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The sources of co-morbidity between major depression and generalized anxiety disorder in a Swedish national twin sample

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ABSTRACT

Background. Prior studies report high levels of co-morbidity between major depression (MD) and generalized anxiety disorder (GAD) and suggest that these disorders are closely related genetically. The personality trait of neuroticism (N) is substantially correlated with risk for MD and GAD.

Method. Bivariate twin models were applied to lifetime diagnoses of modified DSM-IV diagnosis of MD and GAD obtained at personal interview in 1998–2003 with 37 296 twins from the population-based Swedish Twin Registry. A trivariate Cholesky model with N, MD and GAD was applied to a subset (23 280 members of same-sex twin pairs) who completed a self-report questionnaire assessing N in 1972–1973.

Results. In the best-fit bivariate model, the genetic correlation between MD and GAD was estimated at +1·00 in females and +0·74 in males. Individual-specific environmental factors were also shared between the two disorders with an estimated correlation of +0·59 in males and +0·36 in females. In the best-fit trivariate Cholesky model, genetic factors indexed by N impacted equally on risk for MD and GAD in males and females. However, in both sexes, genetic risk factors indexed by N contributed only around 25% to the genetic correlation between MD and GAD.

Conclusion. Genetic risk factors for lifetime MD and GAD are strongly correlated, with higher correlations in women than in men. Although genetic risk factors indexed by the personality trait of N contribute substantially to risk for both MD and GAD, the majority of genetic covariance between the two disorders results from factors not shared with N.

INTRODUCTION

Generalized anxiety disorder (GAD) and major depression (MD) are highly co-morbid in both clinical and epidemiological samples (Gorwood, 2004). The relative contribution of genetic and environmental factors to this co-morbidity has been examined in a series of population-based twin studies (Gorwood, 2004). The first such study was conducted in 1033 pairs of personally interviewed female–female twins from the Virginia Twin Registry (VTR) (Kendler *et al.* 1992). Using a range of definitions of GAD, the genetic correlation between lifetime GAD and lifetime MD was consistently estimated at unity. Thus, from a genetic perspective, MD and GAD seemed to be the same disorder. No shared environmental effects were detected for either disorder and the correlation in individual-specific environmental effects varied across definitions of GAD from +0·19 to +0·51. These results suggested that the reason why individuals at

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high risk would develop MD *versus* GAD was entirely a result of their environmental experiences.

The second study to examine the sources of co-morbidity between MD and GAD was conducted using lifetime diagnoses obtained by a self-report questionnaire from 486 male and female twin pairs obtained from the Swedish Twin Registry (Roy *et al.* 1995). Half of the sample were randomly selected from the registry and half were ascertained though the Swedish Psychiatric Twin Registry so as to contain a twin hospitalized for unipolar or bipolar affective illness. No evidence was found for shared environmental effects on GAD or MD, and the genetic and unique environmental correlations between them were estimated at 1·00 and +0·28 respectively. No evidence was found for sex effects on parameter estimates.

The third study to explore this question examined the 1-year prevalence of MD and GAD in a later wave of female–female twin pairs from the same female twin cohort from the VTR noted above (Kendler, 1996). Again, the genetic correlation between the two disorders was estimated at unity, with the environmental correlation varying widely (from zero to +0·70) depending on the definition of GAD used.

It is also of importance to understand the sources of the co-morbidity between neuroticism (N) and MD. Of particular interest is the personality trait of N, which has been shown to be a strong risk factor for both MD (e.g. Hirschfeld *et al.* 1989; Boyce *et al.* 1991; Kendler *et al.* 1993) and GAD (Hettema *et al.* 2004). In the VTR, levels of N explained about 40% of the co-morbidity between MD and GAD (Khan *et al.* 2005) and a substantial proportion of this effect was due to genetic factors shared between the personality trait and the two disorders (Hettema *et al.* 2006).

In this paper, we examine MD, GAD and N in a large sample of twins from the population-based Swedish Twin Register. An unusual feature of this sample is that personality was assessed approximately 25 years before the interview-based assessment of lifetime history of MD and GAD. Our analyses had two major goals. First, using a bivariate twin design, we aimed to determine the sources of co-morbidity between MD and GAD. In particular, we sought to replicate prior evidence for a high genetic correlation between MD and GAD. Our sample size is large enough to clarify, for the first time, whether the genetic correlation between these two disorders is the same in men and women. Second, using a trivariate twin design, we examined the degree to which the co-morbidity between MD and GAD could be explained by genetic and environmental risk factors that are in common with N.

METHOD

Sample

The sample comes from the Swedish Twin Registry, which contains a nearly complete registration of all twin births in Sweden. In 1972–1973, a questionnaire was sent to all same-sex twin pairs born in 1926–1958. The questionnaire contained nine items selected from the N scale of the short form of the Eysenck Personality Inventory (EPI Form B; Eysenck & Eysenck, 1964; Floderus-Myrhed *et al.* 1980).

The Screening Across the Lifespan Twin (SALT) study completed telephone interviews between March 1998 and January 2003 with all cooperative members of the Registry born in or before 1958 who were alive at the time of contact, obtaining a 74% response rate. The present analyses excluded those (i) interviewed by proxy, (ii) who terminated the interview prior to, or were improperly skipped out of, the MD and GAD sections, and (iii) members of pairs with uncertain zygosity. According to standard Swedish practice, a letter about the study was sent before the telephone call, and informed verbal consent was obtained prior to interview. This project was approved by the Swedish Data Inspection Authority, the Ethics Committee of the Karolinska Institute, and the Institutional Review Board of the University of Southern California. As detailed elsewhere (Lichtenstein *et al.* 2002), zygosity was assigned using standard self-report items and, when validated against biological markers, was found to be 95–99% accurate.

The psychiatric portion of the SALT interview used the computerized Composite International Diagnostic Interview–Short Form (CIDI-SF) adapted from its original design for 12-month prevalence to assess lifetime

prevalence of DSM-IV disorders (APA, 1994; Kessler *et al.* 1998). In the CIDI-SF, the evaluation of MD was shortened by the elimination of criteria A5 (psychomotor agitation/retardation) and C (distress or impairment), and the simplification of criteria A3 (eliminating loss/gain of appetite, inquiring only about weight changes) and A4 (eliminating hypersomnia). The CIDI-SF version adapted for this study contained a skip-out for individuals who, when asked about episodes of sad mood in the last year, volunteered that they were taking antidepressants. Such individuals were assumed to be positive for a history of MD but were unlikely to have manifested symptoms in the past year due to treatment. Because of an oversight, this skip-out was not eliminated when the CIDI-SF was adapted for lifetime prevalence.

In validating the CIDI-SF criteria for MD against 1-year prevalence data with the full CIDI, Kessler and Mroczek (personal communication, 22 February 1994) recommend using a cut-off of four out of eight criteria. We simulated the CIDI-SF assessment of MD in our sample of 7521 personally interviewed twins from the VTR, where we had a complete set of items for DSM-III-R adapted from the Structured Clinical Interview for DSM-IV (SCID; Spitzer & Williams, 1985). Agreement with the full criteria also maximized using a cut-off of four CIDI-SF criteria ($\kappa = +0{\cdot}90 \pm 0{\cdot}01$).

The sample used in this report contained 160 twins who skipped out of the section because they volunteered a history of antidepressant usage. We assessed whether a history of 'taking antidepressants' was a valid substitute for a diagnosis of MD by examining risk for MD in co-twins of twins with (i) neither a diagnosis of MD nor a history of antidepressant usage, (ii) a diagnosis of MD, and (iii) a history of antidepressant usage. As detailed elsewhere (Kendler *et al.* 2006*a*), groups II and III differed significantly from group I but not from each other. Therefore, we considered as affected: twins who either met the criteria for MD or volunteered that they were taking or had taken antidepressants.

To meet criteria for what we call 'narrow' GAD in the CIDI-SF, an individual had to report a period of 6 months or more of excess worry and anxiety, where they either 'worried about things that were not likely to happen' or 'worried about things that were not really serious' and had to report 'different worries on your mind at the same time'. They also had to endorse at least three of five symptoms which included all of the C criteria for GAD in DSM-IV with the exception of C3 ('difficulty concentrating or mind going blank') (APA, 1994). As with MD, the CIDI-SF did not include the 'stress or impairment' criterion for GAD. The CIDI-SF also did not implement criterion F for GAD, in which GAD would not be diagnosed if the entire episode occurred exclusively during a mood disorder.

Using this narrow definition of GAD as a dichotomous category resulted in unstable estimates especially in male twins. Therefore, we also created a 'broad' category of GAD. These individuals meet the same 'worry' criteria noted above, but needed only 1 month or more of excessive worry and had to endorse one or more of the five symptomatic criteria. For all the analyses reported here, GAD was operationalized as a three-category variable: unaffected, broad GAD, and narrow GAD. In all of the five zygosity groups, tests for the multiple threshold model were non-significant ($p > 0{\cdot}10$), indicating that these three categories could be conceptualized as differing levels of severity on the same continuum of liability.

The sample used for the bivariate analyses of MD and GAD included 37 296 individual twins from 26 770 pairs. All five twin zygosity groups [male monozygotic (MZ), female MZ, male dizygotic (DZ), female DZ, and opposite sex DZ] were represented. These pairs could be subdivided into 14 806 with complete information from both twins, 11 534 pairs with complete information on one twin and incomplete or missing information on the co-twin, and 430 pairs with incomplete information on both twins.

The sample used for the trivariate analyses, including MD, GAD and N analyses, included 23 280 individual twins from 14 029 same-sex pairs. These pairs could be subdivided into 7522 with complete information from both twins, 5219 pairs with complete information on one twin and incomplete or missing information on the co-twin, and 1288 pairs with incomplete information on both twins.

Statistical analysis

Bivariate analyses of MD and GAD

The goal of our first analysis was to decompose the covariance in liability to MD and GAD into its genetic and environmental components. We assume that twin resemblance arises from two latent factors: (i) additive genes (A), contributing twice as much to the MZ as to the DZ twin correlation, and (ii) shared or 'common' environment (C), which contributes equally to the correlation in MZ and DZ twins. In addition to 'shared' or 'common' environment, the model also contains individual-specific environment (E), which reflects measurement error and those environmental experiences that make members of a twin pair different in their liability.

Using the software package Mx (Neale *et al.* 2003), we fit models by the method of maximum likelihood to data from all individual twins containing even partial information. This method reduces the impact of cooperation bias and is a binary data maximum likelihood application of the 'missing at random' principle expounded by Little and Rubin (2002). Because prevalence rates changed substantially as a function of age in this sample, our calculation of tetrachoric correlations and model-fitting included an age-dependent threshold that 'subtracted out' the twin resemblance due to their perfect correlation for year of birth.

Twice the difference in log-likelihood between any two nested models yields a statistic that is asymptotically distributed as χ^2 with degrees of freedom equal to the difference in their number of parameters. We used Akaike's information criterion (AIC; Akaike, 1987; Williams & Holahan, 1994) for model selection. The lower its value, the better is the balance between explanatory power and parsimony.

Analyzing all five twin-zygosity groups, including opposite-sex DZ pairs, enables us to examine two distinct sex effects. The quantitative question asks whether the magnitude of genetic effects on MD and GAD is the same in males and females. The qualitative question inquires whether the genetic risk factors for MD or GAD in men and women are the same. The latter question involves the estimation of the parameter r_g, the correlation in the additive genetic effects on the liability to MD in males and females. If r_g, or the genetic correlation, is zero or one, then the genetic factors that influence disease risk in males and females are, respectively, entirely unrelated or identical.

In these bivariate analyses of GAD and MD, we are also able to estimate correlations in the genetic and environmental risk factors for MD and GAD. For example, a genetic correlation of unity between the two disorders means that the same genetic risk factors contribute to risk for the two disorders. An individual-specific environmental correlation of zero would mean that the environmental risk factors for MD and GAD were completely independent of one another.

Trivariate analyses of N, MD and GAD

In the trivariate analyses of N, MD and GAD, we used a Cholesky decomposition because we had an a priori set of 'directional' hypotheses. As depicted in Fig. 1, we were interested in the structure of genetic risk factors for these three phenotypes. In this model, the first or A_1 factor indexes genes that impact on N, MD and GAD through paths p_1, p_2 and p_3 respectively. The second or A_2 factor reflects genes that impact only on MD and GAD through paths p_4 and p_5 respectively. The third or A_3 factor indexes genes that impact only on GAD via path p_6. By using the rules of path tracing, the total genetic covariance between MD and GAD can be broken down into two components: a pathway that includes N (the product of paths p_2 and p_3) and a pathway that is independent of N (the product of paths p_4 and p_5). We are particularly interested in the proportion of total genetic covariance between MD and GAD that is indexed by N. This is equal to: $(p_2 \times p_3)/[(p_2 \times p_3) + (p_4 \times p_5)]$.

Entirely parallel calculations can be made for the environmental contributions to N, MD and GAD. Thus we are also interested in the proportion of total environmental covariance between MD and GAD that is indexed by N. For individual specific environment, this is equal to: $(p_{14} \times p_{15})/[(p_{14} \times p_{15}) + (p_{16} \times p_{17})]$.

RESULTS

Descriptive statistics

The lifetime prevalences of narrow GAD, broad GAD and MD in the sample were, respectively, 2·2, 4·8 and 14·0% in males and 5·0,

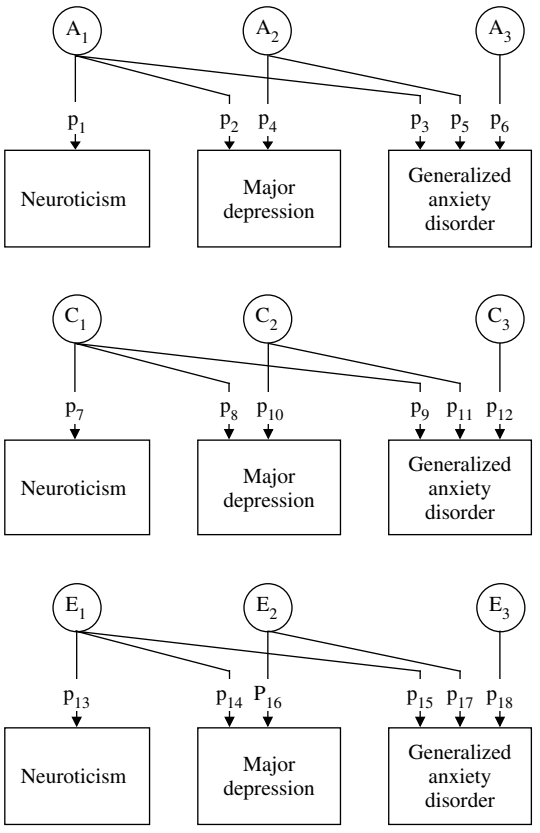

FIG. 1. Trivariate Cholesky decomposition for neuroticism, major depression (MD) and generalized anxiety disorder (GAD). A, additive genetic effects; C, shared (or common) environmental effects; E, individual-specific environmental effects; p, path. Subscripts 1, 2 and 3 refer to factors that are, respectively, shared by all three traits, specific to MD and GAD, and specific to only GAD.

8·8 and 27·0% in females. The odds ratios (and 95% confidence intervals) between MD and, respectively, narrow and broad GAD were 11·5 (9·6–13·9) and 18·4 (13·7–24·7) in males and 7·4 (6·4–8·5) and 9·2 (7·7–11·2) in females. Examining broad GAD and controlling for age and sex, the mean ± S.E.M. N scores for unaffected individuals, individuals with MD only, GAD only, and both MD and GAD were 2·52 ± 0·02, 3·35 ± 0·04, 3·82 ± 0·10 and 3·98 ± 0·07 respectively ($F = 369{\cdot}4$, df = 32 0267, $p < 0{\cdot}0001$).

Model fitting: MD and GAD

Results of model fitting for MD and GAD are outlined in Table 1. We began with a full model (model I) that included quantitative sex effects and the four genetic correlations outlined above. This model had a −2 log likelihood value of 59 956·6 with df = 83 613. In model II, we set to zero all parameters related to shared environment, which resulted in a substantial improvement in the AIC. In model III, we set equal all parameter estimates in males and females. The model fit deteriorated substantially. In models IV–VII, we individually set each of the genetic correlations to unity. The AIC improved when we constrained the MD–GAD genetic correlation to unity in females (model V) but not in males (model IV) and when we set to unity the genetic correlation between males and females for GAD (model VI) but not for MD (model VII). In model VIII, we combined the constraints from models V and VI, which, as expected, further improved the AIC. In models IX and X, we constrained to unity the environmental correlation between MD and GAD in males and females respectively. Both models fit quite poorly.

The parameter estimates for the best-fit model VIII are depicted in Fig. 2. Five results are noteworthy. First, as seen previously in this sample (Kendler *et al.* 2006*a*), the heritability of MD is greater in women than in men. Second, the pattern was reversed for GAD, with heritability estimates slightly higher in males than in females. Third, in females the genetic correlation between MD and GAD was estimated at unity while in males it was lower, here estimated at +0·74. Fourth, the environmental correlation between MD and GAD was moderately higher in males (+0·59) than in females (+0·36). Fifth, as found previously in this sample, the genetic correlation for MD in males and females was substantially lower than unity, here estimated at +0·64 (Kendler *et al.* 2006*a*). Finally, by contrast, the genetic correlation for GAD in males and females was estimated to equal unity.

N, MD and GAD

Here we fitted a trivariate Cholesky model as illustrated in Fig. 1. We began with a full model (model I) that had a −2 log likelihood value of 12 3281·3 with df = 65 766. In model II, we set to zero all the shared environmental parameters. The change in χ^2 was only 1·9 units for df = 12 so the AIC improved substantially to −22·1. In model III, we constrained all parameters to

Table 1. *Results of bivariate model-fitting for major depression (MD) and generalized anxiety disorder (GAD)*

							r_a				r_e					
	MD			GAD			MD–GAD		Sex		MD–GAD		Quantitative			
Model	A	C	E	A	C	E	M	F	GAD	MD	M	F	sex effects	χ^2	df	AIC
I	+	+	+	+	+	+	+	+	+	+	+	+	+	—	—	—
II	+	−	+	+	−	+	+	+	+	+	+	+	+	0·0	6	−12·0
III	+	−	+	+	−	+	+	+	+	+	+	+	−	21·1	10	+1·1
IV	+	−	+	+	−	+	1	+	+	+	+	+	+	4·5	7	−9·5
V	+	−	+	+	−	+	+	1	+	+	+	+	+	0·4	7	−13·6
VI	+	−	+	+	−	+	+	+	1	+	+	+	+	0·0	7	−14·0
VII	+	−	+	+	−	+	+	+	+	1	+	+	+	4·9	7	−9·1
VIII	+	−	+	+	−	+	+	1	1	+	+	+	+	0·4	8	−15·6
IX	+	−	+	+	−	+	+	1	1	+	1	+	+	125·7	9	+107·7
X	+	−	+	+	−	+	+	1	1	+	+	1	+	104·0	9	+86·0

+, Parameter estimated; −, parameter set to zero; 1, parameter set to unity; A, additive genetic effects; C, common or shared environmental effects; E, individual-specific environmental effects; r_a, additive genetic correlation, r_e, individual-specific environmental correlation; M, male; F, female; df, degrees of freedom; AIC, Akaike's information criterion (Akaike, 1987).

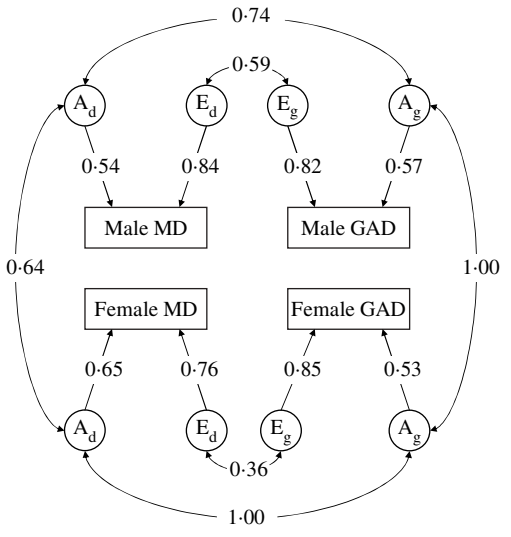

FIG. 2. Parameters for the best-fit model for the bivariate twin analysis of major depression (MD) and generalized anxiety disorder (GAD). A, additive genetic effects; E, individual specific environmental effects. Subscripts d and g refer to MD and GAD respectively.

equality across the sexes. Compared to model II, this resulted in a large increase in χ^2 (30·8 units for df = 9) and a resulting deterioration in AIC (+12·8). Examining the parameter estimates from this model, only two paths had estimates of below 0·15 in both sexes – paths p_{14} and p_{15} in Fig. 1. However, compared to model II, constraining those paths to zero resulted in a large increase in χ^2 (18·9 units for df = 4) and deterioration in the AIC (+10·9). One remaining parameter was estimated at very close to zero (−0·01) in females – path p6. Our final model set that path to zero and, compared to model II, found no change in χ^2 and an improvement of AIC to –2·0.

Parameter estimates for the best-fit model are shown in Fig. 3. Three results are of worthy of comment. First, reassuringly, the broad pattern of findings for MD and GAD are similar to those found with the entire twin sample and depicted in Fig. 2. For example, the genetic correlation of 0·74 and 1·00 between MD and GAD found in the entire sample in males and females respectively is paralleled in these analyses by the absence of GAD-specific genes (path p_6) for females but not males. Furthermore, as in the full sample, the total heritability for MD in this subsample is higher in females than in males with similar estimates (41% and 29% respectively).

Second, N did not account for all of the genetic or environmental contributions to co-morbidity between MD and GAD. In both males and females, the best-fit model indicated that there were genetic factors (path 5) and unique environmental factors (path 17) that were shared between MD and GAD but not shared with N. As outlined above, these estimates permit us to quantify the contribution of N to the co-morbidity between MD and GAD.

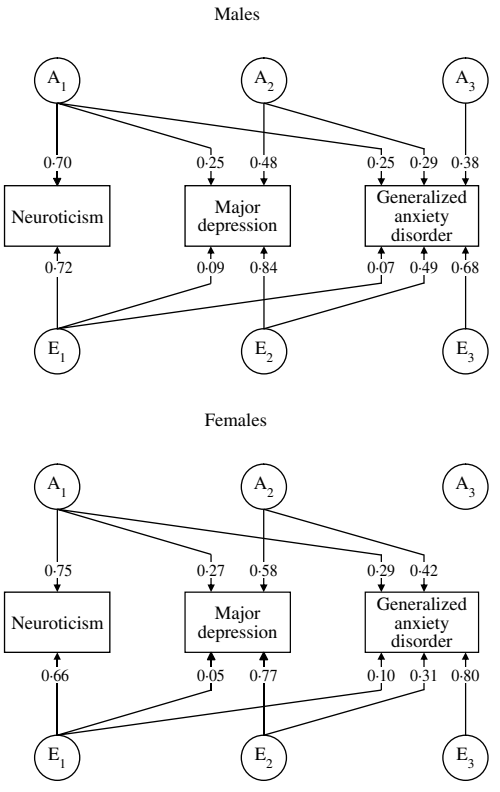

FIG. 3. Parameters for the best-fit model for the trivariate Cholesky decomposition for neuroticism, major depression (MD) and generalized anxiety disorder (GAD). A, additive genetic effects; E, individual specific environmental effects. Subscripts 1, 2 and 3 refer to factors that are, respectively, shared by all three traits, specific to MD and GAD, and specific to only GAD.

The genetic contribution to MD–GAD co-morbidity can be broken down into one set of genetic risk factors shared with N (the product of paths p_2 and p_3) and another set not shared with N (the product of paths p_4 and p_5). In males, the total genetic correlation between MD and GAD is +0·26, of which only +0·06 (or 23%) is shared with N. In females, the total genetic correlation between MD and GAD is +0·32, of which +0·08 (or 25%) is shared with N. Similar calculations can be made for the unique environmental contributions to MD–GAD co-morbidity. In males, environmental risk factors shared with N contribute only about 1% to the total unique environmental correlation between MD and GAD. In females, the parallel figure is about 2%.

Third, these results permit us to determine the degree to which genetic risk factors for N contribute to the etiology of MD (via p_2) and GAD (via p_3). In both males and females, these two paths are very similar in magnitude. Parallel comparisons can be made for unique environmental effects (comparing paths p_{14} and p_{15}). In both males and females, these two paths are small. They are similar in magnitude in males, but in females the path to GAD is twice as large as the path to MD.

DISCUSSION

We sought to address two major questions in this paper. What is the origin of the high levels of co-morbidity between MD and GAD that have been seen in this and previous epidemiological samples? In accord with previous studies (Kendler *et al.* 1992; Roy *et al.* 1995; Kendler, 1996), we found very high genetic correlations between MD and GAD and individual-specific correlations of a more modest nature. These results provide further evidence that the genetic substrates for MD and GAD are closely interrelated.

We also explored possible sex differences in the sources of MD–GAD co-morbidity. Of the three prior studies of this issue, two were in female–female twins only (Kendler *et al.* 1992; Kendler, 1996) and one was conducted in a relatively small twin sample that detected no sex effects but had limited power (Roy *et al.* 1995). In the present bivariate analyses of MD and GAD, we could confidently reject a model constraining parameters to be equal across the sexes. Of particular interest, while the genetic correlation between MD and GAD was estimated at unity in females, in males the value, albeit still high, was lower, at +0·74. Also of note, the pattern of individual-specific environmental correlation between MD and GAD was the reverse – higher in males than in females. Although the best-fit model (Fig. 2) predicted relatively similar phenotypic correlations between MD and GAD in men (+0·63) and women (+0·58), in men, environmental factors are responsible for a substantially higher proportion of that correlation (65%) than in women (40%).

What are the nosological implications of the increasingly compelling evidence for the close

genetic relationship between MD and GAD? In DSM-IV, these two disorders are contained within two different categories: mood and anxiety disorders. The introduction to DSM-IV states that the major subdivisions of the manual are 'based on shared phenomenological features' (APA, 1994, p. 10). In the history of biology, classification of species began with surface similarities (e.g. creatures that flew, that swam in the ocean, etc.), but is now based almost exclusively on shared descent that can increasingly be quantified by DNA sequence analysis. In what might be a roughly parallel move, should psychiatry progress from a classification system based on shared phenomenology to one founded on shared etiology? If such a system is implemented, then at least from the perspective of genetic risk factors, MD and GAD should be placed within the same diagnostic category.

The second question we addressed in these analyses was the degree to which the co-morbidity between MD and GAD could be explained by genetic and environmental risk factors that are in common with the personality trait of N. This is a relevant question because of prior evidence of a substantial genetic relationship between N and MD (Kendler *et al.* 1993, 2006*b*) and N and GAD (Mackintosh *et al.* 2006) as well as findings that, at a phenotypic level, N can explain a substantial proportion of the observed co-morbidity between MD and GAD (Khan *et al.* 2005). Our results were somewhat disappointing. Consistent with prior findings, genes that impacted on levels of N also had a significant impact on liability to both MD and GAD. However, genes shared with N accounted for only a modest proportion of the genetic co-morbidity between MD and GAD. Put another way, in both men and women, the preponderance of the genetic risk factors shared between MD and GAD were *not* shared with N. For environmental risk factors, these figures were much higher. About 98% of the environmental risk factors shared between MD and GAD were *not* shared with N.

We are aware of only one prior study that provides roughly comparable findings. In the VTR, Hettema *et al.* (2006) examined the relationship between N and six different internalizing disorders. Although the model differed in some ways from the one used in this report, they found that between 45% and 50% of the genetic risk factors common to MD and GAD were also shared with N. Several possible factors might explain these differences. In particular, in the report by Hettema *et al.* (2006), N was measured relatively close in time to the personal interviews at which the lifetime history of MD and GAD were assessed. By contrast, in this study, these two measurements were separated by about 25 years, ruling out the possibility that state effects or correlated errors of measurement would bias upward the association between N and MD and/or GAD.

The construct of N has recently been criticized by Ormel *et al.* (2004). We agree that N is, and was designed to be, a broad and non-specific index of emotionality. However, it remains of value to show, especially with our longitudinal design, the sources of the association between N and MD and GAD. Our results enable us to understand the relationship between two different kinds of scientific 'constructs' – personality and psychiatric disorders – each with their own literatures and perspectives.

These results have two potential implications for molecular genetic studies. First, they suggest that for association and linkage analyses, studies of MD should be able to increase power by counting individuals with GAD as 'affected' and vice versa. Second, while N has been an increasing focus of linkage studies in recent years (e.g. Fullerton *et al.* 2003; Nash *et al.* 2004; Neale *et al.* 2005), our results suggest that genes found in this way will not index the majority of genetic risk factors shared between MD and GAD.

Our findings are broadly consistent with a recent study by Mackintosh *et al.* (2006) that examined GAD and N in this same Swedish sample. Using a three-category variable for GAD that differed somewhat from the one implemented here, they reported bivariate analyses between GAD and the personality trait of N in same-sex male and female twin pairs. The level of heritability for GAD and the degree of sharing of genetic and environmental risk factors between N and GAD were very similar to those reported here. The only difference of consequence between the two analyses was that Mackintosh *et al.* did not find evidence for quantitative sex effects.

Limitations

These results should be interpreted in the context of five major methodological limitations. First, no questionnaire data were available on opposite-sex DZ twins so we were unable to examine qualitative sex effects in our trivariate twin modeling. Second, our assessment of N was based on a modest number of items empirically selected from the EPI (Eysenck & Eysenck, 1964), which later evolved into the Eysenck Personality Questionnaire (EPQ; Eysenck & Eysenck, 1975). Therefore, the construct of N that we here used will not be identical to scales for N obtained from other personality instruments. Third, our diagnoses of MD and GAD were based on a slightly shortened version of DSM-IV criteria. Fourth, because of problems with low prevalence, our analyses of GAD are based on a three-category variable of unaffected, broad and narrow GAD. Fifth, MD, GAD and N were, in this sample, obtained on only one occasion. The effects of measurement error and individual-specific environmental effects are therefore confounded.

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DECLARATION OF INTEREST

None.

REFERENCES

Akaike, H. (1987). Factor analysis and AIC. *Psychometrika* **52**, 317–332.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn). American Psychiatric Association: Washington, DC.

Boyce, P., Parker, G., Barnett, B., Cooney, M. & Smith, F. (1991). Personality as a vulnerability factor to depression. *British Journal of Psychiatry* **159**, 106–114.

Eysenck, H. J. & Eysenck, S. B. G. (1964). *Manual of the Eysenck Personality Inventory*. London University Press: London.

Eysenck, H. J. & Eysenck, S. B. G. (1975). *Manual of the Eysenck Personality Questionnaire*. Hodder and Stoughton: London.

Floderus-Myrhed, B., Pedersen, N. & Rasmuson, I. (1980). Assessment of heritability for personality, based on a short-form of the Eysenck Personality Inventory: a study of 12,898 twin pairs. *Behavior Genetics* **10**, 153–162.

Fullerton, J., Cubin, M., Tiwari, H., Wang, C., Bomhra, A., Davidson, S., Miller, S., Fairburn, C., Goodwin, G., Neale, M. C., Fiddy, S., Mott, R., Allison, D. B. & Flint, J. (2003). Linkage analysis of extremely discordant and concordant sibling pairs identifies quantitative-trait loci that influence variation in the human personality trait neuroticism. *American Journal of Human Genetics* **72**, 879–890.

Gorwood, P. (2004). Generalized anxiety disorder and major depressive disorder comorbidity: an example of genetic pleiotropy? *European Psychiatry* **19**, 27–33.

Hettema, J. M., Neale, M. C., Myers, J., Prescott, C. A. & Kendler, K. S. (2006). A population-based twin study of the relationship between neuroticism and internalizing disorders. *American Journal of Psychiatry* **163**, 857–864.

Hettema, J. M., Prescott, C. A. & Kendler, K. S. (2004). Genetic and environmental sources of covariation between generalized anxiety disorder and neuroticism. *American Journal of Psychiatry* **161**, 1581–1587.

Hirschfeld, R. M. A., Klerman, G. L., Lavori, P. W., Keller, M. B., Griffith, P. & Coryell, W. (1989). Premorbid personality assessments of first onset of major depression. *Archives of General Psychiatry* **46**, 345–350.

Kendler, K. S. (1996). Major depression and generalised anxiety disorder. Same genes, (partly) different environments – revisited. *British Journal of Psychiatry* **168** (Suppl. 30), 68–75.

Kendler, K. S., Gatz, M., Gardner, C. & Pedersen, N. (2006*a*). A Swedish national twin study of lifetime major depression. *American Journal of Psychiatry* **163**, 109–114.

Kendler, K. S., Gatz, M., Gardner, C. & Pedersen, N. L. (2006*b*). Personality and major depression: a Swedish longitudinal, population-based twin study. *Archives of General Psychiatry* **63**, 1113–1120.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C. & Eaves, L. J. (1992). Major depression and generalized anxiety disorder. Same genes, (partly) different environments? *Archives of General Psychiatry* **49**, 716–722.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C. & Eaves, L. J. (1993). A longitudinal twin study of personality and major depression in women. *Archives of General Psychiatry* **50**, 853–862.

Kessler, R. C., Andrews, G., Mroczek, D. K., Ustun, B. & Wittchen, H.-U. (1998). The World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF). *International Journal of Methods in Psychiatric Research* **7**, 171–185.

Khan, A. A., Jacobson, K. C., Gardner, C. O., Prescott, C. A. & Kendler, K. S. (2005). Personality and comorbidity of common psychiatric disorders. *British Journal of Psychiatry* **186**, 190–196.

Lichtenstein, P., de Faire, U., Floderus, B., Svartengren, M., Svedberg, P. & Pedersen, N. L. (2002). The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *Journal of Internal Medicine* **252**, 184–205.

Little, R. J. A. & Rubin, D. B. (2002). *Statistical Analysis with Missing Data*. John Wiley & Sons: New York.

Mackintosh, M., Gatz, M., Wetherell, J. & Pedersen, N. (2006). A twin study of lifetime generalized anxiety disorder (GAD) in older adults: genetic and environmental influences shared by neuroticism and GAD. *Twin Research and Human Genetics* **9**, 30–37.

Nash, M. W., Huezo-Diaz, P., Sterne, A., Purcell, S., Hoda, F., Cherny, S. S., Abecasis, G. R., Prince, M., Gray, J. A., Ball, D., Asherson, P., Mann, A., Goldberg, D., McGuffin, P., Farmer, A., Plomin, R., Craig, I. W. & Sham, P. C. (2004). Genome-wide linkage analysis of a composite index of neuroticism and mood-related scales in extreme selected sibships. *Human Molecular Genetics* **13**, 2173–2182.

Neale, B. M., Sullivan, P. F. & Kendler, K. S. (2005). A genome scan of neuroticism in nicotine dependent smokers. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **132B**, 65–69.

Neale, M. C., Boker, S. M., Xie, G. & Maes, H. H. (2003). *Mx: Statistical Modeling*. Department of Psychiatry, Virginia Commonwealth University Medical School: Box 980126, Richmond, VA 23298.

Ormel, J., Rosmalen, J. & Farmer, A. (2004). Neuroticism: a non-informative marker of vulnerability to psychopathology. *Social Psychiatry and Psychiatric Epidemiology* **39**, 906–912.

Roy, M. A., Neale, M. C., Pedersen, N. L., Mathe, A. A. & Kendler, K. S. (1995). A twin study of generalized anxiety disorder and major depression. *Psychological Medicine* **25**, 1037–1049.

Spitzer, R. L. & Williams, J. B. W. (1985). *Structured Clinical Interview for DSM-III-R* (*SCID*). Biometrics Research Department, New York State Psychiatric Institute: New York.

Williams, L. & Holahan, P. (1994). Parsimony-based fit indices for multiple-indicator models: do they work? *Structural Equation Modeling* **1**, 161–189.