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White matter structural integrity differs between people with schizophrenia and healthy groups as a function of cognitive control

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ABSTRACT

A behavioral hallmark of schizophrenia is poor cognitive control. Recent evidence suggests that problems with cognitive control in schizophrenia are related to disconnectivity along major white matter fibers. Although deficits of cognitive control are common in schizophrenia, a proportion of otherwise healthy subjects show poor cognitive control performance. The present study sought to address this potential confound by comparing white matter integrity between a group with schizophrenia and otherwise healthy individuals with either high or low levels of cognitive control (based on working memory span performance). Diffusion tensor imaging was used to evaluate white matter integrity in 24 participants with schizophrenia, 24 healthy participants with high cognitive control (HCC), and 25 healthy participants with low cognitive control (LCC). To test for differences in fractional anisotropy (FA) across major white matter fiber tracts, a voxelwise region of interest analysis was conducted in standardized brain space. In a separate analysis, regions of interest were manually drawn in native brain space to isolate superior longitudinal fasciculus (SLF), a tract implicated in cognitive control performance. The voxelwise analysis demonstrated widespread lower FA in the schizophrenia group compared to the HCC group. With a high degree of concordance, the manual ROI analysis revealed lower FA in the schizophrenia group compared to the HCC group. Taken together, these results provide evidence to suggest that structural differences identified between healthy groups and schizophrenia may not be entirely specific to the disease process and can vary as a function of cognitive control capacity in the comparison group.

1. Introduction

Schizophrenia is characterized by problems with cognitive control. Recent diffusion tensor imaging (DTI) evidence suggests that deficits in cognitive control in people with schizophrenia are associated with white matter structural deviations across the brain (Liu et al., 2013), particularly in frontal and parietal regions (Karlsgodt et al., 2008). Similar frontal and parietal regions are implicated in poor cognitive control in healthy individuals, with lower cognitive control scores linked to lower structural integrity of fronto-parietal connections (Burzynska et al., 2011). Although deficits of cognitive control are a behavioral hallmark of schizophrenia, some healthy subjects from the general population show poor cognitive control performance and similar deficits in the underlying white matter substrates (Hutton and Ettinger, 2006; Karlsgodt et al., 2008). As such, cognitive control ability may be a mediating factor in typical comparisons between healthy individuals and people with schizophrenia, with variance in structural differences related to cognitive control rather than to the disease process of schizophrenia. The present study sought to test this potential confound by identifying groups of healthy participants with either a high level of cognitive control (HCC) or low level of cognitive control (LCC) based on working memory performance and compare white matter structure across HCC, LCC, and a group of subjects with chronic schizophrenia.

Although the etiologies of schizophrenia have yet to be identified, one theory is that schizophrenia is a disease of disconnectivity (Friston, 1998). DTI is well suited to explore this theory, as it allows for assessment of the relationships between structural disconnectivity and cognitive dysfunction. Present day findings using DTI, however, have provided mixed results as to the white matter structural connections related to schizophrenia symptomatology (see Kubicki et al., 2007 for review). Some authors suggest that discrepancies in white matter findings may be due to heterogeneity of patient characteristics (Liu et al., 2013) or methodological factors, including inconsistencies in data acquisition, processing, or analysis (Kubicki et al., 2007; Whitford et al., 2011). This drives a need to systematically remove confounds of both participant and methodological variety from DTI

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analyses of schizophrenia. The present study sought to accomplish this by accounting for the level of cognitive control in the healthy comparison groups through stringent participant matching criteria and by comparing results from multiple DTI analysis types on a single dataset.

Despite inconsistent DTI findings of schizophrenia-specific alterations in white matter, the superior longitudinal fasciculus (SLF; a fronto-parietal tract) has emerged as one of the most reliably identified. Kubicki and Shenton (2009) estimate that SLF is the most consistently identified structure in DTI voxel-based morphometric (VBM) studies, with 33% of the studies reporting schizophrenia-related reductions in SLF integrity. SLF fractional anisotropy (FA; a scalar measure of diffusivity) is reduced in people with schizophrenia as compared to controls (Karlsgodt et al., 2008). Additionally, higher FA values in SLF are correlated with better cognitive control performance in schizophrenia and healthy controls (Karlsgodt et al., 2008). The SLF connects frontal and parietal regions which are structurally and functionally identified as regions mediating cognitive control in healthy samples (Burzynska et al., 2011; Schaeffer et al., 2013). In view of these findings, variability in structural integrity of the SLF likely mediates cognitive control in both schizophrenia and healthy groups.

Based on evidence linking cognitive control and white matter integrity, we sought to test the following hypotheses: (1) That white matter structural integrity (as measured by FA and radial diffusivity (RD)) across the brain would demonstrate the following pattern across groups: for FA, schizophrenia would show lower values than HCC, but not differ from LCC. For RD (which typically shows an inverse relationship with FA), schizophrenia would show higher values than HCC, but schizophrenia and LCC would not differ. (2) That the SLF, a tract identified as being involved in cognitive control, would differ in FA and RD between HCC and the groups with low cognitive control (LCC and schizophrenia), but not between the schizophrenia and LCC groups, who show more similar cognitive control performance. To test these hypotheses, the present study used two complementary DTI analysis approaches. In the first analysis, voxelwise FA values were compared across major white matter tracts using a region of interest approach. In a second analysis, manual fiber tracing was used to isolate bilateral SLF in DTI native space, with the goal of mitigating the effects of spatial transformation and testing a hypothesis (hypothesis 2 above) specific to the SLF. By using these spatially discrete methods (voxelwise in standard space and fiber tracing in native space), we sought to test if between group differences were robust and not a function of analysis type. In summary, the present study sought to identify schizophrenia-specific alterations in white matter integrity though the use of highly specified control groups (HCC and LCC) and two complementary DTI analyses.

2. Method

2.1. Participants

Twenty four subjects with schizophrenia were recruited through outpatient centers in Athens and Augusta, GA, USA. For the comparison groups, a large initial sample of healthy people ($N = 235$; mean age = 31.0, SD = 11.5; 53% female) was recruited via newspaper ads and flyers posted around Athens, GA, USA to participate in the cognitive control screening session of this study. Based on a distribution of cognitive control performance from this large sample, 24 HCC and 25 LCC participants (age matched to schizophrenia subjects; see Table 1 for demographics) returned for DTI acquisition along with the schizophrenia subjects. HCC and LCC participants had no history of psychiatric illness. All participants were interviewed using the Non-Patient or Patient edition of the Structured Clinical Interview for DSM-IV (First et al., 2002a, 2002b) and were free from severe head trauma, or current drug or alcohol abuse (via self-report). Participants were screened for contraindications for MRI (e.g., pacemaker or metal in body). Participants provided written informed consent and were compensated $20 per hour for their participation. The University of Georgia Institutional Review Board approved this study.

Table 1
Participant demographics.

	HCC	LCC	SZ
N	24	25	24
Age (years)	32.6 (13.6)	32.6 (10.3)	38.5 (9.1)
Gender (N female)	6	18	13
Handedness (N right, left, ambidextrous)	21, 2, 1	20, 5, 0	19, 3, 2
Anti-psychotic (atypical, typical, both; N on)	0, 0, 0	0, 0, 0	14, 3, 1
Anti-cholinergics (N on)	0	0	1
Anti-depressants (N on)	0	0	5
Anti-anxiety (N on)	1	0	3

Patient medication: 18 anti-psychotics only, 1 anti-psychotics and anti-cholinergics, 3 on anti-psychotics and anti-depressants, 2 anti-depressants only, and 3 anti-psychotics and anti-anxiety.

2.2. Materials and procedure

2.2.1. Cognitive control screening

Following initial screening, potential healthy comparison group participants ($N = 235$) completed three computer-administered complex span tasks (operation span, reading span, and symmetry span; Unsworth et al., 2005; Unsworth and Spillers, 2010) from which a composite score was derived. The operation span task consists of remembering letters while solving unrelated math operations, the reading span task consists of remembering letters while reading unrelated sentences (and making judgments about them), and the symmetry span task requires the recall of spatial sequences of red squares within a matrix while performing a symmetry-judgment task. The score for each task is the number of to-be-remembered items recalled in the correct order. For cognitive control composite scores, each participant's score was z-transformed (based on the means and standard deviations from a previously defined distribution of over 500 participants; Unsworth et al., 2012) and the three z-scores were averaged. This composite score is a broad measure of cognitive control and reduces the probability that task-specific variance is influencing categorization of cognitive control. Only individuals scoring in the upper (HCC, $z \geq 0.57$) and lower (LCC, $z \leq -0.38$) quartiles were asked to participate in the diffusion MRI portion of the study.

2.2.2. Diffusion MRI data acquisition

Images were acquired at the University of Georgia on a 3T GE Signa Excite HDx MRI system (General Electric Medical Systems, Milwaukee, Wisconsin, USA) with an 8 channel head-coil (Model 800152; Invivo Corporation, Gainesville, Florida, USA). During scanning, head positions were stabilized with foam padding. Diffusion images were acquired using an echo planar imaging sequence (acquisition matrix = 128×128, 55 interleaved slices, voxel size = $2 \times 2 \times 2.4$ mm, FOV = 256×256 mm, TR = 16,100 ms, TE = min-full, 3 $b = 0$ images, 30 diffusion weighted images, $b = 1000$ s/mm^2).

2.2.3. Diffusion MRI preprocessing and analysis

Raw diffusion images were converted from GE DICOM format to NIFTI format using the dcm2nii tool (Rorden, 2007). For each subject, volumes were visually inspected for motion artifacts; volumes distorted by motion were removed from the image series and b value/vector tables (1.5% of total volumes removed; average number of volumes/subject removed = 1). Diffusion tensor image analysis was conducted using the FMRIB Software Library (University of Oxford, Oxford, England; Smith et al., 2004). Diffusion images were corrected for eddy-current-induced distortions. Simple head motion was corrected through an affine registration to the first (of three) non-diffusion weighted images ($b = 0$) acquired prior to the diffusion weighted volumes. Nonbrain tissue was removed using the Brain Extraction Tool (Smith, 2002).