



Increased structural connectivity of the medial forebrain bundle in schizophrenia spectrum disorders is associated with delusions of paranoid threat and grandiosity

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ABSTRACT

In many cases delusions in schizophrenia spectrum disorders (SSD) are driven by strong emotions such as feelings of paranoia or grandiosity. We refer to these extreme emotional experiences as psychotic affectivity. We hypothesized that increased structural connectivity of the supero-lateral medial forebrain bundle (slMFB), a major tract of the reward system, is associated with delusional psychotic affectivity. Forty-six patients with SSD and 44 healthy controls (HC) underwent diffusion weighted magnetic resonance imaging (DW-MRI)-scans. The slMFB and a comparison tract (corticospinal tract) were reconstructed using diffusion tensor imaging (DTI)-based tractography. Fractional anisotropy (FA) was sampled across the tracts. We used a mixed-model analyses of variance controlling for age and gender to compare FA of bilateral slMFB between SSD-patients and HC. Correlations of FA of bilateral slMFB and the PANSS-positive item delusions were calculated. In addition, FA was compared between three clinically homogeneous SSD-subgroups in terms of psychotic affectivity (severe, mild and no PA, sPA, mPA, nPA) and HC. FA of the slMFB did not differ between all SSD-patients and HC. In SSD-patients there was a positive correlation between delusions and FA in bilateral slMFB. Likewise, SSD-subgroups of psychotic affectivity and HC differed significantly in FA of the slMFB. Results were driven by higher FA in the right slMFB in sPA as compared to nPA and to HC. There was no significant effect for the comparison tract. In conclusion, increased structural connectivity of the slMFB may underlie delusional experiences of paranoia and grandiosity in SSD.

1. Introduction

In many cases delusions in schizophrenia spectrum disorders (SSD) are driven by strong emotions (Freeman et al., 2013; Garety et al., 2013; Heinz and Schlagenhauf, 2010; Lake, 2008; Strik et al., 2017). Mostly, the emotional valence is related to anxiety (e.g. an exceptional existential threat such as poisoning or persecution), whilst feelings of grandiosity (e.g. delusions of unrealistic power, or spiritual salvation) occur less frequently (Freeman et al., 2013; Garety et al., 2013; Paolini et al., 2016; Schoretsanitis et al., 2016; Strik et al., 2017). However, the emotional valence may switch rapidly between feelings of threat and power (Strik et al., 2017). Furthermore, in about 20% of SSD-patients paranoid and grandiose delusions co-occur even within the same observation period (Garety et al., 2013). There is also

evidence that paranoia and grandiosity may share functional and structural alterations of the limbic system (Stegmayer et al., 2014b, 2017). These findings are in line with concepts viewing delusions of paranoia and grandiosity as a psychotic mood disorder (Lake, 2008). In this study, we refer to these extreme emotional experiences of either grandiosity or paranoid threat as psychotic affectivity (Lang et al., 2016, 2015a; Schoretsanitis et al., 2016; Stegmayer et al., 2014b, 2017; Strik et al., 2017).

Cognitive models of psychosis suggest that delusional patients base their decisions on limited evidence which is referred to as “jumping to conclusions” (Dudley et al., 2016; Garety and Freeman, 2013). In addition, delusion formation may stem from logical attribution errors assigning salience to neutral or irrelevant stimuli. This is referred to as the incentive salience hypothesis (Heinz and Schlagenhauf, 2010;

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Kapur, 2003; Speechley et al., 2010). On a neurobiological level the incentive salience hypothesis states that delusions in schizophrenia are associated with increased activation of the ventral tegmental area (VTA) and the ventral striatum (Heinz and Schlagenhauf, 2010; Jensen et al., 2008; Knolle et al., 2018; Murray et al., 2008; Romaniuk et al., 2010; Schlagenhauf et al., 2009). This overactivation is thought to be mediated by increased dopaminergic input from the VTA to the ventral striatum, which may lead to prediction errors of salience, attributing meaning to irrelevant stimuli (Heinz and Schlagenhauf, 2010; Kapur, 2003). The bed nucleus of the stria terminalis (BNST) is essential for the attribution of the emotional valence (Lebow and Chen, 2016). Overactivation of the BNST may thus underlie feelings of sustained threat or power in SSD-patients with delusions of paranoia or grandiosity (Avery et al., 2016; Davis et al., 2010; Walker et al., 2009, 2003).

The supero-lateral medial forebrain bundle (slMFB) is a polysynaptic pathway connecting cerebellar regions, brain stem, VTA, the BNST, the ventral striatum and the orbitofrontal cortex (Bracht et al., 2015, 2014b; Coenen et al., 2012, 2018b; Rivas-Grajales et al., 2018b; Schlaepfer et al., 2013; Zhang et al., 2016). Given that all the above mentioned brain regions have been linked to the formation of delusions, the slMFB may play a core role in delusions and in the attribution of their emotional valence (Avery et al., 2016; Coenen et al., 2011; Haber and Behrens, 2014; Heinz and Schlagenhauf, 2010; Lebow and Chen, 2016).

Diffusion weighted MRI (DW-MRI) enables an *in vivo* assessment of white matter microstructure (Jones et al., 2013). The most commonly used DW-MRI-based measure to probe white matter microstructure is the fractional anisotropy (FA). FA is influenced by barriers to diffusion of water molecules which may be related to anatomical alterations in white matter microstructure (Jones et al., 2013). Whole brain approaches such as Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006)) compare white matter microstructure on a voxel-by-voxel level whilst tractography approaches average diffusion properties such as FA across tracts of interest for a specific research question (Jones et al., 2013). Given that schizophrenia is considered as a disorder of dysconnectivity (Friston, 1998), DW-MRI has been used extensively to study white matter microstructure alterations in schizophrenia (Ellison-Wright and Bullmore, 2009; Fitzsimmons et al., 2013). Whilst mainly decreases of FA have been reported (Fitzsimmons et al., 2013; Kelly et al., 2018), focal increases in FA have been linked to the presence of specific psychotic symptoms such as auditory verbal hallucinations or formal thought disorders (Hubl et al., 2004; Viher et al., 2018).

Two previous DW-MRI-studies reconstructed the striato-nigro-striatal (SNS)-tract (a segment of the slMFB) in schizophrenia. One study did not find group differences of structural connectivity based on a probabilistic fiber tracking approach (Bracht et al., 2014a). Another tractography study investigated chronic schizophrenia patients and found higher tract-dispersion (TD, an index of white matter morphology (Savadjiev et al., 2014)) but no differences of FA in the right SNS-tract (Rivas-Grajales et al., 2018a). However, to date no tractography study reconstructed the slMFB to investigate its role in the pathophysiology of delusional psychotic affectivity.

It was the first aim of this study to explore the neurobiological correlates of delusions in patients with schizophrenia spectrum disorders (SSD). Multiple training studies suggest that repeated neuronal activity induces structural plasticity that may lead to increases in FA (Piervincenzi et al., 2017; Salminen et al., 2016; Scholz et al., 2009; Steele et al., 2013). Given that the incentive salience hypothesis (Heinz and Schlagenhauf, 2010; Kapur, 2003) postulates an overactivation of the VTA and the ventral striatum (Heinz and Schlagenhauf, 2010; Jensen et al., 2008; Murray et al., 2008; Romaniuk et al., 2010) in delusion formation such increases in focal activity may lead to structural alterations of the slMFB in delusional psychotic patients. Thus, we hypothesized a positive correlation

between the severity of delusions (as measured by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987)) and FA of the slMFB.

Dimensional assessments of psychopathology aid disentangling the heterogeneity of clinical presentations in psychosis, adding specificity to studies on the pathobiology of psychosis. One concept, the Systems Neuroscience of Psychosis (SyNoPsis) views psychosis to result from a fundamental communication breakdown of the language, the affectivity or the motor domain (Strik et al., 2017). SyNoPsis postulates that the neurobiology of specific psychosis symptoms is ideally studied contrasting patients with these symptoms with patients without these symptoms; instead of comparing all patients to healthy controls (Strik et al., 2017). The SyNoPsis instrument is the Bern Psychopathology Scale (BPS) that rates the global severity of impairments in the language, affectivity and the motor domain (Strik et al., 2010).

It is the second aim of this study to explore the role of the slMFB for psychotic affectivity in patients with SSD. In line with previous studies (Lang et al., 2016, 2015a; Schoretsanitis et al., 2016; Stegmayer et al., 2014b, 2017) we used the BPS to stratify patients into subgroups with severe, mild and no psychotic affectivity (sPA, mPA, nPA). We hypothesized increased FA in the slMFB in SSD-patients with sPA as compared to subgroups with mPA, nPA and HC.

Specificity of putative findings was tested twofold. First, a comparison tract (corticospinal tract, CST) was reconstructed. We did not expect any significant differences of FA in the CST between sPA, mPA, nPA and HC. Second, we stratified SSD-patients according to the severity in other psychopathological domains (motor and language) (Bracht et al., 2012; Steinau et al., 2017; Strik et al., 2017, 2010). We did not assume slMFB-microstructure to differ between subgroups of those comparison domains.

2. Methods

2.1. Participants

Forty-six patients with SSD (schizophrenia = 37, schizoaffective disorder = 2, and schizophreniform disorder = 7) according to the Diagnostic and Statistical Manual of Mental Health (DSM-5) and 44 healthy controls matched for age, gender and years of education have been included in the study. Patients were recruited at the inpatient and outpatient departments of the University Hospital of Psychiatry and Psychotherapy, Bern. Inclusion criterion for all participants was right-handedness as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Exclusion criteria were contraindications to perform an MRI, neurological disorders or a history of head injuries with subsequent loss of consciousness or a history of substance use disorder other than nicotine. Exclusion criterion for controls was a history of a psychiatric disorder (as assessed with the Mini International Neuropsychiatric Interview (MINI)) (Sheehan et al., 1998). All but four patients were taking antipsychotic medication. Chlorpromazine equivalents were calculated to assess the current antipsychotic dosage. (Woods, 2003) The study was approved by the local ethics committee (KEK-BE 025/13) and adhered to the Declaration of Helsinki. All participants provided written informed consent. Demographic details are given in Table 1.

2.2. Psychopathological assessment

Psychopathology was assessed at the day of the MRI-scan using the PANSS (Kay et al., 1987), the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) and the BPS (Strik et al., 2010). In the present study, the severity of psychotic affectivity was assessed using the BPS global score of the affectivity domain. SSD-patients were rated on a seven-point Likert

Table 1
Clinical and demographic characteristics.

	Schizophrenia spectrum disorder	Healthy controls	Analyses
Age (y)	38.2 ± 11.5	38.8 ± 13.6	T(88) = -0.23, <i>P</i> = .815
Gender (women)	37%	41%	X ² (1) = 0.15, <i>P</i> = .701
Right handedness	100%	100%	
Education (years)	13.4 ± 3.1	14.1 ± 2.7	T(88) = -1.24, <i>P</i> = .220
Duration of illness (years)	12.3 ± 12.4		
Number of episodes	6.8 ± 7.2		
PANSS positive	18.4 ± 6.3		
PANSS negative	18.5 ± 5.0		
PANSS total	36.4 ± 9.1		
PANSS_P1 (delusions)	3.5 ± 1.7		
PANSS_P5 (grandiosity)	2.3 ± 1.3		
PANSS_P6 (suspiciousness)	2.4 ± 1.3		
CAINS (sum score)	18.8 ± 11.0		
SANS (global score)	9.4 ± 5.0		
CPZ (mg)	403.4 ± 347.3		

scale ranging from -3 (most severe psychotic anxiety, i.e. paranoid threat) to +3 (most severe psychotic grandiosity, i.e. delusions of power), while 0 represents normal affectivity (Lang et al., 2016; Schoretsanitis et al., 2016; Stegmayer et al., 2014b, 2017). Importantly, the severity of psychotic affectivity is rated based on the global clinical impression and does not result from the sum of single items. For example, the presence of few but severe affective signs (e.g. an isolated but severe paranoid threat of poisoning) would still result in a high global severity score of the affectivity domain. Internal consistency and external validity of the BPS has been demonstrated repeatedly (Bracht et al., 2012; Lang et al., 2016, 2015a, 2015b; Schoretsanitis et al., 2016; Stegmayer et al., 2014b, 2017; Steinau et al., 2017; Strik et al., 2010).

SSD-patients were grouped into clinically homogeneous subgroups according to the severity of psychotic affectivity based on the BPS affectivity domain global score. We defined three patient subgroups: The first subgroup incorporates SSD-patients with severe (sPA, global scores of the affectivity domain = -3, -2, +2, +3), the second group includes SSD-patients with mild psychotic affectivity (mPA, global scores of the affectivity domain = -1, +1), and the third group consists of SSD-patients with normal affectivity (no psychotic affectivity, nPA, global scores of the affectivity = 0). This approach is in line with previous studies of our group (Lang et al., 2015b; Stegmayer et al., 2014b, 2017).

The global scores of the language and the motor domain of the BPS were used to collate SSD-patients into subgroups of two comparison domains. Three patient subgroups were defined for both the motor and the language domain according to their global rating scores of the BPS (first group: -3, -2, +2, +3; second group: -1, +1; third group 0). For instance, stupor is rated as motor inhibition (-) and psychomotor agitation is rated as motor disinhibition (+) whilst mutism is rated as language inhibition (-) and increased speech production is rated as language disinhibition (+). In both domains we did not expect differences of FA in the sLMFB. For a detailed description of the language and the motor domains we refer to the original publication of the BPS (Strik et al., 2010) and to its applications (Bracht et al., 2012; Stegmayer et al., 2014a; Viher et al., 2018).

2.3. MRI-acquisition

MRI-scans were acquired on a 3 Tesla MRI-scanner (Siemens Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany) with a 12-channel radio frequency headcoil for signal reception.

3D-T1-weighted (Modified Driven Equilibrium Fourier Transform Pulse Sequence; MDEFT) images for each subject have been obtained, resulting in 176 sagittal slices with 256 × 256 matrix points with a non-cubic field of view (FOV) of 256 mm, yielding a nominal isotropic

resolution of 1 mm³. Further scan parameters were as follows: Repetition time (TR) = 7.92 ms, echo time (TE) = 2.48 ms and flip angle = 16°

For DTI measurements, a spin echo planar imaging (EPI) sequence (59 slices, FOV = 256 × 256 mm², sampled on a 128 × 128 matrix, slice thickness = 2 mm, gap between slices = 0 mm, resulting in 2 mm³ isotropic voxel resolution, TR/TE = 8000/92 ms) covering the whole brain (40 mT/m gradient, 6/8 partial Fourier, GRAPPA factor 2, bandwidth 1346 Hz/Px) was used. Diffusion-weighted images (DWI) were positioned in the axial plane parallel to the AC-PC line. Diffusion encoding gradients (b-value = 1300s/mm²) were applied along 42 directions. In addition, four non-diffusion weighted scans (b-value = 0 s/mm²) were collected. We used a balanced and rotationally invariant diffusion-encoding scheme over the unit sphere to generate the DTI data. Acquisition time was 6 min.

2.4. Diffusion MRI data pre-processing

DWI-data were pre-processed using ExploreDTI v4.8.3 (Leemans et al., 2009). We used a B-matrix rotation to correct for motion artefacts and eddy current distortions (Leemans and Jones, 2009). Field inhomogeneities were corrected as described in Wu et al. (Wu et al., 2008). DWIs were non-linearly warped to the MDEFT-image using the fractional anisotropy map from the DWIs as a reference. Warps were calculated using Elastix (Klein et al., 2010). This results in corrected DWIs being localized in the same (undistorted) space as the MDEFT-image. A single diffusion tensor model was fitted to the diffusion data for calculation of quantitative parameters such as FA (Basser et al., 1994). Diffusion properties (FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD)) were sampled along the tracts.

2.5. Tractography

Whole brain tractography was performed using ExploreDTI v4.8.3 (Leemans et al., 2009) and applying an algorithm similar to that of Basser et al. (Basser et al., 1994). Termination criteria were an angle threshold >45° and FA <0.2. Tracts were reconstructed based on anatomical landmarks as described in Bracht et al. (Bracht et al., 2015). For reconstruction of the sLMFB one horizontal region of interest (ROI) was placed on the DWI surrounding the ventral tegmental area (VTA). Anatomical borders were laterally the substantia nigra, anteriorly the mammillary bodies and posteriorly the red nucleus. A second ROI was drawn on structural images surrounding caudate and putamen on a coronal section at the height of the nucleus accumbens (NAcc) (Bracht et al., 2015) (see Fig. 1 and supplementary material, S1). For reconstruction of the comparison tract (corticospinal tract) the

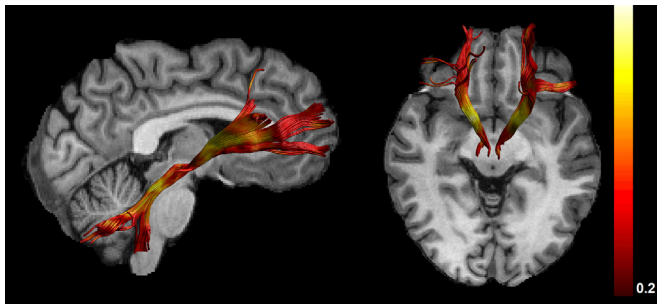


Fig. 1. demonstrates reconstructions of the sLMFB for an individual participant with view from the right side (left image) and view from above (right image). FA metrics are superimposed on the reconstructed tracts.

precentral gyrus was encircled. A second ROI was drawn at the height of the pons on color coded DWI-images, where fibers of the corticospinal tract descend (Bracht et al., 2018) (see supplementary material, S2).

2.6. Group comparison between SSD-patients and healthy controls

Two-sample t-tests were used to compare demographic differences between SSD-patients and healthy controls (see Table 1). A mixed-model ANCOVA was used to investigate group differences in FA of the left and the right sLMFB between HC and SSD. Group (SSD and HC) was entered as independent variable, mean-FA as dependent variable, hemisphere (left-right) as “within-subject” variable and age and gender as covariate.

2.7. Correlations between FA of the sLMFB and delusions

Across all patients, we calculated Spearman correlations between FA of left and right sLMFB and the PANSS-positive item delusions (PANSS_P1). Spearman correlations instead of Pearson correlations were used since PANSS-items are rather ordinal than continuous variables. Alterations in FA and AD may rather stem from axonal properties such as fiber coherence (Mezer et al., 2013), whilst MD and RD may be more sensitive to myelin changes (Song et al., 2002). Thus, where a main effect of FA (our primary outcome measure) was seen, results were followed-up with corresponding analyses of MD, RD and AD.

Exploratory correlations between FA of left and right sLMFB and chlorpromazine equivalents (Woods, 2003) and duration of illness as well as psychopathology measures related to depression (Bracht et al., 2015, 2014b; Coenen et al., 2011; Schlaepfer et al., 2013) and negative and positive symptoms (Bopp et al., 2017; Bracht et al., 2014a) were calculated to improve specificity and to complement our analyses (results are presented in the supplementary material, S5).

2.8. Group comparisons between sPA, mPA, nPA-subgroups and HC

ANOVAS were used to explore clinical and demographic differences between sPA, mPA, nPA, and HC. In order to investigate group differences in FA of the left and the right sLMFB between those clinically homogeneous subgroups in terms of psychotic affectivity a mixed-model ANCOVA was used. Group (sPA, mPA, nPA and HC) was entered as independent variable, mean-FA as dependent variable, hemisphere (left-right) as “within-subject” variable and age and gender as covariates. Significant main effects were followed up with post-hoc ANCOVAs including age and gender as covariates. Post-hoc tests were corrected for multiple comparisons using a False Discovery Rate correction (Benjamini and Hochberg, 1995). Where a main effect of FA (our primary outcome measure) was seen, results were followed-up with corresponding analyses of MD, RD and AD.

To enhance specificity of putative findings all analyses have also

been performed for the comparison tract (corticospinal tract). Further, we stratified SSD-patients into severely, moderately and unaffected patients of psychopathological comparison domains (the motor domain and the language (associative) domain) (Bracht et al., 2012; Strik et al., 2017; Viher et al., 2018). We did not assume homogeneous subgroups of those comparison domains to differ in sLMFB-microstructure.

Tract-specific group comparisons were complemented using whole brain TBSS analyses (see supplementary material, S10). Statistically we complement our analyses providing bootstrap confidence intervals for correlations and for effect sizes of subgroup comparisons (see supplementary material, S12 and S13).

3. Results

3.1. Group comparison between SSD-patients and healthy controls

Groups (SSD, HC) did not differ regarding age, gender, handedness and years of education (see table 1). The mixed-model ANCOVA for FA of the sLMFB controlling for age and gender did not show a significant main effect of group for FA comparing all SSD-patients with HC ($F(1, 86) = 1.10, P = .297, \eta^2 = 0.012$). Neither was there a main effect for FA of hemisphere ($F(1, 86) = 0.25, P = .618, \eta^2 = 0.003$) nor a group $\times$ hemisphere interaction effect ($F(1, 86) = 0.30, P = .586, \eta^2 = 0.003$). There were no significant effects for the comparison tract (see supplementary material, S6).

3.2. Correlations with delusions

Across the whole group there was a positive correlation between delusions (PANSS_P1) and FA of the left ($Rho = 0.337, P = .022$) and of the right ($Rho = 0.399, P = .006$) sLMFB (see Fig. 2).

Follow-up analyses demonstrated negative correlations between delusions (PANSS_P1) and MD of left ($Rho = -0.537, P < .001$) and right ($Rho = -0.467, P = .001$) sLMFB, as well as between delusions and AD of the left ($Rho = -0.488, P = .001$) and the right ($Rho = -0.326, P = .029$) sLMFB, and delusions and RD of the left ($Rho = -0.455, P = .002$) but not of the right ($Rho = -0.288, P = .055$) sLMFB. There were no significant correlations between delusions (PANSS_P1) and FA of the comparison tract (see supplementary material, S3).

3.3. Group comparisons between sPA, mPA, nPA and healthy controls

SSD-patients were grouped into sPA ($n = 16$), mPA ($n = 20$) and nPA ($n = 10$). Subgroups (sPA, mPA, nPA and HC) did not differ regarding age ($F(3, 89) = 0.26, P = .855$), gender ($\chi^2(3) = 0.48, P = .922$) or years of education ($F(3, 89) = 0.98, P = .408$). SSD-subgroups (sPA, nPA, mPA) differed significantly regarding PANSS-positive total scores, which were driven by higher PANSS-items delusions, excitement and suspiciousness/persecution and hostility in the sPA group (for demographic details and group comparisons see supplementary material, S7).

The mixed-model ANCOVA controlling for age and gender comparing FA of the sLMFB showed a significant main effect of group (sPA, mPA, nPA, HC) ($F(3, 84) = 3.06, P = .033, \eta^2 = 0.098$), but no significant main effect of hemisphere ($F(1, 84) = 0.24, P = .629, \eta^2 = 0.003$), nor an interaction effect of group $\times$ hemisphere ($F(3, 84) = 1.74, P = .166, \eta^2 = 0.058$).

The observed main effect was not present in the comparison tract (corticospinal tract) (see supplementary material, S9). Anatomical specificity of the main effect of group for FA of the sLMFB was shown by a significant group $\times$ tract (levels tract (sLMFB) and control tract (CST) interaction ($F(3, 84) = 3.99, P = .010^*$). Furthermore, the FA in the sLMFB did not differ between groups stratified according to the psychopathological comparison domains, i.e. motor and language (see supplementary material, table S11).

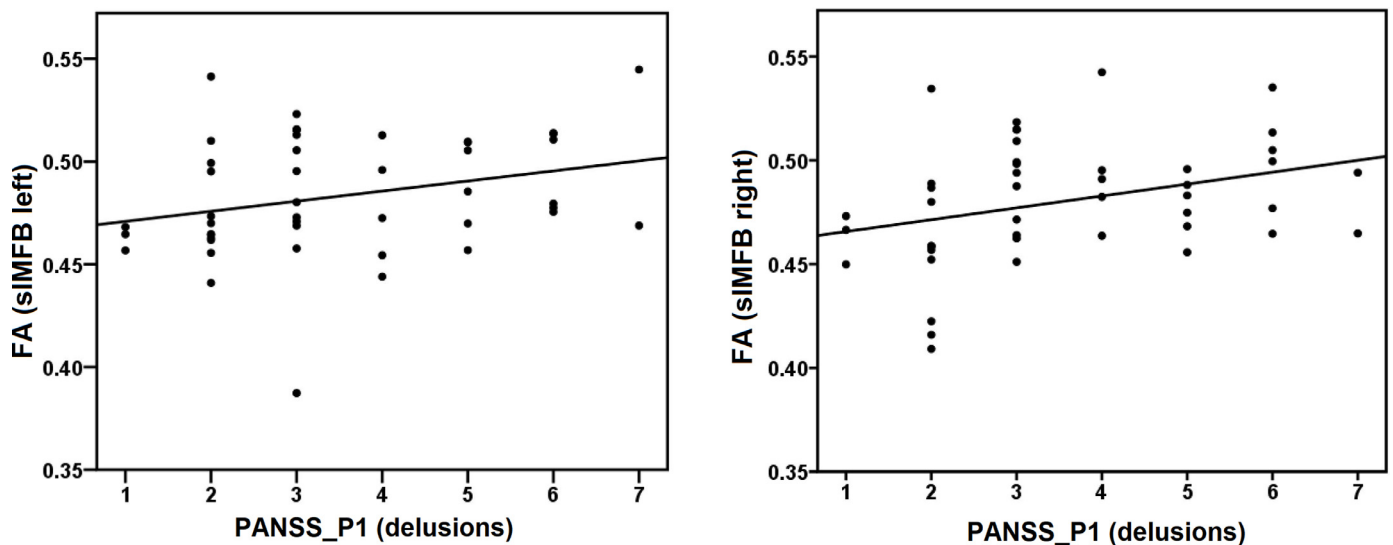


Fig. 2. demonstrates correlations between delusions PANSS_P1 (delusions) and FA of the left ($Rho = 0.337$, $P = .022$) and of the right ($Rho = 0.339$, $P = .006$) sIMFB across all SSD-patients.

Table 2

Results of post-hoc ANCOVAs comparing FA between sPA, mPA, nPA and HC controlling for age and gender are displayed. Displayed p-values are corrected for multiple comparisons using a False Discovery Rate (Benjamini and Hochberg, 1995).

Left sIMFB Contrast (mean FA $\pm$ SD)	Statistics	η^2
sPA (0.49 ± 0.04) vs HC (0.48 ± 0.03)	$F(1,59) = 1.87$, $P = .266$	.032
sPA (0.49 ± 0.04) vs mPA (0.49 ± 0.03)	$F(1,35) = 0.01$, $P = .992$	<.001
sPA (0.49 ± 0.04) vs nPA (0.47 ± 0.01)	$F(1,25) = 3.26$, $P = .204$	.129
mPA (0.49 ± 0.03) vs HC (0.48 ± 0.03)	$F(1,63) = 2.25$, $P = .247$	.036
mPA (0.49 ± 0.03) vs nPA (0.47 ± 0.01)	$F(1,29) = 6.10$, $P = .08$	.190
nPA (0.47 ± 0.01) vs HC (0.48 ± 0.03)	$F(1,53) = 1.02$, $P = .38$	.020
Right sIMFB Contrast (mean FA $\pm$ SD)	Statistics	
sPA (0.50 ± 0.02) vs HC (0.48 ± 0.02)	$F(1,59) = 7.86$, $P = .042^*$	.123
sPA (0.50 ± 0.02) vs mPA (0.48 ± 0.03)	$F(1,35) = 5.05$, $P = .096$	.136
sPA (0.50 ± 0.02) vs nPA (0.46 ± 0.02)	$F(1,25) = 11.49$, $P = .0036^*$	.343
mPA (0.48 ± 0.03) vs HC (0.48 ± 0.02)	$F(1,63) < 0.001$, $P = .992$	<.001
mPA (0.48 ± 0.03) vs nPA (0.46 ± 0.02)	$F(1,29) = 1.21$, $P = .376$	.044
nPA (0.46 ± 0.02) vs HC (0.48 ± 0.02)	$F(1,53) = 2.20$, $P = .257$	.042

Post-hoc ANCOVAs controlling for age and gender comparing FA of left and right sIMFB between sPA, mPA, nPA and HC demonstrated increases in FA for the right sIMFB in sPA as compared to HC and nPA (see Table 2). All P-values are corrected for multiple comparisons using a False Discovery Rate correction (Benjamini and Hochberg, 1995).

Secondary analyses for significant post-hoc ANCOVAs demonstrated decreased MD for the right sIMFB comparing sPA with nPA, and sPA with HC. There were no significant group differences for AD and RD (see supplementary material, S8).

Distribution of FA across BPS-global scores of affectivity are best explained by a quadratic regression model. Plotting FA-values across subgroups a U-shaped distribution with increases of FA in SSD-patients with both paranoia and grandiosity can be seen (see Fig. 3, and supplementary material, S4).

4. Discussion

Delusions are thought to result from dopamine-driven aberrant salience (Heinz and Schlagenhauf, 2010; Kapur, 2003). Here, we explored for the first time whether the sIMFB as a major white matter pathway of the reward system was linked to delusions of psychotic affectivity. Our study has two main findings. First, we demonstrated an

association between the severity of delusions and white matter microstructure of both left (FA, MD, RD, AD) and right (FA, MD, AD) sIMFB. Second, we found increased structural connectivity (as measured by increased FA and reduced MD) in the right sIMFB in sPA compared to nPA and to HC. All findings were specific for the sIMFB (and not present in a comparison tract). Further, group differences of FA in the sIMFB were specific for the sPA group and disappeared when stratifying SSD-patients across psychopathological comparison dimensions (motor and language domain).

The identified positive correlation between FA in bilateral sIMFB in SSD-patients and the severity of delusions corroborates the theoretical concept of the incentive salience hypothesis suggesting that increased (dopaminergic) input from the VTA to the ventral striatum attributes salience to otherwise neutral stimuli (Heinz and Schlagenhauf, 2010; Kapur, 2003). An overactivation of the VTA and the ventral striatum (Heinz and Schlagenhauf, 2010; Jensen et al., 2008; Murray et al., 2008; Romaniuk et al., 2010) may induce structural neuroplasticity (Salminen et al., 2016; Scholz et al., 2009; Steele et al., 2013; Stuber et al., 2008) leading to structural alterations as suggested by our findings of increased FA (and decreased MD, RD and AD) in the sIMFB in delusional psychotic patients. However, our study design does not allow for conclusions on the direction of causality between functional

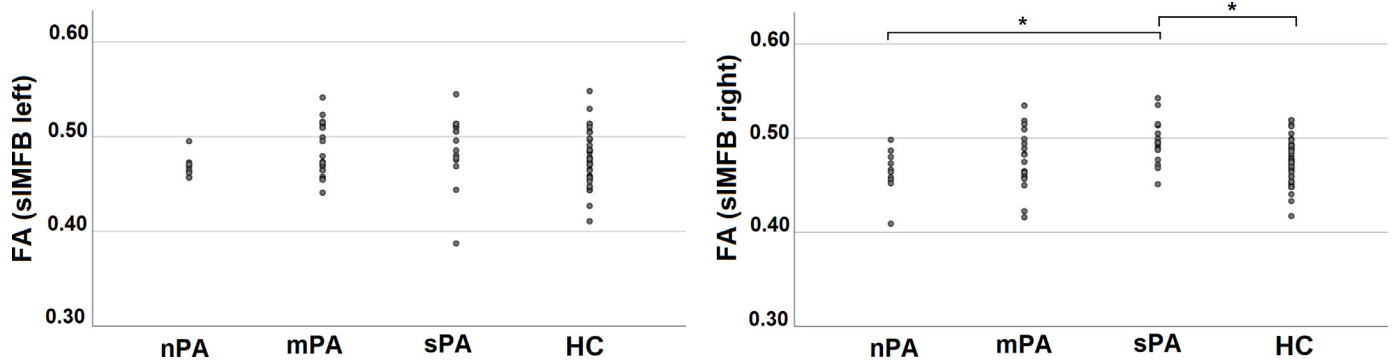


Fig. 3. Mean-FA of the left sIMFB (left side) and the right sIMFB (right side) for homogeneous groups of psychotic affectivity. SSD-patients with sPA show increased FA in the right sIMFB compared to nPA and HC.

and structural alterations in SSD-patients with delusions.

We complemented our analyses approach using a dimensional approach to stratify SSD-patients into homogeneous subgroups in terms of the severity of psychotic affectivity (Lang et al., 2016; Schoretsanitis et al., 2016; Stegmayer et al., 2014b, 2017; Strik et al., 2017). We found increased FA and reduced MD of the right sIMFB in SSD-patients with sPA as compared to nPA and HC. There was a U-shaped FA-distribution of bilateral sIMFB demonstrating increases of structural alterations with increases of either grandiosity or paranoia (see supplementary material, S4). Similar distributions of structural and functional alterations in SSD-patients with sPA have been reported for the volume of the ventral striatum and for the perfusion of the amygdala (Stegmayer et al., 2014b, 2017). Thus, grandiosity and paranoia may share structural and functional alterations of the limbic and the reward system.

Given that the sPA-subgroup had higher FA-values and more pronounced delusions than other PA-subgroups, the reported correlation between delusions (PANSS_P1) and FA across all SSD-patients is also captured by the identified group differences in FA between subgroups of PA. Rather than assessing the presence or severity of delusions, the BPS focusses on the emotional valence of delusions and therefore provides clinically relevant additional information. Our sPA-subgroup consisted mainly of SSD-patients with paranoid threat. This is corroborated by higher PANSS_P6 (persecution) and PANSS_P7 (hostility) values in the sPA-subgroup and points to a predominant paranoid syndrome in the sPA subgroup of this sample. Nevertheless, increases of FA are also seen in sPA with grandiosity (see supplementary material, S4).

Previous fMRI and arterial spin labelling (ASL)-studies suggest that paranoia in psychosis may underlie increased amygdala activation and decreased functional connectivity between the prefrontal cortex and the amygdala (Hall et al., 2008; Hoptman et al., 2014, 2010; Pinkham et al., 2015; Stegmayer et al., 2017). These changes in functional connectivity could rely on structural alterations of pathways connecting the prefrontal cortex with the amygdala such as the uncinate fasciculus (Bracht et al., 2009; Von Der Heide et al., 2013) or the anterior thalamic radiation (Coenen et al., 2012). Even though the anterior thalamic radiation runs medially of the sIMFB there is a partial overlap in the anterior limb of the internal capsule. Thus, given the current resolution of DTI it cannot be excluded that lateral segments of the ATR contribute to our results as well. The sIMFB does not only connect to core regions of the reward system but also to relay stations of the motor system such as the cerebellum (Coenen et al., 2018a). Thus, the sIMFB may play an essential role for the preparation of motor related responses to experiences of psychotic affectivity such as fight or flight reactions in SSD-patients with paranoid experiences.

Deep brain stimulation (DBS) is used to stimulate the sIMFB in treatment resistant depression (Coenen et al., 2018a; Fenoy et al., 2018; Schlaepfer et al., 2013). Interestingly, in rare cases psychotic symptoms

of grandiosity have been attributed to DBS-stimulation of the sIMFB (Coenen et al., 2009). It is possible that reduced structural connectivity of the sIMFB in depression (Bracht et al., 2014b) is being successfully reversed by sIMFB-DBS. Therefore, structural connectivity of the sIMFB may reflect a continuum from severe anhedonia to experiences of intense emotions such as psychotic affectivity as suggested by our findings of increased FA in sPA-SSD patients.

We identified increases in FA (and decreases in MD) in the sIMFB in sPA. Alterations in FA and AD may rather stem from axonal properties such as fiber coherence (Mezer et al., 2013), whilst MD and RD may be more sensitive to myelin changes (Song et al., 2002). Thus, identified changes in sPA may be due to myelin alterations. However, changes in diffusion properties are unspecific and do not allow conclusions on changes in “fiber integrity” (Jones et al., 2013). Novel sub-compartment specific white matter mapping techniques may lead to more informative neurobiological conclusions (Bracht et al., 2016; Vanes et al., 2018).

Using TBSS we identified widespread distributions of FA reductions predominantly localized in the corpus callosum comparing all SSD-patients with HC (see supplementary material S10). This is in line with a broad body of literature (Fitzsimmons et al., 2013; Kelly et al., 2018). On the other hand, increases of FA (as identified in the sIMFB in sPA) have been linked to positive psychotic symptoms (Hubl et al., 2004; Viher et al., 2018). Thus, our results corroborate both concepts pointing to global white matter alterations in schizophrenia and concepts linking overactivation of functionally connected brain regions to increases of structural connectivity.

4.1. Limitations

This study has some limitations. First, the sample size of SSD-PA subgroups is small. Second, there are non-significant trends for demographic and clinical differences between SSD-PA subgroups which may have contributed to group differences. Third, even though smoking may have an impact on FA in schizophrenia we did not collect these data (Gons et al., 2011; Zhang et al., 2010). Fourth, cross-sectional designs do not enable statements on causality and neuroplasticity. Thus, we cannot conclude on sIMFB-microstructure as a state or a trait marker. Fifth, a non-significant finding in the comparison tract does not proof the absence of an actual effect.

5. Conclusions

In conclusion, this is the first tractography study to investigate the role of the sIMFB for experiences of delusional psychotic affectivity in SSD. Our results suggest an association between experiences of paranoid threat and grandiosity in SSD with white matter microstructure of the sIMFB. Our results thus corroborate the important role of the reward system in the pathophysiology of delusions (Heinz and

Schlagenhauf, 2010; Kapur, 2003). Further, this study argues for investigating patients with distinct homogeneous behavioral phenotypes in order to study the neurobiology of psychotic symptom dimensions (Insel et al., 2010; Strik et al., 2017).

Declaration of Competing Interest

Dr. Walther received honoraria from Lundbeck, Lilly, Janssen, and Otsuka. All further authors report no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102044.

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