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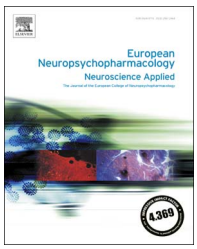

Childhood abuse and white matter integrity in bipolar disorder patients and healthy controls

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Abstract
Childhood trauma has a negative impact on the developing brain and increases the risk for almost all psychiatric disorders including bipolar disorder. White matter abnormalities may play a role in the persistently increased risk for bipolar disorder following childhood trauma.

We therefore examined the influence of childhood abuse and neglect on white matter integrity using diffusion tensor imaging (DTI), quantified as fractional anisotropy (FA), in patients with bipolar I disorder ($N = 251$) and healthy controls ($N = 163$). Bipolar patients experienced more childhood abuse (30.6% vs 8.0%; $p < 0.001$) and childhood neglect (36.3% vs 22.7%; $p = 0.003$) than controls. Childhood abuse had different effects on whole brain FA in patients with bipolar disorder compared to healthy individuals ($F[1,410] = 3.060$; $p = 0.006$). Specifically, whereas patients with bipolar disorder with childhood abuse had lower FA in widespread regions of the brain relative to patients without childhood abuse ($t[249] = 2.28$; $p = 0.024$), no differences were found between healthy individuals with and without abuse ($t[161] = -0.18$; $p = 0.986$). Differences in mean FA significantly mediated the association between childhood abuse and bipolar disorder. In contrast, childhood neglect was not significantly associated with FA in patients with bipolar disorder nor in healthy controls.

Together, these results show that childhood abuse but not neglect is associated with lower integrity of white matter microstructure across the brain in patients with bipolar I disorder but not in healthy

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individuals. Therefore, white matter integrity might be involved the relationship between childhood abuse and bipolar disorder, even though the directionality cannot be proven due to the cross-sectional design of our study.

1. Introduction

Exposure to trauma during childhood can have long-lasting detrimental effects on the developing brain and is one of the main risk factors for psychiatric disorders such as bipolar disorder (Isvoranu et al., 2016; Kessler et al., 2010). Childhood abuse, in particular physical and sexual abuse, is associated with an increased risk of bipolar disorder and within this patient group, with poor disease outcomes (Agnew-Blais and Danese, 2016; Carr et al., 2013). However, the pathophysiological mechanisms underlying this increased risk for bipolar disorders following childhood abuse remain incompletely understood (Carr et al., 2013; McCrory et al., 2010; Schäfer and Fisher, 2011).

Several studies have shown that childhood trauma is associated with brain abnormalities, including altered amygdala activity (Hentze et al., 2016) and amygdala volume (Souza-Queiroz et al., 2016) in patients with chronic depression and bipolar disorder. Moreover, childhood trauma is associated with alterations in functional connectivity between the amygdala and prefrontal cortex (Souza-Queiroz et al., 2016) and between the prefrontal and temporal cortex (Demir-Lira et al., 2016).

It has been suggested that these functional abnormalities in brain connectivity are the result from abnormal white matter microstructure which shapes brain connectivity (Greicius et al., 2009). Indeed, some studies have found childhood trauma to be associated with lower integrity of white matter microstructure in patients with bipolar disorder and schizophrenia, assessed with diffusion tensor imaging (DTI) (Benedetti et al., 2014; Poletti et al., 2015). Moreover, a longitudinal study showed that trauma-related reductions in white matter integrity at baseline were related to an increased risk for psychopathology over a period of five years (Huang et al., 2012). It may therefore be hypothesized that childhood trauma results in white matter abnormalities in susceptible individuals, which may subsequently increase the risk for the development of psychiatric illness later in life. Notably, for bipolar disorder, there is an extensive body of research showing that white matter integrity is generally decreased and is involved in the underlying pathophysiology of this disorder (Benedetti et al., 2011; Sexton et al., 2009). Moreover, this decrease in white matter integrity is attenuated by treatment with lithium (Abramovic et al., submitted for publication). However, the evidence for a relation between childhood trauma and abnormal white matter in bipolar disorder is still limited. Moreover, it is unclear whether an association between childhood trauma and white matter integrity is the same in patients with bipolar disorder and in healthy individuals.

In the current study, we investigated whether childhood trauma is associated with integrity of the white matter microstructure in patients with bipolar disorder and healthy controls. Integrity of white matter microstructure was assessed using DTI and quantified as fractional anisotropy (FA). Childhood trauma was assessed using the validated childhood trauma questionnaire (CTQ) (Bernstein and Fink, 1998). Since childhood abuse and neglect are thought to have differential effects on the brain (Cakir et al., 2016; Kuhlman et al., 2015), we performed separate analyses to assess the association between childhood abuse and childhood neglect on the brain. Childhood abuse in particular is strongly associated with bipolar disorder (Carr et al., 2013; Leverich et al., 2002; Maniglio, 2009; Du Rocher Schudlich et al., 2015; Romero et al., 2009). We hypothesized that childhood abuse would be associated with decreased white matter integrity in the brain of patients with bipolar disorder.

2. Experimental procedures

2.1. Participants

Data from the Dutch Bipolar Cohort (DBC) study were used. This study is a collaboration between the University Medical Center Utrecht (UMCU), various health care institutes in the Netherlands and the University of California Los Angeles (UCLA)(Verkooijen et al., 2016). The DBC collected data from bipolar type I patients and healthy controls. All participants were over 18 years old, had at least three grandparents of Dutch descent and none were pregnant during neuroimaging. Participants who had previously experienced head trauma or were diagnosed with a neurological or major somatic disorder were excluded. An independent radiologist evaluated all MRI scans. Participants with any structural brain abnormalities were excluded from further analyses. In healthy controls, diagnosis of bipolar disorder or a psychotic disorder was an exclusion criterion, as well as presence of a first or second degree relative with a bipolar or psychotic diagnosis. Any other type of psychiatric disorder was not an exclusion criterion in order to avoid the recruitment of a 'super-normal control sample', that is not representative of the general population. Similarly, since comorbid psychiatric disorders are common, we did not exclude bipolar patients who had other psychiatric comorbidities.

Participants were assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al., 1998). A subgroup of patients and controls completed the MRI protocol. The ethical review board of the UMC Utrecht approved the DBC study. Written informed consent was obtained from all participants prior to participation. Individuals with data on childhood trauma and diffusion tensor imaging (DTI) scan were selected (n = 251 patients with bipolar disorder; n = 163 controls).

2.2. Childhood trauma questionnaire (CTQ)

Childhood abuse was assessed using the 25-item version of the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The

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