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Parenting and adolescents' psychological adjustment: Longitudinal moderation by adolescents' genetic sensitivity

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Abstract

We examined whether adolescents' genetic sensitivity, measured by a polygenic index score, moderated the longitudinal associations between parenting and adolescents' psychological adjustment. The sample included 323 mothers, fathers, and adolescents (177 female, 146 male; Time 1 [T1] average age = 12.61 years, *SD* = 0.54 years; Time 2 [T2] average age = 13.59 years, *SD* = 0.59 years). Parents' warmth and hostility were rated by trained, independent observers using videotapes of family discussions. Adolescents reported their symptoms of anxiety, depressed mood, and hostility at T1 and T2. The results from autoregressive linear regression models showed that adolescents' genetic sensitivity moderated associations between observations of both mothers' and fathers' T1 parenting and adolescents' T2 composite maladjustment, depression, anxiety, and hostility. Compared to adolescents with low genetic sensitivity, adolescents with high genetic sensitivity had worse adjustment outcomes when parenting was low on warmth and high on hostility. When parenting was characterized by high warmth and low hostility, adolescents with high genetic sensitivity had better adjustment outcomes than their counterparts with low genetic sensitivity. The results support the differential susceptibility model and highlight the complex ways that genes and environment interact to influence development.

Rates of internalizing and externalizing problems increase across adolescence and have negative consequences for interpersonal relationships with friends and family, academic performance, and physical health (Thapar, Collishaw, Pine, & Thapar, 2012). Psychologists working from a variety of theoretical traditions concur that parenting quality influences adolescents' psychological adjustment such that warm, supportive, and otherwise sensitive parenting behaviors promote well-being, whereas hostile, angry, and coercive parenting behaviors appear to thwart it (e.g., Barber, Stolz, & Olsen, 2005; Maccoby, 2000; Patterson, DeBaryshe, & Ramsey, 1989). Another body of research has demonstrated that certain genetic characteristics also influence adolescents' psychological adjustment (for a review, see Plomin, DeFries, Knopf, & Neiderhiser, 2013). These perspectives have recently been brought together with the idea that genes moderate the influence of the environment on psychological adjustment (e.g., Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). In other words, genes and the quality of one's environment are both dynamically linked forces that interact to contribute to psychological well-being, that is, Gene × Environment (G × E) interaction. Based on this proposition, in the current study we examined whether adolescents' genetic sensitivity moderated the prospective associations between exposure to parental behaviors, ranging from high warmth and low hostility to low warmth and high hostility, and adolescents' psychological adjustment, including depressed mood, anxiety symptoms, and feelings of hostility (e.g., anger and irritability). To address these issues, we used longitudinal, multimethod data from a community sample of young adolescents and both of their biological parents.

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Adolescent Adjustment: G × E Research

Research has shown that an individual's genetic makeup can moderate the effect of parenting behavior on psychological adjustment (for reviews, see Caspi et al., 2010; Horowitz & Neiderhiser, 2011; Plomin et al., 2013). These findings were originally interpreted to support the diathesis–stress model, which hypothesizes that individuals carrying more *risk* alleles on certain *vulnerability* genes are more susceptible to environmental stressors (e.g., more depressive symptoms and higher

rates of antisocial behavior) compared to individuals without these genetic variants. More recently, this model has been refined and presented as a framework of differential susceptibility (Belsky & Pluess, 2009, 2013; Boyce & Ellis, 2005). The differential susceptibility framework hypothesizes that individuals carrying more risk or *plasticity* alleles on certain candidate genes are particularly sensitive to environmental influences regardless of valence such that they exhibit more positive outcomes in response to supportive environments and more negative outcomes in response to stressful environments. That is, according to the differential susceptibility hypothesis, risk alleles may be better characterized as plasticity or *sensitivity* alleles that moderate the effect of the environment on certain outcomes in a for-better *and* for-worse fashion (Belsky & Pluess, 2009, 2013).

Most existing G × E research involving adolescent adjustment has focused on genes from the dopaminergic system, involved in reward sensitivity and sensation seeking (e.g., Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Stice, Yokum, Burger, Epstein, & Smolen, 2012) and the serotonergic system, linked to sensitivity to punishment and displeasure (e.g., Caspi et al., 2010). Neuropsychological research has shown that variants in dopamine and serotonin genes expressed in the limbic system and particularly the amygdala were associated with increased emotional sensitivity to the environment. For instance, in a functional magnetic resonance imaging study, carriers of two short alleles (SS) in the serotonin transporter linked polymorphic region gene (*5-HTTLPR*) had heightened amygdala reactivity to emotionally salient stimuli compared to individuals carrying a short and a long allele (SL) or two long alleles (LL; Walsh et al., 2012). Similarly, individuals with short alleles had more difficulty disengaging from emotionally related stimuli than individual with long alleles (Beevers, Wells, Ellis, & McGeary, 2009). In another study, individuals with the A1 allele of the Taq 1 polymorphism of dopamine receptor D2 (*DRD2*) were more sensitive to reward than individuals without this allele (Lee, Ham, Cho, Lee, & Shim, 2007).

Some research has shown that variants of *5-HTTLPR* interact with environmental stressors to predict psychological adjustment in a manner consistent with the differential susceptibility model. For example, in a sample of young adults, Taylor et al. (2006) found that individuals with SS alleles reported greater depressive symptoms if they experienced early family adversity, such as physical or verbal abuse or observed aggression between other family members, or recent adversity assessed by a checklist of stressful life events in the past 6 months. In addition, compared to those with SL or LL genotypes, SS individuals had significantly fewer depressive symptoms if they reported supportive early family environments (e.g., physical affection, feeling cared for, and well-organized and well-managed households) or few recent stressful life events. In a study of adolescents, Li, Berk, and Lee (2013) reported that *5-HTTLPR* moderated the link between family support (e.g., parental closeness, communication, and feeling loved) and depressed mood and suicide ideation or attempts for boys, but not for girls. Specifically, among boys with poor family support, youth with at least one short allele had more symptoms of depression and higher scores on suicide ideation or attempts relative to boys with two long alleles; however, in the presence of high family support, boys with SS alleles had the fewest depression symptoms relative to SL and LL carriers.

Although research on G × E using single candidate genes has yielded useful information, results have been inconsistent and difficult to replicate (Duncan & Keller, 2011). This approach is giving way to a growing consensus that complex mental health outcomes have a significant polygenic component, in which genetic influences operate as a function of combined additive effects of a number of variants (Sullivan, Daly, & O'Donovan, 2012). Thus, some researchers are beginning to use additive scoring methods to account for cumulative genetic effects across a series of relevant candidate genes (see Belsky & Israel, 2014). Similar to other kinds of indices, several risk or protective factors are combined to create a single score of overall risk or protection (e.g., Evans, Li, & Whipple, 2013). Despite advantages of the polygenic index approach, its disadvantages include the possibility that the effect of one candidate gene variant could cancel out the effect of another. In addition, it may be more difficult to trace the underlying biological processes linking genotype to phenotype when variants from different candidate genes are combined.

Several recent studies have found support for the differential susceptibility hypothesis using cumulative genetic index scores, created by summing polymorphic variation across a set of candidate genes that, individually, have been shown to contribute small effects to outcomes of interest (e.g., *5-HTT* and depression; see Caspi et al., 2010). For example, Masarik et al. (2014) found that a cumulative genetic index made up of variants in five dopaminergic and serotonergic genes moderated the longitudinal link between individuals' exposure to parenting behaviors in adolescence and behavior toward a romantic partner in adulthood. Moreover, these results were consistent with the differential susceptibility hypothesis because individuals who had higher scores on the cumulative genetic index were (a) more likely to behave in a hostile fashion toward their romantic partner in adulthood if they were exposed to higher levels of parental hostility in adolescence and (b) more likely to behave in a positive, supportive, and engaging fashion toward their adult romantic partner if, during adolescence, they experienced similarly supportive behaviors from their parents. Similarly, Simons et al. (2012) found that a cumulative genetic index score comprising variants on the dopamine receptor D4 (*DRD4*) and the *5-HTT* gene interacted with a composite measure of a hostile/demoralizing social environment (e.g., harsh parenting, caregiver substance use, racial discrimination, and community crime) to predict aggression and delinquency in African American adolescents. Consistent with the differential susceptibility hypothesis, when the social environment was adverse, genetically sensitive adolescents were more aggressive than adolescents with low scores on genetic sensitivity, yet

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when social adversity was low, they were less aggressive than adolescents who were low on genetic sensitivity. In another study, Wickrama and O'Neal (2013) reported that adolescents who had high scores on a genetic index of plasticity had more depressive symptoms when their parents had disrupted marriages than adolescents with low genetic plasticity scores. Compared to their counterparts with low plasticity scores, adolescents with high plasticity scores had fewer depressive symptoms when parents had consistently stable marriages. Similarly, Dalton, Hammen, Naijman, and Brennan (2014) found that a cumulative plasticity score made up of alleles in two candidate genes (brain-derived neurotrophic factor [*BDNF*] Val66Met and *5-HTTLPR*) interacted with family environmental quality (combined score of marital, mother–child and father–child relationships) to predict adolescents' depressed mood at age 15 (but not at age 20 or 25), consistent with the differential susceptibility model. Finally, in a study by Belsky and Beaver (2011) that examined adolescents' emotional regulation, adolescents' cumulative genetic plasticity scores interacted with mothers' parenting to predict males', but not females', emotional regulation, also consistent with the differential susceptibility model. These studies provide support for the differential susceptibility hypothesis using cumulative genetic index scores of sensitivity. To date, however, research has not examined the moderating role of adolescents' polygenic sensitivity separately for mothers' and fathers' behavior and for both internalizing and externalizing problems. The current study is uniquely positioned to extend our understanding in this area.

The Present Study

The goal of the present study was to contribute to the emerging literature on genetic moderation of the environment on adolescent adjustment in a number of ways. First, most previous G × E research has relied heavily on a diathesis–stress perspective. The current study, in contrast, draws upon the differential susceptibility framework (Belsky & Pluess, 2009, 2013) to test the proposition that adolescents' polygenic sensitivity would moderate the impact of both positive and negative parenting on adolescents' adjustment. In other words, we examined whether adolescents hypothesized to be more genetically sensitive would have worse psychological adjustment if exposed to hostile, angry, and controlling parenting behaviors, but better adjustment (i.e., less depression, anxiety, and hostility) if exposed to warm, supportive, and nurturing parenting behaviors.

Second, rather than relying on one candidate gene, we added to a growing body of research that uses a cumulative genetic index score to represent the additive effect of variation in a set of candidate genes (see Belsky & Israel, 2014). Specifically, we examined genetic variation across four commonly studied dopaminergic and serotonergic candidate genes: (a) *5-HTT* gene (*5-HTT* has been linked to increased emotional sensitivity, Walsh et al., 2012); (b) ankyrin repeat and kinase domain containing 1 gene/*DRD2* gene (*ANKK1/DRD2*); (c) *DRD4* gene (*DRD2* and *DRD4* have been associated with impulsivity and reward sensitivity; Eisenberg et al., 2007; Lee, 2007; and drug and alcohol use; Brody et al., 2012); and (d) catechol-*O*-methyltransferase (*COMT*) gene (*COMT* has been linked to increased emotional sensitivity and hostile attribution bias; Gohier et al., 2014).

Third, most previous work on G × E involving parenting and adolescent adjustment outcomes has been cross-sectional or has relied on retrospective reports of earlier parenting (for reviews, see Duncan & Keller, 2011; Karg, Burmeister, Shedden, & Sen, 2011), leaving open the possibility of shared method variance and biased recall. In contrast, we used prospective, longitudinal data from multiple reporters. Fourth and finally, relatively little attention has been given to fathers' role in adolescent risk for emotional and behavioral problems in general (Phares, Fields, Kamboukos, & Lopez, 2005; Reeb & Conger, 2011), and we know of no studies that have examined polygenic sensitivity as a moderator of the links between fathers' parenting and adolescents' adjustment. To address this gap in the literature, the current study included independent observer ratings of both mothers' and fathers' parenting behaviors, and we tested whether effects for mothers and fathers differed.

In sum, using longitudinal, multimethod data from a community sample, the current study examined adolescent polygenic sensitivity as a moderator of the prospective associations between mothers' and fathers' parenting behaviors and adolescent adjustment. Consistent with the differential susceptibility hypothesis, we expected that adolescents with high levels of polygenic sensitivity would have (a) higher levels of depression, anxiety, and hostility when parenting behaviors were marked by high levels of hostility and low levels of warmth; and (b) lower levels of depression, anxiety, and hostility when parenting behaviors were characterized by low levels of hostility and high levels of warmth. In contrast, adjustment scores for adolescents with low levels of polygenic sensitivity would be relatively unrelated to levels of parental hostility and warmth.

Method

Participants

Data were derived from the first two waves of a prospective, longitudinal, and multi-informant study of family members living in the rural Midwest (see Conger & Conger, 2002). The ethnic/racial background is exclusively European American and White, reflecting the demographics of the region at study initiation. Starting in 1989, a seventh-grade "target" adolescent, a close-aged sibling, and their biological parents were visited in their homes by trained interviewers. At study initiation, a total of 451 families were eligible to participate. In the present report, we focus on a subsample of target participants with complete data on measures of adolescent polygenic sensitivity, parenting behaviors, and adolescent adjustment corresponding to the 1989 at Time 1 (T1) and 1990 at Time 2 (T2) assessments ($N = 323$: female $n = 177$; male

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$n = 146$). The average age of targets in this subsample was 12.61 ($SD = 0.54$) and 13.59 ($SD = 0.59$) years at T1 and T2, respectively. The average age of mothers was 37.98 ($SD = 4.13$) and 38.94 ($SD = 4.10$) at T1 and T2, respectively, and the average age of fathers was 39.87 ($SD = 5.00$) and 40.89 ($SD = 4.89$) at T1 and T2, respectively.

Procedure

Target adolescents were initially recruited from 34 public and private schools from eight counties in central Iowa in 1989. In brief, names and addresses of seventh-grade students and their parents were collected from schools in communities of 6,500 or fewer people. Letters were sent to families explaining the project, and families were later contacted by telephone and asked to participate. Families without telephones were contacted in person. Seventy-eight percent of the families eligible for the study agreed to participate ($N = 451$).

Trained interviewers visited each family at home at T1 and T2 and conducted the assessments, which lasted for approximately 2 hr on each of two occasions. During the first visit, each family member completed a set of questionnaires that focused on individual family member characteristics and experiences, quality of family interactions, and family economic circumstances. During the second visit, which usually occurred within 2 weeks of the first visit, family members were videotaped as they participated in semistructured interaction tasks designed to stimulate family interaction and elicit information about social skills and emotional responses. We assessed the quality of parenting behaviors toward the target adolescent from the 30-min family discussion task. Family members discussed questions about family life such as important family events, approaches to parenting, and household chores.

Measures

Parenting quality. Observers rated verbal and nonverbal behavior by the mother and father to the target adolescent at T1 using the Iowa Family Interaction Rating Scales (Melby & Conger, 2001). Before rating any of the videotaped interactions, observers received 200 hr of training and passed extensive written and viewing reliability tests. Once reliability was established, all observers attended at least two training sessions each week to ensure continued reliability. Approximately 20% of the videotaped interaction tasks were randomly assigned for rating by a second, independent observer. The primary and secondary ratings were then used to generate estimates of interobserver reliability using intraclass correlation coefficient (ICC) procedures (see Choukalas, Melby, & Lorenz, 2000). The Iowa Family Interaction Rating Scales have been utilized in a variety of cross-sectional and longitudinal studies examining diverse topics such as economic stress, parenting, adolescent development, and romantic relationships, and have acceptable reliability and validity (Melby & Conger, 2001).

Several behavioral codes were used to measure the quality of mothers' and fathers' parenting behavior toward the target adolescent at T1. Each behavior was rated on a scale from 1 (*the behavior is not at all characteristic*) to 9 (*the behavior is highly characteristic*). Mother and father hostility, angry coercion, and antisocial behavior were left in their original scoring format whereas warmth/support, listener responsiveness, positive assertiveness, positive communication, and prosocial behavior were reverse scored. Thus, high scores on parenting quality represent more hostility and less warmth by parents toward their adolescent child; likewise, low scores on parenting quality represent less hostility and more warmth by parents toward their adolescent child. These eight behavioral codes were averaged together separately for mothers (coefficient $\alpha = 0.86$; interobserver ICC = 0.92) and fathers (coefficient $\alpha = 0.86$; interobserver ICC = 0.93). As shown in Table 1, the average parenting quality score for mothers was 3.25 ($SD = 1.40$) and 3.63 ($SD = 1.19$) for fathers.

Adolescent adjustment. Symptoms of adolescent depression, anxiety, and hostility were assessed using the self-reported Symptom Checklist-90—Revised subscales, which have demonstrated reliability and validity (Derogatis, 1983). At T1 and T2, adolescents indicated the degree of discomfort regarding adjustment problems on a scale of 0 (*not at all*) to 4 (*extremely*) during the past week. The 13-item depression subscale had adequate reliability ($\alpha = 0.87$ at T1, $\alpha = 0.85$ at T2), as did the 10-item anxiety subscale ($\alpha = 0.82$ at T1, $\alpha = 0.83$ at T2), and the 6-item hostility subscale ($\alpha = 0.82$ at T1, $\alpha = 0.77$ at T2). Example items include "feeling blue" and "low in energy or slowed down" (depression); "nervousness or shakiness inside" and "feeling tense or keyed up" (anxiety); and "temper outbursts you cannot control" and "having urges to beat, injure, or harm someone" (hostility). Items corresponding to each subscale were averaged together to reflect symptoms of depression, anxiety, and hostility at T1 and T2 (see Table 1 for descriptive statistics).

Polygenic sensitivity. The polygenic sensitivity index is based on genotyping of saliva samples that were obtained from target participants in later waves of assessment (2007–2010) with Oragene™ (DNA Genotek, Ontario, Canada) collection kits. DNA was isolated with DNAdvance™ DNA Isolation Kits (Beckman Coulter, Brea, CA) using a Beckman-Coulter Biomek® FX workstation according to company protocols. Methods for genotyping are outlined in Haberstick et al. (2014). The Taq1A polymorphism has previously been studied in association with *DRD2*, but it has been suggested that *ANKK1* (downstream from *DRD2*) may be responsible for some of the effects attributed to *DRD2* (see Neville, Johnstone, & Walton, 2004); thus, we refer to this genotype as *ANKK1/DRD2*.

Based on past research (e.g., Belsky & Pluess, 2009, 2013), we consider the following alleles to confer sensitivity: short allele of *5-HTTLPR* in *5-HTT* (accounting for single nucleotide polymorphism rs25531); A1 allele of the Taq1A

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Table 1. *Correlations among study variables with descriptive statistics*

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Time 1: Predictors																	
1. Adolescent depression	—																
2. Adolescent anxiety	**.78**	—															
3. Adolescent hostility	**.67**	**.69**	—														
4. Adolescent composite maladjustment	**.90**	**.90**	**.89**	—													
5. Maternal parenting quality	.07	.09	.13	.11	—												
6. Paternal parenting quality	.08	.10	.15	.13	**.47**	—											
7. Average parenting quality	.09	.11	.16	.14	**.88**	**.83**	—										
8. Adolescent polygenic sensitivity	−.02	.01	−.02	−.01	.02	.02	.02	—									
9. Adolescent sex (male)	−.13	.02	.07	−.01	.01	−.01	−.00	.05	—								
Time 1: Family SES																	
10. Maternal education	−.04	−.03	−.08	−.06	−.15	**−.19**	**−.19**	.02	.04	—							
11. Paternal education	−.04	−.11	−.08	−.08	−.09	**−.25**	**−.19**	−.10	−.05	**.44**	—						
12. Average parent education	−.05	−.09	−.09	−.08	−.13	**−.26**	**−.23**	−.06	−.01	**.79**	**.90**	—					
13. Family income to needs ratio	.02	.02	−.03	.00	−.14	−.15	−.16	.05	−.01	**.32**	**.25**	**.33**	—				
Time 2: Outcomes																	
14. Adolescent depression	**.53**	**.45**	**.36**	**.49**	.11	.05	.09	.04	**−.18**	−.02	.03	.01	.02	—			
15. Adolescent anxiety	**.42**	**.44**	**.37**	**.45**	.13	.07	.12	.00	−.04	−.10	−.08	−.11	−.03	**.70**	—		
16. Adolescent hostility	**.38**	**.44**	**.51**	**.50**	.13	.10	.13	−.00	.02	.03	−.00	.01	.02	**.62**	**.64**	—	
17. Adolescent composite maladjustment	**.50**	**.51**	**.48**	**.55**	.14	.08	.13	.01	−.07	−.03	−.02	−.03	.00	**.88**	**.88**	**.87**	—
M	0.63	0.51	0.61	0.58	3.25	3.63	3.44	2.91	0.45	13.27	13.62	13.44	2.93	0.47	0.39	0.48	0.44
SD	0.61	0.53	0.68	0.54	1.40	1.19	1.11	1.21	0.50	1.63	2.23	1.65	2.18	0.48	0.48	0.54	0.44
Minimum	0.00	0.00	0.00	0.00	1.00	1.20	1.10	0	0	9	8	10	−3.95	0.00	0.00	0.00	0.00
Maximum	3.33	2.60	4.00	2.90	7.80	7.93	6.70	6	1	18	20	19	19.03	2.50	3.50	3.33	2.66

Note: $N = 323$. Adolescent composite maladjustment was the average of adolescent depression, anxiety, and hostility. Average parent education was the average of maternal and paternal years of education. Average parenting quality was the average of maternal and paternal parenting quality. Bold coefficients are significant at $p < .001$; underscored coefficients are significant at $p < .05$.

polymorphism (rs1800497) in *ANKK1/DRD2*; seven-repeat allele of exon-3 variable number tandem repeat in *DRD4*; and the methionine allele of the Val158Met polymorphism (rs4680) in *COMT*. Each polymorphism received a score of "0" if no sensitivity allele was observed, a score of "1" if one of these alleles was observed, and "2" if two of these alleles were observed. Finally, these scores were summed to create an index of polygenic sensitivity that ranged from 0 to 6 in our sample ($M = 2.91$, $SD = 1.21$). Please see Appendix A for information on a new statistical approach we used to test whether linear or nonlinear (e.g., dominant/recessive) scoring of candidate genes and simple summing of the genes was most appropriate for creating the polygenic index score. Based on examination of duplicate controls and Mendelian inconsistencies among family members, genotype error rates were less than 1% for all four polymorphisms; and allele and expected genotype distributions were in Hardy–Weinberg equilibrium. Moreover, the allele frequencies were consistent with other Caucasian populations (see http://alfred.med.yale.edu; Rajeevan, Soundararajan, Kidd, Pakstis, & Kidd, 2012).

Control variables. Adolescents' sex, mothers' and fathers' education, and family income to needs ratio were included as controls in our tests of study hypotheses because these variables have been shown to correlate with parenting quality and adolescent adjustment (Berg-Nielsen, Vikan, & Dahl, 2002; Conger, Conger, & Martin, 2010; Kessler et al., 2005; Nolen-Hoeksea & Hilt, 2009). Adolescents' sex was dummy coded 1 = *male* and 0 = *female*. Mothers' and fathers' education at T1 was measured as the number of years of education completed, which ranged in our sample from 8 to 20 years (PhD or other professional degree). The income to needs ratio was created using guidelines from the US Department of Health and Human Services and indicates family income relative to the poverty line for a family of a particular size. For example, a score of 1.0 indicates the family is at the poverty line, and a score of 2.0 indicates the family income is two times higher than the poverty line. At T1, total family income, including all wages, salaries, and other sources of income (e.g., self-employment income, farm net income, and supplemental security income), was divided by the US Department of Health and Human Services poverty guideline (for 1989) for a family of a given size to create the income to needs ratio.

Statistical analyses

Following preliminary descriptive and correlational analyses, predictors of adolescent adjustment outcomes (Symptom Checklist-90—Revised depression, anxiety, and hostility scales) were examined using linear regression models in IBM SPSS Statistics Software 22 (Chicago). To account for the temporal order of causality, we used an autoregressive approach (see Cohen, Cohen, West, & Aiken, 2003) to model change in adolescent depressive, anxiety, and hostility symptoms from T1 to T2. In addition to baseline adolescent symptoms, all regression analyses controlled for sociodemographic variables, including adolescent sex, parent educational attainment, and family income to needs ratio.

A moderated multiple regression framework (Aiken & West, 1991) was used to model the multiplicative interactions between parenting quality[1] and adolescent cumulative genetic sensitivity as predictors of adolescent adjustment over time. In our statistical models ($y_i = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i} + \varepsilon_i$), the outcome variable y_i (T2 adolescent adjustment) was examined as a function of independent variables in the model (X_1 = parenting quality, X_2 = adolescent polygenic sensitivity) and the moderating effects indicated by the interaction ($X_3 = X_1 \times X_2$). To assist in the interpretation of moderation effects and reduce multicollinearity between product terms, continuous independent variables (with the exception of polygenic sensitivity), were grand mean centered prior to conducting moderation analyses. Models were estimated by entering the main effects of all study variables simultaneously in the first step and adding the two-way G × E between parenting quality and genetic sensitivity in the second step. The R^2 was examined in each step, and tests of the change in explained variance, or ΔR^2, were used to assess the significance of moderation effects (Cohen et al., 2003).

The interpretation and post hoc testing of significant interaction effects followed methods outlined in Cohen et al. (2003), such that significant moderating effects were examined by graphically plotting and calculating the simple slopes of parenting at each level of the polygenic sensitivity score observed in our sample.

We also conducted formal tests to compare the fit of the weak and strong differential susceptibility models and the weak and strong diathesis–stress models using procedures developed by Widaman et al. (2012) and Belsky, Pluess, and Widaman (2013). Finally, we conducted a series of supplementary analyses to investigate potential bias arising from failure to include moderating effects of covariates in our primary analyses.

Results

Preliminary analyses

Descriptive statistics and bivariate correlations among all study variables are presented in Table 1. As expected, adolescent depressive symptoms, anxiety symptoms, and hostility scores were significantly and highly correlated at T1 (rs = .67 to .78, all ps < .001) and at T2 (rs = .62 to .70, all ps < .001), and these psychological adjustment scores showed moderate levels of stability from T1 to T2 (rs = .36

1. As explained in greater detail in the Results section, we first fit regression models that included maternal parenting behaviors and paternal parenting behaviors as two separate predictors of adolescent adjustment. In our final models, however, we averaged maternal and paternal parenting behaviors together to represent an overall quality of parenting variable because the effect of parenting on adolescent adjustment did not differ significantly as a function of parent (i.e., mother vs. father).

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to .53, all *p*s < .001). Adolescents' sex (1 = *male*, 0 = *female*) was statistically negatively correlated with depressive symptoms, indicating that males reported fewer depressive symptoms than females. Measures of parental education and family income to needs ratio were negatively correlated with indices of parenting quality (*r*s = –.09 to –.26, with all but one $p < .05$), indicating that higher levels of education and income were associated with higher levels of warmth and lower levels of parental hostility toward the target adolescent.

In accordance with guidelines for testing gene–environment interactions (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007), correlational analyses revealed no significant bivariate associations between adolescent polygenic sensitivity scores and parenting quality for mothers ($r = .02, p = .83$) or fathers ($r = .02, p = .92$), suggesting that evocative effects of genetic sensitivity on parenting did not account for the observed findings. Furthermore, polygenic sensitivity did not correlate significantly with any of the variables in the study, as shown in Table 1 (*r*s = –.10 to +.05, all *p*s > .05).

Predicting adolescent adjustment

As noted in Table 1, adolescent depressive symptoms, anxiety symptoms, and hostility scores were significantly and highly correlated at T1 (*r*s = .67 to .78, all *p*s < .001) and T2 (*r*s = .62 to .70, all *p*s < .001), suggesting that adolescent depression, anxiety, and hostility symptoms tend to be comorbid. These three individual outcomes may collectively represent an overall dimension of adolescent maladjustment. Therefore, we created a measure of "composite maladjustment" by computing the average of adolescent depression, anxiety, and hostility at T1 and at T2; however, we also conducted regression models separately for each of the three outcomes to ensure that the composite score of maladjustment did not mask findings for any of the three components that went into the composite. In the following sections, we first report findings from models using the composite score of adolescent maladjustment, and then report findings for the separate depression, anxiety, and hostility models.

Adolescent composite maladjustment. The first regression model we fit to predict adolescent composite maladjustment at T2 (i.e., the average of depressive symptoms, anxiety symptoms, and hostility scores) had eight predictors: maternal and paternal education, family income to needs ratio, adolescent sex, adolescent composite maladjustment at T1, maternal and paternal parenting quality, and adolescent polygenic sensitivity. This initial model had strong fit to the data, $R^2 = .315, F(8, 314) = 18.07, p < .0001$. Both for theoretical reasons and because maternal and paternal parenting quality were highly correlated ($r = .47$) as were maternal and paternal education ($r = .44$), we hypothesized that maternal and paternal parenting quality would predict adolescent adjustment similarly and that maternal and paternal education would also have similar effects on adolescent adjustment; thus, we constrained these pairs of regression weights to invariance across parents. This constrained main effects model had strong fit to the data, as shown in the first column of Table 2, with $R^2 = .312, F(6, 316) = 22.45, p < .0001$. It is important that the change in R^2, $\Delta R^2 = .003$, was nonsignificant, $F(2, 314) = 0.76$, *ns*, supporting our hypothesis that neither maternal and paternal education nor maternal and paternal parenting differed in their effects on child composite maladjustment.

When we added the Parenting Quality × Adolescent Polygenic Sensitivity interaction to this model, the explained variance increased to $R^2 = .334$, and the increase in explained variance was significant, $\Delta R^2 = .022, F(1, 315) = 4.88, p = .03$. To test whether maternal and paternal education had different effects and whether the main and interactive effects of maternal and paternal parenting quality had differential effects on adolescent composite maladjustment, we relaxed the equality constraints on these three pairs of coefficients. With the constraints relaxed, the increase in explained variance was nonsignificant, $\Delta R^2 = .006, F(3, 312) = 0.90$, *ns*, supporting the constrained model as the optimal model for the data.

Parameter estimates for the constrained model are shown in the leftmost data columns in Table 2, which shows that prior levels of composite maladjustment (T1) had a significant effect on later composite maladjustment (T2; $B = 0.44$, $SE = 0.04$), $t(315) = 11.73, p < .001$. The results also showed that parenting quality had a significant main effect ($B = –0.11$, $SE = 0.05$), $t(315) = –2.39, p = .02$. The Parenting Quality × Polygenic Sensitivity interaction was significant and in the predicted direction ($B = 0.05$, $SE = 0.01$), $t(315) = 3.21, p = .0015$. No other effects, which reflect the effects of predictors for persons at the sample mean, were significant at $p < .05$.

As shown in Figure 1, simple slopes derived from the model for adolescent composite maladjustment were plotted for all levels of adolescent polygenetic sensitivity observed in our sample. The slope for polygenic sensitivity score of 0 was negative and statistically significant ($B = –0.11$, $SE = 0.05, p = .02$). This statistically significant, inverse relation of parenting quality with composite maladjustment is difficult to explain and awaits replication in independent samples. The slopes for gene index scores from 1 to 3 were nonsignificant, ranging from a nonsignificant $B = –0.06$ ($SE = 0.04$, $p = .06$) for index value of 1 to a $B = +0.03$ ($SE = 0.02, p = .13$) for an index value of 3. The slopes for genetic index values of 4 ($B = 0.08$, $SE = 0.03$, $p = .002$), 5 ($B = 0.12$, $SE = 0.04$, $p = .0007$), and 6 ($B = 0.17$, $SE = 0.05$, $p = .0006$) were all significant. These significant slopes were generally consistent with the for-better or for-worse pattern predicted by differential susceptibility theory. That is, for adolescents high on genetic sensitivity, the combination of high parental hostility and low parental warmth was associated with higher than average levels of composite maladjustment, whereas the combination of low parental hostility and high parental warmth was associated with lower than average levels of composite maladjustment.

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Table 2. *Gene × Environment interactions of adolescent polygenic sensitivity and parenting quality predicting change in adolescent adjustment at Time 2*

	Composite Maladjustment		Depression		Anxiety		Hostility	
	Time 2		Time 2		Time 2		Time 2	
Predictors	*B* (*SE*)	β	*B* (*SE*)	β	*B* (*SE*)	β	*B* (*SE*)	β
Main effects								
Intercept	0.45 (0.06)	—	0.46 (0.06)	—	0.42 (0.06)	—	0.48 (0.07)	—
Average parent education[a]	0.01 (0.01)	0.04	0.02 (0.01)	0.06	−0.01 (0.01)	−0.05	0.02 (0.02)	0.07
Family income to needs ratio[a]	0.00 (0.01)	0.01	0.00 (0.01)	0.00	−0.00 (0.01)	−0.00	0.01 (0.01)	0.04
Adolescent sex (male)	−0.07 (0.04)	−0.08	–0.13 (0.05)	–0.13	−0.06 (0.05)	−0.06	−0.03 (0.05)	−0.03
Adolescent Time 1 symptoms[a,b]	**0.44** (0.04)	**0.55**	**0.40** (0.04)	**0.51**	**0.39** (0.05)	**0.43**	**0.41** (0.04)	**0.51**
Average parenting quality[a]	–0.11 (0.05)	–0.28	−0.08 (0.05)	−0.19	−0.10 (0.05)	−0.23	–0.15 (0.06)	–0.30
Adolescent polygenic sensitivity	0.01 (0.02)	0.02	0.02 (0.02)	0.06	−0.00 (0.02)	−0.01	0.00 (0.02)	0.00
R^2	.312		.299		.205		.268	
Interaction effects								
Parenting × Polygenic Sensitivity	0.05 (0.01)	0.38	0.04 (0.02)	0.27	0.04 (0.02)	0.31	**0.06** (0.02)	0.**41**
R^2	.334		.310		.219		.293	
ΔR^2	.022		.011		.015		**.025**	

Note: $N = 323$.
[a]Predictor was sample mean centered for analyses to enhance interpretability of parameter estimates. Composite maladjustment was the average of adolescent depression, anxiety, and hostility.
[b]Adolescent Time 1 symptoms correspond with Time 2 symptoms in each regression model (e.g., composite maladjustment at Time 1 predicted composite maladjustment at Time 2, depression at Time 1 predicted depression at Time 2). Average parent education was the average of maternal and paternal years of education. Average parenting quality was the average of maternal and paternal parenting quality. The ΔR^2 value for the Parenting × Polygenic Sensitivity interaction predicting composite maladjustment was significant at $p < .002$. The ΔR^2 value for the Parenting × Polygenic Sensitivity interaction predicting depression and anxiety were significant at $p < .05$. The ΔR^2 value for the Parenting × Polygenic Sensitivity interaction predicting hostility was significant at $p < .001$. Bold coefficients are significant at $p < .001$, and underscored coefficients are significant at $p < .05$.

Depressive symptoms. As with composite maladjustment, the initial model for depression had strong fit to the data, $R^2 = .303$, $F(8, 314) = 17.06$, $p < .0001$, and constraining effects of maternal and paternal education and maternal and paternal parenting to equality did not affect model fit significantly, $\Delta R^2 = .004$, $F(2, 314) = 1.01$, *ns*. The resulting main effects model had strong fit to the data, as shown in Table 2, with $R^2 = .299$, $F(6, 316) = 22.45$, $p < .0001$. When we added the Parenting Quality × Adolescent Polygenic Sensitivity interaction to this model, explained variance increased to $R^2 = .310$, and the increase in explained variance was significant, $\Delta R^2 = .011$, $F(1, 315) = 4.88$, $p = .03$. Follow-up tests indicated that the interactive effects of maternal and paternal parenting did not differ significantly, $F(1, 314) > 1$, *ns*.

Parameter estimates for the constrained model are presented in Table 2, which shows that male adolescents had significantly lower levels of depression than females ($B = –0.13$, $SE = 0.05$), $t(315) = –2.74$, $p = .007$, and that prior levels of depressive symptoms had a significant effect on later depressive symptoms ($B = 0.40$, $SE = 0.04$), $t(315) = 10.76$, $p < .001$. The Parenting Quality × Polygenic Sensitivity interaction was significant and in the predicted direction ($B = 0.04$, $SE = 0.02$), $t(315) = 2.21$, $p = .03$. No other effects, which reflect the effects of predictors for persons at the sample mean, were significant at $p < .05$.

Simple slopes derived from the model for adolescent depression are not presented here due to space constraints. The plot of simple slopes was very similar to the pattern shown in Figure 1 and is available upon request. The slopes for gene index scores from 0 to 3 were nonsignificant, ranging from a nonsignificant $B = –0.08$ ($SE = 0.05$, $p = .12$) for index value of 0 to $B = +0.03$ ($SE = 0.02$, $p = .20$) for an index value of 3. The slopes for genetic index values of 4 ($B = 0.06$, $SE = 0.03$, $p = .02$), 5 ($B = 0.10$, $SE = 0.04$, $p = .01$), and 6 ($B = 0.14$, $SE = 0.05$, $p = .01$) were all significant. Again, the significant slopes were consistent with the for better or for worse pattern predicted by differential susceptibility theory.

Anxiety symptoms. For the analysis of adolescents' anxiety symptoms, we followed the same model testing steps that

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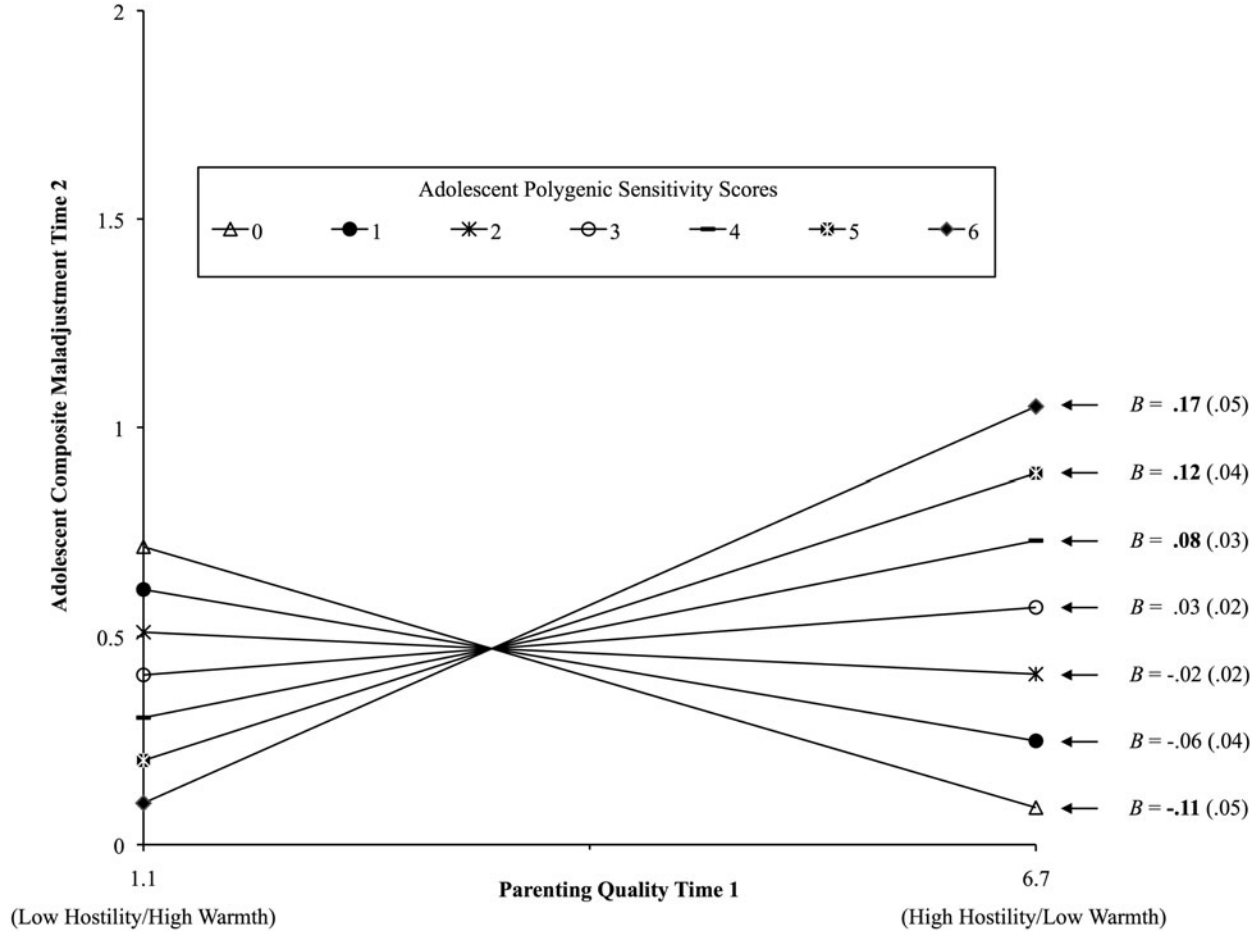

Figure 1. Adolescents' polygenic sensitivity interacted with parenting quality at Time 1 to predict adolescent composite maladjustment at Time 2, controlling for adolescent composite maladjustment at Time 1, average parental education, family income to needs ratio, and adolescent sex. Composite maladjustment was the average of adolescent depression, anxiety, and hostility; *B* is the unstandardized simple slope estimates for each score on the polygenic sensitivity index (standard errors). Bold if statistically significant ($p < .05$).

we used for composite maladjustment and depressive symptoms. For anxiety symptoms, the initial model had good fit to the data, $R^2 = .211$, F (8, 314) = 10.50, $p < .0001$, and constraining effects of maternal and paternal education and maternal and paternal parenting to equality did not affect model fit significantly, $\Delta R^2 = .006$, F (2, 314) = 1.31, *ns*. The resulting constrained model (with maternal and paternal parenting quality and maternal and paternal education constrained to invariance) had good fit to the data, with $R^2 = .205$, F (6, 316) = 13.55, $p < .0001$. Adding the constrained Parenting Quality × Adolescent Polygenic Sensitivity interaction to this model increased explained variance to $R^2 = .219$, and the increase in explained variance was significant, $\Delta R^2 = .015$, F (1, 315) = 5.93, $p = .02$. As in previous analyses, relaxing equality constraints on maternal and paternal predictors led to a nonsignificant increase in explained variance, $\Delta R^2 = .008$, F (3, 312) = 1.04, *ns*, supporting the constrained model as the optimal model for the data.

Parameter estimates for the constrained model are presented in Table 2, and show that prior level of anxiety symptoms had a significant effect on later anxiety symptoms ($B = 0.39$, $SE = 0.05$), t (315) = 8.55, $p < .001$. The Parenting Quality × Polygenic Sensitivity interaction was significant and in the predicted direction ($B = 0.04$, $SE = 0.02$), t (315) = 2.44, $p = .02$. No other effects were significant at $p < .05$.

The plot of simple slopes derived from the adolescent anxiety model is not shown here, but was very similar to that presented in Figure 1 and is available upon request. Similar to depression, the slopes for polygenic sensitivity index scores from 0 to 3 were nonsignificant, ranging from a nonsignificant $B = –0.10$ ($SE = 0.05$, $p = .08$) for index value of 0 to $B = +0.03$ ($SE = 0.02$, $p = .20$) for an index value of 3. The slopes for polygenetic index values of 4 ($B = 0.07$, $SE = 0.03$, $p = .02$), 5 ($B = 0.11$, $SE = 0.04$, $p = .01$), and 6 ($B = 0.15$, $SE = 0.06$, $p = .01$) were all statistically significant. The statistically significant slopes were again consistent with predictions under differential susceptibility.

Hostility. Analyses of adolescent hostility took the same form as analyses for composite maladjustment, depression, and

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anxiety. The initial model had good fit to the data, $R^2 = .272$, F (8, 314) = 14.66, $p < .0001$, and constraining effects of maternal and paternal education and maternal and paternal parenting to equality did not affect model fit significantly, $\Delta R^2 = .004$, F (2, 314) = 0.71, *ns*. The resulting constrained model (with mothers' and fathers' education constrained to equality and mothers' and fathers' parenting constrained to equality) had good fit to the data, with $R^2 = .268$, F (6, 316) = 19.33, $p < .0001$. Adding the constrained Parenting Quality × Adolescent Polygenic Sensitivity interaction to this model increased explained variance to $R^2 = .293$, and the increase in explained variance was significant, $\Delta R^2 = .025$, F (1, 315) = 11.05, $p = .001$. As with previous analyses, relaxing the invariance constraints (a) from maternal and paternal education to adolescent hostility, (b) from maternal and paternal parenting quality to adolescent hostility, and (c) from the interaction effect of maternal and paternal parenting quality by the polygenic index to adolescent hostility led to a nonsignificant increase in explained variance, $\Delta R^2 = .005$, F (3, 312) = 0.73, *ns*, supporting the constrained model as the optimal model for the data.

Parameter estimates for the constrained model are presented in Table 2, which shows that prior level of hostility had a significant effect on later hostility ($B = 0.41$, $SE = 0.04$), t (315) = 10.60, $p < .001$. The results also showed that parenting quality had a significant main effect ($B = –0.15$, $SE = 0.06$), t (315) = –2.48, $p = .01$. The Parenting Quality × Polygenic Sensitivity interaction was significant and in the predicted direction ($B = 0.06$, $SE = 0.02$), t (315) = 3.22, $p = .001$. No other effects were significant at $p < .05$.

The plot of simple slopes derived from the adolescent hostility model is not shown here, but was very similar to that presented in Figure 1 and is available upon request. Contrasting with results for depressive and anxiety symptoms, the slopes for polygenic sensitivity scores of 0 and 1 were statistically significant, $B = –0.15$ ($SE = 0.06$, $p = .01$), and $B = –0.09$ ($SE = 0.04$, $p = .05$), respectively. These statistically significant, inverse relations of parenting quality with the hostility outcome are difficult to explain and await replication in independent samples. Slopes for polygenic sensitivity values of 2 and 3 were nonsignificant. Finally, the slopes for polygenic sensitivity values of 4 ($B = 0.10$, $SE = 0.03$, $p = .002$), 5 ($B = 0.16$, $SE = 0.05$, $p < .001$), and 6 ($B = 0.22$, $SE = 0.06$, $p < .001$) were all statistically significant. These statistically significant slopes for adolescents high on polygenic sensitivity were once again generally consistent with predictions under differential susceptibility.

Comparative fitting of differential susceptibility and diathesis–stress models

As a final step in our main analyses, we tested whether differential susceptibility or diathesis–stress models fit the data better. We used the model comparison methods outlined by Widaman et al. (2012; see also Belsky et al., 2013) to determine whether the data fit best with weak or strong versions of the differential susceptibility model or with weak or strong versions of the diathesis–stress model. In brief, the weak differential susceptibility model has the same number of parameter estimates and the same fit to data as the regression models shown in Table 2. The remaining models (strong differential susceptibility and the weak and strong diathesis–stress models) are restricted models, placing theoretical constraints on parameters originally estimated in the weak differential susceptibility model.

When we fit the competing models to our data, only the weak differential susceptibility model exhibited acceptable fit to the data. When any of the more restricted models were fit to the data, parameter estimates had poor properties, including large standard errors; moreover, model fit to data was worse. Thus, the weak differential susceptibility model appeared to be most optimal for all four adolescent outcomes (composite maladjustment, depression, anxiety, and hostility: see Table 2).

One benefit of the Widaman et al. (2012) method of model fitting is that point and interval estimates of the crossover point in the G×E can be obtained. As shown in Table 1, average parenting quality had a sample $M = 3.44$, $SD = 1.11$, and ranged from 1.10 to 6.70. According to the diathesis–stress model, the crossover point should be at (or near) the most positive point on the environmental predictor, parenting (i.e., near 1.0), whereas the differential susceptibility model predicts a crossover point near the middle of the parenting distribution. The results for adolescent composite maladjustment revealed that the crossover point fell very close to the sample mean, with point estimate of 3.41 ($SE = 0.35$), and an interval estimate, 95% confidence interval (CI) [2.73, 4.09], that fell well within the range of scores observed in our sample, providing clear support for differential susceptibility.

For the separate outcomes, adolescents' depressive symptoms had a crossover point that was a little over 0.5 *SD* below the sample mean, 2.80 ($SE = 0.60$), and an interval estimate, 95% CI [1.62, 3.99], that fell completely within the range of observed scores. For adolescents' anxiety symptoms, the point estimate, 3.53 ($SE = 0.47$), fell very close to the sample mean, and the interval estimate, 95% CI [2.60, 4.45], was fairly narrow. The results for hostility were similar to those for anxiety, with a point estimate of 3.41 ($SE = 0.35$) that was very close to the sample mean and an interval estimate, 95% CI [2.74, 4.09], that was well within the range of the data. These collective results provide clear support for predictions under the differential susceptibility model relative to the diathesis–stress model.

Supplementary analyses

Potential moderation by other covariates. As noted by Keller (2014), researchers may incorrectly attribute significance to interactive effects of genes and environmental factors (e.g., based on significant G × E effects) in cases in which the true underlying effect is the result of interactions of genes with other covariates. This possibility led us to consider other potential covariate interactions in our statistical models. We did so because the environmental factor we investigated (par-

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enting quality) was correlated, albeit at relatively low levels, with the covariates of parent education and family income to needs ratio, as shown in Table 1.

To investigate this issue of interpretational confounding between predictors and covariates of interest, we considered first parental education, fitting a series of models with the three two-way interactions among parental education, parenting quality, and adolescent polygenic sensitivity, and the three-way interaction of these effects. Across the four adolescent outcome variables (composite maladjustment and the separate depression, anxiety, and hostility outcomes), none of the two-way interactions were statistically significant, and the three-way interactions had F values below 1.0. Only one two-way interaction neared statistical significance: the Parent Education × Parenting Quality effect on hostility, F (1, 313) = 3.13, p = .07. It is important to note that in this equation, the hypothesized G × E (Polygenic Index × Parenting Quality) was still significant, F (1, 313) = 14.32, $p < .0001$.

Next, we turned to family economic circumstances, and fit models with the three two-way interactions among family income to needs ratio, parenting quality, and adolescent polygenic sensitivity, and the three-way interaction of these effects. Across the four outcome variables, none of the two-way interactions was statistically significant, and the three-way interactions had nonsignificant F values below 1.0. Only one two-way interaction neared significance: the Income to Needs Ratio × Polygenic Sensitivity effect on hostility, F (1, 313) = 3.45, p = .06; however, in this equation, the hypothesized G × E (Polygenic Index × Parenting Quality) remained significant, F (1, 313) = 14.01, $p < .0001$.

Finally, we examined effects associated with adolescents' sex to determine if the moderating effect of adolescent polygenic sensitivity might operate differently for boys and girls. Here, we tested a series of models with the three two-way interactions among parenting quality, adolescent polygenic sensitivity, and sex, and the three-way interaction of these factors, controlling for symptoms at T1, parent education, and family income to needs ratio. None of the two-way interactions involving adolescent sex nor the three-way interactions were statistically significant for any of the four outcome variables (all Fs < 1.0); thus, there was no evidence that the patterns of G × E results for composite maladjustment, depression, anxiety, and hostility differed by adolescent sex. In sum, we could find no evidence that failure to include interactive effects of covariates in our models led to positive bias in the estimation of G × E interactive effects of parenting quality and adolescent genetic sensitivity.

Testing differences among genetic markers. Difficulties with interpretation can arise when an additive, linear polygenic index score is used in analyses of G × E. For instance, it is possible that the effect of one genetic marker in a candidate gene (i.e., allele) may counteract the effect of another, or the results obtained using the polygenic index can be driven by effects of only one or two genetic markers, masking the lack of effect of the remaining ones. Furthermore, we summed allelic scores across four candidate genes (*5-HTT, DRD2, DRD4*, and *COMT*), each of which was scored assuming linear gene action for the allele of interest. That is, when no "risk" or "susceptibility" allele was present, participants received a score of 0, a score of 1 when one risk/susceptibility allele was present, and a score of 2 when two risk/susceptibility alleles were present. If, in reality, a given genetic marker had a nonlinear (e.g., dominant/recessive) effect, using this type of linear scoring method could possibly mask the true underlying genetic effect on the phenotype.

For the reasons just stated, we devised a new analytic approach to test for departures from linearity for each genetic marker on the candidate genes and for differential effects of each candidate gene. The method is explained in Appendix A, along with results of model comparisons testing nonlinearity of effects and differential effects for the candidate genes. As shown in Table A.1 in Appendix A, we found no evidence for nonlinearity of effects in each of the four genetic markers nor did we find evidence that certain candidate genes influenced the adolescent outcomes differently. These results support our use of an additive, linear summation of the genetic markers in our polygenic index as reported in Table 2.

Discussion

We investigated whether adolescents' genetic sensitivity moderated longitudinal associations between mothers' and fathers' parenting behaviors toward their adolescent children and adolescents' internalizing and externalizing problems 1 year later. Overall, results supported the differential susceptibility model (Belsky & Pluess, 2009, 2013). Adolescents' genetic sensitivity, assessed by a composite polygenic score of four dopaminergic and serotonergic genes (*5-HTT, ANKK1/DRD2, DRD4*, and *COMT*) significantly moderated the associations between observational measures of mothers' and fathers' parenting behaviors and adolescents' depressed mood, anxiety symptoms, and hostility 1 year later. Compared to adolescents who had low scores on the polygenic sensitivity index, adolescents with high polygenic sensitivity scores were more depressed, more anxious, and more hostile when they experienced high levels of negative parenting (i.e., the combination of high parental hostility and low parental warmth/support), yet were less depressed, less anxious, and less hostile when they experienced high levels of positive parenting (i.e., the combination of high parental warmth/support and low parental hostility). These effects were observed even after controlling for adolescents' baseline levels of adjustment at 13 years of age. That is, these significant G × E effects held for rank-order change in adolescent outcomes across a 1-year lag between measurements. Adolescents with higher polygenic sensitivity scores were more affected in terms of their psychological adjustment by both positive (i.e., "for better") and negative aspects (i.e., "for worse") of parenting than were adolescents who had lower scores on polygenic sensitivity.

We conducted formal tests to determine whether the weak or strong versions of the differential susceptibility or diathesis–stress models best fit the data (Belsky et al., 2013; Widaman et al., 2012). The results from model fitting indicated that

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only the weak differential susceptibility model provided an acceptable fit to the data. Moreover, the crossover point of the G × E fell very close to the mean of parenting quality in all models; and in all cases, the point estimates and interval estimates fell well within the range of parenting scores in our sample. Together, these findings provide clear support for the differential susceptibility model relative to the diathesis–stress model. Rather than "eyeballing" slopes for different levels of the polygenic index score and crossover points to determine which model was best supported by the data, we formally tested each of the four possible G × E models and determined that the weak differential susceptibility model best fit the data. We also obtained point and interval estimates of the crossover point that yields crucial information for adjudicating relative fit between differential susceptibility and diathesis–stress predictions (Widaman et al., 2012).

It is important to note that we found general support for the differential susceptibility hypothesis for positively valenced parental behaviors (warmth, support, and positive communication) as well as negatively valenced parental behaviors (hostility, angry coercion, and antisocial behavior). That is, our measure of parenting (E) ranged from high levels of parental warmth combined with low levels of parental hostility toward the adolescent to high levels of parental hostility combined with low levels of parental warmth toward the adolescent. Much of the previous G × E research has focused solely on negative aspects of parenting or other measures of environmental adversity or has assumed that the absence of parental hostility is equivalent to the presence of parental warmth (see Caspi et al., 2010; Duncan & Keller, 2011, for reviews), and our research corrected for this gap in the literature. In short, consistent with past research, we found that mothers' and fathers' parenting had longitudinal influences on adolescents' adjustment (see Barber et al., 2005; Maccoby, 2000, for reviews). Our novel contribution to this literature was that these associations were moderated by adolescents' polygenic sensitivity across a set of serotonergic and dopaminergic genes.

The mechanisms by which adolescents' genetic sensitivity moderates the association between parenting and adolescents' psychological adjustment have not been definitively identified in the literature. However, by examining the neuropsychological functioning of the serotonergic and dopaminergic systems, we can propose some plausible hypotheses. The serotonergic system has been linked to punishment and displeasure (e.g., Caspi et al., 2010), and the dopaminergic system has been associated with reward sensitivity and sensation seeking (e.g., Dreher et al., 2009; Stice et al., 2012). As noted by Belsky and Pluess (2009), variants in genes from these systems expressed in the limbic system and, in particular, the amygdala, have been associated with increased emotional sensitivity to the environment. Thus, adolescents who, for reasons having to do with genetics, are particularly sensitive to reward (e.g., parental warmth and support) as well as punishment (e.g., parental hostility and angry-coercion) may be more affected in their psychological adjustment compared to adolescents with less genetic sensitivity.

Another potential mechanism by which adolescents' genetic makeup moderates the association between parenting and adolescents' psychological adjustment might involve DNA methylation and subsequent changes in genetic expression in response to certain environmental stimuli. For example, Beach, Brody, Todorov, Gunter, and Philibert (2010) found significant and lasting differences in methylation levels in the promoter region of the serotonin transporter gene in DNA of males and females with certain genotypes who also experienced child abuse (see Vijayendran, Beach, Plume, Brody, & Philibert, 2012). Additional neuropsychological and epigenetic research is needed to more fully understand how genetic characteristics are linked to sensitivity to the environment and, in turn, moderate environmental influences.

In the current study, we used polygenic sensitivity scores to move beyond methodological and conceptual problems of testing single candidate genes (see Duncan & Keller, 2011, for a review). Although the single candidate gene approach arguably makes it easier to trace specific biological processes involved in genes moderating environmental effects, we felt that the polygenic index score approach, which was predicated on the notion that complex psychological constructs are influenced by small effects of a number of genetic variants rather than by a single candidate gene variant (Evans et al., 2013; Sullivan et al., 2012), was the most efficacious approach. There is some debate in the field about whether to use linear or nonlinear (dominant/recessive) scoring to create polygenic index scores (e.g., Aliev, Latendresse, Bacanu, Neale, & Dick, 2014). As noted in our Appendix A analyses, we developed a new method to test which approach was most appropriate for creating the polygenic sensitivity index. The results indicated that linear scoring of each candidate gene was most appropriate. We also showed that each of the four genetic markers in the polygenic sensitivity index had effects of similar magnitude. Further, we ruled out several potential problems with polygenic scores. Our analyses showed no evidence that one candidate gene in the index was driving the index or that any individual gene cancelled out the effect of another.

The results showed that adolescents' genetic sensitivity, measured by the polygenic index score, moderated the links between parenting and adolescents' adjustment, including depressed mood, anxiety symptoms, and hostility. Further, we found that the interactive effects of mothers' and fathers' parenting and adolescents' genetic sensitivity did not differ significantly across parents. Research on whether associations between parenting quality and adolescents' adjustment outcomes vary for mothers and fathers is limited (Phares et al., 2005; Reeb & Conger, 2011), and even less is known about fathers' parenting in G × E research on adolescents' adjustment. Our findings are notable for demonstrating statistically that adolescents' genetic sensitivity moderated the influence of parenting on adolescents' psychological adjustment similarly for mothers and fathers.

Our final set of analyses examined the role of covariates in G × E. Researchers have noted that results from regression analyses to test G × E can be misinterpreted if relevant Covariate × Gene Index interactions are not considered in the models (e.g.,

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Keller, 2014). To investigate this potential problem, we tested all possible two- and three-way interactions among adolescents' sex, parental education, and family income to needs ratio with parenting quality and adolescent polygenic sensitivity. The interactions between polygenic sensitivity and parenting remained statistically significant in all analyses in which covariate interactions were included, and none of the additional covariate interactions were statistically significant. Thus, the moderating effect of adolescent genetic sensitivity did not differ by adolescent sex, parents' education level, or families' economic circumstances. For the case of adolescent sex, we found no evidence to suggest that parenting was more impactful for (a) father–son versus father–daughter dyads; or for (b) mother–son versus mother–daughter dyads. Some previous research has found higher rates of G × E for parenting and adjustment for boys (Li et al., 2013) and others for girls (Dalton et al., 2014), and most research has not even considered adolescent sex differences (see Duncan & Keller, 2011; Karg et al., 2011, for reviews). Further research is needed on possible differences in these processes for male and female adolescents.

In addition to considering the role of covariates in G × E, behavioral geneticists have pointed out the importance of ruling out gene–environment correlations when interpreting G × E (Caspi & Moffitt, 2006; Jaffee & Price, 2007). Our analyses showed that there was little evidence to suggest an evocative genetic effect on the part of the adolescent because adolescents' genetic sensitivity was not significantly associated with either mothers' or fathers' parenting or with any of the remaining covariates in the study. In other words, adolescents who were high on polygenic sensitivity did not elicit different levels of maternal or paternal warmth or hostility compared to adolescents who were low on polygenic sensitivity. Instead, adolescents' genetic sensitivity moderated the effect that parenting behaviors had on their adjustment.

To summarize the strengths of this study, we found support for the differential susceptibility hypothesis using prospective, longitudinal data, in contrast to most previous G × E research, which has used retrospective reports of parenting or has been cross-sectional in design (for reviews, see Duncan & Keller, 2011; Karg et al., 2011). We also controlled for the level of adolescents' internalizing and externalizing behaviors at T1; thus, our significant G × E results indicate that adolescent polygenic sensitivity moderated the link between parents' behavior and rank-order change in adolescents' adjustment. Moreover, we assessed both positive and negative dimensions of parenting for both mothers and fathers, whereas previous research has primarily focused on mothers' parenting behaviors only and/or has tended to assess only negative aspects of parenting behaviors (or other aspects of early family adversity). Another strength is that our data consisted of independent measures of parenting behavior (trained observer report) and adolescent adjustment (self-report). Hence, the results are unlikely to be explained by shared method variance. In addition, we demonstrated that the results were not explained by gene–environment correlation, because genetic sensitivity of adolescents did not elicit particular types of behavior from their parents. We also showed, as suggested by Keller (2014), that our results were not confounded by other Covariate × Polygenic Sensitivity interactions. Finally, much of the previous research in this area has focused on single candidate genes (Caspi et al., 2010; Duncan & Keller, 2011; Karg et al., 2011). We used a polygenic sensitivity index that takes into account that most genetic influence on complex psychological variables operates by additive effects of a number of genetic variants, each with a small effect (Sullivan et al., 2012). Further, we conducted statistical tests to show that an additive rather than a dominant or recessive summing method was the most appropriate one to create our polygenic sensitivity index.

Despite these strengths, there are several limitations to this study. Our sample was Caucasian in ethnicity and from rural America. It is important to note, however, this relatively homogeneous sample is advantageous for genetic analyses because it avoids problems of population stratification and spurious associations due to ethnic group differences (Cardon & Palmer, 2003). In addition, we used a community sample, and it is possible that genetic sensitivity would operate differently in extreme levels of family adversity or for adolescents' with clinical diagnoses. Finally, our sample size was somewhat smaller than ideal for G × E investigations. It will be important for future research to replicate these results in larger samples that are more diverse in terms of ethnicity, geographic regions, and mental health.

In conclusion, our findings indicate that adolescents' genetic sensitivity moderated the links between both mothers' and fathers' parenting and adolescents' internalizing and externalizing problems. These findings further support the idea that variations in how individuals respond to their environments are, at least in part, related to their genes. One implication of this is that intervention programs might need to be tailored to address the potentially different learning styles and reward systems for those children and adolescents who are high on genetic sensitivity and for those who are low on genetic sensitivity (van IJzendoorn & Bakersman-Kranenburg, 2015). Future research on the practical implications of differential genetic sensitivity is needed. Our results highlight the importance of assessing adolescents' genetic characteristics when investigating associations between parenting and adolescents' psychological adjustment and demonstrate one of the complex ways that nature and nurture work together to influence development.

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Appendix A

Testing differential effects of genetic markers

When using candidate genes in G × E investigations, researchers must decide whether to use additive, dominant, or recessive scoring of a given genetic marker. Further, if multiple candidate genes are assessed and a summative polygenic index is calculated, interpretation can be confounded if genetic markers across different candidate genes have differential effects. For example, different candidate gene markers (i.e., alleles) could have significantly different effects on the phenotype of interest. Moreover, different candidate genes may interact differently with the environmental variable of interest (E). In both cases, a significant G × E finding with the use of a polygenic index score might be driven by the effects of only one or two genetic markers. Another possibility is that the effects of one genetic marker may be counteracted by opposite effects of another. We conducted various tests described below to determine if an additive approach for scoring each genetic marker was justified and whether differential effects across candidate genes might compromise the use of our polygenic sensitivity index.

Each candidate gene included in the polygenic index score was scored 0, 1, or 2 for the number of risk or susceptibility alleles, with identity of the sensitivity allele being based on prior research (e.g., Belsky & Pluess, 2009). A dominant gene-action scoring method would be a dummy variable with scores of 0 (if the individual had zero risk/susceptibility alleles) or 1 (if the individual had 1 or 2 risk/susceptibility alleles). A recessive gene-action scoring method would be a dummy variable with scores of 0 (if the individual had 0 or 1 risk/susceptibility alleles) or 1 (if the individual had 2 risk/susceptibility alleles). If both dominant and recessive scores for an allele are in the same regression model and have equal regression weights, this is consistent with an assumption of linearity of gene action for the genetic marker of interest.

We fit three regression models for each adolescent outcome (depression, anxiety, and hostility). The first model, termed the disaggregated model, included eight gene main effects (i.e., dominant and recessive dummy codes for each of the four genes) and eight G × E product terms (i.e., the product of average parenting quality with the dominant and recessive dummy codes for each gene). The disaggregated model also contained the other five predictors shown in Table 2 (average parent education, family income to needs ratio, adolescent sex, adolescent symptoms at T1, and average parenting quality), so it had a total of 21 regression slope estimates.

The second model, the linear gene effect model, constrained effects of each genetic marker to linearity, constraining the regression weights for the dominant and recessive dummy codes to equality for each genetic marker main effect (four restrictions), and constraining the regression weights for the dominant and recessive G × E effects for each genetic marker to equality (four additional restrictions). The linear gene model constrained each gene to have a linear effect on the outcome, but estimated effects could differ across candidate genes. Thus, the linear gene effect model had 13 slope estimates: effects for four covariates, one environmental main effect, four gene main effects, and four G × E product terms.

The third model, the equal gene effect model, placed further restrictions on gene effects, constraining the four genetic main effects to have identical effects (three restrictions), and the four G × E effects to have identical effects (three additional restrictions). The equal gene effect model for a given outcome had the same fit to the data and the same number of parameter estimates as the corresponding model shown in Table 2. The advantage of the linear and equal gene effect models is that one obtains tests of restrictions on parameter estimates. For example, if one or more restrictions were significant in the linear gene effect model, this would imply that at least one genetic marker had a nonlinear effect. If one or more restrictions were significant in the equal gene effect model, individual genes might have significantly differential effects.

The results of fitting these three models are provided in Table A.1. We show the model R^2 for a model and its test of significance, an F test, and its degrees of freedom in Table A.1. For the linear and equal gene effects models, we present the change in explained variances (ΔR^2) and the test of its significance. We also list the adjusted (or shrunken) R^2, which contains a correction for model complexity. Finally, we show the number of restrictions that were statistically significant at $p < .05$ for a given nested model.

For composite maladjustment, the disaggregated model had good fit to the data ($R^2 = .3438$). The nested, restricted linear model had a lower R^2, but the change in explained variance ($\Delta R^2 = .0065$) was small, especially considering the 8 restrictions, and was nonsignificant ($F < 1$). Because none of the eight restrictions was significant, gene effects did not depart significantly from linearity. Then, the nested and even more restricted equal gene effect model had a still lower R^2, but the change in explained variance ($\Delta R^2 = .0036$) was again small, associated with 6 additional restrictions, and was nonsignificant ($F < 1$). Because none of the 14 restrictions in the equal model was significant, gene effects did not depart significantly from linearity or from equality across candidate genes. This pattern of results clearly supports the use of the linear and additive polygenic index across the four genetic markers when predicting change in composite maladjustment.

The results for the depression, anxiety, and hostility outcomes are also shown in Table A.1. The results of model comparisons were very similar to those for adolescent composite maladjustment. For all three of the separate outcomes, the linear gene effect model fit only slightly and nonsignificantly worse than the disaggregated model, and the highly constrained equal gene effect model fit only slightly and nonsignificantly worse than the linear model. For all of these outcomes, because none of the 8 restrictions in the linear model and none of the 14 restrictions in the equal model was significant, effects of genetic markers did not depart significantly from lin-

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Table A.1. *Model comparisons testing linearity and equality of effects of individual genetic markers predicting change in adolescent adjustment*

		Model Fit		Change in Model Fit			
Outcome Variable	Regression Model	R^2	F $(df)^a$	ΔR^2	F $(df)^b$	Adj. R^2	Sig. Restrict.
Composite maladjustment	Disaggregated	.3438	7.51 (21, 301)	—	—	.2981	—
	Linear gene effect	.3373	12.10 (13, 309)	.0065	0.37 (8, 301)	.3094	0 of 8
	Equal gene effect	.3337	22.54 (7, 315)	.0036	0.28 (6, 309)	.3189	0 of 14
Depression	Disaggregated	.3301	7.06 (21, 301)	—	—	.2834	—
	Linear gene effect	.3196	11.16 (13, 309)	.0105	0.59 (8, 301)	.2909	0 of 8
	Equal gene effect	.3096	20.18 (7, 315)	.0100	0.76 (6, 309)	.2942	0 of 14
Anxiety	Disaggregated	.2376	4.47 (21, 301)			.1845	
	Linear gene effect	.2226	6.80 (13, 309)	.0150	0.74 (8, 301)	.1898	0 of 8
	Equal gene effect	.2194	12.65 (7, 315)	.0032	0.21 (6, 309)	.2020	0 of 14
Hostility	Disaggregated	.3041	6.26 (21, 301)			.2256	
	Linear gene effect	.2987	10.12 (13, 309)	.0054	0.29 (8, 301)	.2692	0 of 8
	Equal gene effect	.2932	18.67 (7, 315)	.0055	0.40 (6, 309)	.2775	0 of 14

Note: $N = 323$. The disaggregated model has eight gene main effects (dominant and recessive predictors for each of four genetic markers) and eight Gene × Environment (G × E) interaction effects (dominant and recessive scores for each genetic marker interacting with average parenting quality). The linear model has a total of eight restrictions, restricting the four genetic markers main effects to linearity and the four G × E interactions to be linear genetic effects. The equal gene effect model has six additional restrictions, constraining the main effects of the four candidate genes to have equal effects (three restrictions), and constraining the four G × E interactions to have equal effects (three restrictions). Adj. R^2, the population estimate of R^2 corrected for model complexity or the number of predictors; Sig. Restrict., the number of individual restrictions on parameter estimates that were significant at $p < .05$.

[a]All F ratios for overall model fit were significant at $p < .0001$.

[b]None of the F ratios for change in model fit associated with restrictions was statistically significant at $p < .05$.

earity nor did the four candidate genes depart from equality in terms of their magnitude on the outcome.

It is interesting that, for all four outcomes, the explained variance, indexed by R^2, decreased when moving from the disaggregated to the linear gene effect and then to the equal gene effect models, as must happen when a more restricted model is fit to the data. However, the adjusted R^2, which has a correction for model complexity, showed the reversed pattern of changes, being highest for the most restricted and most efficient model, the equal gene effect model, for each of the four outcome variables. Taken together, these analyses support the use of the linear additive polygenic index employed in the primary analyses reported in this manuscript.

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