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White matter organization and neurocognitive performance variability in schizophrenia

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ABSTRACT

Background: White matter alterations in schizophrenia are associated with deficits in neurocognitive performance. Recently, across task within-individual variability (WIV) has emerged as a useful construct for assessing the profile in cognitive performance in schizophrenia. However, the neural basis of WIV has not been studied in patients with schizophrenia.

Methods: Twenty-five patients with schizophrenia (SZ) and 27 healthy comparison subjects (HC) performed a computerized neurocognitive battery (CNB) and underwent diffusion tensor imaging (DTI). WIV for performance accuracy and speed on the CNB was calculated across-tasks. Voxel-wise group comparisons of white matter fractional anisotropy (FA) were performed using tract-based spatial statistics (TBSS). The relationship between accuracy and speed WIV on the CNB and white matter FA was examined within the regions that differentiated patients and healthy comparison subjects.

Results: SZ had higher WIV for performance accuracy and speed as compared to HC. FA in SZ compared to HC was reduced in bilateral frontal, temporal and occipital white matter including a large portion of the corpus callosum. In white matter regions that differed between patients and comparison subjects, higher FA in the left cingulum bundle and left fronto-occipital fasciculus were associated with lower CNB speed WIV for HC, but not SZ. Accuracy WIV was not associated with differences in white matter FA between SZ and HC.

Conclusions: We provide evidence that WIV is greater in patients with SZ and that this greater within-individual variability in performance in patients is associated with disruptions of WM integrity in specific brain regions.

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1. Introduction

Schizophrenia is a complex disorder with persistent neurocognitive dysfunction (Saykin et al., 1994; Gur et al., 2001a). Disrupted communication within and between brain regions may underlie these neurocognitive disturbances. Specifically, disruptions in brain white matter (WM) organization may alter neural communication critical for neurocognitive performance. WM abnormalities in SZ are related to myelin dysfunction (Davis et al., 2003), changes in oligodendrocytes (Segal et al., 2007), and hyperglutamatergic states (Chang et al., 2007). The availability of diffusion tensor imaging (DTI) has facilitated the in vivo study of WM alterations in SZ. WM disruptions, as measured by fractional anisotropy (FA) using DTI, are widespread throughout the brain in SZ. These disruptions include reduced FA in the corpus callosum, arcuate fasiculus, the internal capsule and the cingulum bundle (Kyriakopoulos et al., 2008). The specific constellation of affected areas remains unclear and varies by study. Several studies report that WM alterations in SZ are associated with deficits in neurocognitive performance (Szeszko et al., 2008; Phillips et al., 2009; Spoletini et al., 2011). For example, reductions in WM FA were associated with impairment in task switching (Kubicki et al., 2002) and cognitive flexibility (Perez-Iglesias et al., 2010). While these studies begin to illuminate the disruption of specific brain–behavior relationships in SZ, it is possible that focal microstructural WM alterations may affect general cognitive performance, rather than the specific tasks examined in these studies. We assess the relationship between across task within-individual variability (WIV), a measure associated with general cognitive ability, and WM integrity in major brain WM tracts of in patients with SZ compared to HC.

WIV reflects within-person differences in neurocognitive performance across a range of tests, and has been used to assess the stability in cognitive processing (Snitz et al., 2006; Holtzer et al., 2008; MacDonald et al., 2009). WIV has emerged as a useful construct for assessing the architecture of cognitive performance in disorders such as ADHD (Leth-Steensen et al., 2000) and SZ (Kaiser et al., 2008; Carroll et al., 2009; Rentrop et al., 2010; Cole et al., 2011; Roalf et al., in press). Typically, WIV is measured across-trials within a given domain (Stuss

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et al., 2003; Klein et al., 2006; Rentrop et al., 2010), and it is limited to measures of performance speed. However, WIV can also be calculated across neurocognitive domains within a single testing session, providing a broad index of brain function for accuracy or speed (Reichenberg et al., 2006; Holtzer et al., 2008; Cole et al., 2011). A large study of SZ patients, their unaffected siblings and healthy individuals found greater across-task WIV in patients compared to their unaffected siblings, who showed more variability than healthy individuals (Cole et al., 2011). Recently, we showed a similar pattern of increased WIV in patients with SZ and their unaffected relatives in both performance accuracy and speed as compared to HC (Roalf et al., in press). Furthermore, we noted an increase in WIV in patients over time, indicating an inability to maintain consistency across tasks that involve a range of cognitive processing domains. Since WM connectivity is needed for maintaining the integrity of communication across regions, variability in neurocognitive performance may be related, in part, to WM availability (for review see MacDonald et al., 2009). To our knowledge the neural basis of WIV has not been measured in patients with SZ. Here we evaluate the relationship between brain WM integrity and neurocognitive performance using across-task WIV and hypothesize that disruptions in brain white matter will be related to higher WIV in patients with SZ.

2. Methods and materials

2.1. Participants

Patients who met DSM-IV diagnosis of schizophrenia (SZ; n = 25) and healthy comparison subjects (HC; n = 27) were recruited to the Schizophrenia Research Center of the University of Pennsylvania Perelman School of Medicine. Participants received the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient or Non-patient Edition (SCID-I; First et al., 2002). Patients were rated with regard to general psychiatric symptoms, negative symptoms, and positive symptoms using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), the Scales for Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and Positive Symptoms (SAPS; Andreasen, 1984b). All scales were completed by trained raters and ratings are presented in Table 1. HC were excluded for any history of an axis I diagnosis, axis II cluster A personality disorder, or family history of axis I psychotic disorder in a first-degree relative. All subjects were excluded for any history of neurological disorder, head trauma with loss of consciousness, lifetime history of substance dependence, substance abuse within the preceding 6 months, any medical condition that might affect brain function or any contraindication for MRI. Written informed consent was obtained after all procedures were fully explained, in compliance with guidelines established by the University of Pennsylvania Institutional Review Board and the Declaration of Helsinki.

Table 1
Demographic characteristics and clinical scales for healthy comparison subjects and patients with schizophrenia.

	Healthy comparison (n = 27)	Schizophrenia (n = 35)
Age, years	30.44 (7.72)	36.76 (8.93)
Education, years	15.38 (2.60)	13.80 (2.72)*
Parental EDU, years	13.39 (2.44)	13.35 (3.12)
Sex, % M	51.80%	60.0%
Handedness, % R	96.1%	80.0%
Race (C/AA/O)	16/6/3*	7/16/2
SANS	n/a	22.18 (14.44)**
SAPS	n/a	14.90 (15.80)
BPRS	n/a	29.05 (8.49)
DTI motion (mm)[a]	0.33 (0.11)	0.37 (0.08)
Medication		
Atypicals		21
Typicals	n/a	3
Unmedicated		1

* p<.05: healthy comparison subjects > patients with schizophrenia.
** Correlated with speed WIV (r = .45, p<.05; n = 20).
[a] A metric of average relative motion displacement from previous time point using Jenkinson et al. (2002) method.

Participants' characteristics are presented in Table 1. There were no significant differences in sex distribution [$\chi^2(1) = 0.35$, $p = 0.55$] and handedness [$\chi^2(1) = 0.32$, $p = 0.07$], but the race [$\chi^2(1) = 10.40$, $p = 0.01$] distributions differed between diagnostic groups. HC were younger [$t(50) = 2.73$, $p < .01$] and more educated [$t(49) = 2.14$, $p = .04$] than SZ; however, groups did not differ with respect to parental education [$t(43) = 0.05$, $p = 0.96$]. Most SZ were medicated with a regimen of first-generation antipsychotics or second-generation antipsychotics (n = 22), two patients were unmedicated and medication information was unavailable for one patient.

2.2. The computerized neurocognitive battery (CNB)

The CNB was validated in healthy people (Gur et al., 2001b) and individuals with SZ (Gur et al., 2001a). It evaluates the neurocognitive domains of abstraction and mental flexibility, attention, working memory, verbal memory, face memory, spatial memory, language reasoning, nonverbal reasoning, spatial processing, emotion processing and sensorimotor processing speed. Details regarding the test administration and a description of individual tests have been published (Gur et al., 2001b, 2010). Two performance indices are calculated for each domain: accuracy and speed. The tasks included in the current study include: 1) Penn Conditional Exclusion Test; 2) Continuous Performance Test; 3) Letter n-back; 4) Immediate and Delayed Face Memory Test, 5) Immediate and Delayed Word Memory Test; 6) Immediate and Delayed Spatial Memory Test; 7) Penn Verbal Reasoning Test; 8) Matrix Reasoning Test; 9) Judgment of Line Orientation Test, 10) Emotion Identification Test; 11) Simple Motor Speed Test; and 12) Sensorimotor Speed Test. Some individuals did not have data for all CNB tasks as some tasks were added after initiation of the study and some data was lost due to computer or tester error.

2.3. Across-task intra-individual variability

Within-person across-test variability was calculated as in previous studies (Holtzer et al., 2008; Roalf et al., in press) for CNB accuracy and speed. Variability scores were only calculated for subjects who completed a minimum of five CNB tests. Twenty-three patients with SZ and eighteen HC were included in this analysis. Of these, 19 patients and 17 controls completed all CNB tests. Briefly, raw scores for each CNB test were z-transformed based on the sample as a whole. These transformed scores were then used to calculate variability using the following equation:

$$\text{Within} - \text{individual variability} = \sqrt{\sum_{k=1}^{K} \frac{(Z_{ik} - A_i)^2}{(K-1)}}$$

where Z_{ik} is the kth CNB test score for the ith individual and is

$$A_i = \sum_{k=1}^{K} \frac{Z_{ik}}{K}$$

the individual's mean z-transformed score based on all of the CNB tests performed. An analysis of covariance (ANCOVA) was applied, with diagnostic group serving a between-subjects factor and age was used as a covariate. All behavioral statistical analyses were carried out using SPSS v.20 (IBM).

2.4. Neuroimaging acquisition

Diffusion weighted images were collected using a 3.0 Tesla MRI scanner (Siemens Tim Medical Solutions, Erlangen, Germany) with