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Sulcogyral patterns and morphological abnormalities of the orbitofrontal cortex in psychosis

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ABSTRACT

Three types of OFC sulcogyral patterns have been identified in the general population. The distribution of these three types has been found altered in individuals at genetic risk of psychosis, first episode psychosis (FEP) and chronic schizophrenia. The aim of this study was to replicate and extend previous research by additionally investigating: intermediate and posterior orbital sulci, cortical thickness, and degree of gyrification/folding of the OFC, in a large sample of FEP patients and healthy controls. OFC pattern type was classified based on a method previously devised, using T1-weighted magnetic resonance images. Cortical thickness and local gyrification indices were calculated using FreeSurfer. Occurrence of Type I pattern was decreased and Type II pattern was increased in FEP patients for the right hemisphere. Interestingly, controls displayed an OFC pattern type distribution that was disparate to that previously reported. Significantly fewer intermediate orbital sulci were observed in the left hemisphere of patients. Grey matter thickness of orbitofrontal sulci was reduced bilaterally, and left hemisphere reductions were related to OFC pattern type in patients. There was no relationship between pattern type and degree of OFC gyrification. An interaction was found between the number of intermediate orbital sulci and OFC gyrification; however this group difference was specific to only the small subsample of people with three intermediate orbital sulci. Given that cortical folding is largely determined by birth, our findings suggest that Type II pattern may be a neurodevelopmental risk marker while Type I pattern may be somewhat protective. This finding, along with compromised orbitofrontal sulci thickness, may reflect early abnormalities in cortical development and point toward a possible endophenotypic risk marker of schizophrenia-spectrum disorders.

1. Introduction

The orbitofrontal cortex (OFC) is a region known to be involved not only in somatosensory and emotion processing but various higher-order cognitive functions, including moral judgement, decision-making and social cognition (Zald and Rauch, 2006). Morphological abnormalities of the OFC have long been associated with schizophrenia pathology (Pantelis and Brewer, 1996), but only recently have researchers begun to characterise the nature of such abnormalities, whether they confer risk for the development of psychosis, and the subsequent implications for illness outcome.

A number of studies have investigated OFC volumetric differences between schizophrenia patients and healthy controls. Although findings are somewhat inconsistent, evidence generally suggests that reductions in both total and subregional OFC volumes are common in chronic schizophrenia and first episode psychosis (FEP) (e.g., Kawasaki et al., 2004; Nakamura et al., 2008; Takayanagi et al., 2010) with evidence of progressive grey matter OFC reductions from initial illness onset (Pantelis et al., 2003). These findings along with evidence of altered neurodevelopmental trajectories (Pantelis et al., 2007), reduced cortical thickness (e.g., Schultz et al., 2010), and surface size (Crespo-Facorro et al., 2000), and abnormal neuronal activation (e.g., Pauly et al., 2008) of orbitofrontal regions, has led to the hypothesis that specific abnormalities in the OFC may contribute to the risk of developing psychosis. Thus, investigation of OFC sulcogyral folding patterns has become an area of interest. Such investigation offers the hope of discovering a potential early detectable risk marker, given that cortical folding is completed shortly after birth (Chi et al., 1977) and sulcogyral patterns remain relatively

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of varience; CSF, cerebrospinal fluid; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders 3rd Edition Revised; FEP, first episode psychosis; ICV, intercranial volume; IOS, intermediate orbital sulcus; LGI, local gyrification index; LOS, lateral orbital sulcus; LOSc, lateral orbital sulcus caudal; LOSr, lateral orbital sulcus rostral; MNI, Montreal Neurological Institute; MOS, medial orbital sulcus; MOSc, medial orbital sulcus caudal; MOSr, medial orbital sulcus rostral; NART, National Adult Reading Test; NOS, not otherwise specified; OFC, orbitofrontal cortex; PANSS, Positive and Negative Syndrome Scale; POS, posterior orbital sulcus; TOS, transverse orbital sulcus.

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stable throughout life despite natural volumetric changes with age (Magnotta et al., 1999). Gyral and sulcal formation has been linked to cytoarchitecture of underlying structures (e.g., Xu et al., 2010), neuronal connectivity (e.g., Herculano-Houzel et al., 2010) and genetic influences (e.g., Bartley et al., 1997). Abnormal gyrification of regions such as the anterior cingulate (e.g., Yucel et al., 2002) and prefrontal cortex (e.g., Harris et al., 2004a) has previously been implicated in psychosis and schizophrenia.

Despite the heterogeneity of sulcogyral pattern in the OFC, 'H', 'K' and 'X' shaped formations have frequently been reported, but only recently have the anatomical characterisations of OFC sulci and gyri been operationally defined (Chiavaras and Petrides, 2000). Three predominant pattern types have been identified in healthy individuals; Type I is most common (found in 56% of hemispheres), Type II is less common (30% of hemispheres), while Type III is uncommon (14% of hemispheres; see Methods and materials section, Fig. 1 for examples of pattern types) (Chiavaras and Petrides, 2000). Altered OFC sulcogyral pattern distributions have been found in chronic schizophrenia (Nakamura et al., 2007, 2008) and FEP (Chakirova et al., 2010; Takayanagi et al., 2010), where Type III was more common and Type I less common in patients, specifically in the right hemisphere. Chakirova et al. (2010) also found individuals at high genetic risk of schizophrenia who later developed the illness had significantly reduced incidence of Type I when compared to at risk individuals who had not converted to psychosis within the 10 year follow-up period. For chronic schizophrenia patients, having a Type III classification in either hemisphere has been associated with poorer socio-economic status, worse verbal comprehension, a 'negative emotionality' trait and more severe symptoms compared to patients without Type III expression (Nakamura et al., 2007). OFC pattern type has been found to be independent of volumetric changes (Nakamura et al., 2008; Takayanagi et al., 2010).

The aim of this study was to replicate and extend previous research by investigating the OFC sulcogyral pattern distribution in a large sample of FEP patients and healthy controls. This study extends previous research by investigating differences in the number of intermediate and posterior orbitofrontal sulci, cortical grey matter thickness and degree of gyrification in the OFC, and how these parameters relate to OFC pattern type.

2. Methods and materials

2.1. Participants

One hundred and three individuals with FEP (aged 16–30) were recruited from the Early Psychosis Prevention and Intervention Centre, Orygen Youth Health, an outpatient service in Melbourne. Recruitment of this sample has been previously described (Velakoulis et al., 2006). Briefly, FEP patients were included in the study if they: were currently psychotic (the presence of at least one of: delusions, hallucinations, disorder of thinking or speech, or disorganised, bizarre or markedly inappropriate behaviour), had a DSM-III-R diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder, based on standardised structured clinical interviews (American Psychiatric Association, 1987; McGorry et al., 1989), plus review of medical records. Individuals with other psychotic disorders, including psychosis NOS, delusional disorder, bipolar disorder and major depression with psychotic features, were not included in order to minimize variability within the patient sample.

Control participants (aged 15–36) were recruited by approaching ancillary hospital staff and via advertisement. Both FEP patients and controls were screened for comorbid medical and psychiatric conditions by way of clinical, physical and neurological assessments. Participants from either group were excluded if they had a history of: serious head injury, seizures, a neurological disease, impaired thyroid function, corticosteroid use, or if they met criteria for alcohol or substance abuse or dependence according to the DSM-III-R. This study was approved by the Melbourne Health Mental Health Research and Ethics Committee. Written informed consent was obtained from all participants or a parent/guardian where appropriate. Basic demographic data was collected including age, handedness and height. All participants performed the National Adult Reading Test (NART) (Nelson, 1982) to provide an indicator of premorbid IQ. All FEP patients were administered the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and illness duration and chlorpromazine equivalent antipsychotic dose at the time of scanning were recorded.

A total of 178 participants were initially recruited into the study. Of this sample, 169 (FEP = 96; controls = 73) were included in the final analysis. Nine participants were excluded because of poor image quality, due to movement artefact.

2.2. MRI acquisition

High-resolution anatomical T1-weighted images were acquired on a 1.5 T Signa scanner (General Electrical Medical Systems, Milwaukee, Wisconsin) at the Royal Melbourne Hospital. A 3-dimensional volumetric spoiled-gradient recalled echo in the steady-state sequence generated 124 contiguous, 1.5-mm coronal sections. Imaging parameters were: echo time, 3.3 ms; repetition time, 14.3 ms; flip angle, 30°; matrix size, 256 × 256; field of view, 24 × 24-cm matrix; and voxel dimensions, 0.938 × 0.938 × 1.5 mm.

2.3. OFC sulcogyral pattern classification

The classification technique was based on that devised by Chiavaras and Petrides (2000). To summarize, visual classification of each hemisphere was based on the continuity/discontinuity of the medial orbital sulcus (MOS) and lateral orbital sulcus (LOS), in regard to the joining of the rostral and caudal regions, respectively (see Fig. 1). For Type I the MOS is disconnected while the LOS is intact, for Type II both the MOS and LOS are continuous, and for Type III both the MOS and LOS are disconnected. In rare instances where the MOS was continuous but the LOS was disconnected, this pattern was deemed a Type III, given that the interrupted LOS is the distinguishing feature of the Type III pattern. All skull-stripped brains were first aligned along the

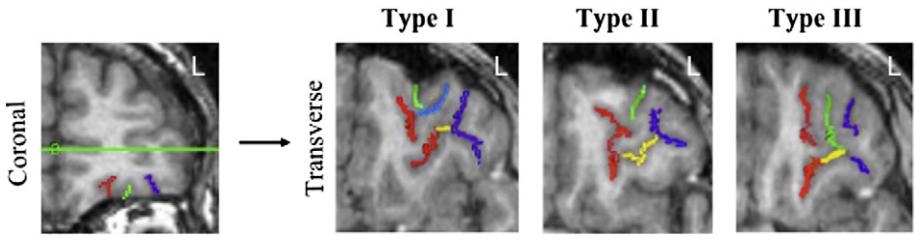

Fig. 1. Examples of the three different OFC pattern types. To determine Type, sulci are first traced on the coronal slices (left panel), and then viewed on the transverse images (right panel). Type I: medial orbital rostral and caudal regions (red) are disconnected while the lateral orbital sulcus (purple) is continuous. Type II: rostral and caudal regions of the medial and orbital sulci are connected, respectively. Type III: rostral and caudal regions of the medial and orbital sulci are disconnected, respectively. The additional sulci depicted are: transverse orbital sulcus (yellow), Intermediate orbital sulci (green and blue).