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Research report

Association between age of disease-onset, cognitive performance and cortical thickness in bipolar disorders

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ABSTRACT

Objectives: Neuroimaging studies in patients with bipolar disorder (BD) have indicated a number of structural brain changes, including reduced cortical thickness. However, the effects of the course of illness, clinical and cognitive variables on cortical thickness in BD patients have not yet been evaluated.
Methods: A total of 67 individuals (32 patients with euthymic BD and 35 healthy and age-matched controls) underwent 3D-anatomical magnetic resonance imaging (MRI). Whole-brain cortical thickness and group differences were assessed using the Freesurfer software. Course of disease variables, clinical and cognitive parameters were correlated with cortical thickness measures.
Results: We found reduced cortical thickness in BD patients compared with controls in the frontal and temporal lobes and in several limbic areas. We also report significant associations between cortical thickness and age of disease-onset, speed of cognitive processing, executive function and depression severity in BD patients.
Conclusions: Cortical thickness reduction across frontal and limbic areas is a structural correlate of affective symptom severity and cognitive impairments in BD as well of age of disease-onset. We may assume that frontal lobe structural abnormalities are present in bipolar disorder, and might lead to dysfunctional cognitive functioning. The causality and functional relevance beyond mere correlation, however, is yet to be established. Our findings encourage further longitudinal studies in BD patients and in healthy at-risk subjects in order to discern the temporal order and development of morphological changes and clinical symptoms.

1. Introduction

Bipolar disorder (BD) is one of the most severe mental diseases, affecting about 1–2% of the worldwide population. The disorder is ranked as sixth most important cause of disability among all other diseases (Schmitt et al., 2014). Current pathophysiological models propose that several neurotransmitter disturbances, genetic risk factors, neurophysiological changes and environmental factors contribute to the development of BD (Anderson et al., 2012). Of interest in current neuroimaging studies is the investigation of potential links between symptom severity and sociodemographic factors and functional and structural brain abnormalities. We therefore systematically explored in the current study potential cortical thickness substrates of cognitive and clinical symptoms in BD patients.

Several non-invasive methods permit the investigation of the structure of the cortex, including volumetric measures with voxel-based morphometry (VBM) (Ashburner and Friston, 2000), measures of diffusion tensors with diffusion-tensor imaging (DTI)

Abbreviations: BD, Bipolar disorder; BDI, Beck Depression Inventory; BRMAS, Beck Rafaelsen Mania Scale; CON, controls; GM, gray matter; TL-D, tower of London; TMT, Trail Making Test; VBM, Voxel-Based Morphometry; WM, white matter; MOF, medial orbitofrontal cortex; PA, pars opercularis of the inferior frontal cortex; Pre, precuneus; STG, superior temporal gyrus; Cu, cuneus; rAC, rostral anterior cingulate

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(Le Bihan et al., 2001) and measures of cortical thickness (Fischl et al., 2001). Cortical thickness is defined as the local or average distance between the white matter surface and the pial surface of the cortex. Cortical thickness is related with the number of neurons and the neuropil within an ontogenetic column, and the cohort of cortical neurons that originate from a single neuronal progenitor (Rakic, 2008). Measurement of cortical thickness has been acknowledged to probe alterations in brain growth and maturation (Magnotta et al., 1999; Salat et al., 2004; Sowell et al., 2001; Sowell et al., 2003).

Reviews and meta-analyses of structural imaging studies of BD have shown a high variability of the topography of morphological changes across studies (Andreasen, 1997; Ellison-Wright and Bullmore, 2010; Selvaraj et al., 2012). Reported abnormalities include increased volumes of lateral cerebral ventricles and the III ventricle, extended cortical sulci, increased subcortical hyperintensity and frontal (particularly prefrontal) white matter and cerebellar volume reduction (Andreasen, 1997; Ellison-Wright and Bullmore, 2010; Selvaraj et al., 2012). The meta-analysis by Ellison-Wright and Bullmore (2010) revealed gray matter reductions in paralimbic regions (anterior cingulate and bilateral insula) in bipolar disorders, and a recent meta-analysis by Selvaraj et al. (2012) showed reduced gray matter in a cluster encompassing the right insula, middle temporal gyrus, superior temporal gyrus, temporo-polar area, pars opercularis and pars triangularis, inferior frontal gyrus, and claustrum.

Cortical thickness in BD has only been investigated by a small number of studies (Bouras et al., 2001; Foland-Ross et al., 2011; Fornito et al., 2008; Fornito et al., 2009; Lyoo et al., 2006; Qiu et al., 2008; Rimol et al., 2010). These studies indicate a reduction of cortical thickness in BD in comparison with controls, but the location of these reductions has been partly inconsistent across studies. However, the majority of studies revealed frontal cortical thickness reductions (Bouras et al., 2001; Foland-Ross et al., 2011; Fornito et al., 2008; Fornito et al., 2009; Lyoo et al., 2006; Rimol et al., 2010), particularly in prefrontal areas (Foland-Ross et al., 2011), in the cingular cortex (Foland-Ross et al., 2011; Fornito et al., 2009; Lyoo et al., 2006), in the paracingular cortex (Fornito et al., 2008) and in the middle frontal cortex (Lyoo et al., 2006). In a post-mortem study by Bouras et al., (2001), they found cortical thickness reduction and reduced neuronal density in subgenual parts of the anterior cingulate. Several studies observed reduced temporal lobe cortical thickness in BD, as described by Lyoo et al. (2006), Qiu et al. (2008) and Rimol et al. (2010), and reduced fusiform cortex thickness as well as changes in parietal and occipital cortical thickness (Lyoo et al., 2006).

An even smaller number of studies have explored the functional significance of any changes in cortical thickness through the correlation with course of illness variables, clinical and cognitive symptoms and states. There are links between cortical thickness in frontal cortices and age (Brambilla et al., 2001; Lyoo et al., 2006) and gender (Najt et al., 2007) but not in all studies (Lyoo et al., 2006). Moreover, Moorhead et al. (2007) reported a significant association between the number of episodes of illness in BD patients and reduction of cortical thickness in temporal lobes, in particular in the hippocampus. Lyoo et al. (2006) showed an inverse correlation between cortical thickness in left middle frontal cortices and disease duration in BD patients. However, Rimol et al. (2010) did not find significant effects of medication, duration of illness or symptom severity on cortical thickness parameters. Furthermore, Nery et al. (2009) observed that acute depressive symptom severity was associated with orbitofrontal cortical thickness decreases in comparison with remitted patients. Few authors linked cognitive functioning with cortical thickness measures: Hartberg et al. (2011) reported a negative correlation between temporal-pole cortical thickness and working memory performance in BD patients and Gutierrez-Galve et al. (2011) reported associations between frontal cortex thickness and volume reductions and premorbid intelligence (IQ) in BD patients (I and II), but no associations with current IQ, visual memory and executive functioning.

In sum, potential direct associations between structural brain changes and clinical (cognitive functioning, affective symptoms) and sociodemographic variables are of particular interest for current pathophysiological models and treatment options of BD. To our knowledge, while a few studies have assessed the effects of some of these variables on cortical thickness, none of the previous work investigated all of them in association with cortical thickness measures. We therefore examined potential structural substrates of cognitive and clinical symptoms in BD patients. We hypothesize that cortical thickness may be associated with symptom severity, course of illness and cognitive functioning in BD.

2. Methods and materials

2.1. Participants

We included 32 remitted BD patients (mean age: $M=44.03$ (SD: 10.69) years) diagnosed with bipolar I disorder according to DSM-IV criteria (APA, 1994). All patients were outpatients of the Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Goethe-University, Frankfurt, Germany. Acute manic or depressive episode was excluded if the interview showed that the patient fulfilled diagnostic criteria for a depressive or manic episode, as well as if any comorbidity disturbances of axis I or II disorders (including substance abuse or dependence) were observed. All patients had history of recurrent manic and depressive episodes (see Table 1 for further details).

The control group included 35 healthy controls (CON) (mean age: $M=42.06$ (11.45) years) was matched with the groups of patients for handedness (all right handed; The Edinburgh Inventory; (Oldfield, 1971)), age, gender and education. Statistical tests (ANOVA, Scheffé post-hoc contrast analyses) for differences between the groups regarding age and years of education revealed no significant differences ($p > 0.05$). Chi-square test showed that gender distribution was equal across groups ($p > 0.05$). Exclusion criteria for control participants were any psychiatric disorder according to DSM-IV, left-handedness, any neurological pathology and inability to provide informed consent. None of the controls had any positive family history of affective disorders (first – second degree).

The anatomical MRI scans were reviewed by a neuroradiologist who did not find pathology, i.e., focal or local atrophy, lacunar infarcts or extensive microangiopathy. Participants were provided with a description of the study and gave written informed consent before participation. Experimental procedures were approved by the ethical board of the medical department of the Johann Wolfgang Goethe-University, Frankfurt/Main, Germany.

2.2. Assessment of psychopathology and cognitive performance

The Structured Clinical Interview for DSM-IV (SCID-I and SCID-II; German version: (Wittchen et al., 1996) was carried out with all participants. Current psychopathology was assessed using the German version of the Beck Depression Inventory II (BDI II; (Hautzinger et al., 2006) and the German version of the Bech Rafaelsen Mania Scale (BRMAS; (Bech, 1981). Remitted state was defined as BD patients who had a BDI II score of < 18 and a BRMAS score of < 7 and as BD patients who did not fulfill the criteria for an acute affective episode in the SCID interview.