ORIGINAL ARTICLE

Parenting and Adolescent Antisocial Behavior and Depression

Evidence of Genotype × Parenting Environment Interaction

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Background: Little is known about the interplay of genotypes and malleable risk factors in influencing adolescent psychiatric symptoms and disorders. Information on these processes is crucial in designing programs for the prevention of psychiatric disorders.

Objective: To assess whether latent genetic factors and measured parent-child relationships interact (G × E) in predicting adolescent antisocial behavior and depression.

Design: We characterized risk of antisocial behavior and depression in adolescents by means of a genetically informed design. We used in-home questionnaire and observational measures of adolescent outcomes and environmental moderators (parenting), and a latent variable behavior genetic analytic model.

Setting: A nationally distributed sample recruited from random-digit dialing and national market panels.

Participants: A total of 720 families with at least 2 children, 9 through 18 years old, stratified by genetic relatedness (monozygotic and dizygotic twins, full biological siblings in nondivorced and stepfamilies, and half-siblings and biologically unrelated siblings in stepfamilies).

Main Outcome Measures: Antisocial behavior and depressive symptoms.

Results: There was an interaction of genotype and both parental negativity and low warmth predicting overall antisocial behavior, as well as aggressive and nonaggressive forms of antisocial behavior, but not depression. Genetic influence was greater for adolescent antisocial behavior when parenting was more negative or less warm. Genotype-environment correlation was partialled out in the analysis and thus did not account for the results.

Conclusion: This study demonstrates, on the basis of careful measurement and appropriate analytic methods, that a continuous measure of parenting in the normative range moderates the influence of genotype on antisocial behavior.

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Antisocial behavior and depression are associated with staggering personal and social costs. Despite a wealth of research identifying correlational risk factors for these disorders, the specific causal roles of these factors have been obscured by complex etiology. The etiology of both disorders clearly includes genetic factors, although the specifics of gene-environment interplay are still unclear.[1,2] One promising line of research investigates the moderating effects of genes on individuals' sensitivity to environmental risk factors, known as gene-environment interaction (G × E). For both antisocial behavior and depression, a small number of previous studies have found evidence of G × E; the environments involved in reports to date include mainly adverse family circumstances for antisocial behavior, and a range of factors including stressful life events for depression.[3-13]

Two main G × E research strategies are being pursued. From a "bottom-up" approach, recent molecular genetic studies have reported allele × environment (E) interactions (sometimes termed *measured G × E*) predicting antisocial behavior/conduct disorder and depression.[6-9] The direction of the interaction effects suggests that the alleles investigated lead individuals to be more sensitive to environmental risk. For the monoamine oxidase A allele interactions predicting antisocial behavior/conduct disorder, effect sizes reported to date are small on average (T. Moffitt, PhD, e-mail communication, February 20, 2005). Thus, although the allele × E strategy is promising for studying specific

genes, it is likely that a number of alleles contribute in various small ways to sensitivity to environmental risk.

A more immediately beneficial approach for preventing disorder is represented by "top-down" studies of genotype-environment interaction (often referred to as *latent G×E*). In such studies, genetic relatedness is typically inferred by means of a twin, adoption, or other family-based design, and the entire genotype contributes to the estimation of the interaction. Genotype × E findings indicate that sensitivity to the environment is moderated by the sum across many allele × E interactions that, individually, may be difficult to identify reliably. The presence of genotype × E interaction indicates that individuals who both have a risk-conferring genotype and experience a certain environment are disproportionately likely to develop a disorder.

The potential contribution of this second approach is greatest when the environmental term refers to a specific, measured aspect of the environment that is potentially malleable through preventive intervention. Two reported genotype × E interactions predicting antisocial behavior and depression exemplify this approach. In a twin study, family dysfunction was found to interact with genotype to predict antisocial behavior in adolescence.[3] In a twin-sibling study, researchers found that maternal punitive discipline interacts with genotype in predicting adolescent depression (Jennifer Y. F. Lau, PhD, and Thalia C. Eley, PhD, unpublished data, 2006). These findings of "genotype × malleable E interaction" are exciting because a number of preventive interventions have been demonstrated to be effective—and even cost-effective[14]—in improving family cohesion and decreasing harsh discipline as a means of improving child and adolescent outcomes.[15,16]

Demonstration of intervention efficacy is only the first stage in implementing an effective public health strategy. As with any treatment, a question naturally arises concerning the appropriate target population. Should resources be targeted toward a small group of high-risk individuals, or a larger group of moderately at-risk individuals, or applied universally?[17,18] There is a dual pitfall: On the one hand, intervention may be provided to a large number of children who do not require it, decreasing cost-effectiveness of the program; on the other hand, insufficient intervention may be provided to children at elevated levels of risk.[19] To the extent that genotype × malleable E studies can offer information on whether different levels of sensitivity to particular forms of environmental risk are found in the population, decisions regarding targeting can be made on a more informed basis.

For example, in the presence of such interaction, more intensive intervention is required for children who have both a risk-conferring genotype and risk-conferring experiences (eg, harsh parenting), compared with children with elevated risk status in only the genotype or only the environment. Moreover, from a research design perspective, trials whose sampling frames do not take into account such genotype × E interactions may be underpowered to detect intervention impact. If an intervention effectively addresses the environmental risk factor, its effect on the negative outcome for the whole population may be small if the majority of the environmentally at-risk population is not genetically at risk. For any individual it is not possible now to directly estimate genetic risk for psychiatric disorders. Although these effects are estimated for a large sample in this study, intervention studies will still be required to use a proxy for genetic risk: the presence of specified psychiatric disorders in blood relatives.

The examination of genotype × E interaction is important in one other respect. Notably, findings across several domains of development have suggested a limited role for family environmental influences that have a common effect across siblings.[20] Instead, findings have indicated that environmental factors tend to make siblings different from one another (ie, nonshared environmental influence). These findings have led to controversial arguments regarding the (un)importance of familywide environmental factors such as parenting.[21,22] Nonetheless, it has been troubling that despite the large amount of variance in behavior and personality accounted for by nonshared environmental influence in behavior genetic studies, researchers have not been able to identify the specific environmental factors responsible for these effects.[23] Notably, much previous behavior genetic research, including our own, has used analytic models that assume no genotype × E. If such interactions are present, however, most previous estimates of heritability and nonshared environment have been inflated, while the influence of shared environment has been underestimated. Thus, genotype × E effects may have been responsible for results that have bedeviled researchers for the past 2 decades.

For the results of a genotype × malleable E study to be maximally valid, generalizable, and useful, there are several study design requirements. First, the environmental variable should be selected and measured carefully by state-of-the-art techniques. In most previous reports of G × E, environmental variables were not easily malleable (eg, socioeconomic status) or were distal risk factors for child maladjustment[24] (eg, divorce) rather than the proximal risk factor impinging on the child (eg, harsh, negative parenting). In addition, some studies have used retrospective reports and/or single measures, methods, and reporters with potential for systematic bias (Jennifer Y. F. Lau, PhD, and Thalia C. Eley, PhD, unpublished data, 2006).

Second, the risk-conferring environment should be assessed in a continuous manner if appropriate. For example, several previous reports of allele × E interaction focus on a categorical definition of extreme childhood maltreatment that applies to relatively few families.[6,10] Although it is possible that G × E occurs only when the abusive extreme of negative parenting is compared with the rest of the spectrum of parenting quality, it would be important information for both preventive intervention[19] and gene detection if G × E is found when the entire range of parenting is considered as a continuous spectrum. From a public health perspective, G × E involving fairly widely distributed environmental risk factors will be a more useful guide to targeting prevention than risks affecting relatively few extreme cases. In addition, we note that the use of a continuous measure for the psychiatric disorder (the phenotype of interest) avoids a potential

methodological problem that may result in inaccurate tests of G × E (see Eaves[25]).

Third, G × E studies must account for the potential confound of gene-environment correlation (rGE), which refers to a joint distribution of genes and environments that is nonrandom. The most important reason for rGE is genetic influence on exposure to environmental risk. Research has demonstrated child and adolescent genetic influence on several risk factors for antisocial behavior and depression, such as life events[26] and parenting.[27,28] If genes are partly responsible for environmental exposure (ie, rGE), then G × E results may in fact be due to an interaction between one set of genes influencing pathological behavior and a second set of genes influencing environmental exposure. Until the recent development of analytic techniques that account for rGE while analyzing G × E, researchers have had to limit investigation of G × E to environmental experiences on which children's genetic influences were small or nonexistent (eg, severe child maltreatment). Ironically, given that proximal, interpersonal processes (eg, parental negativity) are most susceptible to the influence of children's genetic influence (through genetically influenced behavior such as child irritability), it is these proximal risk processes that have by necessity been neglected by G × E research.

This is, to our knowledge, the first study of G × E concerning the influence of family environment on psychiatric symptoms in which proximal, malleable family relations are carefully measured, an ordinary range of family environments is examined, the moderator is considered as a continuous variable, and the potential confound of GE correlation is accounted for within the model. Moreover, the national sample included twins and nontwin siblings in both nondivorced families and stepfamilies; thus, results are not likely due to the particularities of families with twins. We examine both parental negativity and parental warmth as moderators of latent genetic factors in accounting for variance in adolescent antisocial behavior and depressive symptoms. These environmental variables are selected for analysis because an extensive literature of randomized controlled clinical trials suggests that they are modifiable with cost-effective interventions.[14,29] Given evidence of distinct aggressive and nonaggressive (ie, delinquent) subtypes of antisocial behavior, we additionally examined the presence of G × E for aggressive and delinquent forms on antisocial behavior separately.

METHODS

SUBJECTS

The data for this study were from the first wave of the Nonshared Environment in Adolescent Development project. Families were sampled by means of random-digit dialing and commercial market panels with family information to identify certain family types (eg, twins, stepfamilies, and nondivorced families). The resulting sample consisted of a total of 720 families with same-sex adolescent sibling pairs (51.6% boys) from 47 states in the United States. Eligibility for the study required sibling pairs to be no more than 4 years apart in age, and no younger than 9 or older than 18 years (mean±SD age: older child, 14.5±2.2 years; younger child, 12.9±2.2 years). The sample was composed of monozygotic (n=93 families) and dizygotic (n=99 families) twins (12 twin pairs were unable to be classified) and full siblings (n=95 families) from nondivorced families; and full siblings (n=182 families), half-siblings (n=109 families), and genetically unrelated siblings (n=130 families) from stepfamilies. The families came from 47 states and had a wide range of income (median annual family income, $25 000-$35 000; Hollingshead Four-Factor Indicator of socioeconomic status, lower working class to upper-middle class) and education (mean years of education, 13.6 for mothers, 14.0 for fathers). Ninety-four percent of mothers and 93% of fathers were European American. For details on sample and measurement, including information on reliability and scale content, see previous publications from this study.[30-32]

MEASURES

Data were collected in two 3-hour home visits, separated by no more than 2 weeks. Participants signed informed consent forms, and the project was approved by the George Washington University institutional review board. In addition to questionnaires, interview teams collected 90 minutes of videotaped interaction from the 2 sessions, during which dyads discussed sources of conflict in their relationship.

Antisocial behavior was measured by adolescent self- and parent report on reliable scales: the Behavior Problems Index,[33] adapted from the Child Behavior Checklist[34]; and a 9-item subscale (eg, "stole," "lied or cheated," or "skipped school") from the Behavior Events Inventory.[35] These measures included items assessing behaviors that corresponded to *DSM-IV* criteria for conduct disorder (eg, argued, disobedient at home or school, and destructive toward objects). Antisocial behavior was also coded by observers from videotaped, 10-minute interactions between all possible combinations of dyads among the 2 parents and 2 siblings. Videotape coding used a global coding system adopted from previous research[35] to assess disruptive and disrespectful behaviors (eg, rude, noncompliant, uncooperative, hostile, coercive, and aggressive). To gauge aggressive and delinquent forms of antisocial behavior, we used subsets of items from the Behavior Problems Index based on comparison of items with *DSM-IV* conduct disorder subtype criteria, content validity, and interitem correlations. A 6-item subscale assessed delinquency (eg, cheat/lie), and a 4-item subscale assessed aggression (eg, bullied/cruel/mean). Adolescent self-report of depression, rather than parent report, was used given the adolescent's unique knowledge of his or her own depressive symptoms (eg, mood, cognition). Adolescents completed the Child Depression Inventory[36] and the depression subscale of the Behavior Problems Index. The antisocial and depression measures contain items that capture some, but not all, of the criteria for the *DSM-IV* diagnoses of conduct disorder and depression.

Parental negativity and parent-child conflict have been demonstrated in a number of previous studies to be related to level and change in both internalizing and externalizing disorders. These associations are found for parent and child report of parental negativity and parent-child conflict,[37,38] as well as for observer ratings.[39,40] Parental negativity was measured by means of 5 scales reported on by both parents and children: the Parent-Child Disagreement, Punitiveness, and Yielding to Coercion Scales of the Parent Discipline Behavior Inventory[35]; the symbolic aggression subscale of the Conflict Tactics Scale[41]; and 4 items from the Parent-Child Relationship Inventory[35] relating to the frequency of conflict and fights. Parental warmth was measured by an 11-item scale from the Parent-Child Relationship survey[35] referring to parent's closeness and rapport with the child; 2 scales were used from the Expression of Affection

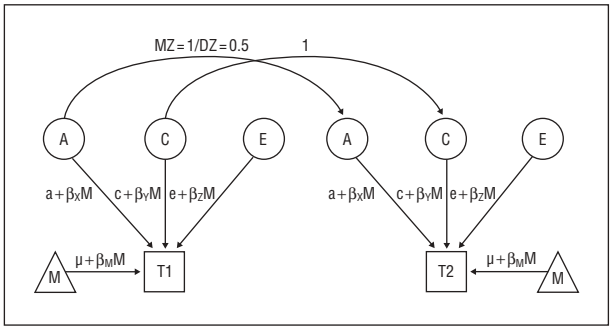

Figure 1. Path diagram for the gene-environment interaction model. A, C, and E indicate latent genetic, shared environment, and nonshared environment; T1, twin 1 outcome score; T2, twin 2 outcome score; a, c, and e, unmoderated (ie, values at the mean of the centered moderator) genetic, common environment, and nonshared environmental components; β_X, β_Y, and β_Z, moderated components of a, c, and e, respectively; β_M, main effect of moderator; DZ, dizygotic; M, moderator; MZ, monozygotic; and μ, grand mean.

Inventory[35] to measure the direct expression of affection and shared activities. Observers' ratings of parental negativity and warmth were also included.

All scales were standardized before being aggregated with a domain (antisocial behavior, depression, negativity, or warmth). Preliminary analyses confirmed that measures within a domain were at least moderately correlated. Composite ratings of antisocial behavior and parental negativity and warmth were formed across all available raters (parent, child, and observation) for each child. All measures were treated as continuous variables. The α values for the composites scores (with individual reporter and observer ratings considered as items) were 0.70 to 0.81 for parental negativity, 0.66 to 0.74 for parental warmth, 0.62 to 0.68 for depression, 0.62 to 0.69 for antisocial behavior, 0.69 to 0.71 for delinquency, and 0.57 to 0.69 for aggression.

The mean score for father's and mother's negativity (or warmth) was used as the child-specific moderator variable in these analyses. Thus, we combined mother and father negativity into 1 score, separately for each child, and we combined mother and father warmth into 1 score, separately for each child. Child-specific scores, rather than an average family score, were used for parenting across both children to (1) maximize the sensitivity of the moderator to differences between children and (2) reduce the number of analyses. The decision to combine mother and father scores was based on the conception that the overall amount of parental negativity (or low warmth) from both parents will impact children with a genetic liability to maladjustment more than other children. Moderate to strong interparental correlations (for older and younger siblings, respectively: r=0.44 and 0.45 for warmth and r=0.64 and 0.60 for negativity) support the examination of an overall parenting effect. Separate analyses were conducted for negativity and warmth, and for depression and antisocial behavior, yielding 4 sets of analyses.

ANALYTIC APPROACH

The analytic model used in this study (**Figure 1**) was developed by Purcell[42] and deserves comment. In gene-environment research, genes and environments may each be measured or unmeasured (also termed *latent*) but estimated through covariance models.[43] The present analytic model incorporates a latent variable representing genotype and 3 environmental variables: a specified, measured aspect of the environment (here, parenting); a latent dimension of environmental influences that are shared across siblings; and a latent dimension representing environmental influences that are not shared (as well as measurement error). It is the measure of parenting, not the latent residual measure, that is entered into the interaction term with genetic factors. As a consequence, the analysis herein of genotype × E might be more appropriately specified as genotype × parenting.

Three points follow: First, whether a specific environmental variable interacts with genetic factors does not indicate whether other environmental factors interact with genetic factors. That is, a failure to detect an interaction of parenting with genetic factors does not rule out the possibility of other genotype × E interactions. Second, the analytic model disentangles the effect of G × parenting interaction from the potentially confounding effects of rGE involving parenting.[3,42] Parenting is measured and included as a main effect and thus is partialled out of the outcome variable. The variance common to G and E (parenting) has already been partialled out of the outcome variable when all the variance in E (parenting) was partialled. Thus, if G × E effects are found to predict the outcome variable, these effects cannot be masking GE correlation predicting the outcome variable. Third, the model allows for the use of the environmental measure in a continuous format. Many previous treatments of G × E have dichotomized a sample into high and low levels of a moderator and then essentially compared the degree of genetic influences in the 2 subsamples. Such an approach reduces power and relies on the cutoff point (typically the median) reflecting a meaningful division of the sample.

The analytic model extends the classic behavioral genetic design to incorporate the mean effect of the specific environmental moderator variable (M: parental negativity or warmth) and interaction terms (β). Therefore, each path coefficient is a combination of both the main effect and the interaction effect. For instance, the interaction term on the genetic component is denoted as β_X, and thus the path coefficient for the genetic contribution is $a + \beta_X M$. Similarly, the interaction terms for shared and nonshared environment are β_Y and β_Z, respectively, and the corresponding path coefficients are $e + \beta_Y M$ and $e + \beta_Z M$. The proposed model estimates 7 parameters: those of the main effects of a, c, and e; the interaction effects on these, β_X, β_Y, and β_Z; and finally the main effect of the moderator. If each of the interaction terms is significant, the proportion of variance due to genetic influences (A), shared environmental influences (C), and nonshared environmental influences (E) will change with variations in the moderator. However, if they are not significant, then the levels of genetic, shared environmental, and nonshared environmental influences are not contextually dependent and thus remain the same regardless of moderator levels. For the purpose of this article, lowercase letters (a, c, and e) refer to the unstandardized terms for genetic, shared environmental, and nonshared environmental influences that are not involved in interactions with parental negativity. Terms with β (β_X, β_Y, and β_Z) refer to the interactions of genetic, shared environmental, and nonshared environmental influences with parental negativity; uppercase letters (A, C, and E) are standardized values and refer to the proportions of the variance explained by genetic influences, shared environmental influences, and nonshared environmental influences at varying levels of parental negativity.

All model fitting was conducted by means of the structural equation model-fitting package Mx.[44] Nested models were compared with the full model by using the difference between the fit statistic (minus twice the log likelihood) values to produce a χ^2 statistic.

RESULTS

For the measure of depression (Child Depression Inventory), more than 10% of youth respondents (154 of 1440) reported at least 16 depressive symptoms (which has recently been suggested as an optimal cutoff[45]). No cut-

Table 1. Fit Statistics of Structural Equation Modeling for Full and Nested Models for Depression*

Model	Fit Statistics			Comparison With Full Model		
	–2LL	*df*	AIC	χ^2	*df*	*P* Value
Parental negativity						
ace-$\beta_Y\beta_Z$-β_M	3603.115	1331	944.319	0.992	1	.99
ace-$\beta_X\beta_Z$-β_M	3603.292	1331	941.292	0.177	1	.67
ace-$\beta_X\beta_Y$-β_M	3606.979	1331	944.979	3.864	1	.049
ace-β_Z-β_M	*3603.456*	*1332*	*939.465*	*0.341*	*3*	*.84*
ace-$\beta_X\beta_Y\beta_Z$	3727.439	1331	1065.452	124.336	1	.00
Parental warmth						
ace-$\beta_X\beta_Y\beta_Z$-β_M	3267.049	1173	921.049			
ace-$\beta_Y\beta_Z$-β_M	3267.078	1174	919.078	0.029	1	.86
ace-$\beta_X\beta_Z$-β_M	3267.059	1174	919.059	0.010	1	.92
ace-$\beta_X\beta_Y$-β_M	3268.712	1174	920.712	1.663	1	.20
ace-β_M	*3272.486*	*1176*	*920.486*	*5.438*	*3*	*.14*
ace-$\beta_X\beta_Y\beta_Z$	3299.229	1174	951.229	32.180	1	.00

Abbreviations: a, c, and e, unmoderated genetic, common environment, and nonshared environmental components; AIC, Akaike information criterion; β_X, β_Y, and β_Z, moderated components of a, c, and e, respectively; β_M, main effect of moderator; –2LL, fit statistic (minus twice the log likelihood).
*Best-fitting models are shown in italics.

offs are available for the antisocial measures. However, to give a sense of the sample characteristics, 615 youths reported having been verbally aggressive and 285 reported having been physically aggressive in the past 24 hours on the Behavior Events Inventory. The phenotypic correlations for parental negativity were 0.31 with depression and 0.68 with antisocial behavior. Parental warmth correlated at –0.15 and –0.32 with depression and antisocial behavior, respectively. Parental negativity and warmth correlated at –0.24, and antisocial behavior and depression correlated at 0.29. All of these correlations were significant at $P<.001$.

PARENTAL NEGATIVITY AND DEPRESSION

The interactions both between parental negativity and genetic factors (a) and between parental negativity and shared environmental factors (c) could be dropped from the model without a significant deterioration in the fit (**Table 1**). The interaction between parental negativity and nonshared environmental influences could not be dropped from the model. These results indicate that the magnitude of the effects of nonshared environmental influences is contextually dependent; that is, as parental negativity increases, the role of nonshared environmental factors changes. These changes are illustrated graphically in **Figure 2**A, which portrays unstandardized, rather than standardized, components of variance for each level of the moderator. Numerical standardized estimates at various levels of the moderator are presented in **Table 2**.

A focus on standardized components, as is typical in most behavior genetic reports, can lead to misinterpretation.[42] Because this point is important and underappreciated, we digress momentarily for an illustration: Consider in a hypothetical case that there are very low levels of variance in the phenotype at one level of the moderator, but a large degree of phenotypic variance at another level of the moderator. A component of variance, eg, genetic factors, may account for all of the small amount of variance at the first point but for only half the variance at the second point. A standardized estimate does not yield a sense of the absolute magnitude of the variance accounted for, but only the proportion of variance. Thus, a

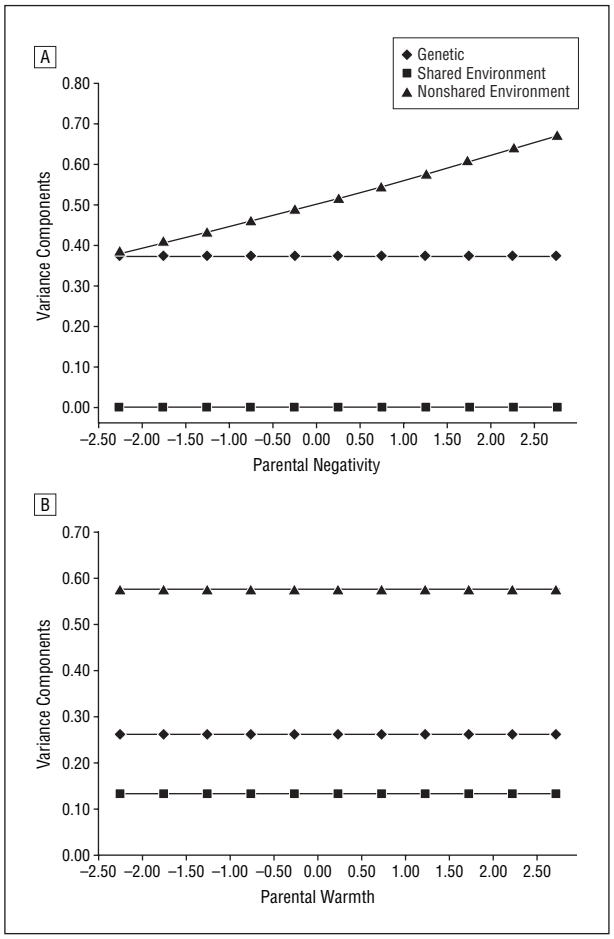

Figure 2. The absolute contribution of genes and shared and nonshared environment to variance in depressive symptoms across the range of parental negativity (A) and parental warmth scores (B), based on the parameter estimates from the best-fitting model.

Table 2. Parameter Estimates for A, C, and E by Level of Moderator (Parental Negativity/Warmth)

	Depressive Symptoms			Antisocial Behavior		
Parenting, SD Units	A	C	E	A	C	E
Negativity						
–2	0.49	0.00	0.51	0.45	0.33	0.22
–1	0.45	0.00	0.55	0.45	0.34	0.21
0	0.42	0.00	0.58	0.44	0.35	0.21
1	0.39	0.00	0.61	0.44	0.36	0.20
2	0.35	0.00	0.65	0.43	0.37	0.20
Warmth						
–2	0.27	0.13	0.60	0.90	0.01	0.09
–1	0.27	0.13	0.60	0.82	0.06	0.12
0	0.27	0.13	0.60	0.60	0.23	0.17
1	0.27	0.13	0.60	0.27	0.54	0.19
2	0.27	0.13	0.60	0.07	0.75	0.18

Abbreviations: A, C, and E, proportions of the variance explained by genetic influences, shared environmental influences, and nonshared environmental influences.

Table 3. Fit Statistics of Structural Equation Modeling for Full and Nested Models for Antisocial Behavior*

	Fit Statistics			Comparison With Full Model		
Model	–2LL	*df*	AIC	χ^2	*df*	*P*
Parental negativity						
ace-$\beta_X\beta_Y\beta_Z$-β_M	*2687.529*	*1311*	*65.529*			
ace-$\beta_Y\beta_Z$-β_M	2693.996	1312	69.996	6.467	1	.01
ace-$\beta_X\beta_Z$-β_M	2697.289	1312	73.289	9.760	1	.00
ace-$\beta_X\beta_Y$-β_M	2696.171	1312	72.171	8.642	1	.00
ace-$\beta_X\beta_Y\beta_Z$	3258.448	1312	634.448	570.914	1	.00
Parental warmth						
ace-$\beta_X\beta_Y\beta_Z$-β_M	2964.774	1160	644.774			
ace-$\beta_Y\beta_Z$-β_M	2984.790	1161	662.790	20.017	1	.00
ace-$\beta_X\beta_Z$-β_M	2974.644	1161	652.644	9.870	1	.002
ace-$\beta_X\beta_Y$-β_M	*2965.880*	*1161*	*643.880*	*1.106*	*1*	*.29*
ace-$\beta_X\beta_Y\beta_Z$	3061.285	1161	739.285	96.511	1	.00

Abbreviations: a, c, and e, unmoderated genetic, common environment, and nonshared environmental components; AIC, Akaike information criterion; β_X, β_Y, and β_Z, moderated components of a, c, and e, respectively; β_M, main effect of moderator; –2LL, fit statistic (minus twice the log likelihood).
*Best-fitting models are shown in italics.

standardized estimate of heritability in this example would be 1.0 at the first point and 0.5 at the second point. Without understanding the magnitude of the variance or variance components at each level of the moderator, one may then infer that genetic factors are twice as strong at the first point as the second point, when in fact genetic factors would account for more actual variance at the second point.

From Figure 2A, it appears that both genetic and nonshared environmental influences play a role at lower levels of parental negativity, although there is little variance in depression itself at these lower levels. At higher levels of parental negativity, the absolute amount of variance in depression accounted for by nonshared environmental factors increases. The absolute contribution of genetic influences to variance in depression remains constant, although the proportion of phenotypic variance due to genetic factors decreases as a consequence of the increasing influence of the nonshared environment influences. Thus, the standardized estimate, reflecting the proportion of variance due to nonshared environmental figures, declines as parental negativity increases (Table 2).

PARENTAL NEGATIVITY AND ANTISOCIAL BEHAVIOR

For antisocial behavior, it was not possible to drop any of the interaction effects without a significant reduction in the fit of the model (**Table 3**). Therefore, genetic, shared environmental, and nonshared environmental influences are all dependent on the level of parental negativity. The extent to which the influence of these variables varies over different levels of parental negativity can be seen in **Figure 3**A.

Although the variance in antisocial behavior was small in families where parental negativity was low (at 2 SDs below the mean), A, C, and E account for 45%, 33%, and 22% of the variance in antisocial behavior, respectively (Table 2). As parental negativity increases, the relative contribution of A (ie, the standardized estimate) remains about the same, while the relative contribution of C increases

and that of E decreases. When parental negativity is at its mean, A is estimated to account for 44% of variance, C for 35%, and E for 21%. At 2 SD units above the mean of parental negativity, the A, C, and E parameters are estimated as 43%, 37%, and 20%, respectively. Figure 3A demonstrates that the unstandardized estimates—reflecting the contribution of each factor to the actual variance in antisocial behavior at each level of parental negativity—increase as parental negativity increases. In other words, each of the factors accounts for more variance in antisocial behavior at high levels of parental negativity than it does at low levels of parental negativity. The importance of genetic and shared environmental factors increases more steeply than does the importance of nonshared environmental influences. Combining the information from Table 3 and Figure 3A, it appears that across increasing levels of parental negativity, the variance in antisocial behavior due to genetic factors increases, although the relative contribution made by genetic factors remains constant.

PARENTAL WARMTH AND DEPRESSION

For depression, parental warmth did not significantly moderate any of the parameters. Thus, Figure 2B consists of flat lines for each parameter, indicting that the absolute (as well as relative) variance accounted for by each does not change across levels of parental warmth.

PARENTAL WARMTH AND ANTISOCIAL BEHAVIOR

Parental warmth does significantly moderate the genetic and shared environmental factors predicting antisocial behavior. The interaction term with nonshared environmental influences could be dropped from the model. Figure 3B depicts the variance components attributable to each parameter across levels of parental warmth. At low levels of warmth, almost all of the variance is accounted for by genetic factors (90%; Table 2). As parental warmth increases, the contribution from genetic factors declines precipitously and is near zero at high levels of parental warmth. At the same time, the contribution of shared environmental influences is close to zero at low levels of warmth, but increases to account for 75% of variance in antisocial behavior at high levels of warmth.

SUBTYPES OF ANTISOCIAL BEHAVIOR

Results of analyses using aggression and delinquency subtypes for the G × E term were very similar to the results for overall antisocial behavior. The best-fitting models included an interaction between parenting (either negativity or warmth) and genetic factors. These results are not displayed herein but are available from the first author.

COMMENT

The central finding of this study is that parental negativity and warmth moderate the influence of genetic factors on adolescents' antisocial behavior (including both aggressive and nonaggressive subtypes), but not on depression. For antisocial behavior, genetic influence was greatest at higher levels of parental negativity and low levels of warmth. The consistency of the findings across both warmth and negativity, which are only modestly correlated, provides important replication within our study. Moreover, this consistency for genetic factors stands in contrast to the different ways that negativity and warmth moderated the effects of environmental factors.

This is not, of course, the first study to report genotype × E interaction predicting antisocial behavior. Cadoret and colleagues[4,46] demonstrated G × E effects on antisocial behavior in research with an adoption design; however, that study lacked measures of proximal family process. A recent report found evidence of G × E in a twin sample for antisocial symptoms.[3] In that study, environment was measured via a brief parent-report scale of general family functioning; thus, the results did not provide a clear intervention target. Finally, the E-risk study found that parental maltreatment disproportionately elevated the level of conduct problems for children with elevated genetic risk[10]; however, the limitations of a focus on parent maltreatment has been noted earlier. Thus, the finding here for genotype × E interaction predicting antisocial behavior is consistent with previous stud-

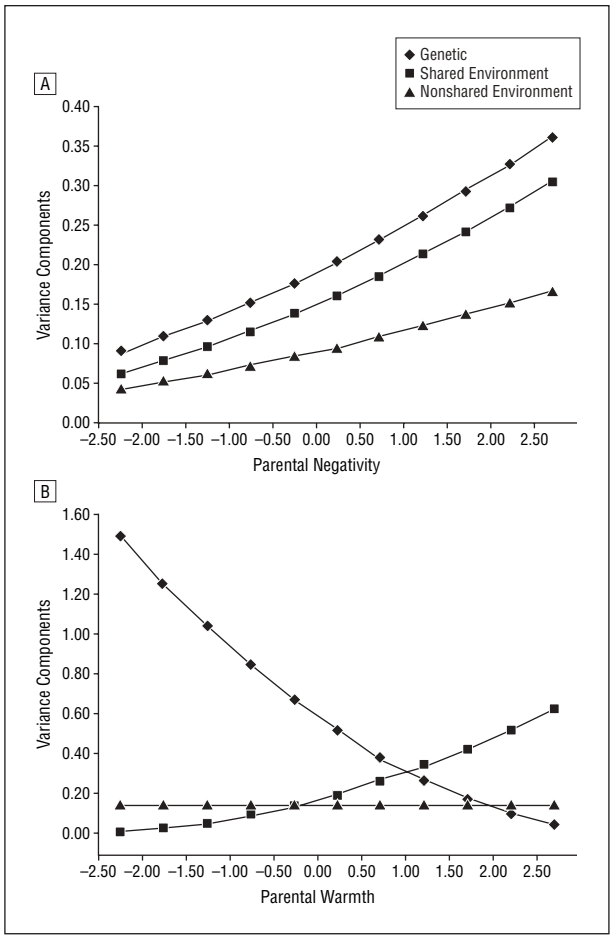

Figure 3. The absolute contribution of genes and shared and nonshared environment to variance in antisocial behavior across the range of parental negativity (A) and parental warmth scores (B), based on the parameter estimates from the best-fitting model.

ies, although the measures, sample, and analysis in this study allow for levels of confidence, generality, and specificity not realized previously. Moreover, the evidence of genotype × E for both aggressive and delinquent forms of antisocial behavior represents a new contribution to the literature.

As noted earlier, one possible reason why genetic factors are especially important for antisocial behavior in the context of negative parenting is that certain genetic factors confer a vulnerability to environmental adversity. At low levels of parental negativity, the genetic liability to problem behavior is not triggered. However, at high levels of parental negativity, some children may experience parental negativity as particularly threatening. For example, children with a genetically influenced temperamental style, such as a proclivity toward anger[47] or low effortful control,[48] may respond to harsh parenting with emotional or behavioral outbursts. Child oppositionality at home may lead through developmentally ordered sequences (ie, to disobedience at school and then to association with other oppositional children) to generalized antisocial behavior.[49]

The mechanisms (and specific genes) through which genotypes moderate sensitivity to low parental warmth may be different than for negativity. For example, parental warmth throughout development has been linked to competent peer and social skills in several studies.[50-52] In addition, adolescents' ability to respond competently to peer and school challenges is likely based, in part, on genetically influenced traits and temperamental styles.[53] Youths who lack both the supportive context of parental warmth and competence-promoting traits and temperament may have few resources available to help them respond competently to challenging or negative peer situations and influences, and thus may be disproportionately likely to adopt an antisocial orientation.

The absence of findings from this study of G × E for depression does not indicate, of course, that no such interaction accounts for meaningful variance in depression. First, even null results should be confirmed and replicated. Second, some previous research, although with certain weaknesses, has found evidence of genotype × E interaction predicting depression in females.[5] Unfortunately, very large samples are required to detect all but the most overwhelming sex differences in G × E. However, in support of the null finding for depression, we note that previous reports of G × E for depression have generally concerned stressful life events or social support, not parenting.[6,8,11-13,53] For adolescents, an environmental measure that reflects only parenting may not represent as salient a context as an overall measure of negative life events including family, school, and peer difficulties. The hypothesis is that the overall load of stress overwhelms biopsychological resources and leads to depression. In contrast, the dynamics leading to antisocial behavior seem to be more narrowly defined: it is the specific experience of parental negativity and lack of warmth that exacerbates the effects of genetic liability on antisocial behavior.

This study has implications and limitations that should be considered. For antisocial behavior (both aggressive and delinquent subtypes), it appears that a *multiplicative combination* of adverse parenting and genetic risk may identify the highest risk group. For the targeting of depressive symptoms, an *additive combination* of genetic risk and parental negativity may define the highest risk group. For researchers interested in identifying specific genes associated with antisocial behavior, these results suggest that efficiency, as well as greater consistency of results, can be obtained by limiting samples to individuals who have experienced elevated levels of parental negativity and/or low levels of parental warmth. This is, to our knowledge, the first study with appropriate controls to indicate that selection of samples maximizing genetic effects on antisocial behavior does not require assessment of childhood abuse history.

One limitation of the analyses in this study is the ambiguity regarding direction of effects. The same type of analysis could have been performed using the interaction of maladjustment and genetic factors to predict parental negativity, which would have supported an interpretation of "child effects," or more precisely, "active GE correlation."[54-56] Longitudinal analyses, which could help decide the direction of effects, were underpowered due to the sample size of the Nonshared Environment in Adolescent Development project in wave 2.

A second limitation is the relative undersampling of low-income families in the Nonshared Environment in Adolescent Development project. This is due in large part to the eligibility requirement that participating families have 2 parents who had been married for at least 5 years. The result of this sample bias is that the study does not fully represent higher levels of parental negativity that are relatively more prevalent in economically stressed and unstable families. Such a bias, however, likely reduces our ability to detect interaction effects and thus implies that the findings are conservative estimates of genotype × E.

On the other hand, the methods in this study contain a number of strengths, as described previously. Although we can hold a fairly high level of confidence in these results, replication of these findings would provide further confirmation that the role of genetic factors in the development of adolescent antisocial behavior, but not depression, depends on levels of parental negativity and warmth within the normative range.

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