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Tract-based diffusion tensor imaging in patients with schizophrenia and their non-psychotic siblings

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Abstract
Structural brain abnormalities have consistently been found in patients with schizophrenia. Diffusion tensor imaging (DTI) has been shown to be a useful method to measure white matter (WM) integrity in this illness, but findings in the earlier disease stages are inconclusive. Moreover, the relationship between WM microstructure and the familial risk for developing schizophrenia remains unresolved. From 126 patients with schizophrenia, 123 of their non-psychotic siblings and 109 healthy control subjects, DTI images were acquired on a 1.5 T MRI scanner. Mean fractional anisotropy (FA) was compared along averaged WM tracts, computed for the genu, splenium, left and right uncinate fasciculus, cingulum, inferior fronto-occipital fasciculus, fornix, arcuate fasciculus, and inferior longitudinal fasciculus. Fractional anisotropy (FA) was assessed for its unique environmental and familial (possibly heritable) aspects associated with schizophrenia, using structural equation modeling for these white matter tracts. The results of this study show that young adult (mean age 26.7 years) patients with schizophrenia did not differ in mean FA from healthy controls along WM fibers; siblings of patients showed higher mean FA in the left and right arcuate fasciculus as compared to patients and controls. With increasing age, an excessive decline in mean FA was found in patients as compared to siblings and healthy controls in the genu, left uncinate fasciculus, left inferior fronto-occipital fasciculus, and left inferior longitudinal fasciculus. Moreover, symptom severity was negatively correlated to mean FA in the arcuate fasciculus bilaterally in patients with schizophrenia. In young adult patients with schizophrenia integrity of individual tract-based (corticocortical) fibers can (still) be within normal limits. However, changes in the arcuate fasciculus may be relevant to (the risk to develop) psychosis, while a general and widespread loss of fiber integrity may be related to illness progression.

1. Introduction

Schizophrenia is a highly heritable disorder (Gottesman, 1991) characterized by structural brain abnormalities, particularly in the frontotemporal regions (Hulshoff Pol and Kahn, 2004).

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In view of the prominent involvement of these areas in schizophrenia, it can be assumed that the connections between them are affected as well. Connecting fibers can be studied with diffusion tensor imaging (DTI), where fractional anisotropy (FA) (Basser and Pierpaoli, 1996) is frequently used as an index for the microstructural integrity of white matter (WM) fiber bundles.

Indeed, DTI studies in schizophrenia, mostly applying voxel-based or region of interest (ROI) analyses have found decreased WM integrity, particularly – and as expected – in the frontal and temporal lobe and in the fiber tracts connecting these areas (see meta-analysis: Ellison-Wright and Bullmore, 2009; reviews: Kanaan et al., 2005; Kubicki et al., 2007). More recently, tract-based analyses have been used, allowing the detection of subtle differences in the FA value that span complete tracts (Jones, 2008). Some of these studies reported lower FA in WM fiber tracts in patients compared to healthy control subjects (Kubicki et al., 2008; Nestor et al., 2008; Phillips et al., 2009; Fitzsimmons et al., 2009; Voineskos et al., 2010; de Weijer et al., 2011a, 2011b), while others did not (Jones et al., 2006; Mori et al., 2007; Shergill et al., 2007; Price et al., 2008; Rosenberger et al., 2008; Szeszko et al., 2008; Chan et al., 2010; Mandl et al., 2010). This discrepancy may be due to differences in illness chronicity of the patients in the various studies. In fact, the studies reporting decreased FA were conducted in chronically ill (for at least 10 years) patients. Indeed, several studies have shown that differences in FA between patients and controls only become evident with increasing age of the sample (Friedman et al., 2008; Maddah et al., 2008; Rosenberger et al., 2008; Mandl et al., 2010), although this finding is not universal (Kubicki et al., 2007; Voineskos et al., 2010).

In view of the high heritability of the disorder, one may expect that first-degree family members, who share some of the genetic risk to develop the disorder with their affected probands, also show (some of the) brain abnormalities found in the patients. Indeed, in a recent meta-analysis we found that healthy relatives shared some of the volume loss with affected family members (Boos et al., 2007), and including progressive brain tissue loss (Gogtay et al., 2007; Brans et al., 2008).

WM integrity abnormalities have been suggested to be present in family members of patients in several studies, using voxel-based analysis (Table 1). Specifically, decreased FA in the frontal lobe has been reported in siblings, parents and monozygotic twin pairs (Camchong et al., 2009; Hao et al., 2009); decreased FA in the hippocampus in siblings (Hao et al., 2009), in the cingulum and angular area in subjects who had one first-degree relative with schizophrenia (Hoptman et al., 2008), and in the anterior limb of the internal capsule in subjects who had one or more first- or second degree relatives with schizophrenia (Muñoz Maniega et al., 2008). One study reported increased FA in WM close to the right middle and superior frontal gyri (Hoptman et al., 2008). Thus, while there is some indication of decreased FA in subjects at increased familial (and genetic) risk for the illness, the affected areas differ between studies, and increased FA has also been reported. These studies applied a voxel-based approach to examine changes in FA in family members of patients with schizophrenia. However, the results of a recent study (Melonakos et al., 2011) showed that VBM analysis is not optimal to study WM in schizophrenia. These authors suggested that other (more sophisticated) analysis methods, such as tract-based analysis, should be utilized to detect subtle microstructural abnormalities. Tract-based analysis uses DTI tractography (Mori and van Zijl, 2002) to reconstruct complete WM fiber bundles and then average the FA values along the complete reconstructed tract. Thus, with tract-based analysis group comparisons are performed at the level of complete reconstructed fiber tracts, instead of comparing groups at a voxel level (i.e. VBM). Compared to tract-based analysis, voxel-based analysis has the advantage of keeping partial volume effects with gray matter and white

Table 1 DTI studies in individuals at high risk for schizophrenia.

Study	Subject	Age	Sex (M/F)	DTI-analysis	Results
Wang et al. (2010)	22 PFH/46 NFH pts, 100 nc	24.0/24.2, 25.6	7/15 25/2, 52/48	VBA	In patients: lower integrity in left temporal lobe en right CC, NB: no relatives
Hao et al. (2009)	34 sibpairs, 32 nc	25.4/25.8, 26.6	20/14 20/14, 19/13	VBA	Compared to controls: pts and relatives lower FA in prefrontal cortex and HP, pts lower FA in left anterior CC
Camchong et al. (2009)	22 HR, 30 nc	48.5, 43.8	8/14, 18/12	VBA	Compared to controls: relatives lower FA in medial frontal wm
Maniega et al. (2008)	22 HR, 31 pts, 51 nc	35, 30, 37	27/8 13/17 16/21	VBA	Compared to controls: lower FA in pts in left and right unicinate and left arcuate, left and right anterior limb of internal capsules. Lower FA in alic in relatives but no frontotemporal disconnectivity of uncinate/arcuate
Hoptman et al. (2008)	22 HR, 23 pts, 37 nc	23.1, 20.1, 36.8	17/20 7/15 16/7	VBA	Compared to controls: lower FA in cingulate and angular gyri, higher FA in right middle/superior frontal gyri

PHF=positive family history; NFH=negative family history; pts=patients; nc=normal controls; VBA=voxel-based analysis; CC=corpus callosum; HR=high risk; alic=anterior limb of the internal capsules.