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Variation in Brain-Derived Neurotrophic Factor (BDNF) Gene is Associated with Symptoms of Depression

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Abstract

Background—Brain-derived neurotrophic factor (BDNF) is putatively involved in the pathophysiology of depression. This study examined associations between BDNF genotype at the Val66Met locus, depression symptoms, and serum BDNF levels.

Methods—Twenty-eight subjects in the primary study (25 female, 3 male) completed diagnostic interviews, self-report questionnaires, and provided blood samples for serum BDNF quantification and buccal cell samples for genotyping. Data from a second sample of 189 subjects (94 female, 95 male) were also analyzed.

Results—The Val/Val genotype was associated with higher scores on the Cognitive-Affective factor of the Beck Depression Inventory-II (BDI-II) in the primary sample. No evidence was found for association between genotype and serum BDNF in this sample. Consistent with the primary study, Val/Val genotype was associated with higher total BDI-II scores, Cognitive-Affective factor scores, and Somatic-Vegetative factor scores, in the second sample. Serum BDNF measures were not available for the second sample.

Limitations—The mechanism through which BDNF genotype translates into (putative) differences in depression symptoms is not known.

Conclusions—In contrast to case-control association studies, we demonstrate two changes in the operationalization of the phenotype. Additionally, we found an association between Val/Val genotype and higher levels of depression symptoms. This result is distinct from an association between BDNF genotype and *diagnosis* of depression, and it may help to clarify our understanding of genetic liability to depression, which will ultimately lead to more nuanced and effective treatment strategies.

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Keywords

Val66Met; BDNF; depression; serum; mood; genetic

Introduction

Brain-derived neurotrophic factor (BDNF) is one of the mammalian neurotrophin-family proteins. Neurotrophins are structurally similar to one another, and they share an important functional role: they are essential for neuronal viability and differentiation. Neurotrophins are also important for synaptic plasticity; for review, see (McAllister et al., 1999). In the human brain, the hippocampus has notably high expression of BDNF. The hippocampus is also well-known for its role in synaptic plasticity and memory (Murer et al., 1999; Murer et al., 2001). Recent research has also implicated the hippocampus in mood disorders (Videbech and Ravnkilde, 2004), and there is some evidence that BDNF partially mediates the role that the hippocampus plays in the pathophysiology of depression (Duman, 2002; Groves, 2007).

Evidence for a Role of BDNF in Depression in Humans

Three lines of research in humans support the role of BDNF in the pathophysiology of depression and/or in the effective treatment of depression: First, serum BDNF levels have been reported to be lower in depressed patients than controls (Aydemir et al., 2006; Karege et al., 2002), and treatment with antidepressant medication normalizes serum BDNF levels of depressed patients (Gonul et al., 2005; Shimizu et al., 2005). Furthermore, a negative correlation has been found between serum BDNF and depression severity among depressed patients (Gonul et al., 2005; Shimizu et al., 2003). Second, a postmortem study of subjects that were depressed at the time of death found a significant difference in concentration of hippocampal BDNF protein between antidepressant-treated and antidepressant-untreated subjects (Chen et al., 2001). This finding is particularly interesting because depressed humans reportedly have lower hippocampal brain volumes than controls (Videbech and Ravnkilde, 2004), and it is possible that BDNF mediates the reduction in hippocampal volume seen in depressed patients (Duman, 2002; Groves, 2007). Third, there is evidence that variation in the human BDNF gene may be associated with depression-related traits. However, the findings from these studies have been mixed, and a definitive understanding of the effect of variation in the BDNF gene on depression awaits further research (Gratacos et al., 2007). Excellent reviews of evolving theory about BDNF's role in depression are available (Groves, 2007; Martinowich et al., 2007), and are beyond the scope of this report.

Inconsistencies in the Literature regarding BDNF Val66Met Polymorphism and Depression

Given the putative role of BDNF in the pathophysiology of depression, there has been much interest in a functional BDNF single nucleotide polymorphism, Val66Met. Findings from the association studies regarding Val66Met are mixed, and a meta-analysis of case-control studies failed to find support for an association between Val66Met and diagnoses of depression (Gratacos et al., 2007). However, a possible explanation for the lack of consensus among studies may be that Val66Met is associated with depression-related traits that are not reliably or completely captured by the diagnostic criteria for depression.

Hypotheses of the current study

This study was designed to test for an association between the BDNF gene at the Val66Met locus and a quantitative measure of depression. This phenotype is distinct from the phenotype of diagnosis of clinical depression, and it may provide more specific information about the symptoms of depression that are (putatively) influenced by Val66Met. This study was also designed to test for an association between Val66Met and serum BDNF levels. We pursued

this methodology because serum BDNF may be a more proximal phenotype to BDNF genotype than depression is; consequently, genotypic differences in serum BDNF levels might be more easily detected in association studies than differences in depression scores.

Materials and Methods

Primary Sample

Participants were 28 freshmen at the University of Colorado at Boulder and provided written informed consent. Participants were recruited by letters, phone, and email. Nineteen of the participants (17 female, 2 male) had experienced an episode of depression prior to study participation (none were currently depressed), and 9 participants (8 female, 1 male) had never experienced an episode of depression. Diagnoses were obtained using the Structured Clinical Interview for DSM-IV (First et al., 1997). There were no differences between the two groups on the variables of age, gender, or ethnicity (*t*-tests, ns). Mean age of the sample was 18.1 years (range: 18–19), and 89% of participants were white, 4% were Hispanic, and 7% did not state ethnicity. Participants were excluded for the following reasons: diagnosis of bipolar disorder, diagnosis of psychotic disorder, diagnosis of substance dependence, current psychotropic drug use and/or current psychotherapy. Participants completed the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996), provided buccal cell samples for genotyping (Freeman et al., 1997; Walker et al., 1999), and also provided blood samples for serum BDNF quantification. Taqman® SNP Genotyping Assays and the 7500 real-time PCR system from Applied Biosystems were used to determine genotype. Serum BDNF was assayed with an ELISA kit (BDNF Emax Immunoassay Kit from Promega, Madison, WI), and absorbencies were measured at 450 nm using an automatic microplate reader. The genotype of one participant could not be determined; thus 27 participants' data were used for all analyses.

Because of the small sample size, Met/Met homozygotes and Val/Met heterozygotes were grouped together for all analyses, and they were compared to Val/Val homozygotes using *t*-tests. Given the finding of a trend toward association between Val66Met and total BDI-II score, additional analyses were conducted in order to determine which items of the BDI-II were driving the relationship between total BDI-II score and Val66Met. To this end, published reports of the factor structure of the BDI-II were examined to identify the most appropriate factor structure for our sample (considering demographic similarity and sample size). Based on these criteria, we chose the two factor structure identified by Dozois et. al. (Dozois et al., 1998). We used Dozois et al.'s results to create individual scores for factors 1 (Cognitive-Affective factor) and 2 (Somatic-Vegetative factor), for each participant.

Replication Sample

Given the small sample size of our primary study and the high rate of unreplicated associations that have been published in the literature, we decided to analyze the association between the Val66Met genotype and BDI-II scores in another dataset. One extant dataset was identified that contained both BDI-II scores and BDNF genotype data, and it was selected based on the presence of these data. The sample consisted of 189 participants between the ages of 18 and 55 that were recruited from the Denver metropolitan area to participate in a study on the genetics of smoking behavior (Hutchison et al., 2007). All participants provided written informed consent and completed a battery of self-report tobacco-use assessments as well as the BDI-II. Of the 189 participants, 50% were male, 75% were Caucasian, 4% were African-American, 2% were Asian-American, 11% were Hispanic, and 7% were Native American. The mean age of participants was 28.2 years (SD=10.8). Participants smoked an average of 16 cigarettes per day at baseline (SD = 7.8). In this sample, there were 56 sibling pairs, and we used a conservative method to control for this dependence in the data. We randomly dropped one sibling from each sibling pair and re-ran the analyses on the reduced sample.

Results

Primary Study

Val/Val genotype was associated with higher factor 1 (Cognitive-Affective) scores, $t(23) = 2.315, p = .032$, in the primary sample. In addition, there was a trend toward association between total BDI-II scores and Val/Val genotype, $t(23) = 2.315, p = .074$. There was no evidence of association between factor 2 (Somatic-Vegetative) scores and genotype or between serum BDNF levels and genotype. See Table I.

Replication Sample

Findings from the original sample were replicated in the second sample; higher scores on the Cognitive-Affective factor of the BDI-II were associated with the Val/Val genotype, $t(187) = -2.71, p = .0074$. In addition, higher total BDI-II scores and Somatic-Vegetative factor scores were associated with the Val/Val genotype. See Table II. Given that the replication sample included 56 pairs of siblings, we also conducted analyses of the association between the Val66Met genotype and BDI-II scores after randomly removing one sibling from each pair of siblings. Results were consistent with findings from the full sample, though the statistical significance of the relationship between genotype and the Somatic-Vegetative factor was only a trend ($p = .055$).

Effect Sizes of Results

Effect sizes were calculated for all statistical tests that were significant, and are presented in Tables I and II. The metric of the effect size reported is r^2 , which, in this case, describes the proportion of variance in BDI-II score (or BDI-II factor score) that is accounted for by differences in BDNF genotype. Estimations of variances accounted for range from 3.1% – 19%.

Discussion

Our results indicate that the Val66Met SNP in the human BDNF gene may account for a modest amount of the population variance in severity of depression as measured by the BDI-II; variance accounted for in these samples ranged from 3.1% – 19% depending on sample (primary or replication) and the specific outcome measure used. These results are consistent with two published reports that used self-report measures of anxiety- and depression-related traits and that *did* find an association with Val66Met (Lang et al., 2005; Sen et al., 2003), with Val as the risk allele. It is noteworthy that the use of a quantitative phenotype, in contrast to dichotomous diagnoses of depression, yielded significant results, which lends support to the hypothesis that variation in the BDNF gene at the Val66Met locus is associated with depression-related traits. Furthermore, it is possible that these traits are not reliably captured by diagnoses of depression.

There was no evidence of association between the Val66Met genotype and serum BDNF. Thus, it is unlikely that a large amount of variation in baseline level of serum BDNF is determined by BDNF genotype at the Val66Met locus. However, it may be the case that baseline levels of serum BDNF are a less important phenotype than changes in serum BDNF levels in response to various stimuli. For example, future studies could determine if BDNF genotype mediates *changes* in serum BDNF levels in response to environmental variables such as social stress.

Limitations

Primary limitations are sample size and composition, potential linkage disequilibrium (between alleles at the Val66Met locus and other alleles), potential population stratification in our

samples, and uncertainty about the mechanism through which BDNF genotype translates into (putative) differences in depression symptoms.

Recommendations

Researchers often look for direct relationships between BDNF genotypes and phenotypes such as depression. However, an alternative strategy is to examine the effect on phenotype of the interaction between BDNF genotype and relevant environmental variables. In other words, gene-by-environment interactions may demonstrate genetic effects more clearly, and they may provide clues about the mechanism through which genotype translates into phenotype. Indeed, recent research in mice demonstrated a dramatic gene-by-environment interaction (Krishnan et al., 2007) in a study that used transgenic BDNF Val66Met mice. Krishnan et. al. elegantly showed that the development of a socially anxious phenotype, in response to social defeat (the relevant environmental variable), depended on BDNF genotype. Furthermore, Val/Val and Met/Met mice did not differ from one another in their levels of social anxiety in the absence of the social stressor. Thus, a large phenotypic effect of the Val66Met polymorphism would have gone undetected if the relevant environmental variable were not included in the study. In turn, we recommend including environmental variables in future association studies.

In sum, studies that test for gene-by-environment effects could shed light on the mechanism through which variation in the BDNF gene contributes to variation in the phenotype of depression. In addition, a focus on quantitative phenotypes instead of dichotomous diagnoses may aid in our understanding of genetic liabilities to psychopathology because specific symptom clusters that are associated with genotype can be identified. In turn, understanding specific liabilities to depression may be useful to patients in the context of psychoeducation, and may ultimately lead to more effective treatment strategies.

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Table I

Comparisons of Psychological Variables and Serum BDNF Levels by Genotype (Val/Val vs. Met Allele Carriers) Using *t*-tests – Data from Primary Sample (N=27)

Measure	Mean values (s. d.)		p value	Effect Size (r^2)
	Val/Val	Val/Met + Met/Met		
BDI-II	8.5 (7.6)	4.9 (2.2)	.074 ¹	.14 ²
BDI-II Cognitive-Affective Factor	4.1 (4.2)	1.7 (1.2)	.032 ¹	.19
BDI-II Somatic-Vegetative Factor	5 (4.3)	3.4 (1.4)	.17 ¹	
Serum BDNF protein (nanograms/ml)	32.7 (7.2)	29.3 (7.0)	.27	

¹ Unequal variances assumed in these *t* tests because ratios of variances all exceed 4:1.

² Only a *trend* toward association was found for this *t*-test; thus, caution is advised in interpretation of this effect size.

Abbreviations: BDI-II Beck Depression Inventory-II.

Table II
 Comparisons of Psychological Variables by Genotype (Val/Val vs. Met Allele Carriers) Using t-tests – Data from Replication Sample (N=189 for full sample, N=133 when one sibling is removed from each pair)

	Mean values (s. d.)			
Measure	Val/Val	Val/Met +Met/Met	p value	Effect Size (r ²)
Data from Full Replication Sample (N=189)				
BDI-II	10.7 (7.5)	7.6 (4.7)	.0042	.043
BDI-II Cognitive-Affective Factor	3.0 (2.7)	1.67 (1.2)	.0074	.038
BDI-II Somatic-Vegetative Factor	3.5 (2.2)	2.7 (1.7)	.0146	.031
Data from Replication Sample with one Sibling Removed (N=133)				
BDI-II	10.8 (7.9)	7.6 (4.9)	.0226	.039
BDI-II Cognitive-Affective Factor	4.7 (4.3)	3.1 (2.8)	.0290	.036
BDI-II Somatic-Vegetative Factor	5.9 (4.0)	4.5 (2.9)	.0547	.028 ^I

^I Only a *trend* toward association was found for this *t*-test; thus, caution is advised in interpretation of this effect size.

Abbreviations: BDI-II Beck Depression Inventory-II.