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Research paper

Dysfunctional decision-making related to white matter alterations in bipolar I disorder

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ABSTRACT

Objective: This study investigated how frontal white matter (WM) alterations in patients with bipolar I disorder (BD-I) are linked to motivational dysregulation, often reported in the form of risk-taking and impulsivity, and whether structure–function relations in patients might differ from healthy subjects (HC).
Method: We acquired diffusion data from 24 euthymic BD-I patients and 24 controls, to evaluate WM integrity of selected frontal tracts. Risk-taking was assessed by the Cambridge Gambling Task and impulsivity by self-report with the Barratt-Impulsiveness Scale.
Results: BD-I patients displayed significantly lower integrity in the right cingulum compared to HC. They also showed more risk-taking behavior and reported increased trait-impulsivity. Risk-taking was negatively associated with WM integrity in the right cingulum. Impulsivity was not related to WM integrity in investigated tracts. Together with age and sex, FA in the cingulum explained 25% of variance in risk-taking scores in all study participants. The left inferior fronto-occipital fasciculus (IFOF) was specifically predictive of risk-taking behavior in BD-I patients, but not in HC.
Limitations: The employed parameters did not allow us to specify the exact origin of WM changes, nor did the method allow the analysis of specific brain subregions. Also, sample size was moderate and the sample included patients with lifetime alcohol dependence/abuse, hence effects found need replication and have to be interpreted with caution.
Conclusion: Our results further strengthen recent models linking structural changes in frontal networks to behavioral markers of BD-I. They extend recent findings by showing that risk-taking is also linked to the cingulum in BD-I and HC, while other prefrontal tracts (IFOF) are specifically implicated in risk-taking behavior in BD-I patients. Meanwhile, self-reported impulsivity was not associated with WM integrity of the tracts investigated in our study.

1. Introduction

Bipolar-I disorder (BD-I) is a severe chronic mental disease, with recurring episodes of mania, hypomania and depression. Early onset is common, with first symptoms occurring during adolescence or young adulthood (Leboyer et al., 2005; Tozzi et al., 2011). Still, to this day, BD-I is often under- or misdiagnosed, preventing patients from receiving optimal treatment (Knežević and Nedić, 2013). Previous research tried to identify markers characteristic for BD-I, such as biological or behavioral abnormalities that might aid in earlier, more precise diagnosis as well as in the development of appropriate treatment. Microstructural characteristics of white matter (WM) were suggested as biological markers (Chiang et al., 2009), resulting in a multitude of studies investigating WM alterations in BD-I patients. Studies have shown some consistent results, with a majority reporting changes in frontal brain regions (Schneider et al., 2012; Strakowski et al., 2012), not only in BD patients but also risk populations, such as unaffected first-degree relatives of BD patients (Linke et al., 2013; de Zwarte et al., 2014). This led to the conclusion that altered structural brain connectivity is a vulnerability and disease marker

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of BD psychopathology. Meanwhile, there is an astonishing lack of empirical evidence for the functional relevance of these changes in BD-I patients. Hence, further research seems to be essential, as a deeper understanding of the functional repercussions of frontal WM changes in BD-I might contribute to behavioral intervention methods that have the potential to alter brain structure and function.

Non-invasive diffusion tensor imaging (DTI) has made it feasible to study the brain's WM on a microstructural level, making it an appropriate method to study the neurobiological underpinnings of BD-I. Fractional anisotropy (FA) is a common DTI outcome measure (Basser and Pierpaoli, 1996), affected by altered myelination, varying axonal integrity or inflammation processes (O'Donnell and Pasternak, 2014). In DTI studies on BD, decreased WM integrity was shown for the left cingulum (Nortje et al., 2013; Sarrazin et al., 2014), near the right anterior and subgenual cingulate cortex, the right hemispheric parahippocampal gyrus (Vederine et al., 2011), the corpus callosum (CC) body and splenium, the anterior arcuate fasciculi (Sarrazin et al., 2014), the uncinate fasciculi (UF) (Benedetti et al., 2011; Linke et al., 2013) and the right posterior temporoparietal WM (Nortje et al., 2013). Still, others reported no changes in FA but an increased number of fibers and fiber density, respectively, in the UF (Houenou et al., 2007; Torgerson et al., 2013). Despite some variations in results, WM changes in BD-I patients appear to be especially profound in frontal and frontolimbic areas, with widespread disturbances encompassing regions involved in emotional and motivational processing (Schneider et al., 2012; Strakowski et al., 2012). This raises the question if these structural changes are related to consistent behavioral disturbances observed in BD.

Such a prominent feature of BD-I is motivational dysregulation (Strakowski et al., 2010; Adida et al., 2011) as indicated, e.g., by increased impulsivity and risk-taking. For several reasons, these behaviors seem to be particularly suitable for studying the functional relevance of WM integrity in BD-I patients. First, frontal WM integrity indeed predicts response inhibition capacities (the flip side of impulsivity) in healthy individuals (King et al., 2012). Secondly, BD patients across all illness stages show significantly impaired response inhibition, heightened impulsivity and increased risk-taking in comparison to HC (Adida et al., 2011; Saddichha and Schuetz, 2014). Similar but weaker patterns were found for individuals with a high genetic risk for BD or with hypomanic personality traits (Wessa et al., 2015). Finally, BD patients exhibit WM alterations especially in those tracts that were previously linked to behavioral variations of risky and impulsive behavior in HC (King et al., 2012; Peper et al., 2013) and other patient populations (Garibotto et al., 2010; Liu et al., 2010). Many of the affected tracts form part of a frontal network assumed to play a pivotal role in higher executive functions, inhibitory control and motivational processes (Phillips and Swartz, 2014). Thus, motivational dysregulation, as seen in elevated impulsivity and risk-taking, is suggested to represent the functional repercussions of mostly frontal WM changes (Hasler et al., 2006; Phillips and Swartz, 2014), a claim that needs further clarification in BD.

To our knowledge, only two studies examined the functional relevance of structural WM changes in BD and those did not explicitly focus on frontally located WM tracts but instead, examined WM changes on a whole-brain scale or restricted analyses to tracts that emerged as significant group differences between BD patients and healthy controls. Previously, we reported reduced FA in the right anterior limb of the internal capsule (ALIC) to be associated with elevated risk-taking in BD-I, healthy relatives and HC, while UF FA correlated negatively with risk-taking in HC but not BD-I (Linke et al., 2013). In siblings of BD-I patients, self-reported trait-impulsivity negatively correlated with FA in the right temporal lobe (Mahon et al., 2013). However, studies included only behavioral measures or self-reports and the dimension of the potentially existing structure–function relationship in BD and whether it differs from HC need to be elucidated on in depth.

Thus, the objective of this study was to investigate the functional implications of frontal WM changes in BD-I for self-reported impulsivity and risk-taking in a gambling task. In line with previous studies, we hypothesized that BD-I patients would show reduced FA in frontal white matter tracts (cingulum, inferior fronto-occipital fascicles (IFOF), UF and CC) as well as increased self-reported impulsivity and risk-taking scores. We also assumed that reduced frontal WM integrity would relate to increased impulsivity and increased risk-taking in BD-I patients and HC. We further explored if BD-I patients and HC would exhibit differential relationships between WM integrity and impulsivity and risk-taking, respectively.

2. Materials and methods

2.1. Participants

We recruited a sample of 24 euthymic BD-I patients and 24 healthy controls (HC), which were matched in age, gender and years of education (see Table 1). Recruitment was done using media announcements, registry offices and support groups. All potential participants underwent a telephone screening assessing exclusion criteria for this study. For BD-I patients, these exclusion criteria encompassed i) current or lifetime comorbid mental disorder with the exception of lifetime alcohol abuse or dependence, which did not lead to exclusion from this study ii) any Axis-II personality disorder iii) cardiac or neurological problems iii) head trauma resulting in medical treatment or loss of consciousness iv) any MRI contra-indications. Patients with a lifetime diagnosis of alcohol abuse or dependency were only invited if they reported abstinence for at least 6 months ($n=5$). At the day of testing, clinical diagnosis was determined by trained raters (BK, VS) using the Structured Clinical Interview (SCID-I and II) for DSM-IV, the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960) and

Table 1
Sample characteristics.

	BD-I patients ($n=24$)		Control subjects ($n=24$)		Patients vs. controls		
	M	SD	*M*	SD	Statistics	df	*P*-value
Gender (female/male)	(10/14)		(10/14)		$\chi^2=0.00$	1	ns[a]
Age: years	44	10	44	10	$t=0.056$	46	ns
Intelligence score[b]	101	12	103	12	$t=-0.747$	46	ns
Working memory[c]	57	30	62	31	$U=257$	46	ns
Years of education	15	2	15	2	$t=0.262$	46	ns
Current mood ratings							
YMRS	0.63	1.1	0.08	0.3	$U=222$	46	0.016
HAMD	1.2	1.5	0.3	0.6	$U=184$	46	0.045
Neuropsychological data							
Risk taking[d]	0.57	.14	0.46	.13	$F=8.479$	1/42	0.006
Impulsivity (BIS-11 total)[e]	62	8	55	8	$F=9.047$	1/42	0.004

BD-I=Bipolar -I Disorder, *M*=mean, SD=standard deviation, HAMD=Hamilton Depression Rating Scale, df=degrees of freedom, ns=non-significant, YMRS=Young Mania Rating Scale.

[a] Non-significant *p*-values are >0.05.
[b] Raw scores were standardized by IQ transformation.
[c] Raw scores were standardized by T transformation.
[d] Values displayed as percentage of total points bet in CGT.
[e] Higher values represent higher self-reported overall trait-impulsivity.