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Extensive white matter abnormalities in patients with first-episode schizophrenia: A diffusion tensor imaging (DTI) study

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ABSTRACT

Background: Previous voxelwise Diffusion Tensor Imaging (DTI) investigations of white matter in first-episode schizophrenia (FESZ) have been limited to the analysis of Fractional Anisotropy (FA) and mean diffusivity (MD), with their findings inconsistent in terms of the anatomical locations and extent of abnormalities. This study examines white matter abnormalities in FESZ, compared with healthy controls, using a tract-based spatial statistics (TBSS) approach applied to multiple measures of tract integrity, and correlates these findings with symptom severity.

Methods: Seventeen first-episode patients with schizophrenia and seventeen age- and gender-matched healthy controls (HC) participated in this imaging study where FA, MD, and axial and radial diffusivities were compared between the two groups using TBSS.

Results: First-episode patients with schizophrenia showed lower FA values in the genu and body of corpus callosum, the internal capsule, the external capsule, the fornix, the superior, inferior fronto-occipital fasciculus, the cingulum, and the uncinate fasciculus compared with HC. Increased MD and radial diffusivity were shown in virtually all white matter regions. There was no significant difference, however, observed for axial diffusivity between the two groups. Pearson correlation analysis showed that the FA values of the right inferior fronto-occipital fasciculus were positively correlated with positive symptoms, negative symptoms, and total correct items of the Wisconsin Card Sorting Test. FA values of right external capsule also showed significant positive correlation with category completed scores of the WCST.

Conclusions: These data suggest extensive, possibly myelin related white matter disruptions in FESZ.

1. Introduction

Previous functional and structural studies have suggested a loss of normal connectivity in schizophrenia (Wernicke, 1906; Weinberger et al., 1992; McGuire and Frith, 1996). White matter lesions could be the basis of this disconnectivity in schizophrenia (see review in Shenton et al. (2001)). Postmortem and genetic studies further suggest that schizophrenia might be related to myelin abnormalities (Uranova et al., 2001; Davis et al., 2003; Uranova et al., 2004), although axonal abnormalities might be involved as well (Mendelsohn et al., 2006).

Diffusion tensor imaging (DTI) techniques make it possible to investigate micro-structural white matter abnormalities *in vivo*. With this technique, Fractional Anisotropy (FA), a deviation from isotropic diffusion of water molecules, as well as mean diffusivity (MD), a scalar measure of the total diffusion within a voxel, can be measured (Basser and Jones, 2002). Previous DTI studies in first-episode schizophrenia (FESZ) and chronic schizophrenia report FA reductions, along with increased MD in various white matter tracts and regions (Kubicki et al., 2007; Kyriakopoulos and Frangou, 2009). These abnormalities could support 'the disconnectivity hypothesis' in schizophrenia.

Studies of FESZ are particularly important, since this population of patients is much less confounded by medication, effects of aging, and long-term substance abuse, as well as long-term effects of having a chronic illness. In addition, if white matter abnormalities are reported consistently at the onset of schizophrenia, such reports might suggest information relevant to the neurodevelopmental origin of schizophrenia.

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However, if white matter abnormalities are not present in FESZ, or are less extensive than in chronic schizophrenia, white matter abnormalities might be more related to late development or degeneration.

DTI findings of FESZ thus far, however, remain inconsistent and therefore inconclusive. While several studies have shown no differences between FESZ patients and HC (Price et al., 2005, 2008; Friedman et al., 2008; White et al., 2009), other studies have shown evidence for widespread white matter abnormalities (Federspiel et al., 2006; Hao et al., 2006; Price et al., 2007; Cheung et al., 2008). Further, only a few studies report no FA abnormalities but these studies were able to identify group differences in other diffusion indices such as geometric indices partitioning the diffusion into linear, planar and spherical diffusion measures, and displacement values using high *b*-value ($b > 3000$ s/mm^2) diffusion-weighted imaging methods, which provide a fuller account of white matter integrity and more specific axonal pathology (Mendelsohn et al., 2006; Chan et al., 2010). There is thus a need to investigate further DTI findings in FESZ.

To examine the anatomical location of DTI abnormalities in FESZ, voxel-based analysis (VBA) has advantages over a region of interest (ROI) approach. ROI methods are limited to localized white matter regions or tracts, whereas VBA is able to analyze the whole brain at once. VBA has shown, in fact, the most positive findings in FESZ (Federspiel et al., 2006; Hao et al., 2006). These findings, however, remain inconsistent when it comes to specific tracts (reported locations usually do not overlap) and the extent of white matter abnormalities.

Moreover, most VBA studies in FESZ are limited to an analysis of FA and MD. FA and MD may not be sufficient for investigating specific axonal or myelin abnormalities. In mouse DTI studies, axonal damage without myelin damage has been associated with a decrease in axial diffusivity (Sun et al., 2006), whereas demyelination has been associated with an increase in radial diffusivity without changes in axial diffusivity (Song et al., 2005). An investigation of these measures could serve to inform the nature of white matter pathology in schizophrenia (Smith et al., 2006, 2007; Seal et al., 2008).

Tract-Based Spatial Statics (TBSS, version 1.2) (Smith et al., 2006; Smith and Nichols, 2009) is believed to reduce some of the methodological problems of previous VBA approaches that were associated with misalignment and smoothing problems. TBSS also takes into account non-normal distributions of FA in certain brain regions (Smith et al., 2007). Accordingly, because of the range of functions that TBSS is capable of performing, we investigated white matter abnormalities in FESZ using TBSS. Additionally, we combined TBSS skeleton with white matter atlases (Mori et al., 2005), a method that makes possible ROI analyses as a way to confirm TBSS results (Karlsgodt et al., 2009).

2. Methods and materials

2.1. Subjects

Seventeen patients with FESZ were recruited by referrals from clinicians at Beth Israel Deaconess Medical Center-Massachusetts Mental Health Center and Children's Hospital, Harvard Medical School, Massachusetts. Seventeen healthy controls (HC) were recruited through newspaper advertisements and advertisements on the websites (www.bostoncidar.org and www.schizophrenia.com). All subjects were part of Boston CIDAR (the Center for Intervention Development and Applied Research) study. DSM-IV diagnoses were based on interviews with the Structured Clinical Interview for DSM-IV-TR (SCID), Research Version (First et al., 2002a) and information from patient medical records. HC were group matched to FESZ for age, gender and parental socioeconomic status (PSES). Using the Structured Clinical Interview for DSM-IV-TR, Non-patient Edition (First et al., 2002b), HCs were excluded if: 1) they currently met the criteria for any psychosis, major depressive disorder, dysthymic disorder, bipolar disorder, obsessive compulsive disorder, post traumatic stress disorder, dissociative disorders, anorexia nervosa, bulimia nervosa, or developmental disorders, 2) they had a history of any psychosis, major depression (recurrent), bipolar disorder, obsessive compulsive disorder, post traumatic stress disorder, developmental disorders, or psychiatric hospitalization, 3) they had current or past use of antipsychotics for any psychiatric condition (other past psychotropic medication use acceptable, but must have been off medicine for at least 6 months before participating in the study, except for prn medications like sleeping medications or anxiolytic agents, like beta-blockers for performance anxiety, tremors, etc.), 4) they had any history of electroconvulsive therapy, 5) there was evidence of any prodromal symptoms, or schizotypal or other Cluster A personality disorders, or 6) they reported having a first-degree relative with psychosis.

Exclusion criteria for all subjects were: sensory-motor handicaps, neurological disorders, medical illnesses that significantly impair neurocognitive function, diagnosis of mental retardation, education less than 5th grade if under 18 or less than 9th grade if 18 or above, not fluent in English, DSM-IV substance abuse in the past month, DSM-IV substance dependence, excluding nicotine, in the past 3 months, current suicidality, no history of ECT within the past five years for patients and no history of ECT ever for controls, or study participation by another family member.

Thirteen patients were receiving antipsychotic medication at the time of testing. Medication dose equivalent to chloropromazine at the time of the scan was 393.3 mg (SD = 358.2)(Woods, 2003). Premorbid intellectual abilities were estimated using the reading subtest from the Wide Range Achievements Test-4 (WRAT-4) (Wilkinson and Robertson, 2006), and current intellect was estimated with two subtests from the Wechsler abbreviated Scale of Intelligence (WASI) (32). Socioeconomic status (SES) of schizophrenia and HCs, and those of their parents (PSES), were evaluated using the Hollingshead (1965) (33) two-factor index. Clinical symptoms were measured using The Brief Psychiatric Rating Scale (BPRS) (34). The 64-card computerized version of the Wisconsin Card Sorting Test (WCST) (35) was also administered by trained neuropsychological testers under the supervision of a psychologist. All patients were scanned at Brigham and Women's Hospital. The study was approved by the local IRB committees at Harvard Medical School, Beth Israel Deaconess Hospital, Brigham and Women's Hospital, and at the Veteran Affairs Boston Healthcare System, Brockton campus, and all study participants gave written informed consent prior to study participation.

2.2. MRI acquisition

Diffusion data were acquired on a 3 Tesla GE Echospeed system (General Electric Medical Systems, Milwaukee, WI). Diffusion-weighted images were acquired using an echo planar imaging sequence, with the following parameters: TR 170,00 ms, TE 78 ms, FOV 24 cm, 144×144 matrix, 1.7 mm slice thickness. A double echo option was used to reduce eddy-current related distortions. To reduce impact of EPI spatial distortions, an 8 Channel coil and ASSET (Array Spatial Sensitivity Encoding techniques, GE) with a SENSE-factor (speed-up) of 2 was used. Eighty-five axial slices parallel to the AC–PC line covering whole brain were acquired in 51 directions with b = 900 s/mm^2. Eight baseline scans with b = 0 s/mm^2 were also acquired. Diffusion-Tensor Images (DTIs) were estimated from the diffusion-weighted images using least-squares method.

2.3. Tract-based spatial statistics

For voxelwise statistical analysis, Tract-Based Spatial Statistics (TBSS) version 1.2 was used. Diffusion tensor images (FA, trace, axial and radial diffusivity) were pre-processed using the FMRIB Software Library (FSL, Oxford), including skull stripping and eddy current correction Briefly, FA maps were first created for each subject using FSL. Then, FA maps were aligned into a common (Montreal Neurologic Institute 152 standard) space using the nonlinear