Diffusion tensor imaging in the early phase of schizophrenia

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White Matter Fibertracking in First-Episode Schizophrenia, Schizo-Affective Patients and Subjects at Ultra-High-Risk for Psychosis


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Abstract

There is increasing evidence for white matter pathology in schizophrenia. The aim of this study was to examine whether white matter abnormalities found with diffusion tensor imaging (DTI) in previous schizophrenia studies are present in the early phase of the illness.

DTI was performed at 3 Tesla of ten male patients with a first (8) or second (2) psychotic episode of schizophrenia or schizo-affective disorder, ten male patients at ultra-high risk for psychosis with (pre)psychotic symptoms, and ten healthy controls. Fibertracts found abnormal in other DTI studies (uncinate and arcuate fasciculus, anterior and dorsal cingulum, subdivisions of the corpus callosum) were calculated and visualized; tract-specific measurements (fractional anisotropy and trace) were performed.

No differences were found between the healthy subjects and two patient groups.

These preliminary findings suggest that there is no white matter pathology of these association tracts detectable with DTI in the early stages of schizophrenic illness in males. Our findings are in contrast with DTI abnormalities found in some other first-episode studies. This discrepancy in findings may be related to differences in subject characteristics and DTI methodology. Possible effects of age, gender, level of education and illicit substance use on DTI findings in schizophrenia are discussed.
2.1.1 Introduction

Abnormal brain development in schizophrenia is thought to lead to 'dysconnectivity' between brain areas associated with positive and negative symptom dimensions and cognitive dysfunctioning [1, 2, 3]. The neuroanatomical substrate for this dysconnectivity may be dysplastic white matter tracts as a result from abnormal development in utero [2], demyelination during adolescence [1, 3] and adulthood [3], or an arrest in the normal process of myelination during brain maturation in adolescence and middle age [3].

With diffusion tensor imaging (DTI), brain white matter structure can be assessed in a more detailed manner in vivo than with conventional MRI [4]. In DTI the magnetic resonance signal is made sensitive to the movement (or diffusion) of water molecules. A DTI index called fractional anisotropy is increased by myelination [5, 6], coherence of fiber tracts [7], and by the structural integrity of fibers, their diameter and packing density [4].

Subjects at ultra high-risk (UHR) for conversion to psychosis are characterized by defined trait or state factors including attenuated or brief limited psychotic symptoms [8, 9, 10]. Studies in UHR subjects and first psychotic episode patients can provide insight in the early pathophysiological mechanisms in schizophrenia-like disorder. Eight DTI studies in patients with a recent onset of schizophrenia have been reported so far [11, 12, 13, 14, 15, 16, 17, 18] and have reported abnormalities in several white matter areas. To our knowledge, no DTI studies in UHR patients have been reported. One diffusion weighted study in first-degree relatives of schizophrenia patients found diffusion abnormalities in gray matter structures not detectable with conventional MRI [19]. In chronic schizophrenia patients, several DTI studies found reduced anisotropy in numerous brain regions [20, 21, 22, 23]. One study found also increased anisotropy in a subgroup of patients [24].

Many DTI studies in schizophrenia examined regions of interest (ROI) or used a voxel-by-voxel approach in gray-scale anisotropy images, in which it can be difficult to locate abnormalities to specific fibertracts. Advanced applications of DTI make it possible to calculate and visualize the probable trajectories of white matter fiber bundles (referred to as ‘fibertracking’; [25]) and allow tract-specific measurements. To our knowledge, this is the first DTI study, which applies fibertracking to examine white matter tracts in UHR patients as well as patients with a first or second psychotic episode of schizophrenia or related disorder. Associ-
ation fibertracts connecting cortical regions may be primarily involved in schizophrenia [26] and we hypothesized that fractional anisotropy of association fibertracts, previously found to be abnormal in schizophrenia, would be altered in both patient groups compared to healthy controls. Furthermore, antipsychotic medication use is a major confounder in schizophrenia research and we hypothesized that there would be a positive correlation between duration and dose of antipsychotic treatment and white matter fractional anisotropy, as found previously [22, 23]. Such a relation would be consistent with possible pro-myelination effects of some atypical antipsychotics, which have been found to increase brain neurosteroid and apolipoprotein D levels and blood lipid levels, which in turn are thought to stimulate myelination in the brain [3].

2.1.2 Methods

Subjects

This study was approved by the local and national medical ethics committees. Male patients diagnosed with a first or second psychotic episode of schizophrenia, schizo-affective disorder or schizophreniform disorder (referred to next as schizophrenia-like disorders) were recruited from the open-ward inpatient and day-care units of the Adolescent Clinic of the Academic Medical Center. These patients were approached when they were deemed clinically able to give informed consent. Ultra-high-risk patients were recruited from a naturalistic, longitudinal study program related to the Adolescent Clinic, with an 18 month follow-up. These patients are referred by mental health services. Inclusion criteria for these patients were defined according to criteria used in other studies [8, 9, 10]: attenuated psychotic symptoms (e.g. odd beliefs, paranoid ideation) or brief psychotic moments with spontaneous remission in less than one week; and/or a decline in functioning in the past year (30% reduction in Global Assessment of Functioning scale) plus a genetic risk (1st degree relative with schizophrenia-like disorder or a schizotypal personality disorder); or two ‘basic symptoms’ (cognitive, perceptual, emotional and social disturbances; [10]). We included only males as white matter abnormalities may be gender-specific [27]. Male healthy control subjects were recruited through local advertisements and were matched for educational level, age and handedness.
Exclusion criteria for all subjects were: history of a demonstrable neurological or endocrine disease which may affect brain structure, history of a head trauma with loss of consciousness for more than 15 minutes, mental retardation according to DSM-IV criteria (prior to onset of the first psychotic episode for schizophrenia-like patients), gross brain abnormalities on conventional MRI other than atrophy or ventricular enlargement, and any standard exclusion-criterion for MRI scanning (e.g. non-removable metal objects). Additional exclusion criterion for the UHR subjects was a current or past psychotic disorder. Additional exclusion criteria for healthy controls were: a personal or family history of a major psychiatric illness, or a lifetime diagnosis of alcohol or other substance abuse or dependence. After complete description of the study, written informed consent was obtained from all subjects.

Clinical Measures

Clinical discharge diagnoses (including substance abuse or dependence) of patients with schizophrenia-like disorder were made according to DSM-IV criteria by two clinical psychiatrists with the use of all available clinical information, including a history taken from a significant other (Longitudinal Expert Assessment of Diagnosis procedure; [28]). An estimate of duration of illness, defined as the time between the start of the first psychotic episode and MRI scanning, was based on an interview and all medical records.

For the UHR patients, fulfilment of the inclusion criteria and diagnoses according to DSM-IV criteria were determined by a clinical psychiatrist and a research psychologist with the Structured Interview for Prodromal Syndromes (SIPS; [9]) and the Bonn Scale for the Assessment of Basic Symptoms (BSABS; [10]). Estimates of total duration of antipsychotic medication use in both patient groups were based on an interview and all medical records. Positive, negative and general symptoms were assessed by trained raters with the Positive and Negative Syndrome Scale (PANSS) in the schizophrenia-like and UHR patients.

Healthy controls were screened in a clinical psychiatric interview by a psychiatry resident. Handedness was determined with the Annett Handedness Questionnaire [29]. Educational level was defined according to the educational levels of the Dutch high school system: ‘skilled professional training’ (requires average or below average IQ), and Bachelor’s or Master’s level.
DTI Protocol and Postprocessing

DTI and T1 MRI images were acquired on a Philips Intera 3 Tesla whole-body MRI scanner (Philips Intera, Philips Medical Systems, Best, The Netherlands). First a localizer scan was done. Whole brain DTI images were then acquired using single-shot spin-echo echo-planar-imaging (EPI). Slice orientation was (para)transversal, tilted slightly to coronal according to the line touching the inferior of the genu and inferior of the splenium of the corpus callosum. DTI acquisition was along 16 noncollinear directions and each direction was scanned twice and then averaged to improve signal-to-noise ratio. Slice thickness was 3 mm, no gap. Other parameters were: FOV 230–256 mm (depending on head size), echo-time 94 msec., TR (repetition time) 4831–6248 msec. (depending on the number of slices, which varied with head size; TR did not vary within a scan; this variation in TR did not affect DTI results, since the T1-weighting factor, which is governed by TR, is divided out in the postprocessing of the DTI image data), diffusion sensitivities of \( b = 0 \) and \( b = 1000 \text{s/mm}^2 \), image matrix \( 256 \times 256 \). Scantime was about 6 minutes per subject for the diffusion series, total scantime was less than 30 minutes.

Subjects were positioned with their heads thoroughly fixated by inserting cushions between their ears and the head coil. No motion artefact correction was performed, because scans were acquired back-to-back and no displacement was visually detected. Since DTI measurements were acquired with single-shot EPI sequences, motion artefacts like blurring or ghosting did not occur. After reconstruction, the diffusion-weighted images were transferred to a workstation, where eigenvalue and eigenvector maps of the diffusion tensor were calculated. Fractional anisotropy (FA) images were reconstructed, including FA images color-coded for main diffusion direction (x, y or z). The acquired diffusion tensor images formed a basis to construct a full brain white-matter tractography for each individual separately. The algorithms presented by Basser et al. formed the basis for the construction of the pathways that follow the white matter fiber bundles in the brain [30]. We used Basser and colleagues’ fourth-order integration through the interpolated tensor field to generate the fiber paths. We chose a whole-brain seeding approach, where many individual fiber tracts are generated throughout the entire brain. The individual starting points are seeded uniformly over the brain and then using these as start locations each fiber bundle is traced in both directions until a stopping condition is met. We have used two criteria for the stopping condition. First, the FA in each voxel has to be at least
0.2. This value was suggested as the optimal FA value for fiber tracking by Mori and colleagues [31] and Kunimatsu and colleagues [32]. Secondly, the bending angle of the tract is not allowed to exceed 45 degrees. These stopping criteria also serve to diminish noise induced errors [30]. This process resulted in a tractography for each subject containing around 30,000 fibers which were composed of around 1.2 million points in total.

**DTI Quantification**

We examined association fiber tracts which showed abnormalities in previous DTI studies in schizophrenia patients: the dorsal cingulum [33, 14], the anterior cingulum [34, 12, 35], the uncinate fasciculus [36, 24] and the arcuate fasciculus [36, 24], the genu of the callosum [24] and the splenium of the callosum [24, 37, 38].

DTI data of each individual subject were analyzed with in-house developed software, Diffusion Tensor Imaging Interactive (DTII) [39]. The software allows interactive extraction of fiber bundles through positioning of three boxes; only the fiber bundle(s) that passes through all three boxes are extracted and visualized. DTII allows visualization of the fiber tracts overlaid on the anatomical T1 MRI-images and the (color-coded) FA-images, in one or more slice-views. In accordance with hypotheses that FA reduction in schizophrenia-like disorder results from myelination abnormalities [1, 3] FA and the ‘trace’ (the average diffusion in all three main directions) were measured in the most ‘homogeneous’ part of each fiber-bundle, i.e. the thickest part with the least branching off of small fibers. Fasciculi were segmented and visualized in the following manner. One box was placed in the ‘starting point’ of the fasciculus, another box was placed in the ‘end point’, and one measurement box was placed between the other two boxes. Mean FA and trace of the section of the fiber tract in the measurement box were measured. Specifics on the boundaries used for each bundle are described below. To locate the bundles the following references were used: publications of studies on these bundles in schizophrenia patients, two DTI atlases [25, 40], one neuropathological atlas [41]. For reliability purposes, the size of the three boxes was maintained the same across subjects for each bundle. The spatial position of the boxes was defined by their location relative to structures in the T1 scan, to the bundle itself, and to the other boxes.

Before actual measurements, inter-rater reliability for each bundle
was determined in ten subjects. Intra-class correlation (ICC) was calculated and was required to be 0.90 or more for each fibertract before actual measurements were performed. Actual measurements were then done by one rater (B.P.). Boundaries of the measured bundles and their ICC were as follows:

**Corpus callosum (see figure 1 in appendix):** Similar to Brambilla and colleagues [42], we divided the corpus callosum in 4 regions: splenium (posterior one-third of the mid-sagittal length), genu (anterior one-third), and anterior truncus and posterior truncus (each one-half of the middle one-third). First, the measurement box (5.6 mm wide, left-right direction) was placed in the middle of the corpus callosum, where its fibers cross from the left to right hemisphere. The two other boxes were then placed adjacent to the measurement box, each one covering the whole left or right hemisphere; this visualized the complete corpus callosum. The sagittal view of the T1 scan was then placed in the middle of the corpus callosum. Next, the measurement box was resized to the length of the corpus callosum in the T1 scan. The anterior-posterior length of the measurement box was for the splenium, posterior truncus, anterior truncus and genu 2.6 cm, 1.3 cm, 1.3 cm and 2.6 cm respectively. The height (superior-inferior) was minimized to exclude the fornix from the measurements. Inter-rater reliability (ICC) was 0.95 for the total corpus callosum, 0.97 for the splenium, 0.97 for the posterior truncus, 0.93 for the anterior truncus, and 0.94 for the genu.

**Uncinate fasciculus (see figure 2 in appendix):** The uncinate fasciculus connects the orbito-frontal lobe (OFL) to the temporal pole (TP). The midsagittal slice of the T1 structural MRI was used for reference. The uncinate was traced and measured by placing one box in the OFL, another box in the TP, and the measurement box (3.9 cm³: 1.4×1.5×1.9) in the segment of the fasciculus containing the vertical (inferior to superior) fibers in the temporal pole and the first part of the horizontal fibers in the prefrontal lobe. ICC was 0.95 for the left and 0.92 for the right.

**Arcuate fasciculus (see figure 3 in appendix):** The arcuate fasciculus connects each frontal lobe with its hemisphere. One box was placed in the frontal part and the other box in the temporal part, both clearly identified in the coronal plane of the color-coded FA images. The measurement box (10.2 cm³: 2.3×1.7×2.7) was placed in the parieto-temporal part of the long fibers, where the horizontal parietal part of the bundle curves downward vertically to the temporal lobe. ICC for the left was 0.97 and for the right 0.98.

**Dorsal cingulum (see figure 4 in appendix):** The cingulum runs from
the frontal lobe to the temporal lobe and interconnects parts of the limbic system. The midsagittal slice of the T1 structural MRI was used for reference. One box was placed just anterior to the genu of the corpus callosum, another on the splenium of the corpus callosum. The measurement box was 40 mm long from anterior to posterior (9.0 cm³: 4.0 × 1.6 × 1.4), and was placed with its anterior side to the dorsal side of the genu of the corpus callosum, which is in accordance with Kubicki et al. [33]. It was then moved to superior to include the dorsal cingulum. ICC was 0.99 for the left and 0.94 for the right.

Anterior cingulum (see figure 5 in appendix): The midsagittal slice of the T1 structural MRI was used for reference. The measurement box (2.3 cm³: 1.1 × 1.6 × 1.3) was placed with its posterior side to the dorsal side of the genu of the corpus callosum. The other box was placed just anterior to the measurement box and the third box was placed on the splenium of the corpus callosum; this corresponds to Wang et al. [34]. The measurement box was then moved superior to cover the anterior cingulum. ICC was 0.94 for the left and 0.90 for the right.

Statistical Analyses

Data were analysed using SPSS version 11.5 (www.spss.com). Repeated-measures analysis of variance (ANOVA) with group as between-subjects factor was used to test for differences in FA and trace between groups. The uncinate fasciculus and arcuate fasciculus were analyzed with side and fibertract (uncinate and arcuate) as within-subjects factors. The cingulum was analyzed with side and part of the cingulum (dorsal or anterior) as within-subjects factors. The corpus callosum was analyzed with the four sub-regions as within-subjects factors. In the case of a significant group or hemisphere effect or a group-by-hemisphere interaction, independent t tests were used to compare group differences, and paired t tests were used to test for hemispheric asymmetry. Level of significance was set at p < 0.05.

Associations between illness duration, antipsychotic medication dose and duration, PANSS scores and diffusion measurements were calculated with Spearman’s rank correlation (rₚ). A Bonferroni correction was applied for number of comparisons (i.e. fibertract measurements), setting level of significance for correlations at p < 0.05/12 (=0.004).
2.1.3 Results

Ten patients with schizophrenia-like disorder, ten UHR patients and ten controls were included (see table 2.1.1). Eight schizophrenia-like patients were diagnosed with schizophrenia, and two with schizoaffective disorder. Eight patients experienced a first psychotic episode and two patients a second (all referred to next as first-episode patients). There were three patients with a history of cannabis dependence, two with cannabis abuse, one with cannabis dependence and amphetamine abuse, one with cannabis dependence and cocaine abuse and alcohol abuse. Eight patients used atypical antipsychotic medication and two typical antipsychotic medication. Median duration of illness was 0.9 years (range 0.3–2.6).

The DSM-IV diagnoses of the UHR patients were: depressive disorder (2), schizoid personality disorder (1), preliminary diagnosis of bipolar disorder (1); six received no diagnosis. Nine UHR patients experienced attenuated positive symptoms, of whom three also experienced brief limited intermittent psychotic symptoms and two had a first-degree relative with schizophrenia-like disorder plus reduced functioning; one patient had (pre)psychotic basic symptoms (thought-blockages and unstable ideas of reference). Three UHR patients had used antipsychotic medication (one risperidone and two olanzapine). One patient used an antihistamine drug, one had used antidepressants, one had used benzodiazepines, one had used methylphenidate as a child. Two patients had a history of cannabis abuse, and one a history of amphetamine, XTC (3,4 methylene-dioxymethamphetamine) and cannabis abuse. There were no significant differences between the groups in age or educational level.

There were no differences in FA or trace between the first-episode patients, UHR subjects and controls in any of the fibertracts (see table 2.1.2). There was a significant effect of hemisphere in FA (F=44.84, df=1, p<0.001) and trace (F=5.35, df=1, p=0.03) of the cingulum in controls and patients grouped together. Follow-up paired t tests showed that, in controls and patients grouped together, there was a left>right asymmetry of FA in the dorsal (t=5.75, df=29, p<0.001) and anterior (t=4.45, df=29, p<0.001) cingulum, and a left>right asymmetry of trace in the dorsal cingulum (t=2.70, df=29, p=0.01).

As substance use by some patients was a possible confounder, post-hoc analyses were performed to explore differences between patients with and without substance use. We applied a bonferroni correction (p=0.05/12=0.004) as 12 new repeated measures ANOVA’s were per-
Table 2.1.1: Characteristics of Patients and Healthy Controls.

<table>
<thead>
<tr>
<th></th>
<th>First-Episode Patients (N=10)</th>
<th>Ultra-High-Risk Patients (N=10)</th>
<th>Healthy Controls (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>21.2 ± 3.0</td>
<td>21.6 ± 2.8</td>
<td>21.1 ± 2.8</td>
</tr>
<tr>
<td>Educational level (n)</td>
<td>3 / 4 / 3</td>
<td>3 / 2 / 5</td>
<td>2 / 4 / 4</td>
</tr>
<tr>
<td>Handedness R/L (n)</td>
<td>8 / 2</td>
<td>10 / 0</td>
<td>8 / 2</td>
</tr>
<tr>
<td>Age at onset (years ± SD)</td>
<td>20.1 ± 2.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antipsychotic medication (n)</td>
<td>10</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Duration antipsychotic medication (weeks)</td>
<td>33.5 (7.1–97)</td>
<td>14 (10, 12 and 20)</td>
<td>-</td>
</tr>
<tr>
<td>Dose antipsychotics c</td>
<td>2.4 (1.3–5.0)</td>
<td>1.1 (0.7–1.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

a Professional skilled training/ Bachelor’s level/ Master’s level.

b Median (min.–max.).

c At time of MRI scanning, median (min.–max.) mg/day in haloperidol equivalents; two patients using quetiapine were excluded, because estimation of the haloperidol equivalent of quetiapine was not deemed valid.

formed [(cingulum, arcuate-uncinate, corpus callosum) × (trace or FA) × (UHR or first-episode patients)].

There were no differences in FA or trace between the first-episode patients with and without substance use. Similarly, UHR patients with substance use were compared with UHR patients without substance use. There were three UHR patients with a history of substance abuse. In addition, one patient was not diagnosed as such, but had used cannabis frequently for some time. Therefore we compared the four UHR patients with substance (ab)use with the six patients without substance (ab)use. There was a trend for the corpus callosum (F=8.1, df=1, p=0.022), where trace of the genu was higher in UHR patients with substance (ab)use (t=-2.9, df=5.5, p=0.032; equal variances not assumed).

Further post-hoc ANOVA’s comparing first-episode patients and UHR patients without substance use with controls showed that there was a trend for a difference in trace in the corpus callosum (F=6.2, df=2, p=0.010). In first-episode patients without substance use trace was lower in the splenium compared with controls (t=4.4, df=11.0, p=0.002; equal variances not assumed), and in UHR patients without substance use trace was lower in the posterior truncus (t=3.1, df=7.6, p=0.016; equal vari-
ances not assumed) and the genu of (t=2.4, df=13.5, p=0.033; equal variances not assumed) compared with controls. There were no differences in trace in the other fibertracts, nor FA differences, between the two patient groups without substance use and controls. Neither were there differences in trace or FA between the two patients groups with substance use and controls.

In first-episode patients, FA in the right arcuate fasciculus was non-significantly related to duration of antipsychotic medication use ($r_s = -0.65$, $p=0.043$). When the three UHR patients with a history of antipsychotic use were included, the correlation became weaker ($r_s = -0.47$, $p=0.103$). There appeared a trend for a relation between FA in the right anterior cingulum and duration of antipsychotic medication use ($r_s = -0.59$, $p=0.033$). There was no significant relation between FA or trace and dose of antipsychotic medication or duration of illness in any of the fibertracts.

In the patient groups combined, there was a trend for a correlation between positive symptom scores and FA of the left anterior cingulum ($r_s = 0.53$, $p=0.017$). Trace in the left uncinate correlated with positive symptom scores ($r_s = 0.51$, $p=0.021$), trace in the right uncinate with general and total symptom scores ($r_s = 0.48$, $p=0.030$ and $r_s = 0.47$, $p=0.037$ respectively), trace in the splenium of the corpus callosum with positive symptom scores ($r_s = 0.47$, $p=0.038$).

### 2.1.4 Discussion

With diffusion tensor fibertracking we found no significant differences in FA or trace of four association tracts between first-episode patients with schizophrenia or schizoaffective disorder, UHR patients and control subjects. We did not find significant relations between FA or trace and antipsychotic medication use.

Our finding of lack of DTI abnormalities in first-episode patients contrasts with findings of reduced FA in other first-episote or recent-onset studies. Hao et al. found reduced FA in the the anterior cingulum [12], Karlsgodt and colleagues found reduced FA in the arcuate fasciculus [18], Szeszko et al. found abnormalities approximately corresponding to the arcuate fasciculus and uncinate fasciculus [17]. However, Price et al [15] applied fibertracking and found no differences between recent-onset patients and controls in mean FA in the uncinate fasciculus. The spread of
the FA distribution along the tract was skewed in the patients, which is thought to represent reduced FA in the core of the tract. In accordance with another first-episode study [13] we found no abnormalities in the genu or splenium of the corpus callosum. In contrast, Cheung et al. did find reduced FA in the splenium of the corpus callosum in medication-naive first-episode patients [16].

There may be several explanations for this discrepancy in findings between DTI studies in young-adult patients with schizophrenia-like disorder. First, the lack of differences between patients and controls in our

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**Table 2.1.2: White Matter Diffusion Tensor Measurements in Four Association Fibertracts**

<table>
<thead>
<tr>
<th>Fibertract</th>
<th>First-episode Patients (N=10)</th>
<th>Ultra-High-Risk Patients (N=10)</th>
<th>Healthy Controls (N=10)</th>
<th>F</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncinatus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractional anisotropy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>0.479 ±0.050</td>
<td>0.477 ±0.044</td>
<td>0.477 ±0.053</td>
<td>0.15</td>
<td>2</td>
<td>0.86</td>
</tr>
<tr>
<td>right</td>
<td>0.467 ±0.034</td>
<td>0.494 ±0.044</td>
<td>0.485 ±0.041</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td></td>
<td></td>
<td></td>
<td>0.35</td>
<td>2</td>
<td>0.71</td>
</tr>
<tr>
<td>left</td>
<td>0.248 ±0.014</td>
<td>0.249 ±0.008</td>
<td>0.244 ±0.009</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>right</td>
<td>0.245 ±0.006</td>
<td>0.239 ±0.007</td>
<td>0.245 ±0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arcuatus</strong></td>
<td></td>
<td>(analyzed with uncinatus)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fractional anisotropy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>0.503 ±0.031</td>
<td>0.501 ±0.029</td>
<td>0.508 ±0.035</td>
<td></td>
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<tr>
<td>right</td>
<td>0.502 ±0.046</td>
<td>0.505 ±0.025</td>
<td>0.503 ±0.027</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td>(analyzed with uncinatus)</td>
<td></td>
<td></td>
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<tr>
<td>left</td>
<td>0.226 ±0.013</td>
<td>0.225 ±0.008</td>
<td>0.228 ±0.006</td>
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<td></td>
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<tr>
<td>right</td>
<td>0.224 ±0.011</td>
<td>0.222 ±0.009</td>
<td>0.266 ±0.007</td>
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<tr>
<td><strong>Cingulum</strong></td>
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<td></td>
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<td>1.21</td>
<td>2</td>
<td>0.31</td>
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<tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>dorsal left</td>
<td>0.536 ±0.072</td>
<td>0.572 ±0.053</td>
<td>0.561 ±0.043</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dorsal right</td>
<td>0.498 ±0.049</td>
<td>0.563 ±0.049</td>
<td>0.516 ±0.043</td>
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<td></td>
<td></td>
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<tr>
<td>anterior left</td>
<td>0.483 ±0.060</td>
<td>0.498 ±0.055</td>
<td>0.496 ±0.047</td>
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<td>anterior right</td>
<td>0.437 ±0.063</td>
<td>0.480 ±0.060</td>
<td>0.409 ±0.049</td>
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<td>0.92</td>
<td>2</td>
<td>0.41</td>
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<tr>
<td>dorsal left</td>
<td>0.250 ±0.028</td>
<td>0.245 ±0.012</td>
<td>0.243 ±0.010</td>
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<tr>
<td>dorsal right</td>
<td>0.243 ±0.016</td>
<td>0.232 ±0.009</td>
<td>0.242 ±0.007</td>
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<tr>
<td>anterior left</td>
<td>0.254 ±0.032</td>
<td>0.247 ±0.009</td>
<td>0.240 ±0.011</td>
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<tr>
<td>anterior right</td>
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<td>0.238 ±0.014</td>
<td>0.245 ±0.011</td>
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Table 2.1.2: (continued)

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<th>First-episode Patients (N=10)</th>
<th>Ultra-High-Risk Patients (N=10)</th>
<th>Healthy Controls (N=10)</th>
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<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
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<td>Fractional anisotropy</td>
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<td>0.706 ± 0.018</td>
<td>0.680 ± 0.020</td>
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<td>genu</td>
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<td>0.651 ± 0.039</td>
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<td>Trace</td>
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<td></td>
<td>2.66</td>
<td>2</td>
<td>0.09</td>
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<tr>
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<td>0.291 ± 0.014</td>
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<tr>
<td>posterior truncus</td>
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<td>0.312 ± 0.027</td>
<td>0.332 ± 0.014</td>
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<tr>
<td>anterior truncus</td>
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<td>0.295 ± 0.020</td>
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<tr>
<td>genu</td>
<td>0.284 ± 0.019</td>
<td>0.280 ± 0.017</td>
<td>0.292 ± 0.025</td>
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</table>

study may result from lack of power due to the small sample size. However, one first-episode study finding differences included ten patients [11], whereas the study finding no differences included twenty patients [13].

Secondly, level of education of the subjects may be an important confounder, although subjects were matched carefully on educational level. In our study, seven out of ten first-episode patients and seven out of ten UHR patients had received education at a Bachelor’s or Master’s level. A structural MRI study in first-episode patients with a high level of education found no differences compared with healthy controls in cerebral white matter volume [43], while other first-episode studies did [44, 45]. High educational level has been associated with good outcome [46, 47], which in turn has been associated with a relative lack of brain abnormalities at illness presentation [48] and in the course of the illness [49]. Educational level was not mentioned in four of the first-episode or recent-onset DTI studies [11, 13, 14, 15], and was somewhat higher in controls in one study [12]. Parental socio-economic status or years of education was matched in three studies [16, 17, 18].

Third, a gender effect may be involved. We included males only and the seven DTI studies showing abnormalities included both males and fe-
males. Post-mortem studies suggest that female patients have more white matter abnormalities than male patients [50, 51]. It is well known that there are gender differences in brain anatomy and this should be taken into account in MRI studies. However, the other negative study [13] also included males and females.

Fourth, there had been considerable use of illicit drugs in our group of first-episode patients, mainly cannabis. In the other studies only sporadic cannabis use by patients was reported [14], or patients with substance dependence [12, 15] or abuse [11] or ‘psychostimulant use’ [16] were excluded; in one study one third of patients had a comorbid diagnosis of substance abuse [17]; two studies did not report on illicit drug use by patients [13, 18]. In another DTI study in a larger sample of first-episode patients we found increased FA in the uncinate fasciculus, which was restricted to patients with a history of illicit drug use, in particular cannabis use before age 17 (Peters et al, submitted). DeLisi et al. [52] found increased FA in young adult subjects with adolescent cannabis use. These findings could mean that adolescent cannabis use increases white matter anisotropy through some effect on brain development. Alternatively, schizophrenia patients with early cannabis use may represent a subgroup of patients with a distinct pathophysiology. Post-hoc analyses in the present study showed virtually no differences between patients with and without substance use (mainly cannabis). It is therefore unlikely that our results were confounded by substance use. There was a trend that patients without substance use had lower trace in parts of the corpus callosum. DTI differences between schizophrenia patients with and without substance use are probably subtle and should be studied further in larger samples.

Fifth, our recent-onset patients were younger (2.2–7.3 years on average) than the patients in all but one of the other first-episode DTI studies. Age was similar in one study [18]. Duration of illness of patients was shorter in three of these studies [14, 16, 17], similar to ours in another [12], slightly longer in another [18], and not mentioned in two studies. Perhaps increasing age during young adulthood in schizophrenia is accompanied by an abnormal decrease in FA due to abnormal brain maturation. This may be independent of any progressive brain abnormalities developing after onset of the first psychotic episode.

Finally, methodological differences in postprocessing and quantification of the DTI images may play a role in the conflicting results. Five first-episode studies [11, 12, 14, 16, 17] employed a voxel-by-voxel analysis. The accuracy of voxel based techniques is limited by possible misclassi-
fication of brain tissue, errors in inter-subject co-registration [53], and possible type I errors of a large number of comparisons (although this was addressed in these studies with a cluster-size threshold). Karlsgodt et al. [18] performed region-of-interest measurements after employing an advanced tract-based intersubject co-registration method. Interestingly, the two first-episode studies employing fibertracking or a conventional region-of-interest method found no differences in mean FA [13, 15].

In studies using conventional FA images, instead of fibertracking algorithms, measurements may be influenced by fibertracts crossing the tract of interest. For instance, measurements in the uncinate fasciculus are likely to include part of the anterior commissure and the inferior occipito-frontal fasciculus [41]. With our interactive fibertract selection with three boxes we could easily segment the uncinate fasciculus from the inferior occipito-frontal fasciculus.

There were some trends for correlations between DTI indices and positive and general symptom scores, but not negative symptom scores. Whether white matter diffusion abnormalities are specifically related to positive symptoms and not negative symptoms should be further examined in larger samples.

Our fibertracking study has some limitations. Fibertracking is a relative new tool to investigate white matter anatomy and it is influenced in certain regions by crossing fibers. Also, the anatomical boundaries for our measurements were defined for the most part by the fibertracts, thus using the dependent variable to define its boundaries. Furthermore, we did not measure fibertract diameter and it is possible that there were differences in fibertract diameter between the groups. In addition, the voxels in our study were not collected isotropically and isotropically-acquired voxel are preferred for fibertracking. As to the quality of the DTI and fiber tracking, we remark that in all cases we could reconstruct fibertracts consisting of densely packed parallel fiber lines. Erroneous fiber lines, wandering away in unlikely directions, which signal the influence of noise, were very infrequent, and they were not taken into account in the measurement.

Little has yet been done about the validation of DTI. Larger studies and especially neuroanatomical and pathological comparisons with brain specimens are lacking in this stage of research. Still it could provide us in the future an important part of the diagnostic chain when we could link fibertracking to functional MRI and neurophysiological data and neuropsychological performance tests.
2.1.5 Conclusion

To our knowledge, this is the first DTI study comparing young-adult schizophrenia and schizoaffective patients as well as UHR patients with healthy controls using white matter fibertracking. We found no DTI abnormalities in four association fibertracts in neither patient group. Larger longitudinal studies including neuroleptic naïve patients are needed to determine the effect of age, illness duration, gender, illicit drug use and medication on DTI measurements in schizophrenia. Longitudinal studies in UHR patients can determine which DTI abnormalities are associated with transition to psychosis. More advanced imaging and quantification methods, in particular high-field-strength imaging with higher resolution and tract-specific measurements through fibertracking, may give better insight in which white matter pathways are implicated in the pathophysiology of schizophrenia.

2.1.6 Acknowledgments

The authors thank Dr. Harry Uylings (Dept. Anatomy & Neuroscience, VU University Medical Center, Amsterdam) for his kind and insightful advice on the boundaries and trajectory of the uncinate fasciculus.

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