Accelerated reductions of cortical thickness in never treated schizophrenia patients with disease duration over 5 years

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Aims and objectives

Since the hypothesis of neuroprogressive changes in schizophrenia was put forward by Kraepelin in his concept of dementia praecox [1], the possibility of progressive brain changes in schizophrenia has been of sustained interest.

Across longitudinal studies of first episode patients, a complex pattern of structural alterations has been described over the course of illness, with fronto-temporal cortex changes being most consistently observed [2, 3]. However, these studies are restricted to early illness course for the foreseeable future because of the decades required to track lifespan effects, and they are all conducted with patients treated with antipsychotic medications that may adversely impact brain anatomy [4]. Thus, questions about how different brain regions may be altered over the longer-term course of schizophrenia and whether they represent treatment effects remain unresolved.

In this circumstance, cross-sectional studies concentrating on examining structural changes in relation to age or disease duration in chronic patients never treated with antipsychotic medication may provide important insights about longer-term changes in brain anatomy over the illness course [5, 6], without the confounding influences of antipsychotic and other psychiatric medications. In developing countries, such samples can still be identified and studied. Recently, 17 Chinese medication-naïve chronic patients were found with grey matter volume (GMV) reduction and cortical thinning in the temporal lobe [7]. However, in that study, the potential relationship between morphometric changes and age or illness duration was not reported. In a similar sample from India, McCreadie et al found no relations between duration of untreated illness and size of lentiform nuclei and ventricle-hemisphere ratio abnormalities but relations to neocortical volumes and thickness were not examined [8].

In the present study, we conducted MRI studies on never-treated chronic schizophrenia patients with illness duration ranging from 5 to 47 years. We sought first to identify brain regions with altered cortical thickness or GMV relative to matched controls, and then determined whether within those regions there were group differences in age-related changes in brain anatomy.
Methods and materials

Participants

Twenty-five never-treated chronic schizophrenia patients were recruited at the Mental Health Centre of the West China Hospital. The ethics committee of West China Hospital approved the study and all participants gave written informed consent to their participation. Diagnoses of schizophrenia were determined by the consensus of two experienced clinical psychiatrists using the Structured Interview for DSM-IV Axis I Disorders (SCID). Duration of untreated illness was evaluated by the Nottingham Onset Schedule [9] (with information provided by the patients, family members and other sources). Psychopathology ratings were obtained using the Positive and Negative Syndrome Scale (PANSS) [10].

Healthy controls (n=33) were recruited from the same area via poster advertisements. The SCID-Non-Patient Version was used to establish the lifetime absence of psychiatric illness, and there was no known history of major psychiatric illness in their first-degree relatives.

All participants were Han Chinese and right-handed. Patients and control subjects were matched in age, sex, and years of education (Table 1). No participants had a history of significant systemic or neurological illness. The following exclusion criteria applied to both groups: (1) age younger than 18 years and older than 80 years; (2) history of substance abuse; (3) pregnancy; or (4) major physical illness such as cardiovascular disease and hepatitis, as assessed by clinical evaluations and medical records.

Data Acquisition

MRI examinations were performed on a 3-Telsa GE Signa EXCITE scanner (General Electric, Milwaukee, USA) with an 8 channel phase array head coil. High resolution T1-weighted images were acquired with a volumetric three-dimensional spoiled gradient recall (SPGR) sequence (TR=8.5 ms, TE=3.4 ms, flip angle=12°). A field of view of 240 × 240 mm² was used with an acquisition matrix comprising 256 readings of 128 phase-encoding steps, producing 156 contiguous 1.0 mm coronal slices. The final matrix of T1-weighted images was automatically interpolated in plane to 512 × 512, yielding an in-plane resolution of 0.47 × 0.47 mm². T1- and T2-weighted magnetic resonance images were inspected by an experienced neuroradiologist; no scan artifacts or gross brain abnormalities were observed in any participant.
**Imaging processing**

Cortical modeling and volumetric segmentation of structural MRI data were performed with the FreeSurfer package (version 5.1.0, http://surfer.nmr.mgh.harvard.edu/). Cortical thickness was measured as the difference between equivalent vertices in the pial and grey-white matter surfaces [11]. Briefly, the main process included automated registration to Talairach space, segmentation of the subcortical white matter and gray matter volumetric structures, intensity normalization, tessellation of gray matter and white matter boundaries, and automated topology correction and surface deformation following intensity gradients to optimally place the gray/white and gray/CSF borders defined at the location with the greatest shift in signal intensity [11-15].

Since the surface-based analysis was restricted to the cortical mantle, we used volumetric analysis to assess deep grey matter using the Diffeomorphic Anatomical Registration using the Exponentiated Lie algebra (DARTEL) toolbox [16]. The processing steps were as follows: setting the image origin to the anterior commissure manually; using the DARTEL toolbox to produce a high-dimensional normalization protocol; and using standard smoothing with an isotropic Gaussian kernel with full width-half maximum (FWHM) of 8 mm.

**Statistical Analysis**

Vertex-wise cortical maps were compared between patients and controls using a general linear model with age, sex and total intracranial volume included as covariates. Non-parametric cluster-wise correction for multiple comparisons was performed using the FreeSurfer Monte Carlo simulation tool with a corrected cluster-forming threshold of p<0.05 [17]. While for GMV, inter-group comparison was performed using the two sample t test, covarying for age, sex and intracranial volume. Clusters with an empirical p<0.05 were regarded statistical significance, fully corrected for multiple comparisons across space with false discovery rate (FDR).

To identify differential relationships between anatomical measures and age in regions where group differences had been detected, we first extracted and averaged values of cortical thickness and GMV in these regions for each subject. Aging effects on the human brain were suggested to follow a nonlinear trajectory in both schizophrenia patients [18], and the healthy [19]. Therefore, nonlinear regression analyses using a quadratic model of age effects in relation to anatomic measures were conducted for each group, and compared between groups to determine whether there was a significant differential rate of age-related change in patients and controls. This was achieved by conducting F tests to determine whether the shape of regression curves were significantly different [20]. Effect of duration of illness was examined with the same model in patients as age because these two are highly corrected.
Table 1: Demographic and Clinical Characteristics of Chronic but Never-Treated Schizophrenia Patients and Healthy Controls. SD, standard deviation.

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Schizophrenia patients (n=25)</th>
<th>Healthy controls (n=33)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td>Age (years)</td>
<td>46.68</td>
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<td>Education (years)</td>
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<td>Duration of illness (years)</td>
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<td>Age of onset (years)</td>
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<tr>
<td>Negative symptoms</td>
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<td>6.59</td>
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<tr>
<td>Positive symptoms</td>
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<td>7.34</td>
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<tr>
<td>General psychopathology symptoms</td>
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<td>2.12</td>
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<tr>
<td>Paranoid</td>
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</table>
Results

**Patient-Control differences in cortical thickness**

Compared to healthy controls, patients showed significantly decreased cortical thickness in bilateral ventromedial prefrontal cortices (vmPFC) extending laterally to orbitofrontal cortices, and in left superior temporal gyrus (STG) and right pars triangularis, while increased cortical thickness was found in the left superior parietal lobe (SPL) extending to occipital cortex (p<0.05, Figure 1).

**Age-related changes in cortical thickness**

Schizophrenia patients had a significant age-related decline of cortical thickness in bilateral vmPFC, left STG and right pars triangularis, but no significant relationship with age was found in the left SPL. In healthy controls, measurements in regions of bilateral vmPFC, left STG and right pars triangularis showed no significant association with age, whereas left SPL cortical thickness decreased with age (Figure 2, Table 2).

In direct group comparison of age-related changes in areas of interest, we observed a faster decline of cortical thickness in right vmPFC, left STG and right pars triangularis with aging and significantly reduced age-related cortical thinning of left SPL in patients relative to controls (p<0.05). A trend for greater age-related cortical thickness reduction was observed in left vmPFC in patients relative to controls (p=0.053, Table 2).

When these effects were examined in relation to disease duration in patients, we found that cortical thickness of bilateral vmPFC, left STG and right pars triangularis exhibited significant duration-associated reduction (p<0.05), similar to modeled age-related effects.

**Voxel-based morphometry analysis of GMV**

Patients had larger GMV in left putamen extending to insula and in right putamen, but smaller GMV in right lingual gyrus extending to cuneus and in right middle temporal gyrus (MTG), relative to healthy controls (Figure 3). GMV of bilateral putamen was not significantly associated with age in either group, or with duration of illness in patients. GMV of right MTG decreased significantly in relation to age in both patients and controls, but there was no significant group difference in these effects.
**Fig. 1:** Cortical Differences between Chronic but Never Treated Schizophrenia Patients and Healthy Controls with significance determined by Monte Carlo Simulation. Increased cortical thinning in patients is indicated by blue/cool color and reduced thinning relative to controls is indicated by red/warm color. L, left hemisphere; R, right hemisphere.

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Fig. 2: Quadratic Models of Cortical Thickness Change with Age in Regions Where Significant Differences of Overall Cortical Thickness Were Observed between Chronic but Never-Treated Schizophrenia Patients and Healthy Controls. L, left hemisphere; R, right hemisphere.

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Table 2: Average Rate of Reduced or Increased Cortical Thickness per Year for Chronic but Never-Treated Schizophrenia Patients and Healthy Controls. a L, left hemisphere; R, right hemisphere. b +, Increase; -, Decrease.

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Fig. 3: Differences in Grey Matter Volume between Chronic but Never-Treated Schizophrenia Patients and Healthy Controls. Increased cortical volume in patients is indicated by red/warm color and reduced volume relative to controls is indicated by blue/cold color. L, left hemisphere; R, right hemisphere.

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Conclusion

By studying this unique sample of chronic but never-treated schizophrenia patients, the current study adds important new evidence about grey matter changes over the course of schizophrenia without the potential confounding influences of antipsychotic treatment.

Surface-based analysis demonstrated cortical and subcortical alterations in schizophrenia patients involving prefrontal, temporal and parietal lobe regions. More importantly, age-related effects suggest a more rapid rate of cortical thinning in right vmPFC, right pars triangularis and left STG in patients than control subjects, whereas age-related changes in posterior SPL were less than in controls. Volumetric analysis demonstrated significant abnormalities in cortical and subcortical gray matter, notably including increased bilateral putamen volume in patients, but these effects did not have differential aging effects in schizophrenia patients.

Thus, the most important finding of our study is that age-related changes in cortical thickness suggestive of a neuroprogressive process in schizophrenia were found in prefrontal and temporal cortices, while abnormalities in other areas including putamen and parietal cortex did not show accelerated age-related changes suggesting different pathological or compensatory processes.
References


