Symptoms of Anxiety and Depression in a Volunteer Twin Population

The Etiologic Role of Genetic and Environmental Factors

Kenneth S. Kendler, MD; Andrew Heath, DPhil; Nicholas G. Martin, PhD; Lindon J. Eaves, DSc

We examined the etiologic role of genetic and environmental factors in 14 symptoms of anxiety and depression reported by 3,798 pairs of adult twins from the Australian National Health and Medical Research Council Twin Register. Multifactorial multiple-threshold models fit the individual symptom scores well. For a substantial majority of the symptoms, the variance in liability was best explained by only genetic factors and environmental influences specific to the individual, where 33% to 46% of the variance was due to genetic factors. For four symptoms, it was not possible to choose definitively between models that, in addition to specific environment, included genetic vs familial environmental effects. These results provide strong evidence for the role of genetic factors in the etiology of symptoms of anxiety and depression as reported in a general population. Evidence for an etiologic role of familial environmental factors was much weaker. If familial environmental factors play any role in the production of these symptoms, they are more important in symptoms of depression than of anxiety, and the factors that predispose to these symptoms are only modestly correlated in males and females.

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Although symptoms of anxiety and depression are among the most common complaints seen in psychiatric and general medical practice, relatively little is known about their etiology. Family and twin studies have suggested that genetic factors probably play an etiologic role in anxiety and depressive disorders; much less is known about the etiologic role of genetic factors in symptoms of anxiety and depression as experienced in the general population. However, certain environmental variables, including stressful life events, early parental loss, and specific patterns of parental behavior, have been hypothesized to predispose to the development of symptoms of anxiety and depression.

In this report, we examine the etiologic role of genetic and environmental factors in the determination of the 14 symptoms of anxiety and depression from the anxiety and depression scales of the Delusions-Symptoms-States Inventory (DSSI). The sample studied was a large volunteer twin population from the Australian National Health and Medical Research Council (NHMRC) Twin Register. This study represents an extension of an earlier investigation of this sample by Jardine et al that focused on the total scale scores and their covariation with the trait of neuroticism. The goal of this report is to clarify the role played by genetic and environmental factors in the etiology of specific symptoms of anxiety and depression as experienced in the general population. Specifically, we were interested in testing two opposing hypotheses: that either genetic factors or family environment is responsible for the similarity of symptom scores of twins.

SUBJECTS AND METHODS

Subjects and Questionnaire

Between November 1980 and March 1982, an extensive questionnaire was mailed to 6,967 twin pairs aged 18 years and over from the Australian NHMRC Twin Register. After reminders to nonrespondents, questionnaires were returned by both members of 3,810 pairs, a 56% pairwise response rate.

Zygosity was diagnosed by questionnaire response, which, if ambiguous, was resolved by having the twins send in recent photographs of themselves. In other twin populations, this method of zygosity determination has been shown to be approximately 95% accurate.

Among the items contained in the mailed questionnaire were the anxiety and depression scales of the DSSI (Table 1). The 14 items were answered on a four-point scale (0 to 3) with the categories labeled as follows: none, a little, a lot, and unbearably. These scales, which were intended to measure state rather than trait characteristics, were developed and validated by Bedford et al. In
a sample of 96 twins from the NHMRC Twin Register who were asked to return two questionnaires at a mean interval of three months. The mean (±SD) correlation (Kendall τ) between their scores on the individual items was 0.42 ± 0.10.

Analysis

Our method of analysis can be divided into three parts. First, we determined whether any obvious differences between twins, such as sex, birth order, age, and zyosity, affected symptom scores to a sufficient degree that they needed to be incorporated into further analyses.

Second, we examined whether the observed response distribution could be fitted to a multiple-threshold model. This approach hypothesizes that for each item there exists a normally distributed liability that determines the response. To analyze four response categories, three thresholds were required. As the scores for males and females differed significantly on many items, it was often necessary to postulate separate sets of thresholds for males and females. In several cases, the number of individuals endorsing the most extreme answer (ie, 3, or unambiguously) on an item was very small or zero. In these circumstances, it sometimes became necessary to combine the two most extreme responses (ie, 2 and 3, or a lot and unambiguously) together into a single category. In addition, when the number of extreme responses was small, slight deviations from expectation in these responses could cause the multiple-threshold model to fail. Therefore, in the few situations where the multiple-threshold model did not fit well to the data using all responses, response categories 2 and 3 were also combined into a single category and the data reanalyzed.

The fit to the multiple-threshold model was determined in two ways. First, the fit was examined for the 70 individual tables of 14 symptoms by five zyosity groups. Second, the fit was examined for each item over all five zyosity groups. This was determined by the fit of what we term the "full model." Because this model contained five parameters to fit to the five polychoric correlations from each zyosity group, this was a "perfect fit" model. This model would be rejected only if the combined fit to the multiple-threshold model over all five zyosity groups were inadequate.

In the third part of the data analysis, we fitted various genotype-environment models to the observed data, assuming a multiple-threshold model. These genotype-environment models assume that the underlying liability is due to the combined additive action of many genes and/or many environmental events, each of small effect. The models and their application are derived from the school of biometrical genetics. As this approach is probably unfamiliar to most readers, we will briefly describe it here. Eysenck and Eaves give a more detailed presentation of these methods.

In our models, variation in liability is seen as resulting from four parameters, two genetic and two environmental. Additive genetic variance (VA) is the proportion of variance in liability that results from the additive effects of alleles at each locus. Domiance genetic variance (VD) is the proportion of total variance that results from the nonadditive effects of two alleles at a locus. The proportion of total variance in liability due to VA and VA + VD is the narrow and broad heritability, respectively.

Common environmental variance (EC) is that proportion of variance in liability that results from environmental events shared by both members of a twin pair. Because most such events presumably result from the twins having been reared in the same family, EC is sometimes referred to as familial environmental variance. A wide variety of variables could contribute to EC, including general rearing environment, specific parental personality traits, socioeconomic class, school attended, or geographic location of rearing environment. Specific environmental variance (ES) is that proportion of variance in liability that results from environmental events that are not shared by both members of a twin pair. Variables that might contribute to ES would include aspects of the rearing environment unique to one member of a twin pair, random developmental processes, environmental "accidents," experiences unique to each twin that occur after their separation. The variance component and measurement error. Three of these parameters (VA, VD, and EC) contribute and one (ES) does not contribute to similarity between relatives.

The mean scores on many of the items differed in males and females. It was therefore necessary in model fitting to permit the thresholds to differ for the two sexes. If the thresholds differed, but all the genotype environment parameters were the same for both sexes, then this was equivalent to the "isocorrelational model" of Cloninger et al.

In addition, we considered two further situations in which VA or EC might differ in the two sexes. First, the same genes or the same common environmental events could influence liability in the two sexes, but the magnitude of their effect might differ in the two sexes. These models, termed the VA(0), VA(1), and the EC(0), EC(1), respectively, correspond to the "environmental model" of Cloninger et al.

Second, the genes and/or common environmental events that influence liability might differ in the two sexes (ie, the "independent model" of Cloninger et al). In these models, which we term VA(0), VA(1), VA(0,1), and EC(0), EC(1), EC(0,1), respectively, two new parameters are introduced: VA(0,0) and VA(1,1). These two parameters represent the covariance between additive genetic effects and common environmental effects, respectively, in males and females. From VA(0,0) and EC(0), new parameters can be calculated, which we define as the correlation in additive genetic effect (rGA) and the correlation in common environmental effects between the two sexes (rCE). In other words, rGA and rCE measure the degree to which the same genes or the same common environmental variables affect liability in males and females.

The contributions of each of the genetic and environmental parameters to the correlation of liability in each zyosity group are given in Table 2. We have assumed that EC contributes equally to the correlation in monositygotic (MZ) and dizygotie (DZ) twins; ES, by definition, makes no contribution to the resemblance of twin pairs.

In studies of twins only, the effects of EC and VA are confounded. As a result, the fit of unconstrained VA, EC, GS and VA, EC, GS models are identical. However, VA and EC have opposite effects on the pattern of correlations between MZ and DZ twins. Given the presence of VA, VA will increase EC and decrease the ratio of the correlations between MZ and DZ twins. Therefore, although the fit of the two models is identical, their predictions regarding MZ and DZ correlations are opposite. As parameters in these models are variance estimates, any model that results in a significant negative estimate of EC or VA is automatically rejected. In fitting what we have termed the VA, EC/VD, ES model, we first estimate EC. If estimates of EC are negative, we interpret this as evidence that the VA, VA, ES model is to be preferred and, therefore, obtain estimates of VA. Because of the strong negative correlations between estimates of VA and VA in the twin design, when VA is present, estimates of VA are often negative. To provide more reasonable estimates of VA and VA in this situation, we estimate these two parameters when both are constrained to be greater than or equal to zero.

Evaluating Specific Models

The initial step in the evaluation of specific genotype-environment models is to obtain the maximum likelihood estimate of the observed responses on a symptom given the specific parameters of the model. The fit of the specific model is then tested, by a likelihood ratio test, against what we term the full model. Because the difference in log likelihoods between two models has an approximate χ2 distribution (two-tailed test) with the df equal to the difference in the number of parameters between the full and reduced models. Only when the parameters of one of the models compared is a subset of the parameters of the other model can the fit of the two models be directly compared.

We use two criteria in deciding on a best model. (1) The model gives a likelihood that is not significantly less than that obtained using the full model. (2) For addition of further parameters does not significantly increase the likelihood of the model. Using these criteria, we strive to arrive at the most parsimonious model that can account for the observations. Under certain circumstances, these rules will not permit an unambiguous identification of a best-fit model. This will occur when model cannot be rejected against the full model and cannot themselves be directly compared because they contain different parameters. In this situation, we are left with two possible models to explain the data.
whether we could find evidence for either genetic dominance or (the VA, Third, tit, number On interested in determining whether the VA, was established the following animaJsaG MZ.·VA Indicates additive *Allitems were scored on a four-point scale: 0, not at all; 1, a little; 2, a lot; and 3, unbearably.

<table>
<thead>
<tr>
<th>Table 1.—Items of the ‘State Anxiety-Depression’ Subscale of the Delusions-Symptoms-State inventory*</th>
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<tr>
<td><strong>Item Name</strong></td>
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<th>Table 2.—Contribution of the Genotype-Environment Factors to the Correlation in Liability by Zygosity Group*</th>
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<td>DZ OS</td>
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*VA indicates additive genetic variance; VD, dominance genetic variance; EC, common environmental variance; ES, specific environmental variance; MZ, monozygotic twins; DZ, dizygotic twins; OS, opposite sex. Subscript letters indicate sex influence on liability. In models with VA, VA = VA = VA, in models with EC, EC = EC = EC, in models with VA, VA = VA, in models with EC and EC, EC = (EC × EC). |

On the principle of parsimony and small differences in goodness of fit, it is often possible to prefer one of the models over the other. Based on results from studies on a wide variety of traits in animals and on studies of personality variables in man, we established the following principles to guide our interpretation of the results. First, because of its simplicity and wide applicability, the VA, ES model was judged the most likely to fit the data. Second, the major alternative explanation to the VA, ES model was considered to be the EC, ES model. We were particularly interested in determining whether this model could adequately explain the liability in symptoms as would be predicted by a number of theorists. These two models are particularly important theoretically because they represent the two extreme explanations for family resemblance for psychiatric symptoms. The first (the VA, ES model) assumes that all similarity between relatives is genetic in origin. The second (the EC, ES model) assumes that all similarity between relatives results from environmental factors. Third, if neither the VA, ES nor the EC, ES model provided an adequate fit for the data, we were interested in determining whether we could find evidence for either genetic dominance or sex-limited gene expression.

In this study we evaluated multiple statistical tests. To determine whether the number of significant results is in excess of chance expectation, we followed a method previously outlined that provides an overall significance level for the number of specific results with a P value less than .06 or .01 as a function of the total number of tests performed. The term significance will be used to denote P values of less than .05.

**RESULTS**

*Sample*

Of the 3,310 pairs of twins who returned questionnaires, 3,798 (99.7%) provided responses from both twins to all 14 anxiety and depression items. The division of these 3,798 twins into their five sex and zygosity groups is given in Table 3. As frequently noted in volunteer twin studies, both female and MZ twins are more common than would be expected in the general population. In addition, there is a slight, but statistically significant, difference in the age distribution of the zygosity groups.

**Effect of Sex, Birth Order, Age, and Zygosity on Item Scores**

Females scored higher than males for all items (Table 4). The difference was significant for ten of the 14 items, a finding far in excess of chance expectations. Firstborn twins had slightly lower symptom scores than secondborn twins, but these differences were significant for only two of the 14 items, a result not different from chance expectation. The correlation between symptom score and age was calculated separately for each sex. Of the 28 correlations, 21 were statistically significant (19 negative and two positive). The substantive significance of these correlations, however, is slight because their magnitude was uniformly low. The mean absolute value of the 21 significant correlations was .062. For these items, age accounted for less than 1% of the total variance in symptom scores.

The effect of zygosity on symptom scores was also analyzed separately for the two sexes. None of the 28 differences in symptom scores between male and female MZ and DZ twins was significant. The effect of sex on mean symptom scores is often large and must be incorporated into further analyses as differences in thresholds between the sexes. We judged the effects of birth order, age, and zygosity to be either absent or small enough to require no special treatment in further model fitting.

**Testing Assumptions of the Twin Method**

The questionnaire contained information on the frequency of contact of members of a twin pair. The MZ twins had more frequent contact than DZ twins and female twins had more frequent contact than male twins (Kruskal-Wallis one-way analysis of variance, \( \chi^2 = 155.52, df = 4, P < .001 \). If the greater similarity of item scores of the MZ compared with DZ twins was due to more frequent
generate a meaningful goodness of fit test for the full model. Of the remaining 13 items, the full model fit well in 11, was rejected at the .05 level in one (Anx1), and was rejected at the .01 level in one (Dep5). For the two items where the full model failed to fit, all items were collapsed into three response categories, and the responses were retested for the model now fit (Table 6). For Dep7, the fit of the full model improved ($\chi^2 = 47.45, df = 31, P = .00$) but still was not significant. As the failure of one or even two of 13 items at the .05 level does not exceed chance expectation, we concluded from both methods of testing that the multiple-threshold model adequately accounted for the observed response pattern.

### Fitting Genotype-Environment Models

The likelihood ratio tests of the specific models against the full model for the anxiety and depression items are given in Table 6. The parameter estimates of the best-fit model or models for the items are seen in Table 7.

To illustrate the model-fitting method, we examined in detail the results for two symptoms, chosen to provide examples of the two major outcomes of model fitting: Anx2, “pain or tension in head,” and Dep2, “depressed without knowing why.”

### Estimations of Polychoric Correlations and Fit of the Multiple-Threshold Model

The polychoric correlation and its SE could be estimated using all four response categories for 53 of the 70 tables of the 14 individual item scores of each of the five sex-syzygy groups (Table 5). For 14 of the tables, small expected cell frequencies required that the data be collapsed into three response categories. For three of the tables, it was not possible to estimate accurately a polychoric correlation even when the data were collapsed into three categories.

By a $\chi^2$ goodness of fit test, the multiple-threshold model was rejected at the .05 level in ten of the 67 tables. This is significantly in excess of chance expectation. However, at the .01 level, the multithreshold model was rejected in only two of the tables, a result not different from that expected by chance.

The fit of the multiple-threshold model was also assessed by a $\chi^2$ goodness of fit test for each item across all five syzygy groups with the full model: $V_{D_{2}}, V_{A_{2}}, E_{C_{2}}, E_{D_{2}}, V_{E_{2}}, E_{S_{2}},$ and ES; with sex-dependent thresholds. This fit could be tested for all items except Dep7 (see Table 1 for explanation of items). For this item, the very low endorsement rate (Table 4) made it impossible to

### Table 3.—Sample of Twin Pairs Studied

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<th>item.</th>
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<th>items except Dep7 (see Table 1 for</th>
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<th>216 Arch Gen Psychiatry—Vol 43, March 1986</th>
<th>Anxiety and Depression—Kendler et al</th>
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</table>
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environmental effects) was rejected as an adequate fit in all 13 symptoms. This was also the case of the \( EC_u, EC_p, ES_u, ES_p \) model, which permitted the common environmental effects to differ in magnitude across sexes.

3. Values of ES (i.e., random environmental effects) for all models were greater than 0.44 and were frequently greater than 0.5.

4. Models with sex-independent thresholds provided an adequate fit in five items (Anx2, Anx7, Dep1, Dep5, and Dep6), but in two of these (Anx7 and Dep3) the adoption of sex-dependent thresholds resulted in a significant improvement in fit.

5. The VA, ES model was the single best-fitting model for seven symptoms (Anx1, Anx5, Anx6, Anx7, Dep2, Dep6, and Dep6). The narrow heritabilities for these items ranged from 0.34 to 0.46.

6. The best-fitting models for the other six symptoms can be divided into three groups: (a) Although the VA, ES model for Anx2 was the simplest one not rejected against the full model, the addition of \( EC_v, EC_d \) resulted in a significant improvement in fit. \( \chi^2 = 4.36, df=1, P = .037 \). Estimates for EC in this model were negative, indicating that the VA, ES model was the preferred one. However, an unrestricted estimate of VA and VD (Table 9) resulted in negative estimates for VA. When VA and VD were constrained to be greater than or equal to 0, the improvement in fit over the VA, ES model was still significant \( \chi^2 = 4.34, df=1, P = .037 \). VA and VD were estimated to be 0 and 0.326, respectively. (b) Anx4 was the only symptom for which the VA, ES model was rejected. It was not possible to choose definitively between two models (Table 7). The VA, ES/VD, ES model resulted in negative estimates of EC, indicating that the VA, ES model was to be preferred. As with Anx2, unrestricted application of the VA, VD, ES model resulted in negative estimates of VA. When VA and VD were constrained to be greater than or equal to 0, VA was estimated to be 0 and VD as 0.468. The fit of this constrained VA, VD, ES model against the full model was still good \( \chi^2 = 4.34, df=3, P = .18 \). Parameter estimates from the \( VA_u, VA_p, VA_{up}, ES_u, ES_p \) model resulted in a low correlation of the additive genetic effects between the two sexes (\( r_{up} = .32 \)) and a higher narrow heritability in males than in females. (c) In Anx6, Dep1, Dep2, and Dep6, it was not possible to choose definitively between two possible best-fit models, one of which was \( EC_u, EC_p, EC_{up}, ES_u, ES_p \). The correlation between the common environmental variables influencing liability in the two sexes (\( r_{up} \)) varied in these symptoms from .278 (Dep6) to .443 (Anx6). In three of the symptoms (Anx6, Dep2, and Dep6) the other possible model was the VA, ES model with narrow heritabilities ranging from .33 to .40. In Dep1, the other possible best-fit model was \( VA_u, VA_p, ES_u, ES_p \).

**COMMENT**

Our major goal for this study was to determine whether the similarity of twins for individual symptoms of anxiety and depression could be explained by genetic or by familial-environmental factors. The results strongly support the role of genetic factors in explaining twin resemblance for the large majority of symptoms. Contrary to prediction, evidence of a role for familial-environmental factors in influencing symptom scores was either absent or weak.

**The Sample**

This study was carried out on a large twin registry in which enrollment had been voluntary. To be included in the sample, both members of a twin pair had to complete and return the questionnaire. As is usual in such studies, more female than male and more MZ than DZ twins were included. In populations of European origin, approximately equal numbers of MZ and DZ pairs of the same sex are found in the population. However, in our sample, 1.5 times as many MZ than DZ same-sex pairs were observed (Table 3). Martin and Wilson argued that this inequality could result if sample selection were based on traits that were in part genetic. They also predicted that, despite such selection, means and variances of the MZ and DZ samples for the trait influencing selection should still be similar. An alternative explanation, put forward by Lykken et al., is that for social reasons MZ twins are more cooperative with twin research. This model predicts that for any trait influencing selection, the variance in MZ twins in the sample should exceed that found for DZ twins.

No systematic differences were found in the means or variances in the symptom scores between MZ and same-sex DZ twin pairs. If the symptoms of anxiety and depression influence the probability of cooperation, these results are consistent with the model of Martin and Wilson but not of Lykken et al. Fortunately, there is a more direct way to test whether symptoms of anxiety and depression were directly affected by the sampling procedures of the registry. Henderson et al. collected a random population sample of 390 individuals in Australia. Although not directly matched for age or sex composition, this sample can serve as a rough guide to the degree to which the symptoms of anxiety and

### Table 5—Polychoric Correlations (= SE) for Individual Items for Each Sex and Zygosity Group*

<table>
<thead>
<tr>
<th>Item</th>
<th>MZ Females</th>
<th>DZ Females</th>
<th>MZ Males</th>
<th>DZ Males</th>
<th>DZ OS</th>
</tr>
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<tbody>
<tr>
<td>Anx1</td>
<td>389.4 ± .032</td>
<td>163.5 ± .046</td>
<td>333.5 ± .053</td>
<td>148.4 ± .074</td>
<td>087.5 ± .044</td>
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<tr>
<td>Anx2</td>
<td>329.4 ± .053</td>
<td>109.7 ± .076</td>
<td>344.3 ± .096</td>
<td>-0.07 ± .132</td>
<td>005.5 ± .076</td>
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<tr>
<td>Anx3</td>
<td>372.4 ± .042</td>
<td>245.5 ± .056</td>
<td>393.4 ± .061</td>
<td>018.5 ± .092</td>
<td>064 ± .054</td>
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<tr>
<td>Anx4</td>
<td>435.4 ± .053</td>
<td>040.8 ± .087</td>
<td>555.6 ± .086</td>
<td>305.3 ± .133</td>
<td>047 ± .083</td>
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<tr>
<td>Anx5</td>
<td>354.4 ± .037</td>
<td>215.4 ± .053</td>
<td>351.4 ± .066</td>
<td>177.5 ± .092</td>
<td>202 ± .052</td>
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<tr>
<td>Anx6</td>
<td>331.4 ± .059</td>
<td>227.5 ± .052</td>
<td>318.5 ± .063</td>
<td>192.5 ± .086</td>
<td>125.5 ± .051</td>
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<tr>
<td>Anx7</td>
<td>458.4 ± .047</td>
<td>206.5 ± .070</td>
<td>390.5 ± .065</td>
<td>229.5 ± .122</td>
<td>233 ± .069</td>
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<tr>
<td>Dep1</td>
<td>387.4 ± .042</td>
<td>289.5 ± .056</td>
<td>229.2 ± .080</td>
<td>177.5 ± .107</td>
<td>122 ± .061</td>
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<tr>
<td>Dep2</td>
<td>313.4 ± .039</td>
<td>228.5 ± .051</td>
<td>383.5 ± .065</td>
<td>222.5 ± .092</td>
<td>118 ± .053</td>
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<tr>
<td>Dep3</td>
<td>504.4 ± .067</td>
<td>144.5 ± .109</td>
<td>346.5 ± .143 4 212 ± .098</td>
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<tr>
<td>Dep4</td>
<td>480.4 ± .043</td>
<td>232.6 ± .085</td>
<td>419.4 ± .073</td>
<td>277.5 ± .104</td>
<td>215 ± .062</td>
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<tr>
<td>Dep5</td>
<td>395.4 ± .048</td>
<td>247.6 ± .065</td>
<td>392.5 ± .078</td>
<td>095.5 ± .112</td>
<td>152 ± .061</td>
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<tr>
<td>Dep6</td>
<td>435.4 ± .055</td>
<td>260.5 ± .081</td>
<td>328.5 ± .099</td>
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<td>104 ± .061</td>
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<tr>
<td>Dep7</td>
<td>377.4 ± .104</td>
<td>284.1 ± .133</td>
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*MZ represents monozygotic; DZ, dizygotic; and OS, opposite sex. For explanation of items, see Table 1. Polychoric correlations were calculated by maximum likelihood, with six thresholds.

For these tables, because of small expected cell frequencies, it was not possible to estimate accurately the polychoric correlations and the SE from the original 4 x 4 tables. Therefore, the values were obtained from 3 x 3 tables with four thresholds combining the scores for responses of "a lot" and "unbearable." In tables where the polychoric correlation and its SE could be calculated using both 4 x 4 and 3 x 3 tables, the results were uniformly very similar.

For these tables, even if converted to 3 x 3, it was not possible to calculate a meaningful polytomous correlation with SE. This resulted from either rare or a very small number of pairs concordant for scores greater than 0.
depression reported by the twins are representative of those reported in the general population.

The distribution of total anxiety and depression scale scores was very similar for the twin and random population sample. For nine of the specific symptoms, no significant differences were found in the two groups; for four symptoms the twins scored significantly higher and for one significantly lower. However, for all but one symptom, the magnitude of the difference in scores for the two groups was small and reached statistical significance only because of the large sample size of twins. These results suggest that the symptoms of anxiety and depression reported in the NHMRC Twin Register are probably representative of those experienced by the general population of Australia.

The Fit of the Multiple-Threshold Model

Though the multiple-threshold model in psychiatry has traditionally been applied to diagnostic categories, the model is equally applicable to levels of severity of a single symptom. As measured by both individual polychoric correlations and the fit for each symptom across the five zygosity groups, the multiple-threshold model failed to fit the symptom scores no more than would be expected by chance. This finding is consistent with the hypotheses that (1) many genes and many environmental events, each of small effect, are responsible for the liability of these symptoms, and (2) the four response categories for each symptom can be represented by thresholds on a normally distributed continuum of liability.
The Fit of Genotype-Environment Models

Models that were fitted to the responses of twin pairs to these 14 items contained five types of parameters: sex-independent or sex-dependent thresholds, VA, VO, VA and VO; and ES parameters. However, Reich et al. noted that for the range of heritabilities found for these items, the power of the multiple-threshold model to distinguish between monogenic and polygenic modes of inheritance is low. In the context of their conclusions, our results support, but by no means prove, a polygenic-multifactorial mode of transmission for symptoms of anxiety and depression in the general population.

Table 8.—Further Analysis of Symptoms With Evidence of VD*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Constraints</th>
<th>df of $\chi^2$</th>
<th>VA</th>
<th>VO</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anx2</td>
<td>VA, VO</td>
<td>None</td>
<td>3</td>
<td>1.18</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>VA, VO and</td>
<td>3</td>
<td>1.70</td>
<td>0</td>
<td>326</td>
</tr>
<tr>
<td>Anx4</td>
<td>VA, VO</td>
<td>None</td>
<td>3</td>
<td>4.52</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>VA, VO and</td>
<td>3</td>
<td>4.94</td>
<td>0</td>
<td>458</td>
</tr>
</tbody>
</table>

*For explanation of abbreviations, see Table 6. †All models include sex-dependent thresholds.

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comparing the correlation in liability of MZ twins with that of the same DZ twins measured twice over a given time span. Monozygotic twins share all of their genetic variance and all of their common environmental variance. An individual tested twice over time shares with himself all the genetic and common environmental variance and the specific environmental variance due to events that occurred prior to the first testing.

Although the sample size of individuals measured twice was small, the correlation of a twin with himself over time for all the items tested was higher, often substantially so, than that found between MZ twins. Because sizes in the range of those used in this study (ie, multiple-threshold analysis with VA and EC permitted to vary across sexes) has not been fully examined, a detailed examination of the power of the twin study using conventional methods of analysis was carried out. Three conclusions of this previous study are relevant to our results. First, contrary to expectation, the twin design is more powerful in detecting common environmental than additive genetic effects. The inability of the current study to detect clearly the twin method assume that such evidence cannot be attributed to inherent limitations of the twin method.

Second, the twin design is relatively weak for the detection of VD. Only with the sample size of those used in this report is the method likely to detect even large amounts of VD. Even these results are critically dependent on assumptions about gene frequencies and an absence of common environmental effects. Third, when the role of specific environment is as large as found for VD in this study (ie, at least .50), the twin method has low power for resolving the effect of VA and EC when one of them accounts for most of the remaining variance in liability. For example, when analyzing normally distributed quantitative data by the method of variance components in a population of half MZ and half DZ twins where ES equals .5, VA equals .4, and EC equals .1, an EC, ES model could be rejected at the .05 level in 96% of cases with a total of only 900 twin pairs. However, to reject a VA, ES model at the same level would require 11,458 twin pairs. These results suggest that even in those items in which a VA, ES model was the unambiguous best fit, common environmental factors could be contributing 10% of the variance in liability and remain undetected.

The Validity of the Twin Method

An assumption of the twin method that is often criticized is that the contribution of common environment to the similarity of MZ and DZ twins is the same. Evidence does support the view that the social environment of MZ twins is more similar than that of DZ twins. Critics of the twin method assume that such evidence demonstrates that environmental factors are responsible for the greater similarity of MZ twins and hence is proof that the twin method is biased. However, another interpretation of these findings is possible: MZ twins behave more similarly than DZ twins, thereby creating for themselves a more similar social environment. A recent review found nine studies that examined the validity of these two hypotheses. Using different twin populations and several different experimental paradigms, all nine studies coincided in supporting the second hypothesis; the similarity in social environment of MZ twins is the result and not the cause of their behavioral similarity.

In the adult twins from the NHMRC Twin Register, MZ twins on average had more frequent personal contact than did DZ twins. This closer degree of personal contact could cause their greater similarity in symptoms of anxiety and depression. This hypothesis predicts that twins with more frequent contact should have more similar symptom scores than twins with less frequent contact. However, no overall relationship between similarity of contact and similarity in symptom scores was found. A review of the relevant literature and results from the NHMRC Twin Register both support the validity of the assumptions of the twin method.

Comparison With Studies of Personality Traits

It is worthwhile to compare the results of this study with previous twin studies on normal personality traits. Many studies, using a variety of psychometric scales, have found evidence for genetic control of a trait variously called neuroticism, stress reaction, or anxiety. When genetic models such as those used in this report have been applied to this personality dimension, results have consistently suggested that only VA and ES are needed to explain the observed variation. The validity of these results is critically dependent on assumptions about the assumptions of the twin method. These findings suggest that the "dichotomy" between psychiatric symptoms and personality traits may be neither as clear-cut nor as useful as is commonly thought.

Limitations of the Current Analysis

Our study has at least three potentially important limitations. First, it is uncertain whether the etiologic factors underlying the commonly experienced symptoms of anxiety and depression are similar to those involved in the fully syndromal states of anxiety and depression. We emphasize again that the results of this report apply only to syndromal anxiety and depression as reported in the general population. Only further research will clarify which, if any, of the conclusions of this report are applicable to the fully syndromal states of panic disorder, anxiety disorder, and/or major depression.

Second, the symptoms analyzed in this study were obtained by a self-report questionnaire rather than by personal interview. Bed ford et al found substantial correlations between clinician-rated anxiety and depression and scores on the respective subscales of the DSSI. Nonetheless, the results of this study might have differed had the symptoms been assessed by clinical interview rather than by self-report.

A third potential limitation is that this report contains only univariate analyses. Scores on many of the specific items were significantly correlated. It would be of interest to examine the pattern of these correlations and to determine the degree to which they were due to correlated genetic and/or environmental factors. However, the large numbers of symptoms and the required analysis of cross-polychoric correlations makes this analysis technically difficult. We hope the results of a multivariate analysis will be the subject of a further report.

CONCLUSIONS

A viewpoint implicit in much of contemporary psychiatry is that genetic and biologic factors play a major etiologic role in the severe psychiatric disorders, such as schizophrenia and the affective disorders; however, in minor psychiatric disturbances, such as symptoms of anxiety and depression, psychological and social factors are considered to be of overriding etiologic importance. The results of this study are not consistent with this viewpoint. Though this study demonstrates that specific environmental factors not shared by members of a twin pair play a major role in the etiology of symptoms of anxiety and depression as experienced in the general population, an etiologic role for familial factors could not be unambiguously demonstrated for any of the items studied. In fact, familial factors equally influencing liability in males and females could be ruled out for all symptoms. Though these results do not eliminate a possible role for common environmental variables, they do suggest...
that factors such as rearing environment and culture play a smaller role than has previously been thought in the etiology of common symptoms of anxiety and depression. By contrast, for a majority of the symptom items studied herein, genetic factors could be unambiguously shown to contribute substantially to liability.

Specifically, for nine of the items, the best-fit model predicted a broad heritability of between .33 and .46. Though these figures are substantially lower than the reported heritability of liability for schizophrenia, they are not much smaller than that often found for human personality variables. Furthermore, they are similar to the heritability found in this sample for the entire anxiety and depression scales by Jardine et al. Our demonstration of a major role for genetic factors in the etiology of symptoms of anxiety and depression indicates that genetically mediated biologic processes play an important role in determining liability to symptoms of anxiety and depression as experienced in the general population.

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John D. Mathews, MD, PhD, assisted in establishing the register, and A. Scott Henderson, MD, collected the psychiatric symptoms data. Rosemary Jardine, PhD, and Marilyn Olsen provided substantial help in preparing the data.

References