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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 tracti 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; Knochel 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 × 256 and field of view was 256 × 256 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 × 230 mm^2, TR 10,800 ms, TE 84 ms, voxel size 1.8 × 1.8 × 1.8 mm^3, b-value 1000 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× B0 and 73× B). The proportion of scans with 76 directions was balanced between the groups (78% in the controls,

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