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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).