Brain Structural Abnormalities in a Group of Never-Medicated Patients with Long-Term Schizophrenia

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Data Supplement

Volumetric Changes in Never-Medicated Patients with Long-Term Schizophrenia: Voxel-based Morphometry Analysis with DARTEL

Imaging Processing

All the 3-dimensional high resolution T1-weighted images of the 25 never-medicated patients with long-term schizophrenia and 33 matched healthy comparison subjects were firstly converted to NIFTI format and then were manually reoriented to center on the anterior commissure. Then grey matter volume was calculated using the Diffeomorphic Anatomical Registration using the Exponentiated Lie algebra (DARTEL) toolbox (1), as implemented in Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). All images were segmented into gray matter, white matter, and cerebrospinal fluid and the segmentation procedure would be further refined by high dimensional warping algorithm implicated in the toolbox. This algorithm involves the creation of a study-specific template, with which the segmentation of each individual image was conducted and a more accurate

inter-subject registration was achieved, designed to maximize accuracy and sensitivity (2, 3). The produced grey matter images were modulated to account for volume changes resulting from the normalization process. The homogeneity was also checked across the samples using an algorithm implicated in VBM8 toolbox complementarily. Standard smoothing with an isotropic Gaussian kernel with full width-half maximum of 8 mm was adopted to correct nonlinear grey matter volumes for individual brain size for the following statistical analysis.

Statistical Analysis for Voxel-based Morphometry

Voxel-wise based inter-group comparison of grey matter volume maps 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).

The SPM toolbox MarsBar (marsbar.sourceforge.net) was used to engage the extraction of clusters and data of regions of interest. The averaged grey matter volume values in regions with significant group differences were extracted for each subject and modeled with age and duration of illness using quadratic regression in both groups. Pearson correlation was conducted between these values and age of onset. With age and sex included as covariates, these values were also partially correlated with PANSS scores (including total scores, subscales and each factor score), and years of education.

Findings for Voxel-based Morphometry

Relative to healthy comparisons, schizophrenia patients showed grey matter enlargement in left putaman extending to insula and right putaman, and grey matter reduction in right lingual gyrus extending to cuneus, and in right middle temporal gyrus ($p<0.05$, Figure 3).

When modeled with age, only grey matter volumes of right middle temporal gyrus exhibited age-related decline in both groups (Figure S1, Table S1), but no significant difference was observed between these two declined curves ($p>0.05$). Besides, volumes of right middle temporal gyrus was also found with a significant decline with illness duration in patients ($p<0.05$). Volumes of bilateral putamen and right lingual gyrus exhibited no significant association with age or illness duration. The mean values of grey matter volume were found not correlated to onset age for all regions.

In the exploratory analysis, only volumes of right lingual gyrus exhibited a significantly negative association with PANSS activation factor scores ($p<0.05$), while others were not significantly correlated with total score, subscales or any factor score of PANSS. Grey matter volumes were found not significantly associated with years of education in any region in patients.

An interesting finding in the voxel-based morphometry analysis is that bilateral putamen showed larger grey matter volume in schizophrenia without the confounding effect of antipsychotic treatment. A detailed discussion has been given in the main text.

As for regions with grey matter reduction, the lingual gyrus is believed to play an important role in vision and dreaming, and its volume reduction has been previously reported to be involved in positive symptoms like hallucinations (4). A recent study also reported patients with predominantly positive symptoms had pronounced grey matter reduction with lingual gyrus involved (5). Consistent with these data, our findings, that grey matter volume reduction of this region and its negative association with activation, support the notion that lingual gyrus plays a role in the psychopathologic model of schizophrenia.

Middle temporal gyrus is a region involved in semantic memory processing and language processes (6, 7), in which abnormalities may account for cognitive deficits in semantic function to some extent. Additionally, grey matter loss in this region has also been suggested to be related to auditory and related abnormalities in higher cognitive function in schizophrenia (8). Duration of illness was negatively associated with volume measures of this region, suggesting possible progressive changes in this region. However, age-related analysis exhibited negative result. Future studies with large sample size may help to clarify this question.

In summary, with the advantage for analysis of subcortical gray matter, volumetric analysis displayed some interesting grey matter changes in this unique sample of never-medicated patients with long-term schizophrenia. It is noteworthy that these findings could not be directly used to compare with results with surface-based analysis due to different methodological factors that may influence the results (9). Furthermore, volume measures were influenced by both cortical thickness

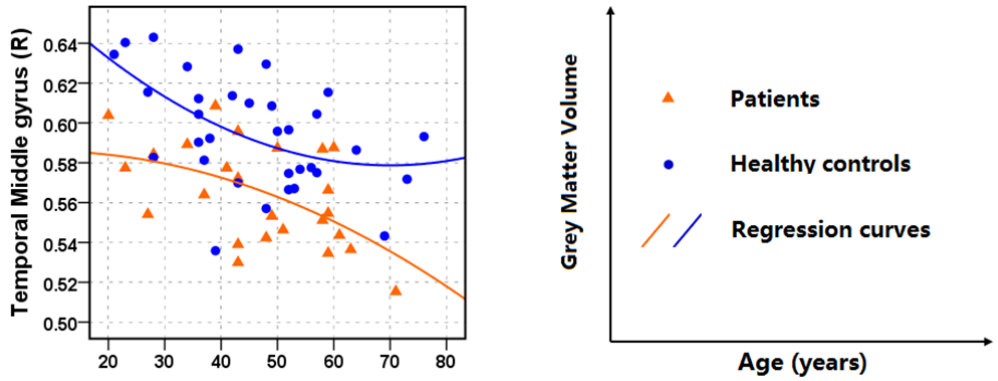
and surface area, and volume was more closely related to surface area than cortical thickness (10). While cortical thickness and surface area are believed to be genetically and phenotypically independent (10), the volumetric results should not used to explain findings reflected by cortical thickness analysis.

Table S1. Differences in Gray Matter Volume between Never-Medicated Patients with Long-Term Schizophrenia and Healthy Comparison Subjects[a]

	Coordinates (MNI)			
	x	y	z	t
Patients > Healthy Comparisons				
Left putamen	-35	5	-12	4.63
	-29	12	4	3.28
Right putamen	30	11	1	4.28
Patients < Healthy Comparisons				
Right middle temporal gyrus	68	-19	-12	4.67
Lingual gyrus	23	-69	1	4.79
	9	-81	9	4.09

[a] Differences are significant at $p<0.05$ with correction for multiple comparisons with false discovery rate.

Figure S1. Quadratic Regression Curves of Grey Matter Volume of Right Middle Temporal Gyrus in Both Never-Medicated Patients with Long-Term Schizophrenia and Healthy Comparison Subjects.

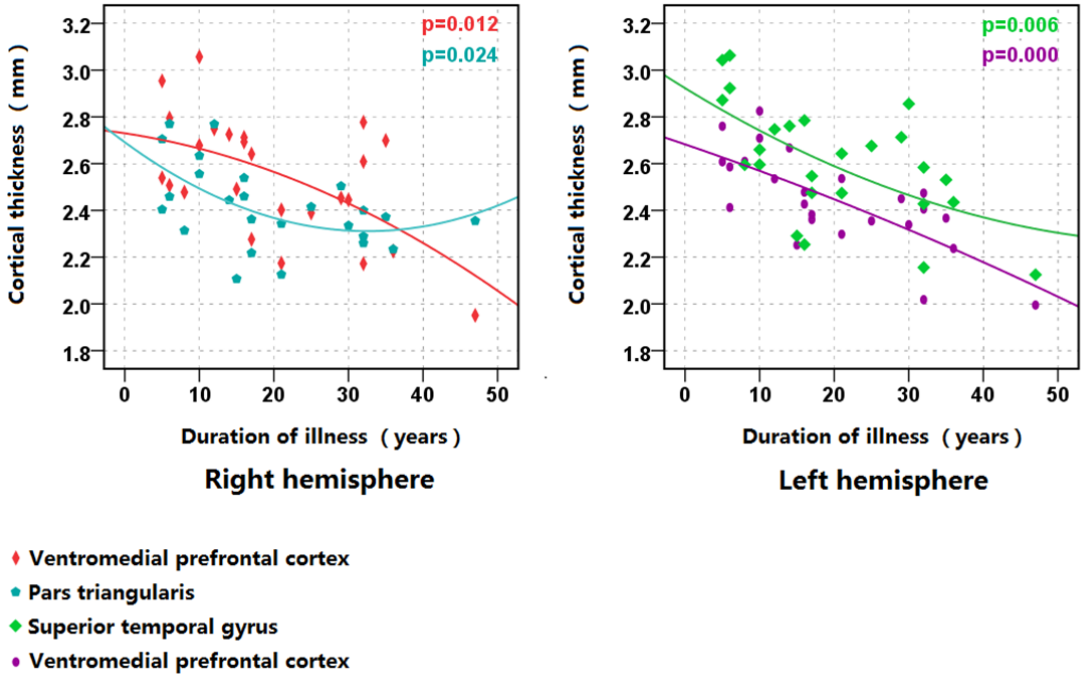


Both schizophrenia patients and healthy comparisons showed significantly grey matter volume reduction over age in right middle temporal gyrus. However, there is no significant difference between the rates of decline between groups.

Findings for Effects of Duration of Untreated Illness on Differences in Cortical Thickness

When effects on cortical thickness were examined in relation to disease duration rather than age, modeled effects were similar in terms of change over the age-span. cortical thickness of bilateral ventromedial prefrontal cortices, left superior temporal gyrus and right pars triangularis was characterized by significant decrease over the illness course ($p<0.05$). No significant association was observed between the cortical thickness of left superior parietal lobe and the duration of untreated illness in patients ($p>0.05$, Figure S2).

Figure S2. Scatter Plots and Quadratic Regression Slopes of Cortical Thickness in Regions Where Group Differences Were Detected with Duration of Illness in Never-Medicated Patients with Long-Term Schizophrenia



Age-related Cortical Differences in Healthy Comparison Subjects with a Larger Sample

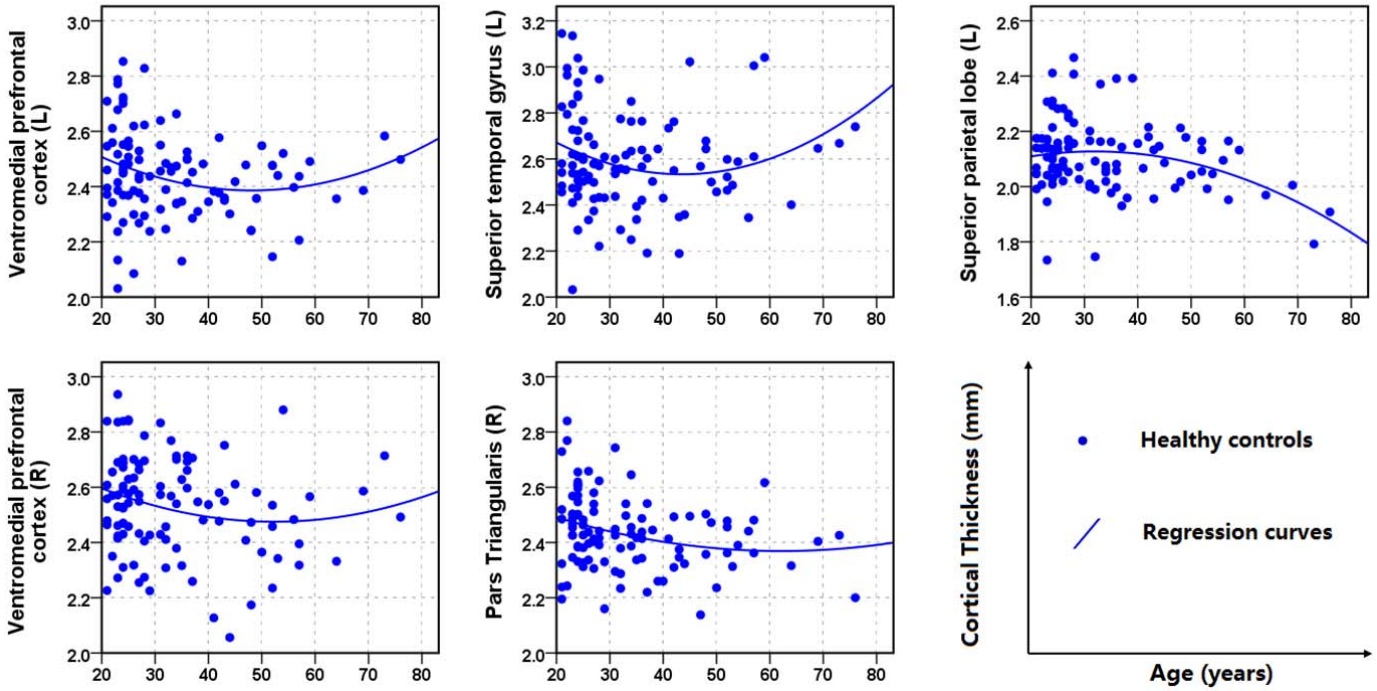
To help establish the representativeness of our healthy comparison data, we further calculated cortical thickness of another healthy sample with the same age range in our previous studies. Subsequently, an integrated sample of 102 healthy subjects was analyzed using similar quadratic regression on aging and cortical thickness of regions where significant group differences have been detected, to see if there were changes in age-related patterns in comparison subjects as reported in the manuscript. Detailed demographic characteristics of the combined healthy sample were given below (Table S2).

With the same nonlinear models, we found that cortical thickness of left superior parietal lobe showed significant age associated decline over time ($p<0.05$), whereas those of other regions, including bilateral ventromedial prefrontal cortices，left superior temporal gyrus and right pars triangularis, did not show any significant associations with age ($p>0.05$). These findings were just the same as those we presented in main text. The regression slopes for these regions have been shown in Figure S3.

Table S2. Demographic Characteristics of the Larger Sample of Healthy Comparisons

Characteristics	**Healthy Comparison Subjects (n=102)**	
	Mean	SD
Age (years)	33.73	12.64
Education (years)	12.54	4.08
	N	%
Gender		
Female	50	49.02
Male	52	50.98

Figure S3. Quadratic Regression Models of Age-related Changes in Cortical Thickness in 102 Healthy Comparison Subjects in Regions Where We Detected Significant Differences in Age-related Changes in Cortical Thickness between Never-Medicated Patients with Long-Term Schizophrenia and Healthy Comparisons.



The cortical thickness of left superior parietal lobe showed significant age-associated decline in the larger group of comparison subjects ($p<0.05$), while cortical thickness of bilateral ventromedial prefrontal cortices, right pars triangularis and left superior temporal gyrus still did not show a significant association with age ($p>0.05$).

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