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A combined diffusion tensor imaging and magnetic resonance spectroscopy study of patients with schizophrenia

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ABSTRACT

Diffusion tensor imaging (DTI) studies in schizophrenia consistently show global reductions in fractional anisotropy (FA), a putative marker of white matter integrity. The cingulum bundle, which facilitates communication between the anterior cingulate cortex (ACC) and hippocampus, is frequently implicated in schizophrenia. Magnetic resonance spectroscopy (MRS) studies report metabolic abnormalities in the ACC and hippocampus of patients. Combining DTI and MRS offers exploration of the relationship between cortical neuronal biochemistry and the integrity of white matter tracts connecting specific cortical regions; however, few studies have attempted this in schizophrenia. Twenty-nine schizophrenia patients and twenty controls participated in this 3 T imaging study in which we used DTI and tract-based spatial statistics (TBSS) to assess white matter integrity and MRS to quantify metabolites in the ACC and hippocampus. We found FA reductions with overlapping radial diffusivity (RD) elevations in patients in multiple tracts, suggesting white matter abnormalities in schizophrenia are driven by loss of myelin integrity. In controls, we found significant negative correlations between hippocampal *N*-acetylaspartate/creatine and RD and axial diffusivity (AD) as well as a significant negative correlation between FA and ACC glutamate + glutamine/creatine in the hippocampal part of the cingulum bundle. It is possible that the extent of myelin damage could have resulted in the absence of DTI–MRS correlations in our patient group. In conclusion, we demonstrate the potential utility of a multi-modal neuroimaging approach to help further our understanding of the relationship between white matter microstructure and neurochemistry in distinct cortical regions connected by white matter tracts.

1. Introduction

Schizophrenia is a complex and disabling mental disorder characterized by disturbances in perception, behavior, and cognition. According to the disconnection hypothesis of schizophrenia, these functional disturbances may be the result of abnormal interactions between spatially distinct brain regions that are structurally connected by white matter tracts (Andreasen, 1999; Bartzokis, 2002; Friston, 1998). Support for this hypothesis has come from numerous postmortem reports of white matter abnormalities (Hof et al., 2003; Stark et al., 2004; Uranova et al., 2001, 2004; Vostrikov et al., 2007), decreased expression of myelin-related genes and proteins (Flynn et al., 2003; Hakak et al., 2001; McCullumsmith et al., 2007), and recent functional neuroimaging studies that have shown aberrations in the temporal correlations of brain activity between different regions (Lynall et al., 2010; Skudlarski et al., 2010; Whitfield-Gabrieli et al., 2009). Furthermore, diffusion tensor imaging (DTI) studies of schizophrenia have consistently shown global reductions in fractional anisotropy (FA), a putative marker of white matter integrity, in the fasciculi connecting discrete regions, particularly the fronto-temporal and fronto-parietal connections (Fitzsimmons et al., 2013; Kubicki et al., 2007; Kuswanto et al., 2012; Pettersson-Yeo et al., 2011; Samartzis et al., 2014).

The cingulum bundle is one fronto-temporal connection frequently implicated in schizophrenia. This major association tract contains fibers connecting the frontal, parietal, and temporal cortices and facilitates communication between two important components of the cortico-limbic network: the anterior cingulate cortex (ACC) and the hippocampus. We previously demonstrated the role of the ACC and hippocampus in psychosis and treatment response (Lahti et al., 2006, 2009) and recently reported alterations in function, neurochemistry, and volume in these regions in schizophrenia patients (Kraguljac et al., 2013; Reid et al., 2010). Furthermore, others have shown that integrity of the cingulum bundle is correlated with measures of memory, attention, and executive function (Kubicki et al., 2009, 2005; Lim et al., 2006; Nestor et al., 2013, 2007; Roalf et al., 2013; Takei et al., 2009), suggesting white matter disruptions may compromise cognitive processes in schizophrenia.

While DTI studies have provided abundant evidence of FA reductions in schizophrenia patients, only a few studies have attempted to

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relate the microstructural differences measured by DTI to the underlying neurochemistry measured by proton magnetic resonance spectroscopy (MRS) (Chiappelli et al., 2015; Rowland et al., 2009; Steel et al., 2001; Tang et al., 2007). These studies focused primarily on MRS measurements in predominantly white matter rather than in related cortical regions. This is an important distinction because aberrant functional interactions between discrete regions could stem from isolated cortical neuronal abnormalities, from abnormal white matter connections, or from both. Thus, an important question is to determine how these alterations are related to each other.

MRS permits the non-invasive measurement of neurometabolites, such as *N*-acetylaspartate (NAA) and glutamate. NAA is an abundant amino acid almost exclusively localized within neurons. Although the exact physiological nature of NAA remains a topic of investigation, NAA appears to have a role in neuronal osmoregulation (Baslow, 2002, 2003a, 2003b) and myelin synthesis (Arun et al., 2010; Chakraborty et al., 2001; Madhavarao et al., 2005; Moffett et al., 2007; Wang et al., 2009). NAA produces a robust MRS signal that is a putative marker of neuronal health (Moffett et al., 2007). MRS evidence suggests NAA is reduced in frontal and hippocampal regions in schizophrenia patients (Kraguljac et al., 2012b). Glutamate, on the other hand, is the major excitatory neurotransmitter. Recent MRS studies suggest levels of glutamate and/or glutamine are elevated in the prodromal and early stages of schizophrenia (Bustillo et al., 2010; de la Fuente-Sandoval et al., 2013; de la Fuente-Sandoval et al., 2011; Theberge et al., 2002, 2007), in unmedicated patients (Kegeles et al., 2012; Kraguljac et al., 2013), and in non-remitted symptomatic first-episode patients following treatment (Egerton et al., 2012) but unchanged or reduced below normal in chronic and medicated patients (Kraguljac et al., 2012a; Lutkenhoff et al., 2010; Reid et al., 2010; Rowland et al., 2013; Theberge et al., 2003). Elevated glutamate levels may reflect an excitotoxic process that potentially accounts for the observed structural deficits in schizophrenia (Kraguljac et al., 2013; Olney et al., 1999) that in turn may manifest as NAA reductions.

Two of the previous studies combining DTI and MRS in schizophrenia have reported correlations between FA and NAA in white matter in patients and controls (Steel et al., 2001; Tang et al., 2007), which is consistent with a recent study in healthy individuals that found white matter NAA explained a significant proportion of variability in FA (Wijtenburg et al., 2013). However, despite the evidence for glutamatergic abnormalities in schizophrenia, these studies either did not report correlations (Steel et al., 2001; Tang et al., 2007) or find evidence of correlations (Rowland et al., 2009) between glutamate and FA. Furthermore, none of these studies reported axial diffusivity (AD) and radial (RD) diffusivity, which have been linked to axonal and myelin integrity, respectively (Song et al., 2003, 2002), and may better reflect underlying pathology than FA alone. In fact, schizophrenia patients appear to have elevated RD in the presence of reduced FA without abnormal AD (Abdul-Rahman et al., 2011; Ashtari et al., 2007; Lee et al., 2013; Levitt et al., 2012; Ruef et al., 2012; Scheel et al., 2013; Seal et al., 2008), suggesting FA differences may be driven by loss of myelin integrity.

In the present study, we sought to investigate the relationship between white matter microstructure and gray matter neurometabolites in schizophrenia patients. We used DTI to quantify FA, AD, and RD across the whole brain and proton MRS to quantify NAA, glutamate and glutamine (Glx), and choline in the ACC and hippocampus. First, to replicate previous DTI studies, we sought to determine whether patients showed microstructural abnormalities compared to healthy controls. We hypothesized that patients would have reduced FA and elevated RD. Second, we planned to explore whether white matter integrity of the cingulum was related to regional cortical neurochemistry. Since NAA is presumed to be a marker of neuronal integrity, we hypothesized that NAA would positively correlate with FA and negatively correlate with RD, reflecting a relationship between cortical neuronal health and white matter integrity. Given the evidence of elevated glutamate levels in schizophrenia that may account for structural deficits (Kraguljac et al., 2013; Olney et al., 1999), we hypothesized that abnormalities in white matter integrity, that is reduced FA and elevated RD, would be associated with higher levels of Glx in patients.

2. Methods

2.1. Participants

29 patients with schizophrenia and schizoaffective disorder (14 unmedicated and 15 medicated) and 20 controls were included in this study. Patients were recruited from the psychiatry clinics and emergency room at the University of Alabama at Birmingham. Of the 14 unmedicated patients, 6 were antipsychotic-naïve, and 8 were off medications for 21.3 ± 40.8 months (range: 0.5–120 months). Controls without personal or family history in a first-degree relative of significant DSM-IV-TR Axis I disorders were recruited by advertisement in the university's newspaper. Exclusion criteria were major medical conditions, substance abuse within 6 months of imaging, neurologic disorders, previous serious head injury with a loss of consciousness for more than 2 min, and pregnancy. Patients' symptom severity was assessed using the 20-item Brief Psychiatric Rating Scale (BPRS) and its positive and negative subscales. Diagnoses were established by a psychiatrist and confirmed through review of patient medical records and the Diagnostic Interview for Genetic Studies (DIGS). All participants gave written informed consent. Before signing consent, all patients were evaluated for their ability to provide consent by completing a questionnaire probing their understanding of the study. The Institutional Review Board of the University of Alabama at Birmingham approved this study.

2.2. MR imaging

Imaging was performed on a 3 T head-only MRI scanner (Siemens Magnetom Allegra, Erlangen, Germany) using a circularly polarized transmit/receive head coil. A sagittal scan was acquired for anatomical reference (MPRAGE, TR/TE/TI = 2300/3.93/1100 ms, flip angle = 12°, matrix = 256 × 256, 1 mm isotropic voxels). Two diffusion-weighted runs were acquired, each non-collinearly distributed along 30 directions [b = 1000 s/mm^2, TR/TE = 9200/96 ms, field of view = 246 × 246 mm, matrix = 112 × 112, 60 slices, interleaved acquisition, 2.2 mm slice thickness with no gap (2.2 × 2.2 × 2.2 mm voxel size), bandwidth = 1396 Hz]. Five images with no diffusion gradients (b0; b = 0 s/mm^2) were also acquired. Slices were aligned along the anterior commissure–posterior commissure line.

MRS data were also acquired from the ACC of 26 patients and 18 controls and from the hippocampus of 23 patients and 18 controls. The majority of these participants have been included in our previous MRS studies (Hutcheson et al., 2012; Kraguljac et al., 2012a; Kraguljac et al., 2013). T1-weighted images (GRE, TR/TE = 250/3.48 ms, flip angle = 70°, 5 mm slice thickness, 1.5 mm gap, matrix = 512 × 512) were acquired to prescribe MRS voxels in the bilateral dorsal ACC (2.7 × 2.0 × 1.0 cm) and the left hippocampus (2.7 × 1.5 × 1.0 cm) as described previously (Hutcheson et al., 2012; Reid et al., 2010). Manual shimming was performed, and chemical shift selective pulses were used to suppress the water signal. Water-suppressed spectra were collected with the point-resolved spectroscopy sequence [PRESS; TR/TE = 2000/80 ms (Schubert et al., 2004), 1200 Hz spectral bandwidth, 1024 points, ACC: 256 averages (8 min 32 s), hippocampus: 640 averages (21 min 20 s)].

2.3. DTI processing

Pre-processing was performed with FMRIB Software Library (FSL, version 4.1) (Smith et al., 2004). The 2 30-direction datasets and 5 b0 volumes were merged, eddy current-corrected using the first b0 volume as a reference, and skull-stripped. The gradient vectors were corrected for slice angulation and image rotation (Leemans and Jones, 2009).