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Cortical complexity in bipolar disorder applying a spherical harmonics approach

Igor Nenadic[a,d,*], Rachel A. Yotter[a,b], Maren Dietzek[a], Kerstin Langbein[a], Heinrich Sauer[a], Christian Gaser[a,c]

[a] Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany
[b] Section of Biomedical Image Analysis, University of Pennsylvania, Philadelphia, USA
[c] Department of Neurology, Jena University Hospital, Jena, Germany
[d] Department of Psychiatry and Psychotherapy, Philipps University Marburg & Marburg University Hospital/UKGM, Marburg, Germany

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ABSTRACT

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 (Brodmann 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

* Correspondence to: Department of Psychiatry and Psychotherapy, Philipps University Marburg & Marburg University Hospital/UKGM, Rudolf-Bultmann-Str. 8, 35037 Marburg, Germany.
E-mail address: nenadic@staff.uni-marburg.de (I. Nenadic).

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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: $F_{(1,42)}$=1.991, p=0.166) or gender (Chi-square 1.504, p=0.220; Fisher's exact test, two-tailed 0.358), estimated premorbid IQ (MWT-B; BP mean 112.6, SD 12.2; HC (n=25, for one HC data were missing) mean 109.5, SD 10.8; ANOVA $F_{(1,41)}$=0.742; p=0.394), or handedness (laterality quotient based on EHI; BP mean 73.1, SD 48.1; HC (n=25) mean 77.4, SD 26.5; ANOVA $F_{(1,41)}$=0.145; p=0.706). All patients met DSM-IV-R criteria, as diagnosed by a board-certified psychiatrist (I.N.), and as confirmed through chart review they also met DSM-5 criteria. Most patients had BP I disorder (n=15; of those n=14 with previous psychotic features) and n=3 had BP II. At the time of scanning, patients were euthymic, as defined through the absence of an affective episode (depressive, hypomanic, manic, or mixed affective episode), as well as Young Mania Rating Scale (YMRS) scores of 7 or below (range 0–7; mean 3.33, SD 2.57) and Hamilton Depression scale (HAMD) of max. of 7 (range 0–7; mean 2.67, SD 2). None of the patients had psychotic symptoms at the time, and only two had a previous history of (but not concurrent) alcohol abuse. Patients were on stable medication with either lithium (n=10), a mood-stabilising antipsychotic such as quetiapine (n=5) or olanzapine (n=2), as mono-therapy or in combination (quetiapine with aripiprazol: n=1), n=2 received additional valproate, n=1 patient was on gabapentin, and n=1 was off psychotropic medication. None of the study participants had (another) psychiatric condition (other than those described for the bipolar group), a neurological or major / poorly controlled general medical condition, a history of traumatic brain injury, or intellectual disability (defined as a pre-morbid IQ < 80). In addition, healthy controls had no history of first-degree psychotic or affective disorders, and had never sought psychotherapeutic treatment.

We obtained high-resolution T1-weighted structural MRI scans on a 3 T Siemens Tim Trio scanner (Siemens Healthcare, Erlangen, Germany) using a MPRAGE sequence (TR 2300 ms, TE 3.03 ms, a=9°, 192 contiguous sagittal slices, field-of-view 256 mm, resolution 1x1×1 mm^3). All subjects passed visual inspection and a quality assurance protocol for both acquisition and automated extraction of the cortical surface. For extraction of the cortical surface, we applied FreeSurfer routines (Fischl, 2012), and then used our previously described method for calculating local cortical complexity based on FD (Nenadic et al., 2014; Yotter et al., 2011). We averaged cortical complexity measures across Desikan atlas regions (Desikan et al., 2006).

Table 1
Regional fractal dimension (FD) measures across in bipolar disorder (BD) and healthy controls (HC).

	Left hemisphere		Right hemisphere	
	HC	BP	HC	BP
Bank superior temporal sulcus	2.8335	2.9050	2.8072	2.9203
Caudal anterior cingulate	2.3733	2.0563	2.4129	2.0705
Caudal middle frontal	2.7699	2.7032	2.7506	2.6276*
Corpus callosum	2.2328	2.5047	2.2349	2.5019
Cuneus	2.6122	2.7675	2.6608	2.7757
Entorhinal	2.7207	2.4307	2.6648	2.3563*
Fusiform	2.5548	2.4726*	2.4828	2.4776
Inferior parietal	2.6885	2.6533	2.7102	2.6650
Inferior temporal	2.4445	2.5631	2.4037	2.5664
Isthmus cingulate	2.1681	2.7454	2.1675	2.7276
Lateral occipital	2.4951	2.5231	2.4842	2.5388
Lateral orbitofrontal	2.3378	2.3826*	2.2983	2.3494
Lingual	2.6823	2.6523	2.6712	2.6547
Medial orbitofrontal	2.4562	2.4409	2.4562	2.4327
Middle temporal	2.6764	2.9293	2.6441	2.9349
Parahippocampal	2.9537	2.6106	2.8662	2.5579
Para central	2.5731	2.9344	2.5508	2.8721
Pars opercularis	2.7883	2.2232	2.7298	2.2384
Pars orbitalis	2.8977	2.2938	2.9334	2.2279*
Pars triangularis	2.8130	2.6108	2.8313	2.5714
Pericalcarine	2.7744	2.8554	2.7614	2.7884
Postcentral	2.7669	2.5348	2.7620	2.5480
Posterior cingulate	2.5371	2.4559*	2.4873	2.4356
Precentral	2.7624	2.6129	2.7730	2.6041
Precuneus	2.5947	2.7671	2.5821	2.6942*
Rostral anterior cingulate	2.1618	2.3734	2.1874	2.3783
Rostral middle frontal	2.5621	2.5625	2.5374	2.5712
Superior frontal	2.4055	2.7758	2.4164	2.7660
Superior parietal	2.6762	2.7256	2.6571	2.6988
Superior temporal	2.8462	2.4500	2.8299	2.4443
Supramarginal	2.5848	2.4840	2.5991	2.4618
Frontal pole	2.8112	3.2251	2.7916	3.2985
Temporal pole	2.6860	2.4818	2.6938	2.4670
Transverse temporal	2.6369	1.9541	2.5925	1.9446

* $p < 0.05$

For statistical assessment, we tested our main hypothesis by applying a general linear model across all ROIs at a threshold of $p < 0.05$ (uncorrected), bearing in mind our regional hypothesis for prefrontal ROIs. In addition, we performed an exploratory vertex-wise analysis to provide a spatially refined overview of results ($p < 0.05$, uncorr.). Finally, we also computed overall fractal dimension across each of the two hemispheres to test for a global effect.

3. Results

Region-of-interest analysis showed increased cortical complexity in bipolar patients compared to healthy controls (as indicated by our fractal dimension measure) in left lateral orbitofrontal cortex and right precuneus, and decreases in FD in the right caudal middle frontal, right entorhinal cortex, right pars orbitalis, and in the left hemisphere FD reductions in the fusiform cortex, and posterior cingulate cortex regions of interest. While bipolar disorder patients also showed reduction of cortical complexity in bilateral caudal anterior cingulate ROIs, these differences did not reach significance. An overview of the results for each ROI is given in Table 1.

Vertex-wise analysis of cortical complexity confirmed a wide-spread pattern of group differences in medial temporal and rostral / lateral prefrontal areas (see Fig. 1 for spatial distribution of findings).

There was no group difference for global cortical complexity in either left hemisphere (BP mean 2.5895, SD 0.0018; HC mean 2.6017, SD 0.0010; T-Test, p=0.163) nor right hemisphere (BP mean 2.5986, SD 0.0015; HC mean 2.6058, SD 0.0008; T-Test, p=0.335).

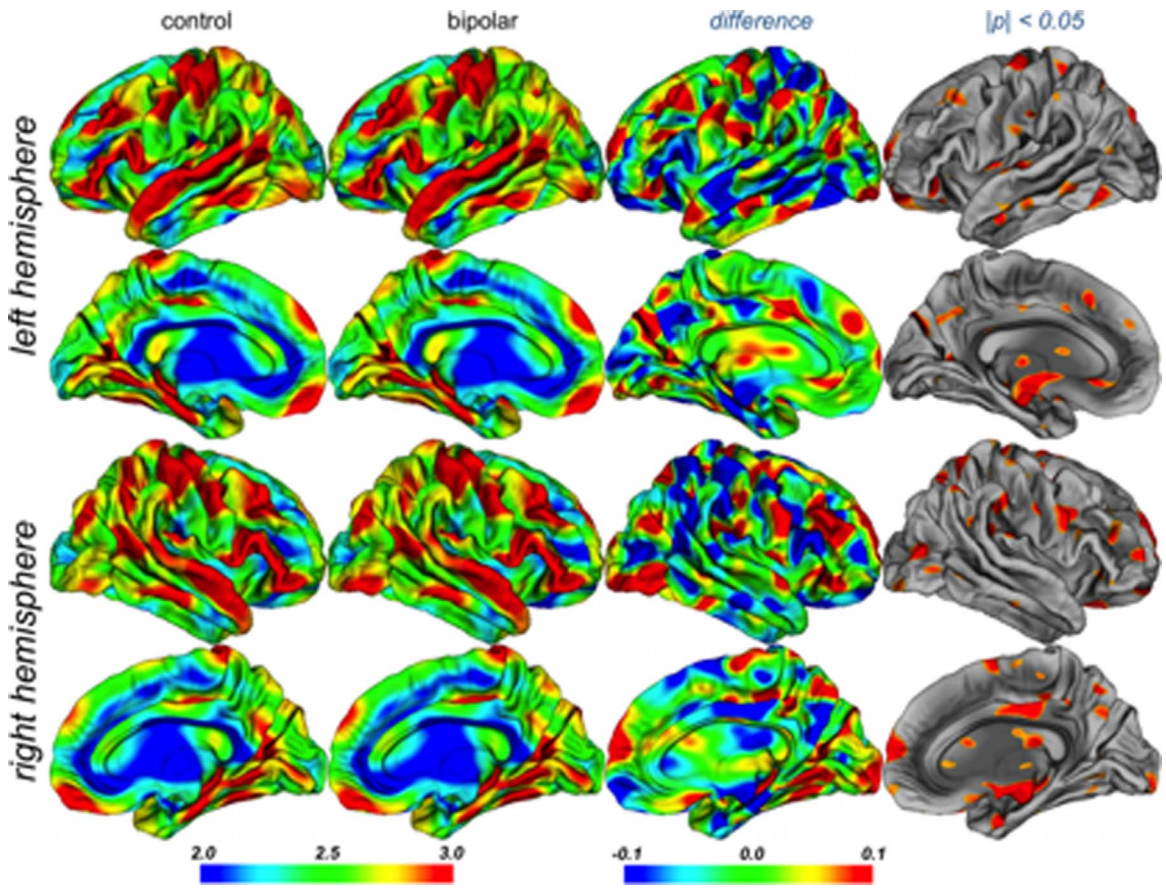

Fig. 1. Vertex-wise analysis of cortical complexity based of fractal dimensions (FD) in patients with bipolar disorder vs. healthy controls: columns (from left to right) depict vertex-wise values for healthy controls, bipolar patients, the difference map, and statistical differences between groups.

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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