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Cortical thinning in bipolar disorder and schizophrenia

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ABSTRACT

Although schizophrenia (SZ) and bipolar disorder (BD) share some clinical features such as psychotic symptoms and cognitive dysfunctions, little is known about possible pathophysiological similarities between both diseases. Therefore, we investigated the potential topographical overlap and segregation of cortical thickness abnormalities in SZ and BD patients.

We analyzed 3D-anatomical magnetic resonance imaging datasets with the FreeSurfer 5.1.0 software to examine cortical thickness and volumes in three groups of participants: $n = 34$ BD patients, $n = 32$ SZ patients and $n = 38$ healthy controls.

We observed similar bilateral cortical thickness reductions in BD and SZ patients predominantly in the pars opercularis of the inferior frontal gyrus and in the anterior and posterior cingulate. We also found disease-specific cortical reductions in the orbitofrontal cortex for BD patients and in dorsal frontal and temporal areas for SZ. Furthermore, inferior frontal gyrus cortical thinning was associated with deficits in psychomotor speed and executive functioning in SZ patients and with age at onset in both groups.

Our findings support the hypothesis that thinning of the frontal cortex may represent a biological feature shared by both disease groups. The associations between cognitive deficits and the reported findings in SZ and to a lesser degree in BD patients add to the functional relevance of our results. However, further studies are needed to corroborate a model of shared pathophysiological disease features across BD and SZ.

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1. Introduction

A major goal of recent structural imaging studies in schizophrenia (SZ) and bipolar disorder (BD) patients has been to detect potential overlap in structural and functional imaging markers. According to some studies, both diseases share frontal and subcortical abnormalities, which supports the spectrum-hypothesis of psychotic disorders (Ellison-Wright and Bullmore, 2010). However, other studies suggest that gray matter (GM) density reductions are unique to SZ (see i.e. Hirayasu et al., 2001) and support Kraepelin's dichotomy concept (Kraepelin, 1919). Only few researchers compared cortical thickness between SZ and BD patients directly (Hulshoff et al., 2012; Rimol et al., 2012). Those who did proposed a similarity in cortical thinning mainly in frontal regions (Rimol et al., 2012). Rimol and colleagues suggested that SZ patients are affected more severely than BD patients, showing

more widespread temporal, occipital and parietal volume reductions and a decrease in cortical thickness (Rimol et al., 2012). Hulshoff and colleagues compared shared and segregated brain abnormalities in patients with SZ and BD and suggested that a smaller volume of overlapping white matter (WM) and common areas of thinner cortex indicated that both disorders share genetic and neurodevelopmental pathways (Hulshoff et al., 2012). Furthermore, Janssen and colleagues observed frontal thinning in adolescents with BD and SZ (Janssen et al., 2014).

Current knowledge indicates that deficits in several cognitive domains may be associated with cortical thinning in SZ (Ehrlich et al., 2012; Hartberg et al., 2010; Oertel-Knöchel et al., 2013) and BD (Gutierrez-Galve et al., 2011). In BD, significant associations have been reported between course of illness and sociodemographic variables, such as gender (Najt et al., 2007) or age (Brambilla et al., 2001; Lyoo et al., 2006) and cortical thickness in temporal lobes (for episodes of illness, see Moorhead et al., 2007) and in frontal lobes (for years of illness, see Lyoo et al., 2006). Padmanabhan et al. assessed a large sample of schizophrenia, schizoaffective and bipolar I patients ($n = 455$) and observed that positive symptoms of psychosis were

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significantly associated with reductions in cortical thickness in frontal and temporal areas across groups, and that negative symptoms correlated with right frontal cortex thinning (Padmanabhan et al., 2015). However, the functional relevance of structural abnormalities may depend on which symptoms or cognitive domains are being assessed (Gutierrez-Galve et al., 2011; Lyoo et al., 2006; Rimol et al., 2010).

In the current study we directly compared cortical thickness and volumes in BD and SZ patients to healthy controls. As a main hypothesis, we suggest that SZ and BD share frontal cortical thinning and volume reductions. Additionally, we suggest that decreases in cortical thickness are directly associated with cognitive and clinical features of psychosis.

2. Material and methods

2.1. Participants

We examined 32 SZ patients ($M_{age} = 39.56$ years ($SD = 10.90$)), 34 euthymic BD I patients ($M_{age} = 43.93$ years ($SD = 10.87$)) and 38 healthy controls ($M_{age} = 40.86$ years ($SD = 11.91$)). All patients were treated as outpatients at the time of the study and had been in remission for a minimum of one month. None of the patients had any comorbid axis I or II disorder (including substance abuse or addiction). To confirm the diagnoses in the patient groups and to ensure that none of the control participants was affected by a psychiatric disorder according to DSM-IV (APA, 1994) we conducted the Structured Clinical Interview for DSM IV Disorders (SCID-I and SCID-II; German version; (Wittchen et al., 1996)). The controls had no family history of affective disorder or psychosis. The three groups were matched for handedness (all were right handed as assessed using the Edinburgh Handedness Inventory, (Oldfield, 1971)), age, gender and years of education. The two patient groups were matched for duration of disease and age at disease onset.

Crystallized intelligence was assessed using the German equivalent of the “Spot-the-Word test” (Mehrfachwahl-Wortschatz-Intelligenz-Test ((MWT-B; (Lehrl, 2005). Psychomotor speed and executive functioning were tested using the Trail Making Test (TMT A and TMT B (Reitan et al., 1988).

Current psychopathological symptoms in SZ patients were assessed using the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987)) and the Revised Hallucination Scale (RHS; (Morrison et al., 2002)). We applied the remission criteria defined by Andreasen et al. (2005). To define remission, we used the following PANSS (Kay et al., 1987) items: delusions, unusual thought content, hallucinations, conceptual disorganization, mannerisms and posturing, blunted affect, social withdrawal and lack of spontaneity. According to the criteria by Andreasen et al., the ratings of these items had to be mild or less over a 6-month period (Andreasen et al., 2005). For the euthymic BD patients we evaluated symptom severity using the German version of the Beck Depression Inventory (BDI II; (Hautzinger et al., 2006) for depressive symptoms (BDI II score of <10) and the German version of the Bech-Rafaelsen Mania Scale (BRMAS; (Bech, 1981)) for mania symptoms (BRMAS score of <7).

All patients had been on stable medication for at least four weeks prior to measurement (see Supplemental material Table S1 for further details). None of the BD or SZ patients received any benzodiazepines and none of them were without medication. To compare different substances and doses, chlorpromazine (see the formula by (Woods, 2003)) and amitriptyline equivalents (Ali, 1998) were computed.

2.2. Data acquisition and image processing

MRI measurements took place at the Goethe-University Brain Imaging Center, Frankfurt, Germany. We acquired a high-resolution, T1-weighted MDEFT sequence (Deichmann et al., 2004) for anatomical brain imaging (176 slices, $1 \times 1 \times 1$ mm, matrix size 256×256 , slice thickness 1 mm, flip angle: 16°) covering the entire brain of each

participant on a Siemens Magnetom Allegra 3 Tesla MRI system (Siemens Medical Systems, Erlangen, Germany). All anatomical T1-weighted MRI scans were reviewed by a neuroradiologist who did not find any neurological or other pathology (i.e. focal or local atrophy, lacunar infarctions or extensive microangiopathy).

Analysis of structural MRI data was performed using the software tools of MATLAB® (The Mathworks Inc., Natick, MA, USA), FreeSurfer® (Version 5.1.0) (FreeSurfer Troubleshooting Reconstruction Work Flow; <http://surfer.nmr.mgh.harvard.edu/>) and a FreeSurfer application (Qdec®).

2.3. Data preprocessing

Cortical thickness was estimated at each vertex across the brain surface using the semi-automated approach of the FreeSurfer 5.1.0 software (Dale et al., 1999; Fischl et al., 1999). This procedure included reconstruction of the gray matter (GM)–white matter (WM) boundary and the cortical surface (Dale et al., 1999; Han et al., 2006; Rosas et al., 2002), a calculation of the distance between those surfaces at each point across the cortical mantle (Dale et al., 1999), a transformation of all data into the Talairach space and an automatic stripping of the skull and subcortical structures (see Segonne et al., 2004). The smoothing algorithm by Dale et al. (1999) was used to alleviate the voxel-based nature of the initial curvature and potential topological defects were corrected using an automated topology fixer (see Segonne et al., 2005). The anatomies were further registered to a reference brain (an average template that included anatomical data sets) to visualize the results. The surfaces were spherically inflated and registered to a common space spherical deformation guided by automatically defined cortical features that were derived from a population atlas (Fischl et al., 1999). The resulting surfaces were transferred to Talairach space, allowing direct, anatomically accurate measurements of thickness. For quality control, all segmentations were inspected, manually corrected and re-inspected as described by Fischl et al. (2001) and Goldman et al. (2009).

We used the resulting surfaces to compile all surface data into 33 cortical regions of interest (see Desikan et al., 2006; Fischl et al., 2001). Each subject's reconstruction was again visually inspected for gross topological inaccuracies. Cortical thickness was calculated for each vertex in the triangulated surfaces by finding the point on the white matter surface that was closest to a given point of the pial surface (and vice versa) (Fischl and Dale, 2000; Han et al., 2006). An average normal control surface was generated and thickness data from each subject were smoothed using a standard Gaussian filter and mapped to the average surface.

2.4. Statistical analysis

Extracted values for cortical thickness and volumes as provided by the QDEC® application of all participants were fitted into three independent ANCOVA models as independent variables, with patient diagnosis (CON, BD, SZ) as a fixed factor and intracranial volumes (ICV) as a covariate. We also conducted independent ANOVAs to compute group comparisons of cognitive and clinical data. All group differences were deemed significant on a threshold level of $p < 0.05$ after a correction for multiple comparisons using the false discovery rate (p^{FDR} ; (Genovese et al., 2002)).

We performed bivariate correlation analyses (Spearman rank correlation, 2-tailed; (Pearson product moment correlation, 2-tailed) between all structural imaging parameters that differed significantly between groups and cognitive, clinical and course of illness variables. We also conducted bivariate correlation analyses between the thickness values and the medication scores as well as years of medication. All correlation analyses were corrected for multiple comparisons using the Bonferroni correction (p_{Bonf}).

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