



## Short communication

# Interaction between *BDNF* rs6265 Met allele and low family cohesion is associated with smaller left hippocampal volume in pediatric bipolar disorder



Cristian Patrick Zeni<sup>a,\*</sup>, Benson Mwangi<sup>a</sup>, Bo Cao<sup>a</sup>, Khader M. Hasan<sup>b</sup>,  
Consuelo Walss-Bass<sup>a</sup>, Giovana Zunta-Soares<sup>a</sup>, Jair C. Soares<sup>a</sup>

<sup>a</sup> Department of Psychiatry and Behavioral Sciences, University of Texas Center of Excellence on Mood Disorders, Houston, TX, USA

<sup>b</sup> Department of Diagnostic and Interventional Imaging, UT Houston Medical School, Houston, TX, USA

## ARTICLE INFO

## Article history:

Received 10 July 2015

Received in revised form

10 September 2015

Accepted 18 September 2015

Available online 25 September 2015

## Keywords:

Bipolar disorder

BDNF

Family functioning

Gene-environment

Hippocampus

Neuroimaging

Pediatric

## ABSTRACT

**Background:** Genetic and environmental factors are implicated in the onset and evolution of pediatric bipolar disorder, and may be associated to structural brain abnormalities. The aim of our study was to assess the impact of the interaction between the Brain-Derived Neurotrophic Factor (BDNF) rs6265 polymorphism and family functioning on hippocampal volumes of children and adolescents with bipolar disorder, and typically-developing controls. **Methods:** We evaluated the family functioning cohesion subscale using the Family Environment Scale-Revised, genotyped the BDNF rs6265 polymorphism, and performed structural brain imaging in 29 children and adolescents with bipolar disorder, and 22 healthy controls. **Results:** We did not find significant differences between patients with BD or controls in left or right hippocampus volume ( $p=0.44$ , and  $p=0.71$ , respectively). However, we detected a significant interaction between low scores on the cohesion subscale and the presence of the Met allele at BDNF on left hippocampal volume of patients with bipolar disorder ( $F=3.4$ ,  $p=0.043$ ). None of the factors independently (BDNF Val66Met, cohesion scores) was significantly associated with hippocampal volume differences. **Limitations:** small sample size, cross-sectional study. **Conclusions:** These results may lead to a better understanding of the impact of the interaction between genes and environment factors on brain structures associated to bipolar disorder and its manifestations.

© 2015 Elsevier B.V. All rights reserved.

## 1. Introduction

The most consistently reported contributing factor to bipolar disorder (BD) occurrence in children and adolescents (Pediatric Bipolar Disorder – PBD) is the presence of BD in first-degree relatives (Pavuluri et al., 2006). Specifically, 60% of phenotypic variance in BD has been attributed to genes. The *BDNF* val66met polymorphism (rs6265) has been consistently implicated in the pathophysiology of BD (Geller et al., 2004). This genetic variation is located on the chromosome 11p13 and results into a valine (G) to methionine (A) substitution at codon 66. BDNF is a molecule related to neuronal survival, growth and differentiation-neural and synaptic plasticity (Grande et al., 2010). Previous studies have extensively discussed the impact of BDNF in many aspects of BD, and BDNF polymorphisms have been associated with alterations in

brain structure and function (Kapczynski et al., 2008). Furthermore, neuroimaging studies have demonstrated that BDNF allelic variations are associated with different anterior cingulate and hippocampal volumes, and abnormal hippocampal activation (Matsuo et al., 2009; Szeszko et al., 2005). However, there has been a failure to replicate many candidate gene associations findings, including those for BDNF, probably due to the small effect size of individual genes in such a heterogeneous disorder as PBD (Gottesman and Gould, 2003). Assessment of the impact that interactions between candidate genes and environmental factors have on structural brain changes implicated in BD episode onset and disease progression, may be an important intermediate step towards understanding BD pathophysiology.

Families of children with BD present high levels of dysfunction, possibly due to the rollercoaster of emotions caused by BD mood swings (Miklowitz, 2004). Low cohesion has been the most consistent finding across studies assessing the relationships between families with BD (Nader et al., 2013; Belardinelli et al., 2008; Romero et al., 2005). Cohesion can be defined as the emotional

\* Correspondence to: Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center, 1941 East Road Houston, TX, 77054, USA.  
E-mail address: [Cristian.P.Zeni@uth.tmc.edu](mailto:Cristian.P.Zeni@uth.tmc.edu) (C.P. Zeni).

bonding that family members have toward one another, and strong emotional bonds are expected to promote family support. Psychosocial treatment models for PBD focusing on family functioning such as the Family Focused Treatment have promoted lower relapse rates and reductions in mood symptoms. Following such interventions, the presence of low cohesion was associated with lower response in terms of overall psychiatric severity (Weinstein et al., 2015).

Hippocampus plays a key role in mood and behavior regulation, and the association between abnormal hippocampal volumes and BD has been extensively reported in the literature of adult BD (Frey et al., 2007). Available data suggests children and adolescents with BD present a decrease in hippocampal volumes when compared to healthy controls (Frazier et al., 2005; Blumberg et al., 2003), but other studies fail to detect such differences (Chang et al., 2005; Dickstein et al., 2005; Chen et al., 2004). These conflicting results may reflect methodological differences across studies, the effect of illness evolution (i.e., the recently reported negative correlation between the right hippocampal volume and the duration of bipolar disorder in adolescents – Inal-Emiroglu et al., 2015), or the participation of environmental factors.

We report in this article an interaction between genetic and environmental factors impacting brain structures in pediatric bipolar disorder. Specifically, we assessed the interaction between the BDNF val66met polymorphism and family functioning-cohesion on hippocampal volume. We hypothesized that both gene and family functioning would predict differences in hippocampal volumes, and a synergistic effect would be observed when the Met allele and worse family functioning are combined.

## 2. Material and methods

### 2.1. Sample

This study was approved by the local institutional review board at The University of Texas Health Science Center at Houston. Written informed assent and consent were obtained from all subjects and their guardians.

The inclusion criteria for the patient group was DSM-IV diagnosis of bipolar disorder [bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified (NOS)] through a structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (APA, 1994). Patients were included if they were 8–18 years old, male or female, and free of any psychotropic drugs for at least two weeks prior to MRI scans. The exclusion criteria were: history of substance abuse, pregnancy, neurologic disorders, head injury with loss of consciousness, family history of hereditary neurologic disorders, and presence of metallic objects in the body impeding MRI. The inclusion criteria for healthy controls were no history of any personal psychiatric or neurologic disorders, or in first-degree relatives.

### 2.2. Diagnostic and functioning assessment

Participants were evaluated for DSM-IV-TR Axis I disorders using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (Sheehan et al., 2010). A senior psychiatrist (JCS) reviewed all clinical information, including history of medical and neurological conditions, and confirmed that all subjects met DSM-IV-TR diagnostic criteria for bipolar disorder, and that healthy controls would not have any Axis I DSM-IV disorder.

Family functioning ratings were assessed using the parent-rated scale Family Environment Scale (FES – Moos and Moos, 2002). This is a likert scale which provides information about

family strength and problem areas. The FES is composed of 90 items distributed in 10 subscales (Cohesion, Expressiveness, Conflict, Independence, Achievement Orientation, Intellectual-Cultural Orientation, Active-Recreational Orientation, Moral-Religious Emphasis, Organization, and Control). These can be grouped into three dimensions (Family Relationship, Personal Growth, and System Maintenance). Due to our small sample size, we only assessed the effect of cohesion, since this subscale has been the most consistently altered factor in family functioning of BD (Nader et al., 2013; Belardinelli et al., 2008; Romero et al., 2005).

### 2.3. Magnetic resonance imaging (MRI) acquisition and processing protocol

All structural MRI images were visually inspected for gross artifacts, hippocampal volumetric measurements were extracted through a standard procedure using Freesurfer software (Postelnicu et al., 2009; Fischl, 2012) version 5.3 (<http://surfer.nmr.mgh.harvard.edu>). Freesurfer volumetric measurements have successfully been used in previous pediatric neuroimaging studies (Ecker et al., 2010). All the analyses were performed considering volumes for the hippocampus corrected according to each participant total intracranial volume, due to the high variation in our age range, and also to account brains size variability between males and females.

### 2.4. BDNF gene polymorphism determination

Blood was drawn by venipuncture and DNA extracted from white blood cells using the PUREGENE kit (Gentra Systems). The BDNF genotype (rs6265) was determined using a TaqMan<sup>®</sup> primer-probe assay ID C\_11592758\_10. PCR amplification was performed at 50 °C for 2 min, 95 °C for 10 min, and then 50 cycles of 95 °C for 15 s, and 60 °C for 1 min. The amplification products were analyzed using an Applied Biosystems Prism 7900 sequence detection system and SDS 2.2 software (Applied Biosystems). TaqMan<sup>®</sup> assays were performed in duplicate by an individual unaware of the clinical status of the subjects. In subsequent analyses, individuals with Val/Met or Met/Met genotypes were combined (Met carriers) and compared with individuals with the Val/Val genotype.

### 2.5. Statistical analysis

Analysis-of-variance (ANOVA) was performed with corrected left and right hippocampal volumes as outcome variables. Independent variables were genotypes: Val/Val, or Met carriers, and high/low cohesion scores. Categorization of scores was based on the normative data of the scale (Moos and Moos, 2002). Thus, there were three groups in our analysis: healthy controls, patients with BD and low cohesion scores, and patients with BD and high cohesion scores. Age and gender were included in the analysis as covariates. Post-hoc analysis was performed between the three diagnosis-cohesion groups with Bonferroni correction.

## 3. Results

The study participants included 29 children and adolescents with a DSM-IV diagnosis of bipolar disorder, and 22 healthy controls. Characteristics of the sample are shown in Table 1. Specifically in BD, 18 patients (62%) presented comorbid attention-deficit/hyperactivity disorder, 12 (41%) presented disruptive behavior disorders, and 9 (31%) presented anxiety disorders.

We did not find significant differences between patients with BD or controls in left or right hippocampus volume ( $p=0.44$ , and  $p=0.71$ , respectively). Also, no significant differences were

Download English Version:

<https://daneshyari.com/en/article/6230843>

Download Persian Version:

<https://daneshyari.com/article/6230843>

[Daneshyari.com](https://daneshyari.com)