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Neuroticism, major depression and gender: a population-based twin study

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ABSTRACT

Background. A portion of the genetic risk factors for the personality trait neuroticism (N) may also increase risk for major depression (MD). Females have both higher levels of N and higher rates of MD than males, suggesting that these traits may be more genetically correlated in females.

Methods. Structured interviews, including a lifetime assessment for MD by DSM-III-R criteria, were administered to 863 male–male MZ (monozygotic), 649 male–male DZ (dizygotic), 506 female–female MZ, 345 female–female DZ, and 1408 opposite-sex twin pairs. N was assessed using the short-form of the Eysenck Personality Questionnaire. A sex-limited Cholesky model was fitted which allowed us to decompose into additive genetic, common environmental, and individual-specific environmental components two main classes of correlations: within-sex between-variable and between-sex within-variable.

Results. Our best-fitting model contained only additive genetic and individual-specific environmental factors for both N and MD. The within-sex genetic correlations between N and MD were estimated at +0·68 in men and +0·49 in women. This model fitted only slightly better than one in which the N–MD within-sex genetic correlation was constrained to be equal across the sexes, and estimated at +0·55. There may be sex-specific genes influencing both N and MD.

Conclusion. Our best-fitting model failed to establish a significant sex difference in the genetic correlation between N and MD. These results, as well as evidence for sex-specific genetic factors for both traits, have implications for the diagnosis, classification, and treatment of the affective disorders, and molecular genetic approaches to the study of these traits.

INTRODUCTION

Early writers such as Kraepelin, Kretschmer and Schneider observed and described personality configurations associated with more severe psychopathology (Kraepelin, 1921; Kretschmer & Sproft, 1936; Schneider & Hamilton, 1958). More recently, dimensional psychometric constructs have been correlated with the liability to affective disorders in clinical, family and twin studies. One of these, neuroticism (N), is one of three orthogonal traits, along with extraversion (E) and psychoticism, comprising Eysenck's theory of personality (Eysenck & Eysenck, 1985). Defined as the general vulnerability to neurotic breakdown under stress, and as measured by the Eysenck Personality Questionnaire, it has good psychometric properties, including item and construct validity, longitudinal stability, consistent correlations between self and observer ratings, and cross-cultural validation (Eysenck & Eysenck, 1985).

Several twin studies have shown that N is heritable, with estimates ranging from 0·30 to 0·60. Most studies (Floderus-Myrhed *et al.* 1980; Martin & Jardine, 1986; Pedersen *et al.* 1988; Rose *et al.* 1988; Tellegen *et al.* 1988; Eaves *et al.* 1989; Tambs *et al.* 1991; Lake *et al.* 2000) have established the importance of only additive

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genetic (A) and individual-specific environmental (E) factors in the aetiology of N. Only one (Macaskill *et al*. 1992) found that common or family environmental factors (C) are significant. In another study, the heritability of N was higher in women, and declined with age (Viken *et al*. 1994), although in most studies, there is no sex difference in heritability.

N and major depression (MD) have been associated in clinical, family and twin studies, but the nature of their relationship has been the subject of some controversy (Chodoff, 1972; Akiskal *et al*. 1983). Depressed subjects, even when recovered, have increased N or N-like traits compared to normal controls (Kendell & DiScipio, 1968; Hirschfeld *et al*. 1983; Reich *et al*. 1987). High N scores prospectively predict the later onset of MD in never-ill subjects who are either unselected (Nystrom & Lindgard, 1975), or who are at high risk because of pregnancy or family history of depressive illness (Boyce *et al*. 1991). One twin study did (Kendler *et al*. 1993*a*), while two clinical studies did not (Duggan *et al*. 1987; Zeiss & Lewinsohn, 1988) find support for an enduring increase in N as a consequence of a depressive episode (a scar effect). Studies correlating N and MD in the same individual are complicated by the fact that the state of being depressed tends to cause an increase in concurrent N score (Coppen & Metcalf, 1965), underscoring the importance of epidemiological samples in studying the relationship between the two traits.

Several studies have examined the correlation between familial aetiological factors for N and MD. Maier *et al*. showed that male but not female healthy relatives of depressed probands had higher N scores than relatives of control probands (Maier *et al*. 1992), while two studies failed to demonstrate a significant difference (Katz & McGuffin, 1987; Ouimette *et al*. 1992). In two twin studies, the covariation between N and MD was largely due to additive gene effects common to both (Jardine *et al*. 1984; Kendler *et al*. 1993*a*).

Gender, personality and psychopathology

Multiple epidemiological studies have consistently demonstrated greater incidences and prevalences of MD in women (Regier *et al*. 1988; Kessler *et al*. 1994; Weissman *et al*. 1996; Kendler & Prescott, 1999). Cross-national studies have shown this to be the case in several other Western and Non-Western countries as well as the United States (Weissman *et al*. 1996). However, these sex differences may be attenuated after accounting for the presence of anxiety or externalizing disorders. Breslau *et al*. (1995) showed that the hazard rates to onset of MD between men and women were not significantly different when lifetime history of anxiety disorder was entered as a time-dependent covariate. Traditional cultures, such as the Old Order Amish and orthodox Jewish communities provide the natural experiments of societies in which externalizing disorders such as substance abuse and sociopathy are strongly proscribed, and where the prevalence of MD is the same in men as in women. The social conditions that obtain within these communities may preclude the masking of MD by gender related behaviours such as substance abuse and sociopathy (Egeland *et al*. 1983; Lowenthal *et al*. 1995).

Although the presence of anxiety and externalizing disorders may contribute to the sex difference in the incidence of MD, they are in turn related to personality. Eysenck & Eysenck (1985) postulated that individuals with high N are more likely to develop psychiatric disorders in general, and that high N conjoined with high E predisposes to conduct problems, while with low E predisposes to anxiety and depression. This is supported by findings that men have higher mean E scores and incidences of externalizing disorders, while women have higher mean N scores and incidences of mood and anxiety disorders (Floderus-Myrhed *et al*. 1980; Martin & Jardine, 1986; Pedersen *et al*. 1988; Rose *et al*. 1988; Tellegen *et al*. 1988; Eaves *et al*. 1989; Tambs *et al*. 1991; Kessler *et al*. 1994; Viken *et al*. 1994).

As the expression of MD may be modulated by the presence of other disorders that correlate with gender, and as these disorders are also related to personality factors such as N, the impact of personality on MD may therefore be in part mediated by gender. The robust gender differences in incidences of MD and externalizing disorders and in levels of N naturally lead to the questions of whether the relationship between N and MD may be different in men than in women, and whether this may explain the gender difference in MD. We therefore sought to evaluate the degree to which the phenotypic

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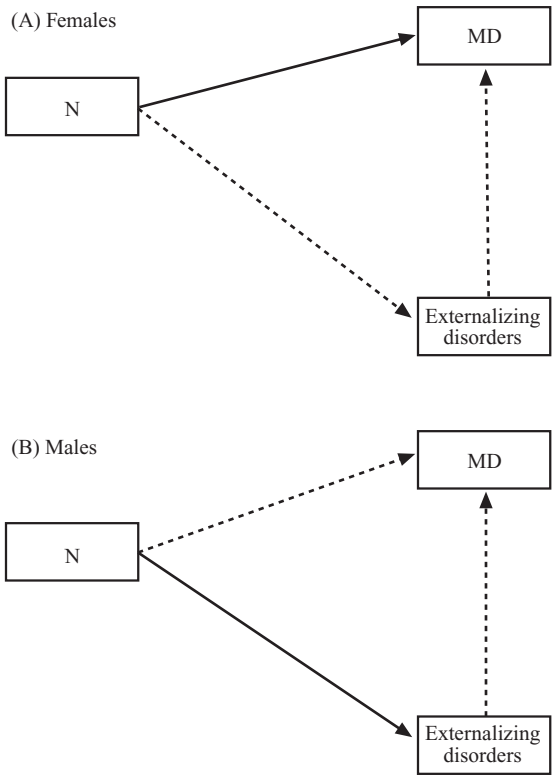


FIG. 1. Developmental pathways from neuroticism (N) to major depression (MD) and externalizing disorders in females (A) and in males (B). Solid arrows represent stronger pathways, while dashed arrows represent weaker pathways.

correlation between N and MD is due to genetic factors common to both traits, and to compare the genders with respect to this genetic correlation. We hypothesized that as the presence of externalizing disorders may be both a cause of MD as well as a result of N in men, there would be a closer genetic relationship between N and MD in women. This formulation is schematically represented in Fig. 1.

METHOD

Subjects

In this report, we included twins deriving from two studies of Caucasian twins ascertained through the population-based Virginia Twin Registry – formed from a systematic review of all birth certificates in the Commonwealth of Virginia. The female–female (FF) twin pairs used in this study cover the birth years 1934–1974. Twin pairs became eligible to participate if both members had previously responded to a mailed questionnaire, the response rate to which was 64%. Eighty-eight per cent of our sample was first interviewed face-to-face in 1988–1989, an average of 16 months after their first assessment. In this report, we utilize the third wave of interviews (FF3), which were returned by 1906, or 78% of the 2440 women to whom the questionnaires were originally sent. Assessments of both N and MD were derived from telephone interviews.

The male–male and male–female twin pairs, covering the birth years 1940–1974 were ascertained in a separate study beginning in 1993 (details outlined elsewhere) (Kendler & Prescott, 1999) in which we succeeded in interviewing by telephone 73% of those eligible. In this study, we included a total of 3771 twin pairs from these two samples, where both members were personally interviewed. This includes 863 male–male MZ (monozygotic), 649 male–male DZ (dizygotic), 506 female–female MZ, 345 female–female DZ and 1408 opposite-sex pairs. Zygosity was determined in same-sex pairs on the basis of a discriminant function of questionnaire responses about physical similarity and blood-type developed in the FF sample (Kendler *et al.* 1992) and validated in the male sample by polymorphic markers (mean, 11·5 (S.D. 11·9) markers per pair). Using this discriminant function, we could confidently assign zygosity to more than 93% of MM pairs. The remainder were assigned by genotyping ($N = 65$) or review of photographs, audiotapes, and interview responses ($N = 32$).

Measures

As outlined elsewhere (Kendler *et al.* 1992), lifetime MD was assessed by a structured psychiatric interview based on the SCID (Spitzer & Williams, 1985). Our assessment differed from the standard SCID in two major ways. First, we assessed last-year history for MD and a lifetime history for MD prior to the last year in two separate sections. An individual who was positive for one or more episodes of DSM-III-R MD (American Psychiatric Association, 1987) in either of these sections is here defined as positive for lifetime MD. Secondly, SCID questions for MD were modified so that, from the 'A criteria' for depression, we independently noted the presence of the 14 disaggregated symptoms (i.e. separately assessing weight loss, weight gain,

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decreased appetite and increased appetite). Neuroticism was assessed using the 12 items of the short-form of the Eysenck Personality Questionnaire. As described elsewhere, the test–retest reliability of N over 17 months in our female sample was +0·69. Mean (S.D.) N in males was 2·72 (2·89) and in females, 3·30 (2·81).

Interviewers had a master's degree in a mental health field or a bachelor's degree plus 2 years of relevant clinical experience and received extensive training. Members of a twin pair were interviewed by different interviewers, who were blind to co-twin diagnosis. Inter-rater reliability among 53 randomly selected FF subjects was $\kappa = 0{\cdot}96$ ($\pm 0{\cdot}05$) for DSM-III-R MD. Written informed consent was obtained prior to face-to-face interviews and verbal assent prior to telephone interviews.

Statistical analysis

We constructed a sex-limited bivariate structural-equation twin model to describe the relationship between N and MD. We used Cholesky factorization to decompose the covariation between the two measures into its additive genetic, common environmental, and individual-specific environmental components (Neale & Cardon, 1992). This model incorporates two sets of latent factors: (1) genetic and environmental common factors influencing personality and lifetime history of major depression; and (2) genetic and environmental specific factors that influence only personality. Comparing the resemblance of MZ and DZ twin pairs permits estimates of each source's contribution to individual differences in expression of a trait or the liability to a disorder, as well as to the covariation between traits. Sex differences in sources of covariation between two traits are indicated if the cross-twin cross-trait correlation is smaller for opposite-sex than for same-sex DZ pairs. If men and women have completely separate sources of covariation, these correlations will be 0 in opposite-sex pairs. Age was not included in our model because it accounted for only very small proportions of variance in the variables of interest in the female–female sample (Kendler *et al.* 1993*a*).

A 4×4 correlation matrix, with polychoric and product-moment correlations between N and MD in each of two twins, was calculated separately for female MZ and DZ, male MZ and DZ, and opposite-sex twin pairs using the test version of the computer program PRELIS 2 (Jöreskog & Sörbom, 1996). Models were fit to these matrices by asymptotic, weighted, least squares using the computer program Mx (Neale, 1994). Parameter estimates of these models were used to calculate the correlations between the additive genetic (r_g) common environmental (r_c) and individual-specific environmental (r_e) factors contributing to N and MD separately in females and males. We also estimated the cross-sex correlations between genetic factors within each trait as well as across traits (e.g. female N and male MD). Choosing the best-fitting model was based on the Akaike information criterion (AIC) (Akaike, 1987), which equals χ^2 minus twice the degrees of freedom (df), and reflects both the goodness-of-fit and parsimony of the model. The goal was to produce the model with the most negative value for the AIC.

RESULTS

The correlation matrices

Table 1 depicts the matrices of correlations for N and MD in male and female MZ and DZ twins and opposite-sex twins. Several conclusions can be immediately drawn from this. First, in MZ twins, the correlation between N and MD within individuals is higher than that between twins for either trait. As MZ differences are a result of only environmental factors, this sug-

Table 1. *The matrices of correlations between neuroticism* (*N*) *and major depression* (*MD*) *in female, male and opposite-sex twins* (*dizygotic correlations are above the diagonal, monozygotic correlations are below the diagonal*)

	Twin 1 N	Twin 1 MD	Twin 2 N	Twin 2 MD
Females				
Twin 1 N		0·355	0·100	0·112
Twin 1 MD	0·273		0·034	0·154
Twin 2 N	0·350	0·135		0·351
Twin 2 MD	0·148	0·393	0·283	
Males				
Twin 1 N		0·511	0·178	0·071
Twin 1 MD	0·391		0·098	0·116
Twin 2 N	0·374	0·211		0·457
Twin 2 MD	0·254	0·300	0·374	
Opposite sex				
Twin 1 N		0·456	0·108	0·082
Twin 1 MD			0·046	0·104
Twin 2 N				0·389
Twin 2 MD				

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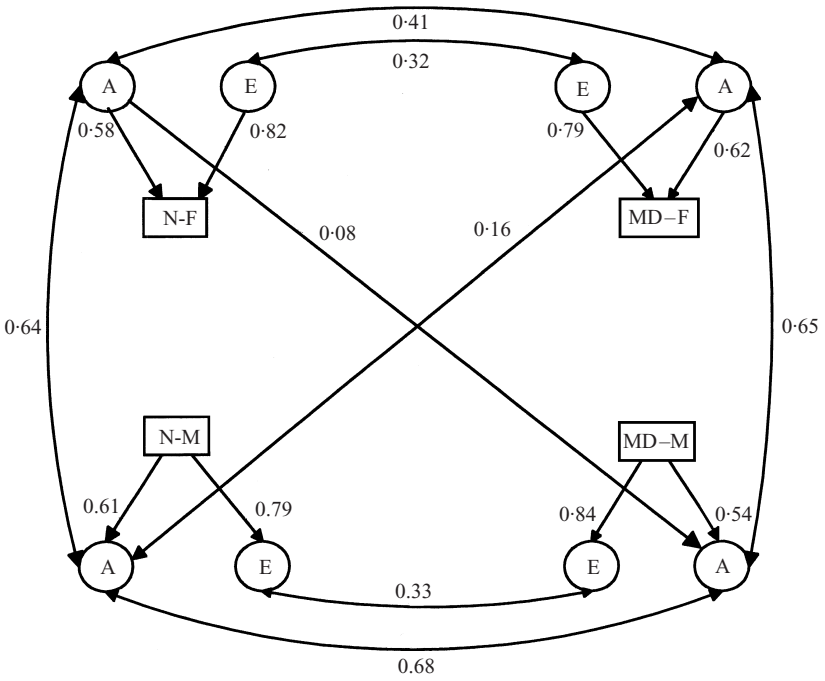


FIG. 2. The best-fitting bivariate two-sample twin model for neuroticism and major depression in females (above) and males (below). Observed variables are depicted in squares and latent variables in circles. Observed variables are current neuroticism (N) and lifetime history of major depression (MD) as assessed at personal interview. Latent variables are additive genetic (A) and individual-specific environmental factors (E). Arrows represent causal paths from the latent to the observed variables, and their associated figures are standardized regression coefficients. Arcs represent correlations between latent variables, and associated figures are their respective correlation coefficients. The arcs connecting additive genetic factors represent r_g, the genetic correlation between N and MD, while the arcs connecting individual-specific environmental factors represent r_e, the environmental correlation.

gests that individual-specific experiences are contributing to the covariation between N and MD. Secondly, the cross-twin, N–MD correlations are smaller than the cross twin correlations for either N or MD separately. This implicates the role of non-genetic factors in the covariation between the two traits. The importance of genetic factors, on the other hand, is evidenced by the observation that the cross-twin, N–MD correlations in MZ twins are greater than in DZ twins. Furthermore, the within-person as well as cross-twin correlations between N and MD are greater in male than female MZ twins, indicating that there may be sex-differences in the factors contributing to the covariation of the two traits. Finally, the opposite-sex twins had an N–MD correlation that was lower than in the male DZ but similar to that of the female DZ twins, suggesting the possibility that the genetic factors influencing the covariation between N and MD may in part be sex-specific.

Model fitting

The full model, model 1, includes additive genetic, common environmental and individual-specific environmental sources (ACE) of the variances of N and MD, as well as the covariation of the two traits. This model had an excellent fit to the data. In it, the within-sex N–MD correlations r_g, r_c, and r_e, were respectively, 0·41, 0 and 0·32 in females, and 0·68, 0 and 0·33 in males. As the parameter estimates for C were zero, we eliminated these paths and r_c in model 2, the AE model. Model 2, depicted in Fig. 2, had the same fit to the data and identical parameter estimates, but was preferable because of its greater parsimony, embodied in a more negative AIC ($-48{\cdot}83$). In this model, the cross-sex genetic correlation was 0·64 for N and 0·65 for MD (out of 1·0 possible), indicating that the additive genetic components of N and MD are correlated, but not identical. The correlation

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Table 2. *Results of bivariate twin modelling for neuroticism and major depression*

Model	Description	Females			Males			df	χ^2	AIC
		r_g	r_c	r_e	r_g	r_c	r_e			
1	ACE	0·41	0	0·32	0·68	0	0·33	26	15·168	−36·832
2*	AE	0·41	0	0·32	0·68	0	0·33	32	15·168	−48·832
3	AE, r_g equal in F and M	0·55	0	0·38	0·55	0	0·24	34	20·044	−47·956
4	AE, r_g set to 0 in F	0	0	0·45	0·61	0	0·29	33	45·892	−20·108
5	AE, r_g set to 0 in M	0·36	0	0·32	0	0	0·46	33	67·882	1·882
6	AE, r_g set to 0 in F and M	0	0	0·46	0	0	0·59	34	95·589	27·589
7	AE, r_g set to 1 in F	1	0	0·13	0·75	0	0·30	33	75·86	9·86
8	AE, r_g set to 1 in M	0·51	0	0·27	1	0	0·31	33	59·18	−6·82
9	AE, r_g set to 1 in F and M	1	0	0·13	1	0	0·31	34	113·177	45·177

F, Female; M, male.
* Best fit by AIC.

for the additive genetic components of variance of N in females and MD in males was 0·08 (95% CIs = 0·034 to 0·158), while that for MD in females and N in males was 0·16 (95% CIs = 0·074 to 0·266).

To determine whether the gender differences between r_g observed in this model were significant, we constrained r_g to be equal across the sexes to form model 3. This resulted in a worse fit to the data, and although it had more degrees of freedom, this model had an AIC of −47·96, which is only a slightly less negative than model 2 (see Table 2). We tried to improve on the fit of model 2 by constructing submodels in which we set the within-sex r_g to zero, indicating no relationship between genetic factors influencing N and MD. This was done for females in model 4, for males in model 5, and for both sexes in model 6. All of these resulted in substantial worsening of fit to the data. We next tested models in which within-sex r_g was set to one, indicating that the genetic factors influencing N and MD were the same. This was done for females in model 7, for males in model 8, and for both sexes in model 9. Again, all of these resulted in substantial worsening of fit to the data.

DISCUSSION

This study was designed to examine the impact of gender on the genetic correlation between neuroticism and major depression. We know of no previous studies addressing this question. Contrary to our *a priori* hypothesis, we did not find evidence of a greater genetic relationship between these domains in women than in men. The model in which the genetic correlation between N and MD was allowed to differ across the sexes had a more negative AIC than the model in which the male and female correlations were constrained to be equal. This difference, however, was less than one unit of AIC. We are therefore unable to reject with confidence the reduced model in which there is no difference between the male and female genetic correlations. Our results are indeed surprising given the apparent closer relationship between N and internalizing disorders such as MD in women. They suggest that the genetic correlation between temperamental factors and affective illness is unrelated to the observed levels of either.

We also found evidence of significant genetic heterogeneity for both N and MD across the sexes. There was a cross-sex genetic correlation of only 0·64 for N and 0·65 for MD (out of 1·0 possible), indicating that some of the genes influencing the two traits are not shared by the sexes. One previous study of N did (Eaves *et al.* 1989), although a recent study of over 45000 twins did not find evidence of sex-specific genetic factors (Lake *et al.* 2000). The magnitude of genetic and environmental factors for N, however, may be similar across the sexes (Floderus-Myrhed *et al.* 1980; Pedersen *et al.* 1988; Rose *et al.* 1988; Tellegen *et al.* 1988; Eaves *et al.* 1989; Tambs *et al.* 1991). Two previous analyses of the subjects in this study found evidence of sex-specific genetic factors for MD (Kendler & Prescott, 1999; Kendler *et al.* 2000). We found a smaller genetic correlation between male N and female MD, estimated at 0·16, and an even smaller one between female N and male MD, estimated at 0·08. Both of these correlations

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were significant however, as the lower limits of their confidence intervals were greater than zero. These indicate substantial genetic differences between N and MD across the sexes.

The genetic heterogeneity evidenced in this study may play a greater role in the sex difference in prevalence of MD than differing magnitudes in the contribution of temperamental genes to the overall liability to MD across the sexes. Genetic heterogeneity is consonant with theories attempting to explain the sex difference in depression on the basis of sexual dimorphisms in putative biological risk factors (Paykel, 1991; Bebbington, 1996). One aspect of this is sex-specific exposure to gonadal hormones *in utero*, leading to a differential organization of the early central nervous system. Prenatal hormone exposure may play a role in aggression, sexual orientation and identity, cognition and personality, in both sexes (Collaer & Hines, 1995). Genes contributing to N and MD, if expressed differently in males than females, may contribute to a sex difference in liability to MD. Sex differences in hormonal exposure during adulthood may also contribute to a difference in liability to MD (Paykel, 1991; Bebbington, 1996; Seeman, 1997), although this is difficult to study because of other sex-related confounding factors (Paykel, 1991). Nevertheless, this notion has face validity based on findings that both oestrogen and androgens may modulate neurochemical systems relevant to the aetiology of affective disorders, including those of serotonin, dopamine, norepinephrine, neuropeptides (Halbreich, 1990; Rubinow & Schmidt, 1996; Rubinow *et al.* 1998) and monoamine oxidase (Chakravorty & Halbreich, 1997).

A high degree of overlap between genes influencing N and MD within the sexes may have implications for both the nosology as well as treatment of affective disorders. In recent years, there has been some controversy over the use of trait criteria in the nosology of affective disorders. For example, depressive personality disorder was moved to an appendix of DSM-IV (Phillips *et al.* 1998), and the concepts of bipolar II disorder and bipolar IV, or hyperthymic personality, have become increasingly popular (Akiskal *et al.* 2000). Both the proliferation of diagnostic categories and the ascendancy of a spectrum concept in the bipolar disorders have been driven by clinical experience suggesting that 'soft' forms of the illness are responsive to medications used in the more severe forms (Akiskal & Pinto, 1999). As the current study suggests that there is a substantial overlap between the genetic risk factors for N and MD, individuals with high N may benefit from interventions used to treat MD in at least some cases. This may ameliorate impairment and/or distress caused by N itself, as well as protect against the later onset of MD. A similar rationale has been proffered for the treatment of Schizotypal Personality Disorder with antipsychotics (Siever, 1994). An implication of this is the utility of N or N-like traits not only as psychometric variables, but also in clinical assessment. Clearly, however, much work would be needed to establish meaningful parameters by which this would be operationalized.

In recent years, it has been suggested that molecular genetic studies of psychiatric illness would benefit from a shift away from phenotype definition using operationalized psychopathological categories (Leboyer *et al.* 1998; Stoltenberg & Burmeister, 2000). Endophenotypes may be able to exploit the genetic information available in clinically unaffected relatives who may carry susceptibility genes, and may thereby provide greater statistical power in linkage and association studies (Stoltenberg & Burmeister, 2000). As N or N-like traits are influenced by genes relevant to the aetiology of MD, they may be useful endophenotypes in genetic studies of affective disorders (Lake *et al.* 2000). Future directions will necessitate the testing of these putative endophenotypes in linkage and association studies, and comparing the power of these strategies to traditional methods. The genetic heterogeneity of both N and MD across sex suggests that both N-like traits and categorical definitions of MD may evidence linkage with and/or association to different susceptibility loci in women than in men. Furthermore, the substantial non-overlap of N and MD across sexes may make the use of N-like traits of limited utility as endophenotypes in unaffected relatives of the opposite sex. Again, these would need to be confirmed in future studies.

Limitations

The results of this report should be interpreted in the context of seven potentially important methodological limitations. First, diagnostic

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assessments and personality questionnaires were conducted largely by telephone. However, there was little difference in the assessment of psychiatric disorders or in the heritability of MD by telephone as opposed to face-to-face interviews in a previous study of these female twins (Kendler *et al.* 1992).

Secondly, we did not assess mania in our first interview of male twins, because of its low prevalence in general population samples. Therefore, no distinction was made between MD and bipolar disorder. In female twins, however, removing individuals with a history of bipolar disorder from analysis had a very small impact on the prevalence and heritability of MD (Kendler & Prescott, 1999).

Thirdly, there may have been excess resemblance between MZ twins due to non-genetic factors such as social expectations to have more frequent contact, thereby leading to over-estimations of heritability. Such a violation of the equal environment assumption, upon which twin studies are predicated, has not been ruled out for N. Several studies, however, have demonstrated that twin studies of MD do not violate this assumption (Kendler *et al.* 1993*b*; Hettema *et al.* 1995).

Fourthly, in the analyses presented here, we included all individuals, including those who had had recent onsets of MD. This may have artifactually increased the within-person and cross-twin N-MD correlations because of the tendency of the state of MD to increase concurrent N. However, when we performed the above analyses while excluding all subjects who had experienced an episode of MD in the last year, the effect of the exclusion was unequal across the sexes, thereby introducing a source of bias. This resulted in a best-fitting model in which r_g was constrained to be equal across the sexes, and included only A and E. However, the difference in AIC between this model and the AE model in which r_g was allowed to be free was minimal. In this latter model, r_g was greater in males. The effects of excluding last year MD may have resulted from diminished power by decreasing the sample size.

Fifthly, the method of structural equation modeling of twin data is predicated on several assumptions. These include: (1) all variables are treated as unitary factors, whose components behave in the same way with other variables; (2) the relationships between variables are linear; and (3) each dependent variable is determined by the sum of the effects of proximate antecedent variables (Wright, 1968; Neale & Cardon, 1992).

Finally, the results presented here are derived from a sample of Caucasian twins, and cannot be generalized to other ethnic groups.

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