

Anatomical and Functional Brain Abnormalities in Drug-Naive First-Episode Schizophrenia

Wenting Ren, M.S.

Su Lui, M.D., Ph.D.

Wei Deng, M.D.

Fei Li, M.D.

Mingli Li, M.D.

Xiaoqi Huang, M.D.

Yuqing Wang, Ph.D.

Tao Li, M.D.

John A. Sweeney, Ph.D.

Qiyong Gong, M.D., Ph.D.

Objective: The authors sought to explore whether anatomical and functional brain deficits are present in similar or different brain regions early in the course of schizophrenia, before antipsychotic treatment, and whether these deficits are more severe or otherwise different in patients with prominent negative symptoms.

Method: A total of 100 drug-naive first-episode schizophrenia patients and 100 matched healthy comparison subjects underwent structural and resting-state functional MRI scanning. Gray matter volume and amplitude of low-frequency fluctuations during resting-state functional studies were measured.

Results: Group comparisons of gray matter volume showed significant differences mainly in thalamo-cortical networks, while alterations in the amplitude of low-frequency fluctuations were observed in fronto-parietal and default mode networks. Thus, different brain regions had alterations in gray matter volume and resting state physiology. These changes did not correlate with

the duration of untreated illness, nor with acute clinical symptom severity. Patients with prominent negative symptoms had greater regional alterations in brain anatomy, particularly in the left dorsolateral prefrontal cortex, while the pattern of functional alterations was unrelated to severity of negative symptoms.

Conclusions: Anatomical and resting-state functional deficits were observed in different brain regions, indicating that anatomical and functional brain abnormalities are significantly dissociated in the early course of schizophrenia. The lack of association of these abnormalities with illness duration and episode severity suggests that these anatomical and functional changes may be early-evolving features of the illness that are relatively stable early in the course of illness. The different structural deficits of regional gray matter observed in patients with prominent negative symptoms may provide unique insight into the early regional neuropathology of this symptom dimension in schizophrenia.

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Schizophrenia is a serious psychiatric illness with onset typically during adolescence and early adulthood and a lifetime incidence of about 1% in the general population (1). In recent decades, many studies have reported anatomical and functional brain abnormalities, most often in fronto-striato-thalamic networks, in schizophrenia patients relative to healthy comparison subjects (2). However, results of neuroimaging studies have been inconsistent, partly because of potential confounders associated with medication, long duration of illness, and small sample sizes (3–5). Recent data suggest that schizophrenia may be a progressive brain disorder (6–10). The extent to which these progressive changes may be due to the effects of antipsychotic medication, substance abuse, and other secondary factors remains unclear (11). Studies of antipsychotic-naive first-episode schizophrenia are important not only as a starting point for evaluating the progression of brain alterations and for assessing brain anatomy and function before they can be influenced by potential confounders, but also to better specify the brain regions where functional and anatomical changes

are seen at the onset of illness in order to provide important, novel information relevant to models of pathogenesis (2).

One important question that remains largely unanswered is how anatomical and functional brain deficits are related early in the course of schizophrenia. Previous anatomical studies have revealed reductions of gray matter volume mainly in the thalamus and the temporal and frontal cortex (3–5), perhaps most notably in the temporal cortex in drug-naive first-episode schizophrenia (12–15). In contrast, the major functional deficits revealed by functional MRI (fMRI) in drug-naive first-episode schizophrenia patients have been localized more widely in prefrontal, temporal, and parietal regions (16–18), especially in the ventromedial prefrontal cortex (19) and in the default mode network, where deficits have been related to specific clinical features (20, 21). Thus, while there are overlaps and differences in brain regions where structural and functional abnormalities have been identified, few studies have examined these deficits together in the same sample. Another important question is whether anatomical and functional deficits are different in patients

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with prominent negative symptoms, which is important because these patients have different clinical manifestations and a diminished treatment response (22, 23).

Voxel-based morphometry (VBM) is a useful automatic technique for investigating the anatomy of the human brain (3, 15, 24, 25), and resting-state fMRI can be used to detect regional functional alterations. In resting-state fMRI, the amplitude of low-frequency (0.01–0.08 Hz) fluctuations of the blood-oxygen-level-dependent (BOLD) signal is considered to be physiologically meaningful and related to spontaneous neural activity (26). The two techniques have been widely used to explore morphometric and functional deficits in a range of psychiatric disorders, including schizophrenia.

Our aim in this study was to characterize alterations of gray matter volume and amplitude of low-frequency fluctuation in 100 drug-naïve first-episode schizophrenia patients, the interrelationship of these abnormalities, and their relationship with illness duration and negative symptom severity.

Method

Participants

A total of 214 right-handed individuals were recruited for this study, including 107 treatment-naïve first-episode schizophrenia patients and 107 healthy comparison subjects. The study was approved by the local research ethics committee, and written informed consent was obtained from all participants. Diagnoses of schizophrenia and duration of illness were determined by the consensus of two experienced clinical psychiatrists using the Structured Interview for the DSM-IV Axis I Disorder, Patient Edition (SCID). Psychopathology ratings were obtained using the Positive and Negative Syndrome Scale (PANSS) (27).

Healthy comparison subjects were recruited by poster advertisement. All comparison subjects were screened using the nonpatient edition of the SCID to confirm the lifetime absence of psychiatric illnesses. In addition, comparison subjects were interviewed to exclude individuals with a known history of psychiatric illness in first-degree relatives. The following exclusion criteria applied to all participants: history of drug or alcohol abuse, pregnancy, and any physical illness such as hepatitis, cardiovascular disease, or neurological disorders, as assessed by interview and review of medical records. Brain MR images (T_1 -weighted and T_2 -weighted images) were inspected by an experienced neuroradiologist, and no gross abnormalities were observed in any participant. Seven patients and seven comparison subjects with excessive head motion (translation of more than 1.5 mm or rotation of more than 1.5°) were excluded, resulting in samples of 100 patients and 100 comparison subjects for statistical analyses. There were no significant differences between groups in age, sex, height, weight, and years of education (see Table S1 in the data supplement that accompanies the online edition of this article) or in head motion during scanning. For analyses of associations of brain measures with negative symptom severity, patients were divided into two subgroups: 36 patients with prominent negative symptoms (a score ≥ 20 on the negative symptom subscale of the PANSS [27, 28]; 20 of them were female, and the mean age was 24.8 years) and 64 patients without prominent negative symptoms (a score < 20 on the negative symptom scale of the PANSS; 39 of them were female, and the mean age was 24.1 years). The mean time since onset of psychotic symptoms was 6.25 months (SD=11.0; range=0.1–46

months). For analyses of illness duration effects, patients were divided into two subgroups: 24 patients with untreated illness of a duration greater than 1 year (12–24 months, N=11; 24–36 months, N=11; 36–46 months, N=2) and 76 patients with a duration of untreated illness < 12 months.

Data Acquisition

Scanning was conducted on a 3-T GE Signa EXCITE scanner (General Electric, Milwaukee). High-resolution T_1 -weighted volumetric three-dimensional images were obtained using a spoiled gradient recall sequence, and amplitudes of low-frequency (0.01–0.08 Hz) fluctuations of the BOLD signal were obtained using a gradient-echo echo-planar imaging sequence. The detailed scan parameters and methods for data analysis are presented in the online data supplement.

Data Analysis

VBM analyses of T_1 MR images were performed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) and the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm>). The amplitude of low-frequency fluctuation was calculated using Data Processing Assistant for Resting-State fMRI (DPARSF), version 2.1, implemented with the MATLAB toolbox (<http://www.restfmri.net>). Voxel-wise group comparisons of gray matter volume and amplitude of low-frequency fluctuation were performed using two-sample *t* tests. For analyses comparing subgroups of patients in relation to negative symptoms and illness duration, voxel-based comparisons of gray matter volume and amplitude of low-frequency fluctuation were conducted using one-way analysis of variance comparing the two patient groups and the comparison group, followed by post hoc *t* tests. The statistical results of gray matter volume were corrected for multiple comparisons using the false discovery rate and those of amplitude of low-frequency fluctuation were corrected using the AlphaSim program (29). Our statistical threshold was a *p* value of 0.05, corrected for multiple comparisons. The average gray matter volume and amplitude of low-frequency fluctuation values of all voxels in brain areas in which abnormalities were detected were extracted, averaged, and correlated with PANSS scores, age, and untreated duration of illness. All analyses examining relationships of brain measures with clinical data were controlled for age and sex.

To test the influence of skull stripping on morphometric measures, the normalized images from 20 patients with the highest and 20 with the lowest VBM gray matter volume were selected, and the nonbrain tissue, including scalp, skull, and dura, were removed blindly and manually by an experienced neuroradiologist. The average gray matter volume of all voxels in abnormal areas revealed by VBM were extracted from these manually skull-stripped images and compared with the values of VBM findings from those without manual skull stripping using a paired *t* test. No significant difference was revealed between the findings with and without manual skull stripping.

Results

Relative to the comparison group, the patient group showed significantly decreased gray matter volume in the left paracentral and left inferior parietal lobules, and increased gray matter volume in the left and right thalamus, anterior cingulate cortex, insula, and orbital frontal gyrus ($p < 0.05$ corrected with false discovery rate) (Table 1; Figure 1). For the amplitude of low-frequency fluctuation analysis, a decreased amplitude of low-frequency fluctuation was observed mainly in the right inferior and

TABLE 1. Differences in Gray Matter Volume and Amplitude of Low-Frequency Fluctuation Between Drug-Naive First-Episode Schizophrenia and Healthy Comparison Subjects^a

Measure, Comparison, and Region	Coordinates			Cluster size	t
	x	y	z		
Gray matter volume					
Patients > healthy subjects					
Left thalamus	9	−31	−5	99	4.85
Left insula	−38	−6	3	855	4.60
Right thalamus	−8	−31	−6	12	5.18
Right insula	36	−16	−2	308	4.73
Right anterior cingulate	5	42	13	546	3.86
Right orbital frontal gyrus	6	53	−20	763	3.96
Healthy subjects > patients					
Left paracentral lobule	−14	−25	67	76	4.51
Left inferior parietal lobule	−56	−36	39	385	4.32
Amplitude of low-frequency fluctuation					
Patients > healthy subjects					
Left putamen	−24	−3	12	165	5.62
Left occipital gyrus	−36	−72	−6	356	4.47
Right putamen	27	−6	9	102	4.18
Right occipital gyrus	39	−81	9	56	4.00
Right calcarine sulcus	18	−93	0	38	3.53
Healthy subjects > patients					
Left superior frontal gyrus	−24	9	57	129	5.26
Left inferior parietal lobule	−42	−51	51	54	4.30
Left rectus	0	63	−18	19	4.57
Right inferior parietal lobule	45	−54	51	128	5.21
Right inferior frontal gyrus	48	12	21	127	4.52
Right precuneus	6	−54	15	37	4.21
Right insula	42	9	−12	31	4.16

^a Differences are significant at $p < 0.05$ with correction for multiple comparisons.

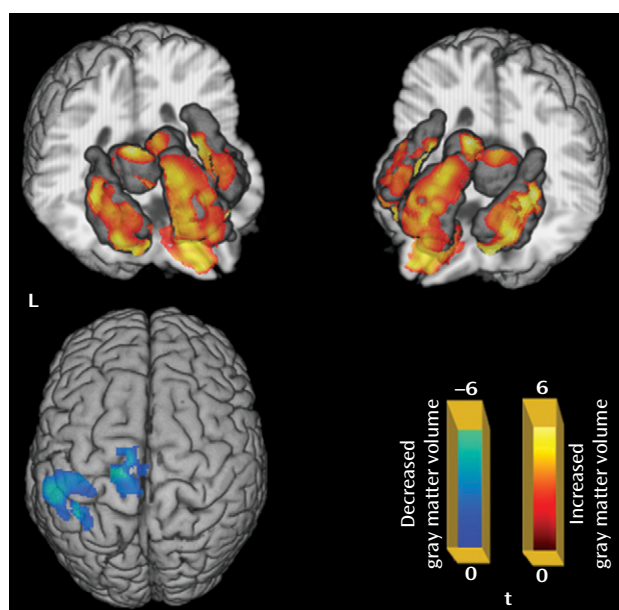
left superior frontal gyrus, the medial frontal gyrus bilaterally, the inferior parietal lobule bilaterally, and the precuneus, while an increased amplitude of low-frequency fluctuation was observed bilaterally in the putamen and occipital regions ($p < 0.05$ corrected with AlphaSim) (Table 1; Figure 2).

Subgroup analysis revealed that the patients with prominent negative symptoms showed significantly decreased gray matter volume in the right postcentral gyrus and the left inferior parietal lobule, and increased gray matter volume in the left and right thalamus, insula, and dorsolateral prefrontal cortex relative to comparison subjects ($p < 0.05$ corrected with false discovery rate) (Figure 3; see also Table S2 in the online data supplement). Relative to comparison subjects, patients without prominent negative symptoms showed significantly decreased gray matter volume in regions including the right middle temporal gyrus, the left middle frontal gyrus, the left postcentral gyrus, and the right middle occipital gyrus, and increased gray matter volume in the left and right thalamus, insula, anterior cingulate cortex, and left inferior frontal gyrus ($p < 0.05$ corrected with false discovery rate) (Figure 3; see also Table S2 in the data supplement). The direct comparison between patients without and with prominent negative symptoms revealed smaller gray

matter volume in the middle frontal gyrus bilaterally and the left superior frontal gyrus in patients without prominent negative symptoms. For the amplitude of low-frequency fluctuation analysis, patients with and without prominent negative symptoms showed similar patterns of decreased amplitude of low-frequency fluctuation mainly in the left and right medial and middle prefrontal gyrus and the right inferior parietal gyrus, and increased amplitude of low-frequency fluctuation in the putamen and occipital regions bilaterally ($p < 0.05$ corrected with AlphaSim) (Figure 4; see also Table S2 in the data supplement). Although the patients without prominent negative symptoms showed more regions with decreased function in the medial prefrontal cortex and the left parietal regions relative to comparison subjects, direct comparisons between the patients with and without prominent negative symptoms revealed no significant difference. Patients with longer and shorter duration of illness did not differ significantly in either the anatomical or functional brain data.

To examine the overlap between gray matter volume and amplitude of low-frequency fluctuation findings, the regions with significant abnormalities in gray matter volume and amplitude of low-frequency fluctuation were overlaid on the same template. There was no overlap of

FIGURE 1. Differences in Gray Matter Volume Between Drug-Naive First-Episode Schizophrenia Patients and Healthy Comparison Subjects^a



^a Significant group differences were identified by *t* test ($p < 0.05$ corrected for multiple comparisons with false discovery rate). The regions in blue indicate areas with decreased gray matter volume in first-episode schizophrenia, including the left postcentral gyrus extending to the paracentral lobule and the left inferior parietal gyrus; regions in red indicate areas with increased gray matter volume in first-episode schizophrenia, including the left and right thalamus, anterior cingulate cortex, insula, and orbital frontal gyrus.

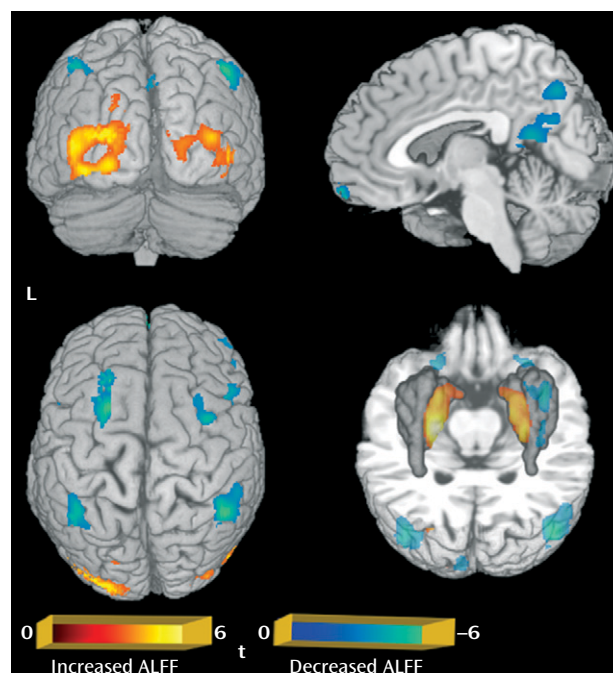
areas with alteration in analyses of gray matter volume and amplitude of low-frequency fluctuation (see Figure S4 in the data supplement). Furthermore, the average gray matter volume values within the regions with abnormal functional measures were not significantly correlated with the amplitude of low-frequency fluctuation values in either the whole patient group or in subgroups defined by negative symptom severity or illness duration.

Significant positive correlations were observed between untreated illness duration and severity of psychotic symptoms, including PANSS positive symptom scores ($r = 0.59$, $p < 0.05$) and ratings of thought disturbance ($r = 0.48$, $p < 0.05$), activation ($r = 0.45$, $p < 0.05$), paranoia ($r = 0.50$, $p < 0.05$), and anergia ($r = 0.44$, $p < 0.05$). However, no significant correlations were observed between illness duration or positive symptom severity and either changes of gray matter volume or amplitude of low-frequency fluctuation in the patient group.

Discussion

Using the largest sample of drug-naive first-episode schizophrenia patients studied to date with MRI, this study revealed both cerebral anatomical and functional deficits early in the course of illness. However, there was no overlap in the regions with anatomical and functional

FIGURE 2. Differences in the Amplitude of Low-Frequency Fluctuation During Resting-State Functional Imaging Between Drug-Naive First-Episode Schizophrenia Patients and Healthy Comparison Subjects^a

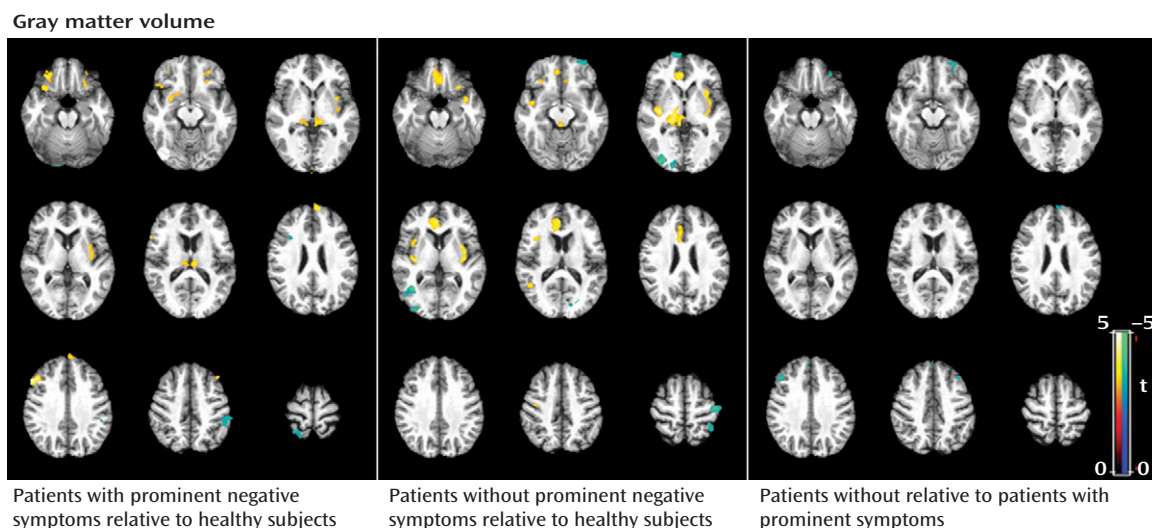


^a Significant group differences were identified by *t* test ($p < 0.05$ corrected for multiple comparisons with the AlphaSim program). The regions in blue showed a decreased amplitude of low-frequency fluctuation in first-episode schizophrenia, seen mainly in the right inferior and left superior frontal gyrus, the medial frontal gyrus, and the left and right inferior parietal lobule and precuneus; regions in red indicate areas with an increased amplitude in first-episode schizophrenia, including the left and right putamen and occipital regions. ALFF=amplitude of low-frequency fluctuation.

abnormalities. Gray matter volume changes mainly involved thalamo-cortical networks, while functional changes reflected in the amplitude of low-frequency fluctuation were observed within a fronto-parietal network and the default mode network. Not only did different brain regions show abnormalities in anatomy and physiology measures, but average gray matter volume values within regions having anatomical abnormalities were not significantly associated with the amplitude of low-frequency fluctuation values in those regions. Brain changes in anatomy and function did not correlate with the duration of untreated illness or with positive symptom severity, but some anatomical differences, notably including the increased gray matter volume of the left dorsolateral prefrontal cortex, were identified that varied in relation to negative symptom severity.

It is noteworthy that the patient group showed widespread increases in gray matter volume in multiple brain areas, including the left and right thalamus, insula, anterior cingulate cortex, and orbital frontal gyrus. These findings differ from those of some previous studies that reported decreased gray matter volume within thalamo-cortical networks in chronic as well as first-episode

FIGURE 3. Differences in Gray Matter Volume Between Healthy Comparison Subjects and Drug-Naive First-Episode Schizophrenia Patients With and Without Prominent Negative Symptoms^a

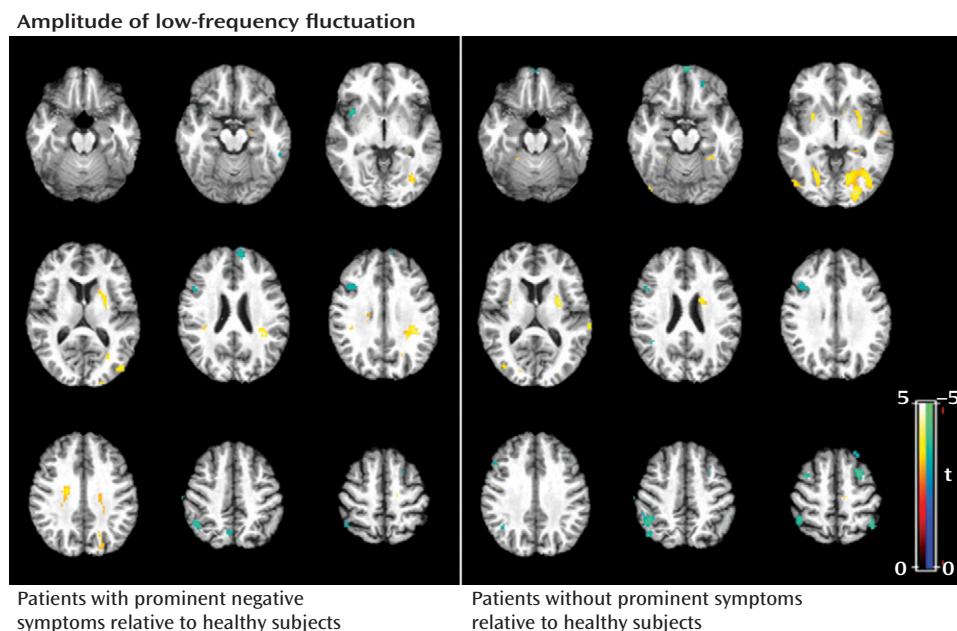


^a The regions in blue denote areas with decreased gray matter volume and those in yellow indicate increased gray matter volume in the comparisons indicated ($p < 0.05$ corrected with false discovery rate). Relative to healthy comparison subjects, patients with prominent negative symptoms showed significantly decreased gray matter volume in the right postcentral gyrus and the left inferior parietal lobule and increased gray matter volume in the left and right thalamus, insula, and dorsolateral prefrontal cortex. Relative to healthy comparison subjects, patients without prominent negative symptoms showed significantly decreased gray matter volume in regions including the right middle temporal gyrus, left middle frontal gyrus, left postcentral gyrus, and right middle occipital gyrus, and increased gray matter volume in the left and right thalamus, insula, anterior cingulate cortex, and left inferior frontal gyrus. The direct comparisons between patients without and with prominent negative symptoms revealed smaller gray matter volume in the left and right middle frontal gyrus and the left superior frontal gyrus in patients without prominent negative symptoms.

schizophrenia patients (3–5, 8, 12–15). In fact, our previous study in a smaller sample ($N=68$) of drug-naive first-episode schizophrenia patients also revealed decreased gray matter volume in the right temporal and anterior cingulate cortex (12). Several factors merit consideration in explaining the regionally greater gray matter volume seen in the present study relative to several previous studies. Differences in patient characteristics across studies may be important, as some other studies have also reported increased gray matter volume in schizophrenia, including a report of such effects in the orbital frontal gyrus and anterior cingulate cortex in a study of 169 patients (30). One patient characteristic that the present data suggest may be important is severity of negative symptoms. This sample had a higher proportion of patients with prominent negative symptoms (36%) than the sample in our previous study (12%) (12). The results of the present study indicate that patients without prominent negative symptoms have more regions with decreased volume, especially in right temporal regions, than patients with prominent negative symptoms close to the time of illness onset, which may partly explain the discrepancy with our previous findings (12). Second, as the patients in the present study were early in the course of illness (average illness duration=6.25 months), possible early-course neuronal pathology, such as preapoptotic osmotic changes or hypertrophy, could increase regional volumes (31). Progressive gray matter volume loss might be expected after antipsychotic treatment (6–10) or in relation to secondary

factors or course of illness effects (6, 32), which could contribute to the absence of reported hypertrophy in previous studies of patients who had a longer duration of illness before MRI scans were obtained (11). Of note, anatomical and functional changes did not correlate with untreated illness duration or with positive symptoms, and the direct comparison between patients with long and short untreated illness durations revealed no significant differences. These findings suggest a relatively static or slowly evolving process of anatomical changes, which is consistent with a recent study of treated schizophrenia patients (33) in suggesting the absence of progressive loss of gray matter volume during the early illness course before treatment has begun. Thus, the structural and functional brain changes observed in first-episode patients may be associated with neurodevelopmental problems such as neuronal overgrowth or a deficit in normal pruning during neurogenesis, as suggested by previous studies (34, 35) or, alternatively, with early illness pathophysiology effects, possibilities that need to be examined in future studies following at-risk individuals. Third, this study had a large sample and may have had the statistical power to detect hypertrophic effects not reported frequently in previous studies. Finally, this study used VBM8, which provides a more optimized method of segmentation and normalization than the VBM2 method in the analysis of gray matter volume (12). Furthermore, with concern for potential influences of skull-stripping artifacts, especially in the orbital frontal gyrus where deskulling is difficult, we

FIGURE 4. Differences in the Amplitude of Low-Frequency Fluctuation Between Healthy Comparison Subjects and Drug-Naive First-Episode Schizophrenia Patients With and Without Prominent Negative Symptoms^a



^a The regions in blue denote decreased and those in yellow denote increased amplitude of low-frequency fluctuation in the comparisons indicated ($p < 0.05$ corrected with false discovery rate). Patients with and without prominent negative symptoms showed similar patterns of decreased amplitude of low-frequency fluctuation, mainly in the left and right middle and inferior frontal gyrus and the right inferior parietal lobule, and increased amplitude in the left and right putamen and occipital regions.

contrasted computerized and manual skull stripping in a subsample of 40 participants and found no differences, indicating that artifacts induced by skull stripping procedures are not likely a cause of the group differences between patients and comparison subjects observed in this study. Although the exact mechanism for increased gray matter volume in first-episode schizophrenia before drug treatment is unclear, our findings indicate that regions within thalamo-cortical networks show early anatomical changes in the course of schizophrenia. Further research is needed on potential neuroinflammatory and other mechanisms that might contribute to these changes in brain anatomy and on how these anatomical changes influence clinical presentation and course of illness.

Deficits in the thalamus and frontal cortex have been widely reported in previous neuroimaging studies of schizophrenia (4, 9, 36–39). Alterations in the thalamus have been proposed to be associated with heterogeneous symptoms in schizophrenia, such as hallucinations, delusions, disorganized behaviors and speech, and thought disorder (5, 36). In contrast, prefrontal abnormalities have been related to negative symptoms and some deficits in higher cognitive function (40). Several other regions with altered gray matter volume were also identified in the present study, including the insula, inferior parietal lobule, and anterior cingulate cortex (41). All these regions are located in thalamo-cortical networks, where abnormalities are believed to be central to the pathogenesis of schizophrenia (10, 42, 43).

In contrast, in the analysis of functional data, abnormalities were located within fronto-parietal and default mode networks, which are thought to be important for decision making, working memory, and general monitoring of internal and external environments (20, 44, 45). In particular, the decreased amplitude of low-frequency fluctuation in medial prefrontal areas and the inferior parietal lobules bilaterally were consistent with previous studies in drug-naïve schizophrenia patients (19). More interestingly, a small cohort study of antipsychotic-naïve patients with first-episode schizophrenia showed significantly increased synchronous regional brain function after 6 weeks of antipsychotic treatment, especially in the left and right prefrontal, medial frontal, and parietal cortex, the left superior temporal cortex, and the right caudate nucleus (46). These regions include areas where pre-treatment alterations were observed in the present study, consistent with the possibility that some of these changes may be shorter-term alterations associated with acute psychosis. Functional deficits in the medial frontal gyrus are thought to be part of the core pathogenesis of schizophrenia and may underlie a number of symptoms, including apathy, lack of emotion, and blunted affect (47). Besides medial prefrontal regions, we also observed an increased amplitude of low-frequency fluctuation in inferior parietal regions bilaterally. Both inferior parietal regions and prefrontal areas bilaterally play a key role in high-level cognitive and executive processing (48, 49), and functional activation studies have shown that deficits in

these regions are greater during than after episodes of psychosis (50).

It is interesting that the regions with anatomical and functional changes were so strikingly dissociated and that gray matter volumes in affected regions were not significantly associated with the amplitude of low-frequency fluctuations. Previous studies have also reported different anatomical and functional abnormalities in the same patients (12, 19, 51), although one recent study (52) showed reduced linkage between regional gray matter volume and functional activation in schizophrenia patients. One possible explanation is that fMRI may reflect physiological alterations related to acute psychosis, while changes in brain anatomy reflect more stable and long-standing alterations. This possibility is supported by previous findings that functional changes in fronto-parietal and default mode networks were normalized after 6 weeks of antipsychotic treatment and clinical remission (46), while anatomical deficits in thalamo-cortical networks are more stable and show slow and modest progressive change over the course of illness (7–9). While the possibility that fMRI changes more directly reflect psychosis-related neurophysiological changes is appealing, the lack of correlation with positive symptoms on the PANSS and with illness duration suggests that BOLD signal alterations may better track the presence than the severity or duration of psychosis.

Although there were many overlaps in anatomical findings in patients with and without prominent negative symptoms, it is noteworthy that patients with prominent negative symptoms showed more pronounced gray matter volume alterations in some regions, notably the left dorsolateral prefrontal cortex (53). On the other hand, no differences were seen in the pattern of functional alteration between patients with and without prominent negative symptoms, suggesting that the impact of psychosis on brain physiology may be similar regardless of the severity of more persistent negative symptoms.

In summary, this study provides evidence that anatomical and functional deficits are seen in different brain regions in a large sample of antipsychotic-naïve first-episode schizophrenia patients. An important caveat is that resting-state studies do not evaluate the functional integrity of all brain regions equally; default mode regions, for example, normally show more robust effects associated with the resting state, and thus sensitivity to illness effects may be greater in these regions. Activation studies in different regions of interest can provide complementary information with resting-state studies of structure-function relationships. Findings from the present study, along with future work clarifying the causes of the functional and structural changes reported and their dissociation, may provide new insight into the underlying neuropathology of the early course of schizophrenia.

Received Sept. 2, 2012; revisions received Nov. 13, 2012, and Feb. 4, 2013; accepted March 4, 2013 (doi: 10.1176/appi.ajp.2013.12091148). From the Huaxi MR Research Center, Department of Radiology, Center for Medical Imaging, West China Hospital of Sichuan University, China; the Department of Radiation Oncology, Cancer Hospital (Institute), Chinese Academy of Medical Science/Peking Union Medical College, Beijing; the Department of Psychiatry, Stat Key Lab of Biotherapy, West China Hospital of Sichuan University, Chengdu, China; and the Departments of Psychiatry and Pediatrics, University of Texas Southwestern Medical Center, Dallas. Address correspondence to Dr. Lui (lusuwcoms@tom.com) or Dr. Gong (qiyonggong@hmrc.org.cn).

Wenting Ren and Wei Deng contributed equally to this study.

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