Genetic Covariation Between Neuroticism and the Symptoms of Anxiety and Depression

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A genetic analysis of the trait of neuroticism and symptoms of anxiety and depression in 3,810 pairs of adult MZ and DZ twins is reported. Differences between people in these measures can be explained simply by differences in their genes and in their individual environmental experiences. There is no evidence that environmental experiences that are shared by cotwins, such as common family environment or social influences, are important. There are differences between the sexes in gene action affecting neuroticism, and genetic effects become more pronounced with age in females. The lack of evidence for dominance variance affecting neuroticism contrasts well with the detection of considerable genetical nonadditivity for extraversion in the same sample and reinforces the view that these two traits are not only statistically, but also genetically, quite independent.

An analysis of the causes of covariation between anxiety, depression, and neuroticism shows that additive gene effects are more important causes of covariation than environmental factors. Genetic variation in symptoms of anxiety and depression is largely dependent on the same factors as effect the neuroticism trait. However, there is also evidence for genetic variation specific to depression.

Key words: multivariate genetical analysis, neuroticism, anxiety, depression, twins

INTRODUCTION

While the major affective disorders indisputably have a substantial genetic etiology [Gershon et al, 1976], the data on the genetics of anxiety and minor depression are much less clear. We consider here some of the difficulties faced in the genetic investigation of the neuroses, then present findings on the distribution of the

trait of neuroticism and the symptoms of anxiety and depression in a large sample of twins.

Medical genetics has achieved greatest success when the disorders studied are clear-cut, dichotomous states, being either present or absent, as in Huntington chorea. With a group of disorders such as the neuroses, there are the problems of unreliable diagnosis and of clinical heterogeneity within this one category. The latter issue has recently come to assume even greater importance with the possibility that some neurotic states may be variants of the affective disorders. Recent findings with the dexamethasone suppression test [Carroll et al, 1981; Coppen et al, 1983] must raise this possibility in studying the genetics of anxiety and depression.

A further impediment is the reliability of reporting symptoms experienced at any time in the individual's past. For a group of disorders with such an evanescent pattern, the cotwin or other relative may not be simultaneously symptomatic. One may therefore wish to inquire if a given symptom has been experienced at some time in the respondent's past. In the present context, the reliability of reporting previous symptoms could be systematically biased in first-degree relatives and perhaps most of all in monozygotic (MZ) twins. The ascertainment problem may also apply to the investigator, who should be blind to the clinical status of the index twin when the cotwin is being examined. Where studies have been based on samples in which one twin has reached psychiatric treatment for neurosis, the sample size has usually been modest, as is evident in the review by Shields [1976]. In our study we have examined symptoms rather than diagnoses and we have restricted our examination to current symptoms rather than lifetime prevalence.

Lastly, there may have been confusion between traits and symptoms when ascertaining what attributes are shared by both twins. This is evident in studies using instruments such as the Middlesex Hospital Questionnaire which mixes both [Young et al, 1971]. Foulds [1965, 1974] has emphasised the desirability of distinguishing between personality traits and symptoms. In their heuristic theory of neurosis, Slater and Slater [1944] suggested that what is inherited is a deficiency in multiple attributes of personality which confer resistance to environmental insults. Consequently, the neurotic constitution is likely to be determined by a large number of genes of small effect. Because this predisposition is a stable attribute, whereas symptoms tend to fluctuate in their severity, one might expect the correlation of twins to be greater for the trait of neuroticism than for individual symptoms.

The evidence collected so far suggests a substantial genetic component in the etiologically important trait of neuroticism [Newman et al, 1937; Slater and Cowie, 1971; Eaves and Eysenck, 1976; Eaves and Young, 1981]. For the neurotic disorders themselves, the dominant theories of causation have been overwhelmingly in experiential domain, although Freud [1937] made it clear that to him the cause lay in interaction between constitutional and experiential factors. There is evidence for a genetic component in anxiety disorders but much less clear evidence for minor or neurotic depression [Shields, 1976; Young et al, 1971; Slater and Shields, 1969]. In the study by Slater and Shields [1969], there were 62 MZ and 84 DZ twins, at least one in each pair having reached a psychiatric consultation. There was striking concordance in MZ twins for anxiety neurosis and personality disorder, but for other diagnoses, mainly consisting of minor depression, there was little agreement. Schepank [1971, 1973] has tried to avoid the diagnostic problem by considering instead the concordance for individual symptoms. In a clinical series of 21 MZ and 29 DZ

pairs, he found evidence for a genetic component in symptoms both of anxiety and of depression. A much larger study based on 587 pairs of twins has also found evidence for a substantial genetic component in both these symptoms [Eaves and Young, 1981]. Torgersen [1983] in a study of 229 same-sex twins found evidence for a genetic component in neurosis only for male twins and for twins admitted to psychiatric hospitals. He has argued that different findings on the importance of genetic factors in the neuroses may be due to differences in sample selection.

We have used the Australian NH&MRC Twin Register to conduct a study in a large sample free of the selection effects found in a treated population. The purpose was to examine the concordance for neuroticism and for states of anxiety and of depression. Neuroticism was chosen for reasons of parsimony as one personality trait which is closely associated with vulnerability to neurotic symptoms under stress [Henderson et al, 1981]. States of anxiety and depression were chosen because they are by far the most prevalent psychiatric symptoms in Western populations, yet the genetic contribution to their etiology remains uncertain. Our results suggest that for neuroticism and for symptoms of anxiety and depression, variation is due only to additive genetic effects together with environmental experiences unique to the individual.

SAMPLE AND MEASUREMENTS

Subjects

A questionnaire containing the following items was mailed to all twins aged 18 years and over who were enrolled on the Australian NH&MRC Twin Register: general health, a personality test, symptoms of anxiety and depression, drinking and smoking habits, and sleep patterns. Only data for the neuroticism scale of the Eysenck Personality Questionnaire [Eysenck and Eysenck, 1975], and the anxiety and depression scales of the Delusions-Symptoms-States Inventory [Bedford et al, 1976] will be analysed here. Between November 1980 and March 1982, questionnaires were mailed to 5,967 adult twin pairs throughout Australia and, after one or two reminders to nonrespondents, completed questionnaires were returned by both members of 3,810 pairs, a 64% pairwise response rate. With this response rate from an enrollment which is already voluntary and unsystematic, there is ample scope for bias from population frequencies. We shall compare below the distributions of scores in our sample with those obtained in random samples in Australia.

Prior to mailing the questionnaire to the entire adult sample, a pilot questionnaire had been mailed to 100 pairs of adult twins in order to assess likely response rate and any problems in construction of the questionnaire. When the main study was conducted some months later, 96 individuals from the pilot sample returned a second questionnaire and these duplicate responses have been used to assess the short-term repeatability of the personality measures.

Diagnosis of zygosity of same-sex pairs was based on their response to the following questions:

1. As children, were you and your twin mistaken by people who knew you:
(a) Frequently   (b) Sometimes   (c) Rarely
2. "Nonidentical twins are no more alike than ordinary brothers and sisters. Identical twins on the other hand have such a strong resemblance to each other in stature,

colouring, features of the face, etc. that people often mistake one for the other." Having read the above statement, do you think you are:

(a) Identical   (b) Nonidentical

If twins differed in their response to these two questions, they were asked to send recent photographs of themselves. This method of zygosity diagnosis has been found by other workers [Cederlöf et al, 1961; Nichols and Bilbro, 1966; Martin and Martin, 1975; Kasriel and Eaves, 1976] to be about 95% correct as judged against diagnosis based upon extensive typing, and this is approximately the same reliability as obtained by typing for the most common six or seven blood group polymorphisms. The sex, zygosity, and age distribution of the twin sample is shown in Table I.

Tests

Delusions-Symptoms-States Inventory: Anxiety and Depression Scales (DSSI/sAD). The DSSI/sAD [Bedford et al, 1976] consists of seven state of anxiety and seven state of depression items. Each item is scored 0, 1, 2, or 3 according to the degree of distress claimed—ie, "none," "a little," "a lot," or "unbearably." The possible range of scores is thus 0–21 for both the anxiety and depression scales. This screening instrument was chosen because its reliability and validity have been established [Bedford and Foulds, 1977] and it is brief. Unlike other screening instruments, it provides separate scores for states of anxiety and states of depression. It had previously performed well in our hands in the course of an epidemiological study of neurosis and the social environment, proving itself to be a high-threshold instrument for the detection of states of anxiety or depression in a general population [Henderson et al, 1981]: only 3% of men and 3.5% of women had scores of 7 or more for depression, and only 1.0% and 5.6% for anxiety. It has been used here as an appropriate instrument for measuring symptoms by self-report in a large postal survey.

Eysenck Personality Questionnaire (EPQ). We wished to include a measure of vulnerability to anxiety or depression, which the construct of neuroticism is claimed to tap [Eysenck and Eysenck, 1969]. The EPQ [Eysenck and Eysenck, 1975] yields scores for three dimensions of personality, extraversion, psychoticism, and neuroticism, along with a fourth factor, the lie scale, which is a measure of social desirability or the tendency to "fake good." The neuroticism (N) scale consists of 23 items of the Yes/No type and is scored 0 or 1 according to whether the response is stable or

TABLE I. Age, Sex, and Zygosity Composition of the Sample

	MZ females	MZ males	DZ females	DZ males	DZ opposite-sex
Number of pairs	1,233	567	751	352	907
Mean age (years)	35.66	34.36	35.35	32.26	32.90
Standard deviation	14.27	14.02	14.27	13.88	13.85
Age range	18–88	18–79	18–84	18–83	18–79

neurotic. Thus total neuroticism scores could range from 0 to 23 in the direction of increasing neuroticism.

RESULTS

Scaling

In a genetic analysis it is most appropriate to choose a scale where there is no genotype-environment interaction so that genetic and environmental effects are additive. Jinks and Fulker [1970] have shown that MZ twins provide the opportunity to test for one important type of such interaction. Because MZ twins are genetically identical, the absolute difference between cotwins is a measure of the specific individual environmental influences (including errors of measurement) to which that pair has been subjected (E_1), while the pair sum is a measure of their genetic value (G) and/ or the environmental influences which they have shared and which make them different from other twin pairs (E_2). Thus regression of absolute within-pair differences on pair sums provides a test for any systematic interactions between genotype and individual environmental influences. Martin and Eysenck [1976] showed that such interactions could be detected with great sensitivity but they could nearly always be removed by a transformation of the scale of measurement which lessened departure from normality.

The anxiety and depression scales both show a extreme "reverse-J" shape distributions (Figs. 1, 2) which produce significant and substantial linear regressions. These may be reduced by logarithmic transformation and although this results in an increase in quadratic regression components, more extreme transformation ($\log_{10}(\log_{10}(x+1))$) or $\log_{10}\sqrt{(x+1)}$) produces no greater improvement so we regard the $\log_{10}(x+1)$ transformation as the more appropriate for both scales.
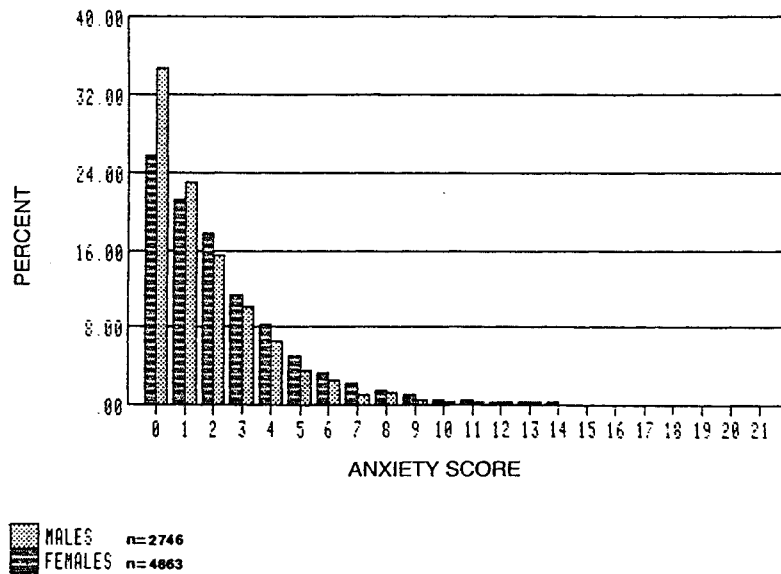

Fig. 1. Distribution of anxiety scores.
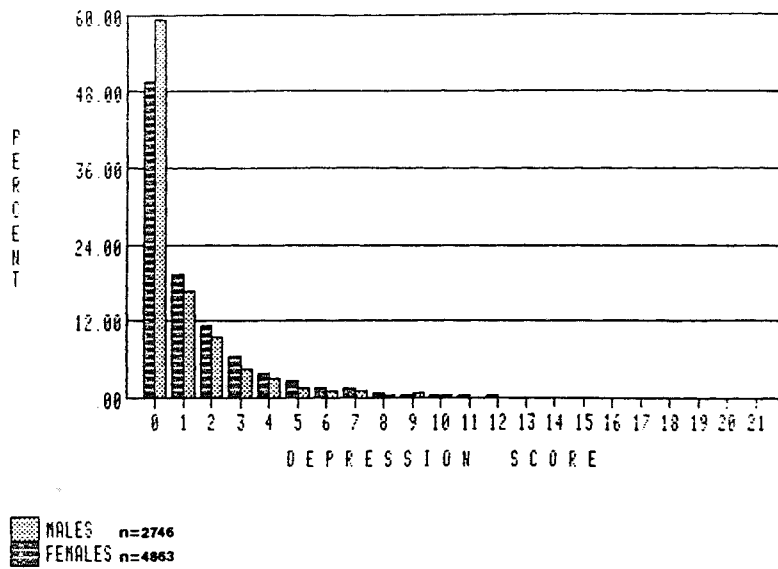
Fig. 2.   Distribution of depression scores.
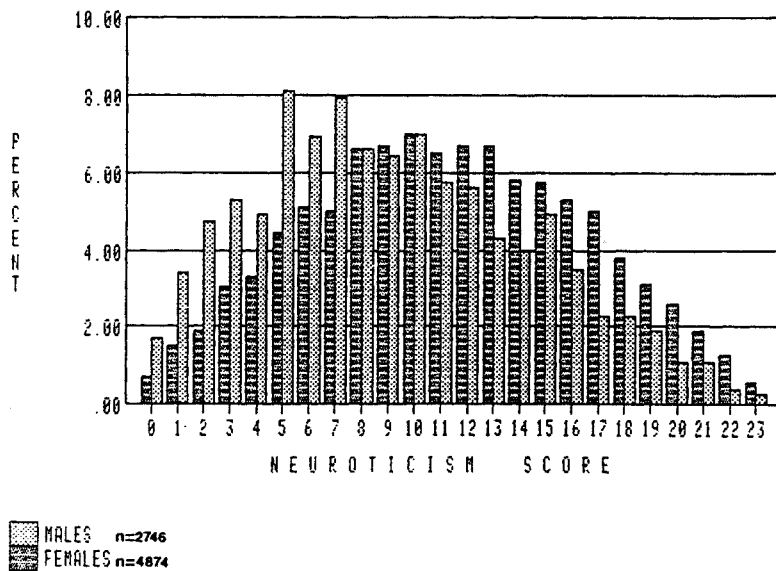
Fig. 3.   Distribution of neuroticism scores.

Neuroticism scores show a reasonably symmetric distribution but with an appreciable number of observations at the extremes producing a "basement-ceiling" effect (Fig. 3). This results in a quadratic sum-difference regression which can be almost entirely removed by angular transformation ($\arcsin\sqrt{p}$) [Snedecor and Cochran, 1980].

Although we choose these transformations for the sake of convenience in the

genetical analysis, they are no more arbitrary than the raw scales of measurement, given that we have no information about the precise relationship of the traits in question to evolutionary fitness [Eaves et al, 1977; Lord and Novick, 1977]. In most cases transformations have a negligible effect on the results of fitting models to variance components, but when there are extreme deviations from normality, as for the anxiety and depression scales, the results may differ markedly [Martin and Eysenck, 1976].

Distribution of Scores and Sex Differences

Females have significantly greater mean anxiety, depression, and neuroticism scores than males and a greater variance than males in the DSSI/sAD scales (Table II). These inequalities are observed for both the raw and transformed scores.

The distribution of neuroticism scores in the twin sample is similar to those from other Australian samples ascertained with less potential for bias [Eysenck et al, 1980].The distributions of anxiety and depression scores in the twin sample are similar to those observed in a random sample of Canberra electors [Henderson et al, 1981). These comparisons do not suggest that there are serious anomalies due to ascertainment bias in the distributions of twin scores.

An assumption fundamental to the twin method is that MZ and DZ twins have been drawn from the same population and we can test this by comparing their distributions. The only significant differences we observe are between the neuroticism means of male MZ and DZ twins (which is quantitatively trivial), and that the variance of raw depression scores is significantly greater ($P < 0.05$) in DZ females than MZ females. However, this latter difference becomes nonsignificant after transformation.

It is sometimes suggested that the twin method is invalid because DZ twins may have less similar environments than MZ pairs. If this inequality were real and influenced the traits under study, then we should expect to find that the total variance of DZ twins was greater than that of MZ's. Models that attempt to account for greater MZ similarity by reference to "different environmental effects for MZ and DZ twins" and which do not predict different total variances, invariably have to include parameters that are genetical in all but name. Even granted that the variance ratio test for inequality is not very powerful in detecting such differences, the total variances of MZ and DZ groups for the traits examined here are so similar that any such differential environmental effects must be of minor importance.

TABLE II. Means and Variances for Raw and Transformed Variables (Significant sex differences are indicated)

		Females (N = 4,857)		Males (N = 2,733)	
		Mean	Variance	Mean	Variance
Anxiety:	Raw	2.360***	6.917***	1.817	4.884
	Log (x+1)	0.4150***	0.0967***	0.3411	0.0900
Depression:	Raw	1.501***	6.401***	1.119	4.410
	Log (x+1)	0.2647***	0.0967***	0.2066	0.0824
Neuroticism:	Raw	11.32***	27.04	9.116	26.42
	Arcsin	44.50***	212.6	38.29	213.7

***$P < 0.001$.

Test-Retest Reliability

The 96 individuals who completed both the pilot and main questionnaires were typical of the total sample in age and distribution of scores except that the males tended to have lower neuroticism scores than those of the total sample (7.6 vs 9.1).

Estimates of repeatability [Falconer, 1981] or test-retest reliability were obtained by analysis of variance of scores from the pilot and main questionnaires. Mean squares between (MS_{bi}) and within (MS_{wi}) individuals were used to calculate intra-class correlations $R_i = (MS_{bi} - MS_{wi})/(MS_{bi} + MS_{wi})$.

The repeatability of the neuroticism scale is high (0.85 in females, 0.83 in males), and this is consistent with previous results [Eysenck and Eysenck, 1975]. Because the time interval between the completion of the pilot and the main study ranged from 1 to 10 months (mean 3 months), it is unlikely that memory would be an important factor in this result. The repeatabilities of the anxiety (0.63, 0.62) and depression (0.66, 0.58) scales are no lower than one would expect of symptoms that fluctuate in their severity. This sensitivity to change has also been reported by Bedford et al [1976]. In a longitudinal study of a general population sample (n = 230), Henderson et al [1981] administered the DSSI/sAD on two occasions 4 months apart. The anxiety scores correlated 0.62 and the depression 0.54.

Correction for Sex Differences and Regression on Age

To investigate the causes of individual differences in personality scores, we first calculate between- and within-pairs mean squares from a separate analysis of variance of each of the five twin groups. However, sex and age effects can bias these mean squares and consequently the components of variance estimated from them.

Where there is a sex difference in means, the within-pairs mean square (WMS) of DZ opposite-sex pairs is inflated by an amount of $n/2 \ (\overline{M}-\overline{F})^2$, where there are n pairs, $\overline{M}$ is the male mean and $\overline{F}$ is the female mean. Since significant sex differences in means were found for all variables (Table II) we correct for this by calculating the residual WMS (with $n-1$ df) given by $n/(n-1) \ (WMS - 1/2 \ (\overline{M} - \overline{F})^2)$.

If a variable is strongly age-dependent, this regression will inflate the between-pairs mean squares (BMS) of both MZ and DZ groups. There are significant negative correlations with all variables, indicating that individuals become less neurotic, anxious, and depressed with increasing age. However, even the largest of these (−0.17 with depression in males) would produce only a trivial inflation of the BMS so we have made no correction for this source of variance.

We may also examine whether twins become more or less similar with advancing years by correlating absolute within-pair differences with age. All correlations are small and nonsignificant for anxiety. For neuroticism the only significant correlation observed is in DZ females (0.12, P < 0.01), and this indicates that genetic differences become more pronounced with age; no such efect is apparent in males. Eaves and Eysenck [1976] also found that genetic differences in neuroticism increase with age but they did not look for differences between the sexes in age-dependent gene expression. For depression, both MZ and DZ males become more similar with advancing age (−0.18, P < 0.001; −0.13, P < 0.05), but no such effect was found in females. While this latter finding is open to a number of interpretations, it is clear that if environmental circumstances of cotwins become more different as they get older, these do not appear to produce any greater differences in the personality variables we have measured.

Genetical Analysis

Between- and within-pairs mean squares for each variable are the appropriate diagonal elements from the ten 3×3 mean-products matrices shown in Appendix I.

A simple model for the possible sources of variance contributing to mean squares from a twin study is shown in Table III. E_1 is environmental variance within families, specific to the individual and shared with no one else, not even members of the same family. It also includes measurement error. E_2 (or B) pairs is environmental variation shared by cotwins but differing between twin pairs and will include cultural and parental treatment effects. V_A is the genetic variance due to the additive effects of genes in the absence of assortative mating. V_D is the genetic variance due to dominant gene action. Martin et al [1978] have shown that only with the very large number of twin pairs available in the present study would there be a reasonable chance of detecting dominance, and for this reason we include it in the models we test.

A sensible hierarchy of models is first to fit E_1 alone. Failure of this most simple model will indicate that there is significant between families variation to be explained. A model including both E_1 and E_2 will test whether the between-families variation is entirely environmental in origin; the $E_1 V_A$ model will test whether it is entirely genetic. If both two-parameter models fail, then models including three sources of variation, either $E_1 E_2 V_A$ or $E_1 V_A V_D$, may be tested.

The method of fitting these models to twin mean squares by the method of iterative weighted least squares is described in detail by Eaves and Eysenck [1975] and illustrated extensively in Eaves et al [1978]. Models are first fitted to the mean squares for males and females separately and then to all eight statistics together. A chi-square to test heterogeneity of fit of a given model over sexes can then be calculated by adding the separate chi-square values for males and females and subtracting the result from the corresponding chi-square for the combined male and female data. If there is no significant heterogeneity then we may proceed to fit the model to all ten mean squares including those from the DZ opposite-sex twins. If the heterogeneity is significant then different models must be considered for males and females.

The results of fitting these models to mean squares for anxiety, depression, and neuroticism are shown in Tables IV, V, and VI. In every case a model (E_1) postulating that all variation was due to individual environmental experiences failed badly and is omitted from summary tables. The $E_1 E_2$ model also failed badly in all cases but one: both the $E_1 E_2$ and $E_1 V_A$ models adequately describe the data for depression in males.

TABLE III. Contributions of Environmental and Genetic Sources of Variation to Twin Mean Squares

Mean square		E_1	E_2	V_A	V_D
MZ:	Between pairs	1	2	2	2
	Within pairs	1	0	0	0
DZ:	Between pairs	1	2	3/2	5/4
	Within pairs	1	0	1/2	3/4

E_1 = Individual environmental variance.
E_2 = Shared environmental variance.
V_A = Additive genetic variance.
V_D = Dominant genetic variance.

TABLE IV. Results of Model Fitting to Log-Transformed Anxiety Scores

Model	$\hat{E}_I$	$\hat{B}$	$\hat{V}_A$	$\hat{V}_D$	df	χ^2	h^2
Female							
$E_I B$	0.068***	0.030***	—	—	2	25.47***	
$E_I V_A$	0.061***	—	0.037***	—	2	0.23	0.38 ± 0.02
$E_I B V_A$	0.060***	−0.002	0.039***	—	1	0.16	
$E_I V_A V_D$	0.060***	—	0.033**	0.004	1	0.16	
Male							
$E_I B$	0.064***	0.024***	—	—	2	15.06**	
$E_I V_A$	0.058***	—	0.031***	—	2	1.29	0.35 ± 0.03
$E_I B V_A$	0.056***	−0.010	0.042***	—	1	0.26	
$E_I V_A V_D$	0.056***	—	0.012	0.020	1	0.26	
Female and Male							
$E_I B$	0.067***	0.028***	—	—	6	45.37***	
$E_I V_A$	0.060***	—	0.035***	—	6	6.70	0.37 ± 0.02
$E_I B V_A$	0.059***	−0.004	0.040***	—	5	6.23	
$E_I V_A V_D$	0.059***	—	0.027**	0.009	5	6.23	
Female and Male and opposite-sex							
$E_I B$	0.071***	0.024***	—	—	8	67.68***	
$E_I V_A$	0.060***	—	0.034***	—	8	10.36	0.36 ± 0.02
$E_I B V_A$	0.059***	−0.008	0.043***	—	7	7.33	
$E_I V_A V_D$	0.059***	—	0.020*	0.016*	7	7.33	

*0.01 < P < 0.05; **0.001 < P < 0.01; ***P < 0.001.

TABLE V. Results of Model Fitting to Log-Transformed Depression Scores

Model	$\hat{E}_I$	$\hat{B}$	$\hat{V}_A$	$\hat{V}_D$	df	χ^2	h^2
Female							
$E_I B$	0.069***	0.028***	—	—	2	22.04***	
$E_I V_A$	0.062***	—	0.035***	—	2	1.20	0.36 ± 0.02
$E_I B V_A$	0.062***	−0.000	0.035***	—	1	1.20	
$E_I V_A V_D$	0.062***	—	0.034**	0.001	1	1.20	
Male							
$E_I B$	0.056***	0.021***	—	—	2	2.46	
$E_I V_A$	0.052***	—	0.025***	—	2	1.85	0.32 ± 0.04
$E_I B V_A$	0.053***	0.010	0.013	—	1	0.46	
$E_I V_A V_D$	0.053***	—	0.044**	−0.021	1	0.46	
Female and male							
$E_I B$	0.065***	0.026***	—	—	6	54.72***	
$E_I V_A$	0.059***	—	0.032***	—	6	30.31***	
$E_I B V_A$	0.059***	0.003	0.028***	—	5	30.22***	
$E_I V_A V_D$	0.059***	—	0.037***	−0.006	5	30.22***	
Female and male and opposite-sex							
$E_I B$	0.069***	0.023***	—	—	8	76.11***	
$E_I V_A$	0.060***	—	0.032***	—	8	33.70***	
$E_I B V_A$	0.059***	−0.002	0.034***	—	7	33.21***	
$E_I V_A V_D$	0.059***	—	0.028***	0.005	7	33.21***	

*0.01 < P < 0.05; **0.001 < P < 0.01; ***P < 0.001.

If we consider the male and female data separately then we see that the E_1V_A model gives an excellent fit for all variables and that in no case (including depression in males) is this improved significantly by addition of E_2 or V_D to the model. We may conclude, then, that variation in these variables is determined mainly by individual environmental and additive genetic effects, and that if family environment or genetic dominance play any part, they are too small to be detected by even this powerful experiment [Martin et al, 1978]. The proportion of total variation due to genetic causes is the heritability and for an E_1V_A model is calculated as $h^2 = \hat{V}_A/(\hat{E}_1 + \hat{V}_A)$. These values are given in Tables IV–VI and range from 0.32 for depression in males to 0.51 for neuroticism in females.

When the E_1V_A model is fitted to the combined male and female data, it fails badly for depression. We find that the chi-square for heterogeneity of fit over sexes is highly significant ($\chi_2^2 = 27.26$, $P < 0.001$), and inspection of the parameter estimates shows that there are larger E_1 and V_A components for males than females. Although heterogeneity chi-squares are not significant for either anxiety ($\chi_2^2 = 5.18$, $P < 0.10$) or neuroticism ($\chi_2^2 = 3.71$, $P > 0.10$), parameter estimates appear to differ somewhat between the sexes.

A model incorporating different sized environmental and genetical components for males and females has been developed by Eaves [1977] and illustrated in Eaves et al [1978]. It estimates different genetical components for males and females, denoted as V_{AM} and V_{AF}, and a component V_{AMF} which is the covariance between the genetical effects acting in males and the genetical effects acting in females. If the genes affecting a trait in males are quite different from those affecting the trait in females, then we expect $\hat{V}_{AMF}$ to be zero. If the genes acting in males and females

TABLE VI. Results of Model Fitting to Arcsin-Transformed Neuroticism Scores

Model	$\hat{E}_1$	$\hat{B}$	$\hat{V}_A$	$\hat{V}_D$	df	χ^2	h^2
Female							
E_1B	125.1***	90.47***	—	—	2	51.1***	
E_1V_A	104.7***	—	110.5***	—	2	0.42	0.51 ± 0.02
E_1BV_A	104.8***	1.218	109.2***	—	1	0.42	
$E_1V_AV_D$	104.8***	—	112.8***	−2.436	1	0.42	
Male							
E_1B	141.8***	76.75***	—	—	2	28.5***	
E_1V_A	118.9***	—	100.3***	—	2	1.72	0.46 ± 0.03
E_1BV_A	116.5***	−26.36	128.8***	—	1	0.27	•
$E_1V_AV_D$	116.5***	—	49.68	52.72	1	0.27	
Female and male							
E_1B	130.3***	86.13***	—	—	6	86.7***	
E_1V_A	109.1***	—	107.4***	—	6	5.85	0.50 ± 0.02
E_1BV_A	108.4***	−8.230	116.2***	—	5	5.30	
$E_1V_AV_D$	108.4***	—	91.49***	16.46	5	5.30	
Female and male and opposite-sex							
E_1B	140.9***	71.98***	—	—	8	136.0***	
E_1V_A	110.9***	—	102.1***	—	8	18.4*	
E_1BV_A	107.6***	−24.06	128.9***	—	7	12.26	
$E_1V_AV_D$	107.6***	—	56.72**	48.13**	7	12.26	

*$0.01 < P < 0.05$; **$0.001 < P < 0.01$; ***$P < 0.001$.

TABLE VII. Parameter Estimates (± SE) and Heritabilities (h^2) From Fit of Models Incorporating Different Sized Environmental and Genetic Effects in Males and Females (Estimates of variance within individuals between occasions (MS_{wi}) from reliability data are included for comparison with E_1 estimates)

		MS_{wi}	E_1	V_A	V_{AMF}	h^2	χ^2
Anxiety	Females	0.037		0.038 ± 0.002		0.39 ± 0.02	
			0.060 ± 0.002		0.023 ± 0.006		$\chi_6^2 = 2.15$ (P = 0.91)
	Males	0.039		0.030 ± 0.003		0.33 ± 0.03	
Depression	Females	0.036	0.062 ± 0.002	0.036 ± 0.003		0.37 ± 0.02	
					0.022 ± 0.006		$\chi_5^2 = 8.73$ (P = 0.12)
	Males	0.032	0.053 ± 0.003	0.026 ± 0.003		0.33 ± 0.03	
Neuroticism	Females	27.2	104.2 ± 3.9	108.0 ± 5.6		0.51 ± 0.02	
					59.4 ± 13.9		$\chi_5^2 = 5.78$ (P = 0.33)
	Males	38.5	117.4 ± 6.4	95.4 ± 8.0		0.45 ± 0.03	

TABLE VIII. Variance Accounted for (%) in Each Measure by Fluctuating Environment and Errors of Measurement, Stable Individual Environmental Experiences, and Additive Genetic Effects

		Anxiety		Depression		Neuroticism	
		Females	Males	Females	Males	Females	Males
Individual environment	Error and fluctuating	38	44	37	29	13	18
	61	67	63	67	49	55	
	"Stable"	23	23	26	38	36	37
Genetic		39	33	37	33	51	45

are exactly the same but produce scalar differences in the two sexes then we expect the correlation between the effects ($r_{MF} = V_{AMF}/\sqrt{V_{AM} \cdot V_{AF}}$) to be one.

The results of fitting a model which specifies environmental and genetic effects of different size in males and females are shown in Table VII. For anxiety, a common E_1 parameter is specified for both sexes but fitting separate V_A parameters for males and females causes a significant reduction in chi-square ($\chi_2^2 = 8.21$, $P < 0.05$) from the E_1V_A model fitted to all ten statistics. Fitting different E_1 and V_A parameters produces even larger reductions in chi-square for depression ($\chi_3^2 = 24.97$, $P < 0.001$) and neuroticism ($\chi_3^2 = 12.64$, $P < 0.01$).

The correlation r_{MF} is 0.67 for anxiety, 0.73 for depression, and 0.58 for neuroticism. Only the correlation for neuroticism is significantly less than unity, but all suggest that there may be some differences between males and females in the genetical effects acting on these traits. There is also evidence that those effects that are common to both sexes have a smaller effect on the genetic variance in males.

Estimates from the reliability data of within-individuals mean squares, which include the effects of fluctuating environment and measurement error, are also shown in Table VII. The breakdown of sources of variation in both sexes is shown for each variable in Table VIII. We may subtract the values of the within-individuals mean square from the estimate of E_1 and so estimate the proportions of variance due to nonrepeatable and to "systematic" individual environmental differences.

Correlations Between Anxiety, Depression and Neuroticism Scores

Correlations between the transformed DSSI/sAD and neuroticism measures are shown in Table IX and are all around 0.6 in both sexes. However, we should like to know whether these intercorrelations arise primarily from environmental or genetic sources and whether there are any genetic effects that are unique to a given variable and do not influence the others.

We know from the univariate analyses that for anxiety, depression, and neuroticism, individual environment (E_1) and additive gene effects (V_A) are important causes of trait variation in both sexes, although there are differences in the importance of these effects in males and females. We may now investigate the extent to which these two sources of variation are responsible for trait covariation by using the genetical analysis of covariance structure developed by Martin and Eaves [1977]. Detailed explanations and applications of this maximum likelihood technique can be found elsewhere [Eaves et al, 1977; Fulker, 1978; Martin et al, 1979, 1981; Clifford et al, 1981].

The genetical analysis of covariance structure is a technique that simultaneously tests hypotheses concerning both the sources and the structure of covariation. Just as

TABLE IX. Correlations Between the Transformed Personality Variables for Females (upper triangle) and Males (lower triangle)

		Anxiety log (x+1)	Depression log (x+1)	Neuroticism arcsin
Anxiety	log (x+1)	—	0.66	0.61
Depression	log (x+1)	0.60	—	0.58
Neuroticism	arcsin	0.60	0.57	—

univariate models were fitted to mean squares, multivariate models are fitted to the between- and within-pairs mean products matrices shown in Appendix I.

The model we shall fit contains a single general factor causing covariation between anxiety, depression, and neuroticism plus a variance component specific to each trait for both the E_1 and V_A sources of covariation. For each source then, we estimate three factor loadings and three specific variance components, or 12 parameters in all. Each mean-products matrix contributes three mean squares from the diagonal and three off-diagonal mean products, making 24 unique statistics from the four between- and within-pairs matrices of MZ and DZ twins of the same sex. We are thus left with 12 degrees of freedom to test the goodness of fit.

Maximum likelihood estimates of factor loadings and specific variance components from each source are obtained. The proportions of variance in each measure accounted for by these estimates are shown in Table X. In both sexes the model gives an excellent fit to the data, and all parameter estimates are significantly greater than zero ($P < 0.01$).

The results suggest that genetic variation in the symptoms of anxiety and depression is largely dependent on the effects of the same genes which determine variation in the trait of neuroticism. This follows from the finding that the specific genetic components of variation in the two symptoms are small, nearly all of their genetic variance being due to the common factor. However, it is interesting that there is still substantial specific genetical variation for neuroticism, and it is possible that this may be manifest relatively independently of the two symptoms we have considered.

A factor of individual environmental effects also appears to influence all three variables, although specific E_1 variation is equally or more important in most cases. The proportion of variance due to error or fluctuating environment in anxiety and depression (Table VIII) is equal to or slightly greater than the specific environmental variance, which suggests that some of this fluctuating environment may contribute to E_1 factor variance. The specific variance component for neuroticism, on the other hand, is somewhat greater than the unrepeatable variance, so that there may be systematic environmental experiences influencing the neuroticism trait which do not influence the symptoms we measure.

TABLE X. Proportions of Variance Accounted for by Environmental (E_1) and Genetic (V_A) General Factor and Specific Variance in Transformed Anxiety, Depression, and Neuroticism Scores (Fit of model is indicated)

	Individual environment		Genetic	
	Factor	Specific	Factor	Specific
Females				
Neuroticism arcsin	0.20	0.29	0.35	0.16
Anxiety log (x+1)	0.35	0.27	0.35	0.03
Depression log (x+1)	0.33	0.31	0.30	0.06
	$\chi^2_{12} = 6.90$ (P = 0.86)			
Males				
Neuroticism arcsin	0.22	0.32	0.34	0.12
Anxiety log (x+1)	0.31	0.35	0.30	0.04
Depression log (x+1)	0.33	0.35	0.23	0.09
	$\chi^2_{12} = 12.52$ (P = 0.40)			

TABLE XI. Genetic and Environmental Correlations Between Transformed Anxiety, Depression, and Neuroticism Scores (Females upper triangle, males lower triangle)

Environmental	Females		
	Neuroticism arcsin	Anxiety log (x+1)	Depression log (x+1)
Males			
Neuroticism arcsin	—	0.47	0.45
Anxiety log (x+1)	0.44	—	0.54
Depression log (x+1)	0.45	0.48	—

Genetic	Females		
	Neuroticism arcsin	Anxiety log (x+1)	Depression log (x+1)
Males			
Neuroticism arcsin	—	0.80	0.76
Anxiety log (x+1)	0.81	—	0.88
Depression log (x+1)	0.73	0.79	—

Genetic and environmental correlations of the variables are shown in Table XI. In both sexes, genetic correlations are much higher (around 0.8) than corresponding environmental correlations (around 0.4).

DISCUSSION

While previous studies on the etiology of neuroses and minor depression have yielded conflicting results [Slater and Shields, 1969; Torgersen, 1983], our large twin study has provided a clear answer to the causes of individual differences in neuroticism and the symptoms of anxiety and depression. Our data suggest that population variation in these measures is due only to additive genetic effects and the influence of environmental factors which are unique to the individual. We find no evidence that environmental influences shared by members of the same family, such as social class and parental treatment, are important in the development of neuroticism, anxiety, and depression. Workers who postulate that early environmental experiences are a major influence on anxiety and depression in adulthood [eg, Parker, 1979, 1981a,b] must recognise that such experiences are not necessarily shared by cotwins; experience from parents is more likely to be a function of the child's genotype than of family environment [Eaves et al, 1978; Eaves, 1976].

There are no significant differences in total variances of MZ and DZ twins, and this would suggest that MZ twins have been treated no more similarly than their DZ counterparts. Although there is no suggestion that the twin sample differs from other more randomly ascertained samples, it is possible that selection bias against more extreme cases may cause underestimation of the genetic variance [Martin and Wilson, 1982].

Anxiety and depression scores appear to be influenced largely by the same genes in both sexes, but these have greater effect in females than in males. Environmental variance for depression is also greater in females, a result previously found by Eaves and Young [1981]. There are also slight differences between the sexes in

environmental and genetic contributions to variance in neuroticism, but these are not surprising in view of the striking evidence we find for the action of different genes on neuroticism in males and females. The correlation of age with absolute within-pair differences in DZ females also indicates that genetic differences in neuroticism become more pronounced as females get older; a similar result has been found by Eaves and Eysenck [1976].

We find no evidence that dominant gene action affects the expression of neuroticism or the symptoms of anxiety and depression; the significant estimates of V_D obtained for anxiety and neuroticism from the fit of the $E_1V_AV_D$ model to all ten statistics are almost certainly artifacts of the sex-limited gene expression affecting these traits. Much of the evidence for dominance comes from the reduction of the DZ correlations relative to their MZ counterparts. In our data, a substantial proportion of DZ twins are of opposite sex, and any sex differences in gene expression will reduce the DZ opposite-sex correlation and hence mimic the effects of dominance in the pooled data. The interpretation is supported by the lack of evidence for dominance when the sexes are analysed separately.

Our results for neuroticism are similar to those of Floderus-Myrhed et al [1980]. Eaves and Young [1981] reanalysed their data from 12898 Swedish same-sex twin pairs and found that both age and sex affected the expression of additive genetic and environmental differences, but that there was no evidence for dominance. The fact that both the present study [Martin and Jardine, 1984] and that analysed by Eaves and Young [1981] have detected significant contributions of dominance or other nonadditive genetic variation for extraversion demonstrates that there is sufficient power to detect dominance variance for neuroticism in these two studies if it exists in moderate quantity. That it does not suggests that these two personality dimensions are not only statistically independent but are also quite different in fundamental biological aspects. This finding may have important implications for the continuing controversy about the physiological basis of Eysenck's personality dimensions. Gray [1970] has argued that a 45° rotation of Eysenck's extraversion and neuroticism dimensions is justified on several biological grounds. Our genetical analysis ascribes quite different origins to the genetic variation for E and N. Since rotation would obscure this distinction, our results may favour Eysenck's position.

The significant and substantial correlations between anxiety, depression, and neuroticism replicate a previous finding that neuroticism is a trait which is closely associated with vulnerability to neurotic symptoms [Henderson et al, 1981]. Our analysis of the causes of genetical and environmental covariation of these measures shows that additive genetic effects are equally, if not more important in their covariation than individual environmental factors and that genetic correlations are much higher (0.8) than environmental correlations (0.4). While the distinction between personality traits and symptoms may be justified because symptoms are often transitory and take different forms [Foulds, 1965, 1974], the fact that correlations between neuroticism and the two symptoms are as high as between the symptoms themselves provides little evidence for this distinction.

Nevertheless, there are also substantial genetic effects on neuroticism (16% of the total in females, 12% in males) which are independent of the two symptoms we have measured. It is interesting to speculate that the general factor (30% in females, 23% in males) and specific components (6% in females, 9% in males) of genetic variance for depressive symptoms may distinguish between forms of depression which

are heterogeneous in their etiology and in their item profile symptoms. In a future paper [Kendler et al, in preparation] we shall investigate the causes of variation in the responses of our twin sample to the individual items of the anxiety and depression scales, with a view to detecting and characterizing such heterogeneity.

There is a certain view abroad, though seldom ventured in print, that is dismissive of the results of twin studies on the rather vague grounds that "twins are not typical of the population" and that there are "special environmental effects" in twins which "make it impossible to generalize." These criticisms have repeatedly been formalized, tackled, and generally dismissed, most recently by Kendler [1983]. Twin studies are a powerful first step for assessing the broad causes of trait variation. Indeed, they are beset with far fewer problems than nuclear-family studies, many of which are rendered almost worthless by the inextricability of genetic and environmental variance [Eaves et al, 1978]. Nevertheless, the importance of twin studies is enhanced if it can be shown that their results are generalizable to other relationships. To this end, further studies are in progress to examine symptoms of anxiety and depression in the relatives of certain subsamples of our very large twin sample.

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APPENDIX I. Mean Products Matrices for the Transformed Anxiety, Depression, and Neuroticism Scores

	MZ females between 1,228 df		
	330.30	4.4175	4.0954
Neuroticism arcsin	104.96	.13371	.09509
Anxiety log (x + 1)	1.1982	.05983	.12820
Depression log (x + 1)	1.1647	.03232	.06063
MZ females within 1,229 df			

	MZ males between 565 df		
	315.18	4.1190	3.4697
	115.65	.12219	.07395
	1.1616	.05706	.10310
	1.1665	.02764	.05397
MZ males within 566 df			

	DZ females between 749 df		
	264.70	3.6399	3.5327
	157.57	.11675	.08109
	1.9503	.08064	.11795
	1.8274	.04999	.08120
DZ females within 750 df			

	DZ males between 350 df		
	263.16	2.9354	2.8184
	183.94	.09708	.05346
	1.9195	.07612	.09118
	1.5822	.03385	.05875
DZ males within 351 df			

	Opposite-sex between 899 df		
	228.45	3.1143	2.9562
	174.26	.10568	.07114
	2.3166	.08276	.10786
	2.0929	.05045	.08259
Opposite-sex within 899 df			

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