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SHORT COMMUNICATION

White matter correlates of the disorganized speech dimension in schizophrenia

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Abstract Disorganized speech is related to functional abnormalities in schizophrenia. To test the association between formal thought disorders (FTDs) and white matter microstructure, we applied a behavioral rating and diffusion tensor imaging in 61 patients with schizophrenia spectrum disorders. The Bern Psychopathology Scale was used to rate the dimension of language abnormalities ranging from negative FTDs, basically unaltered speech, to positive FTDs. Tract-based spatial statistics indicated increased fractional anisotropy in left hemispheric pathways of the language system in patients with negative FTDs. Thus, altered white matter properties in relevant fiber tracts may represent vulnerability to specific formal thought disorders.

Keywords Formal thought disorders · Language system · Bern Psychopathology Scale · Diffusion tensor imaging · Tract-based spatial statistics

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Introduction

Disorganized speech or formal thought disorders (FTDs) are prominent in many psychiatric conditions, including depression, mania, personality disorders and even in healthy controls, but have been mostly linked to schizophrenia [1, 2]. Since Bleuler first described "loosening of associations" as a significant symptom in schizophrenia [3], FTDs are one of the hallmarks, affecting speech and language comprehension [4]. The prevalence of FTDs in schizophrenia ranges 5–91%, with 50% in the largest study in schizophrenia [5, 6].

FTDs in schizophrenia are linked to structural brain abnormalities predominantly in the left superior temporal gyrus (STG), angular gyrus, inferior operculum and orbitofrontal cortex [7–10], and to functional abnormalities in the left superior and middle temporal gyrus [7, 11, 12].

Despite clear associations of FTDs with aberrant structure and function of the cortex, the relationship between white matter and FTDs is poorly understood. For example, WM abnormalities correlated with functional MRI activation in the language network in schizophrenia patients [13]. Likewise, WM abnormalities in language-related pathways were related to linguistic deficits in childhood-onset schizophrenia [14]. Furthermore, aberrant WM properties of single fiber tracts were associated with language deficits in schizophrenia [15–17].

All these studies suggest a link of FTDs in schizophrenia with disturbed WM in cerebral language pathways. However, no study investigated the association of WM with FTDs, possibly owing to the nature of current FTDs rating scales. Factor analytic studies support a dimensional approach to FTDs, ranging from normal speech to FTDs [5]. Furthermore, FTDs may comprise more than one dimension [18]. Most frequently, studies reported a disorganized factor with incoherence and tangentiality and a negative factor of FTDs with poverty of speech and speech content [5]. Newer

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scales differentiate positive and negative FTDs and acknowledge the subjective experience of thought disorders [1, 19]. Indeed, positive and negative FTDs are associated with specific neuropsychological profiles and outcomes [5, 20].

Here, we applied the Bern Psychopathology Scale (BPS), which organizes schizophrenia symptoms in three neurobiologically informed dimensions, i.e., language, limbic and motor [19]. The symptom severity is rated on a Likert scale ranging from severe inhibition (negative FTDs) to severe disinhibition (positive FTDs). Positive FTDs include loose association and increased speech production while negative FTDs include reduced speech production, concretism and inhibited thinking/blocking [19]. The distinction of inhibited and disinhibited language symptoms in the BPS is supported by cluster analysis and differential associations with positive and negative syndrome ratings [21, 22]. Thus, the distinction of FTDs in a negative and positive pole may reveal biological correlates, because different mechanisms could underlie the two ends of severe FTDs. In other words: it is unlikely that one pathophysiological pathway would result in two opposing thought disorders, i.e., negative versus positive. Therefore, we hypothesize that the BPS language dimension will demonstrate a linear relationship with WM microstructure in the cerebral language system.

Materials and methods

Subjects

Sixty-one patients with schizophrenia (37 men, 24 women) were recruited at the inpatient and outpatient departments of the University Hospital of Psychiatry Bern, Switzerland. Inclusion criteria were diagnoses of schizophrenia, schizoaffective disorder or schizophreniform disorder according to the structured clinical interview (SCID) and DSM-5 criteria. Exclusion criteria were any substance-related addiction other than nicotine, past or current medical or neurological condition, histories of head trauma with loss of consciousness or electroconvulsive treatment and specific exclusion criteria for magnetic resonance imaging (MRI) scans (e.g., metallic implants, pregnancy and claustrophobia).

The severity of each core domain of the BPS was rated on a seven-point scale ranging from −3 (inhibition) 0 (not present) to 3 (disinhibition) [19]. This bipolar structure of symptom dimensions has proved valid in schizophrenia and extends the positive–negative dichotomy of schizophrenia symptoms [21, 23–25]. Further assessment of schizophrenia symptoms included the Positive and Negative Syndrome Scale (PANSS) [26]. All but four patients received antipsychotics, and dosages were computed as chlorpromazine equivalents (CPZ) [27]. Demographic and clinical characteristics are summarized in Table 1. The protocol was approved by the local ethics committee, "Kantonale Ethikkomission Bern" (KEK-BE 025/13) and adhered to the declaration of Helsinki. All participants provided written informed consent.

MRI acquisition

Imaging was performed on a 3T MRI scanner (Siemens Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany) with a 12-channel headcoil. For DTI measurements,

Table 1 Demographic and clinical characteristics

Variables	Group 1 ($n = 7$)	Group 2 ($n = 42$)	Group 3 ($n = 12$)	One-way ANOVA	All patients ($n = 61$)
	M (SD)			*p*	*M* (SD)
Age (years)	41.5 (13.2)	35.9 (11.4)	39.3 (9.8)	0.387	37.3 (11.3)
Education (years)	12.1 (2.9)	13.2 (2.9)	14.5 (5.5)	0.366	13.3 (3.6)
Duration of illness (years)	11.8 (15.0)	10.7 (11.6)	15.2 (11.7)	0.536	11.7 (12.0)
Number of episodes	7.0 (9.9)	5.6 (6.2)	9.1 (8.5)	0.337	6.5 (7.2)
PANSS-Pos	13.7 (5.4)	15.7 (5.9)	22.3 (6.7)	0.003	16.8 (6.5)
PANSS-Neg	24.3 (4.7)	18.3 (5.9)	15.2 (3.8)	0.003	18.4 (5.9)
PANSS-Total	75.1 (17.7)	67.4 (18.1)	72.8 (19.5)	0.452	69.3 (18.3)
CPZ (mg)	382.9 (375.8)	426.4 (338.7)	289.0 (192.6)	0.427	394.4 (319.8)
BPS language dimension	−2.3 (0.5)	0.1 (0.9)	2.3 (0.5)	0.000	0.3 (1.5)
BPS affect dimension	−0.6 (1.3)	−0.7 (1.2)	−0.2 (1.4)	0.369	−0.6 (1.2)
BPS motor dimension	−1.6 (0.5)	−0.7 (1.2)	0.8 (1.2)	0.000	−0.5 (1.3)

Group 1: patients with a BPS language score of −3 and −2. Group 2: patients with a BPS language score of −1, 0 and +1. Group 3: patients with a BPS language score of +2 and +3

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

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). The axial slices were positioned in the plane parallel to the AC-PC line and measured along 42 directions with a b = 1300 s/mm^2. The sequence included 4 images without diffusion weighting (e.g., b = 0 s/mm^2; the first and every subsequent 12th image). We used a rotationally invariant and balanced diffusion-encoding scheme over the unit sphere to generate the DTI data. Acquisition time was 6 min.

Data analysis

Image processing

DTI analyses were performed using the Functional Magnetic Resonance Imaging of the Brain's Diffusion Toolbox (FMRIB) Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl), including the tract-based spatial statistics (TBSS) software [28, 29]. The image of each subject was first corrected for head movement 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 used (using "BET-tool" of FSL) [30]. All subjects' FA data were coregistered to a 1-mm^3 Montreal Neurological Institute (MNI) standard space. The alignment was performed applying FMRIB's nonlinear image registration tool [31]. A mean FA image was prepared and thinned in order to create a mean FA skeleton for group comparisons. To prevent the inclusion of nonskeletal voxels, we used a FA threshold of 0.2. Each subject's aligned FA data were then projected onto the skeleton. The resulting data were subjected to voxel-wise between subject statistics.

Statistical analysis

Statistical analysis for WM microstructure was carried out with TBSS, applying a nonparametric approach with permutation test theory in a general linear model (GLM) design matrix [29]. Within the GLM framework, we examined the association between the language dimension and FA, with age, CPZ, and the ratings of the BPS affectivity and motor dimensions as covariates of no interest. Correction for multiple comparisons was achieved with threshold-free cluster enhancement (TFCE) correction and 5000 permutations [32]. A TFCE-corrected p value <0.05 was considered as statistically significant. Localization was performed in clusters with more than 100 voxels using the Johns Hopkins University (JHU)-ICBM-DTI-81 WM labels atlas and the JHU-WM tractography atlas in MNI space [33, 34].

Results

FA values were significantly inverse associated with the BPS global language score (r = −0.380, p = 0.003; see Fig. 1). The distinction in a positive and negative pole of the BPS score was crucial, as the same analysis between FA values and the BPS global language score did not show a significant correlation when neglecting the positive and negative signs (r = 0.120, p = 0.356).

We detected a negative linear association between the BPS global language score and WM microstructure in

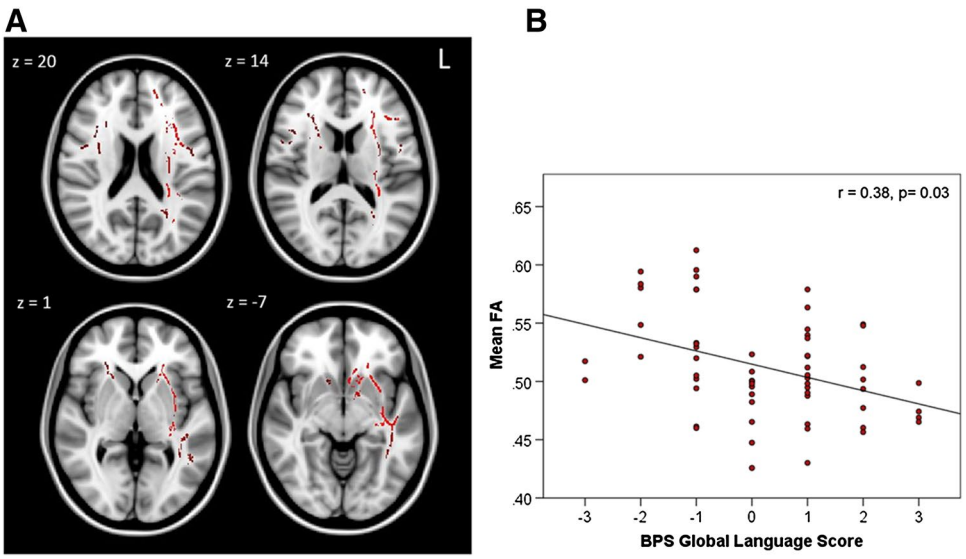

Fig. 1 **a** Correlation of white matter microstructure and language dimension of the BPS. The TBSS image shows the negative correlation between the language dimension of the BPS and FA values within the areas indicated in *red* at $p < 0.05$ corrected for multiple comparison. Covariates included age, CPZ, BPS ratings of affectivity and motor behavior. *Z* indicates the coordinates of the image slices in mm. **b** Correlation of mean FA of significant regions with the score of the language dimension of the BPS

Table 2 Location of significant correlations between white matter microstructure (FA) and the language dimension of the BPS

Location	Center of gravity (mm coordinates)			Cluster size	*p*
FA (negative linear relationship)	X	Y	Z		
Body of corpus callosum	−5.4	−9.6	30.4	635	0.044
Splenium of corpus callosum	−8.5	−42.6	24.2	307	0.047
Anterior limb of internal capsule R	20.9	11.8	9.0	199	0.049
Retrolenticular part of internal capsule L	−30.8	−30.1	7.5	365	0.042
Anterior corona radiata R	25.5	25.0	8.0	303	0.048
Anterior corona radiata L	−23.4	23.6	9.6	450	0.042
Superior corona radiata L	−23.4	−10.6	28.3	262	0.045
Posterior corona radiata R	21.8	−44.7	31.9	105	0.049
Posterior corona radiata L	−24.0	−37.5	27.4	317	0.042
Posterior thalamic radiation L	−34.5	−46.5	6.5	257	0.046
External capsule L	−29.6	2.7	−0.4	799	0.043
Superior longitudinal fascicle R	34.7	−2.2	23.5	191	0.049
Superior longitudinal fascicle L	−36.8	−25.5	28.2	678	0.042
Anterior thalamic radiation R	21.1	15.7	8.1	120	0.048
Anterior thalamic radiation L	−22.3	23.2	9.5	110	0.042
Corticospinal tract L	−22.8	−25.5	39.3	154	0.043
Forceps minor	−15.1	46.5	15.0	173	0.045
Inferior fronto-occipital fascicle R	25.7	26.8	5.0	178	0.048
Inferior fronto-occipital fascicle L	−33.0	−9.4	−2.1	727	0.043
Inferior longitudinal fascicle L	−41.5	−30.3	−7.0	270	0.045
Uncinate fascicle L	−28.0	10.9	−8.0	113	0.041

predominantly left hemispheric clusters of the temporal and frontal lobe (see Fig. 1; Table 2). Higher FA values were associated with more BPS language inhibition in important tracts for language processing, such as the uncinate fascicle, the superior and inferior longitudinal fascicle and the inferior fronto-occipital fascicle ($p < 0.05$, corrected for multiple comparisons).

Discussion

This is the first study to demonstrate a direct link between WM abnormalities in a predominantly left fronto-temporal language network and FTDs in schizophrenia. The fiber tracts associated with FTDs included the left uncinate fascicle, superior and inferior longitudinal fascicle and the inferior fronto-occipital fascicle.

Our findings within WM are in line with the existing literature, linking FTDs in schizophrenia to structural and functional brain abnormalities in the language system [7, 8, 11, 12]. Previous studies demonstrated associations of WM properties with semantic processing [16], a disorganized thoughts factor [15] and a broad clinical factor including several positive symptoms [17]. For example, the left uncinate fascicle connects Broca's region with the temporal lobe [35]. In fact, language performance such as semantic tasks was shown to rely on uncinate WM integrity [35–37]. Likewise, FTDs severity in schizophrenia was associated with functional deviation of the language network in Broca's area [12]. Thus, WM abnormalities in the uncinate fascicle may contribute to poor integrity of the language network and consequently to FTDs.

However, there was no simple correlation with FTDs severity in the BPS when collapsing positive and negative FTDs. In contrast, the linear brain–behavior association with WM microstructure was only detected with the BPS language score ranging from inhibition (negative FTDs) to normal speech (no FTDs) and disinhibition (positive FTDs). Particularly, patients with behavioral inhibition of language had highest FA values, suggesting that structural specialization of language tracts with increased FA may increase vulnerability for negative FTDs. In contrast, lower FA in language tracts increases vulnerability to positive FTDs. Thus, the finding indicates distinct pathobiology of positive and negative FTDs, regarding the association of WM abnormalities and aberrant behavior.

Some limitations of this study require discussion. Age may impact frontal and parietal WM structure [38–40],

but the effect of other variables, such as antipsychotic treatment, is still under debate [41–43]. Nevertheless, we included both variables as covariates of no interest into our analysis. In addition, we included the BPS affect and motor dimensions as covariates to rule out any unspecific effects of schizophrenia syndrome severity.

In conclusion, we found a direct link between a dimension of FTDs in schizophrenia and disturbed WM in language-related pathways. Further studies need to address the functional consequences of aberrant WM in language pathways at the level of cerebral network activity.

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Compliance with ethical standards

Conflict of interest The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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