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Research report

The details of structural disconnectivity in psychotic disorder: A family-based study of non-FA diffusion weighted imaging measures

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ABSTRACT

Background: Diffusion tensor imaging (DTI) studies in psychotic disorder have shown reduced FA, often interpreted as disturbed white matter integrity. The observed 'dysintegrity' may be of multifactorial origin, as changes in FA are thought to reflect a combination of changes in myelination, fiber organization and number of axons. Examining the structural substrate of the diffusion tensor in individuals with (risk for) psychotic disorder may provide better understanding of the underlying structural changes.
Methods: DTI scans were acquired from 85 patients with psychotic disorder, 93 siblings of patients with psychotic disorder and 80 controls. Cross-sectional group comparisons were performed using Tract-Based Spatial Statistics (TBSS) on six DTI measures: axial diffusivity (AXD), radial diffusivity (RD), mean diffusivity (MD), and the case linear (CL), case planar (CP) and case spherical (CS) tensor shape measures.
Results: AXD did not differ between the groups. RD and CS values were significantly increased in patients compared to controls and siblings, with no significant differences between the latter two groups. MD was higher in patients compared to controls (but not siblings), with no difference between siblings and controls. CL was smaller in patients than in siblings and controls, and CP was smaller in both patients and siblings as compared to controls.
Conclusion: The differences between individuals with psychotic disorder and healthy controls, derived from detailed diffusion data analyses, suggest less fiber orientation and increased free water movement in the patients. There was some evidence for association with familial risk expressed by decreased fiber orientation.

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1. Introduction

White matter integrity changes in psychotic disorder can be examined by measuring fractional anisotropy (FA). However, the FA provides information on white matter integrity combining myelination, fiber organization and number of axons in a single measure, making it a rather non-specific measure (Mori and Zhang, 2006; O'Donnell and Pasternak, 2015). A systematic review on voxel-wise diffusion-weighted imaging (DWI) studies in psychotic disorder reported reduction of FA in the left frontal lobe and the temporal lobe (Ellison-Wright and Bullmore, 2009). In addition, lower FA in the splenium of the corpus callosum and the cingulum bundle may also be associated with psychotic disorder (Domen et al., 2013; Fitzsimmons et al., 2014). A more recent study found decreased FA in the right temporal lobe in a group with schizotypal personality disorder (Y. Sun et al., 2016). Furthermore, a review on early onset schizophrenia showed a widespread lower FA in patients relative to controls (Tamnes and Agartz, 2016). The available evidence for individuals at higher than average genetic risk suggest that white matter integrity is reduced, compared with healthy controls, in the corpus callosum (Knochel et al., 2012), the inferior longitudinal fasciculus, the left inferior fronto-occipital fasciculus (Oestreich et al., 2015) and the superior longitudinal fasciculus (K. A. Clark et al., 2011; Nakamura et al., 2012; H. Sun et al., 2015), although not all studies agree (Domen et al., 2013).

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As described above, FA alterations may have several origins. Therefore, additional DWI measures that provide more specific information on white matter integrity in psychotic disorder may be of interest. The axial diffusivity (AXD) describes the diffusion of water diffusion parallel to the white matter tracts (λ1, see Fig. 1) and may reflect axonal function related to the number of axons. A decrease in AXD may be indicative of axonal injury/loss (Song et al., 2003). The radial diffusivity (RD) measures the diffusion of water perpendicular to the white matter tracts and may be a marker for myelin content; an increase in RD indicates demyelination (Giorgio et al., 2008; Song et al., 2005). Previous literature suggests that the disruption of connectivity in psychotic disorder may be associated with dysfunction in myelin maintenance and repair and less with a decrease in the number of axons (Davis et al., 2003; Ruef et al., 2012). Indeed, higher RD in the bilateral cortico-spinal tracts, left arcuate fasciculus (de Weijer et al., 2013) and right superior longitudinal fasciculus (Ruef et al., 2012) have been reported.

Mean diffusivity (MD) measures the total water diffusion; increased MD may indicate an increase in the cellular or interstitial fluid compartments (Narr et al., 2009). Psychotic disorder has consistently been associated with increased ventricular enlargement and an overall increase in cerebrospinal fluid (Shenton et al., 2001). This cerebrospinal fluid increase may originate from specific white matter alterations, such as demyelination. For example, previous studies on psychotic disorder have found an increase in free water movement (increased RD and MD) for commissural fibers and projection fibers (Scheel et al., 2013).

AXD and RD are related to respectively diffusion parallel and perpendicular to the of fiber tracts, while geometrical measures (tensor shapes) take all three eigenvalues into account (Fig. 1). With the tensor shape representation method, more knowledge on white matter composition can be provided by specifying the linear (CL), spherical (CS), and planar (CP) tensor shape measures (Westin et al., 2002). An increase in CL may be related to increased anisotropy, which is associated with fibers being more oriented in one primary direction. In highly organized and myelinated white matter regions, such as the corpus callosum, CL will be high (Alexander et al., 2000; Westin et al., 2002).

CS is related to the diffusion of water in any direction, having no profound preferable direction. In highly isotropic matter, such as cerebrospinal fluid, the CS will be high because water molecules can go in any direction not having one distinct preference. The more isotropic, the more spherical (CS towards one) the tensor becomes. CP is probably associated with fiber orientation and structure (Alexander et al., 2000). High CP reflects areas with increased complexity of the fiber orientation (Westin et al., 2002). The more crossing, kissing and twisting of the fibers in a plane, the more complex the fiber structure becomes and the higher the CP. High CP can, for example, be found in the arcuate fasciculus, because of the crossing and twisting of fibers and overlap of gray matter (Alexander et al., 2000).

Previously, we examined FA in the same sample as described in the present study, and found dispersed FA was reduced in the patient group (Domen et al., 2013). We now examined structural disconnectivity at a more fine-grained level, using the above-described six DWI measures. It was hypothesized that individuals with (risk of) psychotic disorder have altered DWI shape measures and that these are caused by alterations in fiber complexity and increased isotropic diffusion.

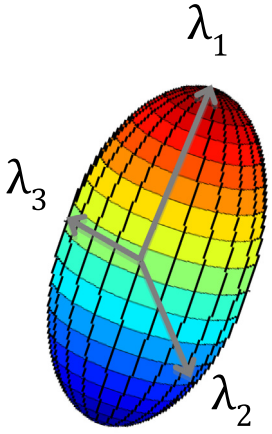

Fig. 1. Diffusion tensor model depicted by three eigenvectors.

2. Results

2.1. Demographics and clinical data

Table 1 shows the demographic characteristics. Patients had a lower educational level compared to controls and siblings, and the proportion of males in the patient group was different from the control group. The frequency of lifetime cannabis and other drug use was higher in patients than in controls and siblings (Table 1).

Most of the patients were receiving antipsychotic medication (second generation: n = 67; first generation: n = 3). The mean current dosage of antipsychotic medication in terms of standard haloperidol equivalents was 5.5 mg (mg) (SD = 4.6). A total of 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.

2.2. Whole brain differences in DWI measures

The reported skeleton mean values were calculated in R and the reported number of voxels were derived from *randomise* ($P < 0.05$ and $P < 0.01$; see Supplemental information) and this is true for all measures presented below.

Table 1
Demographical characteristics.

	Controls (n = 80)	Siblings (n = 93)	Patients (n = 85)
Age (years)	30.8 ± 10.8	29.4 ± 8.8	28.3 ± 7.0
Handedness	76.3	73.9	72.9
Education (level)	5.4 ± 1.8	5.1 ± 2.1	4.1 ± 2.0
Male sex (%)	29 (36%)	49 (53%)	58 (68%)
Age of onset (years)	–	–	22.8 ± 6.4
Illness duration (years)	–	–	5.4 ± 3.6
Antipsychotics[a]	–	–	6692.71 ± 6254.18
Cannabis (lifetime)[b]	7.8 ± 21.9	19.3 ± 37.2	44.0 ± 47.0
Other drugs (lifetime)[b]	0.90 ± 4.7	6.2 ± 31.4	42.4 ± 90.8
Alcohol[c]	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 ± standard deviations are reported.
Abbreviations: PANSS, Positive and Negative Syndrome Scale
[a]Lifetime exposure in haloperidol equivalents.
[b]Lifetime mean number of times of substance use.
[c]Weekly consumption during last 12 months.

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