Diffusion tensor imaging in the early phase of schizophrenia

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White Matter Connectivity and Psychosis in Ultra-High-Risk Subjects: a Diffusion Tensor Fiber Tracking Study


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Abstract

This study assessed with Diffusion Tensor Imaging (DTI) whether ultra-high-risk subjects who later develop a psychotic disorder (UHR-P) show abnormalities in association white matter fiber tracts as compared to UHR subjects who do not convert to psychosis (UHR-NP) and healthy controls. Seventeen male UHR subjects and ten male healthy controls were included and baseline DTI scans were collected before clinical follow-up. The uncinate and arcuate fasciculi, anterior and dorsal cingulate, and subdivisions of the corpus callosum were calculated and visualized, and tract-specific measurements were performed. At 24-month follow-up seven UHR subjects had developed a first psychotic episode. Fractional anisotropy in baseline DTI scans, including left-right asymmetry measures, did not differ between the groups. Thus, DTI measures of these association white matter tracts were not biological markers of psychosis in our UHR sample. Abnormalities of these fiber tracts may develop around or after onset of psychosis. However, further DTI studies in UHR subjects are needed in larger samples.
### 2.3.1 Introduction

Schizophrenia may be a neurodevelopmental disorder leading to dysconnectivity between brain areas associated with positive, negative and disorganization symptoms. The neuropathological substrate of dysconnectivity may be dysplastic white matter tracts as a result from abnormal development in utero (Bullmore et al., 1997) or abnormal myelination during adolescence (Bartzokis 2002; Flynn et al., 2003). Subjects at ultra-high-risk for psychosis (UHR) are defined by trait and state markers including brief or attenuated psychotic symptoms and around 30% of these subjects have been found to convert to psychosis within one to three years (Cannon et al., 2008). Brain imaging may be helpful in identifying biological markers predictive of transition to psychosis, with diffusion tensor imaging (DTI) making it now possible to obtain an indication of the microstructural integrity of brain white matter tracts. A DTI index called fractional anisotropy (FA) is thought to be a marker of the structural integrity of fibers (Beaulieu 2002), the degree of myelination (Gulani et al. 2001), coherence of fiber tracts (Ono et al. 1995), and fiber diameter and packing density (Beaulieu 2002); changes in this index could indicate changes in any of these characteristics of the white matter microstructure or a combination of them.

DTI studies in first-episode schizophrenia patients have found FA to be reduced in several parts of the brain (e.g. Hao et al., 2006; Federspiel et al., 2006; Mendelsohn et al., 2006; Szeszko et al., 2008; Cheung et al., 2008, Karlsgodt et al., 2008). In a recent DTI fiber tracking study we found no significant differences between first-episode patients, UHR subjects and healthy controls in the uncinate and arcuate fasciculi, splenium and genu of the corpus callosum, and cingulate (Peters et al., 2008); in this study clinical follow-up of conversion to psychosis in the UHR subjects had not yet been performed. A recent longitudinal structural MRI study showed reduction of white matter volume in the left parietal lobe of UHR individuals who developed a psychotic disorder (Walterfang et al., 2008a). A disadvantage of this study is the use of voxel-by-voxel analyses in which it can be difficult to localize abnormalities to specific fiber tracts.

In the present study, we aimed to investigate with DTI fiber tracking whether fiber tracts are differentially compromised in UHR subjects who later develop a psychotic disorder as compared to UHR subjects who do not convert to psychosis. In our previous report (Peters et al., 2008) baseline fiber tract measures in UHR subjects, collected before clinical follow-
up, were compared to schizophrenia patients. In the present study, the same baseline fiber tract measures were analyzed, but now UHR subjects who converted to psychosis during clinical follow-up are compared to UHR subjects who did not convert to psychosis and to healthy controls. As it has been previously postulated that schizophrenia arises from disturbed development of cerebral asymmetry (Crow et al. 1989), left-right asymmetry of fiber tracts was included in the analyses. To our knowledge this is the first DTI fiber tracking study to examine whether white matter abnormalities are predictive of transition to psychosis in UHR subjects.

### 2.3.2 Methods

#### Subjects

UHR subjects were consecutively recruited from an ongoing naturalistic, longitudinal study program with a 24 month follow-up (European Prediction of Psychosis Study (EPOS; Klosterkötter et al., 2005)). Help seeking subjects, referred by mental health services when psychotic symptoms or an increased risk for developing psychosis was suspected, were screened for being at UHR for psychosis by a clinical psychiatrist and research psychologist. Subjects were considered to be at UHR after assessment with the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2002) when they met criteria of showing: 1) attenuated psychotic symptoms (e.g. odd beliefs, paranoid ideation) and/or 2) brief psychotic symptoms with spontaneous remission in less than one week and/or 3) a decline in functioning in the past year (30% reduction in the Global Assessment of Functioning scale) plus a genetic risk (1° degree relative with schizophrenia-like disorder or a schizotypal personality disorder in the identified patient) and/or 4) two ‘basic symptoms’ (cognitive, perceptual, emotional and social disturbances; Klosterkötter et al., 2001). Exclusion criteria were: a previous psychotic episode for more than one week, (mild) psychotic symptoms due to an organic etiological factor or due to drug use. Diagnosis of psychosis in the past was assessed with the Structured Clinical Interview for Diagnosis Axis I (SCID-I, sections B and C; Spitzer et al., 1992). At 9, 18 and 24 months follow-up subjects were assessed for potential transition to psychosis with the SIPS. If a transition was suspected, diagnosis was confirmed with the SCID.
Table 2.3.1: Characteristics of UHR subjects and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Ultra-High-Risk Psychosis</th>
<th>Ultra-High-Risk No-Psychosis</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
</tr>
<tr>
<td>Mean age (S.D.)</td>
<td>22.6 (3.9)</td>
<td>21.2 (3.2)</td>
<td>21.1 (2.8)</td>
</tr>
<tr>
<td>Educational level (n)</td>
<td>2 / 5</td>
<td>4 / 6</td>
<td>2 / 8</td>
</tr>
<tr>
<td>Handedness R/L (n)</td>
<td>7 / 0</td>
<td>9 / 1</td>
<td>8 / 2</td>
</tr>
<tr>
<td>History of antipsychotic medication (n)</td>
<td>3</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Duration antipsychotic medication (weeks)</td>
<td>(10, 20, 38)</td>
<td>(12)</td>
<td>-</td>
</tr>
</tbody>
</table>

* Professional skilled training / Bachelor’s level or Master’s level

Both groups were compared with healthy controls to determine whether differences were deviations from normality. Healthy control subjects were recruited through local advertisements, and were included after a clinical psychiatric interview. Exclusion criterion for healthy controls was a personal or family history of a major psychiatric illness. Only males were included as post-mortem studies suggest that there are gender specific effects on white matter abnormalities in schizophrenia (Highley et al., 1999).

Exclusion criteria for all subjects were: metal objects in the body, history of a neurological or endocrine disease which may affect brain structure, history of head trauma with loss of consciousness for more than 15 min., mental retardation according to DSM-IV criteria, gross brain abnormalities on conventional MRI other than atrophy or ventricular enlargement.

This study was approved by the local and national medical ethics committees and all participants of the study gave written informed consent.

DTI acquisition and post-processing

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). Baseline DTI and T1 images of the UHR subjects were
collected on inclusion in the UHR study program. As we aimed to assess whether white matter abnormalities are predictive of psychosis repeat MR scanning at follow-up was not included in our study. Whole brain DTI images were acquired using single-shot spin-echo echo-planar-imaging (EPI). Acquisition parameters and post-processing are described in detail elsewhere (Peters et al., 2008). In brief, DTI acquisition was along 16 non-collinear directions and each direction was scanned twice. Slice orientation was (para)transversal, and whole brain images were collected covering both cerebral hemispheres. Acquisition parameters were: TR (repetition time) 3312–6260 ms. (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 during post-processing of the DTI image data), echo-time 94 ms., field-of-view (FOV) 230–256 mm (depending on head size), diffusion sensitivities of b=0 and b=1000 s/mm², acquisition matrix 112 × 112, image matrix 256 × 256. Number of slices ranged between 38–46, slice thickness was 3 mm, no gap.

After reconstruction the diffusion-weighted images were transferred to a workstation, where eigenvalue and eigenvector maps of the diffusion tensor were calculated, and FA images were reconstructed. The algorithms presented by Basser et al. (2000) formed the basis for the construction of the fiber tracts. 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 starting points are seeded uniformly over the brain. Then using these points as start locations each fiber bundle is traced in both directions until a stopping condition is met. The stopping condition was defined as 1) FA in each voxel had to be at least 0.2 and 2) the bending angle of the tract was not allowed to exceed 45° within a voxel.

**DTI Quantification**

We examined association fiber tracts which showed abnormalities in previous DTI studies in schizophrenia patients: the uncinate and arcuate fasciculi, the genu and splenium of the callosum, the dorsal and anterior cingulate. DTI data of each individual were analyzed with in-house developed software: Diffusion Tensor Imaging Interactive (DTII) (Blaas et al., 2005), which is described in detail by Peters et al. (2008). In brief,
the software allows interactive extraction and visualization of fiber bundles through positioning of three boxes. Only the fiber bundle that passes through all three boxes is extracted and visualized. One box is placed in the ‘starting point’ of the fasciculus, one box is placed in the ‘end point’, and the measurement box is placed between the other two boxes. Mean FA of the section of the fiber tract in the measurement box is measured. In accordance with the hypothesis that FA reduction in schizophrenia results from myelination abnormalities (Bartzokis 2002) FA was measured in the most ‘homogeneous’ part of each fibre-bundle, i.e. the thickest part with the least branching off of small fibers. Before actual measurements, inter-rater reliability for each bundle was determined in ten subjects. Intra-class correlation (ICC) of FA values was required to be 0.90 or more for each bundle before actual measurements were performed by one rater (B.P.), who was blind for subject status.

In brief, the measured regions of the fiber tracts were as follows:

**Uncinate fasciculus (see figure 2 in appendix):** the uncinate fasciculus connects the orbitofrontal lobe to the temporal pole. The uncinate was traced and measured by placing one box in the orbitofrontal lobe, and another box in the temporal pole; the measurement box \((1.4 \times 1.5 \times 1.9\, \text{cm}^3)\) was placed 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 frontal lobe.

**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, another other box in the temporal part; the measurement box \((2.3 \times 1.7 \times 2.7\, \text{cm}^3)\) 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.

**Corpus callosum (see figure 1 in appendix):** we divided the corpus callosum in 4 regions: splenium (posterior one-third of the mid-sagittal length), genu (anterior one-third; see figure 1 in appendix), and anterior truncus and posterior truncus (each one-half of the middle one-third). The measurement box \((5.6\, \text{mm wide, left-right direction})\) was placed mid-sagittally in the corpus callosum, where its fibers cross from the left to right hemisphere.

**Dorsal cingulum (see figure 4 in appendix):** the cingulum trajectories 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 at the splenium of the corpus callosum. The measurement box was 40 mm long from anterior to posterior (4.0 × 1.6 × 1.4 cm³), and was placed with its anterior side at the dorsal edge of the genu of the corpus callosum, and was then moved superiorly to include the dorsal cingulum. This corresponds to the section examined by Kubicki et al. (2003).

*Anterior cingulum (see figure 5 in appendix):* one box was placed just anterior to the measurement box, another box was placed at the splenium. The measurement box (1.1 × 1.6 × 1.3 cm³) was placed with its posterior side at the dorsal edge of the genu of the corpus callosum. The measurement box was then moved superiorly to include the anterior cingulum. This corresponds to the location studied by Wang et al. (2004).

**Statistical analysis**

Data were analyzed using SPSS version 14.0 (www.spss.com). Repeated-measures analysis of variance with group as between-subjects factor was used to test for differences in FA between groups. The uncinate fasciculus and arcuate fasciculus were analyzed with side (left and right) and fiber tract (uncinate and arcuate) as within-subjects factors. The corpus callosum was analyzed with the four sub-regions as within-subjects factors. The cingulum was analyzed with side and part of the cingulum (dorsal or anterior) as within-subjects factors. In 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.

Because in the DTI acquisition the FOV and number of slices differed between subjects depending on headsize, which lead to a variation in voxel size, we assessed if variation in voxel size affected the FA measurements, as found previously (Kim et al., 2006). To this end, we examined whether voxel size differed between the groups and whether voxel size was related to FA in each fibertract (Spearman’s rho correlation). In case of a significant correlation, voxel size was included as a covariate in the analysis of variance.

Between group differences in age were analyzed with independent sample t-tests, and between group differences in educational level and handedness were analyzed with Chi-square tests (Fisher’s exact test for counts less than five). Level of significance was set at \( p < 0.05 \).
2.3.3 Results

Demographic data

Seventeen UHR subjects and ten controls were included. Seven UHR subjects developed a psychotic disorder at follow-up (UHR-P) and ten did not (UHR-NP). The mean time to transition to psychosis in the UHR-P group was 15.5 months (S.D. = 7.0; range 8 to 24). Diagnoses of UHR-P subjects were: schizophrenia (2), schizoaffective disorder (1) and schizophreniform disorder (4). UHR-P subjects, UHR-NP subjects and controls did not differ in mean age (55.9 years (S.D. = 6.3), 54.5 years (S.D. = 6.5), 54.4 years (S.D. = 5.2) respectively; $F(2) = 0.76, P = 0.48$), educational level ($X^2(2) = 1.0, P = 0.86$) or handedness ($X^2(2) = 1.7, P = 0.60$) (see table 2.3.1). Three UHR-P subjects had used antipsychotic medication in the past (duration 13, 23 and 61 weeks), and one UHR-NP subject (12 weeks).

DTI Results

Voxel size was different between the three subject groups (on average UHR-P 13 mm$^3$, UHR-NP 13 mm$^3$, controls 14 mm$^3$), and voxel size correlated with FA in the right anterior cingulate (rho = - 0.37, $P = 0.055$); there were no trends for such a correlation in the other fiber tracts. Voxel size was therefore included as a covariate in the analyses of the cingulate only.

The UHR-P, UHR-NP and control groups did not differ in FA of the uncinate or arcuate fasciculi ($F(2) = 0.07, P = 0.93$), nor in FA of the four subdivisions of the corpus callosum ($F(2) = 1.67, P = 0.21$), nor in FA of the dorsal or anterior cingulate ($F(2) = 0.04, P = 0.96$) (see table 2.3.2). There were no significant hemisphere-by-group interactions.

Closer observation of the data showed that both UHR-P and UHR-NP subjects had higher FA than controls in the right anterior cingulate (see figure 2.3.1). This difference between the UHR-P, UHR-NP and controls in the right anterior cingulate was tested separately in a posthoc analysis of variance without voxel size as a covariate, and was found statistically significant ($F(2) = 3.44, P = 0.049$). When voxel size was included as a covariate this difference was no longer statistically significant ($F(2) = 1.33, P = 0.28$). Finally, we performed an analysis of variance, with voxel size
Figure 2.3.1: Boxplots of fractional anisotropy in the left and right anterior cingulate (mean, 50% and 95% confidence intervals) in ultra-high-risk (UHR) subjects with transition to psychosis at clinical follow-up, UHR subjects without transition and healthy controls. The observed difference in the right anterior cingulate was not statistically different when correcting for the slightly larger voxel sizes in the controls, which depended on head size.

as a covariate, including the right and left anterior cingulate to test for differences in left-right asymmetry; there was no hemisphere-by-group interaction ($F(2) = 1.27, P = 0.30$).

2.3.4 Discussion

In our sample of subjects with ultra-high-risk symptoms for psychosis, DTI measures of the uncinate and arcuate fasciculi, subdivisions of the corpus callosum and dorsal and anterior cingulate did not appear to be biological markers for transition to psychosis. Due to the small sample size, these findings should be considered tentative.

A structural MRI study in UHR subjects found that a lack of leftward bias of anterior paracingulate folding was present in subjects that devel-
Table 2.3.2: Fractional anisotropy in four white matter tracts.

<table>
<thead>
<tr>
<th></th>
<th>Ultra-High-Risk Psychosis ( (n = 7) )</th>
<th>Ultra-High-Risk No-Psychosis ( (n = 10) )</th>
<th>Healthy Controls ( (n = 10) )</th>
<th>( F )</th>
<th>( df )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cingulate(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dorsal left</td>
<td>0.559 (0.053)</td>
<td>0.560 (0.068)</td>
<td>0.561 (0.043)</td>
<td>0.04</td>
<td>2</td>
<td>0.96</td>
</tr>
<tr>
<td>dorsal right</td>
<td>0.519 (0.030)</td>
<td>0.538 (0.062)</td>
<td>0.516 (0.043)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anterior left</td>
<td>0.489 (0.053)</td>
<td>0.484 (0.064)</td>
<td>0.496 (0.047)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anterior right</td>
<td>0.473 (0.042)</td>
<td>0.460 (0.067)</td>
<td>0.409 (0.049)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left-right asymmetry</td>
<td></td>
<td></td>
<td></td>
<td>1.18</td>
<td>2</td>
<td>0.33</td>
</tr>
<tr>
<td>Uncinate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>0.485 (0.034)</td>
<td>0.473 (0.044)</td>
<td>0.477 (0.053)</td>
<td>0.07</td>
<td>2</td>
<td>0.93</td>
</tr>
<tr>
<td>right</td>
<td>0.474 (0.061)</td>
<td>0.485 (0.035)</td>
<td>0.485 (0.041)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left-right asymmetry</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
<td>2</td>
<td>0.97</td>
</tr>
<tr>
<td>Arcuate ( (analyzed with uncinate) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>0.500 (0.031)</td>
<td>0.501 (0.022)</td>
<td>0.508 (0.035)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right</td>
<td>0.511 (0.030)</td>
<td>0.497 (0.043)</td>
<td>0.503 (0.027)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left-right asymmetry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpus callosum</td>
<td></td>
<td></td>
<td></td>
<td>1.69</td>
<td>2</td>
<td>0.21</td>
</tr>
<tr>
<td>splenium</td>
<td>0.693 (0.051)</td>
<td>0.697 (0.021)</td>
<td>0.680 (0.020)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>posterior truncus</td>
<td>0.531 (0.046)</td>
<td>0.552 (0.038)</td>
<td>0.542 (0.029)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anterior truncus</td>
<td>0.555 (0.023)</td>
<td>0.569 (0.036)</td>
<td>0.564 (0.027)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>genu</td>
<td>0.631 (0.042)</td>
<td>0.658 (0.030)</td>
<td>0.638 (0.029)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left-right asymmetry</td>
<td></td>
<td></td>
<td></td>
<td>N.A.(^b)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Analyzed with voxel size as a covariate as voxel size was slightly larger in controls and correlated with FA in the right anterior cingulate (Spearman’s \( \rho = -0.37, P = 0.055 \)).

\(^b\) N.A. = not applicable, due to midsagittal measurements.
oped psychosis at follow-up as well as subjects that did not convert to psychosis (Yücel et al., 2003a). Another structural MRI study in UHR subjects found bilateral thinning of the rostral anterior cingulate gray matter to be predictive of transition to psychosis (Fornito et al., 2008), and longitudinal assessments found that gray matter reductions occurred in the cingulate gyri around transition to psychosis (Pantelis et al. 2003). Indeed, Wood and colleagues (2008) have concluded in a review that frontal lobe measures such as cortical thickness in the anterior cingulate show most promise in defining subjects to develop psychosis, in addition to cognitive measures sensitive to prefrontal dysfunction. Our preliminary results suggest that DTI measures of white matter in the anterior cingulate do not indicate a liability for psychosis, and are not predictive of onset of psychosis in UHR subjects. In support of this, Hao and colleagues (2009) recently found reduced FA in the anterior cingulate in patients but not their healthy siblings. Early developmental abnormalities in the anterior cingulate may be restricted to gray matter. Later on in the course of the illness, around or after onset of the first psychotic episode, white matter alterations in the anterior cingulate (Wang et al., 2004; Hao et al., 2006) could perhaps result from synaptic dysfunction in gray matter (Keshavan et al., 2005) causing retrograde axonal or myelin pathology.

The absence of corpus callosum abnormalities in both UHR groups in our study is in contrast with a structural MRI study in UHR subjects, which found that decreased thickness of anterior sections of the genu was predictive of transition to psychosis (Walterfang et al., 2008). DTI and structural MRI are fundamentally different MRI parameters, and volumetric abnormalities may not necessarily lead to DTI abnormalities. Moreover, an inverse relationship between white matter volume and fractional anisotropy has been reported in chronic good-outcome patients, and was suggested to reflect a protective mechanism where lower volume is compensated by higher fiber directionality (Mitelman et al., 2006). In first-episode schizophrenia patients fiber tracking has revealed reduced FA in both the genu and splenium (Price et al. 2007; Gasparotti et al. 2009), while two voxel-by-voxel DTI studies found abnormalities only in the splenium (Federspiel et al., 2006; Cheung et al., 2008), and three voxel-by-voxel studies were negative for the corpus callosum (Price et al. 2005; Hao et al., 2006; Szeszko et al. 2008). Thus, the location and timing of corpus callosum DTI abnormalities in schizophrenia are not clear at this moment and require further study. In the study of Price and colleagues (2007) FA in the corpus callosum was lower in females than in males irrespective of control or patient status, a finding which is confirmed by post-mortem
research (Highley et al., 1999). Our study only included males, which may partially explain the lack of corpus callosum abnormalities.

We found no differences in the uncinate fasciculus. This is in line with a negative fiber tracking study of the uncinate in first-episode patients (Price et al. 2008), though indications were found in this study for reduced FA in the core of the tract. A region-of-interest study in chronic patients found no FA reductions in the uncinate (Kubicki et al. 2002), but left-greater-than-right FA asymmetry present in the controls lacked in patients. In contrast, a post-mortem study found a right-greater-than-left asymmetry of fiber number in the uncinate of both healthy controls and schizophrenia patients (Highley et al. 2002). Thus, at present the evidence for uncinate abnormalities in schizophrenic illness is not strong and conflicting.

Finally, we found no DTI abnormalities in the arcuate fasciculus. This corresponds with a longitudinal structural MRI study which showed increased white matter volume in the area of the arcuate in UHR subjects with transition to psychosis at follow-up (Walterfang et al., 2008). In first-episode patients Karlsgodt and colleagues did find reduced FA in the arcuate fasciculus (2007), and arcuate abnormalities were confirmed in chronic patients (Burns et al., 2003; Buchsbaum et al., 2006; Shergill et al., 2007). These findings suggest that changes in arcuate microstructure may develop around or after transition to psychosis and not before transition.

Limitations

Our study has several limitations. We did not take into account the functional heterogeneity of the anterior cingulum (Yücel et al. 2003b), although our dorsal part corresponds to the dorsal ‘cognitive’ part defined by Fornito and colleagues (2008), and our anterior part corresponds to a section of the ‘affective’ rostral part measured in that study. Also, the subdivisions of the corpus callosum we examined were quite large. More detailed parcellation of functional subdivisions with structural MRI has shown that axonal projections to heteromodal association cortices may be particularly involved in psychosis (Keshavan et al., 2002).

Another limitation is the small sample size, possibly resulting in false-negative findings. Therefore we cannot confirm the null hypothesis, we can only conclude that there is not enough evidence to reject it. However, the FA differences and its effect sizes we found were small and large
samples would be required to detect significant differences. For instance, the effect sizes of the differences between the UHR-P and UHR-NP subjects in the dorsal cingulate were 0.02 (left) and 0.41 (right), requiring a minimum sample size of 200 subjects to reach 80% power.

Although our UHR subjects were free of antipsychotic medication at time of MR scanning, previous use of antipsychotics may be a confounder, in particular because more UHR-P subjects had used antipsychotics than UHR-NP subjects. In the literature, four DTI studies found FA not to be correlated with medication dose (Foong et al. 2000; Kubicki et al., 2002; Kubicki et al., 2003; Kumra et al. 2005), while in three studies there was a significant correlation (Minami et al., 2003; Okugawa et al., 2004; Rotarska-Jagiela et al. 2007); all except one of these studies examined chronically treated patients. Kanaan et al. (2009) found no differences between age-matched chronically and briefly medicated patients. To explore a medication effect in our population, we have previously examined correlations between duration and dosage of antipsychotic medication and fractional anisotropy in both first-episode patients and UHR subjects (Peters et al., 2008). No significant correlations were found. This may be related to the relatively short time our patients had been treated with antipsychotic medication. Taking together the literature and our earlier findings, there is little evidence for an effect of antipsychotic medication on FA, especially in briefly medicated patients. Therefore we chose not to control for antipsychotic medication in our small sample. Future longitudinal studies in first-episode, neuroleptic naïve patients will be necessary to gain further insight in the effect of antipsychotic medication on white matter anisotropy.

Our fiber tracking procedure has also some limitations. In certain regions fiber tracking is influenced by crossing fibers, although this source of error was minimized by using three boxes to extract the tracts of interest. Also, the anatomical boundaries for our measurements were defined for the most part by the fiber tracts, thus using the dependent variable to define its boundaries. Furthermore, we did not measure fiber tract diameter and it is possible that there were differences in fiber tract diameter between the groups. Finally, the voxels in our study were not collected isotropically and isotropically-acquired voxels are preferred for fiber tracking. In addition to this, voxel sizes in our data set varied between subjects due to variations in the field-of-view and number of acquired DTI slices, which depended on head size. The UHR subjects had consistently smaller voxel sizes compared to the controls, and voxel size was negatively correlated to FA in the right anterior cingulate. FA of the
anterior cingulate in our study was increased in the right hemisphere of UHR subjects, in particular in the UHR-P subjects, but when voxel size was taken into account in the analysis this difference was no longer significant. As brain volume reductions are found in the early phase of schizophrenia (Keshavan et al., 2005; Wood et al., 2008), and because variation in voxel size can affect FA measurements (see also Kim et al., 2006), we conclude that varying voxel size according to head size should not be employed in DTI studies in UHR or schizophrenia patients.

We remark that in all cases we could reconstruct fiber tracts 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 measurements. Moreover, by analyzing fiber tracts we were able to test specific hypotheses concerning involvement of specific tracts in the development of psychosis. This method reduced the chance of finding false positive results.

2.3.5 Conclusions

DTI measurements in the uncinate and arcuate fasciculi, the dorsal and anterior cingulum bundle, and subdivisions of the corpus callosum did not appear to be biological markers for transition to psychosis in our UHR sample. This does not concurs with the findings from structural MRI studies which indicate that gray matter abnormalities in the anterior cingulate are potentially predictive of transition to psychosis. Our results support the hypothesis that the structural integrity of white matter tracts is not disrupted before the onset of psychosis. DTI abnormalities of white matter tracts may develop around or after onset of psychosis. However, our study had some methodological limitations and our results need replication in larger samples.

2.3.6 References

Chapter 2


