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Brain-derived neurotrophic factor (BDNF) Val66Met and adulthood chronic stress interact to affect depressive symptoms

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ABSTRACT

Background: *BDNF* Val66Met by chronic stress interaction has been studied using childhood stress as a moderator, but has not been widely studied using chronic stress in adulthood.
Methods: Two independent samples were used: Duke-CG (238 Caucasians) and MESA (5524 Caucasians, African Americans and Hispanics). Chronic stress in Duke-CG was operationalized as having primary caregiving responsibility for a spouse or relative with diagnosed Alzheimer's disease or other major dementia; chronic stress in MESA was defined using chronic burden score constructed from self-reported problems of health (self and someone close), job, finance and relationships. CES-D scale was the measure of depression in both samples. The *BDNF* Val66Met by adulthood chronic stress interaction predicting CES-D was examined using linear regression, adjusted for covariates.
Results: The main effect of *BDNF* Val66Met genotype on CES-D scores was non-significant (ps $>$ 0.607) but the adulthood chronic stress indicator was significant (ps $<$ 0.001) in both samples. The *BDNF* Val66Met genotype by adulthood chronic stress interaction was also significant (ps $<$ 0.039) in both samples. The impact of chronic stress in adulthood on CES-D scores was significantly larger in Val/Val genotype individuals than Met carriers.
Conclusion: We found in two independent samples that depression levels increased significantly more as a function of adulthood chronic stress Val/Val genotype carriers than Met carriers. Individuals with the Val/Val genotype and chronic stress exposure could be targeted for interventions designed to reduce risk of depression if this finding is confirmed in future studies.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is one of the mammalian neurotrophin-family proteins that supports the survival of existing neurons, contributes to the growth and differentiation of new neurons and synapses (Huang and Reichardt, 2001), and protects against stress-induced neuronal damage (Radecki et al., 2005). In the brain, it is active in the hippocampus, cortex, and basal forebrain — areas vital to learning, memory, and higher thinking (Yamada and Nabeshima, 2003). Studies have reported that BDNF may be involved in the pathophysiology of depression and/or the effective treatment of depression. The role of BDNF in depression is also supported by studies that indicate the variation in the human *BDNF* gene associated with depression, although the findings are mixed.

BDNF protein is encoded by the *BDNF* gene in humans on chromosome 11. *BDNF* Val66Met (rs6265) — is a SNP with a G/A allele polymorphism, resulting in variation between valine and methionine at codon66 (Bath and Lee, 2006; Egan et al., 2003). The Val/Val genotype has been reported to be associated with increased CNS gene expression relative to Val/Met and Met/Met (McHughen et al., 2010). Findings from studies that examine the association between this functional *BDNF* Val66Met and depression are mixed. Some studies have found such an association (Czira et al., 2011; Duncan et al., 2009; Hwang et al., 2006; Licinio et al., 2009; Ribeiro et al., 2007; Sen et al., 2003; Taylor et al., 2007; Verhagen et al., 2010), others have not (Chen et al., 2008; Gratacos et al., 2007; Hong et al., 2003; Schumacher et al., 2005; Surtees et al., 2007). Even among the studies finding an association between *BDNF* Val66Met and depression, the risk conferred by the genotype is inconsistent. Some studies showed that individuals with the Val/Val (G/G) genotype had an increased depressive trait, such as major depression disorder (Licinio et al., 2009; Ribeiro et al., 2007), scores on Beck Depression Inventory — II (BDI — II) (Duncan et al., 2009), and depression facet scores in neuroticism (Sen et al., 2003), whereas others report that

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Met/Met (A/A) subjects have more severe symptoms of depression (Czira et al., 2011; Hwang et al., 2006; Taylor et al., 2007; Verhagen et al., 2010). These reported associations of both alleles with increased levels of depression indicate that the reported association of the Val/Val genotype with increased CNS gene expression (McHughen et al., 2010) does not result in a straightforward association of that genotype with resistance to depression. Instead, they raise possibility that environmental factors moderate the influence of Val66Met on BDNF expression and hence the association of *BNDF* genotype with indices of depression.

Chronic stress is one such environmental factor that is a trigger for several psychiatric disorders, including depression (Kendler et al., 1999). Chronic stress has neurotoxic effects, including damage to hippocampal cells (Sapolsky, 2000) that may underlie symptoms of depression. Existing evidence supports the involvement of *BDNF* Val66Met in stress-sensitivity, depressive states and the development of brain structures related to emotional processing and depression, like the hippocampus and amygdala (Gatt et al., 2007; Joffe et al., 2009; Shirayama et al., 2002; van Wingen et al., 2010). The association between *BDNF* Val66Met and intermediate traits or depressive symptoms may be moderated, therefore, by chronic stress. The effect of this interaction on depression remains unclear, but a few studies have found that childhood stress moderates *BDNF* Val66Met effects on depressive symptoms. Gatt *et al.* (Gatt et al., 2009) reported a significant interaction of *BDNF* Val66Met and early life stress predicting hippocampal and amygdala volumes and working memory among Europeans. Consistent with the reported increased gene expression associated with the Val/Val genotype, the combination of *BDNF* Met carriers and exposure to early life stress predicted reduced gray matter in hippocampus and poorer working memory. Another recent study found that childhood stressful life events were associated with an affective memory bias (a potential cognitive intermediate phenotype for depression) but only in European young men carrying the *BNDF* Met allele (van Oostrom et al., 2012). One study showed that childhood sexual abuse had a greater impact on depressive symptoms in Met carriers of *BDNF* gene than in Val/Val group among Spanish young adults (Aguilera et al., 2009). These findings suggest that effects of childhood stress on depression and related phenotypes are more pronounced in *BNDF* Met carriers.

It is possible, however, that the importance and the effects of chronic stress that occurs during childhood on adult depressive symptoms may be quite different from the effects of chronic stress in adulthood. Jaffee *et al.* (Jaffee et al., 2002) have shown that risk factors experienced during childhood (e.g., perinatal insults, caretaker instability) were associated with juvenile-onset depression, whereas, these risk factors were less related to adult-onset depression. BDNF levels fluctuate (lower in childhood and rise in early adulthood) and have different functions throughout development, suggesting that effects on gene expression vary during development and may have different effects on behavioral outcomes at different life stages (Perea et al., 2012). Therefore, the interaction of *BDNF* Val66Met and adulthood chronic stress may exhibit a different impact on depression compared with its interaction with childhood stress. Perea *et. al* (Perea et al., 2012) recently reported that among Spanish undergraduate students the chronic stress during college years (an adulthood stress) was associated with increased negative affectivity (an underlying construct for both depressive and anxiety disorders) regardless of the *BDNF* Val66Met genotype, while, in this same sample, greater stress during childhood was associated with greater negative affectivity only in Met carriers. In contrast to these studies showing a larger impact of childhood stress on depression among Met carriers, Perroud et al. (Perroud et al., 2008)reported a larger impact of childhood trauma on risk of violent suicide attempt in adulthood among persons with the Val/Val genotype.

Taken altogether, the findings reviewed above suggest that the *BNDF* Met allele might confer increased vulnerability to depression after chronic stress exposure during childhood, but the interaction between *BDNF* Val66Met and chronic stress in adulthood has received much less attention. Moreover, several studies (Duncan et al., 2009; Licinio et al., 2009; Ribeiro et al., 2007; Sen et al., 2003) that have shown that the Val/Val genotype per se was associated with increased depressive traits or symptoms as a main effect (not moderated by childhood stress exposure). In the present paper, therefore, we evaluate the impact of the interaction of *BDNF* Val66Met and chronic stress in adulthood on depressive symptoms, first, in a U.S. sample where chronic stress is defined as caregiving for a relative with Alzheimer's disease or other dementia; and, second, in a public-access database – the Multi-Ethnic Study of Atherosclerosis (MESA) – in which chronic stress is evaluated using a measure of chronic burden, *i.e.*, health problems (self and someone close), job, finance and relationship problems.

2. Methods

2.1. Participants

2.1.1. Duke CG

The Duke Caregiving (Duke-CG) participants were enrolled in 2001–2004 and detailed study procedures are described elsewhere (Kring et al., 2010). Briefly, caregivers, defined as having the primary responsibility for care of a spouse or relative with diagnosed Alzheimer's disease or other major dementia, were recruited using flyers, advertisements in the local media, and community outreach efforts. Controls were identified by asking caregivers to nominate two to five friends with similar demographic factors (*e.g.,* gender, age, and race) who lived in their neighborhood. Informed written consent forms approved by the Duke University Medical Center Institutional review board were obtained from all subjects. A questionnaire battery was given to participants during the home visit by a nurse and returned on their visit to the General Clinical Research Center at Duke University Medical Center. The clinic visit was scheduled during the same week as the in-home visit, and consisted of a general physical examination, and a blood sample was drawn for genotyping. The frequency of the Met allele in African Americans was insufficient (0 Met/Met and 6 Val/Met) for statistical analyses; therefore, African-Americans were excluded in the present study The 238 Caucasians with non-missing values on all measures of interest were included in the present study, consisting of 122 caregivers and 116 controls.

2.1.2. MESA

MESA is a federally funded multi-center, longitudinal cohort study of the factors that influence the progression of mild subclinical cardiovascular disease (CVD) to severe subclinical and clinical CVD in a multi-ethnic group of subjects (Bild et al., 2002). Information on the sampling frame and study design has been previously reported (Bild et al., 2002). Briefly, subjects without a history of clinical CVD, were recruited from six U.S. communities. Institutional review board approval was obtained at all MESA sites. Adults weighing $>$ 300 pounds were not eligible for participation. MESA data included four ethnic groups: Caucasian, Chinese, African-American and Hispanic. The frequency of the Met allele was much higher in an Asian sample (47%) than the frequencies of 17–21% that have been observed in western samples (Kim et al., 2007), therefore, we excluded Chinese samples in this study. The data used in the present study includes the first examination between July 2000 and August 2002 for self-reported ethnic groups Caucasian, African-American, and Hispanic. This resulted in 5524 MESA participants for the current study.