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ORIGINAL ARTICLE

Cortical folding in Broca's area relates to obstetric complications in schizophrenia patients and healthy controls

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Background. The increased occurrence of obstetric complications (OCs) in patients with schizophrenia suggests that alterations in neurodevelopment may be of importance to the aetiology of the illness. Abnormal cortical folding may reflect subtle deviation from normal neurodevelopment during the foetal or neonatal period. In the present study, we hypothesized that OCs would be related to cortical folding abnormalities in schizophrenia patients corresponding to areas where patients with schizophrenia display altered cortical folding when compared with healthy controls.

Method. In total, 54 schizophrenia patients and 54 healthy control subjects underwent clinical examination and magnetic resonance image scanning on a 1.5 T scanner. Information on OCs was collected from original birth records. An automated algorithm was used to calculate a three-dimensional local gyrification index (*l*GI) at numerous points across the cortical mantle.

Results. In both schizophrenia patients and healthy controls, an increasing number of OCs was significantly related to lower *l*GI in the left pars triangularis ($p < 0.0005$) in Broca's area. For five other anatomical cortical parcellations in the left hemisphere, a similar trend was demonstrated. No significant relationships between OCs and *l*GI were found in the right hemisphere and there were no significant case–control differences in *l*GI.

Conclusions. The reduced cortical folding in the left pars triangularis, associated with OCs in both patients and control subjects suggests that the cortical effect of OCs is caused by factors shared by schizophrenia patients and healthy controls rather than factors related to schizophrenia alone.

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Introduction

The increased prevalence of pre- and perinatal complications in schizophrenia patients is supportive of a neurodevelopmental origin of the illness (Lewis & Murray, 1987; Weinberger, 1987; Marenco & Weinberger, 2000). Subtle deviances from normal brain development may be reflected in altered brain morphology (Fatemi & Folsom, 2009). In schizophrenia patients, smaller hippocampi, larger ventricles and reduced cortical thickness and volume have relatively consistently been reported (Honea *et al*. 2005; Steen *et al*. 2006; Glahn *et al*. 2008). In animal models, various obstetric complications (OCs) have been demonstrated to cause both brain morphological alterations and behavioural aberrances that parallel those observed in schizophrenia (for review, see Boksa, 2004). In magnetic resonance imaging (MRI) studies of schizophrenia patients, OCs have been related to smaller hippocampi (van Erp *et al*. 2002; Schulze *et al*. 2003; Ebner *et al*. 2008), larger lateral ventricles (McNeil *et al*. 2000; Falkai *et al*. 2003) and reduced cortical volume (Cannon *et al*. 2002). Taken together, these findings suggest that early somatic trauma such as OCs may

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exert an influence on neurodevelopment, detectable in the brain decades later. However, the brain morphological alterations reported in schizophrenia may also reflect medication use (Smieskova *et al*. 2009), illness progression (van Haren *et al*. 2007; Tanskanen *et al*. 2008), genetic variation (van Haren *et al*. 2008) or other illness-related factors.

Alterations in cortical folding patterns may be a brain morphological correlate of aberrant neurodevelopment. The process of cortical gyrification is under genetic control (Piao *et al*. 2004), but environmental factors have also been demonstrated to be of importance (Bartley *et al*. 1997). The early stages of gyrification appear around gestational week 16, with a rapid increase in cortical gyrification in the third trimester of pregnancy (Armstrong *et al*. 1995). The gyrification index (GI), defined as the ratio between the pial and the arachnoideal surface as observed in coronal slices of post-mortem brains or MRI scans (Zilles *et al*. 1988), demonstrates a steady increase until postnatal week 6, from which the GI remains by and large stable (Armstrong *et al*. 1995). The human gyrification process may be a result of tension-based mechanisms. Visco-elastic tension exerted by cortical fibres draw regions with greater connectivity closer together (forming gyri) and thereby reduces the transit time of the action potentials (van Essen, 1997; White *et al*. 2010). Cortical folding patterns may thus convey information on underlying cortical organization and complexity. As a consequence, gyrification measures demonstrate properties related to both neurodevelopment and cortical organization, aspects that are of importance in schizophrenia.

Several studies on gyrification abnormalities in schizophrenia have been conducted with heterogeneous findings as a result. Prefrontal hypergyria (higher GI) (Vogeley *et al*. 2000, 2001; Falkai *et al*. 2007; Harris *et al*. 2007), lower prefrontal (Bonnici *et al*. 2007) and global (Sallet *et al*. 2003; Cachia *et al*. 2008) GI, as well as negative findings (Highley *et al*. 2003) have been reported. Gyrification abnormalities have been reported to be present before adult illness onset (Harris *et al*. 2004*a*, *b*). A flattening of sulcal curvature together with peaking of gyral curvature has been reported in childhood- and adolescence-onset schizophrenia patients (White *et al*. 2003). It is, however, uncertain if early somatic trauma such as OCs influences the gyrification process in schizophrenia. To our knowledge, thus far only one scientific study (Falkai *et al*. 2007) has examined the relationship between OCs and gyrification in schizophrenia. Falkai *et al*. found no effect of OCs on a two-dimensional (2D) based GI in schizophrenia patients ($n=29$) and their relatives (of which 21 relatives were healthy and 13 had psychosis) (Falkai *et al*. 2007).

The human brain cortex is a highly complex three-dimensional (3D) structure. Measuring cortical folding from 2D coronal MRI slices might lead to loss of information related to buried sulci and gyral anomalies in sublobar regions. In the present study, we used a 3D surface-based automated algorithm to calculate the local GI (*l*GI) in each vertex across the whole cortical mantle (http://surfer.nmr.mgh.harvard.edu/fswiki/LGI) (Schaer *et al*. 2008). With this method, subtle localized deviances in cortical folding may be detected with submillimetre precision.

Hypotheses

Based on findings from the previous scientific literature, we hypothesized: (1) that OCs would be related to cortical folding, as measured by a 3D surface-based *l*GI; (2) that this relationship would be different in schizophrenia patients and healthy control subjects; (3) that the hypothesized difference would correspond to areas where schizophrenia patients demonstrate altered cortical folding as compared with healthy controls.

Method and materials

Subject characterization

This study was part of the Human Brain Informatics Project (HUBIN) at the Karolinska Institutet, Stockholm, Sweden. HUBIN is a comprehensive database of genetic, brain morphological, neuropsychological and clinical information obtained from schizophrenia patients and healthy subjects. The subject inclusion took place between 1999 and 2003. All participants gave written informed consent. The project was approved by the Research Ethics Committee at Karolinska Institutet and the Swedish Data Inspection Board ('Datainspektionen'). The study was performed in accordance with the Helsinki Declaration.

The subject sample consisted of unrelated Caucasian men and women currently resident in the Stockholm area and has previously been thoroughly described (Jonsson *et al*. 2006; Haukvik *et al*. 2009). Briefly, invited patients from three out-patients clinics underwent a comprehensive clinical assessment protocol including structured interviews (Spitzer, 1988; Wing *et al*. 1990) and reviews of medical records to obtain a DSM-III-R and DSM-IV diagnosis as previously described (Ekholm *et al*. 2005; Vares *et al*. 2006). The patients fulfilled DSM-IV criteria for schizophrenia ($n=50$) or schizoaffective disorder ($n=4$). Handedness was ascertained by means of asking the patients which hand they used when writing, using scissors and throwing/catching a ball. Control subjects were

Table 1. *Demographic, clinical, and obstetric characteristics in schizophrenia patients and healthy control subjects*

	Patients ($n=54$)		Controls ($n=54$)		Statistics
	Mean (S.D.)	Range	Mean (S.D.)	Range	p value
Age at MRI (years)	41.9 (8.0)	25–57	41.5 (8.9)	19–56	N.S.
Age at illness onset (years)	24.9 (5.6)	15–39	N.A.		N.A.
Duration of illness (years) $n=53$	16.8 (9.3)	0.4–41	N.A.		N.A.
Years of schooling (years) $n=36$ p, 38 c	12.5 (2.74)	8–19	14.2 (2.89)	10–22	0.012
WAIS R $n=36$ p, 38 c	44.9 (14.0)	9–66	51.9 (9.53)	28–68	0.016
SAPS $n=46$	3.9 (2.72)	0–10	N.A.		N.A.
SANS $n=53$	7.6 (5.1)	1–22	N.A.		N.A.
Birth weight (g)	3494 (635)	1770–5630	3397 (665)	1460–4720	N.S.
Head circumference (cm) $n=105$	33.8 (1.5)	30–37	33.7 (1.6)	28–36	N.S.
Gestational age (weeks)	39.2 (1.9)	32–42	39.4 (2.2)	31–43	N.S.
Maternal age (years)	27.5 (5.6)	17–43	27.9 (4.6)	18–39	N.S.
Obstetric complications	6.0 (5.3)	0–28	5.5 (4.6)	0–23	N.S.
	n	%	n	%	
Gender					
Male	37	68	33	61	N.S.
Female	17	32	21	39	
Handedness $n=105$ (right/left/ambidextrous)	48/2/2	92/4/4	48/3/2	90/6/4	N.S.
Antipsychotics (typical/atypical/none)	25/26/3	46/48/6	N.A.		N.A.

MRI, magnetic resonance imaging; p, patients; c, controls; WAIS, Wechsler adult intelligence scale; SAPS, Scale for the assessment of positive symptoms; SANS, Scale for the assessment of negative symptoms; N.A., not applicable; N.S., not significant.

recruited from hospital staff, their relatives or from a population register. The control subjects included in the present study were interviewed by the same trained psychiatrist (E.G.J.) and had no previous or current psychiatric disorders according to a semi-structured diagnostic interview. They were matched to the patients by age and gender (on a group level).

Exclusion criteria for all subjects were a history of head trauma with loss of consciousness >5 min, current treatment for substance abuse and/or somatic disorders affecting brain function. Demographic characteristics, duration of illness, age at onset and use of antipsychotic medication are described in Table 1.

MRI acquisition

Magnetic resonance images were obtained at the MR Research Centre at Karolinska Institutet, Stockholm, Sweden, using a 1.5 T GE signa Echo-speed (USA) scanner. T1-weighted images were obtained using a 3D spoiled gradient recalled pulse sequence with the following parameters: 1.5 mm coronal slices; no gap; 35 flip angle; repetition time 24 ms; echo time 6.0 ms; number of excitations $=2$; field of view 24 cm; acquisition matrix 256×192. All scans included were visually judged to be without obvious motion artefacts. A trained neuroradiologist evaluated all scans to be without gross pathology.

MRI post processing

Cortical reconstructions were obtained from T1-weighted images using the automated computer software FreeSurfer version 3.0.2. We used the *l*GI algorithm (http://surfer.nmr.mgh.harvard.edu/fswiki/LGI) to compute vertex-wise measurements of local gyrification at more than 150.000 vertices in each hemisphere across the cortical mantle. In addition, measurements of the average *l*GI were calculated in 34 pre-defined anatomical cortex parcellations (Desikan *et al*. 2006) in each hemisphere, which together cover the whole cortex (Supplementary Table S1). The *l*GI method is adapted from the classical GI (2D-GI), which is the ratio of the total pial cortical surface over the perimeter of the brain delineated on coronal sections. The present method, *l*GI, iteratively quantifies GI in circular 3D regions of interest (ROI). After the creation of an outer envelope that tightly wraps the pial cortical surface, local measurement of circular GI is computed for each vertex of the outer surface as the ratio of corresponding ROI on the hull and pial

meshes is created (http://surfer.nmr.mgh.harvard.edu/fswiki/LGI). Delineation of the ROI on both the outer surface (ROIO) and pial surface (ROIP) uses a matching algorithm based on geodesic constraints, so that the ROIP takes into account the entire patch of the cortical surface delineated by the ROIO circular perimeter. This means that, at the end of the computational process, individual *l*GI cortical maps reflect the amount of cortex buried within the sulcal folds in the surrounding circular region. The method has been thoroughly described and validated (Schaer *et al*. 2008).

Assessment of OCs

Information on OCs was collected from hospital birth records. Subjects were born between the years of 1943 and 1982. Obstetric care in Sweden has been of high quality for all this period and the birth records were very detailed. The information was scored according to the McNeil–Sjöström scale (McNeil & Sjostrom, 1995) by a physician (U.K.H.), who was blinded to patient/control status and MRI results. The McNeil–Sjöström scale rates OCs according to severity at an ordinal scale from 1–6, where severity level 1 signifies a 'not harmful or relevant' event and level 6 signifies 'very great harm to or deviation in offspring'. The scale has been constructed for the use in studying the effect of OCs in clinical case–control studies, in which individual complications (e.g. low birth weight, prematurity or placental abruption) occur too infrequently to be assessed separately (McNeil *et al*. 1994). In the present study, the number of OCs with severity scores of $\geqslant 3$ was calculated for each individual subject to form one continuous variable. Scores <3 are considered not to be harmful to the foetus (McNeil & Sjostrom, 1995; Haukvik *et al*. 2010). Obstetric characteristics are presented in Table 1.

Statistical analyses

Statistical differences in demographic and obstetric variables between patient and control groups were evaluated using χ^2 tests, independent-sample t tests and Mann–Whitney non-parametric tests in SPSS version 16.0 (SPSS Inc., USA). The main analyses were performed vertex-wise as well as with predefined cortical areas (parcellations).

At first, vertex-wise analyses of case–control differences in *l*GI across the whole cortical mantle were conducted contrasting schizophrenia patients and healthy controls, with *l*GI as the dependent variable, with age and gender as covariates. Thereafter, vertex-wise analyses with OCs as independent variable (with age and gender as covariates) and *l*GI as the dependent variable were conducted in patients and control subjects both separately and combined. The vertex-wise analyses were conducted using a general linear model within the FreeSurfer program and a false discovery rate (FDR) of 0.05 was applied to adjust for multiple comparisons (Genovese *et al*. 2002).

Second, case–control differences of average *l*GI-values for 34 pre-defined cortical parcellations in each hemisphere (total number of parcellated regions were 68), which together cover the whole cortical mantle, were investigated using multiple linear regression analyses with average *l*GI-values for each parcellation as the dependent variable and diagnosis, age and gender as independent variables. Thereafter, the relationship between OCs and average *l*GI in each of the 68 parcellations was explored using multiple linear regression analyses with OCs, age, gender and diagnosis as independent variables and average *l*GI-values for each parcellation as the dependent variable. The analyses were performed in patients and control combined. The diagnosis*OCs interaction term was added to the analysis for the parcellations in which OCs were related to the *l*GI at $p<0.05$. All parcellation regression analyses were performed in SPSS, and Bonferroni correction was applied to adjust for the number of multiple regression analyses (α level = 0.05/68 parcellations, Bonferroni corrected p value = 0.00076).

Results

Demographic and obstetric variables

Demographic variables were similar in patients and control subjects, with the exception of years of schooling and IQ. There were no differences between patients and control subjects regarding number of OCs or any of the other obstetric variables (Table 1).

Local gyrification in patients versus *controls*

There were no significant differences in *l*GI between patients and controls after adjustment for multiple comparisons. Uncorrected results (at $p<0.05$) demonstrated lower *l*GI in patients than in healthy controls in several regions across both hemispheres (for details, see Supplementary Information and Supplementary Fig. S1).

Local gyrification in relation to OCs in patients and controls

In both schizophrenia patients and healthy controls, increasing number of OCs was significantly related to lower *l*GI in the left pars triangularis ($p<0.0005$) from the parcellation analyses (Fig. 1). This result remained

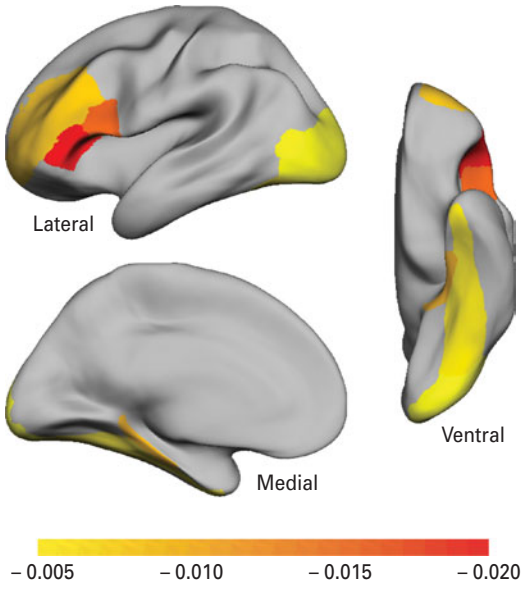

Fig. 1. The effect of increasing number of obstetric complications (OCs) on average local gyrification in pre-defined cortical areas in the left hemisphere significant at $p < 0.05$, from the linear regression model with age, diagnosis, gender and continuous OCs. The red area remains significant after Bonferroni correction for multiple tests. The colour map represents *B* values for OCs, with the corresponding *p* values listed in Supplementary Table S1.

significant after Bonferroni correction (Supplementary Table S1). Five other parcellations in the left hemisphere (fusiform, lateral occipital, parahippocampal, rostral middle frontal and pars opercularis) displayed a similar relationship to OCs (Fig. 1), equally in both groups, but these findings did not remain significant after Bonferroni adjustment for multiple testing (Supplementary Table S1). There was no diagnosis × OCs interaction effect (data not shown). There were no significant relationships between OCs and *l*GI in the right hemisphere (Supplementary Table S1). Current antipsychotic medication (standardized as Haloperidol equivalent dosages) did not have a statistically significant effect on *l*GI and neither did the use of typical *versus* atypical antipsychotic medication (data not shown). From the vertex-wise analyses, no significant relationships between *l*GI and OCs remained after adjustment for multiple comparisons using FDR (see Supplementary Information and Supplementary Fig. S2 for uncorrected results).

Discussion

This is the first scientific study to investigate the relationship between OCs and a 3D *l*GI in schizophrenia. The main finding was that increasing number of OCs in a dose–response fashion was significantly related to lower *l*GI in the left pars triangularis in both schizophrenia patients and healthy control subjects. A similar trend, also for both groups, was demonstrated in five other parcellations in the left hemisphere, whereas no relationship between OCs and *l*GI was demonstrated in the right hemisphere.

Effects of OCs on cortical folding

Studies of gyrification in premature infants have demonstrated increased temporal gyrification bilaterally as compared with term infants (Kesler *et al*. 2006) and higher sulcation index (a measure of cortical folding), when related to brain surface, in preterm intra-uterine growth restriction infants compared with 'normal' preterm infants (Dubois *et al*. 2008). Although the present subject sample included three subjects born prematurely, the results are not directly comparable, as the range of obstetric severity is much larger in the present sample. However, previous findings suggest that gyrification deviances may be related to adverse conditions during foetal brain development.

Only one previous study has investigated the effect of OCs on gyrification in schizophrenia (Falkai *et al*. 2007). From the 2D GI in six coronal MRI sections (three in the frontal and three in the parietal lobe), Falkai and colleagues did not find any relationship between OCs and gyrification in schizophrenia patients. The methodological differences may explain why the results in the present study differ from those of Falkai and colleagues. In the present study, the 3D surface-based approach allowed searching for multiple local alterations in gyrification across the whole cortical mantle. It is worth noting that the same definition and categorization of OCs were applied, OCs being scored with the McNeil–Sjöström scale in both studies. This increases the comparability of the studies and furthermore supports the present use of a surface-based local gyrification method to investigate cortical folding patterns.

Smaller prefrontal and temporal cortical volumes have been reported in schizophrenia patients with a history of foetal hypoxia (Cannon *et al*. 2002). Both cortical folding patterns and cortical thickness affect cortical volume, but their relationship is uncertain. We have previously investigated the present subject sample for association between OCs and cortical thickness and found no association in schizophrenia patients or in healthy controls (Haukvik *et al*. 2009) for the entire cortex, or for frontotemporal regions specifically. Moreover, Schaer *et al*. (2009) have reported that congenital heart disease (presumed to cause lower oxygen delivery to the brain) in patients with 22q11 deletion syndrome was related to altered

cortical folding patterns in the brain but not to cortical thickness. Janssen *et al*. (2009) reported more widespread cortical thickness reductions than gyrification abnormalities in adolescent onset psychosis and concluded that the cortical thickness reductions in schizophrenia appear to be caused by factors occurring after cortical folding development is finished. Taken together, the previous and the current findings suggest that cortical folding patterns may be a more robust brain morphological correlate or even a marker for early neurodevelopmental aberrances than are measures of cortical thickness.

Pars triangularis

The relationship of OCs and *l*GI in the left pars triangularis is of particular interest, as pars triangularis together with pars opercularis are included under Broca's area. Broca's area is important to different aspects of neurocognitive functioning such as language formation (Bhojraj *et al*. 2009), semantic encoding (Demb *et al*. 1995), semantic retrieval (Badre & Wagner, 2007), syntactic processing (Friederici *et al*. 2003) and syntactic working memory (Fiebach *et al*. 2005). Aberrations in neurocognitive domains related to Broca's area have been reported in schizophrenia (for review, see Mesholam-Gately *et al*. 2009). Language impairments have been reported in populations with a history of OCs. Children who have suffered preterm birth or had a very low birth weight demonstrate reduced verbal fluency as measured by the controlled word association test and the animal naming test (Arnoudse-Moens *et al*. 2009). Very low birth weight children have impaired language skills when compared with a term-born control group as measured by recalling sentences and word fluency test (Taylor *et al*. 2004). In children suffering from perinatal asphyxia, verbal IQ has been found to be related to initial arterial pH (Stevens *et al*. 1999). Thus, schizophrenia patients as well as otherwise healthy subjects who have suffered OCs may have impaired cognitive function related to Broca's area.

Increased metric distortion (as an indirect measure of cortical displacement and convolution) in the left pars triangularis (Wisco *et al*. 2007) and reduced sulcal index in Broca's area (Cachia *et al*. 2008) have been described in schizophrenia patients as compared with healthy controls. In contrast, Janssen *et al*. (2009) have reported no relationship between *l*GI and adolescent-onset psychosis and control status in the pars triangularis by using the same *l*GI algorithm as in the present study. In the pars opercularis, which is located adjacent to the pars triangularis, post-mortem findings demonstrated no abnormalities in laminar neuronal densities, glial density, cortical thickness or somal size in schizophrenia patients as compared with healthy controls (Selemon *et al*. 2003). In the present study, the same relationship between higher number of OCs and lower *l*GI was found in pars triangularis and in pars opercularis, but for pars opercularis the p value of 0.021 did not remain significant after adjustment for multiple comparisons. The cytoarchitecture in pars opercularis and pars triangularis has been reported to be more alike than between other cortical parcellations (Amunts & Zilles, 2006), but it is uncertain if the post-mortem findings reported by Selemon *et al*. (2003) in the pars opercularis are identical with the cytoarchitecture of the pars triangularis. Nevertheless, the relationship between OCs and cortical folding in pars triangularis was equal in patients with schizophrenia and healthy controls and, accordingly, reflects alterations that are independent of a diagnosis of schizophrenia.

Limitations

The time window between birth and MRI scanning at adult ages allows for confounding effects on the brain from different environmental or disease-related factors. One such factor may be medication use. In the present study, we found no effect of dosage or type of current antipsychotic medication on *l*GI. In addition, since the significant effect of OCs on *l*GI found in the left pars triangularis of the brain was also found in control subjects, illness-related confounding effects can be ruled out.

In the current study, we used cerebral MRI with a voxel-size of 1 mm in plane and 1.5 mm thickness. The slice thickness of the MRI does, however, not constitute a large limitation, since preprocessing involves the construction of 1 mm isotropic voxels. The cortical surfaces were then reconstructed at submillimetre levels using validated protocols implemented in the FreeSurfer software and served for the computation of *l*GI using previously published algorithms (Schaer *et al*. 2008).

Conclusions

The results from the present study demonstrate a statistically significant relationship between OCs and the *l*GI, with a higher number of OCs related to a lower GI in the pars triangularis of the left hemisphere of the brain in both schizophrenia patients and healthy control subjects. A similar trend was found for five other cortical anatomical areas in the left hemisphere, alike for both groups. The findings suggest that a relationship between OCs and cortical folding may be caused by factors shared by schizophrenia patients and healthy controls rather than factors related to schizophrenia alone.

Note

Supplementary information accompanies this paper on the Journal's website (http://journals.cambridge.org/psm).

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Declaration of Interest

None.

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