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Reduced cortical thickness in first episode schizophrenia

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ABSTRACT

Objective: Previous morphometric studies are suggesting altered cortical thickness mainly in prefronto-temporal regions in first episode schizophrenia. In an extension of these earlier studies, we used an entire cortex vertex-wise approach and an automated clustering for the detection and exact quantification of cortical thickness alterations in first episode schizophrenia.
Methods: A group of 54 patients with first episode schizophrenia according to DSM-IV and 54 age and gender matched healthy control subjects were included. All participants underwent high-resolution T1-weighted MRI scans on a 1.5 T scanner. Cortical thickness was estimated as the distance between the gray–white matter border and the pial surface using an automated computerized algorithm (Freesurfer Software). Statistical cortical maps were created to estimate differences of cortical thickness between groups based on this entire cortex analysis.
Results: Significant cortical thinning was observed in first episode schizophrenia patients relative to controls in a number of cortical areas including the dorsolateral and frontopolar cortices, the anterior cingulate cortex, a ventrolateral–orbitofrontal cluster, as well as the superior temporal cortices and superior parietal lobe. Cortical thinning within these regions was on average 4.4–5.7% with strongest reductions in orbitofrontal regions (7.1%).
Conclusions: The present findings suggest widespread reduction of cortical thickness, mostly in heteromodal cortices of fronto-temporal networks to be present at an early stage of schizophrenia. Taken together, the present morphometric data in first episode schizophrenia provide further evidence for potential neurodevelopmental deficits and disruption of cortical maturation in this disorder.

1. Introduction

1.1. Previous evidence for cortical thinning in schizophrenia

In recent years, a wealth of literature has been accumulated with regard to morphometric changes in schizophrenia using voxel-based morphometric approaches (Honea et al., 2005; Williams, 2008). More recently available automated data analysis strategies focusing on cortical thickness are adding complemental information to these data. There is now growing evidence for reduced cortical thickness predominantly in fronto-temporal regions in chronic schizophrenia (Kuperberg et al., 2003; Nesvag et al., 2008).

In first episode schizophrenia patients reduced cortical thickness could be demonstrated for the anterior cingulate cortex (Fornito et al., 2008) and the prefrontal cortex (Venkatasubramanian et al., 2008) using surface-based regions of interest (ROI) analyses. However, using a ROI strategy, Wiegand et al. (2004) could not demonstrate differences in prefrontal cortical thickness between first episode patients and matched healthy controls.

Narr et al. (2005a,b) computed cortical thickness as a three-dimensional shortest distance from the gray–white

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matter boundary to the gray matter–CSF boundary and resampled the data to a 0.33 mm^3 voxel size to obtain distance measures at a sub-voxel resolution. They examined cortical thickness in first episode schizophrenia separately for lateral cortical and mesial cortical regions. The study demonstrated cortical thinning of frontal and temporal but also occipital areas.

In addition, reduced cortical thickness could also be demonstrated for unaffected siblings of patients with schizophrenia (Goldman et al., 2009) suggesting a potential relationship of these cortical alterations findings to the genetic liability for developing schizophrenia.

However, to date there were no studies based on a two-dimensional cortical surface model, which investigated cortical thickness using an entire cortex and vertex-wise comparison to detect brain areas with a significant cortical thinning in first episode schizophrenia. A two-dimensional surface model most likely reflects the genuine two-dimensional structure of the human cerebral cortex (Dale et al., 1999). Vertex-wise analysis of cortical thickness allows for an entire cortex exploratory data analysis without any a priori constraints and it is therefore not restricted to a limited brain region as a search space for anatomical alterations. Subsequently, clusters of statistically significant vertex-wise findings can be defined. Average cortical thickness data extracted from these clusters can then be used for the exact comparison of cortical thickness differences between diagnostic groups. Hence, significant cortical thickness differences can be quantified independently from predefined cortical parcellation schemes or manual tracing.

1.2. Objectives and hypothesis

Previous surface-based studies (Kuperberg et al., 2003; Nesvag et al., 2008) used atlas based anatomical parcellations or manual tracing of brain regions to define anatomical labels, which are mapped to the individual subjects for data extraction and group comparisons.

In an methodological extension of these earlier studies we performed an entire cortex vertex-wise analysis and employed an automated clustering approach to detect and quantify potential differences of cortical thickness between first episode schizophrenia patients and healthy controls. According to previous studies we hypothesized cortical thinning to be present in mainly prefronto-temporal cortical areas.

2. Subjects and methods

2.1. Participants

Fiftyfour patients with first episode schizophrenia and 54 matched healthy controls were included. All participants were right-handed (Annett, 1967) and groups were matched according to age and gender. Diagnoses were established based on the Structured Clinical Interview for DSM-IV (M. R.) and were confirmed by two independent psychiatrists (R.S. and Ch.S.). All patients met DSM-IV criteria for schizophrenia and had no second psychiatric diagnosis. They were in remission from a psychotic episode and on stable medication, mostly with second-generation antipsychotics.

All healthy controls were screened using a semi-structured interview, which included screening questions for axis I disorders, such conditions in first-degree relatives, on neurological and major medical conditions and also for major medical, neurological and psychiatric history. None of the healthy subjects had first-degree relatives with a psychiatric disorder according to DSM-IV. Exclusion criteria for all healthy controls were history of psychiatric disorder, current psychiatric disorder, neurological or other significant medical disorders potentially influencing neurocognitive function, and first-degree relatives with psychiatric disorders according to DSM-IV. All participants gave written informed consent to the study approved by the Ethics Committee of the Friedrich-Schiller University. Sociodemographic and psychopathological data are given in Table 1.

2.2. MRI-acquisition

We acquired high-resolution anatomical T1-weighted data on a 1.5 T Siemens Magnetom Vision whole-body system with the standard CP transmit/receive head coil by using a three-dimensional spoiled gradient echo sequence: 1 mm sagittal slices with TR = 15 ms, TE = 5 ms, flip angle 30°, FOV = 256, matrix = 256 mm × 256 mm, number of sagittal slices = 192.

All scans were inspected for motion artefacts and a neuroradiologist confirmed absence of gross pathological findings.

2.3. MR scan processing and calculation of cortical thickness

We used the FreeSurfer software package (version 4.0.5, http://surfer.nmr.harvard.edu) for processing of images (Dale et al., 1999; Fischl et al., 1999). The implemented processing stream includes removal of non-brain tissue, transformation to Talairach-like space, and segmentation of gray–white matter tissue. White and gray matter boundary is tessallated and topological defects are automatically corrected. After intensity normalization, and transition of gray–white matter, pial boundary is indicated by detecting the greatest shift in intensity through surface deformation. The entire cortex of each subject was then visually inspected and any inaccuracies in segmentation were manually edited. After creation of the cortical representations the cerebral cortex is parcellated into anatomical structures. Cortical thickness is computed by finding the shortest distance between a given point on the estimated pial surface and the gray–white matter boundary and vice versa and averaging these two values (Fischl and

Table 1
Demographic and clinical data.

Parameter	Controls ($n = 54$)	Patients ($n = 54$)	p
M/F	40/14	40/14	
Age (year)	26.6 (6.3)	26.4 (7.7)	0.903
Education (year)	12.4 (1.2)	11.5 (1.6)	0.002
PANSS total score	n.a.	75.9 (22.3)	
PANSS positive	n.a.	18.3 (7.2)	
PANSS negative	n.a.	18.3 (5.7)	

Data expressed as mean (SD). p-values resulting from two sample t-test. n.a.: Not applicable; PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987).

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Dale, 2000). As the generated cortical maps are not limited to the voxel resolution of the original data, they are capable of detecting sub-millimeter differences between diagnostic groups. Measurements of cortical thickness have been validated against manual measurements in schizophrenia (Kuperberg et al., 2003).

2.4. Statistical analysis

2.4.1. Statistical cortical maps

Each thickness measurement of each vertex of the subjects' surface was mapped on a common spherical coordinate system using a spherical transformation. Maps were smoothed using a Gaussian kernel of 10 mm. We used a general linear model controlling for the effect of age to estimate differences in cortical thickness between the groups at each vertex of the surface. Right and left hemispheres were tested separately.

2.4.2. Monte Carlo simulation and clustering

Monte Carlo simulations were performed in order to identify significant contiguous clusters of significant vertex-wise group differences ($p<0.05$).

2.4.3. Quantification of cortical thinning

To quantify neuroanatomical alterations, we extracted the mean cortical thickness values from the significant clusters of all subjects. We compared the mean thickness values between patients and healthy controls using the student's *t*-test.

All results were corrected for multiple comparisons using the False Discovery Rate method (Genovese et al., 2002).

3. Results

3.1. Automated clustering

Cluster analysis revealed four clusters in the left hemisphere and five clusters in the right hemisphere, which demonstrated significantly reduced cortical thickness in first episode schizophrenia (Fig. 1, Table 2). These clusters comprised prefronto-temporal, anterior cingulate and parietal cortical areas. Reduced cortical thickness in the left cortex included inferior parietal (BA 43), ventro- and dorsolateral prefrontal (BA 44–47; 9), superiorfrontal (BA 6;8), frontopolar (BA 10) and temporal (BA 20;21) areas.

Whereas the right parietal lobe was not affected, left superior (BA 5) and inferior (BA 39) parietal areas showed significant thinner cortex in first episode patients. On the right hemisphere cortical thinning was found in ventrolateral (BA 47) and dorsolateral (BA 46;9) prefrontal, Broca's area (BA 44), orbitofrontal (BA 11), superiorfrontal (BA 6;8) and frontopolar (BA 10) regions. In addition, parts of the anterior cingulate cortex (BA 24) demonstrated thinner cortex in patients with first episode schizophenia. Furthermore

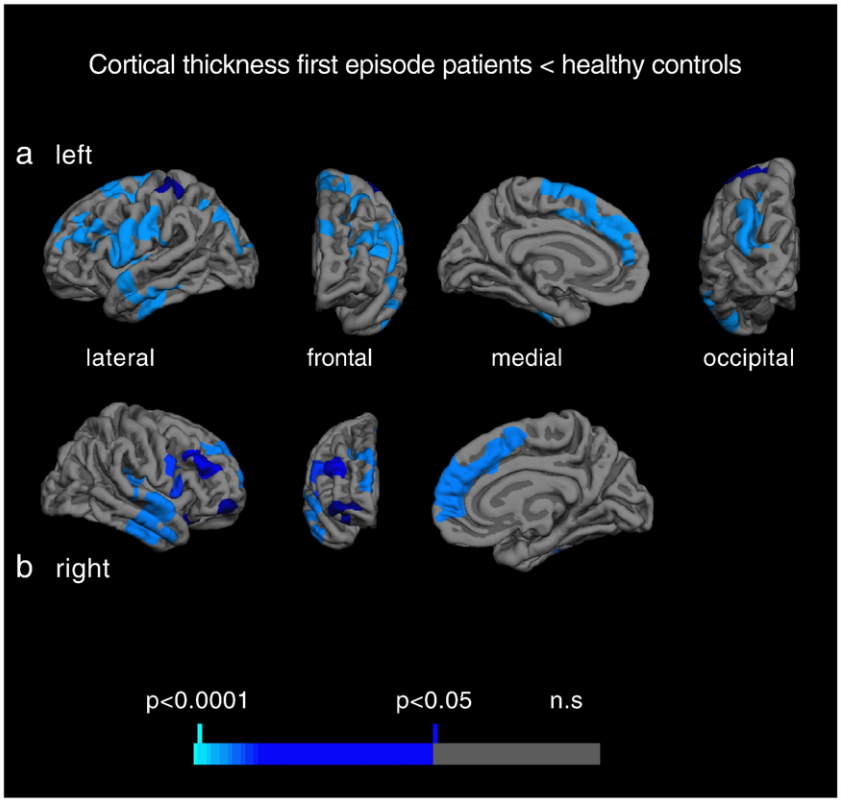

Fig. 1. Cortical statistical maps displaying cortical thickness differences between patients with first episode schizophrenia and healthy control subjects for left (a) and right (b) hemisphere in lateral, frontal, medial and posterior view, respectively (*p*-values corrected for multiple comparisons).

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Table 2
Significant clusters for the left and right hemisphere, cluster size in mm^2, *p*-values from the Monte carlo simulation and clustering as cluster wise probability (CWP), resulting from the vertex-wise comparison of cortical thickness between patients and healthy controls.

Cortical area	Brodmann area	Size in mm^2	CWP
Left hemisphere			
Prefronto-temporal	20;21;43–47	8409	0.0001
Superior frontal	6;8–10	4417	0.0001
Inferior parietal	39	2247	0.0001
Postcentral/superior parietal	3;5	970	0.0360
Right hemisphere			
Temporal/supramarginal	20–22;40	4155	0.0001
Superior frontal/anterior cingulate	6;8–10; 24	3928	0.0001
Pars opercularis	44; Broca' s area	1828	0.0004
Rostral middle frontal (dorsolateral prefrontal)	46	1584	0.0014
Ventrolateral prefrontal/ orbitofrontal	11;47	1261	0.0083

temporal (BA 20–22) and supramarginal (BA 40) cortical areas were affected by cortical thinning.

3.2. Quantification of cortical thinning

Cortical thinning ranged from 1.7 to 7.1% (Table 3). Right dorsolateral prefrontal areas demonstrated the weakest (1.7%) and right ventrolateral–orbitofrontal regions the strongest cortical thinning (7.1%). The other brain regions appeared to be affected to a similar degree (4.4–5.7%), whereas inferior parietal regions were stronger affected than temporal and superiorfrontal areas.

4. Discussion

We present the first surface-based entire cortex analysis of cortical thickness in first episode schizophrenia. Our analysis revealed significant reduced cortical thickness in prefronto-temporal, anterior cingulate and parietal cortex areas in patients with first episode schizophrenia.

Table 3
Quantification of cortical thickness differences between patients and healthy controls, expressed as percentage cortical thinning, *p*-values FDR adjusted.

Cortical area	Mean in mm (SD)		Difference in %	*p*
	Patients	Controls		
Left hemisphere				
Prefronto-temporal	2.02 (0.14)	2.13 (0.15)	5.2	0.000
Superior frontal	2.43 (0.15)	2.54 (0.12)	4.3	0.000
Inferior parietal	2.64 (0.22)	2.80 (0.20)	5.7	0.000
Postcentral/superior parietal	2.02 (0.14)	2.13 (0.15)	5.2	0.000
Right hemisphere				
Temporal/supramarginal	2.78 (0.17)	2.92 (0.15)	4.8	0.000
Superiorfrontal/anterior cingulate	2.62 (0.17)	2.74 (0.11)	4.4	0.000
Pars opercularis	2.49 (0.14)	2.62 (0.15)	5.0	0.000
Rostral middle frontal (dorsolateral prefrontal)	2.36 (0.11)	2.40 (0.07)	1.7	0.017
Ventrolateral prefrontal/ orbitofrontal	2.61 (0.42)	2.81 (0.29)	7.1	0.005

Our results are in line with the studies by Narr et al. (2005a,b), although a direct comparison can only be performed with some limitations due to different methodological approaches of the studies. In addition, our findings are consistent with previous ROI based analyses of cortical thinning in medial prefrontal areas.

Venkatasubramanian et al. (2008) showed cortical thinning in medial prefrontal regions with a surface-based ROI approach. In addition, our results displaying cortical thinning of the anterior cingulate cortex are in line with the study of Fornito et al. (Fornito et al., 2008), who performed a surface-based ROI analysis of the anterior cingulate cortex in first episode schizophrenia.

4.1. Cortical thinning as neuroanatomical correlate for functional deficits in schizophrenia

It is striking that our findings of cortical thinning affected predominantly those cortical areas, which play a major role in the integration of heteromodal neuronal input. The heteromodal association cortices comprise primarily prefrontal, superior temporal and inferior parietal cortical areas. They are suggested to play a critical role in the pathophysiology of schizophrenia (Buchanan et al., 2004). The heteromodal cortices constitute neuronal networks, which are responsible for the integration of multisensory input as well as for planning, conducting and evaluating behavior. Dysfunction of these brain areas has been associated with core symptoms of schizophrenia such as lack of attention, disorganisation and reality distortion (Pearlson et al., 1996; Ross and Pearlson, 1996). VBM studies already revealed gray matter density decrease in heteromodal association areas (Buchanan et al., 2004; Nakamura et al., 2008).

In addition, fMRI studies demonstrated that patients with schizophrenia showed an aberrant neuronal activation in this heteromodal prefronto-temporo-parietal association network, in particular during cognitive control and executive processing (Koch et al., 2008; Schlösser et al., 2008).

In extension to these findings the present results indicate cortical thinning in a similar network consisting of primarily prefronto-temporo-parietal areas in first episode schizophrenia. Hence, cortical thinning of the heteromodal association cortices might be one underlying neuroanatomical alteration leading to functional core deficits in schizophrenia.

4.2. Quantification of cortical thinning and cytoarchitectural correlates

Although we found that the degree of cortical thinning was largely comparable between the different regions the right dorsolateral prefrontal cortex (DLPFC) was found to be less affected than the other brain regions. Studies investigating cortical thickness in chronic schizophrenia demonstrated a more or less homogeneous cortical thinning of the affected brain areas (Kuperberg et al., 2003; Nesvag et al., 2008). Sun et al. (2009) demonstrated an increasing surface contraction in dorsolateral prefrontal areas but not ventrolateral and orbitofrontal areas after two years of illness in first episode schizophrenia. Thus, cortical thinning in dorsolateral

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prefrontal areas might progress in the course of schizophrenia. The present data are cross-sectional and, therefore, direct inference of a temporal progression of these alterations is not possible. However, an integrated view of the different cross-sectional time points at which previous (Kuperberg et al., 2003; Nesvag et al., 2008) and the current study were performed is possible. This leads to the conclusion that the magnitude of cortical thinning varies across time and among different brain regions, which might reflect a dynamic spatiotemporal process.

In addition, apart from a different velocity of cortical thinnning, differing cellular and cytoarchitectural processes might underlie cortical thinning. Postmortem studies demonstrated smaller neuron size and neuronal density in schizophrenia (Benes and Bird, 1987; Benes et al., 1986), but also higher neuronal density was found (Selemon et al., 2003; Selemon et al., 1995). Selemon postulated regionally specific cellular processes as basis for cortical alterations in schizophrenia. He suggested the loss of neuropil in the DLPFC as the cytoarchitectural substrate for cortical thinning (Selemon et al., 2003). Other authors assume that accelerated synaptic pruning might be an underlying pathophysiological process, which could be responsible for cortical alterations in schizophrenia (Sun et al., 2008). Huttenlocher and Dabholkar (1997) demonstrated that the climax of synaptogenesis in humans is reached by the age of about one year. Subsequently, late in childhood there is progressive synaptic pruning that extends until midadolescence. These processes occur earlier in auditory than in prefrontal cortical areas. To which extent these different cellular processes play a role in the pathophysiological course of schizophrenia, and whether these processes run in parallel or separately, remains unclear at this time.

4.3. Comparison of the method to VBM

Surface-based data analysis strategies might provide additional information which could not be acquired from voxel-based volumetric studies so far. Gray matter density analyzed by VBM methods always reflects a three-dimensional marker, which amalgamates influences of the cortical surface, folding and thickness. Therefore, it could not be separated if a decrease in gray matter density is related to alterations of the cortical surface, intensity of cortical folding, cortical thickness or to all three parts. In contrast, analyses of cortical thickness provide the possibility to examine in vivo a specific neuroanatomical one-dimensional marker also used in postmortem studies (Benes et al., 1986; Selemon et al., 2003).

Given that cortical thinning in schizophrenia ranges within tenth millimeter dimensions (Kuperberg et al., 2003), surface-based methods might provide an additional and accurate means to quantify potential cortical thickness alterations. Surface-based methods allow to determine cortical thickness in sub-millimeter dimensions and might therefore even detect subtle anatomical alterations (Fischl and Dale, 2000). Hence, an in vivo analysis of cortical thickness might provide additional insight into the exact nature of potential gray matter alterations in schizophrenia, which have been suggested by previous VBM studies (Honea et al., 2005; Williams, 2008).

A major challenge for the future develolpment of in vivo brain imaging techniques remains the exploration of submacroscopic neuroanatomical processes. The detection of a particular cortical layer (Augustinack et al., 2005) succeeded with high-resolution 7 T MR imaging on autopsied human material. Further technical progress could make such high-resolution MRI applicable in the clinical setting. It would allow the detection of pathophysiological processes on a submacroscopic level in vivo and would fundamentally extend our pathophysiological knowledge of mental diseases like schizophrenia.

5. Concluding remarks

In conclusion, our data demonstrate, that even patients with first episode schizophrenia show a discrete but distinct and under functional aspects well characterizable pattern of cortical thinning. The automated clustering approach used in our study for the exact quantification of cortical thickness alterations provides a deeper insight into how different brain regions are affected in first episode schizophrenia. Against the background of a potentially varying velocity of cortical thinning during the progress of schizophrenia an automated clustering appears to be an appropriate method to reflect these pathological processes in different stages of the disorder. In which brain region cortical thinning progresses during the course of schizophrenia has to be clarified by further, in particular longitudinal, studies.

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Contributors

Drs. Schlösser, Sauer, Schultz, Koch and Wagner were involved in the design of this study and contributed to the writing of the manuscript. Dr. Schultz performed the cortical thickness data analyses. Dr. Gaser and Dr. Reichenbach contributed technical expertise to the MRI imaging processing and cortical thickness analysis. Dr. Roebel and Dr. Nenadic were involved in diagnosing subjects and psychopathological data collection. Ms. Schachtzabel was involved in the recruitment of subjects. Dr. Schultz wrote the first draft of the manuscript. All authors approved the manuscript for submission.

Conflict of interest

All of the authors reported no financial interests or potential conflicts of interest.

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