

Mothers' Early Depressive Symptoms and Preschoolers' Behavioral Problems: The Moderating Role of Genetic Influences

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Abstract As a stressful environment in families, mothers' depressive symptoms might increase children's risks of developing behavioral problems by exacerbating genetic influences. Using data from the nationally representative Early Childhood Longitudinal Study-Birth Cohort data of approximately 750 pairs of twins, we examined whether genetic influences on preschoolers' behavioral problems depended upon mothers' depressive symptoms. Results indicated that the genetic etiology for both internalizing and externalizing behaviors varied with maternal depressive symptoms at 9-months child age. Genetic effects on externalizing behaviors increased as mothers' depressive symptoms increased; however, genetics effects on internalizing behaviors increased when depressive symptoms either increased or decreased from the median level. These different patterns of interactive effects suggest potentially different mechanisms for the etiology of children's externalizing and internalizing behaviors.

Keywords Maternal depression · Behavioral problems · Diathesis–stress · Differential susceptibility

Introduction

Mothers' depressive symptoms are associated with heightened risks of developing both internalizing and externalizing behavior problems among their offspring

[1, 2]. These detrimental effects are over and beyond the effects of many contextual risk factors such as family poverty and adverse life events, and they are particularly detrimental in the first few years of children's lives [3]. Despite the well-established body of literature compiled across the past few decades documenting the association between mothers' depressive symptoms and children's behavioral problems, questions have been raised about how these associations might function differently depending on children's individual differences [2, 3]. In particular, recent developments in behavioral genetics have led to burgeoning interest in examining how specific genetic variants may moderate the influences of mothers' depressive symptoms on child development [4]. However, given the complex set of genes responsible for children's behavioral problems, a quantitative genetic approach is needed to examine how genetic variation as a whole might moderate the impact of mothers' depressive symptoms on children's behavioral problems. In the current study, using data from a large nationally representative sample of American twins, a quantitative genetic approach was employed to test the hypothesis that influences of mothers' depressive symptoms on preschoolers' internalizing and externalizing behavioral problems are moderated by genetic influences.

Genetic Influences of Behavioral Problems

Substantial heritability for children's behavioral problems has been identified by existing behavioral genetics studies, although the degree of reported heritability tends to vary across studies [5–7]. For example, heritability estimates for internalizing have ranged from modest (e.g., 17 and 37 % [8]) to large (e.g., 77 % [9]), with larger estimates derived from studies of older children [8]. Similarly, substantial genetic contributions have been detected for children's

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externalizing behaviors, with estimates ranging from 48 to 66 % [7, 10–13]. As with internalizing behaviors, heritability estimates for externalizing behaviors also increase with child age [14].

Genetic Influences by Maternal Depression Interactions

The expression of genetic effects in children's behavioral problems, however, maybe contingent upon gene–environment interactions [15–17]. The link between specific genes (e.g., 7-repeat DRD4 allele, 5-HTT) and children's behavioral problems has been shown to be stronger in undesirable environments (e.g., insensitive parenting, low social support [15, 16]. As a prevalent and stressful environment in the family context [3, 18], mothers' depressive symptoms might increase children's risks of developing behavioral problems by exacerbating their genetic influences. Children with a brain-derived neurotrophic factor (BDNF) methionine allele who also had a mother who was depressed during their lifetime had significantly more memory for negative self-descriptive traits (i.e., a cognitive marker of depression vulnerability) than did children with the same genotype with mothers who had no history of depression [4]. However, this is the only study to date that has demonstrated the interaction between mothers' depressive symptoms and children's genetic liabilities for behavioral problems. Findings from observational studies also provide tentative support for this moderated link. It has been shown, for example, that mothers' early depressive symptoms interact with a genetically-based characteristic—children's negative emotionality at age 6 months—to predict later behavioral problems [19].

The Application of Quantitative Genetic Approach in Exploring Gene × Environment Interaction

While quantitative genetic studies have been consistently employed to estimate genetic main effects on behavioral problems, there has been relatively a smaller body of studies to test for gene-by-environment in the prediction of children's behavior problems [20, 21]. By allowing the amount of variance attributed to genes to differ as a function of the measured environment, the quantitative genetic approach, instead of pinpointing a particular gene responsible for the G × E interaction, focuses on how the aggregate contribution of genes to children' behavioral problems is moderated by mothers' depressive symptoms. Particularly given that multiple genes are likely to influence the phenotype of children's behavioral problems [22, 23] 2005, quantitative genetic studies might be a more appropriate and sensitive approach to captures G × E effects. This approach has been increasingly applied in

developmental and family studies interested in G × E [21, 24, 25]. However, to our knowledge, the current study is the first one that examines how genetic variations in children's behavioral problems could be moderated by mothers' depressive symptoms using a quantitative gene approach. To be noted, in the quantitative genetic approach, heritability estimates often include effects that act through the environment. Heritability estimate represents a correlation between the genetic component and the phenotypic behaviors and this association should not be interpreted as evidence for direct causation.

Domain-Specificity of Gene-by-Maternal Depression Interactions

Different patterns of G × E interactions might apply to different domains of development. Prior research on G × E effects suggest that interactive effects might only exist in some domains, and developmental theories used to explain such interactive effects also suggest domain specificity. For instance, Bakermans-Kranenburg and Van IJzendoorn [15] observed interactive effects of the DRD4 gene and maternal sensitivity for externalizing but not internalizing behaviors. Similarly, other research has found that G × E interactions were consistent with the diathesis–stress hypothesis (i.e., individuals with vulnerabilities in certain genetic makeup are disproportionately more likely to be negatively affected by adverse environment [26]) for academic and social competence but consistent with the differential susceptibility hypothesis (i.e., the same genotypes may confer responsively to both positive and negative environment [27, 28] for moral internalization [29]). Therefore, whether gene-by-maternal depression effects would differ across internalizing and externalizing behaviors is another primary care of inquiry in the current study.

The Current Study

The current study uses data from the Early Childhood Longitudinal Study-Birth Cohort (ECLS-B) to examine two research questions. First, in order to determine if the G × E interaction patterns should be examined separately for children's internalizing and externalizing behaviors, we first wanted to examine to what extent genetic influences on preschoolers' internalizing and externalizing behaviors are correlated. We expect that genetic influences on them are not correlated [4, 15]. Second, are the genetic influences on preschoolers' behavioral problems moderated by mothers' depressive symptoms (i.e., a G × E interaction)? We hypothesized that mothers' depressive symptoms would exacerbate children's genetic influences for developing internalizing and externalizing behaviors [4, 19].

Methods

Sample

Participants were drawn from the twin sample of a nationally representative longitudinal study—the ECLS-B. All children born in 2001 were sampled for the study via registered births from the US National Center for Health Statistics. Several subsamples, including twins, were oversampled in ECLS-B to increase analytic power. More detailed information regarding recruitment of the cohort is available in Bethel et al. [30]. Data from approximately 750 pairs of twins (out of 800 twin pairs in total) whose zygosity information is available were included in the study. Among these children, 61 % were White; 16 % were African American; 16 % were Hispanic; 3 % were Asian; and 4 % were of mixed race. Among all the parents, 8.0 % of them had less than high school; 16.5 % had high school diploma or equivalent; 6 % had diploma from vocational-technical program; 25.7 % had ever been in a college; 21.2 % had bachelor's degree; 3.9 % had joined graduate school with no degree; 10.8 % had master's degree; 7.3 % had doctoral or professional degree. This educational distribution suggests the current sample is slightly better educated than US population estimates, with a higher percentage of parents having a bachelor's degree or above. *N*'s are rounded to the nearest 50 children throughout the manuscript per NCES requirements for ECLS-B restricted-use data.

Measures

Bivariate correlations among study variables are summarized in Table 1.

Zygosity

Twin's zygosity was assessed using the method described in Tucker-Drob et al. [25]. At age 2-years, trained investigators rated the similarity of same-sex twins on six aspects of physical appearance (e.g., hair texture, facial appearance, earlobe shape) when the twins were X years old, and these ratings were used to identify twins as monozygotic (MZ) or dizygotic (DZ). This method of determining zygosity has been validated in prior studies [31]. Same-sex pairs who would have received a DZ

diagnosis were excluded from analyses if there was a medical reason for their dissimilarity (as reported by their mothers).

Maternal Depressive Symptoms

At child age 9 months, mothers' depressive symptoms (e.g., feel unusually bothered; poor appetite) were assessed with a modified version of the Center for Epidemiologic Studies-Depression Scale (CES-D [32]). Ratings for the 12 items ranged from 1 (rarely or never) to 4 (most or all). Higher mean scores indicated more depressive symptoms ($\alpha = .88$). The mean score was 17.33 (SD = 5.70).

Children's Behavioral Problems

Children's internalizing and externalizing symptoms at the preschool wave were assessed using a modified version of the Preschool and Kindergarten Behavior Scales (PKBS-2 [33]). Early care and education provider (ECEP) interviews were conducted by phone using computer-assisted interview (CAI) instruments. The child care provider was asked to consider eight child externalizing behaviors (e.g., "displays aggressiveness"; "is impulsive"; $\alpha = .82$) and evaluate whether each had been observed within the past 3 months (1 = "very often," 5 = "never"). Two items measured children's internalizing behaviors ("child seems unhappy;" and "child worries"; $\alpha = .88$). Responses were recoded such that higher mean scores indicated more externalizing behaviors. The mean scores were 1.93 for internalizing behaviors (SD = .75) and 2.15 for externalizing behaviors (SD = .80). Although multiple informants or assessments are recommended to measure children's phenotypic behavior problems, we used teachers' reports instead of mothers' reports or children's self-reports (a) to eliminate potential bias that might result from the influence of mothers' depressive symptoms on their assessments of their children and (b) to ensure measures are developmentally appropriate, as the age of our child sample precludes valid self assessments of social-behavioral well-being.

Analysis Plan

The analyses in the current study proceeded in three steps. First, to determine the extent to which the genetic

Table 1 Bivariate correlations among study variables

Variables	1	2	3	4
1. Maternal depression at 9-months	–			
2. Child internalizing behaviors at preschool	.04**	–		
3. Child externalizing behaviors at preschool	.10***	.28***	–	

contribution for internalizing and externalizing behaviors is correlated, a bivariate correlated factors model was fit for internalizing and externalizing behaviors. Second, to examine the proportion of genetic contribution to preschoolers' behavioral problems, we fit univariate main effects models for internalizing and externalizing behaviors. Third, two univariate interaction models then were fit for internalizing and externalizing behaviors respectively to determine if the genetic influences of behavioral problems were contingent on mothers' depressive symptoms (i.e., $G \times E$ effect). Primary analyses followed biometric modeling procedures specified by Prescott [32] for analyzing twin data. All models were conducted using Mplus 7.1 [34]. Full information maximum likelihood (FIML) estimation was used to handle missing data.

Results

To What Extent Are the Genetic Contribution for Internalizing and Externalizing Behaviors Correlated?

To determine the extent of shared genetic contributions for preschoolers' internalizing and externalizing behaviors, a bivariate correlated factors model was fit between internalizing and externalizing behaviors. The path diagram of

the bivariate model is shown in Fig. 1. The model fit the data well: $\chi^2(df = 17) = 17.66, p = .41$; comparative fit index (CFI) = .99, root mean square error of approximation (RMSEA) = .01 (CI .00–.06). However, the correlation between the genetic factors (A) of internalizing and externalizing behaviors was not significant ($r = -.34, p = .64$). This indicates that different sets of genes may be important for internalizing versus externalizing behaviors during preschool. Thus, separate models were examined for children's internalizing and externalizing behaviors.

What Are the Genetic Influences on Internalizing and Externalizing Behaviors among Preschoolers?

Two biometric structural equation models were fit to determine the magnitude of genetic influences on preschoolers' internalizing and externalizing behaviors respectively. The path diagram of the biometric model is in Fig. 2. In each model, the variation in children's internalizing or externalizing behaviors were decomposed into additive genetic factors (A), shared environmental factors (C), and non-shared environmental factors (E).

Estimates from the univariate models for children's internalizing and externalizing behaviors are shown in Table 2 (columns titled main effects models). The genetic influences for internalizing behaviors were not significant ($\beta = .22, p = .51$). Based on the estimated parameter

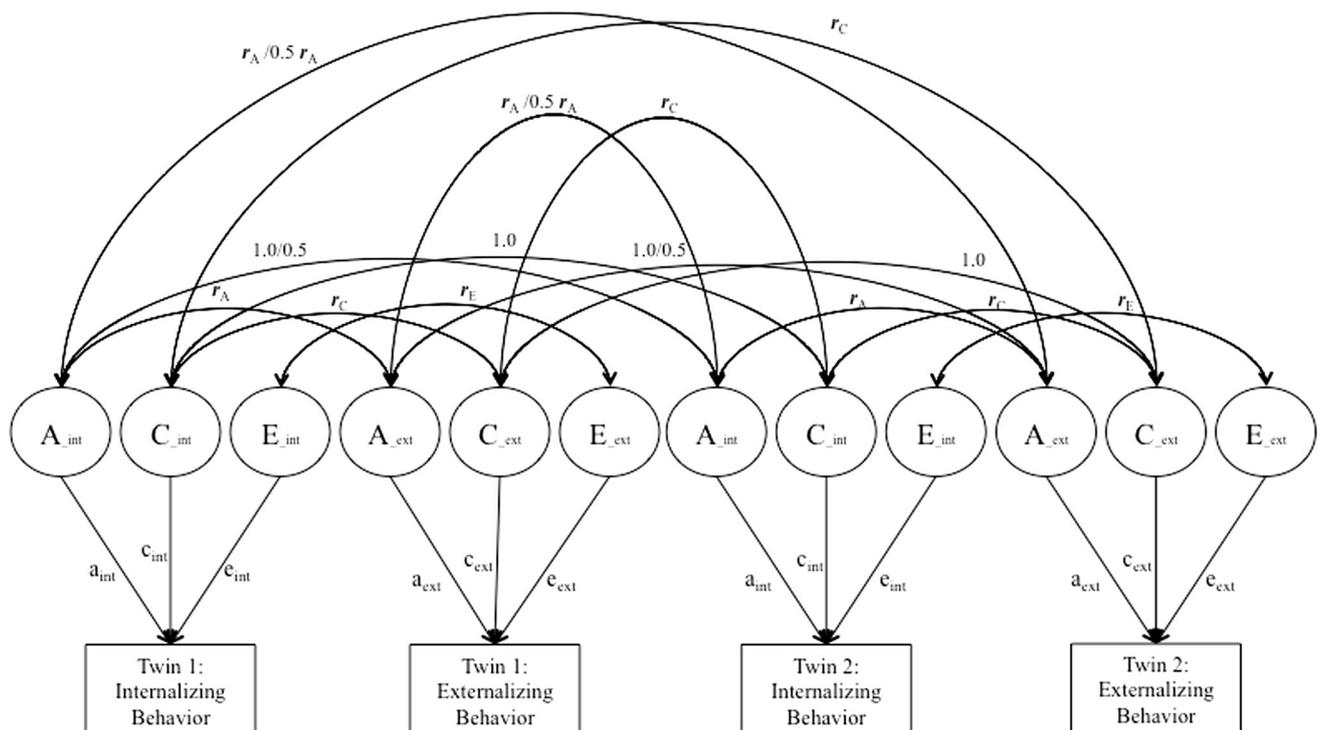


Fig. 1 ACE path diagram of the bivariate two factor model

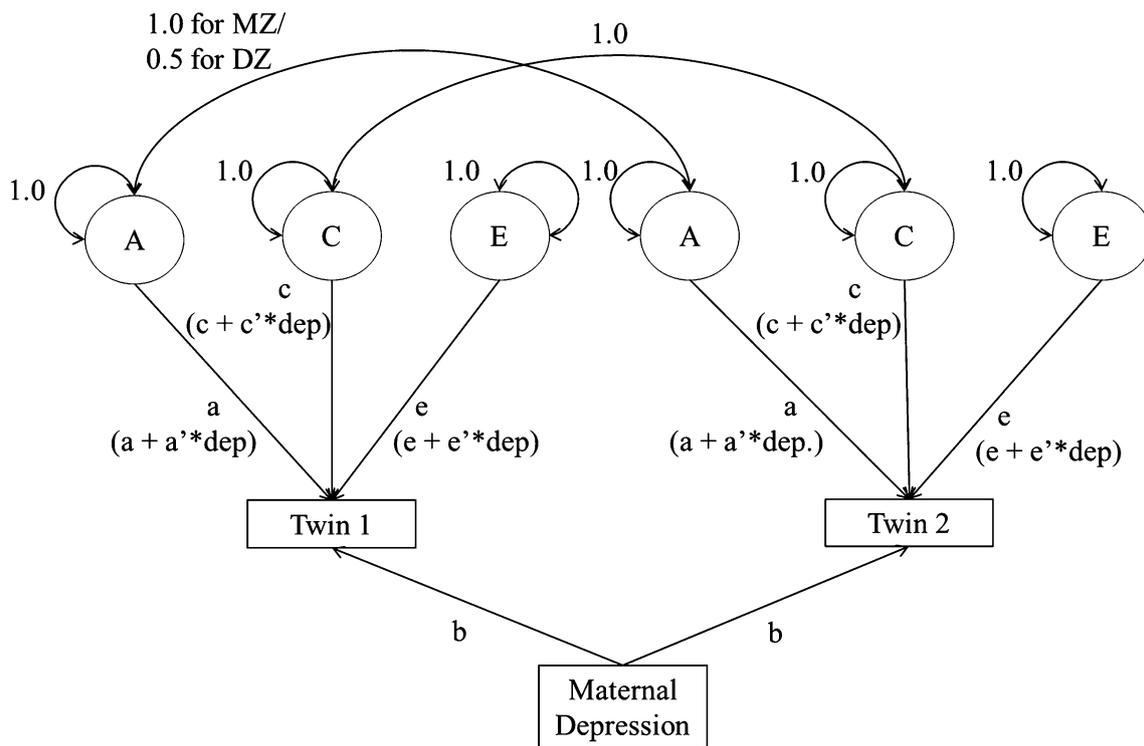


Fig. 2 ACE path diagram of the biometric model

Table 2 Estimates from the biometric structural equation models for internalizing and externalizing behaviors

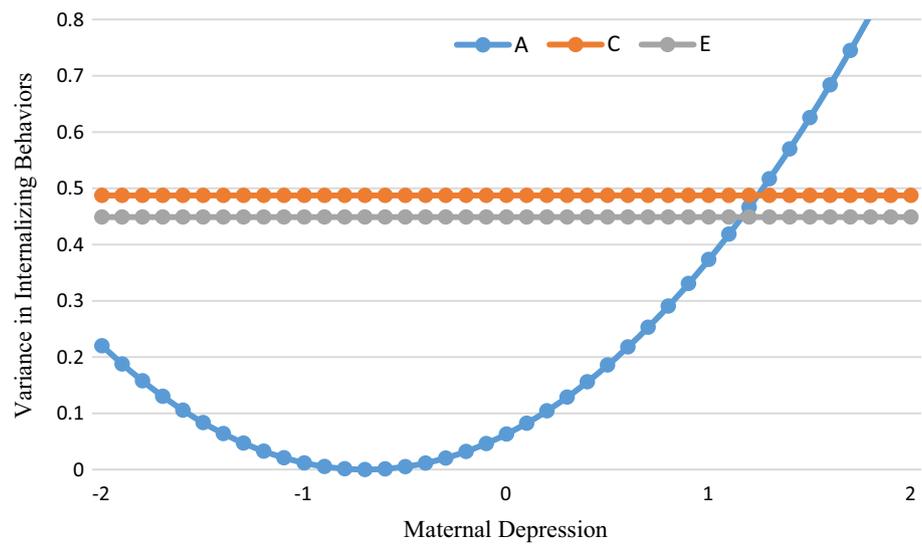
	Internalizing				Externalizing			
	Main effect model		Interacting effects model		Main effect model		Interacting effects model	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
a	.200	.366	.251	.199	.778	.080	.756	.075
a'			.360	.093			.141	.067
c	.754	.075	.698	.071	.322	.165	.359	.138
c'			-.100	.105			-.130	.113
e	.671	.046	.670	.036	.524	.039	.491	.037
e'			-.066	.048			-.002	.039
s	.052	.052	.077	.059	.134	.050	.173	.054
AIC	3985.416		3773.13		3870.527		3650.41	
BIC	4016.967		3817.62		3902.078		3694.903	
Log-likelihood	-1985.708		-1876.56		-1928.264		-1815.21	
df	3				3			
p value	<.001				<.001			

Estimates in bold indicate significant at level of $p < .05$

coefficients, approximately 56 % of variance in internalizing behaviors were explained by shared environment ($\beta = .75, p < .05$), and 44 % was explained by non-shared environment ($\beta = .67, p < .05$). The main effect of maternal depression on children's phenotypic internalizing behaviors was not significant ($\beta = .06, p = .25$).

In the main effect model for externalizing behaviors, both genetics ($\beta = .78, p < .05$), shared environment ($\beta = .33, p < .05$), and non-shared environment ($\beta = .52, p < .05$) explained significant proportion of the variance in externalizing behaviors. The main effect of maternal depression on children's externalizing behaviors was

Fig. 3 Genetic and environmental contributions to children's internalizing behaviors at preschool as a function of maternal depression at 9-month



significant ($\beta = .17, p < .01$). In sum, according to the main effects models, genes significantly contributed to the variance in children's externalizing but not internalizing behaviors.

Does Maternal Depression Moderate Genetic Influences?

Two univariate models integrating interactive effects of maternal depression and A, C, E components were examined to determine whether the genetic influences on preschoolers' behavioral problems were conditioned by maternal depression. The path diagram of the biometric interaction model resembles those tested in the above univariate models with the exception that each biometric path was modeled as both the main effect (a, c, and e) and interactive effects with maternal depression (a', c', and e'; see symbols in parenthesis in Fig. 2). Estimates for the interaction models for children's internalizing and externalizing behaviors are presented in Table 2 (columns titled interaction effects). The interaction terms between maternal depression and genetic influences of both internalizing and externalizing behaviors were significant (internalizing behaviors: $\beta = .35, p < .05$; externalizing behaviors: $\beta = .143, p < .05$). Comparisons of model fit indicators (AIC, BIC, log-likelihood) suggest that the interaction models fit better than the main effect models (see the bottom rows of Table 2 for a summary of model comparisons).

For internalizing behaviors, maternal depression moderated the variance genetic contributions for children's internalizing behaviors. To unpack these interactive effects, we plotted the amount of variance in children's internalizing behaviors accounted for by genetic, shared-,

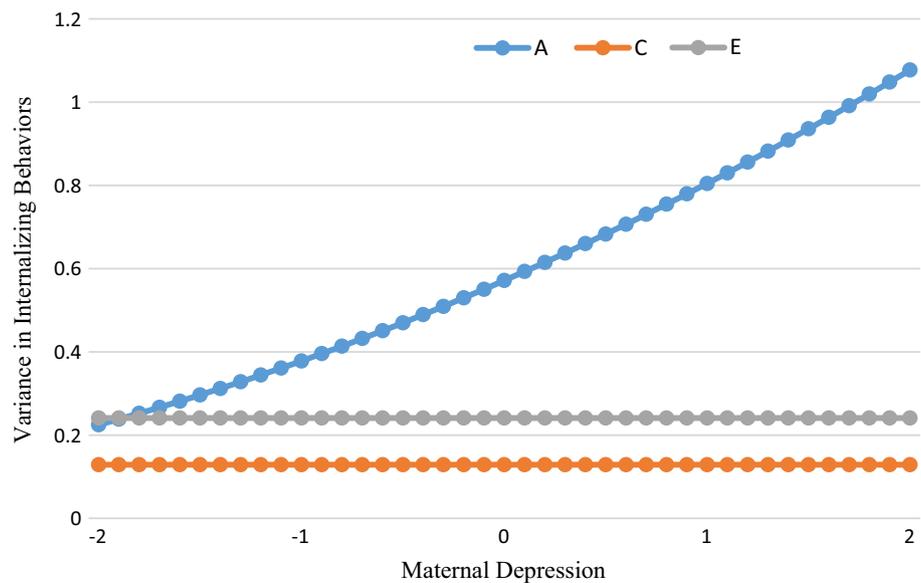
and non-shared environmental influences as a function of mothers' depressive symptoms (see Fig. 3). The genetic component of children's internalizing behaviors varies in a U-shape as maternal depression is plotted from low to high. This suggests that, when mothers' depressive symptoms are at the median level, the set of genes responsible for internalizing behaviors neither increase nor decrease the risk of developing internalizing behaviors; when mothers' depressive symptoms are low or high, genetic contributions for internalizing behaviors increase.

Maternal depression also moderated the variance in genetic contributions to children's externalizing behaviors. As shown in Fig. 4, when mother's depressive symptoms are higher, more variance in children's externalizing behaviors is accounted for by genes. This indicates that maternal depression exacerbates the genetic risks of developing externalizing behaviors.

Discussion

Individual differences have long been hypothesized to moderate the effects of maternal depression on child development [3, 35]. By employing quantitative genetic models, the current study explored individual differences in the form of children's genetic influences for behavioral problems at the aggregate genetic level. Significant interactions between genetic influences and maternal depression were detected for both internalizing and externalizing behaviors among preschoolers. Decomposition of these interactive effects showed unique patterns for internalizing and externalizing problems. Specifically, the genetic contributions for children's internalizing behaviors increased when mothers' depressive symptoms were both high and

Fig. 4 Genetic and environmental contributions to children's externalizing behaviors at preschool as a function of maternal depression at 9-month



low, whereas the genetic contributions for children's externalizing behaviors increased as mothers' depressive symptoms increased.

Maternal depression has been robustly associated with children's internalizing problems as early as early childhood [2, 36]. Our analyses elucidated a more complex picture of these relations by not only including main effects of mothers' depressive symptoms but also integrating interaction effects to determine how maternal depression may alter the magnitude of genetic contributions to the development of internalizing behaviors. Surprisingly and at odds with some prior findings [8, 9, 13], the main effects of genetic influences on children's internalizing behaviors were not significant. This null finding could be attributed to, first, the fact that teachers' reports of internalizing behaviors, instead of mothers' reports, were used in the current study. Teachers generally report fewer internalizing behaviors during early childhood than mothers, and there is also evidence that teacher reports display less variance as well [37]. Also, it has been suggested in prior research that the genetic contribution to internalizing behaviors seem to be weaker when internalizing behaviors are reported by teachers than reported by mothers [13]. Moreover, this null finding may be confounded by the age period and the assessment methods in the current study. Heritability estimates seemed to dramatically increase throughout childhood and the use of others' reports instead of self-reports seem to overestimate familial influences over other influences [14, 38]. These results should be interpreted with caution for the aforementioned reasons.

Moving to the interaction model, our study suggests maternal depression modifies genetic influences on children's internalizing behaviors at the aggregate genetic

variation level. This suggests that globally significant patterns of $G \times E$ effects may be obscured when interactions are examined at the level of a single genetic polymorphism rather than on the aggregate level. More importantly, the genetic component of children's internalizing behaviors varies in a U-shape as maternal depression varies from low to high. Thus, when mothers' depressive symptoms are at the median level, our findings suggest that genetic influences contribute minimally to the development of internalizing behaviors. In contrast, as mothers' depressive symptoms deviate from mean levels (in either high or low directions), the genetic influences on children's internalizing behaviors increase. This distinct curvilinear pattern of genetic influence, often referred to as an "orchid effect," is in line with the prediction of the differential susceptibility model [27, 39]. Differential susceptibility posits some individuals are more sensitive to environments that are both positive/supportive and negative/risk environments than other individuals. The observed greater genetic variance at the extremes of environmental experience and minimal genetic variance for average environments in the study is consistent with this hypothesis. This observed "orchid effect" differs from the "diathesis–stress effects" found in Hayden and her colleagues' work [4] where a single genetic polymorphism was examined. This inconsistency may be due to either the analyses of the aggregate variation level of genetic influences rather a single genetic polymorphism or the range of environmental influences spanned in these studies. This proposal was less often seen in research on maternal depression, given that the lower end of mothers' depressive symptoms scale was barely studied or conceptualized as the "positive environment". However, replication is needed before substantive interpretations of these results are made.

Our findings also revealed a $G \times E$ effect between mothers' depressive symptoms and the genetic contribution of children's externalizing behaviors, although the shape of this interaction differed from that of internalizing behaviors. Specifically, as mothers' depressive symptoms increased, so too did the genetic influences on developing externalizing behaviors. This is in accord with the prediction of the diathesis–stress hypothesis [26], wherein individuals with vulnerabilities in certain genetic makeup are disproportionately more likely to be negatively affected by adverse environments. This pattern of “diathesis–stress” interaction coincides with those observed at the behavioral level whereby children's genetically influenced characteristics (such as negative emotionality) are exacerbated when mothers' depressive symptoms are high [19, 40].

Inconsistent with prior findings [41, 42], the correlation between the genetic factors of internalizing and externalizing behaviors was not significant in the current study. This null finding is likely to be related to young age we examined in the study. Among 5–9 years old, <10 % of phenotypic correlation between internalizing and externalizing disorders was explained by genetic factors; among 12–15 years old, this percentage increased to proximately 20 % [42]. In another adolescent sample, approximately 45 % of the observed covariation between depressive symptoms and antisocial behaviors were explained by genetic liability [41]. These findings suggest that the genetic covariation between internalizing and externalizing behaviors may increase as children develop. However, this null finding may also be due to biased sampling or a lack of power in testing these relations and future study is needed to replicate these results.

Taken as a whole, the current study suggests that the genetic contributions for preschoolers' internalizing and externalizing behaviors vary as a function of one important environment factor—maternal depression. These results, however, should be interpreted with some caveats. First, maternal depression is examined as an environmental risk factor, as suggested by prior research [18]. Yet maternal depression is more than just an environmental factor, as its effects on children may involve both environmental risks and heritable ones (i.e., passive $G \times E$ correlation). Second, although the sample was diverse and nationally representative, generalizing to less advantaged populations, clinical samples, or groups from different cultures should be done with caution. Third, to minimize bias in maternal reports on both their depressive symptoms and child outcomes, teachers' reports of children's behavior problems were used in the current study. However, heritability estimates may vary in part due to instrumental variation and the use of single informant may limit the contextual validity of this measure. Thus, the measurements used in future behavior genetic studies of children's behavior

problems should be diversified given these concerns. Fourth, as $G \times E$ interactions are often hard to replicate, the current study falls short for not including a replication or partial replication of findings. Thus, continued research is necessary to replicate the findings in the current study. Fifth, without genetic information at the molecular level, the detected interaction effects and post hoc simple slopes are only capable of suggesting the possibility of the presence of differential susceptibility or diathesis–stress hypothesis but not capable of firmly proving the existence of these effects. The integration of quantitative and molecular genetic studies is needed in the future to future examine these research questions. Last but not least, although we failed to find the correlation between genetic contributions of children's internalizing and externalizing behaviors, this null finding must be interpreted with caution and continued research is necessary to examine these relations in larger samples or if family context (e.g., SES) moderates the genetic attributes of children's co-occurring behavior problems.

In conclusion, findings from the current study extend our understanding on how genetic influences of children's behavior problems at the aggregate level, rather than the single genetic polymorphism level, may be conditioned by maternal depression. More interestingly, different interaction patterns emerged for preschoolers' internalizing (i.e., differential susceptible pattern) versus externalizing behaviors (i.e., diathesis–stress pattern). Replications of these effects is needed in future studies before any confirmative conclusion is made.

Summary

This study demonstrates that the genetic etiology for both internalizing and externalizing behaviors varied with maternal depressive symptoms at 9-months child age. Genetic effects on externalizing behaviors increased as mothers' depressive symptoms increased; however, genetics effects on internalizing behaviors increased when depressive symptoms either increased or decreased from the median level. These different patterns of interactive effects suggest potentially different mechanisms for the etiology of children's externalizing and internalizing behaviors.

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