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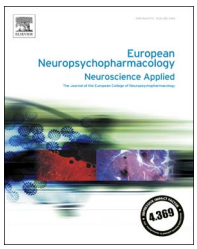

White matter disruptions in patients with bipolar disorder

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Abstract
Bipolar disorder (BD) patients show aberrant white matter microstructure compared to healthy controls but little is known about the relation with clinical characteristics. We therefore investigated the relation of white matter microstructure with the main pharmacological treatments as well its relation with IQ. Patients with BD (N = 257) and controls (N = 167) underwent diffusion tensor imaging (DTI) and comprehensive clinically assessments including IQ estimates. DTI images were analyzed using tract-based spatial statistics. Fractional anisotropy (FA) and Mean Diffusivity (MD) were determined. Patients had significantly lower FA and higher MD values throughout the white matter skeleton compared to controls. Within the BD patients, lithium use was associated with higher FA and lower MD. Antipsychotic medication use in the BD patients was not associated with FA but, in contrast to lithium, was associated with higher MD. IQ was significantly positively correlated with FA and negatively with MD in patients as well as in controls. In this large DTI study we found evidence for marked differences in FA and MD particularly in (but not restricted to) corpus callosum, between BD patients and controls. This effect was most pronounced in lithium-free patients, implicating that lithium affects white matter microstructure and attenuates differences associated with bipolar disorder. Effects of antipsychotic medication intake were absent in FA and only subtle in MD relative to those of lithium. The abnormal white matter microstructure was associated with IQ but not specifically for either group.

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1. Introduction

Converging evidence from magnetic resonance imaging studies suggests that deviations in local white matter volume as well as abnormal structural connectivity play a role in the pathogenesis of BD (O'Donoghue et al., 2017; Bellani et al., 2016; Benedetti and Bollettini, 2014). However, little is known about the influence of clinical characteristics like psychotropic medication on white matter microstructure or whether potential changes in white matter microstructure is related to level of intelligence in patients with Bipolar disorder (BD).

Whereas there is general consensus that lithium has a normalizing or preserving effect on brain volume, leading to attenuated differences between patients and controls (Bearden et al., 2007; Germaná et al., 2010, Singh and Chang, 2012; Hafeman et al., 2012; Abramovic et al., 2016, Hibar et al., 2017), such a role is much less clear for lithium in studies of white matter microstructure. Lithium was positively associated with clusters in the corpus callosum (CC; Walterfang et al., 2009), the left anterior corona radiate and two small peripheral tracts in the frontal orbital cortex (Haarman et al., 2016), however, samples have been small and negative findings have been reported as well (Versace et al., 2008). Also, the effect of other psychotropic medication on brain structure remains unclear. We previously reported that smaller total brain volume in BD patients may be attenuated by lithium, and not by antipsychotic medication use (Abramovic et al., 2016). Thus far, few studies reported on the role of psychotropic medication on white matter measurements. To our knowledge, there is only one study showing a lower connectivity in parietal and occipital cortices following antipsychotic treatment (Szeszko et al., 2014). Considering that more than half of patients with BD are prescribed antipsychotic medication (Kessing et al., 2016), the relation of these drugs with white matter microstructure is warranted. A secondary advantage is that such studies may inform on schizophrenia patients as well, where such studies cannot be performed as the number of patients who are not on antipsychotics is usually too small.

A second topic of interest in the context of white matter microstructure is the potential relationship with IQ as both IQ and white matter volume contribute to the clinical phenotype of bipolar disorder (Forcada et al., 2011). Studies in controls have shown that intelligence is positively related to connectivity in the fiber tracts connecting frontal and parietal areas (Schmithorst et al., 2005). In addition, connectivity in the splenium and left-side inferior longitudinal and arcuate fasciculi predicted level of intelligence (Clayden et al., 2011; Barbey et al., 2013; Gläscher et al., 2010; Schmithorst et al., 2005; Navas-Sánchez et al., 2014). BD has been associated with lower intelligence (Trotta et al., 2015; Frangou et al., 2005; Vreeker et al., 2016). Therefore, we set out to investigate whether white matter deficits we may find in BD are associated with IQ.

We use diffusion tensor images to estimate fractional anisotropy (FA) and mean diffusivity (MD) in white matter tracts on a voxel level. FA is a measure for directional diffusion, which is an indication of the distribution of water molecules in the cellular compartments. Because water is more restricted in white matter due to the myelin sheets, FA is usually higher in intact white matter tracts than in grey matter, cerebrospinal fluid or disrupted fibers. MD reflects the average rate of water diffusion, which is usually higher in damaged tissue (Madden et al., 2012). As tissue damage often leads to more free diffusion and less restriction, lower FA is often (but not always) related to higher MD.

The aim of the current study is to investigate differences in white matter microstructure between BD patients and controls and whether they are related to lithium and antipsychotic treatment and IQ. Based on previous studies suggesting abnormalities in the white matter microstructure in patients with bipolar disorder, we expected to find widespread decreases in FA and increases in MD in white matter tracts of patients compared to control subjects. Also, we expected to find less profound deviations in FA in patients on lithium compared to non-using patients.

2. Experimental procedures

2.1. Participants

In this cross-sectional study, 262 patients with BD type I and 169 control subjects participated.

Control subjects did not have BD, schizophrenia or any other psychotic disorder, nor had their first-degree relatives. Inclusion criteria for all participants were: a minimum age of 18 years old, at least three Dutch-born grandparents, and a good understanding of Dutch language. Subjects with a history of head trauma or a neurological illness were excluded.

The current sample is a subsample of a larger cohort, which was recruited at the University Medical Center Utrecht (UMCU), the Netherlands, as part of a collaboration between the University of California Los Angeles (UCLA) and several Dutch health care institutes. The cohort investigates genetic and phenotypic information of patients with bipolar disorder type I, first-degree relatives and controls. All scans were performed at the same scanner located in the University Medical Center Utrecht. Subjects were scanned between June 2011 and July 2014.

The diagnoses of patients were confirmed with the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002). Also, the Questionnaire for Bipolar Illness Leverich et al., 2001; Suppes et al., 2001) was used. Mood status was assessed at inclusion through self-report using the 30-item Inventory of Depressive Symptoms-Self Report ($IDS\text{-}SR_{30}$; Rush et al., 1996) and the Altman Self-Rating Mania Scale (ASRM; Altman et al., 1997). Mean and standard deviation of these measures were added to Table 1. We measured substance abuse in patients using the CIDI, while it was assessed in controls with the MINI. None of the subjects was admitted at the moment of assessment. Control subjects were screened for psychiatric diagnoses using the M.I.N.I. (Mini International Neuropsychiatric Interview; Sheehan et al., 1998). Interviews were conducted by at least one well-trained independent rater.

Four subtests of the Dutch version of the WAIS-III (Wechsler D., 1997) were used to estimate current IQ, being Digit Symbol Coding (processing speed), Block Design (visuospatial capacities), Arithmetic (working memory) and Information (general knowledge). The combination of these four subtests has been shown to reliably estimate IQ in schizophrenia patients ($R^2 = 0.90$) and controls ($R^2 = 0.86$) (Blyler et al., 2000). We have also performed the DART, which is the Dutch version of the National Adult Reading Test (Schmand et al., 1991), as an estimation for premorbid IQ. This data was available for 210 patients and 151 controls. Written informed consent was obtained from all participants. The Humans Ethics

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