A Longitudinal Twin Study of Personality and Major Depression in Women

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Objective: To elucidate the nature of the etiologic relationship between personality and major depression in women.

Design: A longitudinal twin design in which twins completed a time 1 questionnaire and, 15 months later, were personally interviewed for the occurrence of major depression during the last year and completed a time 2 questionnaire. Both questionnaires contained short forms assessing neuroticism and extraversion.

Participants: 1733 twins from female-female pairs ascertained from the population-based Virginia Twin Registry.

Results: Extraversion was unrelated to lifetime or 1-year prevalence of major depression. Neuroticism was strongly related to lifetime prevalence of major depression and robustly predicted the prospective 1-year prevalence of major depression in those who, at time 1, denied previous depressive episodes. However, controlling for levels of neuroticism at time 1, levels of neuroticism at time 2 were moderately elevated in those who had had an episode of major depression between times 1 and 2 ("scar" effect) and substantially elevated in those experiencing an episode of major depression at time 2 ("state" effect). In those who developed major depression, levels of neuroticism did not predict time to onset. In the best-fit longitudinal twin model, the proportion of the observed correlation between neuroticism and the liability to major depression that is due to shared genetic risk factors was estimated at around 70%, that due to shared environmental risk factors at around 20%, and that due to a direct causal effect of major depression on neuroticism (via both "scar" and "state" effects) at around 10%. Approximately 55% of the genetic liability of major depression appeared to be shared with neuroticism, while 45% was unique to major depression.

Conclusion: In women, the relationship between neuroticism and the liability to major depression is substantial and largely the result of genetic factors that predispose to both neuroticism and major depression.

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Since the first descriptions of major depression (MD), many authors have suggested that a certain type of personality or temperament is at high risk for developing the disorder. Kraepelin, Kretschmer, and Schneider all suggested that certain personality types are predisposed to develop depression. While some studies have focused on personality constructs derived from psychoanalytic or interpersonal etiologic theories of MD, we examine the relationship between MD and two major dimensions of personality—neuroticism (N) and extraversion (E). Originally conceptualized by Eysenck, N and E have been identified cross-culturally as major personality traits by nearly all subsequent investigators. Neuroticism was designed to reflect emotional instability, vulnerability to stress, and anxiety-proneness, and E to measure socialability, liveliness, and the level of ease and pleasure felt in the company of others.

Individuals who experience episodes of depression, with considerable consistency, demonstrate high levels of N and low levels of E. Two plausible hypotheses can explain these observations. First, N or E (or the factors that influence them) may predispose to MD. Second, suffering from MD may influence the reported levels of N and

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MATERIALS AND METHODS

METHODS

The twins described herein are a subset of a larger cohort previously described in detail. In brief, female/female twin pairs from the population-based Virginia Twin Registry were selected if at least one member responded to a previously mailed questionnaire. Questionnaires covering a variety of risk factors for psychiatric illness were then mailed to this sample, for an individual response rate of approximately 64%. Responses were obtained from 1176 eligible pairs. Attempts were then made to personally interview both members of these pairs at least 1 year after they completed the questionnaire. We succeeded in interviewing 2163 or 92% of the eligible twins, including both members of 1033 pairs, with nearly all interviews completed face to face. At the time of the personal interview, a second questionnaire covering many of the same items as the previous mailed questionnaire was left with the respondent with instructions to complete the questionnaire and return it by mail as soon as possible. These second questionnaires were returned by 1842 twins or 69% of those interviewed. The mean (±SD) and median time between the completion of the personal interview and the second questionnaire was 16.6±30.4 days and 1.0 days, respectively. Interviews were conducted by trained social workers who were blind to the status of the co-twin. Zygosity was determined blindly with standard questions, photographs, and, when necessary, DNA analysis. Figure 1 shows the data collection strategy on which this article is based.

These analyses are restricted to twins who (1) completed the personality section of the time 1 questionnaire and (2) whose completed time 1 questionnaire preceded their time 2 personal interview by at least 12 months (n=2033). In several of our epidemiologic analyses and in our genetic analyses, we further restricted the sample to those twins who also returned, with a completed personality section, their time 2 questionnaire; of a total of 1733 individual twins, zygosity was known in 707 pairs of whom 423 were monozygotic (MZ) and 284 were dizygotic (DZ).

Neuroticism and E were assessed with 12 and eight items, respectively, empirically chosen from the Eysenck Personality Questionnaire. The test-retest reliability of N and E over 17 months in this sample was +0.69 and +0.78, respectively. We will refer to N and E at the first and second assessments as N1, E1, N2, and E2. Last year and lifetime prevalence of MD was assessed by one of us (K.S.K.) with a blind review of the personal interview that contained an adapted version of the depression section of the Structured Clinical Interview for DSM-III-R diagnosis. For the last year, onsets and offsets of episodes of MD were estimated in units of a month. Therefore, "current MD" indicates that the individual met the criteria for MD in the month of the interview.

Interrater reliability was assessed in 53 jointly conducted interviews. Each of these interviews was blindly reviewed; chance-corrected agreement (k) for the DSM-III-R diagnosis of major depression was + 96±.04 (P<.001).

In several of our analyses, it is important to exclude twins who had episodes of MD before our first assessment. We had two methods of accomplishing this. First, our time 1 self-report questionnaire contained items screening for a previous episode of MD. Specifically, twins were first asked if they ever in their life experienced the following five key symptoms of MD for at least 2 weeks: depressed mood, appetite disturbance, decreased energy, feelings of worthlessness, and difficulty concentrating. They were then asked if they ever had a period when they experienced at least three of these symptoms at the same time. In this report, a positive answer to this latter question, given by 21.9% of the twins, was interpreted as evidence of a prior episode of MD.

Second, in the personal interview at the second assessment, we separately evaluated whether the twins had experienced an episode of MD during and before the last year. The period before the last year will always include the period before the time 1 assessment so that excluding twins who reported such an episode should eliminate all cases in which the onset of MD was before the first assessment. However, a few subjects with an onset in the few months after the first assessment will also be eliminated, because in many twins, the period between the first and second assessments was a few months over 1 calendar year. By this definition, 27.1% of the sample met the criterion of having had one or more episodes of MD before the first assessment. The agreement between the questionnaire and interview methods of assessing prior history of MD, while highly statistically significant, was only moderate (k=+29±.03) and somewhat lower than that found by Bremet et al (k=+.41). However, in that study, a personal structured interview was used at both time points. While the percentage of patients who admitted to having a history of episodes of depression at the first assessment and confirmed that report at the second assessment was similar in both studies (31.3% in our study and 47.8% in that of Bremet et al), finding no history of MD based on our questionnaire was not as good a predictor of finding no history of MD at follow-up as the personal interviews in the study of Bremet et al. While 20.3% of our sample who denied having prior episodes of depression by questionnaire later admitted to them at personal interview, the corresponding figure in the study by Bremet et al was 10.5%. Finally, in certain analyses, we eliminated 37.8% of the sample who had reported having previous MD either on the time 1 self-report questionnaire or during the time 2 face-to-face interview.

In other analyses, we wished to eliminate individuals who were suffering from MD at the first assessment. This could be accomplished only approximately. We actually assessed, at personal interview, the history of MD in the preceding 13 months. In those twins who were interviewed 13 months after their time 1 questionnaire, we eliminated those who reported depression in that 13th month. For twins who were interviewed more than 13 months after their time 1 questionnaire, we eliminated all twins with any prior history of MD as reported on the questionnaire. Although overinclusive, this was the only way we could ensure that the time 1
questionnaire responses were not influenced by state effects of current MD. We repeated these analyses, eliminating twins who, in their personal interviews at time 2, reported having episodes of MD before the last year, and the results were similar.

REGRESSION ANALYSES

Logistic regression analyses were conducted using MD as the dependent variable, and linear regression analyses were conducted when personality traits were the dependent variable. Age and zygosity were included as control variables, the latter because of previous evidence of a modest difference in the rate of MD in MZ vs DZ twins. In these analyses, including those in which each twin’s history of MD was used to predict her co-twin’s personality, the nonindependence of observations among members of a twin pair must be taken into account. While this nonindependence does not influence the accuracy of the regression coefficients, it does produce spuriously low SEs. The SEs in these analyses were corrected upward as a function of the proportion of the sample who were complete twin pairs and the magnitude of the correlation of the dependent variable in those twin pairs. All tests of significance reported herein are based on these corrected SEs. If the results of logistic regression analyses were significant, the effect of the independent variable was measured by the relative risk for the dichotomous dependent variable with every SD increase in score of the independent variable.

We performed five kinds of regression analyses, which we termed descriptive, causal, prodromal, state, and scar (see Table 1 for an outline). In the descriptive analyses, we sought to describe the overall association between N, E, and MD, and therefore included all individuals using their personality scores to predict lifetime or last year MD. In the causal analyses, we wished to determine if N or E either (1) directly caused MD or (2) was an index for a set of latent risk factors that directly caused MD. Therefore, in these analyses, we eliminated twins with one or more episodes of MD prior to or at time 1 and examined whether N1 or E1 could prospectively predict the new onset of MD in the year before the time 2 interview. In the prodromal analyses, our goal was to determine if any of the putative causal relationships between N, E, and MD could result from these personality measures reflecting prodromal symptoms of depression. Therefore, in individuals who went on to develop an episode of MD, we tested whether N1 and E1 predicted the time to onset of their episode. In the state analyses, we sought to determine if being in an episode of MD influenced personality scores. We eliminated twins who were experiencing an episode of MD at their first assessment (so that this assessment was not influenced by state effects of MD), and then, controlling for their time 1 personality score, determined if being in an episode of MD at their time 2 assessment influenced time 2 personality scores. In the scar analyses, our goal was to determine if personality was influenced by prior episodes of MD. Therefore, we eliminated twins who had had an episode of MD before or at their time 1 assessment (so that their personality was unaffected by possible earlier scar effects) and twins who were in an episode of MD at their time 2 assessment (the presence of which would contaminate the scar and state effects). In the remaining sample, we determined if having had an episode of MD in the year between the time 1 and time 2 assessments influenced the time 2 personality scores, after controlling for the time 1 personality scores.

A LONGITUDINAL TWIN MODEL

We constructed a longitudinal structural-equation, twin model to study the relationship between personality, as assessed at two time points, and the 1-year prevalence of MD, which occurs between these two time points. We used a multifactorial-threshold model for MD, the strengths and limitations of which have been discussed elsewhere. The model incorporates familial environmental factors influencing both MD and personality; however, as no evidence of such factors was found, these influences will not be considered here, to simplify presentation of the model.

As depicted in Figure 2, top, the model incorporates two sets of latent factors influencing N: (1) genetic and environmental common factors that influence personality as assessed at both time points and 1-year prevalence for MD and (2) genetic and environmental specific factors that influence only personality assessed at time 1, personality assessed at time 2, or 1-year prevalence of MD. In addition, the model contains two direct causal paths. The first path, termed α, assesses the direct impact of personality measured at time 1 on the subsequent 1-year prevalence of major depression after controlling for the impact of genetic and environmental risk factors common to both N and MD. This path was included in the model to evaluate whether N is related to the risk of developing MD because N directly predisposes to MD or whether the association occurs because N is an index of genetic and environmental factors that also influence the liability to MD. The second causal path, termed β, assesses the direct impact of episodes of MD in the last year on personality as assessed at time 2. Holding constant the common risk factors, this path is an expression of the direct causal effect of MD on personality. This causal effect reflects the combined impact of both scar effects of episodes of MD in the year between time 1 and time 2 and state effects of individuals who are in an episode of MD at the second assessment. In addition, to ensure identification of the two causal paths, we assumed that the common and specific genetic factors and the common environmental factors produced an equal influence on N at time 1 and time 2. This was a reasonable assumption to make because our sample included subjects in early to middle adult life and the period between the two points of measurement was relatively short. In addition, analyses in this and other samples (A. C. Heath, DPhil, N. Martin, PhD, unpublished results, 1991) indicate that in adults, genetic influences on personality are stable for periods ranging from 1 to 8 years. Because N2 has an extra causal effect from the last year prevalence of MD, the model allowed the specific environmental influences on N for time 1 and time

Continued on next page
2 to differ. Age was not included in the model because it accounted for only very small proportions of variance in the variables of interest.

A 6x6 correlation matrix, with tetrahedral, bilaterial, and prodrom-moment correlations between variables (personality at time 1, 1-year prevalence of MD, and personality at time 2) in each of two twins, was calculated separately for MZ and DZ twin pairs using the beta test version of the computer program PRELIS II. Models were fit to these matrices by asymptotic, weighted least squares using Mx29, choosing the best-fitting model based on the Akaike information criterion (AIC),30 which equals $x^2$ minus twice the degrees of freedom, 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.

Figure 1. A “time-line” of the data collection strategy used in this study. At time 1, twins completed a mailed self-report questionnaire (SRQ) that included an assessment of extraversion (E), neuroticism (N), and screening questions for a prior history of major depression (MD). At time 2, a median of 14.7 months and at least 12 months later, the twins underwent personal interviews, when their history of MD during the preceding year was assessed in detail (including the time of the onset and recovery from depressive episodes) as was their lifetime history of MD before the preceding year (including their age at onset and duration of worst episode, but not detailed dates of all episodes). At the time of the personal interview they were given an SRQ with the same items used to assess N and E at time 1. The median time from the completion of the second SRQ and the personal interview was 1 day.

E. Several studies have evaluated the second hypothesis, and most,8,10,17 but not all,18,19 suggest that being depressed increases levels of N and decreases levels of E.

One approach to evaluating a causal link between N or E and MD is to measure personality when subjects are well. Some studies find14,20-23 (and other studies do not17,24-26) personality differences between depressed patients in remission and control subjects.

This approach has at least three potential flaws. First, since N is a strong predictor of outcome in depression,27 a population of cases in remission is selected for those with less deviant personalities.8 Second, depression may produce an enduring “scar” persisting after clinical recovery28,29 so that personality in patients in remission may be more a consequence than a cause of MD. Third, the personality features associated with MD in samples from psychiatric facilities may reflect help-seeking attributes, since only a minority of patients with MD seek specialist care.30

Two other methodologic approaches may be more definitive: longitudinal investigations and family/genetic studies. If certain personality traits predispose to MD, then they should predict episodes of depression, particularly in individuals with no prior history of MD. In four studies examining this question, all found that N or N-like traits predicted future episodes of MD.31-34 Two studies examined individuals with no prior episodes of depression and both found that N predicted the first onset of MD, while E did not.33,34

Since both personality10,35 and the predisposition to MD36 are influenced by familial/genetic factors, a genetic epidemiologic approach may provide insight into the relationship between these two traits that are free of the confounds found in clinical studies. Of the six studies using this approach, three support the hypothesis that N or N-like traits reflect the familial vulnerability to MD,12,37,38 while three found no such evidence.39-41 Two found evidence that low levels of E or E-like traits have a familial relationship with MD,12,30 while four did not.37-39,41

<table>
<thead>
<tr>
<th>Table 1. Types of Regression Analyses Performed*</th>
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<td>Scar</td>
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*LT indicates lifetime; MD, major depression.
measured at the same time as 1-year and lifetime prevalence of MD were assessed at personal interview. We address the following specific questions from an epidemiologic perspective.

1. Are future episodes of MD predicted by N or E and is this effect present in individuals without prior episodes of depression?
2. Could the apparent predictive effect result from N or E, reflecting prodromal symptoms of depression?
3. Are N or E altered by being in an episode of MD (eg, a "state" effect)?
4. Do prior episodes of MD influence N or E (eg, a "scar" effect)?

Using a longitudinal genetic-epidemiologic model for the relationship between personality and MD, this association can be broken down into the following four components: (1) genetic factors that influence both personality and liability to MD; (2) environmental factors that influence both personality and the liability to MD; (3) a direct causal effect of personality on MD; and (4) a direct causal effect of MD on personality.

RESULTS

EPIDEMIOLOGIC ANALYSES

Descriptive, Causal, and Prodromal Analyses

The results of the descriptive, causal, and prodromal analyses for N are shown in Table 2. In the descriptive analyses, both N1 and N2 were highly significantly and positively related to lifetime and to 1-year prevalence of MD. An increase of 1 SD in N conveys a 50% to 60% higher lifetime risk and 100% to 130% higher 1-year risk of developing MD. Neuroticism measured at either time predicts 1-year MD more strongly than lifetime MD, and N2, assessed around the time of the personal interview, more strongly predicts both lifetime and 1-year MD than does N1 obtained 17 months before.

In the causal analyses in which twins with MD before the first assessment were eliminated from the sample, N1 strongly and significantly predicted the new onset of MD in the year prior to the time 2 assessment. A 1-SD increase in N produces a 90% to 100% increase in the risk of developing subsequent MD.

In the prodromal analyses N1 did not predict time to onset of a subsequent episode of MD. This suggests that the association between N1 and 1-year prevalence of MD is unlikely due to N reflecting prodromal symptoms of depression. The same results were obtained if the sample was restricted to those who had no prior history of MD.

For E, the descriptive, causal, and prodromal analyses revealed only nonsignificant relationships with MD (Table 2).
State and Scar Analyses

As seen in Table 3, the state analyses indicate that meeting criteria for MD at time 2 highly significantly increases levels of N2. The scar analyses demonstrate that one or more episodes of MD between times 1 and 2 produced a modest but significant increase of N2. By contrast, neither the state nor the scar analyses produced any significant effect on E assessed at time 2.

Genetic Epidemiologic Models

These analyses were restricted to the sample of 707 pairs with complete information available in both twins. The mean (±SD) age of this subsample was 30.5±7.6 years, and the mean and median time between completion of the time 1 and time 2 questionnaires were 17.3±5.7 months and 14.7 months, respectively. Of the 1414 twins in this sample, 136 (9.6%) reported one or more episodes of MD in the year prior to the time 2 assessment, with the mean and median time from the first assessment to first onset being 8.6±6.2 months and 7.8 months, respectively. Controlling for age and zygosity, membership in this subsample did not significantly influence either the frequency of or the twin concordance for 1-year prevalence of MD ($\chi^2=1.04$ and 0.52, respectively; $df=1$; NS for both). Although MZ twins had more frequent contact with one another than did DZ twins, after controlling for zygosity, this had no effect on similarity between twins in 1-year prevalence of MD in this sample ($\chi^2=0.39$; $df=1$; NS).

Simple Regression Models

Previous family studies assessed the association between the proband's lifetime history of MD and relatives' personalities, sometimes controlling for the relatives' histories of MD.2,3,7-10 We performed similar analyses using personality as assessed at time 2 in two ways ($df=1$; 610 for both): controlling either for the twin's current status of depression or for her lifetime history of MD. In both analyses, each twin's history of MD was used to predict her cotwin's personality corrected for the correlated observations in twin pairs. With zygosity, age, and the twin's current status of depression as control variables, the cotwin's lifetime history of MD significantly predicted the level of N ($t=5.14$) but not E ($t=.58$; $P=.57$). If lifetime history of MD is used as a control variable instead of current status, the results were similar—the cotwin's lifetime history of MD significantly predicted her twin’s level of N ($t=3.39$; $P=.001$) but not E ($t=.38$; $P=.70$).

| Table 2. The Ability of Neuroticism and Extraversion to Predict Risk for Major Depression (MD) Based on 'Descriptive,' 'Causal,' and 'Prodromal' Regression Analyses* |
|---------------------------------|---------------------|---------------------|----------|---------------|----------|--------|--|
| **Type of Analyses** | **Exclusion Criteria** | **Sample** | **Key Variable** | **Neuroticism** | **Extraversion** | **b** | **RR** | **P** |
| **Descriptive** | None | Total | 2025 | 636 | N1 | LTMD | 1.46 | 1.51 | .0000 |
| | None | With MD | 1733 | 543 | N2 | LTMD | 1.84 | 1.64 | .0000 |
| | None | Independent | 2025 | 209 | N1 | 1-y MD | 2.40 | 1.97 | .0000 |
| | None | Dependent | 1733 | 175 | N2 | 1-y MD | 3.02 | 2.27 | .0000 |
| | Previous MD by SRQ | 1579 | 118 | N1 | 1-y MD | 2.34 | 1.89 | .0000 |
| | Previous MD by interview | 1477 | 88 | N1 | 1-y MD | 2.48 | 1.98 | .0000 |
| | Previous MD by SRQ or interview | 1260 | 60 | N1 | 1-y MD | 2.33 | 1.86 | .0000 |
| | Prodromal† | No 1-y MD | 206 | 209 | N1 | TTMD | 0.11 | .95 |
| **Causal** | None | Total | 2022 | 685 | E1 | LTMD | -0.21 | .19 |
| | None | With MD | 1733 | 543 | E2 | LTMD | -0.20 | .25 |
| | None | Independent | 2022 | 209 | E1 | 1-y MD | -0.22 | .38 |
| | None | Dependent | 1733 | 176 | E2 | 1-y MD | -0.27 | .32 |
| | Previous MD by SRQ | 1577 | 118 | E1 | 1-y MD | -0.56 | .10 |
| | Previous MD by interview | 1475 | 88 | E1 | 1-y MD | -0.50 | .19 |
| | Previous MD by SRQ or interview | 1258 | 60 | E1 | 1-y MD | -0.91 | .07 |
| | Prodromal† | No 1-y MD | 206 | 209 | E1 | TTMD | 0.07 | .96 |

*Numbers vary between analyses of neuroticism and extraversion because a few subjects completed one scale but not the other. ($\chi^2$ or t values for regression analyses are available on request.) RR indicates relative risk (only presented if regression analysis is statistically significant); LT, lifetime; TTMD, time to major depression; SRQ, self-report questionnaire; N1 and N2, neuroticism at time 1 and time 2 assessments, respectively; and E1 and E2, extraversion at time 1 and time 2 assessments, respectively.

†Linear regression. All others are logistic regression analyses.
Twin Model Fitting

Because prior analyses indicated no relationship between E and MD (which was confirmed by model fitting), our analyses focused solely on N. Three patterns in the correlation matrices for MZ and DZ twins for N1, last year MD, and N2 (Table 4) are worthy of note. First, within individual twins, the cross-trait correlations are similar in both zygoitys groups. For example, the mean correlations between N1 and N2 for MZ and DZ twin pairs are .68 and .69, respectively, while the mean correlations between N1 and last year MD are .36 and .41, respectively. Second, the cross-twin, within-trait correlations are substantially higher in MZ than in DZ twins for N1 (+.41 vs +.13), last year MD (+.41 vs +.25), and N2 (+.43 vs +.17). Third, the cross-twin, cross-trait correlations are substantially higher in MZ vs DZ twins. The mean correlation between N1 in one twin and last year MD in her cotwin was .30 in MZ twins and .13 in DZ twins.

A Longitudinal Twin Model for N and MD

The full model (model 1, Figure 2, top) fit well ($\chi^2=28.60; df=28; P=.43; AIC=-27.40$). Since univariate analyses provided no evidence of familial environmental effects on N (results available on request) or last year MD, in model 2, we set all these paths, both for the common and specific factors, to zero. This resulted in little change in the fit of the model and a substantial improvement in the AIC ($\chi^2=29.22; df=32; AIC=-34.78$). In model 3, we set $\alpha$ (the causal path coefficient from N1 to last year MD) to zero. This resulted in almost no change in the fit of the model and a further improvement of the AIC ($\chi^2=29.27; df=33; AIC=-36.73$). In model 4, $\alpha$ was allowed to be free but $\beta$ (the state/scare path coefficient from preceding year MD to N2) was set to zero. This resulted in a worse fit and a less favorable AIC ($\chi^2=30.23; df=33; AIC=-35.77$) than that seen in model 3. In model 5, we set both $\alpha$ and $\beta$ to zero, but this resulted in a substantial worsening of the fit of the model and an accompanying deterioration in the AIC ($\chi^2=34.64; df=34; AIC=-33.36$). For model 6, we returned to model 3 but set the genetic specific paths to N1 and N2 to zero (termed $\alpha_s$, in Figure 2, top). This resulted in a modest worsening in the fit of the model and a small improvement in the AIC ($\chi^2=31.15; df=34; AIC=-36.85$). No further improvements in fit were possible (details available on request), so that model 6 was the best-fitting model. The fit of model 6 was only modestly preferable to several other models, especially 3.

The parameter estimates for the best-fit model 6 are seen in Figure 2, bottom. The correlation between last year MD and N2 can be decomposed into the following three components: shared genetic risk factors (+.329), shared environmental risk factors (+.094), and direct causal effects of MD on N (+.052). This model suggests that of the total correlation of N and the liability to MD, approximately 70% is due to shared genetic risk factors, 20% to shared environmental risk factors, and 10% to a direct causal effect of MD on N. The model clarifies the degree of overlap in the genetic and the environmental risk factors for MD and N. The proportion of variance in liability to MD due to genetic factors shared with N and those unique to MD are 0.264 and 0.205, respectively, so that of the total heritability of liability to MD, approximately 55% is shared with N and 45% is unique to MD. The proportion of variance in liability to MD that results from environmental risk factors shared with N compared with those factors unique to MD are estimated at 0.033 and 0.498, respectively. Of the total estimated environmental contribution to the liability to MD, approximately 95% is unique to MD and 5% is shared with N.

**Table 3. The Ability of Current or Prior Episodes of Major Depression (MD) to Influence Neuroticism or Extroversion Scores Based on 'State' and 'Scar' Regression Analyses**

<table>
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<tr>
<th>Types of Analyses</th>
<th>Exclusion Criteria</th>
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<th>Key Variables</th>
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<th>$P$</th>
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<td>MD2, E1, E2</td>
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<tr>
<td>Scar</td>
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<td>1-y MD, E1, E2</td>
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</table>

*MD1 and MD2 indicate twins meeting criteria for MD at the time 1 and time 2 assessments, respectively; N1 and N2, neuroticism at time 1 and time 2 assessments, respectively; E1 and E2, extraversion at time 1 and time 2 assessments, respectively; and SRQ, self-report questionnaire. (The $b$ values for regression analyses are available on request.)

The goal of this study was to clarify, from both an epidemiologic and genetic-epidemiologic perspective, the re-
relationship between MD and two important personality dimensions, N and E.

EXTRAVERSION AND MD

In this general-population, female-twin sample, we found no evidence for a significant relationship between E and MD. Levels of E did not significantly predict lifetime or 1-year prevalences nor did E prospectively predict first onset of MD. Neither the state of being depressed nor the scar of previous episodes of MD significantly altered levels of E. These results are inconsistent with those from clinical studies that found depressed patients to demonstrate decreased levels of E and that episodes of MD lower levels of E. This discrepancy might be partly due to differences in scale content, as all of these clinical studies used the Maudsley Personality Inventory, which, in contrast to the more recent Eysenck Personality Questionnaire, included items reflecting impulsivity to assess E. However, both the general population studies that found that E did not predict future episodes of MD used an E scale containing impulsivity items.

Consistent with four of the previous family studies to address this issue, we also found that a twin's level of E was unrelated to her cotwin's history of MD. Of the two studies reporting such a relationship, one used no control group and compared relatives of depressed probands with population norms, and the other used an instrument with two major E-like traits, one of which (shy vs venturesome) modestly differentiated relatives of depressed from those of control probands, while the other (reserved vs outgoing) did not. Given that our sample size was considerably larger than those in other studies, our negative finding is not likely to be due to low statistical power. While further research is needed to reach a definitive conclusion, our results suggest that it is unlikely that E as measured in the Eysenck Personality Questionnaire is substantially related to the familial liability to MD.

NEUROTICISM AND MD

An Epidemiologic Perspective

In our epidemiologic analyses, we found strong and consistent associations between MD and N. Neuroticism was strongly related to both lifetime and 1-year prevalence of MD. Levels of N prospectively strongly predicted new onsets of MD, and these results were not sensitive to the method used for screening out individuals with prior episodes of depression. Consistent with previous prospective studies, these results provide strong evidence that N, or factors indexed by N, are causally related to the development of MD.

The ability of N to predict MD could, however, arise, because N is a sensitive index of prodromal symptoms of depression. If so, then in those who develop an episode of MD, N should predict time to onset. However, we found no relationship between N and time to onset of MD. The ability of N to predict episodes of MD does not appear to result from N reflecting prodromal symptoms of depression.

Other mechanisms may contribute to the relationship between MD and N. In most but not all studies, levels of N were higher in patients with depression than in those in remission. We found a similar effect in individuals in whom a true baseline measure of N was available. In understanding the relationship between N and MD, the influence of the state of depression on levels of N should be taken into account.

Episodes of MD may also produce enduring scars on personality. In contrast to previous unsuccessful attempts to detect scars on depression-related cognitions, interpersonal functioning, or personality, we found modest statistical support for a scar effect on N. We cannot, however, rule out that this effect is due to residual mild symptoms of depression or does not endure beyond a year. Our data show that individuals with an episode of MD in the preceding year who report being recovered have modestly higher levels of N than can be predicted from their baseline levels of N.

A Genetic Epidemiologic Perspective

Consistent with the results of three previous family studies, we found that controlling for a twin's current or lifetime history of MD, her level of N was strongly predicted by her cotwin's history of MD. Of the three studies that did not find such a relationship, two had no control group and used only previously published population norms, and one studied a small number of adolescent offspring of depressed patients and controls. Our results provide considerable support for the hypothesis that N reflects the familial liability to MD.

We attempted a more definitive resolution of this
issue by developing a genetic epidemiologic model for N and MD with three major goals in mind. First, we wished to quantify the importance of the various sources for the association between N and the liability to MD. Second, we wanted to move beyond the descriptive epidemiologic models to clarify the roles played in this association by genetic and environmental factors. Third, we wished to test whether N was indeed directly causative of MD or whether N was itself an index for genetic and/or environmental risk factors that in turn predisposed to MD.

To address these questions, we developed a model that took advantage of both the twin and longitudinal structure of our data. In particular, we wished to capture the temporal sequence of the three key variables—N assessed at time 1, 1-year prevalence of MD occurring between time 1 and time 2, and N assessed at time 2 (Figure 2, top). This model was not ideal for three reasons. First, it did not include the information we had on the lifetime history of MD before the first assessment. However, we did not record the beginning and end of all episodes of MD before the previous year so that we lacked sufficient details to enable us to include them satisfactorily in the model. More standard trivariate twin models for the relationship between N, as assessed at two time points, and lifetime MD were tested, and provided qualitatively similar results in suggesting that genetic factors accounted for most of the observed association.

Second, scar and state effects were confounded. Their effects could be disentangled in the epidemiologic analyses by excluding subsamples of twins. This cannot be easily done in structural equation models in which the correlational structure may be sensitive to truncation effects that occur when selected subsamples are eliminated. Third, to simplify the model, we eliminated a correlation between the specific genetic factors that influence N at the first and second assessments. These specific factors were not included in the final model, and fitting a more complex model that allowed for this correlation produced no substantive changes in results.

The best-fitting submodel contained genetic and individual specific environmental risk factors that were common to MD and both measurements of N, individual specific environmental factors unique to MD and N, and individual specific genetic factors unique to MD (Figure 2, bottom). In addition, the best-fitting model contained no direct causal path from N to MD, suggesting that the causal effect of N on the liability to MD is entirely mediated through the genetic and environmental risk factors common to both traits.

However, the best-fitting model did contain a causal path from MD to N that represented the combined effects of scar and state. Although present, the magnitude of this causal relationship was small, accounting for only a modest proportion of the overall correlation between N and the liability to MD.

The correlation between N and the liability to MD was “decomposed” using the best-fitting model and sug-

gested that most of the observed correlation was due to genetic factors that influenced both traits. Individual specific environmental experiences were found that increased both levels of N and the risk for MD, but their effect was relatively modest. The genetic risk factors involved in N and MD were, in our results, much more closely related than were their environmental risk factors.

Limitations

The results of this study should be interpreted in the context of three potential methodologic limitations. First, the sample is restricted to women. Given gender differences both in personality and the risk for MD, it would be unwise to assume that the causal relationships between the two would be the same across sexes.

Second, our epidemiologic causal analyses were based on eliminating those twins from our sample who had experienced previous episodes of MD. As with recall of other medically relevant information, we and others found that the reliability of the one-time assessment of a lifetime history of MD is only moderate. Some individuals who denied having had prior episodes of MD probably had such episodes and were falsely considered new-onset cases. We addressed this problem by defining as previously affected those individuals who responded to any one of two different assessments of prior episodes of MD. We are somewhat reassured that when using this broad definition of prior episodes our results did not substantially differ from those using either assessment alone (Table 2).

Third, personality was assessed in this study by self-report. Such assessments in this sample agree well with those reported by the cotwin. Furthermore, the magnitude of genetic and environmental influences on N and E were very similar when assessed by self- vs informant-reports.

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