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White matter microstructure in schizophrenia: Associations to neurocognition and clinical symptomatology

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ABSTRACT

Background: Diffusion tensor imaging (DTI) studies in schizophrenia report widespread aberrations in brain white matter (WM). These appear related to poorer neurocognitive performance and higher levels of negative and positive symptomatology. However, identification of the most salient WM aberrations to neurocognition and clinical symptoms is limited by relatively small samples with divergent results.
Methods: We examined 53 well-characterized patients with schizophrenia and 62 healthy controls. All participants were administered a computerized neurocognitive battery, which evaluated performance in several domains. Patients were assessed for negative and positive symptoms. Fractional anisotropy (FA) of WM cortical regions and WM fiber tracts were compared across the groups. FA values were also used to predict neurocognitive performance and symptoms.
Results: We confirm widespread aberrant WM microstructure in a relatively large sample of well-characterized patients with schizophrenia in comparison to healthy participants. Moreover, we illustrate the utility of FA measures in predicting global neurocognitive performance in healthy participants and schizophrenia patients, especially for reaction time. FA was less predictive of clinical symptomatology.
Conclusions: Using a standardized computerized neurocognitive battery and diffusion tensor imaging we show that behavioral performance is moderated by a particular constellation of WM microstructure in healthy individuals that differs in schizophrenia.

1. Introduction

Disruptions in brain white matter (WM) organization in schizophrenia may alter neural communication critical for sustaining neurocognitive performance and may relate to the manifestation of clinical symptoms. Diffusion tensor imaging (DTI) has facilitated *in vivo* study of WM integrity, as measured by fractional anisotropy (FA). Reduced FA has been documented in multiple brain regions in schizophrenia (Kyriakopoulos et al., 2008). Studies of patients with chronic schizophrenia reported significant, widespread WM microstructural aberrations (Kyriakopoulos et al., 2008; Thomason and Thompson, 2011; Asami et al., 2014), while more recent investigations of early-onset psychosis (Epstein et al., 2013; Lee et al., 2013) and psychosis in adolescence (White et al., 2007; Davenport et al., 2010) have identified focal WM abnormalities. Typically, these findings are limited to major WM fiber tracts and recent evidence indicates that reductions in cortical WM microstructure are associated with cognition (Nazeri et al., 2013). However, the specific constellation of affected brain regions varies across studies and there is likely regional specificity that relates to neurocognition or clinical symptomatology.

Impaired cognition, a core feature of schizophrenia (Gur et al., 2001a), is associated with WM abnormalities (Gur et al., 2001a; Kubicki et al., 2007; Szeszko et al., 2008; Phillips et al., 2009). Global deficits in cognition are reflective of domain-specific impairments, which are associated with aberrant WM microstructure including working memory (Sugranyes et al., 2012), executive and motor function (Perez-Iglesias et al., 2010), and verbal and visual learning abilities (Liu et al., 2013). We recently reported smaller correlations between a global measure of neurocognition, across task within-individual variability, and WM microstructure in schizophrenia as compared to healthy participants (Roalf et al., 2013). Higher within individual variability in performance speed on a computerized neurocognitive battery was associated with lower FA in the left cingulum bundle and left inferior frontal-occipital fasciculus in healthy people, but not in patients with schizophrenia. Since WM connectivity is essential for maintaining effective communication among regions, deficits in neurocognitive performance may be related, in part, to complex patterns of disrupted WM microstructure.

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Table 1
Demographic characteristics and neurocognitive performance by diagnosis.

	Controls (n = 62)		Patients (n = 53)		
	Percentage	Proportion	Percentage	Proportion	p-value
Gender (% Female)	51.6	32 F, 30 M	35.8	19 F, 34 M	0.09
	Mean (SD)	Range	Mean (SD)	Range	p–value
Age (years)	36.1 (8.6)	25–55	38.7 (9.8)	25–55	0.14
Education (years)	14.9 (2.4)	10–20	13.3 (2.6)	6–20	<0.001
Parental Education (years)	13.9 (3.1)	6.5–20	13.4 (3.0)	6–19.5	0.46
Handedness (% Right)	88.7%		81.1%	–	0.38
SANS Global Average	–	–	1.4 (0.9)	0–3.3	–
SAPS Global Average	–	–	1.4 (1.0)	0–3.5	–
Comorbid Diagnoses‡					
SZ only	–	–	22	–	–
SZ + 1	–	–	18	–	–
SZ + 2	–	–	12	–	–
SZ + 3	–	–	1	–	–
Age of Onset	–	–	22.0 (6.4)	9–37	
Medication (Atypical/Typical)	–	–	27/7	–	–
Medication (CPZE)*	–	–	428.4 (439.4)	–	–
GNP Accuracy (z-score)	0.0 (0.6)	−2.0-1.3	−0.6 (0.9)	−2.9–0.6	–
GNP Speed (z-score)	0.0 (0.6)	−2.0–0.9	−0.9 (1.1)	−3.2–0.9	–

‡ Comorbid diagnoses included: Mood disorders, Substance Dependence and Substance Use.
* Sixteen patients were receiving mood stabilizers, but not antipsychotics; six patients reported no antipsychotic medication; antipsychotic dosage was unknown for two patients.

The relation of WM findings and clinical variables has also been evaluated, including symptoms (Paillere-Martinot et al., 2001), medications (Lieberman et al., 2005) and treatment response (Marques et al., 2014). Clinical variables contribute to heterogeneity beyond demographic variables such as age and sex, which are associated with brain maturation tractography patterns (Asato et al., 2010; Ingalhalikar et al., 2014). Clinical findings evaluating major symptom dimensions suggest that positive symptoms, such as hallucinations, are related to increases in FA (Hubl et al., 2004; Seok et al., 2007), but see (Asami et al., 2014), while negative symptoms (Bai et al., 2009) and poor outcome (Mitelman et al., 2007) are associated with lower FA. A recent study correlated clinical symptoms with global and regional measures of FA and reported significant associations between lower FA in the left hemisphere and negative, but not positive, symptoms (Asami et al., 2014). Most of these investigations have focused on localized WM regions or tracts. Given the inconsistency in previous findings and limited sample sizes, better estimates of the relation between WM microstructure and clinical symptoms are needed.

While DTI is a powerful neuroimaging technique for measuring white matter structure, methodological concerns often make group inference challenging. For example, spatial normalization, or inter-subject registration, is affected by high data dimensionality and the orientation component of the tensors (Ingalhalikar et al., 2010). Several options exist for spatial normalization (Alexander et al., 2001; Cao et al., 2006; Zhang et al., 2006; Yang et al., 2008; Yeo et al., 2008), including a deformable registration using orientation and intensity descriptors (DROID; Ingalhalikar et al., 2010). DROID capitalizes on the structural geometry of the diffusion tensor (Westin et al., 2002) and incorporates orientation information to improve the matching of white matter fiber tracts by accounting for the underlying fiber orientation (Ingalhalikar et al., 2010). Here, DROID is used to register all data to a common template; this method is efficient and produces robust results.

The goal of this study was to 1) evaluate WM microstructural abnormalities in a large sample of patients with schizophrenia and healthy controls, and 2) relate these measures to neurocognitive performance and clinical symptoms. We hypothesized that: A) patients with schizophrenia will have lower FA values in diffuse cortical WM and along WM fiber tracts compared to healthy controls; B) prediction of performance using brain WM microstructure will result in non-overlapping networks in controls and patients; C) abnormalities in WM regions and tracts will be associated with greater symptom severity.

2. Materials and methods

2.1. Participants

The sample included 53 patients with schizophrenia and 62 healthy controls recruited through the Penn Schizophrenia Research Center. Table 1 presents the sample characteristics. Participants underwent standard medical, neurological and psychiatric screening and received the Structured Clinical Interview (SCID) for DSM-IV-TR Axis I Disorders, Patient or Non-patient Edition (First et al., 2002). Patients met DSM-IV diagnosis of schizophrenia and healthy controls did not meet any axis I diagnosis or axis II cluster A personality disorder, and did not have a family history of axis I psychotic disorder in a first-degree relative. All patients had a primary diagnosis of schizophrenia; 18 patients had a history of one comorbid condition, 12 patients had two comorbid conditions, and one had three comorbid conditions. Comorbid conditions included Mood (16 patients), Substance Dependence (17 patients), or Substance Use disorders (9 patients). These counts reflect total comorbidities and are not mutually exclusive.

Potential participants in either group were excluded for any medical condition that might affect brain function, any history of neurological disorder, head trauma with loss of consciousness, lifetime history of substance dependence, substance abuse within the preceding 6 months, or any contraindication for MRI. Symptoms were rated with the Scales for Assessment of Negative Symptoms (SANS; (Andreasen, 1984a) and Positive Symptoms (SAPS; (Andreasen, 1984b). The average of patients' global items was used as a dependent measure. Trained clinical research assessors completed all evaluations and scales. The sample was predominately right-handed and the proportion was similar in each diagnostic group ($\chi^2(1) = 0.77$, $p = 0.38$; 88% of controls and 81% of patients). Written informed consent was obtained after all procedures were fully explained, in compliance with guidelines of the University of Pennsylvania Institutional Review Board and the Declaration of Helsinki.

2.2. Computerized Neurocognitive Battery (CNB)

The CNB examines performance accuracy and speed (response time) in five neurocognitive domains including executive function (abstraction and mental flexibility, attention, working memory), episodic memory (verbal, face, spatial), complex cognition (language reasoning,