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Reduced brain cortical folding in schizophrenia revealed in two independent samples

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ABSTRACT

The cerebral cortex is highly convoluted, and principal folding patterns are determined early in life. Degree of cortical folding in adult life may index aberrations in brain development. Results from previous studies of cortical folding in schizophrenia are inconsistent. Here we investigated cortical folding patterns in the hitherto largest sample of patients with schizophrenia drawn from two independent cohorts. Magnetic resonance imaging scans were acquired from 207 patients and 206 healthy subjects recruited to two separate research projects in Sweden and Norway. Local gyrification index (*l*GI) was estimated continuously across the cortex using automated methods. Group differences in *l*GI were analyzed using general linear models. Patients had lower *l*GI in three large clusters of the cortex with peak differences found in the left precentral gyrus, right middle temporal gyrus, and right precuneus. Similar, although not completely overlapping results were found when the two cohorts were analyzed separately. There were no significant interaction effects between age and diagnosis and gender and diagnosis. The finding of reduced degree of folding in large regions of the cerebral cortex across two independent samples indicates that reduced gyrification is an inherent feature of the brain pathology in schizophrenia.

1. Introduction

The first clinical manifestation of schizophrenia usually occurs in late adolescence or early adulthood, but genetic and epidemiological findings suggest that the disease process involves alterations in early brain development to the developing brain (Weinberger, 1987; Rapoport et al., 2012). Neurodevelopment occurs in a programmed and gradual fashion with cortical neurons migrating to their destination before birth (Bystron et al., 2008). Major cortical folding patterns are mainly determined before birth and undergo only minor changes in childhood and adolescence. Importantly, the degree of folding relative to brain size remains relatively stable from early childhood (Armstrong et al., 1995; Zilles et al., 2013), and is thus a suitable subject for investigation of early brain development. A range of methods for measuring cortical folding has been developed (Mangin et al., 2010; White et al., 2010). The most widely used method is the gyrification index (GI), i.e. the ratio between the folded cortical surface and an outer cerebral surface tightly warping the brain without entering the sulci (Zilles et al., 1988). One of the authors of the present paper (MS) has developed an automated method for measuring vertex-wise gyrification in three-dimensional (3D) space across the entire cortex based on magnetic resonance imaging (MRI) data (Schaer et al., 2008).

Findings from MRI studies of gyrification in schizophrenia have been mixed, as reviewed by White and Hilgetag (2011). Both reduced (e.g. Sallet et al., 2003) and increased (e.g. Falkai et al., 2007) GI have been found using manual or automated methods on coronal sections of MR images, and one study did not find significant group differences (Highley et al., 2003). Higher GI in prefrontal cortex has been found among high-risk patients who later developed schizophrenia compared to those who did not (Harris et al., 2004, 2007). Studies using the automated *l*GI method have shown reduced folding in the right prefrontal cortex among patients with adolescent onset (Janssen et al., 2009) and adult onset schizophrenia (Palaniyappan et al., 2011), and reduced

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folding in the left insula and medial parieto-occipital cortex in adult onset schizophrenia (Palaniyappan and Liddle, 2012).

Given the discrepant findings in the literature, it is still unclear if, where, and to what extent the cortex is abnormally folded in schizophrenia. In the present study, the automated *l*GI method was applied to a large group of patients with schizophrenia and healthy subjects drawn from a Swedish sample with predominantly long-term treated patients, and a Norwegian sample with a high proportion of patients with recent onset schizophrenia. Our aim was to test if patients and controls differed in degree of cortical folding across two large independent samples.

2. Materials and methods

2.1. Participants

A total of 207 patients with schizophrenia (N = 165), schizoaffective disorder (N = 34) or schizophreniform disorder (N = 8) and 206 healthy control subjects were recruited as part of the Human Brain Informatics (HUBIN) project in Stockholm, Sweden between 1999 and 2003, and the Thematically Organized Psychosis (TOP) project in Oslo, Norway between 2003 and 2008. Details regarding subject recruitment and clinical procedures have been described and evaluated previously (Ekholm et al., 2005; Engh et al., 2010). Patients were assessed for lifetime psychiatric diagnoses according to DSM-IIIR or DSM-IV based on hospital case notes and structured clinical interviews (Spitzer et al., 1988; First et al., 2002) performed by trained psychiatrists or psychologists. Symptoms were rated according to the Scale for the Assessment of Negative Symptoms, SANS (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms, SAPS (Andreasen, 1984) in Sweden, and the Positive and Negative Syndrome Scale, PANSS (Kay et al., 1987) in Norway. Current doses of antipsychotic medication were converted to defined daily doses according to guidelines provided by the World Health Organization (http://www.whocc.no/atcddd/). See Table 1 for details regarding demographic and clinical data.

Healthy control subjects were recruited based on population registers (Sweden and Norway) or among hospital staff (Sweden only). The controls had no psychotic disorders as determined by a structured clinical interview (Spitzer et al., 1986) in Sweden, and by the Primary Care Evaluation of Mental Disorders (Spitzer et al., 1994) in Norway, and no severe mental disorders among first-degree relatives. Exclusion criteria were a history of head trauma with loss of consciousness for more than 5 min, or somatic disorders affecting brain function. After complete description of the study, all subjects gave written informed consent to participate. The HUBIN study was approved by the Research Ethics Committee at Karolinska Institutet, and the TOP study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Both studies were conducted according to the Helsinki declaration.

2.2. MR methods

2.2.1. Scan acquisition

Imaging data was collected using 1.5 T MR systems (GE Signa in Sweden and Siemens Magnetom Sonata in Norway). In Sweden, T1-weighted volumes were acquired using a three dimensional spoiled gradient recalled (SPGR) pulse sequence with the following parameters: 124 coronal slices, 35° flip angle, repetition time 24 ms, echo time 6.0 ms, voxel size 0.86 × 0.86 × 1.50 mm. In Norway, two T1-weighted volumes were acquired using a magnetization prepared rapid gradient echo (MPRAGE) pulse sequence (Siemens tfl3d1_ns) with the following parameters: 160 sagittal slices, 7° flip angle, repetition time 2730 ms, echo time 3.93 ms, voxel size 1.33 × 0.94 × 1 mm and averaged during post-processing to increase the signal to noise ratio. All MRI scans were found to lack gross pathology when evaluated by a neuroradiologist.

2.2.2. MR image processing

MRI data were processed using FreeSurfer, v 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). 3D representations of the pial and the gray/white matter border were estimated using automated procedures (Dale et al., 1999; Fischl et al., 1999, 2001). Topological defects were manually edited, and the individual brain surfaces were morphed to a

Table 1
Demographic and clinical data.

	Swedish sample (n = 201)			Norwegian sample (N = 212)			Test[a]
	Patients (n = 95)	Controls (n = 106)	Test	Patients (n = 112)	Controls (n = 100)	Test	ns[b]
Gender (% men)	73.7	67.9	ns	58.9	42.0	$X^2 = 11.6$; $p = 0.003$	$X^2 = 16.8$; $p < 0.001$[c]
Age (y)	42.2 (7.1)	41.5 (9.0)	ns	31.8 (8.6)	37.6 (10.2)	$t = 4.5$; $p < 0.001$	$t = 8.2$; $p < 0.001$[d]
Age at onset (y)[e]	24.6 (5.9)	na		27.1 (8.3)	na		$t = 2.5$; $p = 0.013$
Duration (y)[f]	17.4 (8.7)	na		4.7 (5.0)	na		$t = 12.5$; $p < 0.001$
Education (y)	12.5 (2.8)	14.1 (2.9)	$t = 3.8$; $p < 0.001$	13.1 (2.7)	14.2 (2.3)	$t = 3.2$; $p = 0.002$	ns[g]
PANSS positive	na	na		14.4 (5.5)	na		
PANSS negative	na	na		14.5 (6.3)	na		
PANSS general	na	na		30.9 (7.7)	na		
PANSS total score	na	na		59.9 (15.8)	na		
SANS total score	28.0 (19.0)	na		na	na		
SAPS total score	18.6 (26.5)	na		na	na		
AP medication (DDD)[h]	0.9 (0.7)	na		1.6 (1.2)	na		$t = 5.2$; $p < 0.001$

All data shown as mean (SD) unless otherwise specified. Abbreviations: ns, not significant; y, years; na, not applicable; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative symptoms; SAPS, Scale for the Assessment of Positive Symptoms; AP, antipsychotic; DDD, defined daily doses. Missing data: Age at onset: 2, Duration of illness: 2, Education: 11; PANSS general and PANSS total score: 1, SANS total score: 42, SAPS total score: 43, AP medication: 1.

[a] Tests for differences between samples.
[b] Test for difference in the patient-control ratio between samples.
[c] Test for difference in gender distribution between samples irrespective of diagnostic group.
[d] Test for difference in mean age between samples irrespective of diagnostic group.
[e] Age at onset of illness was defined as onset of psychotic symptoms according to any source.
[f] Duration of illness was defined as the time difference between age at onset and age at investigation.
[g] Test for difference in mean education between samples irrespective of diagnostic group.
[h] In the Swedish sample, 88 patients received antipsychotic medication (40 typical, 41 atypical, and seven a combination of typical and atypical), while seven patients received no antipsychotic medication at the time of investigation. In the Norwegian sample, 100 patients received antipsychotic medication (six typical, 83 atypical, and eleven a combination of typical and atypical), while eleven patients did not receive antipsychotic medication at the time of investigation.

common coordinate system for vertex-wise cross-subject analysis (Fischl and Dale, 2000).

2.2.3. Local gyrification index (lGI)

Based on the pial surface reconstruction, an algorithm for measuring 3D *l*GI at each vertex across each hemisphere was performed. Details of the *l*GI computation can be found in the validation paper (Schaer et al., 2008) and at https://surfer.nmr.mgh.harvard.edu/fswiki/LGI.

The *l*GI method is adapted from the classical 2D GI (Zilles et al., 1988). First, an outer envelope that tightly wraps the pial cortical surface is created. Second, local measurement of circular GI is computed for each vertex of the outer surface as the ratio of corresponding regions of interest (ROI) on the outer envelope and pial surface. Delineation of the ROI on both the outer surface (ROI_O) and pial surface (ROI_P) uses a matching algorithm based on geodesic constraints, so that the ROI_P delineates the entire patch of the cortical surface within the circular perimeter of the ROI_O. Thus, at the end of the computational process, individual *l*GI cortical maps quantify the amount of cortex buried within the sulcal folds in the surrounding circular region.

For statistical analysis, individual *l*GI maps were registered to the *fsaverage* template included in FreeSurfer and smoothed using an iterative nearest neighbor averaging procedure, with full width at a half maximum of 5 mm.

2.3. Statistical analysis

Differences in demographic and clinical variables between patients and controls within and across each sample were analyzed using Chi-square test and Student's T-test in the software IBM SPSS Statistics, v.20 (SPSS Inc., Chicago, IL, USA).

Differences in *l*GI between patients and controls in the two samples separately and combined were analyzed by fitting a general linear model at each vertex on the surface. Age and sex were included as covariates in the separate samples, and age, sex and sample were controlled for in the combined sample analysis. Non-parametric cluster-wise correction for multiple comparisons was performed using the Monte Carlo simulation tool embedded in FreeSurfer (Hagler et al., 2006) with an initial cluster-forming threshold of $p < .05$. Clusters with an empirical $p < .05$ were regarded significant, fully corrected for multiple comparisons across space. Group comparisons were also rerun after excluding patients with schizoaffective disorder.

Mean *l*GI within clusters showing significant group differences in the combined sample were obtained for estimation and comparison of commonly reported effect sizes and post-hoc analyses to test the relative contribution of age, gender, and diagnosis, as well as age × diagnosis and gender × diagnosis interactions on variation in *l*GI. For the latter purpose a generalized linear model was fitted in SPSS, with age, sex, and diagnosis in addition to age × diagnosis and sex × diagnosis as predictors. Sample was entered as an additional covariate. Age was centered on the mean within the entire sample. To test for any association between *l*GI and age at onset and duration of illness, partial correlation analyses controlling for gender and sample were performed. Since age was highly correlated with age at onset and duration of illness ($r = .44$ and $r = .72$, respectively), patients were split into arbitrarily chosen age groups (19–24, 25–29, 30–34, 35–39, 40–44, and 45–49 years) in the partial correlation analyses between *l*GI and age of onset and duration of illness. To test for associations between *l*GI and clinical measures (dose of antipsychotic medication, dose of medication × duration of illness as proxy for cumulative dose, and severity of positive and negative symptoms), partial correlation analyses were performed. Due to differences in distribution of medication types and choice of symptom scales across samples, type of medication and sample were entered as covariates in the analyses. The level for statistical significance was adjusted for multiple comparisons using the Bonferroni correction (alpha = 0.05/number of tests).

3. Results

3.1. Demographic and clinical variables

Patients and controls in the Swedish sample were older than patients and controls in the Norwegian sample (Table 1). Duration of illness was longer and dose of antipsychotic medication was lower among Swedish compared to Norwegian patients. Norwegian patients were younger than Norwegian controls.

3.2. Whole cortex analysis

In the combined sample, patients had significantly lower *l*GI in three clusters; left lateral pericentral cortex, right temporo-occiptal cortex and right medial parietal cortex (Fig. 1, *upper panel*). Similar clusters were found when the Swedish and Norwegian samples were analyzed separately. In the Swedish sample, all three clusters were smaller, but were similar in location when compared to those in the combined sample (Fig. 1, *middle panel*). In the Norwegian sample, the cluster in the left pericentral region was confined to the precentral gyrus, the cluster in right temporal cortex included parts of the lateral frontal cortex, while the right medial parietal cluster was similar in location and magnitude to that in the combined analysis (Fig. 1, *lower panel*). There were no regions with significantly higher *l*GI among patients. Information on location and size of significant clusters are shown in Table 2. Removing the schizoaffective disorder patients did not change the results.

3.3. Cluster-wise analyses

Higher age was related to lower mean *l*GI within the left pericentral and right temporo-occipital clusters (Table 3). Women had lower *l*GI in all three clusters. There were no significant age × diagnosis or sex × diagnosis interaction effects. For patients aged 25–29 years, later onset of illness was related to lower *l*GI and longer duration of illness was related to higher *l*GI in the left pericentral cluster, while for patients aged 30–34 years, later onset was related to lower *l*GI and longer duration was related to higher *l*GI in the left pericentral and right medial parietal clusters (Table 4). Age of onset or duration of illness was not related to *l*GI in the right temporo-occipital cluster. There were no significant correlations between *l*GI and type, dose or duration of antipsychotic medication, or severity of positive or negative symptoms when adjusting for multiple comparisons.

4. Discussion

4.1. Group differences

The main finding of this study was reduced cortical folding in three large brain regions in patients with schizophrenia. The findings were similar, although not entirely overlapping, in the two samples. Previous studies from our group have demonstrated reduced cortical thickness in prefrontal and temporal regions (Nesvåg et al., 2008; Rimol et al., 2010) and reduced cortical area in circumscribed regions of the brain (Rimol et al., 2012) among the patients. Interestingly, the latter study found reduced cortical area in the left pericentral and right lateral temporal regions, similar to regions with reduced *l*GI in the present study. Post-mortem studies have demonstrated that cortical area in the brain of an adult monkey is dependent on the number of proliferative units in the developing brain, while cortical thickness is dependent on the number and size of neurons within each proliferative unit (Rakic, 1988). Although cortical area and thickness are both highly heritable, the genetic correlation between them is weak (Panizzon et al., 2009). Given that gyrification measures the amount of surface enclosed in a restricted space, it is not surprising to find results in similar direction and location using either gyrification or measuring regional areas. In healthy adults, cortical thickness is determined by complex maturational changes

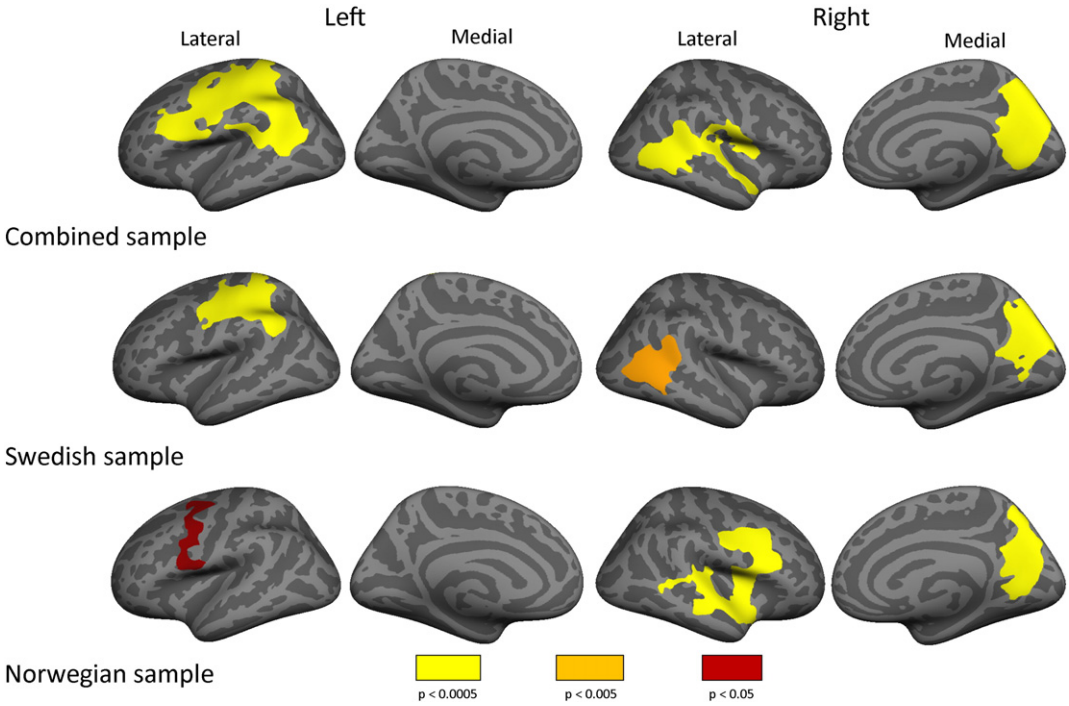

Fig. 1. Color maps showing clusters with significantly lower local gyrification index (*l*GI) in patients with schizophrenia compared with controls from two independent cohorts, one Swedish sample from the Human Brain Informatics (HUBIN) project, and one Norwegian from the Thematically Organized Psychosis (TOP) research project. Corrected cluster-wise significance levels in the combined, Swedish and Norwegian samples are shown in yellow ($p < 0.0005$), orange ($p < 0.005$), and red ($p < 0.05$).

that occur during adolescence (Shaw et al., 2008), whereas cortical surface area is less affected by maturational changes (Raznahan et al., 2011). This may explain the weak correlation between cortical thickness and gyrification or cortical area (Hogstrom et al., in press). In neurodevelopmental disorders, such as schizophrenia, the maturational mechanisms for cortical thickness and gyrification or area may be differentially affected, thus potentially even decreasing the already weak correlation. Previous work from our group on a smaller, but overlapping sample from the Swedish cohort, demonstrated that a history of obstetric complications affected cortical folding (Haukvik et al., 2012), but not cortical thickness (Haukvik et al., 2009). In a large diagnostically heterogeneous sample from the Norwegian cohort, Haukvik et al. (2013) found that birth weight was correlated with cortical area across diagnostic groups, but not with cortical thickness. This suggests that reduced cortical folding and reduced cortical area represent similar pathophysiological mechanisms in schizophrenia, which presumably involves early alterations in neurodevelopment, while reduced cortical thickness is related to other pathophysiological processes.

Our finding of reduced gyrification in left pericentral and right temporo-occipital cortex is partly convergent with two previous studies using the automated *l*GI method in patients with adolescent onset (Palaniyappan et al., 2013a) and adult onset schizophrenia (Palaniyappan and Liddle, 2012). Hypogyria in bilateral insular, left frontal and right temporal regions have been linked to lack of response to antipsychotic medication in first-episode psychosis patients (Palaniyappan et al., 2013b). Furthermore, Cachia et al. (2008) found that medication-resistant hallucinations were related to reduced folding of the left pericentral cortex. In the present study, no significant correlation was found between severity of positive and negative symptoms and degree of cortical folding. However, our cross-sectional study did not allow for investigation of relationships with longitudinal outcome measures, such as response to treatment.

4.2. Relationship with age

Whereas increasing age was related to decreasing *l*GI in the left pericentral and right medial parietal clusters, age was not related to *l*GI in the right temporo-occipital cluster. Reduced cortical gyrification with increasing age may be due to reduced sulcal depth (Kochunov et al., 2005). In a study of gyrification in healthy adults aged between 20 and 85 years, *l*GI was negatively correlated with age in all major lobes of the brain, including regions in which groups differed in the present study (Hogstrom et al., in press). In a recent longitudinal study assessing trajectories of *l*GI change with age in a large sample of

Table 2
Description of clusters with significant group differences in local gyrification index.

Sample	Cluster	Location of peak vertex	Area (mm^2)	CWP
Combined	Left pericentral	Left precentral gyrus	12,480	0.0001
	Right temporo-occipital	Right middle temporal gyrus	5940	0.0001
	Right medial parietal	Right precuneus	5165	0.0001
Swedish	Left pericentral	Left supramarginal gyrus	6156	0.0001
	Right temporo-occipital	Right middle temporal gyrus	2579	0.0048
	Right medial parietal	Right precuneus	3612	0.0002
Norwegian	Left pericentral	Left precentral	1796	0.047
	Right fronto-temporal	Right caudal middle frontal gyrus	6851	0.0001
	Right medial parietal	Right precuneus	3506	0.0002

Abbreviations: *l*GI, local gyrification index; CWP, cluster-wise probability (of group difference in *l*GI).

Table 3
Influence of age, gender and diagnosis on variation in mean local gyrification index per cluster[a].

	Left pericentral cluster			Right temporo-occipital cluster			Right medial parietal cluster		
	B	Test[a]	p	B	Test[b]	p	B	Test[b]	p
Intercept	3.35	50,500	<0.000001	3.55	22,334	<0.000001	3.23	29,628	<0.000001
Age (10 years)[c]	−0.064	48.0	<0.000001	−0.065	19.2	0.00001	0.010	0.73	0.39
Gender (women)[d]	−0.052	8.22	0.004	−0.155	28.1	<0.000001	−0.050	4.66	0.031
Diagnosis	−0.062	14.2	0.0002	−0.080	9.32	0.002	−0.073	12.6	0.0004
Sample (Swedish)[e]	0.036	6.27	0.012	0.425	351.2	<0.000001	−0.24	173.6	<0.000001
Age ∗ diagnosis	−0.013	1.00	0.32	−0.015	0.464	0.50	−0.016	0.89	0.35
Gender ∗ diagnosis	0.026	1.05	0.31	0.080	3.76	0.053	−0.003	0.007	0.93

[a] Generalized linear models with mean *l*GI within each cluster as dependent variable, age, gender and diagnosis as covariates, and age–diagnosis and gender–diagnosis as interaction terms. Sample was entered as covariate in all models, but the parameter estimates for sample is not shown in the table.
[b] Wald Chi-square.
[c] Age was centered on the mean within the entire sample and divided by 10 to obtain test values for a 10 years interval.
[d] Test values are presented for women when men are set to zero.
[e] Test values are presented for the Swedish sample when the Norwegian sample is set to zero.

healthy children, adolescents and young adults, Mutlu et al. (2013) found a linearly decreasing *l*GI with age in most cortical regions, with the exception of the medial prefrontal and cuneus/precuneus regions where *l*GI did not correlate with age. As such, the localization of our two clusters with decreased *l*GI with age and the cluster without significant age-related decrease is largely in agreement with the topological distribution of the trajectories reported by Mutlu et al. The absence of significant age × diagnosis interaction effect in the present study suggests that group differences in *l*GI are independent of age.

4.3. Relationship with age at onset and duration of illness

Age at onset was negatively correlated with *l*GI in two of three clusters, but confined to younger patients. This was an unexpected finding, given that patients with early onset of disease presumably have more perturbations in brain morphology. However, the finding indicates that timing of disease onset may not be strongly related to cortical folding. Age, age at onset and duration of illness are highly correlated, which makes it difficult to disentangle the specific contribution of each of the variables. Putative associations between cortical gyrification and onset/duration of illness may better be studied using a prospective design. In the two-year longitudinal study of adolescent-onset schizophrenia patients by Palaniyappan et al. (2013a), patients had higher *l*GI in the left lateral frontal cortex and lower lGI in the right lateral temporal cortex at baseline. Longitudinally, however, patients showed more reduction than controls in lateral frontal cortex *l*GI, while patients and controls had similar reductions in right lateral temporal *l*GI. Although based on a small sample, the results indicate that early onset of schizophrenia may be related to higher *l*GI in the frontal cortex, and that the association between duration of illness and *l*GI differs across the cortex. Our finding of a relationship between higher *l*GI and earlier onset among the younger patients is partly supported by studies of subjects at high risk for developing psychosis, where hypergyria in right prefrontal cortex was found in subjects who later developed schizophrenia compared to subjects who did not (Harris et al., 2004, 2007), while hypogyria in left hemisphere were found in high-risk subjects compared to controls (Jou et al., 2005).

4.4. Strengths and limitations

We applied a validated, automated 3D method with high spatial resolution in the hitherto largest sample of patients with schizophrenia drawn from two independent cohorts. Limitations include the use of different MR scanners and acquisition parameters in the two samples, differences in age and duration of illness within and across samples, and inadequate data to investigate effects of antipsychotic medication and symptoms for variation in *l*GI.

4.5. Conclusions

Results from the present study suggest that reduced gyrification in left pericentral, right lateral temporal, and right medial parietal cortex is an inherent factor of the brain pathology in schizophrenia, which might serve as a quantitative phenotype in genetic association studies.

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Table 4
Relationships[a] between mean local gyrification index per cluster and age at onset and duration of illness.

	Left pericentral cluster				Right temporo-occipital cluster				Right medial parietal cluster			
	Onset		Duration		Onset		Duration		Onset		Duration	
Age, years	r	p	r	p	r	p	r	p	r	p	r	p
19–24 (N = 30)	−0.16	0.41	0.035	0.86	−0.12	0.55	0.022	0.91	0.031	0.88	−0.07	0.72
25–29 (N = 28)	**−0.58**	**0.002**	**0.55**	**0.003**	−0.39	0.052	0.36	0.072	0.099	0.63	−0.17	0.41
30–34 (N = 36)	**−0.52**	**0.002**	**0.46**	**0.006**	**−0.48**	**0.004**	**0.42**	**0.014**	0.18	0.31	−0.20	0.26
35–39 (N = 27)	−0.13	0.54	0.081	0.70	−0.28	0.28	0.19	0.35	−0.091	0.67	0.099	0.64
40–44 (N = 36)	0.12	0.52	−0.17	0.35	0.096	0.59	−0.11	0.53	0.18	0.32	−0.16	0.37
45–49 (N = 42)	0.026	0.87	−0.067	0.681	−0.062	0.70	−0.015	0.92	0.15	0.35	−0.16	0.33

[a] Partial correlation coefficients between mean *l*GI within each cluster and age at onset of illness and duration of illness, controlling for gender and sample. Nominally significant coefficients are marked by bold text. Abbreviations: N, number of patients within each age interval.

Contributors

Ragnar Nesvåg performed clinical investigation of participants, performed literature search and statistical analyses, and wrote the first draft of the manuscript. Marie Schaer, Lars T. Westlye and Marie-Christine Ottet performed statistical analyses. Unn K. Haukvik, Elisabeth H. Lange, Cecilie B. Hartberg and Erik G. Jönsson performed clinical investigation of participants. Lars M. Rimol, Ingrid Melle, Ole A. Andreassen, Ingrid Agartz and Stephan Eliez participated in study design. All authors contributed to and have approved of the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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