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Gyrification of Broca's region is anomalously lateralized at onset of schizophrenia in adolescence and regresses at 2 year follow-up

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ABSTRACT

Gyrification of the human cerebral cortex starts in the foetus and progresses in early infancy; the pattern of folding in later life provides a lead to early developmental aberration. By studying gyrification at illness onset in adolescence we hoped to clarify the pathophysiology of schizophrenia. Here we find 1) an area of hypergyria includes Broca's area and extends into the Sylvian fissure to encroach on the anterior insula in the left hemisphere, and 2) an area of hypogyria in the superior temporal lobe approximates to Wernicke's area but is located in the right hemisphere and encroaches on the posterior insula. In Broca's/anterior insula area, right lateralization was present in healthy controls but patients were left lateralized: at two year follow-up gyrification had decreased in patients while it increased in controls, and the reduction predicted impaired category fluency. Progressive change was unaccompanied by cortical thinning (investigated only in the brain regions showing baseline changes in gyrification) indicating that the disease process affecting these brain regions (insula, inferior frontal and superior temporal) is not primarily degenerative. A deviation in the lateralized development of peri-Sylvian areas for language production and comprehension appears critical to the pathophysiology of schizophrenia and may point to its species-specific origin.

1. Background

In healthy individuals, though major gyri are established in the prenatal period, progressive change in the degree of folding across the cortex continues during puberty and beyond (Raznahan et al., 2011; Shaw et al., 2012). In normal development some brain regions assume a more folded ('buried') structure than others, with some evidence that these age related changes may be abnormal in schizophrenia (Palaniyappan et al., 2011). Anomalies of gyrification have been found in schizophrenia (White and Hilgetag, 2011) but their direction, regional localization, gender-specificity and lateralization have varied, and no change (Highley et al., 2003) has also been reported. Localized hypergyria (increase in the amount of folded relative to unfolded cortex) in the frontal pole generally to the right and in males but not females has been observed in some studies (Vogeley et al., 2000; Narr et al., 2004; Harris et al., 2007) with reductions elsewhere in the left prefrontal cortex (Sallet et al., 2003) and the insula (Palaniyappan et al., 2011; Palaniyappan and Liddle, 2012). A previous study in adolescents indicates regional variations in frontal gyrification in early onset schizophrenia, though this study only examined regions found to have cortical thinning (Janssen et al., 2009). To date, the time of onset and the progressive course of gyrification changes in schizophrenia are unclear.

Most consistent structural alterations in schizophrenia are localized to language-related brain regions around the Sylvian fissure (insula including inferior frontal and superior temporal regions) (Glahn et al., 2008; Francis et al., 2012). Further, impaired verbal fluency in patients with schizophrenia (Henry and Crawford, 2005) and in individuals at a high-risk of developing psychosis (Magaud et al., 2010; Lin et al., 2011) suggest that the neuroanatomical abnormalities relate specifically to the neural mechanisms underlying production and comprehension of spoken language (Crow et al., 2012). Further, the structural changes involving insula, inferior frontal and superior temporal regions are associated with the clinical expression of schizophrenia (Palaniyappan et al., 2012a, 2012b).

Several groups have reported progressive structural abnormalities in schizophrenia (Vita et al., 2012), and these changes are associated with poorer cognitive functioning (Ho et al., 2003). In particular, longitudinal studies have endorsed the view that schizophrenia with

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onset in adolescence is likely to be a progressive neurodevelopmental disorder with volumetric changes contributing to poor prognosis (Arango et al., 2012). Volumetric studies of this clinical group indicate that prominent longitudinal brain changes occur in those brain regions where baseline differences already exist at the onset (Reig et al., 2009, 2011), suggesting that the anatomical defects observed at an early stage of adolescent-onset schizophrenia may progress with time. Nevertheless, our previous work suggests that volumetric measures do not sufficiently distinguish the contribution of an atrophic, degenerative process from an early developmental aberration with a deviant maturational trajectory (Voets et al., 2008). While gyrification is largely influenced by factors affecting cortical maturation (Mangin et al., 2010), both age-related and disease related cerebral atrophy are accompanied by significant cortical thinning (Salat et al., 2004; Yao et al., 2012).

Here we examined the gyrification pattern of the entire cortical surface in normal adolescents and individuals with onset of schizophrenia at this age. Given our previous observations in an adult sample, we predicted that prominent gyrification defects will be distributed around the Sylvian fissure and include the insula (hypothesis 1), with reduction or reversal of normal gyral asymmetry in the patient group. We expected that the regions that show abnormal gyrification patterns at an early phase of the illness will continue to show progressive change in the grey matter (hypothesis 2); to this end, follow-up scans were obtained and longitudinal change in gyrification was quantified in regions showing baseline abnormalities. While there are no established means of disentangling developmental effects from an atrophic degenerative effect, we explored whether progressive changes in gyrification are also accompanied by progressive thinning in the same brain regions. We also examined the relationship between verbal fluency and the progressive change observed in regions showing abnormal gyrification in patients.

2. Methods

2.1. Participants

25 adolescents satisfying DSM-IV criteria (American Psychiatric Association, 1994) for schizophrenia and 25 healthy controls were recruited from the Oxford Regional Adolescent Unit and the surrounding catchment area. The present study reports data from a sample of 18 patients (10 males and 8 females, age 14.2 to 18.4 years) and 19 controls (9 males and 10 females, age 13.5 to 17.8 years), for whom a follow-up scan after an average interval of 2.18 years was available. The Oxford Psychiatric Research Ethics Committee approved the study and participants or their legal custodian provided written informed consent. The diagnosis of schizophrenia was made on the basis of Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997) carried out by ACJ. Average age of onset of schizophrenia was 14.8 years (SD = 1.35 years). All patients were receiving treatment with atypical antipsychotic medications. Chlorpromazine equivalents were calculated using a standard algorithm (Woods, 2003). We also calculated an approximate interscan antipsychotic exposure value (daily-dose × year) as a product of average CPZ equivalent dose (from the doses prescribed at the two time points) and the interscan interval in years.

The healthy control group was age and gender matched to the patients. The controls came from the same general practice catchment as patients, with a cross section of various social classes. General Practitioners initially selected the controls. From both groups, subjects with a history of current substance abuse or pervasive developmental disorder, significant head injury, neurological or other major medical disorders were excluded. All participants were assessed for Intelligent Quotient (IQ) using the Wechsler Abbreviated Scale of Intelligence (WASI) (Vocabulary, Similarities, Block Design, Matrix Reasoning subtests) and for category fluency using the Category Fluency subtests from the Delis–Kaplan Executive Function System (DKEFS) (Delis et al., 2004). Handedness was assessed with the Edinburgh Handedness Questionnaire (Oldfield, 1971).

2.2. Image acquisition

Baseline and follow-up magnetic resonance scans were collected using Siemens Sonata 1.5-T imaging system using a 3D FLASH sequence. T1-weighted images of isotropic voxel size $1 \times 1 \times 1$ mm^3, TR 12 ms, TE 5.6 ms in a matrix of $256 \times 256 \times 208$ mm^3 were collected.

2.3. Surface extraction

Surface extraction and cortical parcellation for each individual structural image were carried out using FreeSurfer version 4.5.0 (Fischl et al., 1999). The preprocessing followed the standard description available at http://surfer.nmr.mgh.harvard.edu/. Further details of surface generation in this sample have been previously described (Voets et al., 2008). The preprocessing generated images comprising multiple vertices across the whole cortical surface. Cortical thickness was computed in accordance with the standard procedure using Freesurfer (Fischl et al., 1999).

2.4. Computing gyrification

Cortical gyrification was quantified with Schaer's Local Gyrification Indices (LGIs) (Schaer et al., 2008) as previously described (Palaniyappan et al., 2011). This method is described in detail in Supplementary material. The LGI obtained for each vertex on pial surface is a continuous measure that reflects the amount of cortex buried in a locality of 25 mm radius around each vertex, given by the ratio of the inner folded contour to the outer perimeter of the cortex.

2.5. Statistical analysis

2.5.1. Whole brain analysis at baseline

Using a General Linear Model (GLM) approach provided by the Query Design Estimate Contrast (QDEC) interface of Freesurfer, we calculated vertex-wise group differences in gyrification for both hemispheres after surface smoothing using a Gaussian kernel of 15 mm. Age and gender were used as covariates as both of these have been shown previously to affect the LGI. As a group difference in the degree of global folding could also contribute to the variance observed in regional gyrification, we examined the use of hemispheric mean gyrification computed from all vertices included in each hemisphere separately as a covariate in the GLM. As we did not find a significant effect of this variable in the group comparisons the results are reported with only age and gender as covariates. To correct for multiple testing across the cortical surface, we used Monte Carlo analyses with 10,000 simulations at a cluster-inclusion threshold of $p = 0.01$, and report clusters that survive a cluster-wise probability of $p = 0.001$. Region of interest masks were generated using the Freesurfer programme from clusters that emerged as significant from the whole brain analysis. These masks were mapped on to individual surfaces to extract mean LGI and mean thickness within each cluster.

2.6. Asymmetry analysis

We quantified the degree of lateralisation of the observed gyrification abnormalities by creating cluster based mirror image masks for the opposite hemisphere using the Freesurfer average image (fsaverage), in line with our previous study (Palaniyappan and Liddle, 2012). Asymmetry index ([Left − Right] / [Left + Right]) was computed using mean LGI values for each significant cluster that emerged during the whole brain analysis. In addition to the whole brain analysis, we also performed a subsidiary group comparison of