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Increased parahippocampal and lingual gyrification in first-episode schizophrenia

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ABSTRACT

Objective: Cerebral gyrification is attributed to a large extent to genetic and intrauterine/perinatal factors. Hence, investigating gyrification might offer important evidence for disturbed neurodevelopmental mechanisms in schizophrenia. As an extension of recent ROI analyses of gyrification in schizophrenia the present study is the first to compare on a node-by-node basis mean curvature as a sensitive parameter for the identification of local gyrification changes of the whole cortex 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. Mean curvature was calculated dividing the sum of the principal curvatures by two at each point of the curved surface as implemented in the Freesurfer Software package. Statistical cortical maps were created to estimate gyrification differences between groups based on a clustering approach.
Results: A significantly increased gyrification was observed in first-episode schizophrenia patients relative to controls in a right parahippocampal–lingual cortex area. The cluster encompassed a surface area of 750 mm². A further analysis of cortical thickness of this cluster demonstrated concurrent significant reduced cortical thickness of this area.
Conclusions: This is the first study to reveal an aberrant gyrification of the medial surface in first-episode schizophrenia. This finding is in line with substantial evidence showing medial temporal lobe abnormalities in schizophrenia. The present morphometric data provide further support for an early disruption of cortical maturation in schizophrenia.

1. Introduction

There is an overwhelming body of evidence for morphometric cerebral alterations in schizophrenia resulting from voxel based studies (Honea et al., 2005; Shenton et al., 2001; Williams, 2008). These studies indicated a decrease in gray matter density mostly in fronto-temporal regions. More recently available surface-based analysis strategies allow for the examination of cortical shape parameters such as cortical thickness and gyrification. Cortical thinning has been shown in subjects at high risk for psychosis (Jung et al., 2009). In addition, reduced cortical thickness was found in chronic (Kuperberg et al., 2003; Nesvag et al., 2008; Schultz et al., 2010a) and first-episode schizophrenia (Narr et al., 2005; Schultz et al., 2010b; Venkatasubramanian et al., 2008) for fronto-temporal and also parieto-occipital areas.

In particular, the analysis of cerebral gyrification in schizophrenia might offer valuable clues to the pathogenesis of schizophrenia in terms of a neurodevelopmental origin.

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1.1. Gyrification as an important neurodevelopmental cortical marker in schizophrenia

In the course of brain maturation the human cerebral cortex changes from a lissencephalic to a gyrencephalic shape. The process of this shaping is terminated to a very large degree before the age of 2 years (Armstrong et al., 1995). Hence, cortical gyrification might be attributed to a large extent to genetic and intrauterine/perinatal factors. Therefore, investigating gyrification might offer important evidence for early neurodevelopmental mechanisms in schizophrenia.

1.2. Postmortem evidence and in vivo MRI evidence

Postmortem studies in schizophrenia found a hypergyria in prefrontal (Vogeley et al., 2000) and temporal (Highley et al., 1998) areas, but also reduced gyrification in the posterior cingulate cortex (Wheeler and Harper, 2007).

MRI-studies demonstrated an increased prefrontal gyrification in high risk individuals (Harris et al., 2007; Stanfield et al., 2008). Vogeley et al. (2001) showed a higher right frontal gyrification in affected siblings with schizophrenia or schizoaffective disorder than in the unaffected siblings. Accordingly, the frontal gyrification was significantly higher in schizophrenia patients as well as unaffected relatives compared to control subjects (Falkai et al., 2007). Wisco et al. (2007) found a higher cortical folding in Broca's area in patients with chronic schizophrenia applying an automated surface-based method. In contrast, a reduced sulcal cortical folding could be demonstrated in frontal areas including Broca's area and temporal cortices of patients with resistant auditory hallucinations (Cachia et al., 2008). Interestingly, a recent study of Hubl et al. (2010) demonstrated a higher volume of the Heschl's gyrus in patients with auditory hallucinations. Accordingly, a recent ROI study of the entorhinal cortical shape demonstrated a positive correlation between the degree of cortical folding and severity of positive symptoms in schizophrenia (Schultz et al., 2010c). The study of Sallet et al. (2003) showed a decreased cortical folding globally measured for each hemisphere and for a frontal and posterior region using a manual tracing method. Due to methodical reasons the analyses did not include midsagittal structures. McIntosh et al. (2009) found a reduced prefrontal gyral cortical folding in 28 patients with schizophrenia using a ROI approach measuring ventral and dorsal prefrontal gyrification.

1.3. Gyrification in first-episode schizophrenia

To date only a limited number of studies examined gyrification in first-episode schizophrenia. Fornito et al. (2008) performed a region of interest analysis of the anterior cingulate cortex using a surface-based method. This study could demonstrate cortical thinning of the anterior cingulate, but no difference in mean curvature of this region in first-episode schizophrenia. In accordance with the study of Fornito et al. (2008) Wiegand et al. (2005) did not find differences in prefrontal gyrification in a sample of 17 first-episode patients. Harris et al. (2004) examined gyrification in four lobar regions using a manual tracing method. In this study a higher gyrification of the right temporal lobe could be demonstrated. Narr et al. (2004) measured the mean cortical folding of five predefined cortical regions. Results demonstrated a higher cortical folding in a right prefrontal area of male patients with first-episode schizophrenia and a trend towards a higher cortical folding in an occipital area.

1.4. Limitations of previous studies and advantages of entire cortex analysis

Heterogeneities in study results might be due to methodical differences (e.g. different anatomical levels of resolution, i.e. ROI vs. lobar vs. sulcal; manual tracing vs. automated methods) and to variance in the study group regarding the status of illness (e.g. chronic vs. first-episode patients). Recent studies examining gyrification in first-episode schizophrenia used either ROI based analyses (Fornito et al., 2008; Wisco et al., 2007) or compared the mean values of cortical folding of four or five predefined anatomical areas (Harris et al., 2004; Narr et al., 2004), which were more or less grossly structured and did not cover the medial cortical surfaces. They thus excluded potential alterations of medial temporal lobe structures, which belong to the most consistent morphological findings in schizophrenia (Honea et al., 2005).

1.5. Objectives and hypothesis

Based on these methodological considerations we provided for the first time a vertex-wise analysis of local gyrification changes in first-episode patients covering the entire cortex in order to detect even subtle gyrification differences in schizophrenia. Mean curvature as a sensitive and automated approach for the whole brain identification of local gyrification changes (Luders et al., 2006) was assessed in a first-episode patients sample, in which we previously reported significant cortical thickness reduction in a number of cortical areas including dorsolateral and ventrolateral prefrontal areas, lateral temporal, anterior cingulate and inferior parietal regions (Schultz et al., 2010b).

According to previous literature (Harris et al., 2004; Narr et al., 2004; Wisco et al., 2007) we hypothesized aberrant gyrification in prefrontal and temporal regions.

2. Subjects and methods

2.1. Participants

We studied 54 patients with first-episode schizophrenia and 54 healthy controls closely matched for age and gender. All participants were right-handed (Annett, 1967). Diagnoses were established by a clinical psychiatrist (M. R.) based on the Structured Clinical Interview for DSM-IV and were confirmed by 2 independent psychiatrists (R. S. and C. C. S.). All patients met DSM-IV criteria for schizophrenia and had no second psychiatric diagnosis. First-episode schizophrenia was defined according to the criteria of the German Research Network for Schizophrenia (Gaebel et al., 2004), where first episode was pragmatically defined as the first inpatients treatment of psychotic symptoms. Age at onset was defined as the onset of definite psychotic symptoms and was estimated based on the clinical interview performed by

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experienced psychiatrists (M. R., I. N., C. C. S.). Duration of untreated psychosis (DUP) was defined as the period of the onset of definite psychotic symptoms (i.e. age at onset) and the beginning of an adequate treatment (Norman and Malla, 2001). Patients in remission according to the PANSS related remission criteria of Andreasen et al. (2005) were analyzed. They were on stable medication, mostly with second-generation antipsychotics. Healthy volunteers were screened for major medical, neurological and psychiatric history. None of the healthy subjects had a current or history of a psychiatric disorder or first-degree relatives with a psychiatric disorder according to DSM-IV. Exclusion criteria for all participants were neurological disease or damage, and medical disorders potentially influencing neurocognitive function. 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 brain scans in a 1.5 T Siemens Magnetom Vision whole-body system using a three-dimensional, rf-spoiled gradient echo sequence with the following parameters: TR = 15 ms, TE = 5 ms, flip angle 30°, FOV = 256 mm × 256 mm, matrix = 256 × 256, number of sagittal slices = 192, with 1 mm thickness each.

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

2.3. MR scan processing

We used the FreeSurfer software package (version 4.0.5, http://surfer.nmr.harvard.edu) for image processing (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 tessellated and topological defects are automatically corrected. After intensity normalization, transition of gray/white matter and 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.

Table 1
Demographic and clinical data. 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).

Parameter	Controls (n = 54)	Patients (n = 54)	p
M/F	40/14	40/14	
Age (y)	26.6 (6.3)	26.4 (7.7)	0.903
Education (y)	12.4 (1.2)	11.5 (1.6)	0.002
PANSS total score	n.a.	75.9 (22.3)	
PANSS pos	n.a.	18.3 (7.2)	
PANSS neg	n.a.	18.3 (5.7)	
Duration of untreated psychosis (mth)	n.a.	2.5 (1.1)	
Age at onset (y)	n.a.	26.1 (7.7)	

2.4. Calculation of cortical curvature as a measure for local gyrification changes

Mean curvature represents a sensitive and automated approach for identifying very local changes in gyrification (Luders et al., 2006). Cortical curvature was calculated for each vertex of the tessellated pial surface as implemented in the FreeSurfer software. A given surface in a three-dimensional space has at each point an infinite number of possible curvatures. Of these possible curvatures two mutually orthogonal tangent directions will represent the extremal curvatures. These two curvatures are the maximal (k1) and minimal curvatures (k2), which collectively describe the principal curvatures (Pienaar et al., 2008). The principal curvatures at a given point of a surface measure how the surface bends by different amounts in different directions at that point. The mean curvature used in the present study is calculated dividing the sum of the principal curvatures by 2.

2.5. Statistical analysis

2.5.1. Statistical cortical maps

Each curvature measurement of each vertex of the subjects' surface was mapped on a common spherical coordinate system using a spherical transformation. We transferred the signed values for the curvature in unsigned values using the Matlab software. Higher values indicate a more steeply peaked curvature and values approaching zero a more flattened curvature. 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 curvature between the groups at each vertex of the surface. Right and left hemispheres were tested separately.

2.5.2. Monte Carlo simulation and clustering

Monte Carlo simulations with 10,000 iterations were performed in order to identify significant contiguous clusters of significant vertex-wise group differences ($p<0.05$).

2.5.3. Quantification of gyrification differences

To quantify and compare mean curvature, we extracted the mean curvature values of the significant parahippocampal–lingual cluster. We compared the mean curvature values between patients and healthy controls using the student's t-test.

2.5.4. Computation and comparison of cortical thickness of the right parahippocampal–lingual cluster

We defined the parahippocampal–lingual cluster from the entire cortex gyrification analysis as an anatomical label, mapped this label to all subjects and mean cortical thickness of this label was then calculated as described in Schultz et al. (2010a) using automated analysis tools implemented in the Freesurfer Software package. We compared the mean right parahippocampal–lingual cortical thickness using a GLM controlling for the effect of age.

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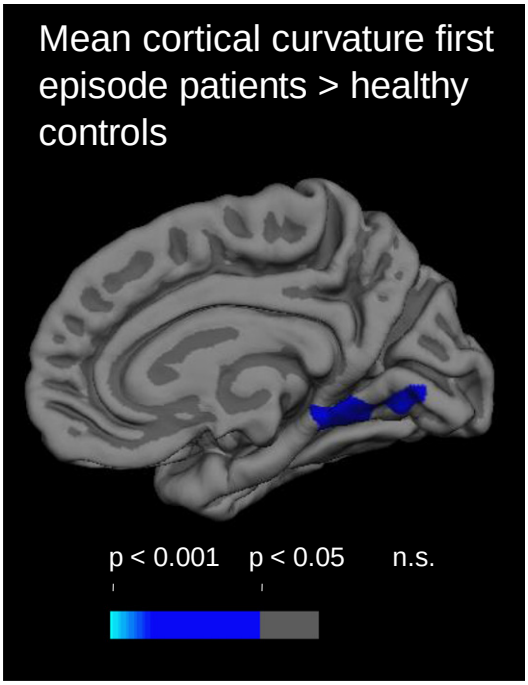

Fig. 1. Cortical statistical map displaying cortical mean curvature differences between patients with first-episode schizophrenia and healthy control subjects, medial surface of the right hemisphere, p-values corrected for multiple comparison.

2.5.5. Correlations of right parahippocampal–lingual curvature and cortical thickness

We performed partial correlations controlling for the effect of age between the mean curvature of the right parahippocampal–lingual cluster and mean cortical thickness of the right parahippocampal–lingual cluster and the mean thickness values of the clusters resulting from our recent entire cortex analysis of cortical thickness in the same patient group (Schultz et al., 2010b). The partial correlations were performed for the whole subject group and for patients and healthy controls separately.

2.5.6. Correlation of right parahippocampal–lingual curvature and clinical variables

Partial correlations controlling for the effect of age between parahippocampal–lingual gyrification and PANSS total score and subscores, age at onset and DUP were performed to assess a potential relationship of clinical variables and altered gyrification.

3. Results

3.1. Entire cortex analysis of local gyrification

The entire cortex analysis revealed one cluster with a significant higher mean curvature in patients with first-episode schizophrenia (Fig. 1). The cluster showed a surface area of ca. 750 mm² and comprised parts of the right parahippocampal and lingual cortex. Table 2 summarizes the characteristics of the cluster.

Table 2
Significant cluster for the right hemisphere, cluster size in mm², p-values from the Monte carlo simulation and clustering as cluster wise probability (CWP), resulting from the vertex-wise comparison of mean curvature between patients and healthy controls.

Cortex area	Size in mm²	Talx	Taly	Talz	CWP
Parahippocampal–lingual	750.35	18.2	-43.8	-3.7	0.0112

3.2. Quantification of gyrification differences

Patients showed a significant increased mean curvature of the parahippocampal–lingual region ($p<0.001$). Fig. 2 visualizes the results.

3.3. Comparison of cortical thickness of the right parahippocampal–lingual cluster

A significantly ($p<0.022$) reduced mean cortical thickness in patients (mean thickness = 2.40 mm ; SD = 0.18) in comparison to controls (mean thickness = 2.48 mm ; SD = 0.17) was found.

3.4. Correlations of right parahippocampal–lingual curvature and cortical thickness

The partial correlation between right parahippocampal–lingual curvature and right parahippocampal–lingual cortical thickness demonstrated a significant inverse correlation for the whole group ($p<0.001$; $r=-0.328$), in patients ($p<0.007$; $r=-0.369$), but not in controls ($p<0.414$; $r=-0.115$).

For the whole subject group, but not for patients and controls separately, a significant (Bonferroni corrected) inverse correlation of the right parahippocampal–lingual curvature was found with the mean cortical thickness of the following clusters: right pars opercularis ($p<0.002$; $r=-0.301$), right temporal/supramarginal ($p<0.003$; $r=-0.281$), left superior frontal ($p<0.003$; $r=-0.283$) and left postcentral/superior parietal ($p<0.002$; $r=-0.300$). That means that a higher parahippocampal–lingual gyrification is associated with lower cortical thickness of these regions.

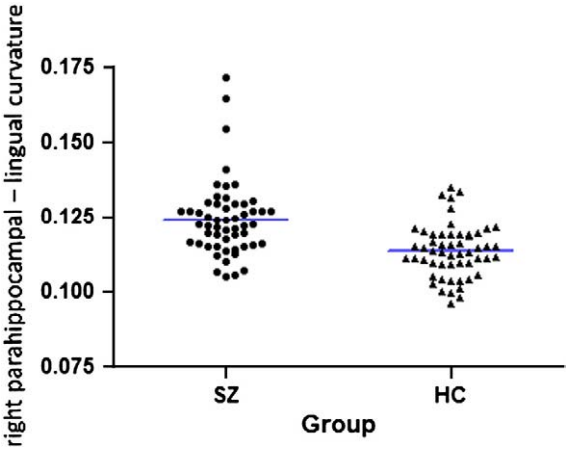

Fig. 2. Scatter plot of the mean curvature values for patients and healthy controls; blue lines showing the average mean curvature of the groups; abbr.: SZ: Patients with first-episode schizophrenia; HC: healthy controls.

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3.5. Correlation of right parahippocampal–lingual curvature and clinical variables

The partial correlations with parahippocampal–lingual curvature and PANSS total score and subscores (negative, positive, general) did not reveal significant results.

The partial correlation between age at onset and parahippocampal–lingual gyrification yielded a significant inverse correlation ($p<0.006$; $r=-0.375$). DUP did not show a significant correlation with parahippocampal–lingual gyrification.

4. Discussion

To our best knowledge, we present the first study using an entire cortex approach to compare on a vertex-wise basis mean curvature as a sensitive parameter for the identification of local gyrification changes in first-episode schizophrenia. We demonstrate hypergyria of a right parahippocampal and lingual cortical region in patients compared to healthy volunteers. Our finding of an increased gyrification is in line with a number of preceding studies showing hypergyria in schizophrenia (Harris et al., 2004; Narr et al., 2004; Vogeley et al., 2000; Wisco et al., 2007). We additionally demonstrated concurrent reduced cortical thickness of this right parahippocampal–lingual cortical area in first-episode schizophrenia reflecting a complex disturbance of cortical development of this area.

4.1. Hypergyria and mechanical models of brain development

Findings of hypergyria in schizophrenia fit well to mechanical models of brain development. These models suggest that due to centripetal forces generated by corticocortical connections in brain maturation a higher curvature is associated with a reduced cortical thickness (Hilgetag and Barbas, 2005). The inverse correlation between right parahippocampal–lingual curvature and cortical thickness found in the current study gives further support to mechanical models. The correlations are of moderate size indicating that other factors might impact the interplay of these anatomical parameters. The process of gyrification is closely related to the forming of cortico–cortical connections and is considered to be a major mediator for the interplay of cortical curvature and thickness (Hilgetag and Barbas, 2006; Van Essen, 1997). Misconnections might lead to focal hypergyrification (Narr et al., 2004). Thus, hypergyrification might be seen as an expression of deficient brain development and might be associated with functional deficits and symptoms in schizophrenia. In accordance, Stanfield et al. (2008) found an association of higher right prefrontal gyrification and schizotypical cognitions in high risk individuals.

Previous evidence of morphometric and functional MRI-studies suggests that the altered gyrification and thickness of the right parahippocampal region and the lingual gyrus which was detectable in the present study might be relevant for pathophysiological processes in schizophrenia.

4.2. Structural alterations of the parahippocampal region in schizophrenia

Several voxel based morphometry studies (VBM) demonstrated a decreased gray matter density of the parahippocampal area (Chua et al., 2007; Glahn et al., 2008) and the amygdala/hippocampal complex (Breier et al., 1992) in schizophrenia. Additionally, diffusion tensor imaging (DTI) analyses revealed reductions of fractional anisotropy (FA) in the right medial temporal lobe adjacent to the right parahippocampal gyrus (Schlosser et al., 2007).

Moreover, postmortem findings of the temporolimbic region including the parahippocampal gyrus (Arnold, 1997, 2000; Arnold et al., 2005) demonstrated reduced cortical thickness and a smaller neuron size. Findings indicative of a neurodegenerative process have, however, not been demonstrated. In addition, synaptic pathology of excitatory glutamatergic neurotransmission has been shown for this region in schizophrenia (Harrison and Eastwood, 1998). Hence, the present in vivo data of an aberrant gyrification and reduced cortical thickness of this region corroborates postmortem as well as MRI findings and is supportive of a neurodevelopmental origin of schizophrenia.

4.3. Structural alterations of the lingual region in schizophrenia

The lingual cortex demonstrated structural alterations with a deformation based analysis (Gaser et al., 1999) and high-dimensional shape transformations approach in schizophrenia (Davatzikos et al., 2005).

Moreover, Borgwardt et al. (2010) demonstrated reduced gray matter volume in the right lingual cortex in monozygotic twins with schizophrenia.

The present data demonstrate an increased gyrification and reduced cortical thickness of the lingual gyrus and extend previous data of aberrant morphology of the lingual region in schizophrenia.

The post hoc analysis of cortical thickness of the parahippocampal–lingual cluster revealed a significant cortical thickness reduction in patients, whereas this difference did not get unveiled using a vertex-wise entire cortex approach. This observation demonstrates that due to the high amount of comparisons for entire cortex analysis (i.e. 150,000 comparisons per hemisphere) and the need for the correction for multiple comparisons alterations of lower significance do not get unveiled whereas with a ROI approach they reach significance level.

4.4. Putative functional role of structural disturbances of the right parahippocampus and lingual cortex in schizophrenia

A substantial number of fMRI studies demonstrated that both the right parahippocampus and right lingual cortex are critically involved in several processes relevant for schizophrenia. The right parahippocampus has been demonstrated to be activated in topographical learning and spatial navigation (Aguirre et al., 1996; Kupers et al., 2010) — processes that have repeatedly been shown to be impaired in the context of the disorder (Piskulic et al., 2007). Moreover, the right parahippocampus and lingual gyrus has been shown to be involved in right hemispheric dominated networks mediating emotional functions. The meta-analysis of Li et al. (2009) indicated that the right parahippocampus is intensively involved in disturbed emotional face processing in schizophrenia. In addition, the study of Seiferth et al. (2008) showed that the right lingual gyrus was hyperactivated during emotion discrimination in high-risk subjects. The right

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parahippocampus and lingual gyrus might also mediate some language related functions. Rankin et al. (2009) demonstrated that the right parahippocampus is critically involved in the detection of sarcasm. This finding might corroborate the view that higher order language functions such as comprehension of humor and sarcasm which have been shown to be disturbed in schizophrenia (Mitchell and Crow, 2005) are more right lateralized. Additionally, in high risk subjects disturbed activation in the right lingual gyrus has been demonstrated performing an fMRI sentence completion task (Whalley et al., 2006).

In summary, both structures – the right parahippocampus and lingual cortex – have been found to be involved in several emotional and cognitive processes, which are of putative relevance for schizophrenia and which are driven by right hemispheric dominated networks. It can be assumed that structural disturbances in terms of hypergyria and reduced cortical thickness of the right parahippocampal and lingual cortex as important nodes of these networks might lead to functional alterations of the subserving processes.

4.5. Relation of right parahippocampal–lingual gyrification and age at onset

The partial correlation between age at onset and parahippocampal–lingual gyrification yielded a significant inverse correlation, i.e. higher parahippocampal–lingual gyrification was associated with earlier onset of psychosis. Age at onset has been conceptualized as an important clue to the etiology of schizophrenia with an association to altered brain developmental processes (DeLisi, 1992). Earlier age at onset is considered to be associated with a poorer treatment outcome (Crespo-Facorro et al., 2007) and is related to heritability of schizophrenia (Hare et al., 2010). As the forming of cerebral gyrification is mostly related to genetic and early pre - and perinatal factors, the association of parahippocampal–lingual curvature and age at onset thus corroborates both the notion of age at onset as an important clinical surrogate and curvature as an important endophenotypical imaging surrogate for an early brain maldevelopment in schizophrenia. The finding that DUP as a marker for pathophysiological processes occurring around the phase of clinical manifestation is not associated with parahippocampal–lingual curvature strengthens this assumption.

4.6. Methodological considerations and potential limitations of the study

In the present study the authors provided an automated curvature based approach for the assessment of local gyrification of the entire cortex. This methodological approach might entail several advantages. (1) It does not exclude any putatively altered regions from the analysis, which might be an advantage in comparison to ROI analysis. (2) The analysis is fine grained: 150,000 values per hemisphere were compared in this study enabling to detect even subtle gyrification differences. (3) After the extraction of the surfaces no manual or other methodological procedures (e.g. spherical ROI definition) are needed. Thus, for relatively new imaging techniques (i.e. automated computation of local gyrification on a surface) with a limited number of studies the use of whole cortex vertex-wise analysis as a more exploratory approach seems to be of high methodological relevance.

As a consequence of the high amount of comparisons resulting from the vertex-wise entire cortex approach, a sufficient handling of multiple comparisons has to be performed. For the present study, a conservative simulation and cluster approach has been chosen to avoid false positive findings. However, the risk is that smaller differences of gyrification aberrations might not get unveiled. This could be a potential explanation for the lacking alterations of gyrification in the present study in frontal areas, which have been shown in a former ROI based analysis (Wisco et al., 2007). On the other hand, findings surviving the multiple comparison procedures of a whole cortex comparison can be regarded as predominantly robust and might therefore be of major clinical relevance.

5. Conclusion

To our knowledge, we present the first vertex-wise analysis of local gyrification changes of the entire cortex in first-episode schizophrenia. Significant alterations were found for regions of the medial surface. Both affected areas, the parahippocampal region and the lingual cortex, are of high pathophysiological relevance for schizophrenia. Thus, our data provided new *in vivo* evidence for an early maturational deficit of these cortical areas in schizophrenia.

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Our sponsor, recognized in the acknowledgments, served no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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 mean curvature data analyses. Dr. Gaser and Dr. Reichenbach contributed technical expertise to the MRI imaging processing and mean curvature 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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