Published in final edited form as:
J Abnorm Psychol. 2010 May ; 119(2): 320–330. doi:10.1037/a0019035.

Posttraumatic Stress Disorder and the Genetic Structure of Comorbidity

Erika J. Wolf,
National Center for PTSD, VA Boston Healthcare System and Department of Psychology, Boston University

Mark W. Miller,
National Center for PTSD, VA Boston Healthcare System, Department of Psychology, Boston University, and Department of Psychiatry, Boston University School of Medicine

Robert F. Krueger,
Departments of Psychology and Psychiatry, Washington University in St. Louis

Michael J. Lyons,
Department of Psychology, Boston University

Ming T. Tsuang, and
Department of Psychiatry, University of California, San Diego and Harvard Institute of Psychiatric Epidemiology and Genetics

Karestan C. Koenen
Department of Society, Human Development, and Health and Department of Epidemiology, Harvard School of Public Health

Abstract

This study used structural equation modeling to examine the genetic and environmental architecture of latent dimensions of internalizing and externalizing psychiatric comorbidity and explored structural associations between posttraumatic stress disorder (PTSD) and these dimensions. Data were drawn from the Vietnam Era Twin Registry and included lifetime diagnoses for PTSD and a range of other psychiatric disorders for 3,372 male–male twin pairs. Examination of the phenotypic structure of these disorders revealed that PTSD cross-loaded on both Internalizing and Externalizing common factors. Biometric analyses suggested largely distinct genetic risk factors for the latent internalizing and externalizing comorbidity dimensions, with the total heritability of the Externalizing factor (69%) estimated to be significantly stronger than that for Internalizing (41%). Nonshared environment explained the majority of the remaining variance in the Internalizing (58%) and Externalizing (20%) factors. Shared genetic variance across the 2 dimensions explained 67% of their phenotypic correlation (r = .52). These findings have implications for conceptualizations of the etiology of PTSD and its location in an empirically based nosology.

Keywords

posttraumatic stress disorder; structure of comorbidity; behavioral genetics; structural equation modeling

Correspondence concerning this article should be addressed to Mark W. Miller, National Center for PTSD (116B-2), VA Boston Healthcare System, 150 South Huntington Avenue, Boston, MA 02130. mark.miller5@va.gov.

Comorbidity (i.e., the co-occurrence of two or more diagnoses) is highly common among mental disorders (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Epidemiologic studies have shown that psychiatric disorders co-occur in patterns that constitute broad classes, or spectra, of psychopathology; disorders within a given spectrum are thought to reflect the manifestation of a common vulnerability to psychopathology of that type (Krueger, 1999; Markon, 2009; Watson, 2005). These common factors, or latent dimensions of psychopathology, are modeled through factor analysis of the covariation among diagnoses. Recent studies suggest that the covariation of the anxiety and unipolar mood disorders is accounted for by a common factor termed *internalizing*. A second factor, termed *externalizing*, has been found to underlie the frequent co-occurrence of the substance-use disorders and antisocial personality disorder (ASPD; Krueger, 1999; Krueger, Caspi, Moffitt, & Silva, 1998; Krueger, Chentsova-Dutton, Markon, Goldberg, & Ormel, 2003; Krueger, McGue, & Iacono, 2001; Miller, Fogler, Wolf, Kaloupek, & Keane, 2008; Slade & Watson, 2006; Vollebergh et al., 2001). Data from children suggest that attention-deficit hyperactivity disorder may also covary primarily with disorders in the externalizing spectrum (Coolidge, Thede, & Young, 2000; Dick, Viken, Kaprio, Pulkkinen, & Rose, 2005; Young et al., 2009). These factors constitute essential components of the structure of mental illness and may provide useful targets for future genetic association and biomarker discovery studies. Further, these dimensions have been proposed as organizing rubrics for the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM–V*) and the *International Classification of Diseases* (11th ed.; *ICD–11*); specifically, the internalizing, or "emotional disorders" (Goldberg, Krueger, & Andrews, 2009), and externalizing domains have been advanced as part of a metastructure that would reorganize the *DSM* and *ICD* according to the common factors underlying classes of related disorders (Goldberg et al., 2009; Krueger & South, 2009). This study examined the relative contributions of genetic and environmental influences to the internalizing and externalizing dimensions of psychopathology using data from the Vietnam Era Twin Registry (VETR).

One prior twin study examined the genetic and environmental structure of a wide array of disorders spanning both the internalizing and externalizing spectra. Kendler, Prescott, Myers, and Neal (2003) reported that a single genetic factor was associated with liability to major depression, generalized anxiety disorder (GAD), and phobic disorders, whereas a second genetic factor explained the majority of shared liability to substance-use disorders, antisociality, and conduct disorder. The authors examined the extent to which the same genetic and environmental effects contributed to the development of multiple disorders within the internalizing and externalizing spectra, but they did not estimate directly the heritability of the common factor underlying these spectra. Doing so would offer several potential advantages. First, if notable heritability of the latent dimensions is observed, then the internalizing and externalizing spectra can be conceptualized as endophenotypic traits that may represent continuous genetic liability factors better than putatively discrete, individual *DSM* constructs. Second, the analysis of common factors is more conceptually consistent with the goal of examining the heritability of comorbidity, given that the primary unit of analysis in this approach is disorder overlap (i.e., covariance) rather than individual disorders. Third, the latent modeling or "common factor" approach separates true nonshared environmental variance (environmental effects making each twin unique) from variance attributed to the unreliability of a specific individual diagnosis, whereas the two sources of variance are conflated in traditional biometric modeling approaches (see the following).

Three prior studies, focusing on externalizing disorders, have examined the genetic and environmental contributions to a *latent* psychopathology factor. Two of these studies found that a single genetic factor explained approximately 80–85% of the variance in externalizing, also termed "behavioral disinhibition" by Young et al. (Krueger et al., 2002; Young, Stallings, Corley, Krauter, & Hewitt, 2000), whereas the third study reported

somewhat lower heritability estimates for the behavioral disinhibition factor (.43–.58; Young et al., 2009). No prior study has estimated the differential genetic and environmental contributions to the common factor underlying internalizing comorbidity or simultaneously modeled these influences on both the internalizing and externalizing latent dimensions. This is an important step in understanding the conceptual status of the internalizing and externalizing latent dimensions. If both dimensions are phenotypically coherent and heritable, then both dimensions can be well conceived of as heritable sources of observed comorbidity (i.e., as endophenotypic constructs that account for comorbidity by channeling genetic influences shared among disorders within a specific spectrum).

This study was designed to address this gap in the literature by modeling the genetic and environmental influences on both internalizing and externalizing psychopathology factors using psychiatric diagnostic data from the VETR, a large twin registry of mono- and dizygotic male–male twin pairs who served in the military during the Vietnam era and who have undergone extensive diagnostic assessments since then. We hypothesized that model fitting would reveal evidence for one genetic factor primarily associated with an internalizing comorbidity factor and a second, distinct, genetic factor linked to the externalizing dimension. In light of prior evidence for a moderate correlation between the internalizing and externalizing factors (in the r = .40–.60 range; Krueger, 1998, 1999; Slade & Watson, 2006; Vollebergh et al., 2001), we expected to find overlap in the genetic influences on internalizing and externalizing. We also examined the residual genetic and environmental structure of the individual mental disorders that comprise the two psychopathology factors, as prior work has demonstrated the presence of independent, disorder-specific genetic and environmental effects (e.g., a genetic effect specific to alcohol-use disorders and a separate genetic effect specific to drug-use disorders; Kendler et al., 2003).

The second aim of this study was to compare explicitly the heritability of internalizing versus externalizing psychopathology. Prior work suggests that the heritability (h^2) of individual internalizing disorders (which has generally been found to be in the .10–.35 range; Hettema, Prescott, Myers, Neale, & Kendler, 2005; Kendler et al., 2003) tends to be weaker than the heritability of individual externalizing disorders (in the .18–.66 range; Kendler et al., 2003) or the externalizing common factor (h^2 = .43–.84; Krueger et al., 2002; Young et al., 2000, 2009). Based on this, we hypothesized that the heritability of the latent externalizing dimension would be greater than that of the latent internalizing dimension. The use of the common factor approach lends itself to this comparison particularly well, as latent variables contain only true-score variance; error variance has been removed by virtue of including multiple indicators (i.e., diagnoses) of the common factor. Error variance is estimated in the portion of indicator residual variance (reflecting variance in each diagnosis that is not captured by the common factor) that is due to disorder-specific nonshared environmental effects. Although it is impossible to distinguish between measurement error and disorder-specific nonshared environmental effects on each individual diagnosis, the use of latent psychopathology dimensions does allow for the separation of true nonshared environmental effects from measurement error on the latent dimensions. This partitioning of true-score and error variance is a compelling approach to estimating the heritability of internalizing and externalizing psychopathology as there is more true-score variance to be explained in the common factor relative to the individual disorders (thus, estimates of heritability are likely to be underestimated when individual disorders are examined because of their greater unreliability). Consistent with this, Kendler, Karkowski, and Prescott (1999) demonstrated that when measurement unreliability is controlled for (i.e., by having multiple assessment points), heritability estimates increase relative to when it is not. The use of common factors may exert the same type of effect on the heritability estimates relative to the use of individual disorders.

The third aim of the study was to clarify the association between posttraumatic stress disorder (PTSD) and internalizing and externalizing. Prior studies (Cox, Clara, & Enns, 2002; Miller et al., 2008; Slade & Watson, 2006) that have examined this issue have found PTSD to align with a subset of the internalizing disorders characterized by worry, rumination, and depressive disorders, the *anxiousmisery* (Krueger, 1999) or *distress* (Krueger & Markon, 2006; Slade & Watson, 2006; Watson, 2009) disorders: depression, dysthymia, and GAD. Further, these studies suggested that PTSD covaries more strongly with the anxious-misery disorders than with disorders characterized by paroxysmal fear (i.e., the fear disorders: panic disorder and the phobias; Krueger, 1999). However, other research suggests a substantive link between PTSD and disorders of the externalizing spectrum. Specifically: (a) PTSD shares genetic influences with disorders of both the internalizing and externalizing spectra (Chantarujikapong et al., 2001; Koenen, Fu, et al., 2008; McLeod et al., 2001; Scherrer et al., 2008; Xian et al., 2000); (b) adults with PTSD are more likely to have histories of childhood externalizing disorders (Gregory et al., 2007; Koenen et al., 2005; Koenen, Moffitt, et al., 2008; Koenen, Moffitt, Poulton, Martin, & Caspi, 2007), compared with adults with other types of anxiety disorders (Gregory et al., 2007); and (c) many individuals with PTSD exhibit a predominantly externalizing pattern of comorbidity characterized by problems in the domain of impulse control, antisociality, and substance abuse (Miller, Greif, & Smith, 2003; Miller, Kaloupek, Dillon, & Keane, 2004; Miller & Resick, 2007). Accordingly, we hypothesized that the best fitting model would be one in which PTSD cross-loaded on both Internalizing and Externalizing factors.

Method

Participants

The sample included 1,874 monozygotic (MZ) and 1,498 dizygotic (DZ) male–male twin pairs from the VETR (a total of 6,744 individuals). As previously described (Eisen, Neuman, Goldberg, Rice, & True, 1989; Henderson et al., 1990), this nationally distributed sample included active military duty twin pairs from the Vietnam War era (born between 1939 and 1957). These data are from the 1992 Harvard Twin Study of Drug Abuse and Dependence. The response rate was 79.6%. The mean age of the sample in 1992 was 44.6 (*SD* = 2.8). Participants reported their ethnicity as follows: White, non-Hispanic (90.4%); African American (4.9%); Hispanic (2.7%); and Native American; or other (2.0%). Zygosity was determined with a questionnaire and blood-group typing methodology, achieving 95% accuracy (Eisen et al., 1989).

Measures

The data that were analyzed were lifetime *DSM–III–R* (American Psychiatric Association, 1987) diagnoses for PTSD, major depression, dysthymia, GAD, panic disorder, ASPD, alcohol abuse/dependence, and substance abuse/dependence. The diagnoses were obtained over the telephone using the Mental Health Diagnostic Interview Schedule (Version III—Revised; DIS–III–R; Robins, Helzer, Cottler, & Golding, 1998). Details of the assessment procedure have been reported previously (Koenen et al., 2002; Lyons et al., 1998); the reliability of the diagnoses was assessed by having a second rater re-interview 146 participants over a period of, on average, 466 days (± 50.5; Koenen et al., 2002; Slutske et al., 1998, 2001). Disorders from the externalizing spectrum tended to have higher Kappa coefficients (*M* = .57) relative to disorders from the internalizing spectrum (*M* = .36; Koenen et al., 2002; Slutske et al., 1998, 2001). Rates of psychopathology are presented in Table 1 for the full sample.

Statistical Analysis

The diagnostic data examined for the phenotypic and biometric analyses were three-level categorical variables: Each diagnosis was coded as *absent* (no symptoms), *subthreshold* (one or more symptom present but did not meet full diagnostic criteria on the DIS–III–R), or *present* (full diagnostic criteria met). Individuals never exposed to trauma (54% of the full sample) were coded as negative for the PTSD diagnosis. Diagnostic data were missing for some participants (maximum amount of missing data for any diagnosis was 0.6% of the full sample for the PTSD diagnosis), but data from these participants were still included in the analyses, as we employed statistical estimators that model missingness directly (see the following). All structural analyses were conducted with the Mplus 5.11 (Muthén & Muthén, 2007) statistical modeling software.

Phenotypic analyses—We first examined the phenotypic structure of comorbidity in this sample using confirmatory factor analysis. To do so, we selected one twin from each twin pair at random and compared the fit of two competing models (described in the following) in this subsample. The advantage of examining a subsample versus all participants at once is that the former approach allowed us to use an estimator which yields more standard fit statistics for evaluating model fit, as the latter approach would require the use of the robust maximum likelihood estimator to account for the nonindependence of twin pairs and would yield fewer such statistics. A second advantage is that it affords consistency in the estimation process employed across the phenotypic and biometric analyses. In the first model, we specified a two-factor structure to the disorders in which major depression (the marker indicator), dysthymia, GAD, PTSD, and panic disorder were specified to load on the Internalizing factor and ASPD (the marker indicator), alcohol abuse/dependence, and drug abuse/dependence were specified to load on the Externalizing factor. We did not model latent anxious-misery versus fear factors, as panic disorder was the only diagnosis available which would have been expected to load on the fear factor. We then compared the fit of the traditional two-factor model with a less restricted comparison model in which PTSD was allowed to cross-load on both the Internalizing and Externalizing factors.

We used the WLSMV estimator, a mean and variance adjusted weighted least squares estimator (because of the categorical nature of the data), and missing data were modeled directly under this estimator (as opposed to eliminating missing observations pairwise or listwise). We evaluated the fit of the models using statistics from the absolute (χ^2), parsimony (root-mean-square error of approximation [RMSEA]), and comparative-fit (Tucker–Lewis index [TLI] and comparative fit index [CFI]) classes of indices, following cutoff guidelines recommended by Hu and Bentler (1999). Specifically, RMSEA values less than .06 and CFI and TLI values ≥.95 were considered to be indicative of good model fit. We examined the relative fit of the two phenotypic models using a chi-square difference-testing approach. A significant difference in the chi-square values between two models indicates that the nested model containing a subset of free parameters from the parent model significantly degrades model fit (i.e., eliminating paths that are actually necessary degrades model fit).

Biometric analyses—We retained the best fitting measurement model from the phenotypic analyses to use in biometric analyses examining the relative contributions of genetic and environmental influences on latent internalizing and externalizing comorbidity. All biometric models were tested with the mean and variance adjusted weighted least squares estimator, consistent with the phenotypic analyses. We examined the fit of a series of four biometric models. In the first model, we examined the fit of an independent pathway model in which the variance and covariance of the individual diagnoses (i.e., not the latent psychopathology dimensions) were parsed into additive genetic effects (A), common

environmental effects (C), and unique or nonshared environmental (E) effects. Two sets of ACE factors were modeled: one set to explain the variance and covariance of the individual internalizing disorders and the second set for the individual externalizing disorders. In addition, we parsed variance remaining in each diagnosis into disorder-specific genetic and environmental effects. The independent pathway model provided a useful baseline to compare the fit of the more parsimonious common pathway (i.e., latent phenotype) models.

We then tested a series of three common pathway models. Figure 1 displays the models that were tested in this common pathway model-testing sequence. In the first common pathway model (the simple ACE model), we parsed variance in the Internalizing and Externalizing comorbidity factors into their genetic and environmental determinants. Separate ACE factors were modeled for the two latent comorbidity factors. Preliminary results indicated that the common environmental pathway to internalizing was negligible, consistent with other twin investigations of the genetic and environmental contributions to internalizing disorders (Hettema et al., 2005; Kendler et al., 2003). Given that parameter estimates close to the boundary of acceptable values (i.e., zero) can cause a model to fail, this pathway was set to zero in all common pathway models. In the second common pathway model, we evaluated whether there was shared genetic variance contributing to both internalizing and externalizing psychopathology. To do so, we fit a Cholesky model (the Cholesky-A model) to the data in which the first latent genetic factor (A_1 in Figure 1) was allowed to also predict the Externalizing factor (Path a1-b in Figure 1), whereas a second set of ACE factors was retained as unique predictors of the Externalizing factor (A_2, C_2, and E_2 in Figure 1). Finally, we examined the fit of a third common pathway model (the Cholesky-AE model) in which the first genetic (A_1) and nonshared environment factors (E_1, i.e., those associated with the Internalizing factor) were allowed to cross-predict the Externalizing factor (Pathways a1-b and e1-b in Figure 1, respectively) and unique genetic (A_2) and environmental (C_2 and E_2) factors were also set to predict the Externalizing factor (Pathways a2, c2, e2, in Figure 1).[1]

The fit of each model was examined using the same fit indices and cutoffs described for the phenotypic models. The necessity of the cross genetic pathway (a1-b in Figure 1) in the second common pathway model and of the cross nonshared environment pathway (e1-b in Figure 1) in the third common pathway model were evaluated by constraining these paths to zero (one at a time) to determine if doing so degraded model fit, as determined by a significant Wald chi-square statistic.

Results

Phenotypic Analyses

The model in which major depression, dysthymia, GAD, panic disorder, and PTSD were set to load on the Internalizing factor, whereas ASPD, alcohol abuse/dependence, and drug abuse/dependence were set to load on the Externalizing factor yielded good model fit, $\chi^2(16, N = 6744) = 153.21$, $p < .001$, RMSEA = .05, CFI = .99., TLI = .99. The model which allowed PTSD to cross-load on both the Internalizing and Externalizing factors also yielded good model fit, $\chi^2(15, N = 6744) = 93.75$, $p < .001$, RMSEA = .04, CFI = 1.0, TLI = .99. The chi-square difference test to compare the fit of the two models revealed that the less restrictive parent model in which PTSD was allowed to cross-load on both the Internalizing and Externalizing comorbidity factors provided significantly better fit to the data than did the nested model in which PTSD was set to load only on the Internalizing factor: $\Delta\chi^2(\Delta df =$

[1]Note that we never fit a model in which shared variance between Internalizing and Externalizing was estimated to be due to the first common environment factor (C_1), because this pathway was set to zero.

1, $N = 6744$) = 46.22, $p < .001$.[2] The completely standardized factor loadings for this best fitting model are shown in Figure 2;[3] all diagnostic indicators loaded significantly on their respective factors. The correlation between the latent Internalizing and Externalizing variables in the best fitting model was $r = .52$.

To examine the uniqueness of the PTSD cross-loading on the Externalizing factor, we ran a series of four additional phenotypic models in which we allowed the other internalizing disorders to cross-load on the Externalizing factor (each in separate analyses) to determine if doing so significantly improved model fit. We set the following criteria to evaluate if the model with the cross-loading provided significantly better fit than the model without it: (a) The cross-loading disorder must load positively on both the Internalizing and Externalizing factors and must not result in a Heywood case (i.e., out of range parameter estimates); (b) the parameter estimate for the cross-loading disorder on the Externalizing factor must achieve the same minimum level of statistical significance as all other loadings on the factor (i.e., $p < .001$); (c) all fit statistics must indicate acceptable model fit in the model with the cross-loading; (d) the nested chi-square test must be statistically significant at the $p < .001$ level, given the atheoretical nature of these comparisons, the large sample size, and that the model with the PTSD cross-loading achieved this degree of improvement in model fit; and (e) the 95% confidence interval (CI) for the parameter estimate of the cross-loading disorder on the Externalizing factor must not contain the value zero.

The results of this series of analyses revealed that major depression, dysthymia, and GAD failed to meet the most basic of criteria outlined in the preceding paragraph in that all three of these disorders loaded negatively and/or nonsignificantly on the Externalizing factor (cross-loading for major depression = −.14, $p < .001$; for dysthymia = −.12, $p < .001$; and for GAD = −.01, $p = .72$), and the models with major depression and dysthymia resulted in Heywood cases. The analysis examining the panic disorder cross-loading on the Externalizing factor yielded a good-fitting model with a positive and significant cross-loading (path = .13, $p = .01$), but the statistical significance of this path was less than that of every other indicator on the factor, including that of PTSD in the prior analysis (all other indicators of Externalizing loaded at the $p < .001$ level). This result failed to meet Criterion B (see above). The 95% CI for this parameter estimate was .03–.22, which, although it did not include the value zero, clearly approached this value (in contrast, the 95% CI for the model with the PTSD cross-loading was .15–.27). Finally, although the chi-square difference test comparing the model with the panic disorder cross-loading to the model without it was significant, $\Delta\chi^2(\Delta df = 1, N = 6744) = 5.96$, $p = .01$, this difference failed to meet our Criterion D. In sum, although panic disorder evidenced a significant cross-loading on the Externalizing factor, the validity of this association was dubious given that it failed to reach the same level of statistical significance as the other indicators and failed to produce a change in chi-square at the a priori determined level of significance, and because its CI closely approached the null value. Together, this suggested that the model was not sufficiently robust for further testing. The model in which PTSD cross-loaded on Internalizing and Externalizing was retained as the best fitting model to use in subsequent common pathway biometric analyses.

[2]We also examined the relative fit of the two models using the complete dataset clustered within twin pairs and the use of the robust maximum likelihood estimator to account for the nonindependence of twin pairs. These results replicated those presented in the main text of the article by demonstrating that the model with the PTSD cross-loading on the Externalizing factor yielded superior fit to the model without this cross-loading, as judged by the log-likelihood difference test, and the lower Akaike Information Criterion and Bayesian Information Criterion values for the former model.

[3]The factor loadings shown in Figure 2 were estimated as part of the biometric analyses but do not differ greatly from the factor loadings obtained in the phenotypic analyses.

Biometric Analyses

Cross-twin cross-diagnostic polychoric correlations for each diagnosis are listed separately for MZ and DZ twins in Table 1. The cross-twin correlations for the common Internalizing factor were $r = .44$ and $r = .16$ for MZ and DZ twins, respectively. The cross-twin correlations for the Externalizing factor were $r = .91$ and $r = .57$ for MZ and DZ twins, respectively. This pattern of correlations provides initial evidence of (a) genetic effects for both common factors, (b) nonshared environment effects for the Internalizing factor, and (c) common environment effects for the Externalizing factor. This pattern provides no evidence of common environmental effects for the Internalizing factor and suggests negligible contributions of the nonshared environment to the Externalizing factor.

In the first biometric model (the independent pathway model), one set of latent ACE factors was modeled as predictors of major depression, dysthymia, GAD, panic disorder, and PTSD, and a second set of latent ACE factors was modeled as predictors of ASPD, alcohol abuse/dependence, drug abuse/dependence, and PTSD (this was the independent pathway model most directly comparable to the phenotypic and common pathway models); residual genetic and environmental effects distinct to each diagnosis were also calculated. This model did not yield adequate model fit (see Table 2). Next, we examined the fit of the most basic common pathway model (the simple ACE model) in which one set of ACE factors was modeled as predictors of the Internalizing factor (with the c_1 pathway set to zero); a separate set of ACE factors was modeled as predictors of the Externalizing factor, and the residual variances of the individual disorders were parsed into their genetic and environmental components. This model also did not provide good fit to the data (see Table 2), however, its fit, in terms of RMSEA, TLI, and CFI, was identical to that of the independent pathway model (see Table 2). Given that the common pathway model is, by definition, more parsimonious than the independent pathway model, it was judged to be superior to the independent pathway model, as it achieved equal fit with fewer estimated parameters; therefore, the common pathway model was retained for subsequent refinement.[4]

We next sought to improve the fit of the common pathway model by fitting models that allowed for shared genetic and/or environmental variance; common etiological variance seemed likely, given the phenotypic correlation between the two dimensions. To evaluate this, we added a diagonal path reflecting shared genetic variance across the Internalizing and Externalizing common factors, in addition to modeling genetic and environmental contributions specific to the Externalizing factor (the Cholesky-A model). This model fit the data well (see Table 2),[5] and the Wald chi-square test indicated that constraining this cross genetic path to zero significantly degraded model fit, thus this cross genetic path was retained in the subsequent model. We then tested the fit of a third common pathway model (the Cholesky-AE model) in which we added a diagonal path reflecting overlapping nonshared environmental variance across the Internalizing and Externalizing factors, in addition to the path reflecting common genetic effects. This model provided excellent fit to the data (see Table 2), and the Wald chi-square test indicated that constraining the cross nonshared environmental pathway to zero significantly degraded model fit; thus, this cross

[4]Akaike Information Criterion and Bayesian Information Criterion values are often used to determine whether an independent versus common pathway model provides better fit, as these statistics take into account both model fit and model parsimony. However, these fit statistics are based on maximum likelihood estimation and are not applicable to the present study, which is based on weighted least squares estimation (because of the categorical nature of the data). In addition, although the common pathway model is nested within the independent pathway model, a simple nested chi-square test would not be appropriate for determining the superiority of one model over the other as this statistic does not take model parsimony into account and is unduly influenced by sample size. Thus, we compared the fit of the two models by examining root-mean-square error of approximation, Tucker-Lewis index, and comparative fit index values, in consideration of model complexity versus parsimony.

[5]Although the chi-square value for this model is significant, this is unlikely to indicate poor model fit given that other fit statistics are consistent with good model fit. Rather, significant chi-square values are often obtained with large sample sizes because of minor (not substantive) differences between the specified model and the data.

path was retained as part of this final, best-fitting model.[6] Standardized parameter estimates from this best fitting model are provided in Figure 2. Finally, we tested if the total heritability for the Internalizing versus Externalizing factors was equivalent. To do so, we imposed a model constraint on the best fitting model in which the genetic path for Internalizing was set to be equal to the sum of the genetic paths for Externalizing and compared the fit of this model with the best fitting model without this constraint. Imposing the constraint yielded significantly poorer model fit, Wald $\chi^2(1, N =) = 10.43$, $p = .001$.

Table 3 lists the proportion of variance in the common psychopathology factors explained by the genetic and environmental factors in the best fitting model. Results suggested that one genetic factor contributed to the majority of genetic variance in Internalizing ($h^2 = .41$), whereas a second genetic factor contributed to the majority of genetic variance in Externalizing (h^2 for genetic variance unique to Externalizing = .40). The first genetic factor also explained an additional 29% of the variance in Externalizing (i.e., there was overlapping genetic variance across the two comorbidity factors), yielding a total heritability for the Externalizing common factor of .69. Overlapping nonshared environmental effects explained 58% of the variance in Internalizing and 5% of the variance in Externalizing; in addition, nonshared environment factors specific to the Externalizing spectrum explained an additional 15% of the variance in that dimension. In total, 34% of the variance in Externalizing was shared with Internalizing (29% due to shared genetic effects and 5% due to overlapping nonshared environmental effects), and this overlap was mostly (85%) due to shared genetic effects. Finally, 9% of the variance in Externalizing was due to common environmental effects, whereas there were no common environmental effects for Internalizing.

Another way to quantify these factor-specific and overlapping genetic and environmental effects across Internalizing and Externalizing is to calculate the phenotypic correlation between the Internalizing and Externalizing factors using tracing rules and then determine the proportion of the phenotypic correlation that is due to correlated genetic versus environmental effects. We calculated the phenotypic correlation between Internalizing and Externalizing as $r = .52$. The proportion of the phenotypic correlation attributable to shared genetic effects was 67% (i.e., $r_g = .35$), whereas the proportion of the phenotypic correlation attributable to overlapping nonshared environmental effects was 33%. The correlation between the genetic factors affecting Internalizing and Externalizing (r_A) was .66, whereas the correlation between the nonshared environmental factors affecting Internalizing and Externalizing (r_E) was .50.

Table 4 lists the genetic and environmental determinants of the residual variance components for each diagnosis. The total residual variance for each diagnosis is the amount of variance in each indicator unexplained by the common factors. The table shows that for most disorders, the majority of residual variance was accounted for by the nonshared environment, which also included measurement error. Significant disorder-specific genetic effects were evident only for ASPD, GAD, and panic disorder. Disorder-specific common environmental effects were evident only for alcohol abuse/dependence, drug abuse/dependence, and PTSD.

[6]To examine whether the ordering of common factors affected model results, we ran a complementary analysis to this best fitting model in which the Externalizing factor was modeled as the first common factor and the Internalizing factor was modeled second. Results revealed identical total genetic and environmental effects on the two common factors as in our main analysis.

Discussion

This study modeled the relative strength of genetic and environmental influences on the common factors underlying the internalizing and externalizing dimensions of psychopathology. Analyses revealed that 41% of the variance in the common factor underlying disorders of the internalizing spectrum was accounted for by one genetic factor, whereas a second, distinct, genetic factor explained 40% of the variance in externalizing. These findings suggest that genes contribute in a broad and coherent manner to increase the likelihood of developing one or more of a range of related mental disorders. The first genetic factor likely corresponds to the heritable component of trait negative emotionality (i.e., the primary personality substrate for the internalizing disorders; Brown, 2007; Brown, Chorpita, & Barlow, 1998; Krueger et al., 2001; Mineka, Watson, & Clark, 1998; Watson, 2005) and is likely manifested in symptoms marked by high distress but little specificity for any single *DSM* diagnosis (i.e., generalized distress; Watson, 2009). The second factor may reflect the heritable component of trait disinhibition (i.e., the primary personality substrate for externalizing; Dick et al., 2008; Krueger et al., 2001, 2002; Krueger, Markon, Benning, & Kramer, 2005; Miller, Vogt, Mozley, Kaloupek, & Keane, 2006; Young et al., 2000, 2009). This dimension may manifest cognitively in executive function deficits (Coolidge et al., 2000; Young et al., 2009), particularly in the domain of response inhibition (Young et al., 2009). Analyses also revealed evidence of substantial genetic effects that were shared between the two dimensions of psychopathology, with 29% of the variance in Externalizing accounted for by the first genetic factor; this suggests that the biological risk factors for the development of internalizing and externalizing disorders are not fully distinct and implies that some genes may increase the risk for disorders in both spectrums. This overlap is consistent with prior studies of the phenotypic structure of comorbidity that have found moderate correlations between internalizing and externalizing factors (Krueger, 1999; Krueger et al., 1998; Slade & Watson, 2006; Vollebergh et al., 2001). This likely reflects the contribution of negative emotionality to both spectra and illustrates the ubiquity of negative emotionality in mental disorders (Khan, Jacobson, Gardner, Prescott, & Kendler, 2005; Lahey, 2009; Miller et al., 2006, 2008; Mineka et al., 1998).

Stronger heritability estimates were obtained for the Externalizing factor (total = .69) than for the Internalizing factor (.41), with the nonshared environment accounting for the largest proportion of variance (58%) in Internalizing and the largest proportion of environmental variance in Externalizing (20%). This suggests that disorders of these spectra were more strongly linked to unique life experiences that operated on the individual twin (such as the effects of war zone deployment and combat exposure) rather than common environmental factors which operated on both members of the twin pair. In addition, this study suggests that some of the nonshared environment factors that give rise to the internalizing spectra also contribute to the externalizing dimension. This suggests that individual life experiences, such as trauma exposure, may operate on an individual's genetic diathesis toward either internalizing or externalizing psychopathology, thus increasing the likelihood that such vulnerability will be manifested (Resick & Miller, 2009).

In contrast to the role of the nonshared environment, the common environment exerted no effects on the Internalizing factor and relatively modest effects on the Externalizing factor (with 9% of the variance in Externalizing attributable to the common environment). The common environment exerted its greatest effect on risk for the development of individual disorders from the externalizing spectrum, including alcohol and drug abuse/dependence and PTSD. This suggests that factors common to both members of the twin pair, such as immediate family environment, socioeconomic status, and community factors, such as exposure to crime and illicit drugs, may serve to shape the particular manifestation of externalizing psychopathology; that is, whereas genetic and nonshared environmental

factors may increase the risk for externalizing psychopathology broadly, common environmental factors may determine the specific expression of such psychopathology. The primacy of genetic and nonshared environmental factors (over the common environment) has been shown previously in biometric analyses of individual disorders (Hettema et al., 2005; Kendler et al., 2003), but to our knowledge, no prior study has simultaneously modeled the genetic and environmental influences on the common factors underlying both internalizing and externalizing comorbidity.

One possible explanation for the finding of greater heritability of the externalizing spectrum is that this is a function of the greater reliability of the assessment of externalizing relative to internalizing disorders in these data (Koenen et al., 2002; Slutske et al., 1998, 2001). This would mean that there was more error among the internalizing disorders and, therefore, a limit on the amount of true-score internalizing disorder variance available to be explained by the genetic and environmental factors. As a result, we may have underestimated the genetic and environmental influences on internalizing relative to externalizing. Although these data cannot quantify the extent to which the greater internalizing disorder unreliability explains this factor's lower heritability (see Kendler et al., 1999), the use of latent factors in this study minimizes this problem relative to other approaches that do not separate error from true-score variance. In other words, although this study cannot control for differential reliability in the assessment methods, it can capitalize on this information and limit its effects on the parameters of interest.

Findings of this study help clarify the location of PTSD within the broader structure of common mental disorders. On the basis of theory and prior evidence (Miller et al., 2003, 2004; Miller & Resick, 2007), we had hypothesized a significant relationship between PTSD and disorders of both the internalizing and externalizing spectra (i.e., that the best fitting model would include significant loadings of PTSD on both internalizing and externalizing). Results were consistent with this hypothesis and showed that although PTSD covaried more strongly with disorders of the internalizing spectrum, it also evidenced a significant, albeit more modest, relationship with externalizing that was important to overall model fit. Although it is possible that the modest association between PTSD and the Externalizing factor was statistically significant merely as a result of the large sample size, the chi-square difference test demonstrated the superiority of the model with the PTSD cross-loading. Further, no other internalizing disorder yielded this same pattern of cross-loading on the Externalizing factor, suggesting the discriminant validity of the PTSD–externalizing association relative to the other internalizing disorders. This finding is consistent with a "multiformity" model (Krueger & Markon, 2006; Neale & Kendler, 1995; Rhee, Hewitt, Corley, Willcutt, & Pennington, 2005) in which PTSD is conceptualized as arising as a function of latent liabilities toward either internalizing or externalizing. In addition, PTSD evidenced a much weaker association with the Internalizing factor relative to the magnitude of the loadings of the other internalizing disorders on that factor, a finding which has been reported previously (Cox et al., 2002). Together, these findings add to a growing body of research which call into question the current placement of PTSD within the anxiety disorders section of *DSM–IV* (Resick & Miller, 2009). They are consistent with the hypothesis that PTSD may arise from individual diatheses that span the spectrum of human variation in vulnerability to psychopathology and result in extensive heterogeneity in the phenotypic expression of posttraumatic psychiatric disturbance. They also support calls for PTSD to be moved out of the anxiety disorders in *DSM–V* into its own class of disorders defined by the causal conditional nature of their relationship to serious adverse life events (i.e., a spectrum of traumatic-stress disorders; Miller, Resick, & Keane, 2009; Resick & Miller, 2009).

Finally, results of this study illustrate the advantages of studying the common factors underlying broad classes of psychopathology in future genetic research. Such factors can be conceptualized as endophenotypic traits that reduce psychometric error and thereby reflect high-fidelity representations of the dimensions underlying the diagnoses of interest. As such, they can be expected to map more directly and completely onto their biologic substrate and yield substantially increased predictive power for biomarker association analyses compared with analyses that focus on identifying biomarkers of individual disorders. Recent work of this type using factor or other composite indicators of internalizing and externalizing psychopathology has already begun to prove useful in identifying specific genes associated with these broad spectra of disorders (Dick, 2007; Dick et al., 2008; Hettema et al., 2008; Stallings et al., 2005).

Limitations

The primary limitations of this study are those inherent to the twin study method, such as assumptions about the nature of the genetic and environmental associations between MZ versus DZ twins (i.e., that MZ twins share 100% of their genes, whereas DZ twins share 50%, and that environmental effects can be split into those effects that are completely shared by members of the twin pair and those with no overlap across members of a twin pair). In addition, the fact that all participants were male military veterans from the Vietnam War era and that analyses were based on lifetime diagnostic data raises questions about whether results would generalize to other samples or diagnostic indicators based on current symptoms. This latter concern is offset by evidence that the structure of mental illness is consistent across studies, regardless of the use of current/past year (e.g., Krueger et al., 2003; Slade & Watson, 2006; Vollebergh et al., 2001) or lifetime (e.g., Krueger, 1999; Krueger et al., 2001) psychiatric diagnoses. As is the case with any structural equation model study, it is conceivable that there are other phenotypic and biometric models that we did not test which might provide equivalent or improved model fit relative to our best fitting model. In addition, as noted earlier, it is unclear to what extent the differential reliability of the internalizing and externalizing disorders affected the relative magnitude of the etiological pathways. These limitations are arguably offset by the strengths of this study, including the ability to simultaneously model latent internalizing and externalizing psychopathology factors and to quantify the overlapping and unique etiologic variance of the two factors.

Conclusions

This study provides evidence for two distinct genetic factors that differentially give rise to internalizing versus externalizing comorbidity. Further, diagnostic comorbidity across the internalizing and externalizing dimensions is largely explained by a common genetic factor that predicts both classes of disorders. The nonshared environment explained the largest proportion of environmental variance in the two common psychopathology factors. Results also showed that PTSD shares phenotypic and etiological links with both the internalizing and the externalizing spectra of psychopathology. This suggests the need to further examine and refine models of comorbidity and conceptualizations of the influence of genetic and environmental effects on posttraumatic psychopathology.

Acknowledgments

Funding for this study was provided by National Institute of Mental Health Grants K08MH070627 and MH78928 to Karestan C. Koenen, by National Institute of Mental Health Grant 5F31MH074267 to Erika J. Wolf, and by a VA Merit Review Award to Mark W. Miller. Additional funding was provided by the American Foundation for Suicide Prevention, National Institute on Drug Abuse, and the Robert Wood Johnson Foundation. The United States Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry. The funding sources had no further role in study design; in the collection,

analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. None of the authors of this article has a conflict of interest, including no specific financial interests, relationships, or affiliations relevant to the subject of this article. Numerous organizations have provided invaluable assistance in the conduct of this study, including the Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University. Most important, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution, this research would not have been possible.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3. Washington, DC: Author; 1987. rev

Brown TA. Temporal course and structural relationships among dimensions of temperament and *DSM–IV* anxiety and mood disorder constructs. Journal of Abnormal Psychology. 2007; 116:313–328. [PubMed: 17516764]

Brown TA, Chorpita BF, Barlow DA. Structural relationships among dimensions of the *DSM–IV* anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. Journal of Abnormal Psychology. 1998; 107:179–192. [PubMed: 9604548]

Chantarujikapong SI, Scherrer JF, Xian H, Eisen SA, Lyons MJ, Goldberg J, True WR. A twin study of generalized anxiety disorder symptoms, panic disorder symptoms and post-traumatic stress disorder in men. Psychiatry Research. 2001; 103:133–145. [PubMed: 11549402]

Coolidge FL, Thede LL, Young SE. Heritability and the comorbidity of attention deficit hyperactivity disorder with behavioral disorders and executive function deficits: A preliminary investigation. Developmental Neuropsychology. 2000; 17:273–287. [PubMed: 11056845]

Cox BJ, Clara IP, Enns MW. Posttraumatic stress disorder and the structure of common mental disorders. Depression and Anxiety. 2002; 15:168–171. [PubMed: 12112721]

Dick DM. Identification of genes influencing a spectrum of externalizing psychopathology. Current Directions in Psychological Science. 2007; 16:331–335.

Dick DM, Aliev F, Wang JC, Grucza RA, Schuckit M, Kuperman S, Goate A. Using dimensional models of externalizing psychopathology to aid in gene identification. Archives of General Psychiatry. 2008; 65:310–318. [PubMed: 18316677]

Dick DM, Viken RJ, Kaprio J, Pulkkinen L, Rose RJ. Understanding the covariation among childhood externalizing symptoms: Genetic and environmental influences on conduct disorder, attention deficit hyperactivity disorder, and oppositional defiant disorder symptoms. Journal of Abnormal and Child Psychology. 2005; 33:219–229.

Eisen S, Neuman R, Goldberg J, Rice J, True W. Determining zygosity in the Vietnam Era Twin Registry: An approach using questionnaires. Clinical Genetics. 1989; 35:423–432. [PubMed: 2736790]

Goldberg DP, Krueger RF, Andrews G. Emotional disorders: Cluster 4 of the proposed meta-structure for *DSM–V* and ICD-11. Psychological Medicine. 2009; 39:2043–2059. [PubMed: 19796429]

Gregory AM, Caspi A, Moffitt TE, Koenen K, Eley TC, Poulton R. Juvenile mental health histories of adults with anxiety disorders. American Journal of Psychiatry. 2007; 164:301–308. [PubMed: 17267794]

Henderson WG, Eisen S, Goldberg J, True WR, Barnes JE, Vitek ME. The Vietnam Era Twin Registry: A resource for medical research. Public Health Reports. 1990; 105:368–373. [PubMed: 2116638]

Hettema JM, An SS, Bukszar J, van den Oord EJ, Neale MC, Kendler KS, Chen X. Catechol-O-methyltransferase contributes to genetic susceptibility shared among anxiety spectrum phenotypes. Biological Psychiatry. 2008; 64:302–310. [PubMed: 18436194]

Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Archives of General Psychiatry. 2005; 62:182–189. [PubMed: 15699295]

Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modeling. 1999; 6:1–55.

Kendler KS, Karkowski LM, Prescott CA. Fears and phobias: Reliability and heritability. Psychological Medicine. 1999; 29:539–553. [PubMed: 10405076]

Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Archives of General Psychiatry. 2003; 60:929–937. [PubMed: 12963675]

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month *DSM–IV* disorders in the National Comorbidity Survey replication. Archives of General Psychiatry. 2005; 62:617–627. [PubMed: 15939839]

Khan AA, Jacobson KC, Gardner CO, Prescott CA, Kendler KS. Personality and comorbidity of common psychiatric disorders. British Journal of Psychiatry. 2005; 186:190–196. [PubMed: 15738498]

Koenen KC, Fu QJ, Ertel K, Lyons MJ, Eisen SA, True WR, Tsuang M. Common genetic liability to major depression and posttraumatic stress disorder in men. Journal of Affective Disorders. 2008; 105:109–115. [PubMed: 17540456]

Koenen KC, Fu QJ, Lyons MJ, Toomey R, Goldberg J, Eisen SA, Tsuang M. Juvenile conduct disorder as a risk factor for trauma exposure and posttraumatic stress disorder. Journal of Traumatic Stress. 2005; 18:23–32. [PubMed: 16281192]

Koenen KC, Harley R, Lyons MJ, Wolfe J, Simpson JC, Goldberg J, Tsuang M. A twin registry study of familial and individual risk factors for trauma exposure and posttraumatic stress disorder. The Journal of Nervous and Mental Disease. 2002; 190:209–218. [PubMed: 11960081]

Koenen KC, Moffitt TE, Caspi A, Gregory A, Harrington H, Poulton R. The developmental mental-disorder histories of adults with posttraumatic stress disorder: A prospective longitudinal birth cohort study. Journal of Abnormal Psychology. 2008; 117:460–466. [PubMed: 18489223]

Koenen KC, Moffitt TE, Poulton R, Martin J, Caspi A. Early childhood factors associated with the development of posttraumatic stress disorder: Results from a longitudinal birth cohort. Psychological Medicine. 2007; 37:181–192. [PubMed: 17052377]

Krueger RF. The structure of common mental disorders. Archives of General Psychiatry. 1999; 56:921–926. [PubMed: 10530634]

Krueger RF, Caspi A, Moffitt TE, Silva PA. The structure and stability of common mental disorders (*DSM–III–R*): A longitudinal-epidemiological study. Journal of Abnormal Psychology. 1998; 107:216–227. [PubMed: 9604551]

Krueger RF, Chentsova-Dutton YE, Markon KE, Goldberg D, Ormel J. A cross-cultural study of the structure of comorbidity among common psychopathological syndromes in the general health care setting. Journal of Abnormal Psychology. 2003; 112:437–447. [PubMed: 12943022]

Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: Modeling the externalizing spectrum. Journal of Abnormal Psychology. 2002; 111:411–424. [PubMed: 12150417]

Krueger RF, Markon KE. Reinterpreting comorbidity: A model-based approach to understanding and classifying psychopathology. Annual Review of Clinical Psychology. 2006; 2:111–133.

Krueger RF, Markon KE, Benning DB, Kramer M. Linking antisocial behavior, substance use, and personality: An integrative quantitative model of the adult externalizing spectrum. Journal of Abnormal Psychology. 2005; 116:645–666. [PubMed: 18020714]

Krueger RF, McGue M, Iacono WG. The higher-order structure of common *DSM* mental disorders: Internalization, externalization, and their connections to personality. Personality and Individual Differences. 2001; 30:1245–1259.

Krueger RF, South SC. Externalizing disorders: Cluster 5 of the proposed meta-structure for *DSM–V* and ICD-11. Psychological Medicine. 2009; 39:2061–2070. [PubMed: 19796431]

Lahey BB. Public health significance of neuroticism. American Psychologist. 2009; 64:241–256. [PubMed: 19449983]

Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, Meyer JM, Tsuang M. A registry-based twin study of depression in men. Archives of General Psychiatry. 1998; 55:468–472. [PubMed: 9596050]

Markon KE. Modeling psychopathology structure: A symptom-level analysis of Axis I and II disorders. Psychological Medicine. 2009; 11:1–16.

McLeod DS, Koenen KC, Meyer JM, Lyons MJ, Eisen S, True W, Goldberg J. Genetic and environmental influences on the relationship among combat exposure, posttraumatic stress disorder symptoms, and alcohol use. Journal of Traumatic Stress. 2001; 14:259–275. [PubMed: 11469155]

Miller MW, Fogler JM, Wolf EJ, Kaloupek DG, Keane TM. The internalizing and externalizing structure of psychiatric comorbidity in combat veterans. Journal of Traumatic Stress. 2008; 21:58–65. [PubMed: 18302181]

Miller MW, Greif JL, Smith AA. Multidimensional Personality Questionnaire profiles of veterans with traumatic combat exposure: Externalizing and internalizing subtypes. Psychological Assessment. 2003; 15:205–215. [PubMed: 12847781]

Miller MW, Kaloupek DG, Dillon AL, Keane TM. Externalizing and internalizing subtypes of combat-related PTSD: A replication and extension using the PSY-5 scales. Journal of Abnormal Psychology. 2004; 113:636–645. [PubMed: 15535795]

Miller MW, Resick PA. Internalizing and externalizing subtypes in female sexual assault survivors: Implications for the understanding of complex PTSD. Behavior Therapy. 2007; 38:58–71. [PubMed: 17292695]

Miller MW, Resick PA, Keane TM. *DSM–V*: Should PTSD be in a class of its own? British Journal of Psychiatry. 2009; 194:90. [PubMed: 19118339]

Miller MW, Vogt DS, Mozley SL, Kaloupek DG, Keane TM. PTSD and substance-related problems: The mediating roles of disconstraint and negative emotionality. Journal of Abnormal Psychology. 2006; 115:369–379. [PubMed: 16737401]

Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. Annual Review of Psychology. 1998; 49:377–412.

Muthén, LK.; Muthén, BO. Mplus user's guide. 4. Los Angeles, CA: Muthén & Muthén; 2007.

Neale MC, Kendler KS. Models of comorbidity for multifactorial disorders. American Journal of Human Genetics. 1995; 57:935–953. [PubMed: 7573055]

Resick PA, Miller MW. Posttraumatic stress disorder: Anxiety or traumatic stress disorder? Journal of Traumatic Stress. 2009; 22:384–390. [PubMed: 19774665]

Rhee SH, Hewitt JK, Corley RP, Willcutt EG, Pennington BF. Testing hypotheses regarding the causes of comorbidity: Examining the underlying deficits of comorbid disorders. Journal of Abnormal Psychology. 2005; 114:346–362. [PubMed: 16117572]

Robins, LN.; Helzer, JE.; Cottler, L.; Golding, E. National Institute of Mental Health Diagnostic Interview Schedule Version III— Revised. St. Louis, MO: Department of Psychiatry, Washington University in St. Louis; 1998.

Scherrer JF, Xian H, Lyons MJ, Goldberg J, Eisen SA, True WR, Koenen KC. Posttraumatic stress disorder; combat exposure; and nicotine dependence, alcohol dependence, and major depression in male twins. Comprehensive Psychiatry. 2008; 49:297–304. [PubMed: 18396190]

Slade T, Watson D. The structure of common *DSM–IV* and ICD-10 mental disorders in the Australian general population. Psychological Medicine. 2006; 36:1593–1600. [PubMed: 16882356]

Slutske WS, Eisen S, Xian H, True WR, Lyons MJ, Goldberg J, Tsuang M. A twin study of the association between pathological gambling and antisocial personality disorder. Journal of Abnormal Psychology. 2001; 110:297–308. [PubMed: 11358024]

Slutske WS, True WR, Scherrer JF, Goldberg J, Bucholz KK, Heath AC, Tsuang MT. Long-term reliability and validity of alcoholism diagnoses and symptoms in a large national telephone interview survey. Alcoholic Clinical and Experimental Research. 1998; 22:553–558.

Stallings MC, Corley R, Dennehey B, Hewitt JK, Krauter KS, Lessem JM, Crowley TJ. A genome-wide search for quantitative trait loci that influence antisocial drug dependence in adolescence. Archives of General Psychiatry. 2005; 62:1042–1051. [PubMed: 16143736]

Vollebergh WA, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders. Archives of General Psychiatry. 2001; 58:597–603. [PubMed: 11386990]

Watson D. Rethinking the mood and anxiety disorders: A quantitative hierarchical model for *DSM–V*. Journal of Abnormal Psychology. 2005; 114:522–536. [PubMed: 16351375]

Watson D. Differentiating the mood and anxiety disorders: A quadripartite model. Annual Review of Clinical Psychology. 2009; 5:221–247.

Xian H, Chantarujikapong SI, Scherrer JF, Eisen SA, Lyons MJ, Goldberg J, True WR. Genetic and environmental influences on posttraumatic stress disorder, alcohol and drug dependence in twin pairs. Drug and Alcohol Dependence. 2000; 61:95–102. [PubMed: 11064187]

Young SE, Friedman NP, Miyake A, Willcutt EG, Corley RP, Haberstick BC, Hewitt JK. Behavioral disinhibition: Liability for externalizing spectrum disorders and its genetic and environmental relation to response inhibition across adolescence. Journal of Abnormal Psychology. 2009; 118:117–130. [PubMed: 19222319]

Young SE, Stallings MC, Corley RP, Krauter KS, Hewitt JK. Genetic and environmental influences on behavioral disinhibition. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2000; 96:684–695.

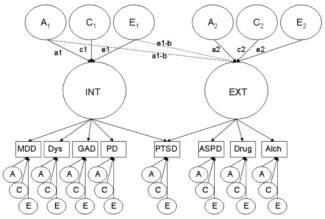

Figure 1.

Common pathway model testing sequence. The figure shows the model testing sequence for one twin. Identical models were simultaneously evaluated in the second twin from each pair but are not depicted in the figure for the sake of presentation clarity. Common factors are denoted by circles and observed indicators by squares. The first common pathway model (the simple ACE model) included the paths depicted by solid black lines (Paths a1–e1 and a2–e2). The c1 pathway was set to zero in all models. The second common pathway model (the Cholesky-A model) added the path denoted by the long-dotted line (Path a1-b) and the third common pathway model (the Cholesky-AE model) added in the path denoted by the short-dotted gray line (Path e1-b). A = additive genetic; C = common environment; E = nonshared environment; INT = internalizing; EXT = externalizing; MDD = major depressive disorder; Dys = dysthymia; GAD = generalized anxiety disorder; PD = panic disorder; PTSD = posttraumatic stress disorder; ASPD = antisocial personality disorder; Drug = drug abuse/dependence; Alch = alcohol abuse/dependence.

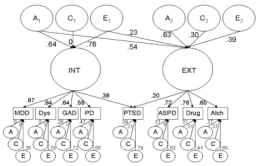

Figure 2.

Standardized results from best-fitting biometric model. All values are completely standardized parameter estimates. All paths are statistically significant at the $p < .001$ level with the following exceptions: All paths fixed or estimated to be 0 or .01 were not significant, the residual genetic paths to PTSD and alcohol abuse/dependence were not significant, the residual common environment path to PTSD was significant at the $p = .006$ level, and the residual genetic path to ASPD was significant at the $p = .03$ level. A = additive genetic; C = common environment; E = nonshared environment; INT = internalizing; EXT = externalizing; MDD = major depressive disorder; Dys = dysthymia; GAD = generalized anxiety disorder; PD = panic disorder; PTSD = posttraumatic stress disorder; ASPD = antisocial personality disorder; Drug = drug abuse/dependence; Alch = alcohol abuse/dependence.

Table 1

Lifetime Prevalence Rates of Psychopathology and Polychoric Cross-Twin Diagnostic Correlations for Monozygotic Versus Dizygotic Twins

		Alch		ASPD		Drug		DYS		GAD		MDD		Panic		PTSD	
Disorder	**%**	**MZ**	**DZ**	**MZ**	**DZ**	**MZ**	**DZ**	**MZ**	**DZ**	**MZ**	**DZ**	**MZ**	**DZ**	**MZ**	**DZ**	**MZ**	**DZ**
Alch	54.6	.54	.36	.37	.18	.41	.20	.23	.09	.15	.04	.21	.07	.14	.01	.20	.06
ASPD	2.7	.35	.20	.50	.25	.43	.26	.23	.14	.13	.09	.23	.14	.12	.05	.19	.10
Drug	10.1	.38	.20	.43	.27	.70	.52	.26	.16	.20	.00	.27	.15	.19	.03	.21	.13
DYS	2.4	.21	.11	.23	.14	.25	.18	.35	.16	.31	.11	.35	.17	.29	.13	.27	.13
GAD	2.2	.10	.12	.15	.05	.07	.12	.22	.04	.27	.06	.28	.06	.19	.05	.24	.03
MDD	9.2	.24	.13	.22	.13	.23	.15	.36	.10	.31	.07	.37	.14	.33	.08	.31	.12
Panic	1.6	.22	.04	.13	.08	.22	.13	.27	.12	.28	.26	.28	.15	.39	.04	.18	.13
PTSD	9.6	.15	.14	.20	.13	.19	.13	.16	.11	.14	.07	.19	.13	.17	.00	.25	.19

Note. MZ = monozygotic; DZ = dizygotic; Alch = alcohol abuse/dependence; ASPD = antisocial personality disorder; drug = drug abuse/dependence; dys = dysthymia; GAD = generalized anxiety disorder; MDD = major depressive disorder; Panic = panic disorder; PTSD = posttraumatic stress disorder. Percentages are based on dichotomous diagnoses, whereas the polychoric correlation matrix is based on three-level (negative, subthreshold, threshold) variables. Correlation coefficients ≥ .09 are significant at the $p < .05$ level.

J Abnorm Psychol. Author manuscript; available in PMC 2011 May 19.

Table 2

Biometric Model Testing Results

Pathway	χ^2 (*df*)	RMSEA	CFI	TLI	Model constraint	Wald test (*df*)
1. Independent pathway	2,289.46* (110)	.11	.91	.92		
2. Common pathway: Simple ACE	2,426.59* (116)	.11	.91	.92		
3. Common pathway: Cholesky-A	331.13* (123)	.03	.99	.99	Path a1-b = 0	486.56* (1)
4. Common pathway: Cholesky-AE	238.43* (122)	.02	1.0	1.0	Path e1-b = 0	95.54* (1)

Note. A = additive genetic; C = common environment; E = nonshared environment; *df* = degrees of freedom; RMSEA = root-mean-square error of approximation; CFI = comparative fit index; TLI = Tucker-Lewis index. *N* = 6,744. Best fitting model is the Cholesky-AE model. The paths described in the Model Constraint column can be found in Figure 1.

* $p < .001$.

J Abnorm Psychol. Author manuscript; available in PMC 2011 May 19.

Table 3

Variance Accounted for in the Internalizing and Externalizing Factors by the Genetic and Environmental Factors

	Genetic factors			Common env. factors			Nonshared env. factors		
Common factor	**A1**	**A2**	**Total h^2**	**C1**	**C2**	**Total c^2**	**E1**	**E2**	**Total e^2**
Internalizing	.41		.41	0		0	.58		.58
Externalizing	.29	.40	.69		.09	.09	.05	.15	.20

Note. env. = environment; A = additive genetic; C = common environment; E = nonshared environment; h^2 = heritability.

Table 4

Disorder-Specific Residual Variance Components

Diagnosis	Disorder-specific genetic variance	Disorder-specific common env. variance	Disorder-specific nonshared env. variance	Total residual variance
Alch	.07	.14	.36	.57
ASPD	.10	0	.38	.48
Drug	0	.26	.17	.43
Dys	0	0	.11	.11
GAD	.08	0	.51	.59
MDD	0	0	.07	.07
Panic	.22	0	.44	.66
PTSD	0	.10	.62	.72

Note. env. = environment; Alch = alcohol abuse/dependence; ASPD = antisocial personality disorder; drug = drug abuse/dependence; dys = dysthymia; GAD = generalized anxiety disorder; MDD = major depressive disorder; Panic = panic disorder; PTSD = posttraumatic stress disorder.