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ORIGINAL ARTICLE

Cortical morphology and early adverse birth events in men with first-episode psychosis

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Background. Reduced cortical gray-matter volume is commonly observed in patients with psychosis. Cortical volume is a composite measure that includes surface area, thickness and gyrification. These three indices show distinct maturational patterns and may be differentially affected by early adverse events. The study goal was to determine the impact of two distinct obstetrical complications (OCs) on cortical morphology.

Method. A detailed birth history and MRI scans were obtained for 36 patients with first-episode psychosis and 16 healthy volunteers.

Results. Perinatal hypoxia and slow fetal growth were associated with cortical volume (Cohen's $d = 0.76$ and $d = 0.89$, respectively) in patients. However, the pattern of associations differed across the three components of cortical volume. Both hypoxia and fetal growth were associated with cortical surface area ($d = 0.88$ and $d = 0.72$, respectively), neither of these two OCs was related to cortical thickness, and hypoxia but not fetal growth was associated with gyrification ($d = 0.85$). No significant associations were found within the control sample.

Conclusions. Cortical dysmorphology was associated with OCs. The use of a global measure of cortical morphology or a global measure of OCs obscured important relationships between these measures. Gyrification is complete before 2 years and its strong relationship with hypoxia suggests an early disruption to brain development. Cortical thickness matures later and, consistent with previous research, we found no association between thickness and OCs. Finally, cortical surface area is largely complete by puberty and the present results suggest that events during childhood do not fully compensate for the effects of early disruptive events.

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Key words: Birthweight, cortical gray matter, imaging, obstetric complications, perinatal hypoxia, psychosis.

Background

A substantial body of evidence indicates abnormal brain morphology in those with a psychotic illness (Karlsgodt *et al.* 2010). Reduced cortical gray-matter volume is among the most commonly reported abnormality in this population (Ellison-Wright & Bullmore, 2010; Bora *et al.* 2011; De Peri *et al.* 2012). Cortical gray-matter volume is a composite measure comprised of cortical thickness and total cortical surface area. Further, total cortical surface area is the sum of the area of the gyral surface of the cortex and the area of the cortex within the sulci and is therefore influenced by the degree cortical folding or gyrification. The use of gray-matter volume as an index of cortical integrity can obscure potentially important abnormalities in these three underlying components.

The three components of the cortex show distinct maturational patterns (Giedd & Rapoport, 2010; Raznahan *et al.* 2011). Maximum gyrification is achieved before 2 years of age whereas surface area and cortical thickness peak shortly before puberty (Giedd & Rapoport, 2010; Zilles *et al.* 2013). All three measures show a shallow global reduction during adolescence and early adulthood (Raznahan *et al.* 2011) but changes may accelerate during later adulthood (Bonnici *et al.* 2007; Palaniyappan *et al.* 2011; Lemaitre *et al.* 2012) and may be observed in specific cortical regions in younger samples (Sun *et al.* 2009; Palaniyappan *et al.* 2011, 2013*a*, *b*). This developmental variability suggests that the timing of any disruption to cortical maturation may differentially affect the three

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measures. The early maturation of gyrification suggests that abnormalities in this measure may reflect pre- or perinatal adverse events. On the other hand, the development of surface area throughout childhood and relative stability thereafter suggests abnormalities reflect either obstetrical or childhood influences. Finally, the sensitivity of cortical thickness to environmental influences (Merkley *et al.* 2008; Habets *et al.* 2011) suggests that this measure may be a poor index of obstetrical complications (OCs).

The cognitive, behavioral and psychiatric consequences of OCs are well documented (Rees & Inder, 2005; Gluckman *et al.* 2008; Volpe, 2012). Two distinct complications that are associated with an increased risk for psychosis are intra-uterine growth retardation (IUGR) and perinatal hypoxia. The consequences of these two complications can be developmentally similar but neuroanatomically distinct (Rees & Inder, 2005; Volpe, 2012). IUGR can result from a range of factors during gestation and is associated with reduced brain growth. Some (Hultman *et al.* 1999; Dalman *et al.* 2001; Gunnell *et al.* 2003) but not all (Jones *et al.* 1998; Ichiki *et al.* 2000) studies suggest IUGR increases the risk for psychosis. Perinatal hypoxia can also result from a range of factors but exerts its influence on the fully developed neonatal brain. Several studies suggest an increased risk for psychosis in those who experienced perinatal hypoxia (Zornberg *et al.* 2000; Clarke *et al.* 2006; Byrne *et al.* 2007).

Studies of pediatric populations indicate an association between slow fetal growth and a range of neurodevelopmental difficulties (Indredavik *et al.* 2005; Schlotz & Phillips, 2009). This risk is not limited to significantly low birthweight (<2500 g) but appears to operate across the full range of weights (Haukvik *et al.* 2013). Perinatal hypoxia is also associated with developmental problems (Zornberg *et al.* 2000; Dalman *et al.* 2001; Lindström *et al.* 2006; Millichap, 2008). Relatively brief periods of perinatal hypoxia may result in neuronal death, white- and gray-matter damage and reduced neuronal growth (Rees & Inder, 2005; Volpe, 2012). This can lead to developmental delays and cognitive impairment in the absence of gross structural brain abnormalities and motor disorders (Rennie *et al.* 2007). Both slow fetal growth and perinatal hypoxia are associated with cortical abnormalities (Rees & Inder, 2005; Volpe, 2012). What is less clear is which aspects of cortical morphology are affected by these two complications and whether or not these complications differ in the effect they have on cortical morphology. Pediatric studies that have investigated cortical morphology indicate an association between slow fetal growth and reductions in cortical gray-matter volume, cortical surface area and gyrification but not global cortical thickness (Martinussen *et al.* 2005; Dubois *et al.* 2008; De Bie *et al.* 2011; Raznahan *et al.* 2012; Walhovd *et al.* 2012). There have been relatively few studies of these associations in patients with psychosis.

Patients with psychosis show reductions in cortical surface area both regionally (Goghari *et al.* 2007; Voets *et al.* 2008; Gutierrez-Galve *et al.* 2010; Rimol *et al.* 2012) and globally (Palaniyappan *et al.* 2011; Colibazzi *et al.* 2013). A study of the relationship between surface area and OCs in patients with psychosis indicated less surface area in those with lower birthweight (Haukvik *et al.* 2013). Cortical thickness also tends to be reduced in patients with psychosis (Goldman *et al.* 2009; Schultz *et al.* 2010; Takayanagi *et al.* 2011). Cortical thickness is sensitive to a range of environmental risks during childhood and adolescence but not with pre- or perinatal events (Merkley *et al.* 2008; Haukvik *et al.* 2009; Woodward *et al.* 2009; Kuhn *et al.* 2010, 2011; Habets *et al.* 2011; Lopez-Larson *et al.* 2011).

Studies of gyrification in psychosis indicate an increase in regions of the frontal lobes (Vogeley *et al.* 2001; Narr *et al.* 2004; Falkai *et al.* 2007; Harris *et al.* 2007; Wisco *et al.* 2007) with an overall reduction in global cortical folding (Sallet *et al.* 2003; Jou *et al.* 2005; Cachia *et al.* 2008; Palaniyappan & Liddle, 2012). Two studies included measures of both gyrification and OCs (Falkai *et al.* 2007; Haukvik *et al.* 2012) and both defined OCs as the total number of complications. No significant association was found in one study (Falkai *et al.* 2007) whereas the other indicated a significant correlation between more OCs and less frontal gyrification (Haukvik *et al.* 2012).

Only one study of psychosis included measures of cortical morphology and both hypoxia and IUGR (Cannon *et al.* 2002*b*). This report indicated reduced cortical gray-matter volume in those with perinatal hypoxia and this effect was greater if IUGR was included in the analysis. However, cortical gray-matter volume was not separated into its two component parts – surface area and thickness. A related study (Haukvik *et al.* 2009) failed to detect an association between hypoxia and cortical thickness suggesting that reduced surface area might explain the significant findings of Cannon *et al.* (2002*b*). No previous reports have assessed the relationship between perinatal hypoxia and either cortical surface area or cortical gyrification.

The first goal of this study was to determine the associations between two distinct OCs and cortical gray-matter volume. The second goal was to assess the relationship between these two OCs and the three components of global cortical anatomy. Specifically, slow fetal growth and perinatal hypoxia should be associated with early-maturing aspects of the cortex such as gyrification and surface area but not with late-maturing aspects such as cortical thickness.

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Table 1. *Demographic characteristics and brain measures in patients and controls*

	First-episode psychosis	Healthy control	Statistical analyses
Number of participants	36	16	
Mean age at the MRI scan, years (S.D.)	19.6 (2.9)	19.4 (2.2)	$t = 0.32$, $p = 0.75$
Ethnicity (% white)	67%	81%	$\chi^2 = 1.15$, $p = 0.34$
Mean premorbid (NAART) IQ (S.D.)[a]	99.5 (8.4)	106.6 (4.9)	$t = 3.63$, $p < 0.01$
Mean percentile birthweight (S.D.)[b]	5.8 (2.4)	6.5 (2.7)	$t = 0.88$, $p = 0.39$, $d = 0.26$
Median percentile birthweight	36.5 percentile	45.0 percentile	
Number (%) $\leqslant$10 percentile weight	8 (22.2%)	2 (12.5%)	
Gestational age (<38:38–42 weeks)	3:33	0:16	
Mean birthweight, g (S.D.)	3363 (464)	3521 (618)	$t = 1.02$, $p = 0.31$, $d = 0.31$
Number with perinatal hypoxia (%)	9 (25%)	3 (19%)	$\chi^2 = 0.24$, $p = 0.73$, $d = 0.20$
Total cortical gray volume, cm^3 (S.D.)	513 (46)	534 (39)	$t = 1.59$, $p = 0.12$, $d = 0.48$
Mean cortical thickness, mm (S.D.)[c]	2.62 (0.08)	2.66 (0.08)	$t = 1.55$, $p = 0.12$, $d = 0.47$
Total cortical surface area, cm^2 (S.D.)	1960 (110)	2010 (260)	$t = 0.82$, $p = 0.42$, $d = 0.24$
Mean gyrification index (S.D.)	3.06 (0.10)	3.07 (0.14)	$t = 0.22$, $p = 0.82$, $d = 0.07$

[a] North American Adult Reading Test.
[b] Values are the square root of percentile birthweight for gestational age.
[c] Estimated marginal means after covarying for age.

Method

Participants

Thirty-six males aged 14–26 years were recruited from an early-psychosis intervention program (Table 1). At the time of the MRI scan, 11 (31%) had never received an antipsychotic medication and 25 received risperidone ($N = 16$), olanzapine ($N = 8$) or quetiapine ($N = 1$) for a mean duration of 6.7 weeks (S.D. = 3.1, range 1–14 weeks). Exclusion criteria were substance-induced psychosis, significant head injury, neurological disorder, a history of steroid drug use, or mental retardation. Consensus DSM-IV diagnoses were based on a Structured Clinical Interview for DSM-IV (SCID), a comprehensive assessment at referral and after 6–12 months, and an interview with at least one family member. Twenty-three patients (64%) received a diagnosis of schizophrenia or schizophreniform disorder and 13 (36%) were diagnosed schizoaffective, bipolar or major depression with psychosis. Patients who were using stimulant drugs at presentation were reassessed after 1 month of abstinence to help rule out substance-induced psychosis. Twenty-four patients (67%) were white, five (14%) South Asian, four (11%) East Asian, and three (8%) Native American. Sixteen healthy male controls were similar to patients in age and ethnicity. Controls had no history of psychosis in themselves or in a first-degree relative and other exclusion criteria were the same as for patients. All participants provided written, fully informed consent.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the University of British Columbia Ethics Review Board and with the Helsinki Declaration of 1975, as revised in 2008.

Pregnancy and birth complications

Birth history for all participants was assessed using a detailed structured maternal interview (Smith *et al.* 2001). The present dataset was included in a previous study in which hospital birth records were used to determine the accuracy of maternal report (Smith *et al.* 2009). In agreement with previous studies (Rice *et al.* 2007; Adegboye & Heitmann, 2008) the correlation between birth records and maternal report was very high for birthweight [intra-class correlation coefficient (ICC) = 0.99] and gestational age (ICC = 0.94). Each patient was assigned a percentile birthweight based on gender-specific birthweight-for-gestational-age values (Oken *et al.* 2003). A rating of probable hypoxia indicated that one or more of the following problems occurred during labor and delivery and was 'potentially clearly harmful or relevant' (scored $\geqslant 4$) according to the McNeil–Sjorstrom Scale (McNeil & Sjöström, 1994); emergency cesarean section, breech delivery, labor greater than 18 h, or difficulty breathing at birth. Agreement between birth records and maternal report for this hypoxia rating was high ($\kappa = 0.70$).

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Brain imaging

Image acquisition and preparation

All scans were acquired with a GE Signa Excite 1.5 T scanner (GE Medical Systems, USA). A T1 weighted 3D FSPGR IR prepped series for volumetric assessment was performed for ROI seeding in structural space with the following parameters: TR = 11.5 ms, TE = 5 ms, FOV 26 cm^2, NEX = 1, 124 slices, acquisition and reconstruction matrices = 256 × 256, voxel dimensions = 1.1056 × 1.1056 × 1.6 mm, and inter-slice thickness = 1.5 mm. All image processing was performed on an Apple MacPro Tower Quad Core Intel computer, OS X v. 10.5.8. Raw images were converted to NIFTI format with MICRON dcm2nii (Mac OS X version) shareware before they were processed. All images were skull-stripped and run through brain extraction pipelines in FSL with the brain extraction tool (BET). Whole brain volume was extracted from the skull using FSL Brain Extraction Tool, v. 4.0.5 (Smith *et al.* 2002). Preprocessing of images was performed using the methods of Dale *et al.* (1999).

Cortical surface area, thickness and gyrification

Measures of cortical gray-matter volume, cortical surface area, cortical thickness, and gyrification index were obtained using FreeSurfer v. 4.3 (http://freesurfer.net/). The total cortical surface area of each hemisphere was obtained using the FreeSurfer pipeline. After affine registration and signal intensity normalization, images were spherically transformed or inflated to reveal the sulcal surface, and then the entire surface was opened or flattened across the hemispheres. This transformed image was used to compute hemisphere cortical (pial) surface area. Global cortical surface area was the sum of the two hemispheres. Following cortical surface inflation, mean cortical thickness for each hemisphere was automatically derived from a deformable template based on a generalized gray-white tissue boundary (Fischl & Dale, 2000). FreeSurfer was used to calculate the gyrification index in each hemisphere. Briefly, the gyrification index algorithm measures the pial surface area of the hemisphere and divided this by the outer smoothed surface area of the hemisphere, which excluded the area contained within sulci. The mean of the left and right hemisphere measurements were used for global cortical thickness and global gyrification index.

Analyses

All analyses and the evaluation of statistical assumptions were performed using PASW statistical package, v. 18 for Mac (www.spss.com.hk/statistics/). All brain measures were normally distributed in both groups and variances did not significantly deviate from homogeneity. A significant association was found between greater age and thinner cortical gray matter ($r = -0.56$, $p < 0.01$) and age served as a covariate for analyses of cortical thickness. Total cortical gray-matter volume, total cortical surface area and the gyrification index were not significantly associated with age.

Percentile weight-for-gestational age was normally distributed in the control sample but positively skewed in patients (Shapiro-Wilk: $p = 0.04$). No outliers were present and the distribution was normalized using a square root transformation (Shapiro-Wilk: $p = 0.50$). Only three patients and no controls were born before 38 weeks of gestation and a statistical analysis of prematurity was not feasible. In order to assess whether the three prematurely born patients influenced the results, analyses were computed both with and without these patients. Birthweight was normally distributed in the control sample but not in patients (Shapiro-Wilk: $p < 0.01$). Inspection of the data revealed one patient with a birthweight of 1049 g whereas all other participants ranged from 2608 to 4819 g. In order to control the effects of this outlier, birthweight for this case was adjusted upwards as recommended by Tabachnick & Fidell (2007). Birthweight for this case was changed from 1049–2558 g (50 g below the next lowest birthweight). With this adjustment, which retains the ordinal structure of the data, birthweight was normally distributed in patients (Shapiro-Wilk: $p = 0.50$). The association between percentile birthweight and each brain measure was assessed using Pearson correlations.

Nine patients had a history of perinatal hypoxia but only three controls had this birth complication. Because of the limited number controls with hypoxia, analyses were computed between three groups (patients with hypoxia, $N = 9$; patients with no hypoxia, $N = 27$; controls with no hypoxia, $N = 13$). There was no significant variability between these groups for age. *Post-hoc* analyses were made using Tukey's honestly significant difference (HSD) contrasts. Finally, sequential regression analyses were computed in order to determine whether perinatal hypoxia explains variance in the brain measures after accounting for the effects of percentile birthweight.

Results

Preliminary analyses

No differences were found between patients and controls for age, ethnicity, percentile birthweight, absolute birthweight, or perinatal hypoxia (Table 1). Each of the four cortical measures (volume, surface area, thickness, gyrification) tended to be smaller in patients than in

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Table 2. *Association between perinatal hypoxia and each cortical measure*

Cortical measure	Patient, hypoxia ($N = 9$)	Patient, no hypoxia ($n = 27$)	Control, no hypoxia ($n = 13$)	F	p
Total gray volume, cm^3 (S.D.)	485 (49)	522 (41)	531 (42)	3.28	0.05
Mean cortical thickness, mm (S.D.)	2.66 (0.08)	2.60 (0.08)	2.64 (0.08)	2.62	0.08
Total surface area, cm^2 (S.D.)	1828 (202)	2009 (157)	2006 (149)	4.45	0.02
Mean gyrification index	2.97 (0.11)	3.09 (0.09)	3.06 (0.15)	4.19	0.02

Values for cortical thickness are estimated marginal means obtained after covarying for age.

controls but differences were not statistically significant. No cortical measure was associated with the duration of untreated psychosis, or duration of antipsychotic treatment (all Spearman $r < 0.2$). Further, there were no significant group differences in mean percentile birthweight, mean absolute birthweight, or in the proportion with perinatal hypoxia. In addition, there were no diagnostic group differences (schizophrenia *v.* schizoaffective/mood) in any cortical or obstetrical measure. Perinatal hypoxia was not significantly associated with percentile birthweight (point-biseral $r = 0.05$) or birthweight (point-biseral $r = -0.11$). Inter-correlations between the four cortical measures were similar in patients and controls. Patients with a history of perinatal hypoxia were more likely to smoke cigarettes than patients without this history (78% *v.* 30%, $\chi^2 = 6.44$, $p = 0.02$). However, cigarette smoking was not significantly related to any cortical measure or to percentile birthweight (all p values > 0.20).

Percentile birthweight

Lower percentile birthweight in patients was associated with less cortical gray-matter volume ($r = 0.41$, $p = 0.01$, Cohen's $d = 0.89$). Importantly, an analysis of the relationship between percentile birthweight and the three components of gray-matter volume revealed a significant association with reduced cortical surface area ($r = 0.34$, $p = 0.04$, $d = 0.72$) but not with cortical thickness (partial $r = 0.12$, $p = 0.50$, $d = 0.24$) or gyrification ($r = 0.23$, $p = 0.18$, $d = 0.47$). Associations between percentile birthweight and the cortical measures in the control sample were all low and non-significant (cortical volume: $r = 0.05$, surface area: $r = -0.08$, cortical thickness: $r = 0.01$, gyrification: $r = 0.11$).

Hypoxia

A one-way ANOVA revealed significant variation in cortical gray-matter volume across perinatal hypoxia groups (Table 2). *Post-hoc* comparisons using Tukey's HSD test indicated significantly less cortical gray matter in patients with perinatal hypoxia than in the controls with no hypoxia ($p = 0.05$, $d = 1.02$). There tended to be less cortical gray matter in patients with perinatal hypoxia than patients with no hypoxia but this difference did not reach statistical significance ($p = 0.08$, $d = 0.86$). The volume of gray matter in patients and controls with no hypoxia was similar (Table 2).

Of the three components of cortical gray-matter volume, perinatal hypoxia was associated with significantly decreased cortical surface area and less gyrification but not with cortical thickness (Table 2). *Post-hoc* contrasts revealed less total cortical surface area in patients with hypoxia than in either patients ($p = 0.02$, $d = 1.07$) or controls ($p = 0.04$, $d = 1.03$) with no hypoxia. Gyrification was lower in patients with hypoxia than in patients with no hypoxia ($p = 0.02$, $d = 1.26$) but not lower than in controls with no hypoxia ($p = 0.16$, $d = 0.67$).

The cumulative effects of lower percentile birthweight and perinatal hypoxia

The preceding analyses indicate that percentile birthweight was unrelated to perinatal hypoxia and that both were related to cortical gray-matter volume in patients with first-episode psychosis. A sequential regression analysis was computed to determine whether hypoxia improves the prediction of cortical gray-matter volume over that of percentile birthweight alone. The results indicate that both percentile birthweight and perinatal hypoxia significantly predict total cortical gray-matter volume and that hypoxia does so after accounting for percentile birthweight (Table 3, Fig. 1).

Further analyses were computed in order to assess associations for the three components of total cortical gray-matter volume. The combination of percentile birthweight and perinatal hypoxia was significantly associated with total cortical surface area (Table 3). These two OCs accounted for 32% of the variability in cortical surface area. Percentile birthweight and perinatal hypoxia predicted a small and non-significant 7% of the variability in cortical thickness after accounting for the effects of age. Finally, perinatal hypoxia accounted for 26% of the variability in gyrification

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Table 3. *Sequential regression of percentile birthweight and perinatal hypoxia on global cortical measures in the patient sample*

Dependent variable	Independent variables	*B*	S.E.	*β*	R^2 change	*p*	Results after the entry of all variables
Total cortical gray-matter volume	Percentile birthweight	7642	2942	0.407	0.166	0.014	$R^2 = 0.306$ adjusted
	Perinatal hypoxia	−38 922	15 082	−0.375	0.140	0.014	$R^2 = 0.264$ $p = 0.002$
Total cortical surface area	Percentile birthweight	2573	1225	.339	0.115	0.043	$R^2 = 0.315$ adjusted
	Perinatal hypoxia	−18 821	6057	−0.448	0.200	0.004	$R^2 = 0.274$ $p = 0.002$
Total mean cortical thickness	Age	−0.023	0.005	−0.641	0.411	0.000	$R^2 = 0.483$ adjusted
	Percentile birthweight	0.004	0.006	0.091	0.008	0.497	$R^2 = 0.434$ $p < 0.001$
	Perinatal hypoxia	0.060	0.030	0.253	0.064	0.055	
Total cortical gyrification index	Percentile birthweight	0.010	0.007	0.228	0.052	0.180	$R^2 = 0.315$ adjusted
	Perinatal hypoxia	−0.126	0.035	−0.513	0.262	0.001	$R^2 = 0.273$ $p = 0.002$

The first row in each block shows the results after entering the first variable and second and third rows show the adjusted results when subsequent variables were included in the model.

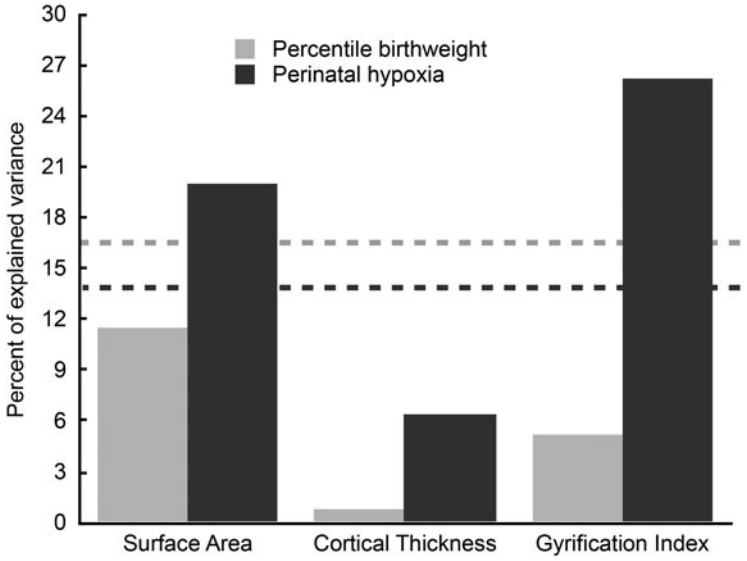

Fig. 1. Results from the sequential multiple regression analysis for two obstetrical predictors of three components of total cortical gray-matter volume. The dashed lines reflect the degree to which total cortical gray-matter volume was predicted by percentile birthweight (gray) and perinatal hypoxia (black).

after accounting for the non-significant 5% of variance subsumed by percentile birthweight.

Exploratory regression analyses were computed to determine whether the global reduction in surface area and gyrification reflected a reduction across all regions of the cortex. Analyses for each cortical lobe revealed that percentile birthweight and perinatal hypoxia significantly predicted less cortical surface area in the right and left frontal, temporal, parietal and insula regions and in the right occipital lobe (explained variance: 14–36%, $\beta = -0.34$ to -0.48) but not the left occipital lobe (explained variance = 9%, $\beta = -0.26$). After controlling the non-significant variance subsumed by percentile birthweight, perinatal hypoxia significantly predicted a lower gyrification index in all cortical regions (explained variance: 12–27%, $\beta = -0.34$ to -0.52) except the left frontal, left insula and left occipital lobes (explained variance: 9%, 10% and 4%, $\beta = -0.31$, -0.31 and -0.20, respectively). Finally, Freesurfer-generated cortical maps were created to determine whether focal abnormalities were superimposed on the global abnormalities. These maps suggest that perinatal hypoxia was associated with focal regional reductions in gyrification (Fig. 2). However, maps of cortical surface area failed to reveal any focal regional abnormalities associated with lower percentile birthweight or perinatal hypoxia.

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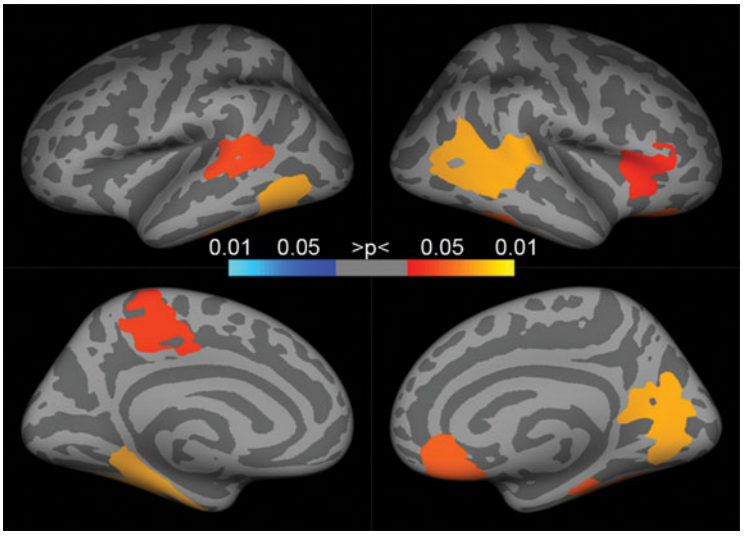

Fig. 2. The cortical maps depict focal differences in the amount of cortical folding between patients with a history of perinatal hypoxia and those with no history of hypoxia. Colored regions show mean differences after controlling for multiple comparisons using a cluster inclusion criteria of $p = 0.05$. The yellow end of the spectrum indicates less gyrification in the group with perinatal hypoxia and blue indicates more gyrification. Images were generated using Freesurfer and displayed on an inflated average image (fsaverage). The left hemisphere is on the left and lateral surface on top.

Supplementary analyses

Two previous studies assessed the impact of the number rather than the type of OC on brain morphology (Falkai *et al.* 2007; Haukvik *et al.* 2012). The present results failed to detect a significant association between the total number of complications and any of the brain measures (all Spearman r values < 0.20).

Studies of psychosis tend to analyze slow fetal growth as a dichotomous rather than continuous variable. In order to assess the impact of this method, patients were grouped as small ($\leqslant$10th percentile, $N = 8$) or appropriate (>10th percentile, $N = 28$) for gestational age and the data were re-analyzed. Patients who were small for gestational age had significantly less cortical volume than those appropriate for gestational age (481 *v.* 522 cm^2, $p = 0.02$, Cohen's $d = 0.97$) but no significant differences were found for cortical surface area, thickness, or gyrification.

A large psychiatric literature has reported the correlates of low birthweight. Low birthweight may result from slow fetal growth or from the premature birth of a normally developing fetus. These two complications can have distinct developmental consequences (Smith *et al.* 2001; Rees & Inder, 2005) and the use of birthweight confounds these risks. In the present study, all analyses were repeated after substituting absolute birthweight for percentile birthweight. These analyses tended to result in similar but attenuated associations.

Finally, three patients but no controls were born prematurely and may have affected the results. In order to assess this possibility, all analyses were recomputed after excluding these three participants. The omission of premature patients had minimal impact on effect sizes and did not alter the statistical significance of any of the results.

Conclusions

The present results indicate a significant, moderately strong association between a history of obstetrical complications and global cortical morphology in young men with first-episode psychosis. Consistent with previous results (Cannon *et al.* 2002*a*), both slow fetal growth (lower percentile birthweight) and perinatal hypoxia contributed to the prediction of cortical gray-matter volume and the effect of these two risks was additive. Importantly, this finding was extended to include specific aspects of cortical morphology. These results indicate an association between the type of OC and the pattern of cortical dysmorphology. Perinatal hypoxia was associated with a smaller cortical surface area and with less cortical gyrification but was not related to cortical thickness. On the other hand, slower fetal growth was associated with less cortical surface area but not with either cortical thickness or gyrification. The effects of slow fetal growth and hypoxia on cortical surface area were additive and accounted for nearly one third of the variability in surface area.

The results also suggest that the use of a global index of OCs or the use of a global index of cortical gray-

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matter integrity will both obscure the potentially important associations between specific OCs and specific aspects of cortical morphology. In the present study, when gray-matter volume was used as a measure of cortical abnormality, perinatal hypoxia and percentile birthweight were equally likely to predict abnormality (Fig. 1). However, when gray-matter volume was separated into its three component parts, the effects of perinatal hypoxia were distinct from those of slow fetal growth. Likewise, when the total number of complications was included as a global measure of OCs no association was found with any cortical measure. This suggests it is the type of complication that may be important.

Cortical surface area, cortical thickness and gyrification mature at different times and differ in their sensitivity to subsequent positive or negative environmental exposures (Gluckman *et al.* 2009; Luders *et al.* 2012; Raznahan *et al.* 2012). This suggests that the pattern of cortical abnormality in adulthood may result from an interaction between early adverse events, the neurodevelopmental processes that are occurring at the time of the events, and environmental conditions or exposures that occur during development.

Cortical surface area continues to develop up to puberty but appears to be a relatively robust indicator of early adverse events (Raznahan *et al.* 2012) and shows minimal global reduction from puberty up to early adulthood (Raznahan *et al.* 2011). Low birthweight predicts smaller global cortical surface area (De Bie *et al.* 2011; Haukvik *et al.* 2014) and a very interesting study of twins (Raznahan *et al.* 2012) suggested that the effects of slow prenatal growth on adult cortical surface area may be largely independent of genetic and childhood factors. The present results extend these findings and suggest that both slow fetal growth and perinatal hypoxia are associated with smaller cortical surface area.

Cortical thickness continues to develop into adulthood and is sensitive to a range of risks including psychosocial trauma, cannabis use (Habets *et al.* 2011; Lopez-Larson *et al.* 2011), cigarette smoking (Kuhn *et al.* 2010), traumatic brain injury (Merkley *et al.* 2008), antipsychotic medication, and duration of psychotic illness (van Haren *et al.* 2009; Mattai *et al.* 2010; Sprooten *et al.* in press). This suggests that cortical thickness should be a poor index of early adverse events. The results from the present report and from several previous studies were consistent with this hypothesis and failed to detect an association between cortical thickness and OCs (Merkley *et al.* 2008; Haukvik *et al.* 2009, 2014; Kuhn *et al.* 2010, 2011; Habets *et al.* 2011; Lopez-Larson *et al.* 2011). There is however some evidence that being born with a very low birthweight (<1500 g) increases the risk for thinner cortices in some regions (Martinussen *et al.* 2005; Nagy *et al.* 2011; Skranes *et al.* 2012). The present sample was assessed at the onset of illness and therefore the impact of illness-related variables was reduced. In addition, no association was found between cortical thickness and either the duration of untreated psychosis or the duration of antipsychotic treatment. This suggests that illness-related factors did not influence the present results.

Cortical gyrification is completed before 2 years of age and appears to be relatively stable until young adulthood. Changes to gyrification may occur in some cortical regions (Palaniyappan *et al.* 2011, 2013*a*) but there are minimal global changes (Raznahan *et al.* 2011). This suggests that global abnormalities in cortical folding are likely to reflect exposure to very early adverse events (Zilles *et al.* 2013). The present finding of a strong association between perinatal hypoxia and gyrification is consistent with this hypothesis.

Most studies of fetal growth or birthweight in patients with psychosis used a dichotomized measure and compared patients with slow fetal growth (<10th percentile) or low birthweight (<2500 g) with all other patients. Recent findings suggest that risk extends across the range of birth weights and is not restricted to significantly low weights (Abel *et al.* 2010; Haukvik *et al.* 2013). The present results support this observation and also suggest that the use of percentile birthweight is a more sensitive index of variability in fetal growth than a dichotomous measure. In addition, the use of birthweight can confound the effects of slow fetal growth and premature birth (Smith *et al.* 2001). In the present study, a reanalysis of data using absolute birthweight instead of percentile birthweight resulted in attenuated associations.

It is noteworthy that a significant association between OCs and cortical abnormalities were observed in the absence of significant cortical differences between patient and control groups. A plethora of studies using a range of measurement techniques have documented cortical abnormalities in patients with psychosis. Methodological differences between these studies make it difficult to draw firm conclusions at the present time. Global cortical differences between patients and healthy controls tend to be small and the present study had limited statistical power for identifying small group differences. However, the results suggest a strong relationship between OCs and some aspects of cortical morphology. Because of this, the proportion of a research sample that experienced an OC will influence the probability of detecting cortical abnormality and failure to assess these early events will result in substantial unexplained variability between studies. This raises the question of whether is

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it possible to identify those with a history of early disruptive events based on the pattern of adult brain morphology. The strength of the present finding tentatively suggests that this may be an achievable goal.

A large pediatric and psychiatric literature has documented the developmental, medical and psychiatric consequences of OCs. These include poor psychosocial adjustment (Kunugi *et al.* 2001), cognitive difficulties (Freedman *et al.* 2012), poor academic performance (De Bie *et al.* 2011), a range of medical problems (Barker, 2006), and an increased risk for psychosis (Cannon *et al.* 2002*b*). The link between OCs and adult cortical morphology suggests that cortical measures should also have clinical correlates and this hypothesis has received some recent support. Reduced gyrification in some cortical regionals predicts poor treatment response (Penttilä *et al.* 2009; Palaniyappan *et al.* 2013*b*), disorganization (Palaniyappan & Liddle, 2012), and increased neurological soft signs (Gay *et al.* 2013). Others suggest an association between decreased cortical surface area and both cognitive difficulties (Gutierrez-Galve *et al.* 2010; Colibazzi *et al.* 2013) and increased symptom severity (Palaniyappan *et al.* 2011). Clearly, the consequences of OCs are not specific to psychosis. However, these results suggest that the identification of those who experienced early pathogenic events and those with cortical dysmorphology could potentially explain some heterogeneity in psychotic disorders.

The present findings were obtained using reliable and accurate measures of both OCs and cortical morphology and this confers confidence in the results. In addition, males only were included in order to remove gender-specific variability in cortical maturation. Finally, the use of a young sample at the onset of illness reduced the likelihood that results would be confounded by age-, treatment- or illness-related factors.

The present study also has some limitations. The sample size was relatively small and this limits the ability to detect small effects. However, the effect sizes for all predicted associations were large and in the predicted direction. By contrast, correlations in the control sample were small suggesting failure to detect a statistically significant effect for that group was not a result of small sample size. The inclusion of only men increased the probability of detecting associations but limited the generalizability of the findings. Gender differences in both adult cortical morphology and in the age-related sequence of cortical development are complex and not well documented. These differences are dynamic in young adults, when the cortex is undergoing substantial gender-specific maturational changes. The investigation of this variability requires detailed gender-specific analyses using large samples of both men and women and awaits further study. Adverse birth events exert their influence on both clinical and non-clinical populations and appear to be relevant for a range of adult psychiatric disorders (Abel *et al.* 2010). Because of this, a range of diagnoses was included in the present study. The finding of large effects in the face of this diagnostic heterogeneity suggests the observed associations are not diagnosis-specific. Nevertheless, there may be diagnostic differences in the strength of these associations and further research is needed to assess that possibility.

The use of maternal report can be unreliable for some birth events and therefore could have been a limitation of the present study. However, our findings from an earlier study of OCs (Smith *et al.* 2009) were in agreement with previous research (Rice *et al.* 2007; Adegboye & Heitmann, 2008) and indicated that maternal report using a standardized interview is very accurate for birthweight and gestational age and for serious perinatal events that are likely to result in hypoxia (Smith *et al.* 2009).

Adverse events during childhood and adolescence were not systematically assessed in the present study. The pediatric and psychiatric literature suggests the developmental consequences of early adverse events can be ameliorated or exacerbated by later environmental circumstances (Gluckman *et al.* 2008; Luders *et al.* 2012). Exposures such as psychosocial stress, drug use and head injury appear to increase the risk for psychosis and may have a negative impact on some aspects of cortical morphology. Other exposures such as meditation may reduce age-related changes (Gluckman *et al.* 2008; Luders *et al.* 2012) and therefore may mitigate the effects of early adverse events. These factors were not systematically assessed in the present study and the extent to which they interact with OCs to influence the course of illness and cortical morphology requires further study. Finally, the clinical implications of our findings were not tested and more research is needed to explore the ramifications of OC-related cortical abnormalities.

In summary, aspects of global cortical morphology in first-episode psychosis are related to early environmental events. The present results suggest that cortical surface area and gyrification but not cortical thickness are influenced by pre- and perinatal adversity. Other research suggests that cortical thickness is affected by adverse events during childhood and adolescence. Together, these findings suggest that the impact of an adverse event during neurodevelopment will depend on both the type of event and on the maturational level of the cortex at the time of the event.

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Declaration of Interest

Dr Honer reports receiving consulting or advisory board fees from Roche and Lundbeck/Otsuka. Dr MacEwan has received consulting fees or sat on paid advisory boards for: Apotex, AstraZeneca, BMS, Janssen, Lundbeck, Otsuka, Pfizer and Sunovion. He also received fees lectures sponsored by AstraZeneca, BMS, Janssen, Otsuka and Eli Lilly, and has received grants from Janssen Pharmaceuticals. Dr Kopala reports receiving consulting or advisory board fees from BMS, Otsuka, and Sunovian. Grant support was obtained from BMS while lecture fees were received from AstraZeneca and BMS. All other authors declare that they have no conflicts of interest.

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