ORIGINAL ARTICLE

Personality and Major Depression

A Swedish Longitudinal, Population-Based Twin Study

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Context: Prior studies suggest that the personality traits of neuroticism and extroversion may be related to the liability to major depression (MD).

Objective: To clarify the magnitude and nature of the association between neuroticism and extroversion and the risk for MD.

Design: Longitudinal population-based twin cohort.

Setting: General community.

Participants: A total of 20 692 members of same-sex twin pairs from the population-based Swedish Twin Registry who completed a self-report questionnaire assessing neuroticism and extroversion in 1972 and 1973 and were personally interviewed for lifetime history of MD more than 25 years later.

Main Outcome Measure: Lifetime history of modified *DSM-IV* MD.

Results: Levels of neuroticism strongly predicted the risks for both lifetime and new-onset MD. Twin modeling indicated that the association between neuroticism and MD resulted largely from shared genetic risk factors, with a genetic correlation of +0.46 to +0.47. Levels of extroversion were weakly and inversely related to the risks for lifetime and new-onset MD. This effect disappeared when we controlled for the level of neuroticism. Twin modeling produced similar results.

Conclusions: Results from both longitudinal and genetic analyses support the hypothesis that neuroticism strongly reflects the liability to MD. This association arises largely because neuroticism indexes the genetic risk for depressive illness. However, substantial proportions of the genetic vulnerability to MD are not reflected in neuroticism. By contrast, extroversion is only weakly related to risk for MD.

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ALTHOUGH THE ASSOCIATION between personality and the risk for major depression (MD) could arise from multiple processes,[1,2] it is of particular interest to determine whether some dimension of personality reflects an enduring liability to depressive illness. The most powerful natural experiment with which to evaluate such an association would incorporate both longitudinal and genetic designs. Ideally, personality would be measured in a large, representative sample early in adult life when most individuals are free of a history of depressive illness. Years later, the lifetime history of MD would be assessed.

We herein report the results of such a study. In 1972 through 1973, a questionnaire that contained short scales for the personality traits of neuroticism and extroversion was sent to all same-sex twin pairs in Sweden born from 1926 through 1958. More than 25 years later, their lifetime history of MD was assessed at a personal interview.

Using this unique sample, we address the following 3 questions: (1) Do the personality traits of neuroticism and extroversion predict the lifetime history of MD? (2) Do the personality traits of neuroticism and extroversion predict the first onset of MD? (3) Using twin modeling, to what extent is the correlation between neuroticism and extroversion and the liability to MD the result of shared genetic vs shared environmental risk factors?

METHODS

SAMPLE

The design of this study is illustrated in **Figure 1**. The sample comes from the Swedish Twin Registry, which contains a nearly com-

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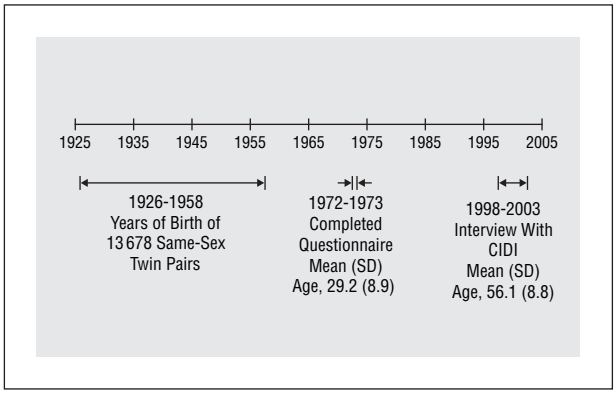

Figure 1. The design of this study, examining twins born from 1926 through 1958, who completed questionnaires containing assessments of the personality traits of neuroticism and extroversion in 1972 through 1973 and who were personally interviewed with portions of the Composite International Diagnostic Interview Short Form from March 1998 through January 2003.

plete registration of all twin births in Sweden. In 1972 through 1973, a questionnaire was sent to all same-sex twin pairs born from 1926 through 1958. The questionnaire contained 18 items selected from the short form of the Eysenck Personality Inventory (Form B), 9 each from the Neuroticism and Extroversion scales.[3,4] These questions were picked from the larger pool of Eysenck Personality Inventory items because of their ability to differentiate between the upper and lower total score quartiles in 400 individuals.[3]

The Screening Across the Lifespan Twin (SALT) Study completed telephone interviews between March 1998 and January 2003 with all cooperative members of the Swedish Twin Registry born in or before 1958 who were alive at the time of contact, obtaining a 74% response rate. The present analyses excluded those interviewed by proxy, those who terminated the interview before or were improperly skipped out of the depression section, and 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 before the 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,[5] zygosity was assigned using standard self-report items that, when validated against biological markers, were 95% to 99% accurate.

The psychiatric portion of the SALT Study interviews used the computerized Composite International Diagnostic Interview–Short Form (CIDI-SF), which was adapted from its original design for 12-month prevalence to assess lifetime prevalence of *DSM-IV* disorders.[6,7] 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 and inquiring only about weight changes) and A4 (eliminating hypersomnia). The CIDI-SF version adapted for this study contained a skip-out item for individuals who, when asked about episodes of sad mood in the preceding year, volunteered that they were taking antidepressants. Such individuals were assumed to have a history of MD but were unlikely to have manifested symptoms in the preceding year owing to treatment. Because of an oversight, this skip-out item 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, Ronald Kessler, PhD, and Daniel Mroczek, PhD (written communication, February 22, 1994), recommend using a cutoff of 4 or more of the 8 criteria. We simulated the CIDI-SF assessment of MD in our sample of 7521 personally interviewed twins from the Virginia Twin Registry, in which we had a complete set of items for *DSM-III-R* adapted from the Structured Clinical Interview for *DSM-III-R*.[8] Agreement with the full criteria also maximized using a cutoff of 4 or more CIDI-SF criteria (mean±SE κ, 0.90±0.01).

The sample used in the present report included 160 twins who skipped out of the section because they volunteered a history of antidepressant medication use. We assessed whether a history of antidepressant use was a valid substitute for a diagnosis of MD by examining the risk for MD in co-twins of twins with (1) no diagnosis of MD and no history of antidepressant use, (2) a diagnosis of MD, and (3) a history of antidepressant use. As detailed elsewhere,[9] groups 2 and 3 differed significantly from group 1 but not from each other. Therefore, we considered as affected the twins who met criteria for MD or volunteered that they were receiving or had received antidepressant medication.

STATISTICAL ANALYSIS

The neuroticism and extroversion scores were standardized for the regression analyses so that the odds ratio (OR) reflected the alteration in the risk of MD with every increase of 1 SD in the personality dimension. For twin modeling, we first regressed out the effects of age that required linear effects for neuroticism but linear and quadratic effects for extroversion. We then treated neuroticism and extroversion as polychotomies, recategorizing them into 9 approximately equal categories each.

Initial analyses of the relationship between personality and the risk for lifetime MD were conducted by logistic regression using the SAS procedure GENMOD,[10] correcting for the twin structure of the data by using the method of generalized estimating equations. Covariates used were sex and year of birth. The association between personality and the first onset of MD was assessed using a Cox proportional hazards regression model as operationalized in PROC PHREG in SAS software, version 8.2.[10] Subjects with onset of MD before 1974—who represented 19.7% (n=611) of those with onset of depression in these data—were deleted from these analyses so that all subjects studied had no history of MD prior to their personality assessment. For all analyses of MD in this sample, sex was treated as a covariate. Because the hazard rate based on birth year was a complex nonlinear function of birth year that could not be easily modeled as a standard covariate in a simple functional form, we instead treated birth year as a stratifying variable.

In bivariate twin analysis, the major goal is to decompose the covariance between 2 traits or disorders, such as neuroticism and MD, into that which is due to additive genetic effects (A), common environment (C) (those environmental experiences shared by members of a twin pair that tend to make them similar), and individual specific environment (E) (those environmental experiences not shared by members of a twin pair that therefore tend to make them dissimilar). Basically, bivariate analysis subdivides a phenotypic liability correlation between 2 traits into that due to (1) the same additive genetic effect predisposing to both traits (the additive genetic correlation or r_a), (2) the same common or familial environmental factors predisposing to both disorders (the common environmental correlation or r_c), and (3) the same individual-specific environmental risk factors predisposing to both disorders (the individual-specific environmental correlation or r_e). Using the software package Mx,[11] we fit models by the method of maximum likelihood to data from all individual twin pairs, including those with partial data. This method reduces the impact of cooperation bias and is a maximum likelihood application of

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the "missing at random" principle expounded by Little and Rubin.[12] Because prevalence rates changed substantially as a function of age in this sample, our calculation of correlations and model fitting included an age-dependent threshold that subtracted out the twin resemblance due to their perfect correlation for year of birth.

Because we had available to us only same-sex twin pairs with information on personality from 1972 through 1973 and on MD, we were able to examine only quantitative sex effects, in which we tested whether the magnitude of genetic and environmental effects on personality and MD are the same in men and women. Twice the difference in log-likelihood between the 2 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 the Akaike information criterion (AIC)[13] for model selection. Lower AIC values indicate better balance between explanatory power and parsimony.

For MD, age was used as a linear modifier variable for the threshold. Thresholds were allowed to differ across sexes for MD and the personality variables. Although desirable, it was computationally infeasible to obtain standard error estimates given the sample size and complexity of the model. We previously examined possible violations of the equal environment assumption for MD in this sample and found no evidence in its support.[9]

RESULTS

DESCRIPTION OF THE SAMPLE

Merging the data sets representing responses to the mailed questionnaire from 1972 through 1973 and completion of the SALT Study interviews identified 23 455 individuals, of whom 20 692 had valid measures of neuroticism, extroversion, and zygosity. In 7831 pairs, we had complete information on personality and MD in both members, whereas the remaining pairs had varying degrees of partial information. The mean (SD) age of this sample at the completion of the questionnaire and personal interview was approximately 29.2 (8.9) and 56.1 (8.8) years, respectively.

Of the 20 692 individuals in the sample, 4331 (20.9%) reported a lifetime history of MD. The risk for MD was significantly greater in this sample in women than in men (OR, 1.99; 95% confidence interval [CI], 1.82-2.17; χ^2_1=234.1; P<.001). Examining the mean (SD) raw personality scores as a function of sex and lifetime history of MD, we obtained the following for neuroticism: for unaffected men, 2.15 (2.05); for affected men, 3.15 (2.37); for unaffected women, 2.92 (2.36); and for affected women, 3.90 (2.42). Parallel results for extroversion were as follows: for unaffected men, 4.26 (2.05); for affected men, 4.12 (2.12); for unaffected women, 3.28 (2.14); and for affected women, 3.42 (2.20).

ASSOCIATION BETWEEN PERSONALITY AND LIFETIME MD

By logistic regression, controlling for sex and the linear and quadratic effects of birth year, neuroticism was robustly and significantly related to the risk for lifetime MD (χ^2_1=520.3; P<.001; OR, 1.49; 95% CI, 1.44-1.55). The same analyses with extroversion revealed a more modest but significant inverse relationship (χ^2_1=22.0; P<.001; OR, 0.92; 95% CI, 0.89-0.95). Because neuroticism and extroversion were negatively correlated (polychoric r=–0.30), we also conducted the analysis with both neuroticism and extroversion as predictors. The association between MD and neuroticism remained unchanged (χ^2_1=502.2; P<.001; OR, 1.50; 95% CI, 1.45-1.56), whereas the association with extroversion disappeared (χ^2_1=2.1; P=.15; OR, 1.03; 95% CI, 0.99-1.07). We also examined for interactions in the prediction of MD between sex and neuroticism, sex and extroversion, and neuroticism and extroversion. None were significant (all P>.05; χ^2_1 values of 3.1, 0.2, and 0.4, respectively).

ASSOCIATION BETWEEN PERSONALITY AND FIRST ONSET OF MD

In these analyses, we censored individuals with an onset of MD before 1974. In the individuals with depressive onsets in the resulting subsample, the mean (SD) number of years between the personality assessment and their onset was 17.4 (7.8). By Cox proportional hazards model, the level of neuroticism significantly predicted the risk for a first onset of MD (χ^2_1=199.5; P<.001; hazard ratio [HR], 1.31; 95% CI, 1.26-1.36). Parallel analyses with E showed a much weaker effect (χ^2_1=4.6; P=.03; HR, 0.96; 95% CI, 0.92-0.99). When neuroticism and extroversion were included as independent variables, neuroticism remained strongly predictive of depressive onsets (χ^2_1=196.9; P<.001; HR, 1.32; 95% CI, 1.27-1.38), whereas extroversion was no longer significantly associated with risk (χ^2_1=2.7; P=.10; HR, 1.04; 95% CI, 0.99-1.08). We examined for interactions with sex, which were nonsignificant for extroversion (χ^2_1=1.4; P=.23; HR, 1.05; 95% CI, 0.97-1.15). However, neuroticism was significantly more strongly predictive of future depressive onsets in men than in women (χ^2_1=9.6; P=.002; HR, 1.14; 95% CI, 1.05-1.23). No significant interaction was seen between neuroticism and extroversion in the prediction of future depressive episodes (χ^2_1=0.9; P=.88; HR, 1.02; 95% CI, 0.98-1.06).

TWIN ANALYSES—CORRELATIONS

The within- and across-twin polychoric correlations between neuroticism and lifetime MD for the 4 twin types in this sample (monozygotic [MZ] female, dizygotic [DZ] female, MZ male, and DZ male) are seen in **Table 1** below the diagonal in each of the four sections of the table. Six patterns are noteworthy. First, the correlations for neuroticism are substantially higher in the MZ than in the DZ pairs in women (0.56 vs 0.27) and men (0.48 vs 0.22). Second, the same pattern is seen for MD (women, 0.45 vs 0.18; men, 0.31 vs 0.15). Third, for both neuroticism and MD, the twin correlations are moderately higher in women than in men. Fourth, the within-twin correlations between neuroticism and MD consistently range from 0.20 to 0.29. Fifth, the cross-twin cross-trait correlations between neuroticism and MD are substantially higher in MZ than in DZ pairs in both sexes. Sixth, the cross-twin cross-trait correlations between neuroticism and MD in MZ pairs (0.20 and 0.25 in women and

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Table 1. Within- and Between-Twin Polychoric Correlations for Neuroticism, Extroversion, and Lifetime MD*

Zygosity	Sex	Variable	Pers T1	MD T1	Pers T2	MD T2
MZ	Female	Pers T1		–0.07	0.55	–0.02
		MD T1	0.25		–0.04	0.45
		Pers T2	0.56	0.25		–0.04
		MD T2	0.20	0.45	0.25	
DZ	Female	Pers T1		0.03	0.18	–0.01
		MD T1	0.23		0.03	0.18
		Pers T2	0.27	0.11		–0.02
		MD T2	0.08	0.18	0.25	
MZ	Male	Pers T1		–0.04	0.46	–0.04
		MD T1	0.26		–0.03	0.31
		Pers T2	0.48	0.18		–0.04
		MD T2	0.21	0.31	0.29	
DZ	Male	Pers T1		–0.03	0.24	0.00
		MD T1	0.28		0.02	0.15
		Pers T2	0.22	0.10		–0.02
		MD T2	0.10	0.15	0.20	

Abbreviations: DZ, dizygotic; MD, major depression; MZ, monozygotic; Pers, personality trait (neuroticism or extroversion); T1, twin 1; T2, twin 2.
*Results for neuroticism are below the diagonal of empty data cells, whereas results for extroversion are those above the diagonal.

Table 2. Model-Fitting Results for Bivariate Twin Analysis of Neuroticism or Extroversion and Lifetime MD

		Neuroticism		Extroversion	
Model	*df*	χ^2*	AIC	χ^2*	AIC
1 ACE; r_a, r_e; f ≠ m					
2 AE; r_a, r_e; f ≠ m	6	1.44	–10.56†	0.01	–11.99
3 AE; r_a, r_e; f = m	10	17.12	–2.88	11.08	–8.92
4 AE; r_a = 0, r_e; f ≠ m	8	177.31	161.31	6.18	–9.83
5 AE; r_a = 1, r_e; f ≠ m	8	133.47	117.47	193.75‡	177.75
6 AE; r_a, r_e = 0; f ≠ m	8	12.38	–3.62	1.23	–14.77†

Abbreviations: A, additive genetic effects; AIC, Akaike information criterion; C, common environment effects; E, individual-specific environment effects; f = m, parameters constrained to be equal in female and male subjects; f ≠ m, parameters allowed to differ between female and male subjects; MD, major depression; r_a, additive genetic correlation; r_e, individual-specific environmental correlation.
*Calculated as –2 log-likelihood.
†Indicates best-fit model.
‡Model fit here was r_a = –1.00.

0.21 and 0.18 in men) are only slightly less than the within-twin cross-trait correlations.

The within- and across-twin polychoric correlations between extroversion and lifetime MD for the 4 twin types are seen in Table 1 above the diagonal. The correlations for MD are the same as those noted in the preceding paragraph. Three patterns are noteworthy. First, the correlations for extroversion are substantially higher in the MZ than in the DZ pairs in women (0.55 vs 0.18) and men (0.46 vs 0.24). Second, the within-twin correlations between extroversion and MD are low, varying from –0.07 to 0.03. Third, the cross-twin cross-trait correlations between extroversion and MD are slightly more negative in the MZ than in the DZ pairs in both sexes.

MODEL FITTING FOR NEUROTICISM

The full model (model 1), which allowed for quantitative sex effects, produced a –2 log-likelihood value of 112 344.59 (*df*, 43 938). In model 2, we constrained to 0 all shared environmental parameters. As seen in **Table 2**, this resulted in a very small increase in χ^2 and a substantial decline in the AIC. In model 3, we constrained the genetic and environmental paths to be equal in men and women, but this resulted in a moderate jump in χ^2 and a resulting deterioration of the AIC. In models 4 and 5, we constrained the values of r_a to be equal to, respectively, 0 and 1 in men and women. Both of these models fit quite badly, indicating that neuroticism and MD shared some but clearly not all their genetic risk factors in common. Model 6 constrained the values of r_e to 0, which produced a modest increase in χ^2 and a parallel deterioration in the AIC. We tried to fit a model constraining r_e to unity. We were repeatedly unable to get this model to converge, although the indirect evidence indicated that this model would fit very poorly indeed. For neuroticism and lifetime MD, model 2 produced the best overall fit by a wide margin.

The parameter estimates from model 2 are seen in **Figure 2**. In accord with our prior analyses of a larger sample of Swedish twins, of which the present sample is a subset,[9] heritability for MD is higher in women (42%)

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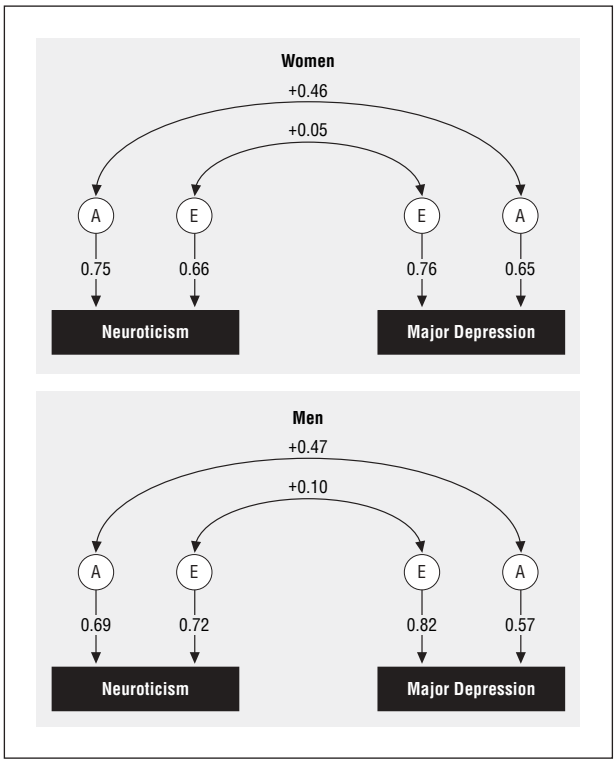

Figure 2. Parameter estimates from the best-fit model 2 (described in Table 2) for the bivariate twin analysis of neuroticism and lifetime major depression. A indicates additive genetic effects; E, individual specific environmental effects.

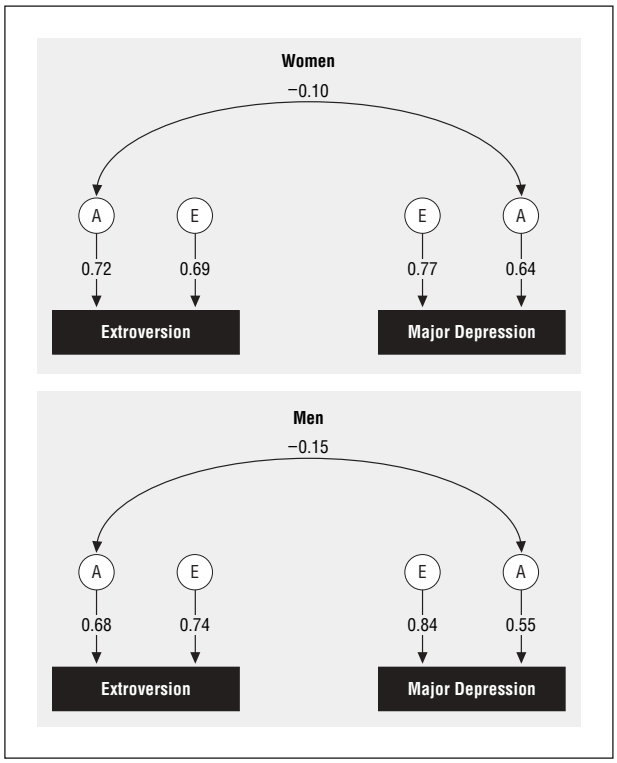

Figure 3. Parameter estimates from the best-fit model 6 (described in Table 2) for the bivariate twin analysis of extroversion and lifetime major depression. A indicates additive genetic effects; E, individual specific environmental effects.

than in men (32%). The same pattern is seen for neuroticism, in which heritability is greater in women vs men (56% vs 49%). The genetic correlation between neuroticism and MD is substantial and slightly higher (+0.47) in men than in women (+0.46). The environmental correlation is low in both sexes.

Using this model, we can decompose the correlations in liability between neuroticism and MD, which are estimated to be 0.25 in women and 0.24 in men. In women, 91% of the correlation between neuroticism and liability to MD is due to genetic factors and only 9% to environmental factors. In men, the figures are 76% and 24%, respectively.

MODEL FITTING FOR EXTROVERSION

The full model (model 1), which allowed for quantitative sex effects, produced a –2 log-likelihood value of 113 339.15 (*df*, 43 939). In model 2, we constrained to 0 all shared environmental parameters. As seen in Table 2, this resulted in virtually no change in χ^2 and a substantial decline in the AIC. In model 3, we constrained the genetic and environmental paths to be equal in men and women. This produced a moderate jump in χ^2 and a resulting deterioration of the AIC. In models 4 and 5, we constrained the values of r_a to be equal to, respectively, 0 and 1 in men and women. Model 4 fit only slightly worse than model 2, whereas model 5 fit very poorly. In model 6, we constrained the values of r_e to 0; this produced a small increase in χ^2 and an improvement in the AIC. We attempted to fit a model with r_e constrained to unity but, as with neuroticism and MD, this model would not converge. For extroversion and lifetime MD, model 6 produced the best overall fit.

The parameter estimates from the best-fit model 6 are seen in **Figure 3**. As with neuroticism, extroversion is more heritable in women than in men. The negative genetic correlation between extroversion and the liability to MD is modestly greater in men (–0.15) than in women (–0.10). The best-fit model predicts that the correlation in liability between extroversion and lifetime MD is quite modest (–0.046 in women and –0.056 in men) but is due entirely to genetic factors.

MODEL FITTING FOR NEUROTICISM AND EXTROVERSION

Given the evidence from the regression-based models that the impact of extroversion on MD was substantially attenuated when neuroticism was included in the model, we examined whether the same pattern of results would emerge in the twin analyses by fitting a series of trivariate twin models to data on neuroticism, extroversion, and lifetime MD (**Table 3**). We were guided by results from the prior bivariate models and so did not fit models constraining r_a or r_e to unity. The full model (model 1), which allowed for quantitative sex effects and all possible genetic and environmental correlations, produced a –2 log-likelihood value of 201 932.39 (*df*, 64 985). As outlined in Table 3, the AIC was improved by model 2, which dropped all shared environmental paths. Working from model 2, in model 3 we attempted to constrain all the

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Table 3. Model-Fitting Results for Trivariate Twin Analysis of Neuroticism, Extroversion, and Lifetime MD

Model	*df*	χ^{2*}	AIC
1 ACE; r_as, r_es; f ≠ m			
2 AE; r_as, r_es; f ≠ m	12	1.84	–22.16
3 AE; r_as, r_es; f = m	21	26.09	–15.91
4 AE; f ≠ m; r_e (extroversion-MD) = 0†	14	2.10	–25.89‡
5 AE; f ≠ m; r_e (neuroticism-MD) = 0§	16	13.11	–18.89
6 AE; f ≠ m; r_e (neuroticism-E) = 0§	16	160.83	128.83
7 AE; f ≠ m; r_a (extroversion-MD) = 0§	16	8.72	–23.28
8 AE; f ≠ m; r_a (neuroticism-MD) = 0§	16	177.93	145.93
9 AE; f ≠ m; r_a (neuroticism-extroversion) = 0§	16	273.73	241.73

Abbreviations: A, addititive genetic effects; AIC, Akaike information criterion; C, common environment effects; E, individual specific environment effects; f = m, parameters constrained to be equal in female and male subjects; f ≠ m, parameters allowed to differ between female and male subjects; MD, major depression; r_a, additive genetic correlation; r_e, individual-specific environmental correlation.

*Calculated as –2 log-likelihood.

†All other r_e and r_a values are estimated.

‡Indicates best-fit model.

§The r_e (extroversion-MD) value was constrained to be 0, and all other r_e and r_a values were estimated.

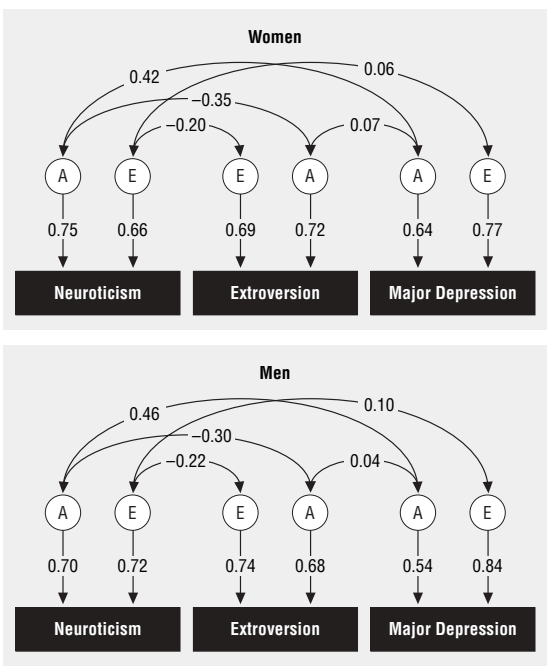

Figure 4. Parameter estimates from the best-fit model 4 (described in Table 3) for the trivariate twin analysis of neuroticism, extroversion, and lifetime major depression. A indicates additive genetic effects; E, individual specific environmental effects.

remaining genetic and environmental parameters to equality in men and women. This results in a substantial deterioration of the AIC. In model 4, we set r_e to 0 between extroversion and MD, which further improved the AIC. Working from model 4, we tried in models 5 through 9 to individually set all the remaining genetic and environmental correlations in the model to 0. None of these models provided an improved fit over that observed in model 4. The parameter estimates from the best-fit model 4 are seen in **Figure 4**.

The parameters for neuroticism and MD changed very little from those seen in Figure 2. The genetic and environmental correlations between neuroticism and extroversion were negative, with the genetic correlation being stronger in both sexes. In contrast to the pattern seen in Figure 3, when neuroticism was included in the model, the genetic correlation between extroversion and MD was now positive, albeit very modest, in both men (0.04) and women (0.07).

COMMENT

The goal of this report was to clarify, from an epidemiologic, longitudinal, and genetic perspective, the relationship between MD and the important personality dimensions of neuroticism and extroversion. This sample has 3 methodological strengths. First, it is large and representative. Second, the personality measures were obtained at least 25 years before the assessment of lifetime MD. Third, the sample is genetically informative.

We first examined the association between personality and the lifetime risk for depression from an epidemiologic perspective. Neuroticism was robustly related to the risk for lifetime MD. By contrast, the relationship between extroversion and MD was weak and negative, indicating that introversion was marginally related to the risk for MD. When both personality traits were included in the analysis, the effect of extroversion disappeared, suggesting that the weak association between extroversion and MD was mediated through the inverse correlation between neuroticism and extroversion. Using a longitudinal design, we then examined the ability of these personality traits to predict first onsets of MD. The results closely resembled those found in the simpler association analyses. Examined on their own, neuroticism strongly and extroversion only weakly predicted new onsets of depressive illness. When examined together, the predictive power of neuroticism was unchanged, whereas that of extroversion became nonsignificant. In neither set of analyses did neuroticism and extroversion interact in the prediction of MD, consistent with the results of some[14] but not other[15] studies of the prediction of depression.

These results are consistent with previous prospective investigations based on samples that were typically smaller and/or less representative. Those studies reported that neuroticism or neuroticism-like traits consistently predicted future depressive episodes[16-20] and/or specifically first onsets of MD.[18-20] By contrast, prospective studies of extroversion have not found this personality trait to be predictive of future depressive episodes.[16,18-20]

We next examined the association between personality and MD using twin modeling. For neuroticism and MD, the best-fit model included only genes and individual specific environment. Parameter estimates differed moderately between men and women. The genetic correlation between neuroticism and MD, estimated to be +0.46 in women and +0.47 in men (+0.45 in both sexes), substantially exceeded the environmental correlation (+0.05 in women and +0.10 in men).

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These results can be usefully compared with those obtained in the single previous comparable study[21] that examined lifetime MD and neuroticism assessed at the same time in 3771 same- and opposite-sex twin pairs from the population-based Virginia Twin Registry. The best-fit model estimated the genetic correlations between neuroticism and lifetime MD to be 0.41 in women and 0.68 in men. The parallel environmental correlations were 0.32 and 0.33, respectively. However, a second model that constrained the genetic correlations to equality in both sexes (at the value of 0.55) fit nearly as well the best-fit model.

The most striking difference between the 2 studies is the much lower estimates for environmental correlations in the Swedish sample. This discrepancy probably arose from the difference in the timing of the assessments of neuroticism and MD: contemporaneous in the Virginia sample and separated by 25 years or more in the Swedish sample. Two possible short-term effects that affect both neuroticism and MD and are not shared by a twin with the co-twin are probably increasing the neuroticism-MD correlation in the Virginia sample. One such effect could arise as a result of correlated errors of measurement (eg, a Virginia twin adopted a "plaintive" set and exaggerated his level of neuroticism and his probability of experiencing a depressive episode). Alternatively, negative environmental experiences might increase the level of negative affect in the twin, which in turn could have short-term effects on neuroticism (as suggested by Hirschfeld et al[22]) and alter the probability of reporting MD.[23] Whatever mechanism is at work, when the assessment of personality and MD are separated by a long time, these short-term environmental effects drop out and most of the correlation arises from genetic sources.

A number of gene-finding studies[24-26] have begun to study neuroticism with the hope that genes located thereby will also affect the risk for MD. What can we say about these efforts in light of the genetic correlations (r_a) of +0.46 to +0.47 that we have found between neuroticism and MD? The relationship between statistical estimates of a genetic correlation and the number and phenotypic effects of actual susceptibility genes is approximate at best.[27] Technically, what we really want to know is not the genetic correlation but a related yet distinct statistic: the proportion of genetic variance for MD that is reflected by neuroticism. Unfortunately, the relationship between this figure and r_a is not straightforward and depends on theoretical assumptions, the empirical bases of which are poorly known (Kristen Jacobson, PhD, and Michael Neale, PhD, unpublished data, September 2004). Although a plausible estimate for a value for this figure is approximately r_a, it could be considerably lower. The most optimistic interpretation of our findings would then be that the genetic risk factors for MD can be divided approximately equally into those that could be successfully found through studies of neuroticism and those that could not be localized using this approach.

Although statistically robust, the magnitude of the correlation between neuroticism and the liability to MD in our sample (approximately 0.25) was far from overwhelming. Clearly, important aspects of the liability to MD are poorly reflected by neuroticism. What might these be? Among individuals with a history of depressive illness, 1 epidemiologic study found that melancholic features were inversely correlated with prior levels of neuroticism.[28] Genetic and environmental risk factors that affect one's liability to neuroticism may bear little relationship to those that influence one's susceptibility to the endogenous features of depressive illness.

Modeling results for extroversion and MD differed markedly from those seen with neuroticism and MD. The modest genetic relationship between introversion and MD was transformed to a modest relationship between extroversion and MD when neuroticism was added to the model. Consistent with the results of the regression analyses, when the analysis controls for levels of neuroticism, a person's level of extroversion tells us very little about that individual's genetic risk for MD. Our findings can be usefully contrasted with recent results for social phobia. Although the risk for social phobia results from a genetic liability to high levels of neuroticism and low levels of extroversion (Oscar J. Bienvenu, MD, John Hettema, MD, PhD, Michael Neale, PhD, Carol Prescott, PhD, and K.S.K., unpublished data, July 2005), only the genetic risk for neuroticism is of substantial etiologic relevance for MD.

These results should be interpreted in the context of 5 major methodologic limitations. First, no questionnaire data were available on opposite-sex DZ twins, so we were unable to examine qualitative sex effects in our twin modeling. Second, our assessments of personality were based on a modest number of items empirically selected from the Eysenck Personality Inventory,[4] which later evolved into the Eysenck Personality Questionnaire.[29] The personality dimensions that we assessed may not be identical to the scales for neuroticism and extroversion obtained from other personality instruments. Third, our diagnosis of MD was based on a slightly shortened version of *DSM-IV* criteria for MD. Although these shortened criteria agreed very well with the full criteria, it is possible that some subtypes of depression (eg, those with atypical vegetative symptoms) were underrepresented in our sample. Fourth, it can be questioned whether twins are representative of the general Swedish population with respect to their risk for MD. We have previously shown that twins in Sweden are representative of the general population with respect to their rates of hospitalization for MD.[30] Fifth, neuroticism and MD were, in this sample, obtained on only 1 occasion. The effects of measurement error and individual-specific environmental effects are therefore confounded.

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