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The Role of BDNF Genotype, Parental Depression, and Relationship Discord in Predicting Early-Emerging Negative Emotionality

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Abstract

The brain-derived neurotrophic factor (BDNF) gene is a plausible candidate for early-emerging negative emotionality (NE), and evidence suggests that the effects of this gene may be especially salient in the context of familial risk for child maladjustment. We therefore examined whether the BDNF val66met polymorphism was associated with child NE in the context of parental depression and relationship discord. A sample of 413 three-year-old children was assessed for NE using standardized laboratory measures. Parents completed clinical interviews and a measure of marital satisfaction. Children with at least one BDNF met allele exhibited elevated NE when a parent had a history of depressive disorder, or when relationship discord was present. In contrast, this allele was associated with especially low NE when parent depression was absent, and when the parental relationship was not discordant. Findings suggest that the BDNF met allele confers increased child sensitivity to both positive and negative familial influences.

Keywords

emotional development; personality; depression; genetics

Advances in the field of molecular genetics in recent decades suggest the possibility of identifying the genetic bases of mood disorder. However, despite a well-funded and substantial body of research, no consistent evidence has emerged linking specific genes directly to depression, and uncertainty about the best strategies for future research continues to pose a significant challenge to the field. In particular, some experts question the wisdom of continuing to rely on study designs aimed at linking genes to cases of major depression (Hasler, Drevets, Manji, Charney, 2004). As an alternative, a number of investigators have argued for an increased focus on endophenotypes (heritable traits associated with a disorder that precede its onset, and are present in unaffected relatives), as such “intermediate” characteristics are thought likely to map more closely onto an underlying genetic etiology than discrete diagnoses (Gottesman & Gould, 2003).

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While a number of depression endophenotypes have been proposed (Hasler et al., 2004), temperamental negative emotionality (NE) may be one of the most promising. Understanding whether individual differences in temperament have implications for adjustment is a long-standing interest among psychopathologists, and much of this work has focused on the role of NE in depression. NE is an early-emerging, heritable, and stable trait (Durbin, Hayden, Klein, & Olino, 2007; Goldsmith, Buss, & Lemery, 1997) comprised of several lower-order constituents including proneness to sadness, anger, and fear. High NE has been linked to depression in adults (Brown, Chorpita, & Barlow, 1998) and children (Anthony, Lonigan, Hooe, & Phillips, 2002) and longitudinal studies have found NE or NE-like behaviors predict later depression (e.g., Kendler, Gatz, Gardner, & Pederson, 2006). Furthermore, a few studies have found elevated NE in the never-depressed relatives of depressed patients (e.g., Lauer et al., 1997). This literature supports the notion that NE is what has been referred to as a psychopathological endophenotype or "intermediate phenotype" for depression (Hassler et al., 2004).

The brain-derived neurotrophic factor (BDNF) gene is a plausible candidate gene for NE (Willis-Owen et al., 2005). BDNF is a nerve growth factor that is assigned a central role in many neurobiological models of the pathophysiology of depression (Duman & Monteggia, 2006). Several lines of research support its importance in mood disorders. BDNF levels are altered in depressed individuals (Shimizu et al., 2003), and antidepressant medications are thought to exert their effects in part by influencing BDNF levels (Gonul et al., 2005). Furthermore, animal studies indicate that stress alters BDNF expression in the hippocampus (Smith, Makino, Kvetnansky, & Post, 1995), a brain region with critical etiological and treatment significance in depression (Warner-Schmidt & Duman, 2006). The BDNF gene, located on chromosome 11p13, has a G to A single nucleotide polymorphism (SNP) at nucleotide 196 (rs6265) that results in an amino acid substitution of valine (val) to methionine (met) at codon 66 (val66met). This substitution changes the 5-prime pro-region of the human BDNF protein and appears to lower depolarization-induced secretion of BDNF, leading to a decrease in available BDNF, possible CNS impairment, and other negative neurobiological effects (Chen et al., 2004; Egan et al., 2003). Previous studies have associated this polymorphism with hippocampal volume (Pezawas et al., 2004) and HPA axis activity (Schule et al., 2006), further supporting links to depression vulnerability. Critical to the present discussion, the met allele of the BDNF gene has been associated with depression in the context of childhood adversity and genetic risk. For example, Kaufman et al. (2006) reported that BDNF met allele genotype interacted with serotonin transporter genotype and maltreatment to predict child depression, and Aguilera et al. (2009) found that the met allele moderated the association between childhood adversity and depressive symptoms in adulthood.

Given these findings, it is plausible that a relationship between BDNF and depression could arise from the effects of BDNF on NE. However, since BDNF expression is "experience-dependent" (i.e., modulated by an array of contextual factors, see Duman & Monteggia, 2006), the relationship between the BDNF met allele and NE should be explored as a function of context. This would be consistent with a burgeoning literature linking genes to the development of dispositional vulnerability to internalizing disorders under conditions of early contextual risk (Fox et al., 2005), and would also be consistent with the work of Kaufman and colleagues (2006) and Aguilera et al. (2009) on this BDNF polymorphism. Indeed, the evidence that context plays a critical role in modulating BDNF raises the intriguing possibility that the BDNF met allele serves as a marker of "differential susceptibility to the environment" (Belsky & Pluess, 2009; Ellis & Boyce, 2008), or the biological predisposition to be susceptible to a wide spectrum of contextual factors. With respect to genetic influences, reviews of gene-environment interaction research have led several authors to conclude that certain polymorphisms may not function simply as

vulnerability genes, but may instead perform a more complex role in enhancing biological plasticity, increasing an individual's responsivity to adverse and supportive contexts (Belsky & Pluess, 2009). In such cases, the same allele will be linked to both positive and negative outcomes, depending on context.

To address these issues, we examined whether BDNF genotype at the val66met site was associated with NE in a large community sample of preschool-aged children. We studied young children as depression is extremely rare in the preschool years, and we wanted to ensure that NE was not a consequence of prior or concurrent depressive disorder. Most studies of temperament in young children use parent reports of child temperament. However, as such measures can be influenced by an array of parent characteristics (de Los Reyes & Kazdin, 2005), we used observer ratings of child NE elicited during a structured laboratory visit. As we hypothesized that the BDNF-NE association may vary as a function of context, we examined whether two well-established risk factors for child maladjustment, parental mood disorder and relationship discord, moderated the association between BDNF genotype and child NE. Children of depressed parents and children whose parents experience relational discord are at elevated risk for an array of adjustment problems, including depression (Goodman & Gotlib, 1999; Repetti, Taylor, & Seeman, 2002). Also, parental depression and relationship discord are relatively common even in a community samples (Glenn, 1998; Kessler et al., 2005), increasing the relevance of findings to a greater number of children compared to studies looking at the effects of more extreme and uncommon cases of adversity (Kaufman et al., 2006).

Method

Participants

The sample was 413 Caucasian children (218 males) from an original sample of 559 children and their parents[a]. The mean age of children was 42.1 months (*SD* = 3.1). Potential participants were identified via a commercial mailing list. Eligible families had a child between three and four years of age, with no significant medical conditions or developmental disabilities, and at least one English-speaking biological parent. Most of the participants came from middle-class families, as measured by Hollingshead's Four Factor Index of Social Status (*M* = 45.0; *SD* = 10.8) (Hollingshead, 1975). The vast majority (96.6%) of children came from two-parent homes, and children were of average cognitive ability as indexed by the Peabody Picture Vocabulary Test (*M* = 103.4, *SD* = 13.5) (Dunn & Dunn, 1997).

Genetic Assessment

When participants came to the laboratory for behavioral assessment, buccal cells were collected from the inside of each child's cheek for genetic analysis. The Qiagen DNA Micro-Kit (Qiagen Valencia, CA, USA) was used to isolate genomic DNA (gDNA) from individual buccal cells according to manufacturer instructions. Individual gDNA isolates were used to genotype the val66met polymorphism in the BDNF gene using the polymerase chain reaction–restriction fragment length polymorphism method described by Bueller and colleagues (2006). In our sample, 195 children (47%) were homozygous for the val/val genotype, 191 (46%) were heterozygous, and 27 (7%) were homozygous for the met/met genotype. Because of the relative infrequency of the met/met genotype in White samples

[a]To reduce the possibility of population stratification, all non-White children or those of unknown ethnicity in the original sample of 559 were excluded from the current study (N = 72). An additional 74 children from the original sample did not give a DNA sample. Other than ethnicity, these 146 children did not differ from the 413 participants on any demographic or study variables other than negative emotionality (NE); those in the present study had lower NE than those not participating at trend-level significance, t (557) = 1.93, p <.10.

(and associated low power), analyses contrasted children with the val/val genotype with those with at least one met allele.

Laboratory Temperament Assessment

Each child participated in a standardized laboratory visit comprised of 12 episodes drawn from the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995). The visit lasted approximately two and a half hours and was videorecorded through a one-way mirror for coding. A female experimenter led each child through the tasks. A description of each episode and the traits typically elicited is provided below.

Risk Room (NE, behavioral inhibition [BI], activity)—Before leaving the main experimental area, the experimenter invited the child to explore a set of novel and ambiguous stimuli (e.g. cloth tunnel, balance beam, Halloween mask, etc.).

Tower of Patience (NE, inhibitory control, interest)—The child and experimenter took turns building a tower with large blocks. During each of her turns, the experimenter adhered to a schedule of increasingly lengthy delays before placing her block on the tower.

Arc of Toys (NE, positive affect, interest)—The child was allowed to play freely by him or herself with toys for a few minutes. The experimenter then returned and asked the child to put the toys away.

Stranger Approach (NE, BI)—The experimenter left the child alone in the main experimental area. After a brief delay, an unfamiliar male research assistant entered the room and spoke to the child in a neutral tone while gradually walking closer.

Car Go (positive affect, interest)—The child and experimenter played with two remote controlled cars.

Transparent Box (NE, persistence, interest)—The child selected a toy, which the experimenter locked in a transparent box. The child was then left to work to open the box with a set of keys that were, unbeknownst to the child, inoperable. After a few minutes, the experimenter returned with the correct key, and helped the child access the toy.

Exploring New Objects (NE, BI)—The child explored a set of novel and ambiguous stimuli, including a mechanical spider and bird, and sticky, soft gel balls.

Pop-up Snakes (positive affect)—The experimenter showed the child what appeared to be a can of potato chips, actually containing coiled spring snakes. The experimenter encouraged the child to surprise his or her mother with the snakes

Impossibly Perfect Green Circles (NE, persistence)—The child was repeatedly asked to draw a circle on a large piece of paper. After each drawing, the experimenter mildly criticized each circle.

Popping Bubbles (positive affect, interest)—The child and experimenter played with a bubble-shooting toy.

Snack Delay (inhibitory control)—The child was instructed to wait for the experimenter to ring a bell before eating a snack. The experimenter adhered to a schedule of varied delays before ringing the bell.

Box Empty (NE)—The child was given a gift-wrapped box, under the pretense that an appealing toy was inside. The child was left alone to discover that the box was empty by before the experimenter returned with several small toys for the child to keep.

Coding—Sadness, anger, and fear were coded during each episode, regardless of the emotion a given episode was specifically designed to elicit (Durbin et al., 2007). Thus, this coding scheme captured atypical and common emotional behaviors while also increasing scale reliability by generating ratings of affect for all tasks. For sadness, fear, and anger, each relevant display of facial, vocal, and bodily affect was coded on a three-point intensity scale. Ratings for the affective displays in each channel were summed within each episode, the totals for the 12 episodes were then summed, and the three channels were aggregated to create scores for sadness, fear, and anger reflecting facial, vocal, and bodily indicators. The NE scale was the composite of these total scores across the 12 episodes. Coders did not have access to other study data on children, including BDNF genotype. Coefficient alpha for NE was .82, and the intraclass correlation for interrater reliability (N = 35) was .74. Male and female children were not significantly different in NE, t (411) = −.84, p = .40.

Parental Psychopathology

Parents were interviewed by Masters-level clinicians using the Structured Clinical Interview for DSM-IV, non-patient version (SCID-NP; First, Spitzer, Gibbon, & Williams, 1996). If a parent could not be interviewed, we obtained information from the co-parent using a family history method. Based on audiotapes of 30 assessments (20 with mothers and 10 with fathers), interrater reliability (indexed by kappa) for lifetime mood disorder was .93. Of the 413 children, we had diagnostic information on 399 mothers and 392 fathers. Direct SCID interviews were obtained from all of the mothers and 328 (83.7%) fathers. For analyses in the present study, major depressive disorder (MDD) and dysthymic disorder (DD) were collapsed into a single category reflecting depressive disorder. Of the mothers, 133 (33.3%) had a lifetime history of MDD or DD, while 63 (16.1%) of the fathers had a history of either MDD or DD. Children were considered to have a family history of depressive disorder if either parent had a diagnosis of MDD or DD (N = 164; 41.1%).

Parental Relationship Discord

The Dyadic Adjustment Scale (DAS; Spanier, 1976), completed by 281 mothers and 250 fathers, was used as a measure of relationship satisfaction. This measure was not available from either parent for 81 children in the present report (71 due to missing questionnaire data; the other 10 cases were single-parent households). The lower score of the two (indicating greater discord) was used when both parents completed the DAS. Following Beach et al. (2005), we adopted a categorical approach to our treatment of our measure of discord. As scores below 100 are considered to reflect a discordant relationship, couples with either parent endorsing a score lower than 100 were classified as discordant (N = 79: 23.8%) while all others were classified as non-discordant (N = 253; 76.2%).

Results

Table 1 shows descriptive statistics for all major study variables for the two child BDNF genotype groups. Groups based on genotype did not differ in NE. BDNF genotype was also unassociated with parental depression, relationship discord, and child sex (all ps > .17). We initially entered child sex as a factor in all regressions, but as no interaction term between child sex and BDNF genotype or the moderator variables was significant, it was dropped from all models.

Multiple regression was used to examine whether parental depression interacted with BDNF genotype to predict child NE. To test interactions between child genotype and parental depression, these variables were entered in the first step, and the interaction term (the product of the two predictors) was entered in Step 2. The interaction term was significant (b = .15, SE = .05, pr = .15, $p < .01$), indicating that the BDNF-child NE association differed depending on the presence of parental depression. Figure 1 depicts this interaction, which shows that parental depression is associated with child NE most strongly when children have at least one copy of the met allele of the BDNF gene.

Next, post hoc tests using the least squares difference method were used to compare children's NE scores in the two genotype groups with and without a depressed parent. Within the val/val genotype group, children with and without a depressed parent did not differ on NE (mean difference = .01, p = .75). Conversely, among children with a met allele, those with a depressed parent displayed significantly greater NE than those with the same genotype but without a depressed parent (mean difference = .16, $p < .01$). The children with both a met allele and a depressed parent also exhibited significantly greater in NE than those with the val/val genotype with a depressed parent (mean difference = .08, p = .04) and without a depressed parent (mean difference = .09, $p < .01$). In contrast, children with a met allele who did not have a depressed parent had significantly lower NE than those with the val/val genotype with (mean difference = −.08, $p < .05$) and without (mean difference = −.07, $p < .05$) a depressed parent.

We next used multiple regression to examine whether child BDNF genotype interacted with parental relationship discord in predicting child NE[b]. To test interactions between child genotype and parental relationship discord, these variables were entered in the first step, and the interaction term (the product of the two predictors) was entered in Step 2. The interaction between BDNF genotype and parental discord (b = .20, SE = .07, pr = .16, $p < .01$) was significant, indicating that the BDNF-child NE association differed depending on whether parental relationship discord was present.

We again conducted post hoc tests using the least squares difference method to compare children's NE scores in the two genotype groups with and without parental relationship discord. A pattern similar to that found examining parental depression-BDNF interactions emerged; within the val/val genotype group, children with and without parental relationship discord were similar on NE (mean difference = .04, p = .36). Children with a met allele with parental relationship discord exhibited significantly greater NE than those with the same genotype but without parental discord (mean difference = .15, $p < .01$). Children with a met allele and parental relationship discord also displayed significantly greater NE than those with the val/val genotype with parental discord (mean difference = .13, $p < .05$) and, at trend level, greater NE than children with the val/val genotype without parental discord (mean difference = .08, p = .06). In contrast, children with a met allele without parental discord exhibited a trend for lower NE than children with the val/val genotype without parental relationship discord (mean difference = −.07, $p < .05$). However, children with a met allele without parental discord were not significantly different from val/val children with parental discord (mean difference = −.02, p = .68).[c]

[b]Results using the dimensional measure of DAS were similar (available from first author by request).

[c]To examine whether the influence of depression or relationship discord could account for the effects of the other, multiple regression was used to determine whether either two-way interaction would remain significant when both were in the same model. After entering child genotype, parental relationship discord, and parental depression, both the BDNF-parental depression (b = .14, SE = .06, pr = .14, $p < .05$) and BDNF-relationship discord (b = .16, SE = .07, pr = .14, $p < .05$) interaction terms remained significant and virtually unchanged from models examining their individual effects, indicating that the two interactions are independent.

Discussion

We examined whether BDNF genotype was associated with NE in children with and without established familial risk factors for adjustment problems. Children homozygous for the val/val genotype exhibited similar, intermediate levels of NE, regardless of parental depression. In contrast, children with the met/met or val/met genotype and a depressed parent exhibited especially high levels of NE, while those with non-depressed parents had especially low levels of NE. A similar pattern emerged for children with a BDNF met allele with parental relationship discord. Our work extends the extant literature implicating the met allele of this gene in predicting risk for negative outcomes under contextual adversity (Aguilera et al., 2009; Kaufman et al., 2006); more specifically, our findings indicate that BDNF genotype has similar effects in the context of two established, common vulnerability factors for child maladjustment, and that having at least one copy of the met allele of the BDNF gene may increase child sensitivity to contextual influences, both good and bad. Ellis and Boyce (2008) recently proposed that the effects of some biological characteristics may be bivalent, rather than univalent; in other words, some characteristics may have both risk-augmenting and risk-protective effects depending on external contexts. These authors refer to this phenomenon as “biological sensitivity to context.” Recently, Belsky and Pluess (2009) outlined specific statistical and other evidentiary criteria for demonstrating that a given factor heightens susceptibility to context, rather than simply increasing vulnerability, providing a very brief list of published studies identifying factors that meet these criteria. Our findings indicate that the BDNF met allele is an additional factor that predisposes children to respond strongly to context “for better *and* for worse” (Belsky & Pluess, 2009).

We have deliberately not described our findings as reflecting a gene-environment interaction (GXE), as this would imply that the effects of parental depression and marital discord are environmentally mediated, which we cannot conclusively establish in our data. Having a depressed parent indicates the possible presence of a diverse array of biological and environmental risk factors that may increase depression vulnerability, including genetic susceptibility, dysregulated activity in neurobiological systems, and modeling of negative affect, among other mechanisms (Goodman & Gotlib, 1999). Parental relationship discord similarly reflects a diverse array of risk factors (O’Brien, Margolin, John, & Krueger, 1991). Despite this ambiguity about the nature of the contextual moderators examined, our findings are no less compelling than others presented within a GXE framework. The stressors regarded as “environmental” in most studies of GXE are rarely, if ever, known to be environmentally mediated. Because the word ‘environment’ so strongly implies a non-biological basis, use of the term ‘gene-context interaction’ may be more appropriate for many studies (see also Gagne, Vendlinski, & Goldsmith, 2009, for a more detailed consideration of this issue).

A recent study examining the relationship between the BDNF val66met polymorphism and neuroticism (Willis-Owen et al., 2005) failed to find that BDNF genotype and stress interacted in predicting neuroticism. However, the sample and methods were very different from those used in the present study; for example, neuroticism and stress were assessed using self-report measures. Additionally, we studied young children, and age may be an especially important consideration in testing whether genetic influences are moderated by contextual effects. Such interactions may be less evident in older samples (Surtees et al., 2006), perhaps because of maturational processes that decrease biological plasticity in response to contextual influences later in development, or because children have relatively little control over the context in which they are raised as well as limited skills for coping with adversity.

Although our sample size was large compared to other genetic studies using laboratory-based phenotypes, it is still relatively small for a genetic association study. However, incorporating measures of environmental pathogens that moderate genetic effects may increase power by specifying conditional-effect genes, thus reducing the need for very large samples (Moffitt, Caspi, & Rutter, 2006). Additionally, improving measurement of relevant phenotypes is another means to bolster power in molecular genetic studies (Uher & McGuffin, 2008) that we have capitalized upon in the present study by using objective, laboratory-based measures of NE.

In sum, we found that family context moderated the association between BDNF genotype and measures of child NE derived from standardized laboratory assessments. Our findings raise the intriguing possibility that the met allele of the BDNF gene may serve as both a risk and a protective factor by amplifying the effects of both positive and negative familial contexts (Belsky & Pluess, 2009; Ellis & Boyce, 2008). While speculative, although individuals with a copy of the met allele appear to be at greater risk in the context of adversity, they may also derive especially powerful benefits from psychosocial interventions, raising the possibility of developing targeted preventions and early intervention efforts for this group.

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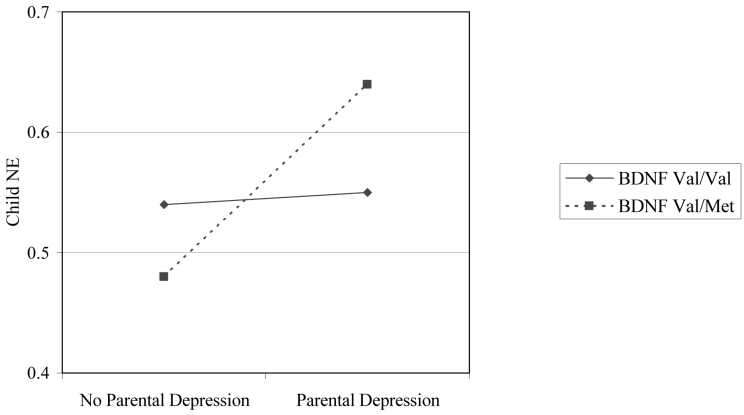

Figure 1.
Laboratory measures of negative emotionality at different BDNF genotypes and in the presence and absence of parental depression (N = 400).
Note: NE = negative emotionality; BDNF = brain derived neurotrophic factor; Val = valine; Met = methionine.

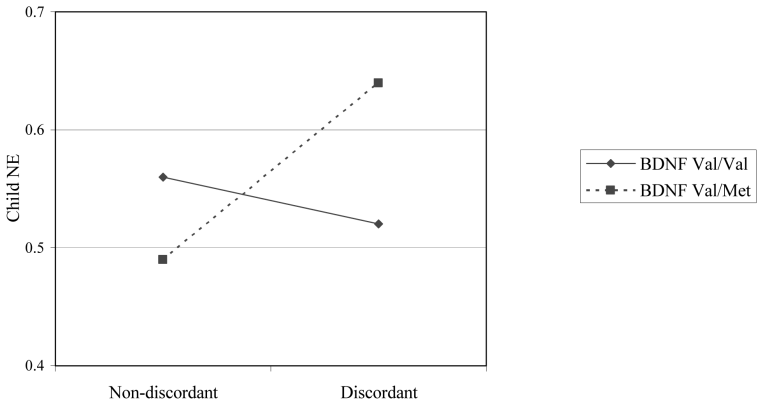

Figure 2.

Laboratory measures of negative emotionality at different BDNF genotypes and in the presence and absence of parental relationship discord (N = 332).

Note: NE = negative emotionality; BDNF = brain derived neurotrophic factor; Val = valine; Met = methionine.

Table 1

Study variables by child BDNF genotype.

	Val/Val (N = 195)			Val/Met & Met/Met (N = 218)		
Variable	**M**	**SD**	**N**	**M**	**SD**	**N**
NE	.55	.27		.54	.24	
Child Sex (Male)			100 (51%)			118 (54%)
Parental Depression			78 (40%)			86 (39%)
Relationship Discord			32 (16%)			47 (22%)

Note: Val = valine; Met = methionine; NE = negative emotionality.

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