

# Diffusion tensor imaging in schizophrenia: Relationship to symptoms

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## Abstract

In this diffusion tensor imaging (DTI) study, the authors investigated white matter integrity in schizophrenia and the relationships between white matter alterations and specific symptoms of the disorder. We compared DTI images of 25 schizophrenia patients and 25 matched healthy controls and performed voxel-wise correlational analyses using the patient's DTI data and their severity scores of positive and negative symptoms. We found diffuse deficits in multiple types of white matter tracts in schizophrenia, and an inverse relationship of DTI fractional anisotropy (FA) values with positive symptom scores in association fibers, supporting a “disconnection” hypothesis of positive symptoms in schizophrenia.

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## 1. Introduction

Increasing evidence suggests the presence of white matter abnormalities in schizophrenia at the molecular (Davis et al., 2003), structural magnetic resonance

imaging (MRI) (Takase et al., 2004) and neuropathologic levels (Zai et al., 2005). These observations “underscore the importance of evaluating white matter fiber tract abnormalities in schizophrenia” (Kubicki et al., 2005) which may contribute to the hypothesized disordered connectivity between brain regions in schizophrenia (Friston, 1998). A number of recent studies have applied diffusion tensor imaging (DTI), a magnetic resonance imaging method sensitive to white matter integrity, to the study of schizophrenia; using the apparent diffusion coefficient (ADC) or fractional anisotropy (FA) measures, the majority of these find white matter deficits associated with the disease (Kubicki et al., 2007; Mori et al., 2007; Shergill et al., 2007; Buchsbaum et al., 2006; Rose et al., 2006; Jones et al., 2005b; Kitamura et al.,

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2005; Kubicki et al., 2005; Kanaan et al., 2005; Kumra et al., 2005; Szeszko et al., 2005).

Symptom profiles in schizophrenia vary considerably between different individuals (Kirkpatrick et al., 2001). Thus, in order to address possible heterogeneity in the underlying pathophysiology, recent studies have examined correlations between different aspects of the disease and DTI data, through examination of specific symptoms and symptom groups (Shin et al., 2006; Hubl et al., 2004; Wolkin et al., 2003), or via performance on tests of cognitive ability (Lim et al., 2006; Nestor et al., 2004). Recent studies have also looked at the relationship between structural data (including DTI) and the Positive and Negative Symptom Scales (PANSS) scores (Mitelman et al., 2006; Okugawa et al., 2006; Shin et al., 2006; Minami et al., 2003; Foong et al., 2000; Paillere-Martinot et al., 2001). Shin et al. reported that a small area of white matter near the right insula showed a positive correlation between the PANSS negative symptoms and ADC. In this study, we compared FA between patients with schizophrenia and matched healthy controls, and performed a voxel-wise correlational analysis with the patients' PANSS scores.

## 2. Methods

### 2.1. Subjects

Participants were 25 outpatients with chronic schizophrenia (mean age 34.2 (sd=11.7), range 19–58, seven female, two non-right handed) and 25 healthy controls (mean age 34.7 (sd=13.6), range 21–64, nine female, three non-right handed). All subjects provided written informed consent to participate after the procedures were fully explained to them, and all procedures were approved by Yale University and Hartford Hospital institutional review boards. Diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID) (Williams et al., 1992) and review of the case file, and symptoms were rated using the Positive and Negative Symptom Scales interview (Kay et al., 1987). Healthy participants were interviewed using the SCID to ensure they were free from DSM-IV Axis I or Axis II psychopathology, and assessed separately to determine that there was no history of psychosis in any first-degree relative. All participants were screened for safety to enter the MRI environment.

### 2.2. Acquisition of images

Diffusion tensor images were acquired on a 3-Tesla Siemens Allegra scanner equipped with a single channel

transmit/receive head coil. Images were collected using a single-shot spin-echo EPI with a twice-refocused balanced echo sequence to reduce eddy current distortions, TR/TE=5800/87 ms, FOV=20 cm, acquisition matrix=128×96, reconstruction matrix=128×128, 8 averages,  $b=0$  and 1000 s/mm<sup>2</sup> along 12 noncollinear directions, 45 contiguous axial slices with 3 mm slice thickness, and peripheral arterial pulse gating to minimize effects from cerebrospinal fluid (CSF) and blood flow. Field map images were acquired using a dual gradient echo sequence ( $\Delta TE=2.46$  ms).

### 2.3. Analysis of images

DTI images were preprocessed using custom software. Susceptibility-induced geometric distortion was corrected using a 1-D correction algorithm (motion correction was also employed as part of this routine) along the phase-encoding direction with the separately-acquired field map (Jezzard and Balaban, 1995). The software used a weighted linear least square method to calculate FA maps (Salvador et al., 2005). Intracranial voxels were separated out using a brain extraction tool-generated brain mask.

FA maps were reoriented in SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2/>) and normalized using the iterative approach below:

- 1) B0 (T2) images from each subject were initially normalized to the T2 template (MNI space) in SPM2.
- 2) Normalization parameters obtained from the above step were applied to the corresponding FA image of each subject.
- 3) All resulting FA images (in standard space) were averaged to form an initial FA template.
- 4) Each FA image in “raw space” was again normalized to this initial FA template and then averaged together to form a final FA study-specific template.

Following the creation of the final template, the original (raw) FA maps were normalized to this template using an affine registration (12 parameters) before conducting the group comparison. This is a robust approach that utilizes a study-specific template, ensuring that individual voxels may be competently compared across subjects. Normalized FA maps were smoothed with a 10 mm<sup>3</sup> full-width half maximum Gaussian kernel. Currently, despite many VBM studies, there is no clear consensus between an optimum smoothing kernel size. We chose the above smoothing kernel based on previous data published by Jones et al. (2005a) and also that fit our empirical processing criteria.

Statistics were calculated using a parametric two-sample *t*-test on a voxel-by-voxel basis, and masked at an FA cutoff of 0.18 to reduce partial volume effect from the CSF and gray matter. The use of an FA threshold allows a valid comparison of voxels which have significant FA values and is similar to the gray matter threshold typically used in VBM analyses. Clusters of fifty voxels or greater, surviving a false discovery rate (FDR), (Genovese et al., 2002) corrected threshold of  $p < 0.001$  were considered significant.

The correlational analysis was performed as a series of single regression correlations (Pearson) in SPM2, with the PANSS positive, negative, or general score as the covariate, and masked using the same convention as the *t*-test described above. Positive and negative correlations contrasts were created, and in this preliminary analysis an uncorrected threshold of  $p < 0.01$  was considered significant. Significant clusters were identified by specific white matter tract through meticulous comparison to the MRI Atlas of Human White Matter (Mori et al., 2005) and verified in three dimensions by five anatomically knowl-

edgeable independent raters (regions were labeled based on a majority opinion).

### 3. Results

#### 3.1. Full-brain voxel-based analysis

There was no significant between-group difference in age, sex, or handedness. PANSS scores were unavailable for two patients, leaving  $n = 23$  for this analysis. The mean values of the PANSS positive, negative, and general scores were 16.2(SD=6.1), 18.3(7.1), and 34.6 (10.7), respectively.

In the whole brain comparison between schizophrenic patients and healthy controls, there were no voxels in which FA was significantly lower in controls. Significant reductions in the FA of the patient group at a FDR corrected cutoff of  $p < 0.001$  were diffuse and found in multiple fiber tract types (see Fig. 1). Deficits in projection fibers were seen in midbrain white matter (corticopontine or corticospinal fibers), which extended contiguously up

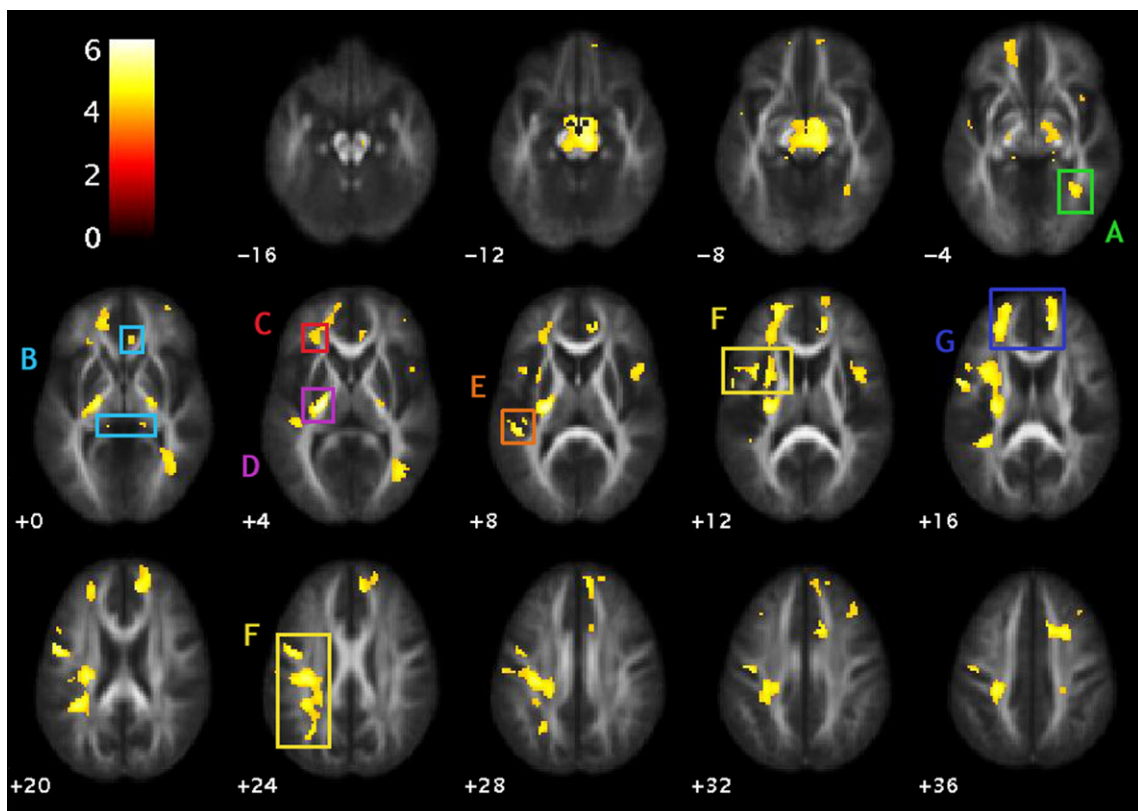


Fig. 1. Contrast of DTI FA values for 25 controls > 25 schizophrenia patients,  $p < 0.001$  corrected, 10 mm smoothing, displayed over the study-specific average normalized FA template. Tracts with significant differences between groups are labeled by letter: A, inferior fronto-occipito fasciculus; B, cingulum; C, anterior thalamic radiation; D, posterior limb of the internal capsule; E, inferior longitudinal fasciculus; F, superior longitudinal fasciculus; G, forceps minor.

through the posterior limb of the internal capsule (PLIC) and into the corona radiata of the cerebral hemispheres, bilaterally but stronger on the left. Lower FA was seen in association fibers in the cingulum (bilaterally in the medial temporal area and in right frontal portions), in temporal portions of the left inferior longitudinal fasciculus, and in the left anterior thalamic radiation. Commissural fibers were significantly different in the forceps minor of the frontal lobe. There was also a large, highly significant difference between groups in the right inferior fronto-occipito fasciculus.

### 3.2. Correlation/regression analysis

In the correlation/regression analysis, negative correlations of FA values with PANSS positive symptom scores were seen in the left uncinate fasciculus, right sagittal stratum, and the left superior longitudinal fasciculus (see Fig. 2). Positive correlations with PANSS negative symptom scores were found in one small area near the right insula, but in a different fiber tract than that reported by Shin et al. (2006). There were no significant results in the positive correlation with positive scores, the negative

correlation with negative scores, nor was there significant correlation with PANSS general scores in either direction.

## 4. Discussion

We report diffuse differences in white matter integrity between schizophrenia patients and matched healthy controls. Using robust normalization methods and carefully matching results to specific white matter tracts, our findings both support disconnection hypothesis-based expectations in association and callosal fibers and detect unanticipated deficits in projection fibers. Projection fibers are not typically the target of white matter studies of schizophrenia, but in their review of white matter lesion-induced deficits, Aralasmak et al. (2006) report that PLIC lesions have been variously associated with apathy, impaired consciousness and verbal memory loss. We attempted to properly attribute observed differences to the white matter tracts in which they were found and not to adjacent gray matter structures or areas, which in certain cases (especially in the region of the basal ganglia/internal capsule) can be potentially misleading. In the area of inferior fronto-

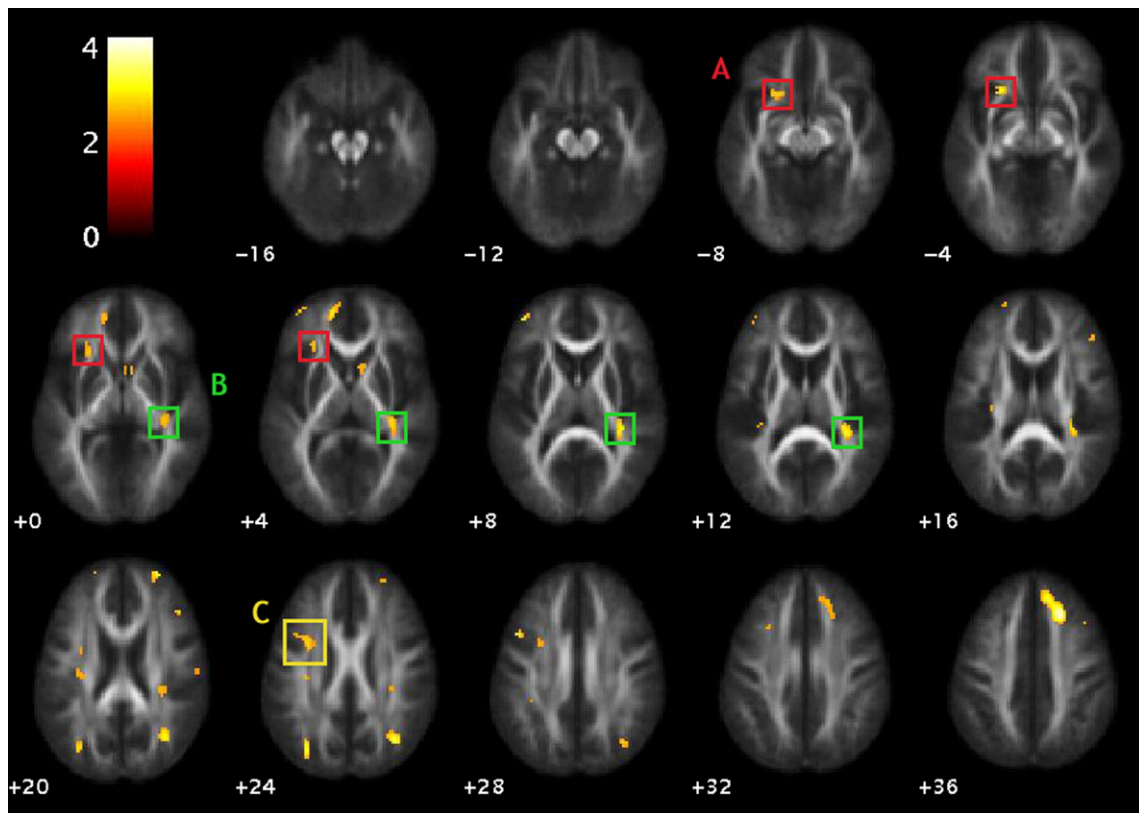


Fig. 2. Negative correlation between PANSS  $p$ -score and FA values for 23 schizophrenia patients, masked at FA cutoff 0.18,  $p < 0.01$ . Tracts which reached a significant negative correlation are labeled by letter: A. uncinate fasciculus; B. sagittal stratum; C. superior longitudinal fasciculus.

occipito fasciculus, more specific classification of results was not possible in the current state of DTI resolution and probabilistic tract identification.

Our correlational analysis with positive symptom scores in 23 schizophrenia patients highlighted deficits in association white matter tracts. Relationship between white matter deficits and PANSS scores are still largely disparate. Studies by Foong et al. (DTI whole brain) and Minami et al. (DTI-ROI based) did not detect any DTI related changes with symptom scores. Other studies using both structural and DTI whole brain measures have shown close relationships between overall PANSS scores and white matter anomalies/disruptions (Mitelman et al., 2006; Paillere-Martinot et al., 2001). Correlation results from this study on the other hand have demonstrated a negative relationship between the FA values of rather specific white matter tracts and positive symptom scores. Even though we used a continuous spectrum of symptom scores as a correlate measure over the whole brain, unlike some of the above studies, future studies with greater numbers of subjects that extend the range of symptom scores are needed to validate and elaborate on these promising preliminary findings.

The heterogeneous nature of the manifestations of schizophrenia encourages approaches that investigate pathophysiology by subdividing the patient sample using symptom or deficit measures, in order to disentangle changes associated with aspects of pathology that may have unique physiologic underpinnings. From our data, positive symptoms of the disorder appear to be associated with differential white matter fractional anisotropy values in specific association fibers. These results are consistent with a “disconnection” hypothesis of positive symptoms in schizophrenia.

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#### Contributors

Drs. Calhoun, Mathalon, and Pearlson designed the study. Ms. Skelly wrote the protocol and managed the literature searches and analyses. Ms. Skelly, Mr. Meda and Drs. Kim and Calhoun undertook the statistical analysis, and Ms. Skelly and Dr. Pearlson wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

#### Conflict of interest

No author has any conflict of interest to report.

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