduced FA, but not  $D_m$ , was present in the UF of schizophrenia compared with healthy controls. Affective psychosis was intermediate between schizophrenia subjects and healthy controls, but not

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### Contributors

Toshiro Kawashima, M.D., Ph.D. and Motoaki Nakamura, M.D., Ph.D. designed the study and wrote the protocol. Toshiro Kawashima also wrote the first draft of the manuscript. Sylvain Bouix, Ph.D., Marek Kubicki, M.D, Ph.D. and Carl-Fredrik Westin, Ph.D. supervised the MRI data acquisition and processing, and provided guidance on technical aspects of diffusion tensor imaging. Dean F. Salisbury, Ph.D. performed recruitment, diagnosis, and clinical assessment of participants, and managed acquisition of DTI data. He also aided in statistical analyses and edited multiple versions of the manuscript. Martha E. Shenton, Ph.D. and Robert W. McCarley, M.D. provided guidance on the study design, implementation of the study, statistical analyses, and edited multiple iterations of the manuscript. All authors contributed to and have approved the final manuscript.

### Conflict of interest

None of the authors have any conflicts of interest that require disclosure.

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significantly different from either. For CB, there was no significant group difference for FA or  $D_m$ . These findings suggested that UF, but not CB, white matter integrity is altered at the early stage of illness in schizophrenia although it may not be specific to schizophrenia. The CB abnormalities reported in chronic schizophrenia may develop during the later course of the disease.

## Keywords

Diffusion tensor imaging; Schizophrenia; Affective psychosis; Uncinate fasciculus; Cingulum bundle; Fractional anisotropy

## 1. Introduction

There is considerable evidence suggesting that aberrant neuronal connectivity may play a significant role in the pathogenesis of schizophrenia (e.g. Andreasen et al., 1996; McGlashan and Hoffman, 2000; Meyer-Lindenberg et al., 2001; Weinberger et al., 1992). Several diffusion tensor imaging (DTI) studies have shown impaired white matter integrity in the brains of schizophrenia within prefrontal and temporal lobes (e.g. Buchsbaum et al., 1998) as well as abnormalities within the fiber bundles connecting these regions, including the uncinate fasciculus (UF) (Burns et al., 2003; Kubicki et al., 2002; Mori et al., 2007; Park et al., 2004b), cingulum bundle (CB) (Hao et al., 2006; Kubicki et al., 2005; Kubicki et al., 2003; Mitelman et al., 2007; Mori et al., 2007; Park et al., 2004b; Sun et al., 2003; Wang et al., 2004), and arcuate fasciculus (Burns et al., 2003; Kubicki et al., 2005). In addition, diffusion abnormalities in the occipito-frontal fasciculus (Buchsbaum et al., 2006; Kubicki et al., 2005), the corpus callosum (Ardekani et al., 2003; Brambilla et al., 2005; Buchsbaum et al., 2006; Foong et al., 2000; Foong et al., 2002; Kubicki et al., 2005; Park et al., 2004b), the internal capsule (Buchsbaum et al., 1998; Kubicki et al., 2005; Park et al., 2004b; Szeszko et al., 2005), fornix (Kubicki et al., 2005; Kuroki et al., 2006a), the optic radiations (Butler et al., 2006; Hao et al., 2006), the superior cerebellar peduncles (Hao et al., 2006; Okugawa et al., 2006; Park et al., 2004b), the middle cerebellar peduncles (Okugawa et al., 2004; Okugawa et al., 2005), and in whole white matter (Lim et al., 1999; Minami et al., 2003; Mitelman et al., 2006) have been reported in schizophrenia, suggesting widespread white matter abnormalities.

The UF is the major fiber tract connecting the inferior frontal and anterior temporal lobes (Ebeling and von Cramon, 1992; Petrides and Pandya, 1988; Ungerleider et al., 1989), and patients with chronic schizophrenia lack the normal left-greater-than-right anisotropy asymmetry in the uncinate fasciculus (Burns et al., 2003; Kubicki et al., 2002). This lack of asymmetry in the size of the uncinate fasciculus in patients with schizophrenia has also been detected in a post-mortem histological study (Highley et al., 2002). A recent study by Price and coworkers has reported DTI abnormalities in left UF in patients with first-episode schizophrenia (Price et al., 2008).

The CB is the white matter tract that connects the cingulate cortex with other brain regions including premotor and prefrontal regions, other cortical association regions, the thalamus, and medial temporal structures such as the presubiculum and parahippocampal gyrus (Mufson and Pandya, 1984). Several DTI studies report decreased fractional anisotropy (FA) in CB in patients with chronic schizophrenia (Kubicki et al., 2003; Sun et al., 2003; Wang et al., 2004).

The purpose of the present study was to determine whether UF and CB white matter integrity are altered at the early stage of illness and are specific to schizophrenia. We investigated UF and CB using DTI in patients with schizophrenia within 4 years of first hospitalization, patients

with affective psychosis within 4 years of first hospitalization, and in psychiatrically healthy control subjects.

## 2. Materials and methods

### 2.1 Subjects

Fifteen patients with schizophrenia (3 women), 15 patients with affective psychosis (5 women), and 15 healthy control subjects (4 women) participated in this study. The affective psychosis patient group (all psychotic) included 12 patients with bipolar disorder in a manic phase and three with major depressive disorder. The patients were recruited from inpatients at McLean Hospital, a private psychiatric hospital affiliated with Harvard Medical School. Healthy control subjects were recruited through newspaper advertisement. After a complete description of the study was provided, written informed consent was obtained from all participants. The study was approved by the local institutional review boards at McLean Hospital, Brigham and Women's Hospital, the VA Boston Healthcare System, and Harvard Medical School.

The protocols for diagnosis and clinical evaluations have previously been described in detail (Hirayasu et al., 1998; Kuroki et al., 2006b; Salisbury et al., 2007; Salisbury et al., 1998). Patients and controls were aged 18 to 44 years, had IQ greater than 75 (measured by the Wechsler Adult Intelligence Scale-third edition (WAIS-III)), were all right-handed, and had a negative history of seizures, head trauma with loss of consciousness, neurologic disorder, and alcohol or drug dependence within 5 years, or abuse within the last year. Medication history, prior to first hospitalization, if present, was assessed by patient report and by reviewing the medical record. Healthy control subjects also had no axis I or II psychiatric disorder or a first-degree relative with axis I psychiatric disorder, according to the Structured Clinical Interview for DSM-IV (SCID) editions for nonpatients (SCID-I/NP) (First et al., 2002a) and personality disorders (SCID-II) (First et al., 1997). Patients were diagnosed on the basis of DSM-IV criteria using the SCID edition for patients (SCID-I/P) (First et al., 2002b) and information from the medical record. All diagnoses were confirmed on re-interview a minimum of 6 months after the initial hospitalization. All patients were scanned within 4 years of first hospitalization. Twelve out of 15 patients with schizophrenia and 12 out of 15 patients with affective psychosis were scanned during their first hospitalization, consistent with *first episode* defined by the literature (Hirayasu et al., 1998; Lieberman et al., 2001). The protocols for diagnosis and clinical evaluations have previously been described in detail (Hirayasu et al., 1998; Kuroki et al., 2006b; Salisbury et al., 2007; Salisbury et al., 1998).

At the time of scan, patients in the schizophrenia group and the affective psychosis group were variously receiving second-generation antipsychotics (9 patients in the schizophrenia group and 13 patients in the affective psychosis group), both first- and second-generation antipsychotics (1 patient in the schizophrenia group), lithium (2 patients in the schizophrenia group and 6 patients in the affective psychosis group), sodium valproate (3 patients in the affective psychosis group), clonazepam (3 patients in the affective psychosis group), gabapentin (2 patients in the affective psychosis group), lamotrigine (1 patient in the affective psychosis group), levetiracetam (1 patient in the affective psychosis group), antidepressants (4 patients in the schizophrenia group and 8 patients in the affective psychosis group), or no drugs or discontinued use of medication (3 patients in the schizophrenia group and 2 patients in the affective psychosis group).

Clinical evaluations within 2–3 weeks of scanning included the Positive and Negative Syndrome Scale; the Mini-Mental State Examination; the information, digits forward, and digits backward subscales of WAIS-III; and the Global Assessment Scale. We also evaluated handedness using the Edinburgh Inventory (Oldfield, 1971) and the socioeconomic status of

patients and control subjects and of their parents using the Hollingshead Two-Factor measure (Hollingshead, 1965).

## 2.2 MRI acquisition and processing

Subjects were scanned with line-scan DTI, which has been described elsewhere (Kubicki et al., 2004; Kuroki et al., 2006a). MR scans were performed with a quadrature head coil on a 1.5-Tesla GE Echospeed system (General Electric Medical Systems, Milwaukee, Wisconsin), which permits maximum gradient amplitudes of 40 mT/m. We began with three orthogonal T1-weighted images used as localizers (sagittal, axial oblique aligned to the anterior commissure – posterior commissure (AC-PC) line, and another sagittal oblique aligned to the interhemispheric fissure). From the last sagittal oblique T1-weighted image, the line-scan DTI sequence in coronal orientation was then aligned perpendicular to the AC-PC line. For each slice, six images with high (1000 sec/mm<sup>2</sup>) diffusion weighting along six noncollinear and noncoplanar directions and two images with low (5 sec/mm<sup>2</sup>) diffusion weighting were collected. The following scan parameters were used: field of view 220 × 165 mm; 128 × 96 scan matrix (256 × 192 image matrix); slice thickness = 4 mm; interslice distance = 1 mm; receiver bandwidth ± 4 kHz; echo time = 64 msec; effective repetition time = 2592 msec; scan time = 60 sec per slice section. We acquired 31–35 coronal slices covering the entire brain, depending on brain size. Total scan time was 31–35 min. After reconstruction, diffusion-weighted images were transferred to Linux workstations using medical imaging software (3D-Slicer version 2.8; an open source development project begun at the Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, MA, U.S.A. and the Surgical Planning Laboratory, Department of Radiology, Brigham and Women's Hospital, Boston, MA, U.S.A.), on which eigenvalues ( $\lambda_1$ ,  $\lambda_2$ , and  $\lambda_3$ ), eigenvectors, mean diffusivity ( $D_m$ ), and FA were calculated. FA, a measure of the fraction of the magnitude of the tensor that can be ascribed to the anisotropic diffusion, and  $D_m$ , the average of three eigenvalues of the tensor, were calculated with the following formulae:

$$FA = \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_1 - \lambda_3)^2}}{\sqrt{2} \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}, \quad D_m = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} (\mu\text{m}^2/\text{msec})$$

The UF and CB regions of interest (ROIs) were automatically defined with a directional threshold method as described elsewhere (Figure 1) (Nakamura et al., 2005). To extract the ROIs from neighboring structures, segmentation was done by thresholding the out-of-plane principal diffusion component ( $\lambda_{1z}$ ), calculated using the following formula:

$$\lambda_{1z} = \lambda_1 \times e_{1z} (\mu\text{m}^2/\text{msec})$$

where  $\lambda_1$  is the largest eigenvalue, and  $e_{1z}$  is the out-of-plane component of the eigenvector associated with the largest eigenvalue ( $\lambda_1$ ). We used 1.1  $\mu\text{m}^2/\text{msec}$  as the common threshold for both bundles for all subjects. This directional threshold was the same as that of our recent study (Nakamura et al., 2005).

For UF, we selected one coronal slice, perpendicular to the AC-PC line, which intersects UF in the anterior temporal stem. This is the densest portion of the UF fiber tract, but sometimes there were two possible slices in which the UF seemed to be distributed densely. In that case, we compared the mean  $\lambda_{1z}$  magnitude above the threshold of 1.1  $\mu\text{m}^2/\text{msec}$  and then selected the one slice that showed the larger  $\lambda_{1z}$  value to focus on the out-of-plane component of the UF. Subsequent manual exclusion of uncertain voxels from the ROI was not needed because we used a higher threshold.

For the CB ROI, we excluded ROI outside of the anterior and posterior boundaries defined by the genu and splenium of corpus callosum and included ROI inside these regions to focus on the out-of-plane component of CB. That is, the most anterior coronal slice in which the corpus callosum was separately seen above and below was the first slice of CB, and the most posterior coronal slice in which the corpus callosum was separately seen above and below was the last slice of CB. There were 9–12 coronal slices that met this criterion for CB slice selection.

For DTI measures, the average values of FA,  $D_m$ , and the cross-sectional area within an ROI were summed over all slices, and then these three DTI measures were averaged by the total number of serial coronal slices for subsequent group comparison.

### 2.3 Statistical analysis

For statistical analyses, we used statistical software (SPSS 16.0 for Windows, SPSS Inc., Chicago, IL, U.S.A.) with a personal computer. One-way analysis of variance (ANOVA) or student t-tests were performed to assess group differences in demographic and clinical characteristics except for gender (Table 1). A chi-square test assessed group differences in gender frequencies. For diffusion measures, repeated-measures ANOVA was applied to mean FA,  $D_m$ , and cross-sectional areas for both UF and CB. We used hemispheres (left and right) as the within-subject factor and diagnostic groups (schizophrenia, affective psychosis, and healthy control) as the between-subjects factor. Post hoc Tukey's Honestly Significant Difference (HSD) tests were performed for the follow-up analyses. The statistical results reported below remained the same after exclusion of the female subjects and when patients with major depressive disorder ( $n=3$ ) were excluded from the affective psychosis group. We also used Spearman  $\rho$  to evaluate the relationship between age and DTI measures in each diagnostic group. To allow comparisons of the relative magnitudes of group differences between UF and CB, effect sizes between each pair of groups were reported for each ROI. Effect sizes, expressed in SD units, were computed using the following formula:

$$d = \frac{M_1 - M_2}{\sqrt{\frac{\sigma_1^2 + \sigma_2^2}{2}}}$$

Exploratory analyses of the relationship between DTI measures and the psychopathologic scales were evaluated using the Spearman  $\rho$  to diminish the effect of any outliers. Herein, we conservatively used  $p < 0.001$  as the cutoff value for statistical significance, considering the presence of multiple comparisons.

### 3. Results

The demographic and clinical characteristics of the present samples are shown in Table 1. There were no significant differences among three groups in terms of age, sex, handedness, parental socioeconomic status, years of education, or two subscales of the WAIS-III. We found significant group differences in subjects' socioeconomic status [ $F(2, 42) = 7.13, p = 0.002$ ]. Patients with schizophrenia had lower socioeconomic status than healthy control subjects [ $p = 0.01$ ]. Patients with affective psychosis also had lower socioeconomic status than healthy control subjects [ $p = 0.003$ ]. These findings are consistent with reduced functioning due to the disorders. We also found significant differences in the Mini-Mental State Examination scores among three diagnostic groups [ $F(2, 42) = 3.99, p = 0.03$ ]. Post hoc HSD tests revealed that the patients with schizophrenia showed lower Mini-Mental State Examination scores compared with healthy controls [ $p = 0.03$ ]. There were no differences in the Global Assessment Scale score, medication dose (chlorpromazine equivalence), or total Positive and Negative Syndrome Scale scores for the two psychiatric groups.



Descriptive statistics of DTI measures and results of repeated-measures ANOVA are summarized in Table 2. Repeated-measures ANOVA showed a significant difference in mean FA bilaterally for UF among the three groups [ $F(2, 42) = 3.68, p = 0.03$ ] (Figure 2). Post hoc HSD tests revealed that patients with schizophrenia showed lower mean FA compared with the healthy control subjects [ $p = 0.03$ , effect size = 0.81 on the left, 0.89 on the right], but not compared with the patients with affective psychosis [ $p = 0.73$ , effect size = 0.08 on the left, 0.42 on the right]. We note that an effect size of 0.81 for the schizophrenia-normal comparison is large, while the effect size of 0.08 for the schizophrenia-affective psychosis comparison is relatively small. Moreover, post hoc HSD tests did not reveal a significant difference in mean FA for UF between patients with affective psychosis and healthy control subjects, although the effect size on the left UF was quite high [ $p = 0.16$ , effect size = 0.89 on the left, 0.28 on the right]. Neither group-by-hemisphere interaction [ $F(2, 42) = 1.21, p = 0.31$ ] nor main effect of hemisphere [ $F(2, 42) = 2.35, p = 0.13$ ] were statistically significant for mean UF FA. There were no group differences in Dm for UF [ $F(2, 42) = 1.04, p = 0.36$ ]. For cross sectional area of UF, there was neither significant group difference [ $F(2, 42) = 0.61, p = 0.55$ ] nor significant group-by-hemisphere interaction [ $F(2, 42) = 1.17, p = 0.32$ ].

For CB, there were no significant group differences in mean FA [ $F(2, 42) = 0.55, p = 0.58$ ; effect size between schizophrenia and healthy control = 0.49 on the left, 0.32 on the right] (Figure 2), Dm [ $F(2, 42) = 1.18, p = 0.32$ ], or cross-sectional area [ $F(2, 42) = 0.64, p = 0.53$ ]. There were significant left > right asymmetries for CB in mean FA [ $F(1, 42) = 35.33, p < 0.001$ ], Dm [ $F(1, 42) = 6.19, p = 0.02$ ], and cross-sectional area [ $F(1, 42) = 39.55, p < 0.001$ ], compatible with previous findings. Neither group-by-hemisphere interactions were significant for mean FA [ $F(2, 42) = 0.15, p = 0.87$ ] nor cross-sectional area [ $F(2, 42) = 2.17, p = 0.13$ ].

We found a negative correlation between age and FA in the right UF [ $r = -0.33, p = 0.03$ ] and in the right CB [ $r = -0.32, p = 0.03$ ] in patients with schizophrenia, although we did not find any significant correlations between age and FA in these same fiber bundles in patients with affective psychosis or in healthy control subjects.

In an exploratory analysis of correlations between UF FA and psychopathologic measures, we found no statistically significant correlations between UF FA reduction and factors or items of the Positive and Negative Syndrome Scale in schizophrenia or in affective psychosis.

#### 4. Discussion

In the present study, we investigated UF and CB using DTI in patients with recent-onset schizophrenia, in patients with recent-onset affective psychosis, and in psychiatrically healthy control subjects to determine whether or not UF and CB white matter integrity were altered at the early stage of illness and were specific to schizophrenia. To our knowledge, no previous study has evaluated the DTI measures directly compared schizophrenia with affective psychosis. Our results suggest that bilateral UF, but not CB white matter integrity is altered at the early stage of illness in schizophrenia. Left hemisphere UF integrity also appears to be abnormal in affective psychosis early in the disease, though this finding was not significantly different from healthy controls, suggesting the sample size was not sufficient, as the effect size was 0.89. This is interesting in light of the putative role of frontal lobe control of mood state stabilization, although manic mood is generally associated more with right frontal lesions, but been reported following left frontal lesions and surgical resections (Pang and Lewis, 1996). Recently our laboratory found that the patients with affective psychosis as well as schizophrenia showed smaller overall neocortical grey matter volumes at the time of their first hospitalization than healthy controls using a semi-automated tissue segmentation of MRI (Nakamura et al., 2007). Taken together, the patients with affective psychosis as well as those with schizophrenia have some structural abnormalities in brains at first hospitalization.

Previous DTI studies have reported UF abnormalities in chronic schizophrenia. Our previous study (Kubicki et al., 2002), for example, showed reduced FA in left UF using the same methods as the present study. Two other studies using voxel-based morphometry analyses have also reported a trend level reduction in left UF FA (Burns et al., 2003) and another study reported significant reduction in bilateral UF FA (Mori et al., 2007) in chronic schizophrenia. Negative correlations between FA values and positive symptom scores of the Positive and Negative Syndrome Scale were also observed in chronic schizophrenia, further supporting a disconnection hypothesis of positive symptoms in schizophrenia (Skelly et al., 2008). In addition, a recent study by Price et al. has reported reduced FA in left UF in patients with first-episode schizophrenia using a probabilistic tractography algorithm (Price et al., 2008). Of further note, FA reduction in UF has been observed in patients with chronic bipolar disorder (McIntosh et al., 2008). Our present findings suggest that UF white matter integrity is altered at an early stage of illness in schizophrenia, bilaterally, and, to a lesser degree, in the early-stage of illness in affective psychosis. Finally, given that some studies report left lateralized findings for UF, as noted above, while other studies report bilateral findings for UF in schizophrenia, further studies are needed to clarify the laterality of abnormal UF in schizophrenia.

Of note, a significant age-related reduction of FA has also been reported in UF, which was more pronounced in patients with chronic schizophrenia than in healthy control subjects (Mori et al., 2007). We also note that a recent study by our group revealed a significant association, bilaterally, in patients with chronic schizophrenia between age at scan and reduced FA in both the uncinate fasciculus and in the cingulum bundle, which was not evident in healthy control subjects (Rosenberger et al., 2008). In addition, a recent volumetric MRI study reported that the individuals with prodromal symptoms who were at ultra high-risk of developing schizophrenia showed significantly lower white matter volume in the right temporal cortex compared to healthy controls (Witthaus et al., 2008). Taken together with these previous findings, our present results suggest that there may be some abnormalities in pathological aging of schizophrenia in right UF which progress following onset of the disease.

Importantly, however, there were no significant group differences in mean FA for CB among schizophrenia or affective psychosis in the early stage of illness, compared with healthy controls. We previously reported CB integrity disruption in chronic schizophrenia (Kubicki et al., 2005; Kubicki et al., 2003; Park et al., 2004a), and several other studies have also reported CB abnormalities in chronic schizophrenia using DTI (Mitelman et al., 2007; Mori et al., 2007; Sun et al., 2003; Wang et al., 2004). Of further note, other studies of first-episode patients with schizophrenia using voxel-based analysis of DTI data have not shown significant differences of FA in CB compared with healthy controls (Cheung et al., 2007; Szeszko et al., 2005). A deteriorating course in schizophrenia (e.g. Salisbury et al., 2007), or perhaps medication effects following the early stage of illness may account for the discrepancy between DTI findings in CB in recent onset versus chronic schizophrenia. In this study, we found that FA in UF but not in CB is decreased in patients with recent-onset schizophrenia using healthy controls as well as affective psychosis. To our knowledge this is the first report demonstrating UF abnormalities in recent-onset schizophrenia using affective psychosis as a comparison group. In addition, our findings suggest that there may be some brain regions, such as UF, that are present at early onset of illness, or even before onset, and thus driven more by neurodevelopmental influences, while some brain regions, such as CB, are not abnormal at early onset of illness but evolve over time and may thus be more associated with progressive aspects of schizophrenia. Longitudinal follow-up DTI studies of a large sample of first-episode patients, however, are needed to determine whether CB abnormalities occur during the chronic course of illness, as suggested by the current cross-sectional study.



The advantage of our method over voxel-based methods is that it is based on directional information obtained only from the diffusion tensor, whereas exploratory voxel-based approaches discard this important information. Nonetheless, because our method works only for the unidirectional portion of fiber bundles and not for their dispersive portions or for fiber crossings, we excluded CB portions outside of the anterior and posterior boundaries defined by the genu and splenium of corpus callosum. However, since we focused on the most frequently investigated regions in DTI studies in chronic schizophrenia, where differences between controls and patients were reported, we believe that this same directional threshold technique, employed here, would have detected differences between first-episode patients and controls if they were present.

In contrast, we have found only a single DTI study by Hao et al. (Hao et al., 2006) that showed lower FA only in the subgenual part of right CB, but not in the whole CB, in patients with first-episode schizophrenia using a voxel-based analysis. However, a voxel-based analysis needs smoothing process to reduce the effect of normalization errors on the statistical analysis. Larger smoothing kernel sacrifices spatial resolution resulting in failure to detect fiber bundles such as CB, while smaller smoothing kernel increases the probabilities of a type I error. The discrepancy for CB findings between the study by Hao et al. and other DTI studies might therefore be due to an error in registration or a type I error.

Of particular interest, the present result in recent onset schizophrenia was consistent with our previous DTI study in antipsychotic-naïve subjects with schizotypal personality disorder, which showed bilateral UF FA reduction but intact CB integrity using the identical methodology as in the present study (Nakamura et al., 2005). Reduced UF FA in schizotypal personality disorder was also significantly correlated with clinical features of ideas of reference, suspiciousness, restricted affect, and social anxiety. Nakamura et al. concluded that the UF but not CB abnormality in schizotypal personality disordered individuals suggested disturbed ventral aspects of fronto-temporal disconnectivity, with more intact frontal lobe function. It may be that in early psychosis more ventral aspects of fronto-temporal disconnectivity are evident, with more frontal lobe regions such as CB being affected later in the course of the illness. Only a longitudinal study, however, of early psychosis patients can address this issue.

In an exploratory analysis of correlations between UF FA and psychopathologic measures, we did not find statistically significant correlations between UF FA reduction and factors or items of the Positive and Negative Syndrome Scale in schizophrenia or in affective psychosis. Although our subjects included some non-first-episode patients, we performed clinical ratings of subjects within 2–3 weeks time of scanning. The fluctuation of clinical stability and the inclusion of some non-first-episode patients in our sample (schizophrenia  $n=3$ , affective psychosis  $n=3$ ), may have contributed to this lack of correlation, although when we evaluated the non-first-episode patients separately, we note that we also found no statistically significant correlations between FA and clinical measures.

A possible limitation of our study is the small number of subjects, although, to date, most diffusion studies in schizophrenia, especially with first-episode patients, have been based on relatively small study groups.

In conclusion, our study found that patients with schizophrenia within 4 years of first hospitalization showed significantly lower mean FA bilaterally for UF compared with healthy controls. Our results suggest that bilateral UF, but not CB white matter integrity, is altered at the early stage of illness in schizophrenia, although the patients with affective psychosis did not differ significantly from either patients with schizophrenia or healthy controls on this measure. Further studies with larger samples within a short interval from first hospitalization

are necessary to address the issue of specificity more definitively. Changes in FA and  $D_m$  longitudinally, and possible medication effects remain to be determined.

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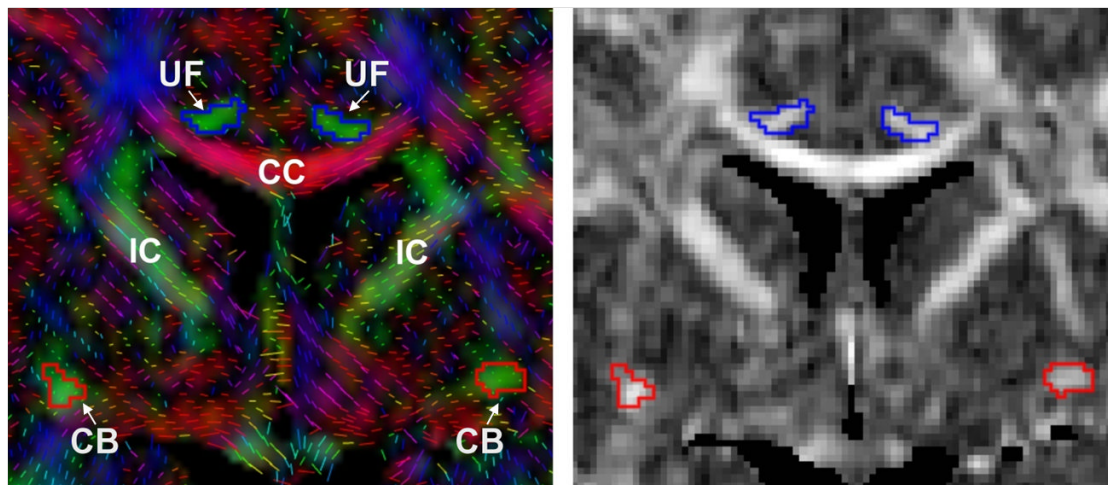
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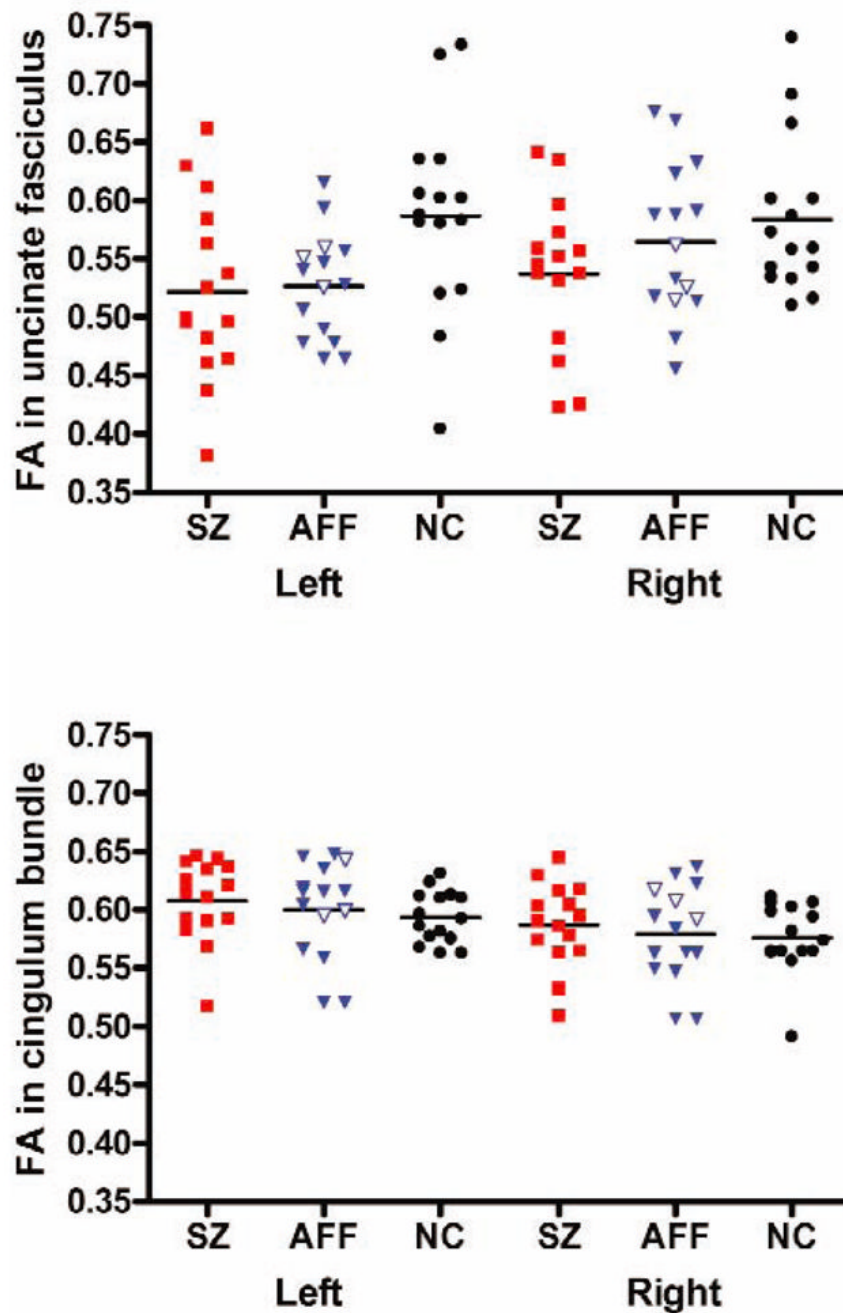




**Figure 1.**

Definition of fiber bundles. **(Left)** Three-directional color-coded fractional anisotropy (FA) map on the coronal plane. Green color means the largest eigenvalues ( $\lambda_1$ ) closely perpendicular to the coronal plane. Red color means  $\lambda_1$  with medial lateral direction. Blue color means  $\lambda_1$  with superior-inferior direction. Colored short straight lines show eigenvalues and eigenvectors in each voxel. We used the out of plane principal diffusion component of maximum diffusivity to define both bundles of uncinatus fasciculus (UF) and cingulum bundle (CB) semi-automatically. **(Right)** Uncinatus fasciculus (red polygon) and cingulum bundle (blue polygon) on FA map on the same coronal plane as left figure. The common threshold ( $1.1 \mu\text{m}^2/\text{msec}$ ) was applied for both bundles in all cases for three diagnostic groups. For measures of diffusion tensor imaging, the average values of FA within a region of interest were summed over all slices, and then they were averaged by the total number of serial coronal slices for subsequent group comparison. CC, corpus callosum; IC, internal capsule.





**Figure 2.**

Group comparison of fractional anisotropy (FA). Scatterplots of FA indicates in the left and right uncinatus fasciculus (**upper**) and cingulum bundle (**lower**) of schizophrenia, affective psychosis, and healthy control groups are shown. Solid triangles indicate patients with bipolar disorder in a manic phase, whereas open triangles indicate patients with major depressive disorder. Repeated-measures analysis of variance showed a significant difference in mean FA bilaterally for uncinatus fasciculus among the three groups [ $F(2, 42) = 3.68, p = 0.03$ ]. Post hoc Tukey's Significant Difference tests revealed that the patients with schizophrenia showed lower mean FA compared with healthy control subjects [ $p = 0.03$ ] but not with the patients with affective psychosis [ $p = 0.73$ ]. In contrast, there were no significant group differences in

mean FA for cingulum bundle [ $F(2, 42) = 0.55, p = 0.58$ ], but there was significant left > right asymmetry [ $F(1, 42) = 35.33, p < 0.001$ ]. Group-by-hemisphere interactions were not significant for mean FA in cingulum bundle [ $F(2, 42) = 0.15, p = 0.87$ ]. SZ, schizophrenia; AFF, affective psychosis; HC, healthy control.

**Table 1**  
Demographic and Clinical Characteristics of the Study Groups

Variable	Schizophrenia (n = 15)	Affective Psychosis (n = 15)	Healthy Control (n = 15)	F or t Test or $\chi^2$ Values	df	P Value
Age [range] (years)	24.5 ± 5.7 [19–42]	24.9 ± 7.2 [19–44]	23.1 ± 4.2 [18–34]	0.39	2, 42	0.68
Sex, male/female (No.)	12/3	10/5	11/4	0.68	2	0.71
Handedness <sup>d</sup>	0.7 ± 0.3	0.6 ± 0.5	0.8 ± 0.2	1.38	2, 42	0.26
Socioeconomic status <sup>b, c</sup>	2.9 ± 1.2	3.1 ± 0.9	2.0 ± 0.0	7.13	2, 42	0.002
Parents' socioeconomic status <sup>b</sup>	1.3 ± 0.6	1.6 ± 0.7	1.3 ± 0.5	1.24	2, 42	0.30
Education (years)	13.5 ± 2.0	14.4 ± 1.6	14.8 ± 1.5	2.24	2, 42	0.12
Mini-Mental State Examination score <sup>d</sup>	28.3 ± 1.4	29.1 ± 1.0	29.4 ± 0.6	3.99	2, 42	0.03
WAIS-III score						
Information	12.6 ± 2.7	13.5 ± 2.9	14.1 ± 2.0	1.25	2, 41	0.30
Digits span	10.7 ± 1.8	11.3 ± 2.4	12.3 ± 2.1	2.15	2, 42	0.13
Global Assessment Scale score	37.8 ± 12.2	46.0 ± 10.0	N/A	1.57	16	0.14
Total Positive and Negative Syndrome Scale score	69.5 ± 16.5	64.2 ± 15.2	N/A	0.85	24	0.40
Medication dose (chlorpromazine equivalent) (mg/d)	186.7 ± 148.2	144.2 ± 95.8	N/A	0.83	21	0.41
Duration of illness from first hospitalization to scan, median (range) (mo)	0 (0–47)	0 (0–17)	N/A	N/A	N/A	N/A
Duration of medication use, median (range) (mo)	0 (0–47)	0 (0–17)	N/A	N/A	N/A	N/A

Data are presented as mean ± standard deviation except for duration of medication use. Statistical significance was determined by a one-factor analysis of variance, chi-square test, or student t-test. Degrees of freedom differ among variables owing to unavailability of data for some subjects. N/A, not applicable; WAIS-III, Wechsler Adult Intelligence Scale-third edition.

<sup>a</sup>Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971). Right-handedness is designated by values above 0.

<sup>b</sup>Patients' and parents' socioeconomic status were assessed using the Hollingshead Two-Factor measure (Hollingshead, 1965). Higher scores indicate lower socioeconomic status.

<sup>c</sup>Post hoc Tukey's Honestly Significant Difference (HSD) tests showed that patients with schizophrenia had significantly lower socioeconomic status overall than healthy comparison subjects (p=0.01), while patients with affective psychosis had also lower socioeconomic status than healthy controls (p=0.003).

<sup>d</sup>HSD tests revealed that Mini-Mental State Examination Score of patients with schizophrenia was lower than that of healthy subjects (p=0.03).

**Table 2**  
Descriptive Statistics of DTI Measures and Repeated-Measures Analysis of Variance

DTI Measures	Side	SZ (n = 15)	AFF (n = 15)	HC (n = 15)	Effect Size		Main Effect of Group		Main Effect of Side		
					SZ vs HC	AFF vs HC	SZ vs AFF	F (2, 42)	p	F (1, 42)	p
UF FA <sup>a</sup>	Left	0.52 ± 0.08	0.53 ± 0.05	0.59 ± 0.08	0.81	0.89	0.08	3.68	0.03	2.35	0.13
	Right	0.53 ± 0.07	0.56 ± 0.07	0.58 ± 0.07	0.70	0.28	0.42				
UF D <sub>m</sub> (μm <sup>2</sup> /msec)	Left	0.84 ± 0.09	0.83 ± 0.05	0.80 ± 0.03	0.56	0.69	0.09	1.04	0.36	2.27	0.14
	Right	0.83 ± 0.07	0.80 ± 0.04	0.82 ± 0.03	0.26	0.68	0.64				
UF Area (mm <sup>2</sup> )	Left	18.5 ± 7.4	22.3 ± 8.4	19.0 ± 9.6	0.05	0.37	0.49	0.61	0.55	0.08	0.78
	Right	17.7 ± 9.9	20.4 ± 16.0	23.1 ± 10.1	0.54	0.20	0.20				
CB FA	Left	0.61 ± 0.03	0.60 ± 0.04	0.59 ± 0.02	0.49	0.20	0.20	0.55	0.58	35.33	< 0.001
	Right	0.59 ± 0.04	0.58 ± 0.04	0.58 ± 0.03	0.32	0.08	0.21				
CB D <sub>m</sub> (μm <sup>2</sup> /msec)	Left	0.79 ± 0.03	0.79 ± 0.03	0.80 ± 0.02	0.40	0.45	0.04	1.18	0.32	6.19	0.02
	Right	0.79 ± 0.03	0.78 ± 0.02	0.80 ± 0.02	0.29	0.87	0.37				
CB Area (mm <sup>2</sup> )	Left	25.3 ± 6.5	22.8 ± 9.9	23.3 ± 5.6	0.33	0.06	0.30	0.64	0.53	39.55	< 0.001
	Right	22.5 ± 5.4	20.7 ± 9.8	18.8 ± 5.0	0.71	0.24	0.22				

Data are presented as mean ± standard deviation. Statistical significance was determined by a repeated-measures analysis of variance. DTI, diffusion tensor imaging; SZ, schizophrenia; AFF, affective psychosis; HC, healthy control; UF, uncinate fasciculus; FA, fractional anisotropy; D<sub>m</sub>, mean diffusivity; Area, cross-sectional area; CB, cingulum bundle.

<sup>a</sup>Post hoc Tukey's Honestly Significant Difference tests indicated that patients with schizophrenia were significantly different from healthy control subjects [ $p = 0.03$ ] but not from the patients with affective psychosis [ $p = 0.73$ ].