



Childhood maltreatment and corpus callosum volume in recently diagnosed patients with bipolar I disorder: Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM)



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ARTICLE INFO

Article history:

Received 18 June 2013

Received in revised form

29 August 2013

Accepted 10 October 2013

Keywords:

Bipolar disorder

First episode mania

Corpus callosum

Childhood trauma

Magnetic resonance imaging

ABSTRACT

Childhood trauma (CT) has been associated with abnormalities in the corpus callosum (CC). Decreased CC volumes have been reported in children and adolescents with trauma as well as adults with CT compared to healthy controls. CC morphology is potentially susceptible to the effects of Bipolar Disorder (BD) itself. Therefore, we evaluated the relationship between CT and CC morphology in BD. We using magnetic resonance imaging in 53 adults with BD recently recovered from their first manic episode, with ($n = 23$) and without ($n = 30$) CT, defined using the Childhood Trauma Questionnaire (CTQ) and 16 healthy controls without trauma. ANCOVA was performed with age, gender and intracranial volume as covariates in order to evaluate group differences in CC volume. The total CC volume was found to be smaller in BD patients with trauma compared to BD patients without trauma ($p < .05$). The differences were more pronounced in the anterior region of the CC. There was a significant negative correlation between CTQ scores and total CC volume in BD patients with trauma ($p = .01$). We did not find significant differences in the CC volume of patients with/without trauma compared to the healthy subjects. Our sample consists of patients recovered from a first episode of mania and are early in the course of illness and reductions in CC volume may occur late in the course of BD. It might mean there may be two sources of CC volume reduction in these patients: the reduction due to trauma, and the further reduction due to the illness.

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1. Introduction

Childhood maltreatment, such as neglect, sexual and physical abuse, is highly prevalent in patients with psychiatric disorders (Arnou, 2004; De Bellis et al., 2011; Fowke et al., 2012). The long term negative consequences of childhood traumatic experiences in adults with mental illness comprise poor outcomes in various domains, including changes in brain morphology, particularly in the hippocampus (Woon and Hedges, 2008), amygdala (Vermetten et al., 2006), prefrontal cortex (Treadway et al., 2009) and corpus callosum (Villarreal et al., 2004).

Among various brain regions, corpus callosum (CC) is of particular interest given its key function in mediating communication between the right and left cerebral hemispheres and in coordinating a number of major cognitive processes, including, attention, arousal, emotion, and higher cognitive abilities (Giedd et al., 1996; Badaruddin et al., 2007). The development of the CC starts in utero, progresses during childhood and early adolescence by a process of myelination and is only completed in early adult life (Giedd et al., 1996; De Bellis, 2005). Therefore, this region may be particularly vulnerable to the effects of stress and trauma during development. The genu, splenium and body of CC have been shown to increase in size from 5 to 8 years of age and continue into early adolescence, accounting for most of the white matter tract increases in the developing brain during this period (Lebel and Beaulieu, 2011). Structural and functional reorganization of the CC, particularly the isthmus, has been reported to occur between 6

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and 8 years of age (Westerhausen et al., 2011). Thus, new challenges and experiences during this period are likely to have a significant impact on the development of the CC (Lebel and Beaulieu, 2011). It can be inferred that different regions of the CC might have different windows of vulnerability to early negative experience, which can result in a reduction in CC size and potential impairment in communication between the two cerebral hemispheres (Clarke and Zaidel, 1994; Teicher et al., 2004).

The most consistent finding in children and adolescents, who experienced psychological trauma seems to be structural abnormalities of the corpus callosum (Rinne-Albers et al., 2013). Decreases in anterior and posterior regions of CC have been reported in maltreated children and adolescents compared to healthy subjects, especially in rostral body, splenium, rostrum and isthmus (De Bellis and Keshavan, 2003; Jackowski et al., 2008). A more recent study reported significant correlations between the degree of exposure to childhood peer verbal abuse with increased mean and radial diffusivity and decreased fractional anisotropy in the CC (Teicher et al., 2010). Childhood trauma is also reportedly associated with delayed myelination of the CC (Kaplow and Widom, 2007). However, a recent study showed no differences in CC mid-sagittal area in adolescents with trauma compared to those without (Mehta et al., 2009). Similar findings have been reported with animal models. An association between CC volume reduction and early life stress has been reported in a few studies with animals (Sánchez et al., 1998; Jackowski et al., 2011), especially in non-handled male rats (Berrebi et al., 1988) and male primates (Coe et al., 2002). On the other hand, others studies have reported no changes in CC with early trauma (Spinelli et al., 2009). Overall, the evidence seems to suggest a potentially causal relationship between early trauma and CC volume.

Furthermore, the neurobiological consequences of early stress may have an important role in the emergence of psychiatric disorders during the course of brain development (Teicher et al., 2003). Findings of smaller CC volume in psychiatric patients related to maltreatment have led to the hypothesis that childhood trauma is associated with a reduction in CC size in these individuals (Kitayama et al., 2007; Van Harmelen et al., 2010). Smaller CC areas also have been largely associated with posttraumatic stress disorder (PTSD) in children (De Bellis et al., 1999; De Bellis et al., 2002) and adults with trauma (Kitayama et al., 2007). Meta-analyses of magnetic resonance imaging (MRI) findings in pediatric samples with PTSD, who had experienced maltreatment, provide evidence of smaller CC volume compared to controls (Karl et al., 2006). This finding is however limited by the fact that PTSD is not the most common consequence of childhood maltreatment and only one third of children who experienced childhood maltreatment develop PTSD (Widom, 1999).

There is reportedly a high prevalence of childhood trauma in patients with psychotic disorders (Larsson et al., 2013), and the frequency of adverse life event appears to be higher and more severe in adults with a diagnosis of bipolar disorder (BD) compared with individuals with no psychiatric diagnoses (Kennedy et al., 2002; Nerila et al., 2005). Traumatic experiences may be considered a predictor of BD (Brietzke et al., 2012) and are strongly associated with a worse clinical presentation, such as, early onset of the disorder (Leverich et al., 2002; Daruy-Filho et al., 2011), high risk for developing alcohol and other substance abuse disorders (Leverich and Post, 2006; Daruy-Filho et al., 2011), rapid cycling (Post et al., 2001) and suicide attempts (Carballo et al., 2008; Daruy-Filho et al., 2011). However, the neurobiological consequences of childhood trauma on a maturing brain in BD patients remain unclear and could be a potential risk factor or disease modifier in BD (Etain et al., 2008).

There are few studies assessing CC volumes in BD. Decreased size of the CC in established BD patients compared to age-matched controls has been reported (Coffman et al., 1990; Brambilla et al., 2004; Arnone et al., 2008; Walterfang et al., 2009a, 2009b); in BD patients with first episode of mania compared to healthy subjects (Atmaca et al., 2007), there was a reduction in the areas of total CC, genu, anterior body, posterior body and isthmus and youths with BD showed smaller middle and posterior callosal regions compared to healthy controls (Lopez-Larson et al., 2010). On the other hand, there are studies in children and adolescents with BD that reported no significant differences in CC area, suggesting that CC abnormalities possibly appear late in the course of bipolar disorder (Yasar et al., 2006; Baloch et al., 2009). A meta-analysis of five studies evaluating CC volume in BD compared to healthy controls, reported a significant effect size ($-.52$, 95% CI = $-.82$, $-.21$) for decreased volume in BD (Arnone et al., 2008), after controlling for age and gender. However, none of these studies evaluated the prevalence and possible influence of childhood trauma on CC morphology in BD.

Although patients with BD demonstrate a high prevalence of childhood trauma and negative effects of such stress, such as poorer cognition even early in the course of illness (Bückner et al., 2013), morphometric studies in this population have not reported or controlled for child maltreatment. The present study examined the relationship between childhood trauma and CC volume in adults with BD, recently recovered from a first episode of mania. We hypothesized that the experience of childhood trauma would be associated with decreased CC volume in BD patients early in the course of illness, compared to BD patients without trauma and matched healthy controls.

2. Subjects and methods

The subjects for this study were drawn from the Systematic Treatment Optimization Program for Early Mania (STOP-EM) Project, details of which have been published elsewhere (Yatham et al., 2009; Torres et al., 2010). Briefly, patients between the ages of 16–34, who experienced their first manic or mixed episode within 3 months preceding enrolment, and met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, (DSM-IV-TR) criteria for bipolar I disorder were recruited. Diagnosis of bipolar I disorder was based on a clinical interview by a trained psychiatrist and a standardized psychiatric examination using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Patients presenting with a history of major medical or neurological illness underlying their manic symptoms or any contraindications to Magnetic Resonance Imaging (MRI) were excluded.

Healthy volunteers matched to patients on age, gender, pre-morbid and IQ, were recruited by advertisement from the community. Healthy subjects were screened using the MINI and excluded if they had history of major Axis I psychiatric disorder in themselves or first-degree relatives. There were only 5 healthy controls with trauma but they were excluded from the analysis due to the small sample size. Therefore, we included only healthy controls without a history of trauma based on Childhood Trauma Questionnaire (CTQ) scores (see description of measure below). Written informed consent was obtained from all patients and healthy subjects in accordance with the Declaration of Helsinki and the informed consent of the participants was obtained after the nature of the procedures had been fully explained. The study protocol was approved by the ethics committee of the University of British Columbia Clinical Research Ethics Board.

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