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Microstructural white matter network-connectivity in individuals with psychotic disorder, unaffected siblings and controls

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ABSTRACT

Background: Altered structural network-connectivity has been reported in psychotic disorder but whether these alterations are associated with genetic vulnerability, and/or with phenotypic variation, has been less well examined. This study examined i) whether differences in network-connectivity exist between patients with psychotic disorder, siblings of patients with psychotic disorder and controls, and ii) whether network-connectivity alterations vary with (subclinical) symptomatology.

Methods: Network-connectivity measures (global efficiency (GE), density, local efficiency (LE), clustering coefficient (CC)) were derived from diffusion weighted imaging (DWI) and were compared between 85 patients with psychotic disorder, 93 siblings without psychotic disorder and 80 healthy comparison subjects using multilevel regression models. In patients, associations between Positive and Negative Syndrome Scale (PANSS) symptoms and topological measures were examined. In addition, interactions between subclinical psychopathology and sibling/healthy comparison subject status were examined in models of topological measures.

Results: While there was no main effect of group with respect to GE, density, LE and CC, siblings had a significantly higher CC compared to patients ($B = 0.0039$, $p = .002$). In patients, none of the PANSS symptom domains were significantly associated with any of the four network-connectivity measures. The two-way interaction between group and SIR-r positive score in the model of LE was significant ($\chi^2 = 6.24$, $p = .01$, $df = 1$). In the model of CC, the interactions between group and respectively SIS-r positive ($\chi^2 = 5.59$, $p = .02$, $df = 1$) and negative symptom scores ($\chi^2 = 4.71$, $p = .03$, $df = 1$) were significant. Stratified analysis showed that, in siblings, decreased LE and CC was significantly associated with increased SIS-r positive scores (LE: $B = -0.0049$, $p = .003$, CC: $B = -0.0066$, $p = .01$) and that decreased CC was significantly associated with increased SIS-r negative scores ($B = -0.012$, $p = .003$). There were no significant interactions between group and SIS-r scores in the models of GE and density.

Conclusion: The findings indicate absence of structural network-connectivity alterations in individuals with psychotic disorder and in individuals at higher than average genetic risk for psychotic disorder, in comparison with healthy subjects. The differential subclinical symptom-network connectivity associations in siblings with respect to controls may be a sign of psychosis vulnerability in the siblings.

1. Introduction

Structural white matter disconnectivity may contribute to the cerebral vulnerability for psychotic disorder (Friston, 1999). Diffusion Magnetic Resonance Imaging (dMRI) in combination with network analysis techniques, allows for the in-vivo study of white matter tracts

Abbreviations: GE, global efficiency; LE, local efficiency; CC, clustering coefficient; DWI, diffusion weighted imaging; PANSS, Positive and Negative Syndrome Scale; SIS-r, Structured Interview for Schizotypy –revised; AP, antipsychotic medication; CIDI, Composite International Diagnostic Interview; ROI, region of interest; AAL, anatomical atlas labeling.

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and testing the 'disconnectivity hypothesis'. The human brain can be considered a small-world network (Sporns et al., 2004) as there is a very short distance between neighboring brain areas and few direct connections to distant areas. This small-world network features a fast system response and enables the interaction between brain areas in an efficient matter (Lago-Fernandez et al., 2000). Wiring cost of the global small world network can be assessed with the density measure, i.e., the ratio of the existing connections to the possible connections. A high density indicates a highly connected network. Furthermore, an efficient structural brain connection requires preserved axonal wiring and an extensive total wiring volume of the network. High clustering and small path lengths reflect efficient information transfer over the network with a high capacity to integrate information across the network (Laughlin and Sejnowski, 2003).

Research on structural network-connectivity in psychotic disorder has provided evidence for alterations in network measures, such as increased characteristic path length (i.e., the average shortest path length between two regions) and a loss of frontal lobe hub regions (van den Heuvel et al., 2010; Zhou et al., 2015). Additionally, studies on the clustering coefficient (CC), a measure of local cohesiveness indicating a stronger local specialization, showed increased (Zhang et al., 2012), decreased (Li et al., 2018) and unchanged (Yeo et al., 2016) CC in patients compared to healthy subjects. Furthermore, decreased local efficiency (LE; i.e., how well information circulates over the network) has been found in the frontal, temporal, (para)-limbic regions and in the putamen in patients with psychotic disorder compared to healthy subjects (Wang et al., 2012; Yan et al., 2015). Previous research also showed reduced global efficiency (GE) in patients with psychotic disorder compared to healthy subjects (Wang et al., 2012; Zhang et al., 2015; van den Heuvel et al., 2013; Collin et al., 2014), indicating a less efficient information circulation over the network in general. Thus, network efficiency is able to provide evidence about information circulation over the structural network, while clustering informs about local specialization of a node. Lastly, with respect to network density, reductions in patients with psychotic disorder (van den Heuvel et al., 2013), as well as absence of differences between patients and controls (van Dellen et al., 2016) have been reported, although the latter study was based on a relatively small sample size (n = 35).

In order to understand how brain connectivity is related to the psychosis phenotype, prior studies have examined symptom-structural network-connectivity relationships. For example, a decrease in GE may result in disrupted integration of the brain networks (Deco et al., 2015), which may be, indirectly, related to impaired cognitive processing and general functioning in patients with psychotic disorder (Yeo et al., 2016). In addition, a negative correlation between structural network GE and LE properties and positive, negative, and total scores of the Positive and Negative Syndrome Scale (PANSS) has been reported (Wang et al., 2012). Notably, all associations between distinct symptom dimensions and network efficiency showed similar directions of effect. In another study, higher positive symptom severity in patients was associated with overall reduction of structural connectivity in the default mode network as measured by the number of tracts connecting the network (Skudlarski et al., 2010). Thus, both general and cognitive/symptomatic functioning have been associated with reduced network efficiency and alterations in CC. Furthermore, reduced asymmetric (specific for a hemisphere) LE has been reported in several frontal regions and the hippocampus in patients with psychotic disorder compared to healthy subjects in a cross-sectional study (Sun et al., 2017). A follow-up longitudinal dMRI study in a smaller sample within the same study, showed increased small-worldness (which may indicate higher local clustering and shorter path lengths between regions) in patients over time (Sun et al., 2016). Additionally, this study indicated that with reduced positive symptoms over time in patients, small-worldness increased, suggesting restoration of global structural integration of the brain network (Sun et al., 2016). There were no studies that reported on the association between density and PANSS symptom scales.

If structural network-connectivity were influenced by genetic vulnerability, first-degree relatives would be expected to have increased levels of altered network-connectivity compared to healthy subjects. Indeed, a previous study reported decreased LE in unaffected parents (first-degree relatives) compared to healthy subjects in the right temporal cortices, left supplementary motor area, left superior temporal pole and left thalamus (Yan et al., 2015). While research in first-degree relatives on LE is limited to this one study (and reports on CC are missing), research on rich club (a tightly interconnected core of regions) organization of structural networks suggests impaired connectivity in siblings (Collin et al., 2014; Schmidt et al., 2016) and parents (Zhao et al., 2017) of patients with psychotic disorder. Studies on help-seeking individuals with an at-risk mental state for psychotic disorder (help-seeking individuals with affective or substance use disorder and a degree of psychosis admixture, some of whom will have a poor prognosis) showed preserved (Schmidt et al., 2016) as well as reduced GE (Choi et al., 2017; Drakesmith et al., 2015). To date, there are no studies examining density in siblings. In addition, while there is little known about associations between symptomatology and brain network topology in patients, there is very little work on associations between subclinical symptomatology and DWI based network-connectivity in siblings.

Therefore, the current study examined structural brain network alterations in individuals with psychotic disorder, siblings without disorder and healthy comparison subjects. It is hypothesized that patients and siblings will show reduced GE, density and LE compared to healthy comparison subjects, in addition to alterations in CC. We also examined whether (subclinical) symptoms in patients and siblings would be associated with decreased network efficiency, density and CC.

2. Methods and materials

2.1. Participants

Data was collected in the context of a multicenter longitudinal study (Genetic Risk and Outcome of Psychosis, G.R.O.U.P.) in the Netherlands. In selected representative geographical areas in the Netherlands and neighboring Belgium, patients were identified through clinicians providing health care for those with psychotic disorder. Siblings were contacted through participating patients. Mailings and advertisements in local newspapers of the same geographical areas were used in order to recruit healthy comparison subjects. All patients had a diagnosis of psychotic disorder, based on DSM-IV (American Psychiatric Association, 2000); schizophrenia (n = 59), schizoaffective disorder (n = 9), schizophreniform disorder (n = 4), brief psychotic disorder (n = 2), and psychotic disorder not other-wise specified (n = 11). Siblings and healthy comparison subjects had no lifetime diagnosis of any non-affective psychotic disorder, based on the CASH. The total sample consisted of 258 participants: 85 patients with a psychotic disorder, 93 siblings without a psychotic disorder, and 80 healthy comparison subjects. Familial relatedness can be found elsewhere (Michielse et al., 2017) and in the supplementary information.

All participants were screened before MRI scanning using the following exclusion criteria: brain injury with unconsciousness > than 1 h, meningitis or other neurological diseases with possible impact on brain structure or function, cardiac arrhythmia requiring medical treatment, and severe claustrophobia. In addition, participants with metal corpora aliena were excluded from the study, as were women with intrauterine device status and suspected pregnancy or pregnancy.

The standing ethics committee approved the study protocol, and all the participants gave written informed consent in accordance with the committee's guidelines.

2.2. Clinical measures

The PANSS (Kay et al., 1987) was used to measure psychotic

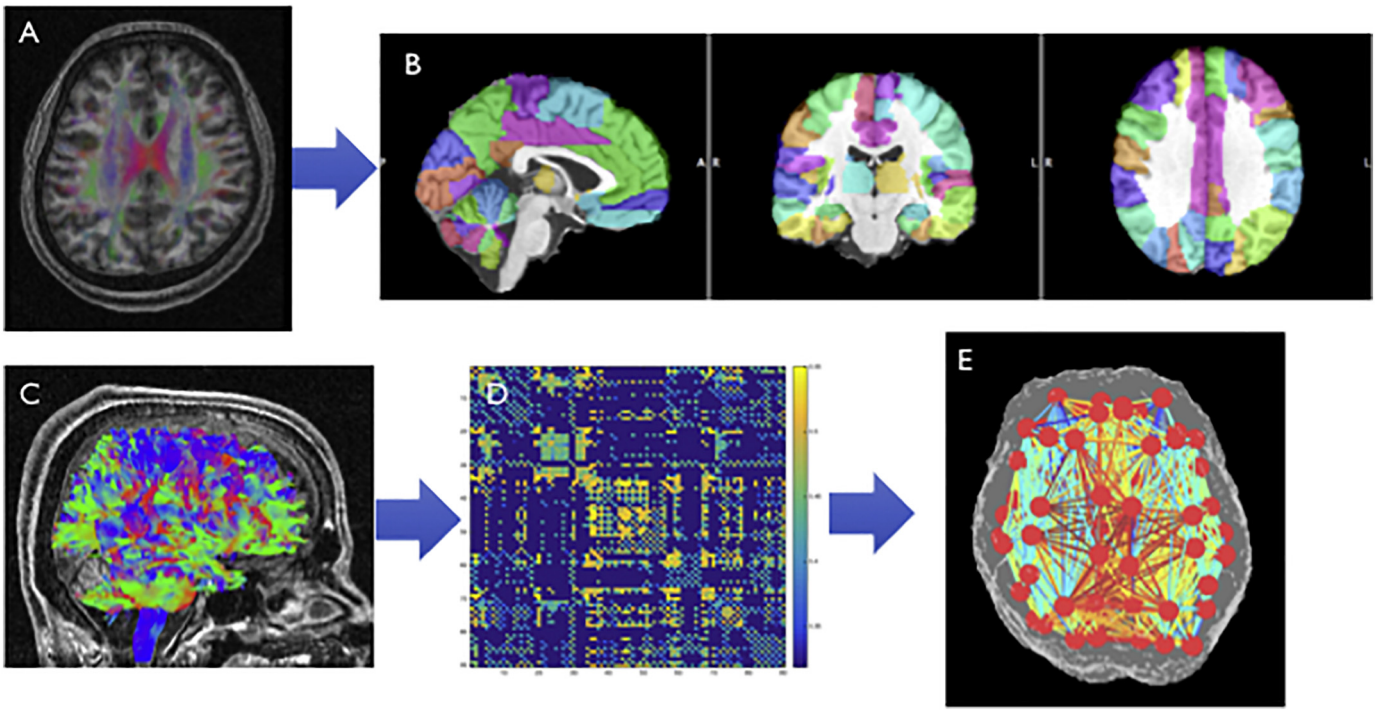

Fig. 1. For each DWI dataset (A) whole-brain deterministic tractography was performed. The automated anatomical labeling atlas (AAL) template with a total of 90 cortical and subcortical brain regions, without cerebellum (B), was co-registered to the DWI tractography image (C). The number of connections between any 2 regions of the AAL template was calculated resulting in a symmetric 90 × 90 weighted connectivity matrix (D). The connectivity matrix can be visualized as a graph, composed of nodes (brain areas) and edges (white matter tracts) (E).

symptoms in patients over the two weeks prior to inclusion. A five-factor model (van der Gaag et al., 2006) for the PANSS yielded positive symptoms, negative symptoms, disorganization symptoms, excitement and emotional distress. The scores of the individual items of the five symptom dimensions were summed. In healthy comparison subjects and siblings, the Structured Interview for Schizotypy –revised (SIS-r) was used for assessing subclinical psychotic symptoms (Vollema and Ormel, 2000). Subclinical positive symptoms were measured by the items referential thinking, psychotic phenomena, derealisation, magical ideation, illusions, and suspiciousness. Negative-disorganized symptoms were covering the items social isolation, sensitivity, introversion, restricted affect, disturbances in associative and goal-directed thinking, poverty of speech, and eccentric behavior. The mean of the positive SIS-r and negative SIS-r items was calculated per participant.

Educational level was defined as the highest accomplished level of education. Handedness was assessed using the Annett Handedness Scale (Annett, 1970). In the patient group, antipsychotic medication use (AP use) was evaluated by patient report and verified with the treating consultant psychiatrist. Best estimate lifetime (cumulative) AP use was determined by multiplying the number of days of AP use with the corresponding haloperidol equivalents and summing these scores for all periods of AP use (including the exposure period between baseline assessment for the G.R.O.U.P study and the moment of baseline MRI scanning), using previously described AP dose equivalents calculations (Andreasen et al., 2010). Substance use was measured with the Composite International Diagnostic Interview (CIDI) sections B-J-L (Robins et al., 1988). Cannabis and other drug use were reported as frequency during the last 12 months as well as lifetime use. Data on lifetime cannabis and other drug use was missing for respectively eight (3% missing) and two participants (1% missing). Information on alcohol use was reported as weekly consumption over the last year and was missing for 33 participants (13%). Additional information on this sample can be found elsewhere (Michielse et al., 2017). CIDI frequency data on lifetime cannabis and other drug use was available for respectively 250 participants (3% missing data) and 256 participants (1% missing data). In the statistical analyses, missing data were omitted from the analyses.

2.3. MRI data acquisition

Methods for data acquisition were identical to those in previously described protocol (Michielse et al., 2017). In short, magnetic resonance imaging scans were obtained using an 3 T Allegra syngo MR A30 (Siemens, Erlangen, Germany). An 1 mm × 1 mm × 1 mm Modified Driven Equilibrium Fourier Transform (MDEFT) sequence and Magnetization Prepared Rapid Acquisition Gradient-Echo (MPRAGE; Alzheimer's Disease Neuroimaging Initiative) anatomical scan was used as reference. A DTI scan at 2 mm × 2 mm × 2 mm resolution with 76 directions and one with 81 directions was used. As a result of a scanner update, two slightly different protocols were used. See supplementary materials for more details.

2.4. DWI processing

Details on processing of the DWI data can be found elsewhere (Michielse et al., 2017) and in the supplementary materials. Processing was conducted in ExploreDTI (Leemans et al., 2009) and after tensor estimation, white matter tracts were reconstructed for each individual dataset, using deterministic fiber tractography (Basser et al., 2000). The tractography in ExploreDTI was done based on an FA threshold of 0.2 and an FA range between 0.2 and 1, a fiber length threshold between 50 and 500 voxels and an angle threshold of 30 degrees.

Parcellation of the whole brain fiber tracts was done using the generally accepted standard automated anatomical atlas labeling (AAL, (Tzourio-Mazoyer et al., 2002)). This procedure provides 90 both cortical and subcortical brain regions of interest (ROI), each representing a node in the network. The reconstructed white matter tracts were represented as unweighted edges between each pair of nodes. The AAL atlas provides adequate cortical coverage and is widely used in both structural and functional connectivity analysis, as shown in Fig. 1.

2.5. Network construction

With the use of the individual brain networks, connectivity measures were computed in order to quantify the network architecture using the Brain Connectivity Toolbox. Connectivity was described in terms of network density, GE, LE, and CC (Rubinov and Sporns, 2010) based on the pass criteria (the direction is unknown, because tractography is bidirectional) per ROI. The pass criteria allowed to include all fibers that pass through or end/start in the ROI. Network density is the fraction of the existing connections to possible connections and is also known as the wiring cost. All connectivity network measures were calculated per individual and statistically analyzed using R version 3.2.3 (Team RC, 2015). GE and density were analyzed at whole brain level, while LE and CC were analyzed as node specific.

2.6. Statistical analysis

2.6.1. Group comparisons of GE and network density

Group comparisons (patients, siblings, healthy comparison subjects) for GE were carried out using a multilevel linear regression model with one GE measure per individual, who belong to a family (level 1). The "lme" (linear mixed effect) command in R was used to fit a mixed-effects models with random intercepts at the family level (Team RC, 2015; Laird and Ware, 1982). Group was treated as a three-level factor. The model included age, sex, handedness, level of education, and cannabis use as a priori hypothesized confounders (in line with previous research (Michielse et al., 2017)). The same was done for network density.

2.6.2. Group comparisons for LE and CC

All analyses were conducted using 90 brain nodes, regions. Group comparisons for LE and CC were done based on 90 regions clustered within individuals (level 1), and individuals clustered within families (level 2). Hence, random intercepts were added to the model for families and individuals within families. Group × ROI interactions in models of LE and CC were examined using Wald-type chi-square tests. The number of voxels was used in the model as an analytic weight to control for the ROI extent (i.e., the error variance for a particular observation was inversely weighted by the number of voxels within the corresponding region). Post-estimation linear hypothesis testing was performed in case of significant group × ROI interactions, to test for differences in slopes between i) patients and healthy comparison subjects, ii) siblings and healthy comparison subjects and iii) patient and siblings. Because we consider the analysis approach exploratory and hence hypotheses-generating, the analysis was conducted for all 90 ROIs and a Bonferroni correction was applied. If the group × ROI interaction were not significant, the main effect of group was investigated in a model without ROI. The analyses were corrected for the previously mentioned confounders.

2.7. Associations with (subclinical) symptoms

2.7.1. Patients with psychotic disorder

In the multiple regression model of GE (dependent variable), the association with the PANSS positive, negative, disorganized, excitement, and emotional distress symptoms (independent variables in separate models) was examined in patients. Bonferroni correction (equal to $p < .01$) was applied to correct for testing the five symptom models.

In the models of LE and CC, the interactions between PANSS symptoms and ROI were tested. In case of significant interactions in any of the five PANSS dimensions, post-hoc estimation was applied for all 90 regions. Analyses were corrected for multiple comparisons, at the level of the five (symptom) interaction tests, using a conservative p-level of $p < .01$, and at the level of 90 regions, with Bonferroni. The multilevel analyses were corrected for age, sex, level of education, illness duration, cannabis use and lifetime AP exposure. If the PANSS symptom × ROI interaction was not significant ($p \geq .01$), main effects of PANSS symptoms on overall LE and CC were investigated in a model without ROI. Bonferroni correction (equal to $p < .01$) was applied to correct for testing the five symptom models.

2.7.2. Siblings and healthy comparison subjects

The associations between SIS-r positive/negative score and GE, LE and CC were separately examined in the total group (combined sibling and healthy comparison group).

In the model of GE, the interactions between group and SIS-r positive and negative symptoms were examined separately. In case of a significant interaction ($p < .05$), stratification was applied per group to investigate association between GE and symptoms.

In the multilevel models of LE and CC, the two group × ROI × SIS-r symptom interactions were tested (for positive and negative symptoms). In case of significant group × ROI × SIS-r interactions ($p < .01$), post-estimation linear hypothesis testing was performed for all 90 regions to test for differences in slopes between siblings and healthy comparison subjects. This analysis was corrected for multiple comparisons with Bonferroni. Confounding factors in the model were age, sex and level of education. If the group x ROI × SIS-r interaction was not significant ($p \geq .01$), the interaction between group and SIS-r symptom was investigated in a model without ROI.

3. Results

3.1. Demographics

There were more men in the patient and sibling group compared to the healthy comparison group. The healthy comparison group had a higher educational level than the patients and siblings. Most patients were not in acute illness phases as evidenced by low PANSS score (Table 1) and by the fact that 58% of the patients were in remission according to the remission criteria of Andreasen (2006).

Table 1
Demographic characteristics.

	Healthy comparison subjects (n = 80)	Siblings (n = 93)	Patients (n = 85)
Age at scan (years)	30.8 (10.8)	29.4 (8.8)	28.3 (7.0)
Sex (% male)	29 (36%)	49 (52%)	58 (68%)
Handedness	76.3 (58.2)	75.1 (58.6)	71.1 (63.9)
Level of education	5.4 (1.8)	5.1 (2.1)	4.1 (2.0)
No. of times cannabis use last year	5.4 (41.5)	7.3 (40.2)	37.0 (97.8)
No. of times non-cannabis drug use last year	4.7 (41.2)	0.4 (4.1)	22.5 (71.0)
PANSS positive	7.3 (1.1)	7.2 (0.9)	10.3 (4.9)
PANSS negative	8.1 (0.9)	8.4 (1.9)	12.0 (5.8)
PANSS disorganization	10.1 (1.1)	10.3 (0.7)	12.5 (4.1)
PANSS excitement	8.3 (1.1)	8.5 (1.3)	9.7 (2.7)
PANSS emotional distress	9.2 (2.0)	9.8 (2.5)	13.1 (5.2)
SIS-r positive	0.46 (0.44)	0.56 (0.40)	–
SIS-r negative	0.25 (0.23)	0.33 (0.24)	–
In remission	–	–	49/84 (58%)
Age of onset (years)	–	–	21.9 (7.1)
Duration of illness (years)	–	–	6.4 (4.0)
Cumulative lifetime AP exposure in mean haloperidol equivalents	–	–	6692.7 (6254.2)
Alcohol use per week frequency	5.0 (7.0)	9.8 (17.3)	5.0 (9.1)

Means (SDs) are reported. Abbreviations: SD = Standard Deviation; PANSS = Positive and Negative Syndrome Scale; SIS-r = Structured Interview for Schizotypy-revised; AP = Antipsychotic. Cumulative lifetime AP exposure is expressed as haloperidol equivalents.
Some data were missing as described in the supplementary materials.

Table 2
Means and group comparison of topological outcome measures.

	Mean (SD)			Group comparison	
	Patients	Siblings	Healthy comparison subjects	χ^2	p-value
Global efficiency	0.68 (0.018)	0.69 (0.020)	0.69 (0.021)	3.50	0.17
Density	0.39 (0.033)	0.40 (0.032)	0.39 (0.034)	4.68	0.10
Local efficiency	0.82 (0.067)	0.82 (0.064)	0.82 (0.065)	198.29	0.14
Clustering coefficient	0.32 (0.065)	0.33 (0.063)	0.33 (0.065)	204.99	0.08

Reported are the mean values and SD (standard deviation) over all regions for local efficiency and clustering coefficient and the χ^2 and *p*-values of the multilevel regression analyses.

The patients were more frequent cannabis and non-cannabis drug users than the siblings and healthy comparison subjects (Table 1). At the time of scanning, seventy patients were receiving AP medication (second generation: $n = 67$; first generation; $n = 3$). The mean current dosage of AP medication in terms of standard haloperidol equivalents was 4.6 mg (SD = 5.0).

3.2. Group comparison of global efficiency (GE) and network density

The GE was not significantly different between the three groups *($\chi^2 = 3.50$, $p = .17$, $df = 2$)*, nor was network density *($\chi^2 = 4.68$, $p = .10$, $df = 2$)* (Table 2).

3.3. Group comparison of local efficiency (LE) and clustering coefficient (CC)

In the model of LE, there was no significant interaction between group and ROI (*$\chi^2 = 198.29$, $p = .14$, $df = 178$*) and neither in the model of CC (*$\chi^2 = 204.99$, $p = .08$, $df = 178$*) (Table 2). There was a significant main effect of group in the model of CC (*$\chi^2 = 9.77$, $p = .008$, $df = 2$*), but not in the model of LE (*$\chi^2 = 1.68$, $p = .43$, $df = 2$*). The CC was equal between healthy comparison subjects and respectively patients (*$B = -0.0032$, $p = .07$*) and siblings (*$B = 0.00069$, $p = .68$*), but significantly different between siblings and patients (*$B = 0.0039$, $p = .002$*). Since there were no significant interactions, no region-specific results were reported.

3.4. Association between topological measures and PANSS scores in patients with psychotic disorder

No significant associations were found between any of the PANSS symptom scores and GE or density measures in patients with psychotic disorder (Table 3). Similarly, the interactions between any of the PANSS symptom scores and ROI in the models of LE and CC were not significant (Table 3). In the main effect analyses, none of the associations between PANSS symptom scores and overall LE and CC were significant at a conservative p-level of $p < .01$ (*LE;* PANSS positive: *$B = 0.00014$, $p = .45$*, PANSS negative: *$B = -0.00023$, $p = .14$*, PANSS disorganization: *$B = 0.000028$, $p = .92$*, PANSS excitement: *$B = 0.000030$, $p = .75$*, PANSS emotional distress: *$B = 0.00018$, $p = .25$*; *CC;* PANSS positive: *$B = -0.000012$, $p = .95$*, PANSS negative: *$B = -0.00020$, $p = .19$*, PANSS disorganization: *$B = -0.00021$, $p = .36$*, PANSS excitement: *$B = -0.00044$, $p = .16$*, PANSS emotional distress: *$B = -0.0000873$, $p = .57$*).

3.5. Association between topological measures and SIS-r scores in siblings and healthy comparison subjects

3.5.1. Global efficiency and density

There was no significant interactions between group and SIS-r positive symptoms and between group and SIS-r negative symptoms in the models of GE and density (Table 4). Main effect analyses of the total group of siblings and healthy comparison subjects showed no significant associations between SIS-r positive (B = 0.0042, p = .45) or negative symptom score (B = 0.0054, $p = .39$) and GE. Similarly, there were no significant associations between SIS-r positive (B = 0.0013, $p = .83$) or negative symptom score (B = −0.0025, $p = .82$) and density in the total group of siblings and healthy comparison subjects.

3.5.2. Local efficiency and clustering coefficient

No significant three-way interactions were found between group, ROI and SIS-r positive symptoms in the models of LE and CC, and neither so with respect to SIS-r negative symptoms. The two-way interaction between group and SIR-r score in the LE model was significant for SIS-r positive symptoms (*$\chi^2 = 6.24$, $p = .01$, $df = 1$*), but not for SIS-negative symptoms (*$\chi^2 = 1.35$, $p = .24$, $df = 1$*). Stratified analyses showed a significant decrease in overall LE with increasing SIS-r positive symptom scores in siblings (*$B = -0.0049$, $p = .003$*), while this association was absent in controls (*$B = 0.00091$, $p = .58$*).

In the model of CC, the interactions between group and respectively SIS-r positive (*$\chi^2 = 5.59$, $p = .02$, $df = 1$*) and negative (*$\chi^2 = 4.71$, $p = .03$, $df = 1$*) symptom scores were significant. Stratified analyses for SIS-r positive symptoms showed a significant decrease in overall CC with increasing SIS-r positive symptoms in the sibling group (*$B = -0.0066$, $p = .01$*), but not in the control group (*$B = 0.0021$, $p = .43$*). Stratified analyses for the SIS-r negative score showed a significant decrease in overall CC with increasing SIS-r negative symptoms in the sibling group (*$B = -0.012$, $p = .003$*), which was not the case for the control group (*$B = 0.0022$, $p = .673$*). There was no significant association between SIS-r positive or negative score and LE and CC in

Table 3
Associations between PANNS symptoms network connectivity measures in patients with psychotic disorder.

	PANSS positive		PANSS negative		PANSS disorganization		PANSS excitement		PANSS emotional distress	
	χ^2*	p-value	χ^2*	p-value	χ^2*	p-value	χ^2*	p-value	χ^2*	p-value
Global efficiency	−0.00080	0.12	−0.00041	0.34	−0.00094	0.14	−0.00096	0.27	−0.00043	0.32
Density	−0.00068	0.99	−0.00075	0.99	−0.00062	0.59	−0.0018	0.25	−0.00015	0.85
Local efficiency x ROI	87.57	0.52	83.32	0.65	68.86	0.94	55.49	0.99	93.41	0.38
Clustering coefficient x ROI	91.00	0.45	83.05	0.66	63.65	0.98	55.63	0.99	87.49	0.53

χ^2 values for local efficiency and clustering coefficient and the *p*-values are derived from multilevel regression analyses.
* For global efficiency and density the B values and *p*-values are provided.

Table 4
Associations between subclinical psychotic symptoms and network connectivity measures in siblings and healthy comparison subjects.

	SIS-r positive		SIS-r negative	
	χ^2*	p-value	χ^2*	p-value
Group x ROI x SIS-r				
Local efficiency	77.85	0.79	64.17	0.98
Clustering coefficient	80.71	0.72	68.57	0.95
Group x SIS-r				
Global efficiency	0.0057	0.14	0.0054	0.39
Density	−0.0080	0.53	−0.021	0.35
Local efficiency	6.24	**0.01**	1.35	0.24
Clustering coefficient	5.59	**0.02**	4.71	**0.03**
Main effect in total group				
Local efficiency	100.90	0.18	103.03	0.15
Clustering coefficient	99.44	0.21	103.05	0.15

χ^2 and p-values of multilevel regression analyses are provided for local efficiency and clustering coefficient. Significant p-values are noted in bold.

* For global efficiency and density the B values and *p*-values are provided.

the total group (siblings and controls) (Table 4).

4. Discussion

In this cross-sectional study, microstructural white matter inter-regional network-connectivity was examined in patients with psychotic disorder, non-psychotic siblings and healthy comparison subjects. Not in line with the hypotheses, the results showed absence of differences in structural network-connectivity properties between patients or siblings with respect to controls. There was, however, a significant difference in CC between siblings and patients, in that siblings had a slightly higher CC. In the symptom-network connectivity analyses, none of the PANSS scores symptoms in patients were associated with the structural network-connectivity measures. Moreover, SIS-r subclinical symptom scores were not associated with regional structural network-connectivity in siblings and healthy comparison subjects. With respect to overall LE and CC, it was shown that in the sibling group higher SIS-r positive symptom scores were associated with lower overall LE and that higher SIS-r positive and negative symptom scores were associated with lower overall CC.

4.1. Group comparison of topological measures

Contrary to the hypothesis and the literature, the current study findings did not show lower GE and LE in patients and siblings compared to healthy subjects. The majority of prior work suggests alterations in structural white matter connectivity (Friston, 1999; Wang et al., 2012; Rubinov and Bullmore, 2013; Wheeler and Voineskos, 2014), with generally lower GE as previously reported in patients with respect to healthy comparison subjects (Wang et al., 2012; Zhang et al., 2015; Collin et al., 2014), while the evidence for alterations in these DWI based network-connectivity measures in siblings is scarce (Collin et al., 2014). The studies on patients included medication naïve first episode patients (Zhang et al., 2015), while the current population had an average illness duration of 6.4 years and almost all patients were medicated. Our study population had a little longer illness duration. Possibly, environmental or illness-related factors may have contributed to the differential findings. The majority of the patients of the current study used cannabis (37 times in total over the last year), while the frequency of cannabis use was much lower in one study (Collin et al., 2014), and another study did not report about cannabis use (Wang et al., 2012). As cannabis use decreases the network efficiency while increasing the CC (Kim et al., 2011), this could potentially have diminished effects on the group level in our study although we corrected for this factor in the analyses. Interestingly, previous analyses on this sample showed alterations in DWI parameters, i.e., decreased fiber orientation and increased free water movement (Michielse et al., 2017) and also lower CC based on fMRI activation (Peeters et al., 2016). These DWI parameter and functional connectivity analyses are different from the current network-based connectivity analyses and show different aspects of brain alterations. In line with the findings in GE, there were no significant differences in network density between groups. While this is not in line with previous research on a selected rich club network showing decreased network density (van den Heuvel et al., 2013), one other small study also reported absence of findings (van Dellen et al., 2016). This suggests that, in terms of the wiring cost of the network, individuals with psychosis (vulnerability) may not differ from healthy comparisons, implying equally energy consuming networks.

In conclusion, whether the absence of GE, density and LE alterations in individuals with (vulnerability for) psychotic disorder is related to technical procedures specific to these DWI based network-connectivity measures, or reflects a true finding has to be investigated further in future studies.

The finding of a non-deviated CC in patients and siblings compared to healthy comparison subjects falls into the mixed findings of previous research, showing increased (Zhang et al., 2012), decreased (Li et al., 2018), and unchanged (Yeo et al., 2016) CC in patients with psychotic disorder compared to healthy comparison subjects. Besides, to our knowledge, there are no reports on CC in siblings of patients with psychotic disorder. While the interaction between group and ROI in the model of CC was not significant, the group by group comparison showed that siblings had a higher CC compared to patients. The inconsistent findings on CC alterations in psychotic disorder may be related to differences in patient characteristics, illness-related factors or other methodological issues. One study investigated medication naïve first-episode patients (Li et al., 2018), while another study did not report on medication use (Yeo et al., 2016). In the current study, most patients were treated with medication, while the group with higher than average psychosis vulnerability (siblings) was not subjected to illness-related factors such as medication use. This makes comparison of the studies difficult as medication and other drug use could heavily influence the structural brain network. Another study applied a structural network approach on anatomical data instead of white matter tracts (Zhang et al., 2012), a different technique that is hard to compare with DWI based network-connectivity.

While several studies have described that disconnectivity may be an important contribution to pathophysiologic alterations in psychotic disorder, reflected by alterations in efficiency and clustering, recent studies have also shown alterations in psychotic disorder at the level of abnormal hub organization (Rubinov and Bullmore, 2013; Wheeler and Voineskos, 2014; Ellison-Wright and Bullmore, 2009). A hub-based (rich-club) approach, using a specific selection of hubs within the brain network, may be considered in future research. However, research into the structural hub organization of brain networks has the limitation of how to define and select the hub regions (van den Heuvel and Sporns, 2011). The whole brain network-based connectivity approach does not use a selection of hub regions. As described earlier, functional connectivity analyses in the current study sample showed lower CC in patients compared to healthy comparison subjects (Peeters et al., 2016), while structural DWI white matter parameters indicated decreased fiber orientation and increased free water movement (Michielse et al., 2017). Combining both functional and structural MRI analyses, via a fusion MRI approach, can be very informative and would be a future step (Zhu et al., 2014). Structural DWI white matter analyses are not based on tractography and are based on parameters derived from the tensor model. Thus, network-based analyses allow for a more detailed investigation of the tracts, but more processing is required. For example, selection of fibers that pass through the region (instead of end) could have resulted in minimizing the effect size of the network-based parameters.

4.2. Association between topological measures and clinical psychotic symptoms

Against a-priori expectations, no significant associations were found between PANSS symptom domains and the network-connectivity properties GE, density, LE or CC in patients with psychotic disorder. This is in line with prior work by Zhang and van den Heuvel, who did not find significant associations between several network properties (strength, CC, characteristic path length, betweenness centrality, GE, shortest path length, and degree) and clinical psychotic symptoms (Zhang et al., 2015; van den Heuvel et al., 2010) in patients. In that study, patients with a first episode of psychosis were included and were medication-naïve, so that potential confounders such as duration of illness, drug use and anti-psychotic medication were minimized (Zhang et al., 2015). A study by Wang and colleagues (Wang et al., 2012) found a negative correlation between the PANSS and GE and LE, but used a general linear model that did not include covariates such as handedness and level of education. Most patients in the current study were in a remitted phase as reflected by the relatively low PANSS scores with little variance and had shorter illness duration than the patients in the study of Wang and colleagues (Wang et al., 2012). Based on the previous literature on patients with psychotic disorder, it could be speculated that alterations in white matter network-connectivity and phenotypic correlates are more likely to be detected at the more severe side of the psychosis spectrum. However, this does not hold when examining individuals at the lower end of the spectrum (see below). It can be questioned if the network-based structural connectivity method was sensitive enough to detect small topological measure variation in relation to symptom variation in this cross-sectional sample of patients with psychotic disorder.

4.3. Association between topological measures and subclinical psychotic symptoms

The current study showed that the interactions between SIS-r positive or negative symptom domains and region in the models of network-connectivity properties GE, density, LE or CC were not conditional on group (siblings, controls). While these region-symptom-group interactions were not significant, the overall network-measure approach combining all regions did show some significant symptom-group interactions. In siblings, significant negative associations between SIS-r positive symptoms and respectively overall LE and CC were found, which was not the case for the healthy comparison subjects. In addition, there was a significant negative association between SIS-r negative symptoms and CC in siblings, but not in controls. This indicates that differential subclinical symptom-global white matter network-connectivity associations may exist, depending on the genetic risk for psychotic disorder. A limited number of studies have examined the association between subclinical symptoms and topological measures in the general population or in siblings of patients with psychotic disorder. One study in help-seeking individuals with an at-risk-mental state in a population-based cohort showed that reduced rich-club organization was associated with an increased severity of negative symptoms as measured by the Scale for the Assessment of Negative Symptoms (Schmidt et al., 2016). In another study, no significant correlation was found between rich club connectivity (integration between hubs) and total subclinical psychotic symptoms measured by the CAPE in siblings (Collin et al., 2014). The CAPE, in contrast to the SIS-r, allows for measurement of separate frequency and distress scales over the past 12 months (Yung et al., 2009), allowing for a broader assessment of subclinical psychotic symptoms since distress from the symptoms can be more informative compared to the frequency. While rich club connectivity does measure a different feature of the structural network architecture, as stated in the previous paragraph, the current findings on subclinical symptoms in individual at higher than average genetic risk (siblings) not being associated with regional efficiency and clustering, may agree with other research findings in individuals at the highest genetic risk level (patients). The finding in siblings that lower overall LE and CC is associated with higher SIS-r positive scores, and that lower CC is associated with higher SIS-r negative symptoms scores, shows that, at the subclinical level, symptom-network connectivity association patterns can be detected and that differential patterns may exist dependent on the background genetic risk level, a finding that warrants replication.

4.4. Methodological considerations

Particular strengths of this study are the relatively large sample size, including a sample of siblings (higher than average genetic risk), which allowed for examination of topological measures in a genetically sensitive design in which illness-related confounding factors were not present.

There were large differences in other (non-cannabis) drug use between the groups. As described in Table 1, the average non-cannabis drug use over the last year was higher in patients (22.5 times) compared to controls (4.7 times) and siblings (0.4 times). While the statistical models included cannabis use as a confounder, non-cannabis drug use may have influenced the results. Of note, there was substantial variation in the amount of non-cannabis use over the last year in patients. In order to not overcorrect on patient status and because of the low variance of non-cannabis use in siblings and of medication use in siblings and controls, the models did not include non-cannabis drug use and medication as confouders.

A problem in region-based analyses of topological measures is the necessity to correct for multiple comparisons, while maintaining sufficient statistical power. As there is no consensus on how to control for these multiple tests, we chose to be conservative. Currently there is no standard methodological approach for structural network analyses.

Topological measures of the structural brain networks are highly dependent on the network density or wiring cost of the network, which is defined as the number of connections divided by the number of possible connections (Griffa et al., 2013). Due to alternatives for setting a threshold of the wiring cost of the network, studies could show different results and make them less generalizable. Moreover, the applied deterministic tractography algorithm could have influenced the results of the network-based connectivity analyses. While this approach was carefully chosen, studies have shown that other algorithms may provide different network-based outcomes (Basser et al., 2000; Zalesky et al., 2011).

5. Conclusions

This cross-sectional study analyzed structural white matter network-connectivity in individuals at different levels of genetic risk for psychotic disorder. The results showed absence of differences in four network-connectivity properties between patients with psychotic disorder, siblings, and healthy comparison subjects, except for an increased CC in the sibling compared against patients. Symptom measurements were not associated with the regional network-properties in patients, while in siblings a higher SIS-r positive symptom score was associated with lower overall LE/CC and a higher SIS-r negative symptom score was associated with lower overall CC. Although the findings were not in line with the a priori stated hypotheses, the current study adds to the literature by providing evidence for absence of network-based connectivity in individuals with (vulnerability for) psychotic disorder. With respect to global network-connectivity parameters, differential patterns of association with subclinical symptoms may exist between siblings and controls.

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Appendix A. Supplementary data

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