Brain Struct Funct
DOI 10.1007/s00429-011-0374-1

ORIGINAL ARTICLE

The visual cortex in schizophrenia: alterations of gyrification rather than cortical thickness—a combined cortical shape analysis

C. Christoph Schultz · Gerd Wagner · Kathrin Koch · Christian Gaser · Martin Roebel · Claudia Schachtzabel · Igor Nenadic · Jürgen R. Reichenbach · Heinrich Sauer · Ralf G. M. Schlösser

Received: 24 June 2011 / Accepted: 12 December 2011

Abstract In light of bottom-up models of disrupted cognition in schizophrenia, visual processing deficits became a key feature for the pathophysiology of schizophrenia. However, morphometric studies focusing on the visual cortex are limited. Thus, the present study sought to provide a combined cortical shape analysis (cortical thickness, folding) of visual areas, which were implicated to be involved in disturbed visual processing in schizophrenia. A group of 72 patients with schizophrenia according to DSM-IV and 72 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 and mean curvature of the V1, V2 and V5/MT+ visual cortex were estimated using an automated computerized algorithm (Freesurfer Software). A GLM controlling for the effect of age was used to estimate differences of cortical shape parameters between the study groups. Significantly increased gyrification of the V1, V2 and the V5/MT+ visual area bilaterally was detected. Conversely, cortical thickness was reduced in patients with schizophrenia only for the V5/MT+ area. This study is the first providing direct in vivo evidence for a disturbed cortical shape of central visual areas in schizophrenia. The present findings of hypergyria are highly indicative for a disrupted corticogenesis of these visual key regions and might constitute a relevant anatomical basis for visual processing deficits in schizophrenia.

Keywords V1 visual cortex · V2 visual cortex · V5/MT+ visual cortex · Cortical thickness · Gyrification · Cortical folding · Mean curvature · FreeSurfer

C. C. Schultz (✉) · G. Wagner · K. Koch · C. Gaser · M. Roebel · C. Schachtzabel · I. Nenadic · H. Sauer · R. G. M. Schlösser
Department of Psychiatry and Psychotherapy, Jena University Hospital, Friedrich-Schiller-University Jena, Philosophenweg 3, 07740 Jena, Germany
e-mail: christoph.schultz@med.uni-jena.de

J. R. Reichenbach
Medical Physics Group, Institute for Diagnostic and Interventional Radiology, Jena University Hospital, Friedrich-Schiller-University Jena, Philosophenweg 3, 07740 Jena, Germany

Introduction

Visual processing deficits in schizophrenia and visual cortex alterations

Schizophrenia is a devastating disease affecting about 1% of the population. In the majority of patients, the disorder begins in late adolescence or early adulthood (Picchioni and Murray 2007; van Os and Kapur 2009). Besides positive symptoms (such as delusions and hallucinations) and negative symptoms (e.g., blunted affect), cognitive deficits are a key feature of the disorder and of major relevance for long-term disability (Meltzer 2004). It has been repeatedly demonstrated that patients suffer from severe deficits in various cognitive domains including working memory, attention and executive functions (Bilder et al. 2000). However, the exact pathophysiological nature of these deficits is a matter of debate. As a potential basis for disturbed cognitive functioning, several studies demonstrated altered sensory input processing in schizophrenia (Butler et al. 2008; Javitt 2000). These findings led to the model of disturbed bottom-up sensory input integration as an important constituent of altered cognitive functioning in schizophrenia (Javitt 2009). In particular, visual processing deficits are considered to be important pathophysiological

Published online: 27 December 2011

features of the disorder (Coleman et al. 2009; Kantrowitz et al. 2009). They are linked to clinical symptoms and outcome measures such as social functioning (Green and Walker 1986; Rassovsky et al. 2011). Visual processing deficits may also be attributed to genetic liability for schizophrenia, as these deficits even occur in first-degree relatives (Yeap et al. 2006). However, in contrast to the established functional data for disturbed visual processing in schizophrenia, the majority of region of interest morphometric studies in schizophrenia have focused on fronto-temporal areas and studies explicitly investigating the visual cortex are limited. As visual processing deficits are regarded as constituting a trait marker for schizophrenia linked to genetic liability (Green et al. 2009), the underlying neuroanatomical alterations might be attributed to disturbed processes of early corticogenesis. As the process of cortical shaping in brain maturation is terminated to a very large degree before the age of 2 years (Armstrong et al. 1995), the measurement of gyrification particularly constitutes an in vivo marker for early disturbed neurodevelopmental processes in schizophrenia, mostly unaltered from net synaptic pruning and cortical aging processes. Volume-based parameters might be vulnerable to such later occurring cortical changes and are thus not exclusively directed to the detection of early disrupted processes of corticogenesis, which might be a potential explanation for the limited evidence of visual cortex alterations resulting from VBM studies in schizophrenia. Cortical shape parameters are thought to constitute indicators for the integrity of corticogenesis (Hilgetag and Barbas 2005). Surface-based morphometry (SBM) MRI studies allow examining cortical thickness and gyrification in vivo. Our recent entire cortex SBM study detected cortical thickness reduction in fronto-temporal areas and in parts of visual cortex areas including lateral occipital, lingual, the temporo-occipital cortex and the parieto-occipital junction in chronic schizophrenia (Schultz et al. 2010b), which is in line with the findings of other SBM studies (Goldman et al. 2009; Kuperberg et al. 2003; Nesvag et al. 2008; Rimol et al. 2010). In addition, hypergyria of a right parahippocampal–lingual area could be shown in first episode schizophrenia (Schultz et al. 2010a). Although these cortical shape findings were not confined to distinct visual cortex areas, they might indicate that cortical shape parameters are sensitive markers for the detection of cortical alterations of the visual system in schizophrenia. Thus, a combined analysis of cortical thickness and gyrification of distinct visual cortex areas, which were implicated to be involved in disturbed visual processing in schizophrenia, might elucidate the exact nature of potential visual cortex alterations and shed light on a potential neuroanatomical basis for visual processing deficits in schizophrenia.

Objectives and hypothesis

Thus, in the current study we intended to specifically investigate SBM of the central parts of the visual system. We sought to examine the cortical shape of the primary visual cortex (V1), the second major visual area V2 and V5/MT+ as a central "higher order" visual area. These areas have repeatedly been shown to be involved in disturbed visual processing in schizophrenia (Green et al. 2009; Martinez et al. 2008). A well-validated and highly accurate surface-based method (FreeSurfer) was used to assess cortical thickness and gyrification differences of the V1, V2 and V5/MT+ visual cortex in an extended cohort of patients with chronic schizophrenia and matched healthy controls. Whereas cortical thickness differences are clearly directed to a reduction of cortical thickness in schizophrenia, both hyper- and hypogyria have been found in schizophrenia even in the same patient group (Palaniyappan et al. 2011), potentially reflecting heterogeneity of gyrification changes in schizophrenia depending on the cortical area analyzed. Thus, a directed hypothesis with respect to gyrification differences cannot definitely be derived from the literature for the different visual areas. We thus hypothesized a reduced cortical thickness and altered gyrification of the V1, V2 and V5/MT+ visual cortex in schizophrenia patients compared to healthy controls.

Subjects and methods

Participants

Seventy-two patients with schizophrenia and 72 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 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. Socio-demographic and psychopathological data are given in Table 1.

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 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 artifacts and a neuroradiologist confirmed absence of gross pathological findings.

MR scan processing

We used the FreeSurfer software package (version 4.0.5, http://surfer.nmr.mgh.harvard.edu) for image processing (Dale et al. 1999; Fischl et al. 1999). The implemented processing stream provides removal of non-brain tissue (Segonne et al. 2004), transformation to Talairach-like space, and segmentation of gray/white matter tissue (Fischl et al. 2002, 2004a). The white and gray matter boundary is tessellated and topological defects are automatically corrected (Fischl et al. 2001; Segonne et al. 2007). After intensity normalization (Sled et al. 1998), transition of gray/white matter is detected by an adapted marching cubes algorithm and the pial boundary is detected by indicating the greatest shift in intensity through surface deformation (Dale et al. 1999; Dale and Sereno 1993; Fischl and Dale 2000). The entire cortex of each subject was then visually inspected and any inaccuracies in segmentation were manually edited. 18 subjects needed manual correction, and 2 of them required corrections in visual cortex areas. After creation of the cortical representations, the cerebral cortex is parcellated into anatomical structures (Desikan et al. 2006; Fischl et al. 2004b).

Table 1 Demographic and clinical data

Parameter	Controls ($n = 72$)	Patients ($n = 72$)	p
M/F	47/25	47/25	
Age (years)	29.0 (8.5)	28.6 (8.9)	0.810
Education (years)	11.4 (1.0)	10.7 (1.2)	0.003
PANSS total score	n.a.	73.6 (24.1)	
PANSS pos	n.a.	18.2 (7.9)	
PANSS neg	n.a.	17.8 (6.3)	
Duration of illness (years)	n.a.	4.3 (5.6)	

Data expressed as mean (SD)

n.a. Not applicable, *PANSS* positive and negative syndrome scale (Kay et al. 1987)

p Values resulting from two sample t test

ROI delineation

To ensure reproducibility of results, we restricted our analyses of visual cortex areas in schizophrenia to ROIs delineated by validated anatomical labels as implemented in the FreeSurfer Software. The delineation of the V1 label is based on the study of Hinds et al. (2008) and corresponds to Brodmann area (BA) 17; the delineation of the V2 label is described by Fischl et al. (2008) and corresponds to BA 18. The delineation of the V5/MT+ label is based on the work of Malikovic et al. (2007). This V5/MT+ area is located close to the intersection of the anterior occipital and the inferior lateral occipital sulci in the region of the temporo-occipital junction. Its major part is found in the depths of sulci. Only a minor part covers the free surface of the occipital gyri.

Figure 1 illustrates the topography of V1, V2 and V5/MT+ visual cortex.

The anatomical labels were mapped to all individual brains for the quantification of average cortical thickness and average mean curvature using automated FreeSurfer tools.

Calculation of cortical thickness

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 Dale 2000). Measurements of cortical thickness have been validated against manual measurements in schizophrenia (Kuperberg et al. 2003).

Calculation of gyrification

Cortical curvature represents a sensitive and automated approach for identifying highly local changes in gyrification (Luders et al. 2006). Mean curvature was calculated for the V1, V2 and V5/MT+ visual cortex area of both hemispheres of the white surface, as implemented in the FreeSurfer software.

Mean curvature is a mathematically defined measure derived from differential geometry (do Carmo 1976). It is a measure of the general extent of the curvature and is

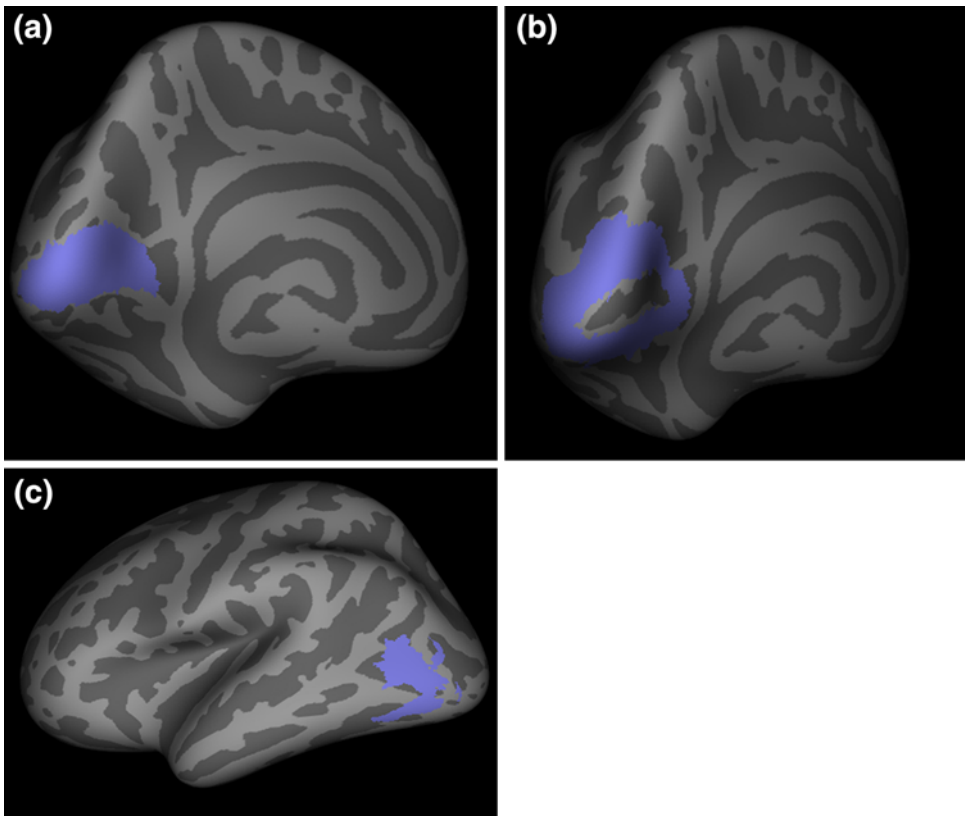

Fig. 1 Topography of the V1 (**a**), V2 (**b**) and V5/MT+ (**c**) visual area (*colored in blue*) displaying the *left* inflated surface

calculated by the mean of the principal curvatures, k_1 and k_2 (Pienaar et al. 2008):

$$\text{Mean curvature} = \frac{1}{2}(k_1 + k_2)$$

For the data analysis, absolute values for the mean curvature were calculated and averaged for each ROI using the unsmoothed curvature data. Higher values represent a more steeply peaked curvature and values approaching zero a more flattened curvature.

Statistical analysis

Comparison of cortical thickness and mean curvature between the groups

Values for the average cortical thickness and absolute mean curvature for each subject of the V1, V2 and V5/MT+ visual cortex for both hemispheres were analyzed using a general linear model controlling for the effect of age. All results were corrected for multiple comparisons using Bonferroni correction. F values were based on pair-wise comparisons between the mean values extracted from the general linear model.

Results

Cortical thickness

We found a significantly reduced cortical thickness in patients with schizophrenia of the left ($p < 0.001$) and right ($p < 0.001$) V5/MT+ visual cortex. The differences in percent were 4% (left) and 3.25% (right). In addition, a strong trend for a reduced cortical thickness was observed for the right V2 area ($p < 0.08$).

Absolute mean curvature

Patients exhibited a significantly higher mean curvature for both hemispheres of the V1, V2 and V5/MT+ cortical area (V1: left $p < 0.003$, right $p < 0.002$; V2: left $p < 0.003$, right $p < 0.002$; V5: left $p < 0.002$, right $p < 0.000$).

For all measures, the exact values are given in Table 2.

There were no significant differences in total brain volume between groups.

We post hoc compared cortical thickness and mean curvature covering the entire cortex. Significant cortical thinning in patients was found in parts of the V5/MT+ visual region in patients. No other significant results were

Table 2 Mean values of the anatomical parameters were compared using a general linear model controlling for the effect of age

Parameter	Unit	Mean (SD)		*F*	*p*
		Controls	Patients		
Left V1 mean curvature	mm^{-1}	0.192 (0.020)	0.206 (0.034)	9.07	**0.003**
Right V1 mean curvature		0.193 (0.018)	0.206 (0.031)	9.64	**0.002**
Left V1 cortical thickness	mm	1.86 (0.09)	1.87 (0.14)	0.07	0.788
Right V1 cortical thickness		1.91 (0.10)	1.91 (0.13)	0.08	0.781
Left V2 mean curvature	mm^{-1}	0.187 (0.015)	0.198 (0.027)	8.99	**0.003**
Right V2 mean curvature		0.187 (0.014)	0.198 (0.026)	9.88	**0.002**
Left V2 cortical thickness	mm	2.09 (0.08)	2.07 (0.12)	2.68	0.104
Right V2 cortical thickness		2.14 (0.10)	2.11 (0.11)	3.05	0.083
Left V5/MT+ mean curvature	mm^{-1}	0.166 (0.016)	0.177 (0.026)	9.90	**0.002**
Right V5/MT+ mean curvature		0.157 (0.013)	0.168 (0.022)	13.04	**0.000**
Left V5/MT+ cortical thickness	mm	2.48 (0.12)	2.38 (0.17)	14.45	**0.000**
Right V5/MT+ cortical thickness		2.46 (0.14)	2.38 (0.17)	11.18	**0.001**

F values are based on the pairwise comparisons among the means. *p* values corrected for multiple comparisons using Bonferroni

Bold values indicate satistically significant *p* values

found in the visual cortex areas at the whole brain level for cortical thickness and mean curvature.

Discussion

The present study examined cortical geometry of central parts of the visual system. An increased gyrification was detected in all of the investigated visual areas, indicating an early disruption of corticogenesis of these cortical regions. Cortical thickness was only significantly reduced for the V5/MT+ area. The combined analysis of cortical thickness and gyrification demonstrated that the different anatomical parts of the visual cortex are differentially affected by alterations of the cortical shape in schizophrenia. Our finding of cortical thickness reduction of the V5/MT+ area is in line with previous studies showing cortical thickness reduction of the temporo-occipital and parieto-occipital junction in schizophrenia (Kuperberg et al. 2003; Schultz et al. 2010b), although these studies were not explicitly directed to the analysis of specific visual cortex areas. In addition, the demonstrated hypergyria of the V1 and V2 area corroborates our recent finding of lingual hypergyria in first episode schizophrenia (Schultz et al. 2010a). However, the present study is—due to different methodical approaches (ROI vs. entire cortex approach) and differences of the study group (first episode vs. chronic patients)—not entirely comparable with our previous study.

Hypergyria as a result of disturbed processes of corticogenesis

Mechanical models of brain development propose that the process of gyrification is closely related to the forming of cortico-cortical connections, which is considered to be a major mediator for the interplay of cortical curvature and thickness (Hilgetag and Barbas 2006; Van Essen 1997). The characteristic convolutions are thought to optimize the neuronal information transfer between the brain regions (Hilgetag and Barbas 2005; Van Essen 1997; Zilles et al. 1988). Animal experiments have demonstrated that misconnections are related to focal hypergyrification (Goldman-Rakic 1980). Thus, hypergyrification might be seen as an expression of deficient brain development in schizophrenia and might be associated with disturbed white matter integrity. Several MRI studies in schizophrenia and high risk subjects demonstrated altered gyrification in the same direction, i.e., a hypergyrification (Harris et al. 2004, 2007; Narr et al. 2004; Stanfield et al. 2008; Vogeley et al. 2001; Wisco et al. 2007) as hypothesized by these mechanical models.

In contrast to the above-mentioned mechanical models of gyrification, other studies suggest the influence of differential cortical growth in brain development to be a driving force of cortical folding processes (Toro et al. 2008; Xu et al. 2010). However, both models propose a close relation of cortical folding processes and brain development. Further in vivo studies evaluating the exact mechanism of the forming of cortical folding are needed.

The potential time course of shape alterations of the visual cortex

Whereas gyrification and not cortical thickness of the V1 and V2 area was altered, we found an alteration of gyrification and cortical thickness of the V5/MT+ area, which might indicate that from lower to higher order visual areas, the complexity of cortical shape disturbance might increase. Although speculative, this observation might shed

light on the potential time course of cortical alterations of the visual cortex in schizophrenia.

With regard to determination of gyrification, it is important to note that until the 26th post-gestational week, the developing brain is lissencephalic. After the 26th week, the cortex morphology changes rapidly reaching the characteristic adult gyrencephalic shape by term at week 40 (White and Hilgetag 2011). Thus, major parts of the process of cortical folding occur during the third trimester. It has additionally been demonstrated that cortical gyrification is largely stable over a wide age range (Armstrong et al. 1995). Based on the findings that major parts of cortical folding processes take place in early brain development, it seems most plausible that cortical folding alterations in schizophrenia may be—to a large extent—due to deficits in early corticogenesis and related genetic, prenatal and early postnatal factors. However, there are also data showing changes in the degree of folding during childhood and throughout adolescence (White et al. 2010). Thus, it cannot be ruled out that cortical folding alterations in schizophrenia are—to a minor part—additionally attributed to these later occurring processes. Further studies are needed to examine at which time point cortical folding alterations in schizophrenia occur and which cortical processes are associated with these cortical folding alterations.

Cortical thickness reduction might additionally be associated with synaptic pruning and related decrease of glial cells due to reduced metabolic requirements (Paus et al. 2008). Net synaptic elimination begins and ends earlier in "lower" cortical areas and primary sensory areas in comparison to "higher" cortical regions, where net synaptic pruning extends until mid-adolescence (Huttenlocher and Dabholkar 1997). Hence, it can be speculated that reduced cortical thickness of the higher order visual cortex V5 might also be a result of pathophysiological processes appearing in the adolescence period. Another putative neuroanatomical process underlying cortical thickness changes might be the degree of intra-cortical myelin. It has repeatedly been demonstrated that intra-cortical myelin increases from birth to adulthood [see for review (Paus et al. 2008)]. A recent in vivo study in humans of Glasser and Van Essen (2011) found an inverse relation of intra-cortical myelin and cortical thickness. It is known from histological studies that heavily myelinated cortical areas are associated with lower cortical thickness (Triarhou 2007). Moreover, in MRI studies a higher degree of cortical myelination might lead to an underestimation of cortical thickness (Paus et al. 2008). Hence, intra-cortical hypermyelination may constitute another process that explains findings of cortical thinning in schizophrenia. Taken together, different neuroanatomical mechanism might underlie cortical thinning in schizophrenia and further studies on this issue are required.

Altered cortical shape of the visual areas and possible functional implications

Our findings indicate that cortical shape parameters and in particular gyrification might be sensitive measures for the detection of cortical alterations of the visual system in schizophrenia. As visual processing deficits are proposed to be a trait marker for schizophrenia, it can be assumed that cortical shape alterations of the investigated visual areas might be a neuroanatomical basis of visual processing deficits in schizophrenia. However, to directly explore a potential link between cortical shape alterations of visual processing deficits further, particularly multimodal, imaging studies are needed allowing to relate visual cortex shape alterations to visual processing deficits in schizophrenia.

Limitations of the study

There is growing evidence that antipsychotic medication affects gray matter volume. A recent study by Ho et al. (2011) demonstrated significant effects of both typical and atypical antipsychotics on total and lobar gray matter volume in a large cohort of more than 200 patients. Hence, to evaluate a potential medication effect on the visual cortical shape measures, the chlorpromazine equivalents of the current antipsychotic medication (at the time point of MRI measurement) were estimated. A partial correlation between the current chlorpromazine equivalent dose and cortical shape values controlling for the effect of age did not yield any significant results, which is in line with studies showing no effect of antipsychotic medication on cortical thickness (Kuperberg et al. 2003; Nesvag et al. 2008) and gyrification (Palaniyappan et al. 2011). However, it cannot be ruled out that statistically significant effects of antipsychotic medication on visual cortical shape measures would be unveiled in a larger patient sample.

Future research directions

Two recent reviews focused on cortical gyrification findings in schizophrenia considering that measures of cortical folding constitute an important cortical marker in schizophrenia (Mangin et al. 2010; White and Hilgetag 2011). In the present study, the authors used a curvature-based approach for estimating gyrification of the visual cortex areas, which has repeatedly been used in clinical samples (Fornito et al. 2008; Gaser et al. 2006; Schultz et al. 2010a). However, it is important to note that other also well-validated methods for measuring cortical folding exist. Most of them are conceptually based on the gyrification index by Zilles et al. (1988), such as the local gyrification index of Schaer et al. (2008). The different

cortical folding measures (curvature based vs. gyrification index based) are not necessarily comparable regarding the relationship to underlying neuroanatomical mechanisms and associated putative pathophysiological processes. Thus, further studies comparing the different cortical folding measures and related neuroanatomical parameters (e.g., white matter connectivity) are needed.

Concluding remarks

This is the first study providing direct in vivo evidence for a disturbed shape of the visual cortex in schizophrenia. The presented findings of hypergyrification are suggestive of a disrupted corticogenesis of these visual key regions and might constitute an anatomical basis for visual processing deficits in schizophrenia.

Acknowledgments This work was supported by the Bundesministerium für Bildung und Forschung, BMBF Grant 01GW0740 and the Interdisciplinary Center for Clinical Research of the University of Jena (IZKF).

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

References

Annett M (1967) The binomial distribution of right, mixed and left handedness. Q J Exp Psychol 19(4):327–333

Armstrong E, Schleicher A, Omran H, Curtis M, Zilles K (1995) The ontogeny of human gyrification. Cereb Cortex 5(1):56–63

Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, Pappadopulos E, Willson DF, Alvir JM, Woerner MG, Geisler S, Kane JM, Lieberman JA (2000) Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. Am J Psychiatry 157(4):549–559

Butler PD, Silverstein SM, Dakin SC (2008) Visual perception and its impairment in schizophrenia. Biol Psychiatry 64(1):40–47

Coleman MJ, Cestnick L, Krastoshevsky O, Krause V, Huang Z, Mendell NR, Levy DL (2009) Schizophrenia patients show deficits in shifts of attention to different levels of global-local stimuli: evidence for magnocellular dysfunction. Schizophr Bull 35(6):1108–1116

Dale AM, Sereno MI (1993) Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. J Cogn Neurosci 5:162–176

Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9(2): 179–194

Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31(3):968–980

do Carmo M (1976) Differential geometry of curves and surfaces. Prentice-Hall, Englewood Cliffs

Fischl B, Dale AM (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA 97(20):11050–11055

Fischl B, Sereno MI, Dale AM (1999) Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 9(2):195–207

Fischl B, Liu A, Dale AM (2001) Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. IEEE Trans Med Imaging 20(1):70–80

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002) Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33(3):341–355

Fischl B, Salat DH, van der Kouwe AJ, Makris N, Segonne F, Quinn BT, Dale AM (2004a) Sequence-independent segmentation of magnetic resonance images. Neuroimage 23(1):S69–S84

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM (2004b) Automatically parcellating the human cerebral cortex. Cereb Cortex 14(1):11–22

Fischl B, Rajendran N, Busa E, Augustinack J, Hinds O, Yeo BT, Mohlberg H, Amunts K, Zilles K (2008) Cortical folding patterns and predicting cytoarchitecture. Cereb Cortex 18(8): 1973–1980

Fornito A, Yucel M, Wood SJ, Adamson C, Velakoulis D, Saling MM, McGorry PD, Pantelis C (2008) Surface-based morphometry of the anterior cingulate cortex in first episode schizophrenia. Hum Brain Mapp 29(4):478–489

Gaser C, Luders E, Thompson PM, Lee AD, Dutton RA, Geaga JA, Hayashi KM, Bellugi U, Galaburda AM, Korenberg JR, Mills DL, Toga AW, Reiss AL (2006) Increased local gyrification mapped in Williams syndrome. Neuroimage 33(1):46–54

Glasser MF, Van Essen DC (2011) Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. J Neurosci 31(32):11597–11616

Goldman AL, Pezawas L, Mattay VS, Fischl B, Verchinski BA, Chen Q, Weinberger DR, Meyer-Lindenberg A (2009) Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Arch Gen Psychiatry 66(5):467–477

Goldman-Rakic PS (1980) Morphological consequences of prenatal injury to the primate brain. Prog Brain Res 53:1–19

Green M, Walker E (1986) Symptom correlates of vulnerability to backward masking in schizophrenia. Am J Psychiatry 143(2): 181–186

Green MF, Lee J, Cohen MS, Engel SA, Korb AS, Nuechterlein KH, Wynn JK, Glahn DC (2009) Functional neuroanatomy of visual masking deficits in schizophrenia. Arch Gen Psychiatry 66(12): 1295–1303

Harris JM, Yates S, Miller P, Best JJ, Johnstone EC, Lawrie SM (2004) Gyrification in first-episode schizophrenia: a morphometric study. Biol Psychiatry 55(2):141–147

Harris JM, Moorhead TW, Miller P, McIntosh AM, Bonnici HM, Owens DG, Johnstone EC, Lawrie SM (2007) Increased prefrontal gyrification in a large high-risk cohort characterizes those who develop schizophrenia and reflects abnormal prefrontal development. Biol Psychiatry 62(7):722–729

Hilgetag CC, Barbas H (2005) Developmental mechanics of the primate cerebral cortex. Anat Embryol (Berl) 210(5–6):411–417

Hilgetag CC, Barbas H (2006) Role of mechanical factors in the morphology of the primate cerebral cortex. PLoS Comput Biol 2(3):e22

Hinds OP, Rajendran N, Polimeni JR, Augustinack JC, Wiggins G, Wald LL, Diana Rosas H, Potthast A, Schwartz EL, Fischl B (2008) Accurate prediction of V1 location from cortical folds in a surface coordinate system. Neuroimage 39(4):1585–1599

Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011) Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 68(2):128–137

Huttenlocher PR, Dabholkar AS (1997) Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 387(2): 167–178

Javitt DC (2000) Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. Audiol Neurootol 5(3–4):207–215

Javitt DC (2009) When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. Annu Rev Clin Psychol 5:249–275

Kantrowitz JT, Butler PD, Schecter I, Silipo G, Javitt DC (2009) Seeing the world dimly: the impact of early visual deficits on visual experience in schizophrenia. Schizophr Bull 35(6): 1085–1094

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13(2):261–276

Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SC, van der Kouwe AJ, Salat DH, Dale AM, Fischl B (2003) Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry 60(9):878–888

Luders E, Thompson PM, Narr KL, Toga AW, Jancke L, Gaser C (2006) A curvature-based approach to estimate local gyrification on the cortical surface. Neuroimage 29(4):1224–1230

Malikovic A, Amunts K, Schleicher A, Mohlberg H, Eickhoff SB, Wilms M, Palomero-Gallagher N, Armstrong E, Zilles K (2007) Cytoarchitectonic analysis of the human extrastriate cortex in the region of V5/MT+: a probabilistic, stereotaxic map of area hOc5. Cereb Cortex 17(3):562–574

Mangin JF, Jouvent E, Cachia A (2010) In-vivo measurement of cortical morphology: means and meanings. Curr Opin Neurol 23(4):359–367

Martinez A, Hillyard SA, Dias EC, Hagler DJ Jr, Butler PD, Guilfoyle DN, Jalbrzikowski M, Silipo G, Javitt DC (2008) Magnocellular pathway impairment in schizophrenia: evidence from functional magnetic resonance imaging. J Neurosci 28(30):7492–7500

Meltzer HY (2004) Cognitive factors in schizophrenia: causes, impact, and treatment. CNS Spectr 9(10 Suppl 11):15–24

Narr KL, Bilder RM, Kim S, Thompson PM, Szeszko P, Robinson D, Luders E, Toga AW (2004) Abnormal gyral complexity in first-episode schizophrenia. Biol Psychiatry 55(8):859–867

Nesvag R, Lawyer G, Varnas K, Fjell AM, Walhovd KB, Frigessi A, Jonsson EG, Agartz I (2008) Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. Schizophr Res 98(1–3):16–28

Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF (2011) Folding of the prefrontal cortex in schizophrenia: regional differences in gyrification. Biol Psychiatry 69(10):974–979

Paus T, Keshavan M, Giedd JN (2008) Why do many psychiatric disorders emerge during adolescence? Nat Rev 9(12):947–957

Picchioni MM, Murray RM (2007) Schizophrenia. BMJ 335(7610): 91–95 (Clinical research ed)

Pienaar R, Fischl B, Caviness V, Makris N, Grant PE (2008) A methodology for analyzing curvature in the developing brain from preterm to adult. Int J Imaging Syst Technol 18(1):42–68

Rassovsky Y, Horan WP, Lee J, Sergi MJ, Green MF (2011) Pathways between early visual processing and functional outcome in schizophrenia. Psychol Med 41(3):487–497

Rimol LM, Hartberg CB, Nesvag R, Fennema-Notestine C, Hagler DJ Jr, Pung CJ, Jennings RG, Haukvik UK, Lange E, Nakstad PH, Melle I, Andreassen OA, Dale AM, Agartz I (2010) Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol Psychiatry 68(1):41–50

Schaer M, Cuadra MB, Tamarit L, Lazeyras F, Eliez S, Thiran JP (2008) A surface-based approach to quantify local cortical gyrification. IEEE Trans Med Imaging 27(2):161–170

Schultz CC, Koch K, Wagner G, Roebel M, Nenadic I, Gaser C, Schachtzabel C, Reichenbach JR, Sauer H, Schlosser RG (2010a) Increased parahippocampal and lingual gyrification in first-episode schizophrenia. Schizophr Res 123(2–3):137–144

Schultz CC, Koch K, Wagner G, Roebel M, Nenadic I, Schachtzabel C, Reichenbach J, Sauer H, Schlosser R (2010b) Complex pattern of cortical thinning in schizophrenia: results from an automated surface based analysis of cortical thickness. Psychiatry Res 182(2):134–140

Segonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, Fischl B (2004) A hybrid approach to the skull stripping problem in MRI. Neuroimage 22(3):1060–1075

Segonne F, Pacheco J, Fischl B (2007) Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. IEEE Trans Med Imaging 26(4):518–529

Sled JG, Zijdenbos AP, Evans AC (1998) A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 17(1):87–97

Stanfield AC, Moorhead TW, Harris JM, Owens DG, Lawrie SM, Johnstone EC (2008) Increased right prefrontal cortical folding in adolescents at risk of schizophrenia for cognitive reasons. Biol Psychiatry 63(1):80–85

Toro R, Perron M, Pike B, Richer L, Veillette S, Pausova Z, Paus T (2008) Brain size and folding of the human cerebral cortex. Cereb Cortex 18(10):2352–2357

Triarhou LC (2007) The Economo-Koskinas atlas revisited: cytoarchitectonics and functional context. Stereotact Funct Neurosurg 85(5):195–203

Van Essen DC (1997) A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature 385(6614):313–318

van Os J, Kapur S (2009) Schizophrenia. Lancet 374(9690):635–645

Vogeley K, Tepest R, Pfeiffer U, Schneider-Axmann T, Maier W, Honer WG, Falkai P (2001) Right frontal hypergyria differentiation in affected and unaffected siblings from families multiply affected with schizophrenia: a morphometric MRI study. Am J Psychiatry 158(3):494–496

White T, Hilgetag CC (2011) Gyrification and neural connectivity in schizophrenia. Dev Psychopathol 23(1):339–352

White T, Su S, Schmidt M, Kao CY, Sapiro G (2010) The development of gyrification in childhood and adolescence. Brain Cogn 72(1):36–45

Wisco JJ, Kuperberg G, Manoach D, Quinn BT, Busa E, Fischl B, Heckers S, Sorensen AG (2007) Abnormal cortical folding patterns within Broca's area in schizophrenia: evidence from structural MRI. Schizophr Res 94(1–3):317–327

Xu G, Knutsen AK, Dikranian K, Kroenke CD, Bayly PV, Taber LA (2010) Axons pull on the brain, but tension does not drive cortical folding. J Biomech Eng 132(7):071013

Yeap S, Kelly SP, Sehatpour P, Magno E, Javitt DC, Garavan H, Thakore JH, Foxe JJ (2006) Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. Arch Gen Psychiatry 63(11):1180–1188

Zilles K, Armstrong E, Schleicher A, Kretschmann HJ (1988) The human pattern of gyrification in the cerebral cortex. Anat Embryol (Berl) 179(2):173–179