RESEARCH PAPER

Acta Neurobiol Exp 2021, 81: 80–95
DOI: 10.21307/ane-2021-009

On the relation of white matter brain abnormalities and the asociality symptoms in schizophrenia outpatients – a DTI study

Przemysław Adamczyk[1]*, Olga Płonka[1], Dawid Kruk[2,4], Martin Jáni[1,3], Piotr Błądziński[4], Aneta Kalisz[4], Stynke Castelein[5,6], Andrzej Cechnicki[2,4] and Miroslaw Wyczesany[1]

[1] Institute of Psychology, Jagiellonian University, Krakow, Poland,
[2] Psychosis Research and Psychotherapy Unit, Association for the Development of Community Psychiatry and Care, Krakow, Poland,
[3] Department of Psychiatry, Faculty of Medicine, Masaryk University and University Hospital Brno, Brno, Czech Republic,
[4] Community Psychiatry and Psychosis Research Center, Chair of Psychiatry, Medical College, Jagiellonian University, Krakow, Poland,
[5] Lentis Research, Lentis Psychiatric Institute, Groningen, The Netherlands,
[6] Faculty of Behavioural and Social Sciences, University of Groningen, Groningen, The Netherlands,
** Email: przemyslaw.adamczyk@uj.edu.pl*
The study was conducted by the Krakow Schizophrenia Research Group, Krakow, Poland

Recent MRI studies have shown that abnormal functional connections in schizophrenia coexist with subtle changes in the structure of axons in the brain. However, there is a discrepancy in the literature concerning the relationship between white matter abnormalities and the occurrence of negative psychopathological symptoms. In the present study, we investigate the relationship between the altered white matter structure and specific psychopathology symptoms, i.e., subscales of Positive and Negative Syndrome Scale (PANSS) and Brief Negative Symptoms Scale (BNSS) in a sample of schizophrenia outpatients. For investigation on white matter abnormalities in schizophrenia, the diffusion tensor imaging analysis of between-group differences in main diffusion parameters by tract-based spatial statistics was conducted on schizophrenia outpatients and healthy controls. Hence, the correlation of PANSS and BNSS psychopathology subscales in the clinical group with fractional anisotropy was analyzed in the 17 selected cortical regions of interest. Presented between-group results revealed widespread loss of white matter integrity located across the brain in schizophrenia outpatients. Results on the white matter relationship with psychopathology revealed the negative correlation between fractional anisotropy in the left orbital prefrontal cortex, right Heschl's gyrus, bilateral precuneus and posterior cingulate cortex and the severity of asociality, as assessed with the BNSS. In conclusion, the presented study confirms the previous evidence on the widespread white matter abnormalities in schizophrenia outpatients and indicates the existence of the subtle but specific association between fractional anisotropy in the fronto-temporo-parietal regions with the asociality.

Key words: schizophrenia, diffusion tensor imaging, white matter, negative symptoms, psychopathology

INTRODUCTION

The brain origins of psychotic symptoms, known as Kraepelin's 'dementia praecox', were further indicated by Bleuer as an essential disintegration of mental processes in schizophrenia (Jablensky, 2010). Nowadays, it resonates with the disconnection theory (Friston, 2002; Friston et al., 2016), where neuropathology of schizophrenia points at abnormal functional connections associated with subtle changes in the structure of axons located across the brain.

Recent evidence implicates that altered white matter (WM) structure in schizophrenia can be regarded as a long-term effect of disturbed myelinogenesis, e.g.

Received 11 September 2020, accepted 29 January 2021

lower levels of oligodendrocyte- and myelin-related proteins (Cassoli et al., 2015; Schoonover et al., 2019), but also as a consequence of excitotoxicity, cytoskeletal abnormalities (Uranova et al., 2004) or disturbances in neurogenesis, e.g. weakened synaptic pruning (Alba-Ferrara and de Erausquin, 2013; Klauser et al., 2016). Finally, the abnormal structural connectivity and microstructural changes on synapses lead to the functional disturbances and manifestation of psychopathological symptoms related to schizophrenia (Friston 2002; Friston et al., 2016).

Apart from positive symptoms (e.g. hallucinations, delusions, paranoid thoughts) and various socio-cognitive deficiencies, negative symptoms (i.e., alogia, apathy, avolition, anhedonia, asociality, blunted affect, and poverty of speech) remain as an extremely important hallmark of the diagnosis and considered a core feature of schizophrenia. Indeed, negative symptoms are believed to be the most stable characteristics for schizophrenia psychopathology (Andreasen, 1982; Harrow and Jobe, 2018), and social anhedonia is recognized as a predictor of later schizophrenia spectrum disorder development in young adults (Kwapil, 1998).

However, despite long and extensive clinical research on negative symptoms, the effectiveness of its treatment remains at the pretty unsatisfactory level of low to moderate, while its neural basis remains largely unknown (Kaiser et al., 2011; Asami et al., 2014; Bijanki et al., 2015; Garcia-Portilla et al., 2015; Shaffer et al., 2015; İnce and Üçok 2018; Strauss et al., 2018; Kochunov et al., 2019).

Hence, the investigation on biomarkers of this phenomenon, including structural changes in brain connectivity, that affect various aspects of brain functioning is of great importance, as the occurrence of negative symptoms has a destructive impact on individual functioning in schizophrenia (e.g. occupational impairment, financial dependence, poor social relationships and worse quality of life) and remains one of the most important scientific and societal problems related to schizophrenic psychosis remediation (Kaiser et al., 2011; Bijanki et al., 2015; Dollfus and Lyne 2017; Correll and Schooler, 2020).

Recently, analyses of WM alterations in the schizophrenic brain are performed using diffusion tensor imaging (DTI). DTI is based on the estimation of the diffusion of water molecules in tissues as this allows a reconstruction of images of brain fibers' cytoarchitecture (Emsell et al., 2016). One of the most widely used DTI measurements is fractional anisotropy (FA), which is generally interpreted as a biomarker of the integrity of WM bundles (Assaf and Pasternak, 2008). Other commonly used parameters are axial diffusivity (AD), regarded as the index of axonal damage; radial diffusivity (RD), a measure of the level of myelinization (Karlsgodt, 2016); mean diffusivity (MD), considered a complex measure of the surrounding cytoarchitecture (Emsell et al., 2016).

Recent data undoubtedly indicate the existence of abnormal WM structure in schizophrenia (Kelly et al., 2018; Koshiyama et al., 2020). In particular, a recent meta-analysis of 29 DTI studies in schizophrenia, including 1963 patients, showed differences in the diffusion parameters between clinical and healthy subjects in 20 tracts in total, indicating the WM alterations in schizophrenia are widespread and affecting the majority of fiber bundles in the brain, with the greatest effect size in the corpus callosum and the anterior corona radiate (Kelly et al., 2018). Other research consistently revealed that WM abnormalities were detected in different structures, in various groups of patients (e.g. medication naïve, after the first episode, chronic) and WM alteration has a potential to be a biomarker used as a diagnostic criterion, even in a prodromal stage of the illness (Pettersson-Yeo et al., 2011; Alba-Ferrara and de Erausquin, 2013).

Yet, regarding the existing DTI studies on the structural biomarkers of the negative symptoms in schizophrenia, the observed inconsistency of the results could be due to the high heterogeneity of clinical images between schizophrenic individuals. The lack of application of detailed clinical assessment of specific negative symptoms is also one of the most important issues.

First of all, two clinical tools were commonly used in a majority of DTI research in schizophrenia the Scale for the Assessment of Negative Symptoms (SANS, Andreasen 1982) or the negative subscale of the Positive and Negative Symptoms Scale (PANSS, Kay et al., 1987; van der Gaag et al., 2006; Liemburg et al., 2013; Stiekema et al., 2016). In brief, most of the studies involving these scales find no association between their scores and reduced WM integrity, i.e., lower FA values (Fujiwara et al., 2007; Skelly et al., 2008; Abdul-Rahman et al., 2011; Choi et al., 2011; Yan et al., 2012; Kelly et al., 2018), whereas some find negative (Whitford et al., 2014; Balevich et al., 2015; Ochi et al., 2020) or positive associations (Camchong et al., 2011; Bijanki et al., 2015).

Furthermore, in some studies (Balevich et al., 2015; Sun et al., 2015) clinical assessment did not seem to be prioritized, as the calculated associations were provided only between a total score of each scale, instead of correlations between particular subscales. The specific investigations on the relationships between diffusion parameters and clinical subscales or even single items concerning negative symptoms are still scarce.

Pieces of evidence indicate that lower FA in the left frontal lobe were related with SANS anhedonia-asociality domain (Asami et al., 2014; Ohtani et al., 2014); SANS avolition were negatively correlated with FA in the corpus callosum (Nakamura et al., 2012); PANSS (N1)-blunted affect was related with lower FA in uncinate fasciculus (Luck et al., 2011); avolition-apathy domain (The Schedule for the Deficit Syndrome (SDS); Kirkpatrick et al., 1989) negatively correlate with FA abnormalities in the reward system, i.e., amygdala-insular connections (Amodio et al., 2017); deficit patients (SDS) revealed a greater reduction in WM integrity than non-deficit patients in the corpus callosum and right posterior thalamic radiation (Tan et al., 2020); patients with persistent negative symptoms exhibit a different pattern of WM abnormalities as compared to patients without negative symptoms (Hovington et al., 2015); WM abnormalities related to the treatment resistance were also associated with the severity of the negative symptoms (Kochunov et al., 2019).

Summarizing, although consistent results revealed the existence of diverse WM abnormalities in schizophrenia in comparison to healthy controls, the association of those changes with the occurrence of the negative symptoms seems still to be not yet fully detected and understood. The above discrepancy of DTI results on negative symptomatology may be more specifically considered as an effect of the inconsistency of the clinical assessments of the same symptoms by different scales. For example, anhedonia is not included in the PANSS, while in the SANS it is rated together with asociality, but with no discrimination on anticipatory and consummatory anhedonia, of which the first one is most characteristic for schizophrenia (Marder and Galderisi, 2017; Yan et al., 2019).

Interestingly, on the contrary to the SANS and PANSS, the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011) rates avolition more precisely as based on both internal subject's feeling and observed behavior, and evaluates both consummatory and anticipatory anhedonia (Marder and Galderisi, 2017). BNSS belongs to the second generation of the negative symptoms scales and consists of 5 specific subdomains of negative symptoms: blunted affect, alogia, asociality, anhedonia, and avolition (Garcia-Portilla et al., 2015; Kumari et al., 2017; Ahmed et al., 2019; Strauss et al., 2019), which may have the potential to separate neurobiological substrates and to become new therapeutic targets (Kirkpatrick et al., 2011). The concurrent validity of both BNSS and PANSS is high and a recent study (Kaliuzhna et al., 2020) revealed that both amotivation factors reach a relatively high negative association with diminished left ventral striatal activation. However, the effect sizes for BNSS were much higher and the authors emphasize that the use of specialized scales like BNSS is crucial in MRI studies directly addressing negative symptoms (Kaliuzhna et al., 2020).

Hence, the primal aim of this study is to investigate the association between WM abnormalities and the severity of specific subdomains of psychopathological symptoms measured by PANSS and BNSS in a sample of schizophrenia outpatients, with a special focus on the specific aspects of the negative symptomatology.

First, we determined the differences in WM diffusivity parameters in the main tracts in the examined clinical group in comparison to healthy controls. Replication of the alternations in WM in a group of patients consistent with those reported in the literature (Kelly et al., 2018; Koshiyama et al., 2020) serves as a rationale for the secondary correlation analysis of the altered DTI parameters with psychopathology.

More specifically, in the present study, we investigate the severity of specific negative symptoms using the five-factor BNSS (Ahmed et al., 2019) and five-factor PANSS (van der Gaag et al., 2006) models with additional application of a 2-factor PANSS negative symptoms structure, i.e., social amotivation and diminished expression (Liemburg et al., 2013). However, BNSS may be regarded as a more specific clinical tool than PANSS, as relies on both clinical and subject internal experience (Marder and Galderisi, 2017) and the 5 subdomains construct model of negative symptoms is clinically well settled (Ahmed et al., 2019, Strauss et al., 2018). On the other hand, since PANSS is one of the most widely used clinical tools in neuroimaging research the referential value of such measurement is indispensable. Therefore, we expect more pronounced BNSS subdomains associations compared to PANSS factors.

Next, based on the reported widespread alternations of WM in schizophrenia (Kelly et al., 2018; Koshiyama et al., 2020) we postulate that WM regions related to the severity of the negative symptoms may be subtle, more diffuse and not restricted only to the main tracts, but expressed beneath the cortical regions with abnormal functional activation. This assumption is supported by studies on grey matter structure and its relation to negative symptoms, eg. blunted affect (Guessoum et al., 2020) or apathy (Bègue et al., 2020). Thus, in the present study, besides commonly used tract-based spatial statistics (TBSS) analysis, we used a novel DTI approach more focused on smaller parts of the WM tracts localized beneath cortical regions of interest (ROI), which ROI-FA values will serve as the basis for secondary analyses of the relationship between WM integrity and specific psychopathology subdomains.

Finally, concluding from available data (Shaffer et al., 2015; Abram et al., 2017; Walton et al., 2018; Li et al.,

2018; Bègue et al., 2020; Brady et al., 2019, Guessoum et al., 2020, Kaliuzhna et al., 2020), we hypothesize, that the most robust association between avolition/anhedonia/asociality symptoms (and/or social amotivation factor) and abnormal WM changes will be manifested within the fronto-temporo-parietal regions, such as orbitofrontal cortex, cingulate gyrus, middle and superior temporal gyrus, and precuneus.

METHODS

Subjects

The study included 30 schizophrenia outpatients (SCH) and 30 sex-, age-, and education-matched healthy controls (CON). The clinical group consisted of people with schizophrenia (27 paranoid subtype, 2 undifferentiated, 1 schizoaffective) as diagnosed with the ICD-10 by an experienced psychiatrist based on clinical interviews and medical documentation; recruited through the local network of outpatient clinics and rehabilitation centers in Krakow, Poland.

The inclusion of patients with undifferentiated schizophrenia and schizoaffective disorder was based on a clinical premise, that diagnostic subtyping has no predictive validity and will be abandoned in future classifications, e.g. ICD-11 (Reed et al., 2019) and that schizoaffective disorder shares similar WM pathologies with schizophrenia (Kaluser et al., 2016).

All participants provided written informed consent for participation in the study. Procedures were designed following the ethical standards of the World Medical Association Declaration of Helsinki (2013) and approved by the Research Ethics Committee of the Institute of Psychology, Jagiellonian University in Krakow, Poland.

All clinical subjects were in a stable psychopathological condition for at least 8-12 weeks before the assessment. The exclusion criterion was a history of head injuries, seizures, substance dependence, or any serious current somatic illnesses. Before MRI data acquisition, the PANSS, Kay et al., 1987; Van der Gaag et al., 2006; Liemburg et al., 2013 and the BNSS, Kirkpatrick et al., 2011; Ahmed et al., 2019 were assessed by experienced psychiatrists. The mean dose of antipsychotics for each subject from the clinical group was calculated as chlorpromazine equivalents (Atkins et al., 1997; Woods, 2003; Gardner et al., 2010).

The Polish adaptation of the Montreal Cognitive Assessment (MoCA, available at www.mocatest.org; Nasreddine et al., 2005) was used as a general measure of basic cognitive skills for all of the subjects. The groups did not differ in terms of sex and age, but they did differ in years of education (CON > SCH), although this difference was not found at the educational level (Chi^2=4.592; P=0.204). As expected, a difference in cognitive performance (MoCA result; CON > SCH) was found, with a lower total score in the SCH group, and revealed the cognitive impairments prominent and characteristic for schizophrenia (Adamczyk et al., 2016).

Demographic and clinical data are presented in Table I. The data were normally distributed.

MRI data acquisition

Magnetic resonance imaging (MRI) was executed using a 3T scanner (Magnetom Skyra, Siemens) at Malopolska Centre of Biotechnology, Krakow, Poland. The acquisition was performed with a 64-channel head coil. The DTI-MRI protocol included T1, T2 and the diffusion sequence. For T1 scans an optimized magnetization-prepared rapid acquisition gradient echo was used with following parameters: voxel size=1 × 1 × 1 mm, FoV=25. 6 × 25.6 cm, TR=1800 ms, TE=2.26 ms. For T2 scans the parameters were: voxel size=1 × 1 × 1 mm, FoV=25.6 × 25.6 cm, TR=3200 ms, TE=410 ms. For DTI scans the following parameters were used: b-values 0, 1000, 2500 s/mm2; in 94 directions, with anterior – posterior phase-encoding direction, 4 b0 images, 100 × 100 image matrix with an in-plane voxel resolution of 2.5 × 2.5 mm, 49 slices; FoV=24 × 24 cm (cerebellum not included); TR=8700 ms; TE=110 ms.

Preprocessing of diffusion data

For DTI data preprocessing and analysis, the FSL package (FMRIB Software Library v5.11) was used. Anatomical images were skull-stripped with BET (Smith et al., 2006). Motion correction was performed using eddy (Andersson and Sotiropoulos, 2016) and distortion correction was performed with FLIRT (Jenkinson et al., 2002). After every step, the quality of data was checked manually by experienced researchers. Voxelwise statistical analysis of the FA data was carried out using TBSS (Smith et al., 2006). First, the tensor model was fitted to diffusion data using FDT, thus resulting in the creation of brain FA images. All subjects' FA data were then aligned into a common space with FNIRT. Next, based on the mean FA image from each subject, the mean FA skeleton was created, which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and used for voxelwise cross-subject statistics. RD (radial diffusivity), AD (axial diffusivity), and MD (mean diffusivity) data were also

Table I. Demographic and clinical data.

Demographic and clinical data	Schizophrenia outpatients (n=30)				Healthy Controls (n=30)				Between-group differences
	Mean	± SD	Min	Max	Mean	± SD	Min	Max	
Demographic data									
sex (male:female)	15:15				15:15				Chi^2=0.00; ns
age	41.97	9.12	27	61	41.80	8.68	27	61	t=-0.07; ns
years of education	14.13	2.61	9	21	16.30	2.91	12	23	t=-3.03; *P*<0.01
MOCA total	23.17	3.91	21	29	27.03	1.95	23	30	t=-4.84; *P*<0.01
Clinical data									
years of illness	17.20	8.57	3	39					
number of episodes	8.83	7.33	1	33					
nr of hospitalizations	8.60	5.57	2	23					
schizophrenia diagnosis (ICD-10):	n	%							
paranoid (F20.0)	27	91							
undifferentiated (F20.3)	2	6							
schizoaffective disorder (F25.0)	1	3							
Type of pharmacotherapy:									
typical anipsychotics	1	3							
atypical antipsychotics	27	91							
typical-atypical mixed	2	6							
anxiolytics	11	37							
antidepressants	4	14							
mood stabilizers	6	20							
chlorpromazine equiv. (mg/day)	425.33	277.74	100	1300					
PANSS:									
total	61.23	16.01	33	96					
positive symptoms	11.30	4.15	5	20					
negative symptomps	16.90	6.40	8	31					
disorganization	9.53	3.95	5	19					
excitment	6.07	2.24	4	11					
emotional distress	9.17	3.17	4	16					
expressive deficits	10.20	7.40	0	25					
social amotivation	11.83	7.60	0	26					
BNSS:									
total	22.03	13.54	1	49					
anhedonia	5.30	3.98	0	12					
asociality	3.30	2.38	0	8					
avolition	3.23	2.36	0	8					
blunted effect	6.30	4.51	0	14					
alogia	2.97	2.51	0	9					

Subjects demographics and clinical data were presented as mean (±SD) for quantitative data. The significance level in all statistical analyses equaled *P*<0.05.

warped, merged, and projected onto the original mean FA skeleton.

Additionally, since TBSS analysis is based on values extracted from voxels contained in the FA skeleton, which does not include the subject's entire WM, it represents only all tracts that are common to the whole group. Thus, besides standard TBSS between-group analysis, we focused on selected regions of interest (ROI) containing cortex and adjacent WM, and extracted values from WM skeletons voxels within those areas (individually for each subject). We assume that correlations between these ROI-FA values and psychopathology can provide more reliable results.

Therefore, to obtain cortical projections of WM results, we decided to test between-group differences in FA values within 17 selected cortical ROI-FA. Regions were selected according to previously published data on brain abnormalities in schizophrenia and revealed as relevant attribution to negative symptom (Shaffer et al., 2015; Abram et al., 2017; Walton et al., 2018; Erp et al., 2018; Li et al., 2018; Brady et al., 2019; Bègue et al., 2020; Guessoum et al., 2020).

The chosen ROIs were identified with the Human Harvard-Oxford Atlas as follows: frontal pole (FP), orbitofrontal cortex (oPFC), inferior frontal gyrus pars opercularis (oIFG), inferior frontal gyrus pars triangularis (tIFG), middle frontal gyrus (MFG), superior frontal gyrus (SFG), anterior cingulate gyrus (aCC), posterior cingulate gyrus (pCC), anterior inferior temporal gyrus (aITG), posterior inferior temporal gyrus (pITG), anterior middle temporal gyrus (aMTG), posterior middle temporal gyrus (pMTG), anterior superior temporal gyrus (aSTG), posterior superior temporal gyrus (pSTG), Heschl's gyrus (HG), temporal pole (TP), anterior supramarginal gyrus (aSupG), posterior supramarginal gyrus (pSupG), angular gyrus (AngG) and precuneus cortex (Prec).

The masks for each ROI were created separately and fitted to the common space. The shared voxels of each ROI mask and the respective mean FA skeleton were extracted individually for each subject. Namely, the FA values from each mask in each subject's FA skeleton image were extracted, averaged, and used for statistical ROI-FA analysis. We decided to obtain only the FA measure from masks as this parameter is widely used in other publications concerning WM and psychopathology in schizophrenia, but not MD, RD, or AD.

Statistical analysis

Voxelwise DTI analyses were performed using nonparametric permutation-based testing with the Randomise command (Winkler et al., 2014) controlling for sex, age and illness duration. The Threshold-Free Cluster Enhancement (TFCE) method was used with Familywise Error (FWE) correction; 10.000 permutations were calculated. $P<0.001$ were considered significant.

Between-group comparison of ROI-FA values (t-tests) was performed using IBM SPSS Statistics for Windows (version 23). The effect size was calculated with Cohen's d with small sample size correction. False discovery rate (FDR) (Benjamini and Hochberg, 1995) was used for multiple testing corrections for all extracted ROIs threshold at α level $P<0.05$.

The relationships between PANSS, BNSS and ROI-FA values were computed using partial Spearman rank-order correlation, controlling for sex, age, illness duration and medication (chlorpromazine equivalent). Besides the calculation with standard five factors PANSS (Kay et al., 1987; Van der Gaag et al., 2006) i.e., positive symptoms, negative symptoms, disorganization symptoms, excitement and emotional distress, the additional analysis was conducted, where the negative symptoms were divided into 2 subdomains – expressive deficits and social amotivation (Liemburg et al., 2013). For BNSS 5-factor model was applied, which includes blunted affect, alogy, anhedonia, avolition and asociality subdomains (Strauss et al., 2018; Mucci et al., 2019). The FDR correction for multiple tests with α level $P<0.05$ was used.

RESULTS

The DTI TBSS results of the between-group comparisons of FA, MD, RD and AD parameters showed widespread differences across most of the WM bundles in the brain (Fig. 1 left-panel). In particular, the FA values were lower and MD, AD, RD were higher for the SCH group as compared to the CON group ($P<0.001$, TFCE, FWR corrected). The structures in which all the parameters changed (FA, MD, RD, AD) were identified bilaterally (i.e., the body and splenium of the corpus callosum, the medial lemniscus, the anterior, posterior and retrolenticular limb of internal capsule, the superior corona radiata, the sagittal stratum, the external capsule, the fornix); they were also identified selectively in the left (i.e., the anterior corona radiata) and right hemisphere (i.e., the superior longitudinal fasciculus, the corticospinal tract, the posterior corona radiata).

Next, the between-group differences on ROI-FA values were detected bilaterally, with lower FA values in the SCH group in the left oPFC ($t58=-3.01$, $P=0.015$), oIFG ($t58=-2.46$, $P=0.038$), tIFG ($t58=-2.95$, $P=0.017$), pCC ($t58=-3.46$, $P=0.004$), pITG ($t58=-2.73$, $P=0.024$), AngG ($t58=-2.54$, $P=0.036$), Prec ($t58=-2.58$, $P=0.034$), and right oPFC ($t50.32=-4.79$, $P<0.001$), oIFG ($t58=-4.99$,

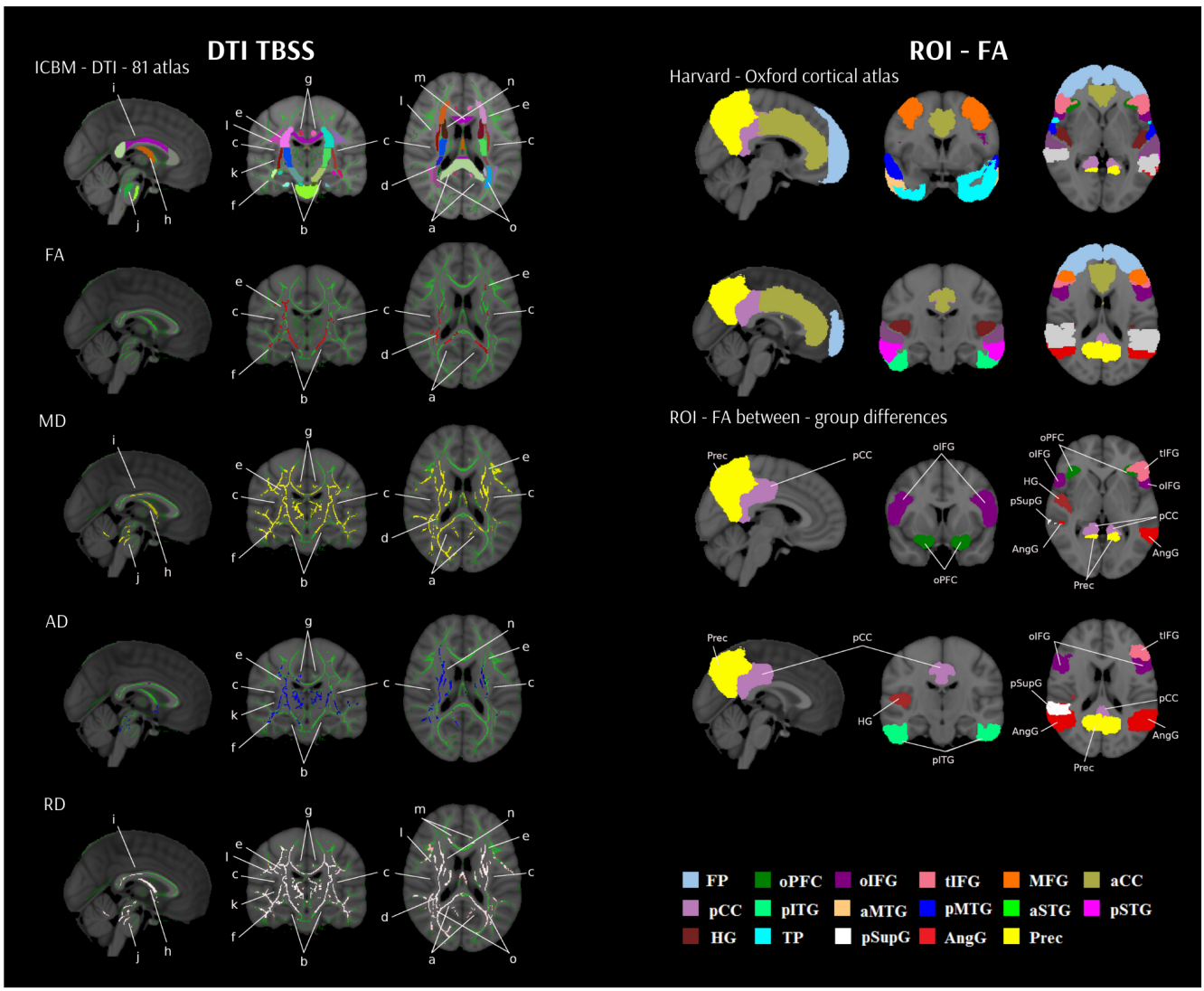

Fig. 1. Between-group differences in DTI parameters and ROI-FA values. Left panel: Differences between clinical (SCH) and control group (CON) in DTI parameters were shown using labels from the ICBM-DTI-81 white-matter labels atlas (left-top) on fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). Images presented in neurological convention with background of mean FA skeleton – green color, and MNI 152 brain. Red color – FA values lower in SCH compared to CON; blue, yellow, light gray – MD, AD, and RD values respectively higher in SCH compared to CON. MNI coordinates of the brain image profile: X, Y, Z=90, 108, 90. Abbreviations for ICBM-DTI-81atlas labels: a) splenium of corpus callosum, b) cerebral peduncle, c) posterior limb on the internal capsule, d) retrorenticular part of the internal capsule, e) superior corona radiata, f) sagittal stratum, g) cingulum, h) fornix, i) body of corpus callosum, j) pontine crossing tract, k) external capsule, l) superior longitudinal fasciculus, m) body of corpus callosum, n) anterior limb of the internal capsule, o) posterior thalamic radiation. Right panel: Differences in ROI-FA values were shown using the Harvard-Oxford cortical atlas and labeled by color (right-top). The clusters with lower FA values in SCH compared to CON (two left-bottom images) are presented in neurological convention with MNI 152 brain background. The top-down MNI coordinates of brain profile images: X, Y, Z=85, 128, 73; 90, 108, 90; 85, 135, 73; 90, 108, 90, respectively.

P<0.001), pCC (t58=-4.39, P<0.001), pITG (t58=-3.7, P<0.001), HG (t58=-3.78, P<0.001), pSupG (t58=-3.37, P=0.004), AngG (t58=-2.5, P=0.036), Prec (t58=-4.1, P<0.001). The data were normally distributed. Detailed data on ROI-FA values are presented in Table II and Fig. 1 (right-panel).

Finally, the correlation analysis of the ROI-FA values with psychopathology has been provided in the above ROIs in which significant between-group differences were found. The negative association between asociality BNSS subscale and several regions after FDR correction for multiple comparisons was revealed. In particular, increased asociality was associated with decreased FA in the left oPFC (r=-0.46, P=0.043), pCC (r=-0.56, P=0.016), Prec (r=-0.49, P=0.035), and the right pCC (r=-0.54, P=0.016), HG (r=-0.54, P=0.016), and Prec (r=-0.70, P<0.001). The detailed correlation results are presented in Table III and Fig. 2.

Table II. ROI-FA between-group differences.

ROIs	Schizophrenia outpatients (n=30)				Healthy controls (n=30)				Between-group differences		
	Mean	±SD	Min.	Max.	Mean	±SD	Min.	Max.	t-test	Cohen's d	FDR Q
Left Hemisphere											
LFP	0.39	0.02	0.35	0.43	0.40	0.02	0.35	0.44	-2.07	-0.53	P=0.077
LoPFC #	0.35	0.02	0.29	0.38	0.36	0.02	0.33	0.42	-3.01	-0.78	P=0.015
LoIFG #	0.44	0.03	0.39	0.51	0.46	0.02	0.42	0.50	-2.46	-0.63	P=0.038
LtIFG #	0.41	0.03	0.35	0.46	0.43	0.03	0.37	0.50	-2.95	-0.76	P=0.017
LMFG	0.47	0.03	0.42	0.53	0.48	0.03	0.41	0.54	-1.69	-0.44	P=0.132
LaCC	0.66	0.03	0.58	0.71	0.67	0.02	0.63	0.71	-1.91	-0.49	P=0.102
LpCC #	0.54	0.03	0.49	0.59	0.56	0.03	0.50	0.64	-3.46	-0.89	P=0.004
LpITG #	0.42	0.03	0.34	0.46	0.44	0.03	0.37	0.50	-2.73	-0.71	P=0.024
LaMTG	0.47	0.03	0.42	0.53	0.48	0.03	0.41	0.54	-1.69	-0.44	P=0.131
LpMTG	0.42	0.03	0.37	0.47	0.43	0.03	0.36	0.49	-1.74	-0.45	P= 0.129
LaSTG	0.37	0.03	0.30	0.43	0.37	0.04	0.32	0.46	-0.99	-0.26	P=0.359
LpSTG	0.33	0.03	0.26	0.40	0.34	0.04	0.27	0.44	-0.66	-0.17	P=0.542
LHG	0.42	0.03	0.36	0.47	0.43	0.03	0.36	0.50	-1.58	-0.41	P=0.156
LTP	0.32	0.02	0.27	0.37	0.34	0.03	0.28	0.37	-2.14	-0.55	P=0.074
LpSupG	0.40	0.03	0.35	0.45	0.41	0.02	0.37	0.45	-1.25	-0.32	P=0.252
LAngG #	0.42	0.02	0.34	0.46	0.43	0.02	0.38	0.47	-2.54	-0.66	P=0.036
LPrec #	0.44	0.02	0.40	0.48	0.45	0.03	0.40	0.50	-2.58	-0.67	P=0.034
Right Hemisphere											
RFP	0.39	0.02	0.35	0.42	0.40	0.02	0.36	0.43	-1.96	-0.51	P=0.092
RoPFC #	0.33	0.02	0.29	0.35	0.35	0.02	0.32	0.41	-4.79	-1.24	P=0.001
RoIFG #	0.44	0.02	0.41	0.48	0.47	0.03	0.41	0.54	-4.99	-1.29	P=0.001
RtIFG	0.42	0.03	0.37	0.50	0.43	0.03	0.35	0.50	-1.45	-0.38	P=0.186
RMFG	0.47	0.02	0.43	0.51	0.49	0.02	0.42	0.53	-2.08	-0.54	P=0.077
RaCC	0.69	0.04	0.62	0.76	0.71	0.03	0.64	0.76	-1.78	-0.46	P=0.125
RpCC #	0.53	0.03	0.48	0.59	0.56	0.03	0.51	0.60	-4.39	-1.13	P=0.001
RpITG #	0.38	0.03	0.32	0.45	0.41	0.03	0.34	0.47	-3.70	-0.96	P=0.001
RaMTG	0.33	0.03	0.28	0.39	0.33	0.03	0.27	0.38	0.15	0.04	P=0.885
RpMTG	0.36	0.02	0.31	0.41	0.37	0.02	0.32	0.41	-1.45	-0.37	P=0.186
RaSTG	0.33	0.03	0.28	0.40	0.34	0.04	0.28	0.40	-1.20	-0.31	P=0.266
RpSTG	0.31	0.03	0.23	0.36	0.32	0.03	0.28	0.38	-0.42	-0.11	P=0.694
RHG #	0.43	0.03	0.37	0.50	0.46	0.03	0.39	0.51	-3.78	-0.98	P=0.001
RTP	0.33	0.02	0.28	0.37	0.34	0.02	0.30	0.38	-2.18	-0.56	P=0.07
RpSupG #	0.41	0.02	0.37	0.45	0.43	0.02	0.38	0.47	-3.37	-0.87	P=0.004
RAngG #	0.42	0.02	0.37	0.48	0.44	0.02	0.38	0.47	-2.50	-0.65	P=0.036
RPrec #	0.46	0.02	0.41	0.50	0.48	0.02	0.41	0.52	-4.10	-1.06	P=0.001

Cohen's d was calculated using Hedge's g. with small sample size correction and controlling for sex. age. illness duration and chlorpromazine equivalent. Results were considered significant with $P<0.05$ after FDR correction. Right hemisphere (R); left hemisphere (L); Used ROIs based on Harvard-Oxford cortical atlas: frontal pole (FP); orbitofrontal cortex (oPFC); inferior frontal gyrus pars opercularis (oIFG); inferior frontal gyrus pars triangularis (tIFG); middle frontal gyrus (MFG); cingulated gyrus anterior (aCC); cingulated gyrus posterior (pCC); inferior temporal gyrus posterior (pITG); middle temporal gyrus anterior (aMTG); middle temporal gyrus posterior (pMTG); superior temporal gyrus anterior (aSTG); superior temporal gyrus posterior (pSTG); Heschl's gyrus (HG); temporal pole (TP); supramarginal gyrus posterior (pSupG); angular gyrus (AngG); precuneus cortex (Prec).

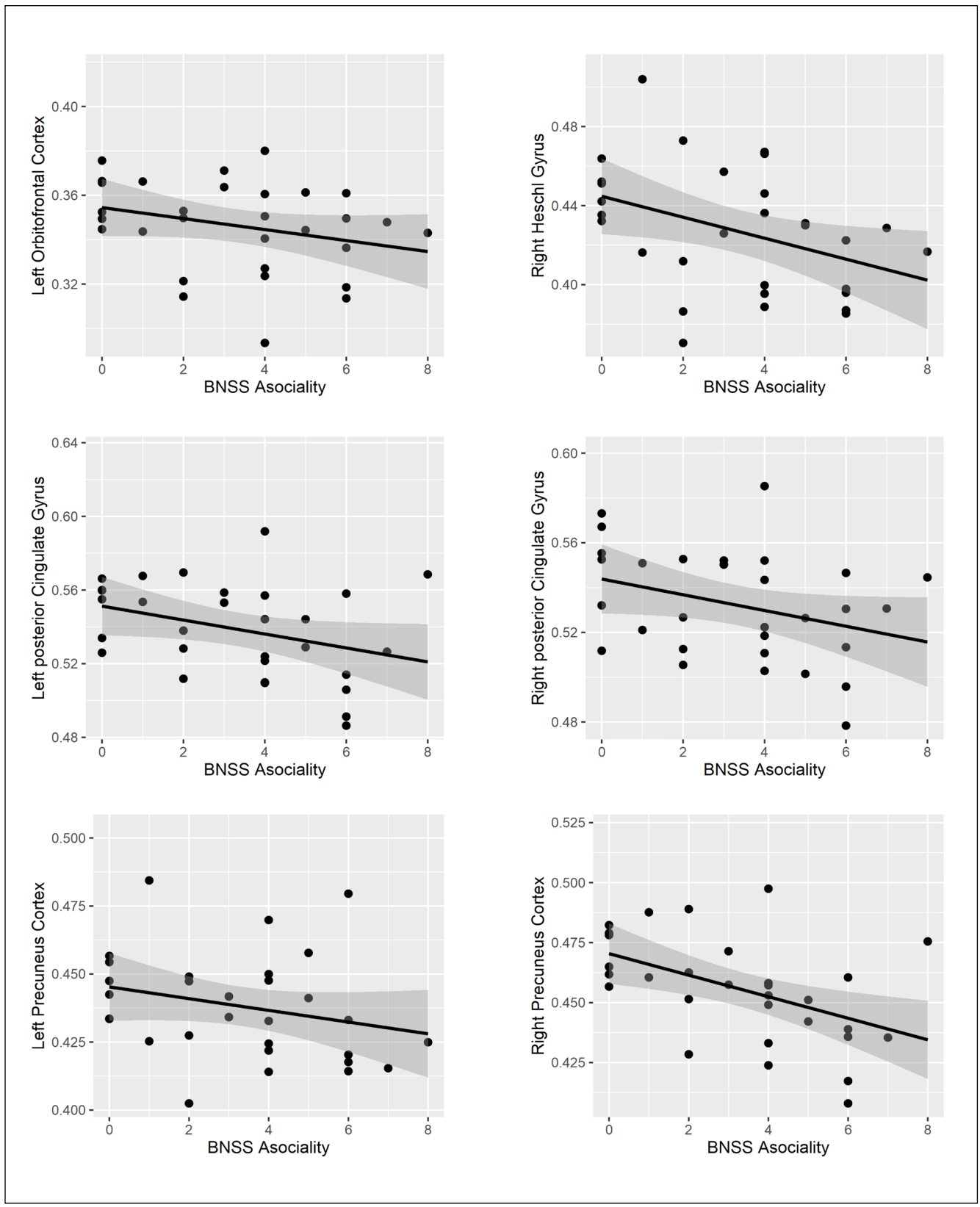

Fig. 2. Correlations between BNSS asociality subscale and fractional anisotropy in selected regions of interest (ROI-FA). Scatter plots of the scores of Brief Negative Symptom Scale (BNSS) asociality in the schizophrenia subjects and its association with the fractional anisotropy (FA) in the selected regions of interest (ROI). The significant Spearman's correlation after FDR correction for multiple comparisons.

Table III. ROI-FA correlations with psychopathology.

Hemisphere / Brain area	BNSS							PANSS					PANSS negative		
	Total	Anhedonia	Distress	Asociality	Avolition	Blunted affect	Alogia	Total	Positive	Negative	Disorga-nization	Excitement	Emotional reactivity	Social amotivation	Expressive deficits
Left hemisphere															
L oPFC	-0.24	-0.39	-0.28	**-0.46#**	-0.25	-0.11	0.09	<0.01	0.18	-0.2	0.11	-0.05	-0.07	-0.27	0.10
L oIFG	-0.09	-0.2	-0.14	-0.24	-0.11	0.01	0.11	-0.16	-0.01	-0.06	-0.2	-0.31	-0.22	-0.04	0.09
L tIFG	-0.14	-0.02	0.03	-0.34	-0.06	-0.03	-0.17	-0.01	0.07	-0.03	0.04	-0.04	-0.14	-0.07	0.03
L pCC	-0.41	-0.31	-0.35	**-0.56#**	-0.33	-0.26	-0.28	-0.29	-0.1	-0.33	-0.2	-0.24	-0.28	-0.27	-0.17
L pITG	-0.31	-0.23	-0.38	-0.4	-0.24	-0.08	-0.25	-0.16	-0.13	-0.32	0.08	-0.04	0.04	-0.41	-0.19
L AngG	-0.25	-0.36	-0.13	-0.41	-0.25	-0.13	0.06	-0.16	-0.2	-0.13	0.06	-0.11	-0.12	-0.12	0.01
L Prec	-0.19	-0.17	-0.09	**-0.49#**	-0.18	-0.01	-0.11	-0.05	0.07	-0.15	0.08	-0.04	-0.1	-0.19	0.11
Right hemisphere															
R oPFC	-0.26	-0.23	-0.3	-0.41	-0.21	-0.22	-0.1	-0.22	<0.01	-0.28	-0.12	-0.22	-0.37	-0.26	-0.13
R oIFG	-0.05	-0.02	-0.1	-0.07	-0.13	-0.01	0.04	-0.14	0.05	-0.02	-0.39	-0.17	-0.04	0.03	0.05
R MFG	-0.15	-0.24	-0.19	-0.41	-0.12	0.06	0.17	0.03	<0.01	-0.03	0.03	0.01	0.13	-0.17	0.17
R pCC	-0.35	-0.31	-0.21	**-0.54#**	-0.28	-0.16	-0.24	-0.2	-0.16	-0.26	-0.14	-0.1	-0.2	-0.25	0.00
R pITG	-0.13	-0.16	-0.25	-0.23	-0.15	0.01	0.02	0.11	0.13	-0.19	0.38	0.06	0.1	-0.26	0.06
R HG	-0.38	-0.38	-0.32	**-0.54#**	-0.34	-0.3	-0.14	-0.45	-0.45	-0.34	-0.21	-0.18	-0.24	-0.18	-0.14
R pSupG	-0.24	-0.22	-0.17	-0.39	-0.18	-0.24	-0.05	-0.23	-0.16	-0.27	0.09	-0.18	-0.21	-0.39	-0.13
R AngG	-0.19	-0.21	-0.09	-0.38	-0.17	-0.08	-0.04	-0.31	-0.24	-0.1	-0.23	-0.34	-0.18	-0.05	-0.05
R Prec	-0.55	-0.51	-0.39	**-0.70#**	-0.45*	-0.34	-0.29	-0.38	-0.29	-0.39	-0.22	-0.11	-0.25	-0.35	-0.17

Partial Spearman's correlations between FA values of selected regions of interest (ROIs with lower FA values in schizophrenia *vs.* controls between-group comparisons) with clinical variables, controlled for age, sex, illness duration and medication. Significant correlations with FDR correction at $P<0.05$ (#). Abbreviations: L – left hemisphere; R – right hemisphere; PANSS – Positive and Negative Syndrome Scale; BNSS – Brief Negative Symptom Scale. Used ROIs based on Harvard-Oxford cortical atlas: orbitofrontal cortex (oPFC); inferior frontal gyrus pars opercularis (oIFG); inferior frontal gyrus pars triangularis (tIFG); middle frontal gyrus (MFG); cingulated gyrus posterior (pCC); inferior temporal gyrus posterior (pITG); Heschl's gyrus (HG); supramarginal gyrus posterior (pSupG); angular gyrus (AngG); precuneus cortex (Prec).

DISCUSSION

In the present study, we aimed at investigating the relationship between the WM integrity abnormalities and psychopathological symptoms in schizophrenia using BNSS and PANSS scales.

First of all, results of between-group comparisons on DTI parameters and ROI-FA values confirmed the existence of essential bilateral and widespread disruptions of WM cytoarchitecture in schizophrenia in line with previous studies (Parnanzone et al., 2017; Kelly et al., 2018; Koshiyama et al., 2020). Thus, the clinical group of outpatients investigated in our study may be regarded as representative, as sharing the abnormal patterns of WM changes similar to those revealed by big-data study on a cohort of people with schizophrenia, e.g. these found in the major tracts of the corpus callosum and the corona radiata (Kelly et al., 2018). Moreover, the presented results on differences in all diffusivity parameters (FA, AD, MD, RD) with the most widespread RD WM alterations are in line with the recent study on 696 schizophrenia patients (Koshiyama et al., 2020). In particular, we found widespread bilateral differences, which indicates a breached microstructural integrity in schizophrenia, i.e., FA values were lower and RD, AD and MD values were higher. Consistently, results from ROI-FA values revealed various bilateral differences in the frontal, temporal and parietal lobes. Moreover, we found a higher general level of diffusivity (MD) in the schizophrenia group in the same regions as the FA-related findings described above, with additional changes in the cingulum and the uncinate fasciculus. Noteworthy, consistent with big-sample studies (Kelly et al., 2018; Koshiyama et al., 2020) the RD changes were the most distributed DTI parameter, as compared to FA, AD, and MD measures. These findings support the evidence that the diffusivity changes in schizophrenia are most possibly a result of myelin disruptions (Cassoli et al., 2015; Mighdoll et al., 2015). The RD is considered a more sensitive measure to detect abnormalities related to myelin disruptions than FA (Joo et al., 2020). This is especially evident in regions that demonstrate a significant number of coherently oriented axons, e.g. corpus callosum (Karlsgodt, 2016). Moreover, molecular studies showed that the dysfunction of oligodendrocytes has an impact on disrupted myelination processes in schizophrenia (Cassoli et al., 2015; Mighdoll et al., 2015). Although, further studies are needed to better determine this phenomenon. At last, the differences that appeared along the axis (AD) indicate the impact of other factors that contribute to WM abnormalities, e.g. an inappropriate neurodevelopmental environment that results in an abnormal process of establishing synapses and pruning axonal connections (Alba-Ferrara and de Erausquin, 2013; Klauser et al., 2016) seemingly provided to the brain disconnection (Friston et al., 2016).

Overall, it should be pointed that presented differentiated findings on the WM abnormalities distribution indicated by various measures (i.e., FA, MD, RD, AD) is seemingly related to the fact, that each of those DTI parameters were concerned specifically sensitive to different biological phenomena (e.g. FA - WM integrity, RD - WM myelination level, AD - WM axonal damage; MD - WM surrounding cytoarchitecture). Although, such an interpretation of the tissue properties based on the DTI parameters is still under debate (Wheeler-Kingshott and Cercignani, 2009). To investigate the exact mechanism underlying different alternations of WM in schizophrenia, further research is needed to better determine the biological characteristics of the brain tissues and their relation to the specific DTI measure (Kelly et al., 2018).

Second, the significant effects on the specific associations of the BNSS asociality with a lower WM integrity was found in the left oPFC, right HG, and bilateral pCC and Prec. This indicates that the abnormal structure of these regions may be concerned as a neurobiological substrate of functional disturbances crucial for the manifestation of specific psychopathological symptoms, i.e., asociality. This is consistent with the previous DTI study (Viher et al., 2016) which revealed that the negative symptoms (DSM-V) were related to the disrupted WM structure in bilateral prefrontal cortices and the right temporal lobe.

However, to the best of our knowledge, apart from the presented findings, there is a lack of other research investigating the relationship between schizophrenia symptoms and abnormalities of WM beneath the specified cortical regions (e.g. ROI-FA). Although, our results are supported by recent research that indicates that alterations of WM tracts may be considered to represent neural underpinning of changes in structural properties of grey matter regions, which are inextricably interconnected at a cellular level. In particular, reductions in cortical thinning were shown to be related to the increased FA in the intracortical WM (Di Biase et al., 2019), elevated RD in adjacent WM was associated with increased cortical folding in the dorsolateral PFC (Schultz et al., 2017) and reduced volume of WM was shown to be related to the volume reduction in the neighboring regions of grey matter (Colibazzi et al., 2013).

Considering abnormal brain structure in schizophrenia, some studies revealed pronounced fronto-temporo-parietal cortical thinning (right STG/TPJ, parahippocampal gyrus, and cingulate cortex) (Bodnar et al., 2014), or smaller volume of the right

parahippocampal gyrus and STG (Benoit et al., 2012) in schizophrenia patients with persistent negative symptoms. At last, the left medial-oPFC cortex thinning was found to be selectively related to negative symptoms severity (Walton, 2018). Interestingly, in a longitudinal study involving at-risk for psychosis adolescents, negative symptoms were found to be related to the increased grey matter loss in the left hemisphere, e.g, STG/SupG, pCC, cerebellum and limbic lobe (McKechanie et al., 2016).

Furthermore, in the case of the functional MRI studies, hypoactivation of the Prec and the pCC was found to be related to the higher scores on the SANS anhedonia/asociality subscale (Shaffer et al., 2015; Guessoum et al., 2020) and avolition/apathy domain (Shaffer et al., 2015), and reduced resting-state functional connectivity in the precuneus was found to be positively correlated with avolition-apathy domains in schizophrenia patients (Forlim et al., 2020). Finally, the above-mentioned disconnectivity between large scale networks, such as frontal-cingulate-parietal connections within the default mode network (DMN) may be considered crucial for negative symptoms manifestation in schizophrenia (Lefort-Besnard et al., 2017).

Noteworthy, the medial PFC, temporal lobe, pCC and precuneus are considered as an essential part of DMN and a social network crucial for social cognition, which deficits partially overlap the asociality concept (Millan et al., 2014; Pelletier-Baldelli and Holt, 2020). Interestingly, the neurobiological basis of the structural and functional associations between precuneus and asociality is recognized to be dependent on the oxytocin level (Churchland and Winkielman, 2012; Kumar et al., 2015; 2019; Strauss et al., 2015). In particular, previous studies showed that the decreased plasma oxytocin level is associated with increased asociality (Strauss et al., 2015) and administration of intranasal oxytocin can reduce asociality symptoms in patients (Churchland and Winkielman, 2012). Complementary, other studies showed that enhancement of the oxytocin transmission can affect functional connectivity between precuneus - amygdala (Kumar et al., 2015) or precuneus - left dorsolateral prefrontal cortex (Kumar et al., 2019) connections. The above findings support the theory on the contribution of the precuneus to the social cognition in schizophrenia, mediated by oxytocin level decrease, which is strongly related to one related deficit of social cognition - the severity of asociality (Guessoum et al., 2020).

Yet, our results on altered WM structure beneath the left oPFC, right HG, bilateral precuneus and pCC seem to be complementary with findings on disturbed oxytocin-related functional connectivity in the DMN, which may be regarded as a potential mechanism of the neural substrate of social cognition deficits in schizophrenia and/or manifestation of asociality-related symptomatology. The pCC and precuneus are midline areas involved in higher-order and social processing (Cavanna and Trimble, 2006; Leech et al., 2012). Therefore, diminished WM connections in these regions might be responsible for disruption in social-motivation processes and turn resulting in increased asociality. This is supported by previous findings on the specific relationship of the anhedonia-asociality domain (assessed with SANS) with disrupted WM integrity in the left superior fronto-occipital fasciculus (Asami et al., 2014), the left posterior oPFC - ACC connections (Ohtani et al., 2014) or right cingulum bundle (Whitford et al., 2014). Finally, the results of the presented BNSS correlations indicate that alterations in the smaller parts of tracts located beneath grey matter (ROI-FA) may be an effective approach for the measurement of the specific associations of brain regions with negative symptoms.

On the other hand, no significant correlation with the negative symptoms subscale of PANSS was found, neither within the five-factor model of PANSS subscales (Van der Gaag et al., 2006), nor the analysis of the additional two specific subdomains of the PANSS negative symptoms, i.e., social amotivation and expressive deficits (Liemburg et al., 2013). The presented BNSS and PANSS results may indicate that the relation of WM disturbances with negative symptoms was indeed indirect and narrow down to specific deficits, e.g. BNSS asociality subscale; supporting the previously mentioned discrepancies between clinical scales (Kumari et al., 2017; Marder and Galderisi, 2017). Importantly, regarding the concurrent validity for the BNSS, SANS or PANSS, it should be pointed out that these clinical scales are highly inconsistent and measure slightly different aspects of the negative symptomatology (Kirkpatrick et al., 2011); e.g. asociality is often understood as social amotivation and therefore is treated by many researchers as one of the elements of the avolition/apathy domain (Kaiser et al., 2017). Interestingly to this issue, an exceptional DTI study on schizophrenia which applied BNSS (Stämpfli et al., 2019), despite revealed subtle between-group fiber density (FD) differences, reported no correlation between negative symptoms, neither for FA nor for FD parameters. Although, in contrast to the present study, in the study of Stämpfli and colleagues (2019), no commonly observed FA WM alterations were found (Kelly et al., 2018) and the BNSS analysis was limited to the two-factor model, i.e., apathy and diminished expression, beyond current five-factor model of BNSS subdomains analysis (Ahmed et al., 2019).

Summarizing, due to some limitations of our study (e.g. limited sample size), the presented results should be interpreted with caution, especially the correlation

analysis. Nevertheless, the presented results may serve as a valuable input for a deeper understanding of WM structure changes and its relation to the specific psychopathology symptoms in schizophrenia. Noteworthy, in the present study on schizophrenia outpatients, we detected characteristic differences in WM parameters in schizophrenia, which served as a rationale for provided correlation analysis of specific PANSS and BNSS symptoms subscales, as of great importance. The presented results of the ROI-FA calculation gave a deeper insight into the associations between WM structure abnormality and the manifestation of psychopathology symptoms. However, the used ROI-FA approach, similar to other methods (e.g. TBSS method focusing on the major WM tracts) is still affected by the problems with precise abnormal brain region alignment and localization accuracy. For a more profound understanding of the nature of WM abnormalities in schizophrenia and its relation with psychopathology, the more sophisticated methods need to be incorporated in further studies, e.g. ROI specified tractography and structural connectivity analysis. The more precise analysis of FA values on particular WM tracts may provide more precise measures of WM abnormalities in schizophrenia. Although, the replication of presented results on a bigger sample in the future is required.

Furthermore, even in our analyses, we controlled the parameters that potentially affected WM integrity in schizophrenia, i.e., sex, age, illness duration, and dosage of antipsychotic medication, these issues require special attention, as still under scientific debate. On the one hand, some studies indicated that WM integrity may be affected by the type of medication or illness duration (Ozcelik-Eroglu et al., 2014; Samartzis et al., 2014). On the other hand, the recent studies on big-sample sizes revealed that the dose of medication (calculated as the chlorpromazine equivalent) did not affect the diffusivity parameters of WM (Kelly et al., 2018; Koshiyama, 2020; Joo et al., 2020; Gurholt et al., 2020).

Nevertheless, another problematic issue concerns nowadays the open-source, big databases where usually lack the full clinical information of patients, e.g. PANSS, BNSS results. Thus, our research strongly suggests the necessity of implementing consistent and more specific clinical scales, e.g. five-factor BNSS, as standard for psychopathology measurement in clinical DTI investigations on schizophrenia.

To summarize, further study on this topic is highly required. In particular, multidisciplinary studies combining functional and structural approaches in one investigation may be an important prospect that allows analysis of the relations between WM abnormalities, altered synaptic transmission, genes, and associated myelination disturbances and psychopathology in schizophrenia. The better organization of the recent knowledge on the relation between the negative symptoms and their biological underpinnings may contribute to the development of more effective neurotherapeutic interventions, i.e., state-of-the-art neurostimulation methods aimed at psychopathological symptoms reduction, e.g. TMS or tDCS, which methods potentially may effects in an improvement of social functioning.

CONCLUSIONS

In the present study, we revealed the association between disrupted WM integrity in the fronto-temporo-parietal regions (the left oPFC, right HG, bilateral Prec and pCC) and specific negative symptoms in schizophrenia, i.e., asociality. Further studies on this topic require big neuroimaging data set and implementation of more specific, consistent and more homogenous clinical scales used in DTI studies on schizophrenia, e.g. five-factor BNSS symptoms scale.

ACKNOWLEDGMENTS

We are thankful to all participants in this study, to Artur Daren for help with neurocognitive assessment, to Jan Godyń and to Mike Timberlake for proofreading the manuscript. This work was supported by the National Science Centre, Poland, grant no 2016/23/B/HS6/00286.

CONTRIBUTORS

PA did the conception and study design with support from AC, SC. PA, OP wrote the MRI scanning protocols. PA, OP and MJ did MRI-DTI data acquisition. PA, OP did neuropsychological assessments. PB and AK did clinical group recruitment and psychiatric assessments. PA, OP, MJ did DTI data pre-processing and analysis. MJ did DTI-PANSS/BNSS correlation analysis. PA, OP, DK, MJ and SC did data interpretation. PA, OP and DK wrote the paper with revisions from MJ, MW, SC.

REFERENCES

Abdul-Rahman MF, Qiu A, Sim K (2011) Regionally specific white matter disruptions of fornix and cingulum in schizophrenia. PLoS One 6: e18652.

Abram SV, Wisner KM, Fox JM, Barch DM, Wang L, Csernansky JG, MacDonald AW, Smith MJ (2017) Fronto-temporal connectivity predicts cognitive empathy deficits and experiential negative symptoms in schizophrenia. Hum Brain Mapp 38: 1111–1124.

Adamczyk P, Daren A, Sułecka A, Błądziński P, Cichocki Ł, Kalisz A, Gawęda Ł, Cechnicki A (2016) Do better communication skills promote sheltered employment in schizophrenia? Schizophr Res 176: 331–339.

Ahmed AO, Kirkpatrick B, Galderisi S, Mucci A, Rossi A, Bertolino A, Rocca P, Maj M, Kaiser S, Bischof M, Hartmann-Riemer MN, Kirschner M, Schneider K, Garcia-Portilla MP, Mane A, Bernardo M, Fernandez-Egea E, Jiefeng C, Jing Y, Shuping T, Gold J, Allen DN, Strauss GP (2019) Cross-cultural validation of the 5-Factor structure of negative symptoms in schizophrenia. Schizophr Bull 45: 305–314.

Alba-Ferrara LM, Erausquin GA de (2013) What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia. Front Integr Neurosci 7: 9.

Amodio A, Quarantelli M, Mucci A, Prinster A, Soricelli A, Vignapiano A, Giordano GM, Merlotti E, Nicita A, Galderisi S (2017) Avolition-apathy and white matter connectivity in schizophrenia: reduced fractional anisotropy between amygdala and insular cortex. Clin EEG Neurosci 49: 55–65.

Andersson JLR, Sotiropoulos SN (2016) An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. NeuroImage 125: 1063–1078.

Andreasen NC (1982) Negative symptoms in schizophrenia. Arch Gen Psychiatry 39: 784.

Asami T, Hyuk Lee S, Bouix S, Rathi Y, Whitford TJ, Niznikiewicz M, Nestor P, McCarley RW, Shenton ME, Kubicki M (2014) Cerebral white matter abnormalities and their associations with negative but not positive symptoms of schizophrenia. Psychiatry Res Neuroimaging 222: 52–59.

Assaf Y, Pasternak O (2008) Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci: MN 34: 51–61.

Atkins M, Burgess A, Bottomley C, Riccio M (1997) Chlorpromazine equivalents: a consensus of opinion for both clinical and research applications. Psychiatr Bull 21: 224–226.

Balevich EC, Haznedar MM, Wang E, Newmark RE, Bloom R, Schneiderman JS, Aronowitz J, Tang CY, Chu KW, Byne W, Buchsbaum MS, Hazlett EA (2015) Corpus callosum size and diffusion tensor anisotropy in adolescents and adults with schizophrenia. Psychiatry Res Neuroimaging 231: 244–251.

Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B 57: 289–300.

Benoit A, Bodnar M, Malla AK, Joober R, Lepage M (2012) The structural neural substrates of persistent negative symptoms in first-episode of non-affective psychosis: a voxel-based morphometry study. Front Psychiatry 3: 42.

Bègue I, Kaiser S, Kirschner M (2020) Pathophysiology of negative symptom dimensions of schizophrenia – Current developments and implications for treatment. Neurosci Biobehav Rev 116: 74–88.

Bijanki KR, Hodis B, Magnotta VA, Zeien E, Andreasen NC (2015) Effects of age on white matter integrity and negative symptoms in schizophrenia. Schizophr Res 161: 29–35.

Bodnar M, Hovington CL, Buchy L, Malla AK, Joober R, Lepage M (2014) Cortical thinning in temporo-parietal junction (TPJ) in non-affective first-episode of psychosis patients with persistent negative symptoms. PLoS One 9: e101372.

Brady RO, Gonsalvez I, Lee I, Öngür D, Seidman LJ, Schmahmann JD, Eack SM, Keshavan MS, Pascual-Leone A, Halko MA (2019) Cerebellar-prefrontal network connectivity and negative symptoms in schizophrenia. Am J Psychiatry 176: 512–520.

Camchong J, MacDonald AW, Bell C, Mueller BA, Lim KO (2011) Altered functional and anatomical connectivity in schizophrenia. Schizophr Bull 37: 640–650.

Cassoli JS, Guest PC, Malchow B, Schmitt A, Falkai P, Martins-de-Souza D (2015) Disturbed macro-connectivity in schizophrenia linked to oligodendrocyte dysfunction: from structural findings to molecules. NPJ Schizophr 1: 15034.

Cavanna AE, Trimble MR (2006) The precuneus: A review of its functional anatomy and behavioural correlates. Brain 129: 564–583.

Choi H, Kubicki M, Whitford TJ, Alvarado JL, Terry DP, Niznikiewicz M, McCarley RW, Kwon JS, Shenton ME (2011) Diffusion tensor imaging of anterior commissural fibers in patients with schizophrenia. Schizophr Res 130: 78–85.

Churchland PS, Winkielman P (2012) Modulating social behavior with oxytocin: How does it work? What does it mean? Horm Behav 61: 392–399.

Colibazzi T, Wexler BE, Bansal R, Hao X, Liu J, Sanchez-Peña J, Corcoran C, Lieberman JA, Peterson BS (2013) Anatomical abnormalities in gray and white matter of the cortical surface in persons with schizophrenia. PLoS One 8: e55783.

Correll CU, Schooler NR (2020) Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. Neuropsychiatr Dis Treat 16: 519–534.

Di Biase MA, Cropley VL, Cocchi L, Fornito A, Calamante F, Ganella EP, Pantelis C, Zalesky A (2019) Linking cortical and connectional pathology in schizophrenia. Schizophr Bull 45: 911-923.

Dollfus S, Lyne J (2017) Negative symptoms: History of the concept and their position in diagnosis of schizophrenia. Schizophr Res 186: 3–7.

Emsell L, Van Hecke W, Tournier JD (2016) Introduction to Diffusion Tensor Imaging. In: Diffusion Tensor Imaging Springer, New York, NY, p. 7–19.

Erp TGM van, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, Pearlson GD, Yao N, Fukunaga M, Hashimoto R, Okada N, Yamamori H, et al. (2018) Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) consortium. Biol Psychiatry 84: 644–654.

Forlim CG, Klock L, Bächle J, Stoll L, Giemsa P, Fuchs M, Schoofs N, Montag C, Gallinat J, Kühn S (2020) Reduced resting-state connectivity in the precuneus is correlated with apathy in patients with schizophrenia. Sci Rep 10: 2616.

Friston K, Brown HR, Siemerkus J, Stephan KE (2016) The dysconnection hypothesis (2016). Schizophr Res 176: 83–94.

Friston KJ (2002) Dysfunctional connectivity in schizophrenia. World Psychiatry 1: 66–71.

Fujiwara H, Namiki C, Hirao K, Miyata J, Shimizu M, Fukuyama H, Sawamoto N, Hayashi T, Murai T (2007) Anterior and posterior cingulum abnormalities and their association with psychopathology in schizophrenia: A diffusion tensor imaging study. Schizophr Res 95: 215–222.

Garcia-Portilla MP, Garcia-Alvarez L, Saiz PA, Al-Halabi S, Bobes-Bascaran MT, Bascaran MT, Muñiz J, Bobes J (2015) Psychometric evaluation of the negative syndrome of schizophrenia. Eur Arch Psychiatry Clin Neurosci 265: 559–566.

Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ (2010) International consensus study of antipsychotic dosing. Am J Psychiatry 167: 686–693.

Guessoum SB, Le Strat Y, Dubertret C, Mallet J (2020) A transnosographic approach of negative symptoms pathophysiology in schizophrenia and depressive disorders. Prog Neuro-Psychopharmacol Biol Psychiatry 99: 109862.

Gurholt TP, Haukvik UK, Lonning V, Jönsson EG, Pasternak O, Agartz I (2020) Microstructural white matter and links with subcortical structures in chronic schizophrenia: a free-water imaging approach. Front Psychiatry 11: 56.

Harrow M, Jobe TH (2018) Long-term antipsychotic treatment of schizophrenia: does it help or hurt over a 20-year period? World Psychiatry 17: 162–163.

Hovington CL, Bodnar M, Chakravarty MM, Joober R, Malla AK, Lepage M (2015) Investigation of white matter abnormalities in first episode psychosis patients with persistent negative symptoms. Psychiatry Res Neuroimaging 233: 402–408.

İnce E, Üçok A (2018) Relationship between persistent negative symptoms and findings of neurocognition and neuroimaging in schizophrenia. Clin EEG Neurosci 49: 27–35.

Jablensky A (2010) The diagnostic concept of schizophrenia: its history, evolution, and future prospects. Dialogues Clin Neurosci 12: 271–287.

Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17: 825–841.

Joo SW, Kim H, Jo YT, Yoon W, Kim Y, Lee J (2020) Shared and distinct white matter abnormalities in schizophrenia and bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry doi: 10.1016/j.pnpbp.2020.110175. Online ahead of print.

Kaiser S, Heekeren K, Simon JJ (2011) The negative symptoms of schizophrenia: Category or continuum? Psychopathology 44: 345–353.

Kaiser S, Lyne J, Agartz I, Clarke M, Mørch-Johnsen L, Faerden A (2017) Individual negative symptoms and domains – Relevance for assessment, pathomechanisms and treatment. Schizophr Res 186: 39–45.

Kaliuzhna M, Kirschner M, Carruzzo F, Hartmann-Riemer MN, Bischof M, Seifritz E, Tobler PN, Kaiser S (2020) Clinical, behavioural and neural validation of the PANSS amotivation factor. Schizophr Res 220: 38–45.

Karlsgodt KH (2016) Diffusion imaging of white matter in schizophrenia: Progress and future directions. Biol Psychiatry Cogn Neurosci Neuroimaging 1: 209–217.

Kay SR, Fiszbein A, Opler LA (1987) The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 13: 261–276.

Kelly S, Jahanshad N, Zalesky A, Kochunov P, Agartz I, Alloza C, Andreassen OA, Arango C, Banaj N, Bouix S, Bousman CA, Brouwer RM, et al. (2018) Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. Mol Psychiatry 23: 1261–1269.

Kirkpatrick B, Buchanan RW, McKenny PD, Alphs LD, Carpenter WT (1989) The schedule for the deficit syndrome: An instrument for research in schizophrenia. Psychiatry Res 30: 119–123.

Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, Marder SR (2011) The Brief Negative Symptom Scale: Psychometric properties. Schizophr Bull 37: 300–305.

Klauser P, Baker ST, Cropley VL, Bousman C, Fornito A, Cocchi L, Fullerton JM, Rasser P, Schall U, Henskens F, Michie PT, Loughland C, Catts SV, Mowry B, Weickert TW, Weickert CS, Carr V, Lenroot R, Pantelis C, Zalesky A (2016) White matter disruptions in schizophrenia are spatially widespread and topologically converge on brain network hubs. Schizophr Bull 43: 425–435.

Kochunov P, Huang J, Chen S, Li Y, Tan S, Fan F, Feng W, Wang Y, Rowland LM, Savransky A, Du X, Chiappelli J, Chiappelli J, Chen S, Jahanshad N, Thompson PM, Ryan MC, Adhikari B, Sampath H, Cui Y, Wang Z, Yang F, Tan Y, Hong LE (2019) White matter in schizophrenia treatment resistance. Am J Psychiatry 176: 829–838.

Koshiyama D, Fukunaga M, Okada N et al. (2020) White matter microstructural alterations across four major psychiatric disorders: mega-analysis study in 2937 individuals. Mol Psychiatry 25: 883–895.

Kumar J, Iwabuchi SJ, Völlm BA, Palaniyappan L (2019) Oxytocin modulates the effective connectivity between the precuneus and the dorsolateral prefrontal cortex. Eur Arch Psychiatry Clin Neurosci 270: 567–576.

Kumar J, Völlm B, Palaniyappan L (2015) Oxytocin affects the connectivity of the precuneus and the amygdala: a randomized, double-blinded, placebo-controlled neuroimaging trial. Int J Neuropsychopharmacol 18: pyu051.

Kumari S, Malik M, Florival C, Manalai P, Sonje S (2017) An assessment of five (PANSS, SAPS, SANS, NSA-16, CGI-SCH) commonly used symptoms rating scales in schizophrenia and comparison to newer scales (CAINS, BNSS). J Addict Res Ther 8: 324.

Kwapil TR (1998) Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. J Abnorm Psychol 107: 558–565.

Leech R, Braga R, Sharp DJ (2012) Echoes of the brain within the posterior cingulate cortex. J Neurosci 32: 215–222.

Lefort-Besnard J, Bassett DS, Smallwood J, Margulies DS, Derntl B, Gruber O, Aleman A, Jardri R, Varoquaux G, Thirion B, Eickhoff SB, Bzdok D (2017) Different shades of default mode disturbance in schizophrenia: Subnodal covariance estimation in structure and function. Human Brain Mapping 39: 644–661.

Li M, Deng W, Das T, Li Y, Zhao L, Ma X, Wang Y, Yu H, Li X, Meng YJ, Meng YJ, Qiang Wang Q, Palaniyappan L, Li T (2018) Neural substrate of unrelenting negative symptoms in schizophrenia: a longitudinal resting-state fMRI study. Eur Arch Psychiatry Clin Neurosci 268: 641–651.

Liemburg E, Castelein S, Stewart R, Gaag M van der, Aleman A, Knegtering H (2013) Two subdomains of negative symptoms in psychotic disorders: Established and confirmed in two large cohorts. Psychiatr Res 47: 718–725.

Luck D, Buchy L, Czechowska Y, Bodnar M, Pike GB, Campbell JSW, Achim A, Malla A, Joober R, Lepage M (2011) Fronto-temporal disconnectivity and clinical short-term outcome in first episode psychosis: A DTI-tractography study. J Psychiatr Res 45: 369–377.

Marder SR, Galderisi S (2017) The current conceptualization of negative symptoms in schizophrenia. World Psychiatry 16: 14–24.

McKechanie AG, Moorhead TWJ, Stanfield AC, Whalley HC, Johnstone EC, Lawrie SM, Owens DGC (2016) Negative symptoms and longitudinal grey matter tissue loss in adolescents at risk of psychosis: Preliminary findings from a 6-year follow-up study. Br J Psychiatry 208: 565–570.

Mighdoll MI, Tao R, Kleinman JE, Hyde TM (2015) Myelin, myelin-related disorders, and psychosis. Schizophr Res 161: 85–93.

Millan MJ, Fone K, Steckler T, Horan WP (2014) Negative symptoms of schizophrenia: Clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. Eur Neuropsychopharmacol 24: 645–692.

Mucci A, Vignapiano A, Bitter I, Austin SF, Delouche C, Dollfus S, Erfurth A, Fleischhacker WW, Giordano GM, Gladyshev I, Glenthøj B, Gütter K, et al. (2019) A large European, multicenter, multinational validation study of the Brief Negative Symptom Scale. Eur Neuropsychopharmacol 29: 947–959.

Nakamura K, Kawasaki Y, Takahashi T, Furuichi A, Noguchi K, Seto H, Suzuki M (2012) Reduced white matter fractional anisotropy and clinical symptoms in schizophrenia: A voxel-based diffusion tensor imaging study. Psychiatry Res Neuroimaging 202: 233–238.

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53: 695–699.

Ochi R, Noda Y, Tsuchimoto S, Tarumi R, Honda S, Matsushita K, Tsugawa S, Plitman E, Masuda F, Ogyu K, Wada M, Miyazaki T, et al. (2020) White matter microstructural organizations in patients with severe treatment-resistant schizophrenia: A diffusion tensor imaging study. Prog Neuro-Psychopharmacology Biol Psychiatry 100: 109871.

Ohtani T, Bouix S, Hosokawa T, Saito Y, Eckbo R, Ballinger T, Rausch A, Melonakos E, Kubicki M (2014) Abnormalities in white matter connections between orbitofrontal cortex and anterior cingulate cortex and their associations with negative symptoms in schizophrenia: A DTI study. Schizophr Res 157: 190–197.

Ozcelik-Eroglu E, Ertugrul A, Oguz KK, Has AC, Karahan S, Yazici MK (2014) Effect of clozapine on white matter integrity in patients with schizophrenia: A diffusion tensor imaging study. Psychiatry Res Neuroimaging 223: 226–235.

Parnanzone S, Serrone D, Rossetti MC, D'Onofrio S, Splendiani A, Micelli V, Rossi A, Pacitti F (2017) Alterations of cerebral white matter structure in psychosis and their clinical correlations: a systematic review of Diffusion Tensor Imaging studies. Riv Psichiatr 52: 49–66.

Pelletier-Baldelli A, Holt DJ (2020) At issue: are negative symptoms merely the "real world" consequences of deficits in social cognition? Schizophr Bull 46: 236–241.

Pettersson-Yeo W, Allen P, Benetti S, McGuire P, Mechelli A (2011) Dysconnectivity in schizophrenia: Where are we now? Neurosci Biobehav Rev 35: 1110–1124.

Reed GM, First MB, Kogan CS, Hyman SE, Gureje O, Gaebel W, Maj M, Stein DJ, Maercker A, Tyrer P, et al. (2019) Innovations and changes in

the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. World Psychiatry 18: 3–19.

Schoonover KE, Farmer CB, Cash AE, Roberts RC (2019) Pathology of white matter integrity in three major white matter fasciculi: A post-mortem study of schizophrenia and treatment status. Br J Pharmacol 176: 1143–1155.

Schultz CC, Wagner G, Schachtzabel C, Reichenbach JR, Schlösser RG, Sauer H, Koch K (2017) Increased white matter radial diffusivity is associated with prefrontal cortical folding deficits in schizophrenia. Psychiatry Res Neuroimaging 261: 91-95.

Shaffer JJ, Peterson MJ, McMahon MA, Bizzell J, Calhoun V, Erp TGM van, Ford JM, Lauriello J, Lim KO, Manoach DS, McEwen SC, Mathalon DH, et al. (2015) Neural correlates of schizophrenia negative symptoms: distinct subtypes impact dissociable brain circuits. Mol Neuropsychiatry 1: 191–200.

Skelly LR, Calhoun V, Meda SA, Kim J, Mathalon DH, Pearlson GD (2008) Diffusion tensor imaging in schizophrenia: Relationship to symptoms. Schizophr Res 98: 157–162.

Samartzis L, Dima D, Fusar-Poli P, Kyriakopoulos M (2014) White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. J Neuroimaging 24: 101–110.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TEJ (2006) Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. Neuroimage 31: 1487–1505.

Stämpfli P, Sommer S, Manoliu A, Burrer A, Schmidt A, Herdener M, Seifritz E, Kaiser S, Kirschner M (2019) Subtle white matter alterations in schizophrenia identified with a new measure of fiber density. Sci Rep 9: 4636.

Stiekema APM, Liemburg EJ, Meer L van der, Castelein S, Stewart R, Weeghel J van, Aleman A, Bruggeman R (2016) Confirmatory factor analysis and differential relationships of the two subdomains of negative symptoms in chronically Ill psychotic patients. PLoS One 11: e0149785.

Strauss GP, Keller WR, Koenig JI, Sullivan SK, Gold JM, Buchanan RW (2015) Endogenous oxytocin levels are associated with the perception of emotion in dynamic body expressions in schizophrenia. Schizophr Res 162: 52–56.

Strauss GP, Nuñez A, Ahmed AO, Barchard KA, Granholm E, Kirkpatrick B, Gold JM, Allen DN (2018) The latent structure of negative symptoms in schizophrenia. JAMA Psychiatry 75: 1271.

Strauss GP, Esfahlani FZ, Galderisi S, Mucci A, Rossi A, Bucci P, Rocca P, Maj M, Kirkpatrick B, Ruiz I, Sayama H (2019) Network analysis reveals the latent structure of negative symptoms in schizophrenia. Schizophr Bull 45: 1033–1041.

Sun H, Lui S, Yao L, Deng W, Xiao Y, Zhang W, Huang X, Hu J, Bi F, Li T, Sweeney JA, Gong Q (2015) Two patterns of white matter abnormalities in medication-naive patients with first-episode schizophrenia revealed by diffusion tensor imaging and cluster analysis. JAMA Psychiatry 72: 678–686.

Tan AS, Chew QH, Sim K (2020) Cerebral white matter changes in deficit and non-deficit subtypes of schizophrenia. J Neural Transm 127: 1073–1079.

Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI (2004) Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophr Res 67: 269–275.

Van der Gaag M, Hoffman T, Remijsen M, Hijman R, Dehaan L, Vanmeijel B, Vanharten P, Valmaggia L, Dehert M, Cuijpers A (2006) The five-factor model of the Positive and Negative Syndrome Scale II: A ten-fold cross-validation of a revised model. Schizophr Res 85: 280–287.

Viher PV, Stegmayer K, Giezendanner S, Federspiel A, Bohlhalter S, Vanbellingen T, Wiest R, Strik W, Walther S (2016) Cerebral white matter structure is associated with DSM-5 schizophrenia symptom dimensions. Neuroimage Clin 12: 93–99.

Walton E, Hibar DP, van Erp TGM, Potkin SG, Roiz-Santiañez R, Crespo-Facorro B, Suarez-Pinilla P, van Haren NEM, de Zwarte SMC, Kahn RS, et al. (2018) Prefrontal cortical thinning links to negative symptoms in schizophrenia via the ENIGMA consortium. Psychol Med 48: 82–94.

Wheeler-Kingshott CA, Cercignani M (2009) About "axial" and "radial" diffusivities. Magn Reson Med 61: 1255-1260.

Whitford TJ, Lee SW, Oh JS, Luis-Garcia R de, Savadjiev P, Alvarado JL, Westin CF, Niznikiewicz M, Nestor PG, McCarley RW, Kubicki M, Shenton ME (2014) Localized abnormalities in the cingulum bundle in patients with schizophrenia: a diffusion tensor tractography study. Neuroimage Clin 5: 93–99.

Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE (2014) Permutation inference for the general linear model. Neuroimage 92: 381–397.

Woods SW (2003) Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 64: 663–667.

World Medical Association (2013) Declaration of Helsinki – ethical principles for medical research involving human subjects. JAMA 310: 2191-2194.

Yan H, Tian L, Yan J, Sun W, Liu Q, Zhang YB, Li XM, Zang YF, Zhang D (2012) Functional and anatomical connectivity abnormalities in cognitive division of anterior cingulate cortex in schizophrenia. PLoS One 7: e45659.

Yan J, Cui Y, Li Q, Tian L, Liu B, Jiang T, Zhang D, Yan H (2019) Cortical thinning and flattening in schizophrenia and their unaffected parents. Neuropsychiatr Dis Treat 15: 935–946.