

The BDNF Val66Met Polymorphism Interacts with Maternal Parenting Influencing Adolescent Depressive Symptoms: Evidence of Differential Susceptibility Model

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Abstract Although depressive symptoms are common during adolescence, little research has examined gene–environment interaction on youth depression. This study chose the brain-derived neurotrophic factor (*BDNF*) gene, tested the interaction between a functional polymorphism resulting amino acid substitution of valine (Val) to methionine (Met) in the proBDNF protein at codon 66 (Val66Met), and maternal parenting on youth depressive symptoms in a sample of 780 community adolescents of Chinese Han ethnicity (aged 11–17, $M = 13.6$, 51.3 % females). Participants reported their depressive symptoms and perceived maternal parenting. Results indicated the BDNF Val66Met polymorphism significantly moderated the influence of maternal warmth-reasoning, but not harshness-hostility, on youth depressive symptoms. Confirmatory model evaluation indicated that the interaction effect involving warmth-reasoning conformed to the differential-susceptibility rather than diathesis-stress model of person-X-environment interaction. Thus, Val carriers experienced less depressive symptoms than Met homozygotes when mothering was more positive but more symptoms when mothering was less positive. The findings provided evidence in support of the differential susceptibility hypothesis of youth depressive symptoms and shed

light on the importance of examining the gene–environment interaction from a developmental perspective.

Keywords Adolescent depressive symptoms · BDNF Val66Met polymorphism · Differential susceptibility · Gene–environment interaction · Maternal parenting

Introduction

Depression is a common mental health problem in adolescence. One recent meta-analysis found the worldwide prevalence of depressive disorder in youth to be 2.6 % (Polanczyk et al. 2015), with other work showing about one third of adolescents manifesting subthreshold depression (Balazs et al. 2013). Both adolescent subthreshold depression and depressive disorder are associated with severe functional impairments (Fröjd et al. 2008), elevated rates of substance abuse (Diego et al. 2003), increased likelihood of adult depression (Pine et al. 1999), and poor physical health (Naicker et al. 2013). Another severe consequence of adolescent depression is suicide (Wild et al. 2004), with more than half of adolescent suicide victims having a depressive disorder at the time of death (Thapar et al. 2012), and subthreshold-depressed adolescents being three times more likely to have suicidal thoughts/ideations than their non-depressed counterparts (Balazs et al. 2013). Given these data on the prevalence and consequences of adolescent depression, identifying its etiological mechanisms is critical for developing empirically-based prevention and intervention programs (Garber 2006).

Many now appreciate that both genetic and environmental factor, as well as the gene–environment interactions ($G \times E$), contribute to the development of depression (Caspi et al. 2003; Rice 2014; Rutter et al. 2009).

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According to the multifactorial model of depression (Kendler et al. 2002), there are multiple genes and environments that may additively or interactively influence depression. A large number of studies have examined $G \times E$ interactions using a candidate-gene approach when investigating adult depression (Lopizzo et al. 2015), but less research on gene–environment interaction has targeted youth. Extant $G \times E$ work on youth depression has mostly focused on the interaction between the serotonin transporter gene-linked polymorphic region (5-HTTLPR) and childhood maltreatment or stressful life events, yielding mixed findings concerning the putative risk allele (Dunn et al. 2011). In this study, for the reasons detailed below, we focused on another candidate gene—the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism, investigating its interaction with maternal parenting in predicting adolescent depressive symptoms while competitively evaluating alternative $G \times E$ models of diathesis-stress and differential-susceptibility.

Parenting and Adolescent Depressive Symptoms

Parent–child relationships often go through significant transformation during adolescence, and parents perceive adolescence as the most challenging and difficult stage of childrearing (Buchanan et al. 1990). Both theories (e.g., separation-individuation theory, Blos 1967; autonomy-relatedness perspective, Cooper et al. 1983) and empirical research (Collins and Laursen 2004; De Goede et al. 2009) suggest that increasing autonomy and independence during adolescence may make the parenting of youth more challenging. Needless to say, not all families cope well with these developmental processes; and maladaptive parenting may foster adolescent psychopathology, including depression (McLeod et al. 2007; Steinberg 2001).

Considerable research highlights distinct parenting dimensions associated with adolescent depressive symptoms. European-American research reveals parental warmth to be negatively and parental harshness and hostility to be positively associated with adolescent depressive symptoms (Ge et al. 1994a, b; Hipwell et al. 2008). Also implicated as important is use of inductive-reasoning, which involves the provision of clear expectations and rationales for parental demands (Natsuaki et al. 2007); it is negatively related to depressive symptoms in European-American adolescents (Ge et al. 1994a, b). Notably, the cited findings involving parenting (i.e., warmth, inductive-reasoning, harshness and hostility) and adolescent depressive symptoms extend to African teenagers (Kim et al. 2003; Natsuaki et al. 2007) and Asian-American ones (Kim et al. 2009, 2013), as well as those from mainland China (Zhang et al. 2015) and Taiwan (Wang et al. 2015). Moreover, a recent meta-analysis revealed that less warmth

or inductive-reasoning and greater hostility increase the risk for youth depressive symptoms (Yap et al. 2014).

Biological Plausibility of BDNF

Val66Met \times Parenting

One important prerequisite for candidate $G \times E$ is its biological plausibility, that is, genes and environment are convergent to one biological pathway underlying the focused psychopathology (Caspi et al. 2010; Moffitt et al. 2006; Rutter et al. 2009). Biological plausibility for the present research resides in the joint effect of BDNF Val66Met and parenting on abnormal BDNF functioning, which has been shown to be involved in depression (Castrén and Rantamäki 2010). Specifically, the Val66Met polymorphism has been shown to reduce intracellular trafficking and activity-dependent secretion of BDNF (Chen et al. 2006; Egan et al. 2003; Kuczewski et al. 2009). Rodent studies indicate that maternal behavior including postnatal maternal separation (negative) and higher quality maternal care (positive) can influence offspring's BDNF expression in brain (Bath et al. 2013; Cutuli et al. 2015; Mashoodh et al. 2012). Noteworthy, too, is accumulating evidence of the diverse role of BDNF on depression in different brain regions (Yu and Chen 2011), such that in the hippocampus BDNF inhibits depression (Duman and Monteggia 2006) whereas in the nucleus accumbens (NAc) it facilitates depression (Groves 2007; Martinowich et al. 2007). Collectively, these results provide the basis for the hypothesis that BDNF Val66Met and maternal parenting interactively influence abnormal BDNF levels in the brain and thus contribute to depressive symptoms.

BDNF Val66Met \times Environment on Depression

Although there is accumulating research on BDNF Val66Met \times Environment on depression, there seems to be no conclusive basis for specifying who (Val vs. Met carriers) are more sensitive to environmental effects related to depression. A meta-analysis of $G \times E$ studies of mostly even if not exclusively adult participants revealed that it was Met-BDNF carriers who were most prone to depression in the face of life stress (Hosang et al. 2014). Notably, though, a study of Chinese adolescents found that it was Val-BDNF carriers who proved most susceptible to depressive symptoms in the face of stressful life events (Chen et al. 2012). Such results would seem to be in line with work with Mexican adolescents (12–17 years) showing BDNF Val/Val homozygotes to be most at risk of depression when facing cumulative psychosocial adversities (Cruz-Fuentes et al. 2014), and with U.S. adolescents indicating that Val-BDNF carriers manifested the most depressive symptoms when victimized by their peers

(Gottfredson et al. 2014). Collectively, the work just cited points to potential developmental, cultural, and ethnic variation in how the BDNF Val66Met polymorphism interacts with the environment in predicting depression. Indeed, the importance of appreciating the importance of developmental stage and perhaps culture and ethnicity as well is evidence that among American Caucasian children of 3-year olds, it is Met carriers who exhibit elevated negative emotionality when a parent has a history of depression or is involved in a discordant intimate relationship (Hayden et al. 2010).

Even if not widely appreciated, the possibility that $G \times E$ interaction effects may vary across development has not gone unnoticed (e.g., Casey et al. 2009; Hyde 2015; Lenroot and Giedd 2011). In fact, Lenroot and Giedd (2011) contended that an “individual’s risk for developing pathology in response to a given stressor may be related to both to their genetic make-up and to the age at which a stressor was encountered” (p. 431). And Hyde (2015) recently suggested that “Future studies that examine three-way $G \times E \times D$ (development) interactions will be the key to uncovering developmental pathways within $G \times E$ interactions” (p. 604). Both observations seem especially pertinent to BDNF-related studies given evidence that human BDNF levels show an inverted-U shape change across development, with levels being low during childhood, peaking during adolescence, and thereafter falling and stabilizing (Casey et al. 2009). This developmental change of BDNF level may explain the apparent inconsistency in the $G \times E$ findings pertaining to BDNF and depression summarized above.

Models of $G \times E$: Diathesis-Stress and Differential Susceptibility

Two theoretical perspectives have informed $G \times E$ research. Initially, work was guided by the diathesis-stress model (Zuckerman 1999), which stipulated that some individuals are more vulnerable to the negative effects of adversity than others, and thus largely focused on negative environments (i.e., maltreatment, stressful life events). Recently, an alternative framework—differential susceptibility—has been advanced and found to fit much $G \times E$ data well. It stipulates that individuals with certain genotype may not only be disproportionately susceptible to the adverse effects of negative environments, but simultaneously benefit the most from positive environmental exposures (Belsky and Pluess 2009, 2013; Ellis et al. 2011).

With regard to differential susceptibility, most studies to date have focused on Caucasian youth, showing that those with short allele of *5-HTTLR* or the less efficient dopamine-related genes are more susceptible to the influences of both positive and negative developmental experiences

(for meta-analyses, see Bakermans-Kranenburg and Van IJzendoorn 2011; Van IJzendoorn et al. 2012). One study of Japanese college students found Met-BDNF carriers to be more sensitive to parenting influences in predicting personality (Suzuki et al. 2011). With a few exceptions (e.g., DiLalla et al. 2009; Buil et al. 2015; Propper et al. 2007; Zhang et al. 2015), most prior research documenting differential-susceptibility-related $G \times E$ interaction has only measured negative or positive environmental conditions (Belsky and Pluess 2013), when it is the full range of environments (from negative to positive) that is required to fully evaluate this conceptual framework (Belsky et al. 2007; Belsky and Pluess 2013; Roisman et al. 2012). It is for this reason that the present effort focuses on both negative and positive parenting.

The Present Study

Given the limited $G \times E$ research on youth depression and the potential developmental difference in $G \times E$ effect across adolescence and adulthood, we examined the interactive effect of BDNF Val66Met polymorphism and maternal parenting on youth depressive symptoms. Given the inconsistent findings on the more susceptible carrier (Met vs. Val), we first conduct an exploratory $G \times E$ test using traditional regression analyses. For the significant $G \times E$ effect, we further carried out a competitive confirmatory approach developed by Widaman and associates (2012), Belsky et al. (2013) to evaluate the relative fit of two competing $G \times E$ accounts (i.e., diathesis-stress versus differential susceptibility).

The competitive model-fitting approach involves a re-parameterized regression model that directly estimates the value of predictor, together with confidence intervals (CI), at which the slopes for the two allelic groups cross. If the crossover point and its CI fall within the range of values of the (parenting) predictor, the $G \times E$ effect conforms to the disordinal form, supporting the differential susceptibility model. Conversely, if the crossover point and its confidence interval (CI) approaches or goes beyond the extreme point of the (parenting) predictor, the $G \times E$ effect conforms to the ordinal form, supporting the diathesis-stress model (Widaman et al. 2012). Thus, the location of the crossover point is the crucial parameter that distinguishes the two competing $G \times E$ models. This confirmatory approach has greater power to evaluate competitive $G \times E$ theories or hypotheses, herein diathesis-stress versus differential susceptibility (Belsky et al. 2013). Moreover, it can distinguish “strong” and “weak” versions of both models. Strong models reflect the fact that for some genotypes the predictor-outcome association is significant but for others it is not, whereas weak models reflect the fact

that predictor–outcome association are significant for multiple genotypic groups, yet prove (significantly) stronger for some than for others.

It should be noted that the $G \times E$ work presented herein focused on *parenting* extends prior research on the current sample that examined the $G \times E$ interaction of BDNF Val66Met and *stressful life events* in predicting adolescent depression (Chen et al. 2012). Because the environmental parameter used in that earlier report was likely related to the parenting predictors used in the current inquiry, the parenting measures used here were residualized (i.e., statistically adjusted) for stressful life events. Thus, we sought to determine whether a *different* and now *independent* environmental exposure—parenting—interacts with BDNF Val66Met in predicting depressive symptoms in the same way that stressful life events did (i.e., with Val carriers proving disproportionately susceptible to environmental influences in a manner consistent with differential susceptibility).

Methods

Participants

The participants of the present study were drawn from the adolescent twins in Beijing Twin Study (BeTwiSt) (Chen et al. 2013), who are recruited from elementary and middle schools in Beijing, China. The second-born child in each twin pair was genotyped. The sample for this study only included adolescents of Han ethnicity, aged 11–17 years ($M = 13.6$, $SD = 1.80$), with genotype data ($N = 780$, 51.3 % female). The adolescent twins are representative of the general youth population of Beijing in terms of basic demographic characteristics (i.e., family socio-economic status, fathers' educational attainment, parents' marital status or marital quality), with the exception that the mothers of twins had more years of education than the general youth sample (Chen et al. 2013).

Procedures

All children and their parents signed informed consents. After explaining the study purpose and procedures, trained research assistants distributed questionnaires to the adolescents in their classrooms after school time. They provided information on personal and family demographics, and self-reported their depressive symptoms and perceived maternal parenting practices. In addition, participants were asked to provide their saliva samples for DNA extraction by Oragene[®] DNA sample collection kits. Ethical approval for the study was obtained from the Institutional Review Board of Institute of Psychology, Chinese Academy of Sciences (CAS).

Measurements

Maternal Parenting

Adolescents reported their mothers' parenting practices during the past 12 months using a 5-point scale ranging from 1 (*never*) to 5 (*always*) that assessed two dimensions of positive parenting: *inductive-reasoning* (e.g., *discipline you with reasoning, explaining and talking*, 6 items, $\alpha = .83$) and *warmth* (e.g., *express warmth and support to you*, 7 items, $\alpha = .86$), and two dimensions of negative parenting: *harshness* (e.g., *hit you, spank you*; 3 items, $\alpha = .62$) and *hostility* (e.g., *yell you, insult you, be angry to you*; 6 items, $\alpha = .84$). These scales, when used in Western adolescent samples, have good psychometric properties (Ge et al. 1996; Kim et al. 2013; Simons et al. 1994). A Chinese version of these measures was generated through a translation and back translation process. Principal component analysis (PCA) of the four dimensions of parenting supported the retention of two broader dimensions: the positive-mothering dimension included inductive-reasoning (factor loading = .95) and warmth (factor loading = .95) and the negative-mothering dimension included harshness (factor loading = .89) and hostility (factor loading = .90). In view of the fact that the SLE score was significantly associated with both positive mothering ($r = -.14$) and negative mothering ($r = .24$), each of the latter were adjusted for their association with the SLE score (i.e., residualized) for reasons outlined at the end of the Introduction. These residualized parenting composites were used in the core regression analyses evaluating parenting-X-BDNF interactions.

Depressive Symptoms

To measure depressive symptoms, the Chinese version (Chen et al. 2000) of the Children's Depression Inventory (CDI) (Kovacs 1992), with good reliability and validity (Mash and Hunsley 2005; Timbremont et al. 2004), was used in the current study. Youth rated depressive symptoms that they had experienced over the past 2 weeks on a 3-point scale. The internal consistency of the CDI in our sample was .86.

Stressful Life Events (SLEs)

SLEs were assessed with a modified version of the Life Events Checklist (Johnson and McCutcheon 1980). This checklist consists of 38 life events that may occur in youngsters' daily life (e.g., "having trouble with teacher", "being difficult with classmates", "lacking friends", "illness or death of family members", "friends, family economic losses", "suspension or expulsion from school"). Each item in the checklist was scored "1" if the target

adolescent indicated a specific event had occurred and “0” if the event had not occurred during the past 12 months. The number of events reported were summed; for purposes of this report, scores ranged from 0 (no SLE) to 6 or more, as done in Chen et al. (2012).

Genotyping

Genomic DNA was extracted from participants’ saliva samples. The BDNF Val66Met polymorphism was genotyped using the SNaPshot method (Applied Biosystems, Foster City, USA) (Kim and Misra 2007). Genomic DNA flanking the SNP (rs6265) was amplified by polymerase chain reaction (PCR) using the primers: 5’-TGATGACCA TCCTTTTCCTT-3’ (forward) and 5’-CACTGGGAG TTCCAATGC-3’ (reverse). The reaction products were analyzed by electrophoresis using an ABI Prism 3730xl DNA analyzer, with the results interpreted using the GeneScan analysis software (ABI). Ten percent of the samples were randomly selected for duplicate genotyping to check accuracy. The error rate was lower than 1 %. All laboratory procedures for genotyping were carried out blind to the measurement of child’s depressive symptoms and perceived maternal parenting.

Statistical Analyses

Multiple imputation (Rubin 1987; Schafer 1997; Schafer and Graham 2002) was employed to accommodate missing data, using the Markov Chain Monte Carlo (MCMC) method. Based on the assumption of missing at random (MAR), we generated one imputed data set for all cases. Because the fraction of missing information was very small for all variables (<4.8 %), imputing only one dataset generates fairly accurate results (Graham 2009).

We firstly conducted standard multiple linear regression to examine G × E:

$$Y = B_0 + B_1X_1 + B_2D_1 + B_3D_2 + B_4(X_1 \times D_1) + B_5(X_1 \times D_2) + B_6X_2 + B_7X_3 + E \tag{1}$$

where Y is the dependent variable, X₁ is the mean-centered residualized parenting score, D₁ is dummy variable (0 = Met/Met and 1 = Val/Val), D₂ is another dummy variable (0 = Met/Met and 1 = Val/Met). B₀ is the intercept, B₄ and B₅ and is the regression coefficient for G × E and represents the difference in the slopes of X₁ in the two genotype groups, B₆ and B₇ are coefficient for two covariates (gender and age), and E is the error term. Given the similarity of regression coefficients between Val/Val and Val/Met, we combined these two groups to one group (Val+), we then conduct regression analyses with one genotype variable (D in Eq. 2, 0 = Met/Met and 1 = Val/Val or Val/Met). B₄ and B₅ are coefficient for two covariates (gender and age) here.

$$Y = B_0 + B_1X_1 + B_2D + B_3(X_1 \times D) + B_4X_2 + B_5X_3 + E \tag{2}$$

Finally, we implemented the Widaman et al. (2012)’s approach, which involves a re-parameterization of standard multiple linear equation (Eq. 2) by centering predictor X₁ at C, the crossover point on X₁ (see Eq. 2).

$$Y = B_0 + B_1(X_1 - C) + B_3((X_1 - C) \cdot D) + B_4X_2 + B_5X_3 + E \tag{3}$$

In Eq. 3, C is the point on X₁ at which the slopes for the two allelic groups cross, B₀ is the estimated Y at the crossover point, and all other symbols were defined as in Eq. (2). The Eq. (3) can also be expressed as following:

$$Y : \begin{cases} D = 0 & Y = B_0 + B_1(X_1 - C) + B_4X_2 + B_5X_3 + E \\ D = 1 & Y = B_0 + B_2(X_1 - C) + B_4X_2 + B_5X_3 + E \end{cases} \tag{4}$$

In Eq. 4, B₁ and B₂ are slopes for the two allelic groups respectively, and other symbols are defined in Eq. (3). In Eq. (4), the point estimates and the corresponding CI of C, are of interest. If C falls within the range of values of X₁ with a relatively narrow confidence interval (CI), the G × E effect conforms to the disordinal form, supporting the differential susceptibility model. Conversely, if C approaches or goes beyond the extreme point on X₁, or has a rather wide confidence interval, then the G × E effect conforms to the ordinal form, supporting the diathesis-stress model (Widaman et al. 2012).

The model presented in Eqs. 3 and 4 is consistent with what Widaman et al. (2012) and Belsky et al. (2013) refers to as the “weak differential susceptibility” model where (a) the crossover point falls *within* the range of environmental measurement and (b) all allelic groups prove susceptible to environmental influence to some extent (i.e., estimates of slopes all different from zero), though one is more so than the other. In contrast, by constraining B₁ = 0 in Eq. 4, the “strong differential susceptibility” model stipulates that the association between environmental conditions and behavioral outcome is non-significant for the non-malleable allelic group, with the reverse being true for the malleable allelic group. Weak and strong diathesis-stress models differ in a similar way from each other, although the crossover point is fixed at the positive end of the environment (i.e., highest positive parenting, lowest negative parenting).

The current inquiry tested all four models (i.e., strong/weak differential susceptibility and diathesis-stress), comparing them on the basis of variance accounted (i.e., R²) and Akaike and Bayesian information criteria (i.e., AIC and BIC, respectively). Models explaining more variance, hence better representing the data are favored. A model

that is more parsimonious is preferred if two models explain comparable amount of variance. Furthermore, smaller values of AIC and BIC indicate better model fit and are particularly useful when comparing non-nested models. Both AIC and BIC penalize for model complexity; therefore, adding unnecessary parameters results in increased AIC and BIC values. Additional statistical details can be found in Widaman et al. (2012) and Belsky et al. (2013).

Results

Three sets of results are presented, the first being preliminary and descriptive, the second involving an exploratory regression analysis and a third the competitive model testing analysis.

Preliminary Descriptive Analyses

The genotype groups were 28 % Val/Val, 51 % Val/Met, and 21 % Met/Met, and in Hardy–Weinberg equilibrium, $\chi^2(1, N = 780) = 1.06, p > .05$. The two gender groups did not differ significantly on genotype frequency, $\chi^2(2, N = 780) = 2.05, p = .36$. Consistent with prior findings of ethnic differences in the distribution of BDNF Val66Met polymorphism (Petryshen et al. 2010; Verhagen et al. 2010), the Met frequency is relatively higher in our Chinese Han sample than that in Caucasian samples.

Means and standard deviations of study variables for the analysis sample and three allelic subgroups are shown in Table 1. One-way ANOVA revealed no statistically significant main effect of BDNF genotype on depressive symptoms. In addition, the main effects of BDNF genotype on maternal warmth-reasoning (positive) and maternal harshness-hostility (negative) were also statistically non-significant, suggesting no genetic influence on individuals' exposure to environment (i.e., gene–environment correlation). The distributions of depressive symptoms and maternal parenting behaviors approached normality, with skewness and kurtosis ranging from -1 to $+1$.

Primary Regression Analyses

Four regression analyses were conducted given that we examined two separate parenting predictors (warmth-reasoning, hostility) and two different ways of parameterizing BDNF (Val–Val vs. Val–Met vs. Met–Met; Val carriers vs. Met–Met) and the resulting $G \times E$ interactions in predicting depressive symptoms, with child gender and age treated as covariates. The results of multiple linear regressions with three genotype grouping are shown in Table 2 and those with two genotype groupings in Table 3. With regard to main effects, inspection of both tables reveal that less positive parenting and more negative mothering predicted, as anticipated, more depressive symptoms, but that there were no main effects of genotype. Most important for purposes of this report, the $G \times E$ interaction proved significant in the models that included the positive, not negative parenting measure; and this was true when three genotypic groups were involved and when two genotypic groups were the focus.

Secondary Model Fitting Analysis

In light of the results of the exploratory regression analyses, the association between positive mothering and depressive symptoms was stronger in Val carriers ($B = -.24, p < .05$) than Met homozygotes ($B = -.12, p < .05$), then the Widaman et al. (2012) competitive model-fitting approach was conducted using the positive parenting predictor and the two BDNF allelic subgroups (Val carriers vs. Met–Met), with a priori hypothesis of Val carriers being more sensitive. As Table 4 and Fig. 1 indicate, the point estimate of the crossover point in model b, $C = 4.05$ ($SE = 5.44$), and its 95 % confidence intervals [$-6.58, 14.73$], fell within the median area of positive mothering (residualized SLE) in this sample (rang from -35 to 22), thus supporting the differential-susceptibility model, rather than diathesis-stress model. Furthermore, constraining the slopes of Met/Met group to zero (i.e., $B_1 = 0$) as strong differential-susceptibility predicted significantly reduced the model fits ($F = 5.70, p < .05$), thus supporting the weak differential-susceptibility model.

Table 1 Means and SD of study variables among different genotype groups and total sample

	Val/Val (n = 221)	Val/Met (n = 402)	Met/Met (n = 157)	Total (n = 780)	F	p
Age (years)	13.50 (1.82)	13.77 (1.85)	13.49 (1.73)	13.64 (1.82)	2.30	.10
Depressive symptoms	39.22 (7.42)	38.88 (7.08)	38.84 (6.31)	38.97 (7.03)	0.20	.82
Mother's warmth-reasoning (positive)	45.40 (11.69)	46.50 (11.35)	45.45 (10.66)	45.98 (11.31)	0.89	.41
Mother's harshness-hostility (negative)	19.78 (6.48)	19.78 (6.32)	20.06 (5.81)	19.84 (6.26)	0.12	.89

Table 2 Standard regression analyses with genotype dummy coding for positive and negative mothering ($N = 780$)

	Mother's positive parenting				Mother's negative parenting			
	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Constant	38.24	0.60	63.80	0.000***	38.40	0.62	62.37	0.000***
Gender	0.94	0.48	1.95	0.051	0.80	0.50	1.61	0.11
Age	0.38	0.13	2.94	0.003**	0.49	0.14	3.63	0.000***
Parenting	-0.12	0.05	-2.38	0.017*	0.26	0.10	2.72	0.007**
D1(Val/Val vs. Met/Met)	0.52	0.69	0.75	0.453	0.59	0.71	0.82	0.411
D2(Val/Met vs. Met/Met)	0.47	0.63	0.76	0.451	0.22	0.65	0.33	0.738
D1 × parenting	-0.11	0.06	-1.69	0.092	0.07	0.12	0.59	0.553
D2 × parenting	-0.13	0.06	-2.19	0.029*	0.01	0.11	0.06	0.953
R^2	0.137				0.079			

Positive and negative mothering were residualized by stressful life events and centered. Met/Met is the reference group

* $p < .05$; ** $p < .01$; *** $p < .001$

Table 3 Standard regression analysis with genotype grouping (Val+ vs. Met/Met) for positive and negative mothering ($N = 780$)

	Mother's positive parenting				Mother's negative parenting			
	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Constant	38.23	0.60	63.88	0.000***	38.39	0.62	62.41	0.000***
Gender	0.95	0.48	1.97	0.050*	0.82	0.50	1.64	0.100
Age	0.39	0.13	2.96	0.003**	0.48	0.13	3.59	0.000***
Parenting	-0.12	0.05	-2.39	0.017*	0.26	0.10	2.73	0.006**
D (Val+ vs. Met/Met)	0.48	0.59	0.82	0.414	0.35	0.61	0.57	0.569
D × parenting	-0.12	0.05	-2.17	0.030*	0.03	0.10	0.27	0.784
R^2	0.137				0.078			

Positive and negative mothering were residualized by stressful life events and centered. Met/Met is the reference group

Val+ represents the combination of Val/Val and Val/Met groups

* $p < .05$; ** $p < .01$; *** $p < .001$

Moreover, the weak differential-susceptibility model (b) explained the largest variance and had the lowest AIC values among the four alternative models. Although the BIC value was smaller in model d, considering the biased tendency of BIC favoring simpler model and small value difference, we proposed that the weak differential-susceptibility is the best model fitting the BDNF × positive mothering, that is, while both Val carriers and Met–Met homozygotes evinced more depressive symptoms when mothers were less positive in their parenting, this association proved stronger in Val carriers.

Discussion

Although there is growing interest in $G \times E$ research on the etiology of depression, most previous studies have focused on adults, informed as they were by diathesis-stress thinking. More recently, researchers have begun to

examine the $G \times E$ on psychopathology among adolescents (Dunn et al. 2011; Mullineaux and DiLalla 2015), with growing evidence for the differential-susceptibility framework (Bakermans-Kranenburg and Van IJzendoorn 2011; Van IJzendoorn et al. 2012). Recall that this person × environment interaction model stipulates that individuals with certain alleles may not just be disproportionately and adversely affected by negative environments, consistent with diathesis-stress reasoning, but also benefit the most from positive environmental conditions.

We examined whether and how BDNF Val66Met polymorphism interacted with both negative and positive maternal parenting in predicting adolescent depressive symptoms, while evaluating which of two theoretical $G \times E$ models (differential susceptibility or diathesis-stress) fit the data better. Recall that we sought to extend prior depression-related, $G \times E$ research on this sample that proved consistent with the differential-susceptibility

Table 4 Re-parameterized regression analyses for mother's positive parenting ($N = 780$)

Parameter	Differential susceptibility		Diathesis-stress	
	Strong: Model a Estimate (SE) 95 % CI	Weak: Model b Estimate (SE) 95 % CI	Strong: Model c Estimate (SE) 95 % CI	Weak: Model d Estimate (SE) 95 % CI
B_0	32.85 (1.85)*** [29.22, 36.48]	32.48 (2.10)*** [28.36, 36.59]	30.58 (1.86)*** [26.94, 34.22]	28.68 (1.83)*** [25.09, 32.28]
B_1	0.00 (–) [–]	–0.12 (0.05)** [–0.22, –0.02]	0.00 (–) [–]	–0.18 (0.03)*** [–0.24, –0.13]
C	1.60 (2.51) [–3.32, 6.51]	4.07 (5.44) [–6.58, 14.73]	22 (–) [–]	22 (–) [–]
B_2	–0.24 (0.02)*** [–0.28, –0.19]	–0.24 (0.02)** [–0.28, –0.19]	–0.14 (0.02)*** [–0.18, –0.11]	–0.22 (0.02)*** [–0.27, –0.18]
R^2	0.130	0.136	0.088	0.134
F	23.13	20.28	18.70	23.95
df	5/771	6/770	4/772	5/771
p	<0.0001	<0.0001	<0.0001	<0.0001
F versus a		5.70	38.11	
df		1770	1771	
p		0.02*	<0.001***	
F versus b			22.02	2.41
df			2770	1770
p			<0.001***	0.121
F versus c				41.55
df				1771
p				<0.001***
AIC	5172.3	5168.6	5207.8	5169.0
BIC	5200.3	5201.2	5231.1	5197.0

The parameters of covariates were not shown here but degree freedom (df) number was counted. B_0 stands for intercept. B_1 represents the slope of group “Met/Met”. B_2 stands for the slope of group “Val+” and C represents the crossover point

F versus a stands for an F test of the difference in R^2 for model a versus other model

F versus b stands for an F test of the difference in R^2 for model b versus other model

F versus c stands for an F test of the difference in R^2 for model c versus other model

* $p < .05$; ** $p < .01$; *** $p < .001$

model when using stressful life events as the environmental predictor (Chen et al. 2012). Recall, too, that to distinguish the putative influence of parenting in the current inquiry from that of life events evaluated in the prior research, we adjusted the measures of parenting for their association with life events. This enabled us to investigate the independent effect of parenting in interacting with BDNF Val66Met in predicting adolescent depressive symptoms.

Main-effect associations linking maternal parenting and adolescent depressive symptoms emerged as expected, with less positive parenting (warmth and inductive-reasoning) predicting more depressive symptoms, as did more negative parenting (harshness and hostility); these results proved, then, consistent with prior research on Western adolescents (Ge et al. 1994b; Kim et al. 2009; Kim et al.

2013) and Chinese youth (Zhang et al. 2015). Also in line with prior work (Verhagen et al. 2010), no main effect of the BDNF Val66Met polymorphism on adolescents' depressive symptoms emerged. Especially important given the $G \times E$ focus of the current inquiry was that no significant association was detected between BDNF genotype and maternal parenting practices, suggesting no gene–environment correlation (rGE). These results ruled out the possible confounding effect of rGE on $G \times E$, at least with respect to the polymorphism central to this inquiry.

The first main and novel finding of the current study involves the significant interaction effect between BDNF Val66Met and maternal positive parenting (warmth-reasoning), but not negative parenting, on adolescents' depressive symptoms. Recall that positive parenting

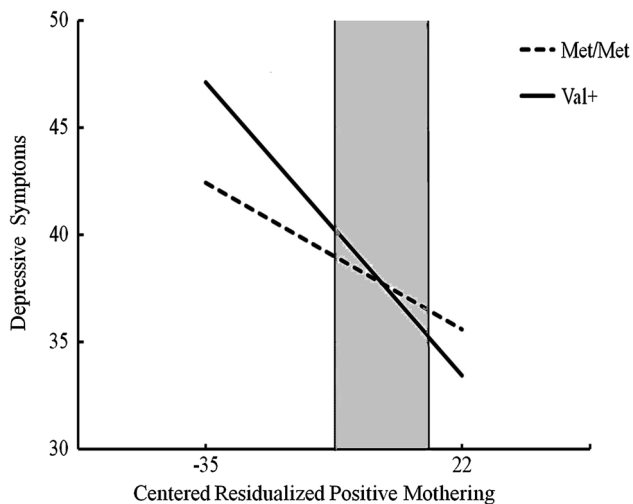


Fig. 1 Plots of predicted depressive symptoms (*Y axis*) as functions of positive mothering (*X axis*) in two genotype groups (Val + vs. Met/Met) under the weak differential-susceptibility model. *Shading* region indicates the 95 % confidence interval for cross-over point. Val+ represents the combination of Val/Val and Val/Met groups

predicted depressive symptoms more strongly for Val carriers (Val/Val or Val/Met) than Met–Met homozygotes, though in both cases more positive mothering was associated with less depressive symptoms and less positive parenting with more symptoms. As a result of this pattern of associations, confirmatory model-fitting analyses of the detected $G \times E$ interaction proved more consistent with the differential susceptibility rather than diathesis stress model. Because the association between positive parenting and depressive symptoms was also evident in the case of Met–Met homozygotes, it was the weak rather than strong version of the differential susceptibility model that fit the data best.

Exactly why a similar interaction did not prove significant in the case of negative maternal parenting remains unclear, though it should be noted that a trend did emerge more or less in line with the positive-parenting results (i.e., stronger association in the case of Val carriers). Conceivably, it could be the case that it would take more extreme forms of negative parenting, like child abuse, to reveal the kind of $G \times E$ interaction detected reliably in the case of positive parenting.

It is important to consider the results reported herein in the context of the developmental stage of our sample. We focused on adolescence because most previous $G \times E$ studies focused on depression were of adults, with earlier reviewed research suggesting that the interaction between BDNF gene and environment may vary across development (e.g., Casey et al. 2009; Lenroot and Giedd 2011). Our findings, together with prior adolescent studies (Chen et al. 2012; Cruz-Fuentes et al. 2014; Gottfredson et al. 2014), support the proposition that BDNF Val66Met \times Environment might vary between

adolescents and adults. Specifically, the Val version of BDNF appears to confer heightened susceptibility to environmental influences in the case of youth, whereas the Met version of BDNF operates in this manner with regard to depression and adversity in the case of adults (see meta-analysis in Hosang et al. 2014).

To the extent that this is indeed the case, it seems likely that different neurobiological mechanisms may underlie BDNF \times Environment interplay in adolescents and adults. One possibility is that environmental stimuli during adolescence might foster depressive symptoms in youth through the ventral tegmental area to nucleus accumbens (VTA-NAc) pathway, whereas environmental influence on adult depression might be mediated through the hippocampus. Recall that research suggests that BDNF has opposite effects in the two brain regions across these developmental epochs (Feder et al. 2009; Krishnan and Nestler 2008). That is, more BDNF in the hippocampus reduces depression (Duman and Monteggia 2006), whereas in the nucleus accumbens (NAc) it facilitates depression (Groves 2007; Martinowich et al. 2007). Another candidate mechanism involves stress-reactivity, as there is also evidence that younger adults carrying Met-BDNF, relative to their Val–Val counterparts, evince blunted hypothalamic–pituitary–adrenal (HPA) axis responses to psychological stressors (Alexander et al. 2010; Shalev et al. 2009).

Collectively, our results along with those just summarized, underscore the importance of examining the $G \times E$ from a developmental perspective. Future $G \times E$ research with longitudinal designs needs to elucidate how specific genetic variants (e.g., BDNF Val66Met) interact with developmental salient experiences (e.g., childhood maltreatment, parenting and peer interactions in childhood and adolescence, and stressors in adulthood) and affect the development and course of psychopathology from childhood to adulthood.

The results reported herein should also be interpreted in light of the ethnicity of our sample (i.e., Chinese Han), considering that previous research has highlighted the very real possibility of racial/ethnic differences in $G \times E$ (Propper et al. 2007). The ethnically homogeneous sampling strategy central to the current work excluded the confounding of population stratification, but it also raised the issue of generalizing our findings to other ethnic youth, given the relatively more common Met in Asian populations compared to Caucasian populations (Petryshen et al. 2010; Verhagen et al. 2010). It is worth noting that previous studies of Europeans and North Americans usually grouped the Val66Met heterozygote and Met/Met homozygote together into a single group for comparison against Val/Val homozygotes. However, this process of genotype grouping may produce inherent biases when examining the effect of genotype. Future studies should

utilize sampling strategies that increase the representation of Met homozygotes to ensure that the main effect of three genotype groups can be appropriately tested (Notaras et al. 2015).

The current study has several strengths. First, we included both negative and positive parenting dimensions to investigate the $G \times E$. Second, we employed a confirmatory and competitive model-testing approach developed by Widaman et al. (2012) to explicitly compare the relative fit of the diathesis-stress and differential susceptibility models of $G \times E$ interactions after conducted exploratory regression analyses. Recall that we adopted this two-stage strategy of inquiry because of inconsistent signals in the $G \times E$ literature regarding which allelic subgroup would prove most susceptible to environmental effects. Had the signal been more consistent, we would have bypassed the exploratory regression approach and gone directly to the confirmatory model testing, as this approach has greater statistical power than standard linear regression (Belsky et al. 2013).

Despite these strengths, our study also has some limitations. First, we only focused on a negative outcome and not a positive (or bipolar) one (e.g., self-esteem, academic achievement), as would be ideal when evaluating differential susceptibility (Belsky et al. 2007). Second, because this $G \times E$ inquiry, like so many, is observational and thus correlational in design, it precludes the drawing of causal inferences regarding the effects of parenting on adolescent depressive symptoms. Experimental studies that evaluate differential response to intervention as a function of genotype are better positioned to do just that, though they can only manipulate positive environmental exposures given ethical constraints on exposing individuals to negative ones for solely scientific reasons (Belsky and Van IJzendoorn 2015; Bakermans-Kranenburg and Van IJzendoorn 2015). Natural experiments such as exposure to divorce, economic depression or natural disasters could serve the latter purpose.

A third limitation of the current work derives from the fact that adolescents provided information on both the environmental predictor and the outcome. Thus their association could partially reflect reporter bias. Fourth, because this study was based on a community sample, the measurements obtained may not adequately capture more extreme negative parenting experiences to which some adolescents are exposed. If so, this would restrict the possibility of detecting stronger effects. A smaller effect size may also be due to period of time on which adolescents reported on the parenting they experienced (i.e., within the past year); conceivably, had a longer—or shorter—period been the focus of measurement, stronger $G \times E$ effects might have emerged. Fifth, we only focused on a single polymorphism. Future work should pursue polygenic

approaches to the study of $G \times E$ interaction (Belsky and Pluess 2013). Finally, we lack direct replication in an independent sample using the same measures; as result, the reported findings should be interpreted with caution.

Conclusion

We found that the BDNF Val66Met polymorphism significantly moderated the influence of maternal warmth-reasoning on adolescent depressive symptoms. Youth carrying the Val-BDNF, relative to their Met–Met counterparts, proved more sensitive to the effects of positive mothering, though both groups showed the expected association between more positive parenting and less depressive symptoms. These findings supported BDNF Val66Met as a genetic susceptibility marker and BDNF as one “plasticity gene”. Future studies can explore whether the BDNF Val66Met polymorphism moderates depressed youth’s responses to intervention program involving the improvement of mothers’ warmth and inductive-reasoning.

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Author contributions LZ performed the statistical analyses; ZL participated in data analyses, and are involved in drafting the manuscript; JC participated in interpretation of the data, and are involved in drafting and revising the manuscript; XL and JZ participated in the design and coordination of the project; Jay Belsky participated in conceiving the study, interpretation of the data and helped to draft the manuscript. LZ, ZL, and JC contributed equally to this work. All authors read and approved the final manuscript.

Conflict of interest The authors declare that they have no conflict of interest.

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