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White matter tract abnormalities in first-episode psychosis

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ABSTRACT

Fibers connecting fronto-temporal and fronto-medial structures that pass through the anterior limb of the internal capsule (ALIC) subserve executive and psychomotor functioning. Both of these functions are adversely affected in schizophrenia, and may be abnormal at illness onset. In a study of first-episode psychosis, we used diffusion tensor imaging (DTI) and cognitive testing to examine ALIC integrity. Fourteen early psychosis patients and 29 healthy volunteers were included. Symptoms were assessed with the Positive and Negative Syndromes Scale (PANSS). All structural and diffusion scans were acquired on a GE Signa 1.5 T scanner. A T1-weighted 3D FSPGR Inversion Recovery imaging series was acquired for manual seeding in structural space. Diffusion tensor imaging (DTI) was performed, and all DTI images were co-registered to structural space. Seeds were manually drawn bilaterally on the coronal plane at a specified location. Diffusion images were post-processed for subsequent Tract-based Spatial Statistics (TBSS) analysis. First-episode psychosis patients had significantly smaller fronto-medial and fronto-temporal AIC tract volumes compared to healthy volunteers on the left and the right (p-values$<$0.04). No differences in mean fractional anisotropy (FA) were seen within either left or right tracts (p-values$>$0.05), nor did TBSS reveal any other differences in FA values between groups in other regions. Relationships between tract volumes and symptom severity were not observed in this study.

1. Introduction

Recent developments in neuroimaging technology, particularly diffusion tensor imaging (DTI), allow for in vivo investigation of white matter structure and integrity. Recent imaging studies support the underlying hypothesis that white matter abnormalities in schizophrenia are central to the emergence of the core symptoms of psychosis. These symptoms include auditory and visual hallucinations, paranoid or bizarre delusions, disorganized thought and speech, and negative symptoms (APA, 1994). This wide range of symptoms is not readily localized to any single cortical or deep gray matter structure. As a result, schizophrenia is increasingly conceptualized as a disorder of connectivity, in which alterations or abnormalities of white matter pathways are part of an underlying pathophysiology of the circuits serving normal functional and cognitive processes (Andreasen et al., 1998; Cho et al., 2008).

The circuits sub-served by frontal—medial and frontal—temporal pathways are involved in executive planning, decision making, emotional attribution, memory and learning (Takahashi et al., 2007; Wager et al., 2008). In patients with schizophrenia, abnormalities in both the volume and the structural integrity of white matter are present, particularly in frontal—temporal areas (Chan et al., 2010; Skudlarski et al., 2010). These observations are supported by the post-mortem findings of decreased myelin-related gene expression and abnormalities of white matter cellular density and organization in the brains of schizophrenia patients (Beasley et al., 2005, 2009; Hakak et al., 2001). Negative symptoms in schizophrenia have been correlated with low fractional anisotropy (FA) in the inferior frontal white matter (Wolkin et al., 2003). Reduced white matter of the cingulum bundle and uncinate fasciculus differentially and specifically predicted deficits in executive functions and memory respectively (Nestor et al., 2008). Additionally, positive symptoms have been inversely correlated with fiber tract integrity in association tracts, such as the left superior longitudinal fasciculus (Skelly et al., 2008).

The anterior limb of the internal capsule (ALIC) is of particular interest as it contains corticothalamic projections that subserve sensory processing, sensory gating and cognitive processes such as memory, attention, and psychomotor control, which are affected in schizophrenia (Mamah et al., 2010; Rosenberger et al., 2012). Dysfunction of ALIC circuits may increase a patient's vulnerability to schizophrenia and provide a basis for the multiplicity of symptoms seen in schizophrenia (Kubicki et

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al., 2005). Multiple abnormalities recently demonstrated within the ALIC in patients with schizophrenia have underscored its potential role in schizophrenia. Specifically, findings of reduced ALIC volume (Lang et al., 2006) and altered fractional anisotropy (Kubicki et al., 2005; Mitelman et al., 2007b) lend support to the potential role of fronto-medial tracts in schizophrenia. Imaging studies in the early phases of schizophrenia are of particular interest as they avoid potential confounds associated with chronic medication exposure and co-morbidities frequently seen in chronic schizophrenia.

Observations of white matter changes in early and first-episode schizophrenia have been inconsistent. Absence of a single or specific cluster of white matter deficits in schizophrenia may reflect methodological issues (scanning protocols, segmentation techniques) or population sampling differences (Peters et al., 2008). Data pertaining to the anterior limb of the internal capsule in drug naïve first episode schizophrenia remains sparse and further data are required to assess its role in the pathophysiology of schizophrenia. In this study, the volume and integrity of the ALIC in drug naïve first episode psychosis patients were investigated with DTI using both region of interest (ROI) tractography and Tract-Based Spatial Statistics (TBSS). TBSS has been proposed as a more robust method of analysis, overcoming alignment and smoothing issues (Smith et al., 2006). In this study, results from ROI tractography were confirmed with TBSS analysis.

2. Methods

2.1. Subjects

A cohort of subjects with first-episode psychosis (FEP) was recruited between 2001 and 2008 from the South Fraser catchment area, under the umbrella of the British Columbia Fraser Health Authority. Of this cohort, a smaller group of fourteen subjects underwent diffusion scanning and were included in the current study. Three of the 14 subjects were antipsychotic-naïve at entry, while the remainder had a median of 4.0 weeks of antipsychotic treatment at entry (see Table 1 for further details). The number of antipsychotic-naïve patients was too small for separate analyses. Twenty-nine healthy volunteers were recruited from the general community between 2001 and 2007. In the subpopulation included in the current study, the age range was 15 to 38 years. Ethical review of this study was provided by the UBC Clinical Research Ethics Board, in accordance with Tri-Council Ethics guidelines. All study participants gave full written consent, and those under age 16 also provided additional consent from a parent or legal guardian. Inclusion criteria for the FEP subjects were presentation of a DSM-IV defined psychosis (all subjects were within their 1st year of illness at study entry), no history of significant head injury (defined by loss of consciousness greater than 5 min), no history of neurodevelopmental disorder (autism, Asperger's syndrome) or central nervous system infection. Exclusionary criteria included inability to provide full written consent, IQ less than 75, diagnosis of substance-induced psychosis and inability to receive MRI (claustrophobia, contra-indicated surgical implants, pregnancy). Consensus DSM-IV diagnoses were based on comprehensive subject assessments and formal SCID interviews, along with interviews with one or more family members at referral. Clinical assessment of illicit substance use was performed at one-month post intake to rule out substance-induced psychosis. Inclusion and exclusion criteria were similar for healthy volunteers, aside a history of any psychiatric disorder.

2.2. Clinical and cognitive measurements

Handedness was evaluated with the Edinburgh Handedness Inventory. Pre-morbid and current intelligence were evaluated with the North American Adult Reading Test (NAART) and the Kaufman Brief Intelligence Test (KBIT) respectively. The Stroop test was conducted to assess attention and processing speed. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess symptom severity.

Table 1
Demographic and clinical characteristics for first-episode patients and healthy volunteers.

Part A. Clinical

Variable	First episode psychosis		Healthy volunteers	
	Mean	Range	Mean	Range
Age (years)	20.9	15–38	23.6	15–38
Education (years)	11.7	9–16	12.1	8–16
Duration of medication at scan (weeks)	8.2	0–35.6	N/A	N/A
Total PANSS score	71.8	47–112	N/A	N/A
IQ (NAART)	100.5	89–116	105.7	90–124
IQ (KBIT)	94.4	77–114	101.9	69–120
Stroop test (word score)	34.9	15–61	46.1	27–65
Stroop test (color score)	35.1	13–57	43.2	18–63
Edinburgh handedness	1.4	−1–2	1.7	−1.8–2
	N	%	N	%
Male	12	86	6	20
Female	2	14	23	80
Ethnicity				
Caucasian	13	93	17	59
Asian	0	0	7	24
First nation	0	0	1	3.4
Hispanic	0	0	1	3.4
Other	1	7	3	10.2

Part B. Treatment

Antipsychotic treatment	FEP subjects only		
	N	Mean dose (mg/d)	Dose range (mg/d)
None	3		
Olanzapine	4	13.1	5.0–10.0
Risperidone	6	1.2	1.0–1.5
Quetiapine	1	100	100.0
Mean week exposure	8.2	Range: 0.0–35.5 weeks	

Cognitive functioning was assessed using the intra-dimensional/extra-dimensional (IDED) task from the CANTAB (Cambridge Neuropsychological Tests and Battery), a computer-based neuropsychological battery (http://www.camcog.com/camcog/default.asp). The IDED paradigm is designed to test cognitive flexibility and attentional set shifting as a probe of frontal lobe performance (Pantelis et al., 2009). Demographic and clinical descriptors are summarized in Table 1.

2.3. Image acquisition

Scans were acquired with a GE Signa Excite 1.5 T scanner (GE Medical Systems, Milwaukee). A T1-weighted 3D FSPGR IR prepped series for volumetric assessment was performed for ROI seeding in structural space with the following parameters; TR = 11.5 ms, TE = 5 ms, FOV 24 cm^2, NEX = 1, 120 slices, acquisition and reconstruction matrices = 256 × 192 and 256 × 256, respectively, voxel dimensions = 0.9375 mm × 0.9375 mm × 2 mm, and interslice thickness = 1 mm. Additional diffusion tensor scans were performed with the following parameters; EPI axial; b value − 1000, tensor 25 directions, TR = 13000 ms, TE = 72.8 ms, NEX = 2, voxel dimensions = 1.25 mm × 1.25 mm × 2.5 mm, FOV = 32 × 32 cm, 58 slices, and acquisition and reconstruction matrices = 128 × 128 and 256 × 256, respectively.

2.4. Region of interest (ROI) manual segmentation

The ROI for the anterior limb of the internal capsule (AIC) was manually selected by a single rater (D.L.) blinded to diagnosis for tractography. Manual segmentation was performed on the T1-SPGR structural scans using the interactive masking tool from the FMRIB Software Library v.