



## Microstructural white matter alterations in psychotic disorder: A family-based diffusion tensor imaging study

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### ABSTRACT

**Background:** There is evidence for microstructural white matter alterations in patients with psychotic disorder, suggesting altered interregional connectivity. Less is known about the presence and role of white matter alterations in well individuals at higher than average genetic risk for psychotic disorder.

**Methods:** 85 patients with psychotic disorder, 93 non-psychotic siblings of patients with psychotic disorder and 80 healthy controls underwent a diffusion tensor imaging (DTI) scanning protocol. In a whole brain voxel-based analysis using Tract Based Spatial Statistics (TBSS), fractional anisotropy (FA) values were compared between the three groups. Effects of antipsychotic medication and drug use were examined.

**Results:** The patients displayed significantly lower mean FA than the controls in the following regions: corpus callosum (genu, body, splenium), forceps major and minor, external capsule bilaterally, corona radiata (anterior, posterior) bilaterally, left superior corona radiata and posterior thalamic radiation bilaterally. Similar FA differences existed between the patients and siblings; the siblings did not differ from the controls.

**Conclusion:** Profound microstructural white matter alterations were found in the corpus callosum and other tracts and fasciculi in the patients with psychotic disorder, but not in siblings and the controls. These alterations may reflect brain pathology associated with the illness, illness-related environmental risk factors, or its treatment, rather than genetic risk.

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### 1. Introduction

There is growing evidence that cerebral vulnerability in schizophrenia may be mediated by altered connectivity between brain regions, rather than focal brain alterations. Indeed, neurophysiological and functional neuroimaging studies have demonstrated pathological functional connectivity (Friston and Frith, 1995; Andreasen et al., 1998; Konrad and Winterer, 2008). Dysconnectivity, in terms of impaired axonal mechanisms and/or abnormal control of synaptic plasticity, may form the core pathology of schizophrenia (Friston, 1998), and may be based in structural alterations. In support of this, volumetric MRI studies have shown decreased white matter volumes of the frontal lobes and temporo-parietal regions and a decreased corpus callosum volume (genu and/or truncus) in schizophrenia patients (Walterfang et al., 2006; Makris et al., 2010; Olabi et al., 2011). Since the late nineties, numerous DTI-studies in patients with a diagnosis of

schizophrenia have been published, showing a decrease in FA, indicative of white matter integrity loss, in several brain tracts, including the fronto-temporal connections, such as the arcuate fasciculus, anterior cingulum bundle, uncinate fasciculus (Burns et al., 2003; Kanaan et al., 2005; Kubicki et al., 2007) and fronto-occipital tracts (Ardekani et al., 2003; Mitelman et al., 2007). A meta-analysis in 2009 concluded that significant reductions were present in frontal deep white matter (genu corpus callosum, cingulum bundle, left anterior thalamic radiation, left corticobulbar tract and left inferior fronto-occipital fasciculus) and temporal deep white matter (splenium corpus callosum, fornix/stria terminalis, left inferior longitudinal fasciculus and left inferior fronto-occipital fasciculus) (Ellison-Wright and Bullmore, 2009). Although most, but not all studies (Steel et al., 2001; Hubl et al., 2004; Price et al., 2005) report FA decreases associated with schizophrenia, there is inconsistency regarding the location of the affected brain regions, which, in part, may be related to differences in scanning protocol, study design (e.g. characteristics of the participants) and analytical techniques.

Structural dysconnectivity in patients with schizophrenia may reflect disease-related pathology, but may also represent expression of genetic risk for the disorder (Marenco and Radulescu, 2010). Thus, volumetric MRI studies in first-degree relatives (McDonald

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et al., 2004; Goghari et al., 2007) and twins (Hulshoff Pol et al., 2006) have shown indirect genetic effects on global gray and white matter volume reduction in schizophrenia. The number of DTI studies examining individuals at higher than average genetic risk for psychotic disorder is scant and sample sizes are, in general, small (number of high-risk individuals ranging from  $n = 16$  to  $n = 34$ ), except for one study (Boos et al., 2012). The available evidence suggests that white matter alterations may be present in first-degree relatives without symptoms (Munoz Maniega et al., 2008; Camchong et al., 2009; Hao et al., 2009; Narr et al., 2009; Clark et al., 2011; Boos et al., 2012; Knoche et al., 2012). The results for so-called “ultra-high risk” samples with (pre)clinical symptoms are conflicting (Peters et al., 2010), which likely is related to lack of consistency in ultra-high risk sample enrichment procedures across studies (van Os and Linscott, 2012) as well as to differences in brain regions studied and methodological approaches, precluding definite conclusions.

In the present large DTI study ( $n = 258$ ), whole-brain, voxel-based analytic techniques were used to examine patients with a psychotic disorder (highest genetic risk group), non-psychotic siblings (higher than average genetic risk group) of patients with a psychotic disorder, and healthy controls (average genetic risk group). We hypothesized that the patients with psychotic disorder would show reduced white matter integrity compared to the healthy controls, particularly in the corpus callosum, fronto-temporal, and fronto-parietal connections, with the siblings showing a pattern of alterations of intermediate severity.

## 2. Methods

### 2.1. Participants

The patients were recruited from an on-going longitudinal MRI study in Maastricht, the Netherlands. In selected representative geographical areas in the Netherlands and Belgium, the patients were identified through representative clinicians providing health care for patients with psychotic disorder. The siblings were contacted through the participating patients. Mailings and advertisements were effectuated in local newspapers of the same geographical area in order to recruit control participants. The total sample consisted of 258 participants: 85 patients with a psychotic disorder, 93 siblings without a psychotic disorder and 80 healthy controls. The sample included 56 families, of which 35 families contributed one patient and one healthy sibling, three families contributed one patient and two healthy siblings, and one family contributed one patient and three healthy siblings. One family contributed two patients, six families contributed two healthy siblings, and one family contributed three healthy siblings. In the control group, 9 families contributed two siblings. In addition, 44 families contributed a single patient, 34 families contributed a single sibling, and 62 families contributed a single control.

Inclusion criteria were: age range 16–50 years a good command of Dutch language and for patients: a diagnosis of non-affective psychotic disorder with illness duration of <10 years. The siblings and the controls did not have a lifetime diagnosis of any non-affective psychotic disorder. In addition, the controls had no first-degree relative with a lifetime diagnosis of any psychotic disorder, assessed using the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992).

Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorder—IV (DSM-IV) criteria (APA, 2000), measured with the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al., 1992). The patients were diagnosed as follows: schizophrenia ( $n = 59$ ), schizoaffective disorder ( $n = 9$ ), schizophreniform disorder ( $n = 4$ ), brief psychotic disorder ( $n = 2$ ), and psychotic disorder not otherwise specified ( $n = 11$ ). Psychopathology in the siblings and controls was also assessed and respectively 18 and 12 participants had a history of a major depressive disorder. None of these met the criteria for a current depressive episode.

All the participants were screened before MRI acquisition for the following exclusion criteria: brain injury with unconsciousness of greater than 1 h, meningitis or other neurological diseases with possible impact on brain structure or function, cardiac arrhythmia requiring medical treatment and severe claustrophobia. In addition, subjects with metal corpora aliena were excluded from the study, as were women with intrauterine device status and (suspected) pregnancy.

The standing ethics committee approved the study protocol, and all the participants gave written informed consent in accordance with the committee's guidelines.

### 2.2. Measures

Level of psychotic symptomatology at the time of scanning was assessed with the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) in all three groups. The five factor model by van der Gaag et al. (2006), was used dividing the PANSS in positive symptoms, negative symptoms, disorganization symptoms, excitement and emotional distress. The scores of the individual items of the 5 symptom dimensions were summed.

Educational level was defined as highest accomplished level of education. Handedness was assessed using the Annett Handedness Scale (Annett, 1970).

In the patient group, antipsychotic (AP) medication use was determined by the patient's report and verified with the treating consultant psychiatrist. Best estimate lifetime (cumulative) AP use was determined by multiplying the number of days of AP use with the corresponding haloperidol equivalents and summing these scores for all periods of AP use (including the exposure period between baseline assessment for the G.R.O.U.P. study and the moment of baseline MRI scanning), using the recently published converting formulas for AP dose equivalents described by Andreasen et al. (2010).

Substance use was measured with the Composite International Diagnostic Interview (CIDI) sections B–J–L (WHO, 1990). Use of cannabis and other drugs was assessed as reported frequency of use during the last 12 months, as well as lifetime use. CIDI frequency data on lifetime cannabis and other drug use was available for respectively 250 participants (3% missing data) and 256 participants (1% missing data).

Alcohol use was defined as the reported number of weekly consumptions during the last 12 months.

### 2.3. Image acquisition

Magnetic resonance imaging scans were obtained at Maastricht University, the Netherlands, using an Allegra syngo MR A30 (Siemens, Erlangen, Germany) operating at 3.0 T. The following anatomical scan parameters were used: Modified Driven Equilibrium Fourier Transform (MDEFT) sequence; 176 slices, 1 mm isotropic voxel size, echo time 2.4 ms, repetition time 7.92 ms, inversion time 910 ms, flip angle 15°, total acquisition time 12 min and 51 s; Magnetization Prepared Rapid Acquisition Gradient-Echo (MPRAGE; Alzheimer's Disease Neuroimaging Initiative) sequence 192 slices, 1 mm isotropic voxel size, echo time 2.6 ms, repetition time 2250 ms, inversion time 900 ms, flip angle 9°, total acquisition time 7 min and 23 s. The matrix size was  $256 \times 256$  and field of view was  $256 \times 256 \text{ mm}^2$ . The number of excitations was one. Two sequences were used because of a scanner update during data collection.

Microstructural anatomy was examined using diffusion tensor imaging with an echo-planar-imaging sequence (field of view  $230 \times 230 \text{ mm}^2$ , TR 10,800 ms, TE 84 ms, voxel size  $1.8 \times 1.8 \times 1.8 \text{ mm}^3$ , b-value  $1000 \text{ s/mm}^2$ , noise level 40, 85 slices, no overlap). As a result of the scanner update, two DTI sequences were used: one with 76 directions (of which 4 T2-weighted (B0) and 72 diffusion-weighted (B)), and one with 81 directions ( $8 \times B0$  and  $73 \times B$ ). The proportion of scans with 76 directions was balanced between the groups (78% in the controls,

75% in the siblings and 69% in the patients ( $\chi^2 = 1.52$ ,  $P = 0.468$ ), preventing any systematic bias. Total acquisition time of the DTI sequence was 15 min.

#### 2.4. Diffusion tensor imaging analysis

Processing of DTI data was effectuated using tract-based spatial statistics (TBSS) v1.2 in FSL 4.1.6 (FMRIB Analysis Group, Oxford, UK, <http://www.fmrib.ox.ac.uk/analysis/research/tbss>). First, standard Siemens DICOM files were transformed into compressed NIFTI format using a custom built in-house software named GIANT (General Image ANalysis Tools developed by EHBMG). Raw data were corrected for head movement and eddy currents invoked during scanning. The B0 volume was skull-stripped using FSL's Brain Extraction Tool (Smith, 2002) and this served as a brain mask for all B volumes.

The next step was fitting a diffusion tensor model at each voxel using data output from the brain extraction, diffusion weighted data and gradient directions following a general linear model (FreeSurfer v4.5.0, <http://surfer.nmr.mgh.harvard.edu>). After tensor fitting the process continued working on FA volumes, eroding them slightly.

Nonlinear registration aligned each FA volume to  $1 \times 1 \times 1$  mm standard FMRIB58\_FA space. The standard FMRIB58\_FA contains a template derived from high-resolution images of 58 participants in a well-aligned population (both males and females ranging between 20 and 50 years of age) (Smith et al., 2006).

After nonlinear transformation of the FA volumes into standard space, a mean FA skeleton from all the participants per group was derived. The mean FA skeleton follows the major white matter tracts in each individual participant (normalized in MNI152 space) and provides a way to compare between (groups of) the participants. The final step of the processing was setting the FA threshold using visual inspection of the FA skeleton, in the present study at a level of 0.25, to include major white matter tracts while removing small peripheral tracts that would cause excess inter-participant variability. In addition, this threshold setting avoided inclusion of regions that are likely to be composed of multiple tissue types or fiber orientations.

#### 2.5. Statistical analyses

Voxel-wise statistical analysis was performed on the mean FA skeleton using a general linear model and applying FSL's randomize (v2.1) permutation-testing script (Smith et al., 2004). The comparisons involved the statistical tests of group differences in FA, yielding a total of six contrasts: i) mean FA is lower (or higher) in the patients compared to the controls, ii) mean FA is lower (or higher) in the siblings compared to the controls, and iii) mean FA is lower (or higher) in the patients compared to the siblings. The a priori hypothesized confounding variables age, sex, handedness, level of education, lifetime cannabis use and lifetime other drug use were used in the statistical model. In addition to tests for regional group differences, stratified gender analyses were carried out.

In addition, associations between AP medication and FA were analyzed in two different ways. First, cumulative AP exposure was added as an additional covariate. Second, in the patients only, cumulative AP exposure was entered as independent (dummy) variable representing the distribution of scores divided by its tertiles (low, medium and high exposure) to examine the effect on FA within the patients.

Lastly, planned sensitivity analyses were performed excluding the siblings and controls with a history of affective disorder.

For the main analysis permutation tests were performed using 50,000 permutations in order to reduce the margin of error to acceptable uncertainty levels ( $P = 0.05 \pm 0.00195$ , i.e. 3.9% of the nominal alpha). With regard to the additional analyses (effects of AP medication and gender, exclusion of affective disorder) 10,000–50,000 permutations were performed. The threshold free cluster enhancement

(TFCE) option was enabled to find clusters without setting an initial cluster level (Smith and Nichols, 2009). Statistical maps (thresholded at  $P < 0.05$ ) were used for assessing differences between groups (corrected for multiple comparisons).

The Johns Hopkins University International Consortium for Brain Mapping (JHU ICBM)-DTI-81 white-matter atlas labels (Mori et al., 2008) were used to label significant voxels and assign a specific tract name. If the voxels did not match with the JHU ICBM labels, they were identified using the JHU white-matter tractography atlas (Hua et al., 2008). A binary mask was created containing the significant clusters in order to extract FA values of the individual participants.

For visualization purposes (see Fig. 1) and to extend the TBSS analyses, from all 38 JHU labeled white matter tracts, skeleton mean FA values were extracted and exported to Stata version 12 (StataCorp, 2009). Regional group differences were tested with multilevel random regression procedures using the Stata XTREG command with adjustment for the a priori hypothesized confounding variables age, sex, handedness, and level of education.

In addition, the data set was transformed from a wide to a long format, resulting in a hierarchically structured data set, with 38 regional FA measures (Level 1) nested in subjects (Level 2) who were part of the same families (Level 3). Because of the three-level grouping structure of the data, compromising statistical independence of the observations, multilevel random regression models were fitted using the XT MIXED command in Stata with FA measures as the dependent variable and subject number and family number modeled as random effects. Mixed models contain both fixed and random effects, the fixed effects being analogous to standard regression coefficients (B).

Main effects of group and group  $\times$  sex interactions in the model of FA were examined, as well as associations between cumulative AP dose and FA in the patient group. The same covariates were used as described above.

### 3. Results

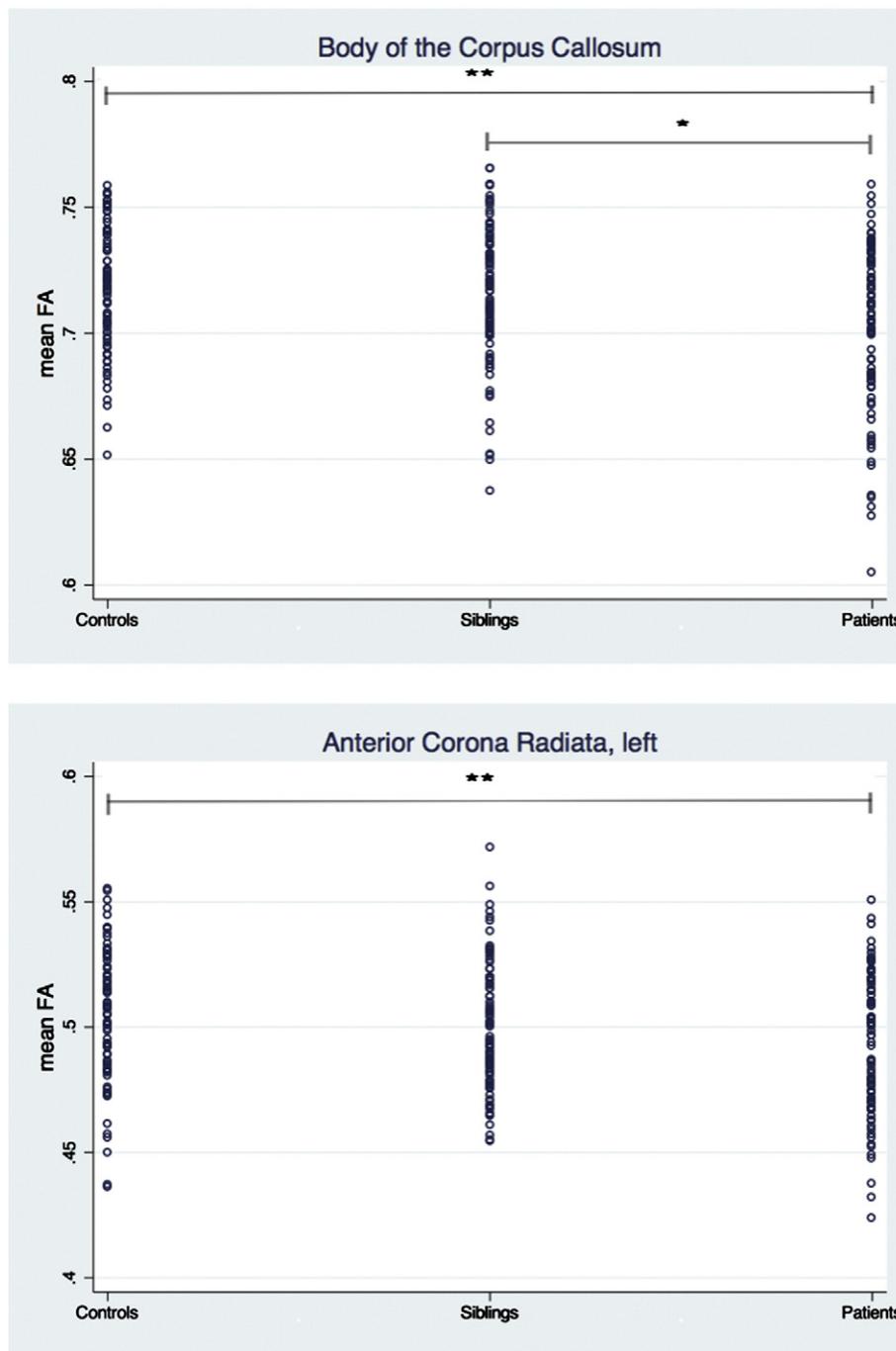
#### 3.1. Descriptive analyses

There were more women than men in the control group, whereas the opposite held for the patient group. The study comprised a relatively stable patient group as reflected by the low PANSS scores (Table 1). The patients were more frequent cannabis- and other drug users than the siblings and controls (Table 1). At the time of scanning, seventy patients were receiving AP medication (second generation:  $n = 67$ ; first generation:  $n = 3$ ). The mean current dosage of AP medication in terms of standard haloperidol equivalents was 5.5 milligrams (mg) ( $SD = 4.6$ ). Furthermore, 16 patients used antidepressants, 6 used benzodiazepines, 5 used anticonvulsants, and 2 used lithium. Three siblings and 3 control participants used antidepressants, and one control participant used benzodiazepines.

#### 3.2. Whole brain group differences in FA

Voxel-wise analysis in TBSS revealed significant differences in mean FA in two out of six comparisons, indicating that the patients had a lower mean FA than the controls and siblings. The number of voxels for each white matter tract with a significant higher FA ( $P < 0.05$ ) in the controls and siblings compared to the patients, was derived and shown in Table 2.

The patients showed a significantly lower FA compared to the control group in the following regions with  $> 250$  voxels and thresholded at  $P < 0.05$ : corpus callosum (genu, body, splenium), forceps major and minor, external capsule bilaterally, corona radiata (anterior, posterior) bilaterally, left superior corona radiata and posterior thalamic radiation bilaterally. At a more conservative threshold ( $P < 0.01$ ), the



**Fig. 1.** Two white matter regions with a significantly lower mean FA value in the patients vs. the controls (\*\*body of the corpus callosum:  $B = -.016$ ,  $P = 0.001$ , anterior corona radiata, left:  $B = -.013$ ,  $P = 0.004$ ) and in the patients vs. the siblings (\*body of the corpus callosum:  $B = .013$ ,  $P = 0.002$ ); controlled for age, sex, handedness and highest level of education.

corpus callosum (genu, body), left external capsule en anterior corona radiata bilaterally remained significant (Fig. 2).

The mean FA values in the brain areas mentioned above showed a gradual decline from the controls to the siblings to the patients (see Fig. 1, results from multilevel random regression procedures in Stata). Although mean FA values in the siblings were generally lower than FA values in the controls, these differences were neither large nor conclusive statistically.

Compared to the siblings, the patients showed a significantly lower FA in the following regions with >250 voxels and thresholded at  $P < 0.05$ : corpus callosum (genu, body), forceps minor, left anterior corona radiata, right superior and posterior corona radiata and the right posterior thalamic radiation. Only a few regions remained significant

using a more conservative threshold, i.e.  $P < 0.01$ : the right body of the corpus callosum and the right superior corona radiata (Fig. 2). All these regions overlapped with those standing out in the comparison between patients and healthy controls.

There were no regions with a higher mean FA in the patients compared to the controls or with a higher mean FA in the siblings compared to the controls.

### 3.3. Additional covariates: cannabis and other drug use

The results described above were controlled for age, sex, handedness, and highest level of education. The analyses were repeated using the additional covariates of cannabis and other drug use. When only

**Table 1**  
Demographic characteristics of the participants.

	Controls (n = 80)	Siblings (n = 93)	Patients (n = 85)
Sex, male (%)	29 (36%)	49 (53%)	58 (68%)
Handedness	76.3	73.9	72.8
Age at scan (years)	30.8 ± 10.8	29.4 ± 8.8	28.3 ± 7.0
Level of education	5.4 ± 1.8	5.1 ± 2.1	4.1 ± 2.0
Age of onset (years)	–	–	22.8 ± 6.4
Illness duration (years)	–	–	5.4 ± 3.6
Antipsychotics <sup>a</sup>	–	–	6692.71 ± 6254.18
Cannabis <sup>b</sup>	7.8 ± 21.9	19.3 ± 37.2	44.0 ± 47.0
Other drugs <sup>b</sup>	0.90 ± 4.7	6.2 ± 31.4	42.4 ± 90.8
Alcohol <sup>c</sup>	5.0 ± 7.0	9.8 ± 17.3	5.0 ± 9.1
PANSS			
Positive symptoms	7.3 ± 1.1	7.3 ± 0.9	10.4 ± 5.0
Negative symptoms	8.2 ± 1.0	8.4 ± 2.0	12.0 ± 5.9
Disorganization	10.2 ± 1.2	10.3 ± 0.7	12.5 ± 4.1
Excitement	8.3 ± 1.1	8.6 ± 1.4	9.7 ± 2.7
Emotional distress	9.2 ± 2.1	9.9 ± 2.6	13.2 ± 5.2

Means ± SDs are reported.

Abbreviations: PANSS, Positive and Negative Syndrome Scale.

<sup>a</sup> Lifetime exposure in haloperidol equivalents.

<sup>b</sup> Mean number of times; life time.

<sup>c</sup> Weekly consumptions on the last 12 months.

cannabis use was added as an additional covariate, the number of significant brain regions showing FA difference between the patients and the controls, as well as the number of voxels per region was comparable to the analysis without cannabis use as a covariate. The right superior longitudinal fasciculus became apparent as an additional area with a significant higher FA in the controls than in the patients (see Table 2).

When both cannabis and other drugs were added as covariates, the number of white matter areas with significant FA differences between the patients and the controls slightly decreased, particularly on the right side of the brain. Effect sizes of the genu and body of the corpus callosum held, whereas the effect size of the splenium was decreased (Table 2). Overall, the effect of drug use on white matter tissue appeared to be minor in this sample.

### 3.4. AP medication

When cumulative AP exposure was added in TBSS as an additional covariate, the number of significant voxels decreased markedly, but significantly lower FA in the patients compared to the controls remained present in the body of the corpus callosum and the right posterior corona radiata (>250 voxels). The patient–sibling comparison did not show significant regional differences.

Cumulative AP exposure was also entered as an independent (dummy) variable (low exposure: n = 22, medium exposure: n = 22 and high exposure: n = 21) to examine the effect on FA within the patients. No significant differences in mean FA values were found when high or medium AP exposure levels were compared to low AP exposure levels.

In addition, analysis in Stata showed that there was no significant association between lifetime AP use and FA ( $B = 1.4 \times 10^{-7}$ ,  $P = 0.68$ ).

### 3.5. Sex differences

Stratified TBSS analyses were done separating the male (n = 29 controls, 49 siblings, 58 patients) and the female subjects (n = 51 controls, 44 siblings, 27 patients). This led to 50% reduction in sample size and to an absence of significant regional differences in mean FA in the patient–control, patient–sibling and control–sibling comparisons.

Since the number of the participants varied considerably between the groups after separating them by sex (e.g. far more male patients than controls, and vice versa for females), the analyses were repeated in equally sized groups, i.e. three groups of 29 males and three groups

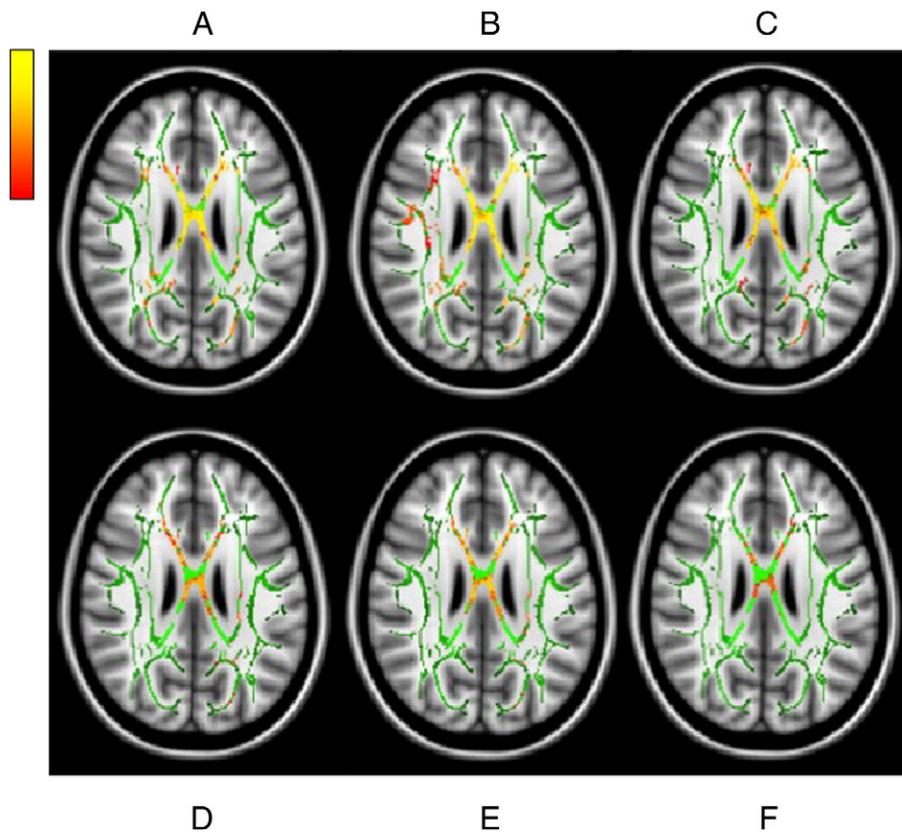
**Table 2**  
Group differences in FA: results from TBSS.

Brain Area	Siblings vs. patients			Controls vs. patients		
	A	A	B	C	C	C
Genu of corpus callosum	826	841	928	800		
Body of corpus callosum	1983	2421	2581	2380		
Splenium of corpus callosum	92	346	412	165		
Forceps major	94	276	326	122		
Forceps minor	1068	1038	1149	984		
Fornix (column and body of fornix)	0	0	0	0		
Anterior limb of internal capsule, right	0	49	398	0		
Anterior limb of internal capsule, left	0	213	48	0		
Posterior limb of internal capsule, right	0	0	22	0		
Posterior limb of internal capsule, left	0	1	0	0		
Retrolenticular part of internal capsule, right	0	4	2	0		
Retrolenticular part of internal capsule, left	0	0	1	1		
Anterior corona radiata, right	0	1037	1049	750		
Anterior corona radiata, left	654	1157	1233	1120		
Superior corona radiata, right	395	241	394	175		
Superior corona radiata, left	221	468	470	382		
Posterior corona radiata, right	339	373	406	0		
Posterior corona radiata, left	13	442	443	416		
Posterior thalamic radiation (incl. optic radiation), right	253	244	255	0		
Posterior thalamic radiation (incl. optic radiation), left	0	313	352	260		
Sagittal stratum (incl. inf. longitudinal fasc. and inferior fronto-occ. fasc), right	149	3	8	0		
Sagittal stratum (incl. inf. longitudinal fasc. and inferior fronto-occ. fasc), left	0	5	46	35		
External capsule, right	0	255	394	0		
External capsule, left	0	371	425	400		
Cingulum (cingulate gyrus), right	0	57	140	127		
Cingulum (cingulate gyrus), left	23	0	0	0		
Cingulum (hippocampus), right	0	0	0	0		
Cingulum (hippocampus), left	0	0	0	0		
Fornix, stria terminalis, right	0	19	27	0		
Fornix, stria terminalis, left	0	4	18	16		
Superior longitudinal fasciculus, right	0	0	269	0		
Superior longitudinal fasciculus, left	0	184	198	173		
Superior fronto-occipital fasciculus, right	103	65	69	0		
Superior fronto-occipital fasciculus, left	0	64	62	0		
Uncinate fasciculus, right	0	50	57	0		
Uncinate fasciculus, left	0	53	58	56		
Tapetum, right	0	35	35	0		
Tapetum, left	0	5	5	5		

The number of voxels with a significant higher FA ( $P < 0.05$ ) in the controls vs. the patients and the siblings vs. the patients. There were no regions with a significant higher FA in the siblings compared to the controls. Results were controlled (A) for age, sex, handedness, highest level of education, (B) age, sex, handedness, highest level of education and cannabis use, (C) age, sex, handedness, highest level of education, cannabis and other drug use.

of 27 females. The total number of significant voxels markedly decreased: 8% (=1291 voxels) left in the female patient–control comparison, and 28% (=1845 voxels) left in the male patient–sibling comparison. In females, the patient group showed significantly lower FA values compared to the controls, but not compared to the siblings, in the genu and body of the corpus callosum and the forceps minor (>250 voxels). In males, the patient group showed significantly lower mean FA values compared to the siblings, but not compared to the controls, following a similar regional pattern as in the whole group analysis, with only the body of the corpus callosum exceeding 250 voxels. There were no significant mean FA differences in the sibling–control comparisons.

In addition, although there was a significant main effect of group in the model of FA (group, linear trend:  $B = -0.004$ ,  $P = 0.02$ ; patients compared to controls:  $B = -0.007$ ,  $P = 0.02$ ; siblings compared to controls:  $B = -0.002$ ,  $P = 0.45$ ), the group × sex interaction was not significant ( $\chi^2: 1.04$ ,  $P = 0.60$ ), suggesting that the effect of group is not conditional on sex.



**Fig. 2.** Axial view of white matter regions, mainly the corpus callosum, in MNI space ( $x: 89, y: 107, z: 98$ ), where the patients have significant lower mean FA values compared to the controls (A, B, C) and the siblings (D, E, F). All the results were controlled for age, sex, handedness, highest level of education, and additionally for cannabis use (B, E) and cannabis and other drug use (C, F). Statistical maps were thresholded at  $P < 0.05$ , with the colormap reflecting the P-values, ranging from 0.05 (red) to 0.00 (yellow).

### 3.6. Exclusion of individuals with a history of affective disorder

Repeating the original analyses excluding siblings (8 males and 10 females) and controls (1 male and 11 females) with a history of affective disorder resulted in an overall increase (+15%) of significant voxels in the patient–control comparison, and an overall decrease (–76%) of significant voxels in the patient–sibling comparison. The regional pattern of patient-related decreased FA was not changed, except for the absence of the left anterior, superior and posterior corona radiata in the patient–sibling comparison. No significant differences in mean FA values were found between the controls and the siblings.

## 4. Discussion

In this whole-brain DTI study, patients with a psychotic disorder, non-psychotic siblings and healthy controls were examined in order to identify microstructural white matter alterations that may be associated with the familial risk for schizophrenia. The results showed a gradual decline of mean FA from the controls to the siblings to the patients. Mean FA values were significantly lower in the patients compared to the controls in several major white matter tracts, while differences between the siblings and the controls did not reach statistical significance. Thus, microstructural white matter alterations may reflect brain pathology associated with the illness, illness related environmental factors, or its treatment, rather than genetic risk.

### 4.1. Findings in the patients

The results support the hypothesis that the patients with psychotic disorder compared to the healthy controls have reduced connectivity

in several brain regions, while no regions with increased FA were identified. This is in line with the majority of the previous evidence suggesting widespread FA decreases in schizophrenia (Kubicki et al., 2007; Ellison-Wright and Bullmore, 2009; Peters et al., 2010). A significantly lower mean FA in the patients in certain brain fasciculi and tracts may indicate dysfunctional axonal connectivity, which has been related to psychotic symptomatology. For example, smaller FA in the left superior longitudinal fasciculus has been associated with positive symptoms (Skelly et al., 2008), in particular hallucinations (Seok et al., 2007) and smaller FA in posterior callosal fibers has been associated with negative symptoms (Seok et al., 2007).

In the present study, the most prominent FA decreases were found in the corpus callosum, in particular the anterior part (genu) of the corpus callosum. The corpus callosum and its postulated role in the dysconnectivity hypothesis in schizophrenia are highlighted in several studies, but there is no consensus about which part of the corpus callosum is most affected; the anterior part (Kubicki et al., 2008) or the more posterior interhemispheric connections (Patel et al., 2011). The results from the present study showed that the anterior–middle part was most affected, but also suggest that the entire corpus callosum may in fact be involved. These FA decreases in the corpus callosum provide additional evidence for aberrant cerebral interhemispheric activity in callosal fibers, further strengthening the theory that disconnection in white matter connective architecture in this part of the brain plays an important role in the core pathology of schizophrenia (Woodruff et al., 1997; Zalesky et al., 2011). Indeed, aberrant connectivity in the corpus callosum has been associated with social cognition and interhemispheric information transfer deficits (Chaim et al., 2010; Miyata et al., 2010), as well as positive and negative symptoms (Hubl et al., 2004; Rotarska-Jagiela et al., 2008).

#### 4.2. Findings in the siblings

Only a few studies with relatively small samples sizes have examined FA in first-degree relatives of patients with psychotic disorder. Clark et al. (2011) found decreased FA in both patients and non-psychotic first-degree relatives in the left and right inferior longitudinal fasciculus, the left inferior fronto-occipital fasciculus and the temporal component of the superior longitudinal fasciculus, using a ROI approach (Clark et al., 2011). The effect sizes for the relatives were intermediate to those for the patients and controls. Other studies have reported significant white matter abnormalities in first-degree relatives compared to controls in the prefrontal cortex and hippocampus (Hao et al., 2009), medial frontal regions (Camchong et al., 2009), the anterior limb of the internal capsule (Munoz Maniega et al., 2008) and the corpus callosum (Knochel et al., 2012). One recent family study, comprising larger samples than hitherto, reported absence of FA alterations in most white matter tracts in siblings as compared to patients with schizophrenia and controls, except for an increased FA in the right arcuate fasciculus (Boos et al., 2012).

Although in the present study, the mean FA in the significant areas between the controls and the patients reflected a dose response effect of familial risk in that the values were highest in the controls and lowest in the patients, with intermediate values for the siblings, there were no significant differences between the sibling and the control group. In addition, there were significant changes in the patient versus sibling comparison, suggesting that the siblings are more similar to the controls than the patients. In other words, the present study does not provide strong evidence for a microstructural white matter intermediate phenotype, but rather suggests that the microstructural white matter alterations are contingent on the expression of psychotic illness. As cross-sectional studies do not allow conclusions on direction of effect, fiber dysconnectivity could in fact arise from the disease process or disease-related differential exposure to environmental risk factors or medication use.

#### 4.3. Antipsychotic medication

Qualitative reviews have suggested that AP use may affect brain structure (Navari and Dazzan, 2009; Smieskova et al., 2009). A recent, fairly large longitudinal study found that white matter volume loss was associated with more extensive use of antipsychotics even after adjustment for illness duration, illness severity, and substance abuse (Ho et al., 2011). However, cross-sectional DTI studies with patients who were either medication-naïve or briefly medicated did not find evidence for a significant association between FA and antipsychotic exposure (Peters et al., 2008; Szeszko et al., 2008). In the present study, extensive TBSS and Stata analyses both supported absence of significant effects of cumulative AP exposure on FA, except for one specific analysis in TBSS, in which AP exposure was added as a covariate and, consequently, the number of significant voxels between the patients and the controls markedly decreased (by 79%). This, however, likely is an effect of the randomize procedure in FSL, where all controls and siblings receive a zero value for AP exposure leading to skewed distributions in the equation and distortion of the results (i.e. controlling for AP is like controlling for patient-status itself). Moreover, despite the voxel reduction in this analysis, significantly lower FA in the patients compared to the controls remained present in the body of the corpus callosum and the right posterior corona radiata (>250 voxels), showing the robustness of FA differences in these areas. Lastly, altered FA values have been detected in AP-naïve patients (Cheung et al., 2008; Zou et al., 2008; Gasparotti et al., 2009), suggesting that AP exposure may at best contribute to, but not fully explain, the white matter alterations.

#### 4.4. Environmental factors

Specific (epi)genetic or environmental effects and/or gene-environment interplay may have contributed to the emergence of

structural dysconnectivity in patients. Evidence for gene effects has come from studies with healthy subjects and studies with patients showing associations between polymorphisms of myelin-associated genes, such as NRG1, ErbB4 and PIK4CA on the one hand, and white matter integrity in the anterior cingulum, the anterior limb of the internal capsule and frontotemporal fibers on the other (McIntosh et al., 2008; Konrad et al., 2009; Wang et al., 2009; Marengo and Radulescu, 2010; Zuliani et al., 2011).

Certain environmental factors, such as childhood trauma (Andersen et al., 2008) and urban upbringing (Lederbogen et al., 2011) have been associated with cerebral alterations in respectively traumatized and non-psychiatric populations. Although these environments are risk factors for schizophrenia (van Os et al., 2010) they have never been examined in relation to cerebral white matter in this patient population. The influence of cannabis on white matter volume in schizophrenia is weak (Cahn et al., 2004; Solowij et al., 2011) but DTI studies have shown both FA increases and decreases in cannabis-using patients with schizophrenia compared to non-using patients (DeLisi, 2008; Peters et al., 2010). Previous analyses on the present study sample have demonstrated that familial predisposition for psychotic disorder is associated with greater cannabis-induced reduction in cortical thickness (Habets et al., 2010). The current DTI results suggest that there is no marked effect of cannabis on microstructural white matter, as the controlling TBSS analyses for cannabis use did not change the results. However, the number of white matter areas that were significantly different between the patients and the controls slightly decreased in the model that included other drug use as a covariate. This may indicate that non-cannabis drug use may have a subtle, though measurable, effect on microstructural white matter in patients with psychotic disorder. To date, there are no other DTI studies reporting on an association between FA and non-cannabis drug use in individuals with psychotic disorder. In healthy (non-psychotic) individuals, other drug use (cocaine, heroin) has been negatively associated with FA in several brain areas, including the corpus callosum (Lane et al., 2010; Bell et al., 2011; Bora et al., 2012). Thus, other drugs may affect the integrity of white matter brain tracts in individuals with psychotic disorder as well as in healthy (non-psychotic) individuals.

The possible influence of environmental risk factors on white matter tissue warrants further investigation.

#### 4.5. Sex differences

Several studies have addressed sex differences in FA in healthy individuals. For the corpus callosum, both higher FA values in women compared to men (Kanaan et al., 2012), higher FA values in men compared to women (Menzler et al., 2011), as well as no sex differences (Sullivan et al., 2001) have been reported. In patients with schizophrenia, the literature on sex differences in FA is limited, but suggests lower values in women compared to men in the genu (Price et al., 2007) and the whole corpus callosum (Rametti et al., 2009). In the present study, the absence of significant group differences in regional FA in males and females separately could be the result of lack of power and markedly unequal group sizes after stratification by sex. Indeed, when stratified analyses were done in equally sized groups, there were patient-control differences in females, but not in males, and sibling-patient differences in males, but not in females. Multilevel analyses in Stata, however, did not yield support for a group  $\times$  sex interaction. The contrasting results between TBSS and Stata analyses could be the result of methodological differences (voxel-wise analyses of aligned FA data projected on the mean FA skeleton, versus multilevel regression analyses on the skeleton mean FAs of 38 regions).

In conclusion, the significant FA reductions in patients may be more female than male driven, which needs replication in larger samples. The absence of reduced FA in the siblings compared to the controls, however, was consistent in all analyses, thus consistently providing evidence for the absence of an intermediated phenotype.

#### 4.6. Methodological considerations

Since FA decreases in cortical and subcortical areas have been found in patients with major depression (Liao et al., 2012), a priori planned sensitivity analyses were done excluding all individuals with a history of affective disorder. Although the number of significant voxels varied, which may be due to a different sex distribution between the groups as the majority of the excluded participants were females, it did not alter the regional pattern of significant white matter tracts.

Structural neuroimaging studies often differ in scanning acquisition and imaging processing. These differences could have contributed to discrepancies in outcome. The present study was the second family study using a 3-T scanner. The signal-to-noise ratio using this field strength is better, as is the visibility of certain details compared to a 1.5-T scanner. Also, the sequence alteration due to a scanner update could in theory have influenced our results. However, we repeated the TBSS analyses, with the number of scan directions as additional covariate. The number and pattern of significant findings was not affected (results available on request).

Other methodological differences are reflected in the type of analyses: hypothesis-generating whole-brain voxel-wise analysis versus the hypothesis-testing ROI approach. It is known that due to image misregistration, smoothing and partial volume effects, whole brain voxel-wise analysis often yields different results compared to the region of interest (ROI) studies (Kyriakopoulos et al., 2008; Jones and Cercignani, 2010).

In DTI studies, different atlases are used in establishing the exact regions of white matter alterations. These atlases differ considerably in the definitions of the boundaries of particular white matter tracts and of the labeling of certain brain regions, in an attempt to account for overlap and crossing fibers. We used two versions of the white matter JHU atlas (Hua et al., 2008; Mori et al., 2008) to include most major white matter tracts. The differences in atlases among the DTI studies hamper between-study comparisons.

## 5. Conclusion

This large cross-sectional DTI study examined white matter integrity in relation to different levels of familial risk for psychotic disorder. There was evidence for patient-specific alterations in microstructural white matter, most profoundly present in the corpus callosum, with no evidence for an intermediate phenotype. The widespread disruptions in white matter in patients with schizophrenia may reflect disease-related dysconnectivity, or disease-related differential exposure to environmental risk factors contributing to the symptoms of schizophrenia.

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#### Contributors

M. Marcelis and Jim van Os designed the study and wrote the protocol. A. Roebroek contributed to the scanning protocol and preprocessing of the data. P. Habets and P. Domen collected the data. E. Gronenschild and P. Habets performed the preprocessing steps. M. Marcelis, Jim van Os and P. Domen managed the analyses. S. Michielse and P. Domen undertook the statistical analysis. P. Domen managed the literature searches and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

#### Conflict of interest

J. van Os has been an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from, Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GlaxoSmithKline, AstraZeneca, Pfizer, and Servier.

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#### Appendix A. Supplementary data

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