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ORIGINAL ARTICLE

Age-Related Reduction in Cortical Thickness in First-Episode Treatment-Naïve Patients with Schizophrenia

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Abstract Substantial evidence supports the neurodevelopmental hypothesis of schizophrenia. Meanwhile, progressive neurodegenerative processes have also been reported, leading to the hypothesis that neurodegeneration is a characteristic component in the neuropathology of schizophrenia. However, a major challenge for the neurodegenerative hypothesis is that antipsychotic drugs used by patients have profound impact on brain structures. To clarify this potential confounding factor, we measured the cortical thickness across the whole brain using high-resolution T1-weighted magnetic resonance imaging in 145 first-episode and treatment-naïve patients with schizophrenia and 147 healthy controls. The results showed that, in the patient group, the frontal, temporal, parietal, and cingulate gyri displayed a significant age-related reduction of cortical thickness. In the control group, age-related cortical thickness reduction was mostly located in the frontal, temporal, and cingulate gyri, albeit to a lesser extent. Importantly, relative to healthy controls, patients exhibited a significantly smaller age-related cortical thickness in the anterior cingulate, inferior temporal, and insular gyri in the right hemisphere. These results provide evidence supporting the existence of neurodegenerative processes in schizophrenia and suggest that these processes already occur in the early stage of the illness.

Keywords Schizophrenia · Cortical thickness · Age-related

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Introduction

The neuropathology of schizophrenia has been investigated for over a century [1]. In the past two decades, the neurodevelopmental hypothesis, being dominant and popular in this field, has provided significant insight into understanding the etiology and pathology of the illness. With substantial supporting data, this hypothesis suggests that etiological and pathogenic factors disrupt the circuits in the brain during early development, and this results in malfunction during late adolescence or early adulthood [2–4]. Meanwhile, evidence of neurodegeneration in schizophrenia has also been reported [5–7]. Studies have revealed progressive gray matter decreases in first-episode [8–13] and chronic [14–18] patients with schizophrenia. In addition, it has been shown that the rate of cortical thickness decay in patients with schizophrenia is considerably faster than that in healthy controls [19–21]. These

results have collectively led to a neurodegenerative hypothesis of schizophrenia, suggesting that neurodegeneration might also be a characteristic component in its neuropathology. This hypothesis can help explain the heterogeneous but commonly deteriorating clinical course of the illness and the apparent ability of treatment to modify its course [22–24], and thus can be complementary to the neurodevelopment hypothesis.

Although a neurodegenerative process is potentially important in understanding the neural mechanisms of schizophrenia, it has been argued that it could be a manifestation of the effects of antipsychotic drug treatment rather than being characteristics of the illness itself [25]. This notion was supported by the fact that most of the aforementioned studies were conducted on individuals who were already on antipsychotic medications, and it has been repeatedly shown that antipsychotic drugs have a profound impact on brain structures and functions [26], both chronically [27, 28] and acutely [29]. Indeed, studies have reported that the progressive cortical decay process is attributable to treatment with antipsychotics [8, 19, 30]. This concept has been further corroborated by even stronger effects reported in animal studies [31]. Furthermore, the neurodegenerative hypothesis is complicated by inconsistent results in the literature [32–34]. For instance, van Haren and colleagues showed that the cortical thickness in patients with schizophrenia progressively decreases across the entire course of the illness relative to healthy controls [19], whereas several other studies have reported no significant age-related changes in either global or regional cortical thickness [33–35].

The confounding effects of antipsychotic drugs on brain structures make it difficult to rigorously test the neurodegenerative hypothesis. To address this issue, in the present study we examined changes in age-related cortical thickness as a function of age in a large sample of first-episode, treatment-naïve patients with schizophrenia. The patient population was not confounded by any antipsychotics or other factors such as times of hospitalization and relapses, and thus could be used to disambiguate the origin of the faster gray matter loss previously reported in schizophrenics [36]. We conclude that there are age-related brain structural changes in patients with schizophrenia which are independent of antipsychotics.

Materials and Methods

Participants

A total of 145 patients with schizophrenia or schizophreniform psychosis were recruited from the inpatient and outpatient units of the West China Hospital of Sichuan University from July 2005 to May 2012. Each patient was assessed based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I Disorders (SCID-P; patient version) and diagnosed accordingly [37]. Patients with schizophreniform psychosis were included in the study only if they were found to meet the DSM-IV diagnostic criteria of schizophrenia after being followed up for at least 6 months and at most 12 months. We performed the follow-up by contacting the family members or the patients by telephone. We interviewed them and checked the medical records if possible to confirm the diagnosis. If a patient and his/her family could not be reached, or a participant no longer met the criteria of schizophrenia, he/she was excluded from the study. All patients were experiencing first-episode psychosis and were treatment-naïve at the time of clinical assessment and MRI scan. The age at the first psychotic episode for each patient was determined by the onset of psychotic symptoms (delusion, hallucination, disorganized speech, or disorganized/catatonic behaviors) or negative symptoms (affective flattening, alogia, or avolition) recorded in the patient's medical history or reported by the patient and/or his/her family members. The duration of untreated psychosis (DUP) was calculated accordingly. The Positive and Negative Syndrome Scale (PANSS) [38] and the Global Assessment Function (GAF) scale [39] were used to assess the severity of clinical symptoms and social function, respectively.

A total of 147 healthy controls were recruited from the local community by poster advertisement. They were interviewed by experienced psychiatrists using the SCID non-patient version to ensure the absence of any major mental disorder. Individuals who were pregnant or had any history of alcohol or drug abuse, or any severe neurological illness such as brain tumor or epilepsy were excluded. All participants were Han Chinese and right-handed, as assessed using Annett's Hand Preference Questionnaire [40]. Brain MRI images of all participants were inspected by an experienced neuroradiologist and no gross abnormality was observed in any participant. This research was approved by the Ethics Committee of West China Hospital of Sichuan University, China, and was in accordance with the Declaration of Helsinki. Written informed consent was given by all participants after being provided with a complete description of the study. Part of the patient sample has been used in other reported studies [41–43].

MRI Data Acquisition and Processing

All participants were scanned on the same scanner, a Signa 3.0-T scanner (U.S. EXCITE, 8-channel head-coil) at Huaxi MR Research Centre, Department of Radiology in West China Hospital of Sichuan University. High-

resolution 3D T1-weighted MRI images were acquired using the 3D spoiled gradient echo sequence with the following acquisition parameters: repeat time (TR) = 8.5 ms, echo time (TE) = 3.93 ms, flip angle = 12°, slice thickness = 1 mm, single-shot, field of view (FOV) = 24 × 24 cm^2, matrix = 256 × 256, voxel size = 0.47 × 0.47 × 1 mm^3. A total of 156 axial slices covering the whole brain were collected for each participant. All scans were inspected for motion artifacts.

Image processing was conducted using the Freesurfer software package (version 5.1.0, http://surfer.nmr.mgh.harvard.edu) [44, 45]. Briefly, preprocessing steps included removal of non-brain tissue, transformation to the Talairach space, and segmentation of gray/white matter. Subsequently, the cortical surface of each hemisphere was inflated to a spherical surface to locate the pial surface and gray/white matter boundaries. The quality of segmentation and surface reconstruction was visually inspected. Topological defects were corrected manually by following the Freesurfer user guidelines. The images from five participants (4 patients and 1 healthy control) had to be manually corrected. Cortical thickness was calculated by finding the shortest distance between a given point on the estimated pial surface and the gray/white matter boundary and *vice versa*. These two values were then averaged [46]. This calculation method has been shown to be highly reliable [45]. The thickness of each vertex on the cortical surface was mapped onto a common spherical coordinate system using a spherical transformation. Maps were then smoothed using a Gaussian kernel with a full-width-at-half-maximum of 10 mm.

Statistical Analysis

The χ^2 test for categorical variables and independent *t*-tests for continuous variables were used to compare differences between two groups. The mean cortical thickness for each hemisphere was first calculated by averaging the cortical thickness of all vertices across the hemisphere. The general linear model (GLM) was used to examine the main effects of diagnosis (i.e. schizophrenia patients or healthy controls) and age, as well as the age × diagnosis interaction on the mean hemispheric cortical thickness. In addition, the partial correlations between mean hemispheric cortical thickness and the age at illness onset, DUP, GAF scores, and PANSS scores after controlling for age and gender were each examined in the patient group. Statistical analyses were performed using the Statistical Package for the Social Science version 15.0 (SPSS Inc., Chicago, IL).

Vertex-wise GLM was performed using the mri_glmfit function in Freesurfer. First, for each vertex we evaluated the rate of cortical thickness change as a function of age by separately regressing cortical thickness against age in patients and healthy controls after controlling for gender. Second, the age × diagnosis interaction was calculated for each vertex to examine the difference in the rate of change of cortical thickness in relation to age between the patient and control groups after controlling for gender at this vertex. The *P* value was corrected at the cluster level using Monte Carlo simulations with 10,000 interactions. Third, clusters exhibiting significant differences in the rate of change of cortical thickness between the two groups were selected as regions of interest (ROIs). The mean cortical thickness of ROIs was calculated using Freesurfer for each participant. Finally, correlations between cortical thickness and DUP, age at disease onset, GAF scores, as well as PANSS scores were separately examined for each vertex after controlling for age and gender in the patient group. Statistical significance of correlations was set at $P < 0.05$ after correction for multiple comparisons using the criteria of false discovery rate (FDR).

Results

Demographic Characteristics and Clinical Profiles

The demographic characteristics of all participants are shown in Table 1. Out of 145 patients, 63 were ≤ 20 years old, 35 were > 20 and ≤ 25, 15 were > 25 and ≤ 30, 25 were > 30 and ≤ 40, and 7 were > 40 and ≤ 45. There was no significant difference in gender, age, and duration of education between the patients with schizophrenia and the healthy controls.

Mean Hemispheric Cortical Thickness

First, we compared the mean cortical thickness of the left and right hemispheres in patients and healthy controls using the independent *t*-test. There was no difference in the mean cortical thickness for either the left ($t = 1.282$, $P = 0.201$) or the right hemisphere ($t = 1.468$, $P = 0.143$) between patients (left hemisphere, 2.54 ± 0.10 mm; right hemisphere, 2.55 ± 0.11 mm) and healthy controls (left hemisphere, 2.53 ± 0.10 mm; right hemisphere, 2.53 ± 0.10 mm).

Second, we tested the effects of age and diagnosis on the mean cortical thickness. There was a significant main effect of age on the mean cortical thickness for both the left ($F = 85.380$, $P < 0.001$) and the right ($F = 76.172$, $P < 0.001$) hemispheres.

There was a significant main effect of diagnosis ($F = 7.550$, $P = 0.006$) and age × diagnosis interaction ($F = 6.742$, $P = 0.010$) on the mean cortical thickness of the right hemisphere. That meant that there was difference in the mean cortical thickness of the right hemisphere between patients and healthy controls considering the

Table 1 Demographic characteristics of first-episode treatment-naïve patients with schizophrenia and healthy controls.

Variables	Patients (n = 145)	Healthy controls (n = 147)	t/χ^2	P
Male:female	69:76	71:76	0.015	0.907
Age (years)	24.5 ± 7.9	25.9 ± 8.5	−1.484	0.139
Range (years)	16–49	16–49		
Duration of education (years)	12.2 ± 3.0	12.8 ± 3.2	−1.484	0.139
Range (years)	5–20	5–20		
Age at onset (years)	23.6 ± 7.9			
Range (years)	12.8–43.9			
Duration of untreated psychosis (months)	10.8 ± 19.2			
Median	[25% quantile, 75% quantile]	4 [1.7, 13.0]		
Range (months)	1–145			
GAF scores	29.5 ± 10.5			
PANSS scores				
Total	93.1 ± 17.3			
Positive	25.2 ± 6.1			
Negative	19.9 ± 8.2			
General psychopathology	48.1 ± 9.6			

effect of age. However, there was no significant main effect of diagnosis (F = 1.806, P = 0.180) or age × diagnosis interaction (F = 1.463, P = 0.228) on the mean cortical thickness of the left hemisphere.

In the patient group, there were no significant correlations between mean cortical thickness and age at disease onset, DUP, GAF scores, or PANSS scores after controlling for age and gender for either hemisphere (Table 2).

Vertex-Wise Analysis of Cortical Thickness

To assess the change of cortical thickness with age in specific brain regions, we regressed cortical thickness against age for individual vertices across the whole brain. There were significant vertex-wise correlations between cortical thickness and age in both patients and healthy controls (Fig. 1). The slope of the regression of cortical thickness against age was predominantly negative across the brain for both groups, suggesting a gradual reduction of cortical thickness with increased age in both healthy participants and patients. In the patient group, regions with significant negative age–cortical thickness slopes were mostly located in the frontal, temporal, parietal, and cingulate gyri. In the control group, regions with significant negative age–cortical thickness slopes were mostly located in the frontal, temporal, and cingulate gyri, albeit to a lesser extent. These results showed that in both patients and healthy controls, the cortical thickness decreased with age, and this trend was considerably more pronounced in patients. However, a cluster located in the temporal gyrus

Table 2 Correlations between mean hemispheric cortical thickness and age at illness onset, DUP, GAF scores, and PANSS scores in the patient group after controlling for age and gender.

	Mean cortical thickness of left hemisphere		Mean cortical thickness of right hemisphere	
	r	P	r	P
Age at onset	− 0.134	0.125	− 0.101	0.248
DUP	0.139	0.113	0.105	0.230
GAF scores	0.008	0.928	0.017	0.849
PANSS scores				
Total	0.111	0.207	0.061	0.489
Positive	0.142	0.105	0.111	0.206
Negative	0.059	0.503	0.045	0.605
General psychopathology	0.130	0.138	0.125	0.155

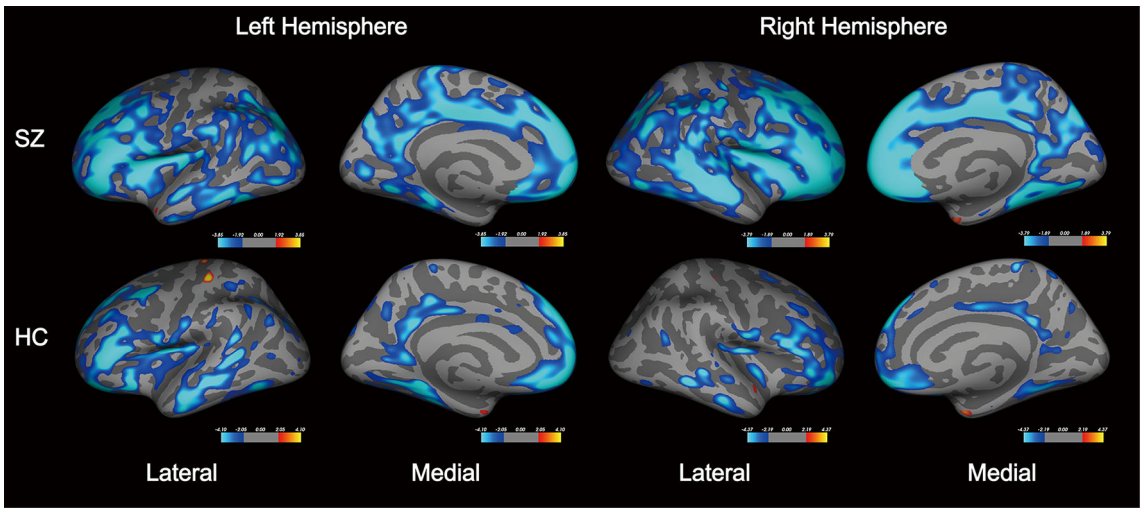

Fig. 1 Vertex-wise correlation between cortical thickness and age in patients with schizophrenia and healthy controls. Blue regions represent negative correlations and red regions represent positive correlations. Color bars show $-\log(P)$. Statistical significance was thresholded at $P < 0.05$, FDR corrected. SZ, patients with schizophrenia; HC, healthy controls.

in each hemisphere showed a significant positive cortical thickness–age slope in both patients and healthy controls.

Statistically significant differences were found in the rate of change of cortical thickness with age (i.e. the regression slope of cortical thickness against age) between the patient and control groups ($P < 0.05$, corrected at the cluster level using Monte Carlo simulations with 10,000 interactions) (Fig. 2). Relative to healthy controls, patients exhibited a significantly smaller age-related cortical thickness in the anterior cingulate, inferior temporal, and insular gyri in the right hemisphere. These three clusters were defined as ROIs. The relationship between mean cortical thickness and age for the three ROIs in patients and healthy controls is shown in Fig. 3.

No brain region showed a slower reduction in cortical gray matter thickness in patients than healthy controls. No vertex showed a significant difference in the absolute cortical thickness between patients and controls after FDR correction for multiple comparisons. In addition, no correlations between cortical thickness and age at disease onset, DUP, PANSS scores, or GAF scores survived the FDR correction for multiple comparisons after controlling for age and gender in the vertex-wise analysis.

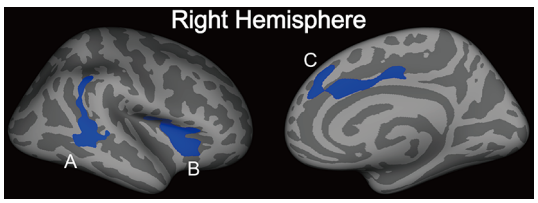

Fig. 2 Regions showing significant differences in the rate of change of cortical thickness as a function of age between the patient and control groups. Statistical threshold was set at $P < 0.05$, corrected at the cluster level using Monte Carlo simulations with 10,000 replications. Significantly faster cortical reduction in patients relative to controls was observed in the temporal and parietal gyrus (A), insula (B), and anterior cingulate gyrus (C). These regions were defined as ROIs.

Discussion

In the present study, we assessed the change of cortical thickness with age in un-medicated patients with schizophrenia and matched controls. Our results showed that the cortical thickness decreased with age in most brain regions in both patients and healthy controls, and the rate of age-related gray matter loss was significantly more pronounced in patients with schizophrenia relative to healthy controls, especially in the right anterior cingulate, inferior temporal, and insular gyri. Because the patients recruited in the study were all at their first psychotic episode and treatment-naïve, this difference cannot be attributed to the effects of antipsychotics. Taken together, these results suggest that schizophrenia can be characterized by an age-related loss of gray matter and this loss is already present in the early stage of the illness.

Age-Related Gray Matter Loss Might be a Characteristic Feature in Schizophrenia

Studies have reported faster gray matter loss in both cortical volume [8, 9, 11, 12, 30, 47] and cortical thickness [19, 48–50] throughout the course of the illness. The finding of the present study further suggests that this process is already manifest in the early stage of the disease, and may occur even before the onset of the illness.

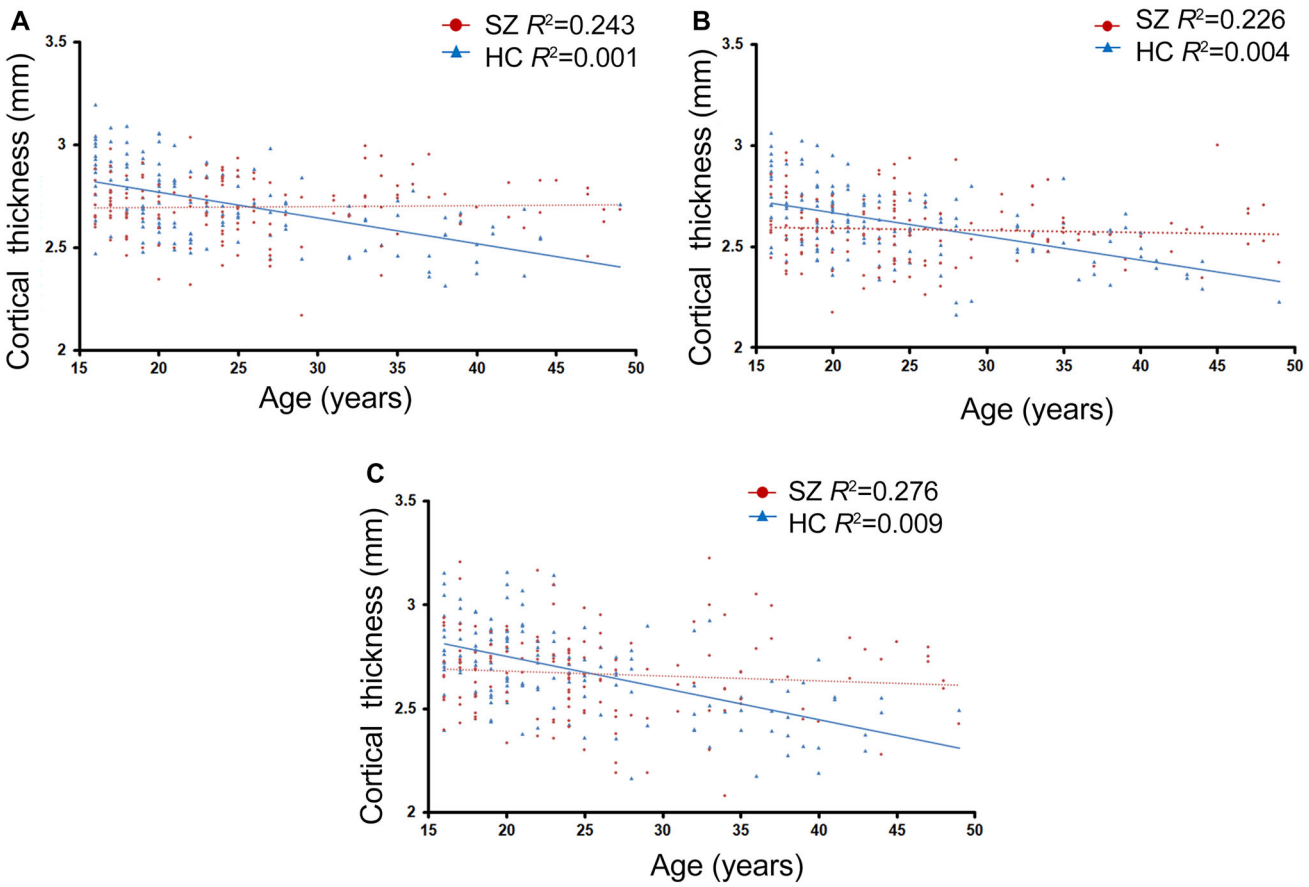

Fig. 3 Regression of mean cortical thickness in ROIs (**A**, temporal and pariental gyrus; **B**, insula; **C**, anterior cingulate gyrus) against age in patients with schizophrenia and healthy controls. SZ, patients with schizophrenia; HC, healthy controls.

Particularly, the present study showed that the insular, anterior cingulate, and temporal cortices in patients demonstrated more pronounced cortical thinning relative to healthy controls. Interestingly, these regions coincide with the functional brain network that exhibits significant degeneration in patients with behavioral variant frontotemporal dementia [51]. Moreover, the insular and anterior cingulate cortices have been found to progressively degenerate before the onset of psychosis [52, 53]. All these results collectively suggest that a neurodegenerative process manifested as age-related gray matter loss might be a key feature in schizophrenia.

Faster Age-Related Cortical Thickness Reduction in Schizophrenia Was Not Due to Antipsychotics

The major controversy over the neurodegenerative hypothesis centers on whether faster gray matter loss in patients in fact results from the effects of antipsychotic drugs. Indeed, use of antipsychotics has been shown to have a profound impact on brain structures, making it difficult to conclude whether any structural abnormalities identified are characteristic of the pathophysiology of the disease or merely a confounding effect of treatment [25, 54, 55]. Furthermore, recent research has shown that reductions in cortical thickness are not consistently reported [35]. In addition, different types of antipsychotic may have different effects on the brain. For instance, typical antipsychotics have been associated with brain tissue loss while atypical antipsychotics have not [56]. Furthermore, the clinical functional outcome as a result of treatment has also been related to structural differences in the brain [19, 57, 58]. These factors may all contribute to the inconsistent results in the literature in terms of the rate of gray matter decay between patients and controls [33, 34]. One important contribution of the present study is that it was conducted on treatment-naïve patients and thus eliminated all the confounding factors noted above. As a result, the finding of more pronounced gray matter loss in this patient group provides important evidence supporting the neurodegenerative hypothesis.

Evidence for the "Two-Hit" Model

Given the strong evidence supporting the developmental origin of schizophrenia, early developmental insult may

account for the dysfunction of the brain which leads to later neurodegeneration in schizophrenia [59, 60]. Therefore, by considering both the neurodevelopmental and neurodegenerative hypotheses, the mechanisms underlying schizophrenia can perhaps be reformulated by progressive developmental models [61, 62], including the "two-hit" model [63, 64]. Specifically, these hypotheses postulate that an early developmental deficit leads to the dysfunction of specific neural networks that account for premorbid signs and symptoms, and the excessive elimination of synapses and loss of plasticity account for the emergence of symptoms. The results of the present study support these models given that the age range of the patients in our study was quite large.

Other Potential Factors that Can Contribute to Faster Cortical Thinning in Schizophrenia

Several factors may contribute to the finding of the present study. One factor is neuronal pruning. The cerebral cortex undergoes progressive thinning from childhood to puberty and early adulthood because of pruning and later becomes steady in normal populations [65]. There is evidence suggesting abnormal pruning in schizophrenia, including reduced synaptic products [66, 67] and reduced spine density and smaller dendritic arbors in the prefrontal cortex [68]. Accelerated neuronal pruning in patients may lead to a faster cortical thinning process in patients. However, since pruning predominantly occurs during the adolescent period, while the age range of the participants in the present study was considerably larger (16–49 years), pruning cannot be the only reason for our finding. Other factors such as neurotoxicity may also cause neuronal shrinkage and thus induce gray matter loss. *N*-Methyl-*D*-aspartate receptor antagonists such as dizocilpine (MK-801) have been found to be neurotoxic, causing cell death, and are used to model schizophrenia [69, 70]. Further studies are needed to determine the exact neurobiological basis underlying the faster cortical thinning process in schizophrenia.

Potential Limitations

It has to be noted that in the present study we used a linear model to test the relationship between cortical thickness and age in patients with schizophrenia and healthy controls, although the developmental trajectories of the cortex can be nonlinear [71]. Linear model analysis assumes the same rate of degeneration before and after onset of the first episode. More sophisticated analysis may be needed to elucidate a possibly more complicated pattern in future studies with a bigger sample set.

Another limitation of the present study is that a cross-sectional design was applied. To eliminate the confounding effects of antipsychotic drugs on brain structures, one could theoretically conduct longitudinal studies on un-medicated patients throughout the course of illness to examine possible neurodegenerative processes. However, such studies are not ethical. Alternatively, cross-sectional designs, particularly with large groups of participants, can also offer valuable information on age-related brain changes. In fact, the cross-sectional study design has frequently been used as an important tool for investigating progressive changes in normal brain development and aging [72], as well as in different diseases [73].

Moreover, we carried out a clinical review to confirm the inclusion/exclusion criteria, although urine tests would have provided a more precise measurement of substance abuse. Some participants could not be included due to inability to comprehend the procedures or to their acute clinical status that made interviewing difficult or unreliable. Some factors including stress, anxiety, smoking, and sleep disruption were not recorded and included in our analysis.

Summary

In conclusion, in the present study we found extensive and excessive age-related gray matter loss in the cortex in first-episode and treatment-naïve patients with schizophrenia. These changes were especially pronounced in the right insular, anterior cingulate, and inferior temporal gyri, and cannot be attributed to antipsychotics. This study offers critical insight into understanding the neuropathophysiology of schizophrenia.

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Conflict of interest Authors declare that they have no conflict of interest.

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