Schizophrenia Bulletin vol. 41 no. 1 pp. 201–210, 2015
doi:10.1093/schbul/sbt177
Advance Access publication December 18, 2013

Altered Cortical Thickness Related to Clinical Severity But Not the Untreated Disease Duration in Schizophrenia

Yuan Xiao[1,5], Su Lui[*,1], Wei Deng[2,5], Li Yao[1,5], Wenjing Zhang[1], Shiguang Li[1], Min Wu[1], Teng Xie[3], Yong He[3], Xiaoqi Huang[1], Junmei Hu[2], Feng Bi[4], Tao Li[2], and Qiyong Gong[1]

[1]Huaxi MR Research Center (HMRRC), Department of Radiology, The Center for Medical Imaging, West China Hospital of Sichuan University, 37 Guo Xuexiang, Chengdu, Sichuan, China; [2]Department of Psychiatry, West China Hospital of Sichuan University, Chengdu, Sichuan, China; [3]State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China; [4]Department of Oncology, West China Hospital of Sichuan University, Chengdu, Sichuan, China

[5]These authors contributed equally to the article.

*To whom correspondence should be addressed; Huaxi MR Research Center (HMRRC), Department of Radiology, The Center for Medical Imaging, West China Hospital of Sichuan University, 37 Guo Xuexiang, Chengdu, Sichuan, China. tel: +86-28-85423960, fax: +86-28-85423503, e-mail: lusuwcums@tom.com

Although previous studies have reported deficits in the gray matter volume of schizophrenic patients, it remains unclear whether these deficits occur at the onset of the disease, before treatment, and whether they are progressive over the duration of untreated disease. Furthermore, the gray matter volume represents the combinations of cortical thickness and surface area; these features are believed to be influenced by different genetic factors. However, cortical thickness and surface area in antipsychotic-naive first-episode schizophrenic patients have seldom been investigated. Here, the cortical thicknesses and surface areas of 128 antipsychotic-naive first-episode schizophrenic patients were compared with 128 healthy controls. The patients exhibited significantly lower cortical thickness, primarily in the bilateral prefrontal and parietal cortex, and increased thickness in the bilateral anterior temporal lobes, left medial orbitofrontal cortex, and left cuneus. Furthermore, decreased cortical thickness was related to positive schizophrenia symptoms but not to the severity of negative symptoms and the untreated disease duration. No significant difference of surface area was observed between the 2 groups. Thus, without the confounding factors of medication and illness progression, this study provides further evidence to support anatomical deficits in the prefrontal and parietal cortex early in course of the illness. The increased thicknesses of the bilateral anterior temporal lobes may represent a compensatory factor or may be an early-course neuronal pathology caused by preapoptotic osmotic changes or hypertrophy. Furthermore, these anatomical deficits are crucial to the pathogenesis of positive symptoms and relatively stable instead of progressing during the early stages of the disease.

Key words: schizophrenia/cortical thickness/first-episode/antipsychotic-naive/MRI

Introduction

Although schizophrenia is one of the leading worldwide causes of disability, the pathogenesis of the disease remains unclear. One hypothesis states that schizophrenia is caused by neurodevelopmental deficits. This hypothesis is supported by evidence including the early age of onset, some genetic deficits, and premorbid evidence that youth at high risk for schizophrenia are characterized by neurocognitive impairments[1,2] and similar but less extensive structural brain abnormalities to those observed in patients with schizophrenia.[3,4] In contrast, another hypothesis was put forth by Kraepelin, who described schizophrenia as a neuroprogressive disorder characterized by early-onset ("dementia praecox") and deteriorating processes.[5] This hypothesis is supported by many longitudinal studies that provide evidence of clinical deterioration and cerebral deficits over time, especially recently reported neuroimaging studies,[6–8] which have shown progressive changes in brain structure in schizophrenia beyond the effects of age. However, the progressive volume loss that is frequently found in these studies is affected by the use of antipsychotic medications,[9,10] the small sample size of both patient and healthy control samples,[11] as well as comorbidities and other secondary disease factors.[12] Specifically, antipsychotic medications may reduce the regional cerebral volume in the frontal, temporal, and parietal lobes in both animals[13,14] and humans.[10,15] Thus, studying antipsychotic-naive

first-episode schizophrenia is crucial as a starting point for evaluating the progression of disease-related changes in the brain and for assessing brain anatomy and function before they can be influenced by potentially confounding factors. It may also help clarify the brain regions in which functional and anatomical changes are observed at disease onset to provide important, novel information that is relevant to models of pathogenesis.[16]

Most of the previous neuroimaging studies have examined gray matter volume in schizophrenic patients.[17,18] Gray matter volume, however, is a product of cortical thickness and surface area; these features are believed to be influenced by different genetic factors related to sulcal or gyral patterning and the thickness of cortical mantle itself.[19] Surface area mainly represents the number of columns within a cortical region,[20] whereas cortical thickness reflects the size, density, and arrangement of neurons, neuroglia, and nerve fibres[21,22] in the cortical columns. Disturbances in neurogenesis, neuronal migration, differentiation, and synaptogenesis have been found in schizophrenia[23,24]; these deficits may affect the arrangement of the cortical laminae and cause morphological changes in the cortical thickness.[25] Furthermore, from a methodological perspective, cortical thickness is measured using a surface-based method rather than volumetric techniques; although volume can be directly measured, partial volume effects must be considered.[26] Thus, measurements of cortical thickness may be more sensitive than volume to provide important and relatively unique information about disease-specific neuroanatomical changes in schizophrenia. However, unlike gray matter volume, cortical thickness in first-episode antipsychotic-naive schizophrenia has seldom been investigated. Several neuroimaging studies have demonstrated significant cortical thinning, primarily in the frontal and temporal regions in both chronic[9,27] and first-episode schizophrenic patients,[22,25] and even in the unaffected first-degree relatives of schizophrenic patient[28,29] although the results are inconsistent. Van Haren et al. found decreased cortical thickness to be related to outcome and medication as well as progressive over time.[9] However, in a recent study, Wheeler et al. found reduced thickness in the bilateral dorsolateral prefrontal cortex in both chronic and first-episode schizophrenic patients, suggesting a structural impairment in schizophrenia that is independent of illness stage or medication exposure.[30] In a recent study of 19 first-episode drug-naive schizophrenic patients, Goghari and her colleagues found an increase in rostral middle frontal thickness in patients after 4- and 8-week atypical antipsychotic treatment.[31] Negative results have also been reported in another study of first-episode schizophrenia.[32] Other than the effects of antipsychotic medication and disease progression, small effect sizes compared with large interindividual differences in smaller samples may contribute to the discrepancies among studies. Another important factor that may contribute to the inconsistent findings is the different proportion of patients with prominent negative symptoms across studies. This is important because these patients have different clinical manifestations and a diminished treatment response.[33,34] Furthermore, different deficits in gray matter volume have been observed between patients with and without prominent negative symptoms.[35]

Thus, this study aimed to investigate differences of cortical thickness and surface area in a large sample of 128 first-episode drug-naive schizophrenic patients and 128 healthy controls. We hypothesized that (1) regional reductions in cortical thickness and surface area would be observed in the early stages of schizophrenia and (2) changes in cortical thickness and surface area would be related to clinical severity and the duration of untreated disease and may be different between patients with and without prominent negative symptoms.

Methods

Participants

One hundred twenty-eight antipsychotic-naive first-episode schizophrenic patients (78 females, mean age 24.3 ± 8.1 years) and 128 healthy controls (65 females, mean age 26.1 ± 8.3 years) were recruited via the Mental Health Centre of West China Hospital, which is the largest hospital in China. The study was approved by the ethics committee of West China Hospital, and written informed consent was obtained from all subjects before participation. Diagnosis of schizophrenia and the duration of untreated disease were determined by consensus between 2 experienced psychiatrists (W.D. and X.H.) using the Structured Clinical Interview for DSM-IV (SCID)-Patient Version. In addition, diagnoses for all the patients were confirmed after ≥1-year follow-up. The Positive and Negative Syndrome Scale (PANSS) score for 1 patient and the disease courses of 10 patients were unavailable at the time of examination due to the severity of the disease in these patients. Healthy controls were recruited from the local area through poster advertisements and screened using the SCID-Non-Patient Version to confirm the lifetime absence of psychiatric and neurological illness. Additionally, healthy subjects were interviewed to confirm that there was no history of psychiatric illness among their first-degree relatives. Exclusion criteria for both groups were (1) the existence of a neurological disorder or other psychiatric disorders; (2) alcohol or drug abuse (DSM-IV); (3) pregnancy; and (4) any chronic physical illness such as a brain tumor, hepatitis, or epilepsy, as assessed by clinical evaluations and medical records. Magnetic resonance (MR) images were firstly inspected by an experienced neuroradiologist (S.L.) after MR examination to check image quality and exclude possible gross cerebral abnormalities in either group. The psychosocial functioning of patients was assessed using the Global Assessment of Functioning

Scale (GAF).[36] The PANSS,[37] which determines positive and negative symptom scores, a total score and general psychopathology symptoms, as well as indices of thought disturbance, activation, paranoid, depression, anergia, and impulsive aggression,[37] was also completed to evaluate the current clinical symptoms of patients. Demographic information of age, gender, handedness, educational years, and clinical data were acquired by 2 experienced clinical psychiatrists (W.D. and X.H.) prior to MR scans. All participants were right-handed as assessed using the Annett Handedness Scale.[38] Demographic and clinical characteristics of all participants are shown in table 1. No significant differences in age, gender, and educational years were found between the 2 groups at the statistical threshold of $P < .05$.

MRI Data Acquisition

High-resolution T1-weighted images were acquired using a 3T MR imaging system (EXCITE, General Electric, Milwaukee) with a volumetric 3D Spoiled Gradient Recall (SPGR) sequence (TR = 8.5 ms, TE = 3.4 ms, Flip angle = 12°, slice thickness = 1 mm) using an 8-channel phase-array head coil. A field of view of $240 \times 240\,mm^2$ was used with an acquisition matrix comprising 256 readings of 128 phase-encoding steps, producing 156 contiguous coronal slices with slice thickness of 1.0 mm. The final matrix of T1-weighted images was automatically interpolated in plane to 512×512, which yields an in-plane resolution of $0.47 \times 0.47\,mm^2$.

Image Processing

We used the CIVET software (version 1.1.9, Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada) to extract cortical thickness and surface area measurements from T1-weighted MR images. The original images were first registered to stereotaxic space[39] using linear transformation,[40] whereas nonuniformity artefacts were corrected using the N3 algorithm.[41] The registered and corrected images were then automatically segmented into gray matter, white matter, cerebrospinal fluid, and background using an advanced neural net classifier.[42] The inner and outer gray matter surfaces, totaling 81 924 polygons (40 962 vertices in each hemisphere), were then automatically extracted from each MR volume using the constrained Laplacian-based automated segmentation with proximities algorithm.[43,44] Cortical thickness was thus defined as the distance between linked vertices of the inner and outer surfaces.[45] Finally, a

Table 1. Demographic and Clinical Characteristics of Antipsychotic-Naive First-Episode Schizophrenic Patients and Healthy Comparison Subjects

	Group				
	SCZ (N = 128)		HC (N = 128)		
Characteristic	Mean	SD	Mean	SD	P
Age (years)	24.26	8.07	26.13	8.35	.07
Education (years)	12.14	2.91	12.92	3.42	.06
Duration of illness (months)	11.49	22.01			
GAF scores	29.42	11.07			
PANSS scores					
Total	96.39	19.15			
Positive symptoms	25.34	6.14			
Negative symptoms	18.44	8.19			
General psychopathology symptoms	46.32	10.01			
Thought disturbance	14.11	3.88			
Activation	9.2	3.41			
Paranoid	10.37	2.87			
Depression	8.58	4.1			
Anergia	8.46	4.3			
Impulsive aggression	16.31	5.33			
	N	%	N	%	P
Gender					
Female	78	60.9	65	50.8	.102
Male	50	39.1	63	49.2	.102

Note: GAF, Global Assessment of Functioning Scale; HC, healthy control participants; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenic patients; SD, standard deviation.

20-mm smoothing kernel was applied to improve sensitivity.[46] These cortical thickness extracting approaches have been validated using both manual measurements[47] and simulation approaches.[45,48] Surface area was measured at the middle cortical surface, which lies at the geometric center between the inner and outer cortical surfaces and thus provides a relatively unbiased representation of sulcal versus gyral regions.[49,50] This gives the surface area of every vertex in the surface mesh, which can be summed to give the lobar surface areas.

Statistical Analysis

Differences in age and education levels between the 2 groups were assessed using 2-sample *t* tests, whereas gender differences were compared using the chi-squared test. A vertex-based 2-sample *t* test was used to investigate cortical thickness and surface area differences between the patient group and the healthy control group, with age and sex as covariates. Significance was set to $P < .05$ corrected for multiple comparisons using false discovery rate correction.

The averaged cortical thickness in regions with altered thickness was extracted and input into SPSS Statistics 17.0 software along with other clinical characteristics. Then, a Pearson correlation analysis was performed considering the averaged cortical thickness in regions with altered thickness, the scaled scores obtained on the PANSS and GAF, and the duration of untreated disease to reveal potential associations between anatomical deficits and clinical symptoms, psychosocial function, and the duration of untreated disease. The level of significance was set to $P < .05$. The averaged duration of untreated disease was 11.5 months (SD = 22.0; range from 0.03 to 144 months). For analysis of the effect of untreated disease duration, we divided the patients into 2 subgroups in terms of the disease course, ie, the shorter course subgroup (with untreated disease duration < 12 months: 81 cases) and the longer course subgroup (with untreated disease duration ≥ 12 months: 37 cases; 12–24 months: 13 cases; 24–36 months: 12 cases; 36–144 months: 12 cases). For analysis of the associations between cortical thickness and negative symptom severity, patients were divided into 2 subgroups: 44 patients with prominent negative symptoms (a score ≥ 20 on the negative symptom subscale of the PANSS[37,51]; 26 females, mean age 24.9 years) and 83 patients without prominent negative symptoms (a score < 20 on the negative symptom subscale of the PANSS; 51 females, mean age 24.0 years). Two-sample *t* tests were performed to explore the differences in cortical thickness between the patient subgroups.

Results

Changes in Patient Cortical Thickness and Surface Area

Compared with controls, patients exhibited significantly reduced cortical thickness, primarily in the right dorsolateral prefrontal cortex (DLPFC), left precentral gyrus, left orbitofrontal cortex (OFC), left inferior frontal gyrus pars triangularis, and right precentral and postcentral gyri ($P < .05$, corrected for multiple comparisons; figure 1, supplementary table 1). In addition, significant cortical thickening was found in the bilateral anterior temporal lobes, the left medial orbitofrontal cortex (med-OFC), and the left cuneus in patients compared with controls ($P < .05$, corrected for multiple comparisons; figure 1, supplementary table 1). No significant difference of surface area was found between the 2 groups.

Correlations Between Changes in Cortical Thickness and Clinical Symptoms

Within the patient group, the average cortical thickness of the regions with reduced cortical thickness, ie, the right DLPFC, bilateral precentral gyri, left OFC, and left inferior frontal gyrus pars triangularis, was negatively correlated with symptom severity, as identified by the PANSS scores. This was especially true for positive symptoms (figure 2), whereas the average cortical thickness within the regions with increased cortical thickness and the right postcentral gyrus was not correlated to the scale scores of PANSS or GAF. Subgroup analysis demonstrated that there was no significant difference in cortical thickness between patients with and without prominent negative symptoms ($P > .05$).

Relationship Between Cortical Thickness and the Duration of Untreated Disease

To investigate the potential effects of duration of untreated disease on cortical thickness, we used a Pearson correlation analysis to quantify the relationship between the duration of untreated disease and changes in cortical thickness. However, no significant correlation was observed between the cortical thickness in each region with altered thickness and the duration of untreated disease ($P > .05$, supplementary table 2). Furthermore, patients with shorter duration of untreated disease (<12 months, 81 cases) exhibited no significant differences compared with patients with longer duration of untreated disease (≥12 months, 37 cases) ($P > .05$).

Discussion

This study includes the largest sample of antipsychotic-naive first-episode schizophrenia to date, and the patients exhibited both regional cortical thinning and thickening in widespread areas, including the bilateral prefrontal and temporal cortices. Furthermore, the cortical thinning of the right DLPFC, left OFC, left inferior frontal gyrus pars triangularis, and bilateral precentral gyri was negatively correlated with the severity of clinical symptoms, as identified by PANSS scores (figure 2). This finding suggests that widespread cortical deficits occurring in the early stages of schizophrenia may be crucial to the pathogenesis of the disease. However, the cortical thickening of the bilateral anterior temporal lobes, left med-OFC,

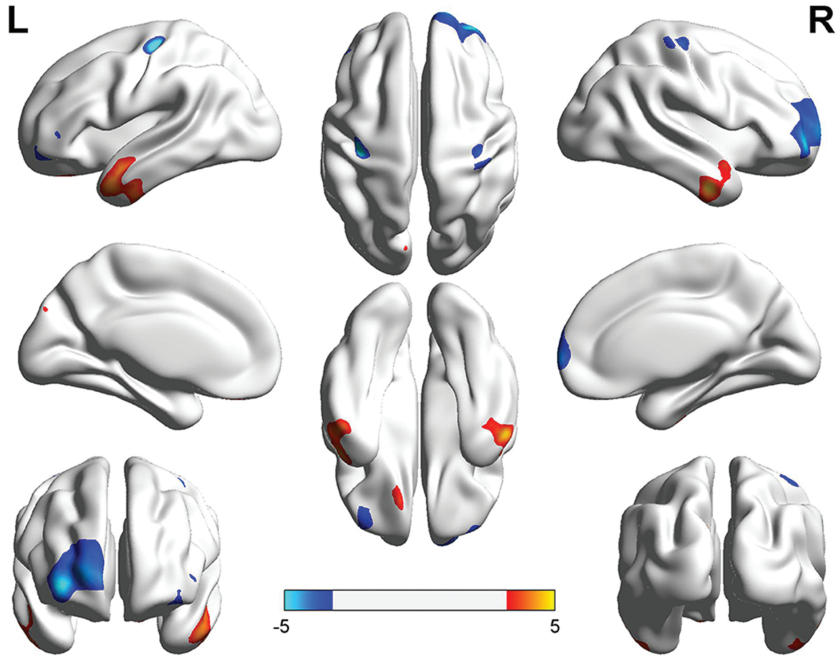

Fig. 1. Differences in cortical thickness between untreated first-episode schizophrenic patients and healthy controls. Significant group differences were identified using a vertex-based 2-sample *t* test with age and sex as covariates ($P < .05$, corrected for multiple comparisons with false discovery rate). Reduced cortical thickness was found in the following regions (labeled in blue): the right dorsolateral prefrontal cortex, left precentral gyrus, left orbitofrontal cortex, left inferior frontal gyrus pars triangularis, and right precentral and postcentral gyri. Increased cortical thickness was observed in the following regions (labeled in red): The bilateral anterior temporal lobes, left medial orbitofrontal cortex, and left cuneus in schizophrenic patients compared with healthy controls.

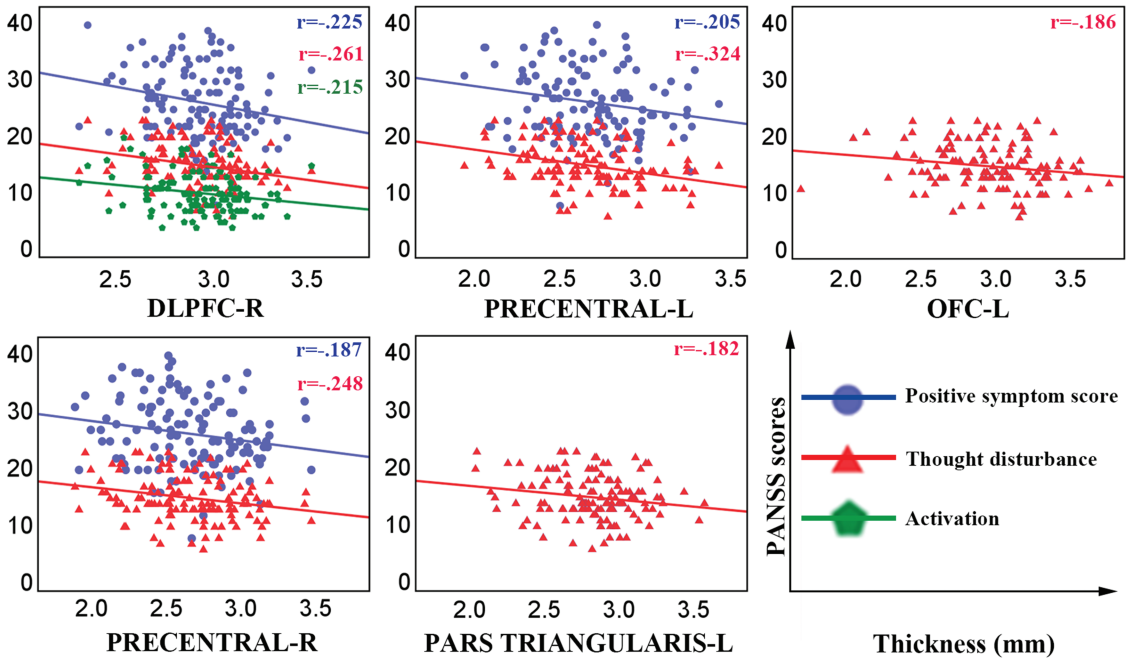

Fig. 2. The relationship between cortical thickness and clinical symptoms in antipsychotic-naive first-episode schizophrenic patients. Scatter plots and regression slopes representing the cortical thickness of the right dorsolateral prefrontal cortex, bilateral precentral gyri, left orbitofrontal cortex, and left inferior frontal gyrus pars triangularis. The cortical thickness of these areas was negatively correlated with the severity of clinical symptoms, as identified by Positive and Negative Syndrome Scale scores for positive symptom scores, thought disturbances, or activation ($P < .05$).

and left cuneus was not correlated with the scale scores. Furthermore, these changes in cortical thickness were not related to the duration of untreated disease ($P > .05$, supplementary table 2) or the severity of negative symptoms. These findings were consistent with a recent meta-analysis,[52] suggesting that the longitudinal gray matter volume decreases in schizophrenic patients are associated with higher cumulative exposure to antipsychotic overtime instead of duration of illness. There was no significant difference of surface area between the 2 groups, which was consistent with the findings in a recent study of schizophrenia,[53] suggesting that the alterations in cortical thickness are more pronounced than those in surface area during the early stage of schizophrenia.

The most prominent cortical thinning was observed in the bilateral prefrontal regions, which agrees with the results of previous studies of cortical thickness or volume in medicated first-episode schizophrenia.[25,30,54] However, previous volumetric studies[35,55] of drug-naive first-episode schizophrenia reported no significant differences in frontal volumes between patients and controls. Negative results of frontal thickness have also been reported in another study of first-episode schizophrenia.[32] Thus, it is still unclear whether the observed changes in the bilateral prefrontal regions are disease related or the effect of medication. In fact, a recent study of 19 first-episode drug-naive schizophrenics found an increase in rostral middle frontal thickness in patients after 4- and 8-week atypical antipsychotic treatment.[31] However, Wheeler et al. found reduced thickness in the bilateral DLPFC in both chronic and first-episode schizophrenic patients, suggesting the structural impairment in schizophrenia is independent of disease stage or medication exposure.[30] By studying the largest sample of antipsychotic-naive first-episode schizophrenics to date, this study further confirmed the cortical thinning of the bilateral prefrontal cortex as an early-course characteristic of schizophrenia before treatment. Furthermore, unlike the negative findings from the volumetric studies of drug-naive first-episode schizophrenia,[35,55] the observed cortical thickness changes of the bilateral prefrontal cortex in these drug-naive first-episode patients provided evidence to support the notion that cortical thickness may be more sensitive than volume to reveal cortical changes,[22,56] especially early in the duration of the disease. In fact, the gray matter volume of a cortical region represents the combination of its cortical thickness and surface area; these features are believed to be influenced by different genetic factors that are related to gyral[57] and/or sulcal patterning and the thickness of the cortical mantle itself.[19,58] Conversely, cortical thickness can provide more details reflecting the size, density, and arrangement of neurons, neuroglia, and nerve fibres[21,22] in cortical columns. Furthermore, cortical volume is measured using volume-based techniques that directly measure cortical volumes, and partial volume effects must therefore be considered[26]; cortical thickness is measured using surface-based techniques that can acquire data at a subvoxel resolution.[54]

The reduced cortical thickness of the right DLPFC, bilateral precentral gyri, left OFC, and left inferior frontal gyrus pars triangularis was negatively correlated with symptom severity, as identified by the PANSS scores. This finding suggests that reduced cortical thickness, especially in the prefrontal regions, may predispose patients to specific symptoms. Thus, the anatomical deficits in the prefrontal and parietal regions may represent core pathology during the early course of schizophrenia. In fact, the prefrontal cortex and, particularly, the DLPFC play an important role in managing many executive functions, such as working memory, response inhibition, and goal-directed behaviors.[59] These cognitive abilities are typically disturbed in schizophrenia. In addition to the DLPFC, the OFC has been proposed to be involved in sensory integration, the representation of affective values of reinforcers, decision making, and expectation.[60] The precentral and postcentral gyri comprise the locations of the primary motor cortex and primary somatosensory cortex, respectively, and have been reported to be inefficient in schizophrenia by fMRI.[61] Furthermore, the left inferior frontal gyrus pars triangularis is part of Broca's area, which plays a role in language and interpersonal information processing. Reduced volumes of the inferior frontal cortex pars triangularis were observed in subjects with first-episode schizophrenia compared with the healthy controls; additionally, these reduced volumes were suggested to represent a risk factor for schizophrenia.[62] Although the exact mechanism of cortical thinning is not yet well understood, a newly published postmortem study provides convincing evidence to support that reduced pyramidal layer thickness may result in the decreased thickness of the frontal lobe in schizophrenia.[63] Pyramidal neurons are the principal output cells of the cortex, and their functions are associated with advanced cognitive functions; therefore, any alterations in these cells may result in aberrant intra- and intergyral connectivity, resulting in the disordered symptoms of schizophrenia. A pathologically extended pruning processes[8] and sublethal apoptotic activity[64] have been suggested to be involved in the process of gray matter loss in schizophrenia. Reduced blood flow in the prefrontal cortex (ie, bilateral DLPFC, medial frontal cortex, and left OFC) and parietal cortex in neuroleptic-naive schizophrenia[65] may also be considered another contributor to cortical thinning.

Another interesting finding was greater cortical thickness of the bilateral anterior temporal lobes, left med-OFC, and left cuneus in patients compared with controls, which appeared to contradict the findings of thinner cortices[25] and reduced gray matter volume[55] in the temporal lobes of first-episode schizophrenic patients. A newly published study of a large sample of first-episode schizophrenic patients also found increased gray matter volumes in the left med-OFC.[35] One possible explanation

is that cortical thickening may represent a compensatory factor[66] that is meant to protect against psychosis related to the early phase of schizophrenia. However, the increased cortical thickness was not correlated to clinical symptoms. Another possible explanation may be associated with the synaptic pruning neurodevelopmental model of schizophrenia,[67] which states that schizophrenia arises from insufficient synaptic pruning.[66,68] Insufficient synaptic or axonal pruning, which leaves more synapses or axon branches intact compared with typical neurodevelopment, may induce cortical thickening in schizophrenia. Third, given that the patients in this study were early in the duration of disease (mean duration of untreated disease = 11.49 months), possible early-course pathology, such as preapoptotic osmotic changes or hypertrophy, could increase regional tissue.[69] However, the exact pathological mechanisms underlying cortical thickening in the early stages of schizophrenia require further study.

No significant correlations were found between altered cortical thickness and duration of untreated disease; additionally, no significant differences in cortical thickness were noted between patients with shorter duration of untreated disease and those with longer duration of untreated disease. This appears to contradict the hypothesis that schizophrenia is a progressive disease in which cerebral structures deteriorate over time.[5] Although progressive clinical symptoms and further decreases in brain tissue have been reported in many longitudinal studies,[6,7,70,71] the results of these investigations were confounded by the effects of antipsychotic medication, substance abuse, prolonged duration of disease and stress, as well as other factors that were secondary to the disease. Although some studies have demonstrated that age-related gray matter reductions occur in schizophrenia,[56] no evidence of disease progression has been found.[56,72,73] Especially, a recent meta-analysis of the effect of antipsychotics on schizophrenia found that the longitudinal gray matter volume decreases in schizophrenic patients were associated with higher cumulative exposure to antipsychotic over time, whereas no effects were observed for duration of illness.[52] Thus, current findings provided the direct evidence to support that the cortical deficits in schizophrenia are relatively stable instead of progressing during the early stages of the disease. In fact, our previous study of first-episode untreated schizophrenia demonstrated that gray matter volume was not correlated with the untreated disease duration.[35] Evidence from a number of clinical studies also contradicts the hypothesis that schizophrenia is a progressive disease. For example, cognitive functioning, which is certainly impaired in schizophrenic patients compared with healthy controls, does not appear to worsen over time.[12,74] On the contrary, most patients exhibit the potential to remit and experience functional recovery. Reports that some schizophrenic patients experience deterioration may reflect poor access or adherence to treatment, the effect of comorbidities, poverty, and a lack of social support.[12] Our findings further suggest that the anatomical changes associated with schizophrenia may be relatively stable or evolve slowly in the early stages of schizophrenia[35] and may thus be considered a relatively objective biomarker for early diagnosis. However, it is possible that different neuropathological mechanisms exist that may be associated with progressive anatomical changes occurring in the later stages of the illness. Because a longitudinal study of antipsychotic-naive schizophrenia is unethical, cross-sectional designs including longer duration of untreated disease, up to as many as 5 or 10 years, may be the optimal way to detect and confirm the relationship between structural neuroanatomical changes and the duration of disease and to reveal the nature of pathophysiological processes in schizophrenia.

No significant correlations were found between altered cortical thickness and the negative symptom subscale of the PANSS; additionally, no significant differences in cortical thickness were noted between patients with and without prominent negative symptoms. These findings suggest that these cortical thickness deficits occurring in the early stages of schizophrenia may be crucial to the pathogenesis of positive symptoms instead of negative symptoms. This is consistent with previous findings in treated and untreated schizophrenia,[35,75,76] which also suggested that negative symptoms have a different mechanism of pathogenesis from positive symptoms. However, the exact pathological mechanisms underlying the negative symptoms in schizophrenia require further study.

Two issues must be addressed to explain the current findings. First, due to the limitations associated with the research methodology, no subcortical regions, which may also be affected by aberrant neurodevelopmental mechanisms, were investigated. For example, the thalamus provides critical inputs to brain regions such as the prefrontal, cingulate, and temporal cortices, and thalamic deficits have been reported in schizophrenic patients via both neuroimaging[8,18] and postmortem studies.[77] Furthermore, although the duration of untreated disease ranged from 0.03 to 144 months, the majority of the durations of untreated disease in our sample were limited to within 36 months (106 cases). Similarly, the distribution of the duration of untreated disease was not symmetrical in our sample. Samples including patients with longer duration of untreated disease, such as 5–10 years, are relatively small. Thus, our study mainly revealed anatomical changes that are specific to the early stages of schizophrenia.

This study provided the first empirical evidence of widespread differences in cortical thickness, including both thinning and thickening, in the largest sample of antipsychotic-naive first-episode schizophrenic patients to date. Furthermore, these anatomical changes were related to the positive symptoms observed in schizophrenia, but not to the duration of untreated disease or the severity of negative symptoms. This finding suggests that these anatomical deficits are crucial to the pathogenesis

of positive symptoms and may be relatively stable in very early stages of the disease. However, it remains unclear whether these deficits are progressive in patients with longer untreated disease duration of schizophrenia. Further study of antipsychotic-naive patients with longer duration of untreated disease may help clarify the effect of disease duration on the brain in the later stages of disease as well as the natural dynamic of disease progression in schizophrenia.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

Funding

National Natural Science Foundation (81222018, 81371527 to S.L., 81030027, 81227002, 81220108013 to Q.G.); the Distinguished Young Scholars of Sichuan (2011JQ0005 to S.L.); the Programs for New Century Excellent Talents in University (NCET-10–0596 to S.L.); the CMB Distinguished Professorship Award (F510000/G16916411 to Q.G.); the National Key Technologies R&D Program (2012BAI01B03 to Q.G.); the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT, IRT1272) of China.

Acknowledgments

Drs Su Lui and Qiyong Gong contributed equally to playing the role of corresponding author, and in particular, Dr Qiyong Gong acknowledges his Visiting Adjunct Professor appointment in the Department of Radiology at the University of Illinois Hospital & Health Sciences System, Chicago, IL, USA. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Woodberry KA, Giuliano AJ, Seidman LJ. Premorbid IQ in schizophrenia: a meta-analytic review. *Am J Psychiatry*. 2008;165:579–587.
2. Giuliano AJ, Li H, Mesholam-Gately RI, Sorenson SM, Woodberry KA, Seidman LJ. Neurocognition in the psychosis risk syndrome: a quantitative and qualitative review. *Curr Pharm Des*. 2012;18:399–415.
3. Jung WH, Kim JS, Jang JH, et al. Cortical thickness reduction in individuals at ultra-high-risk for psychosis. *Schizophr Bull*. 2011;37:839–849.
4. Fornito A, Yung AR, Wood SJ, et al. Anatomic abnormalities of the anterior cingulate cortex before psychosis onset: an MRI study of ultra-high-risk individuals. *Biol Psychiatry*. 2008;64:758–765.
5. Kraepelin E. *Dementia Praecox and Paraphrenia (1919)*. Translated by Barclay RM. Robertson GM, ed. New York, NY: Robert E Krieger; 1971.
6. Arango C, Rapado-Castro M, Reig S, et al. Progressive brain changes in children and adolescents with first-episode psychosis. *Arch Gen Psychiatry*. 2012;69:16–26.
7. Vita A, De Peri L, Deste G, Sacchetti E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry*. 2012;2:e190.
8. Andreasen NC, Nopoulos P, Magnotta V, Pierson R, Ziebell S, Ho BC. Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia. *Biol Psychiatry*. 2011;70:672–679.
9. van Haren NE, Schnack HG, Cahn W, et al. Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry*. 2011;68:871–880.
10. Lieberman JA, Tollefson GD, Charles C, et al. HGDH Study Group. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry*. 2005;62:361–370.
11. Andreasen NC. The lifetime trajectory of schizophrenia and the concept of neurodevelopment. *Dialogues Clin Neurosci*. 2010;12:409–415.
12. Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. *Schizophr Bull*. 2013;39:1363–1372.
13. Konopaske GT, Dorph-Petersen KA, Sweet RA, et al. Effect of chronic antipsychotic exposure on astrocyte and oligodendrocyte numbers in macaque monkeys. *Biol Psychiatry*. 2008;63:759–765.
14. Vernon AC, Natesan S, Modo M, Kapur S. Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. *Biol Psychiatry*. 2011;69:936–944.
15. Smieskova R, Fusar-Poli P, Allen P, et al. The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia?–a systematic review. *Curr Pharm Des*. 2009;15:2535–2549.
16. Agarwal N, Port JD, Bazzocchi M, Renshaw PF. Update on the use of MR for assessment and diagnosis of psychiatric diseases. *Radiology*. 2010;255:23–41.
17. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry*. 2005;162:2233–2245.
18. Bora E, Fornito A, Radua J, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophr Res*. 2011;127:46–57.
19. Panizzon MS, Fennema-Notestine C, Eyler LT, et al. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex*. 2009;19:2728–2735.
20. Rakic P, Swaab D. Defects of neuronal migration and the pathogenesis of cortical malformations. *Progress Brain Res*. 1988;73:15–37.
21. Parent A, Carpenter MB. *Human Neuroanatomy*. 9th ed. Baltimore, MD: Williams & Wilkins; 1995.
22. Narr KL, Toga AW, Szeszko P, et al. Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. *Biol Psychiatry*. 2005;58:32–40.
23. Jakob H, Beckmann H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. *J Neural Transm*. 1986;65:303–326.
24. Arnold SE, Franz BR, Gur RC, et al. Smaller neuron size in schizophrenia in hippocampal subfields that

mediate cortical-hippocampal interactions. *Am J Psychiatry*. 1995;152:738–748.
25. Narr KL, Bilder RM, Toga AW, et al. Mapping cortical thickness and gray matter concentration in first episode schizophrenia. *Cereb Cortex*. 2005;15:708–719.
26. Winkler AM, Kochunov P, Blangero J, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage*. 2010;53:1135–1146.
27. Kuperberg GR, Broome MR, McGuire PK, et al. Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry*. 2003;60:878–888.
28. Oertel-Knöchel V, Knöchel C, Rotarska-Jagiela A, et al. Association between psychotic symptoms and cortical thickness reduction across the schizophrenia spectrum. *Cereb Cortex*. 2013;23:61–70.
29. Gogtay N, Greenstein D, Lenane M, et al. Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. *Arch Gen Psychiatry*. 2007;64:772–780.
30. Wheeler AL, Chakravarty MM, Lerch JP, et al. Disrupted prefrontal interhemispheric structural coupling in schizophrenia related to working memory performance [published online ahead of print July 20, 2013]. *Schizophr Bull*. doi:10.1093/schbul/sbt100
31. Goghari VM, Smith GN, Honer WG, et al. Effects of eight weeks of atypical antipsychotic treatment on middle frontal thickness in drug-naïve first-episode psychosis patients. *Schizophr Res*. 2013;149:149–155.
32. Wiegand LC, Warfield SK, Levitt JJ, et al. Prefrontal cortical thickness in first-episode psychosis: a magnetic resonance imaging study. *Biol Psychiatry*. 2004;55:131–140.
33. Crow TJ. Positive and negative schizophrenic symptoms and the role of dopamine. *Br J Psychiatry*. 1980;137:383–386.
34. Gasquet I, Haro JM, Novick D, Edgell ET, Kennedy L, Lepine JP; SOHO Study Group. Pharmacological treatment and other predictors of treatment outcomes in previously untreated patients with schizophrenia: results from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Int Clin Psychopharmacol*. 2005;20:199–205.
35. Ren W, Lui S, Deng W, et al. Anatomical and functional brain abnormalities in drug-naive first-episode schizophrenia. *Am J Psychiatry*. 2013;170:1308–1316.
36. Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. *Am J Psychiatry*. 1992;149:1148–1156.
37. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res*. 1988;23:99–110.
38. Annett M. A classification of hand preference by association analysis. *Br J Psychol*. 1970;61:303–321.
39. Talairach J, Tournoux P, eds. *Co-planar Stereotaxic Atlas of the Human Brain*. New York, NY: Thieme; 1988.
40. Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr*. 1994;18:192–205.
41. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*. 1998;17:87–97.
42. Zijdenbos AP, Forghani R, Evans AC. Automatic "pipeline" analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. *IEEE Trans Med Imaging*. 2002;21:1280–1291.
43. MacDonald D, Kabani N, Avis D, Evans AC. Automated 3-D extraction of inner and outer surfaces of cerebral cortex from MRI. *Neuroimage*. 2000;12:340–356.
44. Kim JS, Singh V, Lee JK, et al. Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification. *Neuroimage*. 2005;27:210–221.
45. Lerch JP, Evans AC. Cortical thickness analysis examined through power analysis and a population simulation. *Neuroimage*. 2005;24:163–173.
46. Chung MK, Worsley KJ, Robbins S, et al. Deformation-based surface morphometry applied to gray matter deformation. *Neuroimage*. 2003;18:198–213.
47. Kabani N, Le Goualher G, MacDonald D, Evans AC. Measurement of cortical thickness using an automated 3-D algorithm: a validation study. *Neuroimage*. 2001; 13:375–380.
48. Lee J, Lee JM, Kim JH, Kim IY, Evans AC, Kim SI. A novel quantitative validation of the cortical surface reconstruction algorithm using MRI phantom: issues on local geometric accuracy and cortical thickness. *Med Image Comput Comput Assist Interv*. 2006;9:183–190.
49. Van Essen DC, Dierker D, Snyder AZ, Raichle ME, Reiss AL, Korenberg J. Symmetry of cortical folding abnormalities in Williams syndrome revealed by surface-based analyses. *J Neurosci*. 2006;26:5470–5483.
50. Im K, Lee JM, Lyttelton O, Kim SH, Evans AC, Kim SI. Brain size and cortical structure in the adult human brain. *Cereb Cortex*. 2008;18:2181–2191.
51. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.
52. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev*. 2013;37:1680–1691.
53. Voineskos AN, Foussias G, Lerch J, et al. Neuroimaging evidence for the deficit subtype of schizophrenia. *JAMA Psychiatry*. 2013;70:472–480.
54. Schultz CC, Koch K, Wagner G, et al. Reduced cortical thickness in first episode schizophrenia. *Schizophr Res*. 2010;116:204–209.
55. Lui S, Deng W, Huang X, et al. Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. *Am J Psychiatry*. 2009;166:196–205.
56. Kubota M, Miyata J, Yoshida H, et al. Age-related cortical thinning in schizophrenia. *Schizophr Res*. 2011;125:21–29.
57. White T, Andreasen NC, Nopoulos P, Magnotta V. Gyrification abnormalities in childhood- and adolescent-onset schizophrenia. *Biol Psychiatry*. 2003;54:418–426.
58. Bartley AJ, Jones DW, Weinberger DR. Genetic variability of human brain size and cortical gyral patterns. *Brain*. 1997;120 (Pt 2):257–269.
59. Rimol LM, Hartberg CB, Nesvåg R, et al. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biol Psychiatry*. 2010;68:41–50.
60. Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci*. 2005;6:691–702.
61. Kim MA, Tura E, Potkin SG, et al. FBIRN. Working memory circuitry in schizophrenia shows widespread

cortical inefficiency and compensation. *Schizophr Res*. 2010;117:42–51.
62. Iwashiro N, Suga M, Takano Y, et al. Localized gray matter volume reductions in the pars triangularis of the inferior frontal gyrus in individuals at clinical high-risk for psychosis and first episode for schizophrenia. *Schizophr Res*. 2012;137:124–131.
63. Williams MR, Chaudhry R, Perera S, et al. Changes in cortical thickness in the frontal lobes in schizophrenia are a result of thinning of pyramidal cell layers. *Eur Arch Psychiatry Clin Neurosci*. 2013;263:25–39.
64. Glantz LA, Gilmore JH, Lieberman JA, Jarskog LF. Apoptotic mechanisms and the synaptic pathology of schizophrenia. *Schizophr Res*. 2006;81:47–63.
65. Andreasen NC, O'Leary DS, Flaum M, et al. Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naïve patients. *Lancet*. 1997;349:1730–1734.
66. Goghari VM, Rehm K, Carter CS, MacDonald AW 3rd. Regionally specific cortical thinning and gray matter abnormalities in the healthy relatives of schizophrenia patients. *Cereb Cortex*. 2007;17:415–424.
67. Rapoport JL, Giedd JN, Gogtay N. Neurodevelopmental model of schizophrenia: update 2012. *Mol Psychiatry*. 2012;17:1228–1238.
68. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res*. 1982;17:319–334.
69. Adler CM, Levine AD, DelBello MP, Strakowski SM. Changes in gray matter volume in patients with bipolar disorder. *Biol Psychiatry*. 2005;58:151–157.
70. van Haren NE, Hulshoff Pol HE, Schnack HG, et al. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biol Psychiatry*. 2008;63:106–113.
71. Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry*. 2011;68:128–137.
72. DeLisi LE, Hoff AL. Failure to find progressive temporal lobe volume decreases 10 years subsequent to a first episode of schizophrenia. *Psychiatry Res*. 2005;138:265–268.
73. Boonstra G, Cahn W, Schnack HG, et al. Duration of untreated illness in schizophrenia is not associated with 5-year brain volume change. *Schizophr Res*. 2011;132:84–90.
74. Gold S, Arndt S, Nopoulos P, O'Leary DS, Andreasen NC. Longitudinal study of cognitive function in first-episode and recent-onset schizophrenia. *Am J Psychiatry*. 1999;156:1342–1348.
75. Lui S, Li T, Deng W, et al. Short-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia revealed by "resting state" functional magnetic resonance imaging. *Arch Gen Psychiatry*. 2010;67:783–792.
76. Kay SR, Singh MM. The positive-negative distinction in drug-free schizophrenic patients. Stability, response to neuroleptics, and prognostic significance. *Arch Gen Psychiatry*. 1989;46:711–718.
77. Young KA, Manaye KF, Liang C, Hicks PB, German DC. Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia. *Biol Psychiatry*. 2000;47:944–953.