Environmental Adversity and Increasing Genetic Risk for Externalizing Disorders

Brian M. Hicks, PhD; Susan C. South, PhD; Ana C. DiRago, MA; William G. Iacono, PhD; Matt McGue, PhD

Context: Studies of gene-environment interplay in the development of psychiatric and substance use disorders are rapidly accumulating. However, few attempts have been made to integrate findings and to articulate general mechanisms of gene-environment influence in the emergence of psychopathology.

Objective: To identify patterns of gene-environment interplay between externalizing disorders (antisocial behavior and substance use) and several environmental risk factors.

Design: We used quantitative genetic models to examine how genetic and environmental risk for externalizing disorders changes as a function of environmental context.

Setting: Participants were recruited from the community and took part in a daylong assessment at a university laboratory.

Participants: The sample consisted of 1315 male and female twin pairs participating in the assessment of the Minnesota Twin Family Study at age 17 years.

Main Outcome Measures: Multiple measures and informants were used to construct a composite of externalizing disorders and composite measures of 6 environmental risk factors, including academic achievement and engagement, antisocial and prosocial peer affiliations, mother-child and father-child relationship problems, and stressful life events.

Results: A significant gene × environment interaction was detected between each environmental risk factor and externalizing such that greater environmental adversity was associated with increased genetic risk for externalizing.

Conclusions: In the context of environmental adversity, genetic factors become more important in the etiology of externalizing disorders. The consistency of the results further suggests a general mechanism of environmental influence on externalizing disorders regardless of the specific form of the environmental risk.

Arch Gen Psychiatry. 2009;66(6):640-648

Various lines of evidence testify that genetic and environmental factors contribute to psychiatric and substance use disorders.1 Recently, psychiatric genetic research has evolved beyond simple estimates of heritable and nonheritable influences to investigations that begin to delineate the mechanisms of gene-environment interplay. This includes studies using the specific gene × measured environment design,2 with the most well-known example being that variants of the 5-HTT gene increase risk for major depression in the context of stressful life events.3,4 In addition, there is an accumulating literature of quantitative genetic studies5-9 that use twin, adoption, and family designs to delineate processes of gene-environment interplay, such as how the relative contribution of genetic and environmental risk factors changes as a function of the environmental context. Although there has been a veritable explosion in studies of gene-environment interplay in psychopathology in recent years, there have been few attempts to integrate findings in an effort to articulate more general principles of gene-environment influence across different environmental variables and psychiatric disorders.10-12 Key questions that remain unanswered include the following: Is the mechanism of environmental influence the same regardless of the environmental variable such as parenting, peers, or stressful life events? Or, do different environmental variables exhibit varying mechanisms of influence? Also, are the mechanisms of gene-environment influence the same for all types of psychiatric disorders? For example, are processes of gene-environment interplay the same or different for internalizing (major
depression and anxiety disorders) vs externalizing (antisocial behavior and substance use) disorders?

We begin to answer these questions by examining gene-environment interplay processes between externalizing disorders and 6 environmental risk factors in a large adolescent twin sample. By late adolescence, genetic risk for externalizing disorders is largely nonspecific and is primarily attributable to a highly heritable general vulnerability dimension \(h^2 = 0.80\).\textsuperscript{13,15} However, externalizing disorders also exhibit strong associations with environmental variables (such as poor performance and lack of engagement in school,\textsuperscript{16,17} deviant peer affiliation,\textsuperscript{18} harsh discipline,\textsuperscript{19,20} and poor parental monitoring\textsuperscript{21,22}) and with various stressful life events (eg, poverty, parental discord, residential instability, and familial psychopathology).\textsuperscript{23} However, the mechanisms underlying these associations are less well delineated.\textsuperscript{28} For example, do these environmental risk factors cause externalizing symptoms, or does genetic risk for externalizing instigate selection processes that result in greater exposure to these environmental risk factors?

Two gene-environment processes are essential to understanding the etiology of psychiatric disorders. Gene-environment correlations are the first process and refer to the fact that environmental risk is not distributed randomly but rather is, to some extent, a result of an individual’s decisions and actions (specifically, active and evocative gene-environment correlations).\textsuperscript{24,25} For example, the behavior of preadolescents who exhibit childhood disruptive disorders or of adolescents who precociously use substances can initiate a cascade of experiences, including weakened attachment to and increased conflict with parents,\textsuperscript{26,27} poor performance and lack of engagement in school,\textsuperscript{16,17,30} and stronger affiliation with deviant peers,\textsuperscript{31} which increases risk of developing psychiatric and substance use disorders in adulthood. Gene-environment correlations also help account for the finding that almost every putatively “environmental” measure exhibits heritable variance.\textsuperscript{32,33} That is, an individual’s genetically influenced characteristics, such as personality and intelligence, help to shape his or her environment, including exposure to environmental risk factors, which then increases risk for psychiatric disorders.\textsuperscript{28,29}

Gene \(\times\) environment interactions are the second process and refer to the finding that, rather than being uniform across individuals, environmental effects seem to be most influential among a subset of individuals who are genetically at high risk or, alternatively, that the impact of genetic influences varies depending on the environmental context. For example, stressful life events are a risk factor for major depression, but this risk is greater if an individual carries multiple copies of the short allele of the 5-HTT gene.\textsuperscript{3} Twin studies can also be used to identify gene \(\times\) environment interactions. For example, twin studies have shown that parental monitoring,\textsuperscript{34} rural residence,\textsuperscript{35} marriage,\textsuperscript{36} and religiousness\textsuperscript{37} attenuate genetic influences on substance use and abuse, with the corollary being that weaker environmental constraints amplify genetic influences. This provides for the more general hypothesis that, regardless of the specific mechanism, greater environmental stress will increase genetic risk for maladaptive behaviors.\textsuperscript{31} Therefore, although quantitative genetic investigations do not identify specific risk alleles, they can serve as a conceptual framework for measured gene \(\times\) measured environment designs by identifying the environments in which genetic risk is suppressed or amplified.\textsuperscript{37}

Recently, more sophisticated quantitative genetic models have been developed that incorporate gene-environment correlation and gene \(\times\) environment interaction,\textsuperscript{26} a notable advance because the presence of a gene-environment correlation can confound the interpretation of a gene \(\times\) environment interaction.\textsuperscript{11,24} In this investigation, we used these quantitative genetic models to delineate mechanisms of gene-environment interplay in the development of externalizing disorders during late adolescence, a critical development period when etiologic processes are shifting from those of childhood to those of adulthood.\textsuperscript{20,30} In addition, we examined the effects of multiple environmental risk factors that have robust and well-replicated associations with externalizing. Finally, environmental risk factors and externalizing were assessed using multiple methods and informants, providing for excellent measurement of the constructs. With these various methodological strengths, we sought not only to detect a gene \(\times\) environment interaction but (1) to identify patterns of gene-environment interplay across the various environmental risk factors and externalizing and (2) to begin to articulate a general model of gene-environment interplay in the development of externalizing disorders.

**METHODS**

**SAMPLE**

Participants were adolescent male and female twins taking part in the ongoing Minnesota Twin Family Study (MTFS). The MTFS is an epidemiologic longitudinal study of the families of same-sex twin pairs born in Minnesota that was designed to investigate the etiology of substance use disorders and related conditions. A comprehensive description of the design and methods of the MTFS has been provided elsewhere.\textsuperscript{20,36} Briefly, the MTFS includes a younger cohort first assessed at age 11 years and an older cohort who began the study at age 17 years. Twin participants are then offered the opportunity to return for follow-up assessments every 3 to 4 years. Families were initially located using publicly available birth records and databases, targeting the birth years from 1972 to 1984. More than 90% of eligible twin families were successfully located for each target birth year. Families are representative of the Minnesota population for the target birth years in terms of parental occupational status, educational attainment, and history of mental health treatment. Consistent with the demographics of those born in Minnesota during the target years, 96% of the participants were of white race/ethnicity. All twins and their parents provided informed consent or assent (with a parent providing informed consent) as appropriate before participation, and an internal review board approved all study protocols.

Data for the present investigation were collected as part of the assessment at age 17 years for both cohorts (ie, intake assessment for the older cohort and the second follow-up assessment for the younger cohort). The total sample included 1315 twin pairs, including 437 monozygotic (MZ) and 251 dizygotic (DZ) female twin pairs and 418 MZ and 209 DZ male twin pairs. The mean (SD) age of the total sample at the time of assessment was 17.8 (0.7) years. Zygosity was determined by the
MEASURES

Data were primarily collected during the daylong in-person assessment at the Department of Psychology, University of Minnesota. The assessment included structured clinical interviews conducted by trained staff with a bachelor's or master's degree in psychology, self-report questionnaires completed by twins and parents, and a rating form completed by teachers nominated by the family as being knowledgeable about the twins' behavior.

Our measures of externalizing disorders included DSM-III-R symptoms of adult antisocial behavior and alcohol, nicotine, and illicit drug dependence. Adult antisocial behavior (ie, the adult criteria for antisocial personality disorder) was assessed using a modified version of the Structured Clinical Interview for Axis II Personality Disorders.

Substance use disorders were assessed using the Substance Abuse Module of the Composite International Diagnostic Interview. The drug assessment included inhalants, opioids, phencyclidine, and sedatives. The drug class for which the participant endorsed the most symptoms of at least 2 advanced graduate students in clinical psychology. Mothers also reported on the presence of symptoms of drug class for which the participant endorsed the most symptoms of at least 2 advanced graduate students in clinical psychology. Consensus between the diagnosticians regarding the presence or absence of symptoms was reached before assigning symptoms, referring to audiotapes of the interview when necessary. The consensus process yielded uniformly high diagnostic reliabilities of 0.95 for adult antisocial behavior and greater than 0.91 for each substance use disorder.

In addition to the structured interviews, ratings were obtained from up to 3 teachers on a 30-item scale of overall externalizing behavior (eg, items similar to the criteria for oppositional defiant disorder and conduct disorder); 76.3% of the sample had ratings from at least 1 teacher and 61.3% had ratings from at least 2 teachers. The internal consistency reliability for the teacher rating was 0.92; the interrater reliability (intraclass correlation) for the mean of 2 raters was 0.71. Minnesota schools have a policy of placing twins in separate classrooms whenever possible, thereby minimizing the likelihood that members of a twin pair would be rated by the same teacher. All statistical analyses used an externalizing composite variable that was calculated by taking the mean z score of the symptom counts of adult antisocial behavior, nicotine dependence, alcohol abuse or dependence, and drug abuse or dependence and the teacher rating of externalizing behavior.

We also assessed multiple domains of each twin's environmental context, including academic achievement and engagement, antisocial and prosocial peer affiliation, mother-child and father-child relationships, and stressful life events. Academic achievement and engagement represented a composite of twin and mother reports regarding the twin's cumulative grade point average, self- and maternal ratings regarding their expectation of the twin's ultimate educational attainment (eg, complete high school, complete college), and a 7-item scale completed by the twin and mother assessing the twin's attitudes and engagement in school (eg, good attitude about school, enjoys attending school [α = 0.83]). The measure of academic achievement and engagement used in the analyses was the mean z score for ratings of grade point average, academic expectations, and academic attitudes averaged across the twin and mother reports (r = 0.77). Although academic achievement and engagement can also be conceptualized as an outcome or individual differences variable, in the present investigation the construct serves as an indicator of the individual's broader environmental context (in particular, the context actively or evocatively shaped by the individual) that might amplify or suppress risk for externalizing.

Peer affiliation was assessed by twin and teacher reports. Twins completed a 19-item questionnaire assessing antisocial (eg, my friends smoke, drink alcohol, steal, and get in fights [α = 0.85]) and prosocial (eg, my friends work hard in school, are popular with other kids, and are liked by teachers [α = 0.78]) peer affiliation.

Teachers completed similar ratings regarding the twin's antisocial (α = 0.85) and prosocial (α = 0.87) peer affiliation (mean interrater reliability, 0.71). The mean z score of the twin and teacher reports (r = 0.46) was used to calculate composite measures of antisocial/prosocial peer affiliation.

The quality of parent-child relationships was assessed using the Parental Environment Questionnaire, a 50-item self-report questionnaire that assesses multiple dimensions of the parent-child relationship (eg, conflict and involvement [α range, 0.82-0.69]). Twins completed separate Parental Environment Questionnaire ratings regarding their relationship with their mother and father. Parents also rated their relationship with each twin, as well as the quality of the relationship between each twin and the other parent (eg, mother rated the relationship between each twin and the father). Therefore, up to 3 ratings were available for the mother-child and father-child relationships. The measure of mother-child and father-child relationship problems used in the analyses was the mean of the 3 informant ratings on the first principal component among the Parental Environment Questionnaire scales (the scales exhibit a dominant first component [mean correlation across informants, 0.41]). Finally, stressful life events were assessed via a structured interview administered to each twin. Our analyses are limited to what are referred to as "independent" life events. That is, these events are largely independent of the individual's behavior (eg, parent lost a job) as opposed to being in some way dependent on the respondent's behavior (eg, failed a class). The stressful life events measure for this analysis was a tally of 18 life events covering the domains of parental divorce and discord and family money, legal, and mental health problems. Because these events should be concordant for members of a twin pair, the correlation between twin reports provides an estimate of reliability (r = 0.81; interrater reliability, 0.89).

ANALYTIC APPROACH

Structural equation modeling was used to examine gene-environment interplay between the externalizing composite and 6 environmental risk factors. First, we used univariate biometric models to estimate the relative genetic and environmental effects on each variable. These models assume that variance in each measure is attributable to the following 3 independent sources: additive genetic effects (A), shared environmental effects (C), and nonshared environmental effects (E). Estimates of the ACE variance components are derived by comparing the similarity of members of MZ twin pairs relative to that of mem-
nbers of DZ twin pairs, given that MZ twins share all their genes and DZ twins share on average 50% of their segregating genes (A effects are present if $r_{MZ} > r_{DZ}$). Shared environmental effects refer to environmental effects that increase similarity among family members (C effects are present if $r_{DZ} > \frac{1}{2} r_{MZ}$), whereas nonshared environmental effects (including measurement error) contribute to differences between members of a twin pair (E effects are present if $r_{DZ} < 1.0$).

Next, we examined whether the ACE effects on the externalizing composite changed as a function of the environmental context, operationalized as different levels of the environmental risk factors. This gene-environment interplay model (Figure 1) can be conceptualized as a bivariate extension of the univariate model that incorporates additional moderation terms on the ACE effects.38 This gene-environment interplay model estimates the ACE contributions to the covariance between externalizing and the environmental risk factor (eg, the genetic covariance is $a_{ij} \times a_{ij}$), as well as the ACE effects that are unique to externalizing (eg, $a_{ij}$). This allows for the estimation of the gene-environment correlation between externalizing and the environmental variable, which accounts for any selection effects between externalizing and exposure to the environmental risk factor.

If a gene × environment interaction is present, the initial ACE parameters derived from the bivariate model are then adjusted according to the direction (+ or −) and size of the moderation width ($\beta_x$) and the level of the moderator (M [eg, the number of antisocial peers]). Moderation can occur for the ACE effects that overlap between externalizing and the environmental risk factor (eg, $a_{ij} + \beta a_{ij} M$) or for the ACE effects that are unique to externalizing (eg, $a_{ij} + \beta a_{ij} M$). For example, a positive sign for $\beta a_{ij}$ would mean that the unique genetic variance in externalizing would increase in the context of more antisocial peers.

Models were fit to the raw data using full-information maximum likelihood estimation as implemented in the computer program Mx (Department of Psychiatry, Virginia Commonwealth University, Richmond),34 which allows for missing data and yields less biased parameter estimates than other procedures.55 The externalizing composite was log transformed to better approximate normality. We followed standard behavior genetic analytic procedures by regressing all variables on sex, age, and age² and the interactions of sex and the age variables36 before analyses.

Model fit was evaluated using the $-2 \times \log$ likelihood and several information theoretic indexes that balance overall fit with model parsimony, including the Akaike information criterion,37 bayesian information criterion,38 sample size-adjusted bayesian information criterion,39,40 and deviance information criterion.41 The full gene × environment moderation model was compared with the no-moderation model using the likelihood ratio test, which yields a $\chi^2$ statistic. If the full-moderation model provided a better fit to the data, further model-trimming analyses were conducted to identify the most parsimonious model, retaining only the significant moderation effects.

The best-fitting model was judged to be the model that yielded lower values for at least 3 of 4 information theoretic indexes relative to the full model.

**RESULTS**

**PHENOTYPIC CORRELATIONS, TWIN CORRELATIONS, AND UNIVARIATE BIOMETRIC ANALYSES**

Table 1 summarizes the phenotypic correlations among the study variables. Each environmental risk factor was significantly correlated with externalizing (ie, exhibited a main effect). Notably, all of the environmental risk factors were significantly correlated with each other, indicating that adversity in one domain tended to be associated with problems in other domains. However, there was a wide range in the strength of the associations among the environmental risk factors ($r$ range, 0.18-0.57), and none was so high that any measure would be considered redundant.

Table 2 summarizes the MZ and DZ twin correlations for each study variable, as well as the estimates of the ACE variance components from the univariate biometric model. Externalizing was highly heritable, with no shared environmental effects. Each environmental variable exhibited statistically significant heritable variance, although there was a wide estimate range of 0.08 to 0.72. Except for academic achievement and engagement, each environmental variable also exhibited significant shared and nonshared environmental variance.

**GENE-ENVIRONMENT INTERPLAY OF EXTERNALIZING AND ENVIRONMENTAL RISK FACTORS**

Table 3 gives the fit statistics for the models of gene-environment interplay between externalizing and each environmental variable. Each environmental variable exerted large moderation effects on externalizing as evidenced by the highly significant likelihood ratio test results. Follow-up model-trimming analyses showed that each environmental variable moderated the unique additive genetic and nonshared environmental variance in externalizing, with 3 variables also moderating the unique shared environmental variance. These moderating effects on the shared environmental effects (C component) necessitated retaining it in the model, despite the
univariate estimate of C on externalizing being zero. Academic achievement and engagement and both peer affiliation variables also moderated the common additive genetic variance with externalizing (prosocial peers also moderated the common nonshared environmental variance). Because members of a twin pair should not differ on the life events that constitute our measure of independent stressful life events, no genetic effect is expected, so it is inappropriate to estimate the genetic-environment correlation.62 Therefore, for independent stressful life events, we only allowed for moderation on the unique variance in externalizing. Although not ideal, this approach allowed us to examine at least some of the effect of highly relevant environmental stressors (eg, parental discord and poverty and family legal and mental health problems), as well as whether the mechanism of their effect was similar to or different from that of other environmental risk factors.

**Figure 2** shows the mechanisms of gene \times environment interaction on externalizing for each environmental moderator. All environmental variables have been coded such that higher values are indicative of greater adversity. For each environmental variable, greater environmental adversity was associated with substantially greater additive genetic variance in externalizing, with modest to moderate increases in nonshared environmental variance. The figure shows the unstandardized variance estimates, so the ACE variance components do not necessarily sum to 1.0. For 3 environmental variables, there was also a modest moderation effect on the shared environmental variance, with shared environmental variance tending to be greatest at low levels of environmental adversity. Given the consistency of these results, a plausible hypothesis is that moderation of externalizing is due to the overlap among the different environmental variables. To test this hypothesis, we regressed each environmental risk factor on the first principal component among the 6 environmental variables and examined whether the residual variance continued to moderate the ACE effects on externalizing. Although the common variance across the environmental variables accounted for a large portion of the moderation effects, the residual variance of each environmental variable continued to exert significant moderating effects on externalizing (χ² range, 28.6-195.2; P < .001 for all).

Because the additive genetic and nonshared environmental variance of externalizing was moderated, the size of the genetic (r_A) and nonshared environmental (r_E) correlations (ie, the gene-environment correlations) also varied with levels of the environmental risk factor (this situation holds even if only the unique variance of externalizing is moderated).37,38 Because results were consistent across the environmental moderators, we discuss results for mother-child relationship problems as an illustrative example. At low levels of mother-child relationship problems (~2 SDs), the r_E with externalizing was large (r_E = 0.78) but declined as levels of mother-child relationship problems increased (r_E = 0.44 at 0 SD and r_E = 0.29 at 2 SDs). Results for the r_F were similar but of lesser magnitude (r_F = 0.31, r_F = 0.16, and r_F = 0.10 at levels of mother-child relationship problems of ~2 SDs, 0 SD, and 2 SDs, respectively). This indicates that, as environmental adversity increases, externalizing and mother-child relationship problems share less genetic and environmental variance. The

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**Table 1. Phenotypic Correlations Between Externalizing and Environmental Risk Factors**

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<td></td>
</tr>
<tr>
<td>engagement</td>
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<td></td>
<td></td>
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<td>Mother-child relationship</td>
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<td>0.24</td>
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<td>Stressful life events</td>
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<td>0.20</td>
<td>0.25</td>
<td>0.20</td>
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*All correlations are significant at P < .001. Academic achievement and engagement and prosocial peer affiliation have been reverse scored.*

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**Table 2. Twin Correlations and Univariate ACE Estimates**

<table>
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<tr>
<th>Variable</th>
<th>MZ Twin</th>
<th>DZ Twin</th>
<th>ACE Estimate (95% Confidence Interval)</th>
<th>A</th>
<th>C</th>
<th>E</th>
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<td>0.40</td>
<td>0.76 (0.65-0.79)</td>
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<td>Academic achievement and</td>
<td>0.77</td>
<td>0.42</td>
<td>0.72 (0.57-0.79)</td>
<td>0.95 (0.80-0.91)</td>
<td>0.23 (0.20-0.26)</td>
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<td>engagement</td>
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<td>Antisocial peer affiliation</td>
<td>0.70</td>
<td>0.51</td>
<td>0.42 (0.28-0.56)</td>
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<td>Mother-child relationship</td>
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<td>0.49 (0.38-0.62)</td>
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<td>0.75</td>
<td>0.23 (0.15-0.31)</td>
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<td>Stressful life events</td>
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<td>0.80</td>
<td>0.08 (0.01-0.15)</td>
<td>0.75 (0.68-0.80)</td>
<td>0.17 (0.16-0.20)</td>
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*Abbreviations: A, additive genetic effects; C, shared environmental effects; DZ, dizygotic; E, nonshared environmental effects; MZ, monozygotic.*
uncoupling points to a true environmental effect or social causation process on the inherited vulnerability to externalizing, an effect that is most pronounced in the context of extreme environmental adversity.37

Table 3. Fit Statistics for Gene-Environment Interplay Models of Externalizing and Environmental Moderators

<table>
<thead>
<tr>
<th>Modela</th>
<th>−2 × Log Likelihood</th>
<th>df</th>
<th>Akaie</th>
<th>Sample Size–Adjusted Bayesian</th>
<th>Deviance</th>
<th>Bayesian</th>
<th>Change in χ2b</th>
<th>df</th>
<th>P Value</th>
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<td>4702</td>
<td>1166.94</td>
<td>−3874.17</td>
<td>−7020.94</td>
<td>−11 341.79</td>
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<td>4708</td>
<td>1682.09</td>
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<td>1165.13</td>
<td>−3876.98</td>
<td>−7025.09</td>
<td>−11 347.77</td>
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Abbreviations: A, additive genetic effects; C, shared environmental effects; E, nonshared environmental effects; ellipses, base model.

a Full refers to the gene-environment interplay model with all possible moderation parameters. None refers to a bivariate biometric model with no moderation parameters. Lower values for all fit indices are indicative of better fit. The model for stressful life events allowed for unique variance of externalizing only, which was also the best-fitting model.

b The change in χ2 is the difference between the −2 × log likelihood in the base model and the other models tested.

c Moderation effects for best fit.

COMMENT

Our analyses yielded surprisingly consistent findings regarding gene-environment interplay in the emergence of externalizing disorders during late adolescence. Specifically, across 6 environmental risk factors, genetic variance in externalizing increased in the context of greater environmental adversity. This indicates that, as environmental stress increases, genetic differences among people actually become more important in the etiology of externalizing.

This finding is not necessarily intuitive. For example, each environmental risk factor was significantly correlated with externalizing, with evidence of a main effect such that the mean levels of externalizing increase with greater levels of environmental risk. This has led some to conclude that environmental influence is causative and that the greater environmental adversity would obscure genetic influences.12 However, the effect of environmental adversity clearly differs for those who experience it because many individuals under substantial environmental stress do not exhibit externalizing disorders. Therefore, environmental risk factors must also exert differential or moderating effects on the variance of externalizing, and it is these moderating effects on the genetic and environmental variance of externalizing that provide a model for the mechanisms of environmental risk for externalizing psychopathology.37

The finding of a consistent mechanism of gene-environment interplay across the different environmental risk factors suggests a general mechanism of environmental influence on externalizing regardless of the particular manifestation of the environmental risk. The consistency is especially noteworthy given the differences in content of the environmental measures, the use of multiple informants and methods of assessment, and the variations in heritability. Also, the nature of the gene × environment interaction with externalizing was the same regardless of whether the environmental variable conferred distal risk (independent life events) or risk that was proximal and malleable (peers, parent-child relationships, and academic achievement and engagement), with the latter being theorized to be most relevant to gene-environment processes.25 In addition, although all the environmental variables were corre-
lated, the moderation effects were not solely due to the effect of a general environmental risk factor. Finally, our results are consistent with previous studies that have examined single externalizing phenotypes (e.g., conduct problems, alcohol use, and smoking) and environmental moderators (e.g., peers and social and demographic variables). Integrating our results with the broader literature then suggests a general principle of gene-environment interplay such that environments that are more constrained, structured, and less stressful suppress genetic risk, whereas unconstrained and more stressful environments amplify genetic risk for externalizing behaviors (although some have suggested that this general mechanism can be further delineated).

Another possibility is that our measures of environmental risk would have the same moderating effects on the genetic and environmental risk for any form of psychopathology. However, in a separate study of the same sample, gene-environment interplay was examined between internalizing disorders and the same measures of environmental risk, and it was found that the nonshared environmental variance of internalizing increased at higher levels of each environmental risk factor, whereas the genetic and shared environmental variance remained stable (B.M.H., A.C.D., W.G.I., and M.M., unpublished data, June 2008). That is, the same environmental adversity was associated with a different mechanism of gene-environment interplay in the emergence of internalizing behaviors.

Figure 2. Externalizing (EXT) moderated by environmental risk factors. Changes in the unstandardized variance of EXT are given as a function of environmental risk factors for the best-fitting model. All environmental risk factors have been coded such that higher levels are associated with greater environmental adversity.
compared with externalizing psychopathology. Taken together, the pattern of results across these 2 studies provides impressive evidence of convergent and discriminant validity. The intriguing hypothesis then is that the mechanism underlying environmental influence is general but will differ depending on the nature of the disorder.

Some limitations of our study need to be considered. First, although the sample is representative of the Minnesota population from which it was drawn, it does not reflect the racial/ethnic diversity of the broader US population. Also, our sample was limited to late adolescence, so it is unknown whether the same gene-environment interplay processes are present at other developmental stages. Another limitation is ambiguity regarding the direction of causation. That is, our decision to examine the moderating effects of environmental risk on externalizing, although theoretically grounded, is methodologically arbitrary because an argument could be made that externalizing moderates the genetic and environmental influences on the environmental risk factors. However, supplemental analyses showed that, when such effects were present, they were much weaker than the moderation effects on externalizing. Future analyses that use the prospective design of the MTFS will provide further insight into the causative associations between externalizing and these environmental risk factors.

Our results have important implications for gene association and measured gene × measured environment studies. Specifically, studies attempting to detect associations between specific genes and externalizing will be more likely to yield significant results if they also incorporate measures of environmental adversity. Our results can also inform developmental theories of psychopathology. For example, individuals who exhibit an early onset and a persistent course of antisocial behavior and substance use disorders seem to experience both greater genetic and greater environmental risk. A potential mechanism is that gene-environment correlation processes lead to greater exposure to environmental risk, whereas the experience of greater environmental adversity then results in the expression of more genetic vulnerabilities (ie, increased genetic variance via gene × environment interactions). These processes are then likely to magnify over time, channeling individuals into stable developmental trajectories. At present, most gene association investigations examine the link between a specific gene and a lifetime case of a disorder. Given the interplay of these genetic, environmental, and developmental processes, a sensible prediction is that specific genes will be most reliably associated with the developmental characteristics of externalizing disorders, especially an early onset and a persistent course. Externalizing disorders are of substantial public health importance, and continued attempts to integrate multiple processes and approaches should yield important insights into their etiology.

Submitted for Publication: June 2, 2008; final revision received September 17, 2008; accepted September 18, 2008.

Correspondence: Brian M. Hicks, PhD, Department of Psychology, University of Minnesota, 75 E River Rd, Minneapolis, MN 55455 (hicks013@umn.edu).

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grants AA09367, DA05147, and DA024417 from the US Public Health Service.

REFERENCES


