The Structure of Genetic and Environmental Risk Factors for Anxiety Disorders in Men and Women

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Background: The anxiety disorders exhibit high levels of lifetime comorbidity with one another. Understanding the underlying causes of this comorbidity can provide insight into the etiology of the disorders and inform classification and treatment.

Objective: To explain anxiety disorder comorbidity by examining the structure of the underlying genetic and environmental risk factors.

Design: Lifetime diagnoses for 6 anxiety disorders (generalized anxiety disorder, panic disorder, agoraphobia, social phobia, animal phobia, and situational phobia) were obtained during personal interviews from a population-based twin registry. Multivariate structural equation modeling that allowed for sex differences was performed.

Setting: General community sample.

Participants: More than 5000 members of male-male and female-female twin pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders.

Main Outcome Measures: Parameter estimates for best-fitting model.

Results: The full model, which contained 2 common genetic, shared environmental, and unique environmental factors plus disorder-specific factors, could be constrained to equality across male and female study participants. In the best-fitting model, the genetic influences on anxiety were best explained by 2 additive genetic factors common across the disorders. The first loaded most strongly in generalized anxiety disorder, panic disorder, and agoraphobia, whereas the second loaded primarily in the 2 specific phobias. Social phobia was intermediate in that it was influenced by both genetic factors. A small role for shared environmental influences was observed owing to a single common factor that accounted for less than 12% of the total variance for any disorder. Unique environmental influences could be explained by a single common factor plus disorder-specific effects.

Conclusions: The underlying structure of the genetic and environmental risk factors for the anxiety disorders is similar between men and women. Genes predispose to 2 broad groups of disorders dichotomized as panic-generalized-agoraphobic anxiety vs the specific phobias. The remaining associations between the disorders are largely explained by a unique environmental factor shared across the disorders and, to a lesser extent, a common shared environmental factor.

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Twin Registry, suggested significant genetic correlation between GAD and panic disorder and between these syndromes and posttraumatic stress disorder. Contrary to these findings, most family studies of the anxiety disorders reported relative specificity in their familial aggregation.

Like genetic factors, the experience of stressful life events, either shared with other family members or unique to the individual, is etiologically related to the development of anxiety disorders and is likely to have nonspecific effects across disorders. For example, many forms of childhood adversity are associated with adult psychiatric outcomes with little specificity, including the anxiety disorders. Childhood sexual abuse has been found to elevate the risk for adult GAD and panic disorder, as well as other psychiatric and substance use disorders. Similarly, childhood parental loss or separation has been linked to various forms of adult psycho-pathologic characteristics.

In this study, we used multivariate twin analysis to examine the latent structure of the genetic and environmental risk factors that underlie 6 anxiety disorders. We attempted to answer the following questions: (1) How similar is the pattern of genetic and environmental risk factors across the anxiety disorders in men and women? (2) Can one identify shared risk factor domains (genetic, common familial environment, or unique individual environment) that account for the phenotypic correlations (comorbidity) among the anxiety disorders? (3) If shared risk factors exist, how are they structured (ie, how many separate factors are necessary to best describe patterns of comorbidity)? (4) What are the relative roles of risk factors that are common across the anxiety disorders vs those that are disorder specific?

**METHODS**

**SAMPLE AND ASSESSMENT PROCEDURES**

The sample in this study derives from the population-based Virginia Adult Twin Study of Psychiatric and Substance Use Disorders. Female-female (FF) twin pairs, from birth years 1934 to 1974, became eligible if both members previously responded to a mailed questionnaire between 1987 and 1988, the response rate to which was approximately 64%. They were approached for 4 subsequent waves of personal interviews from 1988 to 1997, with individual cooperation rates ranging from 85% to 92%. Between waves 1 and 2, from which the current analyses derive, the pairwise cooperation rate was approximately 90% and the time between the 2 interviews was approximately 13 to 15 months. The male-female (MFFM) twin pairs, covering the birth years 1940 to 1974, were ascertained in a separate study, with an initial cooperation rate of 72.4%, and were approached for 2 waves of interviews from 1993 until 1998. Zygosity was determined by a combination of standard questions, photographs, and DNA analysis. The mean (SD) ages of the FF and MFFM samples at their final interviews were, respectively, 36.6 (8.1) years and 36.8 (9.1) years. Interviewers had a master's degree in a mental health–related field or a bachelor's degree in this area plus 2 years of clinical experience. At each wave, members of a twin pair were interviewed by different individuals who were blind to clinical information about the co-twin. In this report, we examine only same-sex twin pairs and will therefore refer to male pairs as the MM sample.

The phobias were diagnosed using an adaptation of DSM-III criteria, which required the presence of 1 or more of 22 fears that the respondent recognized as unreasonable and that, in the judgment of the interviewer, objectively interfered with the respondent's life. They were grouped according to standard nomenclature as agoraphobia, social phobia, or specific phobia, the last having been further subtyped by the nature of the respondent's fears (animal, situational, or blood injury). Since a low prevalence of GAD and panic disorder had been problematic in previous analyses, modified DSM-III-R diagnostic criteria were used for these conditions. We adopted a broad diagnostic approach to these 2 disorders, reducing the minimum duration from 6 months to 1 month for GAD and requiring a history of panic attacks that met at least 2 symptomatic criteria, peaking within 30 minutes for panic disorder.

We have shown that these approaches reflect the same continuum of liability as the fully syndromal disorders. The diagnostic data used in these analyses came from various waves of the 2 samples. In the FF sample, all diagnoses came from the first wave (2150 participants) except for panic disorder, which was derived from wave 2. In the MFFM sample, approximately 12 to 15 months later. The pairwise cooperation rate was approximately 90% between the 2 interviews. For the MM sample, all diagnoses were obtained from the second wave (2939 participants). Comorbidity in these analyses refers to the lifetime occurrence of 2 or more disorders within an individual.

**STATISTICAL ANALYSES**

We have outlined elsewhere our approach to multivariate genetic analysis. The models described herein are based on a liability threshold model, the strengths and limitations of which have been previously discussed. Like traditional factor analysis, multivariate genetic analysis seeks to explain covariation among multiple variables with a few factors. However, traditional exploratory factor analysis is purely descriptive, whereas multivariate genetic analysis provides insight into the sources of resemblance.

Using the software package Mx, we fit models by the method of maximum likelihood to data from all individual twins, including those with missing data or without an interviewed co-twin. This method can reduce the impact of cooperation bias if the data are “missing at random” as described by Little and Rubin.

For these analyses, we used independent pathway models that contained 2 genetic common (A1, A2), 2 shared environmental common (C1, C2), and 2 unique environmental common (E1, E2) factors in addition to disorder-specific factors. Two factors were used based on indications from other analyses that phobias may be etiologically distinct from the other anxiety disorders and because of computational limitations in trying to model more than 2 factors. Also, to keep computer run-times tractable, we restricted our analyses to the simultaneous modeling of 6 disorders, including data from only 2 of 3 available specific phobia subtypes for these analyses.

We fit this model to both the MM and FF data sets, first allowing all parameters, including thresholds, to vary by sex. We then constrained all of the path estimates (but not the thresholds) to be equal in the 2 sexes. We did this for all of the path estimates en masse to test the global structural equivalence across sexes rather than test each individual pathway. We fit subsequent, simpler submodels with the goal of obtaining an over-
all best-fitting model that best explained the data by taking ma-
imal account of risk factors shared between the anxiety disorders.
To minimize the overall number of tests and therefore type I
error, we compared submodels created by simplifications across
classes of factors (common vs disorder specific) rather than test-
ing the significance of each of the individual path loadings. Twice
the difference in log likelihood between a higher order and sub-
model yields a statistic that is asymptotically distributed as $\chi^2$
with the $df$ equal to the difference in their number of parame-
ters. We used the Akaike information criterion (AIC)\(37\) for
model selection. The lower its value, the better the balance be-
 tween explanatory power and parsimony.

Table 1. Lifetime Prevalence Rates and Comorbidity Among 6 Anxiety Disorders
in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders\(^*\)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lifetime Prevalence, %</th>
<th>Odds Ratio (95% Confidence Interval), Tetrachoric Correlation(^†)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD</td>
</tr>
<tr>
<td>GAD†</td>
<td>14.6</td>
<td>25.8</td>
</tr>
<tr>
<td>Panic</td>
<td>4.8</td>
<td>11.9</td>
</tr>
<tr>
<td>Social phobia</td>
<td>6.3</td>
<td>11.4</td>
</tr>
<tr>
<td>Animal phobia</td>
<td>5.2</td>
<td>10.9</td>
</tr>
<tr>
<td>Situational phobia</td>
<td>9.5</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Abbreviation: GAD, generalized anxiety disorder.
*\(N = 5000\), varying depending on diagnosis.
†Results for men are above the diagonal formed by the ellipses; for women, below.
‡Broad diagnostic criteria.
§Statistically nonsignificant.

include factors that affect the individual anxiety disorders
in a disorder-specific fashion. Model 1 allows for the ef-
effects of the various factors to differ between men and
women, whereas model 2 constrains these to be equal
across the sexes. Model 2 provides a better balance of par-
simony and explanatory power by lower AIC (by 52.3
units) and is not significantly different from model 1 by a \(\chi^2\) difference test (\(\Delta \chi^2 = 37.74\), \(P = .77\)), suggesting that the pattern of genetic and environmental risk factors does
differ significantly between men and women, as had
been seen in prior univariate analyses of these disor-
ders. All subsequent models will therefore ignore sex dif-
f erences in the effects of the latent factors on the disor-
ders.

Models 3a and 3b attempted to simplify the factor struc-
ture by removing the effects of disorder-specific additive
genetics or shared environment. Both provided an
improvement in parsimony via lower AIC compared with
model 2. However, model 4a, in which both were re-
moved simultaneously, provided the most parsimonious
model with the full 2-2-2 structure for the common
factors. However, given the substantial disorder-
specific genetic loading on agoraphobia in the full model,
we tested its significance separately by including it in
model 4b. A comparison between models 4a and 4b shows a
significant effect of this factor (\(\Delta \chi^2 = 4.01\), \(P = .04\)), which
was retained in subsequent submodels.

Models 5a (1-2-2), 5b (2-1-2), and 5c (2-2-1) tested
the hypotheses that 2 vs 1 additive genetic, shared en-
vironmental, or unique environmental common fac-
tors, respectively, are required to best explain the pat-
tern of comorbidity between the anxiety disorders. Model
5a, in which the effects of \(A_2\) were constrained to 0 but
the effects of \(C_2\) and \(E_2\) were retained, provided a slightly
improved AIC but a nearly significant deterioration in
fit as indicated by the \(\chi^2\) difference (\(P = .11\)). Model 5c
(2-2-1) provided the lowest AIC of this class of models,
suggesting that the unique environmental risk factors can
be effectively explained using 1 common factor (\(E_i\)) plus
disorder-specific factors.
Table 2. Multivariate Model-Fitting Results for 6 Anxiety Disorders in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders*

<table>
<thead>
<tr>
<th>Model</th>
<th>Common Factors</th>
<th>Disorder-Specific Factors</th>
<th>−2LL</th>
<th>df</th>
<th>AIC</th>
<th>Δχ²</th>
<th>Δdf</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A₁-A₂-C₁-C₂-E₁-E₂</td>
<td>All A⁺E⁺-C⁺</td>
<td>17537.06</td>
<td>30298</td>
<td>-43108.94</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>A₁-A₂-C₁-C₂-E₁-E₂</td>
<td>All A⁺C⁺-E⁺-E₂</td>
<td>17574.80</td>
<td>30343</td>
<td>-43111.21</td>
<td>37.74</td>
<td>45</td>
<td>.77</td>
</tr>
<tr>
<td>3a</td>
<td>A₁-A₂-C₁-C₂-E₁-E₂</td>
<td>All C⁺E⁺</td>
<td>17576.36</td>
<td>30349</td>
<td>-43121.64</td>
<td>1.56</td>
<td>6</td>
<td>.96</td>
</tr>
<tr>
<td>3b</td>
<td>A₁-A₂-C₁-C₂-E₁-E₂</td>
<td>All A⁺</td>
<td>17574.80</td>
<td>30349</td>
<td>-43123.20</td>
<td>0.0</td>
<td>6</td>
<td>.99</td>
</tr>
<tr>
<td>4a</td>
<td>A₁-A₂-C₁-C₂-E₁-E₂</td>
<td>All E⁺</td>
<td>17579.04</td>
<td>30355</td>
<td>-43130.96</td>
<td>4.24</td>
<td>12</td>
<td>.98</td>
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<tr>
<td>4b</td>
<td>A₁-A₂-C₁-C₂-E₁-E₂</td>
<td>A⁺(ag), All E⁺</td>
<td>17575.03</td>
<td>30354</td>
<td>-43132.97</td>
<td>0.23</td>
<td>11</td>
<td>.99</td>
</tr>
<tr>
<td>5a</td>
<td>A₁-C₁-C₂-E₁-E₂</td>
<td>All A⁺(ag), All E⁺</td>
<td>17584.03</td>
<td>30359</td>
<td>-43133.97</td>
<td>9.00</td>
<td>5</td>
<td>.11</td>
</tr>
<tr>
<td>5b</td>
<td>A₁-A₂-C₁-E₂</td>
<td>All A⁺(ag), All E⁺</td>
<td>17582.27</td>
<td>30359</td>
<td>-43135.73</td>
<td>7.24</td>
<td>5</td>
<td>.20</td>
</tr>
<tr>
<td>5c</td>
<td>A₁-A₂-C₁-C₂-E₁</td>
<td>All A⁺(ag), All E⁺</td>
<td>17577.71</td>
<td>30359</td>
<td>-43140.29</td>
<td>2.68</td>
<td>5</td>
<td>.75</td>
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<tr>
<td>6a</td>
<td>A₁-C₁-C₂-E₁-E₂</td>
<td>A⁺(ag), All E⁺</td>
<td>17589.41</td>
<td>30364</td>
<td>-43138.59</td>
<td>11.70</td>
<td>5</td>
<td>.04</td>
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<tr>
<td>6b</td>
<td>A₁-A₂-C₁-E₁</td>
<td>A⁺(ag), All E⁺</td>
<td>17583.56</td>
<td>30364</td>
<td>-43144.44†</td>
<td>5.85†</td>
<td>5</td>
<td>.32</td>
</tr>
<tr>
<td>7a</td>
<td>A₁-A₂-E₁</td>
<td>A⁺(ag), All E⁺</td>
<td>17604.84</td>
<td>30370</td>
<td>-43135.16</td>
<td>21.28</td>
<td>6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>7b</td>
<td>A₁-A₂-C₁</td>
<td>A⁺(ag), All E⁺</td>
<td>17743.27</td>
<td>30370</td>
<td>-42996.73</td>
<td>159.71</td>
<td>6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>8</td>
<td>A₁-C₁-E₁</td>
<td>A⁺(ag), All E⁺</td>
<td>17624.69</td>
<td>30369</td>
<td>-43113.31</td>
<td>41.13</td>
<td>5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Model 6a and 6b compared the 2 next simpler submodels (1-2-1 vs. 2-1-1) with model 5c. The removal of the effects of A₂ in model 6a produced a significant deterioration in fit (P = .04) and a higher (less negative) AIC, suggesting that 2 additive genetic factors common to all the anxiety disorders best explain the data. Conversely, the improvement in AIC provided by model 6b compared with 5c suggests that 1 shared environmental risk factor common across disorders (vs 2) can adequately explain the data.

Further simplifications to the underlying risk structure beyond model 6b did not produce better fit to the data. Models 7a and 7b, which tested the 2-0-1 and 2-1-0 structures against model 6b, provided worse fit by AIC and could be rejected by the χ² difference test. Model 8, which again tested the significance of the A₁ factor but within the simplified factor structure background, produced a severe deterioration in fit by the χ² difference statistic and thus could also be rejected with confidence.

### PARAMETER ESTIMATES AND VARIANCE PROPORTIONS

Figure 1 and Figure 2 depict the path estimates for the full model for men and women (model 2) and the best-fitting model (model 6b). As can be seen, the overall pattern of loadings is similar between these models, although model 6b provides a substantially improved balance of parsimony and explanatory power and is more easily interpretable. The rest of this section will focus on these latter results. The proportions of variance in liability for the 6 anxiety disorders due to the factors included in this best-fitting model are given in Table 3.

Figure 2 shows that A₁ substantially affects GAD, panic, agoraphobia, and to a lesser extent social phobia, whereas A₂ primarily affects the 2 specific phobia subtypes with less substantial loadings in GAD, panic, and social phobia. This is reflected in Table 3, where A₁ accounts for only approximately 1% of the total variance of the animal and situational phobias, and A₂ accounts for less than 5% of the variance of the first 4 disorders. Agoraphobia alone was found to have a significant proportion of its genetic risk not shared with the other disorders. The total genetic proportion of variance (that is, heritability) was estimated to be approximately 25% to 35% for all disorders except social phobia, in which it accounted for only 10% of the total variance in our data.

The common shared environmental factor, C₁, has loadings of 0.33 or less, accounting for approximately 10% or less of the variance for any of the disorders (Table 3). The common unique environmental factor, E₁, loaded most strongly on agoraphobia but had substantial loadings across all of the disorders except social phobia. Disorder-specific effects were generally higher than those arising from E₂ except for agoraphobia.

### SEX DIFFERENCES IN THE PATTERN OF RISK FACTORS FOR ANXIETY DISORDERS

We applied multivariate structural equation modeling to lifetime diagnoses of 6 anxiety disorders assessed in male and female twins to examine the pattern of genetic and environmental risk factors that underlie their observed comorbidity. In this effort, we sought to answer a series of 4 questions, the last 3 of which will be consolidated for the purposes of discussion.
constraining the path loadings to be equal across the sexes. This produced a nonsignificant deterioration in model fit and a more parsimonious explanation of the data. This is consistent with prior analyses of the individual anxiety disorders in this sample. This finding suggests that despite the nearly 2-fold greater prevalence rate in women, the same underlying liability structure broadly accounts for patterns of comorbidity among the anxiety disorders, independent of sex.

**STRUCTURE OF GENETIC AND ENVIRONMENTAL RISK FACTORS FOR ANXIETY DISORDERS**

We sought to account for the observed comorbidity among the anxiety disorders by starting with a full model that contained 2 factors common to all of the anxiety disorders in each of the risk factor domains (additive genetic, shared environmental, and unique environmental effects), with residual variance explained by disorder-specific factors. By testing successively simpler submodels, we could most parsimoniously explain this comorbidity with a model that contained 4 factors common across the 6 disorders: 2 genetic factors, a single shared environmental factor, and a single unique environmental factor. In this best-fitting model, residual effects were limited (except for agoraphobia-specific genetics) to disorder-specific unique environmental factors that include the effects of measurement error.

The first genetic factor had highest loadings on GAD, panic, agoraphobia, and to a lesser extent, social phobia. A shared genetic diathesis among these disorders is not surprising heuristically and may help to explain their common response to antidepressant medications. However, residual differences among these disorders may be mediated by the relative impact of the second genetic factor and differential effects of the environmental risk factors. One might hypothesize a set of genes that increases the liability of developing a common intermediate phenotype, such as an anxious personality trait, which then interacts with modifier genes or stressful life events to surpass the threshold for the development of 1 or more shared environmental factors.
disorders. Similarly, the finding that the specific phobias load primarily on a second genetic factor uncorrelated with the first suggests that their genetic etiology may be largely distinct from the other disorders. Interestingly, specific phobias do not share the same treatment response to medications as the other disorders studied.

These results have potential implications for the conceptual unity of the anxiety disorders within psychiatric nomenclature. Although heterogeneous in their symptom presentation, age at onset, course of illness, and biological correlates, the results of this study suggest that etiologically, the anxiety disorders possess a relatively simple genetic architecture. Our analyses place agoraphobia and, to a lesser extent, social phobia closer etiologically to GAD and panic disorder than to the specific phobias. Given the way that agoraphobia is defined in relation to panic disorder, this is not surprising. For social phobia, the decision to place it in a separate category from the specific phobias is in part supported by these analyses. In addition, although GAD and panic disorder were created as separate disorders out of the former category of anxiety neurosis, their risk structure is remarkably similar.

Because of computational limitations, we could simultaneously model only 6 disorders and thus did not include all available specific phobia subtypes. To examine the effect of omitting blood-injury phobia on the present results and also understand how it fits into the risk structure, we analyzed a model that substituted it for a subset of 5 internalizing disorders: major depression, their risk structure is remarkably similar. The findings of this analysis have important implications for studies that seek to find the genes that increase liability for the anxiety disorders. For monogenic illnesses, genetic studies have traditionally emphasized the importance of selecting a “pure” phenotype to maximize the power of detecting the effect of the causative gene. To do so may be more difficult (and likely less appropriate) for complex, multifactorial disorders that exhibit nonmendelian inheritance and high rates of comorbidity. Gene-finding studies for the anxiety disorders may benefit from a multivariate approach using a broadened phenotype that includes a range of disorders with shared genetic risk factors. For example, a linkage study39 that used such a broadened phenotype of panic disorder together with other anxiety disorders has reported significant linkage to chromosome 9p31, whereas a family study38 that included panic disorder, bladder problems, severe headaches, mitral valve prolapse, and thyroid conditions found significant linkage on chromosomes 13q. Further developments in gene finding across disorders may be expected from multivariate linkage analysis.40

**LIMITATIONS**

The results of this analysis should be interpreted in the context of several potential limitations. First, these re-
The underlying structure of genetic and environmental risk factors for the anxiety disorders does not significantly differ between men and women. Two genetic factors predispose to 2 broad groups of disorders dichotomized as generalized and panic anxiety plus agoraphobia vs the specific phobias, with social phobia intermediate between these. The remaining associations between the disorders are largely explained by a unique environmental factor shared across the disorders and, to a lesser extent, a common shared environmental factor. In the most parsimonious model, the only disorder-specific factors that contribute significantly are from an agoraphobia-specific genetic factor and unique environmental effects for each disorder. This suggests that the underlying patterns of liability can be broadly understood as follows: individual genetic factors derive from 2 sets of genes that increase risk for the 2 classes of panic-generalized agoraphobic anxiety vs specific phobias. Risk across all of the anxiety disorders may be further increased by life experiences either shared with other family members or unique to the individual, with varying impact (loadings) depending on the disorder. Add to this a set of unique environmental factors that increase the liability for one anxiety disorder independent of another. Although these last factors appear to carry the largest proportion of variance, this is likely an overestimate due to confounding by measurement error, with a compensatory underestimate of the true effects of genes and/or shared environment.

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