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Short Communication

Prefrontal gyrification in psychotic bipolar I disorder vs. schizophrenia

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ABSTRACT

Bipolar disorder and schizophrenia share phenotypic and genotypic features, but might differ in aspects of abnormal neurodevelopmental trajectories. We studied gyrification, a marker of early developmental pathology, in high-resolution MRI scans of 34 patients with schizophrenia, 17 euthymic bipolar I disorder patients with previous psychotic symptoms, and 34 matched healthy controls in order to test the hypothesis of overlapping and diverging prefrontal gyrification abnormalities. We applied a novel, validated method for measuring local gyrification in each vertex point of the reconstructed cortical surface. Psychotic bipolar I patients had higher gyrification in dorsal anterior and infragenual cingulate cortex compared to either schizophrenia or healthy controls, while schizophrenia patients had higher gyrification than controls in anterior medial (BA 10) and orbitofrontal areas, altogether indicating disease-specific alterations in the prefrontal cortex. Our findings indicate gyrification changes in a specific subgroup of bipolar I disorder to affect an area relevant to emotion regulation, and distinct from changes seen in schizophrenia.

1. Introduction

Bipolar disorder with psychotic features and schizophrenia share common clinical features, and identification of shared risk genes has spurred research into exploring common and distinguishing biological markers (Thaker, 2008). Brain structure is one of several putative endophenotypes affected in both disorders, and is influenced both by genetic and environmental factors (Ivleva et al., 2013; Mathew et al., 2014). An influential theory has posited neurodevelopmental differences to be at the core of biological differences between the two disorders (Demjaha et al., 2012).

More recent structural neuroimaging studies have suggested anatomical overlap of pathologies, particularly for bipolar-I-disorder subgroup (Rimol et al., 2010). Bipolar I disorder patients with psychotic features are of particular interest, as they share clinical features like psychotic symptoms, deteriorating disease course, poor outcomes, and enduring affective or cognitive impairment. However, most brain morphometric parameters are prone to state-dependent effects, medication and other factors. In contrast, gyrification reflects a more stable indicator of cortical pathology indicating early pre-/perinatal or childhood developmental disturbances (Zilles et al., 2013). Gyrification has been shown to be increased in schizophrenia (McIntosh et al., 2009; Vogeley et al., 2000), including first-episode cohorts (Harris et al., 2004b), as well as high-risk subjects with subsequent conversion to psychosis (Harris et al., 2004a). One initial study comparing gyrification in schizophrenia and bipolar disorder patients vs. healthy controls found reduced prefrontal gyrification in dorsal and ventral areas (McIntosh et al., 2009), while a more recent study in adolescent patients found schizophrenia and bipolar patients to overlap in prefrontal lobar gyrification changes, but those in schizophrenia extending to other lobes as well (Janssen et al., 2014). The techniques in both studies, however, lack resolution for identifying subregions within the prefrontal cortex, which might show relative specificity for the two diagnostic categories. A more recent study across the spectrum of psychotic disorders, which also included non-psychotic relatives of patients, has furthermore suggested the cingulate cortex to show highest heritability for effects of gyrification (Nanda et al., 2014).

In this study, we compared a narrowly defined group of bipolar-I-disorder (BP) patients with a history of psychotic symptoms vs. schizophrenia patients and controls using a morphometric method to calculate local gyrification in 3D across the cortex. We tested the

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hypothesis, that bipolar patients would show different localization of prefrontal gyrification changes, esp. in medial PFC.

2. Methods

We studied a total of 85 subjects, including 34 patients with DSM-IV schizophrenia (Sz), 17 euthymic bipolar I disorder patients (BP) and 34 healthy controls (HC), all of whom provided written informed consent to study protocols approved by the Ethics Committee of the Medical School of the Friedrich-Schiller-University of Jena, Germany, and compliant with the guidelines set forth in the Declaration of Helsinki. All subjects had capacity to consent, and none of them was undergoing compulsory treatment at the time of study. We have previously described this sample in an analysis using voxel-based morphometry (Nenadic et al., 2015). Patients were all recruited from in-patient and out-patient services of Jena University Hospital and assessed by a board-certified psychiatrist (I.N.). General assessment of all subjects included handedness (Edinburgh Handedness Scale) and IQ estimate (using the MWT-B, a standard German test for pre-morbid IQ assessment (Lehrl, 2005)). None of the subjects had an estimated IQ smaller than 80. Groups did not differ for age (ANOVA; $p=0.294$), gender (Chi^2-Test; $p=0.724$), handedness using the laterality quotient derived from the Edinburgh Handedness Inventory EHI (ANOVA; $p=0.172$), and their estimated (pre-morbid) IQ derived from the German MWT-B scores also did not differ significantly (ANOVA; $p=0.5$) (Table 1).

Patients met diagnosis of either DSM-IV schizophrenia or DSM-IV bipolar I disorder, respectively, established through either SCID-I interview questions with the patient, or (in cases were this was not possible) by chart review. Patients with bipolar I disorder were euthymic at time of scanning, which was defined by: (a) absence of depressive, (hypo)manic, or mixed affective episode (according to DSM-IV criteria), and (b) maximum scores of 7 on the Young Mania Rating Scale (YMRS) and Hamilton Depression Scale (HAMD; 21-item version). In addition, all of the bipolar disorder patients had an established history of psychotic symptoms during previous disease episodes. Psychopathology of schizophrenia patients was assessed using the Scale of Assessment of Positive Symptoms (SAPS), and Scale of Assessment of Negative Symptoms (SANS), which reflected mostly negative and some (residual) positive symptoms. All schizophrenia patients had disease duration of more than 2 years (thus also meeting DSM-IIIR criteria for chronic schizophrenia) and were scanned while in remission.

Most patients were on stable medication. In the bipolar group, $n=5$ were on lithium (monotherapy), $n=4$ on lithium plus a second-generation antipsychotic, $n=6$ on one or two antipsychotics, $n=1$ on valproic acid, and $n=1$ on pregabalin. In the schizophrenia group, $n=4$ were off antipsychotic medication, while the other $n=30$ patients were on one or two second-generation antipsychotic (including aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone), including augmentation therapy with lithium ($n=1$) or an antidepressant ($n=3$).

High-resolution magnetic resonance imaging (MRI) scans were obtained on a 3 Tesla scanner (Siemens Tim Trio, Erlangen, Germany) using an MPRAGE sequence (TR 2300 ms; TE 3.03 ms; alpha 9°; resolution: $1\times1\times1\,mm^3$; 192 sagittal slices; in-plane matrix 256×256), visually inspected for artefacts, and image quality was additionally checked using functions implemented in the VBM toolbox (http://dbm.neuro.uni-jena.de/vbm/check-sample-homogeneity).

Gyrification was calculated using the absolute mean curvature approach (Luders et al., 2006). In this approach, which has been applied in previous studies (Gaser et al., 2006; Luders et al., 2012), the mean curvature is calculated at each vertex of the triangulated mesh network that forms the central surface; the method is robust to induced changes during the normalization process in the preprocessing pipeline.

The cortical surface was extracted using Freesurfer software (http://surfer.nmr.mgh.harvard.edu/). This allows for reconstruction of topologically corrected pial and white matter surfaces which are in the form of triangulated meshes. This also preserves the information regarding the curvature of the extracted surface at each of the vertices of the triangulated mesh (Dale et al., 1999; Fischl et al., 1999). Central surfaces were estimated by averaging the pial and white matter surfaces for each subject. Absolute mean curvature was derived using in-house software (Luders et al., 2006).

Statistical comparison using Statistical Parametric Mapping 8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) was computed using a one way ANCOVA with group (HC, BP, Sz) as the independent variable, local cortical gyrification as the dependent variable and age and gender as nuisance variables. In order to test our specific anatomical hypothesis derived from the literature (increased right PFC gyrification and potential Sz/BP overlap in the ventral PFC (McIntosh et al., 2009; Vogeley et al., 2000), as well as cingulate cortex (Nanda et al., 2014)), we chose a statistical threshold of $p<0.001$ (uncorrected) for the prefrontal areas of interest (i.e. mid/lower dorsolateral prefrontal cortex, anterior cingulate cortices and adjacent medial PFC, i.e. BA 24, 25, 32); results at this threshold for the other remaining cortical areas were thus carried out by means of an exploratory analysis.

Table 1
Demographic details of the study cohorts.

	HC (healthy controls)	**BP-I** (bipolar I disorder w/psychotic symptoms)	**SZ** (schizophrenia)
n	34	17	34
Gender distribution (female/male)	16/18	8/9	13/21
Age (mean and SD)	34.33 (10.62)	37.69 (11.13)	32.97 (8.91)
Age range	20.77–55.49 yrs	23.84–57.77 yrs	21.39–51.43 yrs
Duration of illness: mean (SD)	n/a	9.9 (8.7)	8.9 (5.9)
Age of illness onset (SD)	n/a	27.5 (7.9)	23.9 (5.8)
YMRS score: mean (SD) and range	n/a	2.7 (2.2) 0–7	n/a
HAMD score: mean (SD) and range	n/a	2.7 (2.3) 0–7	n/a
SAPS score: mean (SD) and range	n/a	n/a	20.9 (11.3) 5–42
SANS score: mean (SD) and range	n/a	n/a	44.1 (15.3) 11–74
BPRS score: mean (SD) and range	n/a	n/a	39.1 (7.1) 23–54

3. Results

Patients with psychotic bipolar-I-disorder (BP) had increased local gyrification (compared to healthy controls) in the right anterior infragenual cingulate cortex (BA 24/25) and left dorsolateral prefrontal (BA 9) in BP (see Fig. 1). Comparing schizophrenia and healthy control groups, we found increased gyrification in Sz in the right anterior medial prefrontal cortex (Brodmann area (BA) 10) and orbitofrontal cortex. Direct Sz vs. BP comparison confirmed higher right anterior infragenual cingulate gyrification in BP compared to schizophrenia.

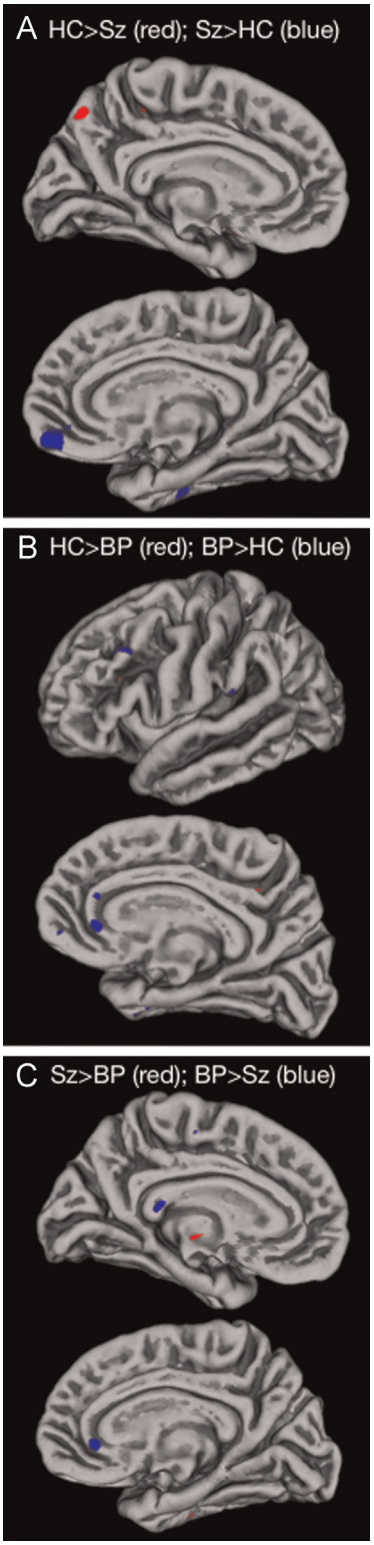

Fig. 1. Cortical surface renderings of differences in local cortical gyrification (vertex-wise analysis, $p < 0.001$, uncorr. for hypothesis-based analysis) for schizophrenia (Sz) vs. healthy controls (HC), euthymic bipolar-I-disorder with previous psychotic features (BP) vs. HC, and direct Sz vs. BP contrasts (red indicating increased and blue decreased gyrification). Hemisphere views with no findings are not displayed. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

While psychotic bipolar disorder and schizophrenia show phenotypic and genotypic overlap, there is little direct comparison for many putative intermediate phenotypes or biomarkers, although such markers are important in elucidating diagnostic boundaries based on biological data. Our results demonstrate that, while both psychotic bipolar-I-disorder and schizophrenia show altered prefrontal gyrification, the anatomical location differs markedly and affect different anatomical systems.

The anterior peri-/infragenual cingulate area showing hypergyrification in psychotic bipolar I disorder is located in the hub of an affective network, integrating and regulating amygdala inputs, and subserving mood regulation (Dumontheil et al., 2008; Etkin et al., 2011). A parsimonious interpretation of the regional pattern would suggest that regional differences in disturbed neurodevelopmental trajectories reflect different genetic or non-genetic early developmental effects, which manifest in different adult neuroanatomy and thus different symptom profiles. Changes in subgenual anterior cingulate cortices might manifest in a predominantly affective phenotype, which also impacts on cognitive function (Wessa and Linke, 2009) and emotion regulation (Lim et al., 2013), while multiple changes across other regions result in negative symptoms and cognitive deficits seen in schizophrenia.

The medial prefrontal and orbitofrontal areas observed to be altered in schizophrenia are located in regions that have been linked to cognitive, psychotic, and negative symptom profiles in previous structural imaging studies (Der-Avakian and Markou, 2012; Goghari et al., 2010; Nenadic et al., 2012). The medial/anterior prefrontal cluster in BA 10 is located in an area subserving various higher cognitive functions, including stimulus-oriented attending and executive tasks, which has been reported to show late maturation well into adolescence and being linked to schizophrenia and other neurodevelopmental disorders (Dumontheil et al., 2008). Similarly, the orbitofrontal cortex in schizophrenia had been implicated in other morphometric studies, especially related to negative symptom dimensions (Nenadic et al., 2010).

Comparing our study with the mentioned previous studies of gyrification, there are some considerable methodological difference. Unlike two previous studies mentioned (Janssen et al., 2014; McIntosh et al., 2009), we used a method to measure gyrification in each vertex, and analysed on a vertex-level and not across an entire lobe. Also, the clinical populations differed, as we have restricted our bipolar disorder sample to a subgroup of (currently euthymic) bipolar I disorder with previous psychotic features, which differs from approaches including bipolar patients irrespectively of subtype. Interestingly, we did not find cingulate cortex changes in gyrification, which featured prominently in a very recent large study of psychosis spectrum patients and their first-degree relatives (Nanda et al., 2014). While using a considerably larger sample than our study, Nanda et al. did not differentiate bipolar disorder subgroups. Therefore, it remains an unresolved issue whether psychotic features, which were inherent in our sample, but not all of the mentioned studies, represent a phenotypic core feature related to the observed prefrontal gyrification changes.

Gyrification is thought to be a relatively stable marker, which is less susceptible to longitudinal changes or confounding factors such as medication. However, several methodological aspects and limitations need consideration when interpreting these results. Different studies have used diverging methods for assessing gyrification, and might thus give different results. Most previous studies on gyrification in schizophrenia have relied on either 2-dimensional methods or techniques that measure gyrification across the whole lobe or part thereof (Harris et al., 2004b; McIntosh et al., 2009). Regional or lobar analysis has now been increasingly superseded by studies of local gyrification, which assesses gyrification in each vertex of a surface-based analyses. But even among the latter methods, different approaches exist, and

the local gyrification index (LGI) implemented in FreeSurfer differs from our curvature-based approach (Luders et al., 2006). This might also affect direction of changes and interpretation with post mortem data. Both of the latter techniques, however, are assumed to tap an inherent geometric feature of the cortex, which forms during early development.

Another methodological restraint of both previous and our own study, is therefore that volatile variables such as concurrent clinical symptoms might not be suitable for correlation with a marker that putatively relates to early neurodevelopment. However, certain clinical features, such as type of psychotic symptoms across the life-span might be viable approaches to relate gyrification to phenotype aspects. Given that all of the patients in our study have experienced psychotic symptoms at some stage of their illness, the detected patterns are unlikely to reflect psychotic features per se, which are overlapping. Rather, the divergence in patterns might relate to the different developmental trajectories towards affective disorder or schizophrenia, respectively.

Limitations of our study include sample size and the restriction of hypothesis-led analysis to prefrontal areas. IQ, which seems to be correlated to gyrification (McIntosh et al., 2009), was not different in our cohorts, making bias unlikely. Given the temporal stability of gyrification, medication and other state-dependent measures are also rather unlikely to have influenced our results. However, since most patients were medicated and the literature lacks clear longitudinal studies of medication effects on gyrification, we cannot exclude medication as a confounding factor.

Taken together, the use of a 3D gyrification measure allows us to differentiate brain areas within the prefrontal cortex that are differentially affected in schizophrenia and psychotic bipolar disorder and might reflect the impact of genetic risk factors on development within different brain anatomical systems.

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Nothing declared.

Conflict of interest

The authors declare that they have no relevant conflicts of interest to declare.

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