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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.