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Regional update

Elucidation of shared and specific white matter findings underlying psychopathology clusters in schizophrenia

Jeanette Lim[a,b,c], Rowena Chin[a], New Fei Ho[a], Max Lam[a], Min Yi Sum[a], Simon Collinson[b], Lisa Phillips[c], Tih-Shih Lee[d], Balázs Zoltán Gulyás[e], Juan Zhou[f], Kang Sim[a,g,*]

[a] Research Division, Institute of Mental Health, 10 Buangkok View, Buangkok Green Medical Park, 539747, Singapore
[b] Department of Psychology, National University of Singapore, 21 Lower Kent Ridge Rd, 119077, Singapore
[c] Melbourne School of Psychological Sciences, University of Melbourne, Parkville, VIC 3010, Australia
[d] Neuroscience & Behavioural Disorders Programme, Duke-NUS Medical School, 8 College Road, 169857, Singapore
[e] Translational Neuroscience Laboratory, Lee Kong Chian School of Medicine, Nanyang Technological University, 11 Mandalay Road, 308232, Singapore
[f] Center for Cognitive Neuroscience, Neuroscience and Behavioral Disorders Program, Duke-NUS Graduate Medical School, 8 College Road, 169857, Singapore
[g] Department of General Psychiatry, Institute of Mental Health, 10 Buangkok View, Buangkok Green Medical Park, 539747, Singapore

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ABSTRACT

Background: Schizophrenia is associated with diverse white matter (WM) brain abnormalities. In this study, we sought to examine the WM microstructural findings which underlie clinical psychopathology clusters in schizophrenia and hypothesized that these symptom clusters are associated with common and unique WM tracts.
Methods: Overall, 76 healthy controls (HC), and 148 patients with schizophrenia (SZ) were recruited and severity of symptomatology in schizophrenia was assessed using the Positive and Negative Syndrome Scale. WM fractional anisotropy (FA) values were extracted from their diffusion tensor images. Psychopathology clusters were first determined using factor analysis and the relationship between these symptom factors and FA values were then assessed with structural equation modelling, which included covariates such as age, sex, duration of illness and medications prescribed.
Results: Patients with schizophrenia had reduced FA in the genu of corpus callosum (gCC) compared to HC. A three-factor model, namely Positive, Negative, Disorganised factors, was determined as the best fit for the data. All three psychopathology factors were associated with decreased FA in the gCC and bilateral cingulate gyrus. Higher Negative factor scores were uniquely associated with decreased FA in the right sagittal striatum and right superior longitudinal fasciculus.
Conclusions: This study found shared and specific WM changes and their associations with specific symptom clusters, which potentially allows for monitoring of such white matter findings associated with clinical presentations in schizophrenia over treatment and illness course.

1. Introduction

The dysconnection hypothesis indicates that schizophrenia is a disorder of brain connectivity (Friston and Frith, 1995). Previous diffusion tensor imaging (DTI) studies have found reductions of fractional anisotropy (FA) in different brain regions involving the frontal, temporal, limbic, parietal and occipital regions in patients with schizophrenia (d'Albis and Houenou, 2015; Peters et al., 2010). Considering the diversity in clinical presentations related to schizophrenia, it would be clinically meaningful to determine white matter findings underlying different symptom clusters (Karlsgodt, 2016).

The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), a common rating tool to assess the nature and level of psychopathology in schizophrenia, was originally designed with three subscales i.e. positive, negative and general psychopathology, and recent factor analyses have generally found five-factor models consisting of Positive, Negative, Disorganised, Depression/Emotional Distress and Excitement/Mania factors (Jiang et al., 2013; van der Gaag et al., 2006; Wallwork et al., 2012). However, the lack of a consistent, consensus five-factor model suggests that a locally and contextually derived model might be more appropriate.

Overall, studies examining the relationship between brain white matter integrity and PANSS factors were limited and most studies have focused mainly on positive and negative symptom subscales and not the

* Corresponding author at: Institute of Mental Health/Woodbridge Hospital 10, Buangkok View, 539747, Singapore.
E-mail address: kang_sim@imh.com.sg (K. Sim).

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full factors. Positive symptoms were associated with increased or decreased FA in different WM structures, particularly in genu of corpus callosum (gCC) and superior longitudinal fasciculus (SLF) (Caprihan et al., 2015; Mitelman et al., 2007). This might be due to different sample sizes as increased FA was usually found in studies with smaller number of subjects (Park et al., 2014; Rotarska-Jagiela et al., 2009). In addition, higher negative symptoms were associated with decreased FA in gCC, inferior fronto-occipital fasciculus (IFOF) and inferior longitudinal fasciculus (ILF) (Arnedo et al., 2015; Sun et al., 2015).

Thus in this study, we sought to examine the patterns of WM anomalies associated with symptom clusters as measured by PANSS amongst our patients with schizophrenia.

2. Methods

2.1. Participants

Out of 244 participants, 96 were healthy controls (HC) and 148 were participants with schizophrenia (SZ). HC were recruited from the community via advertisements and patients with SZ were recruited from the Institute of Mental Health, Singapore. For all participants, presence and absence of psychopathology was established by a board-certificated psychiatrist (K.S.) using information obtained from the clinical history, mental status examination, existing medical records, interviews with significant others as well as the administration of the Structural Clinical Interview (Patient and Non-Patient version) (First et al., 1994) based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000). Patients were eligible for the study if they met DSM-IV criteria for schizophrenia. Participants were excluded if they had any of the following characteristics: (1) a history of any significant neurological illness such as brain trauma or epilepsy and (2) met DSM-IV criteria for alcohol or other substance abuse. Written informed consent was obtained from all participants. The Institutional Review Board of the Institute of Mental Health and National Neuroscience Institute approved the studies.

2.2. Assessment

Basic demographic data were collected. PANSS (Kay et al., 1987) was used to measure the nature and severity of symptomatology. The PANSS consists of 30 items in three subscales, namely positive (seven items), negative (seven items), and general psychopathology (16 items). Higher scores indicate more severe psychopathology.

Magnetic resonance imaging was carried out using a 3-T whole-body scanner (GyroscanAchieva, Philips Medical Systems, Eindhoven, The Netherlands) with a SENSE head coil at the National Neuroscience Institute, Singapore. A regular automated quality control procedure was in place to ensure the stability of a high signal to noise ratio. Whole brain volumetric scans were acquired with a high-resolution, T1-weighted turbo-field echo sequence (repetition time (TR) = 8.4 s; echo time (TE) = 3.8 ms; inversion time (TI) = 3000 ms; flip angle = 8°; field of view (FOV) = 230 mm^2; acquisition matrix 256 × 256) to produce a total of 180 contiguous axial slices of 0.9 mm thickness with no gaps.

Diffusion-weighted images were obtained in the same session using a single-shot echo-planar sequence (TR = 3725 ms; TE = 56 ms; flip angle = 90°; b-factor = 800s/mm^2) in 15 non-parallel directions with the baseline image being acquired without diffusion weighting (b-factor = 0 s/mm^2). Each volume consisted of 42 axial slices of 3.0 mm thickness with no gaps and were parallel to the anterior–posterior commissure line (FOV = 230 mm^2; acquisition matrix 256 × 256 after conversion). Three volumes were obtained to improve the signal-to-noise ratio of the scans. Both structural and DTI scans were acquired sequentially in one single scan time with no position change.

2.3. Imaging processing

The Enhancing Neuro Imaging Genetics through Metal-Analysis (ENIGMA) DTI protocol was used for the pre-processing of the DTI scans and the extraction of mean fractional anisotropy (FA) values (ENIGMA, 2015). Pre-processing involved motion, gradient and eddy current correction following our previous approach (Ho et al., 2017). The FA images were then registered non-linearly to the ENIGMA target brain using FSL (Smith et al., 2004) nonlinear registration algorithm (FNIRT). A modified FSL Tract-Based Spatial Statistics (TBSS; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS; Smith et al., 2006) analytical method was used to project the individual FA values onto the ENGMA-DTI template skeleton, creating skeletonized images for each subject. Following which, the WM regions of interest (ROIs) were extracted from the skeletonized images using John Hopkins University (JHU) DTI atlas (International Consortium of Brain Imaging (ICBM)-DTI-81 white-matter labels atlas) (Mori et al., 2008). Based on extant literature, investigations were limited to average FA values from 11 regions of interest including the genu, body and splenium of corpus callosum (gCC, bCC and sCC), bilateral sagittal striatum (SS; includes IFOF and ILF), bilateral cingulum (cingulate gyrus) (CG), bilateral cingulum (hippocampus) (CHIP) and bilateral SLF. FSL version 5.0 (http://www.fmrib.ox.ac.uk/fsl) was used for the DTI data analyses.

2.4. Statistical analyses

First, FA comparisons between HC and schizophrenia were performed using full factorial univariate analyses including main and interaction effects of group, age, and sex. Subsequently, to determine the optimal number of factors for PANSS, exploratory factor analysis (EFA) was performed on the schizophrenia sample. Two to seven factors were explored using PANSS items as ordinal variables with Geomin rotation.

Four different models were then run to examine the relationship between PANSS factors and WM fractional anisotropy (FA) using exploratory structural equation modelling (ESEM; Asparouhov and Muthén, 2009). The zero-order correlation model allowed for the examination of unadjusted relationships between PANSS factors and FA. Given that past studies have demonstrated the effects of age, sex, duration of illness and medication dosage on WM (Peters et al., 2010), the partial correlation model controlled for these factors. Next, a regression model, including covariates, investigated WM tracts unique to specific symptom cluster. If a WM tract was associated with all dimensions, there might not be unique associations with any dimensions; significant correlations and non-significant regressions across all dimensions might be observed. Therefore, only these significant correlation paths (i.e. common to all symptoms) and significant regressions paths (i.e. specific to a symptom) were retained in the final model. Given the numerous statistical comparisons made in the models, Benjamini and Hochberg's (1995) False Discovery Rate was used to reduce Type I errors.

Fit statistics of a good model include a non-significant χ^2 test, Tucker-Lewis Index (TLI; Tucker and Lewis, 1973) and comparative fit index (CFI; Bentler, 1990) of greater than or equal to 0.90; root mean-squared error of approximation (RMSEA; Jöreskog and Sörbom, 1982) of less than 0.08; and weighted root mean residual (WRMR) of less than 0.90 (Schreiber et al., 2006). The χ^2 difference tests were also used to examine if the models were measuring the same constructs (Satorra and Bentler, 2001). SPSS 22.0 (IBM Corp, 2013) and Mplus 7.0 (Muthén and Muthén, 2012) was used for the analyses.

3. Results

3.1. Study sample

Differences between HC and SZ groups were examined (Table 1). Compared with HC, SZ were more likely to be single and had fewer

Table 1
Demographics, Clinical and White Matter Data for the Study Sample.

	People with schizophrenia included in current study (N = 148)			Healthy controls (N = 96)					
Variable	*n*	%		*n*	%		*t/F*	df	*p*
Sex									
Male	101	68.2		59	61.5		1.187	1	0.276
Ethnicity									
Chinese	133	89.9		82	85.4		3.404	3	0.333
Malay	9	6.1		5	5.2				
Indian	5	3.4		6	6.2				
Others	1	0.7		3	3.1				
Marital Status									
Single	128	86.5		62	64.6		21.692	3	< 0.001***
Married	17	11.5		33	34.4				
Divorced/Separated	3	2.0		0	0				
Widowed	0	0		1	1.0				
	M	*SD*	n	*M*	*SD*	Type of Effect[b]	*t/F*	*df*	*p*
Age	32.95	9.13		32.07	9.86	–	−0.705	242	0.481
Years of Education	11.72	2.34		13.97	2.00	–	7.739	242	< 0.001***
Univariate Analysis[a]			76						
Genu of Corpus Callosum	0.673	0.029		0.674	0.028	Group	4.057	1,216	0.045*
Body of Corpus Callosum	0.615	0.040		0.618	0.037	All	*ns*	*ns*	*ns*
Splenium of Corpus Callosum	0.762	0.024		0.766	0.023	All	*ns*	*ns*	*ns*
Right Sagittal Striatum	0.540	0.030		0.545	0.029	All	*ns*	*ns*	*ns*
Left Sagittal Striatum	0.529	0.027		0.532	0.026	Age	6.524	1,216	0.011*
Right Cingulum (Cingulate Gyrus)	0.550	0.042		0.561	0.039	Group x Age	6.430	1,216	0.012*
						Group	8.571	1,216	0.040*
						Age	6.684	1,216	0.010*
Left Cingulum (Cingulate Gyrus)	0.578	0.038		0.580	0.039	Group x Age	3.993	1,216	0.047*
						Group	3.904	1,216	0.049*
Right Cingulum (Hippocampus)	0.538	0.048		0.538	0.040	Age	4.855	1,216	0.029*
Left Cingulum (Hippocampus)	0.525	0.048		0.525	0.038	All	*ns*	*ns*	*Ns*
Right Superior Longitudinal Fasciculus	0.501	0.032		0.509	0.024	Group x Age x Sex	3.943	1,216	0.048*
						Group	4.583	1,216	0.033*
Left Superior Longitudinal Fasciculus	0.501	0.027		0.506	0.023	Group X Age	4.324	1,216	0.039*
						Group	5.401	1,216	0.021*
Duration of Psychiatric Illness (years)	6.48	7.48		–	–	–			
Daily Dose of Antipsychotics in Chlorpromazine Equivalents	199.90	185.93		–	–	–			
PANSS[c] Total Score	39.89	8.36		–	–	–			
PANSS[c] Positive Score	10.59	3.80		–	–	–			
PANSS[c] Negative Score	8.99	3.02		–	–	–			
PANSS[c] General Psychopathology Score	20.31	3.68		–	–	–			

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] The main and interaction effects of group, sex, and age were explored on white matter fractional anisotropy values.
[b] Only significant main and interaction effects were reported.
[c] PANSS = Positive and Negative Syndrome Scale.

years of education.

For FA, significant main and interaction effects were found (See Supplementary Figures). The SZ group had decreased FA for gCC, bilateral CG and bilateral SLF (Group effect). Those who were older also had decreased FA for left SS, right CG, and right CHIP (Age effect). Post-hoc analyses found that within the control group, as age increased, FA decreased in right CG ($F(1,72) = 13.022$, $p = 0.001$), left CG ($F(1,72) = 6.400$, $p = 0.14$) and left SLF ($F(1,72) = 7.304$, $p = 0.009$), while there were no differences in the schizophrenia group (all $p > 0.05$) (Group x Age). For right SLF, in females, FA decreased as age increased in HC ($F(1,27) = 5.685$, $p = 0.024$) with no significant differences in people with schizophrenia ($F(1,45) = 3.785$, $p = 0.058$) (Group x Age x Sex). There were no differences in males (all $p > 0.05$).

3.2. PANSS factor structure within the sample

First, PANSS items with skewed distributions and high correlations, indicating ceiling and multicollinearity effects (Kline, 2016), were removed (see Supplementary Tables). This was done using an iterative method – the PANSS items with a high number of correlations and skewed distributions were removed until no variable was highly correlated with another (Kline, 2016). 17 PANSS items remained.

Subsequently, to explore two- to seven-factor models, EFA was used on the 17 PANSS items. The three-factor model was the first model with a non-significant χ^2 and CFI, TLI, RMSEA and WRMR above the cut-offs (Table 2). The three-factor model was also significantly different from the two-factor model and not significantly different from the four-factor model. Therefore, the three-factor model provided the most parsimonious fit for the data. The three factors identified corresponded to those in the literature, namely Positive, Negative, and Disorganised (Table 3). In the three-factor model, the correlation between the Positive and Negative factor was 0.105 ($p = 0.117$), the Positive and Disorganised factor was 0.274 ($p < 0.001$) and the Negative and Disorganised factor was 0.453 ($p < 0.001$).

3.3. Symptom clusters and white matter

The three-factor PANSS zero-order correlation, partial correlation, and regression models with the ROIs had poor fit to the data (Table 2). To refine the model, significant shared and specific paths with symptom

Table 2
Model Fit Statistics.

Models	χ^2	*df*	*p*	χ^2 difference	*df*	*p*	RMSEA[a]	RMSEA 90% CI[b]	CFI[c]	TLI[d]	WRMR[e]
Exploratory Factor Analysis											
Two-factor	145.169	103	0.004	–	–	–	0.053	0.0031–0.0072	0.988	0.984	0.769
Three-factor	98.856	88	0.201	53.132	15	< 0.001	0.029	0.000–0.055	0.997	0.995	0.546
Four-factor	75.656	74	0.425	21.963	14	0.079	0.012	0.000–0.049	1	0.999	0.411
Five-factor	62.512	61	0.422	14.384	13	0.347	0.013	0.000–0.0052	1	0.999	0.340
Six-factor	No convergence										
Seven-factor	No convergence										
Exploratory Structural Equation Modelling											
Zero-order Correlation	946.589	297	< 0.001	–	–	–	0.122	0.113–0.130	0.796	0.74	1.829
Partial Correlation and Regression	349.314	298	0.0217	–	–	–	0.034	0.014–0.048	0.985	0.975	0.668
Final Model	238.094	214	0.1239	–	–	–	0.028	0.000–0.046	0.993	0.99	0.643

[a] RMSEA = Root mean-squared error of approximation.
[b] CI = Confidence intervals.
[c] CFI = Comparative fit index.
[d] TLI = Tucker-Lewis index.
[e] WRMR = Weighted root mean residual.

Table 3
Factor Loadings of the Three-Factor Positive and Negative Syndrome Scale (PANSS) Model.

Item	Positive	Negative	Disorganised	R^2
P1 Delusions	0.972***	0.041	0.037	0.978
P2 Conceptual Disorganisation	0.361**	0.112	**0.458***	0.498
P3 Hallucinations	**0.719*****	0.037	0.138	0.602
P7 Hostility	0.035	0.094	0.289*	0.124
N1 Blunted Affect	0.119*	**1.067*****	−0.225*	0.998
N2 Emotional Withdrawal	0.075	**0.840*****	0.032	0.751
N3 Poor Rapport	0.082	**0.475*****	0.470***	0.685
N4 Apathetic Social withdrawal	−0.243	**0.623*****	0.468***	0.836
N5 Difficulty in Abstraction	−0.066	0.581***	**0.481*****	0.800
N6 Lack of Spontaneity	0.030	**0.534*****	0.517***	0.815
N7 Stereotyped Thinking	0.085	0.116	**0.672*****	0.576
G2 Anxiety	0.064	0.054	0.174	0.053
G9 Unusual Thought Content	**0.994*****	0.017	−0.056	0.963
G12 Lack of Judgement and Insight	**0.195***	−0.049	**0.468*****	0.286
G13 Disturbance of Volition	−0.065	0.221	**0.465*****	0.342
G15 Preoccupation	0.334***	−0.072	**0.860*****	0.953
G16 Active Social Avoidance	0.228	**0.290*****	0.579***	0.709

Note. Items in bold corresponded to those found in the literature.
*$p < 0.05$, **$p < 0.01$, ****$p < 0.001$.

clusters were selected (all $p < 0.05$; see Supplementary Tables). In the partial correlation model, all three factors were negatively associated with FA in gCC and bilateral CG. In the regression model, higher Negative factor scores were significantly associated with decreased FA in right SS and right SLF. All other associations were non-significant.

In the final model, both common (i.e. gCC and bilateral CG) and unique (right SS and right SLF) WM tracts were retained, and the model fit was very good (Table 2). Decreased FA in gCC was significantly associated with all three symptom clusters, and decreased FA in right SS and right SLF were significantly associated with the Negative factor (Table 4, Fig. 1). The PANSS item loadings were similar to the three-factor PANSS model (not shown). The variances accounted for in right SS and right SLF were 30.4% and 10.8% respectively.

4. Discussion

Given the heterogeneity of WM findings in schizophrenia, this study evaluated the use of psychotic psychopathology clusters to clarify WM findings underlying these clinical presentations. A three-factor EFA-derived model, consisting of Positive, Negative and Disorganised factors, was the best fit for the PANSS data. Decreased FA in both gCC and bilateral CG were associated with all three symptom clusters. Higher Negative factor scores were also uniquely associated with decreased FA in right SS and right SLF. This suggests that both common and unique patterns of associations were found between psychotic symptom clusters and WM, even after controlling for age, sex, duration of illness and current taken medications.

A three-factor PANSS EFA model with multiple cross-loadings was the best-fitting model in our sample. While previous studies have found five-factor models (Jiang et al., 2013; van der Gaag et al., 2006; Wallwork et al., 2012), the three-factor model (Positive, Negative and Disorganised) is a subset of these five-factor models (Positive, Negative, Disorganised, Excitement/Mania, and Depression/Emotional Distress) as the items within each factor corresponded fairly well to those found in the literature. The majority of the PANSS items removed were related to both the Depression/Emotional Distress and Excitement/Mania factors. Additionally, P7 Hostility and G2 Anxiety had low item loadings in the model, suggesting that the study participants were not experiencing excessive emotional distress or excitement at the time of recruitment. The current findings correspond with van Os and Kapur's (2009) schizophrenia subtype of high scores on Positive, Negative and Disorganised symptoms and lower scores on Mania and Depression. Furthermore, the three-factor model expanded on current findings of similar models of associations with other neurobiological markers including grey matter (Nenadic et al., 2010), blood flow (Liddle et al., 1992), regional glucose metabolism (Schröder et al., 1996), and task-related brain activation (Honey et al., 2003).

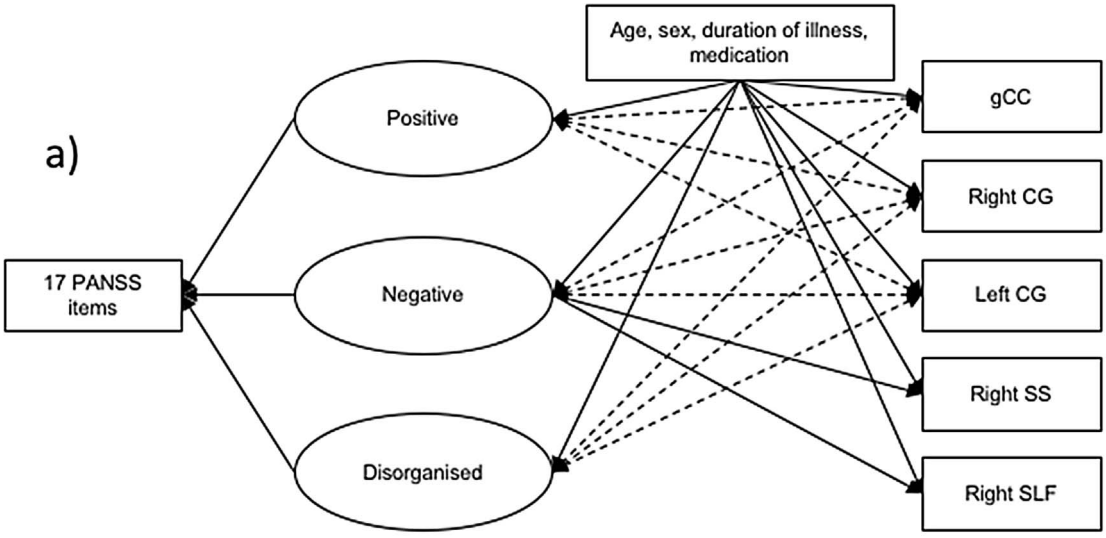
4.1. Shared WM tracts across symptom clusters

The three symptom clusters were associated with reduced FA in gCC and bilateral CG which suggest that common WM anomalies underlie psychotic psychopathology clusters in schizophrenia (Karlsgodt, 2016). The gCC is functionally associated with the frontal lobe and anterior CG (van der Knaap and van der Ham, 2011), and is involved in executive functioning including inhibition of competing semantic and visuospatial information between both hemispheres (Rotarska-Jagiela et al., 2008; et al., 2010). Furthermore, as gCC FA was significantly decreased in people with schizophrenia, this is in line with the notion of interhemispheric dysconnectivity underlying schizophrenia (Crow, 1998). The CG, a prominent WM structure in the limbic system, connects to the prefrontal, premotor, parietal, occipital, parahippocampal cortices and thalamus (Mori et al., 2008). It has been associated with regulating responses in terms of volition, initiation, attention, monitoring and emotional regulation (Allen et al., 2008; Assaf et al., 2006; Ćurčić-Blake et al., 2015). Further research is needed to examine the relationship between regulation of information in schizophrenia symptoms.

Table 4
Final Model of White Matter Fractional Anisotropy Values in the Genu of Corpus Callosum, Right Sagittal Striatum, Bilateral Cingulum (Cingulate Gyrus) and Right Superior Longitudinal Fasciculus on Positive and Negative Syndrome Scale (PANSS) Factors.

	Positive						Negative						Disorganised					
	Unstandardized						Unstandardized						Unstandardized					
Path[a]	Estimate	*SE*	*Z*	*p*	*BH*[b] *p*	*SEst*[c]	Estimate	*SE*	*Z*	*p*	*BH*[b] *p*	*SEst*[c]	Estimate	*SE*	*Z*	*p*	*BH*[b] *p*	*SEst*[c]
gCC[d]	−0.007	0.002	−3.471	< 0.001***	0.002**	−0.238	−0.008	0.002	−3.513	< 0.001***	0.003**	−0.278	−0.009	0.002	−3.903	< 0.001***	0.002**	−0.315
R SS[e]	−0.004	0.002	−1.777	0.076	0.244	−0.145	−0.015	0.003	−4.998	< 0.001***	< 0.001***	−0.492	< −0.001	0.003	−0.102	0.919	0.981	0.010
R CG[f]	−0.007	0.003	−2.531	0.011*	0.045*	−0.176	−0.013	0.004	−3.720	< 0.001***	0.002**	−0.318	−0.008	0.003	−2.774	0.006**	0.024*	−0.203
L CG[g]	−0.010	0.003	−3.595	< 0.001***	0.003**	−0.262	−0.008	0.003	−2.821	0.005**	0.023*	−0.209	−0.010	0.003	−3.725	< 0.001***	0.002**	−0.267
R SLF[h]	−0.002	0.002	−0.722	0.470	0.745	−0.055	−0.011	0.003	−3.345	0.001*	0.004**	−0.359	0.005	0.004	1.526	0.127	0.332	0.177
Age	0.021	0.012	1.705	0.088	0.243	0.180	0.015	0.015	0.983	0.325	0.696	0.132	−0.012	0.019	−0.659	0.510	0.745	−0.109
Gender	−0.456	0.217	−2.103	0.036*	0.128	−0.202	−0.196	0.229	−0.855	0.393	0.738	−0.091	−0.253	0.279	−0.907	0.364	0.714	−0.115
DOI[i]	−0.051	0.017	−2.922	0.003**	0.018*	−0.359	−0.006	0.017	−0.355	0.722	0.958	−0.046	0.018	0.026	0.704	0.482	0.745	0.131
Med[j]	0.074	0.100	0.741	0.459	0.749	0.070	< −0.001	0.128	−0.004	0.997	0.997	0.000	−0.163	0.230	−0.707	0.479	0.745	−0.158

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a]All paths are regression paths except for gCC and bilateral CG, which are correlational paths.
[b]BH = Benjamini & Hochberg False Discovery Rate, corrected for 47 comparisons.
[c]SEst = Standardised estimate.
[d]gCC = Genu of corpus callosum.
[e]R SS = Right sagittal striatum.
[f]R CG = Right cingulum (cingulate gyrus).
[g]L CG = Left cingulum (cingulate gyrus).
[h]R SLF = Right superior longitudinal fasciculus.
[i]DOI = Duration of illness.
[j]Med = Current antipsychotic medication dosage in chlorpromazine equivalents.



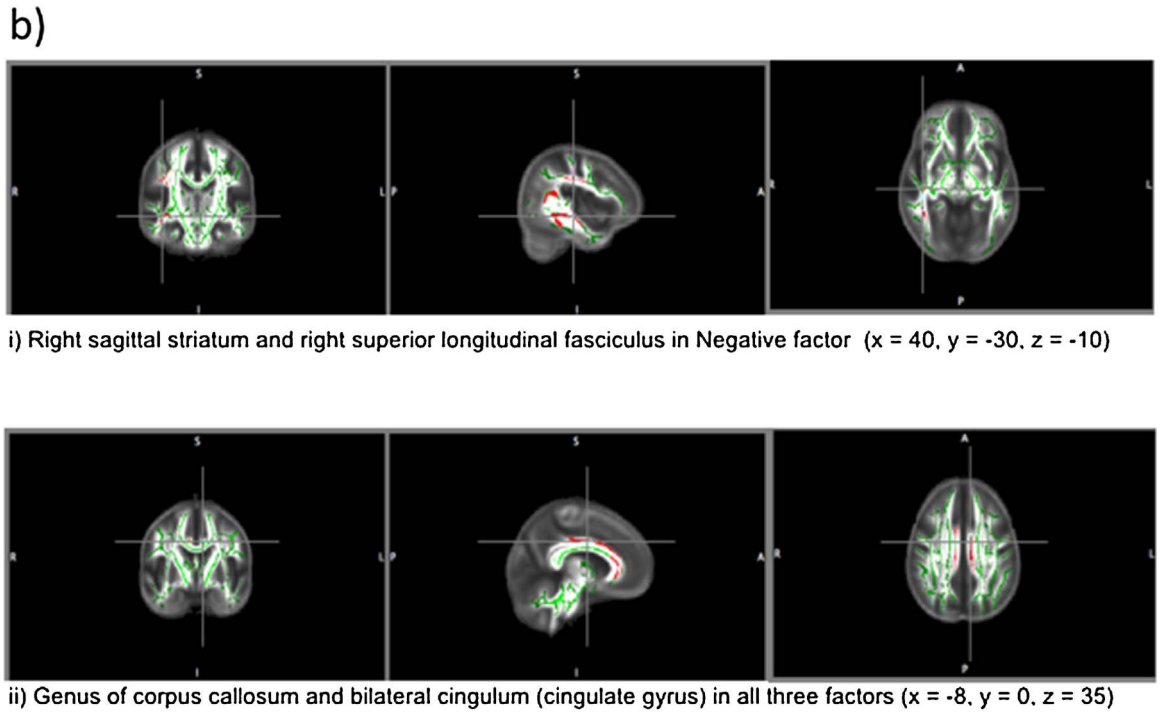


Fig. 1. (a) Final model of Positive and Negative Syndrome Scale (PANSS) factors and white matter fractional anisotropy values with covariates. All three dimensions were correlated with gCC and bilateral CG. Negative factor was uniquely associated with both right SS and right SLF. Age, sex, duration of illness and current antipsychotic medication dosage in chlorpromazine equivalents were included as covariates in the model. Correlational paths are dotted. (b) Significant associations between white matter fractional anisotropy (FA) values and Positive and Negative Syndrome Scale (PANSS) factors. The mean FA image for the study was mapped onto the Enhancing Neuro Imaging Genetics through Metal-Analysis (ENIGMA) Diffusion Tensor Imaging template in green. Significant tracts are identified in red.

4.2. Specific symptom clusters

In terms of the positive symptom cluster, in line with past findings (Ćurčić-Blake et al., 2015; Mitelman et al., 2007), negative associations between Positive factor scores and FA were found in the gCC and bilateral CG. Some suggest that the gCC could be associated with the inability to distinguish the source of generated action, contributing to delusions and hallucinations (Frith, 1996) while the failure in monitoring and regulating responses in CG might lead to misattribution of inner thoughts as hallucinations or elaboration of delusions, and difficulties suppressing auditory cortex activity (Allen et al., 2008).

For the disorganised symptom cluster, past studies had also found associations with gCC and CG (Arnedo et al., 2015; Assaf et al., 2006; Liddle et al., 1992). The combination of poor inhibition of information in the gCC (Schulte and Müller-Oehring, 2010), and difficulties initiating and suppressing semantic responses in the CG (Assaf et al., 2006) in influencing under- and over-production of speech and behaviours might provide an explanation of possible mechanisms of disorganised symptoms.

Regarding the negative symptom cluster, associations with reduced FA in gCC and bilateral CG are in agreement with prior studies (Nakamura et al., 2012; Paillère-Martinot et al., 2001). Both the gCC and CG have been linked to reward networks (anhedonia and amotivation), and impaired processing of diminished emotional expression (DEE) that may underlie negative symptoms (Millan et al., 2014). Specifically, we found right SS and right SLF were also uniquely

associated with negative symptoms. The SS includes the ILF and IFOF (Mori et al., 2008). The ILF, which connects the temporal lobe to the occipital lobe, has been associated with higher-order visual abilities including object and face recognition, as well as emotional responses evoked by visual stimuli (Salvan et al., 2004). In contrast, the IFOF connects the frontal cortex to the posterior temporal-basal area and subsequently to the posterior portion of the occipital gyrus (Martino et al., 2010). The abnormalities in SS/IFOF might contribute to reduced semantic processing (Duffau, 2008) or reduced processing of visual information and emotions (ffytche and Catani, 2005; Xu et al., 2012). More studies are needed to further examine the links between negative symptoms, reduced emotional response to visual stimuli, reduced semantic processing and reduced processing of visual information.

Additionally, the SLF connects the frontal lobe to the three other lobes and include language-related areas including Broca's, Geschwind's and Wernicke's areas (Mori et al., 2008). The SLF is associated with the phonological processing of language (Duffau, 2008). While language areas are commonly associated with the left hemisphere, recent findings have found support against this in healthy controls (Duffau, 2008) and schizophrenia (Sommer et al., 2001). In particular, the lack of asymmetry in language lateralization in schizophrenia has been linked to poor inhibition of information from the right hemisphere (Sommer et al., 2001). Given that negative symptoms are prominent in the prodromal stage (Millan et al., 2014) and language lateralization develops from young (Selnes, 2000), the findings of reduced FA in the right SLF lend weight to the hypothesis that schizophrenia is a result of abnormal neurodevelopmental processes (Rapoport et al., 2012). Therefore, the results supported and expanded on the number of associated tracts in negative symptoms, demonstrating that negative symptoms may be associated with aberrancy of pathways from prefrontal cortex and CG to both dorsal and ventral routes (Millan et al., 2014).

4.3. Conclusion

The strengths of this study lie in the combinatorial use of clinical symptom ratings with neuroimaging measures to examine white matter microstructural findings underlying psychotic psychopathology. However, the study sample size was modest and given the cross-sectional nature of the study, longitudinal studies with larger sample sizes are needed to discern further how these WM tracts and clinical symptoms influence each other over time while considering other covariates such as smoking (Hudkins et al., 2012).

In conclusion, the study allowed for the better characterisation of the complex relationships between brain WM and clinical symptomatology through the identification of shared and unique patterns of associations between brain white matter FA changes and psychotic psychopathology. A deeper understanding of the WM anomalies associated with clinical psychopathology would facilitate delineation of subtypes of illness, and monitoring of these WM findings over treatment and illness course.

Conflict of interest

Nil.

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Contributors

K Sim designed the study and wrote the protocol. J Lim managed the literature searches, undertook statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ajp.2017.08.016.

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