Cortical complexity in bipolar disorder applying a spherical harmonics approach

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A B S T R A C T
Recent studies using surface-based morphometry of structural magnetic resonance imaging data have suggested that some changes in bipolar disorder (BP) might be neurodevelopmental in origin. We applied a novel analysis of cortical complexity based on fractal dimensions in high-resolution structural MRI scans of 18 bipolar disorder patients and 26 healthy controls. Our region-of-interest based analysis revealed increases in fractal dimensions (in patients relative to controls) in left lateral orbitofrontal cortex and right precuneus, and decreases in right caudal middle frontal, entorhinal cortex, and right pars orbitalis, and left fusiform and posterior cingulate cortices. While our analysis is preliminary, it suggests that early neurodevelopmental pathologies might contribute to bipolar disorder, possibly through genetic mechanisms.

1. Introduction
Neurobiological models of bipolar disorder (BP) assume regional alteration in structure and function of limbic and prefrontal areas, including orbitofrontal, ventrolateral and medial prefrontal cortices (Phillips and Swartz, 2014; Price and Drevets, 2012; Wessa et al., 2014). Structural magnetic resonance imaging (MRI) studies using mostly voxel-based morphometry (VBM) have found grey matter deficits in multiple areas, including the ventral / ventromedial (and possibly also dorsomedial) prefrontal cortex, the anterior cingulate cortex, insular cortex and possibly also the hippocampus (Otten and Meeter, 2015; Selvaraj et al., 2012; Wise et al., 2016). Also, cortical thickness in some of these areas, such as the anterior cingulate cortex, superior temporal cortex, and some prefrontal areas (Brodman areas 6, 8, 9, and 10 in most of the studies, and 46 in some), is reduced in bipolar disorder patients compared to healthy controls (Hanford et al., 2016a). In addition, research on subjects at genetic high risk for bipolar disorder has suggested some of these changes, e.g. in the anterior cingulate cortex, insular, and orbitofrontal cortex, are present in first-degree relatives, reflecting the genetic vulnerability to bipolar disorder (Nery et al., 2013). While another study suggested right superior frontal cortical thinning in psychiatrically symptomatic offspring of bipolar disorder patients compared to either unaffected offspring or healthy control offspring (Hanford et al., 2016b), a most recent study did not find such differences in offspring of patients with bipolar disorder, compared to either offspring of patients with schizophrenia or community controls (Sugranyes et al., 2017). However, besides some well-documented trans-diagnostic differences (Hartberg et al., 2011; Redlich et al., 2014), there is also considerable overlap of brain structural changes seen in bipolar disorder compared to unipolar depression (Wise et al., 2016), to schizophrenia (Maggioni et al., 2016), and other psychiatric disorders (Goodkind et al., 2015), pointing to the problem of specificity of findings.

VBM and cortical thickness, while widely used, to do not differentiate timing of structural changes. Rather, they might reflect the sum of multiple effects, including genetic liability, expression of disease phenotype, co-morbidities etc. More recently developed morphometry techniques for the analysis of structural magnetic resonance imaging (MRI) scans have been put forward to tap more specifically early developmental effects on brain structure. Most of the techniques, such as analysis of cortical folding or gyriﬁcation are surface-based morphometry methods, and in part based on the observation that morphometric features like gyriﬁcation tend to develop until early childhood and then stay stable of much of the life-span (Armstrong et al., 2015).
et al., 1995; Zilles et al., 1988). In bipolar disorder, they have shown changes of the cortical folding patterns in prefrontal areas of the anterior/subgenual cingulate cortex (Nenadic et al., 2015), but results have not been consistent (Liao et al., 2008). One older study using a global fractal dimension (FD) approach found increased in the overall grey-white-matter surface (Bullmore et al., 1994), but no studies have assessed novel FD-based measures in 3D, such as applied in other disorders (Nenadic et al., 2014).

In the present study, we used a novel approach for analysis of cortical complexity to test the hypothesis that altered fractal dimension measures can be detected in bipolar disorder, possibly reflecting disturbances in early cortical development especially in those areas implicated by earlier imaging studies.

2. Methods

We analysed high-resolution MRI data from 18 euthymic patients (11 female, 7 male) with DSM-IV bipolar disorder (BP) and 26 healthy controls (HC; 11 female, 15 male), all of which provided written informed consent to a study protocol approved by the Ethics Committee of the Medical School of Friedrich-Schiller-University Jena and in accordance with the Declaration of Helsinki. BP patients were mostly recruited from in-patient and out-patient services of the Department of Psychiatry and Psychotherapy, Jena University Hospital. Cohorts did not differ with regards to age (BP mean age 40.1yrs, SD 10.2; HC mean age 35.6yrs, SD 10.4; ANOVA: disorders (Nenadic et al., 2014).

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4. Discussion

Using a novel spherical-harmonics based approach, we found preliminary evidence for altered cortical complexity in bipolar disorder. In particular, several frontal (left orbitofrontal and right caudal middle frontal) as well as medial temporal (left entorhinal) showed changes, mostly with reduced cortical complexity. Only the right precuneus and left lateral orbitofrontal ROI showed higher cortical complexity in patients. Our findings provide two novel aspects.

First, brain structural alterations in bipolar disorder seem to reflect (at least in part) some neurodevelopmental antecedents. Cortical complexity, similar to gyrification, is an inherent morphometric feature that is more temporally stable than volume or VBM-derived measures of grey matter (Yotter et al., 2011). Previous studies have interpreted changes as indicators of an early neurodevelopmental deficit (Nenadic et al., 2014), possibly arising during intra-uterine or early post-natal brain development. This interpretation is based, in part, on anatomical and embryological studies showing that classical gyrification index rises during intra-uterine brain development, shows another spike in early development (within the first years of life), but then stays stable over much of the life span (Armstrong et al., 1995; Zilles et al., 1988). This is consistent with the notion that many of these surface-based measures, as studied in primates, show considerable heritability, thus pointing to genetic influence on brain development at these stages (Kochunov et al., 2010). However, at least one recent study in humans also suggests changes from adolescence to adulthood (Sandu et al., 2014). FD measures might reflect changes occurring due to differential cortical growth, mostly in early post-natal development, but possibly modified during later brain development (Xu et al., 2010). Unfortunately, methodological differences preclude a direct comparison of our findings to a previous older study in BP (Bullmore et al., 1994), and a recent cortical complexity study addressing gyrification (Liao et al., 2008).

Second, several of the area showing altered complexity are part of established abnormal networks in BP (Phillips and Swartz, 2014), in particular the right hemisphere changes in prefrontal (pars orbitalis / inferior frontal gyrus, caudal middle frontal) and right medial temporal (entorhinal) areas. Some of these fronto-limbic areas are among the best discriminators for BP in machine-learning studies of MRI (Mwangi et al., 2016). Our finding for altered complexity leads us to hypothesise that structural changes in BP occur not only at different stages in time, but far earlier than previously assumed. Recent studies, for example, suggest altered right inferior frontal volume to reflect predisposition to BP (as shown in healthy relatives); yet, regional brain volume in BP changes over the course of illness and improves with treatment (Hajek et al., 2013; Saricicek et al., 2015). Hence, different measures of brain structure, including VBM, cortical thickness, gyrification, and FD-derived cortical complexity might better characterise such changes in BP, which might aid establishing risk profiles and differentiate structural changes related to genetic, illness-related, and treatment-related effects.

Our study is limited mainly through its sample size, which has not allowed us to test whether FD changes are related to subgroups of BP. Further replication and extension of these findings is warranted to characterise putative heterochronicity of brain structural changes in bipolar disorder.

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References


