Impaired Anatomical Connectivity and Related Executive Functions: Differentiating Vulnerability and Disease Marker in Bipolar Disorder

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Background: Bipolar 1 disorder (BD1) has been associated with impaired set shifting, increased risk taking, and impaired integrity of frontolimbic white matter. However, it remains unknown to what extent these findings are related to each other and whether these abnormalities represent risk factors or consequences of the illness.

Methods: We addressed the first question by comparing 19 patients with BD1 and 19 healthy control subjects (sample 1) with diffusion tensor imaging, the Intra-Extra Dimensional Set Shift Task, and the Cambridge Gambling Task. The second question we approached by applying the same protocol to 22 healthy first-degree relatives of patients with BD1 and 22 persons without a family history of mental disorders (sample 2).

Results: In comparison with their control groups, BD1 patients and healthy first-degree relatives of patients with BD1 showed significantly reduced fractional anisotropy (FA) in the right anterior limb of the internal capsule and right uncinate fasciculus. White matter integrity in corpus callosum was reduced in BD1 patients only. In addition, reduced FA in anterior limb of the internal capsule correlated significantly with an increased number of errors during set shifting and increased risk taking and reduced FA in uncinate fasciculus correlated significantly with increased risk taking.

Conclusions: Similar white matter alterations in BD1 patients and healthy relatives of BD1 patients are associated with comparable behavioral abnormalities. Further, results indicate that altered frontolimbic and frontothalamic connectivity and corresponding behavioral abnormalities might be a trait and vulnerability marker of BD1, whereas interhemispheric connectivity appears to be a disease marker.

Key Words: Bipolar disorder, DTI, first-degree relatives, fractional anisotropy, risk taking, set shifting

Bipolar 1 disorder (BD1) is a severe chronic mental disorder with a prevalence of at least 1% and a high heritability of 60% to 80% (1). Recently, it has been suggested that neurodevelopmental disturbances, particularly white matter (WM) alterations, represent an important risk factor for BD1 (2). The investigation of this biological risk factor and its potential relation to neuropsychological abnormalities is extremely important to improve our etiological knowledge of BD1, facilitating early and precise diagnosis and development of new therapeutic agents. However, studies examining BD1 patients cannot distinguish whether observed neurobiological and neuropsychological abnormalities represent risk factors or consequences of the disease. Therefore, investigation of healthy individuals at high risk to develop bipolar disorder, like unaffected first-degree relatives of BD1 patients (BD1-REL), is indispensable. Although longitudinal investigation of such a high-risk sample is the gold standard, cross-sectional studies comprising BD1 patients and BD1-REL also essentially contribute to the differentiation of disease and vulnerability markers.

Previous neuroimaging studies in BD1 patients and BD1-REL using diffusion tensor imaging (DTI) identified alterations in the integrity of corticolimbic and interhemispheric fiber tracts. In more detail, reduced WM integrity in the anterior thalamic radiation (3–5), which passes through the anterior limb of the internal capsule (ALIC) (6) and in the ALIC itself (7–9), has been repeatedly observed during depression, euthymia, and mania. Correspondingly, BD1-REL displayed reduced integrity of the ALIC (9,10), although not all researchers replicated this finding (7). Furthermore, reduced WM integrity in the corpus callosum (CC) has been described in children, adolescents (11,12), and adults with BD1 (8,13–18) during all mood states and in BD1-REL (9,10,19), although results in BD1-REL are less consistent (20,21). For the uncinate fasciculus (UF), which interconnects amygdala, orbitofrontal cortex, and anterior cingulate cortex (22), both reduced (4,5,8,23–25) and increased (24,26) WM integrity was observed in depressed and euthymic BD1 patients but not in BD1-REL.

In addition to aberrant WM tracts, neuropsychological impairments in executive functions, such as set shifting (27,28) and decision making (29), have been suggested to be a trait marker for BD1. Interestingly, WM integrity of the ALIC was shown to be related to impaired set shifting (30–32) and risky decision making (32). Furthermore, WM integrity of the CC also relates to set-shifting (33) and decision-making performance (34–36).

So far, only a few studies have investigated WM integrity in both BD1 patients and BD1-REL with exactly the same methodology. Most of the studies in BD1-REL focused on macrostructural WM alterations revealing reduced WM volume (20,21,37) and

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more WM hyperintensities (38), whereas only three studies on high-risk individuals used DTI (9,10,19). Of these studies, only one included BD1 patients, but no straightforward group-level comparison was calculated; instead, genetic liability was used as a regressor (19). Furthermore, no study has combined the assessment of WM integrity and neuropsychological performance in BD1 patients and BD1-REL.

To extend previous findings, we investigated WM integrity and executive functions in BD1 patients, BD1-REL, and healthy control subjects (HC). First, we expected reduced WM integrity in ALIC, CC, and UF in BD1 patients and unaffected relatives of BD1 patients compared with HC. Second, we predicted impaired set shifting and increased risk taking during decision making in patients and relatives compared with HC. Third, we reasoned that altered WM integrity and impaired executive functions might be related. These hypotheses were examined using DTI with fractional anisotropy (FA) as main outcome measure and standardized neuropsychological tests. To test these hypotheses, we investigated two independent samples: sample 1 consisting of BD1 patients and HC, and sample 2 comprising relatives of BD1 patients and HC. We chose this approach to control for the confounding effect of age, which differed significantly between patients and relatives and significantly influences diffusion parameters (39). However, to strengthen our hypothesis of similar white matter changes in BD1 patients and BD1-REL, we exploratively compared both groups directly.

Methods and Materials

Participants and Diagnostic Assessment

We invited BD1 patients who had already participated in epidemiologic studies at the Central Institute of Mental Health or frequented local support groups and their unaffected first-degree relatives to participate in the study. To recruit HCs matching patients or relatives for age and gender, we drew a large random sample from the registry office of the city of Mannheim and contacted these persons by mail.

All interested persons underwent a telephone screening, assessing the following exclusion criteria: history of neurological or systemic illness with neurological complications, history of previous head trauma with loss of consciousness, lack of fluency in German, metal implants, lifetime or current drug/alcohol dependence, and age $<$18 years or $>$65 years. Unaffected first-degree relatives of BD1 patients and HC were also excluded if they fulfilled criteria of any Axis I or Axis II disorder as defined by the DSM-IV (40), which was verified by two trained clinical psychologists conducting the Structured Clinical Interview for DSM-IV Axis I Disorders and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (41) and attention-deficit/hyperactivity disorder diagnostics (42,43) on the day of testing. Furthermore, HC were excluded if they reported any mental disorder among their first-degree relatives. In addition, trained clinical psychologists rated all participants for mania (Young Mania Rating Scale) (44) and depression (Hamilton Depression Rating Scale) (45). All participants completed the Beck Depression Inventory (46), the Multiple Choice Word Vocabulary Test (47) to measure intelligence, and the digit span subtest from the Wechsler Adult Intelligence Scale (48) to assess working memory. The study was approved by the ethics committee of the Medical Faculty Mannheim of Heidelberg University. All participants gave informed written consent before participation.

Sample 1. From the original 22 patients and 21 HCs who agreed to participate, 3 BD1 patients and 2 HCs had to be excluded due to magnetic resonance imaging artifacts or abnormal brain morphology. In the final sample of 19 BD1 patients and 19 HCs, no significant group differences concerning gender, age, years of education, marital status, current employment, intelligence, working memory, Hamilton Depression Rating Scale scores, or consumption of caffeine, nicotine, and alcohol were observed (Table 1). Although patients were euthymic, they scored significantly higher on the Young Mania Rating Scale and the Beck Depression Inventory (Table 1). Two patients were diagnosed with lifetime but currently remitted panic disorder. Detailed information on clinical characteristics and medication of patients is given in Table 2.

Sample 2. Unaffected first-degree relatives of BD1 patients were recruited through BD1 patients (index patients), who were excluded from study participation to ensure that BD1 patients and BD1-REL were independent. In addition, we verified that index patients and BD1 patients included in sample 1 were not related. If BD1-REL fulfilled inclusion criteria, index patients were invited to verify diagnosis of BD1 and to assess major clinical characteristics (Table S1 in Supplement 1).

Twenty-two BD1-REL and 22 HC (different from HC in sample 1 to ensure independence of both samples) participated. Sample 2 included 9 siblings and 13 children of BD1 patients. Eleven relatives were from simplex families (1 case of BD1 in the family) and the remaining 11 were from multiplex families (2 or more cases of BD1 in the family). Groups did not differ significantly concerning gender; age; years of education; marital status; current employment; intelligence; working memory; consumption of caffeine, nicotine, and alcohol; and current symptoms of depression and mania (Table 1). Please note that characteristics of both samples have already been reported in a previous publication (49).

Neuropsychological Assessment

The Intra-Extra Dimensional Set Shift Task and the Cambridge Gambling Task (CGT) included in the Cambridge Neuropsychological Test Automated Battery (Cambridge Cognition Ltd., Cambridge, United Kingdom) were presented on a high-resolution touch-screen monitor to assess set shifting and risky decision making. Both tasks have been described elsewhere in detail (50,51). In short, to master the Intra-Extra Dimensional Set Shift Task, participants must switch their attention within one dimension (intradimensional shift) or to a previously irrelevant dimension (extradimensional shift [EDS]). For the number of errors during intradimensional shift (pre-EDS errors) and EDS stages (EDS errors), we used *Z* scores standardized for age and gender, which are provided by the Cambridge Neuropsychological Test Automated Battery. We multiplied *Z* scores with −1, so that higher values indicated more perseverative errors, and calculated the mean of these two standardized *Z* scores as a composite measure of set shifting.

During the CGT, participants must decide whether a token is hidden under a red or a blue box and are given the opportunity to win points by betting a percentage of their total points on their choice. Half of the bet options are presented in ascending order (5%, 25%, 50%, 75%, or 95% of their total points) and the other half in descending order to disentangle risk taking from impulsivity. We analyzed risk taking operationalized by the proportion of points gambled on each trial. As for risk taking, no *Z* scores are provided; we used raw values.

DTI Data Acquisition

Magnetic resonance imaging data were acquired on a 3.0 Tesla scanner (Magnetom Trio, Siemens Medical Solutions,