Diffusion tensor imaging in the early phase of schizophrenia

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Preliminary Evidence for Reduced Frontal White Matter Integrity in Subjects at Ultra-High-Risk for Psychosis


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Abstract

Subjects at ultra-high-risk (UHR) for psychosis (n = 10) and recent-onset schizophrenia patients (n = 10) were studied with diffusion tensor imaging to assess the presence of white matter abnormalities. Whole brain voxel-by-voxel analyses were performed. Compared with healthy controls (n = 10), UHR subjects showed reduced fractional anisotropy in frontal white matter clusters, whereas in recent-onset patients fractional anisotropy was reduced in parietal and temporal white matter clusters and in frontal white matter areas at voxel-level. These findings indicate that reduced frontal white matter integrity may predispose to onset of psychosis and that white matter abnormalities occur in parietal and temporal areas around onset of psychosis.
In subjects with a genetic high-risk of psychosis, diffusion tensor imaging (DTI) has shown decreased white matter anisotropy in the cingulate and angular gyri bilaterally (Hoptman et al., 2008) and in the anterior limb of the internal capsules (Maniega et al., 2008). In this study we examined white matter integrity in subjects at ultra-high-risk (UHR) for psychosis with DTI, in comparison with recent-onset schizophrenia patients.

Ten male subjects at UHR for psychosis (mean age 21.6 years, standard deviation (SD) = 2.8) were included after assessment with the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2002) and according to internationally defined criteria (Klosterkötter et al., 2005): attenuated psychotic symptoms (e.g. odd beliefs, paranoid ideation) or brief limited psychosis with spontaneous remission in less than one week; or a decline in functioning in the past year (30% reduction in Global Assessment of Functioning scale) plus a genetic risk (schizotypal personality disorder); or two ‘basic symptoms’ (cognitive, perceptual, emotional and social disturbances). UHR subjects did not use any medication at time of MRI (three subjects used antipsychotic medication in the past). Eight male patients with a recent-onset of schizophrenia and two male patients with schizoaffective disorder (21.2 years, SD = 3.0) were recruited from the Adolescent Clinic, Amsterdam. All recent-onset patients used antipsychotic medication. Ten male healthy controls (21.1 years, SD = 2.8) were included. All participants were matched for handedness and level of education and gave written informed consent as approved by the local and national medical ethics committees.

MR images were acquired with a 3 Tesla Philips scanner. For DTI spin-echo single shot EPI was used, with: TR 4831–6248 msec. / TE 94 msec.; b = 0 and b = 1000 s/mm²; 16 noncolinear directions, each direction scanned twice; slice thickness 3 mm without gap, FOV 230–256 mm, image matrix 256 × 256. All data were processed with Statistical Parametric Mapping Software SPM2 using optimized voxel based morphometry. T1-weighted images were normalized to standard space (Montreal Neurological Institute, MNI). Prior images of white matter (WM) were generated based on the existing (MNI) T1 weighted template in SPM2, and were used for segmentation and stripping. Prior to template creation, Bo and T1-weighted images were co-registered. Thereafter, all Bo images were spatially normalized, based on the customized T1-weighted template and using the obtained deformation fields. Next, the FA images were
co-registered to the spatially normalized Bo image of the corresponding subject. The images were then smoothed with 10 mm FWHM.

ANOVA for group comparisons were thresholded in a successive order, starting at (i) $P < 0.001$ at voxel level, with a minimal cluster size of 50 voxels, and then (ii) individual significant clusters, corrected for multiple comparisons (cluster level, $P_c < 0.05$).

We identified reduced FA values in the UHR patients compared to controls in the right superior frontal lobe WM (T&T coordinates 24, 1, 36; $Z = 5.44$; $P < 0.001$) and left middle frontal lobe WM (-27, 7, 53; $Z = 5.89$; $P_c < 0.05$) (see figure 2.2.1). We identified reduced FA values in the recent-onset schizophrenia patients compared to controls in WM of the parietal lobe bilaterally (24, -66, 51; $Z = 6.71$; $P_c < 0.001$; 22, -65, 35; $Z = 5.6$; $P_c = 0.05$), left superior temporal lobe (-22, 0, 55; $Z = 5.89$; $P_c = 0.048$), right temporal lobe, insula region (26, -26, 14; $Z = 4.20$; $P < 0.001$) and left frontal lobe (-32, 44, 01; $Z = 6.70$; $P < 0.001$) (figure 2.2.2).

Our findings differ from previous DTI studies in genetic high-risk subjects (Hoptman et al., 2008; Maniega et al., 2008). These differences are most likely due to differences in subject characteristics: none of our UHR subjects had a genetic high-risk for schizophrenia, and a large number of subjects in the other studies did not meet UHR criteria.

Our findings concur with a proton magnetic resonance spectroscopy study, which produced evidence for decreased frontal and cingulate (but not temporal) neuronal density and function in UHR subjects (Jessen et al., 2006). Our findings give some support to the suggestion that frontal abnormalities lead to a (genetic) liability of psychosis, whereas parietal, temporal and orbital prefrontal abnormalities are disease related (Cannon et al., 2002; Pantelis et al., 2005). The frontal WM abnormalities in our schizophrenia patients did not survive cluster-level correction and should therefore be considered preliminary. The discrepancy of possible lack of frontal WM abnormalities in our schizophrenia patients and presence of significant frontal WM clusters in the UHR subjects could be related to the clinical heterogeneity of schizophrenia. Little is known about the differences between UHR subjects who are later diagnosed with schizophrenia-like disorder and patients who enter treatment and research programs after onset of the first psychotic episode.
**Figure 2.2.1:** Significant fractional anisotropy differences between ultra-high-risk subjects and healthy controls.

**Figure 2.2.2:** Significant fractional anisotropy differences between schizophrenia patients and healthy controls.

Legend: Clusters of decreased FA are overlaid on a FA image. There were no areas of increased FA in UHR or schizophrenia subjects. Left is left-hemisphere, right is right-hemisphere.
2.2.1 References


