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Cerebral white matter structure is associated with DSM-5 schizophrenia symptom dimensions

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ABSTRACT

Diffusion tensor imaging (DTI) studies have provided evidence of widespread white matter (WM) abnormalities in schizophrenia. Although these abnormalities appear clinically significant, the relationship to specific clinical symptoms is limited and heterogeneous. This study examined the association between WM microstructure and the severity of the five main DSM-5 schizophrenia symptom dimensions. DTI was measured in forty patients with schizophrenia spectrum disorders. Using Tract-Based Spatial Statistics controlling for age, gender and antipsychotic dosage, our analyses revealed significant negative relationships between WM microstructure and two DSM-5 symptom dimensions: Whereas abnormal psychomotor behavior was particularly related to WM of motor tracts, negative symptoms were associated with WM microstructure of the prefrontal and right temporal lobes. However, we found no associations between WM microstructure and delusions, hallucinations or disorganized speech. These data highlight the relevance of characteristic WM disconnectivity patterns as markers for negative symptoms and abnormal psychomotor behavior in schizophrenia and provide evidence for relevant associations between brain structure and aberrant behavior.

1. Introduction

Schizophrenia is characterized by heterogeneous symptom patterns. This heterogeneity has long been explained in terms of clinical subtypes, as in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Tandon et al., 2013). Because these subtypes lack stability and biological correlates, they were eliminated and replaced by psychopathological dimensions in the DSM-5 (Barch et al., 2013; Peralta and Cuesta, 2001). The main symptom dimensions of schizophrenia in the DSM-5 are delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms. The DSM-5 schizophrenia dimensions allow describing the heterogeneity of symptoms in a more valid, reliable and clinically useful way (Tandon et al., 2013).

Brain white matter (WM) abnormalities have been reported as one of the central hallmarks in schizophrenia; thought to contribute to the pathophysiology of the disorder (Davis et al., 2003). Diffusion tensor imaging (DTI) is a non-invasive Magnetic Resonance Imaging (MRI) method that allows the investigation of WM microstructure by quantifying the degree and direction of water diffusion (Basser, 1995; Mori et al., 2005). A number of studies provide evidence of WM abnormalities in schizophrenia, predominantly in the prefrontal and temporal lobe, using most often fractional anisotropy (FA) as an indicator of the integrity of WM (Federspiel et al., 2006; Kubicki et al., 2007). Altered white matter microstructure has been reported across the course of schizophrenia, in subjects at risk for psychosis and in healthy first-degree relatives of schizophrenia patients, suggesting that these alterations are associated both with the biological risk of schizophrenia and with symptom progression (Federspiel et al., 2006; Fitzsimmons et al., 2013; Ohtani et al., 2015).

Several studies have focused on the link between brain WM abnormalities and schizophrenia symptom dimensions. For example, conflicting results were reported for WM associations with the classical positive/negative symptom dimensions probably due to different patient groups (Asami et al., 2014; Cheung et al., 2011; Roalf et al., 2015; Zhang et al., 2016). For other symptom dimensions (e.g. disorganized speech, abnormal psychomotor behavior), only a few studies have investigated the association with aberrant WM integrity (Asami et al., 2013; Bai et al., 2009). In addition, cognitive impairment in schizophrenia was associated with WM microstructure in association fibers such as the right

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cingulum bundle, superior and inferior longitudinal fasciculi and inferior fronto-occipital fasciculus (Liu et al., 2013; Seitz et al., 2016; Zeng et al., 2016). Given the heterogeneity of current results for some symptom dimensions and a lack of studies for others, the question remains whether different dimensions of schizophrenia have specific brain WM correlates. Applying the dimensional approach of the DSM-5 to schizophrenia psychopathology may further help finding neural underpinnings of aberrant behavior (Heckers et al., 2013). Therefore, we aimed to investigate for the first time the association between WM microstructure and all of the five main DSM-5 dimensions in one group of patients with schizophrenia spectrum disorders. We hypothesized in some of the five dimensions an association between symptom severity and WM alteration, particularly in the dimension of abnormal psychomotor behavior, as aberrant motor behavior was consistently linked to WM abnormalities in schizophrenia before (Bracht et al., 2013; Walther et al., 2011).

2. Material and methods

2.1. Participants

Forty patients (25 men, 15 women) with schizophrenia (77.5%), schizophreniform (17.5%) or schizoaffective disorder (5%) were included in the study. All patients were recruited from the inpatient and outpatient departments of the University Hospital of Psychiatry Bern, Switzerland. They were right-handed as determined by the Edinburgh handedness inventory (Oldfield, 1971).

Inclusion criteria were diagnoses of schizophrenia, schizoaffective disorder or schizophreniform disorder according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition. Exclusion criteria were any substance-related addiction other than nicotine, a past or current medical or neurological condition associated with either impaired or aberrant movement or WM abnormalities (e.g. stroke, multiple sclerosis), histories of head trauma with loss of consciousness or electroconvulsive treatment and specific exclusion criteria for MRI scans (e.g. metallic implants, pregnancy and claustrophobia).

The severity of each core domain of the DSM-5 schizophrenia symptom dimensions was rated on a five-point scale ranging from 0 (not present) to 4 (present and severe) (Barch et al., 2013). Dimensional ratings of the severity in our group were: delusions ($M = 2.18 \pm 1.26$), hallucinations ($M = 1.3 \pm 1.51$), disorganized speech ($M = 1.63 \pm 1.37$), abnormal psychomotor behavior ($M = 1.53 \pm 1.52$) and negative symptoms ($M = 2.2 \pm 1.09$). Correlations between the five symptom dimensions were calculated using Spearman rank correlations. Additional assessments included the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) to establish diagnoses and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) for schizophrenia psychopathology. All but three patients received antipsychotic pharmacotherapy. Chlorpromazine equivalent dosages (CPZ) were calculated to evaluate current antipsychotic exposure (Woods, 2003). The demographic and clinical characteristics of the participants are summarized in Table 1.

The protocol was approved by the local ethics committee (KEK-BE 025/13) and adhered to the Declaration of Helsinki. All participants received oral and written information on the planned study. The capacity of the patients to give informed consent was confirmed by their treating psychiatrist. All participants provided written informed consent.

2.2. MRI acquisition

Imaging was performed on a 3 T MRI scanner (Siemens Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany) with a 12-channel radio frequency headcoil for signal reception. For DTI measurements, we used a spin echo planar imaging (EPI) sequence (59 slices, FOV = 256×256 mm^2, sampled on a 128×128 matrix, slice thickness = 2 mm, gap between slices = 0 mm, resulting in 2 mm^3 isotopic voxel resolution) and TR/TE = 8000/92 ms covering the whole brain (40 mT/m gradient, 6/8 partial Fourier, GRAPPA factor 2, bandwidth 1346 Hz/Px). Diffusion-weighted images (DWI) were positioned in the axial plane parallel to the AC-PC line and measured along 42 directions with a b-value = 1300 s/mm^2. The sequence included 4 images without diffusion weighting (e.g. b-value = 0 s/mm^2; the first and every subsequent 12th image). We used a balanced and rotationally invariant diffusion-encoding scheme over the unit sphere to generate the DTI data. Acquisition time was 6 min.

Table 1
Demographic and clinical characteristics.

Variables	*M*	*SD*
Age (years)	37.20	10.40
Education (years)	13.53	3.10
Duration of illness (years)	11.77	11.05
Number of episodes	6.58	7.71
PANSS-Pos	18.25	6.48
PANSS-Neg	18.48	5.41
PANSS-Total	72.43	17.04
CPZ (mg)	411.70	358.47

PANSS, Positive and Negative Syndrome Scale; PANSS-Pos, subscale for positive symptoms; PANSS-Neg, subscale for negative symptoms; PANSS-Total, total score of PANSS; CPZ, chlorpromazine equivalents; M = Mean; SD = Standard deviation.

2.3. DTI processing

DTI analyses were processed using the FMRIB (Functional Magnetic Resonance Imaging of the Brain's diffusion toolbox) Software Library (FSL) (FSL, http://www.fmrib.ox.ac.uk/fsl), including the Tract-Based Spatial Statistics (TBSS) software (Smith et al., 2006; Smith et al., 2004). The images of each subject were first corrected for head movements and eddy currents (using "eddy-tool" of FSL). FA images were created by fitting a tensor model to the raw data (using "FDT") and then a brain extraction tool was applied (using "BET-tool" of FSL) (Smith, 2002). All subjects' FA data were aligned to a 1 mm^3 Montreal Neurological Institute (MNI) standard space. The alignment was performed applying FMRIB's Non-Linear Image Registration Tool (Andersson et al., 2007a; Andersson et al., 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). A mean FA image was prepared and thinned in order to create a mean FA skeleton for later group comparisons. To prevent the inclusion of non-skeletal voxels, we used a FA threshold of 0.2. Each subject's aligned FA data was then projected onto the skeleton. The resulting data was subjected to voxelwise between subject statistics. Additionally to the FA images, other parameters of DTI, mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) were calculated by fitting a tensor model to the data at each voxel. In order to use TBSS in MD, RD and AD images, the nonlinear warps and skeleton projection of the FA images were applied to MD, RD and AD images using the "non_fa" option.

2.4. Statistical analysis

Statistical analyses for WM microstructure were carried out with TBSS, which is based on a non-parametric approach using permutation test theory with a general linear model (GLM) design matrix (Smith et al., 2006). Age, gender and chlorpromazine equivalents were entered as covariates of no interest into the analyses. Within the GLM framework, we examined the association between each of the five symptom dimensions with FA, MD, RD and AD.

Skeletonised FA, MD, RD and AD were tested voxelwise for associations with DSM-5 dimensions using a randomise tool (Winkler et al., 2014) (5000 permutations) with a threshold-free cluster enhancement (TFCE) correction method (Smith and Nichols, 2009). A TFCE corrected p-value < 0.05 (FWE corrected) was considered statistically significant in all of the analyses. The resulting significant skeletal regions were located and labelled by mapping the corrected statistical map to the