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Effects of the Brain-Derived Neurotrophic Growth Factor *Val*66*Met* Variation on Hippocampus Morphology in Bipolar Disorder

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Histological and behavioral research in bipolar disorder (BD) implicates structural abnormalities in the hippocampus. Brain-derived neurotrophic growth factor (BDNF) protein is associated with hippocampal development and plasticity, and in mood disorder pathophysiology. We tested the hypotheses that both the *BDNF val66met* polymorphism and BD diagnosis are associated with decreased hippocampus volume, and that individuals with BD who carry the *met* allele have the smallest hippocampus volumes compared to individuals without BD and *val/val* homozygotes. We further explored localization of morphological differences within hippocampus in BD associated with the *met* allele. Twenty individuals with BD and 18 healthy comparison (HC) subjects participated in high-resolution magnetic resonance imaging scans from which hippocampus volumes were defined and measured. We used linear mixed model analysis to study effects of diagnosis and *BDNF* genotype on hippocampus volumes. We then employed three-dimensional mapping to localize areas of change within the hippocampus associated with the *BDNF met* allele in BD. We found that hippocampus volumes were significantly smaller in BD compared to HC subjects, and presence of the *BDNF met* allele was associated with smaller hippocampus volume in both diagnostic groups. The BD subgroup who carried the *BDNF met* allele had the smallest hippocampus volumes, and three-dimensional mapping identified these decreases as most prominent in left anterior hippocampus. These results support effects of BD diagnosis and *BDNF* genotype on hippocampus structure and suggest a genetic subgroup within BD who may be most vulnerable to deficits in hippocampus and may most benefit from interventions that influence *BDNF*-mediated signaling.
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INTRODUCTION

Histological and molecular studies in bipolar disorder (BD) consistently demonstrate cellular abnormalities within hippocampus. Postmortem studies report decreased hippocampal cell number and density in BD (Benes *et al*, 1998; Bielau *et al*, 2005; Chambers and Perrone-Bizzozero, 2004; Rosoklija *et al*, 2000), and magnetic resonance spectroscopy studies demonstrate reduced levels of *N*-acetylaspartate, a putative marker for neuronal integrity, in the hippocampus of BD patients relative to healthy comparison (HC) subjects (Bertolino *et al*, 2003; Deicken *et al*, 2003). Abnormal levels of biochemical markers related to neuronal sprouting and plasticity (Dowlatshahi *et al*, 2000; Fatemi *et al*, 2001; MacDonald *et al*, 2006), cell signaling (Law and Deakin, 2001), and oxidative metabolism (Konradi *et al*, 2004) have also been observed in the hippocampus in BD.

Consistent with cellular evidence for hippocampal pathology, there is convergent behavioral data supporting hippocampal dysfunction in BD. Impaired performance on tests of episodic verbal memory, a measure of hippocampal function, is one of the most frequently reported cognitive deficits in BD (Cavanagh *et al*, 2002; Clark *et al*, 2001; Deckersbach *et al*, 2004; Glahn *et al*, 2005; Pavuluri *et al*, 2006; van Gorp *et al*, 1999; Wolfe *et al*, 1987). These deficits are present in children and adults with BD, and across mood states. Their presence in youth, during euthymic periods (Clark *et al*, 2001; Sweeney *et al*, 2000; van Gorp

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et al, 1999; Wolfe *et al*, 1987), and in unaffected monozygotic twins of BD patients and non-twin siblings of patients with BD (Gourovitch *et al*, 1999; Keri *et al*, 2001) suggests hippocampal dysfunction may reflect an underlying vulnerability for BD.

Despite these observations, morphometric imaging studies of hippocampus in BD fail to provide consistent evidence of decreased volume. Several studies demonstrate significant decreases in the volume of gray matter in individuals with BD compared to HC patients (Frazier *et al*, 2005; Hauser *et al*, 1989; Noga *et al*, 2001; Strasser *et al*, 2005; Swayze *et al*, 1992). However, other studies report only a trend toward smaller hippocampus volume in BD (Blumberg *et al*, 2003; Brambilla *et al*, 2003), or no difference between BD and HC groups (Altshuler *et al*, 2000; Chang *et al*, 2005; Chen *et al*, 2004a; Hauser *et al*, 2000; Strakowski *et al*, 1999). Variability in these findings may reflect the presence of hippocampal deficits only within particular demographic or clinical subgroups as age, sex, and presence of psychotic symptoms have all been associated with variability in hippocampal volume in BD (Blumberg *et al*, 2003; Chambers and Perrone-Bizzozero, 2004; Frazier *et al*, 2005; Sax *et al*, 1999; Strasser *et al*, 2005; Velakoulis *et al*, 1999). It is also possible that studies may vary in the proportion of individuals within the samples carrying different polymorphic variants in genes associated with hippocampus morphology.

Cellular studies suggest brain-derived neurotrophic growth factor (*BDNF*) has the potential to influence hippocampus morphology in BD. *BDNF* promotes neuron growth and synapse formation (Maisonpierre *et al*, 1990; Thoenen, 1995) and low *BDNF* levels are implicated in hippocampal deficits in animal models of mood disorders (Chen *et al*, 2001; Duman and Charney, 1999; Duman *et al*, 1997; Nibuya *et al*, 1995; Santarelli *et al*, 2003). Decreased levels of *BDNF* protein have since been detected peripherally during depressed and manic episodes, and in brain tissue in postmortem studies of BD (Cunha *et al*, 2006; Knable *et al*, 2004; Neumeister *et al*, 2005). In addition, research in rodents shows medications used to treat BD increase neural *BDNF* levels (Bennett *et al*, 2000; Hashimoto *et al*, 2002), including specific increases within hippocampus (Frey *et al*, 2006; Fukumoto *et al*, 2001).

The *val66met BDNF* polymorphism is a functional variation associated with deficiencies in intracellular trafficking and activity-dependent release of *BDNF* protein (Chen *et al*, 2004b; Egan *et al*, 2003). This allele is also associated with impaired episodic memory, decreased hippocampus recruitment and decreased hippocampus volume in HC groups, major depression, and schizophrenia (Bueller *et al*, 2006; Frodl *et al*, 2007; Hariri *et al*, 2003; Pezawas *et al*, 2004; Szeszko *et al*, 2005). In this study we tested the hypotheses that the *BDNF val66met* variant would influence hippocampus volumes in both HC and BD study groups, and individuals with BD who carry at least one copy of the *met* allele (*val/met* or *met/met* genotype) would have the smallest hippocampus volumes compared to BD *val/val* homozygotes and HC subjects. We also employed a technique to evaluate three-dimensional (3D) hippocampus maps in an effort to localize the areas of change within hippocampus in BD most strongly associated with the *BDNF val66met* polymorphism.

METHODS

Subjects

Subjects included 20 adults with BD (11 female patients: age 21–56 years; race: 18 European Americans; 2 other) and 18 HC participants (12 female patients: age 18–58 years; race: 13 European Americans; 3 African Americans; 2 other). Subjects with BD included 12 *val/val* homozygotes and 8 'met carriers' (seven individuals heterozygous for the *met* allele and one *met/met* homozygote). In the HC group, 12 subjects were homozygous for the *val* allele and 6 subjects were *met* carriers (all heterozygous for the *met* allele). Study participants were recruited through the Veterans Affairs Connecticut Health Care System, West Haven; the Yale School of Medicine, New Haven, CT; and practitioners in the community or from advertisement in local newspapers. All subjects provided written, informed consent for participation in this study protocol as approved by the Yale School of Medicine and Department of Veterans Affairs institutional review boards.

Presence or absence of DSM-IV Axis I disorders was confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders, version 2.0 (First *et al*, 1995). None of the participants had a significant medical or neurologic illness, history of loss of consciousness greater than 5 min, or active drug or alcohol dependence. HC subjects also lacked a personal history of an Axis I disorder.

Mean age of BD onset, as defined by subject report of the first incidence of mood symptoms to satisfy DSM-IV criteria for a depressive or manic/hypomanic episode, was 21 years (SD = 8 years, range = 11–35 years). Mean length of BD illness duration was 18 years (SD = 10 years; range = 2–40 years). Five (25%) of the BD subjects had experienced past psychotic symptoms that occurred within the context of a manic episode. None of the subjects were psychotic at the time of scan. Two (10%) of the BD subjects had a history of panic disorder and 14 (70%) had a history of substance abuse or dependence (including alcohol). All were in remission for at least 1 year (range = 1–27 years), with the exception of one subject who was in remission for 5 months. Average length of time in remission was 11 years. Five (25%) of these subjects had a history of alcohol dependence and 2 had additional comorbid substance dependence (1 cocaine and 1 polysubstance dependence). One subject had a history of cannabis dependence. An additional 8 (40%) BD subjects had a history of substance abuse (4 alcohol and cannabis, 2 alcohol only, 1 cannabis only and 1 abused multiple substances). Eight (40%) of the BD subjects met past criteria for rapid cycling. Six (30%) of the subjects were euthymic at the time of scan, 8 (40%) were depressed, and 5 (25%) were manic or hypomanic. Six (30%) of the BD subjects were unmedicated at the time of scan. Of the remaining 13 subjects, 5 (25%) were prescribed lithium salts, 8 (40%) an anticonvulsant, 6 (30%) an atypical antipsychotic, 6 (30%) an antidepressant, and 1 (5%) levothyroxine.

Genotyping

Blood was collected by venopuncture and frozen at -20°C. Samples were thawed and DNA extracted using Puregene kits (Gentra, Minneapolis, Minnesota). The *BDNF* gene

polymorphism at position 196 (codon 66), G/A (*val/met*) was identified using an ABI TaqMan assay (Applied Biosystems, Foster City, California) (Shi *et al*, 1999).

Acquisition and Processing of Magnetic Resonance Images

Magnetic resonance imaging (MRI) scans were obtained using a single 1.5-T scanner (GE Signa; General Electric, Milwaukee, Wisconsin). Head position was standardized using canthomeatal landmarks and image parameters set at a 3D sagittal spoiled gradient echo sequence (repetition time, 24 ms; echo time, 5 ms; flip angle, 45°; frequency encoding superior/inferior; no wrap; 256 × 192 matrix; field of view, 30 cm; two excitations; slice thickness, 1.2 mm; and 124 contiguous slices).

Hand-tracing of hippocampus region of interest. Prior to tracing of the hippocampus, half of the brain images were flipped in left–right orientation. Personnel blind to subject diagnosis and left–right brain orientation performed the hippocampus delineations. Methods for stripping the skull and segmenting the brain are previously described (Blumberg *et al*, 2003). Total brain volume (TBV) was calculated as volume of cerebral gray matter plus white matter with interrater intraclass correlation coefficients of 0.999, as assessed on 10 scans. The hippocampus was defined by manual tracing performed by one of two trained research personnel whose interrater intraclass reliability coefficients were 0.924 for left hippocampus and 0.902 for right hippocampus traced on 10 brains. Tracings were performed in the coronal plane according to methods previously described (Blumberg *et al*, 2003; Kates *et al*, 1997; Peterson *et al*, 2001). Briefly, the anterior of the hippocampus was defined by the slice at which the temporal horn shifts from a lateral to superior position in relation to the hippocampus. The posterior boundary was defined by the slice in which the splenium of the corpus callosum begins to join the fornix. Final tracings were confirmed in orthogonal views.

Three-dimensional mapping of hippocampus morphology. Three-dimensional mapping of the hippocampus was performed using an extended robust point matching (RPM) nonrigid registration algorithm (Duncan *et al*, 2004; Papademetris *et al*, 2003) that is part of the Yale BioImage Suite image analysis package (Papademetris *et al*, 2006). First, all hippocampal tracings were registered to that of a single subject using RPM. An average transformation from all subjects was then used to warp the single subject's right and left hippocampus to generate new synthetic hippocampus tracings whose shape and size were effectively means of the data set. All original subjects' hippocampus tracings ($N = 38$) were then registered to these templates using RPM. Final registrations were verified visually for accuracy, and a map of local expansion or contraction created based on the determinant of the Jacobian of the displacement field generated by each registration (Staib *et al*, 2006). This analysis produced a Jacobian map where each voxel had a value representing the local volume change required to map an individual subject to the mean template (ie 1 = no volume change, >1 = individual subject is larger than the template, and <1 = individual subject is smaller than the template). These Jacobian maps were checked to ensure transformations were free of singularities (ie $|J| < 0$).

Statistical Analyses

Hippocampus region of interest analyses. Statistical analyses for region of interest (ROI)-based hippocampus tracings were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). All subjects ($N = 38$) were included in a linear mixed model analysis with group (BD *vs* HC) and *BDNF* genotype (*val/val vs met* carriers) (Egan *et al*, 2003; Hariri *et al*, 2003) as the between-subjects factors. Hemisphere (left *vs* right) was included as a within-subjects exploratory factor and all two- and three-way interactions were tested. Subject was used as the clustering factor. Age and sex were included as covariates based on previous reports implicating these factors in hippocampus volume (Blumberg *et al*, 2003; Frazier *et al*, 2005; Pruessner *et al*, 2001). TBV was included as a covariate to account for general scaling effects. Least square (LS) means were calculated from the mixed model for hippocampus volume and plotted to interpret effects of diagnosis and genotype (Figure 1).

Post hoc analyses were conducted to explore potential main effects of clinical variables within the BD group, including illness onset or duration, history of psychosis, history of substance abuse or dependence (treated as a dichotomous variable), rapid cycling, mood state, presence or absence of medications at the time of scan, and effects of individual classes of psychotropic medications on hippocampus volumes in BD.

Three-dimensional mapping of hippocampus morphology. Three-dimensional mapping methods were used to localize effects of *BDNF* genotypes within BD by performing two-sample *t*-tests comparing BD *val/val* homozygotes with BD *met* carriers at all hippocampus voxels. These analyses were performed using the Yale BioImage Suite software package (www.bioimagesuite.org) with morphometric Jacobian

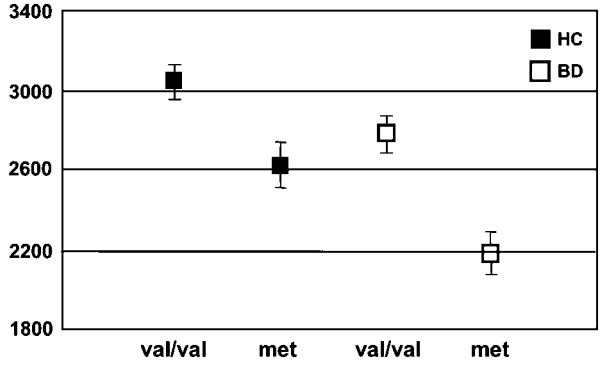

Figure 1 The graph displays LS means and standard errors for hippocampus volumes by *BDNF* genetic variation and diagnosis. Volumes were reduced significantly in association with the presence of the *met* allele and with BD diagnosis. Individuals with BD who carried the *BDNF met* allele had the smallest hippocampus volumes. Sample sizes for each group are as follows: HC *val/val* $N = 12$, HC met (*val/met* genotype) $N = 6$, BD *val/val* $N = 12$ and BD *met* (*val/met* and *met/met*) $N = 7$. BD, bipolar disorder; *BDNF*, brain-derived neurotrophic growth factor; LS, least square.

values as the dependent variables. Significant localized effects of *BDNF* genotype were plotted on a 3D rendering of the mean of the hippocampus tracings for all participants.

RESULTS

There were no significant differences in sex or genotype distribution between diagnostic groups. There was a significant difference in mean age between diagnostic groups as the HC group contained significantly younger subjects than the group with BD ($M_{HC=}28$, SD = 12; $M_{BD=}40$, SD = 9; $p<0.001$). Within the BD group, *met* carriers did not differ from *val/val* homozygotes on any of the clinical variables measured.

The ROI analyses revealed significant main effects of both genotype ($F_{1,31}=13.3$; $p<0.001$) and group ($F_{1,31}=8.1$; $p<0.008$) on hippocampus volume. Carriers of the *BDNF met* allele had significantly smaller LS mean hippocampus volumes than individuals homozygous for the *val* allele ($LSmean_{met}=2433$, $SE_{met}=115$; $LSmean_{val}=2950$, $SE_{val}=86$). In addition, the BD group demonstrated smaller hippocampus volumes than the HC group ($LSmean_{BD}=2458$, $SE_{BD}=100$; $LSmean_{HC}=2925$, $SE_{HC}=100$). BD *met* carriers had the smallest hippocampal volumes compared to BD *val/val* homozygotes and HC subjects ($LSmean_{HCval}=3166$, SE = 134; $LSmean_{HCmet}=2683$, SE = 178; $LSmean_{BDval}=2734$, SE = 125; $LSmean_{BDmet}=2181$, SE = 149) (Figure 1). The ROI analyses of genotype and group remained significant using only the subgroup of European-American subjects ($p<0.001$ and $p<0.01$, respectively). Individual subject data points are illustrated in Supplementary Figure 1. The interaction between genotype and group was not significant. There were also no significant main effects of age, sex, hemisphere, or any of the clinical variables explored on hippocampus volumes ($p>0.12$ for all analyses).

Three-dimensional morphological mapping demonstrated localized decreases in hippocampus volume in BD *met* carriers compared to BD *val/val* homozygotes within the left anterior hippocampus where two regions of difference were evident ($p<0.05$, uncorrected). One region contained an area that survived significance of $p<0.0005$ (Figure 2).

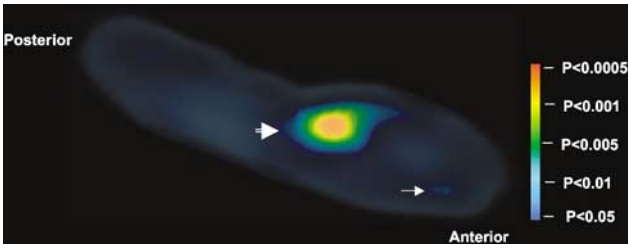

Figure 2 This image demonstrates three-dimensional morphometric mapping of regions of significant difference in BD *BDNF met* carriers compared to BD *BDNF val/val* homozygotes ($p<0.05$, uncorrected). In the left anterior hippocampus, in addition to a small area of decreased volume (small arrow), there was a more prominent area of decreased volume that included a region at the level of significance of $p<0.0005$ (indicated by the large arrow). BD, bipolar disorder; *BDNF*, brain-derived neurotrophic growth factor.

DISCUSSION

In this study, adults with BD had significantly smaller hippocampus volumes than HC subjects. This decrease in volume is consistent with observed reductions in cellular number and density in postmortem studies of hippocampus in BD. In addition, presence of the *BDNF met* allele was associated with reduced hippocampus volume in both HC and BD samples. Hippocampus volume was smallest in the individuals with BD who carried the *BDNF met* allele, as compared to HC subjects and BD *val/val* homozygotes. We suggest the *BDNF met* allele may function as one of several factors that, along with a diagnosis of BD, put the hippocampus beyond a threshold for normal structure and function. Thus, the subgroup with BD that carries the *met* allele may be a subgroup most vulnerable to hippocampus-related deficits.

The effects of the *BNDF met* allele in BD were localized to left anterior hippocampus. This finding is consistent with the neurovegetative, emotional, and cognitive symptoms associated with this disorder. Anterior hippocampus and its nonhuman primate analogue ventral hippocampus (Jay and Witter, 1991; Sasaki *et al*, 2004) have substantial connections with the hypothalamic–pituitary–adrenal (HPA) axis, amygdala, and prefrontal cortex that are implicated in the above symptoms (Bannerman *et al*, 2004). Anterior hippocampus activity has been associated with modulation of the HPA axis (Aihara *et al*, 2007; Colla *et al*, 2007) and hippocampus neurotrophin expression has been proposed to directly mediate this association (Uys *et al*, 2006). Behavioral studies demonstrate specialization of ventral or anterior hippocampus in select memory functions in rodents and in both human and nonhuman primates (Colombo *et al*, 1998; Dolan and Fletcher, 1999; Kjelstrup *et al*, 2002; Sinnamon *et al*, 1978; Stevens and Cowey, 1973; Strange *et al*, 1999). Anterior hippocampus may also be associated with anxiety-related behaviors, such as those seen in post-traumatic stress disorder, which demonstrate reductions in anterior hippocampus activity and volume (Etkin and Wager, 2007; Vythilingam *et al*, 2005). Differences in anterior hippocampus volume have also been associated with schizophrenia (Bilder *et al*, 1995; Narr *et al*, 2004; Pegues *et al*, 2003). Together, these findings raise questions as to whether individuals with BD who have decreased anterior hippocampus volume might represent a clinically distinct subgroup within the heterogeneous presentations of BD. One might expect these individuals to demonstrate abnormalities related to anterior hippocampus-based circuitry, including HPA dysfunction, memory impairment, and symptoms of anxiety or psychosis. This spectrum of symptoms may reflect a phenotypic presentation that exists across psychiatric disorders demonstrating a gene-related neuroanatomical abnormality.

Indeed, decreases in hippocampus volume in association with the *BDNF met* allele are not specific to BD. They have been reported in major depression (Frodl *et al*, 2007) and schizophrenia (Szeszko *et al*, 2005). These studies, in addition to our current findings, suggest the *BDNF met* allele may be associated with hippocampus-related phenotypic features common to several psychiatric diagnoses. Further investigation into *BDNF*-mediated effects may help parse the heterogeneous features of these disorders, as well

as suggest mechanisms that underlie their common symptoms.

Variation in *BDNF* genotype may have contributed to differences in hippocampus volume findings among previous MRI studies in BD (Blumberg *et al*, 2003; Brambilla *et al*, 2003; Chen *et al*, 2004a; Dickstein *et al*, 2005; Frazier *et al*, 2005; Hauser *et al*, 2000; Noga *et al*, 2001; Strakowski *et al*, 1999). Some studies report the *BDNF val* allele may be preferentially transmitted in BD (Neves-Pereira *et al*, 2002), although this finding is not universally reported (Zhang *et al*, 2006). There is also evidence that the *BDNF met* and *val* alleles may be associated with clinical subgroups within BD (Geller *et al*, 2004; Green *et al*, 2006; McIntosh *et al*, 2007), supporting the hypothesis presence of the *val* or *met* alleles may modify different phenotypes within this disorder. McIntosh *et al* (2007) report greater decreases in temporal lobe volumes in BD over a 4-year interval in association with the *BDNF met* allele, suggesting *BDNF* variation has dynamic effects on hippocampus volume during adulthood. Although duration of affective illness (Sheline *et al*, 1999), presence of psychotic symptoms (Strasser *et al*, 2005), age or stage of development (Blumberg *et al*, 2003; Frazier *et al*, 2005; Pruessner *et al*, 2001) and sex (Frazier *et al*, 2005; Pruessner *et al*, 2001) may also influence hippocampus volume, we did not detect significant influences of these factors in this study. However, the group sizes may have limited our power to detect such effects. We also did not detect significant effects of history of substance abuse or dependence on hippocampus volumes, although power may have been limited to detect such effects. Differences in anterior hippocampus volume in association with alcohol dependence have been previously reported (Sullivan *et al*, 1995). Although this study found no association between lifetime alcohol consumption and hippocampus volume, it is possible that alcohol exposure could have influenced our findings.

Our results may have implications for clinical interventions in the treatment of BD as serotonergic antidepressant medications, mood stabilizers such as lithium and valproic acid, and nonpharmacological treatments such as exercise have been shown to upregulate *BDNF* and its associated neurotrophic effects in hippocampus (Duman and Monteggia, 2006; Frey *et al*, 2006; Fukumoto *et al*, 2001; Malberg *et al*, 2000; Manji *et al*, 2000; Santarelli *et al*, 2003). Lithium has also been associated with increases in hippocampus volume in persons with BD (Bearden *et al*, 2008; Yucel *et al*, 2007), including increases specifically within the hippocampus head (Yucel *et al*, 2008). These reports suggest persons with BD who carry the *BDNF met* allele might benefit most from treatments mediated by *BDNF*-related mechanisms. However, it is also possible that *BDNF met* carriers may be more resistant to these treatments if ability to mount a *BDNF*-related response is diminished in these individuals. Since the *BDNF met* allele has been associated with deficits in recovery from stress (Gould *et al*, 1997, 1998; Magarinos *et al*, 1996), it may be alternative strategies, such as stress and anxiety reduction, may be needed to reverse anterior hippocampus abnormalities. In addition, interaction between *BDNF* and serotonin proteins are implicated in neural development and plasticity (Duman, 2002; Peng *et al*, 2008; Sairanen *et al*, 2005). This suggests interaction of *BDNF*- and serotonin-related genes, such as the serotonin transporter gene polymorphisms (*5-HTTLPR*) may modulate hippocampus morphology in mood disorders. Sample sizes limited investigation into interactions between *BDNF* and *5-HTTLPR* in this study, however future study of these interactions is warranted.

In sum, this study of the *val66met* polymorphism provides preliminary evidence that variation in *BNDF* has the potential to influence hippocampus structure in BD, and carriers of the *met* allele may be a subgroup within BD more vulnerable to hippocampus-related deficits. Potential influence of the *BDNF val66met* polymorphism on hippocampus provides one model of a molecular mechanism that may contribute to clinical heterogeneity within BD. Improved understanding of the role of *BDNF* in BD may help to identify a subset of patients who would most benefit from interventions that can target *BDNF*-related mechanisms and modify *BDNF* expression.

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DISCLOSURE/CONFLICT OF INTEREST

The authors declare that except for income received from primary employers no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service aside from those listed below and there are no personal financial holdings that could be perceived as constituting a potential conflict of interests.

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