Accepted Manuscript

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PII: S0278-5846(13)00044-4
DOI: doi: [10.1016/j.pnpbp.2013.02.010](https://doi.org/10.1016/j.pnpbp.2013.02.010)
Reference: PNP 8349

To appear in: *Progress in Neuropsychopharmacology & Biological Psychiatry*

Received date: 9 December 2012
Revised date: 1 February 2013
Accepted date: 12 February 2013

Please cite this article as: Bartholomeusz Cali F., Whittle Sarah L., Montague Alice, Ansell Brendan, McGorry Patrick D., Velakoulis Dennis, Pantelis Christos, Wood Stephen J., Sulcogyral patterns and morphological abnormalities of the orbitofrontal cortex in psychosis, *Progress in Neuropsychopharmacology & Biological Psychiatry* (2013), doi: [10.1016/j.pnpbp.2013.02.010](https://doi.org/10.1016/j.pnpbp.2013.02.010)

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Sulcogyral patterns and morphological abnormalities of the orbitofrontal cortex in psychosis

Running title: Orbitofrontal abnormalities in psychosis

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Word count:

Abstract = 270

Body text = 6,312

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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 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. These findings, 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.

Key Words: Schizophrenia, Sulci, Cortical Thickness, Local Gyrification Index, Endophenotypic Risk Marker

Abbreviations

ANCOVA – analysis of covariance

ANOVA – analysis of variance

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

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 characterize 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 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) have 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 characterizations 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 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., 2008; Nakamura et al., 2007) 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 and colleagues (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 at 10 years follow-up. 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 (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 was 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 (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, 3.3ms; repetition time, 14.3ms; flip angle, 30°; matrix size, 256 x 256; field of view, 24 x 24-cm matrix; and voxel dimensions, 0.938 x 0.938 x 1.5 mm.

2.3. OFC sulcogyral pattern classification

The classification technique was based on that devised by Chiavaras and Petrides (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 regards 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 anterior commissure-posterior commissure plane to adjust for head tilt (using FLIRT rigid body registration to the MNI template) and resampled into 1mm cubic voxels. Images were classified on a LINUX workstation using the biomedical imaging software package Analyze 10.0 (Mayo Clinic). We identified all sulci appearing on the orbital surface, taking note of the number of intermediate orbital sulci (IOS) and posterior orbital sulci (POS). Sulci were highlighted in coronal section slices by slice using the tracing tool, and then viewed in transverse and sagittal planes to aid in the visual classification of OFC pattern type (see Figure 1). Based on the written recommendation of Nakamura (2009; personal communication), a fissure was considered to be a sulcus if it was at least 4mm long and 4mm deep (i.e. visible in 4 coronal and 4 transverse slices). For a sulcus to be continuous with another sulcus it had to be clearly connected in at least 3 slices.

OFC pattern classification for each hemisphere was performed by C.B., who was blinded to sex and group. Inter-rater reliability was performed by C.B. and S.L.W. on 56 randomly selected brains from the Melbourne Neuropsychiatry Centre database. Intra-rater reliability was performed on a subset (N=18) of these brains. Interclass correlation

coefficients (Chronbach's α) were 0.82 and 0.89 for inter- and intra-rater reliability, respectively. Given the precise nature of the classification method, S.L.W. reviewed approximately 38% of hemisphere from the current sample, which were deemed most difficult to classify. Reliability between raters remained high (0.88).

----- Insert Figure 1 about here -----

2.4. Cortical thickness and local gyrification index (LGI) processing

Images were processed using FreeSurfer (v. 4.5.0) automated neuroanatomical segmentation software. This involved motion correction, non-uniform intensity normalization, affine registration to Montreal Neurological Institute (MNI) space and Talairach transformation followed by removal of skull and other non-brain tissue. The white matter boundary was automatically traced, tessellated and smoothed at a 2.0 mm FWHM kernel to produce a surface mesh. The pial boundary was generated from the white mesh by lateral deformation to the cerebrospinal fluid (CSF). Pial and white matter surfaces for each subject were spherically inflated and registered to the manually delineated Desikan brain atlas (Desikan et al., 2006). All boundaries were reviewed for accuracy and manually corrected where needed to produce more accurate surface estimates. Images were then reprocessed to produce final thickness estimates (Fischl et al., 2002).

In addition, these images were also run through the FreeSurfer local gyrification index (LGI) pipeline (Schaer et al., 2008) to examine the degree of cortical folding. The LGI quantifies the amount of cortex buried within the sulci as compared to the amount of cortex that is visible on the outer surface/gyri of the brain. This vertex-wise method uses a morphological closing operation, which is applied to the 3-D mesh of the pial surface using a

sphere of 15mm diameter. The resulting outer-mesh typically consists of a mean number of 55,000 vertices with a mean face area of 0.4mm^2 . The LGI at a given point on the cortical surface is calculated as the ratio between the surface of a circular region of interest (ROI) on the outer surface, centered at this point, and the surface of the corresponding ROI on the pial surface (Schaer et al., 2008). Within each hemisphere, the LGI was automatically computed for 35 cortical parcellation units, according to the Destrieux Atlas (Destrieux et al., 2010).

2.5. Statistical analysis

Data analysis was performed using SPSS statistical software (IBM SPSS 19.0 for Mac, SPSS Inc., Chicago, Illinois). Group differences in demographic variables Age, Height and Premorbid IQ (NART predicted) were analysed with One-way analyses of variance (ANOVAs), while sex and handedness were analysed with Pearson's χ^2 statistics. Pearson's χ^2 statistics were also used to assess pattern type distribution between groups overall and for each of the pattern types individually (hemispheres analysed separately). To assess whether the significant group differences observed in age and IQ (see results section) were potential confounding factors for subsequent OFC pattern Type analyses, we ran separate univariate ANOVAs with age and IQ as the dependent variables and group and OFC pattern Type as the between-subjects factors. Because sex differences in OFC pattern type distribution has not previously been investigated, we also ran Pearson's χ^2 analyses for the control and FEP groups separately to test this. We then examined the role of asymmetry in OFC pattern type and estimated relative risk associated with particular pattern types/combinations, given that only one research group has previously examined this aspect of OFC folding (Nakamura et al., 2007) and findings have yet to be replicated. Additionally, due to the observation that the number of sulci appearing in the OFC region was inconsistent, we ran χ^2 statistics for number

of IOS and POS to investigate potential group effects. Given that previous research has found significant relationships between OFC pattern type and psychopathology (Nakamura et al., 2007), we also conducted separate univariate ANOVAs on the PANSS total score, positive, negative and general sub-scores, and duration of illness (dependent variables) with OFC pattern Type as the fixed factor (hemispheres analyzed separately).

To assess group differences in OFC thickness, separate mixed analyses of covariance (ANCOVAs) were performed for each hemisphere. Mixed ANCOVAs were performed for sulci (orbital medial-olfactory, orbital H-shape, orbital lateral) and gyri (gyrus rectus, orbital gyrus) separately, according to Freesurfer Destrieux Atlas (Destrieux et al., 2010), given that previous research suggests sulci and gyri can be differentially affected in schizophrenia (White et al., 2003). Thus, OFC region was the independent factor, Group and Sex were the between-subjects factors, and intracranial volume (ICV) and age (log transformed to account for normality assumptions) were the covariates. To investigate the relationship between OFC Pattern type and these parameters, mixed ANCOVAs were re-run with OFC pattern type as an additional between-groups variable.

To explore differences in LGI between groups, mixed ANCOVAs were also performed. OFC region (gyrus rectus, OFC H-shape [labelled 'medial' and 'lateral' OFC respectively according to FreeSurfer Desikan-Kiliany Atlas]) (Desikan et al., 2006) was the independent factor, Group was the between-subjects factor, ICV, age (as above) and mean hemispheric LGI (to account for OFC specificity) were the covariates (sex was not used as a covariate given there were no sex effects or interactions with group when analysing mean hemispheric LGI). ANCOVAs were re-run with OFC pattern type included as a factor. We also wanted to test the hypothesis that a greater number of IOS and POS were related to a higher LGI (which takes into consideration sulcal depth and length). This relationship cannot simply be

assumed. For example, with the IOS, some individuals may have very shallow sulci yet possess as many as 3 IOS, while other people may have very deep IOS but possess only one. Thus, to test the relationship between these two indices of OFC morphology we conducted univariate ANCOVAs with the same covariates were run for the OFC H-shape region (i.e. 'lateral' OFC FreeSurfer region, as this encompasses all parts of the OFC where these sulci could be identified) for the IOS and POS respectively.

For primary analyses with a priori defined hypotheses (i.e. OFC pattern type differences between the FEP and control groups, including across hemispheres and relationship with psychopathology), α was set at 0.05 uncorrected, which is in accordance with the method adopted by previous researchers in this area (Chakirova et al., 2010; Nakamura et al., 2007; Takayanagi et al., 2010). For exploratory analyses (i.e. analyses involving number of intermediate and posterior sulci, cortical thickness and LGI), post-hoc tests were adjusted for multiple comparisons using the Bonferroni (backwards) method (Bland, 2000), where the α was set at 0.05. This correction involved the raw p value of each post hoc analysis being multiplied by the number of post hoc analyses run as a result of a significant overall group effect/interaction (incidentally this was always '3'). Thus, if after multiplying the raw p value by 3 it was $\leq$ 0.05 it was deemed significant. Adjusted p values for these post-hoc tests are reported in results (and are indicated to be adjusted). We chose to only correct post hoc analyses given that the Bonferroni method is quite conservative and we wanted to reduce the likelihood of Type II errors.

3. Results

3.1. Demographics

Independent samples *t*-tests showed a significant difference in age and premorbid IQ between groups, whereby control participants were on average slightly older and had a higher IQ than FEP patients (see Table 1 for demographics). Univariate ANOVAs showed no significant interactions between group and OFC pattern type (hemispheres analysed separately) for either age or premorbid IQ.

----- Insert Table 1 about here -----

3.2. OFC pattern type distribution

The distribution of the three OFC pattern types was significantly different between the FEP and control groups in the right hemisphere ($\chi^2=8.53$, $p=.014$), but not the left ($p=.405$). For the right hemisphere, Type I was less common ($\chi^2=5.52$, $p=.019$) while Type II was more common ($\chi^2=7.44$, $p=.006$) in patients compared to controls (see Fig. 2). Findings for Type I and Type II remained significant when OFC pattern type in the left hemisphere was included as a control variable. There was no significant difference in the frequency of Type III classifications between groups ($p=.878$) (see Table 2 for distribution of Pattern type across groups). To ensure that the inclusion of the anomalous Type III pattern (where the MOS was continuous while the LOS was disconnected; previously classified as pattern Type IV by Chakirova et al., 2010) did not impact significantly on the above findings, we re-ran these analyses after excluding individuals with this particular Type III pattern ($n=13$ hemispheres: 8 right, 5 left). Results remained the same (pattern type distribution differed significantly between groups for the right [$\chi^2=8.94$, $p=.011$] but not the left hemisphere [$p=.409$]).

We ran secondary analyses to explore possible sex-specific effects. OFC pattern type distribution was found to be similar between healthy males and females (left: $p=.29$; right:

$p=.36$). However, for the patient group, while males and females had a similar distribution in the right hemisphere ($p=.19$), there was a significantly different distribution in the left hemisphere ($\chi^2=12.55$, $p=.002$), with males having fewer Type Is ($\chi^2=7.86$, $p=.015$ adjusted) and more Type IIs ($\chi^2=11.27$, $p=.003$ adjusted) compared to female patients. Therefore, to ensure that sex was not an influencing factor in the above findings, analyses were re-run for the left hemisphere after dividing the whole sample by sex. There were no significant between-group differences in pattern type distribution in the left hemisphere for males ($p=.26$) or females ($p=.35$).

----- Insert Figure 2 about here -----

We further explored the distribution of OFC patterns across hemispheres. The distribution of the three pattern types differed significantly on the left compared to the right hemisphere for controls ($\chi^2=10.48$, $p=.03$) but not for the FEP group ($p=.447$). In regards to right/left combinations, 43.8% of controls had a Type I/Type I combination. For patients, Type I/Type I was also the most common combination (in 22.9% of cases) but the frequency of this combination was significantly lower than controls ($\chi^2=8.35$, $p=.004$). FEP patients tended to have more Type II combinations than controls, whereby 42.7% of patients had at least one hemisphere that had a Type II ($\chi^2=4.21$, $p=.040$) and 10.4% of patients (compared to 1.4% of controls) had a Type II/Type II combination ($\chi^2=5.58$, $p=.018$). The relative risk for being in the FEP group was 1.58-fold for those who did not have the Type I/Type I combination. If participants had a Type II in either hemisphere the risk was 1.5-fold greater, and if they possessed a Type II/Type II combination there was a five-fold risk that they would be in the FEP group.

----- Insert Table 2 about here -----

3.3. *OFC pattern Type and clinical symptomatology*

There were no significant relationships found between OFC pattern Type and PANSS total or sub-scores, or duration of illness for either the left or right hemisphere in our FEP sample (p ranged from .17 to .93).

3.4. *Number of intermediate and posterior sulci*

We observed that some individuals had more than two IOS or POS, which has not been previously reported (see Table 3). We found there was a significant difference in the number of IOS between groups in the left hemisphere ($\chi^2=9.99$, $p=.007$), but not the right. Compared to controls, there were significantly fewer FEP patients who possessed 3 IOS ($\chi^2=7.79$, $p=.015$ adjusted; see Fig. 3 for an example of an OFC sulcogyral pattern comprising 3 IOS). There was no difference in the number of POS between groups for either hemisphere.

----- Insert Figure 3 about here -----

3.5. *Cortical thickness*

Three (OFC sulcal region: medial, H-shaped, lateral) by 2 (group: FEP, controls) by 2 (sex: male, female) mixed ANCOVAs revealed main effects of group for the left ($F(1,156)=4.90$, $p=.028$) and right ($F(1,156)=5.69$, $p=.018$) hemispheres, whereby FEP patients had reduced cortical thickness in OFC sulci compared to controls (see Table 4). There were no interactions found between group and region. However, when OFC pattern

Type was entered into the analysis it was found to interact significantly with group for the left hemisphere ($F(2,149)=6.69$, $p=.002$; see Fig. 4), but not the right. Post hoc mixed ANCOVAs for each pattern type showed that FEP patients with Type I in the left hemisphere had significantly thinner cortical orbitofrontal sulci in comparison to healthy controls who also had Type I pattern ($F(1,80)=13.60$, $p=.001$ adjusted). There were no significant differences in the post hoc analyses for Types II and III.

There were no significant main effects or interactions with group for any of the analyses involving thickness of the OFC gyri.

----- Insert Figure 4 and Table 4 about here -----

3.6. Local gyrification index

Of the total sample, LGI was successfully calculated for 78 FEP patients and 61 controls for the left hemisphere, and 76 FEP patients and 60 controls for the right hemisphere, thus all LGI analyses were conducted on this available data. There were no main effects or interactions for group and sex for the mean LGI of each hemisphere. There were significant main effects for age and ICV for both left and right hemispheres (data not shown), thus these variables plus mean LGI for a given hemisphere were controlled for in the subsequent analyses.

A 2 (OFC region: gyrus rectus, OFC H-shape) by 2 (group) ANCOVA found a main effect of OFC region for the right ($F(1,130)=8.47$, $p=.004$) hemisphere but not the left ($p=.117$), whereby the OFC H-shape had greater gyrification than the gyrus rectus, as would be expected (see Table 5). There were no main effects or interactions with group for either hemisphere, even after OFC pattern type was entered into the analysis.

Univariate ANCOVAs for the LGI of the OFC H-shape region revealed a significant main effect for number of IOS in the left ($F(2,129)=4.08$, $p=.019$) but not the right hemisphere, where the LGI tended to be higher for individuals who had a greater number of sulci in that area. A significant interaction between number of IOS and group was observed in the left hemisphere ($F(2,129)=3.30$, $p=.040$). While LGI increased slightly as the number of sulci increased for the control group, for the FEP patients, a steeper increment in the LGI was seen as number of sulci increased (see Fig. 5). Post hoc analyses showed that FEP patients had a significantly higher LGI than controls if they possessed 3 IOS in the left hemisphere ($F(1,13)=9.91$, $p=.023$ adjusted). There were no group differences for those who possessed 1 or 2 IOS.

----- Insert Table 5 and Figure 5 about here -----

4. Discussion

The distribution of OFC sulcogyral folding pattern was significantly altered in FEP patients in comparison to healthy controls and this was specific to the right hemisphere, which is consistent with previous research (Chakirova et al., 2010; Nakamura et al., 2007; Takayanagi et al., 2010). However, although the post hoc finding of decreased incidence of Type I in patients was in line with past research (Nakamura et al., 2007; Takayanagi et al., 2010), the increased incidence of Type II is novel. In addition, this is the first study to show that Type I pattern was associated with cortical thinning in OFC sulci of the left hemisphere in FEP patients. Moreover, despite pattern type having no influence on the mean gyrification

index in the OFC, FEP patients who possessed 3 IOS had a higher OFC gyrification index than healthy controls who also possessed 3 IOS.

4.1. Group differences in OFC pattern type distribution

The finding of altered OFC pattern type distribution in FEP is indicative of a potential neurodevelopmental abnormality occurring during the mid-late gestational period. The new finding of a five-fold increased risk for individuals with a Type II pattern in both hemispheres is substantial. The underlying mechanisms by which risk for, or protection against, the development of a psychotic disorder in later life via variations in OFC folding pattern are currently unknown. However, researchers argue that genetic processes have the greatest influence on cortical folding, with preliminary evidence suggesting that the adhesion molecule protocadherin 12 may be related to altered gyrification in schizophrenia based on the relationship with the G/A-Ser640Asn single-nucleotide polymorphism (Gregorio et al., 2009).

Type III pattern was not found to be increased in our FEP patients relative to controls, which is in contrast with previous research in chronic schizophrenia (Nakamura et al., 2008; Nakamura et al., 2007) and FEP (Chakirova et al., 2010; Takayanagi et al., 2010). Despite this, the 27.1% of our FEP patients who had a Type III pattern in the right hemisphere is comparable to that of previous psychosis samples (23-32%) (Chakirova et al., 2010; Nakamura et al., 2007; Takayanagi et al., 2010). Therefore, our lack of a significant group difference in Type III pattern was likely due to the abnormally high incidence of Type III in our control sample (26% compared to 9-10% in previous research) (Chakirova et al., 2010; Nakamura et al., 2007; Takayanagi et al., 2010). The original paper by Chiavaras and Petrides (Chiavaras and Petrides, 2000), which consisted of 50 healthy controls, reported a

much lower incidence of the Type III pattern (see Table 2). In order to account for this finding, we must consider potential discrepancies in the method of classification. For the current study, raters were trained to be especially vigilant in classifying a Type III not only when the LOSr was visibly disconnected from any other sulci, but also when the LOSr was clearly connecting to an IOS or the TOS (as opposed to the LOSe). According to Chiavaras and Petrides (2000) this sub-type (Type III-f) is rare and only found in 1% of hemispheres. To examine the potential for a higher percentage of Type IIIs in controls due to the possibly increased vigilance in identifying Type III-f, we looked at the number of individuals who specifically had this subtype. Only 2.7% of controls (and 6.3% of patients) possessed the Type III-f, implying that the majority of Type III classifications are representative of a truly disconnected LOS.

The deviation from the previously reported norm by our healthy control sample may also account for our significant group difference in Type II pattern, given Type II in the right hemisphere of our control sample was unusually low (11%). Incidentally, the occurrence of Type II in our FEP patients in the right hemisphere (28%) is similar to Chiavaras and Petrides' (Chiavaras and Petrides, 2000) healthy control group (26%). Despite this, there is variability in frequency of right hemisphere Type II pattern within the schizophrenia literature, with Chakirova et al. (Chakirova et al., 2010) reporting 17% in FEP patients, Takayanagi and colleagues (Takayanagi et al., 2010) more than double this amount (38%) also in FEP, and Nakamura et al (Nakamura et al., 2007) finding 34% in their chronic schizophrenia sample. Worth noting, the current study comprised the largest control sample to date. Other possible reasons for differences between study control samples may be due to various unknown prenatal factors or demographics, such as low socioeconomic status or poor cognitive function, which have been previously linked to the Type III pattern (Nakamura et

al., 2007). In this regard it may be that our control group is in some way abnormal, and it is a limitation of this study that such parameters were not collected and hence could not be explored in an attempt to explain the discrepancies between our control group and previous healthy control samples. However, discrepancies may also be due to the different geographical location from which the current sample was selected (southern hemisphere), as opposed to northern regions namely the UK (Chakirova et al., 2010), Japan (Takayanagi et al., 2010) and USA (Nakamura et al., 2008; Nakamura et al., 2007). Variation in skull and brain morphology, including fronto-temporal cortical regions, have been found to differ according to a population-genetic fingerprint displaying a Northwest-Southeast gradient in individuals of European ancestry (Bakken et al., 2011a). Thus, our control sample, which predominantly comprised Australian born individuals (data not shown), may well be representative of the wider Australian community, which in comparison to northern countries may have a higher rate of the Type III and lower rate of Type II pattern. In support of this notion, a similar distribution to that observed in our controls was also found for an independent control sample (n=105) of a different study conducted in our lab, with 29% of controls possessing Type III and 20% possessing Type II in the right hemisphere (unpublished).

There were no relationships found between OFC pattern Type and severity of clinical symptoms in our FEP sample, which is in contrast to the study by Nakamura et al. (2007), which showed a significant relationship between pattern Type III and more severe positive, disorganised and withdrawn symptomatology. It may be that this relationship is dependent on the Type III pattern distribution being altered in patients, which would explain our lack of significant results. However, our findings are in line with that of Takayanagi and colleagues (2011), who also did not find a significant association between type and symptoms in a FEP

cohort, and suggested that pattern Type may affect clinical behavioral outcomes only in the later course of the illness.

4.2. Reduced number of intermediate orbital sulci in FEP

In the left hemisphere, IOS were significantly reduced in number for our FEP group, potentially implying underdevelopment of the neural system in that area. Interestingly, we discovered that a substantial number of individuals had as many as 3, and in two cases 4 IOS, which has not been previously reported. This may be due to our rule of defining a sulcus as 4x4mm (minimum), which was in accordance with that of Nakamura et al (personal communication). It is unknown how other researchers defined a sulcus during their classification process. It should be acknowledged that this complex OFC classification technique has only been mastered by a small number of laboratories worldwide, thus only a handful of sample populations have been assessed. Given this, and the heterogeneity of the OFC in general, anomalies are not surprising. The reduced number of sulci in our FEP patients compared to controls may be related to the delay in which these sulci first appear (40-44 weeks gestation) (Kringelbach and Rolls, 2004), leading to prolonged risk of exposure to prenatal stressors. Premature birth (i.e. <32 weeks gestational age) has been found to alter normal OFC sulcogyral pattern formation (Gimenez et al., 2006). Prematurity along with other obstetric complications have also been linked to abnormal cortical folding in regions other than the OFC (Haukvik et al., 2011). Numerous environmental factors that can effect foetal development, including paternal age, maternal infection, obstetric complications and season of birth, have all been linked to the emergence of schizophrenia-spectrum disorders in later life (Matheson et al., 2011). Thus, further research into OFC sulcogyral patterns, which

specifically takes into account potential birth complications, pre-/post-natal environmental factors and proposed genetic polymorphisms, is needed.

4.3. Compromised cortical thickness of OFC sulci in FEP and relation to OFC pattern Type

Overall thinning of OFC sulci in our FEP sample, relative to controls, may suggest excessive dendritic pruning has potentially occurred. Interestingly, this was a sulci-specific effect, as thickness of OFC gyri were not significantly different between groups. Moreover, sulcal thinning was related to Type I pattern in the left hemisphere for FEP patients. When considering that Type I is significantly more prevalent in healthy controls, it could be postulated that for healthy controls, the Type I pattern provides some unknown protective mechanism/s that may be reducing the likelihood of development of psychosis, however for the FEP patients with a Type I pattern, this mechanism appears to have failed. It may be that the reduced cortical thickness (which is a known characteristic of schizophrenia) impedes on the putative protective effects associated with this particular OFC pattern type in the left hemisphere. What this putative protective mechanism might be is unknown. One speculation is that connectivity may be involved, based on the theory of gyri formation that purports tension-based mechanisms (Van Essen, 1997; White et al., 2010). Type I pattern may be associated with more efficient neural organization of the OFC, and this may potentially be linked to better axonal connectivity with other brain regions and more efficient processing. Reduced structural connectivity (i.e. measure of white matter integrity via fractional anisotropy; FA) and abnormal functional connectivity of pathways/networks specifically involving the OFC have been implicated in schizophrenia (Kubota et al., 2012; Mingoia et al., 2012). Moreover, Kubota and colleagues (2012) found reduced FA values of the thalamo-orbitofrontal pathway to be positively correlated with cortical thickness. In order to test our

theory, future research should explore whether OFC pattern Type is linked to connectivity and assess how this interacts with cortical thickness. Worth noting, no study has found a significant group difference in pattern type distribution when analysing the left hemisphere independently, although a trend can be seen where controls more often possess the Type I pattern. Thus, if OFC Type I is associated with a potential protective mechanism, it seem to be more robust in the right hemisphere, which may also explain why this pattern type was associated with left hemisphere cortical thinning in our patient group.

Cortical thickness findings are unlikely to be confounded by patients having fewer IOS in the left hemisphere, given that no interactions were found between cortical thickness and OFC sulcal region (i.e. medial-olfactory, H-shaped, lateral), and main effects for reduced OFC thickness was bilateral. Reduced cortical thickness of specific sulcal regions, including temporal, parietal, and cingulate sulci, have previously been found in children/adolescents with a psychotic illness (White et al., 2003) and first degree relatives of patients with schizophrenia (Goghari et al., 2007). Thickness reductions in the OFC (where sulci and gyri were analyzed together) have been observed in chronic schizophrenia (Kuperberg et al., 2003) and FEP (Schultz et al., 2010). A number of factors have been found to influence cortical thickness. Cortical thinning of the OFC has previously been associated with higher cumulative intake of typical antipsychotics in schizophrenia patients over 5 years (van Haren et al., 2011). The atypical antipsychotics clozapine and olanzapine however have been shown to have little effect on cortical thickness development over 2 years in childhood onset schizophrenia (Mattai et al., 2010). Our FEP sample had a mean illness duration of 66 days and most were on atypical antipsychotics, thus thinning is less likely due to medication use. Furthermore, recent emerging evidence suggests cortical thinning is largely genetically driven. Aberrations in genetic polymorphisms such as Leu607Phe and Ser704Cys of DISC-1

have been shown to predict the rate of thinning in the right OFC, among other regions (Raznahan et al., 2011). Specific genetic variants within the Prader-Willi and Angelman syndrome region on chromosome 15q12 have also been linked to cortical thickness and cognitive performance in schizophrenia (Bakken et al., 2011b). Taken together, these findings implicate cortical thinning of the OFC as a potential endophenotypic risk marker for psychotic illness and warrants further investigation.

4.4. Local gyrification indices of the OFC and relation to intermediate orbital sulci

Degree of gyrification (i.e. LGI) of the OFC was not significantly different between FEP patients and healthy controls, nor did it interact with OFC pattern type. There was an overall trend for individuals with a greater number of IOS to have a higher LGI for the OFC H-shape region, which was expected. However, this index was significantly higher for FEP patients who possessed three IOS in the left hemisphere, thus suggesting hypergyria (i.e. increased gyrification/folding) of the OFC for these individuals. Only one previous study has investigated the mean gyrification index of the OFC in schizophrenia, but found no significant group effects (Palaniyappan et al., 2011). While both hyper- and hypo-gyria have been previously observed in several frontal (e.g., Palaniyappan et al., 2011; Sallet et al., 2003; Tepest et al., 2012) and temporal (e.g., Harris et al., 2004b; Sallet et al., 2003) regions of patients with a psychotic illness, evidence points towards hypergyria being more localised to anterior brain regions (e.g., Harris et al., 2004b; Palaniyappan et al., 2011). Our findings should be viewed with caution given that, in the LGI analysis only 6 FEP patients and 11 controls possessed 3 IOS; thus, despite statistically significant results, generalizability is limited. Nonetheless, abnormalities in the degree of gyrification may still be possible endophenotypic risk markers, especially considering altered gyrification indices have been

found in UHR individuals (Harris et al., 2004a; Jou et al., 2005). Further research is needed to determine the nature of region-specific abnormalities (hypo- vs. hyper-gyria) and whether hypergyria is dependent on the formation of additional new sulci (rather than the lengthening/deepening of existing sulci). In addition, future research should investigate the comparable degree of risk for psychosis that is contributed by OFC (and other regional) abnormalities, including measures of cortical thickness and gyrification, using a regression model.

4.5. Strengths and limitations

A strength of our study was that we took into consideration potential sex-specific effects on OFC sulcogyral folding. The only significant difference we found was in pattern type distribution in the left hemisphere of male and female patients, whereby males had fewer Type Is and more Type IIs than females, which is similar to previous research in schizophrenia (Uehara-Aoyama et al., 2011). It may be postulated that male patients are driving our pattern type results, particularly given our finding of a 5-fold estimated risk of psychosis for individuals with the Type II/Type II combination. However, sex influences are likely to be minimal, as the sex-difference was only found in the left hemisphere, and no significant group differences in pattern type distribution were observed when the whole sample was split and analysed by sex. One limitation of the current study, in addition to lack of sociodemographic data, is that some of the healthy control participants were recruited via staff who were employed at the hospital, which may be associated with unknown biases, such as higher socioeconomic status or parental education.

5. Conclusions

In conclusion, our findings suggest that having a Type II OFC folding pattern in the right hemisphere may increase the risk of psychosis during the adolescent-early adult years. Possession of the Type I pattern in the right hemisphere may be associated with protective mechanisms, however this putative effect may become compromised when cortical thinning occurs. These findings, in addition to reduced cortical thickness of OFC sulcal regions, and increased gyrification in relation to number of intermediate sulci in the left OFC, may reflect abnormal cortical development in utero and point toward a possible endophenotypic risk marker of schizophrenia-spectrum disorders. Future research should delineate the exact nature of folding pattern abnormalities in various mental illnesses where the OFC is implicated, as this may provide valuable insight into the possible differential neurodevelopmental pathways.

Acknowledgements

This work was supported by the Colonial Foundation and two National Health and Medical Research Council (NHMRC) of Australia Program Grants (566529, 350241). Dr C.F. Bartholomeusz and Dr S. L. Whittle are each supported by NHMRC fellowships (567042 and 1007716, respectively). Christos Pantelis was supported by a NHMRC Senior Principal Research Fellowship (ID: 628386), and a Brain and Behavior Research Foundation (NARSAD) Distinguished Investigator Award.

Conflict of Interest

The authors declare that they have no conflict of interest.

Contributors

Dr Bartholomeusz and Prof Wood conceived the study. Dr Bartholomeusz performed the orbitofrontal sulcogyral pattern classification, wrote the manuscript and was responsible for data analysis and interpretation of results. Dr Whittle was involved in the orbitofrontal cortex sulcogyral classification, data analysis and writing of the manuscript. Ms Montague and Mr Ansell were responsible for freesurfer processing and data management. Assoc Prof Velakoulis, Prof McGorry, Prof Pantelis and Prof Wood provided access to the data and contributed to the writing of the manuscript. Prof Wood was the supervisor of the study and was involved in the planning and interpretation of results. All authors have approved the final version of this manuscript.

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Table 1. Demographics

	FEP (<i>n</i> = 96)	Controls (<i>n</i> = 73)	<i>t</i> / χ^2	p value
Age (yrs)	21.29 $\pm$ 3.25	23.69 $\pm$ 5.42	3.34	.001**
Gender ratio (M/F)	71/25	48/25	1.34	.25
Height (cm)	173.62 $\pm$ 8.94	176.21 $\pm$ 8.85	1.88	.06
Handedness (R/L/mixed)	83/10/3	67/5/1	1.27	.53
Premorbid IQ (NART)	93.80 $\pm$ 14.01	102.04 $\pm$ 10.27	4.08	<.001**
Illness duration (days)	66.41 $\pm$ 106.88	-	-	-
PANSS: Total	84.57 $\pm$ 16.84	-	-	-
Positive	23.32 $\pm$ 6.30	-	-	-
Negative	20.29 $\pm$ 6.95	-	-	-
General	41.11 $\pm$ 8.12	-	-	-
Antipsychotic ^a : <i>N</i> on Typical	24	-	-	-
<i>N</i> on Atypical	66	-	-	-
<i>N</i> on nil	2	-	-	-
Chlorpromazine equiv. dose (mg)	228.99 $\pm$ 120.33	-	-	-

Note: ^aAntipsychotic data was unavailable for 4 participants. ** significant at $p \leq .001$.

Table 2. Distribution of OFC sulcogyral pattern

	FEP (n = 96)	Controls (n = 73)	Past Controls ^b	χ^2	p value
	% (n)	% (n)	% (n)		
Right Hemisphere ^a				8.53	.014*
Type I	44.8 (43)	63.0 (46)	64.0 (32)		
Type II	28.1 (27)	11.0 (8)	26.0 (13)		
Type III	27.1 (26)	26.0 (19)	10 (5)		
Left Hemisphere ^a				1.81	.405
Type I	47.9 (46)	57.5 (42)	48 (24)		
Type II	25.0 (24)	17.8 (13)	34 (17)		
Type III	27.1 (26)	24.7 (18)	18 (9)		

Note: ^aAnalyses displayed for the initial comparison between the current FEP and control groups,

^bChiavaras and Petrides' [17] pattern type distribution in healthy controls (n=50) has been included in the table for ease of comparison, *significant at p<.05.

Table 3. Occurrence of the number of intermediate and posterior orbital sulci

Number of sulci	IOS % (n)		POS % (n)			
	FEP (n=96)	Controls (n=73)	p value	FEP (n=96)	Controls (n=73)	p value
Right Hemisphere			.310			.332
0	0 (0)	1.4 (1)		49.0 (47)	56.6 (34)	
1	35.4 (34)	26 (19)		44.8 (43)	41.1 (30)	
2	54.2 (52)	53.4 (39)		6.3 (6)	9.6 (7)	
3	9.4 (9)	17.8 (13)		0 (0)	2.7 (2)	
4	1.0 (1)	1.4 (1)		-	-	
Left Hemisphere			.007*			.764
0	-	-		55.2 (53)	53.4 (39)	
1	35.4 (34)	20.5 (15)		38.5 (37)	42.5 (31)	
2	58.3 (56)	58.9 (43)		6.3 (6)	4.1 (3)	
3	6.3 (6)	20.5 (15)		-	-	

Note: FEP- first episode psychosis, IOS- intermediate orbital sulcus/sulci, POS- posterior orbital sulcus/sulci,

*significant at $p < .01$

Table 4. Means and standard deviations of cortical thickness for FEP patients and controls

	Left Hemisphere ^a			Right Hemisphere ^a		
	FEP <i>M</i> (SD)	Controls <i>M</i> (SD)	<i>p</i> value ^b	FEP <i>M</i> (SD)	Controls <i>M</i> (SD)	<i>p</i> value ^b
<i>Cortical Thickness</i>						
OFC Gyri:			.486			.227
Gyrus rectus	2.44 (.22)	2.43 (.23)		2.32 (.21)	2.29 (.24)	
Orbital gyrus	2.72 (.20)	2.69 (.21)		2.78 (.22)	2.73 (.21)	
OFC Sulci:			.028*			.018*
Orbital-medial-olfactory sulcus	2.16 (.34)	2.22 (.30)		2.10 (.29)	2.10 (.28)	
Orbital H-shaped sulcus	2.75 (.21)	2.81 (.23)		2.79 (.23)	2.86 (.26)	
Orbital lateral sulcus	2.41 (.31)	2.50 (.30)		2.53 (.29)	2.62 (.28)	

Note: ^aFEP N=91, controls N=71, ^bvalue displayed for main effect of group from the initial ANCOVA (without OFC type as a factor), **p* significant at <.05.

Table 5. Means and standard deviations for local gyrification indices for FEP patients and controls

	Left Hemisphere ^a			Right Hemisphere ^b		
	FEP <i>M</i> (SD)	Controls <i>M</i> (SD)	p value ^c	FEP <i>M</i> (SD)	Controls <i>M</i> (SD)	p value ^c
<i>Local Gyrification Index</i>						
Mean across total hemisphere	3.06 (.25)	3.02 (.29)	.360	3.04 (.13)	3.01 (.16)	.445
OFC region:			.382			.608
Gyrus rectus	2.00 (.13)	2.00 (.12)		2.06 (.09)	2.07 (.10)	
OFC H-shape	2.65 (.19)	2.65 (.19)		2.57 (.14)	2.55 (.15)	

Note: ^afor the left hemisphere FEP N=78, controls N=61, ^bfor the right hemisphere FEP N=76 controls=60, ^cvalue displayed for main effect of group from the initial ANCOVA.

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).

Fig. 2. Distribution of the three OFC pattern types. Type I pattern was significantly less common ($p < .05$) while Type II was significantly more prevalent ($p < .01$) in the right hemisphere of FEP patients when compared to controls.

Fig. 3. Example of a healthy control individual who possesses 3 intermediate orbital sulci (IOS) in the left hemisphere. These IOS are highlighted in green, blue and orange. Slices are 1mm and displayed in the transverse plane.

Fig. 4. Cortical thickness of sulcal regions in the left OFC. A significant interaction ($p < .01$) was found between OFC pattern type and group for cortical thickness of sulcal regions. Means displayed here are the summed means of the three sulcal regions. *A significant difference (adjusted $p < .01$) was observed between patients and controls who possessed a Type I pattern in the left hemisphere.

Fig. 5. Mean local gyrification index for the left OFC H-shape region. A significant interaction ($p < .05$) was found between number of IOS and group. *A significantly higher index was observed in patients compared to controls who possessed 3 IOS (adjusted $p < .05$).

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Highlights

- Orbitofrontal sulcogyral folding pattern distributions are altered in psychosis
- Type II pattern in both hemispheres led to a five-fold risk of psychosis
- Psychosis patients have fewer intermediate orbital sulci
- Orbitofrontal sulci thickness was reduced in patients and related to pattern Type I
- Patients with three intermediate orbital sulci had a higher mean gyrification index

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Title:

Sulcogyral patterns and morphological abnormalities of the orbitofrontal cortex in psychosis

Date:

2013-07-01

Citation:

Bartholomeusz, C. F., Whittle, S. L., Montague, A., Ansell, B., McGorry, P. D., Velakoulis, D., Pantelis, C. & Wood, S. J. (2013). Sulcogyral patterns and morphological abnormalities of the orbitofrontal cortex in psychosis. *PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY*, 44, pp.168-177. <https://doi.org/10.1016/j.pnpbp.2013.02.010>.

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