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Altered topological characteristics of morphological brain network relate to language impairment in high genetic risk subjects and schizophrenia patients

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ABSTRACT

Objective: Evidence suggests relationships between abnormalities in various cortical and subcortical brain structures and language dysfunction in individuals with schizophrenia, and to some extent in those with increased genetic risk for this diagnosis. The topological features of the structural brain network at the systems-level and their impact on language function in schizophrenia and in those at high genetic risk has been less well studied.
Method: Single-subject morphological brain network was constructed in a total of 71 subjects (20 patients with schizophrenia, 19 individuals at high genetic risk for schizophrenia, and 32 controls). Among these 71 subjects, 56 were involved in our previous neuroimaging studies. Graphic Theoretical Techniques was applied to calculate the global and nodal topological characteristics of the morphological brain network of each participant. Index scores for five language-related cognitive tests were also attained from each participant.
Results: Significantly smaller nodal degree in bilateral superior occipital gyri (SOG) were observed in individuals with schizophrenia, as compared to the controls and those at high risk; while significantly reduced nodal betweenness centrality (quantifying the level of a node in connecting other nodes in the network) in right middle frontal gyrus (MFG) was found in the high-risk group, relative to controls. The right MFG nodal efficiency and hub capacity (represented by both nodal degree and betweenness centrality) of the morphological brain network were negatively associated with the wide range achievement test (WRAT) standard performance score; while the right SOG nodal degree was positively associated with the WRAT standard performance score, in the entire study sample.
Conclusions: These findings enhance the understanding of structural brain abnormalities at the systems-level in individuals with schizophrenia and those at high genetic risk, which may serve as critical neural substrates for the origin of the language-related impairments and symptom manifestations of schizophrenia.

1. Introduction

Schizophrenia is a complex and severe brain disorder with the peak age of symptom manifestation in early adulthood (Delisi, 1992). Impaired communication through language is a core component that characterize all its symptoms, including problems in distinguishing between verbalized thought and external speech (verbal auditory hallucinations), in perceiving and interpreting the world around us (delusions), in social interactions and motivation (negative symptoms), and in expressing thought through language (thought disorder) (Kuperberg, 2010).

Schizophrenia is highly heritable, with an estimated risk rate of 79% likely explained by genetic factors (Hilker et al., 2018). A growing body of neuroimaging and clinical studies in patients with schizophrenia and those with heightened genetic risk (siblings/offsprings of patients with schizophrenia who are in the peak age range of symptom manifestation, defined in (Li et al., 2007b)) have consistently shown functional and structural brain abnormalities in regions of language processing pathways (Li et al., 2009). The functional neuroanatomy of the multilevel language processing pathwys in normal controls include the essential sensory input regions (such as superior occipital gyrus (SOG) for visual

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input, and superior temporal gyrus (STG) for auditory input), the conceptual interface center (also referred as the Wernick's area, involving left supratemporal plane and left angular gyrus (AG)), the motor-planning/articulation center (referred as the Broca's area in the left inferior frontal gyrus (IFG)), and other supportive brain regions (Li et al., 2009). Among the regions of the normal language processing pathways, the IFG and SOG are two of the most frequently reported ones for functional abnormalities in patients with schizophrenia and individuals at genetic high risk, during resting-state or language-related tasks (Lieburg et al., 2012; Rajarethinam et al., 2011; Whyte et al., 2006). One of our previous functional MRI studies demonstrated aberrant systems-level topology of the functional brain network for language processing in both patients with chronic schizophrenia and subjects at high genetic risk. These findings included dysfunctioning network hubs in the left IFG and right fusiform regions in the patients and high-risk subjects, as well as a unique pattern of hyperactive and interacting network hubs in the left fusiform and right inferior and middle frontal areas, which was associated with language dysfunction in patients with schizophrenia (Li et al., 2012b).

Structural brain imaging studies across the stages of schizophrenia have also revealed a progressively changing pattern of regional structural anomalies in the brain regions associated with language processing (Sumner et al., 2018). For example, longitudinal investigations in stages from clinical prodromal to conversion to a first episode of psychosis showed that individuals who later converted into psychosis had significantly smaller cortical gray matter (GM) volume in STG and IFG relative to those who did not transition to psychosis (Cannon et al., 2015; Fusar-Poli et al., 2011); the patients who converted showed progressive GM volume reduction in the superior and inferior frontal areas, and reduced corpus callosum WM integrity at the time of a first episode of psychosis (Gasparotti et al., 2009; Gong et al., 2016; Nesvag et al., 2012); whereas patients with chronic schizophrenia showed even greater GM volume decreases in frontal, temporal and cingulate cortices (Dietsche et al., 2017). These consistently identified brain regions, including frontal, temporal, and cingulate cortices, were associated with all stages of schizophrenia, and have critical functions in the normal brain pathways for language processing (Li et al., 2009). However, the voxel-based or region of interest (ROI)-based techniques implemented in these existing studies viewed the brain areas as isolated regions, without having the ability to clarify their intrinsic neural connections and intercommunications that act as an interactive structural brain network.

A recent structural MRI study reported decreased GM coupling between left frontal and bilateral subcortical structures and increased coupling between left temporal and bilateral subcortical regions in patients with schizophrenia relative to controls, by measuring Pearson's correlation of volumes of each pair of 82 cortical and subcortical GM regions (Collin et al., 2013). This study demonstrated altered morphological interconnections among the GM structures in patients with schizophrenia. A structural MRI-based approach has been recently developed to detect the whole-brain structural connectivity patterns by calculating the inter-regional morphological correlations, based on the axon tension theory that axon-connectivity of brain regions has an influence on morphology (Bassett and Bullmore, 2009; He et al., 2007). Multiple investigations have concluded that the variability of human brain in morphometric or morphological features, such as GM tissue density and volume, can imply structural associations and neuronal interactions between brain areas like functional connectivity does (Alexander-Bloch et al., 2013). The techniques for morphological brain network construction have been implemented by a study in population at increased familial risk for developing schizophrenia. In this study, network properties of network size, connectivity density, degree, pathlength, clustering coefficient, betweenness centrality, have been estimated, and people at risk of schizophrenia showed decreased path length and clustering in mostly prefrontal and temporal areas compared to group-matched controls (Tijms et al., 2015). Nevertheless, the systems-level characteristics of such structural brain networks associated with language processing were not investigated.

To understand the topological properties of the morphological neural network and their relationships to language dysfunction in schizophrenia and the genetically high risk subjects, the current study will measure both global and regional (nodal) network characteristics in individuals with chronic schizophrenia, individuals at high genetic risk for schizophrenia, and neurotypical controls. Single-subject morphological brain network will be constructed based on the structural MRI data acquired from a total of 71 subjects (20 patients with schizophrenia, 19 individuals at high genetic risk for schizophrenia, and 32 controls). Among these 71 imaging data, 56 were involved in our previous voxel- and ROI-based studies, reported abnormal regional cortical thickness in bilateral IFG, STG, AG, and abnormal volume of subcortical structures, such as caudate, putamen and thalamus in the patient and high risk groups (Li et al., 2012a; Li et al., 2015). We hypothesize that topological alteration may exist in the high risk and patient cohorts in nodes of the morphological brain network that play critical role for language processing; and the topological features of these identified regions significantly associate with language-related behavioral capacity in the whole study sample.

2. Materials and methods

2.1. Subjects

Seventy-one participants had MRI scans analyzed in the current study, including 32 controls with no history of schizophrenia in themselves or a family member, 19 participants at high genetic risk stage for schizophrenia and 20 individuals with chronic schizophrenia. A participant with high genetic risk was defined as a person within the age range of 16–35, with at least one first-degree biological relative (parent or sibling) with a diagnosis of schizophrenia or schizoaffective disorder. Details of subject diagnostic procedures and characteristics can be found in previous publications (Li et al., 2007a; Li et al., 2007b) and in Table 1. Fifty-six participants of this study were involved in these previous functional MRI studies detailed in (Li et al., 2007a; Li et al., 2007b). The rest of 15 ones were all normal controls. Patients were all inpatients. The patients and high-risk cohorts were recruited by placing advertisements in newspapers and newsletters distributed by multiple chapters of The National Alliance for The Mentally Ill (NAMI), or from an existing pool of subjects who previously participated in other genetic studies on schizophrenia conducted by Dr. DeLisi. Controls were solicited from the community by public advertisement.

A comprehensive neuropsychological assessment battery including language tests was also administered. The detailed description of the battery can be found in (Bertisch et al., 2008). In this battery, receptive

Table 1
Subject characteristics analyzed using one-way ANOVA.

	Controls ($n = 32$)	High-risk ($n = 19$)	Schizophrenia ($n = 20$)	d.f.	p
Age (range)	22.0 ± 5.1 (16–30)	21.1 ± 5.5 (16–30)	37.7 ± 10.3 (20–49)	2	0.001
Male/female (Chi-sq)	18/14	7/12	13/7	2	0.176
Education (years)	14.8 ± 3.0	12.6 ± 2.75	14.5 ± 2.20	2	0.634
Mother's education	13.8 ± 3.5	14.5 ± 2.5	12.5 ± 2.20	2	0.695
Father's education	15.1 ± 2.05	15.0 ± 2.225	14.5 ± 3.25	2	0.942
Full IQ	113.2 ± 17.4	108.07 ± 14.6	105.53 ± 14.3	2	0.88
PPVT	102.5 ± 12.9	101.3 ± 12.2	102.5 ± 16.6	2	0.87
WRAT	104.1 ± 13.1	105.9 ± 9.1	106.6 ± 11.9	2	0.63
WJTA	102.4 ± 14.2	104.5 ± 11.1	103.5 ± 13.3	2	0.67
BNT	103.6 ± 15.7	103.1 ± 16.6	101.5 ± 12.1	2	0.71
CVLT	104.66 ± 12.9	103.9 ± 12.5	105.7 ± 18.7	2	0.76

PPVT: Peabody Picture Vocabulary Test; WRAT: Wide Range Achievement Test; WJTA: Woodcock Johnson Tests of Achievement; BNT: Boston Naming Test; CVLT: California Verbal Learning Test.

language skill was evaluated by the Peabody Picture Vocabulary Test (PPVT), 3rd Edition (Dunn and Dunn, 1997), word decoding skills were assessed by the Wide Range Achievement Test (WRAT), 3rd Edition (Wilkinson, 1993), word retrieval ability was tested by the Boston Naming Test (BNT) (Kaplan et al., 1983), reading comprehension skills were tested by the Woodcock Johnson Tests of Achievement (WJTA), 3rd Edition (Woodcock et al., 2018), and verbal memory capacity was evaluated by the California Verbal Learning Test (CVLT) (Delis et al., 1987).

Approval was attained from the Institutional Review Boards of the Nathan S. Kline Institute for Psychiatric Research and New York University School of Medicine before study commencement. Written informed consents were provided by all participants who were at least 18 years old, and parental/guardian assent was attained for participants younger than 18.

2.2. Imaging acquisition protocol

All magnetic resonance brain images were acquired on a 1.5T Siemens Vision scanner (Erlangen Germany). The high-resolution 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) data were scanned with TR = 11.6 s, TE = 4.9 ms, flip angle = 15°, FOV = 256 × 256 × 307 mm^3, voxel size = 1.0 × 1.2 × 1.2. A high resolution T2-weighted FLAIR data was also acquired from each participant.

2.3. Imaging pre-processing

Each T1-weighted image was pre-processed using Statistical Parametric Mapping Voxel-Based Morphometry 8 tool (SPM-VBM8) (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The images were first segmented into gray matter (GM), white matter and cerebrospinal fluid based on an adaptive Maximum A Posteriori technique. The GM images were normalized to the Montreal Neurological Institute (MNI) space using a high-dimensional "DARTEL" approach and resampled to 1.5 mm isotropic voxels. The voxel-based GM volume maps were then calculated. Spatial smoothing step was not processed, to avoid inducing artifactual signal overlap among spatially adjacent regions. Fig. 1 illustrates the main analytic steps of individual-level analyses.

2.4. Morphological network construction in each individual

The large-scale single-subject morphological network for each participant was created based on the regional GM volume maps. A brain morphological network is defined as a set of nodes and edges interconnecting the nodes, with nodes representing brain regions and edges representing interregional similarity in the distribution of regional GM volume.

To define the network nodes, the GM volume image was parcellated into 246 regions according to the Brainnetome Atlas (Fan et al., 2016). The GM volume value of each of the 246 regions was then calculated. The probability density function of these 246 values was estimated using the kernel density estimation (KDE) with bandwidths chosen automatically. The regional probability density function (PDF) and the Kullback-Leibler divergence-based similarity (KLS) measure between each pair of the 246 regions in their PDFs were then calculated. The network edges were defined as KLS with a consecutive sparsity threshold, S, ranging $0.05 < S < 0.4$ (interval = 0.02). All the following network analyses were performed at each of the threshold level in this range. For each of the network metrics, the estimated values under the range of 0.05–0.4 were integrated with area under curve (AUC). Detailed descriptions of these network construction steps and rationale were provided in (Wang et al., 2016).

2.5. Network topological feature analyses

For each participant, the KLS threshold-based weighted morphological brain network was constructed at each sparsity level (0.05–0.4 with interval of 0.02) (Wang et al., 2016). The global features (global efficiency, E_{glob} and local efficiency, E_{loc}) and nodal features of each region (nodal efficiency e_i, and network hub measures of nodal degree, k_i, and nodal betweenness centrality, b_i) were calculated using the GRETNA toolbox (Wang et al., 2015). The global efficiency of a network is typically interpreted as a measure of the overall capacity for parallel information transfer and integrated processing, while the local efficiency measures the network's average resistance to failure on each of the nodes. In a brain network, a hub, measured by nodal degree or betweenness centrality, represents a node (brain region) with a number of strong connections that greatly exceeds the average (Bullmore and Sporns, 2009). In another word, a hub here means a busy junction

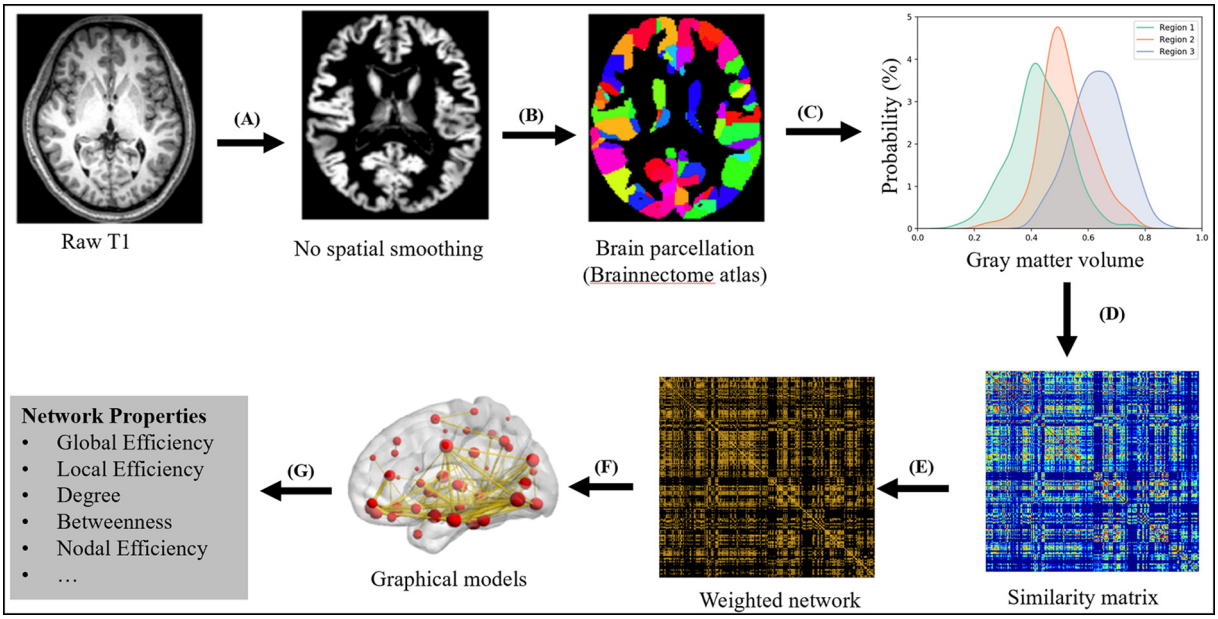

Fig. 1. The flowchart depicting the main analytic process of constructing the single-subject morphological brain network.

that connects a lot of other nodes in the network, but not necessarily a highly efficient node for information transferring. Since the path length of any two nodes in a morphological brain network is determined by their regional GM volume distribution similarity, a hub here represents a brain region that has similar regional GM volume distribution with many other brain regions in the entire network.

To determine if the morphological brain network was organized in a non-random manner, the global features were individually normalized by the corresponding mean of 100 matched random networks generated using a topological rewiring algorithm (Maslov and Sneppen, 2002) which preserved the same number of nodes and edges and the same degree distribution as in a real brain network.

2.6. Group statistical analyses

The demographic, clinical, and language performance indices were analyzed using one way ANOVA and post hoc *t*-tests for between-group comparisons. The topological measures of the morphological brain network, including the global and nodal features, were analyzed using a General linear model (GLM) for between-group comparisons, with age, IQ, antipsychotic treatment duration (months), and sex added as covariates. Bonferroni correction for multiple comparisons (correcting for the number of ROIs) were applied to group comparisons of the network topological measures at the threshold of $p < 0.05$.

In order to determine the degree of association between language performance and brain network topological features, Pearson's partial correlations were implemented where between-group analyses demonstrated significance. These analyses corrected for age, IQ, and sex. False Discovery Rate (FDR) was used to adjust for multiple comparisons of these correlation analyses at the threshold of $p < 0.05$.

3. Results

Findings from the between-groups comparisons on the language measures are described in Table 1. There were no demographic differences, with the exception of age (patients were significantly older than the high-risk subjects and controls), which is expected given the stages of disease and associated age groups. There were no between-group differences within the language assessment.

Group comparisons in the global measures of the morphological brain network did not show significant differences. Table 2 summarized the brain regions that showed significant between-group differences in the nodal measures of the morphological brain network. Individuals with schizophrenia showed significantly smaller nodal degree in bilateral superior occipital gyri (SOG) when compared to both normal controls and the high-risk subjects, and significantly lower nodal efficiency in right SOG when compared to the high-risk subjects. The high-risk group showed significantly reduced nodal betweenness centrality in right middle frontal gyrus (MFG) relative to controls. Additionally, the participants with schizophrenia demonstrated increased nodal betweenness centrality in left striatum and left cuneus compared to controls, and in right precuneus compared to the high-risk subjects.

As shown in Fig. 2, the WRAT standard score was negatively correlated with the right MFG nodal degree, betweenness centrality, and nodal efficiency, whereas it was positively correlated with the right SOG nodal degree in the entire study sample.

Table 2
Brain regions that showed significant between-group differences in nodal features of the morphological brain network.

Groups	Anatomical region	Features	MNI coordinates, mm			*p*
			x	y	z	
NC > SZ	L. superior occipital gyrus	k_i	−11	−88	31	0.016
	R. superior occipital gyrus	k_i	16	−85	34	0.021
NC > HR	R. middle frontal gyrus	b_i	28	55	17	0.012
HR > SZ	L. superior occipital gyrus	k_i	−11	−88	31	0.002
	R. superior occipital gyrus	k_i	22	−97	4	0.007
	R. superior occipital gyrus	e_i	16	−85	34	0.019
SZ > NC	L. striatum	b_i	−28	−5	2	0.021
	L. cuneus	b_i	−13	−68	12	0.029
SZ > HR	R. precuneus	b_i	6	−54	35	0.017

NC = Normal Controls; SZ = Schizophrenia; HR = High-risk subjects; L. = left hemisphere; R. = right hemisphere; k_i = nodal degree; b_i = nodal betweenness centrality; e_i = nodal efficiency.

4. Discussion

In this study, we investigated the topological features of the morphological brain network and their associations with language-related behaviors in patients with chronic schizophrenia, individuals at high genetic risk for schizophrenia, and in neurotypical controls with no family history of schizophrenia. The group of patients showed significantly reduced nodal degree in bilateral SOG relative to the high-risk and control groups, significantly lower nodal efficiency of right SOG when compared to the high risk subjects. The brain-behavior association analyses found that the nodal degree of right SOG was significantly positively correlated with the WRAT performance score in the entire study sample. SOG receives visual inputs from the retina. It is believed that the SOG is one of critical components of the anatomical pathways for visual language-processing, which serve as the demarcation point of the two visual streams, of the dorsal and ventral visual pathways, with the dorsal area containing motion-sensitive neurons, and ventral region specializing for object recognition (Feinberg and Meister, 2015). Our prior fMRI studies have found that individuals with schizophrenia had higher regional brain activation in the bilateral SOG (Li et al., 2007a; Li et al., 2007b). Neural activation deficits in SOG in patients with schizophrenia have also been revealed by other steady-state visual evoked potential, electrophysiological and functional MRI studies (Anderson et al., 2017; Calderone et al., 2013; van de Ven et al., 2017). The findings of the SOG-related topological alterations in patients with schizophrenia and its strong relation with the WRAT performance suggest that the significantly altered nodal features of the SOG in the morphological brain network may relate to the functional abnormalities of the visual input-based language-processing pathways, which further influence the language deficits in schizophrenia.

The results of this study also demonstrated significantly reduced nodal betweenness centrality in right MFG in the high-risk participants relative to controls, and strong negative correlations between the nodal features of right MFG and the WRAT standard scores (measuring word decoding skills). The MFG has previously been found to functionally associate with speech and thought, with differential contributions of left MFG to literacy and right MFG to numeracy (Koyama et al., 2017; Tune et al., 2016). Earlier studies from our group and others have found higher GM volume density in scattered areas located in the right MFG (Li et al., 2012a) and greater right MFG folding (Stanfield et al., 2008) in genetic high-risk participants, relative to controls. Together with these previous studies, findings from the current study suggest that the anomalies of cortical neuron development in right MFG and their compensative influence on literacy and semantic processing may exist early before the onset of schizophrenia symptoms, which may serve as a robust marker for predicting the language impairment and onset of schizophrenia symptoms. With the longitudinal study design and statistically more powerful sample size of group-matched controls and genetically high risk subjects, a future study can focus on validating the power of the right MFG-related neural abnormalities on accurately predicting language impairment and schizophrenia symptom onset in the high risk cohort.

Meanwhile, individuals with schizophrenia demonstrated higher nodal betweenness centrality in left striatum as compared to controls.

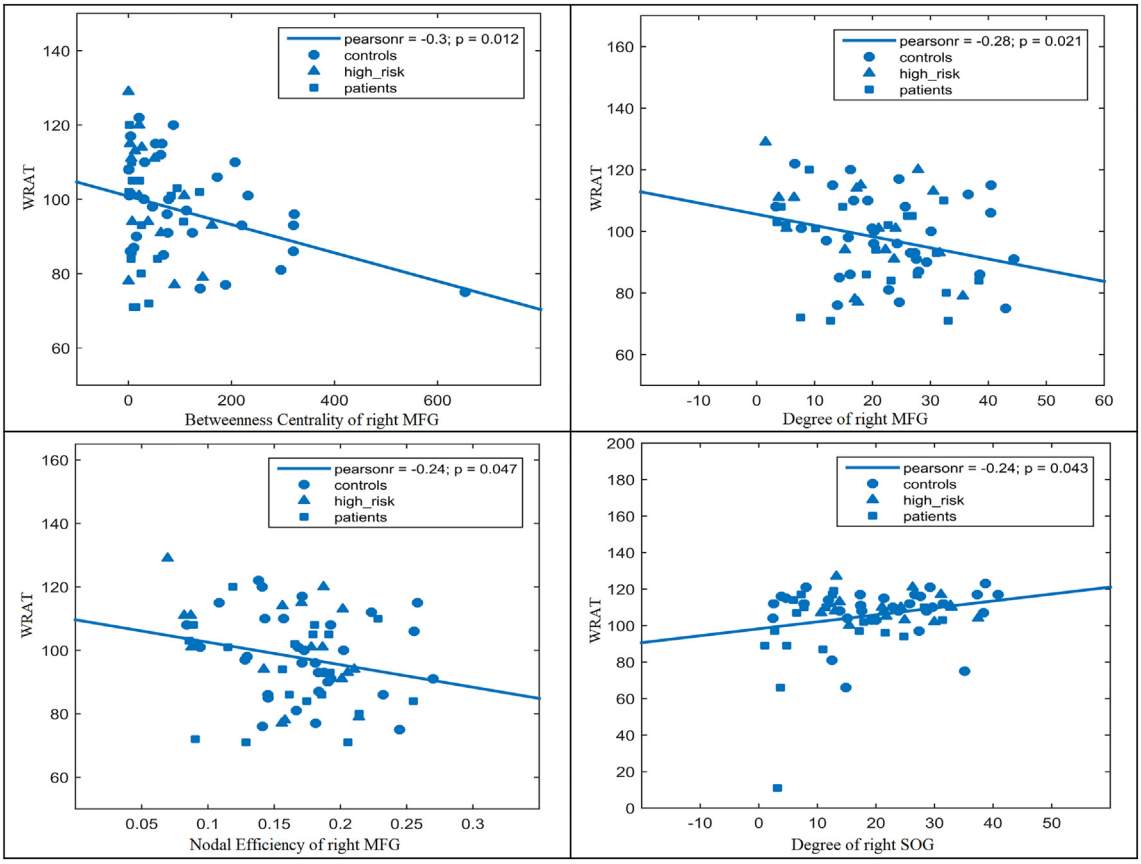

Fig. 2. The topological features at right middle frontal gyrus (MFG) and right superior occipital gyrus (SOG) that differentially associated with the wide range achievement test (WRAT) standard score in the entire study sample.

The striatum is a midbrain structure involved in integrating and modulating a wide range of neurological stimuli and preparing them for language generation (Crosson, 1985). Recent neuroimaging studies have described structural and functional abnormalities in the striatum, particularly the caudate and putamen in patients with chronic schizophrenia, like atypical volumes and gray matter intensity (Stip et al., 2008), atypical cortical-caudate functional connectivity (Bracht et al., 2013), and lower putamen volume associated with poorer verbal learning, working memory, and executive function (Hartberg et al., 2011). One of our previous neuroimaging studies showed significantly decreased volume and widely altered regional surfaces in both the left and right caudate nuclei in individuals with schizophrenia as compared to the neurotypical controls and high genetic risk subjects (Li et al., 2015). Consistent with these findings, the altered striatal nodal feature in the morphological brain network in individuals with schizophrenia suggests robust associations between the structural anomalies in the striatum and the language-related impairments observed in schizophrenia.

This study has several limitations. Both males and females were enrolled in the study. Nevertheless, a meta-analysis describes no language-related significant differences between males and females with schizophrenia (Sommer et al., 2003). In addition, the individuals with chronic schizophrenia were older than the controls and high risk subjects, and were treated by antipsychotic medications. To remove the potential confounding caused by these factors, we included age, treatment duration, and sex as the covariates in group-level analyses.

In summary, the present study reports altered topological features of the morphological brain network and their relationships to language-related deficits in patients with chronic schizophrenia and in those at high genetic risk for the disorder. Our results expand the existing literature in schizophrenia, which has primarily focused on abnormalities in individual cortical and subcortical structures and the pair-wise inter-relationships among these brain regions, without understanding the topological features of the entire structural brain network at the systems-level. These new findings suggest that compared to controls and the high risk subjects, patients with chronic schizophrenia demonstrate topological differences in morphological brain organization especially within bilateral occipital lobes and striatum that may occur as a consequence of the course of illness. Relative to controls, the subjects with high genetic risk showed significantly higher network hub capacity in right MFG, which significantly associate with language-related behavioral deficits. Therefore, topological anomalies in the right MFG as present in the high genetic risk individuals, may indicate early development of precursors that may lead to language impairments, and thus may act as a core marker for the onset of schizophrenia.

Conflict of interests

There is no conflict of interests reported from any of the authors.

Contributors

Dr. Xiaobo Li designed the neuroimaging study, managed the literature searches, and wrote the first draft of the manuscript.

Dr. Kai Wu contributed to data analysis and manuscript writing.

Yue Zhang and Lingyin Kong processed the neuroimaging data and statistical analyses.

Dr. Lynn Delisi provided the general hypotheses and administered the clinical interviews.

All authors contributed to and have approved the final manuscript.

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