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Symptoms of Anxiety and Depression in a Volunteer Twin Population

The Etiologic Role of Genetic and Environmental Factors

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• **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[1-6]; 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,[7-9] early parental loss,[9,10] and specific patterns of parental behavior,[11-15] 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).[16] 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[17] 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 5,967 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 64% 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.[18-21]

Among the items contained in the mailed questionnaire were the anxiety and depression scales of the DSSI[16] (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.[15] In

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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 zygosity, 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.[22,23] 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 unbearably) 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 unbearably) 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 zygosity groups. Second, the fit was examined for each item over all five zygosity 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 zygosity 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 zygosity 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.[24-26] As this approach is probably unfamiliar to most readers, we will briefly describe it here. Eysenck and Eaves[27(chap3-6)] 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. Dominance 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 departure from the rearing environment, 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.[28]

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_M, VA_F and the EC_M, EC_F models, respectively, correspond to the "environmental model" of Cloninger et al.[28]

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_M, VA_F, VA_{MF} and EC_M, EC_F, EC_{MF}, respectively, two new parameters are introduced: VA_{MF} and EC_{MF}. These two parameters represent the covariance between additive genetic effects and common environmental effects, respectively, in males and females. From VA_{MF} and EC_{MF}, two new parameters can be calculated, which we define as the correlation in additive genetic effect (rg_{MF}) and the correlation in common environmental effects between the two sexes (rc_{MF}). In other words, rg_{MF} and rc_{MF} 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 zygosity group are given in Table 2. We have assumed that EC contributes equally to the correlation in monozygotic (MZ) and dizygotic (DZ) twins; ES, by definition, makes no contribution to the resemblance of twin pairs.

In studies of twins only, the effects of EC and VD are confounded.[29] As a result, the fit of unconstrained VA, EC, ES and VA, VD, ES models are identical. However, VD and EC have opposite effects on the patterns of correlations between MZ and DZ twins. Given the presence of VA, VD will increase and EC 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 VD 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, VD, ES model is to be preferred and, therefore, obtain estimates of VD. Because of the strong negative correlations between estimates of VA and VD in the twin design,[29] when VD is present, estimates of VA are often negative. To provide more reasonable estimates of VA and VD 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. Twice the difference in log likelihoods between two models has an approximate χ^2 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) The 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 particularly when two models 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.

Table 1.—Items of the 'State Anxiety-Depression' Subscale of the Delusions-Symptoms-State Inventory*

Item Name	Full Text	Abbreviated Text
Anx1	Recently I have been worried about every little thing.	Worried about everything
Anx2	Recently I have been breathless or had a pounding of my heart.	Breathless or heart pounding
Anx3	Recently I have been so worked up I couldn't sit still.	Worked up, can't sit still
Anx4	Recently, for no good reason, I have had feelings of panic.	Feelings of panic
Anx5	Recently I have had a pain or tense feeling in my neck or head.	Pain or tension in head
Anx6	Recently worrying has kept me awake at night.	Worrying kept me awake
Anx7	Recently I have been so anxious that I couldn't make up my mind about the simplest thing.	Anxious, can't make up my mind
Dep1	Recently I have been so miserable that I have had difficulty with my sleep.	Miserable, difficulty with sleep
Dep2	Recently I have been depressed without knowing why.	Depressed without knowing why
Dep3	Recently I have gone to bed not caring if I never woke up.	Gone to bed not caring
Dep4	Recently I have been so low in spirits that I have sat for ages doing absolutely nothing.	Low in spirits, just sat
Dep5	Recently the future has seemed hopeless.	Future seems hopeless
Dep6	Recently I have lost interest in just about everything.	Lost interest in everything
Dep7	Recently I have been so depressed that I had thoughts of doing away with myself.	Depressed thoughts of suicide

*All items were scored on a four-point scale: 0, not at all; 1, a little; 2, a lot; and 3, unbearably.

Table 2.—Contribution of the Genotype-Environment Factors to the Correlation in Liability by Zygosity Group*

	Factor							
Zygosity Group	VA_M	VA_F	VA_{MF}	VD	EC_M	EC_F	EC_{MF}	ES
MZ males	1	0	0	1	1	0	0	0
MZ females	0	1	0	1	0	1	0	0
DZ males	½	0	0	¼	1	0	0	0
DZ females	0	½	0	¼	0	1	0	0
DZ OS	0	0	½	¼	0	0	1	0

*VA indicates additive genetic variance; VD, dominance genetic variance; EC, common environmental variance; ES, specific environmental variance; MZ, monozygotic; DZ, dizygotic; OS, opposite sex. Subscript letters indicate sex influence on liability. In models with VA, $VA_M = VA_F = VA_{MF}$; in models with EC, $EC_M = EC_F = EC_{MF}$; in models with VA_M and VA_F, $VA_{MF} = (VA_M \times VA_F)^{1/2}$; in models with EC_M and EC_F, $EC_{MF} = (EC_M \times EC_F)^{1/2}$.

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[30] and on studies of personality variables in man,[24-26,31] 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.[9-15] 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 often evaluated multiple statistical tests. To determine whether the number of significant results is in excess of chance expectation, we followed a method previously outlined[32] that provides an overall significance level for the number of specific results with a P value less than .05 or .01 as a function of the total number of tests performed. The term significant will be used to denote P values of less than .05.

RESULTS

Sample

Of the 3,810 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,[33] 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 .082. 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

Table 3.—Sample of Twin Pairs Studied

	N	Age, yr (Mean ± SD)*
Monozygotic females	1,228	35.39 ± 14.29
Monozygotic males	566	34.35 ± 14.04†
Dizygotic females	750	35.29 ± 14.17†
Dizygotic males	352	32.26 ± 13.89
Dizygotic, opposite sex	902	32.77 ± 13.72†

*By one-way analysis of variance, ages differ significantly across groups: $F = 8.243$; $df = 4/3,790$; $P < .0001$.
†Age was unavailable for one pair.

Table 4.—Symptom Scores as a Function of Sex

	Females (n=4,857)		Males (n=2,739)		
Item*	% Scoring >0	Mean ± SD	% Scoring >0	Mean ± SD	P†
Anx1	53.2	0.653 ± 0.702	43.4	0.509 ± 0.637	<.0001
Anx2	16.1	0.191 ± 0.469	11.8	0.133 ± 0.384	<.0001
Anx3	26.2	0.322 ± 0.594	26.2	0.314 ± 0.571	.93
Anx4	13.3	0.160 ± 0.444	9.1	0.107 ± 0.360	<.0001
Anx5	34.4	0.435 ± 0.665	23.1	0.279 ± 0.556	<.0001
Anx6	34.1	0.412 ± 0.631	27.5	0.319 ± 0.560	<.0001
Anx7	16.0	0.195 ± 0.486	12.8	0.151 ± 0.427	.0001
Dep1	24.2	0.229 ± 0.584	16.8	0.197 ± 0.468	<.0001
Dep2	35.1	0.423 ± 0.639	22.8	0.265 ± 0.526	<.0001
Dep3	7.3	0.098 ± 0.389	5.6	0.072 ± 0.320	.009
Dep4	19.5	0.247 ± 0.551	16.3	0.199 ± 0.486	.0005
Dep5	17.8	0.233 ± 0.557	16.9	0.209 ± 0.510	.26
Dep6	12.0	0.148 ± 0.437	10.9	0.133 ± 0.408	.20
Dep7	4.2	0.054 ± 0.287	3.5	0.042 ± 0.238	.16

*For explanation of items, see Table 1.
†By Mann-Whitney U test corrected for ties.

contact of MZ twins, then the frequency of contact of twin pairs should be negatively correlated with their difference in item scores. As age has a strong negative correlation with frequency of contact, partial correlations between frequency of contact and difference in item score was computed for each item with the effect of age removed. The number of significant correlations observed (4/70) did not exceed chance expectations.

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 from each of the five sex-zygosity 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 χ^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 multiple-threshold 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 χ^2 goodness of fit test for each item across all five zygosity groups with the full model: VA_M, VA_F, EC_M, EC_F, EC_{MF}, ES_M, and ES_F 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 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 when applied to all four response categories, the responses were collapsed into three categories and retested. For Anx1, the full model now fit ($\chi^2 = 38.42$, $df = 31$, $P = .168$). For Dep5, the fit of the full model improved ($\chi^2 = 47.45$, $df = 31$, $P = .03$) but still was not adequate. 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: Anx5, "pain or tension in head," and Dep2, "depressed without knowing why."

Anx5.—By likelihood ratio test, all models for this symptom with sex-independent thresholds (ie, the same threshold for both sexes) were strongly rejected against the full model (Table 6). With sex-dependent thresholds (ie, thresholds differing for males and females), the EC, ES model was rejected against the full model, as were all other models without a VA parameter. Of the models not rejected against the full model, the VA, ES model contained the fewest parameters. When the VA, ES model was tested by likelihood ratio test against the three more complex models that were not rejected against the full model, none produced a significant improvement in fit. For example, addition of the parameter EC/VD produced no significant improvement in fit ($\chi^2 = 0.02$, $df = 1$, not significant). Therefore, the VA, ES model with sex-dependent thresholds was unambiguously the best-fit model for this symptom. The proportion of variation in liability to Anx5 due to VA and ES was estimated as 0.351 and 0.649, respectively (Table 7).

Dep2.—As for Anx5, all three models with sex-independent thresholds were strongly rejected against the full model for Dep2 (Table 6). Five models were not rejected against the full model, four of which contained a VA parameter. The simplest model not rejected was the VA, ES model with sex-dependent thresholds. None of the three models containing VA parameters significantly improved the fit over that found with the VA, ES model. The EC, ES and the EC_M, EC_F, ES_M, ES_F models were significantly rejected against the full model. However, the EC_M, EC_F, EC_{MF}, ES_M, ES_F model could not be rejected. Because the parameters of the VA, ES model were not a subset of this more complex model, the two could not be directly tested against one another. Therefore, it was not possible to decide definitively whether the liability to Dep2 in the population was due to additive genetic effects and random environment (with the additive genetic effects accounting for 33.4% of the total variance) or to common environmental effects that differed in the two sexes. If common environmental factors were responsible for the variance in liability in this symptom, then $rc_{MF} = .387$.

Overview of Results

The details of the model fitting for each of the specific items can be seen in Table 6. Here, we will only summarize these results. The low endorsement rate for Dep7 resulted in many very small expected cell frequencies, which prevented definitive calculation of log likelihoods for several models. For the eight models for which a likelihood estimate could be obtained, none could be rejected against the full model (Table 6). Too little information was available in Dep7 to permit further meaningful analysis.

For the other 13 items, the following results were noted.

1. The VA, ES model with sex-dependent thresholds (which ascribes the similarity between twins as due solely to additive genetic effects) provided a good fit for the results in 12 of the 13 symptoms.

2. The EC, ES model with sex-dependent thresholds (which ascribes the similarity between twins as due solely to common

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

Item	MZ Females	DZ Females	MZ Males	DZ Males	DZ OS
Anx1	.395±.032	.163±.046	.333±.053†	.148±.074‡	.087±.044
Anx2	.329±.053	.109±.076	.344±.096	−.007±.132‡§	.005±.076
Anx3	.372±.042	.245±.056	.393±.061	.018±.090‡	.064±.054
Anx4	.435±.053§	.040±.087	.555±.086‡	.305±.133‡	.047±.083
Anx5	.354±.037	.154±.053	.351±.066	.177±.092‡	.202±.052
Anx6	.331±.039	.237±.052	.318±.063	.192±.085‡	.125±.051
Anx7	.458±.047	.206±.073	.390±.085	.239±.122‡	.233±.069
Dep1	.387±.042§	.289±.058	.292±.080	.177±.107‡	.122±.061‡
Dep2	.313±.039†	.238±.051	.383±.065	.222±.090‡	.118±.053
Dep3	.504±.067	.144±.109	.345±.143‡§	...‖	.212±.098
Dep4	.480±.043	.232±.065	.419±.073	.277±.104‡	.215±.062
Dep5	.395±.048	.247±.068§	.392±.078	.095±.112‡§	.152±.061
Dep6	.430±.055	.260±.081	.326±.099	.241±.137‡	.104±.081§
Dep7	.377±.104	.284±.133	...‖	...‖	.045±.147§

*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.

†$P<.01$, by χ^2 goodness of fit.

‡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 4×4 tables. Therefore, the values were obtained from 3×3 tables with four thresholds combining the scores for responses of "a lot" and "unbearably." In tables where the polychoric correlation and its SE could be calculated using both 4×4 and 3×3 tables, the results were uniformly very similar.

§$P<.05$, by χ^2 goodness of fit.

‖For these tables, even if converted to 3×3, it was not possible to calculate a meaningful polychoric correlation with SE. This resulted from either rare or a very small number of pairs concordant for scores greater than 0.

environmental effects) was rejected as an adequate fit in all 13 symptoms. This was also the case of the EC_M, EC_F, ES_M, ES_F model, which permitted the common environmental effects to differ in magnitude across sexes.

3. Values of ES (ie, random environmental effects) for all models were greater than 0.44 and were frequently greater than 0.6.

4. Models with sex-independent thresholds provided an adequate fit in five items (Anx3, Anx7, Dep3, Dep5, and Dep6), but in two of these (Anx7 and Dep3) the addition 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, Anx3, Anx5, Anx7, Dep3, Dep4, and Dep5). 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/VD resulted in a significant improvement in fit ($\chi^2=4.86$, $df=1$, $P=.027$). Estimates for EC in this model were negative, indicating that the VA, VD, ES model was the preferred one. However, an unrestricted estimate of VA and VD (Table 8) 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, EC/VD, ES model resulted in negative estimates of EC, indicating that the VA, VD, 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 as 0 and VD as 0.458. The fit of this constrained VA, VD, ES model against the full model was still good ($\chi^2=4.94$, $df=3$, $P=.18$). Parameter estimates from the VA_M, VA_F, VA_{MF}, ES_M, and ES_F model resulted in a low correlation of the additive genetic effects between the two sexes ($rg_{MF}=.20$) 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_M, EC_F, EC_{MF}, ES_M, and ES_F. The correlation between the common environmental variables influencing liability in the two sexes (rc_{MF}) 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_M, VA_F, ES_M, ES_F.

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,[9-15] 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,[33] 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.[34] However, in our sample, 1.6 times as many MZ than DZ same-sex pairs were observed (Table 3). Martin and Wilson[35] 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,[33] 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[35] but not of Lykken et al.[33] 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[36] 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 6.—Likelihood Ratio Test of Specific Models as Compared With Full Model

Specific Factors	Thresholds†	*df* of χ^2	Anxiety Items 1‡	2	3	4	5	6	7
VA_M, VA_F, VA_{MF}	Sex dep	2	0.36	2.50	2.52	**4.50**	0.18	1.64	0.24
EC_M, EC_F, EC_{MF}	Sex dep	2	18.00§	11.12§	12.08§	18.42§	10.78§	**3.70**	9.12‖
VA_M, VA_F	Sex dep	3	4.52	5.70	7.28	9.36‖	0.32	2.22	0.28
EC_M, EC_F	Sex dep	3	33.76§	16.64§	26.18§	31.50§	13.50§	10.70‖	12.04§
VA, EC/VD	Sex dep	3	2.74	**1.18**	5.74	**4.52**	0.30	2.32	0.68
EC	Sex dep	4	38.06§	18.76§	29.06‖	33.20§	13.62§	11.98‖	13.06‖
VA	Sex dep	4	**6.14**	6.04	**7.50**	11.18‖	**0.32**	**2.54**	**0.68**
VA, EC/VD	Sex ind	6¶	67.48§	29.32§	11.64	33.66§	104.50§	42.00§	13.58‖
EC	Sex ind	7#	103.68§	47.38§	34.34§	63.04§	119.54§	52.64§	25.84§
VA	Sex ind	7#	70.64§	34.14§	13.24	40.54§	104.52§	42.14§	13.60
Minus log likelihood of full model	...	...	7,004.92	3,641.04	5,425.10	3,166.54	5,938.18	5,922.81	3,740.40

*For explanation of abbreviations, see Table 2; dep represents dependent; ind, independent. For explanation of anxiety and depression items, see Table 1. Twice the difference in log likelihoods of the models under comparison has a χ^2 distribution with the *df* equal to the difference in the number of parameters in the two models. For Anx3, Anx7, Dep3, Dep5, and Dep6, more complex models were fit with sex-independent thresholds. For Anx3, Anx7, Dep3, and Dep5, these models produced no significant improvement in fit. For Dep6, the EC_M, EC_F, EC_{MF} model with sex-independent thresholds could not be rejected against the full model ($\chi^2 = 7.16$, $df = 5$, not significant), was not improved significantly by the addition of sex-dependent thresholds ($\chi^2 = 2.32$, $df = 3$, not significant), and was therefore to be considered as one of the best-fit models for this symptom. Certain log likelihoods for Dep7 could not be accurately estimated because of small observed cell frequencies. Values for best-fitting model or models are in boldface.

Table 7.—Parameter Estimates for Best-Fitting Models*

Symptom	Thresholds	VA	VA_M	VA_F	VA_{MF}	EC	EC_M	EC_F	EC_{MF}	ES	ES_M	ES_F
Anx1	Sex dep	.344	...	...	...	...	...	...	...	.656	...	...
Anx2	Sex dep	.574	...	...	...	−.241	...	...	...	.667	...	...
Anx3	Sex ind	.358	...	...	...	...	...	...	...	.642	...	...
Anx4†	Sex dep	.768	...	...	...	−.304	...	...	...	.536	...	...
	Sex dep	...	.552	.400	.093‡	...	...	...	...	...	.448	.600
Anx5	Sex dep	.351	...	...	...	...	...	...	...	.649	...	...
Anx6†	Sex dep	.333	...	...	...	...	...	...	...	.667	...	...
	Sex dep	...	...	...	...	...	.272	.293	.125§	...	.728	.707
Anx7	Sex dep	.437	...	...	...	...	...	...	...	.563	...	...
Dep1†	Sex dep	...	.249	.414	...	...	...	...	...	...	.751	.586
	Sex dep	...	...	...	...	...	.227	.349	.109‖	...	.773	.651
Dep2†	Sex dep	.334	...	...	...	...	...	...	...	.666	...	...
	Sex dep	...	...	...	...	...	.326	.282	.116‖	...	...	...
Dep3	Sex dep	.445	...	...	...	...	...	...	...	.555	...	...
Dep4	Sex dep	.459	...	...	...	...	...	...	...	.541	...	...
Dep5	Sex ind	.385	...	...	...	...	...	...	...	.615	...	...
Dep6†	Sex ind	.398	...	...	...	...	...	...	...	.602	...	...
	Sex ind	...	...	...	...	...	.303	.362	.092‖	...	.697	.638

*For explanation of abbreviations, see Table 6.
†For these symptoms, two best-fit models were found, listed in order of likelihood.
‡Correlation between VA_M and VA_F for second best-fit model for Anx4 is .198.
§Correlation between EC_M and EC_F for second best-fit model for Anx6 is .443.
‖Correlations between EC_M and EC_F for second best-fit model for Dep1, Dep2, and Dep6 are, respectively, .387, .383, .278.

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.[17] 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.

Depression Items						
1	2	3	4	5‡	6	7
1.54	2.18	3.16	0.72	0.72	0.40	. . .
4.56	3.24	12.84§	12.52§	10.54§	4.84	0.26
2.36	3.52	3.18	0.76	1.06	1.90	. . .
9.68‖	13.20§	13.44§	18.58§	14.68§	11.24‖	0.44
6.56	3.74	3.30	1.12	0.70	3.40	6.36
45.48§	13.26§	15.44§	19.14§	16.06§	13.86§	7.58
6.56	3.94	4.62	1.12	1.28	3.62	6.36
68.02§	127.24	11.54	14.38‖	6.00	5.42	8.36
80.50§	139.00§	23.38§	32.30§	20.66§	15.80‖	9.74
68.02§	127.28§	12.66	14.38‖	6.00	5.62	8.36
4,791.91	5,777.80	2,198.22	4,393.23	4,190.71	3,201.56	1,436.74

†Sex dep, 6 for Anx2 through Anx7, Dep1 through Dep4, Dep6, Dep7, and 4 for Anx1 and Dep5.
‡Fit to 3×3 tables where item scores 2 and 3 were combined.
§$P<.01$.
‖$P<.05$.
¶Equals 5 for Anx1 and Dep5.
#Equals 6 for Anx1 and Dep5.

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

		Likelihood Ratio Against Full Model†		Best-Fit Models		
Parameters	Constraints	*df* of χ^2	χ^2	VA	VD	ES
Anx2						
VA, VD	None	3	1.18	−.149	.482	.667
VA, VD	VA and VD≥0	3	1.70	0	.326	.674
Anx4						
VA, VD	None	3	4.52	−.144	.608	.536
VA, VD	VA and VD≥0	3	4.94	0	.458	.542

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

However, Reich et al[22] 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.

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, VD, EC, and ES. In addition, the values of VA and EC were permitted to take different values in the two sexes and to be correlated to a variable degree in the two sexes. We will discuss each of these parameters in turn. Because of insufficient information, little of use can be said about item Dep7, so our discussion will focus on the other 13 items.

Thresholds.—Our analysis detected significant sex differences in thresholds in all but three (Anx3, Dep5, and Dep6) of the 13 items. Not surprisingly, these were the three symptoms for which the mean symptom scores did not significantly differ in males and females (Table 4). For all other items, the thresholds of liability for females were lower than the parallel thresholds for males, corresponding to the higher observed symptom rates in females.

Genetic Factors: Additive Variance (VA).—A simple model consisting of only VA and ES was an adequate fit for 12 and the best fit for seven of the 13 items. This simplest of all genetic models suggests that the liability to symptoms results from only additive genetic effects and random environmental variables. In the seven symptoms for which the VA, ES model was the best fit, the proportion of variance in the liability due to the additive genetic effects (ie, narrow heritability) varied from 0.34 to 0.46.

Of the remaining six items, a VA, ES model was rejected against the full model in only one (Anx4). In one of the items (Anx2), the fit was significantly improved by adding VD to the model. In three others, it was not possible to choose definitively between the VA, ES model and an EC_M, EC_F, EC_{MF}, ES_M, ES_F model. In one item (Dep1), one of the best-fit solutions required that the magnitude of the additive genetic variance differ across sexes. In one further item (Anx4), a best-fit solution required that the correlation between the additive genetic effects in males and females differ significantly from unity. For at least 12 of the items, if genes were contributing to the liability to develop symptoms, then the same genes were contributing in males and females. Furthermore, with the exception of two items, if these genes were contributing to liability, they were contributing the same proportion of total variance in males and females. For most items, the same genes contributed to the underlying liability in both sexes.

Dominance Variance (VD).—This was present in the single best-fit model for one item, Anx2 ("breathless or heart pounding") and in one of the two best-fit models for another item, Anx4 ("feeling of panic"). Because of the large negative correlation between estimates of VD and VA in the classic twin design,[29] it is difficult to determine precise values for VD for these two items. For both items, inclusion of VD resulted in estimates of broad heritability in the range of .35 to .45. The two items in which evidence was found for VD were those most prominently reflecting paniclike aspects of anxiety. If confirmed, these results suggest that the genetic basis of paniclike anxiety, as experienced in a general population, may differ from that of "cognitive" or "physical-tension–like" anxiety (as typified by items Anx1 and Anx7, and Anx3 and Anx5, respectively).

EC.—Contrary to the predictions of several workers,[9-15] an etiologic role for common environmental factors in symptoms of anxiety and depression could not be unequivocally demonstrated. All models that assumed that the similarity of the symptom scores of twins results from familial environmental factors that affected both males and females were clearly rejected for all symptoms. This was true regardless of whether the common environment accounted for the same or differing proportions of variance in liability in the two sexes. Only the most complex model incorporating common environmental effects was not uniformly rejected. This model, which permitted the common environmental events affecting liability in males and females to differ, was not rejected in four symptoms. However, in each of these symptoms, on the basis of both differences in goodness of fit and the principle of parsimony, models that assumed that additive genetic factors were solely responsible for the similarity between twins were preferred. Of these four symptoms, one was from the original anxiety scale of the DSSI (Anx6) and three were from the depression scale (Dep1, Dep2, and Dep6). Though the results of this study regarding the importance of common environment in the etiology of symptoms of anxiety and depression are not conclusive, they suggest that if common environment influences any of these traits, (1) it is more important for depressive than for anxiety symptoms and (2) the factors in the shared family environment that predispose to the development of these symptoms in males and females are only modestly correlated.

ES.—For all items, the greater part of the variance in underlying liability resulted from ES. Environmental events specific to the individual appear to play the major role in the etiology of symptoms of anxiety and depression in the general population. This finding is consistent with previous results that suggest that life events influence the onset of states of depression and anxiety.[7,8] No measures of environmental variables were included in the questionnaire sent to the NHMRC Twin Register. Although it is therefore impossible to delineate further what particular environmental variables are important, it is possible to indicate roughly the time course over which these specific environmental events influence symptoms of anxiety and depression. This can be done by

comparing the correlation in liability of MZ twins with that of the same individual 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 the mean interval between testing was three months, these results suggest that specific environmental events occurring at least three months prior to the time of testing substantially affect symptoms of anxiety and depression. The specific environmental events that affect these symptoms are not entirely the result of either environmental events that occurred in the days or weeks immediately preceding testing or random aspects of the twins' questionnaire responses.

The Power of the Twin Study

The results of this study should be interpreted in the context of knowledge about the power of the twin design. Though the precise power of the methods of analysis used herein (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 more conventional methods of analysis has been carried out.[29] 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 common environmental factors for symptoms of anxiety and depression cannot be ascribed to inherent limitations of the twin method.

Second, the twin design is relatively weak for the detection of VD. Only with the sample sizes in the range 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 the items 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[22,29] 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 95% of cases with a total of only 940 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.[37] 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.[37] 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 on psychiatric symptoms 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.[17,23,32,38-40] 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.[17,23,40] Heritability estimates for this trait are only slightly higher than those reported for the individual symptoms in this report. Given these results, it is particularly interesting that Jardine et al[17] found a high genetic correlation between neuroticism scores and total scale scores for anxiety and depression in the same twins analyzed in this report. 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.[41] We emphasize again that the results of this report apply only to symptoms of 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. Bedford et al[16] 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 rather than the more conventional covariances make 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 demonstrated that specific environmental events 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.[9-15] 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,[38,42] they are not much smaller than that often found for human personality variables.[23,26,31] Furthermore, they are similar to the heritability found in this sample for the entire anxiety and depression scales by Jardine et al.[17] 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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