Probe into Abnormality of Brain Gray Matter Volumes in Schizophrenia Patients and Their Healthy Siblings

Chang Liu[1*], Zhiming Xue[2], Weidan Pu[3]

[1] Brains Hospital of Hunan Province, Changsha, Hunan, China; [2] Mental Health Institute, Second Xiangya Hospital, Central South University, Changsha 410011, China; [3] Medical Psychological Institute, Second Xiangya Hospital, Central South University, Changsha 410011, China.

Correspondance: Chang Liu. Email: liuchang19861121@163.com

ABSTRACT

Objective: To investigate the difference of gray matter volume among schizophrenia patients, unaffected siblings and healthy controls, and explore possible neurophysiological endophenotypes for schizophrenia.

Methods: 27 schizophrenia patients, 26 unaffected siblings, and 27 healthy controls were scanned using three-dimensional structural magnetic resonance imaging. The voxel-based morphometry (VBM) was used to investigate the gray matter volume in three groups.

Results: Compared to healthy controls, unaffected siblings of schizophrenia showed significantly increased gray matter in the left middle occipital gyrus, precuneus, and right thalamus; while patients with schizophrenia had significantly decreased gray matter in the left middle temporal gyrus, superior frontal gyrus, and bilateral inferior temporal gyrus, and increased gray matter in the right thalamus. Furthermore, schizophrenia showed gray matter decreases in the left superior frontal gyrus and bilateral inferior temporal gyrus compared to unaffected siblings. In addition, there was a significantly negative correlation between the level of decreased gray matter in the left superior frontal gyrus and the total PANSS score and positive syndrome score.

Conclusion: The regions of reduced gray matter volume that were observed in unaffected siblings may reflect a compensatory role in providing resilience to schizophrenia, while the specific gray matter abnormalities for patient may be related to the illness itself.

Key Words: Schizophrenia; Sibling; Gray Matter Volume

ISSN:2397-9119

OPEN ACCESS

DOI: 10.20900/mo.20160013

Received: March 15, 2016

Accepted: May 18, 2016

Published: June 25, 2016

website:http://mo.qingres.com

Copyright: ©2016 Cain et al. This is an open access article distributed under the terms of the Creative Commons Attribution License,which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing Interests: The authors have declared that no competing interests exist.

INTRODUCTION

Schizophrenia usually occurs in young adult aged 18-25 years. It is a chronic mental illness characterized by the disorder of thinking, emotion and behavior and the incompliance with its internal and external environment. It is also considered as a functional mental illness because of no organic change. However, people have realized the change of studying the brain structure in the living organisms with the development of neuroimaging technology, which can further investigate the change of brain nerve system of the schizophrenia patients. After nearly 20 years' researches and exploration, the results

of neuroimaging studies confirm that the schizophrenia is not a purely functional disease. The results of brain structure imaging studies further confirm that there exists a difference of morphology and brain structure in the schizophrenia patients. The more direct evidences involving the abnormal brain structure of schizophrenia patients were originated from the voxel-based morphology comparative studies. These studies all showed the reduced gray matter volumes of prefrontal lobe, superior temporal gyrus, hippocampus, and amygdala in the brain of schizophrenia patients, as well as the enlargement of lateral ventricles and the third ventricle.(1,2) Moreover, the previous studies also confirmed that the gray matter loss of prefrontal cortex and superior temporal gyrus cortex existed for patients with first-episode schizophrenia or chronic schizophrenia. (3) The different neuropathology changes in the brain of schizophrenia patients were also found in a lot of autopsy studies, including cortical atrophy, enlarged ventricles, reduced amygdala and hippocampus volumes, structural disorder, hypothalamic cell loss, and volume reduction.

Schizophrenia is commonly considered as a neurodevelopmental mental illness.(4) Such an abnormal neurodevelopment is thought to occur during the process of trimming and correcting the synapses and regulating the neurogenesis in the individual adolescence and early adulthood, which may expose the problems previously hidden and caused by genetics, environment, or interactions so as to result in the schizophrenia. (5) The schizophrenia showed the neurodevelopment defects, so the abnormal brain structure might exist in the healthy groups who have the common genetic background and living environment with the schizophrenia patients. About 50% alleles are the same between the schizophrenia patients and their unaffected siblings (brothers or sisters). After excluding the interference of confounding factors from the incidence (e.g. biological change of patients caused by antipsychotic drugs, chronic disease course, and anxiety and depression from incidence as well as potential neurotoxic effects of mental disease), the more and more studies of healthy siblings of the schizophrenia patients showed also the loss of brain gray matter in the brain of the unaffected siblings of the schizophrenia patients. (6,7) These studies showed that the pathological change of brain structure had existed before the emergence of psychiatric symptoms. However, up to date, these studies have still not revealed the abnormal brain structure of unaffected siblings of schizophrenia patients, and it is even more seldom in China. In this study, the cross-sectional comparison of early schizophrenia patients, unaffected siblings (healthy siblings who have the same parents with the included patients) and healthy volunteers was made using the voxel-based morphology analysis to explore the abnormality of brain gray matter in unaffected siblings (relative to normal control). It aims to discuss that the abnormality of gray matter volume in which brain area is related to the genetic susceptibility of schizophrenia, the abnormality of gray matter volume in which brain area may be the characteristics of the diseases. However, the abnormality of gray matter volume in which brain area might be associated with the compensatory protective effect of healthy siblings on the brain area gray matter abnormality related to its genetic susceptibility.

SUBJECTS AND METHODS

1. Subjects

1.1 Schizophrenic Patients (SCZ) The MRI data and general clinical information of 27 schizophrenia patients were collected in this study. All schizophrenia patients were the inpatients and outpatients from Department of Psychiatry, the Second Xiangya Hospital of Central South University from September 2010 to September 2013. All schizophrenia subjects were assessed with Structured Clinical Interview for DSM-IV (Patient version, SCID-I/P) of the Diagnostic and Statistical Manual of Mental Disorders (8). Inclusion criteria included i) comply with the diagnosis criteria of schizophrenia in DSM-IV, ii) more than one unaffected sibling for each patient who shall be the brothers or sisters of the same parents, iii)18-45 years old and disease course <5 years, iv) Han Nationality, dextromanuality, v) no history of nerve system disease or major physical disease, vi) no history of alcohol or substance abuse or reliance, vii) no history of electric shock treatment, viii) no use of any medication within six hours before the imaging scanning, ix) no contraindication against the MRI tests and no brain abnormalities after the scanning test of MRI, and x) understand the research contents, hope to participate in and be able to complete the whole experiment, and sign the Informed Consent.

1.2 Healthy Siblings (SIB) Twenty six healthy siblings were collected in this study and they were all the brothers or sisters of the same parents with the schizophrenia. The inclusion criteria of the healthy siblings are identical to that of the schizophrenia patients in addition to the incompliance with the diagnosis criteria of DSM-IV schizophrenia. The axis I disorders of all healthy siblings was excluded using SCID-NP.

1.3 Healthy Controls (HC) Twenty seven healthy controls were collected in this study and they were

voluntarily enrolled through the public recruitment and they were all from communities in Changsha and surrounding regions. In addition to the compliance with the said inclusion criteria including items iii) – x), all healthy controls must have no history of mental disease, neurological and psychotic disorders or family disease, severe physical disease and drug abuse and they must not experience any major psychological trauma, and their first-degree relatives have no history of mental disorders. The axis I disorder of all healthy controls was excluded using SCID-NP; the family history of mental diseases of first-degree relatives was excluded with Family History Research Diagnostic Criteria (FHRDC). All subjects (Ss) were informed of the risks and gains before the tests and they signed the informed consent. This study was approved by Medical Research Ethics Committee of the Second Xiangya Hospital of Central South University.

2. Methods

2.1 Acquisition of Structural MRI Data The structural MRI imaging data were acquired in the MRI room of the Second Xiangya Hospital of Central South University by an experienced professional technical staff of the radiology department. Signa Twinspeed 1.5T dual-gradient magnetic resonance imaging system (General Electric, Fair field, Connecticut, USA) of the General Electric Corporation was used to complete the scanning in the standardized head coil. No cognitive task was added during the scanning. The subject lied on his/her back and closed eyes, the subject was instructed to keep the whole body motionless, and try not to think about any particular person or thing. The supportive earplug was used to isolate from the ambient noise, and the supportive foam pad was used to limit the movement of the head. Scanning parameters included repetition time TR (12 ms), echo time TE (4.2 ms), flip angle (15 degrees), field of view (24×24 cm), matrix (512×512), slice thickness (1.8 mm), gap (0 mm), and 170 slices.

2.2 Acquisition of Clinical Data The old field inventory was used to assess the handedness of all subjects. Demography and clinical basic data of the subjects contained age, gender, and educational level. The psychiatric syndrome and severity of the schizophrenia patients were assessed using the Positive and Negative Syndrome Scale (PANSS) (9). This PANSS was used to mainly assess the positive syndrome, negative syndrome and general psychiatric syndrome of the subjects to obtain the total score and factor scores, e.g. Points P, N and G, and record the diagnosis and disease course of the patients. The disease course of the schizophrenia patients averaged 18.32 ± 15.84 months; of which, disease course of 23 patients was < 2 years, disease course of 3 patients was < 3 years, disease course of one patient was < 5 years, which all belonged to the early onset. There were 15 patients who were not administered, 6 patients were taking the Risperidone (2-5 mg), 1 patient was taking the clozapine (200 mg), 3 patients were taking the quetiapine (400-600), and 2 patients were taking the Sulpiride (100-300 mg).

2.3 Processing and Analysis of Structural MRI Data The structural MRI data were analyzed with software MATLAB 7.8 & SPM8 (http://www.fil.ion.ucl.ac.uk/spm) in this study. The structural MRI data were pre-processed with sub-toolkit VBM8 of the SPM8, mainly including standardization, partitioning, adjustment and translation, and other steps, to obtain the calibrated images of brain gray matter and white matter, which represent the brain gray matter volume and white matter volume, respectively. The specific steps were: i) the original T1 images of all subjects were subjected to the Montreal Space Standardization, ii) The standardized brain structural images were partitioned into three portions, including gray matter (GM), white matter (WM) ,and cerebrospinal fluid (CSF), iii) fabricate the average gray matter template of all subjects with DDARTEL, iv) the partitioned brain images of all subjects were standardized, with the voxel size of 1.5×1.5×1.5 mm^3, and v) isotropic 8 mm (full-width at half-maximum, FWHM) Gaussian kernel was used to translate the images of the three groups to obtain the high signal-noise ratio and reduce the individual difference. The translated images were subjected to the comparison of gray matter volumes.

2.4 Statistical Analysis The statistical analysis of structural MRI data was carried out with software package SPM8. The one-way analysis of covariance (ANCOVA) was used to compare and count up the significant difference of gray matter volumes among schizophrenia patients, healthy siblings, and healthy controls. The threshold value of significant difference was set as $P<0.001$ (uncorrected). Then, the significant result was taken from the one-way ANCOVA as the mask, and the gray matter volumes of the samples of the three groups were compared with double-sample t test model, of which, the threshold value was set as $P<0.05$ (FWE correction). The difference of clinical variables between two groups or among three groups were compared with the double-sample t test model or one-way ANCOVA based on SPSS16.0. The correlation coefficient between gray matter volume and clinical variables was calculated with Pearson correlation analysis and the threshold value of significant difference ($P<0.05$).

RESULTS

1. Demographic Characteristics

The demographic data and clinical characteristics of schizophrenia patients, healthy siblings, and healthy controls are detailed in Table 1. No significant differences were found in gender, age and educational level among three groups.

Table 1 Demographic Data and Clinical Characteristics of Schizophrenia Patients, Healthy Siblings, and Healthy Controls (Mean ± SD)

Variable	Schizophrenia Patients(n=27)	Healthy Siblings (n=26)	Healthy Controls (n=27)	Statistical Analysis	
				F/χ2	P
Age (year)	25.44 ± 5.92	25.56 ± 6.44	27.44 ± 7.24	0.793	0.696
Educational years(Year)	12.30 ± 2.73	12.70 ± 2.73	12.96 ± 3.39	0.365	0.456
Gender(Male/female)	15/12	16/11	18/9	0.713	0.700
Disease Course (month)	18.32 ± 15.84	-	-		
Total score (PANSS)	85.78 ± 12.80	-	-		
Total positive score (PANSS)	21.56 ± 4.92	-	-		
Total negative score(PANSS)	23.15 ± 5.75	-	-		
Total score for general mental disease (PNASS)	41.30 ± 6.38	-	-		

Table 2 Brain Areas with Difference of Brain Gray Matter Volumes for Three Groups showed in ANCOVA

Brain Area	Voxel number	MNI Coordinate			Statistical Analysis		Effect Size
		X	Y	Z	F	PFWE,corrected	Cohen's d
Middle Temporal Gyrus	296	-50	-10	-23	12.59	0.346	1.24
Superior Temporal Gyrus	39	-23	-4	58	10.36	0.870	1.03
Inferior temporal gyrus	39	50	-46	-23	9.44	0.958	1.18
Mid-occipital gyri	89	-56	-54	-11	10.36	0.828	1.45
Thalamus	50	18	-18	15	8.76	0.993	

Note: MNI refers to the 3D coordinate positioning system of human brain developed by Montreal Neurological Institute (MNI), of which, the coordinate zero is located in the center of the brain, Axis x represents left/right direction and its value is from negative value to positive value and means the direction from the leftmost to rightmost of the human brain. Axis y represents the front/rear direction and its value is from negative value to positive value and means the direction from the most significant end to the rearmost end of human brain. Axis z represents up/down direction, and its value is from negative value to positive value and means the direction from the top end to the lowest end of the human brain; and the

same below.

2. Comparison of Whole Brain Gray Matter Volumes

The one-way ANCOVA results showed that the brain areas with difference of gray matter volumes were mainly distributed in bilateral inferior temporal gyrus, right thalamus, and left superior temporal gyrus (uncorrected, Table 2). Post-hoc comparison results showed that the gray matter volume in bilateral inferior temporal gyrus, left superior temporal gyrus, and left middle temporal gyrus of the schizophrenia patients reduced and the gray matter volume in right thalamus increased (Table 3, attached figure) compared to healthy controls; the gray matter volume in left middle temporal gyrus, left precuneus and right thalamus of healthy siblings increased (Table 4, attached figure) relative to the schizophrenia patients. The gray matter volume in left superior temporal gyrus and bilateral inferior temporal gyrus of schizophrenia patients reduced (Table 5, attached figure) relative to the healthy siblings.

Table 3 Comparison Result of Gray Matter Volumes between Schizophrenia Patients and Healthy Controls

Brain Area	Voxel Number	MNI Coordinate			Statistical Analysis		Effect Size
		X	Y	Z	t	P	Cohen's d
Healthy Control> Schizophrenia Patients							
Middle Temporal Gyrus	296	-50	-10	-23	4.85	0.000384	1.24
Superior Temporal Gyrus	11	-21	-4	58	3.68	0.013	1.03
Inferior Temporal Gyrus	10	50	-43	-24	3.64	0.014	1.18
Inferior Temporal Gyrus	14	-56	-54	-11	3.58	0.017	1.45
Healthy Controls <Schizophrenia Patients							
Thalamus	50	20	-21	16	3.94	0.06	2.31

Table 4 Comparison Result of Gray Matter Volumes between Schizophrenia Healthy Siblings and Healthy Controls

Brain Area	Voxel Number	MNI Coordinate			Statistical Analysis		Effect Size
		X	Y	Z	t	PFWE,corrected	Cohen's d
Healthy Controls < Healthy Siblings							
Middle Temporal Gyrus	89	-24	-81	39	4.31	0.002	1.24
Thalamus	41	17	-19	15	4.17	0.003	1.03
Precuneus	22	-17	-63	39	4.11	0.004	1.18

Table 5 Comparison Result of Gray Matter Volumes between Schizophrenia Patients and Healthy Siblings

Brain Area	Voxel Number	MNI Coordinate			Statistical Analysis		Effect Size
		X	Y	Z	t	PFWE,corrected	Cohen's d
Schizophrenia Patients< Healthy Siblings							
Middle Temporal Gyrus	39	-24	-6	60	4.35	0.002	1.24
Thalamus	39	50	-46	-23	4.15	0.003	1.03
Precuneus	14	-56	-54	-9	4.15	0.003	1.18

Notes: The left half portion in the figure represents three brain areas with the difference of gray matter volumes between healthy siblings and healthy controls: 1 represents the lateral middle temporal gyrus, 2 represents the left praecuneus, and 3 represents the right thalamus. The right half portion in the figure represents 5 brain areas with the difference of gray matter volumes between schizophrenia patients and healthy controls: 1 represents the left middle temporal gyrus, 2 represents the left inferior temporal gyrus, 3 represents the right inferior temporal gyrus, 4 represents the left superior temporal gyrus and 5 represents the right thalamus. Attached Figure Brain Area with Difference of Gray Matter Volumes among Schizophrenia Patients and Healthy Siblings and Healthy Controls.

3 Correlation Analysis

The correlation analyses of schizophrenia group showed that the gray matter volume of left superior temporal gyrus was significantly negatively correlated with PANSS total score ($r=-8.99$, $P<0.05$) and P total score ($r=-3.54$, $P<0.05$).

DISCUSSION

1. Abnormal Brain Gray Matter Volume of Schizophrenia Patients

The studies showed that the gray matter volume in left superior temporal gyrus, bilateral inferior temporal gyrus and left middle temporal gyrus of schizophrenia patients reduced relative to that of healthy controls. The loss of gray matter volumes in these brain areas indicates that the reduction of gray matter volume of schizophrenia patients mainly occurs in brain area of front temporal lobe, which is consistent with the previous study results. The loss of gray matter volumes exists for both acute or chronic schizophrenia patients and it mainly presents in temporal lobe and frontal lobe. (7,10,11) In particular, the meta analysis result of a structural MRI study showed that the reduction of gray matter volumes existed in many brain areas in the schizophrenia patients, mainly including superior temporal gyrus, inferior temporal gyrus, middle temporal gyrus, anterior cingulated, medial temporal lobe, insular cortex, hippocampus, and parahippocampal gyrus. (10) In addition, the studies on brain structural MRI of first-attacked schizophrenia patients have confirmed that the left middle temporal gyrus might be an early biological marker of schizophrenia,(12) and the relatively consistent brain imaging evidences have proven that the abnormalities of structure (6) and function (13,14) of middle temporal gyrus are existed in schizophrenia patients. The left middle temporal gyrus is mainly responsible for processing of language(15) and concept and the forming of thinking(16). Some studies have confirmed that the inferior temporal gyrus has played an important role in the pathogenesis of the schizophrenia. The related analyses also show that the reduction of gray matter volumes in inferior temporal gyrus is significantly related to the psychotic syndrome severity of schizophrenia, e.g. the severity of positive syndrome. The most common syndromes of schizophrenia include auditory hallucinations, delusion and thinking disorder. The structural MRI studies comparatively have showed the reduction of gray matter volume in the middle temporal gyrus of schizophrenia patients and a recent morphological study has confirmed that the reduction of gray matter volume in middle temporal gyrus of schizophrenia patients is significantly related to the severity of its thinking disorder. In the functional MRI tests of schizophrenia patients, the excessive metabolism occurred in the left temporal lobe of schizophrenia, and it was associated with the severity of its reality distortion symptom (hallucinations and delusions). (17) At the same time, task-related fMRI studies showed the reduction of functional connection of temporal lobe and frontal cortex of schizophrenia

patients and it was associated with its auditory hallucinations.(18) Furthermore, a recent fMRI study for use of language fluency task also shows that the abnormal activation is presented in the middle temporal gyrus of schizophrenia and it is significantly related to the severity of its thinking disorder.(13) Thus, the positive syndrome of schizophrenia patients is associated with the morphologic and functional abnormalities of its temporal lobe and frontal lobe. Both the brain structure study and brain function study have suggested that the middle temporal gyrus may be involved in the neuropathological change of schizophrenia. Therefore, the damage of gray matter volume in middle temporal gyrus may be the important pathologic basis to understand the positive syndrome of schizophrenia patients.

In addition, this study shows the enlargement of gray matter volume of right thalamus apart from the reduction of gray matter volume in left superior temporal gyrus, bilateral inferior temporal gyrus and left middle temporal gyrus in the schizophrenia patients. This study result is inconsistent with the previous study results. After summarizing the brain structural MRI study results of schizophrenia patients using VBM approach, it is found that the schizophrenia-related structural MRI studies in the past mostly reported that the thalamus gray matter volume of schizophrenia patients was significantly lower than that of the healthy controls,(19,20) but there were also the studies related to the reports of the enlargement of thalamus gray matter volume.(21) Such a result may be associated with the heterogeneity of patient samples in this study, for example, the use condition of antipsychotics. There are some points that shall be further explained. In some studies, after the comparison of the abnormalities of gray matter volumes between the administered schizophrenia patients and non-administered patients,(21) the results have showed the decrease of thalamus volume in the first-attacked schizophrenia patients and the enlargement of thalamus volume in the administered schizophrenia patients. In this study, 2/3 patients took the antipsychotic medications, which may be considered that the antipsychotic medications to certain extent lead to the enlargement of brain volume of schizophrenia patients.

2. Abnormality of Brain Gray Matter Volume of Healthy Siblings

Interestingly, there only exists the brain area with the enlarged gray matter volume in left middle temporal gyrus, left precuneus and right thalamus in schizophrenia patients and healthy siblings and no brain area with decreased gray matter volume is found. The structural MRI results of schizophrenia-related unaffected siblings in the past mostly reported that the gray matter volume of schizophrenia patients was significantly lower than that of the healthy controls, but there were also the reports relating to the enlargement of gray matter volume.(7,22) The reasons why such a result may be that most of the healthy siblings included in the past studies are at the age for high incidence of schizophrenia (18-25 years old), with a higher genetic susceptibility. The damage of their brain gray matter similar to schizophrenia is basically the same, which mainly reflects in the decrease of gray matter volume in important brain areas, including frontal lobe, temporal lobe, anterior cingulate, insular cortex and hippocampus; the ages of healthy siblings in this study have all exceeded the high-incidence period of schizophrenia (average age: 25.56 ± 6.44 years old). Compared to the normal controls, the morphologic abnormalities reflected by them are the enlargement of gray matter volumes of brain areas, including mainly left middle temporal gyrus, left precuneus, and right thalamus. Similarly, the functional MRI studies of healthy siblings who are beyond the high-incidence period of schizophrenia showed (23) that they represent the enhancement of functional connection with the brain areas related to the onset of schizophrenia. However, the previous study reports showed that schizophrenia patients and their healthy siblings who are at the schizophrenia high-incidence period mostly showed the reduction of functional connections of these brain areas. The results of a follow-up study suggest (24): it is identical to the gray matter loss of schizophrenia, namely, there also exists the corresponding dynamic change process in the unaffected siblings. This mainly reflects in the gradual normalization of gray matter volumes of cerebral cortex areas in the unaffected siblings in their adulthood. In the high-incidence period, these areas however represent the loss of brain gray matter volumes similar to the schizophrenia. More interestingly, these brain areas are mostly located at the left side, which is relatively consistent with the “lateralization” abnormality of the schizophrenia. The researchers speculate (25) that the dynamic process of “changing abnormality of gray matter volume into normality” can be deemed as a compensation-related change, and the abnormality of gray matter volume emerged in the high-incidence period, however, may only be a kind of state-dependent change. At present, a growing number of researchers believe that the schizophrenia is a neurodevelopmental disorder. The emergence of psychiatric symptoms is mainly associated with the prefrontal cortex excitatory-inhibitory balance disorder resulted from excessive trimming of asymmetric synapses of schizophrenia patients and the decreased precision of inhibitory pathway, and the trimming of nerve branches is considered to be the main reasons for decrease of gray matter. The high-risk incidence period of schizophrenia is consistent with the development period of the important senior cognitive brain area as well as the brain area related to cortical connection. In this period, the schizophrenia patients may easily lead to the onset of

psychiatric symptoms due to the neurodevelopmental disorders and the healthy siblings at the high-risk age bracket of schizophrenia however are subject to brain structure change similar to the schizophrenia. Beyond this high-risk age bracket, the enlargement of gray matter volume of healthy siblings might play the important role of compensatory protection in exempting the healthy siblings from the diseases.

Funding: National Natural Science Fund of China (program numbers: 81401125, 81171287)

REFERENCES

1. Glahn DC, Laird AR, Ellison-Wright I, et al. Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. Biological Psychiatry, 2008, 64(9): 774-781
2. Fornito A, Yücel M, Patti J, et al. Mapping grey matter re-ductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. Schizophrenia Research, 2009, 108(1): 104-113
3. Glahn DC, Laird AR, Thelen SM, Bullmore E. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. The American Journal of Psychiatry, 2008, 165(8): 1015-1023
4. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Archives of General Psychiatry, 1987, 44(7): 660-669
5. Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophrenia Bulletin, 2009.sbn187
6. Hu M, Li J, Eyler L, et al. Decreased left middle temporal·211·Chinese Journal of Clinical Psychology Vol.24 No.2 2016 gyrus volume in antipsychotic drug- naive, first episode schizophrenia patients and their healthy unaffected siblings. Schizophrenia Research, 2013, 144(1): 37-42
7. Honea RA, Meyer-Lindenberg A, Hobbs KB, et al. Is gray matter volume an intermediate phenotype for schizophrenia? A voxel-based morphometry study of patients with schizophrenia and their healthy siblings. Biological Psychiatry,2008, 63(5): 465-474
8. First M, Gibbon M, Spitzer RL, Williams J. User's guide for the structured clinical interview for DSM-IV axis I Disorders—Research version. New York: Biometrics Research Department, New York State Psychiatric Institute, 1996
9. Kay SR, Flszbein A, Opfer LA. The positive and negative syndrome scale(PANSS) for schizophrenia. Schizophrenia Bulletin, 1987, 13(2): 261
10. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. American Journal of Psychiatry, 2014
11. Onitsuka T, Shenton ME, Salisbury DF, et al. Middle and in ferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. American Journal of Psychiatry, 2014
12. Kuroki N, Shenton ME, Salisbury DF, et al. Middle and inferior temporal gyrus gray matter volume abnormalities in first episode schizophrenia: an MRI study. The American Journal of Psychiatry, 2006, 163(12): 2103-2110
13. Li X, Branch CA, Nierenberg J, DeLisi LE. Disturbed functional connectivity of cortical activation during semantic disrimination in patients with schizophrenia and subjects at genetic high-risk. Brain Imaging and Behavior, 2010, 4(1): 109-120
14. Yu R, Chien YL, Wang HLS, et al. Frequency-specific alternations in the amplitude of low-frequency fluctuations inschizophrenia. Human Brain Mapping, 2014, 35(2): 627-637
15. Kiehl KA, Smith AM, Mendrek A, Forster BB, Hare RD, Liddle PF. Temporal lobe abnormalities in semantic processing by criminal psychopaths as revealed by functional magnetic resonance imaging. Psychiatry Research: Neuroimaging, 2004, 130(1): 27-42
16. Wei T, Liang X, He Y, et al. Predicting conceptual processing capacity from spontaneous neuronal activity of the left middle temporal gyrus. The Journal of Neuroscience, 2012,32(2): 481-489
17. Kaplan RD, Szechtman H, Franco S, et al. Three clinical syndromes of schizophrenia in untreated subjects: relation to brain glucose activity measured by position emission tomog-raphy(PET).

Schizophrenia Research, 1993, 11(1): 47-54

18. Lawrie SM, Buechel C, Whalley HC, et al. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. Biological Psychiatry, 2002, 51(12): 1008-1011
19. Portas CM, Goldstein JM, Shenton ME, et al. Volumetric evaluation of the thalamus in schizophrenic male patients using magnetic resonance imaging. Biological Psychiatry,1998, 43(9): 649-659
20. Csernansky JG, Schindler MK, Splinter NR, et al. Abnormalities of thalamic volume and shape in schizophrenia. American Journal of Psychiatry, 2014
21. Gur RE, Maany V, Mozley PD, et al. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. American Journal of Psychiatry, 1998, 155(12):1711-1717
22. Borgwardt SJ, Riecher-Rössler A, Dazzan P, et al. Regional gray matter volume abnormalities in the at risk mental state. Biological Psychiatry, 2007, 61(10): 1148-1156
23. Wang J, Cao H, Liao Y, et al. Three dysconnectivity patterns in treatment-resistant schizophrenia patients and their unaffected siblings. NeuroImage: Clinical, 2015, 8: 95-103
24. Gogtay N, Greenstein D, Lenane M, et al. Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. Archives of General Psychiatry,2007, 64(7): 772-78025
25. Gogtay N, Vyas NS, Testa R, Wood SJ, Pantelis C. Age of onset of schizophrenia: perspectives from structural neuroimaging studies. Schizophrenia Bulletin, 2011,37(3): 504-513