

# Symptoms of Anxiety and Symptoms of Depression

## Same Genes, Different Environments?

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• While traditional multivariate statistical methods can describe patterns of psychiatric symptoms, they cannot provide insight into why certain symptoms tend to co-occur in a population. However, this can be achieved using recently developed methods of multivariate genetic analysis. Examining self-report symptoms in a clinically unselected twin sample (3798 pairs), traditional factor analysis indicates that symptoms of depression and anxiety tend to form separate symptom clusters. Multivariate genetic analysis shows that genes act largely in a nonspecific way to influence the overall level of psychiatric symptoms. No evidence could be found for genes that specifically affect symptoms of depression without also strongly influencing symptoms of anxiety. By contrast, the environment seems to have specific effects, ie, certain features of the environment strongly influence symptoms of anxiety while having little impact on symptoms of depression. These results, which are replicated across sexes, suggest that the separable anxiety and depression symptom clusters in the general population are largely the result of environmental factors.

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Individual psychiatric symptoms are not independently distributed in the population. Rather, symptoms tend to cluster to form recognizable psychiatric syndromes. Although initially the province of the diagnostician, the task of recognizing and describing clinical syndromes has been supplemented, for several decades, by multivariate statistical methods.<sup>1,2</sup> These methods can identify syndromes by showing that certain symptoms often occur together in individuals in a population; however, they provide no insight into why these symptoms tend to covary.

In this article, we apply newly developed methods of multivariate genetic analysis<sup>3</sup> that can move beyond traditional factor analysis to clarify why certain symptoms tend to cluster. We apply these methods to self-report symptoms of anxiety and depression from a large clinically unselected twin sample.<sup>4</sup> Our goal is to understand why certain individuals display depressive symptoms, while for others the symptoms of anxiety are more pronounced.<sup>5-7</sup>

We wish to test two major hypotheses. The first is that certain genes specifically influence the liability to depressive symptoms and other genes specifically influence the liability to symptoms of anxiety. The second hypothesis is

that certain environmental factors are specifically depressogenic and others are specifically anxiogenic.

## METHODS

### Sample

This study is based on completed postal questionnaires, mailed during the period from 1980 to 1982, received from 1978 same-sex female, and 918 same-sex male, and 902 opposite-sex volunteer twin pairs older than the age of 18 years from the Australian National Health and Medical Research Council (NHMRC) Twin Register, Canberra. As described elsewhere,<sup>4</sup> zygosity was determined by questionnaire items shown to be at least 95% accurate. The questionnaire contained a seven-item anxiety and a seven-item depression subscale from the Delusions-Symptoms-States Inventory (DSSI), developed and validated by Bedford et al.<sup>8</sup> Respondents were asked to indicate whether they had experienced symptoms "recently": 1, not at all; 2, a little; 3, a lot; and 4, unbearably. The prevalence of symptoms of anxiety and depression as assessed by this scale was similar in the twin sample and in general population samples from Australia.<sup>4</sup> Frequency of contact among members of a twin pair was shown to be unrelated to concordance for symptoms. To simplify the analyses, the 902 opposite-sex twin pairs were excluded from the multivariate genetic analyses.

Because few individuals checked the most extreme response (unbearably), response categories 3 and 4 were collapsed into a single category for the purposes of these analyses. Furthermore, because of the low response rate, the last item of the depression scale (depressed, thoughts of suicide) was eliminated from the multivariate analysis. Since the full text of these items has been presented previously,<sup>4</sup> in this report, we will use the abbreviated item versions.

### Data Analysis: An Overview

Because of the statistical complexity of some of the material in this article, in this section, a relatively nontechnical overview of the methods of data analysis is presented. More technical aspects are outlined in the "Data Analysis: Methods" section. Finally, the first paragraph of the "Comment" section contains a nontechnical summary of the important results.

There are three major steps to the data analysis presented in this article. First, a traditional factor analysis of the twin responses to the DSSI items is presented. Second, the fit of various models to these responses is examined using multivariate genetic analysis. Third, after the determination of the most appropriate multivariate genetic model, the results of that model are presented in detail.

Factor analysis attempts to account for the observed correlations between a relatively large number of symptoms in terms of the effects of a small number of latent dimensions or factors. Factor analysis utilizes as "raw" data only the cross-correlations of symptoms within individuals. Thus, factor analysis is purely a descriptive technique that can succinctly summarize patterns of symptom covariation. For example, if the DSSI items are providing only a gross measure of overall "psychiatric distress," we would expect a single-factor solution. If the items are able to discriminate between two dimensions of symptomatology (eg, symptoms of anxiety vs depression), at least two factors would be needed to explain the observed pattern of symptoms correlations.

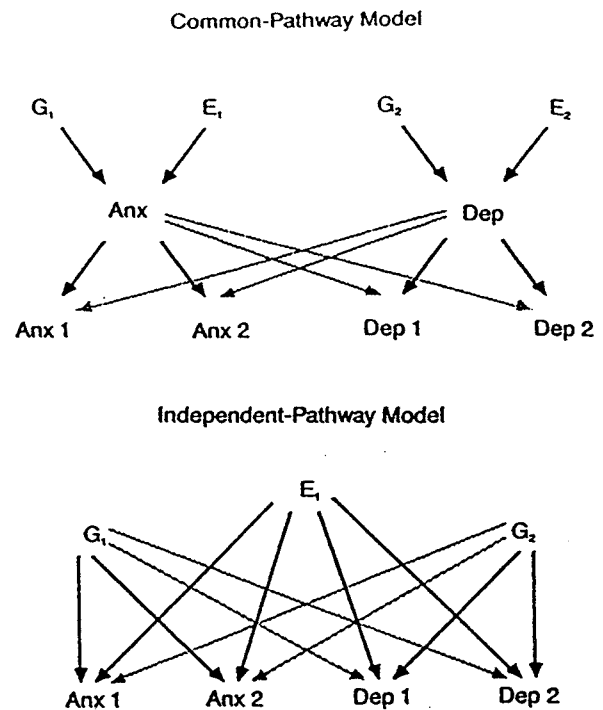
The next step in the data analysis is multivariate genetic

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Relationship, as depicted by schematic path diagrams, among hypothesized genetic factors ( $G_1$  and  $G_2$ ), hypothesized environmental factors ( $E_1$  or  $E_1$  and  $E_2$ ), two hypothesized symptoms of anxiety (Anx 1 and Anx 2), and two hypothesized symptoms of depression (Dep 1 and Dep 2). Strong relationships among variables are represented by black arrows and weak relationships by gray arrows. In common-pathway model, genetic and environmental factors affect symptoms by both acting on same latent variable. That is, one genetic ( $G_1$ ) and one environmental ( $E_1$ ) factor specifically influence latent variable anxiety (Anx), while second genetic ( $G_2$ ) and second environmental ( $E_2$ ) factor specifically influence latent variable depression (Dep). Individual symptoms are in turn influenced by latent variables. In this model, genes and environment, by their influence on latent variables, are equally specific (or nonspecific) in their influence on symptoms of anxiety and depression. In independent-pathway model, genes and environment directly and separately influence individual symptoms. One of many possible configurations is depicted here with this model in which two genetic factors ( $G_1$  and  $G_2$ ) and one environmental factor ( $E_1$ ) directly influence the four symptoms.  $G_1$  is relatively specific for symptoms of anxiety and  $G_2$  for symptoms of depression, but  $E_1$  is nonspecific and influences approximately equally symptoms of both anxiety and depression. Thus, in this specific configuration, genes and not environment are responsible for tendency of symptoms of anxiety to correlate more highly with other symptoms of anxiety than with symptoms of depression, and vice versa. In another possible configuration of independent-pathway model, and one more consistent with results of this article, environmental factors would be relatively specific in their impact on symptoms of anxiety and symptoms of depression while a genetic factor would nonspecifically influence both sets of symptoms.



analysis. This technique can be understood as a generalization of factor analysis that permits the estimation of separate genetic and environmental factors. By using information from the correlations between monozygotic (MZ) and dizygotic (DZ) twin pairs for the same symptom and cross-correlations between and within twins for different symptoms, multivariate genetic analysis permits the separation of the genetic from the environmental impact on symptom covariation.

We wish to test two models in our multivariate genetic analysis that represent different ways in which genes and environment might affect multiple symptoms (Figure). The first, or "common-pathway," model assumes that genes and environment both contribute to one or more intermediate latent variables (eg, liability to "anxiety" and liability to "depression," denoted as "Anx" and "Dep" in the upper section of the Figure), which are in turn responsible for the observed pattern of symptom covariation. In other words, this model assumes that genes and environment act on symptom covariation by a final common pathway.

Under the second, or "independent-pathway," model, genes and environment may have different effects on the pattern of symptom covariation. For example (as pictured in the bottom section of the Figure), there could be two sets of genes—one of which was relatively selective for symptoms of anxiety and the other for symptoms of depression—but environmental influences that predispose equally to both sets of symptoms. It can be shown algebraically that the common-pathway model can be subsumed as a submodel of the independent-pathway model, so that the fit of the two models can be tested statistically (by means of a likelihood ratio  $\chi^2$  test).<sup>15</sup>

The final step in the "Results" section is to present in detail the findings of the most appropriate multivariate genetic model. This presentation permits a detailed comparison of results between the conventional and multivariate genetic factor analyses and an examination of the consistency of the findings across sexes.

#### Data Analysis: Methods

Methods of data summary and analysis designed for continuous variables are inappropriate for discontinuous variables, such as our item scores, which have only three-point scales. The approach that we have used assumes the existence, for each item, of a normally distributed liability that determines the probability of response to

that item. The observed distribution is related to the latent distribution by abrupt "thresholds" superimposed on the latent distribution. With multicategory data as those used in this article, it is possible to test statistically the validity of these assumptions. As described previously,<sup>4</sup> the fit of this "threshold" model to the observed data was good.

The first step in our data analysis was a traditional factor analysis of the twin responses. The sample was subdivided by sex and then into first and second members from each twin pair. A factor analysis was performed separately for each of the four resulting subsamples. Factor loadings were estimated by the unweighted least-squares method.<sup>14</sup> In each analysis, the number of factors extracted was determined by the number of eigenvalues greater than unity. We estimated uncorrelated ("orthogonal") factors for comparability with the multivariate genetic analysis. To select for study one of the infinite number of statistically equivalent solutions ("factor rotations"), we used the simplest technique of fixing to 0 the loadings of one depression item ("lost interest in everything") on the second and third factors, and of an anxiety item ("pain or tension in head") on the third factor.<sup>14</sup> This method of rotation ensured comparability of factor rotations between sexes, between first and second twins, and between the traditional and multivariate genetic factor analyses. These items were chosen by performing varimax rotations<sup>14</sup> on the results from the four subsamples and then selecting the items for which the mean-squared factor loadings were highest on the observed depression and anxiety factors. In fitting three factors, this traditional factor analysis required the estimation of 36 common factor loadings for 13 items on the first latent factor, 12 on the second, and 11 on the third. Item-specific factor loadings, which explain the variance not accounted for by the common factors loadings, were obtained by subtracting from unity the variance accounted for by the common factor loadings. By convention, these item-specific loadings are not tabulated.

Although solutions that permit correlated ("oblique") factors are sometimes preferred for descriptive purposes, our chief interest was in causal analysis for which uncorrelated factors are much simpler to interpret. This is particularly true with respect to the action of different genes that, in the absence of gametic-phase disequilibrium, should be uncorrelated in the population.

Theoretically, the best data summaries for multivariate analysis

Table 1.—Factor Loadings ( $\times 100$ ) of Symptoms of Anxiety and Depression on Phenotypic Factors in Females and Males\*

| Item                               | Females |    |     |        |    |     | Males  |     |     |        |    |     |
|------------------------------------|---------|----|-----|--------|----|-----|--------|-----|-----|--------|----|-----|
|                                    | Twin 1  |    |     | Twin 2 |    |     | Twin 1 |     |     | Twin 2 |    |     |
|                                    | I       | II | III | I      | II | III | I      | II  | III | I      | II | III |
| <b>Anxiety subscale</b>            |         |    |     |        |    |     |        |     |     |        |    |     |
| 1. Worried about everything        | 62      | 37 | 16  | 63     | 28 | 22  | 55     | 37  | 20  | 55     | 33 | 29  |
| 2. Breathless or heart pounding    | 37      | 34 | 0   | 42     | 42 | -8  | 43     | 44  | 1   | 35     | 55 | 0   |
| 3. Worked up, can't sit still      | 57      | 44 | 3   | 61     | 34 | 11  | 50     | 50  | 23  | 57     | 37 | 19  |
| 4. Feelings of panic               | 66      | 40 | -8  | 72     | 27 | 0   | 71     | 29  | 1   | 63     | 42 | 7   |
| 5. Pain or tension in head         | 41      | 44 | 0†  | 41     | 44 | 0†  | 49     | 45  | 0†  | 38     | 59 | 0†  |
| 6. Worrying kept me awake          | 58      | 31 | 39  | 60     | 25 | 51  | 54     | 25  | 58  | 55     | 27 | 56  |
| 7. Anxious, can't make up my mind  | 78      | 32 | -7  | 79     | 21 | -2  | 73     | 16  | 14  | 74     | 34 | 6   |
| <b>Depression subscale</b>         |         |    |     |        |    |     |        |     |     |        |    |     |
| 1. Miserable difficulty with sleep | 68      | 31 | 74  | 72     | 24 | 63  | 68     | 27  | 52  | 68     | 29 | 57  |
| 2. Depressed without knowing why   | 70      | 23 | -3  | 71     | 18 | -2  | 72     | 19  | -2  | 72     | 22 | 1   |
| 3. Gone to bed not caring          | 84      | 1  | 7   | 85     | 7  | 2   | 83     | -3  | -4  | 83     | 11 | 4   |
| 4. Low in spirits, just sat        | 80      | 6  | 1   | 80     | 10 | 2   | 76     | 5   | -5  | 78     | 7  | 2   |
| 5. Future seems hopeless           | 83      | -3 | 8   | 85     | -6 | 9   | 83     | -18 | 7   | 84     | 10 | 4   |
| 6. Lost interest in everything     | 89      | 0† | 0†  | 92     | 0† | 0†  | 86     | 0†  | 0†  | 91     | 0† | 0†  |

\*Orthogonal factors.  
†Parameter fixed to 0.

of our discontinuous data would be 13-way contingency tables, cross-classifying the scores of individuals on each of the 13 items, for factor analysis, or 26-way tables, cross-classifying responses of first and second twins on each of the 13 items, for multivariate genetic analysis. In practice, fitting models to such contingency tables, which would require the repeated numerical integration of the multivariate normal distribution, would be infeasible with current computer resources. Instead, we have obtained maximum likelihood estimates of the "polychoric correlation"<sup>18</sup> between every pair of variables, separately for each twin group (male and female first and second twins for factor analysis; male and female MZ and DZ pairs for the multivariate genetic analysis). We then fitted models to  $13 \times 13$  or  $26 \times 26$  matrices of polychoric correlations. The factor analyses were performed separately on each  $13 \times 13$  matrix, but the multivariate genetic analysis involved simultaneous analysis of two matrices, one for MZ pairs and the other for DZ pairs of a given sex. Models were fitted by unweighted least squares, in the case of the factor analysis, but by weighted least squares, using estimates of the reciprocal of the sampling variance of each polychoric correlation as noniterative weights,<sup>18,20</sup> for the multivariate genetic analysis. The latter approach gives us an approximate  $\chi^2$  goodness-of-fit test of the absolute fit of the model with the number of degrees of freedom equal to the number of unique correlations (650 if we are analyzing two  $26 \times 26$  correlation matrices) minus the number of estimated parameters. We can also compute an approximate likelihood ratio  $\chi^2$  (or " $\chi^2$  difference") test of the relative fit of each model compared with more complete models. For the full model, only a goodness-of-fit test is available. For subsidiary models, the likelihood ratio  $\chi^2$  provides a more powerful test. Thus, it is possible that by a goodness-of-fit test a model may provide an acceptable fit to the data, yet be rejected in favor of a different model by a likelihood ratio test.

In our multivariate genetic analysis using the independent-pathway model, we estimated simultaneously item loadings on the common genetic factors, the common (nonfamilial) environmental factors, and item-specific genetic factors. Loadings on the common genetic factors contribute both to the within-individual and to the between-twin cross-correlations between items. Loadings on the common (nonfamilial) environmental factors contribute to the within-individual but not to the between-twin item cross-correlations. Loadings of the item-specific genetic factors contribute to the correlation between twins for a specific item, but not the cross-correlations between items. Finally, item-specific environmental factors, which explain the residual variance, are obtained by

subtraction. Both common and item-specific loadings are expected to be the same for both members of a twin pair. An independent-pathway model that allows for three common genetic, three common environmental, and item-specific genetic factors requires the estimation of 85 parameters: 36 ( $13 + 12 + 11$ ) common genetic factor item loadings, 36 common environmental factor loadings, and 13 item-specific genetic factor loadings.

Using the common-pathway model, we estimated as before common genetic, item-specific genetic, and item-specific environmental loadings. However, under this model, the item loadings of each common environmental factor are expected to be a constant multiple of the loadings on the corresponding common genetic factor. Therefore, it was necessary to estimate only a single scalar multiplier for each common genetic factor from which loadings on the corresponding common environmental factor could be derived. In the three-factor common-pathway model, it was therefore necessary to estimate only 52 parameters: 36 common genetic loadings, three scalar multipliers, and 13 item-specific genetic loadings.

The previous univariate analysis<sup>4</sup> indicated that the overall effect of common environmental or genetic dominance on symptoms of anxiety and depression in this sample was small or undetectable. If a variable accounts for a small proportion of variance in an item, statistical principles dictate that it cannot make a major contribution to the covariation of that item with other items. Therefore, our multivariate analyses considered only additive genetic and non-familial (or random) environmental effects, both of which were shown, in our univariate analysis, to have a large impact on symptoms of anxiety and depression.<sup>4</sup>

For an estimate of the similarity of factor loadings obtained on different samples (eg, twin 1 vs twin 2 or males vs females), the congruency coefficient ( $r_c$ ) was used.<sup>21</sup>

## RESULTS

### Factor Analysis

Using the eigenvalue criterion, three orthogonal factors were extracted in each case for the first and second members of the male and female twin pairs. The results of this traditional, or phenotypic, factor analysis are seen in Table 1. Factor loadings (which, in an orthogonal solution, are equivalent to the correlation of an item with the underlying latent factor) are given for the rotated solution.

The first phenotypic factor, which accounted for between 45.8% and 50.5% of the total variation, was similar across groups. The congruency coefficients were above .99 for all six possible compari-

Table 2.—Factor Loadings ( $\times 100$ ) of Symptoms of Anxiety and Depression on Genetic and Environmental Factors in Female and Male Twins\*

| Item                                | Genetic Factors |    |     |          | Environmental Factors |     |     |          |
|-------------------------------------|-----------------|----|-----|----------|-----------------------|-----|-----|----------|
|                                     | I               | II | III | Specific | I                     | II  | III | Specific |
| Females                             |                 |    |     |          |                       |     |     |          |
| Anxiety subscale                    |                 |    |     |          |                       |     |     |          |
| 1. Worried about everything         | 51              | 2  | 10  | 33       | 40                    | 32  | 21  | 56       |
| 2. Breathless or heart pounding     | 31              | 39 | -9  | 25       | 29                    | 25  | -1  | 73       |
| 3. Worked up, can't sit still       | 50              | 11 | 2   | 35       | 36                    | 37  | 8   | 59       |
| 4. Feelings of panic                | 59              | 14 | 1   | 20       | 41                    | 26  | -3  | 60       |
| 5. Pain or tension in head          | 33              | 34 | 0†  | 34       | 28                    | 34  | 0†  | 68       |
| 6. Worrying kept me awake           | 40              | 13 | 29  | 29       | 43                    | 25  | 39  | 50       |
| 7. Anxious, can't make up my mind   | 68              | -2 | -10 | 0        | 45                    | 25  | 6   | 51       |
| Depression subscale                 |                 |    |     |          |                       |     |     |          |
| 1. Miserable, difficulty with sleep | 46              | 10 | 45  | 0        | 51                    | 28  | 50  | 0‡       |
| 2. Depressed without knowing why    | 53              | 2  | 13  | 21       | 47                    | 21  | -16 | 61       |
| 3. Gone to bed not caring           | 51              | 18 | 13  | 43       | 71                    | -2  | 1   | 17       |
| 4. Low in spirits, just sat         | 60              | 1  | 17  | 32       | 53                    | 9   | -11 | 46       |
| 5. Future seems hopeless            | 53              | 2  | 1   | 34       | 69                    | -11 | 14  | 32       |
| 6. Lost interest in everything      | 63              | 0† | 0†  | 17       | 66                    | 0†  | 0†  | 37       |
| Males                               |                 |    |     |          |                       |     |     |          |
| Anxiety subscale                    |                 |    |     |          |                       |     |     |          |
| 1. Worried about everything         | 33              | 8  | 46  | 0        | 40                    | 35  | 3   | 63       |
| 2. Breathless or heart pounding     | 42              | 44 | 7   | 0        | 14                    | 28  | -2  | 73       |
| 3. Worked up, can't sit still       | 38              | 22 | 19  | 36       | 31                    | 45  | 13  | 58       |
| 4. Feelings of panic                | 74              | 1  | 15  | 0        | 17                    | 31  | -5  | 55       |
| 5. Pain or tension in head          | 32              | 34 | 0†  | 37       | 24                    | 44  | 0†  | 63       |
| 6. Worrying kept me awake           | 44              | 6  | 23  | 29       | 29                    | 25  | 72  | 0‡       |
| 7. Anxious, can't make up my mind   | 60              | 13 | 18  | 6        | 45                    | 25  | 1   | 57       |
| Depression subscale                 |                 |    |     |          |                       |     |     |          |
| 1. Miserable, difficulty with sleep | 44              | 4  | 29  | 9        | 48                    | 32  | 37  | 50       |
| 2. Depressed without knowing why    | 57              | -7 | 5   | 23       | 39                    | 35  | -8  | 58       |
| 3. Gone to bed not caring           | 57              | -4 | 12  | 5        | 56                    | -3  | 4   | 59       |
| 4. Low in spirits, just sat         | 65              | 1  | -16 | 0        | 48                    | 10  | 4   | 55       |
| 5. Future seems hopeless            | 51              | -1 | 7   | 32       | 68                    | -2  | 2   | 41       |
| 6. Lost interest in everything      | 62              | 0† | 0†  | 0        | 64                    | 0†  | 0†  | 45       |

\*Orthogonal factors, weighted least-square solution.

†Parameter fixed to 0.

‡Parameter value constrained to be positive.

sons across the four groups. The highest factor loadings in all groups were found on four core depression items: "gone to bed not caring," "low in spirits, just sat," "future seems hopeless," and "lost interest in everything." However, the factor was not highly specific for depression as all items loaded positively (ie,  $> +0.30$ ) on this factor. This factor was termed "depression-distress" to signify that depression items consistently loaded highest on this factor, but it was also, in part, a general psychiatric distress factor.

The second phenotypic factor, which accounted for between 6.5% and 10.9% of the total variation, was also quite similar in the four groups. Five of the six possible congruency coefficients were above .96 and the sixth (between male twin 1 and male twin 2) was .93. The four highest loadings in all groups were from among five anxiety items: "worried about everything," "breathless or heart pounding," "worked up, can't sit still," "feelings of panic," and "pain or tension in head." Unlike the first factor, the second factor was relatively specific. The loadings of all anxiety items except "anxious, can't make up my mind" were in excess of .25, while the loadings for the four core depression items never exceeded .11. This factor was termed "general anxiety."

A third factor, which accounted for between 5.6% and 5.9% of the total variation, had in all four groups by far the highest loading on the two insomnia items: "worrying kept me awake" and "miserable, difficulty with sleep." Five of the six possible congruency coefficients were above .90 and the sixth (between female twin 1 and

male twin 1) was .87. This factor was termed "insomnia."

A useful way to quantify the contribution of the first two phenotypic factors to the original anxiety and depression subscales is to compare the proportion of total variance accounted for in the two subscales by the first two factors. Across all four groups, the mean ( $\pm$ SD) proportion of variance in the anxiety and depression subscales accounted for by the "depression-distress" factor was, respectively,  $33.8\% \pm 2.8\%$  and  $63.4\% \pm 1.9\%$ . In other words, the "depression-distress" factor accounted for one third of the total variance of the anxiety subscale, but for nearly two thirds of the total variance for the depression subscale. The mean proportion of variance in the anxiety and depression subscales accounted for by the "general anxiety" factor was, respectively,  $14.1\% \pm 3.0\%$  and  $2.4\% \pm 0.4\%$ . The "general anxiety" factor accounted for over five times as much variance in the anxiety as in the depression subscale.

#### Multivariate Genetic Analysis: Model Fitting

We considered two major multivariate models: the common-pathway and independent-pathway models (Figure). By a  $\chi^2$  goodness-of-fit test, the fit of a "full" independent-pathway model with three genetic and three environmental factors was excellent for both females ( $\chi^2 = 470.8$ ;  $df = 565$ ;  $P = .98$ ) and males ( $\chi^2 = 556.8$ ;  $df = 565$ ;  $P = .59$ ). For females, all subsidiary models with fewer than three genetic and three environmental factors could be

rejected by likelihood ratio  $\chi^2$  tests. For males, all subsidiary models could also be rejected except that which contained all three environmental factors and only the first two genetic factors ( $\chi^2=16.3$ ;  $df=11$ ;  $P=.13$ ).

The two- and one-factor common-pathway models could be rejected at high levels of statistical significance ( $P<.00001$ ) for both males and females. However, the three-factor common-pathway model produced a reasonable fit in both females ( $\chi^2=550.0$ ;  $df=598$ ;  $P=.92$ ) and males ( $\chi^2=638.4$ ;  $df=598$ ;  $P=.12$ ). However, compared with the full independent-pathway model, the three-factor common-pathway model could be rejected by likelihood ratio tests at high levels of significance for both females ( $\chi^2=79.3$ ;  $df=33$ ;  $P<.0001$ ) and males ( $\chi^2=81.6$ ;  $df=33$ ;  $P<.0001$ ).

Finally, we fitted the full independent-pathway model to both sexes simultaneously. The likelihood ratio test of heterogeneity was very highly significant ( $\chi^2=222.9$ ;  $df=85$ ;  $P<.0001$ ), indicating that although this model was appropriate for each sex, the factor loadings differed significantly between females and males.

### Results of Best-Fitting Model

Genetic and environmental factor loadings are given under the full independent-pathway model separately for females and for males (Table 2). Although a slightly simpler model also provided an adequate fit in males (ie, two genetic and three environmental factors), the full model was somewhat superior in fit and had the advantage of simplifying the comparison of the results across sexes. In comparing these results with the phenotypic factor loadings shown in Table 1, it should be remembered that we are now fitting a total of six (three genetic and three environmental) factors rather than three phenotypic factors, so that the individual factor loadings will, in almost all cases, be lower in Table 2 than in Table 1. A comparison of these tables should focus on the pattern rather than the absolute value of the factor loadings.

The first genetic factor, which accounted for 26.7% of the total phenotypic variance in females and 27.3% in males, was very similar in both sexes ( $r_c=.986$ ). The four items with highest loading in both sexes were two anxiety items, "feelings of panic" and "anxious, can't make up my mind," and two depression items, "low in spirits, just sat" and "lost interest in everything." Like the first phenotypic "depression-distress" factor, all items tended to load highly and positively on this factor. Unlike the first phenotypic factor, the average loading for anxiety items was almost as high as that found for depression items. Because of the apparent lack of specificity of this factor, it was termed the "genetic distress" factor.

The second genetic factor accounted for 2.8% of the total variance in females and 3.0% in males and was reasonably similar across sexes ( $r_c=.837$ ). In both sexes, only two items had substantial loadings on this factor: "breathless or heart pounding" and "pain or tension in head." This factor differed from the second phenotypic "general anxiety" factor in having low loadings for other anxiety items, especially "worried about everything" and "feelings of panic." Therefore, this factor was termed the "genetic somatic anxiety" factor.

The third genetic factor, which accounted for 2.9% of the total variation in females and 3.8% in males, was only modestly stable across sexes ( $r_c=.510$ ). In females, substantial loadings were seen only for the two insomnia items. In males, the highest loading was seen on the first anxiety item "worried about everything," followed by the two insomnia items. This factor was broadly similar to the third phenotypic factor and, hence, was termed the "genetic insomnia" factor. The second and third genetic factors, although statistically significant because of the large size of the sample, account for a small proportion of total variance in liability to symptoms in the twin population. The genetic specific loadings, which reflect the genetic influences unique to each symptom, were, on the average, relatively modest, accounting for only 7.8% of the total variation in liability to symptoms in females and 4.0% in males. These results suggest that the majority of genetic variance in these symptoms is accounted for by the three extracted factors.

The first environmental factor, which accounted for 24.5% of the total phenotypic variance in females and 18.8% in males was similar across sexes ( $r_c=.984$ ). In both sexes, the four highest loadings were on the core depression items: "gone to bed not caring," "low in spirits, just sat," "future seemed hopeless," and "lost interest in everything." This factor was relatively similar to the first phenotypic "depression-distress" factor, but the specificity for depres-

sive symptoms was somewhat greater. Therefore, this factor was termed the "environmental depression" factor.

The second environmental factor, which accounted for 5.8% of the phenotypic variance in females and 8.1% in males, was also very similar in the two sexes ( $r_c=.986$ ). In both sexes, the three highest loadings were on the core anxiety symptoms "worried about everything," "worked up, can't sit still," and "pain or tension in head." This factor was quite similar to the second phenotypic "general anxiety" factor in loading more equally on all the anxiety items and hence was termed the "environmental general anxiety" factor.

The third environmental factor, which accounted for 4.0% of the total variance in females and 5.3% in males, was also reasonably similar in males and females ( $r_c=.835$ ). In both sexes, this factor had substantial loadings on only the two insomnia items. This factor was broadly similar to both the "insomnia" and "genetic insomnia" factors and was termed the "environmental insomnia" factor.

For almost all the items, item-specific environmental loadings that represent environmental effects (including measurement error) influencing one item but no others, accounted for a substantial proportion of the total variation. For all items, specific environmental variation accounted for 26.0% of the total phenotypic variation in females and 30.0% in males.

A useful way to contrast the contribution of the first genetic and environmental factors to the anxiety and depression subscales is to compare the proportion of variance accounted for in these subscales by the two factors. The "genetic-distress" factor contributed more to the total variation in the depression than to the anxiety subscale in both females (29.8% vs 24.1%) and males (31.8% vs 23.3%), but the differences were quite small. This is in contrast to the "environmental depression" factor, which contributed more than 2½ times the total variance to the depression than to the anxiety subscale in females (36.3% vs 14.4%). In males, this ratio was over 3:1 (30.0% vs 9.3%). These results support the conclusion that the first genetic factor is nonspecific, while the first environmental factor is relatively specific for symptoms of depression.

### COMMENT

This article represents, to our knowledge, the first application of multivariate genetic methods to individual psychiatric symptoms. We analyzed responses of 3978 twin pairs to the anxiety and depression subscales of the DSSI. Our major goal was to clarify the role of genes vs the environment in the etiology of separable anxiety and depression symptom clusters in the general population. Three major results are noteworthy. First, a traditional factor analysis consistently identified two important factors termed "depression-distress" and "general anxiety." Second, in fitting multivariate genetic models, the common-pathway model could be clearly rejected in favor of the independent-pathway model. Third, fitting the full independent-pathway model produced three factors of particular interest, termed: "genetic distress," "environmental depression," and "environmental anxiety." We could find little evidence that genes influenced specifically either symptoms of depression or symptoms of anxiety. However, certain environments appeared to be specifically depressogenic and others anxiogenic.

### Phenotypic Factor Analysis

In this large volunteer twin sample, the traditional eigenvalue criterion readily identified three phenotypic factors that were stable across four groups (ie, twin 1 and 2 in females and males). After rotation, the first of these phenotypic factors, termed "depression-distress," accounted for about half of the total variation. As the name implies, this factor loaded substantially on almost all items, but loadings were consistently highest on the depression items. The second phenotypic factor, which accounted for between 6% and 11% of the total variance, was termed a "general anxiety" factor. Loadings for this factor were both relatively specific for the anxiety subscale, and were similar

for almost all the anxiety items. The third or "insomnia" factor had highest loadings on the two insomnia items with only quite modest loadings on all other items.

Controversy over the discrimination between symptoms of anxiety and depression has a long history.<sup>6,12,22</sup> Two major viewpoints, which have been termed the "distinct-syndrome" and "unitary-syndrome" positions,<sup>6</sup> have been articulated. The distinct-syndrome position views depression and anxiety as qualitatively distinct, albeit with some overlap of symptomatology. The unitary-syndrome viewpoint, by contrast, argues that these two states are on a single continuum, and that any differences between them are basically quantitative and not qualitative. As recently reviewed,<sup>22,23</sup> empirical studies using a variety of multivariate techniques have tended to support the distinct-syndrome position, although these results are not unequivocal. In addition, follow-up studies have strongly supported the discrimination between anxiety states and depression.<sup>10,23</sup>

Previous multivariate studies of the relationship between anxiety and depression have, with rare exception,<sup>24</sup> been performed on samples obtained in a treatment setting. Such an approach introduces an important possible bias. Individuals with symptoms of both disorders are more likely to present for treatment than those with symptoms from only one disorder. This bias can create a spurious covariation of symptoms. By contrast, no such bias can be operating in the general population sample studied in this article.

The Australian NHMRC Twin Registry represents a large, volunteer twin population, in which reported levels of anxiety and depression do not differ from those observed in the general Australian population.<sup>4</sup> Results from this sample provide some support for the "distinct-syndrome" position in that two phenotypic factors that could be identified as depression and anxiety were extracted from each of the four subject groups. However, these symptom dimensions were not completely independent, as anxiety items consistently loaded positively on the first "depression-distress factor." By contrast, most depression items had very low loadings on the second "general anxiety" factor.

Contrary to expectation, consistent evidence was found for a third "insomnia" factor. We are unaware of any similar results that suggest an insomnia factor can be discriminated from anxiety and depression in the general population. These insomnia items, along with other questionnaire data about sleep duration and quality, are the focus of another report in preparation.

#### Multivariate Genetic Model Fitting

Three aspects of model fitting were examined: (1) the best-fitting model, (2) the required number of genetic and environmental factors, and (3) the consistency of results across sexes. We considered two different models of how genetic and environmental factors might influence symptom covariation. The first, or common-pathway model, assumed that both genes and environment act on symptoms by influencing the same latent variables. The second, or independent-pathway model, permitted genes and environment to influence symptom covariation in different ways. The common-pathway model could be clearly rejected in favor of the independent-pathway model. These findings indicate that in this sample genes and environment are influencing the pattern of covariation of individual symptoms of anxiety and depression in qualitatively different ways.

The previously reported univariate analysis of these symptoms included an examination of the genetic and environmental correlation of liability between sexes.<sup>4</sup> These analyses required the consideration of opposite-sex DZ twin pairs, the inclusion of which in the present multi-

variate analysis would have been extremely cumbersome. In the multivariate genetic analyses, our consideration of sex differences was limited to showing that, although the same model produced the best fit in both sexes, the individual factor loadings differed significantly between the sexes. These results required the separate analysis of results in females and males, which had the advantage of permitting an assessment of the similarity of results across sexes.

#### Results of Best-Fitting Multivariate Genetic Model

The results of the best-fitting multivariate model gave a striking confirmation of the previous finding that genes and environment were influencing symptom covariation in a qualitatively different fashion. Of the three genetic factors, the first two were relatively stable across sexes, while the third was only modestly so. The first "genetic-distress" factor was so named because factor loadings were high on all items with relatively little difference found between depression and anxiety items. Compared with the first phenotypic factor, the first genetic factor was substantially less specific for depression. This "genetic-distress" factor, which accounted for around 27% of the total phenotypic variance and over two thirds of the total genetic variance in both sexes, indicated that genes were largely acting non-specifically to influence the predisposition to symptoms of psychiatric distress.

The second and third genetic factors were quite minor, each accounting for less than 4% of the total phenotypic variance. The second, or "genetic somatic anxiety" factor, loaded highly on only two anxiety items, both of which reflected the somatic symptoms of anxiety. This factor differed from the phenotypic "general anxiety" factor in the low loadings found for several key symptoms reflecting cognitive aspects of anxiety. Although genes seem to "code" specifically for symptoms of anxiety to a modest degree, they apparently influence only the somatic symptoms of anxiety.

The third, or "genetic insomnia" factor, was broadly similar to the third phenotypic factor in loading most prominently on the two insomnia items. Genetic factors that influence complaints of insomnia are, at least in part, separable from those that influence general levels of distress or symptoms of physical anxiety.

Of the three environmental factors, the first two were stable and the third relatively stable across sexes. The first or "environmental depression" factor loaded consistently highest on four core depression items. This factor was more specific for depression than the first phenotypic "depression-distress" factor, as reflected by the fact that the "environmental depression" factor accounted for over 2½ times the total variance in the depression subscale than in the anxiety subscale.

The second, or "environmental general anxiety" factor, was quite similar to the phenotypic "general anxiety" factor. Loadings were consistently highest on both physical and cognitive symptoms of anxiety, while loadings were low on the core depression symptoms. The third, or "environmental insomnia" factor, like the two other insomnia factors, had highest loadings on the two insomnia items. The environmental factors that influence insomnia also appear to be in part separable from those that cause anxiety and depression. This is not surprising in that nighttime noise might be expected to produce precisely this effect.

#### Limitations

One potential limitation of this report is noteworthy. The symptoms studied were obtained by self-report from the general population. As noted above, this has distinct advantages for the kind of multivariate analyses performed. The

use of a population-based sample avoids the possible bias associated with help-seeking behavior. However, it does mean that the results obtained here on symptoms of anxiety and depression cannot necessarily be extrapolated to clinical syndromes. For example, if there were genes specific for panic disorder, individuals with such genes could be rare enough in our sample to prevent detection of a separable "panic" genetic factor.

#### Significance

The results of this study suggest that the tendency in the general population for symptoms of anxiety to co-occur with other symptoms of anxiety and symptoms of depression to co-occur with other symptoms of depression is largely the result of environmental factors. Contrary to our expectation, genetic influences on these symptoms were largely nonspecific. That is, while genes may "set" the vulnerability of an individual to symptoms of psychiatric distress, they do not seem to code specifically for symptoms of depression or anxiety. These findings are consistent with a previous analysis of the total anxiety and depression scale scores performed with the Australian NHMRC Twin Registry data analyzed here.<sup>25</sup> In that report, high genetic correlations were found between transformed total scores on the anxiety and depression subscales, indicating that the same genes were largely responsible for genetic variation in the two subscales.

The one notable exception to the apparent nonspecificity of gene action on symptoms of anxiety and depression was the consistent emergence of a minor "genetic somatic anxiety" factor. These results suggest that genes may be responsible for the frequently observed partial independence of "somatic" from "psychic" symptoms of anxiety.<sup>26</sup>

Because measures of relevant environmental variables

were not obtained on twins from the Australian NHMRC Twin Registry, little further information can be extracted from the registry regarding the particular environmental variables that predispose to symptoms of anxiety vs symptoms of depression. However, as indicated by the results of the univariate genetic analyses of these data,<sup>4</sup> these environmental variables were not shared by members of a twin pair. Therefore, the environmental effects that specifically predispose to symptoms of anxiety vs symptoms of depression could not plausibly be parental characteristics, to which both members of a twin pair would be exposed.<sup>27-29</sup> By contrast, since most life events, except death or illness in relatives, are not shared by members of an adult twin pair, the results of this study are consistent with findings that certain classes of life events specifically precipitate either depression or anxiety.<sup>30-32</sup> This study demonstrates that genetically informative designs such as MZ and DZ twins, when appropriately analyzed, can not only provide insight into the role of genetic and environmental factors in the etiology of individual psychiatric symptoms, but can also clarify the degree to which the clustering of individual psychiatric symptoms into syndromes is the result of genetic vs environmental influences.

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