Published in final edited form as:
Schizophr Res. 2013 January ; 143(1): 172–178. doi:10.1016/j.schres.2012.10.014.

White matter organization and neurocognitive performance variability in schizophrenia

David R. Roalf, Ph.D.[a], **Kosha Ruparel, M.S.**[a], **Ragini Verma, Ph.D.**[b], **Mark A. Elliott, Ph.D.**[c], **Raquel E. Gur, M.D., Ph.D.**[a,c], and **Ruben C. Gur, Ph.D.**[a,c]

[a]Neuropsychiatry Section, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine

[b]Section of Biomedical Image Analysis, University of Pennsylvania Perelman School of Medicine

[c]Department of Radiology, University of Pennsylvania Perelman School of Medicine

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.

Corresponding author: David R. Roalf, Ph.D. Department of Psychiatry, Neuropsychiatry Section, University of Pennsylvania Perelman School of Medicine, 3400 Spruce St., Gates Building 10th Floor, Philadelphia PA, 19104.

Conflict of interest
All of the authors reported no biomedical financial interests or potential conflicts of interest.

Contributors:
Drs. Roalf, Verma, Elliott, R.E. Gur, and R.C. Gur were involved in the design, analysis and contributed to the writing of the manuscript. Ms. Ruparel assisted in the analysis of DTI data, calculation of intraindividual variability and manuscript editing.

Keywords

diffusion tensor imaging; intraindividual variability; cognition; white matter

1.0 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 (Phillips et al., 2009; Spoletini et al., 2011; Szeszko et al., 2008). 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 (Holtzer et al., 2008; MacDonald et al., 2009; Snitz et al., 2006). 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 (Carroll et al., 2009; Cole et al., 2011; Kaiser et al., 2008; Rentrop et al., 2010; Roalf et al., in press). Typically, WIV is measured across-trials within a given domain (Klein et al., 2006; Rentrop et al., 2010; Stuss et al., 2003), 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 (Cole et al., 2011; Holtzer et al., 2008; Reichenberg et al., 2006). 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 evaluating 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.

2.0 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.

Participants' characteristics are presented in Table 1. There were no significant differences in sex distribution [$\chi(1)=0.35$, p=0.55], 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; Gur et al., 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. 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 *k*th CNB test score for the *i*th 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 an eight-channel head coil. T_2-weighted diffusion weighted images were acquired using a single-shot spin-echo-type echo planar imaging (TR = 6500 ms, TE = 99 ms, 90 degree flip angle, 70 slices, voxel size = 1.718mm × 1.718mm × 3.000mm; field of view = 22cm; 40 slices). Gradient encoding pulses were applied in 12 directions with a b-value of 800 s/mm^2, and one diffusion-weighted image was collected with no weighting.

2.5 Image Processing and Statistical Analysis

All images were visually inspected and data was excluded if any of 13 volumes were considered to include noise. Eddy current effects and head motion were corrected using FMRIB's Diffusion Toolbox and skull-stripped using FSL brain-extraction tool (BET; (Smith, 2002). Motion for patients and controls was similar as calculated with a metric of average relative motion displacement from previous time point using Jenkinson's (Jenkinson et al., 2002) method (Table 1). FSL's Diffusion Toolbox (FDT) was used to calculate the diffusion tensor, identify the eigenvalues of the tensor (λ_1, λ_2, λ_3) and measure fractional anisotropy (FA). FA is the scalar value between 0 and 1 that indicates the magnitude of preferred direction of water diffusion in a given voxel and is thought to reflect fiber density, axonal diameter and myelination. Voxelwise statistical analysis was performed on FA maps using Tract-Based Spatial Statistics (TBSS) version 1.2 (Smith et al., 2006; Smith et al., 2007). Data was extracted from white matter fiber tracts using the Johns Hopkins University (JHU) DTI-based White Matter Atlas in FSL (Mori et al., 2005; Wakana et al., 2007). In addition, an exploratory voxel-wise analysis was performed using a FSL's 'randomise' tool, which is a permutation-based inference tool for nonparametric statistical thresholding (Smith et al., 2006), to compare FA values in patients and controls across the entire cerebrum. Detailed description of the analysis steps are documented in the Supplemental Methods.

3.0 Results

3.1 Within-individual variability (WIV) on the Computerized Neurocognitive Battery

Neurocognitive variability is presented in Figure 1. Overall, SZ had greater WIV compared to HC in accuracy [$F(1,38)=12.32$, $p=.001$] and speed [$F(1,37)=18.52$, $p<.001$] on the CNB.

These results were unchanged when WIV was computed for only those subjects with complete CNB, indicating WIV calculation is robust to small amounts of missing data. Accuracy WIV was not associated with SANS, SAPS or BPRS in SZ. Higher speed WIV on the CNB was associated with higher SAPS scores in SZ (r=.45, p<.05; n=20), but there were no associations with SANS or BPRS.

3.2 Diffusion Tensor Imaging data

SZ showed multiple significant reductions in FA compared to HC (Figure 2A). Regions included bilateral frontal, temporal and occipital white matter including a large portion of the corpus callosum (Figure 2B). There were no regions of greater FA in SZ compared to HC. Thus, all follow-up correlations are from regions where SZ had lower FA than HC.

In WM regions that differed between SZ and HC, left cingulum bundle (CB) mean FA and left inferior fronto-occipital fasciculus (IFO) were negatively correlated with CNB speed WIV for HC, but not SZ (Figure 3B, C). No correlations with accuracy WIV survived p<.01 threshold for HC or SZ.

Exploratory voxel-wise analyses confirmed that FA in the LIFO was significantly correlated with speed WIV in HC (p<.05, TFCE corrected), but the correlation within the CB did not survive correction (p<.05, uncorrected). FA in the IFO and CB was not correlated with WIV for CNB speed in SZ.

4.0 Discussion

Our behavioral findings were that patients with SZ showed greater WIV compared to HC on a computerized neurocognitive battery, and that greater speed WIV in patients was associated with a greater incidence of positive symptoms. Neuroanatomically, patients had lower white matter FA in bilateral frontal, temporal and occipital WM including a large portion of the corpus callosum, relative to comparison subjects. The behavioral findings were related to the neuroanatomic differences in that higher mean FA in the left cingulum bundle and left fronto-occipital fasciculus was associated with lower CNB speed WIV for HC, but this relationship was absent in patients. Accuracy WIV was not associated with FA in patients or comparison subjects. The behavioral data on across-task measure of performance variability confirm previous results (Cole et al., 2011; Roalf et al., in press) of more WIV for neurocognitive measures in SZ compared to HC. However, our study is the first to indicate that this increase may be related to specific disruptions in WM integrity in the CB and IFO, two brain regions associated with disrupted neurocognitive function in SZ (Cho et al., 2006; Nestor et al., 2004; Nestor et al., 2007).

Our results confirm and extend prior findings on the neuropsychological deficits in SZ. Like other studies, both accuracy and speed WIV differentiated patients from HC. The increase in accuracy and speed WIV of general neurocognitive performance in patients may reflect the inability to maintain consistency across tasks that involve rapid complex cognitive processing. Our finding that positive symptoms are associated with more variable CNB performance in patients is consistent with a previous study that suggested a unique association between reaction time WIV and positive symptoms in SZ (Vinogradov et al., 1998). Other studies (Cole et al., 2011; Holtzer et al., 2008) suggest that this inconsistency may be a more sensitive index of performance and it may be related, in part, to alterations in WM (Manoach et al., 2007). Thus, WIV could be a particularly sensitive marker of brain function given its relationship to symptoms and brain WM integrity in SZ (Kyriakopoulos et al., 2008).

We report evidence that more anisotropic WM is associated with consistent speed WIV as measured across neurocognitive domains in HC, but not in SZ. While our findings are exploratory, they align with recent findings suggesting the relationship between cognitive performance and FA in the CB and IFO that may be disrupted in SZ. The CB is a major fiber tract that connects limbic and cortical brain regions. The CB has connections with regions associated with memory and executive functioning including the thalamus, amygdala, hippocampus, and dorsolateral and dorsomedial prefrontal cortex (Croxson et al., 2005; Di Rosa et al., 2008; Goldman-Rakic et al., 1984). Reduced FA of the CB in SZ was linked to reduced ability to properly orient attention (Nestor et al., 2007), including longer reaction-times during the Stroop task (Takei et al., 2009), poor executive function, reduced general intelligence and impaired visual memory (Nestor et al., 2008). Importantly, our measure of WIV was calculated over tests that incorporate these domains, suggesting that lower across-task WIV measures may also be associated with WM integrity, particularly in healthy individuals. The lack of association of CB white matter and WIV in patients suggests a disorganization of critical axons that connect the anterior cingulate with the limbic and motor cortices. Perhaps this WM disorganization underlies the increase in WIV, as CB is associated with conflict monitoring (Bush et al., 2002), providing feedback to guide prospective decisions (Carter et al., 2001), and neuroimaging studies indicate that patients have abnormal activity of the CB during neurocognitive task performance (Carter et al., 2001; Ikuta et al., 2012). However, it is also possible that disorganization is the result of neural dysfunctions elsewhere in the brain. For example, patients with SZ have reduced volume in hippocampus, cingulate and frontal brain regions that are innervated by the CB. These volumetric changes may in turn affect WM organization in the CB. (Bush et al., 2002;Carter et al., 2001; Carter et al., 2001; Ikuta et al., 2012). Future studies should focus specifically on the CB, its inputs and targets, as it has now been implicated in many DTI studies of the neurocognitive aspects of SZ.

The IFO forms the main connection between the fusiform and lingual gyri and the prefrontal cortex (Martino et al., 2010). Disruption of the right IFO is associated with deficits in semantic processing (Duffau et al., 2005) and recognition of facial expressions, including emotional content (Philippi et al., 2009; Thomas et al., 2008). Disruption of the left IFO is associated with psychosis (Walterfang et al., 2008), is commonly found in SZ (Clark et al., 2011; Koch et al., 2010; Kyriakopoulos and Frangou, 2009), is associated with poorer outcomes and more negative symptoms (Mitelman et al., 2006), is heritable (Clark et al., 2011) and is associated with subclinical psychotic symptoms in children (Jacobson et al., 2010). Thus, disruptions of IFO are pervasive in SZ and may contribute to the severity of the disorder. Indeed, patients with SZ show disruptions in facial recognition, emotion processing and semantic processing (Irani et al., 2012; Lee et al., 2011; Morris et al., 2009; Wang et al., 2011) for which an intact IFO is critical, and these deficits extend to unaffected family members (Bediou et al., 2007; Eack et al., 2010). Notably, our WIV incorporates measures of emotion identification, face memory and verbal reasoning, further emphasizing that a disruption in the IFO in schizophrenia may affect several aspects of cognition. Reduced IFO FA in patients with SZ suggests a disruption of the pathway connecting association regions of the occipital and parietal lobe with prefrontal cortex. Again, it remains unclear whether changes in IFO white matter are the cause of increased WIV or if disruptions elsewhere in the brain supersede this change. For example, an IFO disruption may be associated with performance variability, as one of its frontal targets, the inferior frontal cortex is disrupted in SZ. (Forstmann et al., 2008)(Cho et al., 2006). Disruption in inferior frontal cortex may directly affect the integrity of IFO white matter afferents. Notably, the IFO is a major WM tract that spans a large portion of the cerebrum; thus more detailed studies of the specific parcels of IFO disruptions would further elucidate this relationship.

The study is limited by the small sample size and the lack of an additional clinical (non-SZ) group. Thus, the lack of association of cognitive performance and IFO or CB integrity may not be specific to SZ. Also, this study focused on WM integrity and it is plausible that disruption in FA is the result of underlying volumetric changes, which are evident in SZ (Davatzikos et al., 2005; Gur et al., 2000). Future studies will consider the interaction of volumetric changes and WM organization to better elucidate these findings. Furthermore, the use of 12 diffusion directions is a methodological limitation as DTI with 30 directions or more provides superior signal-to-noise and allows for increased precision of fiber orientation estimation (Mukherjee et al., 2008). However, 12 diffusion directions provide adequate signal-to-noise for the estimation of FA. Our results are exploratory, but in addition to using an ROI driven approach to associate WIV with WM, we confirmed our results with whole-brain voxel-wise analysis (Figure 3C). As our sample was unmatched for age, we accounted statistically for this difference in both the estimation of FA from the DTI data and when making comparison to WIV. Future studies will examine age-matched comparison samples to avoid potential age effects. The groups differ in education and race, which could be confounding factors. However, this limitation is mitigated as the groups do not differ in parental education and lower educational attainment in SZ is itself the result of reduced neurocognitive function. Finally, we did not account for medication effects or illness duration, but other studies have shown limited correlations between antipsychotic dosage or illness duration and specific neurocognitive functioning or DTI measures in SZ (e.g. Nestor et al., 2007).

To summarize, employing a novel approach to assess global neurocognitive functioning, we found higher across-task within-individual variability and lower FA throughout the brain in patients with schizophrenia. Higher FA in the CB and IFO was associated with lower variability in healthy individuals, but this pattern did not exist in patients with schizophrenia. These results support recent evidence that the disruption of the CB and IFO are related to neurocognitive deficits in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Role of funding source:

Our sponsors, recognized in the acknowledgments, served no role in the study design, collection, analysis, interpretation, writing, or decision to submit this manuscript for publication.

This work was supported by the National Institute of Mental Health (R01MH042191 and T32 MH019112 to [REG]; NIH R01-MH060722 (RCG).

References

Andreasen, NC. The Scale for the Assessment of Negative Symptoms (SANS). Unversity of Iowa; Iowa City, Iowa: 1984a.

Andreasen, NC. The Scale for the Assessment of Positive Symptoms (SAPS). Unversity of Iowa; Iowa City, Iowa: 1984b.

Bediou B, Asri F, Brunelin J, Krolak-Salmon P, D'Amato T, Saoud M, Tazi I. Emotion recognition and genetic vulnerability to schizophrenia. Br J Psychiatry. 2007; 191:126–130. [PubMed: 17666496]

Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR. Dorsal anterior cingulate cortex: a role in reward-based decision making. Proc Natl Acad Sci U S A. 2002; 99(1):523–528. [PubMed: 11756669]

Carroll CA, O'Donnell BF, Shekhar A, Hetrick WP. Timing dysfunctions in schizophrenia span from millisecond to several-second durations. Brain Cogn. 2009; 70(2):181–190. [PubMed: 19282082]

Carter CS, MacDonald AW 3rd, Ross LL, Stenger VA. Anterior cingulate cortex activity and impaired self-monitoring of performance in patients with schizophrenia: an event-related fMRI study. Am J Psychiatry. 2001; 158(9):1423–1428. [PubMed: 11532726]

Chang L, Friedman J, Ernst T, Zhong K, Tsopelas ND, Davis K. Brain metabolite abnormalities in the white matter of elderly schizophrenic subjects: implication for glial dysfunction. Biol Psychiatry. 2007; 62(12):1396–1404. [PubMed: 17693392]

Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. Proc Natl Acad Sci U S A. 2006; 103(52):19878–19883. [PubMed: 17170134]

Clark KA, Nuechterlein KH, Asarnow RF, Hamilton LS, Phillips OR, Hageman NS, Woods RP, Alger JR, Toga AW, Narr KL. Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. J Psychiatr Res. 2011; 45(7):980–988. [PubMed: 21306734]

Cole VT, Weinberger DR, Dickinson D. Intra-individual variability across neuropsychological tasks in schizophrenia: a comparison of patients, their siblings, and healthy controls. Schizophr Res. 2011; 129(1):91–93. [PubMed: 21470829]

Croxson PL, Johansen-Berg H, Behrens TE, Robson MD, Pinsk MA, Gross CG, Richter W, Richter MC, Kastner S, Rushworth MF. Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. J Neurosci. 2005; 25(39): 8854–8866. [PubMed: 16192375]

Davatzikos C, Shen D, Gur RC, Wu X, Liu D, Fan Y, Hughett P, Turetsky BI, Gur RE. Whole-brain morphometric study of schizophrenia revealing a spatially complex set of focal abnormalities. Arch Gen Psychiatry. 2005; 62(11):1218–1227. [PubMed: 16275809]

Davis KL, Stewart DG, Friedman JI, Buchsbaum M, Harvey PD, Hof PR, Buxbaum J, Haroutunian V. White matter changes in schizophrenia: evidence for myelin-related dysfunction. Arch Gen Psychiatry. 2003; 60(5):443–456. [PubMed: 12742865]

Di Rosa E, Crow TJ, Chance SA. Axon bundle spacing in the anterior cingulate cortex of the human brain. J Clin Neurosci. 2008; 15(12):1389–1392. [PubMed: 18974006]

Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. Brain. 2005; 128(Pt 4):797–810. [PubMed: 15705610]

Eack SM, Mermon DE, Montrose DM, Miewald J, Gur RE, Gur RC, Sweeney JA, Keshavan MS. Social cognition deficits among individuals at familial high risk for schizophrenia. Schizophr Bull. 2010; 36(6):1081–1088. [PubMed: 19366983]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patietn Edition (SCID-I/P). Biometrics Research, New York State Psychiatric Institute; New York: 2002.

Forstmann BU, Jahfari S, Scholte HS, Wolfensteller U, van den Wildenberg WP, Ridderinkhof KR. Function and structure of the right inferior frontal cortex predict individual differences in response inhibition: a model-based approach. J Neurosci. 2008; 28(39):9790–9796. [PubMed: 18815263]

Goldman-Rakic PS, Selemon LD, Schwartz ML. Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. Neuroscience. 1984; 12(3):719–743. [PubMed: 6472617]

Gur RC, Ragland JD, Moberg PJ, Bilker WB, Kohler C, Siegel SJ, Gur RE. Computerized neurocognitive scanning: II. The profile of schizophrenia. Neuropsychopharmacology. 2001a; 25(5):777–788. [PubMed: 11682261]

Gur RC, Ragland JD, Moberg PJ, Turner TH, Bilker WB, Kohler C, Siegel SJ, Gur RE. Computerized neurocognitive scanning: I. Methodology and validation in healthy people. Neuropsychopharmacology. 2001b; 25(5):766–776. [PubMed: 11682260]

Gur RC, Richard J, Hughett P, Calkins ME, Macy L, Bilker WB, Brensinger C, Gur RE. A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: standardization and initial construct validation. J Neurosci Methods. 2010; 187(2):254–262. [PubMed: 19945485]

Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, Arnold SE, Bilker WB, Gur RC. Temporolimbic volume reductions in schizophrenia. Arch Gen Psychiatry. 2000; 57(8):769–775. [PubMed: 10920465]

Holtzer R, Verghese J, Wang C, Hall CB, Lipton RB. Within-person across-neuropsychological test variability and incident dementia. JAMA. 2008; 300(7):823–830. [PubMed: 18714062]

Ikuta T, Szeszko PR, Gruner P, Derosse P, Gallego J, Malhotra AK. Abnormal anterior cingulate cortex activity predicts functional disability in schizophrenia. Schizophr Res. 2012

Irani F, Seligman S, Kamath V, Kohler C, Gur RC. A meta-analysis of emotion perception and functional outcomes in schizophrenia. Schizophr Res. 2012

Jacobson S, Kelleher I, Harley M, Murtagh A, Clarke M, Blanchard M, Connolly C, O'Hanlon E, Garavan H, Cannon M. Structural and functional brain correlates of subclinical psychotic symptoms in 11–13 year old schoolchildren. Neuroimage. 2010; 49(2):1875–1885. [PubMed: 19770054]

Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage. 2002; 17(2):825–841. [PubMed: 12377157]

Kaiser S, Roth A, Rentrop M, Friederich HC, Bender S, Weisbrod M. Intra-individual reaction time variability in schizophrenia, depression and borderline personality disorder. Brain Cogn. 2008; 66(1):73–82. [PubMed: 17604894]

Klein C, Wendling K, Huettner P, Ruder H, Peper M. Intra-subject variability in attention-deficit hyperactivity disorder. Biol Psychiatry. 2006; 60(10):1088–1097. [PubMed: 16806097]

Koch K, Wagner G, Dahnke R, Schachtzabel C, Schultz C, Roebel M, Gullmar D, Reichenbach JR, Sauer H, Schlosser RG. Disrupted white matter integrity of corticopontine-cerebellar circuitry in schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2010; 260(5):419–426. [PubMed: 19915989]

Kubicki M, Westin CF, Maier SE, Frumin M, Nestor PG, Salisbury DF, Kikinis R, Jolesz FA, McCarley RW, Shenton ME. Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. Am J Psychiatry. 2002; 159(5):813–820. [PubMed: 11986136]

Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S. Diffusion tensor imaging in schizophrenia. Eur Psychiatry. 2008; 23(4):255–273. [PubMed: 18524546]

Kyriakopoulos M, Frangou S. Recent diffusion tensor imaging findings in early stages of schizophrenia. Curr Opin Psychiatry. 2009; 22(2):168–176. [PubMed: 19553871]

Lee J, Gosselin F, Wynn JK, Green MF. How do schizophrenia patients use visual information to decode facial emotion? Schizophr Bull. 2011; 37(5):1001–1008. [PubMed: 20156852]

Leth-Steensen C, Elbaz ZK, Douglas VI. Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. Acta Psychol (Amst). 2000; 104(2): 167–190. [PubMed: 10900704]

MacDonald SW, Li SC, Backman L. Neural underpinnings of within-person variability in cognitive functioning. Psychol Aging. 2009; 24(4):792–808. [PubMed: 20025396]

Manoach DS, Ketwaroo GA, Polli FE, Thakkar KN, Barton JJ, Goff DC, Fischl B, Vangel M, Tuch DS. Reduced microstructural integrity of the white matter underlying anterior cingulate cortex is associated with increased saccadic latency in schizophrenia. Neuroimage. 2007; 37(2):599–610. [PubMed: 17590354]

Martino J, Vergani F, Robles SG, Duffau H. New insights into the anatomic dissection of the temporal stem with special emphasis on the inferior fronto-occipital fasciculus: implications in surgical approach to left mesiotemporal and temporoinsular structures. Neurosurgery. 2010; 66(3 Suppl Operative):4–12. [PubMed: 20173571]

Mitelman SA, Newmark RE, Torosjan Y, Chu KW, Brickman AM, Haznedar MM, Hazlett EA, Tang CY, Shihabuddin L, Buchsbaum MS. White matter fractional anisotropy and outcome in schizophrenia. Schizophr Res. 2006; 87(1–3):138–159. [PubMed: 16854563]

Mori, S.; Wakana, S.; van Zijl, PCM.; Nagae-Poetscher, LM. MRI Atlas of Human White Matter. 1. Elsevier; Amsterdam, The Netherlands: 2005.

Morris RW, Weickert CS, Loughland CM. Emotional face processing in schizophrenia. Curr Opin Psychiatry. 2009; 22(2):140–146. [PubMed: 19553867]

Mukherjee P, Chung SW, Berman JI, Hess CP, Henry RG. Diffusion tensor MR imaging and fiber tractography: technical considerations. AJNR Am J Neuroradiol. 2008; 29(5):843–852. [PubMed: 18339719]

Nestor PG, Kubicki M, Gurrera RJ, Niznikiewicz M, Frumin M, McCarley RW, Shenton ME. Neuropsychological correlates of diffusion tensor imaging in schizophrenia. Neuropsychology. 2004; 18(4):629–637. [PubMed: 15506830]

Nestor PG, Kubicki M, Niznikiewicz M, Gurrera RJ, McCarley RW, Shenton ME. Neuropsychological disturbance in schizophrenia: a diffusion tensor imaging study. Neuropsychology. 2008; 22(2):246–254. [PubMed: 18331167]

Nestor PG, Kubicki M, Spencer KM, Niznikiewicz M, McCarley RW, Shenton ME. Attentional networks and cingulum bundle in chronic schizophrenia. Schizophr Res. 2007; 90(1–3):308–315. [PubMed: 17150337]

Overall JE, Gorham DR. The brief psychiatric rating scale. Psychological Reports. 1962; 10:799–812.

Perez-Iglesias R, Tordesillas-Gutierrez D, McGuire PK, Barker GJ, Roiz-Santianez R, Mata I, de Lucas EM, Rodriguez-Sanchez JM, Ayesa-Arriola R, Vazquez-Barquero JL, Crespo-Facorro B. White matter integrity and cognitive impairment in first-episode psychosis. Am J Psychiatry. 2010; 167(4):451–458. [PubMed: 20160006]

Philippi CL, Mehta S, Grabowski T, Adolphs R, Rudrauf D. Damage to association fiber tracts impairs recognition of the facial expression of emotion. J Neurosci. 2009; 29(48):15089–15099. [PubMed: 19955360]

Phillips OR, Nuechterlein KH, Clark KA, Hamilton LS, Asarnow RF, Hageman NS, Toga AW, Narr KL. Fiber tractography reveals disruption of temporal lobe white matter tracts in schizophrenia. Schizophr Res. 2009; 107(1):30–38. [PubMed: 19028423]

Reichenberg A, Weiser M, Rapp MA, Rabinowitz J, Caspi A, Schmeidler J, Knobler HY, Lubin G, Nahon D, Harvey PD, Davidson M. Premorbid intra-individual variability in intellectual performance and risk for schizophrenia: a population-based study. Schizophr Res. 2006; 85(1–3): 49–57. [PubMed: 16626941]

Rentrop M, Rodewald K, Roth A, Simon J, Walther S, Fiedler P, Weisbrod M, Kaiser S. Intra-individual variability in high-functioning patients with schizophrenia. Psychiatry Res. 2010; 178(1):27–32. [PubMed: 20447695]

Roalf DR, Gur RC, Almasy L, Richard J, Gallagher RS, Prasad K, Wood J, Pogue-Geile MF, Nimgaonkar VL, Gur RE. Neurocognitive performance stability in a muliplex multigenerational study of schizophrenia. Schizophrenia Bulletin. in press.

Segal D, Koschnick JR, Slegers LH, Hof PR. Oligodendrocyte pathophysiology: a new view of schizophrenia. Int J Neuropsychopharmacol. 2007; 10(4):503–511. [PubMed: 17291369]

Smith SM. Fast robust automated brain extraction. Hum Brain Mapp. 2002; 17(3):143–155. [PubMed: 12391568]

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006; 31(4):1487–1505. [PubMed: 16624579]

Smith SM, Johansen-Berg H, Jenkinson M, Rueckert D, Nichols TE, Miller KL, Robson MD, Jones DK, Klein JC, Bartsch AJ, Behrens TE. Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. Nat Protoc. 2007; 2(3):499–503. [PubMed: 17406613]

Snitz BE, Macdonald AW 3rd, Carter CS. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr Bull. 2006; 32(1):179–194. [PubMed: 16166612]

Spoletini I, Cherubini A, Banfi G, Rubino IA, Peran P, Caltagirone C, Spalletta G. Hippocampi, thalami, and accumbens microstructural damage in schizophrenia: a volumetry, diffusivity, and neuropsychological study. Schizophr Bull. 2011; 37(1):118–130. [PubMed: 19542526]

Stuss DT, Murphy KJ, Binns MA, Alexander MP. Staying on the job: the frontal lobes control individual performance variability. Brain. 2003; 126(Pt 11):2363–2380. [PubMed: 12876148]

Szeszko PR, Robinson DG, Ashtari M, Vogel J, Betensky J, Sevy S, Ardekani BA, Lencz T, Malhotra AK, McCormack J, Miller R, Lim KO, Gunduz-Bruce H, Kane JM, Bilder RM. Clinical and neuropsychological correlates of white matter abnormalities in recent onset schizophrenia. Neuropsychopharmacology. 2008; 33(5):976–984. [PubMed: 17581532]

Takei K, Yamasue H, Abe O, Yamada H, Inoue H, Suga M, Muroi M, Sasaki H, Aoki S, Kasai K. Structural disruption of the dorsal cingulum bundle is associated with impaired Stroop performance in patients with schizophrenia. Schizophr Res. 2009; 114(1–3):119–127. [PubMed: 19505800]

Thomas C, Moya L, Avidan G, Humphreys K, Jung KJ, Peterson MA, Behrmann M. Reduction in white matter connectivity, revealed by diffusion tensor imaging, may account for age-related changes in face perception. J Cogn Neurosci. 2008; 20(2):268–284. [PubMed: 18275334]

Vinogradov S, Poole JH, Willis-Shore J, Ober BA, Shenaut GK. Slower and more variable reaction times in schizophrenia: what do they signify? Schizophr Res. 1998; 32(3):183–190. [PubMed: 9720123]

Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, van Zijl P, Mori S. Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage. 2007; 36(3):630–644. [PubMed: 17481925]

Walterfang M, McGuire PK, Yung AR, Phillips LJ, Velakoulis D, Wood SJ, Suckling J, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGorry PD, Pantelis C. White matter volume changes in people who develop psychosis. Br J Psychiatry. 2008; 193(3):210–215. [PubMed: 18757979]

Wang K, Cheung EF, Gong QY, Chan RC. Semantic processing disturbance in patients with schizophrenia: a meta-analysis of the N400 component. PLoS One. 2011; 6(10):e25435. [PubMed: 22022395]

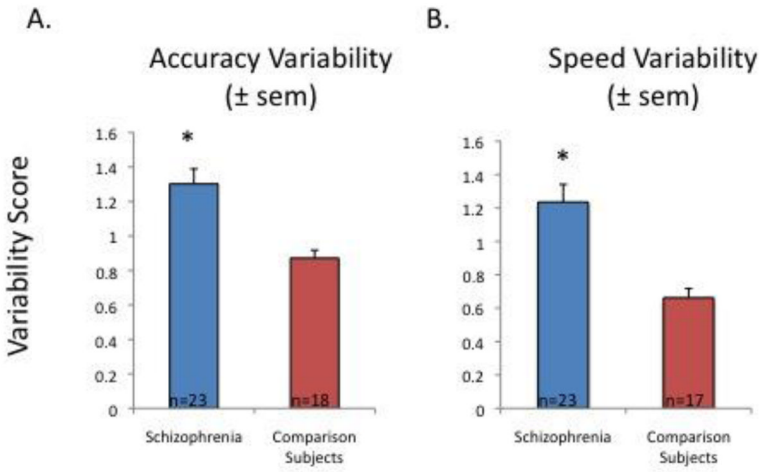

Figure 1.

Within-individual variability (WIV) on a computerized neurocognitive battery. WIV is calculated across a minimum of five neurocognitive tasks. Higher variability scores are indicative of poorer overall performance. *p<.01.

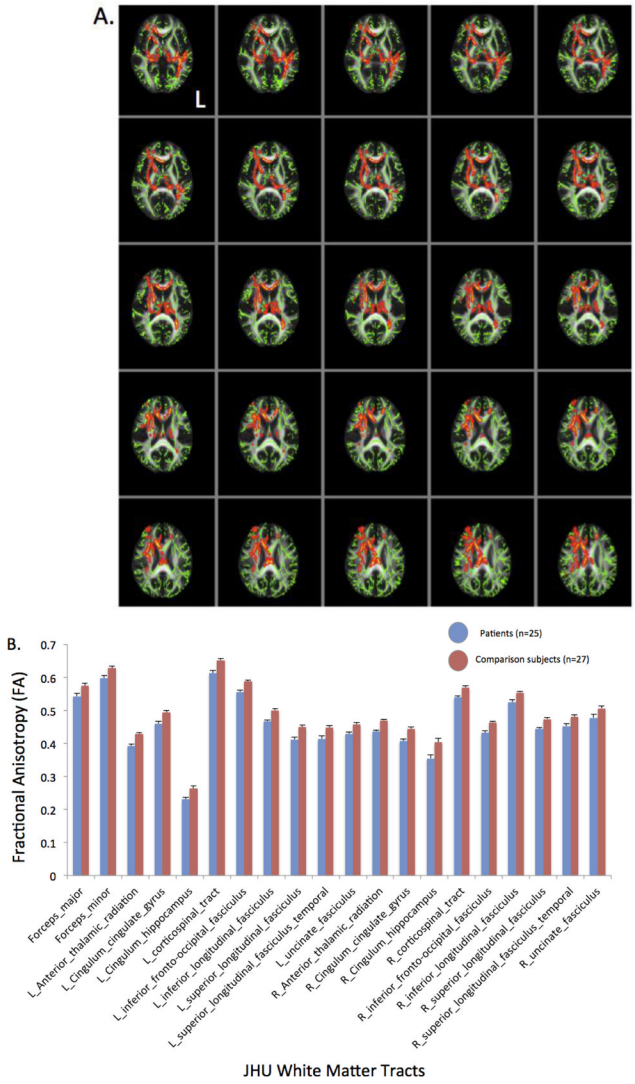

Figure 2.

A. Regions of significant reduction in schizophrenia patients (n=25) relative to healthy comparison subjects (n=27). Results are shown overlaid on the standard FMRI58 FA template with the group mean FA skeleton overlaid (green). Regions showing a significant reduction in FA ($p<.05$, TFCE corrected) in patients as compared to healthy comparison subjects are displayed in red with local enhancement for better viewing in radiological convention (right-left). These results are adjusted for age. B. Significant differences in mean fractional anisotropy for patients (red) and controls (blue) in the major white matter tracts as defined by the JHU White Matter Atlas. Note: L= left hemisphere; R=right hemisphere.

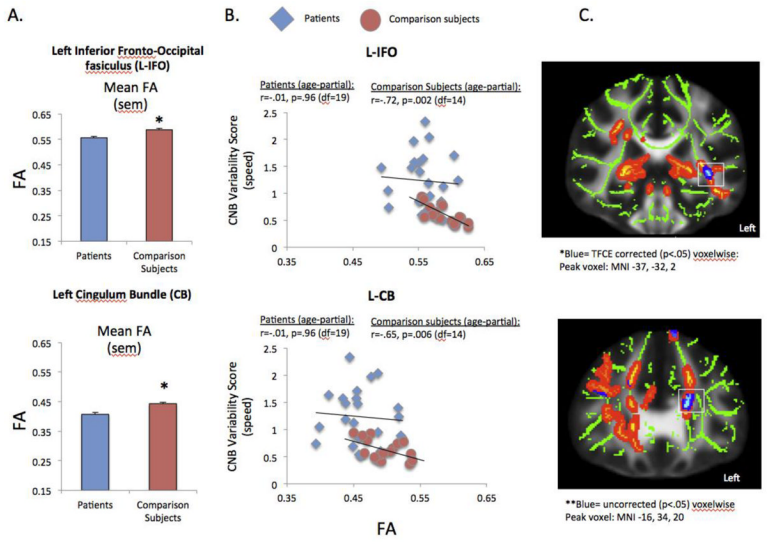

Figure 3.

Correlation between speed WIV and FA in comparison subjects and schizophrenia patients. A) Mean FA in patients and controls in the inferior fronto-occipital fasciculus (IFO) and cingulum bundle (CB); *p<.05. B) Correlation in the inferior fronto-occipital fasciculus (IFO) and cingulum bundle (CB) in patients and controls. FA values were extracted from the comparison>patient analysis from the JHU white matter tract regions-of-interest. C. Significant correlation between speed WIV and FA in healthy controls in a voxelwise analysis for the left inferior fronto-occipital fasciculus and left cingulum bundle (MNI coordinates reported for peak voxel). Regions are displayed with local enhancement for better viewing in radiological convention (right-left).

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)
[a] DTI motion (mm)	0.33 (0.11)	0.37 (0.08)
Medication		
Atypicals		21
Typicals	n/a	3
Unmedicated		1

[a] a metric of average relative motion displacement from previous time point using Jenkinson's method (2002).

* p<.05: healthy comparison subjects > patients with schizophrenia

** correlated with speed WIV (r=.45, p<.05; n=20)