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Comparison of grey matter volume and thickness for analysing cortical changes in chronic schizophrenia: A matter of surface area, grey/white matter intensity contrast, and curvature

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ABSTRACT

Grey matter volume and cortical thickness are the two most widely used measures for detecting grey matter morphometric changes in various diseases such as schizophrenia. However, these two measures only share partial overlapping regions in identifying morphometric changes. Few studies have investigated the contributions of the potential factors to the differences of grey matter volume and cortical thickness. To investigate this question, 3 T magnetic resonance images from 22 patients with schizophrenia and 20 well-matched healthy controls were chosen for analyses. Grey matter volume and cortical thickness were measured by VBM and Freesurfer. Grey matter volume results were then rendered onto the surface template of Freesurfer to compare the differences from cortical thickness in anatomical locations. Discrepancy regions of the grey matter volume and thickness where grey matter volume significantly decreased but without corresponding evidence of cortical thinning involved the rostral middle frontal, precentral, lateral occipital and superior frontal gyri. Subsequent region-of-interest analysis demonstrated that changes in surface area, grey/white matter intensity contrast and curvature accounted for the discrepancies. Our results suggest that the differences between grey matter volume and thickness could be jointly driven by surface area, grey/white matter intensity contrast and curvature.

1. Introduction

Schizophrenia is a complex and heterogeneous disorder. Many efforts have been made to investigate the aetiology of this disease, including research focusing on genetics, early environment, psychology and neurobiology (Straub et al., 1995; Schröder et al., 1996b; Tsuang, 2000). Advanced morphometric analyses based on objective, non-invasive magnetic resonance imaging (MRI) have been increasingly used to investigate the neuroanatomical correlates of schizophrenia. The most widely used morphometric analysis methods are volume-based grey matter measures such as voxel based morphometry (VBM) and surface-based cortical thickness measures by Freesurfer.

VBM is an automated voxel-based whole-brain analysis suitable to detect cortical and subcortical grey matter volume differences between patients and controls (Ashburner and Friston, 2000). Previous VBM studies have demonstrated widespread grey matter deficits in patients with schizophrenia compared with healthy controls. In particular, deficits were found in the superior/medial temporal gyrus, inferior/medial frontal regions, inferior parietal lobe, insula and some sub-cortical regions such as the thalamus, basal ganglia and lateral or sulcal ventricles (Dazzan et al., 2005; Honea et al., 2005; Ellison-Wright et al., 2008; van Erp et al., 2014).

The estimation of cortical thickness is an automated surface-based method for the assessment of brain cortical thickness changes. It represents a methodological alternative to volume measurements for the investigation of subtle cortical changes in the human brain (Dale et al., 1999; Fischl et al., 1999a). Prior studies examining cortical thickness in schizophrenia identified a broad

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pattern of reduced cortical thickness in the prefrontal regions, temporal regions, superior parietal gyrus, hippocampus and cingulate gyrus (Narr et al., 2005; Schultz et al., 2010b; Kubota et al., 2011; van Haren et al., 2011).

It is well established that brain structural changes are important for understanding the pathophysiology of schizophrenia (McCarley et al., 1999; Shenton et al., 2001). Multiple overlapping regions were found using grey matter volume and thickness measures such as the superior temporal and prefrontal areas. However, obvious differences still existed between the two measures. Previous studies compared the spatial overlap between grey matter volume and cortical thickness measures in schizophrenia. They revealed that surface area changes were present in some regions that demonstrated significant grey matter volume reduction but without cortical thinning (Narr et al., 2005; Voets et al., 2008; Hutton et al., 2009). These findings suggest that grey matter volume changes could be partly driven by cortical thinning and that other factors such as surface area may also contribute to the grey matter volume changes. A study by Palaniiyappan and Liddle (2012) demonstrated that changes of cortical thickness, gyrification and surface area could mediate changes of grey matter volume in schizophrenia, but did not account for all the variances of grey matter volume . A recent study by Kong et al. (2012) demonstrated grey/white matter intensity contrast changes which were similar to, but more widespread than, the changes in cortical thickness in schizophrenia, and which overlapped to some extent with the regions showing grey matter volume reduction in VBM studies . Therefore, grey/white matter intensity contrast could also be a contributor to grey matter volume changes and might account for some discrepancies between grey matter volume and thickness. Until now, few studies have combined surface area, grey/white matter intensity contrast and curvature (a measure of gyrification) together to investigate their contributions to the differences in grey matter volume and thickness.

Therefore, in the present study, we first investigated the changes of grey matter volume and thickness in chronic schizophrenia patients compared with healthy controls. We then examined whether the surface area, intensity contrast and curvature contributed to the differences of the changes between grey matter volume and thickness jointly.

2. Methods

2.1. Participants

The participants comprised 22 patients with chronic schizophrenia and 20 age-matched healthy controls with an average age of 53.95 (standard deviation (S.D.)= 8.53) years and 52.75 (S.D.=8.10) years (this sample is part of the study by Herold et al. (2013); 11 patients and one healthy control were excluded after image quality examination before and after performing the surface and volume analyses). The patients were recruited among the inpatients treated at the section of Geriatric Psychiatry at the University of Heidelberg and the residential care St. Thomas e.V., Heidelberg. The majority of patients (68.1%) were chronically hospitalised. Diagnoses of schizophrenia were established using the German version of the Structured Clinical Interview for DSM-IV (Wittchen et al., 1997). The patients had an average duration of illness of 31.54 (S.D.=12.99) years and received an antipsychotic medication with a mean daily dose of 542.53 (S.D.=385.41) mg of chlorpromazine (CPZ) equivalents (Woods, 2003). Clinical evaluation included ascertainment of personal and family history and detailed physical and neurological examination. None of the participants had a lifetime history of neurological or severe systemic illness, head injury or substance abuse. The investigations were approved by the local ethics committee, and written informed consent was obtained from all participants after the procedures of the study had been fully explained. Detailed demographics are presented in Table 1.

2.2. Image acquisition

MRI data were obtained at the German Cancer Research Center on a 3.0 T MRI scanner (Magnetom TIM Trio, Siemens Medical Solutions, Erlangen, Germany) using a high-resolution T1-weighted 3D magnetisation prepared rapid gradient echo sequence (MP-RAGE). Imaging parameters were as follows: image matrix=256 × 256, voxel size=1 × 1 × 1 mm^3, TR=2300 ms, TE=2.98 ms, TI=900 ms, flip angle=9°, and 160 sagittal slices.

Table 1
Demographic and clinical characteristics.

Parameters	Controls (n=20) Mean (S.D.)	Patients (n=22) Mean (S.D.)	t d.f.=40	P value (t-test and χ^2-test)
Age (years)	52.75 (8.10)	53.95 (8.53)	−0.47	0.64
Education (years)	13.70 (1.95)	12.68 (3.27)	1.2	0.23
Sex (M/F)	12/8	16/6		0.38[a]
Duration of illness (years)	n.a.	31.54 (12.99)		
Medication (mg)	n.a.	542.53 (385.41)		

Data expressed as mean (S.D.); S.D.: standard deviation; d.f.: degrees of freedom; n.a.: not applicable.

[a] χ^2-test.

2.3. Grey matter volume

All the T1-weighed MR images were processed using a VBM8 toolbox in SPM8 (The Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm) with the default parameters on the Matlab 7.1 platform (The Mathworks, Natick, MA, USA). Smoothed, modulated and normalised grey matter images were used for statistical analysis. Smoothing was performed using an isotropic Gaussian kernel of 8 mm.

2.4. Cortical thickness

Cortical thickness was calculated using Freesurfer 5.1.0 (http://www.surfer.nmr.mgh.harvard.edu/; version 5.1.0). The technical details of these procedures have been described in prior publications (Dale et al., 1999; Fischl et al., 1999a; Fischl et al., 1999b; Fischl and Dale, 2000; Segonne et al., 2004). In brief, the first stage is to extract the cortical surface, which involves removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of grey/white matter and intensity normalisation (Sled et al., 1998). The second aim of the processing is to model the cortical surface. Segmented white matter volume is then used to derive a tessellated surface representing the grey/white matter boundary (inner surface), which is automatically corrected for topology defects and expanded to model the pial–grey boundary (outer surface) (Fischl et al., 2001; Segonne et al., 2007). Once the cortical models are completed, cortical thickness, surface area and curvature measures can be estimated using the methods of (Fischl and Dale, 2000). Surface measures are smoothed with a 10-mm Gaussian kernel for statistical analysis.

2.5. Grey/white matter intensity contrast

Grey/white matter intensity contrasts were measured automatically based on grey/white matter and grey matter/cerebrospinal fluid boundaries, which were created by Freesurfer. As described in previous studies (Salat et al., 2009; Kong et al., 2012), grey matter intensities were measured at a depth of 30% through the thickness of the cortical ribbon from the grey/white matter border along the normal direction towards the grey matter/cerebrospinal fluid border; white matter intensities were extracted at 1 mm subjacent to the grey/white matter border along surface normal towards white matter. Grey/white matter intensity contrast was represented as intensity 100 × (white matter – grey matter intensity)/((white matter intensity+grey matter intensity)/2), and it was then smoothed with a 30-mm Gaussian kernel as recommended by Salat et al. (2009).

2.6. Comparison of grey matter volume and cortical thickness

To compare the differences in anatomical locations of group changes between the grey matter volume obtained from VBM and cortical thickness obtained from Freesurfer, the Marsbar toolbox (Brett et al., 2002) was used to generate all cluster-specific masks based on VBM results (t-statistic map). We excluded clusters in subcortical regions, as surface-based measures such as cortical thickness, are restricted to cortical regions. The cluster-specific masks were further trimmed using the Automated Anatomical Labelling (AAL) Atlas (Tzourio-Mazoyer et al., 2002) so that each masked cluster was completely in the cortical region and with anatomical specificity. Then these binary masks were used to obtain mask constrained mean grey matter measures based on the voxels included in the cluster using Statistical Parametric Mapping (SPM).

To visualise the VBM-derived group difference in surface space, VBM results were painted onto the surface template in Freesurfer, which involved the following steps: a mask-constrained group difference *t*-statistic map was first registered onto a Freesurfer average image in line with that in Palaniiyappan and Liddle (2012). Then, volume to surface projection was applied to map the *t*-statistical map onto Freesurfer average surface space for visualisation (Voets et al., 2008; Palaniiyappan and Liddle, 2012).

For obtaining surface measures (area, intensity contrast and curvature) in the masked cluster regions, the binary masks of the clusters, instead of the *t*-statistic map above, were registered onto the Freesurfer average image and then mapped to the average surface using volume to surface projection. Subsequently, region of interest (ROI) labels were created using the volume to label routine in Freesurfer, and the ROI labels were then unwarped back to native space of each subject. The surface area, intensity contrast and curvature in these ROI labels were obtained by averaging the respective values from all the vertices included within the defined clusters for each subject (Fig. 1) (Voets et al., 2008; Palaniiyappan and Liddle, 2012).

For ROI analysis based on surface parcellation, regional surface measures (surface area, curvature and intensity contrast) were obtained based on automatically generated cortical parcellation (Desikan et al., 2006). The average surface measures were calculated in each parcellation including corresponding group-difference clusters.

2.7. Statistical analysis

Group differences of basic demographical characteristics and clinical data of the sample were examined with Student's *t*-test and chi-square test using SPSS 18. Grey matter volume differences based on VBM analysis were analysed using *t*-test in SPM8 with the age and intracranial volume as covariates. Regional effects of schizophrenia on cortical thickness were tested by general linear models (GLM) across the entire cortex controlling for age. The results were corrected for multiple comparisons using a false discovery rate (FDR). *P* values less than 0.05 were considered significant. The effects of different measures on the discrepancy regions (regions with grey matter volume reduction but without corresponding cortical thickness changes) were performed using analysis of covariance based on surface-based parcellation and VBM ROI-constrained regions. *P* values less than 0.05 were considered significant. Volume and cortical thickness analyses were repeated with and without age and medication as covariates for detecting the effects of age and medication. The effect of sex was also tested by comparing groups, which were assorted by sex.

3. Results

3.1. Grey matter volume and cortical thickness comparison: co-localisation of significant results

Results demonstrated overlapping grey matter volume and cortical thickness changes in the superior temporal gyrus, pars opercularis and insula in the left hemisphere. In the right hemisphere, overlapping regions were found in the lateral occipital cortex, insula, rostral middle frontal cortex, medial orbitofrontal cortex, superior temporal cortex, and pars opercularis (Fig. 2, Table 2(a)).

Compared with cortical thickness results, however, grey matter volume changes also revealed some regions where grey matter volume significantly decreased but without corresponding evidence of cortical thinning. These regions included the bilateral rostral middle frontal, left precentral, lateral occipital, superior frontal, medial orbital frontal areas and right supramarginal, fusiform areas (Fig. 2, Table 2(b)).

3.2. Discrepancies in the grey matter volume and cortical thickness comparison: surface measures based on surface parcellation

Due to the lack of clear correspondence between grey matter volume derived from VBM and cortical thickness derived from Freesurfer, regional surface area, grey/white matter intensity contrast and curvature measures based on Desikan template parcellation were therefore used to test the differences between groups. The results revealed significantly decreased surface areas in patients

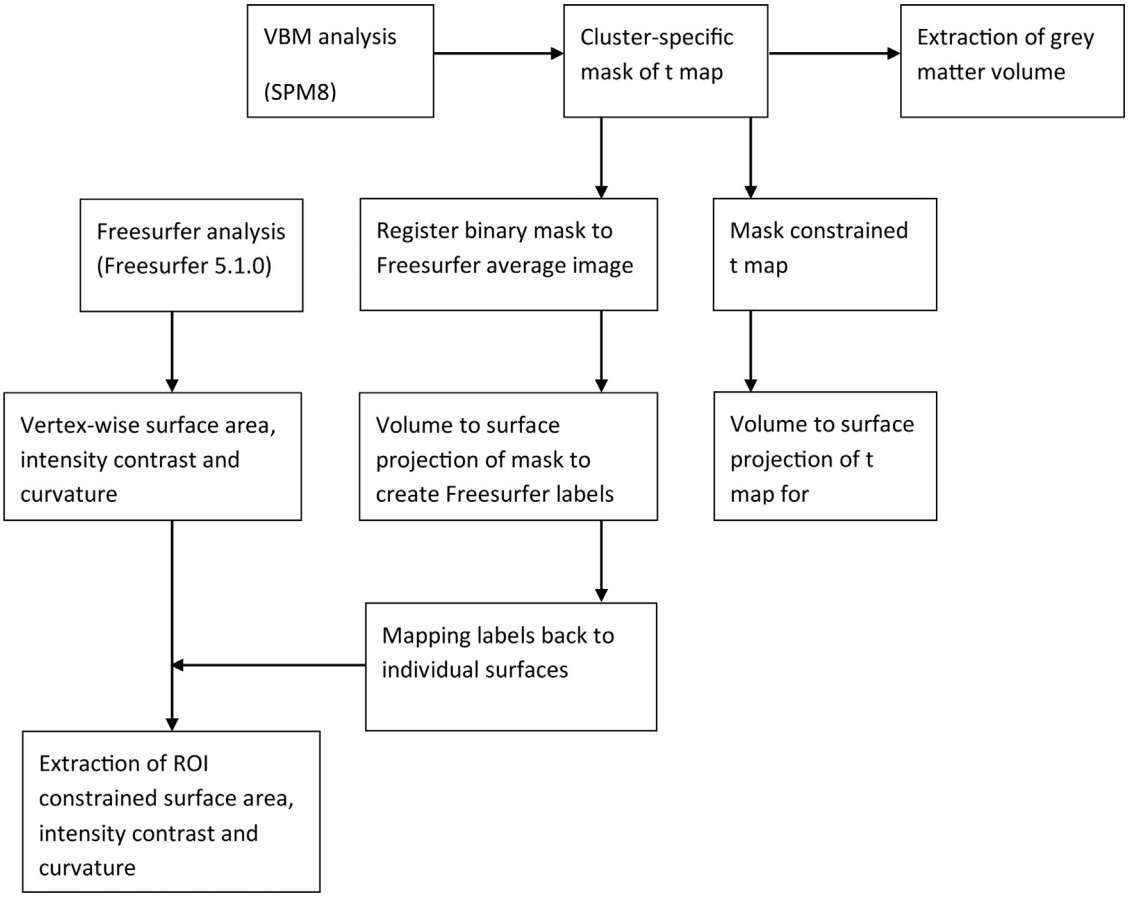

Fig. 1. Chart of the data processing explains voxel based and surface based morphometric analyses.

with schizophrenia compared with healthy controls in five of eight chosen regions showing grey matter volume reduction but without corresponding cortical thickness changes; all of the eight regions demonstrated significantly decreased grey/white intensity contrast compared with controls. However, significant between-group differences in curvature were not found in all eight regions (Table 3).

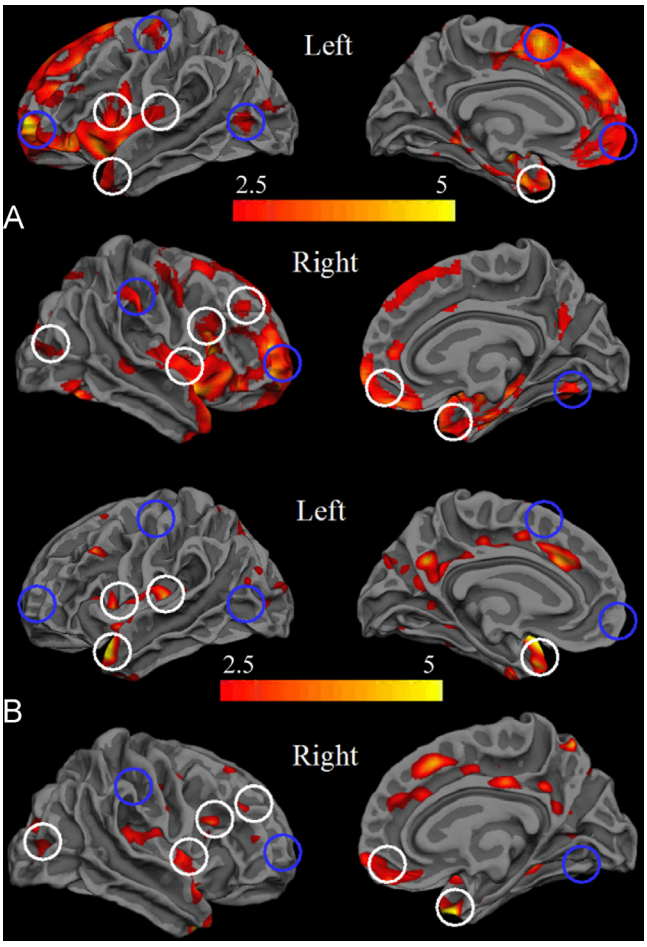

Fig. 2. VBM grey matter volume group difference map rendered onto Freesurfer surface. (A) Projection of the voxel-based grey matter volume group differences onto the average surface template. (B) Surface-based cortical thickness group differences map (colour scale in the map is $-\log^{10}$ (*P*-value)). Blue circles denote regions with significantly decreased volume using VBM but not in thickness. White circles identify regions of cortical change consistent between reduced grey matter volume and thinning cortical thickness. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Discrepancies in the grey matter volume and cortical thickness comparison: surface measures based on VBM-constrained analysis

As the surface-based parcellation could have weakened the significance of surface measures when significant regions were in a small proportion of the corresponding surface atlas, here we further examined the changes of surface area, grey/white matter intensity contrast and curvature based on ROI masks, which were obtained from VBM results. These ROIs were more refined than surface parcellation as they restricted the analyses into the significant regions. Our results demonstrated five regions with dramatic surface area changes among all eight regions, although here the five regions are not completely identical with those based on surface parcellation. Significantly decreased surface area in the left occipital gyurs was observed in the results based on surface parcellation, but the right supramarginal gyrus was observed in ROI analysis. Significantly lower grey/white matter intensity contrasts are still significant in all the regions. Moreover, two regions revealed significantly varied curvature: in the left lateral occipital, significantly decreased mean curvature was observed, but in the left rostral middle frontal gyrus, mean curvature increased dramatically. The mean curvature of right fusiform demonstrated a trend to decrease (Table 4).

3.4. Potential effects of age, sex and medication on cortical thickness and grey matter volume

Our results did not reveal significant age and sex effects on grey matter volume or thickness changes in schizophrenia. The effects of neuroleptic medications were tested in the patients with schizophrenia by modelling them as independent variables in regression analyses. There were no significant effects of medication on volume and cortical thickness analyses in cortical regions.

4. Discussion

In this study, we examined the differences of grey matter volume and cortical thickness in analysing cortical changes in chronic schizophrenia. We found that significant changes in surface area, intensity contrast and curvature accounted for the discrepancies between grey matter volume and cortical thickness jointly.

Although both methods under investigation identified corresponding changes in multiple overlapping regions, for grey matter

Table 2
Identifying the similarities (a) and differences (b) of grey matter volume and cortical thickness in detecting the effects of schizophrenia

Left hemisphere	Talairach coordinates (*x*, *y*, *z*)	Right hemisphere	Tailarach coordinates (*x*, *y*, *z*)
a: Anatomical location of regions showing corresponding voxel-based grey matter volume reductions and surface-based cortical thinning in patients compared to controls			
Pars opercularis	−49.4, 11.9, 9.3	Lateral occipital	30.4, −89.1, 28.6
insula	−33.0, −11.3, 9.4	insula	34.4, 4.3, 1.5
Superior temporal	−45.4, 9.2, −22.7	Pars opercularis	53.2, 18.4, 20.8
		Rostral middle frontal cortex	35.1, 37.2, 29.6
		Medial orbito- frontal cortex	11.3, 49.6, −7.3
		Superior temporal cortex	38.5, 12.8, −23.2
b: Anatomical location of regions showing corresponding voxel-based grey matter volume reductions but no corresponding surface-based cortical thinning in patients compared to controls			
Rostral middle frontal cortex	−21.3, 57.4, 8.2	Supramarginal	59.2, −27.9, 37.5
Precentral gyrus	−40.9, −15.4, 57.1	Rostral middle frontal cortex	21.8, 63.9, −4.8
Lateral occipital	−49.1, −76.7, 4.7	Fusiform gyrus	26.7, −68.2, −2.7
Superior frontal	−8.9, 4.9, 52.3		
Medial orbito- frontal cortex	−9.4, 49.0, −14.8		

Table 3
Surface area (mm^2), grey/white matter intensity contrast and curvature (mm^{-1}) differences between groups based on surface parcellations in the discriminating regions of grey matter volume and thickness.

Region	Healthy controls ($n=20$)	Patients ($n=22$)	P value
Left rostral middle frontal gyrus			
Surface area	5718.5 (114.0)	5333.4 (108.6)	**0.02**
Intensity contrast	39.56 (2.99)	36.87 (2.75)	**0.004**
Curvature	0.171 (0.003)	0.178 (0.003)	0.16
Left precentral gyrus			
Surface area	4786.5 (74.5)	4571.5 (71.1)	**0.03**
Intensity contrast	30.51 (2.44)	28.42 (2.58)	**0.01**
Curvature	0.151 (0.005)	0.145 (0.005)	0.40
Left lateral occipital gyrus			
Surface area	4860.0 (107.8)	4519.9 (102.7)	**0.02**
Intensity contrast	33.19 (2.21)	31.40 (2.87)	**0.03**
Curvature	0.16 (0.002)	0.16 (0.002)	0.95
Left superior frontal gyrus			
Surface area	7332.3 (100.2)	6713.5 (95.5)	**0.00**
Intensity contrast	38.11 (3.16)	36.01 (2.81)	**0.03**
Curvature	0.163 (0.004)	0.159 (0.004)	0.53
Left medial orbitofrontal gyrus			
Surface area	1877.2 (41.6)	1855.4 (39.7)	0.7
Intensity contrast	35.62 (2.54)	32.62 (3.11)	**0.002**
Curvature	0.160 (0.003)	0.161 (0.003)	0.92
Right supramarginal gyrus			
Surface area	3563.5 (69.7)	3505.8 (66.5)	0.5
Intensity contrast	39.69 (3.48)	35.35 (3.64)	**0.00**
Curvature	0.159 (0.003)	0.153 (0.003)	0.18
Right rostral middle frontal gyrus			
Surface area	5635.9 (103.0)	5265.8 (98.3)	**0.01**
Intensity contrast	39.65 (3.69)	36.44 (2.74)	**0.003**
Curvature	0.175 (0.003)	0.176 (0.003)	0.67
Right fusiform			
Surface area	3239.8 (83.5)	3042.1 (79.6)	0.07
Intensity contrast	34.97 (3.04)	32.52 (2.90)	**0.01**
Curvature	0.159 (0.003)	10.158 (0.002)	0.73

Data are expressed as mean (S.D.).

Table 4
ROI-based surface area (mm^2), grey/white matter intensity contrast and curvature (mm^{-1}) results between patients and healthy controls in the discriminating regions of grey matter volume and thickness. Data are expressed as mean (S.D.).

Region	Healthy controls ($n=20$)	Patients ($n=22$)	P value
Left rostral middle frontal gyrus			
Surface area	1015.3 (25.4)	954.2 (24.2)	**0.04**
Intensity contrast	34.49 (2.15)	32.09 (2.53)	**0.002**
Curvature	0.170 (0.004)	0.181 (0.003)	**0.02**
Left precentral gyrus			
Surface area	194.6 (5.3)	173.4 (5.0)	**0.00**
Intensity contrast	34.72 (2.51)	31.77 (2.29)	**0.00**
Curvature	0.151 (0.007)	0.137 (0.007)	0.15
Left lateral occipital gyrus			
Surface area	58.3 (3.2)	54.4.9 (3.1)	0.3
Intensity contrast	34.77 (3.46)	31.41 (3.16)	**0.002**
Curvature	0.155(0.006)	0.132 (0.006)	**0.02**
Left superior frontal gyrus			
Surface area	814.9 (20.0)	713.7 (19.1)	**0.00**
Intensity contrast	34.77 (2.50)	32.08 (2.49)	**0.001**
Curvature	0.166 (0.003)	0.173 (0.003)	0.16
Left medial orbitofrontal gyrus			
Surface area	342.6 (7.8)	332.6 (7.4)	0.4
Intensity contrast	33.99 (2.46)	32.19 (2.87)	**0.04**
Curvature	0.181 (0.004)	0.179 (0.004)	0.75
Right supra- marginal gyrus			
Surface area	133.1 (4.7)	120.8 (4.5)	**0.05**
Intensity contrast	34.12 (2.68)	31.02 (2.36)	**0.00**
Curvature	0.225 (0.003)	0.221 (0.002)	0.27
Right rostral middle frontal gyrus			
Surface area	799.6 (20.5)	710.7 (19.5)	**0.00**
Intensity contrast	34.12 (2.68)	31.02 (2.36)	**0.00**
Curvature	0.176 (0.004)	0.179 (0.004)	0.52
Right fusiform			
Surface area	266.8 (10.6)	255.0 (10.1)	0.4
Intensity contrast	34.31 (3.05)	31.82 (2.60)	**0.007**
Curvature	0.167 (0.004)	0.157 (0.004)	0.09

volume losses in regions like the bilateral rostral middle frontal gyrus, left precentral gyrus, lateral occipital gyrus, superior frontal gyrus, medial orbital frontal areas and right supramarginal and fusiform gyrus, there was no corresponding evidence of cortical thinning.

Based on previous findings, surface area, grey/white matter intensity contrast and curvature could account for some differences between grey matter volume and cortical thickness. In the present study, we used two methods to address this hypothesis: surface area, grey/white matter intensity contrast and curvature derived from anatomic labels on the surface template and VBM ROI-constrained mask in discrepancy regions of grey matter volume and thickness. The former was used to calculate surface area, grey/white matter intensity contrast and curvature in the smallest anatomic labels from Desikan template parcellations that included significantly changed regions. The last method used to directly calculate the surface area, intensity contrast and curvature changes of the significantly changed regions based on the ROI mask. Surface measures derived from the anatomic labels demonstrated five regions with significant surface area changes and all eight regions with significant grey/white intensity contrast changes. However, none of the regions demonstrated significant curvature changes. Given the lack of spatial specificity of large surface parcellation labels, the significance of the results could have been weakened compared with those derived from precise localisation. Therefore, this result was reanalyzed based on the VBM-defined ROIs. Compared with the results from surface anatomic labels, ROI-constrained analysis not only identified similar surface area and grey/white matter intensity contrast changes, but also detected two regions (the left lateral occipital and right fusiform gyrus) with significantly changed curvature. This result suggests that the discrepancies between grey matter volume and thickness could be jointly driven by surface area, grey/white matter intensity contrast and curvature.

Compared with morphometric measures (surface area and curvature), grey/white matter intensity contrast changes (Supplementary Fig. S1.tif for group differences of the intensity contrast), which reflect subtle abnormalities of neural tissue properties, appear to explain the discrepancies in more regions. On the one hand, this suggests that grey/white intensity contrast accounts for the differences between grey matter volume and thickness; on the other hand, it also indicates that grey/white intensity contrast as a subtle neural tissue property is more sensitive than gross morphometric changes. This is supported by previous findings that the grey/white matter intensity contrast is a highly sensitive metric, even more sensitive than cortical thickness (Salat et al., 2009; Kong et al., 2012). In addition, this is also consistent with our further correlational analyses between surface measures (surface area, curvature and intensity contrast) and grey matter volume, which demonstrated that the significant association between intensity contrast and grey matter volume involved more regions, such as in the left lateral occipital cortex and the right rostral middle frontal cortex, and a trend toward an association in left rostral middle frontal cortex and right supramarginal cortex. In contrast, surface area was significantly correlated with grey matter volume in the left medial orbitofrontal cortex, with a trend toward an association in the left rostral middle frontal cortex, and there was no significant association between curvature and grey matter volume.

Although little has been established about the associations between grey/white matter intensity contrast and traditional morphometric changes like volume in the schizophrenia literature, a recent study by Salat et al. (2011) found that hippocampal volume was associated with grey/white matter intensity contrast changes in Alzheimer's disease. Although both previous studies investigating tissue intensity contrast changes in schizophrenia or Alzheimer's disease found more widespread tissue intensity contrast changes than cortical thickness, there were multiple areas of regional overlap between these two measures (Salat et al., 2011; Kong et al., 2012). Therefore, the grey/white matter intensity contrast could be a microstructural marker of pathological mechanisms. However, it is not clear whether grey/white matter intensity contrast changes have similar or different biological mechanisms to those underlying schizophrenia-related differences in grey matter volume and thickness.

In the present findings, there was a varying combination of surface area, grey/white matter intensity contrast and curvature contributing to the discrepancies of grey matter volume and thickness. This could be due to the varied nature of the tissue abnormality across the regions. Although grey matter volume and thickness did not directly reveal the histopathology of the schizophrenia, different abnormalities in the trajectories of the measures could relate to different neurodevelopmental mechanisms of schizophrenia. Our findings demonstrated that different measures were differently affected across the cerebral regions in schizophrenia and suggested that each descriptor could have a distinct cellular mechanism as a result of a distinct origin. This interpretation was supported by our further correlational analyses between surface measures, which demonstrated that these measures were not consistently associated except in some regions such as in left rostral middle frontal cortex and right fusiform gyrus (significant associations between curvature and surface area or intensity contrast were found).

In the present study, we did not find a significant age effect on grey matter volume or thickness in schizophrenia, although some previous studies reported such an effect (Thormodsen et al., 2013). A small range of age in our sample could be the reason for this negative result. We also did not find a significant effect of sex on grey matter volume or thickness in schizophrenia, which is consistent with results of other studies (Nesvag et al., 2008; Kong et al., 2012). The potential effects of antipsychotics have previously been reported (Dazzan et al., 2005; Lieberman et al., 2005; Ho et al., 2011). Consistent with a recent literature review, there was evidence of specific effects of typical but not atypical antipsychotics on basal ganglia volumes and little evidence of effects of antipsychotics on cortical regions (Navari and Dazzan, 2009). In the present study, the changes of grey matter volume and thickness were restricted to cortical regions and the dose of antipsychotic medications was not significantly associated with these cortical changes. Our results confirmed previous findings that antipsychotic medication did not have a significant influence on cortical grey matter changes (Voets et al., 2008; Schultz et al., 2010a).

To the best of our knowledge, this is the first study thoroughly combining the grey/white matter intensity contrast with surface area and curvature to investigate their contributions to grey matter volume changes in cortical regions. Moreover, numerous studies have shown that patients with chronic schizophrenia demonstrated more widespread grey matter changes in cortical regions (Schröder et al., 1996a; Shenton et al., 2001; Schultz et al., 2010a). Additionally, a recent meta-analysis investigating chronic schizophrenia provided evidence of grey matter changes from subcortical to cortical regions during the course of schizophrenia (Ellison-Wright et al., 2008). Therefore, patients with chronic schizophrenia could be an appropriate population in which to compare grey matter changes in cortical regions. Finally, schizophrenia does not just affect mental health; patients with a diagnosis of schizophrenia have a shorter lifespan of 12–15 years than the average population (Van Os and Kapur, 2009). Our sample consists of older patients with an average age of 53 years, and it therefore could provide valuable information. Until recently, most schizophrenia studies focused primarily on younger patients. Older patients with schizophrenia are still underrepresented in clinical research, although an increasing rate of older patients with schizophrenia in the future is expected (Cohen et al., 2008; Saha et al., 2007).

There are also some limitations to the present study. A modest sample size, cross-sectional design and the choice of the smoothing kernel parameter in imaging analysis could potentially affect our

results. Although, we cannot exclude the potential effects of such factors, we aimed to minimise the potential influence by recruiting an age- and sex-matched sample, and using optimised smoothing parameters recommended by previous studies. Longitudinal studies with large samples will be needed to confirm the current findings.

In conclusion, significant changes in surface area, grey/white matter intensity contrast or curvature were found in the discrepancy regions between grey matter volume and cortical thickness, which suggests the differences between grey matter volume and thickness could be jointly driven by surface area, grey/white matter intensity contrast and curvature. In addition, our results also further confirmed that grey matter volume reflects a combination of information obtained from several measures, as grey matter volume can reflect brain morphometric changes in both cortical and subcortical regions. For specific diseases, especially deficits involving subcortical regions such as in schizophrenia, it is better to combine grey matter volume and thickness together for a comprehensive analysis.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2014.12.004.

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