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Interaction between *BDNF* Val66Met and childhood stressful life events is associated to affective memory bias in men but not women

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ABSTRACT

Recent meta-analyses point towards a pathogenic role of the Val66Met variant of the brain-derived neurotrophic factor (BDNF) in major depressive disorder, specifically in males. We investigated whether *BDNF* Val66Met shows a male-specific interaction with childhood stressful life events on affective memory bias, a cognitive susceptibility factor for depression. Healthy volunteers ($n = 430$; 272 females and 158 males) were genotyped for *BDNF* Val66Met (rs6265) and completed the self-referent encoding task and a childhood stressful life events scale. *BDNF* Met carriers reporting childhood events tended to recall a lower proportion of positive words compared to Val/Val homozygotes reporting childhood events. Sex-specific analyses revealed that the *BDNF* genotype × childhood events interaction was significant in male participants and not in female participants. The results suggest that in males, *BDNF* Val66Met interacts with childhood life events, increasing the cognitive susceptibility markers of depression. In females, this effect may be independent of *BDNF* Val66Met.

1. Introduction

Mood disorders are extremely invalidating and result in a high disease burden as well as increased mortality risk due to important impairments in social, emotional and physical functioning. The World Health Organization estimates that major depressive disorder (MDD) will be the number two cause of lost years of healthy life worldwide by the year 2020. It is therefore important to identify risk factors for depression and to understand the underlying biological, environmental and psychological mechanisms of pathogenesis. It is now well established that early life stress contributes to the susceptibility to depression in adulthood (Kendler et al., 1999; Hovens et al., 2009). Besides the involvement of adverse childhood experiences, there is an important genetic contribution to mood disorders (Sullivan et al., 2000). This genetic contribution may have direct effects on depression morbidity, but likely also contributes by moderating the influence of early life stress (Caspi et al., 2010; van IJzendoorn et al., 2010). For example in a recent meta-analysis, Karg et al. (2011) concluded that there is strong evidence for the hypothesis that the 5-HTTLPR variant in the gene encoding the serotonin transporter moderates the relationship between stress and depression. The search for specific genes for depression has, however, remained unsuccessful, potentially due to the high complexity and heterogeneity of MDD and the role of gene–environment interactions in its etiology (Cannon and Keller, 2006). The intermediate phenotype approach (Gottesman and Gould, 2003) promises more successful genetic analyses by studying apparently simpler and less heterogeneous constructs such as increased amygdala activation or hypothalamic–pituitary–adrenal (HPA) axis reactivity, that are linked to the clinically observed mental disorder.

Affective information processing bias is a strong candidate of a cognitive intermediate phenotype for depression (De Raedt and Koster, 2010). This bias is assumed to reflect the cognitive susceptibility to depression and includes selective attention for negative experiences and increased encoding and retrieval of negative memories. Affective bias is assumed to engender and maintain negative thinking, rumination and low mood (Beck, 2008) and has consistently been observed in depressed patients independent of the depressive state (Matt et al., 1992), although some studies have reported negative results (Mogg et al., 1993, 2000; Kerr et al., 2005). Evidence is emerging that affective bias may be heritable, and it has been associated to two candidate depression risk factors, the 5-HTTLPR variant in the gene encoding the serotonin transporter and the Val108/158Met polymorphism in *COMT* (Hayden

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et al., 2007; Williams et al., 2010; Thomason et al., 2010; Perez-Edgar et al., 2010). Affective bias in information procession seems state-independent; it has been observed in patients in remission (Bhagwagar et al., 2004; Joormann and Gotlib, 2007; Ramel et al., 2007) and in highly neurotic, never-depressed individuals (Chan et al., 2007), who are at increased risk of depression. Affective bias has furthermore been found in never-depressed family members of MDD patients at a higher rate than in the general population (Jaenicke et al., 1987; Joormann et al., 2007; Taylor and Ingram, 1999) underlining its potential as an intermediate phenotype.

The depression candidate gene encoding the brain-derived neurotrophic factor, *BDNF*, and its functional variant Val66Met (rs6265) (Chen et al., 2004), may be of particular interest in relation to affective memory processing bias. *BDNF* codes for a neurotrophin that exerts long-term effects on neuronal survival, migration and growth. A large body of evidence supports the involvement of *BDNF* Val66Met in stress-sensitivity, depressive states and the development of brain structures that are implicated in emotional processing and depression, like the hippocampus, amygdala and anterior cingulate cortex (Gatt et al., 2007; Urani et al., 2005; Van Wingen et al., 2010; Joffe et al., 2009; Shirayama et al., 2002). These brain structures mature late and may therefore be more susceptible to adverse events in childhood. Recent studies have found that in *BDNF* Met allele carriers who had a history of childhood stressful life events, these brain structures are reduced in grey matter volume (Scharinger et al., 2010; Gerritsen et al., 2011) and show greater responses to emotional tasks (Montag et al., 2008; Schofield et al., 2009; Lau et al., 2010), compared to Val homozygotes. This evidence suggests a role of the *BDNF* genotype in regulating the effect of childhood stress on brain structures that are involved in emotional processing and in conferring the susceptibility to depression via its effect on affective information processing biases.

Despite this evidence, no direct relationship between *BDNF* Val66Met and major depression was found in a meta-analysis including 2821 depressed patients and 10,843 non-depressed controls (Verhagen et al., 2010). The Val66Met variant turned out to be significantly associated with depression in men, but not in women. One proposed explanation for this gender-specificity is the effect of estrogen on BDNF synthesis (Scharfman and Maclusky, 2005). Most studies addressing the relationship between estrogen and BDNF expression have found that estrogen up-regulates protein expression of BDNF in the brain (Numakawa et al., 2010). Estrogen may therefore have protective effects in the regulation of the effects of stress and BDNF levels in the brain.

In sum, current evidence suggests that *BDNF* Val66Met may interact with early life stress in affecting brain development as well as increased susceptibility to depression. These effects may be different for men and women, since the increased depression risk is observed specifically in males and estrogen regulates BDNF expression in the brain. As empirical evidence is lacking for this hypothesis, we set out to use an intermediate phenotype approach by studying the contribution of *BDNF* Val66Met and childhood stressful life events to the cognitive susceptibility to depression, especially affective memory bias, in a large sample of healthy individuals. We hypothesized that childhood life events would be associated with a greater negative memory bias and a smaller positive memory bias in both men and women. Furthermore, we expected *BDNF* Met carriers reporting childhood stress, and especially men, to demonstrate particularly increased negative memory bias and smaller positive memory bias.

2. Methods

2.1. Participants and study design

Participants were 430 young adults (158 males and 272 females) aged 18–40 years, who were recruited among participants in the Brain Imaging Genetics (BIG) study at the Donders Institute for Brain, Cognition and Behavior of the Radboud University Nijmegen Medical Centre. They were screened using a self-report questionnaire for the following exclusion criteria: a history of somatic disease potentially affecting the brain, current or past psychiatric or neurological disorder, medication (except hormonal contraceptives), current or a history of substance abuse, pregnancy and lactation. Participants were invited to complete a web-based battery at home consisting of several online tasks and questionnaires, and they were asked to donate saliva for genetic analyses. The self-referent encoding task and the life events questionnaire were part of the battery. All participants gave written informed consent and the study was approved by the local medical ethics committee.

2.2. Measures

2.2.1. Self-referent encoding task (SRET)

The SRET (Hammen and Zupan, 1984) was used to assess affective memory bias. In the encoding part of the task, twelve negative and twelve positive trait adjectives were presented on a computer screen, one by one. Participants were asked to press a button indicating whether a word was self-descriptive or not, to ensure self-referent encoding. Subjects were instructed for intentional recall in order to avoid floor effects. After a distraction task (2.5 min), the participants were asked to type as many adjectives as they could remember using the keyboard of their computer for three minutes. The two adjectives at the beginning and at the end of the presented list were used as filler adjectives and were excluded from the analyses in order to avoid primacy and recency effects. Spelling errors were permitted since all adjectives that did not match the word list were checked manually. Two outcome variables were calculated: the proportion of self-referent negative recall and the proportion of self-referent positive recall. These two variables were calculated by dividing the number of adjectives endorsed as self-descriptive in a valence category that was subsequently recalled by the total number of adjectives endorsed as self-descriptive. The proportion of self-referent negative recall was calculated by dividing all self-endorsed and recalled negative adjectives by the total number of self-endorsed adjectives. For example, self-endorsement and recall of two negative adjectives with self-endorsement of eight positive words results in a value of .25; self-endorsement and recall of zero negative adjectives results in a value of 0. Advantage of using this variable is that it controls for group differences in overall rates of endorsement (Symons and Johnson, 1997).

2.2.2. Childhood stressful life events

Stressful life events were assessed retrospectively by using the Life Events Questionnaire (Brugha and Cragg, 1990). Participants were asked to indicate whether they had experienced a set of life events (e.g. parental loss, divorce of parents and/or prolonged separation of parents) before age 16 years, after age 16 and over the last year. We calculated a childhood stressful life events variable by adding up the number of life events before age 16 years.

2.3. Genotyping

The *BDNF* 198G>A (rs6265) polymorphism (Val66Met) was genotyped at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre using Taqman® analysis as described before (Van Wingen et al., 2010). Testing for Hardy–Weinberg equilibrium did not show deviations from the expected distribution of genotypes [$p = .48$].

2.4. Statistical analysis

We first examined the two outcome variables proportion of positive and negative self-referent recall for outliers and skewing. The 'proportion of negative self-referent recall' variable was skewed and could not be normalized by transformation. Therefore, we dichotomized this variable into two groups (negative self-referent recall bias (>0) vs no self-referent recall bias (0)) and analyzed this variable using the method of logistic regression. The outcome variable 'proportion of positive self-referent recall' demonstrated a normal distribution and was analyzed using the method of linear regression analysis.

The main effect terms (*BDNF* genotype and childhood stressful life events) and the cross-product term of *BDNF* genotype and childhood stressful life events were entered into the equation, with the proportion of positive recall as outcome variable. Identical analyses were conducted with negative self-referent recall bias as outcome variable. The analyses were first conducted in the whole group and subsequently in the group of male and female participants separately, in order to test for gender differences. In the whole group, all three *BDNF* genotypes (*BDNF* Val/Val, *BDNF* Val/Met, *BDNF* Met/Met) were tested. In the male and female groups, two genotype groups were tested after combination of heterozygous and homozygous rare variant carriers into one group (*BDNF* Val/Val vs *BDNF* Val/Met or Met/Met), given the small size of the Met-homozygous genotype group. In the whole group, all analyses were adjusted for age and gender. In the male and female groups, all analyses were adjusted for age. Additional analyses were performed to check robustness of the results (e.g. VIF's and distribution of residuals). Standardized regression coefficients (β) are reported. In order to correct for multiple testing, p-values below .0027 were considered significant.