Journal of Affective Disorders 198 (2016) 198–205

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Reduced hippocampus volume and memory performance in bipolar disorder patients carrying the *BDNF* val66met met allele

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ARTICLE INFO

Article history:
Received 29 September 2015
Received in revised form
8 March 2016
Accepted 9 March 2016
Available online 10 March 2016

Keywords:
Bipolar disorder type I
BDNF val66met
Polymorphism
Hippocampus
Volume
Memory
MRI
Bipolar
Major depressive disorder

ABSTRACT

Background: Previous studies investigated the impact of brain-derived neurotrophic factor (*BDNF*) val66met (rs6265) on hippocampus volumes and neurocognition in bipolar disorders (BD), but the results were not consistent. This study aimed to investigate the effect of *BDNF* polymorphism on hippocampus volumes and memory performance in well-characterized adult populations diagnosed with type I BD (BD-I) and major depressive disorder (MDD) compared with healthy controls (HC).

Methods: 48 BD-I patients, 33 MDD patients and 60 HC were genotyped for *BDNF* rs6265 using DNA isolated from white blood cells. Individuals with val/met and met/met genotypes were grouped as met carriers and compared to those with the val/val. Brain segmentations were obtained from structural magnetic resonance imaging (MRI) using the Freesurfer. Memory performance was assessed with the California Verbal Learning Task (CVLT).

Results: We found a significant diagnosis effect and marginal interaction between diagnosis and *BDNF* genotype group for both hippocampus volumes and memory performance. *BDNF* met allele carrier BD patients had smaller hippocampus volumes and reduced performance on multiple CVLT scores compared to MDD patients and HC.

Conclusions: We provide strong evidence for the *BDNF* val66met polymorphism as a putative biological signature for the neuroanatomical and cognitive abnormalities commonly observed in BD patients.

1. Introduction

Bipolar Disorder (BD) is a significantly disabling chronic psychiatric condition with characteristic depressive and manic phases and lifetime prevalence of 3.9% (Kessler et al., 2005; Yatham et al., 2009). BD has long been sought to be associated with a number of neuroanatomical changes in the fronto-limbic regions, hippocampus, basal ganglia and corpus callosum (Chepenik et al., 2009b; Lavagnino et al., 2015; Radaelli et al., 2015; Selek et al., 2013). Notably, the hippocampus – a brain region widely acknowledged for its role in declarative memory (Eldridge et al., 2000) and emotion processing (Houenou et al., 2011) - has been reported to be either reduced (Bearden et al., 2008; Blumberg et al., 2003a; Chepenik et al., 2009b; Hartberg et al., 2011), enlarged (Beyer et al., 2004; Javadapour et al., 2010; van Erp et al., 2012) or unchanged (Altshuler et al., 2000; Bertolino et al., 2003; Brambilla et al., 2003; Chen et al., 2004; Delaloye et al., 2009) compared to healthy controls (HC). The reported discrepancies could arguably be attributed to methodological factors, such as the variety of techniques used to demarcate brain structures and demographic and clinical characteristics of the sample, such as age and gender related brain characteristics (Blumberg et al., 2003b), BD subtype (Strasser et al., 2005) and medication history (Yucel et al., 2008). Thus, further investigation of the hippocampus volume alterations in BD with careful control of the above factors is warranted.

In addition to potential brain abnormalities, the majority of BD patients have significant cognitive impairments that persist during

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http://dx.doi.org/10.1016/j.jad.2016.03.044
0165-0327/

the euthymic and acute phases of the illness (APA, 2002; Bora et al., 2009; MacQueen et al., 2001; Quraishi and Frangou, 2002). Overall, there is evidence of deficits in visuomotor processing speed, verbal memory and executive functioning (van der Werf-Eldering et al., 2011). Impairments of smaller effect size in working memory, and sustained attention have also been reported (Cohen's d = 0.6–0.7) (Albus et al., 1996; Bora et al., 2009; Goldberg et al., 1993; Martínez-Arán et al., 2004; Quraishi and Frangou, 2002). The presence of verbal memory impairment across mood phases may indicate that these deficits are trait markers of the bipolar illness (Gualtieri and Johnson, 2006). In particular, a study comparing manic, hypomanic, depressive and euthymic BD patients showed that manic BD patients had the most robust cognitive deficits of all treatment groups and presented poor immediate and delayed verbal memory performance on the California Verbal Learning Test (CVLT) and executive tasks (Sweeney et al., 2000).

Along with neurocognitive deficits, BD is characterized by high peripheral levels of pro-inflammatory markers (Barbosa et al., 2011) and decreased brain-derived neurotrophic factor (BDNF) levels (Bourne et al., 2013; Cunha et al., 2006). BDNF is a member of the neurotrophin family of growth factors and regulates major cellular processes such as neurogenesis, development, dendritic growth, survival and maturation (Kuipers and Bramham, 2006) as well as complex neuronal processes such as synaptic plasticity and memory consolidation (Post, 2007). The *BDNF* val66met polymorphism (rs6265) has been consistently implicated in candidate gene studies examining the pathophysiology of BD (Bourne et al., 2013; Cunha et al., 2006). This single nucleotide polymorphism is located on chromosome 11p13 and results in a valine (G) to methionine (A) substitution at codon 66 (Bath and Lee, 2006; Green et al., 2006; Hwang et al., 2006; Liu et al., 2008; Neves-Pereira et al., 2002; Sklar et al., 2002). Further, in neuronal and neurosecretory cells the *BDNF* val66met polymorphism can lead to a significant reduction in BDNF trafficking to secretory granules, and as a result, to a reduced BDNF production by the secretory granules (Benjamin et al., 2010; Egan et al., 2003).

A number of studies have linked the BDNF *val/met* polymorphism to abnormal hippocampus volumes across the mood disorder spectrum in both adults (Benjamin et al., 2010; Chepenik et al., 2008; Gatt et al., 2009; Montag et al., 2009; Pezawas et al., 2004) and pediatric populations with BD (Inal-Emiroglu et al., 2015; Peruzzolo et al., 2015). However, findings in this field remain controversial as a recent systematic and meta-analysis review based on 18 independent clinical cohorts comprising 1695 participants showed that the decreased hippocampus volume observed in patients with mood disorders, psychosis and schizophrenia relative to healthy controls did not depend on the BDNF polymorphism (Harrisberger et al., 2015). Notably, the authors reported that most studies were underpowered and did not provide information about treatment regimen, comorbidities, and progress/severity of the disease. These factors should therefore be taken into account in future investigations. To date it is still unclear whether the relationship between *BDNF* polymorphisms and hippocampus volumes is specific to BD as a broad diagnostic group, or whether it is specific to a bipolar subtype. For instance BD type I is viewed as being the most severe form of BD as it involves more pronounced anatomical (Maller et al., 2014) and cognitive impairments (Bourne et al., 2015) than BD type II. In addition a study showed that the number of manic episodes – observed in BD-I and not BD-II- is inversely correlated with performance in learning and memory tests (Bourne et al., 2015).

Thus, in the current study we recruited a well-characterized group of individuals with BD type I and major depressive disorder (MDD) compared to healthy controls (HC). Based on previous studies, we hypothesized that the *BDNF* val66met variant would be associated with abnormalities in hippocampus volumes and memory performance – as measured by the CVLT – in both individuals with BD type I and MDD, as well as healthy controls (HC).

2. Materials and methods

2.1. Participants

The sample included 48 BD-I patients (32 females, age (Mean ± S.D.) = 41.02 ± 12.65 years), 33 MDD patients (23 females, age (Mean ± S.D.) = 39.17 ± 12.42 years) and 60 HC (39 females, age (Mean ± S.D.) = 40.57 ± 12.95 years). Patients were recruited from inpatient and outpatient clinics at the University of Texas Health Science Center at San Antonio campus. HC were recruited through local media advertisements and flyers posted in public areas. All patients met the DSM-IV-R criteria for BD-I or MDD. The diagnosis of BD-I and MDD and the absence of mental disorders among controls were ascertained by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders Axis I (SCID I), which was administered to all participants by an independent psychiatrist or trained research assistant. Based on the SCID assessment 16 BD and 18 MDD patients were classified as euthymic and 20 BD and 15 MDD patients as depressed at the time of testing. Fourteen MDD patients had achieved complete remission, while the remnant of the sample experienced episodes of depression of mild to moderate intensity (based on the SCID diagnosis). The interview also included the Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). All participants had no history of substance abuse in the previous 6-months and no chronic medical issues including cardiovascular and neurological disorders. At the time of enrollment 44 of the 48 participants with BD type I reported taking one or more psychotropics. Primary types of medication included lithium (n = 2), antidepressant (n = 5), anticonvulsants (n = 5), atypical antipsychotics (n = 1) and benzodiazepines (n = 3). Eighteen participants took two or more medications concurrently. There was no medication history data available for 10 of the 44 medicated BD patients. One of the 33 patients with MDD took lithium. HC with a history of any Axis I disorder in the first-degree relatives and use of psychoactive medication less than 2-weeks prior to the start of the study were excluded. All female participants underwent a urine pregnancy test and urine drug screen to exclude participants with pregnancy and illegal drug use. The study protocol was approved by the local Institutional Review Board and informed consent was obtained from all the participants.

2.2. Genotyping

DNA was extracted from white blood cells from blood samples collected from study participants with the Gentra Puregene blood kit (Qiagen, Germantown, MD). val66met (rs6265) genotyping was performed with a 5′-fluorogenic exonuclease assay (C__11592758_10) (TaqMan®, Applied Biosystems, Foster City, CA) or an ABI 7900 Sequence Detection System (Applied Biosystems, Foster City, CA) in duplicates by an individual blind to participants clinical status. Platinum® quantitative PCR SuperMix-UDG (Invitrogen, Carlsbad, CA) on a GeneAmp PCR system 9700 was employed for PCR amplification. Applied Biosystems Prism® 7900 sequence detection system and SDS 2.2 software (Applied Biosystems) were used for analysis of amplification products. In subsequent analyses individuals with *val/met* or *met/met* genotypes were combined (met carriers) and compared with individuals with the *val/val* genotype, because met/met carriers only occupy about 6% of the total sample.

2.3. Hippocampus volume

High resolution T1-weighted brain images were acquired on a Philips 1.5 Tesla MR system (Philips Medical System, Andover, MA, USA). Images were collected by means of an axial three-dimensional fast field echo sequence (field of view 256 mm × 256 mm; repetition time 24 ms; echo time 5 ms; flip angle 40°; slice thickness 1 mm).

After all scans were visually inspected to be valid, cortical and subcortical reconstruction and volumetric segmentation were performed with the Freesurfer software version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). The whole procedure included motion correction, intensity normalization, automated topology corrections and automatic segmentations of cortical and subcortical regions, as documented elsewhere (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 2001, 2002, 2004, 1999; Han et al., 2006; Jovicich et al., 2006; Ségonne et al., 2004). The regions labeled as left and right hippocampus were extracted, and the corresponding volumes were calculated (Fischl et al., 2002). Both left and right hippocampus volumes were scaled by the estimated total intracranial volume for each subject to control for differences in head size.

2.4. Cognitive performance

All participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI), which is a screener of verbal, nonverbal, and general cognitive ability [41], and the Wechsler Test of Adult Reading (WTAR), which is a measure of premorbid intellectual quotient (IQ) (Holdnack, 2001). 116 out of the total 141 participants were administered a revised version of the CVLT – a standardized test measuring verbal learning and declarative memory via a trial list-learning paradigm (Donders, 2008). This version of the CVLT was part of the South Texas Assessment of Neurocognition (STAN) which includes both standardized and computerized neurocognitive tasks (Glahn et al., 2007). In the CVLT task participants are presented orally with 16 words for 5 times and asked to recall as many words as possible in any order (immediate recall). After being presented with an intrusion list (List B), participants are asked to recall the words included in the List A one more time via cues (short delay cued recall) and without cues CVLT short-delay (free recall). After a 20-min delay participants are asked to recall words from List A, both with the aid of categorical cues (long delay cued recall) and spontaneously (long delay free recall). Scores of each CVLT variable represented the number of correctly recalled words. Four subjects were excluded from analyses because they did not complete the whole or part of the CVLT.

2.5. Statistical analyses

Statistical analyses were performed using IBM SPSS statistics (Version 21.0). Normality of each variable was verified. One subject was excluded as an outlier (outside 3 standard deviations) in hippocampus volume. Demographic, clinical and cognitive differences between groups were assessed with chi-square and a series of univariate analyses of variance (ANOVA). A general linear model (GLM) was used with bilateral hippocampus volumes as the dependent variable, and two between-subject factors: diagnosis (BD-I vs. MDD vs. HC) and genotype (met-allele carrier vs. val/val genotype). Hippocampus laterality was a within-subject variable, and age and gender were entered to the model as covariates. The threshold of statistical significance was set at $p < 0.05$ and a Bonferroni correction for multiple comparisons was performed across the three diagnosis groups for *post hoc* tests.

The CVLT data were analyzed using a GLM with two between-subject independent factors: diagnosis (BD-I vs MDD vs. HC) and genotype (0 = met-allele carrier vs. 1 = val/val genotype). Five CVLT performance measures (CVLT trial-1-to-5, short delay cued recall, short delay free recall, long-delay cued recall and long-delay free recall) served as within subject factors. Age and gender were entered as covariates. Linear regression analyses were performed to examine the link between hippocampus volume, CVLT scores, diagnosis, *BDNF* genotype, and the interactions between diagnosis and *BDNF* genotype. Age and gender were entered as predictors and CVLT scores were the outcomes measures.

3. Results

3.1. Demographics and clinical description

Demographics and clinical features for BD, MDD and HC are reported in Table 1. There was no significant difference in age, gender and genotype distribution between the three groups. However, there were different levels of educational attainment across groups ($p < .05$) with BD-I individuals reporting less years of education than HC. Overall HAM-D scores were significantly higher in BD-I, and to a lesser extent MDD patients, compared to HC. YMRS scores were higher in BD-I patients compared to HC and MDD patients.

3.2. Hippocampus volume

We found a main effect of diagnosis on the hippocampus volumes ($F(2,133) = 9.527$, $p < 0.001$), a marginal effect of *BDNF* genotype [$F(1,133) = 3.762$, $p = 0.055$] and a marginal interaction between diagnosis and *BDNF* genotype [$F(2,133) = 3.040$, $p = 0.051$] (Fig. 1a). *Post-hoc* tests with the Bonferroni correction showed that within *BDNF* met carriers, BD-I patients displayed smaller hippocampus volumes compared to HC ($p = 0.01$) and MDD ($p = 0.003$), and MDD patients have similar hippocampus volumes with HC ($p = 0.725$). *BDNF* val/val genotype BD-I patients had similar hippocampus sizes as HC ($p = 0.257$) and MDD patients ($p = 0.747$),

Table 1
Demographic and clinical features of study participants (Mean ± standard deviation (SD)).

	Healthy control (n = 60)	BD-I (n = 48)	MDD (n = 33)	F/X^2	*P-value*
Age (years)	40.57 ± 12.95	41.02 ± 12.65	39.17 ± 12.42	0.21	0.81
Gender (n of females)	39	32	23	0.21	0.9
***BDNF* met carriers**	19	13	8	0.63	0.72
Ethnicity					
Caucasian	25	35	20	18.14	0.02
Hispanic	26	12	13		
Asian	6	0	0		
Other	1	0	0		
Multi-racial	1	0	0		
Missing	1	1	0		
Education (years)[a]	16.51 ± 3.34	13.9 ± 1.87**	15.03 ± 2.99*	9.70	< 0.01
WTAR[b]	38.15 ± 9.33	37.5 ± 7.84	39.29 ± 8.44	0.37	0.7
YMRS	0.28 ± .71	6.65 ± 7.26**	1.94 ± 2.08	8.44	< 0.01
HAM-D	0.93 ± 1.27	12.67 ± 8.11**	10.39 ± 8.77**	50.8	< 0.01

** $P < 0.01$.
* $P < 0.05$.
[a] Total n for the variable "years of education" is 21.
[b] Total n for the variable "WRAT" is 111.

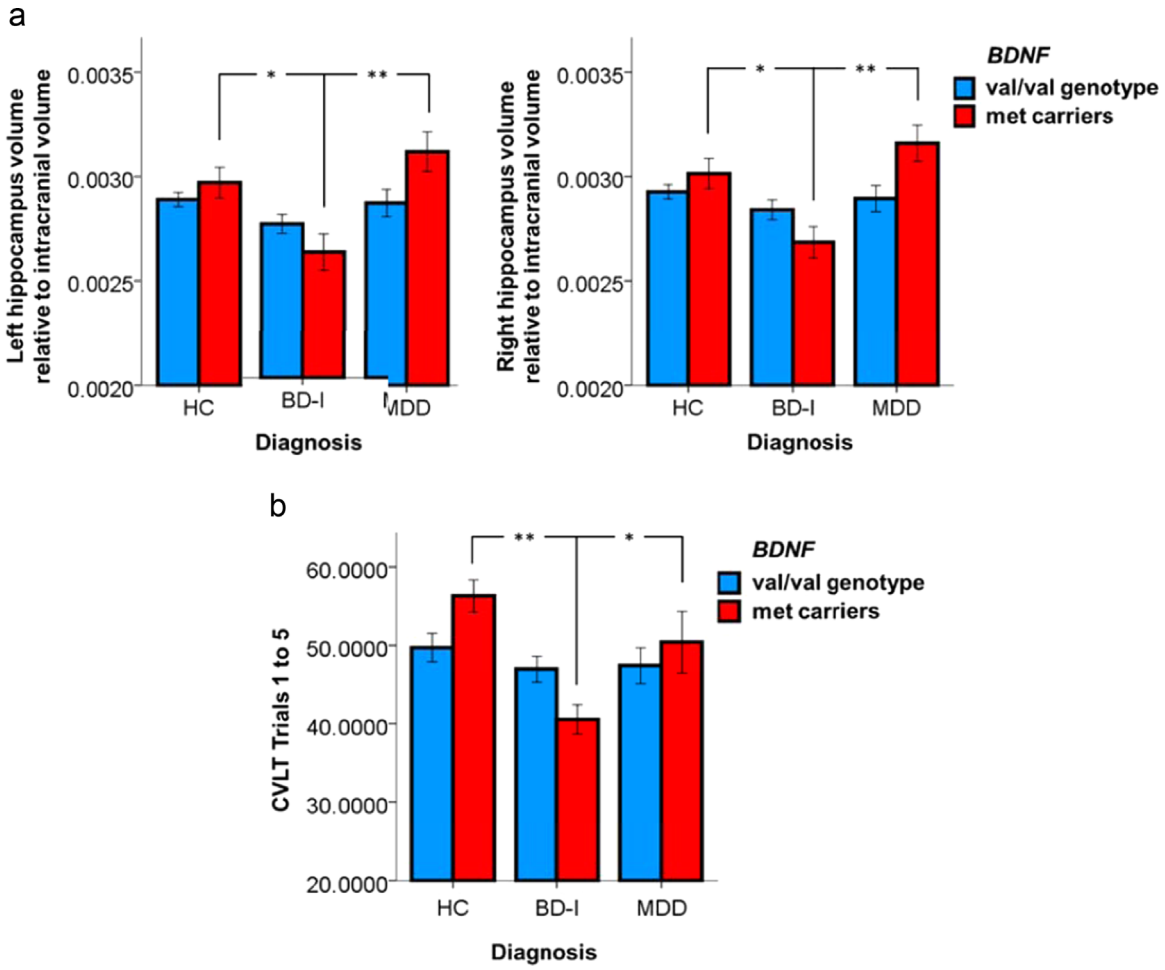

Fig. 1. Reduced hippocampus volume and memory performance in bipolar disorder patients carrying the *BDNF* val66met met allele. (a) Ratios of bilateral hippocampus volumes relative to the intracranial volume in HC, BD-I and MDD patients; (b) Total number of correctly recalled words on the CVLT Trials 1–5. * $p < 0.05$; ** $p < 0.005$.

and MDD patients have similar hippocampus volumes with HC ($p=1$). There was no main effect of laterality on the hippocampus [$F(1,133)=0.072$, $p=0.788$]. Further, we did not find an interaction between laterality and diagnosis [$F(1,133)=0.149$, $p=0.861$] and *BDNF* genotype [$F(1,133)=0.001$, $p=0.971$] and no triple interaction between laterality, diagnosis and *BDNF* genotype [$F(1,133)=0.003$, $p=0.796$].

3.3. Cognitive performance

We found a main effect of diagnosis on all CVLT measures [$F(2,108)=8.139$, $p=0.001$] and a significant interaction between diagnosis and *BDNF* genotype [$F(2,108)=3.509$, $p=0.033$]. However, the *BDNF* genotype main effect did not reach significance [$F(1,108)=0.702$, $p=0.404$]. Bonferroni-corrected *post-hoc* tests showed that among BDNF val/val genotype BD-I patients showed similar memory performance compared with HC ($p=1$) and MDD patients ($p=1$). However, *BDNF* met carrier BD-I patients showed worse memory performance compared to HC ($p < 0.001$) and MDD ($p=0.019$). Fig. 1b shows the scores of CVLT trials 1–5. The other four CVLT scores had a similar pattern (see Supplementary materials Fig. S1). Although there was a main effect of both diagnosis and *BDNF* genotype on the hippocampus volumes and memory performance measured by CVLT tests, a partial correlation analysis adjusted for diagnosis, *BDNF* genotype, age and gender revealed a trend toward a positive correlation between the right hippocampus volume and the long delay free recall score marginally ($r=0.166$, $p=0.081$).

Further regression analysis found that across clinical populations the left and right hippocampus volumes explain an additional variance of less than 0.6% for the immediate learning and short delay scores, and less than 3.5% for long delay scores. By comparison a regression model including the predictors diagnosis, *BDNF* genotype, age and gender explains 20–25% of the total variance in CVLT scores. Across groups the hippocampus volumes did not explain additional variance in CVLT scores ($p > 0.05$). Except the long delay cued recall, the variance in CVLT scores explained by the interaction between diagnosis and *BDNF* genotype was significant for BD and HC ($p < 0.05$), but not for MDD and HC ($p > 0.05$).

4. Discussion

The current study examined the effect of the *BDNF* val66met genotype on hippocampus volumes in patients with BD-I and MDD compared to demographically matched healthy controls. Given the role of the hippocampus in information encoding and memory storage, we also explored the relationship between *BDNF* genotype on memory performance measured by the CVLT. The most important finding of this study is the association between the *BDNF* val66met polymorphism and reduced hippocampus volumes in BD-I patients. Indeed, in our sample, BD patients carrying the met allele of the *BDNF* gene were found to have smaller hippocampus volumes and reduced memory performance compared to HC. This result corroborates previous findings on the link

between the val66met polymorphism and BD-I (Lohoff et al., 2005) and reduced hippocampus volumes and BDNF expression in BD (Chepenik et al., 2009a).

We observed a significant reduction in hippocampus volumes in met carrier BD-I patients. Traditionally, studies on hippocampus abnormalities in BD have been inconsistent. Previous *in vivo* studies showed either no differences in hippocampus volumes between BD patients and HC (Frey et al., 2007), or smaller hippocampus volumes in BD patients (Bearden et al., 2008; Frazier et al., 2005). A post-mortem study demonstrated reduced pyramidal cell size in the hippocampus of BD patients compared with HC (Liu et al., 2007). Given the dearth of genetic studies integrating neuroanatomical data further investigations are needed to determine whether the *BDNF* polymorphism mediates these anatomical abnormalities. An alternative explanation for the divergent findings may be related to the administration of psychotropic medication such as lithium and valproate that are hypothesized to reduce oxidative stress possibly by boosting the expression of the BDNF protein expression (Frey et al., 2006) in a number of brain regions including the hippocampus (Nibuya et al., 1996). It is also compelling that antidepressants and lithium lead to volumetric changes possibly induced by the increased proliferation and maturation of hippocampus cells (Foland et al., 2008; Yucel et al., 2007). Although in our sample, 44 of the 48 BD-I patients were medicated at the time of testing, the significant reductions in hippocampus volumes were observed only in met carrier BD-I patients, and therefore were unlikely to be the effect of medication.

While the presence of memory impairment in BD is well-established (Bearden et al., 2006), less is known about the association between the *BDNF* val66met polymorphism and cognition in BD and related mood disorders. Our lab has previously shown that met carriers displayed a poorer (albeit not statistically significant) memory performance compared to BD patients and HC with the val/val genotype with a smaller sample (Matsuo et al., 2009). Further, cognitive differences between met carriers and those with a val/val genotype have been found on the Wisconsin Card Sorting Test – a test of abstraction and inhibition (Rybakowski et al., 2006, 2003). Studies of patients with schizophrenia showed that met carriers have poorer spatial and verbal memory performance (Egan et al., 2003; Ho et al., 2006) along with smaller hippocampus (Egan et al., 2003; Szeszko et al., 2005), parahippocampus and supramarginal gyrus volumes when compared with val/val carriers (Ho et al., 2006). Notably, we found that BD carrying the *BDNF* met allele displayed worse neurocognitive performance than MDD and HC. By contrast, the memory performance of MDD patients did not differ from that of HC. The latter finding is likely to be due to the fact that the majority of the MDD patients (n=18) included in this study were euthymic, and that approximately half of them (n=14) were in full remission at the time of testing.

The current findings appear to be in line with the neuroprogression model of BD (Berk et al., 2011; Fries et al., 2012). This model proposes to explain the pathological brain rewiring that takes place in the context of severe mental disorders (Berk et al., 2011; Fries et al., 2012; Kapczinski and Streb, 2014), and links recurrent mood episodes with the disruption of the homeostasis between inflammatory mechanisms, oxidative processes, and neuroprotective mechanisms (e.g., BDNF). This disruption has been linked to an increase in the individual's vulnerability to psychological stress, brain atrophy and ultimately cognitive impairment (Berk et al., 2010; Kapczinski et al., 2008). Notably, in BD neuroprogression has been associated with cognitive decline, refractoriness, brain volume changes and a more severe course of illness. (Bauer et al., 2014; Cao et al., 2016). Further these results highlight the importance of *BDNF* on the hippocampus function and may provide a rationale for individualized pharmacological interventions targeting inflammation in subjects carrying the met allele. For instance, met carriers may be more at risk for inflammation and resulting consequences in terms of neuroprogression. Thus, interventions aimed to reduce physiological stress may help reverse neuroanatomical abnormalities.

Our findings supports further investigation into the link between memory performance and hippocampus volumes (Otten and Meeter, 2015). Indeed our regression analyses showed that in BD the hippocampus volume did not significantly contribute to the explained variance in memory performance. Thus, other factors may mediate the link between the hippocampus volumes and memory performance, and may differ across the mood disorder spectrum. Future studies with factorized models are therefore necessary to reveal the specific connections between BD, *BDNF* genotypes, hippocampus volumes and neurocognitive performance.

Our sample has few limitations, such as the MDD sample might not be completely homogeneous (14 out of 33 MDD patients were in remission), and there was a small but significant difference in education levels between groups. Given the high number of missing data (n=20) for the variable education we decided against adding it as a covariate. However, exploratory analyses showed that after adding education as an additional covariate along with age and gender, the main effect of diagnosis on the hippocampus volumes remained significant ($F(2,112)=7.225$, $p=0.001$) and the interaction between diagnosis and *BDNF* genotype approached significance ($F(2,112)=3.060$, $p=0.051$). Similarly, for CVLT, both the main effect of diagnosis ($F(2,91)=4.426$, $p=0.015$) and the interaction between diagnosis and *BDNF* genotype were significant ($F(2,91)=3.254$, $p=0.043$). Furthermore, the BD-I group was the only one who received medication and psychotropic drugs have well-known effects on BDNF expression (Notaras et al., 2015). For instance antidepressant medication leads to increased brain-derived neurotrophic factor (BDNF) receptor trkB signaling (Chi et al., 2010), and lithium has been shown to alter the magnetic resonance imaging (MRI) signal and lead to potential misinterpretation of grey matter volume changes. However, these medicines usually increase the hippocampus volume, and thus, the decreased hippocampus volume observed in our BD-I patients with the met genotype was in the opposite direction of the volumetric effect of these medicines and was less likely to be caused by them. In contrast to previous studies, we did not find significant reduction of hippocampus volumes in healthy met carriers (Bueller et al., 2006; Egan et al., 2003; Pezawas et al., 2004). A potential explanation for the divergence in findings may be due to the different types of image processing and selection of brain structures and reconstruction methods between our study and those studies e.g. manual tracing (Bueller et al., 2006) vs. automatic reconstruction with Freesurfer in our study, and grey matters selected in the regions of interest (ROI) by voxel-based morphometry (VBM) (Pezawas et al., 2004) vs. whole hippocampal volume segmented by Freesurfer in our study. Manual tracing is a rather time-consuming approach that is suitable for large rather than small brain structures. VBM registers every brain to a template and is therefore sensitive to errors such as misalignment of brain structures and tissues. While VBM uses less *a priori* information, but an efficient image segmentation algorithm (Zhang et al., 2001), Freesurfer relies on *a priori* information (Fischl et al., 2002). Notably, a recent study showed that Freesurfer yields more valid results than VBM in terms of hippocampus segmentation (Grimm et al., 2015). Furthermore, in our study, we scaled the hippocampus volumes by the estimated total intracranial volume to control for differences in head size, and corrected our analyses for both age and gender. By comparison, Pezawas et al. (2004) reported grey matter ratio to val/val mean and Bueller et al. (2006) adjusted hippocampal differences only for gender. The results of our study still need to be interpreted with caution due to these limits.

To the best of our knowledge, this is the first study to view anatomical and cognitive features as a function of BDNF polymorphisms in individuals with BD type I, MDD and HC. Our study provides evidence that the val66met polymorphism is associated with reduced memory performance in BD-I patients. The current findings highlight potential differences in the role of *BDNF* val66met polymorphisms in neurocognition across the mood disorder spectrum (MDD vs. BD). Furthermore, they raise questions on the possible link between neurocognitive impairment and BDNF variants across BD subtypes.

Author contributions

Study concept and design: Cao, Bauer, Sharma.

Acquisition, analysis, or interpretation of data: Cao, Bauer, Sharma, Frazier, Nielsen, Mwangi, Lavagnino, Soares.

Drafting of the manuscript: Cao, Bauer, Sharma.

Critical revision of the manuscript for important intellectual content: Cao, Bauer, Sharma, Mwangi, Frazier, Lavagnino, Walss-Bass, Glahn, Kapczinski, Nielsen, Soares.

Statistical analysis: Cao, Bauer.

Administrative, technical, and material support: Zunta-Soares.

Study supervision: Kapczinski, Soares.

Funding sources

The current work was supported by: NIH/NIDA 5 P50 DA018197-05 (DN), through MD Anderson's Cancer Center Support Grant NIH/NIDA DA026120 (DN), and the Toomim Family Fund (David A. Nielsen), NIMH Grant R01 085667, the Dunn Research Foundation and the Pat Rutherford, Jr. Endowed Chair in Psychiatry (Jair C. Soares). The genetic findings are the result of work supported with resources and the use of facilities at the Michael E. DeBakey VA Medical Center, Houston, TX (David Nielsen).

Financial disclosure

Dr. Kapczinski has received grants/research support from AstraZeneca, Eli Lilly, Janssen-Cilag, Servier, CNPq, CAPES, NARSAD, and the Stanley Medical Research Institute; has been a member of speakers' boards for AstraZeneca, Eli Lilly, Janssen and Servier; and has served as a consultant for Servier. Dr. Soares participated in research funded by Forest, Merck, BMS, GSK and has been a speaker for Pfizer and Abbott.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.03.044.

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