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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 3T 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

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CONFLICT OF INTEREST

The authors report no biomedical financial interests or potential conflicts of interest.

CONTRIBUTORS

MAR contributed to study design, data acquisition, analysis, and interpretation and wrote the manuscript. DMW contributed to data acquisition and interpretation. NVK contributed to data interpretation and edited the manuscript. As principal investigator, ACL was responsible for study design and oversaw data acquisition and analysis as well as drafting and critical revision of the manuscript.

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matter microstructure and neurochemistry in distinct cortical regions connected by white matter tracts.

Keywords

diffusion tensor imaging; magnetic resonance spectroscopy; anterior cingulate cortex; hippocampus; *N*-acetylaspartate; cingulum

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; Uranova et al., 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; Lahti et al., 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; Kubicki et al., 2005; Lim et al., 2006; Nestor et al., 2013; Nestor et al., 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 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

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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, b) 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; Theberge et al., 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; Song et al., 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

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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 minutes, 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 3T 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

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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 sec), hippocampus: 640 averages (21 min 20 sec)].

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). Images were visually inspected for sudden motion artifacts. Bad volumes were removed from further analyses for 3 patients and 1 control, and the gradient tables for these participants were updated accordingly. The maximum number of bad volumes was 3, and in no case was the same gradient direction removed from both 30-direction datasets. FSL's dtifit was used to calculate maps of FA. AD and RD maps were calculated from the eigenvalues [AD = λ_1; RD = $(\lambda_2 + \lambda_3)/2$].

Between-group analyses of the FA, AD, and RD data were performed with FSL's tract-based spatial statistics (TBSS) (Smith et al., 2006). All data were aligned into a common space using the nonlinear registration tool FNIRT and a study-specific target image (Andersson et al., 2007a, b). The mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each participant's aligned FA, AD, and RD data were then projected onto this skeleton. FSL's randomise with 10,000 permutations was used to compute voxelwise statistics on the skeletonised FA, AD, and RD, controlling for age and smoking status (Gons et al., 2011; Zhang et al., 2010). TBSS was also used to correlate the MRS metabolite levels with DTI measures, controlling for age, smoking status, and the gray matter fraction in the MRS voxel (see section 2.4 MRS Processing). MRS metabolites were correlated only within the bilateral cingulum, including the cingulate and hippocampal parts. The cingulum mask was created from the whole-group mean FA skeleton mask using the Johns Hopkins University Probabilistic Tractography and White Matter Labels Atlases (distributed with FSL) as guides. In addition, whole-brain DTI measures were correlated with BPRS symptom scores in the patient group. Threshold-free cluster enhancement (TFCE) was used to correct for multiple comparisons, and statistical significance was set at FWE-corrected $p < 0.05$. FSL's cluster command was used to identify the t- and p-values, the cluster sizes, and the MNI coordinates for the peak clusters of significance.

2.4 MRS Processing

MRS spectra were processed in jMRUI (version 3.0) (Naressi et al., 2001) as described previously (Reid et al., 2010). The residual water peak was removed using the Hankel-Lanczos singular values decomposition filter. Spectra were quantified in the time domain by AMARES (advanced method for accurate, robust, and efficient spectral fitting) using prior knowledge derived from in vitro and in vivo metabolite spectra as described previously (Kraguljac et al., 2013). Glx, NAA, and choline (Cho) were quantified with respect to

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creatine (Cr). Signal-to-noise ratio (SNR) and line widths (full-width at half maximum, FWHM) were used to assess spectral quality. Cramer-Rao lower bounds (CRLB) were used as a measure of uncertainty of the fitting procedure. Reproducibility of measurements from the ACC and hippocampus using these methods has been demonstrated previously (Hutcheson et al., 2012; Reid et al., 2010).

To calculate the fraction of gray matter in the MRS voxel, the structural MPRAGE image was co-registered to the MRS localizer images and then segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using SPM8. Binary images of the MRS voxels were created in MATLAB using the MRS raw data headers, and these images were then used to mask the tissue types. Tissue volumes (mL) were calculated in MATLAB. The GM fraction was defined as the proportion of GM to total tissue within the MRS voxel: GM/(GM+WM).

2.5 Statistical Analysis

Statistical analyses were performed in SPSS (version 20). Independent-samples *t*-tests and *chi*-square tests, as appropriate, were used to compare demographics, MRS metabolite levels, SNR, and FWHM between patients and controls. Statistical significance for all tests was $p < 0.05$.

3. RESULTS

3.1 Participants & MRS

Patients and controls did not significantly differ in age, sex, smoking status, parental occupation, MRS metabolite levels, SNR, or FWHM (Table 1). MRS results remained non-significant when controlling for age, smoking, and GM fraction (all $p > 0.29$). CRLB for all spectra were less than 20%.

3.2 TBSS – Patients versus Controls

Patients showed reduced FA in many tracts (Figure 1 and Table 2) with elevated RD in most regions overlapping the FA differences (Figure 2 and Table 3). Given the widespread group differences in FA and RD, many of the significant tracts grouped together in large clusters; therefore, tracts in Figure 1 and Figure 2 were identified using the Johns Hopkins University Probabilistic Tractography and White Matter Labels Atlases (distributed with FSL). FA reductions were observed in bilateral anterior thalamic radiation, bilateral corticospinal tract, bilateral cingulum (cingulate gyrus part), right cingulum (hippocampus part), forceps major, forceps minor, bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral uncinate fasciculus, body of the corpus callosum, genu of the corpus callosum, splenium of the corpus callosum, bilateral superior corona radiata, and fornix. RD elevations were observed in bilateral anterior thalamic radiation, left corticospinal tract, left cingulum (cingulate gyrus part), right cingulum (hippocampus part), forceps major, forceps minor, bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral uncinate fasciculus, body of the corpus callosum, genu of the corpus callosum, splenium of the corpus callosum, bilateral superior corona radiata, and fornix. AD did not significantly differ between the groups.

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In the cingulum, in particular, FA was significantly reduced in patients in the bilateral cingulate gyrus portion of the bundle but only in the right side of the hippocampal part. RD differences in the cingulum were localized primarily to the left cingulate gyrus portion of cingulum and the right anterior cingulate and posterior hippocampal parts. FA was also reduced in the midbrain white matter adjacent to the left substantia nigra and ventral tegmental area, corresponding to projections of the anterior thalamic radiation, but there were no differences in RD in this region.

3.3 TBSS – Correlations with MRS & BPRS

In controls but not patients, there was a significant negative correlation between RD in the left anterior hippocampal part of the cingulum and NAA/Cr measured from the left hippocampus (Figure 3A and Table 4). AD in the same region was also negatively correlated with hippocampal NAA/Cr (Figure 3B and Table 4). Glx/Cr measured from the ACC was also negatively correlated with FA in the hippocampal part of the cingulum (Figure 3C and Table 4). In patients, NAA/Cr and Glx/Cr measurements from the hippocampus and ACC were not correlated with DTI measures. To determine whether these correlations were specific to the cingulum, a mask of the fornix, which is the output tract of the hippocampus, was created, and hippocampal NAA/Cr and Glx/Cr were correlated with DTI measures in the fornix. There were no significant correlations in the fornix of controls or patients. Using Bonferroni correction with a revised $p < 0.0125$ (0.05/4 to reflect two regions and two metabolites), none of the DTI–MRS correlations survived multiple comparisons correction.

In patients, BPRS scores and DTI measures were not significantly correlated.

4. DISCUSSION

In this study, we combined DTI and MRS to examine the relationship between white matter structural integrity of the cingulum and related neurochemistry in cortico-limbic regions connected by this tract. Using TBSS, we found FA reductions in patients in multiple tracts, including the cingulum, with considerable overlap of RD elevations in many of the same tracts. In controls but not patients, we found a significant negative correlation between hippocampal NAA/Cr and RD and AD in the hippocampal part of the cingulum as well as a negative correlation between ACC Glx/Cr and FA in the same region.

Since we were focusing on the cingulum bundle in this study, we considered using deterministic tractography but chose TBSS for several reasons. First, it allowed us to perform whole-brain group comparisons to replicate previous findings. TBSS facilitates group comparisons by focusing on the center of tracts common to the group (individual tract differences are averaged out); this “mean FA skeleton” is an alignment-invariant tract representation. Second, while deterministic tractography would have allowed us to look beyond the center of the tract to identify more focal changes, variability could be introduced during the manual placement of the regions of interest needed to reconstruct the fiber bundle. Third, with deterministic tractography, in order to perform the correlations with MRS, we would be required either to average FA across an entire bundle or to implement an along-tract analysis. With the former, focal differences may be averaged out, and with the latter we would again face the issue of aligning bundles across participants. Finally,

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deterministic tractography also has the limitation of edge effects, which means the ends of the fiber bundle could vary considerably from participant to participant depending on how the bundle is reconstructed and where the streamlines composing the bundle terminate.

Consistent with previous studies, we found FA reductions in fronto-temporal, fronto-parietal, and fronto-occipital tracts (Caprihan et al., 2015; Fitzsimmons et al., 2013; Samartzis et al., 2014; Skudlarski et al., 2013) with concurrent elevations in RD and without significant alterations in 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). White matter abnormalities identified by TBSS have been remarkably consistent across illness stage and medication status. FA reductions and RD elevations have been observed in medication-naïve first-episode patients (Alvarado-Alanis et al., 2015), medicated first-episode patients (Lee et al., 2013), and medicated patients with chronic schizophrenia (Asami et al., 2014; Holleran et al., 2014). These studies, along with our findings, suggest FA differences could be primarily driven by disruption of myelin integrity (Song et al., 2003; Song et al., 2002). Interestingly, the fronto-temporal and fronto-parietal connections are among the last fasciculi to fully myelinate around the common age-of-onset of schizophrenia (Whitford et al., 2012). Dysmyelination in fasciculi could potentially lead to conduction delays of axon potentials, resulting in temporal discoordination between brain regions (Whitford et al., 2012) as observed in functional connectivity studies (Lynall et al., 2010; Skudlarski et al., 2010; Whitfield-Gabrieli et al., 2009). This asynchrony of function may in turn contribute to some of the perceptual, behavioral, and cognitive disturbances characteristic of schizophrenia.

We also observed FA reductions in the midbrain white matter adjacent to the left substantia nigra and ventral tegmental area, corresponding to connections of the anterior thalamic radiation linking the midbrain with the prefrontal cortex (Menke et al., 2010). Our finding is consistent with studies showing reduced FA (Alvarado-Alanis et al., 2015; Cheung et al., 2008) or elevated RD (Lee et al., 2013) in the midbrain of first-episode patients. This is important because the substantia nigra and ventral tegmental area are the primary sites of dopamine synthesis, and patients have elevated dopamine release in the striatum (Abi-Dargham et al., 1998; Laruelle et al., 1996), one of the targets of midbrain dopaminergic neurons. It is possible that dysmyelination of these neurons could contribute to psychotic symptoms (Whitford et al., 2012). However, we must point out that we did not observe significant differences in RD or AD in the midbrain itself, possibly suggesting myelin damage or axonal damage is not present there. Perhaps dysmyelination in other regions of the mesocorticolimbic circuit could affect the white matter of the midbrain. For example, we observed elevated RD in the medial thalamus, anterior limb of the internal capsule, and prefrontal white matter, all of which are part of the connections linking the midbrain to the prefrontal cortex. Alternatively, some other pathology not detected by measurements of RD and AD may be present in the midbrain. Another possibility is that we did not have adequate power to detect RD or AD changes in this midbrain region.

To our knowledge, only a few studies of schizophrenia have combined DTI and MRS. Steel et al. (2001) reported correlations between FA and NAA measured from prefrontal white matter, but the correlations were not consistent across hemispheres within their participant

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groups, which could be due to the poor signal-to-noise ratio at the lower field strength used in their study. Tang et al. (2007) used multi-voxel MRS imaging and DTI and found correlations between FA and NAA in the left medial temporal lobe in a combined patient and control group, consistent with a recent study reporting that white matter NAA explained a significant proportion of the variability in FA measured in the anterior corona radiata of healthy individuals (Wijtenburg et al., 2013). On the other hand, Rowland et al. (2009) acquired high quality spectra at greater field strength yet reported no correlations between FA in the superior longitudinal fasciculus, the major tract connecting frontal and parietal regions, and MRS metabolites measured in middle frontal and inferior parietal cortical regions. Most recently, Caprihan et al. (2015) used MRS imaging to examine supra-ventricular NAA and DTI and TBSS to assess whole-brain FA, RD, and AD in a large group of patients. Like us, they found reduced FA in several regions; however, they did not correlate DTI and MRS measures. Chiappelli et al. (2015) found that, in a combined patient and control group, whole-brain FA and FA of the anterior corona radiata positively correlated with NAA in frontal white matter but negatively correlated with myo-inositol, a marker of glial cells. When the groups were analyzed separately, FA and NAA were positively correlated in patients but not controls while FA and myo-inositol were independently negatively correlated in both patients and controls.

Like Rowland et al. (2009), we measured metabolites in regions predominantly comprising gray matter because we sought to relate cortical neuronal abnormalities to alterations in the white matter connecting these regions. While we did not observe correlations between FA and NAA, we did find a negative correlation between RD and NAA in the left hippocampal part of the cingulum in controls. Importantly, this part of the cingulum is located close to the same region where hippocampal MRS measurements were obtained. Supporting the validity of the results in controls, if RD is indeed a measure of myelin integrity with RD elevations suggesting myelin damage (Song et al., 2003; Song et al., 2002), we would expect that better myelin integrity (that is, lower RD) would be associated with regions with healthier neurons (that is, higher NAA). Since the cingulum provides afferent neuronal projections to the hippocampal region, these data suggest that cingulum myelin integrity could affect hippocampal neuronal integrity. Perhaps further supporting this idea is the absence of a correlation between RD and NAA in patients. Our recent meta-analysis showed reduced NAA levels in the hippocampus of patients (Kraguljac et al., 2012b), so the lack of correlation between RD and NAA in patients might be related to loss of neuronal integrity, loss of myelin integrity, or both. In contrast, the negative correlation between AD and NAA in controls is puzzling because we might expect better axonal integrity (that is, higher AD) to be associated with higher levels of NAA. Nevertheless, the absence of correlations in the fornix, the efferent tract of the hippocampus, suggests some specificity to the hippocampal portion of the cingulum.

Interestingly, we did not observe correlations between DTI measures and Glx/Cr levels in patients as expected, although we did find a negative correlation between ACC Glx/Cr and FA in controls. Importantly, the correlation was in the hypothesized direction: higher levels of Glx/Cr were associated with lower levels of FA. Elevated levels of glutamate could lead to excitotoxicity that may in turn influence the integrity of the myelinated axons of the affected neurons or, perhaps in this case, their associated connections. Oligodendrocytes, the

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glial cells that produce myelin, are vulnerable to glutamate receptor-mediated toxicity (McDonald et al., 1998), and glutamate appears to be elevated in the early stages of schizophrenia and in unmedicated patients (Bustillo et al., 2010; de la Fuente-Sandoval et al., 2013; de la Fuente-Sandoval et al., 2011; Kegeles et al., 2012; Kraguljac et al., 2013; Theberge et al., 2002; Theberge et al., 2007). It is possible that glutamate excitotoxicity could lead to damage of myelin, glia, or the neurons themselves, resulting in the absence of a correlation in our patient group. Another possible reason for the lack of correlation in patients is the mixed unmedicated versus medicated status of the participants. Abnormalities of glutamate or glutamine would be expected to influence the Glx signal, and Glx elevations have been observed in unmedicated patients (Kegeles et al., 2012; Kraguljac et al., 2013), while glutamate and glutamine reductions have been observed in chronic and medicated patients (Lutkenhoff et al., 2010; Theberge et al., 2003). Thus, the mixed medication status, potential underlying abnormalities of the glutamatergic system, and/or the extent of myelin damage could explain the absence of correlations in our patient group. However, interpretations of the DTI–MRS correlations are cautious and speculative. Nevertheless, the presence of the correlations in controls demonstrates the potential utility of this multi-modal MRI approach to help further our understanding of the relationship between white matter microstructure and neurochemistry in distinct cortical regions connected by white matter tracts. Future studies in larger, more homogeneous patient samples could help determine whether this relationship is disrupted in schizophrenia.

Our findings should be considered in the context of the following limitations. First, our patient group had mixed medication status. DTI measurements could potentially be influenced by antipsychotic medication (Minami et al., 2003). However, we note that DTI abnormalities have been observed in medication-naïve patients (Alvarado-Alanis et al., 2015; Cheung et al., 2008; Cheung et al., 2011; Gasparotti et al., 2009; Mandl et al., 2013). Second, although our goal was to explore the relationship between the neuronal biochemistry of two cortical regions and the white matter tract connecting them, the MRS voxels included both gray and white matter, which both contribute to the NAA and Glx signals and have different concentrations (Sailasuta et al., 2008; Wang and Li, 1998). We attempted to control for potential contribution from the white matter to the MRS signal by including the gray matter fraction as a covariate; however, this does not directly rule out partial volume effects. Third, we quantified MRS metabolite ratios using creatine as an internal reference because we did not collect unsuppressed water spectra. Since creatine abnormalities may be present in patients (Öngür et al., 2009), future studies should use absolute quantitation. Other imaging methods, such as magnetization transfer ratio and diffusion tensor spectroscopy, may provide improved ways to measure distinct components of white matter alterations in schizophrenia (Du et al., 2013).

In conclusion, we investigated the relationship between white matter microstructure, and neurometabolites in schizophrenia patients and controls using a multi-modal MRI approach. We used DTI to quantify FA, AD, and RD across the whole brain to characterize white matter integrity and proton MRS to quantify NAA, a marker of neuronal integrity, and glutamate in the ACC and hippocampus. We found FA reductions in patients in multiple tracts that appear to be driven by loss of myelin integrity as evidenced by RD elevations in many of the same regions. In controls but not patients, we found a significant relationship

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between white matter integrity of the hippocampal part of the cingulum bundle and hippocampal NAA/Cr. Taken together, our findings demonstrate the potential utility of this multi-modal neuroimaging approach to help further our understanding of the relationship between white matter microstructure and neurochemistry in distinct regions connected by white matter tracts.

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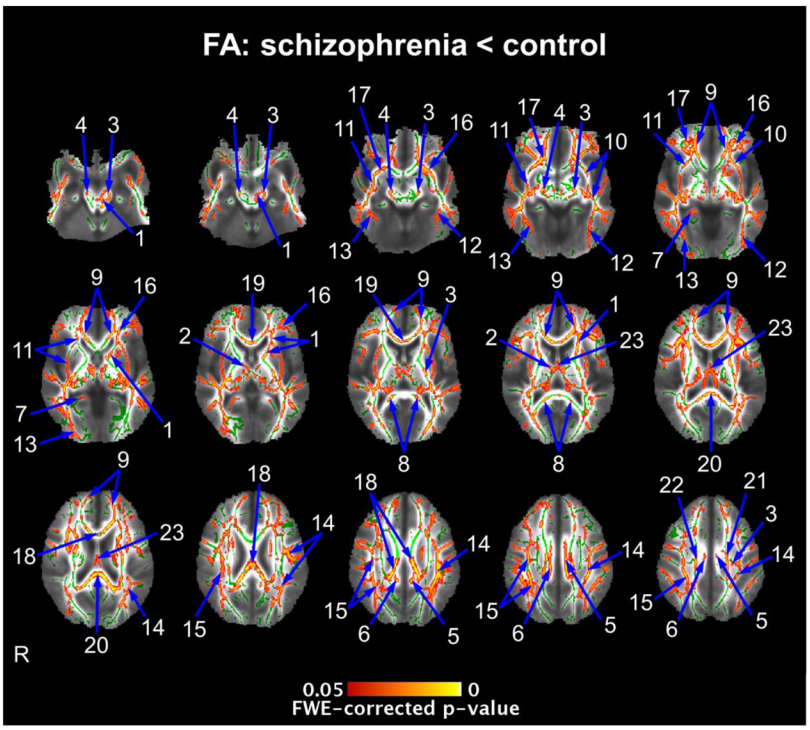

Figure 1.

Regions of significant reduction in fractional anisotropy (FA) in patients with schizophrenia (n = 29) compared to healthy controls (n = 20). Red-yellow indicates $p_{FWE} < 0.05$. Results are overlaid on the study-specific whole-group mean FA image and the whole-group mean FA skeleton (green). Images are displayed in radiological view (left side of the figure is right side of the brain). Tracts were identified using the Johns Hopkins University Probabilistic Tractography and White Matter Labels Atlases (distributed with FSL). 1: anterior thalamic radiation (left), 2: anterior thalamic radiation (right), 3: corticospinal tract (left), 4: corticospinal tract (right), 5: cingulum (cingulate gyrus) (left), 6: cingulum (cingulate gyrus) (right), 7: cingulum (hippocampus) (right), 8: forceps major, 9: forceps minor, 10: inferior fronto-occipital fasciculus (left), 11: inferior fronto-occipital fasciculus (right), 12: inferior longitudinal fasciculus (left), 13: inferior longitudinal fasciculus (right), 14: superior longitudinal fasciculus (left), 15: superior longitudinal fasciculus (right), 16: uncinate fasciculus (left), 17: uncinate fasciculus (right), 18: body of corpus callosum, 19: genu of corpus callosum, 20: splenium of corpus callosum, 21: superior corona radiata (left), 22: superior corona radiata (right), 23: fornix.

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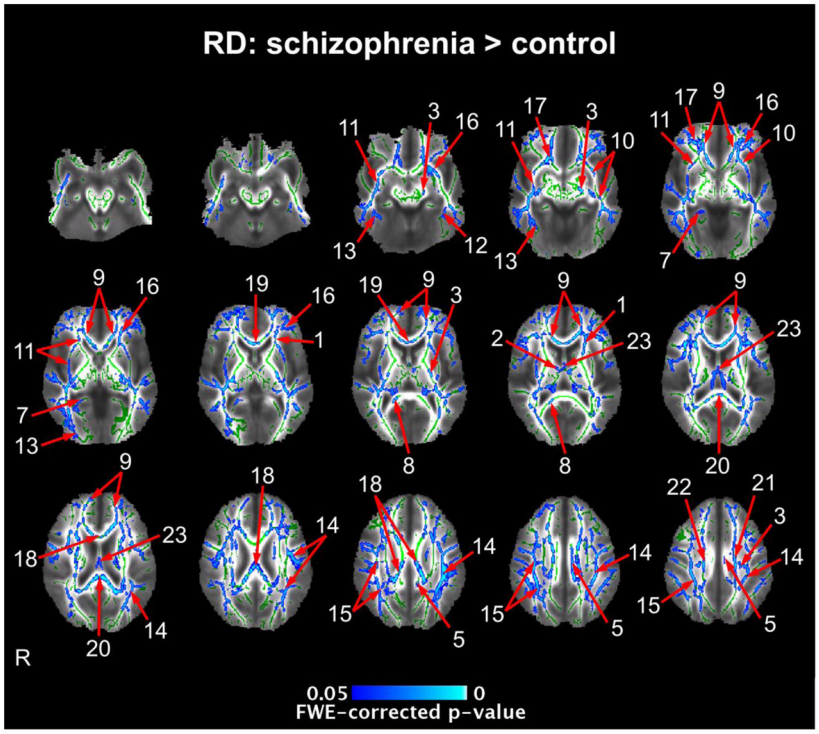

Figure 2.

Regions of significant elevation in radial diffusivity (RD) in patients with schizophrenia (n = 29) compared to healthy controls (n = 20). Blue-light blue indicates $p_{FWE} < 0.05$. Results are overlaid on the study-specific whole-group mean FA image and the whole-group mean FA skeleton (green). Images are displayed in radiological view (left side of the figure is right side of the brain). Tracts were identified using the Johns Hopkins University Probabilistic Tractography and White Matter Labels Atlases (distributed with FSL). Labeling convention is the same as in Figure 1. 1: anterior thalamic radiation (left), 2: anterior thalamic radiation (right), 3: corticospinal tract (left), 4: corticospinal tract (right), 5: cingulum (cingulate gyrus) (left), 6: cingulum (cingulate gyrus) (right), 7: cingulum (hippocampus) (right), 8: forceps major, 9: forceps minor, 10: inferior fronto-occipital fasciculus (left), 11: inferior fronto-occipital fasciculus (right), 12: inferior longitudinal fasciculus (left), 13: inferior longitudinal fasciculus (right), 14: superior longitudinal fasciculus (left), 15: superior longitudinal fasciculus (right), 16: uncinate fasciculus (left), 17: uncinate fasciculus (right), 18: body of corpus callosum, 19: genu of corpus callosum, 20: splenium of corpus callosum, 21: superior corona radiata (left), 22: superior corona radiata (right), 23: fornix.

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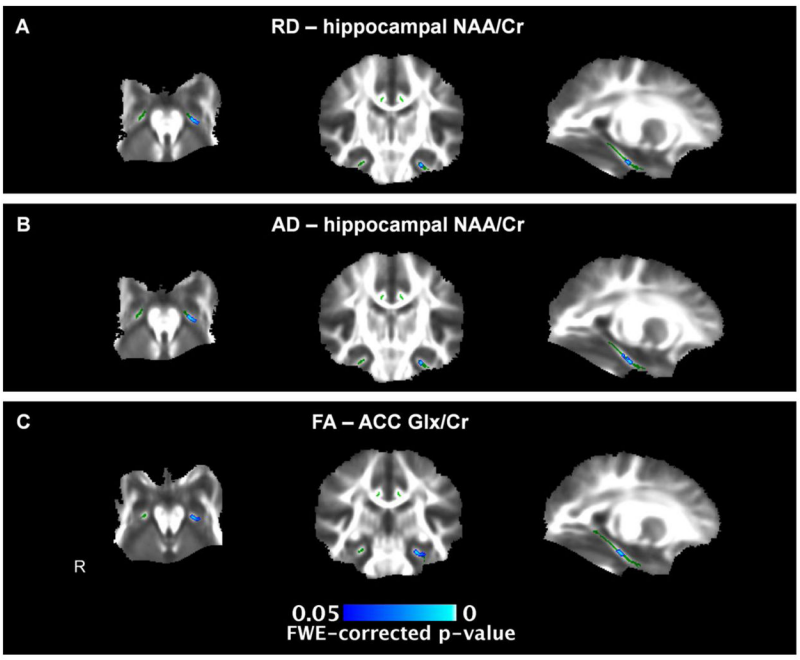

Figure 3.

Correlations between diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS). (A) Significant negative correlation between radial diffusivity (RD) and hippocampal *N*-acetylaspartate/creatine (NAA/Cr) in healthy controls ($n = 18$). (B) Significant negative correlation between axial diffusivity (AD) and hippocampal NAA/Cr in healthy controls ($n = 18$). (C) Significant negative correlation between fractional anisotropy (FA) and glutamate+glutamine/creatine (Glx/Cr) in the anterior cingulate cortex in healthy controls ($n = 18$). Blue-light blue indicates $p_{FWE} < 0.05$. Results are overlaid on the study-specific whole-group mean fractional anisotropy (FA) image and the cingulum mask (green). Images are displayed in radiological view (left side of the figure is right side of the brain).

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Table 1

Demographics and MRS metabolite levels [a, b]

Measure	Patients (n = 29)	Controls (n = 20)	Statistic	p
Age, years	33.8 (11.0)	37.1 (11.1)	$t(47) = 1.03$	0.31
Sex, M/F	20/9	14/6	$\chi^2 = 0.01$	0.94
Parental occupation [c]	9.3 (6.1)	8.2 (4.1)	$t(43) = 0.71$	0.48
Smoker/Non-smoker	21/8	12/8	$\chi^2 = 0.83$	0.36
BPRS [d]				
Total	40.5 (12.6)	–	–	–
Positive	10.1 (5.0)	–	–	–
Negative	6.3 (3.0)	–	–	–
Illness duration, years	13.4 (11.6)	–	–	–
Unmedicated/Medicated	14/15	–	–	–
Anterior Cingulate Cortex [e]				
NAA/Cr	1.33 (0.10)	1.32 (0.12)	$t(42) = 0.17$	0.87
CRLB, %	3.4 (0.5)	3.4 (0.5)		
Glx/Cr	0.70 (0.06)	0.70 (0.08)	$t(42) = 0.10$	0.92
CRLB, %	6.8 (1.3)	6.9 (1.4)		
Cho/Cr	0.80 (0.07)	0.79 (0.06)	$t(42) = 0.67$	0.51
CRLB, %	2.6 (0.4)	2.6 (0.3)		
SNR	10.8 (1.1)	11.1 (1.1)	$t(42) = 0.81$	0.42
Line width (FWHM, Hz)	4.9 (0.8)	5.2 (1.2)	$t(42) = 1.04$	0.30
Hippocampus [f]				
NAA/Cr	1.23 (0.12)	1.25 (0.15)	$t(39) = 0.49$	0.63
CRLB, %	3.7 (0.5)	3.8 (0.9)		
Glx/Cr	0.62 (0.12)	0.61 (0.09)	$t(39) = 0.49$	0.63
CRLB, %	10.4 (2.0)	10.2 (1.7)		
Cho/Cr	0.92 (0.11)	0.89 (0.14)	$t(39) = 0.67$	0.51
CRLB, %	3.1 (0.4)	3.1 (0.7)		
SNR	11.5 (1.1)	11.7 (1.5)	$t(39) = 0.47$	0.64

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Measure	Patients (n = 29)	Controls (n = 20)	Statistic	p
Line width (FWHM, Hz)	8.3 (1.3)	8.2 (1.1)	$t(39) = 0.21$	0.83

[a] Abbreviations: BPRS, Brief Psychiatric Rating Scale; Cho, choline; Cr, creatine; CRLB, Cramer-Rao lower bounds; FWHM, full-width at half maximum; Glx, glutamate + glutamine; Hz, hertz; NAA, *N*-acetylaspartate; SNR, signal-to-noise ratio

[b] Mean (SD) unless indicated otherwise.

[c] Parental occupation determined from Diagnostic Interview for Genetic Studies (1–18 scale). Lower numerical value corresponds to higher socioeconomic status. Information not available for 4 SZ

[d] Scored on a 1–7 scale. Positive: conceptual disorganization, hallucinatory behavior, unusual thought content, and suspiciousness. Negative: emotional withdrawal, motor retardation, and blunted affect.

[e] patients: n = 26; controls: n = 18

[f] patients: n = 23; controls: n = 18

Schizophr Res. Author manuscript; available in PMC 2018 June 01.

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Table 2

Clusters of significantly ($p_{FWE} < 0.05$) reduced fractional anisotropy (FA) in schizophrenia patients compared to controls as identified by tract-based spatial statistics (TBSS) with threshold-free cluster enhancement (TFCE).

	MNI Coordinates			Cluster size	*t*	p_{FWE}
	X	Y	Z			
FA: schizophrenia < control						
Cluster 1	−29	−54	29	46626	5.41	0.003
	32	−20	6		5.01	
	−30	26	20		4.92	
	33	−16	6		4.92	
	40	−9	−27		4.83	
	34	−46	31		4.77	
Cluster 2	−25	12	−33	538	3.60	0.042
	−22	11	−32		3.52	
	−20	10	−30		3.40	
	−30	9	−33		3.31	
	−25	5	−33		3.31	
	−20	9	−28		3.22	
Cluster 3	27	43	31	100	2.54	0.050
	26	37	30		2.52	
	27	34	28		2.45	
	25	34	28		2.35	
	25	40	32		2.28	
	27	41	34		2.23	
Cluster 4	23	48	32	13	2.65	0.050
	22	46	32		2.51	
Cluster 5	19	46	34	5	2.56	0.050

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Table 3

Clusters of significantly ($p_{FWE} < 0.05$) elevated radial diffusivity (RD) in schizophrenia patients compared to controls as identified by tract-based spatial statistics (TBSS) with threshold-free cluster enhancement (TFCE).

	MNI Coordinates			Cluster size	*t*	p_{FWE}
	X	Y	Z			
RD: schizophrenia > control						
Cluster 1	36	−30	2	42476	5.34	0.009
	−13	29	14		4.88	
	−52	−5	13		4.74	
	36	−4	30		4.72	
	32	−22	1		4.58	
	−50	−2	8		4.51	

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Table 4

Clusters of significant ($p_{FWE} < 0.05$) correlation between DTI measures and MRS metabolites as identified by tract-based spatial statistics (TBSS) with threshold-free cluster enhancement (TFCE).

	MNI Coordinates			Cluster size	*t*	p_{FWE}
	X	Y	Z			
Control						
Negative correlation: RD in the cingulum – Hippocampal NAA/Cr						
	−25	−20	−24	43	4.42	0.016
	−32	−25	−25		3.96	
	−29	−22	−24		3.86	
Negative correlation: AD in the cingulum – Hippocampal NAA/Cr						
	−29	−29	−17	76	4.66	0.020
	−25	−20	−24		3.89	
	−25	−26	−19		3.86	
	−30	−24	−23		3.73	
	−26	−23	−23		3.73	
	−32	−25	−23		3.27	
Negative correlation: FA in the cingulum – ACC Glx/Cr						
	−24	−27	−18	44	4.38	0.022
	−24	−25	−18		4.25	
	−30	−26	−20		3.61	
Schizophrenia	–	–	–	–	–	ns