The Structure of the Genetic and Environmental Risk Factors for Six Major Psychiatric Disorders in Women

Phobia, Generalized Anxiety Disorder, Panic Disorder, Bulimia, Major Depression, and Alcoholism

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Background: Although prior family and twin studies have examined the relationship between the genetic and environmental risk factors for pairs of psychiatric disorders, the interrelationship between these classes of risk factors for a broad range of psychiatric disorders remains largely unknown.

Methods: An epidemiologic sample of 1030 female-female twin pairs with known zygosity, ascertained from the Virginia Twin Registry, were evaluated by a personal interview conducted by mental health professionals, assessing lifetime history of phobia, generalized anxiety disorder, panic disorder, bulimia nervosa, major depression, and alcoholism.

Results: A multivariate twin analysis suggested the following: First, genetic, familial-environmental, and individual-specific environmental risk factors each cause a unique pattern of comorbidity among the six disorders. Second, genetic influences on these disorders are best explained by two factors, the first of which loads heavily on phobia, panic disorder, and bulimia nervosa and the second, on major depression and generalized anxiety disorder. Third, unlike other disorders, genetic influences on alcoholism are largely disorder specific. Fourth, familial-environmental influences on these disorders are best explained by a single factor that substantially influenced liability to bulimia nervosa only. Fifth, individual-specific environmental influences on the risk for these psychiatric disorders are best explained by a single factor, with highest loadings on generalized anxiety disorder and major depression and with large-disorder–specific loadings, especially on phobias, panic disorder, and alcoholism.

Conclusions: These results support the following hypotheses: First, each major risk factor domain (genes, family environment, and individual-specific environment) influences comorbidity between these disorders in a distinct manner. Second, genetic influences on these six disorders are neither highly specific nor highly nonspecific. Neither a model that contains a discrete set of genetic factors for each disorder nor a model in which all six disorders results from a single set of genes is well supported. Third, the anxiety disorders are not, from a genetic perspective, etiologically homogeneous. Fourth, most of the genetic factors that influence vulnerability to alcoholism in women do not alter the risk for development of other common psychiatric disorders. These results should be interpreted in the context of both the strengths and limitations of multivariate twin analysis.

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HISTORICALLY, psychiatric diagnostic systems have developed from clinical experience and intuition, which have only recently been guided by rigorously collected empirical evidence.[1] Although most nosologists agree that diagnoses should ultimately be based on etiologic characteristics, this has, with minor exceptions, been an unattainable goal in psychiatry. Genetic epidemiology has, however, begun to address systematically the relationship between the risk factors for the major psychiatric disorders, all of which have been shown to run in families.[2,3] The conceptual and analytic approach to these studies has, however, been largely limited to the consideration of two disorders at a time. For example, family studies have addressed the familial relationship between alcoholism and major depression (MD),[4,5] panic disorder and phobia,[6] and bulimia and MD.[7,8]

However, multivariate methods that permit a more definitive resolution of the structure of the genetic and environmental risk factors for a range of psychiatric disorders are now available.[9] In particular, such methods can be powerfully applied in twin

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METHODS

As part of a longitudinal study of the genetic and environmental risk factors for common psychiatric disorders in women, we personally interviewed 2163 white female twins from the population-based Virginia Twin Registry who were born in the years 1934 to 1971.[16] This sample contained both members of 1033 pairs and had, at interview, a mean±SD age of 30.1±7.6 years. No male twins were studied. The refusal rate during the personal interview phase of this project, which was conducted by interviewers with master's degrees in social work or psychology or bachelor's degrees and 2 or more years' clinical experience, was 8%. Each twin was assessed by an interviewer who was blind to the psychopathologic status of her cotwin. Zygosity was determined by an algorithm based on questionnaire responses, photographs, and, when these sources were ambiguous, DNA polymorphisms,[22] and the algorithm yielded 590 monozygotic (MZ) pairs, 440 dizygotic (DZ) pairs, and three pairs of unknown zygosity. This zygosity distribution (57% MZ and 43% DZ) differs only slightly from that predicted for same-sex twins from records of white twin births in the Commonwealth of Virginia over the years 1940 to 1971 using Weinberg's rule[23] (53.5% MZ and 46.5% DZ). Our epidemiologically derived twin cohort did not suffer from the large excess of MZ twins usually seen in volunteer twin samples.[24] Our analyses herein will focus on the 1030 pairs with known zygosity.

The interview included, in modified form, sections of the Structured Clinical Interview for *DSM-III-R*[25] for MD, GAD, panic disorder, bulimia nervosa, and alcohol dependence. Phobias were assessed by an adaptation of the "Phobic Disorders" section of the Diagnostic Interview Schedule Version III-A,[26] which was based on the *DSM-III* criteria.[27] Phobia was defined as the presence of one of 17 specific fears that the respondent considered to be irrational and that in the interviewer's judgment, produced objective behavioral interference with the respondent's life.[18] Interviewers were trained to record symptoms as not present if they were due to the effects of medical illness or medication.

The diagnoses of MD, bulimia, panic disorder, and GAD were based on a blind review of the interview protocols by one of us (K.S.K.), using *DSM-III-R* criteria.[21] Thus, MD was not diagnosed when depressive symptoms resulted from uncomplicated bereavement. However, for GAD, we followed *DSM-III* convention, requiring only a 1-month minimum duration of illness, rather than *DSM-III-R* convention. Furthermore, the GAD section of the version of the Structured Clinical Interview for *DSM-III-R* from which we worked did not contain questions addressing whether the anxiety or worry affected two or more life circumstances. Thus, we considered twins to meet *DSM-III-R* criterion A for GAD if they responded positively to having had a time when they were "anxious, nervous, or worried more days than not." All diagnoses were made without regard to diagnostic hierarchies. The lifetime prevalence rates for MD, GAD, and any phobia in this sample were 31.4%,[16] 23.6%,[17] and 30.5%,[18] respectively.

Three of the six disorders examined in this sample had relatively low lifetime prevalence rates: bulimia (2.8%),[15] panic disorder (5.9%),[20] and alcohol dependence (9.0%).[19] Both power analyses[9,28] and previous experience in this sample[15,20] indicate that model fitting that is applied to disorders of this rarity usually yields results that are neither definitive nor stable. Therefore, to increase statistical power, the major analyses reported herein were based on broad definitions for these three disorders. For bulimia and panic disorder, cases diagnosed at the possible level were included because a multiple threshold model indicated that the possible cases were on the same continuum of liability as those diagnosed with greater certainty.[15,20] In addition, for bulimia, it was shown that a range of epidemiologic risk factors and patterns of comorbidity were similar for the narrowly and broadly diagnosed cases.[15] To maximize our statistical power for alcoholism, we chose the broad criteria of alcohol dependence, as defined by *DSM-III-R*,[21] or problem drinking, in which the respondent admits to having had or having been considered by others as having a significant drinking problem that is not limited to single isolated incidents. A multiple threshold model indicates that in these data, problem drinking reflects a milder disturbance on the same liability dimension that influences alcohol dependence.[19] For all three disorders, the results from univariate twin analysis were similar for the narrow and the broad definitions of illness. With the broader definitions of illness, the lifetime prevalence of bulimia, panic disorder, and alcoholism in this sample was 5.7%, 11.0%, and 17.3%, respectively.

Our approach to the analysis of twin data has been outlined in detail elsewhere,[9,16] as have the basic principles and goals of genetic multivariate analysis.[18] The models described herein are based on a liability-threshold model, the strengths and limitations of which have been discussed previously.[9,16] Whereas the goal of univariate genetic analysis is to decompose the variance of the liability to a disorder into genetic and environmental components, in multivariate genetic analysis, the focus expands to examine both the variance in liability of individual disorders and the

Continued on next page

studies, which, unlike family studies, can separate the etiologic roles of genetic and familial-environmental factors.

Based on personal interviews with both members of a large number of female-female pairs from a population-based twin registry, we examined the interrelationship between the genetic and the environmental risk factors for MD and several other disorders, examined one at a time.[10-13] In this article, using a multivariate twin analysis, we examined the interrelationship between the genetic and the environmental risk factors for the lifetime prevalence of all of the major psychiatric disorders assessed in this study to date: MD, generalized anxiety disorder (GAD), panic disorder, phobias, bulimia nervosa, and alcoholism. We sought to answer six questions:

1. Is the pattern of comorbidity that is due to genetic factors the same as that due to environmental factors? It is possible that one set of genetic risk factors may be common to several disorders, whereas environmental risk factors are disorder specific.[14] Or, a reverse pattern may be seen. To evaluate this hypothesis, we can formally test whether genetic and environmental risk factors influence these psychiatric disorders by a common pathway.[14]

2. How specific are the genetic risk factors for the common psychiatric disorders in women? Are they very

covariance of liability between disorders. Furthermore, when three or more disorders are simultaneously considered, general and disorder-specific genetic and environmental factors can be estimated. In traditional factor analysis, latent factors are assumed with the goal of explaining the covariation between a large number of variables by a small number of factors. Multivariate genetic analysis is similar to traditional factor analysis in that it seeks to explain covariation between multiple variables with a few factors. However, it differs from traditional factor analysis in that it provides separate estimates of the structure of genetic and environmental sources of covariation. Whereas traditional exploratory factor analysis is a descriptive statistical method, multivariate genetic analysis provides insight into the causes of resemblance.

In univariate analysis, information regarding the variation of liability to illness is obtained by comparing the tetrachoric correlations for that disorder in MZ and DZ twin pairs. In the multivariate case, entire matrices of tetrachoric correlations are used. By comparing the cross-twin, cross-variable correlations in MZ and DZ twins and contrasting them to the cross-twin, within-variable and the within-twin, cross-variable correlations, the covariation of two or more variables can be partitioned into its genetic and environmental components.

For example, if genetic factors are responsible for the comorbidity between two disorders, then the correlation in liability between the two disorders will be similar within individuals (eg, disorder 1 and disorder 2 in twin 1) and across MZ twins (ie, disorder 1 in twin 1 and disorder 2 in twin 2), who share all their genes in common, and both will be about twice as large as that seen in DZ twins, who share on average half their genes in common. If familial-environmental factors (eg, parental rearing style) cause the comorbidity, then the correlation between the two disorders will be similar in individuals and across MZ and DZ twins because MZ and DZ twins reared together share all their familial environment. If individual-specific environmental factors (eg, marital discord) are responsible for the comorbidity, then the liability to the two disorders should be correlated in individuals but not across MZ or DZ twins.

Genetic and environmental factors might influence the covariation between disorders in two different ways. First, genetic and environmental factors might influence the covariation of liability to two disorders by a common pathway through an intermediate phenotype.[14] For example, both genetic and environmental risk factors might influence the psychobiologic state of chronic dysphoria, which can manifest itself in MD and/or GAD. If the common pathway model fits best, this implies that the pattern of comorbidity produced by genetic and environmental factors is the same. Second, in the independent pathway model, genes and the environment contribute to covariation through separate genetic and environmental factors. For example, whereas genes might influence the liability to chronic dysphoria, environmental effects are specifically anxiogenic or depressogenic. If the independent pathway model fits best, this implies that genetic and environmental factors would, if separable, produce different patterns of comorbidity. The common pathway model can be parameterized as a series of constraints imposed on an independent pathway model. Therefore, the fit of the common pathway model can be formally compared with that of the more general independent pathway model.

Two 12×12 tetrachoric correlation matrices and their asymptotic covariance matrices (available on request) were calculated (separately for MZ and DZ twins) by PRELIS II,[29] giving the tetrachoric correlations within and across twins for the six disorders considered. To best describe how genes and environment influence the resemblance among the six disorders, a series of multivariate models were fitted to these matrices using Mx[30] by the method of asymptotic weighted least squares. The fit of the various models were compared by Akaike's information criterion (AIC),[31] with the goal of selecting the model that best combines the principles of both parsimony and goodness-of-fit. For selected comparisons, we also report the χ^2 difference test. Because no stable solution was found in this data for a full three-factor independent pathway model (containing three genetic, three familial-environmental, and three individual-specific environmental factors), we began by fitting two-factor independent and common pathway models.

Previous univariate and bivariate analyses of these disorders have uncovered no consistent evidence for dominance genetic variance. Therefore, in these analyses, we examine only additive genetic factors, which are, for the sake of simplicity, termed genetic. When multiple factors were present in a model, factor loadings were estimated by Mx and then rotated using VARIMAX criterion.[32]

As with univariate analyses, multivariate twin analyses are predicated on the validity of the equal environment assumption that MZ and DZ twins are approximately equally correlated in their exposure to environmental factors of etiologic relevance to the trait under study. This hypothesis has been empirically evaluated in several different ways for the psychiatric disorders assessed in this study,[15-20,33,34] with the results consistently supporting its validity.

nonspecific (ie, one common set of genes influences the liability to all disorders) or highly specific (ie, a different set of genes influences the liability to each disorder)?

3. Previous analyses in this sample suggest that familial-environmental factors are of little etiologic importance in common psychiatric disorders in women.[15-20] Would the greater power of the multivariate method uncover evidence that nongenetic familial factors were etiologically important in these disorders?

4. How specific is the effect of the environmental risk factors that are unique to the individual in these common psychiatric disorders? Are there environmental risk factors that are highly disorder specific in their impact, or is the action of most environmental stressors relatively nonspecific, thus increasing the risk for development of a variety of disorders?

5. The current grouping of GAD, panic disorder, and phobias in the anxiety disorders category[21] suggests that these three disorders might be etiologically related. Are the genetic and environmental risk factors for these three disorders sufficiently related to warrant their inclusion in this overarching nosologic category?

6. Alcoholism, a substance use disorder, is often conceptualized as differing from more typical psychiatric dis-

Table 1. The Comorbidity Between Six Major Psychiatric Disorders as Assessed by the Odds Ratio and the Tetrachoric Correlation*

	Phobia	GAD	Panic Disorder	Bulimia	Major Depression	Alcoholism
Phobia	...	3.00 (2.43-3.71)	5.62 (4.19-7.55)	1.87 (1.28-2.72)	2.24 (1.84-2.72)	2.02 (1.59-2.55)
GAD	.382	...	4.91 (3.69-6.53)	2.28 (1.55-3.35)	8.93 (7.11-11.22)	2.35 (1.84-3.00)
Panic disorder	.520	.484	...	2.32 (1.46-3.70)	3.98 (2.99-5.29)	2.47 (1.82-3.36)
Bulimia	.181	.234	.221	...	2.24 (1.54-3.25)	3.12 (2.10-4.61)
Major depression	.293	.677	.427	.232	...	2.67 (2.12-3.38)
Alcoholism	.237	.281	.275	.316	.329	...

**Tetrachoric correlations are below ellipses and are all positive; odds ratios with 95% confidence intervals are above ellipses. All tetrachorics are significant at P<<.000. GAD indicates generalized anxiety disorder.*

orders. Does alcoholism result from genetic and environmental risk factors that are very similar to or distinct from those that influence typical psychiatric disorders such as MD and panic disorder?

RESULTS

COMORBIDITY BETWEEN DISORDERS

Table 1 depicts the comorbidity between the six disorders assessed in this study, in terms of both odds ratios and tetrachoric correlations. The strongest associations using both measures were found between MD and GAD and between panic disorder and phobia.

MODEL FITTING

The two-factor common pathway model fit poorly (χ^2=180.2, *df*=104) compared with the two-factor independent pathway model (χ^2=138.8, *df*=87) and could be rejected against the more general model using both AIC (−23.8 vs −35.2, respectively) and the χ^2 difference test (χ^2=41.4, *df*=17, *P*<.001).

We then attempted to obtain the best-fitting independent pathway model, first by seeking the optimal number of genetic, familial-environmental, and individual-specific environmental factors, assuming the presence of disorder-specific loadings. Then, when the best factor model was found, we examined evidence for disorder-specific genetic, familial-environmental, and individual-specific environmental loadings. The details of the model fitting are given in **Table 2**.

Model 1 is the full two-factor independent pathway model, which we will now term the 2-2-2 model, with the digits indicating, respectively, the number of genetic, familial-environmental, and individual-specific environmental factors. In models 2 through 4, we attempted to simplify this model by reducing the number of factors from two to one for the individual-specific environment (model 2, a 2-2-1 model), the familial environment (model 3, a 2-1-2 model), and genes (model 4, a 1-2-2 model). Both models 2 and 3 produced a better (or more negative) AIC value than did model 1, indicating a better overall balance of fit and parsimony, with model 3 producing the best result. By contrast, model 4 produced a deterioration (or increase) in the AIC values compared with model 1. It should also be noted that model 4 can be rejected against model 1 by a χ^2 difference test (χ^2=11.8, *df*=5, *P*=.04).

Working from model 3, a 2-1-2 model, we attempted a further simplification by assuming either one individual-specific environmental factor (model 5, a 2-1-1 model) or one genetic factor (model 6, a 1-1-2 model). While model 5 produced an improvement in AIC value over that of model 3, model 6 produced a deterioration that was also highly significant by a χ^2 difference test (χ^2=18.3, *df*=5, *P*=.003).

We then tried to simplify model 5 in three ways: by eliminating the one individual-specific environmental factor (model 7, a 2-1-0 model), by eliminating the one familial-environmental factor (model 8, a 2-0-1 model), or by reducing the number of genetic factors to one (model 9, a 1-1-1 model). However, compared with model 5, models 7 through 9 all produced a worsening of the AIC value, indicating an overall poorer fit. Our results therefore suggest that the most parsimonious description of the covariation of these six common psychiatric disorders in women requires two genetic, one familial-environmental, and one individual-specific environmental factor.

Working from the 2-1-1 model (model 5), we then attempted to eliminate all disorder-specific unique-environmental, familial-environmental, and genetic factors, in models 10, 11, and 12, respectively. Model 10 produced a very large deterioration in the fit of the model. The AIC values for both models 11 and 12 were superior to that of model 5, but model 11 was the better of the two.

We then tried to further simplify model 11 (a 2-1-1 model with no familial-environmental–specific loadings), by eliminating the disorder-specific unique-environmental and genetic loadings in models 13 and 14. Both of these models, however, produced a considerably worse AIC value than did model 11, which was therefore the best-fit model. Of note, model 14 could also be strongly rejected against model 11 by a χ^2 difference test (χ^2=31.3, *df*=6, *P*<.0005).

PARAMETER ESTIMATES

Genetic Factors

The genetic parameter estimates of the best-fitting model 11 are seen in the **Figure**, top. The first genetic factor is dominated by high loadings (eg, >0.50) on phobia, panic disorder, and bulimia. Generalized anxiety disorder and alcoholism have more modest load-

Table 2. Results of a Model Fitting of a Multivariate Twin Analysis of Six Major Psychiatric Disorders*

Model	Additive Genetic Factor		Familial-Environmental Factor		Unique Environmental Factor		Fit of the Model		
	Common Factors, No.	Disorder-Specific Loadings	Common Factors, No.	Disorder-Specific Loadings	Common Factors, No.	Disorder-Specific Loadings	χ^2	*df*	AIC
1†	2	P	2	P	2	P	138.8	87	−35.2
2	2	P	2	P	1	P	143.4	92	−40.6
3†	2	P	1	P	2	P	141.8	92	−42.4
4	1	P	2	P	2	P	150.6	92	−33.4
5†	2	P	1	P	1	P	149.7	97	−44.3
6	1	P	1	P	2	P	160.1	97	−33.9
7	2	P	1	P	0	P	231.4	103	−25.4
8	2	P	0	P	1	P	164.9	103	−41.1
9	1	P	1	P	1	P	171.2	102	−32.8
10	2	P	1	P	1	A	306.6	103	100.6
11†	2	P	1	A	1	P	149.7	103	−56.3‡
12	2	A	1	P	1	P	156.9	103	−49.1
13	2	P	1	A	1	A	306.6	109	100.6
14	2	A	1	A	1	P	181.0	109	−37.0

*AIC indicates Akaike's Information Criterion[31]; P, disorder-specific loadings present; and A, disorder-specific loadings absent.
†Models against which subsequent models are tested.
‡Best-fitting model by AIC.

ings and MD has almost no loading at all on this first genetic factor.

The second genetic factor is dominated by high loadings on MD and GAD. Panic disorder and alcoholism both have modest loadings, whereas the loadings of phobia and bulimia are small.

Disorder-specific genetic factors are nonzero only for GAD, where they are of only modest impact, and for alcoholism, where they constitute the single strongest loading. The liability to alcoholism is substantially influenced by genetic factors that do not contribute to the genetic vulnerability to the other psychiatric disorders considered.

Environmental Factors

As seen in the Figure, bottom, the single familial-environmental factor has a substantial loading only for bulimia, whereas the other loadings are small, with none exceeding 0.20. The single individual-specific environmental factor has high loadings (≈0.60) on GAD and MD, moderate loadings for phobia and panic disorder (≈0.40), and low loadings for alcoholism and bulimia. Although all of the disorders have substantial disorder-specific unique-environmental loadings, this loading is highest for phobia and lowest for MD.

ESTIMATED PROPORTION OF VARIANCE IN LIABILITY DUE TO GENETIC AND ENVIRONMENTAL RISK FACTORS

The Figure presents the path estimates from the best-fitting model. Another useful way to view these results is to divide the sources of variance in liability in each disorder into its component parts. This is displayed in **Table 3**, in which five results are worthy of note. First, with respect to the etiologic importance of genetic factors, the six disorders were divisible into three groups. For bulimia, GAD, and phobia, the estimated total heritability, 30% to 35%, was modest. For MD and panic disorder, total heritability was moderate and estimated at 41% to 44%. By contrast, the total heritability for alcoholism, estimated at 59%, was substantially higher than that for any other disorder.

Second, for both phobia and bulimia, nearly all of the genetic variation was from the first genetic factor. By contrast, for MD, nearly all of the genetic variation was from the second genetic factor.

Third, for alcoholism, over three fourths of the genetic variance was unique to that disorder and was not shared with any other disorders under consideration.

Fourth, using the increased power of multivariate analysis, the role of the familial environment still proved to be of little substantial importance for phobia, GAD, panic disorder, MD, or alcoholism, accounting at most for 4% of the variance in liability. However, for bulimia, our estimates suggest a substantial role for familial-environmental factors.

Fifth, the single individual-specific environmental factor accounted for a substantial proportion of variance only for GAD and MD. Disorder-specific unique environment was important for all disorders but was most important for phobia.

COMMENT

We applied multivariate twin analysis to the lifetime history of six major psychiatric disorders in a personally interviewed, population-based sample of twins from female-female pairs to clarify the structure of the genetic and environmental risk factors underlying these disorders. We examined, in turn, the answers obtained to the six questions outlined above.

GENES AND ENVIRONMENT: COMMON OR INDEPENDENT PATHWAYS?

We began our analysis by considering whether genetic and environmental risk factors for these six common psychiatric disorders acted via common or independent path-

ways. As previously outlined in the ARCHIVES[14] (see Figure therein), the common pathway model predicts that genetic and environmental risk factors should produce the same pattern of comorbidity between disorders, whereas the independent pathway model allows for the various risk factor domains to cause different patterns of comorbidity.

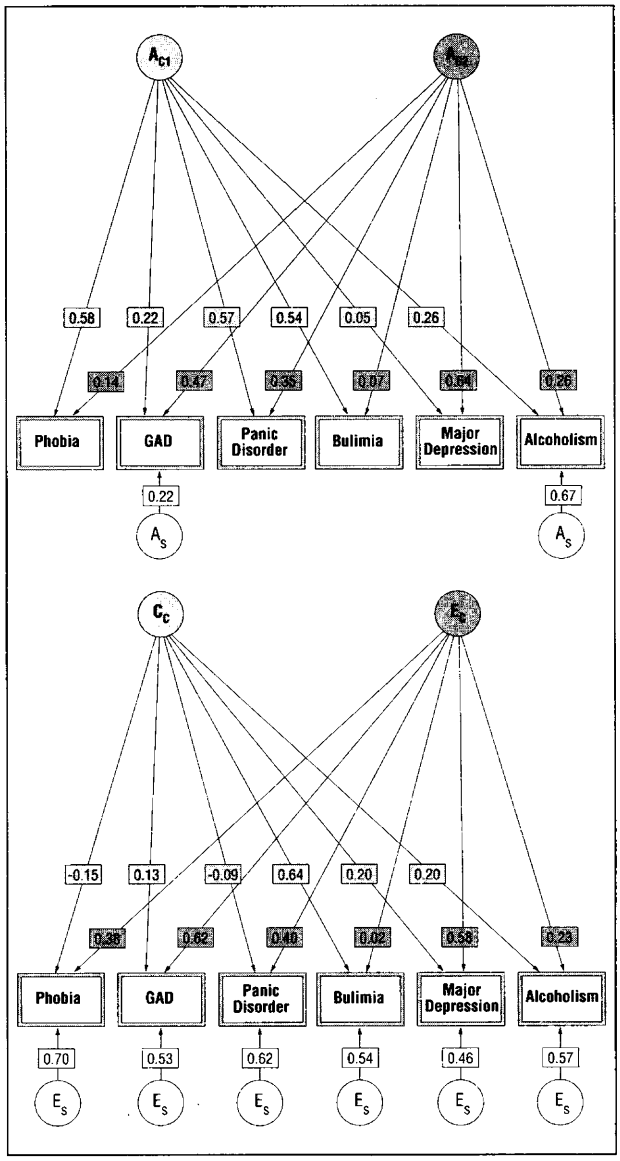
In our analyses, the common pathway model was rejected, suggesting that the genetic and environmental risk factors for these disorders are not influencing comorbidity in the same manner. This result is significant because it suggests that multivariate analyses of these disorders conducted on a phenotypic level may yield incomplete results. The implicit assumption of traditional multivariate analysis in the behavioral sciences, the assumption that the pattern of comorbidity (or covariance for quantitative traits) due to genetic and environmental risk factors is the same, is probably incorrect for the common psychiatric disorders in women.

THE SPECIFICITY OF GENETIC RISK FACTORS

A major goal of this analysis was to clarify the degree of specificity of the genetic risk factors for common psychiatric disorders in women. Consideration of two extreme hypotheses is heuristically useful. First, genetic influences on common psychiatric disorders could be entirely nonspecific. As predicted by unitary models for psychiatric disorders in general[35] or neuroses in particular,[36] genes might code for high or low levels of general liability to illness. Whether one disorder vs another develops in an individual with high liability would result solely from environmental experiences. Second, each of the individual disorders could be genetically distinct. For the six disorders under consideration, there might be six discrete sets of genetic factors that are unrelated to each other.

Previous work in this and other samples suggests that neither extreme hypothesis is likely to be true. For example, contrary to the prediction of the second extreme hypothesis (that of genetically distinct disorders), we and others have found evidence for common genetic and/or familial factors influencing MD and alcoholism,[4,5,13] panic disorder and phobia,[6] bulimia and MD,[7,8,11] and MD and GAD.[10] However, it was previously seen in this data that the genetic risk factors for MD and alcoholism[13] and MD and phobias[12] are partially distinct. Therefore, the first extreme hypothesis (that of one set of nonspecific genetic risk factors) is also unlikely to be true.

The results of our multivariate genetic analysis indeed support neither extreme hypothesis. The genetic risk factors for common psychiatric disorders in women are neither extremely nonspecific nor extremely specific. We found substantial statistical evidence for two genetic factors. The second genetic factor, which loaded most strongly on MD and GAD, was anticipated by a previous analysis[10] that suggested that the genes influencing liability to these two disorders were very closely related. This second genetic factor appears to influence the liability to intermittent and often recurrent episodes of dysphoria.



Top, Parameter estimates from the best-fitting multivariate twin model (model 11 [Table 2]) for the genetic common and disorder-specific factors. The model contains two additive genetic common factors (A_{C1} and A_{C2}), which load most strongly on phobia and panic disorder and on generalized anxiety disorder (GAD) and major depression, respectively. Disorder specific additive genes (A_S) are present for only two disorders, GAD and alcoholism. Bottom, Parameter estimates from the best-fitting multivariate twin model (model 11 [Table 2]) for the environmental common and disorder-specific factors. The model contains one familial-environmental common factor (C_C) and one individual-specific or unique-environmental common factor (E_C). No disorder-specific familial environmental loadings were obtained, whereas every disorder had disorder-specific unique-environmental loadings (E_S).

The validity of a genetically mediated, shared neurobiologic diathesis to GAD and MD is supported by results from both biological and pharmacologic treatment studies of depression and anxiety.[37-40]

The first genetic factor, which loads most heavily on phobia, panic disorder, and bulimia, appears conceptually more problematic. Unlike the second factor, the most prominent clinical manifestations of the disorders that load most heavily on this first factor are acute, short-lived, or even paroxysmal. Both phobia and panic disorder are characterized by a vulnerability to panic attacks.

Table 3. The Proportion of Variance in Liability Accounted for in Six Major Psychiatric Disorders by the Common and Disorder-Specific Genetic and Environmental Risk Factors*

	Genetic Factor					Individual-Specific Environmental Factor		
Disorder	Common Factor 1	Common Factor 2	Disorder-Specific	Total	Familial/Environmental Common Factor	Common Factor	Disorder-Specific	Total
Phobia	0.33	0.02	0.00	**0.35**	0.02	0.14	0.49	**0.63**
GAD	0.05	0.22	0.05	**0.32**	0.02	0.38	0.28	**0.66**
Panic disorder	0.32	0.12	0.00	**0.44**	0.01	0.16	0.39	**0.55**
Bulimia	0.29	0.01	0.00	**0.30**	0.41	0.00	0.29	**0.29**
MD	0.00	0.41	0.00	**0.41**	0.04	0.34	0.21	**0.55**
Alcoholism	0.07	0.07	0.45	**0.59**	0.04	0.05	0.32	**0.37**

**As estimated by the best-fitting twin multivariate model. GAD indicates generalized anxiety disorder; MD, major depression.*

However, bulimia also is marked by short paroxysmal-like disturbances, in this case binging, often followed by purging. The nature of the genetically mediated, shared neurobiologic diathesis to phobia, panic disorder, and bulimia remains to be clarified. Relating the two genetic factors detected in this sample to underlying variations in temperament,[41,42] which are also known to be under genetic influence,[43] would be of great interest.

PSYCHIATRIC ILLNESS AND THE FAMILIAL ENVIRONMENT

Although theorists in the behavioral sciences have long stressed the central role of the family in shaping emotional functioning and personality, empirical evidence from the growing science of human behavior genetics has found little support for this widely held view.[44] Consistent with this trend, the previous univariate analyses in this sample of MD,[16] GAD,[17] bulimia,[15] phobia,[18] alcoholism,[19] and panic disorder[20] uncovered little or no consistent evidence that the liability to these psychiatric disorders was substantially influenced by environmental factors shared in families. Would these conclusions be sustained in our multivariate analysis, which uses important data (eg, the cross-twin cross-disorder correlations) that was excluded from the previous analyses?

The multivariate analyses suggested that with one exception, familial environment played little or no etiologic role. This exception was bulimia nervosa. Previous univariate analysis of this disorder[15] had suggested a moderate familial environment component, but in part because of low rates of the disorder, evidence for this was not significant. Although still limited by the relatively small number of affected twins, our results do suggest that for bulimia, along with genetic factors, familial environmental factors play a significant etiologic role.[45]

PSYCHIATRIC ILLNESS AND THE INDIVIDUAL-SPECIFIC ENVIRONMENT

In accord with earlier analyses, the individual-specific environment appears to be a major risk factor for all of the six disorders considered. Furthermore, our results suggested that like the genetic risk factors, the impact of these environmental risk factors is neither highly disorder-specific nor highly nonspecific. We found evidence for one general environmental factor that was nonspecific in its impact. That is, there appears to be a set of environmental risk factors that increase the liability to a broad range of common psychiatric disorders. Of interest, these nonspecific environmental risk factors played a stronger etiologic role in MD and GAD than in phobia, panic disorder, bulimia, or alcoholism.

In addition, for each disorder, there was evidence for disorder-specific environmental risk factors. That is, our results suggest that a substantial proportion of individual-specific environmental risk factors for psychiatric disorders have an impact on the liability to only one disorder. It was intuitively reasonable that phobias had the highest such loading because many twins recounted idiosyncratic experiences (eg, being locked in a trunk by an older brother or diving into the water onto a corpse) that precipitated phobias but were probably unrelated to the risk for other psychiatric disorders. Our results suggest that environmental experiences that are not shared by a twin with her cotwin constitute a large proportion of the risk factors that are unique to individual psychiatric disorders. However, as detailed below, a certain proportion of what is herein interpreted as individual-specific environment may be error of measurement.

THE UNITY OF ANXIETY DISORDERS

In the *DSM-III*,[27] the old concept of anxiety neurosis was split into two new disorders, one reflecting chronic, free-floating anxiety (GAD) and the other characterized by acute, paroxysmal anxiety attacks (panic disorder). These two diagnoses were combined with phobias, obsessive-compulsive disorder, and posttraumatic stress disorder into the new diagnostic category of anxiety disorders.

Three of these diagnoses were among the six disorders examined in this study. Another goal of this analysis was to determine from the perspective of genetic and environmental risk factors whether the anxiety disorders constituted a cohesive nosologic category. Our results suggested otherwise. Although panic disorder and phobia appeared to share important etiologic factors, GAD was more closely related etiologically to MD than to either anxiety disorder. These results are broadly consistent with previous evidence from family,[46] developmental,[47,48] and biologic[49] studies that suggest important etiologic differences between GAD and panic disorder.

Our results validate the division in the *DSM-III*[27] of the broad category of anxiety neurosis into panic disorder and GAD.

ALCOHOLISM

Alcoholism can be conceptualized as either a psychiatric or a substance use disorder. Genetic factors may exist that influence the absorption, metabolism, or interaction of ethanol with the brain, which have little impact on the liability to psychiatric illness.[50,51] In Asian populations, for example, a variation at the aldehyde dehydrogenase locus (which metabolizes acetaldehyde to acetic acid) influences the risk for alcoholism.[52,53]

One of the most striking results of this analysis was the pattern of genetic risk factors for broadly defined alcoholism. Alcoholism was substantially more heritable than any other disorder. More importantly, although 12% of the genetic variation for alcoholism resulted from each of the two major genetic factors, the remaining 76% was due to genetic factors that are unique to alcoholism. That is, most of the genetic variation that influences vulnerability to broadly defined alcoholism in a general population of women is unrelated to the genetic factors that alter liability to the common mood, anxiety, and eating disorders. Our findings are consistent with the recent findings of Schuckit[54] that a reduced response to a standard dose of ethanol distinguishes offspring of alcoholic parents from those of controls and predicts future risk for alcohol abuse but does not predict future risk for MD or anxiety disorders.

Consistent with an earlier study,[13] the best-fitting multivariate model found that of the remaining disorders, alcoholism was, from a genetic perspective, most closely related to MD. The predicted genetic correlation between broadly defined alcoholism and MD from our multivariate model (.37) was reassuringly similar to that obtained from the previous analysis, which was limited to only these two disorders (.42).[13]

Our results also provided further insight into the environmental risk factors for alcoholism. In accord with previous findings, the family environment appeared to play little etiologic role in alcoholism in women.[19] Furthermore, consistent with earlier work that examined only alcoholism and MD,[13] the individual-specific environmental risk factors for alcoholism appeared to have little relationship to the common set of events that broadly influence vulnerability to most of the psychiatric disorders examined.

LIMITATIONS

The results of this analysis should be interpreted in the context of eight potentially significant methodologic limitations. First, the sample was entirely female. Because of gender differences in prevalence rates and risk factors for common psychiatric disorders,[55] the results obtained herein may not extrapolate to males.

Second, we presented only one of several plausible pathways through possibly appropriate models. We tried a number of different pathways and the results consistently led to the same best-fit model (model 11). In addition, although a full three-factor independent pathway model was not identified, models containing three genetic, familial-environmental, or individual-specific environmental factors were identified and fitted. In these cases as well, the pathway of model fitting led back to the same best-fit model explored above.

Third, differences of opinion exist in the field of structural equation modeling about the proper criteria with which to pick a best model.[56] We have herein relied on the AIC,[31] which, in our experience with genetic applications, provides a good balance between the demands of parsimony on the one hand and explanatory power on the other. Furthermore, in a recent detailed comparison of seven fit indexes in covariance structure analysis, AIC performed the best.[57] At the three key decision points in our model fitting (rejecting the common pathway model, rejecting a single genetic factor, and rejecting the elimination of all genetic-specific loadings), our decision was also supported by the χ^2 difference test. To explore this question further, we calculated three additional fit indexes: the Tucker-Lewis Index,[58] the Comparative Fit Index,[58] and the Consistent AIC.[59] Two of these indexes (the Tucker-Lewis Index and the Comparative Fit Index) agreed with the AIC both in preferring the independent over the common pathway model and in selecting model 11 from the 14 models described in Table 2. By contrast, the Consistent AIC differed substantially, choosing a common pathway model with a single genetic factor. Although the preponderance of the evidence supports our choice of model 11 as the best model for this data, a different interpretation of these results is possible.

Fourth, for maximal conceptual clarity, as well as to aid potential future models for gene action and for assortative mating, we used an orthogonal factor rotation to obtain loadings on the two genetic factors. However, an argument can be made that an oblique rotation might also be informative. Using the PROMAX routine in SAS,[32] an oblique rotation of the two genetic factors produced an overall pattern very similar to that seen in the Figure, top. As expected, most of the higher factor loadings were a bit higher, and the lower loadings, somewhat lower. The two factors were moderately correlated (.45).

Fifth, the lifetime prevalence rates for several of the disorders examined were higher than those obtained in women from the Epidemiologic Catchment Area study.[55] Our rates might be higher for several reasons, including the use of clinician interviewers and specific probes to encourage careful respondent recall and the youthfulness of our cohort. Our results are not outside the range reported by other investigators[18,60-64] and are, for all disorders except GAD, relatively close to those obtained in the National Comorbidity Survey.[65]

Sixth, because of concerns about the power and stability of estimates, we a priori used broad diagnostic criteria for the three rarest disorders in this sample: panic disorder, bulimia, and alcoholism. Previous analyses had indicated that for each of these three disorders, the broad and narrow definitions reflected the same underlying

liability dimension.[15,19,20] Model fitting was repeated with all of the disorders narrowly defined, and broadly similar results were obtained with two exceptions. Evidence was found for two individual-specific environmental factors instead of one. This was unexpected because less statistical power usually results in the identification of fewer rather than more factors. Similar to the single individual-specific environmental factor seen in Table 2, the first factor loaded most strongly on GAD and MD. The second factor was dominated by a single high loading on phobia (0.83) and a more modest loading on panic disorder (0.35). There remains some uncertainty whether there is, in these data, evidence for one or two sets of environmental risk factors that influence vulnerability to more than one psychiatric disorder. A second set of common environmental risk factors that are largely specific to phobia and panic disorder may exist.

As in the analysis presented above, the analysis with narrow definitions of the rare disorders produced robust evidence for a large component of disorder-specific familial risk for alcoholism that was not shared with other disorders. However, with the narrower definition of alcoholism, the model could not clearly identify this component as genetic vs familial-environmental. None of the results in the twins[13,19] or in the twins and their parents[66] provided substantial evidence for familial-environmental risk factors for alcoholism. Therefore, we would argue that the conclusion reached above—that the disorder-specific familial risk factors for alcoholism are genetic—is probably correct.

Seventh, the lifetime prevalence for the six psychiatric disorders assessed in this sample was obtained at a single point in time. Although the interrater reliabilities of our assessments were high,[15-20] considerable evidence in this[67] and other data sets[68,69] indicates that the test-retest reliability would likely be lower. We have test-retest data on lifetime history for only MD and panic disorder in this data set,[67] so it was not possible to fit a full multivariate model to all disorders incorporating error of measurement. With single disorders, unreliability of measurement, if uncorrelated in twin pairs, leads to an overestimation of the individual-specific environment and an underestimation of heritability. This was precisely the effect seen when MD was analyzed based on two times of measurement.[67] Although it will also have that effect in multivariate models, measurement error can in addition produce other more subtle problems. For example, individuals in the interview may demonstrate a consistent self-report or recall bias, so that they are more or less likely to recall and report any disorders they have experienced. If not substantially correlated in twin pairs, such a bias would emerge as a general individual-specific environmental factor. By contrast, if errors of recall or reporting are largely random in nature and might easily affect reporting of one disorder but not another, then they will appear as disorder-specific unique-environmental factors. In our best-fit model, a substantial proportion of what we term individual-specific environmental effects are probably errors of measurement.

Finally, our model has not considered genotype-environment interaction[70] (eg, stressful life events predisposing to MD only individuals with a high genetic liability) or causal models[71] (eg, alcoholism developing as a form of self-medication for social phobia). Although both of the processes may be important in psychiatric disorders and are worthy of further inquiry, they were not included in this report because of the limitations of both our data set and our analytic models.

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