BDNF Val66Met, stress, and positive mothering: Differential susceptibility model of adolescent trait anxiety

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ABSTRACT

Etiological research has indicated the gene–environment interaction (G × E) on adolescent anxiety. This study aimed to examine how the BDNF Val66Met polymorphism interacted with stressful life events and positive mothering to influence youth trait anxiety. The study sample included 780 community adolescents of Chinese Han ethnicity (M = 13.6, 51.3% females). Participants’ trait anxiety, exposure to stressful life events, and mother’s warmth-reasoning were assessed by self-reported questionnaires. We found that BDNF Val66Met polymorphism significantly moderated the influences of stressful life events and mother’s warmth-reasoning on adolescent anxiety. The influences were significantly greater in adolescents carrying one or two Val allele than those with Met/Met genotype. Moreover, the G × E interactions were more consistent with the differential susceptibility than the diathesis–stress model. Adolescents carrying Val allele who were more susceptible to adversity were also more likely to benefit from supportive experiences. These findings provide novel evidence for the role of BDNF Val66Met as a genetic susceptibility modulating the influences of stressful life events and mother’s warmth-reasoning on adolescent anxiety. We speculate that BDNF Val66Met may moderate anxious youths’ responses to mindfulness-based stress reduction program and family-based treatment targeting the enhancement of positive parenting.

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1. Introduction

Anxiety in adolescence is common, with prevalence of anxiety disorder to be 15–20% (Rapee, Schniering, & Hudson, 2009), and of subthreshold anxiety to be about 32% (Balazs et al., 2013). Anxiety is an evolved biological adaptive response to stressful or threatening environment (Marks & Nesse, 1994). However, excessive anxiety is often accompanied with impaired psychosocial functions (Beesdo, Knappe, & Pine, 2009). Trait anxiety, reflecting an individual’s general disposition to experience anxiety–relevant feelings or to show anxiety–related behaviors (Spielberger, 1979), is regarded as one heritable temperament precursor for anxiety disorders (Chambers, Power, & Durham, 2004; Garcia et al., 2013). Investigating the etiological factors (e.g., both genetic and environmental ones), and their interactive mechanisms (i.e., diathesis–stress or differential susceptibility) underlying adolescent trait anxiety, is informative for early prevention and intervention of anxiety.

Accumulated studies have supported the role of gene–environment interaction (G × E) in the etiology of adolescent anxiety (Lau, Gregory, Goldwin, Pine, & Eley, 2007; Vendelinski, Lemery-Chalfant, Essex, & Goldsmith, 2011). Previous inquiry on specific gene by measured environment interactions was guided primarily, if not exclusively, by the diathesis–stress model (Monroe & Simons, 1991), which proposes that, some individuals, due to genetic vulnerabilities, are disproportionately to be adversely affected by negative environment. Recently, one alternative framework—the differential susceptibility hypothesis, which postulates that some individuals are more susceptible than others to both positive and negative environmental influences, has received substantial attention (Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2007; Belsky & Pluess, 2009; Ellis, Boyce, Belsky, Bakermans–Kranenburg, & Van Ijzendoorn, 2011). Although the differential susceptibility hypothesis is partially compatible with the diathesis–stress model, it further contends that susceptible individuals will differ in a ‘for better and for worse’ pattern (Belsky et al., 2007, 2009); that is, from the evolutionary perspective, the
individuals’ increased vulnerability in adverse environments is countered by better functioning in supportive environments (Belsky & Pluess, 2013).

The differential-susceptibility hypothesis has received substantial support in research of G × E on child and adolescent behaviors. For example, a recent meta-analysis has shown that Caucasian youths carrying short allele of 5-hydroxytryptamine promoter-linked region (5-HTTLPR) are more susceptible to the effects of both positive and negative developmental experiences (Van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012). Another meta-analysis revealed that children with the less efficient dopamine-related genes demonstrated higher susceptibility to both positive and negative environmental exposures (Bakermans-Kranenburg & van Ijzendoorn, 2011). With these intriguing findings, Belsky and his colleagues suggested that the putative ‘vulnerability genes’ might be appropriately conceptualized as ‘plasticity genes’ (Belsky et al., 2009; Belsky & Pluess, 2013). In this study, we focused on another potential genetic susceptibility—the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism, and investigated its moderating role on the influences of stressful life events and positive mothering on adolescent trait anxiety.

BDNF is one of the nerve growth factors that plays an important role in neuronal maturation (Waterhouse et al., 2012) and synaptic plasticity (Cowansage, LeDoux, & Monfils, 2010), and has been indicated to be involved in the pathophysiology and treatment of anxiety (Duman & Monteggia, 2006; Martinowich, Manji, & Lu, 2007). The Val66Met polymorphism (SNP, rs6265) within the BDNF gene, which causes the valine-to-methionine substitution at codon 66 in the pro-domain of BDNF, has been shown to affect intracellular trafficking and activity-dependent secretion of BDNF (Egan et al., 2003). Previous studies have revealed null or trivial main effect of BDNF Val66Met polymorphism on anxiety (Frustaci, Pozzi, Gianfagna, Manzoli, & Bocca, 2008).

Rather, accumulating evidence indicated that the BDNF Val66Met may be related to individual differences in susceptibility to contextual influences. In the physiological level, two independent studies with healthy adults found that individuals with BDNF Met allele demonstrated blunted hypothalamic–pituitary–adrenal (HPA) axis responses to psychological stressors, comparing with those carrying Val/Val genotype (Alexander et al., 2010; Shalev et al., 2009). In the neural level, two human studies indicated that BDNF Met-carriers showed a deficit in amygdala-dependent fear conditioning (Hajcak et al., 2009; Lonsdorf et al., 2010). Furthermore, the BDNF Met allele was found to be associated with impaired fear extinction learning in both mice and humans (Soliman et al., 2010). In the behavioral level, Gatt et al. (2009) found that young adults with Met allele demonstrated significant lower anxiety than Val/Val genotype carriers, but only under the condition of more early life stress. Finally, clinical study also indicated that the posttraumatic stress disorder (PTSD) patients with the BDNF Met allele displayed significant poorer response to exposure therapy compared to patients carrying Val/Val genotype (Felmingham, Dobson-Stone, Schofield, Quirk, & Bryant, 2013).

These findings suggest that the BDNF Val66Met polymorphism modulates individual’s susceptibility to both environmental adversity (e.g., stress, fearful stimulating) and environmental enrichment (e.g., fear extinction, psychotherapy), indicating the differential susceptibility mechanism. However, to our knowledge, little research has empirically tested the differential susceptibility model by examining the interaction effects of BDNF Val66Met polymorphism with both positive and negative environments on adolescent anxiety in a single study. Therefore, we aimed to fill this gap by examining two interaction effects—BDNF Val66Met × stress life events and BDNF Val66Met × mother’s warmth-reasoning—on adolescent trait anxiety in this study.

Mounting evidence has demonstrated stressful life events as a salient risk factor for adolescent anxiety (Allen, Rapee, & Sandberg, 2008; Broeren, Newall, Dodd, Locker, & Hudson, 2014; McLaughlin & Hatzenbuehler, 2009). Meanwhile, substantial research has showed that positive parenting, especially positive mothering, is an important source of protection for youths’ anxiety (Bumaru & Kerns, 2014). For example, parental warmth (e.g., care, support and positive affection) and inductive reasoning (e.g., give reasons for decisions and explain rules) are associated with less anxiety in youths (Letcher, Sanson, Smart, & Toumbourou, 2012; McLeod, Wood, & Weisz, 2007; Yap, Pilkington, Ryan, & Jorm, 2014). Parental warmth may reduce child’s belief that the external environment is hostile and threatening, while inductive reasoning—opposite to over-controlling—may encourage child’s autonomy, both of which can increase child’s self-worth and self-competence (Bögels & Brechman-Toussaint, 2006; Drake & Ginsburg, 2012), thus reduce child’s anxiety.

Given that the vast majority of extant studies included either only negative (Belsky et al., 2009) or only positive environment (Hankin et al., 2011; Pluess & Belsky, 2013), simultaneously measuring both negative (i.e., stressful life events, SLEs) and positive environment (i.e., mother’s warmth-reasoning, MWR) endows the current study a strength for testing the differential susceptibility model in a ‘for better and for worse’ fashion. If the differential-susceptibility model is supported, adolescents carrying certain genotype will simultaneously suffer more from stressful life events and benefit more from maternal warmth-reasoning.

In sum, this study aimed to examine two interaction effects—BDNF Val66Met × stress life events and BDNF Val66Met × mother’s warmth-reasoning—on adolescent trait anxiety. Two standard multiple linear regression analyses were conduct to examine the main effects of genotype, environmental factors and the G × E interaction effect. Furthermore, we adopted the bootstrapping regression method to test the robustness of G × E effects. Finally, we used the confirmatory method developed by Widaman et al. (2012) to explicitly evaluate whether the detected G × E interactions were more consistent with the differential susceptibility than diathesis–stress model. Widaman’s method has larger statistical power than traditional exploratory method, especially in differentiating competitive models (Belsky, Pluess, & Widaman, 2013).

2. Method

2.1. Participants

This study was based on the adolescent twin sample of Beijing Twin Study (BeTwISt) (Chen et al., 2013), in which the second child in each twin pairs was genotyped. These children with gene data constituted the sample of the current study (N = 780, 51.3% female). All participants were of Han ethnicity, and aged 11–17 years (M = 13.6, SD = 1.80). Regarding parental educational attainment, 6.8% fathers had primary school degree, 32.8% had junior high school degree, 31.8% had senior high school degree, 26.1% had college degree, and 2.5% had graduate degree. The corresponding percentages for mothers’ educational attainment were 5.4%, 35.3%, 29.5%, 25.2%, and 4.6%. Data on behaviors and environmental exposures were collected by self-reported questionnaires. DNA was collected via saliva sample using Oragene collection kits under the supervision of specially trained research assistants. All children and their parents signed informed consent forms before participation. Ethical approval for the study was obtained from the Institutional Review Board.
2.2. Measures

2.2.1. Trait anxiety
Trait anxiety was assessed using the trait subscale of the State-Trait Anxiety Inventory (STAI-T, Form Y) (Spielberger, 1983). The STAI-T measures an individual’s stable susceptibility or proneness to experience anxious mood or thoughts frequently. Example items included “I feel nervous and restless,” and “I worry too much.” On a 4-point Likert scale ranging from 1 = almost never to 4 = almost always, participants were asked to choose the statement that mostly closely describes how they generally feel. The Chinese version of STAI has been demonstrated reliable and valid (Li & Lopez, 2004). The reliability coefficient of the STAI-T in this study was .89.

2.2.2. Stressful life events (SLEs)
Adolescents reported their stressful life events exposure during the past year based on a modified version of the Life Events Checklist (Johnsson & McCutcheon, 1980). This checklist consists of 38 negative life events that may occur in participants’ daily life, including minor events such as “having trouble with teacher”, and “lack of friends”, and serious ones such as “illness or death of family members”, and “suspension or expulsion from school”. Each item was scored 1 if the specific event had occurred and 0 if the event had not occurred. The number of events that occurred was then added up, and ranged from 0 (no SLEs) to 7 (7 or more SLEs).

2.2.3. Mother’s warmth-reasoning (MWR)
Adolescents reported their mother’s parenting practices using a 5-point scale ranging for 1 (never) to 5 (always). In the behavioral dimension (inductive-reasoning, 6 items), youths reported the frequency with which their mothers used inductive reasoning, open communication, as well as cooperative problem-solving and decision-making with them during the past 12 months. In the affective dimension (warmth, 7 items), youths reported the frequency with which their mothers expressed warmth, support, and positive affects toward them during the past 12 months. These scales have been used in Western adolescents and demonstrated good psychometric properties (Kim et al., 2003; Simons, Whitbeck, Beaman, & Conger, 1994). The Chinese version of two subscales developed through translation and back-translation process was used in the present study. The reliability coefficient was .83 for the inductive reasoning scale, and .86 for the warmth scale. The two subscale were highly correlated in this sample (r = .81), thus combined as one composite scale (i.e., warmth-reasoning, 13 items). The reliability coefficient of the composite scale was .91.

2.3. Genotyping
Genomic DNA was extracted from participants’ saliva samples. The BDNF Val66Met polymorphism (rs6265) was genotyped using a single-base primer extension assay (ABI PRISM SNAPSHOT Multiplex kit; ABI, Foster City, CA, USA) (Kim & Misra, 2007), according to the manufacturer’s instructions. Genomic DNA flanking the SNP (rs6265) was amplified by polymerase chain reaction (PCR) using the primers: 5’-TATGACGACTCTTTCCCTTT-3’ (forward) and 5’-CAGCAGGACTCAGGTTCC-3’ (reverse). The detailed protocol is available from the manufacturer instructions. 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 for errors. The error rate was lower than 1%. All laboratory procedures for genotyping were carried out blind to the measurement of child’s anxiety, SLEs and parenting.

2.4. Statistical analyses
We firstly conducted standard multiple linear regression to examine $G \times X$:

$$Y = B_0 + B_1X + B_2D + B_3(X \times D) + E$$ (1)

Where $Y$ is the dependent variable, $X$ is the mean-centered environmental variable, $D$ is a dummy variable indicating gene group ($0 =$ Met/Met and $1 =$ Val/Val or Val/Met), $B_0$ is the intercept, $B_1$ and $B_2$ represent main effects of environment ($X$) and gene ($D$), $B_3$ is the regression coefficient for $G \times E$ and represents the difference in the slopes of $X$ in the two genotype groups, and $E$ is the error term.

Following Widaman et al. (2012), we re-parameterized the Eq. (1) as:

$$Y = B_0 + B_1(X - C) + B_3((X - C) \times D) + E$$ (2)

where $C$ is the point on $X$ at which the slopes for the two genotype groups cross, $B_0$ is the estimated $Y$ at the cross-over point, and all other symbols are defined as in Eq. (1). The Eq. (2) can also be expressed as following:

$$Y = \begin{cases} 
D = 0 & Y = B_0 + B_1(X - C) + E \\
D = 1 & Y = B_0 + B_2(X - C) + E 
\end{cases}$$ (3)

where $B_1$ and $B_2$ are slopes of $X$ for gene group $D = 0$ (Met/Met) and $D = 1$ (Val+/), respectively, and other symbols are defined as in Eq. (2). In Eq. (3), the point estimates and standard errors (SE) of four parameters $B_0$, $B_1$, $B_2$, and $C$ can be estimated. If $C$ falls within the range of values on $X$, the tested interaction effect is more consistent with differential susceptibility model. Conversely, if $C$ approaches or goes beyond the extreme point on $X$, then the tested interaction is more consistent with diathesis–stress model (Widaman et al., 2012). We further examined whether a priori diathesis–stress model fitted the data better than differential susceptibility model by constraining $C = \text{max}(X)$ or $C = \text{min}(X)$. Finally, we compared the model fits of strong ($B_1 = 0$) and weak ($B_1$ is freely estimated) differential susceptibility models as indicated by Belsky et al. (2013). The proportion of missing values in the dataset was low (5.6% for TAI score, 6.7% for MWR). The non-significant Little’s MCAR test, $\chi^2(780) = 11.67, p = .39$, revealed that the data were missing completely at random (Little & Rubin, 1987). The multiple imputation method ($n = 5$) was used to deal with the missing data (Graham, 2009).

3. Results

The genotype frequencies in our sample were 20% of Met/Met, 52% of Val/Met, and 28% Val/Val (Table 1), which were in Hardy–Weinberg equilibrium, $\chi^2(1, N = 780) = 1.12, p > .05$. There was no significant sex difference in genotype frequency distributions, $\chi^2(2, N = 780) = 1.23, p = .54$. The Met allele frequency was relatively higher in our sample than in Caucasian samples, which was consistent with prior findings of ethnic differences in the distribution of BDNF Val66Met polymorphism (Petryshen et al., 2009; Verhagen et al., 2008).

The means and standard deviations of study variables in the three genotype groups and the total sample are presented in Table 1. One-way ANOVA revealed no significant main effect of BDNF genotype on anxiety, suggesting that the BDNF Val66Met did not directly influence anxiety. In addition, the main effects of BDNF genotype on stressful life events (SLEs) and mother’s warmth-reasoning (MWR) were also non-significant, suggesting no genetic influence on individual’s exposure to environment (i.e., gene–environment correlation).

Because the dominance status of the two alleles (Val vs. Met) was ambiguous, we separately computed correlation coefficients of
Table 1
Means and standard deviations of study variables in the three genotype groups and the whole sample.

<table>
<thead>
<tr>
<th></th>
<th>Met/Met (n = 157)</th>
<th>Val/Met (n = 402)</th>
<th>Val/Val (n = 221)</th>
<th>Total (N = 780)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>13.45 (1.73)</td>
<td>13.77 (1.85)</td>
<td>13.50 (1.82)</td>
<td>13.63 (1.82)</td>
</tr>
<tr>
<td>Trait anxiety inventory (TAI) scores</td>
<td>38.84 (8.39)</td>
<td>38.17 (9.23)</td>
<td>38.40 (9.27)</td>
<td>38.79(9.07)</td>
</tr>
<tr>
<td>Stressful life events (SLEs)</td>
<td>2.62 (2.11)</td>
<td>2.57 (2.17)</td>
<td>2.61 (2.16)</td>
<td>2.59 (2.15)</td>
</tr>
<tr>
<td>Mother’s warmth-reasoning (MWR)</td>
<td>45.48 (10.61)</td>
<td>46.35 (11.22)</td>
<td>45.61 (11.66)</td>
<td>45.60 (11.22)</td>
</tr>
<tr>
<td><strong>F</strong></td>
<td>2.60 (.08)</td>
<td>3.00 (.74)</td>
<td>0.30 (.03)</td>
<td>0.30 (.74)</td>
</tr>
</tbody>
</table>

The regression slope of MWR was nearly two times larger in Val+ group than in Met/Met group (Fig. 1b). To further test the robustness of the interaction effects, we used bootstrapping with 1000 random sample drawing. The bias-corrected, accelerated (BCa) percentile intervals of regression coefficients were estimated (see Table 3). Because zero was not included in the BCa intervals of interaction terms, the interaction effects were considered significant in bootstrapping regressions.

We next fitted the re-parameterized Eq. (3) to the data. The parameter estimates and their SEs are shown in Table 4. For SLEs × BDNF, the point estimate of the crossover point, C = 0.77 (SE = 0.92), and its 95% confidence interval [−1.03, 2.57], fell within the median range of measured SLEs in this sample. Moreover, constraining the crossover point to the lowest value of SLEs (−2.6) (i.e., the diathesis–stress model predicted) significantly reduced the squared R of model (F = 5.96, p < .05). For MWR × BDNF, the point estimate of the crossover point, C = −3.31 (SE = 5.62), and its 95% confidence interval [−14.3, 7.7], also fell within the median range of measured MWR in this sample. Fixing the crossover point to the highest value of MWR (20.6) (i.e., the diathesis–stress model predicted) also resulted significant reduction of squared R (F = 4.02, p < .05). These results led to a conclusion that the two interactions (SLEs × BDNF and MWR × BDNF) were more consistent with the differential susceptibility model than the diathesis–stress model. Finally, our data supported the weak differential susceptibility model as constraining the slopes of Met/Met group to zero (i.e., B1 = 0) significantly reduced the model fits (SLEs: F = 7.79, p < .01; MWR: F = 8.09, p < .01).

4. Discussion

There have been increasing studies of G × X on psychological traits and psychopathology (Dick, 2011; Manuck & McCaffery, 2014). Most of prior G × X research was informed by the diathesis–stress view that some individuals are genetically more vulnerable to adverse environmental effects than others. More recently, an alternative framework—the differential susceptibility hypothesis—in which the individuals who are most adversely affected by negative environment are also most likely to benefit from positive environment, has received increasing support (Belsky & Pluess, 2009, 2013; Breslin, Finy, & Verona, 2013; Ellis & Boyce, 2011). Several putative ‘vulnerability genes’ such as serotonin transporter (5-HTT), monoamine oxidase-A (MAOA), and dopamine receptor (DRD4) have been demonstrated to be associated with differential susceptibility and proposed to be ‘plasticity genes’ (Belsky & Hartman, 2014; Belsky et al., 2009).

This study provided empirical evidence supporting the association between BDNF Val66Met polymorphism and adolescents’ differential susceptibility to anxiety-related negative and positive environments. In other words, we found that the BDNF Val66Met polymorphism significantly moderated the influences of stressful life events and mother’s warmth-reasoning on adolescent trait anxiety. Specifically, compared with BDNF Met/Met carriers, adolescents with Val allele displayed heightened sensitivity to both the detrimental effect of stressful life events—increase of anxiety symptoms, and the beneficial effect of mothers’ warmth-reasoning—decrease of anxiety symptoms. This ‘for better and for
worse' pattern is consistent with the differential susceptibility hypothesis.

Moreover, we further explicitly confirmed that the two discerned $G \times E$s (i.e., SLEs $\times$ BDNF and MWR $\times$ BDNF) fitted the differential susceptibility model better than the diathesis–stress model using the method developed by Widaman et al. (2012). Specifically, adolescents with Val allele displayed increased levels of anxiety when experiencing high stress or low maternal warmth-reasoning, but exhibited decreased levels of anxiety in the context of low stress or high maternal warmth-reasoning. These results suggested that adolescents carrying Val allele who are more susceptible to adversity (high stress or less positive mothering) are also more likely to benefit from supportive (more positive mothering) or benign environments (less stress). In comparison, adolescents carrying Met/Met genotype demonstrated lesser (but not null) sensitivity or susceptibility to environmental adversity and enrichment. These findings suggest that the differential susceptibility conferred by BDNF Val66Met polymorphism is more likely to be a "plasticity gradient" along which individuals vary (Belsky & Pluess, 2009; Ellis et al., 2011).

Our findings are consistent with previous research involving BDNF Val66Met in multiple level processes of anxiety. For example, the BDNF Val66Met had been found to be associated with differential HPA axis reactivity to stress (Alexander et al., 2010; Shalev et al., 2009), differential amygdala-dependent fear conditioning (Hajcak et al., 2009; Lonsdorf et al., 2010), and frontoamgydala-based fear extinction (Soliman et al., 2010), as well as differential response to exposure therapy in PTSD patients (Felmingham et al., 2013). All these studies indicated the association between the BDNF Val allele and heightened susceptibility or plasticity. Together with our results, it is strongly suggested that BDNF Val66Met is a genetic susceptibility that may modulate individual differences in physiological, neural, and behavioral plasticity involved in development and treatment of anxiety.

The biological mechanism underlying the potential role of BDNF on environmental sensitivity remains tentative. One candidate mechanism pertains to the fact that the physiological functions of BDNF in the brain are specifically controlled by the neuronal activity-dependent BDNF expression and secretion (Park & Poo, 2013), which mediated the experience-dependent neuronal and synaptic plasticity (Hong, McCord, & Greenberg, 2008; Kuczewski, Porcher, & Gaiarsa, 2010; Sakata et al., 2013). There has been evidence indicating the essential role of BDNF in mediating fear extinction in hippocampal-infralimbic circuit (Andero & Ressler, 2012; Peters, Dieppa-Perea, Melendez, & Quirk, 2010) and the amygdala-dependent learning of both appetitive and aversive emotional memories (Heldt, Zimmermann, Parker, Gaval, & Ressler, 2014). While the BDNF Val66Met polymorphism has largely been shown to affect activity-dependent secretion of BDNF, recent studies also suggested that environmental

Table 4

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Differential susceptibility (weak)</th>
<th>Diathesis–stress (weak)</th>
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<tbody>
<tr>
<td></td>
<td>SLEs</td>
<td>MWR</td>
</tr>
<tr>
<td>$B_0$</td>
<td>39.48 (1.49)**</td>
<td>39.34 (1.67)**</td>
</tr>
<tr>
<td>$B_1$</td>
<td>0.89 (0.32)**</td>
<td>−0.18 (0.06)**</td>
</tr>
<tr>
<td>$B_2$</td>
<td>1.76 (0.16)**</td>
<td>−0.32 (0.03)**</td>
</tr>
<tr>
<td>$C$</td>
<td>0.77 (0.92)**</td>
<td>−3.31 (5.62)**</td>
</tr>
<tr>
<td>$Fa$</td>
<td>5.96**</td>
<td>4.02**</td>
</tr>
<tr>
<td>$Fb$</td>
<td>7.79**</td>
<td>8.09**</td>
</tr>
</tbody>
</table>

Note: SLEs, stressful life events; MWR, mother's warmth-reasoning.

$Fa$: testing squared $R$ change between weak differential-susceptibility and diathesis–stress models.

$Fb$: testing squared $R$ change between weak and strong differential-susceptibility models.

$^* p < 0.05$.

$^** p < 0.01$.

$^*** p < 0.001$. 

Fig. 1. Plots of predicted anxiety (Y axis) as functions of stressful life events (X axis) (a) and mothers’ warmth-reasoning (b) in two gene groups under the weak differential susceptibility model. Values on X axis are mean-centered.
Stimuli can trigger activity-dependent regulation of BDNF and neural plasticity through epigenetic process (Karpova, 2014). Thus, it is plausible, albeit warranted to elucidate, that the combination of BDNF Val66Met and environmental stimuli (i.e., stress, parenting) affect anxious behavioral plasticity through BDNF mediated neural plasticity.

4.1. Strength and limitations

One strength of the current study is that we measured both negative (i.e., stressful life events) and positive environments (i.e., mothers’ warmth-reasoning), which allows us to better test the ‘for worse and for better’ manner as predicted by the differential susceptibility model (Belsky et al., 2007). Moreover, this measurement strategy extended the knowledge in the issue of susceptibility to specific or general environment (Ellis et al., 2011). Our results indicated that the BDNF Val66Met polymorphism modulated individual susceptibility to at least two anxiety-related environmental factors: stress and parenting, supporting the general susceptibility view. The use of bootstrapping estimation further validated our findings. One limitation of this study is that our data were cross-sectional, which did not allow us to make causal conclusions. Furthermore, both environmental factors and anxiety were measured by self-reports, which may be subject to shared rater bias. Lastly, other than child sex and age, we did not control other potential covariates that may be associated with adolescents’ stress and anxiety as well as their mothers’ parenting.

4.2. Implications

Our findings have several implications. First, our findings highlight the genetic susceptibility × environment interaction model of trait anxiety. Genetic variation (BDNF Val66Met) underlies individual differences in developmental plasticity of anxiety—anxiety increases under adversity and decreases under supportive contexts. This pattern is compatible with the evolutionary perspective, which contends plasticity as a developmental system shaped by natural selection to respond adaptively to both putatively ‘positive’ and ‘negative’ developmental contexts (Ellis & Bjorklund, 2012). Moreover, this view also resonates with the concept of conditional adaptation—the evolved mechanisms that detect and respond to specific features of childhood environments, and entrain developmental pathways that reliably matched those features during a species’ natural selection history (Boyce & Ellis, 2005, p. 290). Thus, the finding of BDNF Val66Met × Environment interaction on anxiety may reflect the genetic modulator underlying individual’s adaptive responses or plasticity to the changing environments.

The second implication pertains to the novel area of research on theranagenetics, which refers to the prediction of psychological or intervention outcomes from genetic markers (Eley, 2014). For the treatments of child and adolescent anxiety, the most widely studied genetic marker to date is the 5-HTTLPR (Hudson et al., 2013). Although more replication studies are needed, Eley et al. (2012) reported initial evidence showing that children with an anxiety disorder carrying the short-short (SS) genotype were significantly more likely to respond to the cognitive behavior therapy (CBT) than those carrying a long allele (SL/LL). Despite being considered as another plausible candidate genetic marker for predicting psychological therapy response, the BDNF Val66Met polymorphism, on the other hand, has not been found to predict differential responses to CBT for anxiety-disordered children (Lester et al., 2012). In contrast, studies have found an association between BDNF Met-66 allele and significantly poorer response to exposure-based CBT for PTSD (Fullana et al., 2012) and obsessive-compulsive disorder (OCD) (Fullana et al., 2012). These studies seem to suggest that detection of significant BDNF Val66Met × intervention on reducing anxiety may depend on the intervention targets. Based on the findings in this study that BDNF Val66Met modulates adolescents’ susceptibility to stressful life events and mothers’ warmth-reasoning, we speculate that the BDNF Val66Met polymorphism may moderate anxious youths’ responses to psychotherapies involving stress management such as the mindfulness-based stress reduction (MBSR) program (Hofmann, Sawyer, Witt, & Oh, 2010), which has been found can reduce subjective and physiological (cortisol concentration) stress level, and anxiety symptoms (Stefanaki et al., 2014). The BDNF Val66Met polymorphism may also modulate family-based treatments involving the enhancement of positive maternal parenting such as warmth and inductive-reasoning (Drake & Ginsburg, 2012). Future studies employing the Gene × Intervention design (Bakermans-Kranenburg & van Ijzendoorn, 2015) are needed to test this conjecture.

5. Conclusion

In conclusion, we found that the BDNF Val66Met polymorphism significantly moderated the influences of stressful life events and mothers’ warmth-reasoning on adolescent trait anxiety. These interaction effects were consistent with the differential susceptibility hypothesis. Youths carrying Val allele demonstrated heightened susceptibility to both negative and positive environments, compared to the Met/Met carriers. 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 anxious youths’ responses to mindfulness-based stress reduction programs and family-based treatments involving the improvement of mothers’ warmth and inductive-reasoning.

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