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Insight and white matter fractional anisotropy in first-episode schizophrenia

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1. Introduction

Impaired insight is a hallmark feature of schizophrenia and is associated with poor treatment adherence (Yalcin-Siedentopf et al., 2014; Rüsch et al., 2009), a more severe course of illness (Johnson et al., 2012; Hoy et al., 2011) and poorer outcome in multiple symptom and functional domains (Margariti et al., 2015; Mohamed et al., 2009). The clinical model of insight encompasses illness awareness, treatment adherence, and the ability to attribute symptoms as pathological as defining features (David, 1990). As such, insight has become a focus of interest as a predictor of outcome, as well a therapeutic target for both pharmacological and psychological interventions (Lysaker et al., 2013).

Structural neuroimaging studies describe a significant association between impaired insight and a range of brain abnormalities involving predominantly prefrontal (Sapara et al., 2007; Shad et al., 2004; Shad et al., 2006), anterior and posterior cingulate (Ha et al., 2004), cuneus and precuneus, and inferior temporal brain regions (Ha et al., 2004). Illness awareness may be mediated by alterations in the dorsolateral prefrontal cortex (DLPFC) and middle frontal gyrus (Shad et al., 2004; Shad et al., 2006; Buchy et al., 2011; Flashman et al., 2001) and gyrus rectus (Flashman et al., 2001) while awareness of the need for treatment may involve medial frontal, precuneus and inferior temporal cortex (Buchy et al., 2011). On the other hand symptom attribution implicates prefrontal abnormalities including thinness of the DLPFC (Buchy et al., 2012) (Asmal, 2016, in press), thickness of the orbitofrontal cortex (Shad et al., 2006; Buchy et al., 2012), as well as grey matter deficits in the precuneus and posterior cingulate gyrus (Morgan et al., 2010).

Functional MRI (fMRI) studies corroborate structural neuroimaging findings, largely through investigating functional correlates of self-reflective processing (van Buuren et al., 2012; van der Meer et al., 2010a) with limited studies involving a behavioural assessment of insight (van der Meer et al., 2013; Shad and Keshavan, 2015). The difficulty patients have reflecting on the illness, on symptom attribution and on the need for medication may involve self-reflective processing deficits (van der Meer et al. 2010a; van der Meer et al., 2013; Lysaker et al., 2011) mediated by cortical midline structures (CMS), namely the anterior and posterior cingulate cortex, cuneus and precuneus, the ventromedial and dorsomedial prefrontal cortex, and insula (van der Meer et al., 2010b; Ćurčić-Blake et al., 2015; Northoff and Bermpohl, 2004; Murray et al., 2012). Findings from fMRI studies examining brain activation in response to self versus other referential stimuli together with a more direct measurement of insight implicate the CMS as well as parietal and temporal cortices (van der Meer et al., 2013; Shad and Keshavan, 2015).

Brain connection irregularities within and between brain regions may be core pathology in schizophrenia (Wheeler and Voineskos, 2014). However, few studies have explored the relationship between white matter tracts and insight in schizophrenia, and none in patients with first episode schizophrenia. Thus far white matter findings in chronic schizophrenia are somewhat conflicting. One study reported no significant association between cognitive insight (cognitive flexibility towards beliefs, judgments and experiences) and DTI measures (FA and mean diffusivity) in 45 people with chronic schizophrenia (Spalletta et al., 2014), while Antonius et al. ($n = 36$) described significant correlations between white matter abnormalities in multiple DTI regions and clinical insight (Antonius et al., 2011). They reported the grey matter region adjacent to the voxels with reduced FA, and found that symptom unawareness was significantly associated with several frontal-temporal lobe regions and symptom misattribution was associated with various parietal and temporal brain regions. Illness chronicity, medication exposure, relatively small sample sizes and the absence of a control group are possible confounders in these chronic samples.

In this study, we performed a DTI analysis of WM tracts in a cohort of first-episode schizophrenia (FES) patients. We were able to avoid potential confounds by selecting a relatively large first-episode sample with minimal or no exposure to antipsychotic treatment and a matched healthy control group. The aim of this study was to identify WM tract differences in FES patients and controls associated with impaired clinical insight. We hypothesized that impaired insight in patients would

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be predicted by reduced FA values, with a predilection for association tracts interconnecting cortical areas, namely the CMS, and frontal-temporal-occipital areas.

2. Methods

2.1. Participants

This was a substudy of a parent study examining clinical, biological and functional outcome of FES in Cape Town, South Africa. We recruited 125 patients into the parent study; the first 25 were excluded from the neuroimaging component because of an approval delay for scans, 4 were lost as a result of scan error, 3 were unable to be scanned because of claustrophobia, and 4 did not complete the Insight assessment, resulting in a sample of 89 FES patients for the DTI study. We recruited 101 controls and 3 were excluded due to scan error, resulting in 98 controls for the DTI study. First-episode schizophrenia spectrum patients were recruited from inpatient services at Tygerberg and Stikland Hospital, and related community clinics in Cape Town, South Africa. For inclusion in the study, schizophrenia participants had to be aged 16 to 45 years, and experiencing a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder based on the Structured Clinical Interview for DSM-IV (SCID) – Patient Edition (First et al., 2012). The healthy control group was matched for age, sex, ethnicity and level of education (Table 1), and had no DSM-IV axis I or II disorder as determined by the by SCID-Non-Patient Edition interviews. Healthy controls were recruited through personal contacts of the families of the patients with FES and advertisements placed in community centres in the same catchment area as the patients. Patients and controls were excluded if they had a serious or unstable general medical condition, mental retardation, overt substance abuse and <7 completed years of schooling. Patients were excluded if they had a lifetime exposure to >4 weeks of antipsychotic medication or were previously treated with a long-acting depot antipsychotic. Each patient was carefully screened with a thorough physical examination and review of the medical history, ECG, urine toxicology screen and structured assessment of symptoms to verify that inclusion criteria were met. Patients and controls were compensated for transport costs incurred during their participation in the study. Participants did not receive any other financial reward.

This study was conducted according to the principles of the Declaration of Helsinki 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/). After the study procedures were fully explained in accordance with the ethical guidelines of the institutional review board, participants provided written informed consent. The parent study was registered on the South African National Clinical Trials Register (www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx), trial number DOH-27-0710-1957.

2.2. MRI-acquisition

All scans were acquired with a 3T Siemens Allegra MRI scanner (Erlangen, Germany). Diffusion-weighted images (DWIs) were acquired with the following parameters: $1.8 \times 1.8 \times 2.0$ mm^3 spatial resolution, field of view (FOV) = 220 m, repetition time (TR) = 8800 ms, echo time (TE) = 88 ms, 65 slices, no distance factor and twofold GRAPPA acceleration. The gradients were applied in 30 directions and b = 1000 mm/s^2 and 3 b = 0 mm/s^2 images were also acquired. The sequence was repeated three times.

2.3. Image processing

The DWIs were pre-processed using the Functional MRI of the Brain (FMRIB) Software Library (FSL) version 4.1.8 (www.fmrib.ox.ac.uk/fsl/; Smith et al., 2004). Raw DTI data were eddy corrected and the images were imported into Matlab R2008b (Mathworks, MA). The three acquisitions were co-registered by using the first b = 0 mm/s^2 as the reference image. Outliers were determined by calculating the *Z*-value of the tensor estimates at the 25th and 75th percentiles. Data points falling outside of >3 standard deviations were discarded. The acquisitions were then averaged and exported to the FSL for further processing. Fitting a tensor model to the diffusion-weighted images created fractional anisotropy and mean, axial and radial diffusivity maps. Brain extraction was performed with FSL BET. A study-specific template was created by affine registration of each individual's FA image to the FMRIB58 template, after which images were concatenated and averaged. The template was then affine registered to MNI space and every subject's FA image was non-linearly registered to the template. These transforms were then applied to the original FA images. Masks were created to delineate white matter regions by utilizing the JHU white matter atlas (Mori et al., 2005), with a FA threshold of 0.2 allowing for extraction of each subject's FA image. The mean of the FA per region was extracted and exported to STATA for statistical analysis. The regions of interest are listed in Supplementary Table 1.

Table 1
Demographic and clinical characteristics for first-episode schizophrenia patients and matched healthy controls.

Characteristic	Patients (n = 89)	Controls (n = 98)	Analysis[a]		
			Test statistic	df	p
Age in years (mean, SD)	25.39(6.59)	25.55(7.25)	t = 1.13	185	0.13
Male, n (%)	67(75.28)	62(63.27)	x^2 = 3.15	1	0.08
Education level, n (%)			x^2 = 0.72	3	0.95
Elementary	6(6.74)	8(8.16)			
Secondary	52(58.43)	52(53.06)			
Matriculation	21(23.60)	28(28.57)			
Tertiary	10(11.24)	10(10.20)			
Treatment naïve, n(%)	48(55.81)				NA
Duration of treatment in days (median, [range])	3(0–28)				NA
DUP in days (median, [range])	21.15(1.15–315.29)				NA
BIS (mean, SD)					
Total	6.0(2.19)				
Symptom attribution	2.29(1.05)				
Illness awareness	1.57(1.37)				
Need for treatment	2.14(1.01)				
PANSS G12 (mean, SD)	4.82(1.11)				
MCCB composite score (mean, SD)	16.18(15.76)	29.81(12.69)	t = 5.88	152	<0.001

SD, Standard deviation; BIS, Birchwood Insight Scale; DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale.
[a] Paired *t*-tests for continuous variables and x^2 test for categorical variables.

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