Higher-Order Genetic and Environmental Structure of Prevalent Forms of Child and Adolescent Psychopathology

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**Context:** It is necessary to understand the etiologic structure of child and adolescent psychopathology to advance theory and guide future research.

**Objective:** To test alternative models of the higher-order structure of etiologic effects on 11 dimensions of child and adolescent psychopathology using confirmatory factor analyses of genetic and environmental covariances.

**Design:** Representative sample of twins.

**Setting:** Home interviews.

**Participants:** A total of 1571 pairs of 9- to 17-year-old twins.

**Main Outcome Measures:** Structured assessments of psychopathology using adult caregivers and youth as informants.

**Results:** The best-fitting genetic model revealed that most genetic factors nonspecifically influence risk for either all 11 symptom dimensions or for dimensions of psychopathology within 1 of 2 broad domains. With some notable exceptions, dimension-specific genetic influences accounted for modest amounts of variance.

**Conclusions:** To inform theory and guide molecular genetic studies, an etiologic model is offered in which 3 patterns of pleiotropy are hypothesized to be the principal modes of genetic risk transmission for common forms of child and adolescent psychopathology. Some common environmental influences were found, but consistent with a “generalist genes, specialist environments” model, there was little sharing of environmental influences. This implies that prevalent dimensions of child and adolescent psychopathology mostly share their genetic liabilities but are differentiated by nonshared experiences.

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All common dimensions of psychopathology in children and adolescents are positively correlated to varying degrees, often substantially.1-3 Similar to other researchers,1,3 we posit that the correlated nature of psychopathology reflects the underlying etiologic structure of psychopathology. In particular, Kendler hypothesized that many genes pleiotropically influence risk for multiple mental disorders. This hypothesis is supported by studies7,8 of adult twins showing that major depressive disorder (MDD) and generalized anxiety disorder (GAD) are substantially influenced by common genes, as are antisocial behavior and multiple forms of substance abuse. Perhaps most importantly, a twin study of categorical mental disorders in adults9 identified 2 broad genetic factors accounting for most of the genetic variance in the mental disorders that loaded on them: an internalizing factor (anxiety disorders and depression) and an externalizing factor (conduct problems, antisocial personality disorder, and substance use disorders).

Less comprehensive studies have been conducted of child and adolescent psychopathology, but consistent with the apparent importance of pleiotropy in adult disorders, bivariate analyses of child and adolescent twins indicate substantial shared genetic influences on several pairs of mental disorders. Furthermore, a broader study of the externalizing domain in older adolescents generally confirmed findings in adults.9,10

The present analyses test the hypothesis that psychopathology dimensions in children and adolescents are highly correlated at the phenotypic level largely because they are correlated at the genotypic level. These analyses are based on the premise that the underlying latent dimen-
sions of prevalent mental disorders are continuous rather than discrete taxa. That is, similar to other researchers, 11-14 we assume that the diagnostic thresholds for prevalent mental disorders represent conventional cutoff points on symptom continua designed to help clinicians make informed dichotomous treatment decisions rather than reflecting qualitatively distinct states of mental health.

The models of the causal structure of child and adolescent psychopathology tested herein are partly derived from previous findings that 2 higher-order internalizing and externalizing factors account for most of the phenotypic correlations among common psychopathology dimensions in children, adolescents, and adults. 3,5-17 Furthermore, based on the sizable phenotypic correlations between the latent internalizing and externalizing factors in these studies, we also tested the novel hypothesis that the phenotypic correlations between the internalizing and externalizing disorders partly reflect their loadings on a factor reflecting general risk for psychopathology. We present the results of separate confirmatory factor analyses (CFAs) of genetic and environmental covariances among 11 prevalent psychopathology dimensions in a representative sample of twin pairs to compare these alternative models of the structure of etiologic influences.

METHODS

PARTICIPANTS

The Tennessee Twin Study 3 is representative of 6- to 17-year-old twins born in Tennessee and living in 1 of the state’s 3 metropolitan statistical areas in 2000-2001. These metropolitan statistical areas include the 28 urban, suburban, and rural counties that surround the cities of Nashville, Memphis, Knoxville, Chattanooga, and Bristol. The Tennessee Department of Health identified 7794 birth records representing all twin pairs born in Tennessee in the eligible age range and used external databases to locate families; 2431 twin pairs were eliminated because they lived outside the 5 metropolitan statistical areas. A random sample was selected from the remaining families, stratified by age and 35 geographic subareas, proportional to the number of listed families in each subarea. Of 4012 selected households, 3592 (89.5%) were located and screened, with 2646 of the screened families being eligible (neither twin was autistic or psychotic, both twins co-resided with the adult caretaker at least 50% of the time during the past 6 months, the twins and caretaker spoke English, and the twins were ≥6 years old at the time of the interview and ≤17 years old at the time of screening). Twelve families were ineligible on the basis of language, indicating little bias. Biological mothers, biological fathers, stepmothers, and grandmothers were eligible to be interviewed as the adult caretaker. Interviews were completed with 2063 adult caretakers (90.8% biological mothers), with a 70% response rate. When the caretaker was interviewed, both twins were interviewed 98% of the time. Caretakers classified 71% of the twins as non-Hispanic white, 24% African American, 2% as Hispanic, and 3% as other groups.

MEASURES

Caretakers were interviewed about all 6- to 17-year-olds and 9- to 17-year-olds were directly interviewed separately using the Child and Adolescent Psychopathology Scale (CAPS). 4 All participants are administered the same items addressing attention-deficit/hyperactivity disorder, oppositional defiant disorder (ODD), conduct disorder (CD), MDD, GAD, separation anxiety disorder (SAD), agoraphobia, social phobia, specific phobia, and obsessive-compulsive disorder (OCD) symptoms. The GAD symptom of difficulty controlling worrying was judged to be too difficult for respondents to report and was not included. The CAPS items that cover DSM-IV symptoms are based on the “stem questions” of the Diagnostic Interview Schedule for Children. 20 Rather than asking Diagnostic Interview Schedule for Children “contingent questions” to address frequency, duration, and severity, respondents are asked to think about how well each stem question describes the youth’s emotion or behavior, how often it occurred, and how serious it was during the last 12 months using a 4-point response scale: 1 indicates not at all; 2, just a little; 3, pretty much; and 4, very much. Similar to the Diagnostic Interview Schedule for Children, multiple items addressing different aspects of compound symptoms were combined by taking the highest score of the combined items. Consistent with the DSM-IV, 9 of 24 CAPS items that define MDD symptoms refer to changes in functioning (“more/less than usual”) during the last year, as do 3 of 11 items that define GAD symptoms. Items were randomized in the CAPS and administered in 2 counterbalanced orders to control order effects. For the 9% of youth who had taken psychoactive medication during the last year, the respondent was asked to rate the youth when not taking medication.

In a previous study, 2 participants were administered a second CAPS interview 7 to 14 days later. Test-retest intraclass correlation mean ratings of each DSM-IV symptom dimension reported by caretakers were as follows: CD=0.89; ODD=0.80; inattention=0.89; hyperactivity-impulsivity=0.88; MDD=0.82; GAD=0.80; SAD=0.76; social phobia=0.65; specific phobia=0.84; agoraphobia=0.77; and OCD=0.73. Test-retest intraclass correlations for youth reports were as follows: CD=0.78; MDD=0.69; GAD=0.65; SAD=0.68; social phobia=0.62; specific phobia=0.83; agoraphobia=0.70; and OCD=0.67. Robust correlations between symptom dimensions and functional impairment indicated external validity for both versions of the CAPS. 4 Although such dimensional psychopathology scores are strongly correlated with categorical diagnoses, 9-21 they focus on global ratings of symptom severity rather than on diagnostic criteria, such as duration, clustering, and age at onset.

Because caretaker and youth reports of symptoms are modestly correlated, many researchers obtain complementary information from multiple informants. 22 Indeed, several studies indicate that the use of multiple informants improves the validity of assessments of psychopathology in children and adolescents, but the optimal informants are different at different ages and for different disorders. Children at least 9 years of age are reliable and valid informants on anxiety, depression, and CD, but not on ODD and attention-deficit/hyperactivity disorder. 23,24 Based on these considerations, parent and youth reports of symptoms of anxiety disorders, depression, and CD were combined using the standard method of taking the higher rating of each symptom from the adult caretaker or youth. 25 Only caretaker ratings defined ODD and attention-deficit/hyperactivity disorder. The present analyses were limited to 1571 pairs of 9- to 17-year-old twins in which both informants were interviewed. To ensure that combining parent and youth reports did not bias findings, the primary models were refit using only parent ratings of all symptom dimensions for 6- to 17-year-old twins with qualitatively identical results (available on request).

STATISTICAL ANALYSES

Mean ratings of the 11 psychopathology dimensions were residualized on age, sex, age-squared, and age×sex. Univariate
bivariate models were used to decompose observed phenotypic variance into variance attributable to additive genetic factors (A), dominance genetic factors (D), environmental factors shared by the twins (C), and environmental factors not shared by the twins plus measurement error (E) and to account for sibling interaction or rater bias (S).\(^\text{27}\) A correlated factors multivariate biometric model\(^\text{27}\) was used to estimate the variances for genetic and environmental components for each psychopathology phenotype and the \(11 \times 11\) covariance matrices among the genetic, and environmental, components of variance.\(^\text{28}\) Model estimation for the 11 psychopathology dimensions was based on the observed \(22 \times 22\) phenotypic covariance matrices for the 11 phenotypes across the 2 co-twins for each type of twin pair.

We then separately tested alternative models of the underlying structure of the genetic and environmental covariances using a series of hierarchical CFAs. We tested models with 1 through 4 factors for each of A and E. In models for A, no factor structure or other restrictions were imposed on E, allowing the E components of each phenotypic dimension to freely correlate. Similar models were tested for E, allowing the A components to correlate freely.

We used standard covariance structure model estimation procedures in Mplus 5.\(^\text{18}\) for bifactorial and hierarchical biometric-CFA models. Such procedures will be maximum likelihood if the raw data are multivariate normal. We compared nested models using the Satorra-Bentler scaled-difference \(\chi^2\) test, however, that test is valid for large samples even if the data are skewed.\(^\text{30}\) We also used information-theoretic indices to compare the fit of alternative etiologic models underlying the observed phenotypic covariance matrices. Under normality, a Bayesian information criterion (BIC)\(^\text{31}\) can be computed for biometric and CFA models, comparing each model to a “saturated” model in which each manifest variable has its own latent dimension. BIC includes a penalty for the number of parameters in the model so that the alternative model with the lower BIC is preferred in the sense of balancing model parsimony with fidelity to the data in representing the observed covariances among the variables. The standardized root mean square residual\(^\text{32}\) quantifies the standardized difference between the observed predicted covariances, with 0 indicating a perfect fit and values less than 0.08 conventionally indicating a good fit. The root mean square error of approximation\(^\text{33}\) estimates the discrepancy between the index model and the true population covariance matrix of the variables. Smaller values of root mean square error of approximation indicate better fit, with values less than 0.05 conventionally indicating close fits.\(^\text{31}\)

### RESULTS

#### UNIVARIATE BIOMETRIC MODELS

For each phenotype, alternative univariate models containing A, E, and either C, D, or S were compared. Because C, D, and S are estimated using the same information, they cannot be included in the same model. The best-fitting model for each phenotype was chosen on the basis of BIC (Table 1). For CD, inattention, and hyperactivity-impulsivity, AE+S models had the lowest BICs, although estimates of S were small (CD = −0.08, hyperactivity-impulsivity = −0.11, and inattention = −0.15). Negative estimates of S are interpreted as reflecting biases due to raters contrasting twin behavior or competition between twins.\(^\text{34}\)

#### MULTIVARIATE BIOMETRIC MODELS

Genetic and nonshared environmental contributions to variance in the 11 manifest psychopathology dimensions, and the correlations among the genetic and nonshared environmental contributions to these 11 phenotypes derived from the correlated factors model, are given in Table 2. The contributions of shared environmental influences on each psychopathology dimension could be set to 0 without loss of fit except for GAD, MDD, SAD, and OCD. Estimates of shared environmental influences for these phenotypes were as follows: MDD = 0.03, GAD = 0.03, SAD = 0.23, and OCD = 0.21. All 6 correlations among these C components were significant, ranging from 0.11 between GAD and OCD to 0.93 between MDD and GAD (available on request); C for these 6 phenotypes was allowed to correlate freely. All multivariate models included S for inattention, hyperactivity-impulsivity, and CD, but because they do not reflect genetic or environmental influences, they were not allowed to correlate.

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**Table 1. Fit Statistics for the Alternative Univariate Biometric Models for Each Observed Dimension of Child and Adolescent Psychopathology Based on Combined Caretaker and Youth Reports**

<table>
<thead>
<tr>
<th>Dimension</th>
<th>ACE</th>
<th>ADE</th>
<th>AE+S</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BIC</td>
<td>RMSEA</td>
<td>BIC</td>
<td>RMSEA</td>
</tr>
<tr>
<td>Generalized anxiety</td>
<td>4382</td>
<td>0.000</td>
<td>4394</td>
<td>0.046</td>
</tr>
<tr>
<td>Major depression</td>
<td>4409</td>
<td>0.000</td>
<td>4427</td>
<td>0.057</td>
</tr>
<tr>
<td>Separation anxiety</td>
<td>5174(a)</td>
<td>0.004</td>
<td>5220</td>
<td>0.090</td>
</tr>
<tr>
<td>Obsessive-compulsive</td>
<td>3882(a)</td>
<td>0.018</td>
<td>3922</td>
<td>0.080</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>4476</td>
<td>0.032</td>
<td>4479</td>
<td>0.032</td>
</tr>
<tr>
<td>Social phobia</td>
<td>5224</td>
<td>0.034</td>
<td>5226</td>
<td>0.031</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>4524</td>
<td>0.000</td>
<td>4525</td>
<td>0.000</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>−1576</td>
<td>0.020</td>
<td>−1570</td>
<td>0.022</td>
</tr>
<tr>
<td>Oppositional defiant</td>
<td>3681</td>
<td>0.000</td>
<td>3687</td>
<td>0.009</td>
</tr>
<tr>
<td>Inattention</td>
<td>5337</td>
<td>0.000</td>
<td>5337</td>
<td>0.000</td>
</tr>
<tr>
<td>Hyperactivity-impulsivity</td>
<td>4098</td>
<td>0.040</td>
<td>4078</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Abbreviations: A, additive genetic influences; BIC, Bayesian information criterion; C, shared environmental effects; D, dominance genetic influences; E, nonshared environmental influences, plus measurement error; RMSEA, root mean square error of approximation; S, sibling interaction or rater bias.

\(a\)Best-fitting model based on the lowest BIC.
The correlations in Table 2 quantify the extent to which the 11 psychopathology dimensions are associated owing to common genetic and common nonshared environmental influences on each pair of dimensions. All 11 psychopathology dimensions were heritable, and substantial genetic correlations accounted for most of the phenotypic correlations among the psychopathology dimensions (Table 2, below the diagonal). In contrast, nonshared environmental influences were substantial, but correlations among these influences for the 11 psychopathology dimensions were substantially smaller (Table 2, above the diagonal).

### MULTIVARIATE TESTS OF ALTERNATIVE HYPOTHESES FOR GENETIC STRUCTURE

Because our theoretical interest is in what the patterns of higher-order genetic and environmental correlations among the psychopathology phenotypes in Table 2 reveal about taxonomy and etiology, the 11-dimension correlated factors model is not informative on this issue; it allows the genetic and environmental influences on the 11 psychopathology dimensions to correlate freely without imposing any higher-order structure on the correlations. Therefore, a series of models was estimated to compare alternative hypotheses regarding theoretically informative patterns of correlated genetic and environmental influences.

#### Model 1

Most previous molecular genetic studies have sought to identify risk polymorphisms for 1 mental disorder at a time, reflecting the implicit extreme assumption that each mental disorder has mostly disorder-specific genetic risks. Therefore, model 1 in Table 3 reflects the extreme view that each dimension of psychopathology has only dimension-specific genetic influences that are uncorrelated with genetic influences on any of the other dimensions.

#### Model 2

This alternative model, which fit better than model 1, tests the hypothesis that all pleiotropic sharing of genetic influences by the psychopathology dimensions is through a single higher-order factor.

#### Model 3

This model tested the hypothesis that genetic components of the 6 anxiety disorders and MDD load on a higher-order internalizing factor and that genetic components of the 4 disruptive behavior disorders load on a higher-order externalizing factor. Model 3 fit significantly better than did model 2 (Table 3), consistent with the hypothesis that at least some genetic factors nonspecifically influence risk for psychopathology dimensions within each of the internalizing and externalizing domains. Based on the results of an earlier phenotypic CFA of the present sample, we tested an untabulated submodel of model 3 in which MDD and GAD were allowed to load on the higher-order internalizing and externalizing genetic factors, but the fit (BIC=5347) did not improve over model 3 (Satorra-Bentler scaled-difference $\chi^2=2.9$, $P=.23$).

#### Models 4 and 5

Importantly, the estimated correlation between the latent internalizing and externalizing genetic factors in model 3 was $r=0.89$, suggesting that many of the same genetic factors affect variability in the psychopathology dimensions in both the internalizing and externalizing domains. Based on this revealing observation, model 4 was formulated to test the addition of a third higher-order genetic factor, global psychopathology, on which all psychopathology dimensions loaded. Correlations among the global, internalizing, and externalizing factors were set to 0 in model 4. As reported in Table 3, model 4 fit significantly better than the 2-factor model (ie, model...
3), suggesting that in addition to the higher-order internalizing and externalizing factors, there is a global genetic factor that influences variability in all 11 psychopathology dimensions. Model 5, which allowed the internalizing and externalizing factors to correlate, fit significantly better than did model 4.

The proportions of genetic variance in each dimension of psychopathology explained by each higher-order factor and by unique genetic influences in model 5 are shown in Figure 1. For 8 of the 11 symptom dimensions, at least 68% of their genetic variance was accounted for by various combinations of the 3 higher-order genetic factors, with a small to modest proportion of their genetic variance being unique to each of these 8 dimensions. Approximately half (52%-54%) of the additive genetic variance of the remaining 4 symptom dimensions was unique to that dimension, with the other half shared with the higher-order genetic factors.

Model 6

We also tested a 4-factor model that included a separate fourth factor for MDD and GAD only that did not fit as well as did model 5.

### Table 3. Fit Statistics for Alternative Hierarchical Multivariate Models of Additive Genetic Influences

<table>
<thead>
<tr>
<th>Alternative Model</th>
<th>Satorra-Bentler Model $X^2$</th>
<th>df</th>
<th>$P$ Value</th>
<th>RMSEA</th>
<th>SRMR</th>
<th>BIC</th>
<th>$X^2$ Test Comparing Models</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unique A on each dimension only (all A components are uncorrelated)</td>
<td>2192.7</td>
<td>443</td>
<td>&lt;.001</td>
<td>0.060</td>
<td>0.191</td>
<td>27981</td>
<td>2192.7 vs 2192.7</td>
<td>1.000</td>
</tr>
<tr>
<td>2. One higher-order factor on which all dimensions load</td>
<td>1058.1</td>
<td>431</td>
<td>&lt;.001</td>
<td>0.043</td>
<td>0.087</td>
<td>27271</td>
<td>2 vs 1: $X^2=821.4$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3. Internalizing and externalizing, correlated</td>
<td>900.9</td>
<td>430</td>
<td>&lt;.001</td>
<td>0.037</td>
<td>0.070</td>
<td>27090</td>
<td>3 vs 2: $X^2=11.1$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4. General, internalizing, and externalizing, no correlation</td>
<td>706.5</td>
<td>422</td>
<td>&lt;.001</td>
<td>0.029</td>
<td>0.061</td>
<td>26888</td>
<td>4 vs 3: $X^2=206.8$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>5. General, internalizing, and externalizing (I and E correlated)</td>
<td>639.1</td>
<td>421</td>
<td>&lt;.001</td>
<td>0.028</td>
<td>0.060</td>
<td>26972</td>
<td>5 vs 4: $X^2=8.0$</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>6. Eleven-factor model (no higher-order structure on A components)</td>
<td>536.2</td>
<td>388</td>
<td>&lt;.001</td>
<td>0.022</td>
<td>0.060</td>
<td>26951</td>
<td>6 vs 5: $X^2=169.7$</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: A, additive genetic variance; BIC, Bayesian information criterion; df, residual degrees of freedom; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; $\Delta$, Satorra-Bentler scaled-difference.

a Internalizing (major depressive disorder and all anxiety dimensions) and externalizing (inattention, hyperactivity-impulsivity, oppositional defiant disorder, and conduct disorder).
b Internalizing (major depressive disorder and all anxiety dimensions), externalizing (inattention, hyperactivity-impulsivity, oppositional defiant disorder, and conduct disorder), and global (all dimensions).
c Higher-order externalizing and internalizing factors were not allowed to correlate in model 4 but were allowed to correlate in model 5.
d Fit statistics for the best-fitting model based on lowest BIC and interpretability.

**Figure 1.** Proportions of genetic variance in combined adult caretaker- and youth-reported dimensions of child and adolescent psychopathology (model 4, Table 3) associated with 3 higher-order latent genetic factors and unique to each specific dimension of psychopathology (gu). Ag indicates agoraphobia; CD, conduct disorder; GAD, generalized anxiety disorder; H/I, hyperactivity-impulsivity; Inatt, inattention; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; SAD, separation anxiety disorder; SoPh, social phobia; and SpPh, specific phobia.
MULTIVARIATE TESTS OF ALTERNATIVE HYPOTHESES FOR ENVIRONMENTAL STRUCTURE

A parallel set of analyses was conducted for the E covariance structure in Table 2, allowing A to correlate freely. As reported in Table 4, a 3 higher-order factor model like that for A fit best, but, as shown in Figure 2, for 8 of the 11 psychopathology phenotypes, most of E was unique (not shared with other dimensions). Exceptions are ODD, which shares half of its E variance with the higher-order factors, and MDD and GAD, which are the only 2 dimensions with high loadings on the global factor.

The results of the present analyses have important implications both for understanding the nature of child and adolescent psychopathology and for the design of future studies of etiology and pathophysiology.

STRUCTURE OF GENETIC INFLUENCES

The present findings support hypotheses derived from studies of adult twins based on categorical diagnoses of mental disorders that 2 sets of pleiotropic genetic fac-

<table>
<thead>
<tr>
<th>Alternative Model</th>
<th>Satorra-Bentler Model X2</th>
<th>df</th>
<th>P Value</th>
<th>RMSEA</th>
<th>SRMR</th>
<th>BIC</th>
<th>X2 Test Comparing Models</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unique A on each dimension only (all A components are uncorrelated)</td>
<td>2192.7</td>
<td>443</td>
<td>&lt;.001</td>
<td>0.071</td>
<td>0.062</td>
<td>28 621</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. One higher-order factor on which all dimensions load</td>
<td>1017.8</td>
<td>432</td>
<td>&lt;.001</td>
<td>0.042</td>
<td>0.064</td>
<td>27 231</td>
<td>2 vs 1: ΔX2=1212.1</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
| 3. Internalizing and externalizing, correlated
d | 870.2 | 431 | <.001 | 0.036 | 0.063 | 27 049 | 3 vs 2: ΔX2=60.0 | <.001 |
| 4. General, internalizing, and externalizing, no correlationb | 619.9 | 421 | <.001 | 0.025 | 0.061 | 26 815 | 4 vs 3: ΔX2=249.5 | <.001 |
| 5. General, internalizing, and externalizing (I and E correlated)b,c | 618.8 | 420 | <.001 | 0.024 | 0.061 | 26 615 | 5 vs 4: ΔX2=1.1 | >.05 |
| 6. Eleven-factor model (no higher-order structure on A components) | 536.2 | 388 | <.001 | 0.022 | 0.060 | 26 951 | 6 vs 4: ΔX2=99.9 | <.001 |

Abbreviations: BIC, Bayesian information criterion; df, residual degrees of freedom; E, nonshared environmental variance; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; Δ, Satorra-Bentler scaled-difference.

a Internalizing (major depressive disorder and all anxiety dimensions) and externalizing (inattention, hyperactivity-impulsivity, oppositional defiant disorder, and conduct disorder).
b Internalizing (major depressive disorder and all anxiety dimensions), externalizing (inattention, hyperactivity-impulsivity, oppositional defiant disorder, and conduct disorder), and global (all dimensions).
c The higher-order externalizing and internalizing factors were not allowed to correlate in model 4 but were allowed to correlate in model 5.
d Best-fitting model based on lowest BIC and interpretability.

Figure 2. Proportions of nonshared environmental variance in combined adult caretaker- and youth-reported dimensions of child and adolescent psychopathology (model 4, Table 3) associated with 3 higher-order latent nonshared environmental factors and unique to each specific dimension of psychopathology (eu).

Ag indicates agoraphobia; CD, conduct disorder; GAD, generalized anxiety disorder; H/I, hyperactivity-impulsivity; Inatt, inattention; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; SAD, separation anxiety disorder; SoPh, social phobia; and SpPh, specific phobia.
ators nonspecifically influence risk for all internalizing or all externalizing psychopathology dimensions during childhood and adolescence. Furthermore, the present findings are consistent with the new hypothesis that a set of highly pleiotropic genetic influences are globally associated to varying degrees with risk of all 11 prevalent forms of child and adolescent psychopathology. Furthermore, all psychopathology dimensions also are influenced by unique genetic factors with varying, but usually small, magnitudes of effect. It is informative that some psychopathology dimensions had slightly more unique than shared genetic variance, but the estimates of unique genetic variance never exceed 55% of the total genetic variance for any dimension of psychopathology.

These findings strongly suggest that most additive genetic factors associated with variation in the common psychopathology dimensions in children and adolescents are not specific to each individual dimension of psychopathology. Rather, the 3 patterns of pleiotropy identified in these analyses seem to be the principal modes of genetic risk transmission for most of the 11 dimensions of child and adolescent psychopathology.

The present findings based on sharing of etiologic influences were not fully consistent with the hypothesis based on studies of mental disorders in adults that anxiety disorders and depression can be parsed into 2 correlated higher-order domains: distress (MDD, dysthymia, GAD, and posttraumatic stress disorder) and fears (specific phobia, agoraphobia, social phobia, and panic disorder). It is possible that separate higher-order fears and distress factors would have been identified in the present study had symptoms of posttraumatic stress disorder been assessed, but it also is possible that the distinction between the distress and fears domains emerges in adulthood only. Still, it is important to note that the internalizing factor in Figures 1 and 2 might be considered a fears factor because MDD and GAD did not load on it in the best-fitting models.

STRUCTURE OF ENVIRONMENTAL INFLUENCES

Nonshared environmental influences jointly influenced multiple correlated psychopathology dimensions to a modest extent, but most of the nonshared environmental variance was unique for most dimensions (Table 1 and Figure 2). Exceptions are ODD, which was found to share half of its nonshared environmental variance with higher-order factors, and MDD and GAD, which had the highest loadings on the global E factor and small unique E variances. This suggests that nonshared environmental influences on MDD and GAD are mostly not unique to them in this age range.

Shared environmental influences were mostly near or at zero, except for modest C for SAD and OCD. Correlations in C across dimensions were sometimes large, but the absolute magnitude of C that these disorders shared was small.

Taken together, these findings indicate that phenotypic correlations among dimensions of child and adolescent psychopathology are primarily, but not entirely, due to correlated additive genetic influences. This does not rule out the possibility of gene-environment correlations and interactions as sources of shared etiologic influences. This is because gene-environment correlations and gene-environment interactions with C are folded into estimates of A in biometric models, whereas gene-environment interactions with E are included in estimates of E. Nonetheless, the present findings on child and adolescent psychopathology are generally consistent with Plomin’s “generalist genes, specialist environments” hypothesis for cognitive abilities. That is, pleiotropic genetic factors tend to promote correlations among phenotypes, whereas environments tend to promote their differentiation.

IMPLICATIONS FOR TAXONOMY AND NEUROBIOLOGY

If the emerging view that common forms of psychopathology are best treated as dimensional phenomena that are dichotomized using data-based but conventional thresholds to facilitate treatment decisions is supported, the present findings have important implications for taxonomy. They support an etiologic explanation for the observation that child and adolescent psychopathology is phenotypically organized within the higher-order internalizing and externalizing domains. As with adult psychopathology, we hypothesize that dimensions of child and adolescent psychopathology within both the internalizing and externalizing domains are highly correlated largely because they share genetic influences. Furthermore, the present findings suggest a genetic explanation for the well-documented but largely ignored robust correlation between the internalizing and externalizing domains of psychopathology. That is, the broad construct of “psychopathology” may have a physical reality in the sense that all 11 psychopathology dimensions were found to share some of the same genetic influences, albeit to varying extents.

LIMITATIONS AND FUTURE DIRECTIONS

The present findings are based on a standard method of combining symptom reports from multiple informants, but additional psychometric research is needed to compare alternative methods of doing so. Although the present findings were replicated using the parent informant only, other methods of combining reports from multiple informants could have yielded different results. Therefore, the paucity of knowledge on the optimal way to combine data from multiple informants is a limitation of the present study that would similarly limit other studies of child and adolescent psychopathology at present.

It is important to attempt to disconfirm the present hypotheses regarding the higher-order genetic structure of child and adolescent psychopathology in future studies for at least 3 reasons. First, consistent with previous recommendations, this hypothesis implies that rather than searching for genetic polymorphisms associated with psychopathology 1 disorder at a time, it would be far more informative to simultaneously search for networks of pleiotropic genetic factors associated with multiple forms of psychopathology (and for the dimension-
specific genetic and environmental factors uniquely associated with each dimension of psychopathology. This would require measuring multiple phenotypes in each study (across both the internalizing and externalizing domains) and conducting genetic association analyses that squarely address the likelihood of widespread pleiotropy. Although the field will eventually discover which genetic variants are associated with multiple psychopathology dimensions even if we mostly study mental disorders 1 at a time, the present hypothesis imposes a testable model on the data that should make gene discovery more efficient and revealing about the biological nature of psychopathology.

Second, there is evidence from the study of somatic characteristics that pleiotropic genes generally have stronger effects than do other genes. This also could be true of genes that are pleiotropically associated with multiple psychopathology dimensions. Because the hypothesized global psychopathology genetic factor is related to many psychopathology dimensions (regardless of which symptoms are exhibited at any point in time), the association between each pleiotropic gene variant with higher-order psychopathy dimensions may be stronger than the association of the same variant with lower-order psychopathology dimensions. Indeed, there is evidence that the heritability of the higher-order latent externalizing factor could be almost twice that of lower-order dimensions. Therefore, the likelihood of detecting gene variants associated with higher-order psychopathology dimensions may be greater than for lower-order dimensions.

Third, because gene variants associated with the higher-order phenotypes simultaneously influence multiple psychopathology dimensions, they increase risk for comorbid mental health problems. Therefore, it is particularly important to discover pleiotropic psychopathology risk genes because comorbid mental disorders are associated with more distress, functional impairment, persistence, and mental health service use than single disorders. It will be important to test the present etiologic hypothesis at the molecular level. In the present analyses, the genetic influences on each psychopathology dimension were latent, inferred from the analyses of twin pairs. If such participants undergo genotyping, however, it should be possible to directly estimate from the measured polymorphisms, although the genotyping and statistical methods for doing so are still under development. In principle, A for each psychopathology dimension could be estimated from the sums of the varying magnitudes of association of all polymorphisms with that phenotype. The variance-covariance matrix of the A components for all psychopathology dimensions could then be computed and subjected to CFA to determine whether the same higher-order factor structure fits the genetic database on measured polymorphisms.

If the present hypothesis is supported at the molecular level, it would likely force a foundational shift in how the neurobiologic systems underlying common forms of psychopathology is conceptualized. Genetic polymorphisms influence risk for psychopathology by encoding protein components of neurons and other relevant biological systems through a chain of processes. If many genetic polymorphisms are pleiotropically associated with variation in all psychopathology dimensions (and within the internalizing and externalizing domains) that would almost certainly mean that those correlated forms of psychopathology share many aspects of their genetically influenced pathophysiology. That is, in contrast to the dominant paradigm in which forms of psychopathology are studied singly as if each were neurobiologically unique, the present genetic hypothesis implies that patterns of dysfunction in neurobiological systems may be related to risk for multiple psychopathology dimensions, likely through transactions with the environment. In turn, this implies that neurobiological studies should consider multiple neurobiological systems and multiple forms of psychopathology at the same time to identify the common and dimension-specific mechanisms underlying psychopathology.

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REFERENCES

12. Waldman ID, Lilienfeld SO, Lahey BB. Toward construct validity in the child-


