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Unique topology of language processing brain network: A systems-level biomarker of schizophrenia

Xiaobo Li, PhD^{1,2,3,4,*}, Shugao Xia, PhD¹, Hilary C. Bertisch, PhD⁵, Craig A. Branch, PhD^{1,2}, and Lynn E. DeLisi, MD⁶

¹Gruss Magnetic Resonance Research Center, Albert Einstein College of Medicine, Bronx, NY

²Department of Radiology, Albert Einstein College of Medicine, Bronx, NY

³Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY

⁴Department of Psychiatry and Behavior Sciences, Albert Einstein College of Medicine, Bronx, NY

⁵New York University Medical School, NY

⁶VA Boston Healthcare System, Harvard Medical School, Brockton, MA

Abstract

Objective—Schizophrenia is a severe and heritable brain disorder. Language impairment has been hypothesized to spur its onset and underlie the characteristic symptoms. In this study, we investigate whether altered topological pattern of the language processing brain network exists and could be a potential biomarker of schizophrenia. We hypothesized that both patients with schizophrenia and the genetic high risk population would show significantly weakened efficiencies of the network hubs for normal language processing, especially at left inferior frontal and bilateral temporal lobes.

Method—Language task-based fMRI data from 21 patients with schizophrenia, 22 genetic high risk subjects and 36 controls were analyzed. Graph theoretic and post hoc analyses of the fMRI data, and correlations between the functional network features and scores of language tests were carried out.

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*Address all correspondence to: Xiaobo Li, PhD, Assistant Professor at Gruss Magnetic Resonance Research Center, Departments of Radiology, Neuroscience, Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Yeshiva University, 1300 Morris Park Avenue, Gruss 204, Bronx, NY 10461, US., Phone: 718-430-4015, Fax: 728-430-3399, xli.nki.cabi@gmail.com, xli.aecom@gmail.com, xiaobo.li@einstein.yu.edu.

Conflict of Interests

All authors reported no actual and potential conflict of interests.

Contributors

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

Dr. Shugao Xia processed the neuroimaging data and statistical analyses.

Dr. Hilary Bertisch administered the neurocognitive assessments.

Dr. Craig Branch designed the MRI scan protocols.

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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Results—Compared to controls, patients with schizophrenia and the high risk subjects showed significantly weakened network hubs in left inferior frontal and right fusiform gyri. A unique topology of super active and intercommunicating network hubs at left fusiform gyrus and right inferior/middle frontal gyri, which were associated with the behavioral language impairment was found in the patient group, compared to the high risk and control groups.

Conclusions—Aberrant systems-level topology of language processing network, especially significantly weakened network hubs in left inferior frontal and right fusiform gyri, may serve as a candidate biomarker of schizophrenia. Supported by existing findings, the hyperactive left fusiform gyrus communicating with right frontal lobe might be the key neurophysiological component causing hallucinations in schizophrenia. These findings provided a new systems-level diagnostic target for the disorder.

Keywords

Schizophrenia; Genetic high risk; Language processing network; fMRI; Graph theoretical techniques

1. Introduction

Schizophrenia is a severe, chronic and heritable brain disorder. First-degree relatives of schizophrenia patients have an almost 10-fold increased risk of developing the disorder (Gottesman and Shields, 1973). According to NIMH report (2012), it affects at least 2.4 million Americans in a given year and more than 24 million people worldwide. The underlying genetic mechanism for the pathogenesis of the disorder is not well understood. Anomalies in language processing have been hypothesized to spur the onset and underlie the characteristic symptoms of schizophrenia (Crow, 1995). Recent functional and structural neuroimaging studies in patients with schizophrenia (Bluhm et al., 2007; Kircher et al., 2001; Sommer et al., 2004; Liemburg et al., 2012), and in those during the prodromal stage prior to illness onset and/or at high genetic risk (Lawrie et al., 1999; Whyte et al., 2006; Rajarethinam et al., 2011), have shown widespread functional and structural abnormalities in the language processing-related brain regions. These may be relevant to the underlying genetic basis for the disorder.

Brain regions work interactively as a network when processing sensory and cognitive information. The anatomical pathways for language processing were first documented by Broca and Wernicke in the 19th Century, and redefined based on results from numerous language task-based functional imaging studies. In this revised model, bilateral superior temporal gyri and occipital cortex serve as auditory and visual input centers (McNealy et al., 2006). The supramarginal gyrus (Brodmann's area (BA) 40) works as a site for phonological encoding in word production, whereas the angular gyrus (BA 39) for memory of visual word forms (Poeppel and Hickok, 2004). These two regions interface with widely distributed conceptual knowledge systems located primarily at the junction of the left temporal, occipital, and parietal lobes, i.e. inferior temporal region (Wernicke's area), fusiform and lingual gyri. The sound, or visual-based system, interfaces not only with the conceptual knowledge systems, but also with frontal motor systems (Broca's area: BA 44, 45) via an auditory-motor interface system in the inferior parietal lobe. This circuit is the primary substrate for phonological and semantic working memory, and likely plays a role in volitional speech production. Structurally, Broca's area is left lateralized. There is a link between Broca's area and the large-scale distributed network for conceptual representation (such as BA 9, 10, 23, 24, 28) (Poeppel and Hickok, 2004). Thus, the whole circuit of language processing is a highly distributed multilevel bidirectional network.

Development of the advanced graph theoretic techniques has allowed us to characterize the important topological properties of the functional brain networks (Bullmore and Sporns, 2009). Studies have revealed that the functional brain networks for sensory and cognitive information processing in normal human brain have a small-world property, which is characterized by a high level of local clustering and short path lengths linking all nodes within the network, and produces optimal organization for rapid synchronization and information transferring with minimal wiring cost (He and Evans, 2010; Rubino and Sporns, 2010). Recent resting-state fMRI studies have reported altered default mode network topological properties in patients with schizophrenia (Bluhm et al., 2007; Liu et al., 2008; Yu et al., 2011). The systems-level topological features of the functional brain networks for language processing in patients with schizophrenia and the high risk population have not yet been investigated.

In this study, we investigated whether altered topological patterns of the language processing network, assessed with a lexical discrimination task (Li et al., 2007b), during fMRI in patients with schizophrenia and the genetic high risk subjects, could be a potential biomarker of schizophrenia. We hypothesized that both patients with schizophrenia and the high risk subjects would show significantly weakened efficiencies of the network hubs for normal language processing, especially at left inferior frontal and temporal gyri.

2. Materials and methods

2.1. Subjects

A total of 93 subjects were involved in the study. Seven subjects were excluded from analyses due to heavy head motion, 3 were excluded due to poor fMRI task response accuracy, 2 with low IQ, and 2 were not able to finish the whole scan protocol. Eventually, a total of 79 subjects were included in analyses (36 normal controls, 22 high risk subjects, and 21 patients with schizophrenia). Basic demographic comparisons among groups were provided in Table 1. The control subjects did not have evidence of any psychotic disorders (schizophrenia, bipolar disorder or psychosis not otherwise specified) upon evaluation, and no history of any psychotic disorder, psychiatric hospitalization or suicide in first or second-degree relatives. Individuals at genetic high risk were those who were within the peak age of risk for schizophrenia, and originated from families in which at least one first-degree relative (parent or sibling) had a diagnosis of schizophrenia and at least one other relative had a psychotic illness (Li et al., 2007b). All subjects underwent an interview using the DIGS (Diagnostic Interview for Genetic Studies; (Nurnberger, Jr. et al., 1994)). Diagnoses were made based on the interview, information from family members, and medical records as appropriate. The normal controls and high-risk subjects were never treated with medication for psychotic symptoms, whereas the patients with were on a combination of conventional and atypical medications. Six patients were siblings of unaffected individuals in the high risk group.

For each subject, select subtests from the age-appropriate Wechsler Intelligence Scale were administered (Wechsler, 2004). The Verbal Comprehension Index (WAIS-VCI) was used as the primary measure of verbal capacity. The Wide Range Achievement Test – Reading (WRAT-Reading) was performed by decoding a list of progressively harder words, as both a measure of reading ability and as an estimate of premorbid IQ (Wilkinson GS, 1993). The Peabody Picture Vocabulary Test (PPVT-III) was also performed as a test of receptive language, where the subject was shown panels of four pictures and asked to point to the one that best describes a word spoken by the examiner (Dunn and Dunn, 1997).

This study received Institutional Review Board Approval for human subjects' research at the Nathan S. Kline Institute for Psychiatric Research, and at New York University School of

Medicine. Participants over the age of 18 gave written informed consent for their participation after being carefully explained the nature of the study and its procedures. Subjects under the age of 18 provided assent, and consent was provided by a parent/guardian for their participation.

2.2. Experimental task

A Visual Word Discrimination task was used in this study. The experimental task has been described in detail in (Li et al., 2007b). Briefly, three types of blocks interleaved in the task. During the Lexical Decision Blocks, English language words (all concrete nouns) were presented on a screen in a random fashion, interspersed with pseudowords matched to the real words for number of letters. Subjects were instructed to use their right hand to press the left button when a word appeared and to press the right button when the letters displayed were not considered to be a real word. During the Non-Linguistic Control Blocks, two kinds of non-linguistic symbols were shown on the screen. The subjects were instructed to press the left button in response to the symbol denoting “left” and the right button in the response to the symbol denoting “right”. The rest blocks contained a blank screen, and subjects were instructed to keep their eyes open, remain relaxed and motionless.

This visual word discrimination task had 10 blocks, where each block comprised 10 stimuli, each presented for 1000 ms with an interstimulus interval of 3000 ms. The task was repeated four times. The stimuli were presented in random order within blocks. The order of blocks within sequences and the order of trials within blocks differed across the 4 runs, but were identical for all subjects.

2.3. MRI Scans

Imaging was performed on a 1.5T MRI system (Siemens Vision systems, Erlangen, Germany). For each experiment 165 functional volumes sensitive to blood oxygen level dependent (BOLD) contrast were acquired with a T2-weighted gradient-echo EPI sequence [TR=2s, TE=50ms, flip angle=85°, Matrix=64×64, FOV=224, pixel size=3.5×3.5]. Each volume was comprised of 22 axial slices of 5mm slice thickness with no gap. A high resolution 3D MPRAGE data was collected for spatial mapping and registration of the fMRI data.

2.4. Data preprocessing

The fMRI data from each subject was preprocessed using the FSL/FEAT tools. Each image data was initially corrected for slice timing, head motion, and spatial intensity, and spatially smoothed with an 8mm full-width and half maximum Gaussian kernel. A high-pass temporal filter of 1/70 Hz was used to remove low-frequency noise. Non-brain structures were extracted using the Brain Extraction Tool. The fMRI data was first aligned to the skull striped T1-weighted image from the same subject using an affine translation, and further registered to the MNI152 template using a linear registration. Nine components were regressed out from each fMRI data, which included the 6 motion correlation parameters and nuisance signals (white matter, cerebrospinal fluid, and global signal). The residual time series of each image data were analyzed to generate the task-related activation map by using FMRIB improved linear regression (FILM) tool. Activation map for each subject and the average map for each group were generated. The Z statistic image was thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < 0.05$.

Seed ROIs were selected from a combination (union) of all the clusters that were activated in average activation maps of the three groups. First, this combined activation map was parcellated according to the AAL template (Tzourio-Mazoyer et al., 2002), which carved the cerebral cortex and subcortical structures into 90 anatomical areas bilaterally (note that

cerebella regions were not considered in this study). As shown from Table 2 and Figure 1(A), 64 seed ROIs (spheres, R=5mm) were identified from the coordinates at peaks of local maximal activations. In this study, we interrogated the components of the fMRI signals in 0.015 – 0.125 Hz, which has been convinced to contain the majority of the task-related hemodynamic signals by multiple studies in block-design task-based fMRI data (Ginestet and Simmons, 2011; Achard et al., 2006; Bassett et al., 2010). According to existing studies, the hemodynamic response associated signals for different tasks may stay in different sub-bands. Thus, in our study, we first tested three wavelet scales, to assess whether signals from different bands would have different sensitivities to the task design. Since our sampling frequency was 2s (TR = 2s) and wavelet k^{th} scale provided information on the frequency band $[2^{-k-1}/\text{TR}, 2^{-k}/\text{TR}]$, we obtained 0.015–0.031Hz, 0.031–0.062Hz and 0.062–0.125Hz, for wavelet scales 2, 3, 4, using the maximum-overlap discrete wavelet transform that had been extensively applied to time-frequency analyses of fMRI signals (Percival and Walden, 2000).

We eventually decided to use the whole band, based on the testing results that did not show significant sensitivity differences among the three sub-bands. Thus averaged wavelet coefficients of the three frequency sub-bands were utilized for functional connectivity analysis. Pearson correlation of the average wavelet coefficients in each pair of the ROIs was calculated. The absolute values of the correlation coefficients were used to construct the functional connectivity matrix.

2.5. Network efficiency

The functional connectivity matrix was then converted into a binary graph, by using the network cost as threshold. The cost C_G of a network (graph), G , was defined as following:

$$C_G = \frac{K}{N(N-1)/2},$$

where N and K were the total number of nodes (ROIs) and edges (functional correlations), respectively; $N(N-1)/2$ was the number of all the possible sub-networks in the graph G (Latora and Marchiori, 2001). We investigated the network properties over a wide range of the cost values from 0.1 to 0.5 using increments of 0.01. According to existing studies, the selected threshold interval would allow the small-world properties to be properly estimated and the sub-networks to be connected with enough discriminatory power in functional connectivity (Achard and Bullmore, 2007). Then we calculated the two global metrics, global efficiency, $E_{glob}(G)$ and local efficiency, $E_{loc}(G)$, defined as:

$$E_{glob}(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{l_{ij}}, \text{ and } E_{loc}(G) = \frac{1}{N} \sum_{i \in G} E_{glob}(G_i),$$

where l_{ij} was the shortest path length between nodes i and j ; $E_{glob}(G_i)$ the global efficiency of the sub-network G_i that was constructed by the set of nodes that were immediate neighbors of nodes i (Latora and Marchiori, 2001). The graph was considered to be a small-world network if it met the following criteria: $E_{glob}(G_{regular}) < E_{glob}(G) < E_{glob}(G_{random})$ and $E_{loc}(G_{random}) < E_{loc}(G) < E_{loc}(G_{regular})$, where $E_{glob}(G_{regular})$, $E_{glob}(G_{random})$, $E_{loc}(G_{regular})$ and $E_{loc}(G_{random})$ were the global and local efficiencies of node- and degree-matched regular and random networks.

We also investigated the nodal efficiency, $E_{nodal}(G,i)$, which was a local measure to evaluate the communication efficiency between a node i and all other nodes in the network G (Latora and Marchiori, 2001).

2.6. Network hubs

We also identified the network hubs in each group. In this study, a node was defined as a hub if the value of a measure, either degree (D) or between-centrality (BC), of this node was significantly higher than the average value over all the nodes in the network. The degree (D_i) of a node i was the number of edges connected to the node i , and the between-centrality (BC_i) of node i was defined as the proportion of all the shortest paths between pairs of other nodes in the network that include node i (Bullmore and Sporns, 2009).

Let h_i^k , $k = 1, \dots, m$; $i = 1, \dots, N$ be the measure of D_i or BC_i of subject k in the group. The

grand sample mean, $\bar{h} = \frac{1}{mN} \sum_{k=1}^m \sum_{i=1}^N h_i^k$, and the grand sample standard deviation,

$SD = \left(\frac{1}{m(N-1)} \sum_{k=1}^m \sum_{i=1}^N (h_i^k - \bar{h})^2 \right)^{1/2}$, in each diagnostic group was calculated. The standardized

measure of node i in each group was then defined as $z_i = \frac{|\bar{h}_i - \bar{h}|}{SD / \sqrt{m}}$, where $\bar{h}_i = \frac{1}{m} \sum_{k=1}^m h_i^k$ for each node i . These standardized values were then tested with a normal distribution. A node i was a network hub if $1 - \Phi(z_i) < \alpha$, where $\Phi(\cdot)$ was the standard normal cumulative distribution function, and $\alpha = 0.05$ the level of significance.

2.7. Group statistic analyses

Group statistic analyses were performed using a General Linear Model from the MATLAB Statistics Toolbox (The MathWorks Inc, Natick, MA). We compared the demographic/cognitive measures, the global features (E_{glob} and E_{loc}) and the average nodal efficiency at each cost value, among three groups using one-way Analysis of Variance (ANOVA). Sex was added as a fixed-effect factor, and age added as a random-effect covariate. Multiple comparisons were corrected by Bonferroni correction at $\alpha = 0.05$. A significance threshold of $P < 0.05$ was applied to each test.

A linear regression analysis was utilized between the nodal efficiency measure of each node and the scores for WAIS, PPVT and WRAT in each group. Again, sex and age effects were controlled, and multiple comparisons were corrected by Bonferroni correction at $\alpha = 0.05$. A significance threshold of $P < 0.05$ was applied to each test.

3. Results

3.1. Clinical and behavior data

From Table 1, the ages of high-risk subjects and normal controls did not differ significantly ($p = 0.320$), while the patients were significantly older than the other two groups ($p = 0.000$). There were no significant between-group differences in sex, handedness, education levels, and performance scores of the language related cognitive tests. All the participants performed the fMRI task with a $>80\%$ accurate response rate.

3.2. Network efficiencies

Figure 1(B and C) illustrated the global features of functional brain networks, the global and local efficiencies, in the three diagnostic groups, over a range of network costs (0.1 – cost

0.5). We observed that the locations of the global and local efficiency curves of the three groups were between the corresponding curves of the random and regular graphs in the range $0.1 < \text{cost} < 0.3$, known as a small-world regime (Achard and Bullmore, 2007). Compared to normal controls, the high-risk subjects and patients showed decreased global efficiencies and increased local efficiencies (not significant though). Figure 1(D) showed that the degree distributions of the three networks followed a truncated power-law of the form $(k) \sim k^{\alpha-1} e^{-k/k_c}$.

Group comparisons of the nodal efficiencies of all the nodes over the small-world regime showed significant differences in the left inferior frontal gyrus (BA44, $p = 0.032$), left middle frontal gyrus (BA46, $p = 0.03$), and right rectus gyrus (BA11, $p < 0.0001$) among three groups. Results of the Post hoc t tests, as shown in Figure 2, demonstrated that compared to controls, both high-risk and patient groups had significantly decreased nodal efficiencies in the left BA44 and BA46; whereas the patient group had significantly increased nodal efficiency in the right BA11, compared to controls and the high risk subjects.

3.3. Network hubs

Table 2 and Figure 3(A–C) detailed the anatomical regions and locations of the network hubs in each group. As a summary, Figure 3D demonstrated that compared to the controls, both the high risk cohort and patients with schizophrenia lost communications among the middle occipital gyrus, angular gyrus, and inferior temporal and fusiform gyri within the right hemisphere, as well as showed significantly reduced between-hemisphere interactions between the left side inferior frontal area (Broca's area) and the right side angular gyrus and the junction of temporal and parietal lobes, i.e. inferior temporal and fusiform gyri. The language processing network in the patient group showed some unique features, i.e. the significantly increased between-hemisphere interactions between the right side middle frontal gyrus and the left side fusiform gyrus, compared to that in the controls and high risk subjects.

3.4. Correlations between network features and language measures

We found both the global and local efficiencies, over the small-world regime ($0.1 < \text{cost} < 0.3$), were positively (but not significantly) correlated with the PPVT and WRAT scores in the whole study population. Significant negative correlations between the PPVT scores and the nodal efficiency of the right side BA 44/45 were present in the high-risk group ($r = -0.51$, $p = 0.02$). In the patient group, significant negative correlations between the WRAT scores and the nodal efficiencies were observed in right sides BA44/45 ($r = -0.48$, $p = 0.031$ for right side), and in left side BA37 ($r = -0.53$, $p = 0.008$).

4. Discussion

To our knowledge, this is the first study to exhibit atypical topological features of the functional brain network for visual language processing in both patients with schizophrenia and the unaffected people with high genetic risk, and it identifies a potential neural intermediate phenotype of the disorder. Specifically, we observed significantly decreased nodal efficiencies in the left side inferior frontal region (left BA44/45/46) in both high-risk and patient groups compared to healthy comparison subjects, and significantly increased nodal efficiency in the right side middle frontal gyrus (BA11) in patients with schizophrenia compared to controls and high risk subjects. Moreover, significant negative correlations between the language testing performance scores and the nodal efficiency of the right side BA 44/45 were presented in both the high-risk and patient groups. The left side inferior frontal region (BA44/45), also referred to as the Broca's area, has been recognized to be a

key component for language recognition, comprehension and speech production (Price et al., 2001). Neuroimaging studies of this brain area in patients with schizophrenia and the genetic high risk subjects have consistently reported abnormal gray matter and white matter morphology (Jou et al., 2005; Pantelis et al., 2003), disrupted local white matter network organizations (van den Heuvel et al., 2011), and significantly less leftward functional activations during language tasks (Li et al., 2007a; Whyte et al., 2006). In line with the existing studies, the findings in the present study suggest that the significantly weakened function of the left Broca's area and its right-shifting pattern greatly contributes to the pathology of language impairment in schizophrenia, and such unique topological feature of the language processing brain network can be a potential biomarker of the disorder. Such similar findings in the unmedicated high risk cohort and a mixture of medicated and unmedicated schizophrenia patients are of particular importance, because they also suggest that the results are unlikely to be affected by medication.

Mapping of the central hubs of the language processing brain networks in the three groups depicted group-specific topological features of the functional brain networks (especially shown in Figure 3D). It demonstrated that compared to the controls, the high risk and patient groups showed significant lack of communications among the hubs in the primary visual region, and the phonological encoding, memory of visual word forms and conceptual knowledge systems (BA 22/37/39/40) within the right hemisphere, as well as significant lack of between-hemisphere interactions between the left side Broca's area and the right side conceptual knowledge systems, i.e. inferior temporal and fusiform gyri. Very interestingly, the language processing network in the patient group showed some unique features of super active between-hemisphere interactions between the right side middle frontal gyrus and the left fusiform gyrus, and significant negative correlations between the WRAT scores and the nodal efficiencies of left fusiform gyrus.

The angular, inferior/superior temporal and fusiform gyri are key regions for language and semantic memory processing, visual perception, multimodal sensory integration (Ahmad et al., 2003). Neuroimaging studies have reported functional and structural anomalies of the inferior/superior temporal area in patients with schizophrenia and the genetic high risk populations (Rajarethinam et al., 2004; Rajarethinam et al., 2011; Jacobsen et al., 1998). The fusiform gyrus also involves in face/body recognition and within-category identification (Minnebusch et al., 2009). Studies have concluded that the bilateral fusiform gyri play different roles from one another, but are subsequently interlinked: the left fusiform gyrus plays the role of recognizing key features in objects; whereas the right fusiform gyrus plays the role in determining what the recognized object is, and have suggested that increased neurophysiological activity in the fusiform gyrus may produce hallucinations (Jan Dirk Blom, 2010). Postmortem and in vivo imaging studies have reported reduced gray matter volumes in bilateral fusiform gyri in patients with schizophrenia compared with controls (Onitsuka et al., 2004), and more severe hallucinations significantly correlated with smaller left hemisphere volumes of fusiform gyrus in schizophrenia patients (Onitsuka et al., 2004). Functional abnormality in the right side fusiform gyrus during emotion discrimination was found in a sample at high risk for psychosis (Seiferth et al., 2008). In agreement with these existing studies, we suggest that impaired central hubs in the right fusiform gyrus directly cause the lack of within- and between-hemisphere communications among the visual cortex, angular gyrus, and inferior/superior temporal gyri in the right hemisphere, as well as the lack of communications between Broca's areas and right side parietal/temporal areas, in both patient and the high risk groups. Such impaired topological organization of the language processing network could be a remarkable intermediate phenotype, and early sign for the onset of the disorder.

Also seen from Figure 3D, a hyperactive network hub in the left fusiform gyrus was uniquely existed in the schizophrenia patient group. It strongly interacted with the abnormal hubs in the right prefrontal lobe, and was significantly negatively correlated with the language testing scores. Based on the numerous findings from existing studies showing the structural and functional impairments of the left fusiform gyrus and its strong correlations with hallucinations in patients with schizophrenia, we suggest that the unique pattern of abnormal between-hemisphere interactions originated from the left fusiform gyrus might be the key neuronal substrates of the symptomology of the disorder.

The present study has some limitations. First, the sample included both male and female subjects. Although a meta-analysis reported no significant difference in language lateralization between men and women (Sommer et al., 2004), sex was still added as a fixed-effect factor in this study to remove the potential confounders. Second, all the patients were medicated. Medication effects to functional brain networks for cognitive information processes have rarely been investigated in patients with chronic schizophrenia, mainly because washing-out periods (times for patients to stop taking medications until the mental and physical effects of the medications are removed) prior to the MRI examinations are not recommended by the physicians of patients with chronic schizophrenia. In addition, the sample size of this study was relatively small. Future work will need a much larger cohort of high-risk individuals, followed longitudinally, to determine who eventually develops schizophrenia and whether the abnormal language processing brain network would have been predictive of the illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Locations of the nodes and the small-world properties of the functional brain networks. The global and local efficiencies (images B and C) were shown as a function of the cost in the networks. The global and local efficiency curves of the functional brain networks of the three diagnostic groups located in between that of the random and regular networks, over a range of 0.1 cost 0.3 (between the vertical dash lines), known as a small-world regime. The random networks were generated by 50 random rewirings of the edges while keeping the same number of nodes and degree distribution as brain networks. The regular networks were generated by 50 random rewiring of the edges along the two sides of the main diagonal (NC = normal controls, HR = high-risk subjects, SCH = schizophrenia patients). Image D illustrated the degree distributions of three groups, which were fitted by an exponentially truncated power of the form $P(k) \sim k^{\alpha-1} e^{-k/k_c}$ (NC: $\alpha = 1.5667$; $k_c = 4.871$; HR: $\alpha = 1.525$, $k_c = 5.092$; SCH: $\alpha = 1.498$, $k_c = 5.246$). One-way ANOVA indicated that there were no significant differences in the fitted parameters (α : $F(2, 80) = 2.86$, $p = 0.063$; k_c : $F(2, 80) = 2.65$, $p = 0.077$) among the three groups.

Figure 2.

Between-group differences in the nodal efficiency of each node in the language processing network. (NC=normal controls, HR=high-risk, and SCH=patients with schizophrenia). MFG: middle frontal gyrus; PrecG: Precentral gyrus; REC: rectus gyrus; ACC: anterior cingulum cortex; MCC: middle cingulum cortex; Cau: caudate; FFG: fusiform gyrus; MOG: middle occipital gyrus; LING: lingual gyrus; L: left hemisphere; R: right hemisphere.

Figure 3.

Network hubs in normal controls (NC), high-risk group (HR) and schizophrenia patients (SCH) (regions were detailed in Table 2). A: Hubs identified with only between-centrality measure; B: Hubs identified with only degree measure. C: Hubs that satisfy both between-centrality and degree criteria; D: The sketch maps of the major pathways of the language processing networks in three groups. The brain networks were constructed at the cost threshold of 0.2 in each group. The colored lines depict the edges connecting the hubs and other brain regions. Specifically, the red lines demonstrated the unique hub connections in the patient group. IFGtri: inferior frontal gyrus (triangular); IFGope: inferior frontal gyrus (opercular); SFGmed: superior frontal gyrus (medial); REC: rectus gyrus; INS: insula; IPG: inferior parietal gyrus; SMG: supramarginal gyrus; ANG: angular gyrus; ITG: inferior temporal gyrus; FFG: fusiform gyrus; LING: lingual gyrus; CAL: calcarine cortex; MOG: middle occipital gyrus; IOG: inferior occipital gyrus; L: left hemisphere; R: right hemisphere.

Table 1

Subject characteristics and cognitive test scores analyzed by one-way ANOVA

	Normal controls (n = 36)	High-risk subjects (n = 22)	Schizophrenia Patients (n = 21)	F	p
Age	22.9±5.4	21.4±5.3	36.7±9.3	46.8	0.000
Male/Female	17/19	8/14	13/8	Chi-sq=9.7	0.093
L/R Handed	2/34	3/19	2/19	--	--
Education(years)	14.2±2.21	12.6±2.75	14.5±2.20	0.815	0.606
Racial composition	21 C ^a , 15 N ^c	15 C ^a , 7 N ^c	17 C ^a , 4 N ^c	Chi-sq=3.1	0.09
WAIS-VCI	107.9±17.5	105.9±12.8	108.6±15.0	0.168	0.846
PPVT-III	102.9±13.6	101.5±12.9	102.5±16.6	0.7	0.932
WRAT	103.7±11.2	106.3±8.5	106.6±11.9	0.596	0.553

C^a: Caucasian; N^c: Non-Caucasian

Table 2

Node ROIs for functional brain network construction. Network hubs in groups of normal controls (NC), high-risk (HR) and patients (SCH) are labeled. (L.=left; R.=right)

Regions	Volume (mm ³) ^a	Peak MNI coordinates [x y z]			Z ^b	Degree	Between-centrality
L. Superior frontal gyrus (dorsal)	2496	-26	-8	56	3.77		
R. Superior frontal gyrus (dorsal)	2984	-28	-4	58	3.85		
L. Superior frontal gyrus (medial)	1176	-4	16	42	3.52		HR
R. Superior frontal gyrus (medial)	2505	4	26	46	3.39		NC, HR,
R. Orbitofrontal gyrus (superior)	1736	22	34	-24	3.44		
L. Middle frontal gyrus	10496	-38	38	26	3.51		
R. Middle frontal gyrus	9064	28	-4	56	3.67		NC,
L. Orbitofrontal gyrus (middle)	1176	-38	52	-10	2.66		
R. Orbitofrontal gyrus (middle)	992	22	36	-22	3.32		
L. Orbitofrontal gyrus (inferior)	6552	-36	24	-4	3.46		
R. Orbitofrontal gyrus (inferior)	3496	38	30	-2	3.01		
L. Inferior frontal gyrus (opercular)	3512	-44	10	2	4.8	NC, HR, SCH	NC
R. Inferior frontal gyrus (opercular)	7862	44	10	22	4.16		
L. Inferior frontal gyrus (triangular)	3592	-44	16	2	4.04	NC, HR, SCH	NC, HR, SCH
R. Inferior frontal gyrus (triangular)	7504	46	12	22	4.02		
R. Rectus gyrus	1040	16	26	-12	2.92	SCH	SCH
L. Precentral gyrus	14040	-46	8	30	5.12		
R. Precentral gyrus	6400	48	10	30	3.75		
L. Supplementary motor area	7056	-6	4	46	5.17		
R. Supplementary motor area	4344	4	8	58	4.38		
L. Postcentral gyrus	8536	-38	-32	40	4.89		
R. Postcentral gyrus	2088	48	-30	44	3.2		
R. Anterior cingulate gyrus	480	8	6	28	3.27		
L. Middle cingulate gyrus	2408	-6	4	44	4.98		
R. Middle cingulate gyrus	4688	12	22	40	3.74		
L. Superior parietal gyrus	3072	-24	-62	50	5.26		

Regions	Volume (mm ³) ^a	Peak MNI coordinates [x y z]			Z ^b	Degree	Between-centrality
L. Inferior parietal gyrus	8536	-40	-32	40	5.03		
R. Inferior parietal gyrus	1008	32	-54	46	3.86		HR,
L. Angular gyrus	1432	-32	-60	32	3.36		
R. Angular gyrus	2496	28	-62	44	4.15		HR,
L. Supramarginal gyrus	944	-54	-24	42	3.65		SCH
R. Supramarginal gyrus	1152	50	-30	44	3.08		
L. Middle temporal gyrus	2024	-42	-64	-4	4.94		
R. Middle temporal gyrus	3168	44	-62	-4	3.25		
L. Inferior temporal gyrus	6576	-42	-64	-10	5.79	NC, SCH	NC,
R. Inferior temporal gyrus	6392	48	-60	-18	4.6		SCH
L. Temporal pole (superior)	336	-50	10	-8	3.08		
L. Fusiform gyrus	7554	-42	-66	-14	5.97	SCH	SCH
R. Fusiform gyrus	6152	40	-68	-18	4.87	NC,	NC,
L. Superior occipital gyrus	896	-26	-70	36	4.21		
R. Superior occipital gyrus	1504	24	-98	4	4.06		
L. Middle occipital gyrus	5264	-26	-94	-4	6.3		
R. Middle occipital gyrus	4216	28	-96	0	5.55	NC, HR,	NC, HR, SCH
L. Inferior occipital gyrus	5856	-28	-94	-6	6.58		
R. Inferior occipital gyrus	7546	24	-96	-4	6.13	NC,	SCH
L. Lingual gyrus	1848	-28	-94	-14	5.68		HR,
R. Lingual gyrus	3280	22	-94	-8	5.58	NC, SCH	NC, SCH
L. Calcarine cortex	1360	-18	-99	-6	5.53		HR,
R. Calcarine cortex	2112	22	-98	-4	5.53	NC, SCH	
L. Parahippocampal cortex	496	-20	-18	-20	2.65		
L. Insula	5608	-46	8	2	4.68	NC, HR, SCH	
R. Insula	4376	34	24	2	4.33		
L. Rolandic operculum	2504	-48	8	2	4.4		
R. Rolandic operculum	728	46	8	14	2.93		
L. Caudate	952	-18	-14	20	2.67		

Regions	Volume (mm ³) ^a	Peak MNI coordinates [x y z]			Z ^b	Degree	Between-centrality
R. Caudate	4104	20	-16	24	3.37		
L. Putamen	1984	-32	-12	-6	3.0		
R. Putamen	3136	26	20	6	3.14		
L. Pallidum	168	-26	-14	-4	2.45		
L. Thalamus	5024	-16	-18	4	3.3		
R. Thalamus	3504	22	-20	12	3.02		
L. Amygdala	504	-28	-6	-18	2.44		
L. Hippocampus	3088	-20	-14	-18	3.53		
R. Hippocampus	1888	28	-36	6	2.99		

^a_i is the number of activated voxels × 27mm³; the ROIs were R=5 spheres with origins located at the peak Coordinates;
^b_i is the z value of the peak.