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The genetic aetiology of somatic distress

N. A. GILLESPIE,[1] G. ZHU, A. C. HEATH, I. B. HICKIE AND N. G. MARTIN

From Queensland Institute of Medical Research, University of Queensland, Joint Genetics Program, Brisbane, Queensland, School of Psychiatry, University of New South Wales, Academic Department of Psychiatry, St George Hospital and Community Health Service, Sydney, New South Wales, Australia; and Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA

ABSTRACT

Background. Somatoform disorders such as neurasthenia and chronic fatigue syndrome are characterized by a combination of prolonged mental and physical fatigue. This study aimed to investigate the heritability of somatic distress and determine whether this dimension is aetiologically distinct from measures of depression and anxiety.

Method. Measures of anxiety, depression, phobic anxiety, somatic distress and sleep difficulty were administered in a self-report questionnaire to a community-based sample of 3469 Australian twin individuals aged 18 to 28 years. Factor analysis using a Promax rotation, produced four factors: depression, phobic anxiety, somatic distress and sleep disturbance. Multivariate and univariate genetic analyses of the raw categorical data scores for depression, phobic anxiety and depression were then analysed in Mx1.47.

Results. Univariate genetic analysis revealed that an additive genetic and non-shared environmental (AE) model best explained individual differences in depression and phobic anxiety scores, for male and female twins alike, but could not resolve whether additive genes or shared environment were responsible for significant familial aggregation in somatic distress. However, multivariate genetic analysis showed that an additive genetic and non-shared environment (AE) model best explained the covariation between the three factors. Furthermore, 33% of the genetic variance in somatic distress was due to specific gene action unrelated to depression or phobic anxiety. In addition, 74% of the individual environmental influence on somatic distress was also unrelated to depression or phobic anxiety.

Conclusion. These results support previous findings that somatic symptoms are relatively aetiologically distinct both genetically and environmentally from symptoms of anxiety and depression.

INTRODUCTION

Somatoform disorders such as neurasthenia and chronic fatigue are characterized by a combination of prolonged fatigue, and disabling neuropsychological and neuromuscular symptoms (Lloyd *et al*. 1990; Angst & Koch, 1991; Hickie *et al*. 1995). Differences between these syndromes are qualitative and reflect variations in duration criteria rather than symptom constructs (Hickie *et al*. 1997). The ICD-10 (World Health Organization, 1992) classification system includes a formal diagnosis of neurasthenia based on mental and physical fatigue of at least 3 months duration. However, despite current international and epidemiological interest in this disorder, DSM-IV continues to include prolonged fatigue syndromes within the 'Undifferentiated Somatoform Disorders-300.81' category (American Psychiatric Association, 1994) and largely discounts the notion of discrete syndromes like neurasthenia.

Critics of the independence of somatic distress disorders base their objections on the comorbidity of such syndromes with conventional measures of anxiety and depression (Wessely & Powell, 1989; Goldberg & Bridges, 1991).

[1] Address for correspondence: Dr Nathan A. Gillespie, Epidemiology Unit, Queensland Institute of Medical Research, Post Office, Royal Brisbane Hospital, Brisbane, QLD 4029, Australia.

Somatic symptoms are moderately correlated with anxiety (0·53) and depression (0·48), although these correlations are smaller than those found between anxiety and depression alone (0·68) (Goldberg, 1996). Fatigue states are frequently co-morbid with anxiety and depressive disorders. Nevertheless, a number of studies (Kroenke *et al*. 1988; Wessely & Powell, 1989; Hickie *et al*. 1990) have demonstrated that a significant proportion of patients with somatic disorders such as chronic fatigue do not meet the criteria for other psychological disorders. Patients with fatigue do not show specific response to antidepressant pharmacotherapy (Vercoulen *et al*. 1996; Hickie *et al*. 2000) and longitudinal data sets have demonstrated that patients tend to maintain their unique characteristics over time (Merikangas & Angst, 1994; Hickie *et al*. 1999*a*). In addition, factor analytical studies have demonstrated a clear separation of fatigue items and questions relating to anxiety and distress (Gillespie *et al*. 1999; Kirk *et al*. 1999).

The objective of this study was to investigate the heritability of somatic distress and determine whether this dimension is aetiologically distinct from other measures of cognitive distress, particularly depression and anxiety.

METHOD

Sample

Twins were drawn from the Australian National Health and Medical Research Council Twin Register (ATR). The ATR is a volunteer register founded in 1978 with approximately 25000 pairs of all types and all ages enrolled and in various stages of active contact. We estimate that this represents 10–20% of living twins in Australia. Numerous analyses have shown that the ATR is typical of the Australian population in many respects including the prevalence of psychiatric symptoms (Kendler *et al*. 1986), although the ATR sample tends to be slightly more middle class and educated than average, particularly for males (Baker *et al*. 1996).

In 1989, an extensive Health and Lifestyle Questionnaire (HLQ) was mailed to 4269 pairs born 1964–1971 (i.e. aged 18–28). The HLQ covered a wide range of health issues affecting younger people, including a 33-item self-report symptom inventory (see Appendix 1) designed to measure recently experienced psychiatric distress. Most of these twins had been recruited when at school some 10 years earlier, so it was not surprising that, despite extensive follow-up efforts, we were unable to re-establish contact with 1000 pairs. Those twins who failed to return a completed questionnaire were followed-up by telephone up to five times, at which point they were asked to complete an abbreviated telephone interview to obtain basic demographic information only. Returned questionnaires with the psychiatric symptom inventory completed were received from 3469 subjects (1374 males and 2095 females). This included 1350 complete twin pairs plus 769 singletons, representing an individual response rate of 53% (3469/6538) and a pairwise response rate of 41%, although these rates improve somewhat after imputation of missing item responses. The mean age of respondents was $23{\cdot}2 \pm 2{\cdot}2$ with an age range of 18 to 28.

Measures

The psychiatric symptom inventory, labelled 'Feelings' in the HLQ, contained 14 anxiety and depression items from the Delusion Symptoms States Inventory (DSSI/sAD) (see Foulds & Bedford, 1975; Bedford & Deary, 1997) as well as a 19 item subset of the 90-item Symptom Checklist (SCL-90) (Derogatis *et al*. 1973). Eighteen items were chosen from four SCL subscales: Anxiety (4 items); Depression (5 items); Phobic Anxiety (PHOB); and Somatic Distress (SOMAT). One item, dealing with early morning awakening or insomnia was chosen from additional items available in the SCL-90. All items were rephrased to conform to the DDSI/sAD format of enquiry, 'Recently I have had …' rather than use the SCL-90 format, 'In the past two weeks ….'. The response set was also changed from a 5-point scale of distress from 'not at all' (0) to 'extremely' (4) (Derogatis *et al*. 1973) to the DSSI/sAD four-point distress scale (1) 'not-at-all' to (4) 'unbearably'.

Zygosity diagnosis

Zygosity of twins was decided on the basis of twins' responses to standard questions about similarity and the degree to which others confused them. Pairs giving inconsistent responses were further interviewed by telephone for clarification. Such procedures have pre-

Table 1. *Inter-factor correlations for the four-factor solution. Female twins are above the diagonal*

		Females ($N = 2219$)			
		1	2	3	4
1	Depression		0·64	0·52	0·64
2	Phobic anxiety	0·63		0·58	0·54
3	Somatic distress	0·54	0·58		0·46
4	Sleep difficulty	0·58	0·56	0·44	
		Males ($N = 1418$)			

viously demonstrated at least 95% agreement with diagnoses based on extensive blood sampling (Martin & Martin, 1975; Ooki *et al.* 1990).

Statistical analysis

The imputation option in PRELIS 2.20 (Jöreskog & Sörbom, 1998) was used to impute missing values using sex and the full 33 items as matching variables. This approach obtains the substitute value from other cases with similar response patterns, provided there are no missing values in the matching variables (see Jöreskog & Sörbom, 1993, pp. 11–12). In order to avoid the possibility of artefactual inflation of twin correlations, imputation was carried out on an individual basis ignoring the paired structure of the data. A total of 168 Feelings item responses were imputed (0·14% of total number of Feelings items), increasing the total effective sample size to 1418 males (3·2% increase) and to 2219 females (5·9% increase). After imputation, both members of 1474 twin pairs plus a further 689 singletons had complete responses for the Feelings items, increasing the individual response rate to 56%.

Many factors may influence participation therefore we examined the possible influence of social class. We compared the distribution of self-reported social class (lower/ middle/ upper) between subjects who did not provide complete responses to the Feelings items *versus* those who did but there were no significant differences ($\chi^2_2 = 0{\cdot}57$, $P = 0{\cdot}75$).

Our first step was to investigate the factor structure of the 33 'Feelings' items. We estimated polychoric correlations between items using PRELIS 2.20 (Jöreskog & Sörbom, 1993) and then factor analysed the resultant matrices (separately for males and females) using a Promax rotation criterion in SAS 6.11 (SAS Institute, 1985). Four readily interpretable factors were extracted in both sexes: depression, phobic anxiety with panic features, somatic distress, and sleep disturbance. Inter-factor correlations are shown in Table 1.

The twin design provided a unique opportunity for split half analysis to test the four factor solution by separating subjects by sex, and then later by separating pairs of twins into two samples according to their order of registration with the NHMRC Twin Registry. Tucker's (1951) congruence coefficient revealed that the four-factor structure was similar for males and females as well as between twin1 and twin2 for complete twin pairs. The factor structure was also similar to that found by Kendler *et al.* (1995*b*) and Lipman *et al.* (1979). Neither increasing the number of extracted factors nor applying an orthogonal rotation led to the emergence of an interpretable anxiety factor. Instead, items denoting general anxiety loaded across the dimensions of depression and phobic anxiety. Since the sleep difficulty factor was based on three items for females and only two items for males it was not included in further analysis. In the current study seven items common to males and females were retained for depression, seven items for phobic anxiety and four items for somatic distress. Internal consistencies (Cronbach alphas) were 0·86, 0·81 and 0·65 for depression, phobic anxiety and somatic distress respectively.

Analysis of raw ordinal data

Analysis of continuous data in recent years has taken advantage of raw data methods using programs such as Mx (Neale, 1999) to make use of complete and incomplete data observations. In the same way that the equality of means and covariance structure is tested when analysing raw continuous data, the extension of raw data methods to ordinal data permits researchers to test hypotheses concerning the equality of response (threshold) distributions within twin pairs, across sex and zygosity. It also allows one to test hypotheses about of the equality and latent causes of correlations. In addition, one can obtain maximum likelihood tests for the equality of thresholds in complete *versus* incomplete pairs, thereby enabling detection of cooperation or volunteer bias which may be

correlated with the target variables (Neale & Eaves, 1993). Raw data methods also have the added advantage of increasing the accuracy of the estimation of the thresholds and thereby improving estimation of the polychoric correlations. The major disadvantage is that computational demands are proportional to the number of categories, resulting in the decision to reduce the number of categories while ensuring no significant loss of information.

Genetic analysis

Genetic analysis was based on the principles of biometrical genetics (see Neale & Cardon, 1992) whose object is to identify the possible ways in which familial aggregation can arise for the variables of interest. The degree to which family members can be more or less alike can be partitioned into four broad causes of variation: additive genetic influence (A), genetic dominance (D), common environment (C) and specific environment factors (E). Additive genetic influences reflect the additive or average effects of individual alleles at loci influencing a trait. Genetic dominance refers to the interaction between alleles at the same locus. Common environmental effects make family members more alike than random pairs of individuals, whereas specific environmental influences refer to aspects of the environment that are unique to the individual.

The total variance in an observed trait is the sum of the additive and non-additive (dominance or epistasis) genetic variance, plus common and unique environmental variance. The correlations for additive and dominant genetic effects between MZ twins are both 1·0 because MZ twins are genetically identical. However, the correlations for additive and non-additive genetic effects between DZ twins are 0·5 and 0·25 respectively, since DZ twins on average share half of their genes. An important assumption of the biometrical model is that twins experience common environment effects equally, therefore $r_c = 1$ for MZ and DZ alike. Non-shared environmental effects are by definition uncorrelated and also reflect measurement error including short-term fluctuations.

The different patterns of intra-pair correlations between MZ and DZ twins can then be used to indicate the presence of genetic and environmental influences. Current methods use structural equation modelling (SEM) as performed by LISREL or Mx (Neale & Cardon, 1992) to decide which combination of the four parameters (A, C, D, and E) provides the most parsimonious explanation of the observed pattern of MZ and DZ twin correlations (McGregor *et al.* 1998), while at the same time estimating the size of the genetic and environmental parameters. This task is made easier given that C and D are entirely negatively confounded in twin studies, so that only one can appear in a given model. Furthermore, detecting dominance is unlikely given the large sample sizes required. Finally, since it is inconceivable for complex behavioural traits to be measured without error, all models fitted include E. Initially, a fully saturated model (ACE or ADE) is tested to evaluate the statistical properties of the data. The effect of dropping one of the parameters is tested using a chi-square difference ($\Delta\chi^2$) for statistical significance.

In the current study, multivariate analyses were performed using a Cholesky decomposition to partition variances in Mx (Neale & Cardon, 1992). The Cholesky decomposition is a method of triangular decomposition where the first variable (depression) is assumed to be caused by a latent variable that can explain the variance in the remaining variables (phobic anxiety and somatic distress) (Page & Martin, 1998). The second variable (phobic anxiety) is assumed to be caused by a second latent variable that can explain variance in the second as well as remaining variable (somatic distress). In this way, the second latent variable is restrained from explaining variance in the first observed variable. This pattern continues until the final observed variable (somatic distress) is explained by a latent variable, which is constrained from explaining the variance in any of the previous observed variables. A Cholesky decomposition is specified for each latent source of variance A, D, C, or E, and as in the univariate case, ACE, ADE, AE, DE, CE, and E models are fitted to the data.

RESULTS

Hypotheses about threshold homogeneity

No differences in threshold liability distributions were observed within twin pairs and across zygosity groups for depression, phobic anxiety

Table 2. *Maximum likelihood estimates of correlations and 95% confidence intervals for liability to depression, phobic anxiety and somatic distress under model* H_{5th}

	Depression		Phobic anxiety		Somatic distress	
	r	95% CI	*r*	95% CI	*r*	95% CI
MZFF	0·33	0·22–0·42	0·39	0·28–0·50	0·25	0·13–0·36
MZMM	0·34	0·20–0·47	0·43	0·27–0·57	0·36	0·19–0·50
DZFF	0·07	−0·06 to 0·19	0·24	0·10–0·37	0·17	0·04–0·31
DZMM	0·23	0·05–0·39	0·19	−0·02 to 0·39	0·32	0·15–0·47
DZFM	0·27	0·10–0·43	0·28	0·06–0·47	0·26	0·08–0·42
DZMF	0·16	−0·04 to 0·34	0·16	−0·06 to 0·36	0·16	−0·04 to 0·35

MZ, Monozygotic; DZ, dizygotic; F, female; M, male.

and somatic distress. Constraining the threshold distributions to be equal in males and females resulted in a significant deterioration in fit for depression ($\Delta\chi^2_4 = 24{\cdot}70$), phobic anxiety ($\Delta\chi^2_4 = 65{\cdot}05$), and somatic distress ($\Delta\chi^2_4 = 39{\cdot}53$) when compared to a model of separate sex thresholds for each of the target variables. We also demonstrated that the observed sex differences in threshold distributions could then be accounted for by a single set of liability thresholds for males plus a displacement to account for the observed higher prevalencies in females for depression ($\Delta\chi^2_3 = 0{\cdot}94$, $\delta = 0{\cdot}19$), phobic anxiety ($\Delta\chi^2_3 = 0{\cdot}34$, $\delta = 0{\cdot}24$) and somatic distress ($\Delta\chi^2_3 = 1{\cdot}38$, $\delta = 0{\cdot}25$). This provided a very strong test of the Multifactorial Threshold Model, since it is far from obvious *a priori* that we would be able to predict so accurately the relative frequencies of males and females in the five categories with a single set of thresholds and a single displacement. We next tested the possibility that volunteering behaviour was correlated with psychiatric liability. If cooperation bias existed then we would have expected the threshold distributions to be different between complete and incomplete twin pairs (Neale & Eaves, 1993). No significant threshold liability differences were found between complete and incomplete twin pairs for depression ($\Delta\chi^2_{38} = 8{\cdot}31$), phobic anxiety ($\Delta\chi^2_{38} = 14{\cdot}30$), or somatic distress ($\Delta\chi^2_{38} = 8{\cdot}86$).

Estimating twin correlations

Twin pair polychoric correlations and their 95% confidence intervals for the three target variables based on MLE's using raw ordinal data methods are shown in Table 2. No significant heterogeneity was found between MZ male and MZ female correlations for any of the target variables, neither was there any significant heterogeneity between any of the same-sex and opposite-sex DZ groups for all of the target variables. Significant heterogeneity was found between MZ and DZ twin pair correlations for depression ($\Delta\chi^2_1 = 9{\cdot}34$) and phobic anxiety ($\Delta\chi^2_1 = 8{\cdot}03$) indicating familial aggregation due to genetic influence on these variables. No significant heterogeneity was found between MZ and DZ twins for somatic distress ($\Delta\chi^2_1 = 0{\cdot}79$), which suggests that familial aggregation for this variable may be explained by mainly shared environmental influence.

Univariate analysis

For each dimension, models were initially fitted separately for males and females, and then jointly to all four same-sex groups. We tested the heterogeneity of fit for models over sex by adding the separate log likelihood values for males and females and then subtracted this value from the log likelihood of the joint fit to males and females (Jardine & Martin, 1984). No significant heterogeneity between sexes was found for either the ACE or AE models. Therefore, univariate analyses were extended to include the data from opposite sex DZ twin pairs with results shown in Table 3.

The AE model for depression when compared to the best fitting saturated model (ADE) provided a good fit to the data ($\Delta\chi^2_1 = 0{\cdot}05$). Dropping the additive genetic variance from the ACE model caused a significant deterioration in fit ($\Delta\chi^2_1 = 9{\cdot}28$). A similar story was seen for phobic anxiety, for which the AE model was preferred ($\Delta\chi^2_1 = 0{\cdot}11$), and suggests that 41% of the variance is genetic. For somatic distress,

Table 3. *Univariate model fitting results using ordinal threshold methods*

	Proportion of variance								
	A	C	E	D	−2LL	df	$\Delta\chi^2$	Δdf	*P*
Depression	0·33	0·00	0·67	—	10720·59	7987	—	—	—
	0·30	—	0·67	0·03	10720·54	7987	—	—	—
	0·33	**—**	**0·67**	**—**	**10720·59**	**7988**	**0·05**	**1**	**NS**
	—	0·24	0·76	—	10729·87	7988	9·28	1	0·002
	—	—	1·00	—	10791·02	7989	70·44	2	0·000
Phobic anxiety	0·37	0·03	0·59	—	7968·50	7979	—	—	—
	0·41	—	0·59	0·00	7968·62	7979	—	—	—
	0·41	**—**	**0·59**	**—**	**7968·62**	**7980**	**0·11**	**1**	**NS**
	—	0·30	0·70	—	7976·54	7980	8·04	1	0·005
	—	—	1·00	—	8051·14	7981	82·64	2	0·000
Somatic distress	0·11	0·17	0·72	—	9563·28	7969	—	—	—
	0·32	—	0·68	0·00	9566·50	7969	—	—	—
	0·32	**—**	**0·68**	**—**	**9566·50**	**7970**	**3·22**	**1**	**NS**
	—	**0·25**	**0·75**	**—**	**9564·08**	**7970**	**0·79**	**1**	**NS**
	—	—	1·00	—	9624·57	7971	61·29	2	0·000

Preferred models are shown in boldtype.

Table 4. *Cholesky decomposition for depression, phobic anxiety and somatic distress based on all six zygosity groups* under model* H_{5th}

A	C	E	D	−2LL	df	$\Delta\chi^2$	Δdf	*P*
A	C	E		26000·29	15285	—	—	—
A		E	D	26002·17	15285	—	—	—
A		**E**		**26003·82**	**15291**	**3·53**	**6**	**NS**
	C	E		26015·20	15291	14·91	6	0·05
		E		26147·97	15297	147·68	12	0·001

*MZF + DZF + MZM + DZM + DZFM + DZMF twins.
Preferred models are shown in boldtype.

only the E ($\Delta\chi^2 = 61{\cdot}29$, $\Delta df = 2$) model departed significantly from the full ACE model, demonstrating that neither the AE nor CE models could be rejected as an explanation for familial aggregation. Since univariate point estimates did not allow us to choose between either a genetic or environmental model as the best explanation for familial aggregation underlying this variable, we turned to multivariate genetic analysis which has increased power to detect genetic and environmental effects by making use of all the covariance terms between variables.

Multivariate analysis

Multivariate genetic analysis was used to estimate the causes of genetic and environmental covariation between depression, phobic anxiety, and somatic distress. As in the univariate case, the heterogeneity of fit of models over sexes was assessed by adding the separate log-likelihoods for males and females and then subtracting this value from the log-likelihood of the joint fit to same-sex male and female data (Jardine & Martin, 1984). Homogeneity was found across sexes for the ACE, AE, and CE models. So, models were fitted to all zygosity groups including opposite sex DZ twin pairs. Table 4 shows model fitting results using a Cholesky decomposition which accounts for all the covariation between phenotypic target variables due to each latent source.

Dropping both the additive genetic and common environmental effects in the case of the E model (which hypothesizes no familial aggregation) was firmly rejected ($\Delta\chi^2_{12} = 147{\cdot}68$). Dropping only shared environmental effects (AE model) caused only a marginal deterioration in

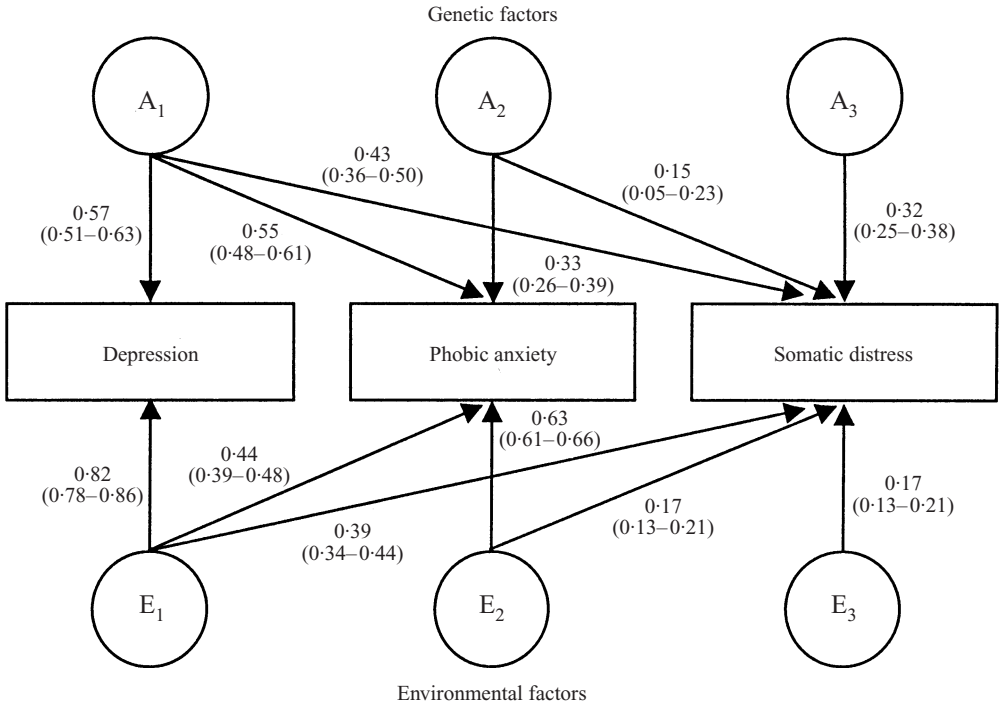

FIG. 1. Path diagram showing path coefficients from latent genetic and environmental influences (circles) to the measured phenotypes (squares) for male and female twin pairs combined.

fit ($\Delta\chi^2_6 = 3{\cdot}53$) indicating that familial aggregation could not be explained best by common environmental effects alone. However, dropping the additive genetic effects (CE model), led to a significant deterioration in fit when compared to the full ACE model ($\Delta\chi^2_6 = 14{\cdot}91$), indicating that familial aggregation for the three target variables can best be explained by additive genetic effects. Calculation of confidence intervals (CIs) for the genetic and environment parameters based on the current raw data methods proved too computationally demanding in Mx. We therefore estimated CIs based on models fitted to 6×6 polychoric correlation matrices for complete pairs only using maximum likelihood. In both cases the parameters were almost identical. We then tried to simplify the genetic and environmental structure by successively dropping parameters but all paths remained significant ($\alpha = 0{\cdot}05$) and were retained. The final model for all twin pairs is shown in Fig. 1.

A common genetic factor (A_1) accounts for 32% ($0{\cdot}57^2$) of the variance in depression scores, 30% ($0{\cdot}55^2$) for phobic anxiety and 18% ($0{\cdot}43^2$) for somatic distress scores. A second, independent genetic factor (A_2) accounts for 11% ($0{\cdot}33^2$) and 2% ($0{\cdot}15^2$) of the variance in phobic anxiety and somatic distress scores respectively. Finally, a third genetic factor (A_3) specific to somatic distress (not shared with measures of depression and phobic anxiety) accounts for 10% ($0{\cdot}32^2$) of the variance in somatic distress scores. Therefore, of the total additive genetic variance contributing to somatic distress, 33% ($10/(18+2+10)$) is specific to somatic distress and not shared with either depression or phobic anxiety.

Individual environmental variance also subsumes measurement errors and so it was expected that paths from the first, second, and third sources of latent non-shared environmental factors (E1, E2 and E3) to depression, phobic anxiety and somatic distress respectively would be large. A non-shared latent environmental factor (E1) accounted for 67% of the variance in depression, 19% for phobic anxiety and 15% for somatic distress. A second non-shared

environmental factor (E2) accounted for 40% and 3% of the variance for phobic anxiety and somatic distress respectively. Finally, a third non-shared environmental latent factor (E3) accounted for 50% of the variance in somatic distress scores. Thus, of the total specific environmental variance, 74% (50/(15+3+50)) is specific to somatic distress and not shared with depression and phobic anxiety.

DISCUSSION

The genetic aetiology of somatic distress is to a considerable extent distinct from other measures of psychological distress such as depression and phobic anxiety. Similarly, non-shared environmental factors influencing somatic distress are largely aetiologically distinct from the specific environmental influences leading to depression and phobic anxiety.

These findings are supported by previous research. Hickie *et al.* (1999*a*, *b*) using the Schedule of Fatigue and Anergia (SOFA - Community), which is a more precise measure of chronic fatigue, found that 44% of the genetic variance in chronic fatigue was not shared by other forms of psychological distress such as anxiety and depression. Kendler *et al.* (1995*b*), used an almost identical measure of somatic distress derived from factor analysis of the SCL and examined the self-report symptoms of panic–phobia and somatic distress in the large American Association of Retired Persons (AARP) volunteer twin sample. They estimated heritability for symptoms of somatic distress to be 49% for males and 36% for females. In the same study, which also used the population-based Virginia Twin Registry, the authors estimated heritability for somatic distress of 28% and 26% for males and females respectively. When the results were adjusted for measurement error and short-term fluctuation, heritability exceeded 50%. Furthermore, the remaining variance in somatic distress, as in the current study, could only be attributed to unique environmental effects that are unshared with co-twins.

Somatic distress disorders such as chronic fatigue and neurasthenia do not appear to be associated with either the characteristic sleep abnormalities (i.e. shortened REM sleep) (Moldofsky, 1993) or hypothalamic–pituitary–adrenal (HPA) axis changes encountered in at least some depressive subtypes (Demitrack *et al.* 1991). Chronic fatigue patients also have a wide range of minor and non-specific immunological changes (Lloyd *et al.* 1994), but of greater severity than encountered in patients with depressive disorders (Lloyd *et al.* 1992). Patients with fatigue states do not show a specific response to anti-depressant pharmacotherapy (Vercoulen *et al.* 1996; Hickie *et al.* 2000), and longitudinal data sets confirm that patients with neurasthenia tend to maintain their unique characteristics over time (Hickie *et al.* 1999*a*; Merikangas & Angst, 1994). These results have important therapeutic implications possibly requiring specific pharmacological and psychological interventions.

Limitations

A potential limitation was the possibility of systematic differences between those who returned *versus* those who did not return completed questionnaires. We tested for response/volunteer bias by examining the threshold distributions between complete and incomplete twin pairs. Sampling issues in a twin study are more complicated than in surveys of unrelated individuals since cooperation is required from pairs of individuals. It is likely that twins will be correlated in terms of their cooperation or volunteering, and may even consult together before choosing to cooperate. The important question is whether cooperation is correlated with the target variables – psychiatric symptomatology. If it is, then to the extent that the target variable aggregates in families, we should expect to find mean scores in single twins (where the co-twin has not cooperated) to be biased in the direction of non-cooperation, compared with the mean for complete pairs (Neale & Eaves, 1993). We found no significant threshold liability differences between complete and incomplete twin pairs for depression, phobic anxiety, or somatic distress, so we concluded that such bias is unimportant in our study.

We also found that within the total sample of respondents, the distribution of self-reported social class did not differ significantly between those responding and those not responding to the Feelings questionnaire. Our results were not surprising. If there were appreciable social class effects on reporting of symptoms, this would

have been detected as a shared environmental variance component ('C'), since twins reared together (both MZ and DZ) must share the effects of the social class in which they were reared. The fact that we were not able to detect any significant common environment effect for our symptoms in the multivariate analysis, argues against social class, or other aspects of the shared environment, having an appreciable impact on the aetiology of these symptoms.

Although self-report symptom scales are widely accepted as reflecting stable aspects of psychological function (Kendler *et al.* 1995*b*) we did not estimate or correct for the temporal instability of the symptoms, which sets an upper limit on the estimates of the genetic and common environment effects. Given the lower internal consistency of the 4-item somatic distress scale compared with the longer and more internally reliable depression and phobic anxiety dimensions, it is likely that the specific individual environment factor loading on somatic distress (E3) which accounts for 50% ($0{\cdot}71^2$) of total variance, is inflated by a large measurement error variance.

Another important limitation is that the items measuring depression, phobic anxiety and somatic distress did not constitute formal clinical diagnoses. Somatic distress may be aetiologically distinct from the more severe and disabling somatic disorder encountered in clinical settings (Hickie *et al.* 1995). However, dimensional models need not be disadvantageous nor should they be restricted to non-clinical samples. Zuckerman (1999) has argued that formal diagnoses while increasing diagnostic reliability do not necessarily contribute to diagnostic validity and instead favours the inclusion of dimensional in addition to formal categorical approaches. Regarding the validity of our somatic distress dimension, there was the possibility that among the subjects categorized as 'somatizers' some may have had genuine physical complaints. This is less likely given the young age of our sample. Furthermore, responses to the four items were sufficiently intercorrelated for a group factor to be extracted, and this factor correlated with the other dimensions of neurosis. The most parsimonious explanation is that there is a somatic distress syndrome, which increases the probability of endorsement of any physical symptom, rather than measuring a syndrome of 'genuine' physical complaint that just happens to encompass these four symptoms.

Many studies, but not all (see Kendler *et al.* 1987), which have investigated psychological and somatic distress using either the SCL-90 or DSSI/sAD scales have focused almost exclusively on smaller clinical samples with varying psychological and somatic complaints. An advantage of using very large non-clinical samples such as the ATR is that they can eliminate the possibility of confounding due to: (*i*) response sets associated with psychiatric out-patients (Dinning & Evans, 1977; Brophy *et al.* 1988); (*ii*) the effects of drug therapy on self-report validity, and (*iii*) 'spurious' covariation of symptoms (see Kendler *et al.* 1987) found in clinical samples whereby individuals with symptoms of both states such as anxiety and depression, are more likely to present for treatment. In addition, the use of population-based samples limits the possibility of bias associated with help-seeking behaviour (Prusoff & Klerman, 1974; Kendler *et al.* 1987).

With regard to the generality of the current findings, Kendler *et al.* (1995*a*) found that with the possible exception of panic–phobia, the level of common psychiatric symptoms and variability reported by twins are in fact similar to those found in the non-twin population. Apart from sex differences, explicit testing of the threshold liability distributions ensured twins were drawn from a homogenous sample. An implied assumption of the genetic models applied is that genetic factors that influence self-report psychiatric symptoms are largely stable in their effect throughout adulthood (Kendler *et al.* 1995*b*). However, gene expression can be quite variable over time, with certain genetic systems 'switching' 'on' and 'off' (see also Eaves *et al.* 1986; Kendler *et al.* 1995*b*) although this is likely to be less of a problem given the tight age range of our sample (18–28).

Conclusion

While there is now strong evidence that depression and phobic anxiety are influenced largely by the same genes, our results suggest that somatic distress, while also sharing common genetic influences with anxiety and phobic depression, is also influenced by distinct genetic and environmental influences.

APPENDIX 1

Questionnaire and item responses for the 'Feelings' section of the HLQ. This is a reduced form of the Delusion States Symptoms (DSSI/sAD) and Symptom Checklist-90 (SCL-90) scales

The following statements describe feelings people may have. For each statement please tick the box which best describes how you are feeling.
(1) Not at all (2) A little (3) A lot (4) Unbearably

		Males ($N = 1414$)				Females ($N = 2218$)			
		%				%			
Measure	Item	1	2	3	4	1	2	3	4
DSSI /S_{AD}									
Anxiety	1 Worried about everything	56	34	7	2	40	42	15	3
	3 Breathless or pounding heart	79	16	4	1	76	19	5	1
	4 So worked up cannot sit still	67	24	7	2	66	26	7	2
	7 Feelings of panic for no reason	88	11	1	1	82	15	2	1
	9 Pain or tension in neck/head	67	23	8	2	53	3	13	3
	11 Worry has kept me awake all night	69	24	6	2	61	28	8	3
	13 So anxious cannot make up mind re simple things	82	15	2	1	79	16	3	1
Depression	2 So miserable have difficulty in sleeping	76	18	5	2	67	23	8	3
	5 Depressed without knowing why	73	20	5	2	58	31	8	3
	6 Gone to bed not caring if I never awake	88	7	3	2	88	8	2	2
	8 Low in spirits sit for ages and do nothing	74	20	5	2	69	22	6	2
	10 Future seems hopeless	76	18	5	2	75	18	5	2
	12 Lost interest in just about everything	83	13	3	1	82	13	4	1
	14 So depressed thoughts of doing away with myself	93	5	1	1	93	5	1	1
SCL-90									
Anxiety	15 Felt nervous or shaky inside	74	22	3	1	68	26	5	1
	27 Felt tense or keyed up	60	31	8	1	51	36	10	2
	32 Felt fearful	88	10	2	1	80	16	3	1
	33 Had spells of terror or panic	95	5	1	0	91	7	2	1
Depression	17 Lost interest in sex, sex is unpleasurable	86	10	3	1	76	17	6	2
	20 Felt 'trapped' or 'caught'	85	11	3	1	82	13	3	1
	21 Blamed myself for things	65	58	6	1	57	34	8	2
	29 Felt that everything is an effort	73	23	4	1	70	24	4	2
	31 Felt worthless	82	14	3	1	77	16	5	2
Phobic anxiety	19 Felt afraid in open spaces or in street	95	4	1	0	94	5	1	0
	23 Afraid to travel on buses or trains	96	3	1	0	94	5	1	1
	24 Avoid certain things that frighten me	88	9	2	1	87	11	2	1
	28 Felt uneasy in crowds	82	14	4	1	83	12	4	1
	30 Felt nervous when left alone	89	9	2	0	78	17	4	1
Somatic distress	16 Felt faint or dizzy	88	10	1	1	77	20	3	1
	18 Had pains in the heart or chest	84	14	2	1	84	13	3	1
	22 Pains in the lower back	52	15	10	1	60	28	9	3
	25 Felt weak in parts of the body	74	21	4	1	73	22	4	1
Awakening	26 Have woken early in the morning	46	35	16	2	46	35	17	3

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