Journal of Affective Disorders 265 (2020) 104–111

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Interactions between the combined genotypes of *5-HTTLPR* and *BDNF* Val66Met polymorphisms and parenting on adolescent depressive symptoms: A three-year longitudinal study

Meiping Wang [1], Xiangjuan Tian [1], Wenxin Zhang *

Department of Psychology, Shandong Normal University, Jinan 250014, Shandong Province, China

ARTICLE INFO

Keywords:
Depressive symptoms;Parenting;5-HTTLPR;BDNF Val66Met;G × G × E;CG × E

ABSTRACT

Background: The importance of multiple genes-environment interaction (G × E) has been highlighted in studies on depressive symptoms. *5-HTTLPR* and *BDNF* Val66Met polymorphisms, with functional interconnection, have been implicated in the pathophysiology of depressive symptoms. However, little is understood about whether the interaction of *5-HTTLPR, BDNF* Val66Met and parenting fits better with the epistatic or cumulative manner.
Methods: 865 adolescents (T1: M_{age} = 12.32, 50.2% girls) were included in a three-year interval longitudinal design. Standardized questionares about parenting and depressive symptoms were collected. Saliva samples were collected for genotyping.
Results: Neither the concurrent nor longitudinal interaction of *5-HTTLPR, BDNF* Val66Met and parenting (G × G × E) showed significant effects on depressive symptoms. The interaction between cumulative genotypes and positive parenting (CG × E) was significant, with the strong differential susceptibility model, for depressive symptoms concurrently but not longitudinally after statistical correction. Adolescents who carried 3 (i.e. SS and Val/Met, L allele and Val/Val) and 4 (i.e. SS and Val/Val), not 1 (i.e. L allele and Met/Met) or 2 cumulative susceptibility alleles (i.e. SS and Met/Met, L allele and Val/Met), reported fewer depressive symptoms if they had experienced higher levels of positive parenting, and more symptoms under lower levels of positive parenting.
Limitations: This study did not examine the *5-HTTLPR* triallelic (rs25531) marker and did not include an external sample.
Conclusions: The combined effects of *5-HTTLPR* and *BDNF* Val66Met polymorphisms functioned in a manner of cumulative rather than epistatic in response to positive parenting on early adolescent depressive symptoms.

1. Introduction

Depression, the third leading cause of “years lived with disability” (YLD) among children and adolescents (Kyu et al., 2016), has consistently been reported to be associated with increased risks for suicide (Esposito and Clum, 2002). Studies have showed that there are dramatically increases both in the lifetime prevalence and levels of depression from early to middle adolescence (Hankin et al., 2015; Thapar et al., 2012). Clearly, it is important to identify the potential mechanisms of depressive symptoms during this period.

A fast-growing research has bolstered the importance of gene-environment interaction (G × E) involved in the etiology of adolescent depressive symptoms (e.g. Comasco et al., 2015; Stocker et al., 2017). It would be better to investigate multiple genetic variants in terms of G × E effects rather than for one single candidate polymorphism (Burmeister et al., 2008). However, G × E work has thus far primarily focused on only one genetic polymorphism because of theoretically sensible reasons (Caspi and Moffitt, 2006), and the most widely studied candidate polymorphism for depressive symptoms has been obtained for the serotonin-transporter-linked polymorphic region (*5-HTTLPR*) polymorphism in the promoter of the *SLC6A4* gene that encodes 5-HTT (see Bleys et al., 2018; Harkness et al., 2015). The *5-HTTLPR* is a 43-base pair insertion/deletion polymorphism that creates two allelic forms, the long (L) allele and the short (S) allele, with the S allele being associated with decreased 5-HTT expression and serotonine reuptake (Lesch et al., 1996). Nevertheless, existing G × E results regarding association between *5-HTTLPR* polymorphism and depressive symptoms have been inconsistent and difficult to replicate (see Culverhouse et al., 2018; Wray et al., 2018). A reasonable corollary of these divergencies is that *5-HTTLPR* polymorphism may operate in

* Corresponding author.
E-mail address: zhangwenxin@sdnu.edu.cn (W. Zhang).
[1] These two authors contributed equally to the study. They should be regarded as joint first authors.

https://doi.org/10.1016/j.jad.2020.01.064
Received 21 November 2019; Received in revised form 9 January 2020; Accepted 14 January 2020
Available online 15 January 2020

conjunction with other genotypes to make some individuals especially sensitive (or not) to contextual conditions toward the likelihood of depressive symptoms (Wegener Sleeswijk et al., 2019). Thus, the approach of G × E using single candidate genes is giving way to a growing consensus that depression has a significant polygenic component, in which genetic influences operate as a function of combined effects of a number of variants (Stocker et al., 2017).

Indeed, extant research has suggested that the serotonin (5-HT) and brain-derived neurotrophic factor (BDNF) systems act synergistically on synaptic plasticity and neurogenesis of a number of brain areas key to depression (Martinowich and Lu, 2008). The most commonly studied functional genetic polymorphism associated with BDNF in depression is Val66Met situating in nucleotide 196, in which there is an amino acid substitution (valine to methionine) at codon 66 (dbSNP number rs6265), with Met variant being associated with lower BDNF activity compared to the Val variation (Egan et al., 2003). Substantial evidence suggests that both *5-HTTLPR* and *BDNF* Val66Met polymorphisms are linked to the brain reward system (e.g. amygdala, Loewenstern et al., 2019) and brain stress system (e.g. hypothalamic-pituitary-adrenal (HPA) axis, Dougherty et al., 2010), which exert powerful control over the inability to experience pleasure, i.e. anhedonia and "behavioral despair", respectively—two strong markers of depression (Martinowich and Lu, 2008). As such, it is theoretically possible that the joint effects of *5-HTTLPR* and *BDNF* Val66Met polymorphisms may affect individuals' sensibility to certain environments toward adolescent depressive symptoms.

Some researchers are beginning to use two analytic approaches so far for illuminating multiple genetic effects on psychological phenotypes: epistatic and cumulative methods (Pearson et al., 2016; Steiger et al., 2016). The former is defined that the effect of one gene (locus) is dependent on the presence of one or more genes, namely genes interact with each other (Tyler et al., 2009). As far as we know, most previous studies on *5-HTTLPR* × *BDNF* Val66Met × environment (G × G × E) have been cross-sectional. And among those, significant work has been limited to individuals with a wide range of age (spanning childhood to adolescence or adolescence to adulthood) or only adults, and restricted to severe, horrendous contextual stress composed of physical or emotional abuse (e.g. Gutierrez et al., 2015). Instead, no significant G × G × E effect has been identified in research with much narrower and younger samples, and normative variability in adversity such as stressful life events, risky family environment (e.g. Aguilera et al., 2009). The other means of explicating the joint effects of multiple loci is through cumulative method, wherein each genotype was assigned a point (0, 1 or 2) according to its number of sensibility alleles and then these values were summed together to generate a cumulative index (Belsky and Beaver, 2011) based on the notion that individual genes have very small effects (Levinson et al., 2014). To our knowledge, only one study using longitudinal data has explored the interaction of cumulative genotypes of *5-HTTLPR* and *BDNF* Val66Met and environment (CG × E), and found that those who carried more cumulative alleles were more sensible to family environment quality exhibiting more or less depressive symptoms at age 15, 20 and 22–25 (Dalton et al., 2014). Although research on the CG × E is sparse, the result was inclined to be significant in samples of older adolescents and in the context of less severe experience. Based on the literature reviewed above, it is plausible to assume that the way in which multiple genes contribute to the manifestations of depression is associated to the developmental stage and the measurement of environments. In conjunction with this, virtually no research has explored these two approaches in one inquiry. The present study is uniquely positioned to extend our knowledge in this area.

We focused on both positive and negative parenting as candidate environmental markers, due to their central importance in G × E studies on depressive symptoms (Van Assche et al., 2017). Influential models hold that parenting quality influences adolescents' depressive symptoms, such that hostile and negative parenting contribute specifically to the development of depression by undermining self-esteem, promoting a sense of helplessness, and prompting development of negative self-schemas, whereas warm, supportive, and otherwise positive parenting appear to thwart it (see Downey and Coyne, 1990; McLeod et al., 2007; Pearson et al., 1994). Importantly, prior research has pinpointed that individuals who carry a certain polygenic burden of multiple alleles are more sensitive to parenting, and then experience depression (Belsky and van IJzendoorn, 2017), but scant research has explored how this process unfolds.

In sum, using a three-year interval longitudinal data from a community sample, the present study seeks to contribute to the emerging literature by examining the G × G × E and CG × E of *5-HTTLPR, BDNF* Val66Met and parenting in depressive symptoms. In light of the limited literature, it remains an open question whether the joint effects of these two polymorphisms may moderate the role of parenting in an epistatic or cumulative manner.

1. Materials and methods

1.1. Participants

All participants in this study were originally recruited from 13 primary schools located in Jinan, P. R. China. At baseline (T1, Grade 6), 933 adolescents (M_{age} = 12.32 ± 0.47 years, 50.2% girls) and their mothers were enrolled. After three years (T2, Grade 9), 865 participants (M_{age} = 15.32 ± 0.46 years, 51.4% girls) were successfully re-evaluated. The final sample (N = 865) consisted of 97.0% Chinese Han ethnicity. No significant differences were found between T1 and T2 in terms of demographic variables (parental education and work, race and gender composition), parenting and depressive symptoms. This study was approved by the local ethics committee. Assent and consent were obtained from adolescents and their parents prior to this data collection.

1.2. Measures

Parenting was measured by Chinese version of Child Rearing Practices of Report (CRPR; Block, 1981), which has well-established psychometric evidence of reliability and validity in Chinese childhood and adolescence samples (Chen et al., 2005). Ratings for each item ranged from 0 (*not all at true*) to 4 (*almost always true*). Based on previous studies (e.g. Zhang et al., 2016b), maternal warmth (4 items) and induction (4 items) were integrated into positive parenting, and maternal rejection (4 items) and punishment orientation (6 items) were combined into negative parenting. Higher scores indicate higher levels of parenting dimension. Cronbach's α for positive and negative parenting were 0.80 and 0.64, respectively.

Adolescent depressive symptoms were evaluated by a 27-item self-report version of the Children's Depression Inventory (CDI; Kovacs, 1992) at T1 and T2. The Chinese version of CDI has manifested good validity and reliability (e.g. Wu et al., 2012). Each of the CDI items was rated on a 3-point scale from 0 (*occasionally*) to 2 (*all the time*), reflecting participants' feelings during the past two weeks. In this study, Cronbach's α were both 0.88 at T1 and T2.

Information on family socioeconomic status (SES) was indicated by five items—mothers' and fathers' education level and occupational prestige, as well as monthly household income, which were all reported by mother at T1. Following previous literature (Akkoyun-Farinez et al., 2018), the items were recoded, standardized and synthesized by factor analysis to compute a composite SES score.

1.3. Genotyping

At T2, the *5-HTTLPR* and *BDNF* Val66Met polymorphisms were genotyped by the analyses of primer extension products generated from amplified genomic DNA using a Sequenom (San Diego, CA, USA) chip-based MALDI-TOF mass spectrometry platform. The *5-HTTLPR* was

Table 1
Descriptive statistics and correlations among study variables

Variables	1	2	3	4	5	6	7	8
1. SES	—							
2. *5-HTTLPR*	0.01	—						
3. *BDNF*	−0.02	−0.05	—					
4. Cumulative genotypes	−0.01	0.51***	0.84***	—				
5. Positive parenting (T1)	0.17***	0.04	0.04	0.05	—			
6. Negative parenting (T1)	−0.15***	−0.05	−0.04	−0.06	−0.48***	—		
7. Depressive symptoms (T1)	−0.05	0.05	0.03	0.05	−0.12***	0.14***	—	
8. Depressive symptoms (T2)	−0.04	−0.01	−0.01	−0.01	−0.10**	0.13***	0.45***	—
M	0.01	—	—	—	3.24	0.98	0.18	0.27
SD	1.00	—	—	—	0.48	0.43	0.21	0.25

Note. ** $p < 0.01$, *** $p < 0.001$.

amplified by polymerase chain reaction (PCR) with forward primer (5′-TCCTCCGCTTTGGCGCCTCTTCC-3′) and reverse primer (5′-TGGGG GTTGCAGGGGAGATCCTG-3′). The *BDNF* Val66Met was amplified by PCR using the forward primer (5′-TCAAGAGGCTTGACATCATTGG-3′) and reverse primer (5′-GCCGAACTTTCTGGTCCTCAT-3′).

1.4. Statistical analysis

The Hardy–Weinberg equilibrium for genotype distributions of each SNP was tested using the χ^2 test for goodness of fit. Bivariate Pearson correlations were conducted to test the associations between variables included in this study. To examined the epistatic effects, concurrent and longitudinal three-way interactions among *5-HTTLPR, BDNF* Val66Met and parenting on depressive symptoms at T1 and T2 (controlling for depressive symptoms at T1) with SES as a covariate were conducted. To test the cumulative effects, concurrent and longitudinal two-way interaction between cumulative genotypes of *5-HTTLPR, BDNF* Val66Met and parenting were performed using depressive symptoms at T1 and T2 (controlling for depressive symptoms at T1) as dependent variables including SES as a covariate. To increase interpretability of the regression estimates and avoid multicollinearity, positive and negative parenting were standardized and tested in separate models. Simple slope analysis was performed to examine the pattern of interaction. And to assess the robustness of results, an internal replication analysis was conducted by randomly splitting the sample into two subsamples. All G × G × E and CG × E effects were assessed using bootstrapping with 1000 sample replicates. Above analyses were conducted in SPSS 25.0. Then, to further support for the robustness of the results, the Comprehensive Meta-Analysis program (CMA; Borenstein et al., 2005) was used to compute the overall effect sizes and *p*-values of the interaction by combining the interactive effects of two randomly split subsamples.

Grounded on previous literature, significant CG × E was further investigated using re-parameterized regression analysis which allows model fit under strong/week differential-susceptibility and strong/week diathesis-stress conditions to be statistically contrasted, with the better fitting model offered as the optimal representation of the data (Widaman et al., 2012). The form was as follows: $Y = (\text{cumulative vulnerability/susceptibility alleles} = 1)(B_0 + B_1(X_1 - C)) + (\text{cumulative vulnerability/susceptibility alleles} = 2)(B_0 + B_2(X_1 - C)) + (\text{cumulative vulnerability/susceptibility alleles} = 3)(B_0 + B_3(X_1 - C)) + (\text{cumulative vulnerability/susceptibility alleles} = 4)(B_0 + B_4(X_1 - C)) + B_5X_2 + E$. Y is the dependent variable of depressive symptoms, X_1 is parenting, X_2 is SES, C is the crossover point where the slopes for groups of allele cross, B_0 is the intercept, B_1, B_2, B_3 and B_4 are the regression weights of parenting for adolescents with 1, 2, 3 and 4 vulnerable/susceptible alleles and B_5 is the regression weight for SES. The re-parameterized regression analysis was performed using R statistical analysis package.

To control Type I error, *p*-values were all adjusted using Benjamini and Hochberg (B-H) procedure (Benjamini and Hochberg, 1995). Additionally, we also performed all analyses when considered gender as an additional controlled variable and obtained virtually identical results. Thus, gender was not included in the final model for parsimony.

2. Results

2.1. Descriptive statistics

The genotype frequencies of the *5-HTTLPR* and *BDNF* Val66Met were SS: 71.4%, SL: 27.4%, LL: 1.2% and Val/Val: 27.1%, Val/Met: 49.3%, Met/Met: 23.6%. The allele distributions for both genotypes in our study are comparable with other studies in Asian sample (He et al., 2010; He et al., 2018). No deviations from the Hardy–Weinberg equilibrium were detected for both two genotypes ($\chi^2 = 5.97$, $p = 0.05$ and $\chi^2 = 0.11$, $p = 0.94$, respectively). Consistent with other research of *5-HTTLPR* (e.g. Belsky et al., 2015) and functional differences across genotypes (Lesch et al., 1996), the LL and SL genotypes were collapsed into an L- allele group and coded as 1, SS genotype was coded as 2. *BDNF* Val66Met was coded as 0 = Met/Met, 1 = Val/Met, 2 = Val/Val based on confirmed empirical evidence, especially those drawing from Chinese sample (e.g. He et al., 2018). Based on previously established method (e.g. Beaver and Belsky, 2012; Wade et al., 2015), the values for each of the genetic polymorphism were added to construct an index of "cumulative alleles", whereby 1 vulnerable/susceptible allele = 50 (5.8%), 2 vulnerable/susceptible alleles = 278 (32.1%), 3 vulnerable/susceptible alleles = 376 (43.5%), 4 vulnerable/susceptible alleles = 161 (18.6%), with higher scores reflecting more genetic vulnerability or susceptibility for depressive symptoms.

Descriptive statistics and intercorrelations of all study variables are summarized in Table 1. There were no significant associations between genetic indexes and parenting, indicating the absence of correlation between genes and environment. Significant positive associations were found between depressive symptoms at two time points, which provided a relative stability of depressive symptoms over time. Additionally, depressive symptoms at T1 and T2 showed significant bivariate correlations with both positive and negative parenting.

2.2. The three-way interaction effects of 5-HTTLPR, BDNF Val66Met and parenting on depressive symptoms

As shown in Table 2, positive parenting and negative parenting negatively and positively predicted depressive symptoms concurrently but not longitudinally. No main effects of *5-HTTLPR* or *BDNF* Val66Met polymorphism on depressive symptoms were found. Neither the significant effects for G × E nor G × G × E among *5-HTTLPR, BDNF* Val66Met and parenting were found concurrently and longitudinally.

2.3. The two-way interaction effects of cumulative genotypes (5-HTTLPR and BDNF Val66Met) and parenting on depressive symptoms

As reported in Table 3, no main effect of cumulative genotypes were observed. Significant CG × E effect regarding positive but not negative

Table 2
Three-way interaction among 5-HTTLPR and BDNF polymorphisms and parenting on depressive symptoms

	Depressive Symptoms (T1)						Depressive Symptoms (T2)					
	△R^2	*b*	*SE*	*t*	*p*	95% CI[a]	△R^2	*b*	*SE*	*t*	*p*	95% CI[a]
Depressive symptoms (T1)							19.8%***	**0.53**	**0.04**	**14.60**	**0.00**	**0.42 to 0.64**
SES	0.3%	−0.01	0.01	−1.48	0.14	−0.03 to 0.01	0.0%	−0.01	0.01	−0.68	0.50	−0.02 to 0.01
Positive parenting (T1)		**−0.03**	**0.01**	**−3.56**	**0.00**	**−0.04 to −0.01**		−0.01	0.01	−1.38	0.17	−0.03 to 0.00
5-HTTLPR		0.03	0.02	1.57	0.12	−0.01 to 0.06		−0.01	0.02	−0.84	0.40	−0.05 to 0.02
BDNF	1.8%**	0.01	0.01	1.11	0.27	−0.01 to 0.03	0.3%	−0.01	0.01	−0.79	0.43	−0.03 to 0.01
5-HTTLPR × positive parenting (T1)		−0.04	0.02	−2.39	0.02	−0.07 to −0.01		0.03	0.02	1.96	0.05	−0.00 to 0.07
BDNF × positive parenting (T1)		−0.02	0.01	−1.61	0.11	−0.04 to 0.01		−0.01	0.01	−0.87	0.38	−0.03 to 0.01
5-HTTLPR × *BDNF*	0.9%	0.01	0.02	0.35	0.73	−0.03 to 0.05	0.5%	−0.02	0.02	−0.93	0.35	−0.07 to 0.03
5-HTTLPR × *BDNF* × positive parenting (T1)	0.3%	−0.03	0.02	−1.55	0.12	−0.07 to 0.01	0.0%	−0.00	0.02	−0.04	0.97	−0.04 to 0.04
Depressive symptoms (T1)							19.8%***	**0.53**	**0.04**	**14.60**	**0.00**	**0.42 to 0.64**
SES	0.3%	−0.01	0.01	−1.48	0.14	−0.03 to 0.00	0.0%	−0.01	0.01	−0.68	0.50	−0.02 to 0.01
Negative parenting (T1)		**0.03**	**0.01**	**4.19**	**0.00**	**0.02 to 0.05**		0.02	0.01	2.02	0.04	0.00 to 0.03
5-HTTLPR		0.03	0.02	1.65	0.10	−0.01 to 0.06		−0.01	0.02	−0.78	0.43	−0.05 to 0.02
BDNF	2.3%***	0.01	0.01	1.16	0.25	−0.01 to 0.03	0.5%	−0.01	0.01	−0.75	0.45	−0.03 to 0.01
5-HTTLPR × negative parenting (T1)		0.02	0.02	0.92	0.36	−0.01 to 0.04		−0.01	0.02	−0.29	0.78	−0.04 to 0.03
BDNF × negative parenting (T1)		−0.00	0.01	−0.40	0.69	−0.02 to 0.01		0.01	0.01	1.12	0.26	−0.01 to 0.03
5-HTTLPR × *BDNF*	0.1%	0.00	0.02	0.12	0.91	−0.04 to 0.05	0.2%	−0.02	0.02	−0.81	0.42	−0.07 to 0.03
5-HTTLPR × *BDNF* × negative parenting (T1)	0.1%	−0.02	0.02	−1.07	0.29	−0.06 to 0.01	0.0%	−0.00	0.03	−0.00	0.99	−0.05 to 0.05

Note. ** $p < 0.01$, *** $p < 0.001$.
Significant results after B-H correction are highlighted by bold face.
[a] 95 % CIs based on bootstrapping.

parenting, on early adolescent depressive symptoms was found even after B-H correction. Furthermore, a simple slope analysis was conducted to identify the interaction effect. As shown in Fig. 1, positive parenting negatively predicted depressive symptoms only among those with 3 (b = -0.03, t = -2.74, p = 0.006, 95% CI = -0.05 to −0.01) and 4 cumulative vulnerability/susceptibility alleles (b = -0.05, t = -3.19, p = 0.002, 95% CI = -0.09 to −0.01) compared to those with 1 (b = 0.01, t = 0.52, p = 0.61, 95% CI = -0.04 to –0.07) and 2 cumulative vulnerability/susceptibility alleles (b = -0.01, t = -0.67, p = 0.51, 95% CI = -0.04 to –0.02). However, the CG × E was not significant longitudinally.

2.4. Internal replication and meta-analysis

To increase precision and also provide evidence of generality and robustness of the interactional results, an internal replication analysis was performed. The CG × E effect identified in the total sample was borderline significant in Subsample 1 (b = −0.02, t = -1.76, p = 0.08, 95% CI = -0.05 to –0.01) and Subsample 2 (b = -0.02, t = -1.95, p = 0.05, 95% CI = −0.05 to −0.00). Similar results were also found in previous published work (Cao et al., 2018).

Moreover, meta-analysis revealed that the combined effect sizes for the association between positive parenting and depressive symptoms amounted to r = -0.16 (p = 0.002) and r = -0.30 (p < 0.001) for

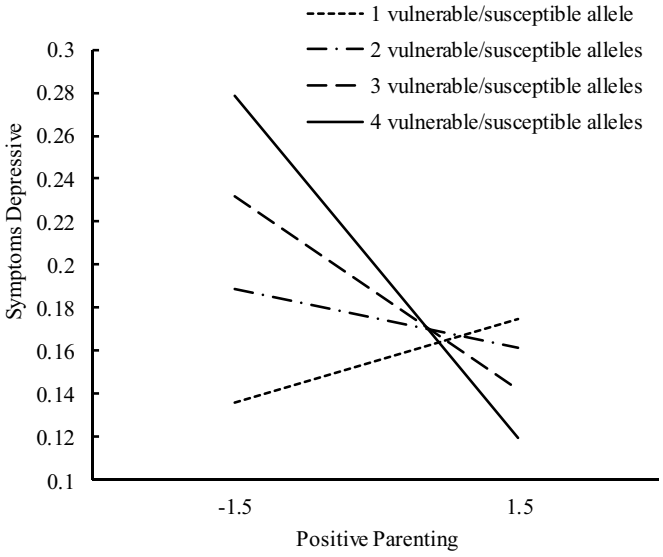

Fig. 1. Interaction between cumulative genotypes and positive parenting in the prediction of early adolescents' depressive symptoms.

Table 3
Two-way interaction between cumulative genotypes and parenting on depressive symptoms

	Depressive Symptoms (T1)						Depressive Symptoms (T2)					
	△R^2	*b*	*SE*	*t*	*p*	95% CI[a]	△R^2	*b*	*SE*	*t*	*p*	95% CI[a]
Depressive symptoms (T1)							19.8%***	**0.53**	**0.04**	**14.60**	**0.00**	**0.43 to 0.64**
SES	0.3%	−0.01	0.01	−1.48	0.14	−0.03 to 0.01	0.0%	−0.01	0.01	−0.68	0.50	−0.02 to 0.01
Positive parenting (T1)		**−0.03**	**0.01**	**−3.55**	**0.00**	**−0.04 to −0.01**		−0.01	0.01	−1.39	0.17	−0.03 to 0.01
Cumulative genotypes	1.7%**	0.02	0.01	1.72	0.09	−0.00 to 0.03	0.3%	−0.01	0.01	−1.08	0.28	−0.03 to 0.01
Cumulative genotypes × positive parenting (T1)	0.7%*	**−0.02**	**0.01**	**−2.48**	**0.01**	**−0.04 to −0.00**	0.0%	0.01	0.01	0.14	0.89	−0.02 to 0.02
Depressive symptoms (T1)							19.8%***	**0.53**	**0.04**	**14.60**	**0.00**	**0.42 to 0.63**
SES	0.3%	−0.01	0.01	−1.48	0.14	−0.03 to 0.01	0.0%	−0.01	0.01	−0.68	0.50	−0.02 to 0.01
Negative parenting (T1)		**0.03**	**0.01**	**4.18**	**0.00**	**0.02 to 0.05**		0.02	0.01	2.02	0.04	−0.00 to 0.03
Cumulative genotypes	2.2%***	0.02	0.01	1.80	0.07	−0.00 to 0.03	0.5%	−0.01	0.01	−1.02	0.31	−0.03 to 0.01
Cumulative genotypes × negative parenting (T1)	0.0%	0.00	0.01	0.11	0.91	−0.02 to 0.02	0.1%	0.01	0.01	0.89	0.38	−0.01 to 0.03

Note. * $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.
Significant results after B-H correction are highlighted by bold face.
[a] 95% CIs based on bootstrapping.

adolescents who carried 3 and 4 cumulative vulnerability/susceptibility alleles, respectively, in a homogeneous set (Q (df = 1) ≤ 0.52, ps > 0.05, I^2s = 0.0%). The combined effect sizes for individuals who carried 1 and 2 cumulative vulnerability/susceptibility alleles were r = 0.06 (p = 0.69) and r = -0.05 (p = 0.46) in a homogeneous set (Q (df = 1) ≤ 3.16, ps > 0.05, I^2s ≤ 68.36%). Importantly, the difference between the more (3 and 4) and fewer (1 and 2) cumulative vulnerability/susceptibility allele groups was significant ($Q_{contrast}$ = 8.60, p = 0.04), supporting that the CG × E with respect to positive parenting was significant and adolescents who carried 3 and 4 but not 1 or 2 cumulative vulnerability/susceptibility alleles were sensitive to positive parenting.

2.5. Reparameterized regression models of cumulative genotypes (5-HTTLPR and BDNF Val66Met) and parenting on depressive symptoms

Finally, to test the specific pattern of CG × E, we re-parameterized the regression models adapted from Widaman et al. (2012). Based on the regression results, we defined adolescents who carried 1 and 2 cumulative alleles as non-vulnerable/susceptible ones, and those who carried 3 and 4 cumulative alleles as vulnerable/susceptible ones. As detailed in Table 4, the strong differential susceptibility model, in which the B_1 and B_2 coefficient were fixed at zero, had fairly strong fit to the data. Specifically, the coefficients for the CG × E were of appreciable significance. The crossover point estimate was approximately near the mean value of positive parenting, and 95% CI also fell well within the range of this variable (−3.08 to 1.58). Additionally, model comparisons showed that the strong differential susceptibility model was the most optimal representation. Moreover, the AIC and BIC values of strong differential susceptibility model were relatively smaller than other three models, thus the best option.

3. Discussion

To advance the understanding of the etiology of adolescent depressive symptoms, the present study investigated the interaction between the combined genotypes (*5-HTTLPR* and *BDNF* Val66Met) and parenting in a longitudinal sample spanning early to middle adolescence—two high-risk phases of this common, debilitating, and potentially lethal disorder. As hypothesized, instead of three-way interaction (*5-HTTLPR* × *BDNF* Val66Met × parenting, epistatic effect), our results support a robust evidence for a two-way interaction between cumulative genotypes and positive parenting (cumulative effect) for depressive symptoms. And the significant CG × E manifested only concurrently but not longitudinally.

Table 4
Results for re-parameterized regression model for depressive symptoms

Parameter	Differential susceptibility		Diathesis-stress	
	Strong (1s)	Week (1w)	Strong (2s)	Week (2w)
B_1	0.00 (—)[a]	0.01 (0.02)	0.00 (—)[a]	−0.00 (0.02)
B_2	0.00 (—)[a]	−0.01 (0.01)	0.00 (—)[a]	−0.02 (0.01)
B_3	**−0.03 (0.01)** **	**−0.03 (0.01)** **	**−0.02 (0.01)** **	**−0.03 (0.01)** ***
B_4	**−0.05 (0.02)** ***	**−0.05 (0.02)** ***	**−0.03 (0.01)** ***	**−0.04 (0.01)** ***
B_5	−0.01 (0.01)	−0.01 (0.01)	−0.01 (0.01)	−0.01 (0.01)
C	0.51 (0.38)	0.61 (0.49)	1.58 (—)[a]	1.58 (—)[a]
95% CI of C	−0.24 to 1.26	−0.37 to 1.58	—[a]	—[a]
R^2	2.5%	2.7%	2.1%	2.5%
$F(df)$	5.62*** (4, 860)	3.89*** (6, 858)	6.06*** (3, 861)	4.37*** (5, 859)
F *vs* .1s *(df)*	—	0.46(2,858)	4.22*(1,860)	—
F *vs* .1w *(df)*		—	—	1.50 (1, 858)
F *vs* .2s *(df)*			—	1.82(2, 859)
AIC	−235.71	−232.64	−233.48	−233.13
BIC	−207.14	−194.53	−209.66	−199.79

Note. * p < 0.05, ** p < 0.01, *** p < 0.001.
R^2, fit of the model.
F vs, tests of the difference in R^2 for two models.
Model 1s, strong differential susceptibility model; model 1w, week differential susceptibility model; model 2s, strong diathesis-stress model; model 2w, week diathesis-stress model.
Significant results after B-H correction are highlighted by bold face.
[a] Parameter fixed at reported value; SE is not applicable, so is listed as —.

3.1. The combined effects of 5-HTTLPR, BDNF Val66Met and parenting on depressive symptoms

In line with prior research and our hypothesis, the current study implies the possibility that the moderating role of the combined genotypes of *5-HTTLPR* and *BDNF* Val66Met operate in a manner of cumulative rather than epistatic in the context of positive parenting in predicting early adolescent depressive symptoms. The present study also underscores the necessity and desirability of simultaneously considering different forms of multiple genetic variants (cumulative vs. epistatic) that work in the etiology of depressive symptoms. Consistent with the strong differential-susceptibility model, early adolescents with more cumulative susceptibility alleles not only exhibited more depressive symptoms when exposed to lower levels of positive parenting but also fewer symptoms when experienced higher levels of positive parenting; whereas for adolescents with non-cumulative susceptibility alleles, their depressive symptoms did not vary as a function of positive parenting.

The underlying mechanisms by which adolescents' cumulative genetic sensitivity moderates the association between positive parenting and adolescents' depressive symptoms have not been explicitly and definitively identified in the existing literature. However, by examining the neuropsychological functioning of the *5-HTTLPR* and *BDNF* Val66Met polymorphisms, we can propose some plausible hypotheses. *5-HTTLPR* S (Dannlowski et al., 2010; Battaglia et al., 2012) and *BDNF* Val/Val carriers (Hajcak et al., 2009) exhibited hyper-amygdala activation to emotional stimuli, which has been demonstrated to increase the risk for depression (Gaffrey et al., 2018). Evidence also indicated that both *5-HTTLPR* SS (Ancelin et al., 2017; Miller et al., 2013) and *BDNF* Val/Val carriers (Alexander et al., 2010; Shalev et al., 2009) showed hyperreactivity of HPA axis in response to stress, which parallels findings in depressed individuals (Keller et al., 2017). These evidences collectively provide the underpinnings of the cumulative role of *5-HTTLPR* and *BDNF* Val66Met polymorphisms in the explanation of the biological mechanisms of depressive symptoms. Here, we argue in favor of the more biologically plausible perspective—additive effect, on the combination of *5-HTTLPR* and *BDNF* Val66Met in terms of sensitivity to positive parenting, but note that it is important to undertake different methods with greater transparency of researchers in reporting their findings (Cohen-Woods and Harkess, 2016).

From another perspective, these results suggest that the prior mixed findings observed in research testing G × E models of *5-HTTLPR* or *BDNF* Val66Met polymorphism for depression may be partially attributable to unknown and unmeasured genetic or non-genetic variation. Our findings also underscore the need for work on polygenic process to explain how genetic influences in question function to apparently make some adolescents more susceptible to parenting than others. Nonetheless, examining genetic effects with multiple genes is not meant to entirely replace the more conventional means of investigating genetic moderation of a single candidate polymorphism, basically because of its specific role in the identification of genetic risk.

Results of the present study suggest that the cumulative genotypes confer increased susceptibility to positive but not negative parenting. Although some literature showed that the genetic ancestry and deleterious environment interacted with each other to influence depressive symptoms (e.g. Van Assche et al., 2016), two studies with community

samples revealed that the *BDNF* Val66Met polymorphism (Zhang et al., 2016a) and *GABAergic* genes (*GABRR1*and *GABRR2* polymorphisms) (Van Assche et al., 2017) significantly moderated the influence of positive but not negative parenting on depressive symptoms during adolescence. A floor effect may account for our results, that is, the restricted variability of negative parenting at the low end of the scale (see Table 1) may fail to determine whether the cumulative genotypes would moderate it. Extreme levels of negative parenting might in turn be linked with cognitive vulnerability and risk for depression (Oppenheimer et al., 2018) and the strongest interactive effects are expected in more severe environmental hazards (Aguilera et al., 2009; Zhang et al., 2016a). To confirm this hypothesis, we investigated the CG × E interaction among adolescents whose negative parenting score were at 1 *SD* above the mean as Aguilera et al. (2009) did and found significant results (Supplementary would be provided on question if necessary.). The present findings suggest that the detection of G × E relies highly on the quality and distribution of environmental exposure. And future G × E work should indisputably focus on a broader spectrum of environments, thereby enabling a comparative evaluation of the interaction.

Our results also revealed that the interaction between cumulative genotypes and positive parenting could predict depressive symptoms concurrently (during the time of early adolescence), but the cumulative genetic susceptibility did not tend to amplify or attenuate the predictive significance of positive or negative parenting longitudinally (during middle adolescence). There are several plausible explanations regarding the longitudinal non-significance of the interaction between cumulative genetic susceptibility and parenting during the time of middle adolescence. Recent evidence demonstrated that specific genetic markers, such as *5-HTTLPR* (Hankin et al., 2011) and *BDNF* Val66Met (Hosang et al., 2014; Lehto et al., 2016) interacted with recent experiences, but not prior life events, to impact depression-related outcomes. Therefore, it is possible that proximal rather than distal parenting would make it easier to detect gene-environment interaction for depressive symptoms. Still, academic achievement—a key developmental task with which almost all adolescents struggle (Steinberg, 2014), particularly for middle adolescents who face tough challenges of the transitional examination to enter senior school (called “Zhongkao” in China), is significantly associated with depression (Jayanthi et al., 2015). Thus, the G × E involving academic factors may make a substantial contribution to the development of depressive symptoms during middle adolescence. Furthermore, there is evidence that DNA methylation, typically acting to repress gene transcription, increases rapidly throughout childhood and adolescence (Lister et al., 2013) and modulates the correlation between parenting and psychosocial and behavioral adaptation (Naumova et al., 2016). It is justified to speculate that DNA methylation within *5-HTTLPR* and *BDNF* Val66Met polymorphisms (e.g. carriers of the SS genotype and Val allele) may contribute to some sort of susceptibility during middle adolescence. In sum, the factors that are responsible for depressive symptoms from early to middle adolescence may largely be dynamic and time-specific.

3.2. Limitations

Despite of several strengths including longitudinal design, multiple genes, internal replication and meta-analysis, it is important to consider the limitations of this study. First, the *5-HTTLPR* triallelic (rs25531) marker, a single nucleotide polymorphism that modifies a subset of L allele, such that L_G, but not L_A allele function similarly to S allele (Hu et al., 2005), is supposed to improve the functional variants at the serotonin transporter promoter region was not tested here. Nevertheless, several studies have demonstrated that the *5-HTTLPR* biallelic polymorphism might be good enough to capture the main functional properties associated with each *5-HTTLPR* genotypic combination (Gutierrez et al., 2015). Second, this paper did not include an external sample to further obtain conclusive results. There has been growing skepticism about the replicability of many of the G × E results (Assary et al., 2018; Dick et al., 2015) and direct independent replication prior to publication is of particular importance (Dick et al., 2015). Although the internal replication and meta-analysis were conducted and succeed in a large part, future studies should include a replication sample to provide sufficient statistical power.

4. Conclusion

In summary, framed in terms of interactions among parenting and biologically plausible genetic factors, the study sheds light on a cumulative rather than epistatic manner of the combined effects of *5-HTTLPR* and *BDNF* Val66Met polymorphisms in response to parenting and supports the hypothesis of differential-susceptibility model, in which adolescents with more cumulative susceptibility alleles were more susceptible to positive parenting than their counterparts. This study highlights the importance of examining the joint effects of multiple genes that have consistently been functionally linked to each other and the use of longitudinal design to illuminate the underlying mechanism of adolescent depressive symptoms.

Ethical approval

This study was approved by the local ethics committee.

Funding sources

This study was supported by the National Natural Science Foundation of China (31671156 and 31500899).

CRediT authorship contribution statement

Meiping Wang: Data curation, Methodology, Writing - original draft, Writing - review & editing. **Xiangjuan Tian:** Data curation, Methodology, Writing - original draft, Writing - review & editing. **Wenxin Zhang:** Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None.

Acknowledgments

The authors would like to express their gratitude to all the adolescents and parents who participated in our current study and also to those research staff that contributed to the study.

References

Aguilera, M., Arias, B., Wichers, M., Barrantes-Vidal, N., Moya, J., Villa, H., van Os, J., Ibáñez, M.I., Ruipérez, M.A., Ortet, G., Fañanás, L., 2009. Early adversity and 5-HTT/BDNF genes: new evidence of gene-environment interactions on depressive symptoms in a general population. Psychol. Med. 39, 1425–1432.

Akkoyun-Farinez, J., Omorou, A.Y., Langlois, J., Spitz, E., Böhme, P., Quinet, M.H., Saez, L., Muller, L., Lecomte, E., Legrand, K., Briançon, S., 2018. Measuring adolescents' weight socioeconomic gradient using parental socioeconomic position. Eur. J. Public Health 28, 1097–1102.

Alexander, N., Osinsky, R., Schmitz, A., Mueller, E., Kuepper, Y., Hennig, J., 2010. The BDNF Val66Met polymorphism affects HPA-axis reactivity to acute stress. Psychoneuroendocrinology 35, 949–953.

Ancelin, M.L., Scali, J., Norton, J., Ritchie, K., Dupuy, A.M., Chaudieu, I., Ryan, J., 2017. Heterogeneity in HPA axis dysregulation and serotonergic vulnerability to depression. Psychoneuroendocrinology 77, 90–94.

Assary, E., Vincent, J.P., Keers, R., Pluess, M., 2018. Gene-environment interaction and psychiatric disorders: review and future directions. Semin. Cell Dev. Biol. 77, 133–143.

Battaglia, M., Zanoni, A., Taddei, M., Giorda, R., Bertoletti, E., Lampis, V., Scaini, S., Cappa, S., Tettamanti, M., 2012. Cerebral responses to emotional expressions and the

development of social anxiety disorder: a preliminary longitudinal study. Depress. Anxiety 29, 54–61.
Beaver, K.M., Belsky, J., 2012. Gene-environment interaction and the intergenerational transmission of parenting: testing the differential-susceptibility hypothesis. Psychiatr. Q. 83, 29–40.
Belsky, J., Beaver, K.M., 2011. Cumulative-genetic plasticity, parenting and adolescent self-regulation. J. Child Psychol. Psychiatry 52, 619–626.
Belsky, J., Newman, D.A., Widaman, K.F., Rodkin, P., Pluess, M., Fraley, R.C., Berry, D., Helm, J.L., Roisman, G.I., 2015. Differential susceptibility to effects of maternal sensitivity? A study of candidate plasticity genes. Dev. Psychopathol 27, 725–746.
Belsky, J., van IJzendoorn, M.H., 2017. Genetic differential susceptibility to the effects of parenting. Curr. Opin. Psychol. 15, 125–130.
Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B Methodol. 57, 289–300.
Bleys, D., Luyten, P., Soenens, B., Claes, S., 2018. Gene-environment interactions between stress and 5-HTTLPR in depression: a meta-analytic update. J. Affect. Disord. 226, 339–345.
Block, J.H., 1981. The Child-Rearing Practices Report (CRPR): a Set of Q Items for the Description of Parental Socialization Attitudes and Values. University of California, Institute of Human Development, Berkeley.
Borenstein, M., Rothstein, D., Cohen, D., 2005. Comprehensive Metaanalysis: a Computer Program for Research Synthesis. Biostat, Englewood. NJ.
Burmeister, M., McInnis, M.G., Zöllner, S., 2008. Psychiatric genetics: progress amid controversy. Nat. Rev. Genet. 9, 527–540.
Cao, C., Rijlaarsdam, J., van der Voort, A., Ji, L., Zhang, W., Bakermans-Kranenburg, M.J., 2018. Associations between dopamine D2 receptor (DRD2) gene, maternal positive parenting and trajectories of depressive symptoms from early to mid-adolescence. J. Abnorm. Child Psychol. 46, 365–379.
Caspi, A., Moffitt, T.E., 2006. Gene-environment interactions in psychiatry: joining forces with neuroscience. Nat. Rev. Neurosci. 7, 583–590.
Chen, X., Chang, L., He, Y., Liu, H., 2005. The peer group as a context: moderating effects on relations between maternal parenting and social and school adjustment in Chinese children. Child Dev. 76, 417–434.
Cohen-Woods, S., Harkess, K.N., 2016. Gene-environment interactions, stress, and depression. Handbook of Psychocardiology. pp. 807–830.
Comasco, E., Gustafsson, P.A., Sydsjö, G., Agnafors, S., Aho, N., Svedin, C.G., 2015. Psychiatric symptoms in adolescents: FKBP5 genotype—early life adversity interaction effects. Eur. Child Adolesc. Psychiatry 24, 1473–1483.
Culverhouse, R.C., Saccone, N.L., Horton, A.C., Ma, Y., Anstey, K.J., Banaschewski, T., Burmeister, M., Cohen-Woods, S., Etain, B., Fisher, H.L., Goldman, N., Guillaume, S., Horwood, J., Juhasz, G., Lester, K.J., Mandelli, L., Middeldorp, C.M., Olie, E., Villafuerte, S., Air, T.M., Araya, R., Bowes, L., Burns, R., Byrne, E.M., Coffey, C., Coventry, W.L., Gawronski, K.A.B., Glei, D., Hatzimanolis, A., Hottenga, J.J., Jaussent, I., Jawahar, C., Jennen-Steinmetz, C., Kramer, J.R., Lajnef, M., Little, K., Zu Schwabedissen, H.M., Nauck, M., Nederhof, E., Petschner, P., Peyrot, W.J., Schwahn, C., Sinnamon, G., Stacey, D., Tian, Y., Toben, C., Van der Auwera, S., Wainwright, N., Wang, J.C., Willemsen, G., Anderson, I.M., Arolt, V., Aslund, C., Bagdy, G., Baune, B.T., Bellivier, F., Boomsma, D.I., Courtet, P., Dannlowski, U., de Geus, E.J.C., Deakin, J.F.W., Easteal, S., Eley, T., Fergusson, D.M., Goate, A.M., Gonda, X., Grabe, H.J., Holzman, C., Johnson, E.O., Kennedy, M., Laucht, M., Martin, N.G., Munafo, M.R., Nilsson, K.W., Oldehinkel, A.J., Olsson, C.A., Ormel, J., Otte, C., Patton, G.C., Penninx, B., Ritchie, K., Sarchiapone, M., Scheid, J.M., Serretti, A., Smit, J.H., Stefanis, N.C., Surtees, P.G., Volzke, H., Weinstein, M., Whooley, M., Nurnberger Jr., J.I., Breslau, N., Bierut, L.J., 2018. Collaborative meta-analysis fnds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. Mol. Psychiatry 23, 133–142.
Dalton, E.D., Hammen, C.L., Najman, J.M., Brennan, P.A., 2014. Genetic susceptibility to family environment: BDNF Val66met and 5-HTTLPR influence depressive symptoms. J. Fam. Psychol. 28, 947–956.
Dannlowski, U., Konrad, C., Kugel, H., Zwitserlood, P., Domschke, K., Schöning, S., Ohrmann, P., Bauer, J., Pyka, M., Hohoff, C., Zhang, W., Baune, B.T., Heindel, W., Arolt, V., Suslow, T., 2010. Emotion specific modulation of automatic amygdala responses by 5-HTTLPR genotype. Neuroimage 53, 893–898.
Dick, D.M., Agrawal, A., Keller, M.C., Adkins, A., Aliev, F., Monroe, S., Hewitt, J.K., Kendler, K.S., Sher, K.J., 2015. Candidate gene-environment interaction research: reflections and recommendations. Perspect. Psychol. Sci. 10, 37–59.
Dougherty, L.R., Klein, D.N., Congdon, E., Canli, T., Hayden, E.P., 2010. Interaction between 5-HTTLPR and BDNF Val66Met polymorphisms on HPA axis reactivity in preschoolers. Biol. Psychol. 83, 93–100.
Downey, G., Coyne, J.C., 1990. Children of depressed parents: an integrative review. Psychol. Bull. 108, 50–76.
Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R., 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257–269.
Esposito, C.L., Clum, G.A., 2002. Psychiatric symptoms and their relationship to suicidal ideation in a high-risk adolescent community sample. J. Am. Acad. Child Adolesc. Psychiatr. 41, 44–51.
Gaffrey, M.S., Barch, D.M., Bogdan, R., Farris, K., Petersen, S.E., Luby, J.L., 2018. Amygdala reward reactivity mediates the association between preschool stress response and depression severity. Biol. Psychiatry 83, 128–136.
Gutiérrez, B., Bellón, J., Rivera, M., Molina, E., King, M., Marston, L., Torresgonzález, F., Morenoküstner, B., Morenoperal, P., Motrico, E., 2015. The risk for major depression conferred by childhood maltreatment is multiplied by BDNF and SERT genetic vulnerability: a replication study. J. Psychiatry Neurosci. 40, 187–196.
Hajcak, G., Castille, C., Olvet, D.M., Dunning, J.P., Roohi, J., Hatchwell, E., 2009. Genetic variation in brain-derived neurotrophic factor and human fear conditioning. Genes. Brain Behav. 8, 80–85.
Hankin, B.L., Jenness, J., Abela, J.R., Smolen, A., 2011. Interaction of 5-HTTLPR and idiographic stressors predicts prospective depressive symptoms specifically among youth in a multiwave design. J. Clin. Child Adolesc. Psychol. 40, 572–585.
Hankin, B.L., Young, J.F., Abela, J.R., Smolen, A., Jenness, J.L., Gulley, L.D., Cohen, J.R., Oppenheimer, C.W., 2015. Depression from childhood into late adolescence: influence of gender, development, genetic susceptibility, and peer stress. J. Abnorm. Child Psychol. 124, 803–816.
Harkness, K.L., Strauss, J., Bagby, R.M., Stewart, J.G., Larocque, C., Mazurka, R., Ravindran, A., Wynne-Edwards, K.E., Rector, N.A., Kennedy, J., 2015. Interactions between childhood maltreatment and brain-derived neurotrophic factor and serotonin transporter polymorphisms on depression symptoms. Psychiatry Res. 229, 609–612.
He, Q., Xue, G., Chen, C., Lu, Z., Dong, Q., Lei, X., Ding, N., Li, J., Li, H., Chen, C., Li, J., Moyzis, R.K., Bechara, A., 2010. Serotonin transporter gene-linked polymorphic region (5-HTTLPR) influences decision making under ambiguity and risk in a large Chinese sample. Neuropharmacology 59, 518–526.
He, S.C., Wu, S., Wang, C., Du, X.D., Yin, G., Jia, Q., Zhang, Y., Wang, L., Soares, J.C., Zhang, X.Y., 2018. Interaction between job stress and the BDNF Val66Met polymorphism affects depressive symptoms in Chinese healthcare workers. J. Affect. Disord. 236, 157–163.
Hosang, G.M., Shiles, C., Tansey, K.E., McGuffin, P., Uher, R., 2014. Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. BMC Med. 12, 7.
Hu, X., Oroszi, G., Chun, J., Smith, T.L., Goldman, D., Schuckit, M.A., 2005. An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. Alcohol. Clin. Exp. Res. 29, 8–16.
Jayanthi, P., Thirunavukarasu, M., Rajkumar, R., 2015. Academic stress and depression among adolescents: a cross-sectional study. Indian Pediatr. 52, 217–219.
Keller, J., Gomez, R., Williams, G., Lembke, A., Lazzeroni, L., Murphy Jr, G.M., Schatzberg, A.F., 2017. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. Mol. Psychiatry 22, 527–536.
Kovacs, M., 1992. Children's Depression Inventory (CDI) Manual. Multi-Health Systems Inc, Toronto.
Kyu, H.H., Pinho, C., Wagner, J.A., Brown, J.C., Bertozzi-Villa, A., Charlson, F.J., Coffeng, L.E., Dandona, L., Erskine, H.E., Ferrari, A.J., Fitzmaurice, C., Fleming, T.D., Forouzanfar, M.H., Graetz, N., Guinovart, C., Haagsma, J., Higashi, H., Kassebaum, N.J, Larson, H.J., Lim, S.S., Mokdad, A.H., Moradi-Lakeh, M., Odell, S.V., Roth, G.A., Serina, P.T., Stanaway, J.D., Misganaw, A., Whiteford, H.A., Wolock, T.M., Wulf Hanson, S., Abd-Allah, F., Abera, S.F., Abu-Raddad, L.J., AlBuhairan, F.S., Amare, A.T., Antonio, C.A., Artaman, A., Barker-Collo, S.L., Barrero, L.H., Benjet, C., Bensenor, I.M., Bhutta, Z.A., Bikbov, B., Brazinova, A., Campos-Nonato, I, Castañeda-Orjuela, C.A., Catalá-López, F., Chowdhury, R., Cooper, C., Crump, J.A., Dandona, R., Degenhardt, L., Dellavalle, R.P., Dharmaratne, S.D., Faraon, E.J., Feigin, V.L., Fürst, T., Geleijnse, J.M., Gessner, B.D., Gibney, K.B., Goto, A., Gunnell, D., Hankey, G.J., Hay, R.J., Hornberger, J.C., Hosgood, H.D., Hu, G., Jacobsen, K.H., Jayaraman, S.P., Jeemon, P., Jonas, J.B., Karch, A., Kim, D., Kim, S., Kokubo, Y., Kuate Defo, B., Kucuk Bicer, B., Kumar, G.A., Larsson, A., Leasher, J.L., Leung, R., Li, Y., Lipshultz, S.E., Lopez, A.D., Lotufo, P.A., Lunevicius, R., Lyons, R.A., Majdan, M., Malekzadeh, R., Mashal, T., Mason-Jones, A.J., Melaku, Y.A., Memish, Z.A., Mendoza, W., Miller, T.R., Mock, C.N., Murray, J., Nolte, S., Oh, I.H., Olusanya, B.O., Ortblad, K.F., Park, E.K., Paternina Caicedo, A.J., Patten, S.B., Patton, G.C., Pereira, D.M., Perico, N., Piel, F.B., Polinder, S., Popova, S., Pourmalek, F., Quistberg, D.A., Remuzzi, G., Rodriguez, A., Rojas-Rueda, D., Rothenbacher, D., Rothstein, D.H., Sanabria, J., Santos, I.S., Schwebel, D.C., Sepanlou, S.G., Shaheen, A., Shiri, R., Shiue, I., Skirbekk, V., Sliwa, K., Sreeramareddy, C.T., Stein, D.J., Steiner, T.J., Stovner, L.J., Sykes, B.L., Tabb, K.M., Terkawi, A.S., Thomson, A.J., Thorne-Lyman, A.L., Towbin, J.A., Ukwaja, K.N., Vasankari, T., Venketasubramanian, N., Vlassov, V.V., Vollset, S.E., Weiderpass, E., Weintraub, R.G., Werdecker, A., Wilkinson, J.D., Woldeyohannes, S.M., Wolfe, C.D., Yano, Y., Yip, P., Yonemoto, N., Yoon, S.J., Younis, M.Z., Yu, C., El Sayed Zaki, M., Naghavi, M., Murray, C.J., Vos, T., 2016. Global and national burden of diseases and injuries among children and adolescents between 1990 and 2013: findings from the global burden of disease 2013 study. JAMA Pediatry 170, 267–287.
Lehto, K., Mäestu, J., Kiive, E., Veidebaum, T., Harro, J., 2016. BDNF Val66Met genotype and neuroticism predict life stress: a longitudinal study from childhood to adulthood. Eur. Neuropsychopharmacol. 26, 562–569.
Lesch, K.P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Müller, C.R., Hamer, D.H., Murphy, D.L., 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274, 1527–1531.
Levinson, D.F., Mostafavi, S., Milaneschi, Y., Rivera, M., Ripke, S., Wray, N.R., Sullivan, P.F., 2014. Genetic studies of major depressive disorder: why are there no genome-wide association study findings and what can we do about it? Biol. Psychiatry 76, 510–512.
Lister, R., Mukamel, E.A., Nery, J.R., Urich, M., Puddifoot, C.A., Johnson, N.D., Lucero, J., Huang, Y., Dwork, A.J., Schultz, M.D., Yu, M., Tonti-Filippini, J., Heyn, H., Hu, S., Wu, J.C., Rao, A., Esteller, M., He, C., Haghighi, F.G., Sejnowski, T.J., Behrens, M.M., Ecker, J.R., 2013. Global epigenomic reconfiguration during mammalian brain development. Science 341, 1237905.
Loewenstern, J., You, X., Merchant, J., Gordon, E.M., Stollstorff, M., Devaney, J., Vaidya, C.J., 2019. Interactive effect of 5-HTTLPR and BDNF polymorphisms on amygdala intrinsic functional connectivity and anxiety. Psychiaty Res. Neuroimaging 285, 1–8.
Martinowich, K., Lu, B., 2008. Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacology 33, 73–83.
McLeod, B.D., Weisz, J.R., Wood, J.J., 2007. Examining the association between

parenting and childhood depression: a meta-analysis. Clin. Psychol. Rev. 27, 986–1003.
Miller, R., Wankerl, M., Stalder, T., Kirschbaum, C., Alexander, N., 2013. The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cortisol stress reactivity: a meta-analysis. Mol. Psychiatry 18, 1018–1024.
Naumova, O.Y., Hein, S., Suderman, M., Barbot, B., Lee, M., Raefski, A., Dobrynin, P.V., Brown, P.J., Szyf, M., Luthar, S.S., Grigorenko, E.L., 2016. Epigenetic patterns modulate the connection between developmental dynamics of parenting and offspring psychosocial adjustment. Child Dev. 87, 98–110.
Oppenheimer, C.W., Hankin, B.L., Young, J., 2018. Effect of parenting and peer stressors on cognitive vulnerability and risk for depression among youth. J. Abnorm. Child Psychol. 46, 597–612.
Pearson, J.L., Cohn, D.A., Cowan, P.A., Cowan, C.P., 1994. Earned-and continuous-security in adult attachment: relation to depressive symptomatology and parenting style. Dev. Psychopathol. 6, 359–373.
Pearson, R., Palmer, R.H.C., Brick, L.A., McGeary, J.E., Knopik, V.S., Beevers, C.G., 2016. Additive genetic contribution to symptom dimensions in major depressive disorder. J. Abnorm. Psychol. 125, 495–501.
Shalev, I., Lerer, E., Israel, S., Uzefovsky, F., Gritsenko, I., Mankuta, D., Ebstein, R.P., Kaitz, M., 2009. BDNF Val66Met polymorphism is associated with HPA axis reactivity to psychological stress characterized by genotype and gender interactions. Psychoneuroendocrinology 34, 382–388.
Steiger, H., Thaler, L., Gauvin, L., Joober, R., Labbe, A., Israel, M., Kucer, A., 2016. Epistatic interactions involving DRD2, DRD4, and COMT polymorphisms and risk of substance abuse in women with binge-purge eating disturbances. J. Psychiatr. Res. 77, 8–14.
Steinberg, L., 2014. Adolescence, 10th ed. McGraw-Hill, New York.
Stocker, C.M., Masarik, A.S., Widaman, K.F., Reeb, B.T., Boardman, J.D., Smolen, A., Neppl, T.K., Conger, K.J., 2017. Parenting and adolescents' psychological adjustment: longitudinal moderation by adolescents' genetic sensitivity. Dev. Psychopathol. 29, 1289–1304.
Thapar, A., Collishaw, S., Pine, D.S., Thapar, A.K., 2012. Depression in adolescence. Lancet 379, 1056–1067.
Tyler, A.L., Asselbergs, F.W., Williams, S.M., Moore, J.H., 2009. Shadows of complexity: what biological networks reveal about epistasis and pleiotropy. Bioessays 31, 220–227.
Van Assche, E., Moons, T., Cinar, O., Viechtbauer, W., Oldehinkel, A.J., Van Leeuwen, K., Verschueren, K., Colpin, H., Lambrechts, D., Van den Noortgate, W., Goossens, L., Claes, S., van Winkel, R., 2017. Gene-based interaction analysis shows GABA ergic genes interacting with parenting in adolescent depressive symptoms. J. Abnorm. Child Psychol. 58, 1301–1309.
Van Assche, E., Moons, T., Van Leeuwen, K., Colpin, H., Verschueren, K., Van Den Noortgate, W., Goossens, L., Claes, S., 2016. Depressive symptoms in adolescence: the role of perceived parental support, psychological control, and proactive control in interaction with 5-HTTLPR. Eur. Psychiatry 35, 55–63.
Wade, M., Moore, C., Astington, J.W., Frampton, K., Jenkins, J.M., 2015. Cumulative contextual risk, maternal responsivity, and social cognition at 18 months. Dev. Psychopathol. 27, 189–203.
Wegener Sleeswijk, A., Heijungs, R., Durston, S., 2019. Tackling missing heritability by use of an optimum curve: a systematic review and meta-analysis. Int. J. Mol. Sci. 20, 5104.
Widaman, K.F., Helm, J.L., Castro-Schilo, L., Pluess, M., Stallings, M.C., Belsky, J., 2012. Distinguishing ordinal and disordinal interactions. Psychol. Methods 17, 615–622.
Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J., Agerbo, E., Air, T.M., Andlauer, T.M.F., Bacanu, S.-A., Bækvad-Hansen, M., Beekman, A.F.T., Bigdeli, T.B., Binder, E.B., Blackwood, D.R.H., Bryois, J., Buttenschøn, H.N., Bybjerg-Grauholm, J., Cai, N., Castelao, E., Christensen, J.H., Clarke, T.-K., Coleman, J.I.R., Colodro-Conde, L., Couvy-Duchesne, B., Craddock, N., Crawford, G.E., Crowley, C.A., Dashti, H.S., Davies, G., Deary, I.J., Degenhardt, F., Derks, E.M., Direk, N., Dolan, C.V., Dunn, E.C., Eley, T.C., Eriksson, N., Escott-Price, V., Kiadeh, F.H.F., Finucane, H.K., Forstner, A.J., Frank, J., Gaspar, H.A., Gill, M., Giusti-Rodríguez, P., Goes, F.S., Gordon, S.D., Grove, J., Hall, L.S., Hannon, E., Hansen, C.S., Hansen, T.F., Herms, S., Hickie, I.B., Hoffmann, P., Homuth, G., Horn, C., Hottenga, J.-J., Hougaard, D.M., Hu, M., Hyde, C.L., Ising, M., Jansen, R., Jin, F., Jorgenson, E., Knowles, J.A., Kohane, I.S., Kraft, J., Kretzschmar, W.W., Krogh, J., Kutalik, Z., Lane, J.M., Li, Y., Li, Y., Lind, P.A., Liu, X., Lu, L., MacIntyre, D.J., MacKinnon, D.F., Maier, R.M., Maier, W., Marchini, J., Mbarek, H., McGrath, P., McGuffin, P., Medland, S.E., Mehta, D., Middeldorp, C.M., Mihailov, E., Milaneschi, Y., Milani, L., Mill, J., Mondimore, F.M., Montgomery, G.W., Mostafavi, S., Mullins, N., Nauck, M., Ng, B., Nivard, M.G., Nyholt, D.R., O'Reilly, P.F., Oskarsson, H., Owen, M.J., Painter, J.N., Pedersen, C.B., Pedersen, M.G., Peterson, R.E., Pettersson, E., Peyrot, W.J., Pistis, G., Posthuma, D., Purcell, S.M., Quiroz, J.A., Qvist, P., Rice, J.P., Riley, B.P., Rivera, M., Saeed Mirza, S., Saxena, R., Schoevers, R., Schulte, E.C., Shen, L., Shi, J., Shyn, S.I., Sigurdsson, E., Sinnamon, G.B.C., Smit, J.H., Smith, D.J., Stefansson, H., Steinberg, S., Stockmeier, C.A., Streit, F., Strohmaier, J., Tansey, K.E., Teismann, H., Teumer, A., Thompson, W., Thomson, P.A., Thorgeirsson, T.E., Tian, C., Traylor, M., Treutlein, J., Trubetskoy, V., Uitterlinden, A.G., Umbricht, D., Van der Auwera, S., van Hemert, A.M., Viktorin, A., Visscher, P.M., Wang, Y., Webb, B.T., Weinsheimer, S.M., Wellmann, J., Willemsen, G., Witt, S.H., Wu, Y., Xi, H.S., Yang, J., Zhang, F., eQTLGen, 23andMe, Arolt, V., Baune, B.T., Berger, K., Boomsma, D.I., Cichon, S., Dannlowski, U., de Geus, E.C.J., DePaulo, J.R., Domenici, E., Domschke, K., Esko, T., Grabe, H.J., Hamilton, S.P., Hayward, C., Heath, A.C., Hinds, D.A., Kendler, K.S., Kloiber, S., Lewis, G., Li, Q.S., Lucae, S., Madden, P.F.A., Magnusson, P.K., Martin, N.G., McIntosh, A.M., Metspalu, A., Mors, O., Mortensen, P.B., MüllerMyhsok, B., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Paciga, S.A., Pedersen, N.L., Penninx, B.W.J.H., Perlis, R.H., Porteous, D.J., Potash, J.B., Preisig, M., Rietschel, M., Schaefer, C., Schulze, T.G., Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Völzke, H., Weissman, M.M., Werge, T., Winslow, A.R., Lewis, C.M., Levinson, D.F., Breen, G., Børglum, A.D., Sullivan, P.F., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat. Genet.. 50, 668–681.
Wu, W., Lu, Y., Tan, F., Yao, S., Steca, P., Abela, J.R., Hankin, B.L., 2012. Assessing measurement invariance of the Children's Depression Inventory in Chinese and Italian primary school student samples. Assessment 19, 506–516.
Zhang, L., Li, Z., Chen, J., Li, X., Zhang, J., Belsky, J., 2016a. The BDNF Val66Met polymorphism interacts with maternal parenting influencing adolescent depressive symptoms: evidence of differential susceptibility model. J. Youth. Adolesc. 45, 471–483.
Zhang, W., Cao, C., Wang, M., Ji, L., Cao, Y., 2016b. Monoamine oxidase a (MAOA) and catechol-o-methyltransferase (COMT) gene polymorphisms interact with maternal parenting in association with adolescent reactive aggression but not proactive aggression: evidence of differential susceptibility. J. Youth. Adolesc. 45, 812–829.