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Brief report

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.

Keywords: Val66Met; BDNF; Depression; Serum; Mood; Genetic

1. 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

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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).

1.1. 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.

1.2. 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.

1.3. 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.

2. Materials and methods

2.1. 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