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A Classical Twin Study of PTSD Symptoms and Resilience: Evidence for a Single Spectrum of Vulnerability to Traumatic Stress

Erika J. Wolf^{1,2}, Mark W. Miller^{1,2}, Danielle R. Sullivan^{1,2}, Ananda B. Amstadter³, Karen S. Mitchell^{1,2}, Jack Goldberg^{4,5}, and Kathryn M. Magruder⁶

¹National Center for PTSD at VA Boston Healthcare System

²Department of Psychiatry, Boston University School of Medicine

³Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University

⁴Seattle Epidemiologic Research and Information Center, VA Puget Sound Health Care System

⁵Department of Epidemiology, University of Washington

⁶Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina

Abstract

Background—To examine shared genetic and environmental risk factors across PTSD symptoms and resilience.

Methods—Classical twin study of 2010–2012 survey data conducted among 3,318 male twin pairs in the Vietnam Era Twin Registry. Analyses included: (a) estimates of genetic and environmental influences on PTSD symptom severity (as measured by the PTSD Checklist) and resilience (assessed with the Connor-Davidson Resilience Scale-10); (b) development of a latent model of traumatic stress, spanning both PTSD and resilience; and (c) estimates of genetic and environmental influences on this spectrum.

Results—The heritability of PTSD was 49% and of resilience was 25%. PTSD and resilience were correlated at $r = -.59$, and 59% of this correlation was attributable to a single genetic factor while the remainder was due to a single non-shared environment factor. Resilience was also influenced by common and unique environmental factors not shared with PTSD, but there was no genetic factor specific to resilience. Confirmatory factor analysis supported development of a revised phenotype reflecting the broader dimension of traumatic stress, with biometric models suggesting increased heritability (66%) of this spectrum compared to PTSD or resilience individually.

Conclusions—Genetic factors contribute to a single spectrum of traumatic stress reflecting resilience at one end and high symptom severity at the other. This carries implications for

Corresponding Author: Erika J. Wolf, PhD, National Center for PTSD at VA Boston Healthcare System, 150 South Huntington Ave (116B-2), Boston, MA 02130, Erika.Wolf@va.gov.

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phenotype refinement in the search for molecular genetic markers of trauma-related psychopathology. Rather than focusing only on genetic risk for PTSD, molecular genetics research may benefit from evaluation of the broader spectrum of traumatic stress.

Keywords

PTSD; resilience; twins; genetic; Vietnam Era Twin Registry; traumatic stress

Resilience refers to the ability to maintain or regain normal psychological and physical functioning in the face of adversity and is often conceptualized as a constellation of adaptive personality traits, beliefs, attitudes, and coping strategies (Ahmed, 2007; Bonanno, 2004; Charney, 2004; Herrman et al., 2011). The construct is of considerable interest to investigators in the field of traumatic stress seeking to identify sources of individual differences in responses to trauma and targets for posttraumatic stress disorder (PTSD) prevention and treatment. However, the conceptual and empirical relationships between resilience and PTSD remain controversial (Aburn, Gott, & Hoare, 2016). A central question, which this study aimed to address, involves the extent to which the two concepts are qualitatively and empirically distinct as opposed to reflecting opposite ends of a single dimension (e.g., negative emotionality; Miller & Harrington, 2011).

The Connor-Davidson Resilience Scale (CD-RISC; Connor & Davidson, 2003) is one of the most widely-used and validated measures of resilience and is comprised of items reflecting personality characteristics, beliefs, and attitudes (Windle, Bennett, & Noyes, 2011). Items include past-month perceptions of: (a) personal competence, high standards, and tenacity; (b) trust in instincts, tolerance of negative affect, and strengthening effects of stress; (c) acceptance of change and secure relationships; (d) control; and (e) spiritual influences (Connor & Davidson, 2003). CD-RISC scores covary with PTSD symptom change (Connor & Davidson, 2003), are altered as a function of pharmacological treatment (Davidson et al., 2005), and are negatively correlated with PTSD severity (e.g., $r_s \sim .50$; Connor, Davidson, & Lee, 2003; Davidson et al., 2012; Pietrzak, Johnson, Goldstein, Malley, & Southwick, 2009). The strength of these associations raise questions about the extent to which these constructs represent opposite ends of a single spectrum of vulnerability versus adaptation to traumatic stress, rather than indexing two distinct constructs. The twin design can be used to address this issue by quantifying the common and distinct genetic and environmental influences on measures of PTSD and resilience.

A longitudinal state birth registry twin study by Amstadter et al. (Amstadter, Myers, & Kendler, 2014) operationalized resilience as the difference between predicted and observed internalizing symptoms. Specifically, they indexed resilience using a linear model in which cumulative exposure to stressful life events was the predictor of internalizing psychopathology. Heritability of this index was estimated at 31%, which increased to 50% when modeled as a latent variable, and was stable across approximately five years (Amstadter et al., 2014). Non-shared environmental factors accounted for the remaining variance. Subsequently, Amstadter et al. expanded their analysis to include diagnoses from the internalizing and externalizing spectra and found that the genetic factor contributing to resilience also explained 42% and 61% of the heritability of depression and generalized

anxiety disorder, respectively, as well as 20% and 18% of the heritability of alcohol abuse/dependence and antisocial personality disorder, respectively (Amstadter, Maes, Sheerin, Myers, & Kendler, 2016). A twin study of depression, anxiety and mental wellness also found that about half of the genetic contribution to depression and anxiety was shared with wellbeing (Routledge et al., 2016). Similarly, twin studies of PTSD have yielded heritability estimates ranging from 24–72% (Sartor et al., 2012; Stein, Jang, Taylor, Vernon, & Livesley, 2002; True et al., 1993; Wolf, Mitchell, Koenen, & Miller, 2014), with evidence suggesting overlapping genetic influence across PTSD and various internalizing disorders (Koenen et al., 2008; Wolf et al., 2010). No study has evaluated the genetic and environmental contributions to CD-RISC, their overlap across both resilience and PTSD, nor modeled the genetic architecture of a broader construct encompassing both traits.

The primary aim of this study was to clarify the relationship between PTSD severity¹ and resilience. Using a bivariate classical twin study design we modeled the shared and unique etiologic sources of influence on PTSD severity and resilience and subsequently examined the extent to which modeling a broad dimension spanning both constructs might yield new insight into the etiology of traumatic stress. We evaluated two competing hypotheses. The first hypothesis was that the phenotypic correlation between PTSD and resilience is attributable primarily to shared genetic underpinnings, as suggested by prior evidence of their associations with the genetic factors underlying the internalizing spectrum. In this case, we would expect scores on the two measures to be explained primarily by a common genetic factor. The alternative hypothesis was that the phenotypic correlation is largely attributable to psychometric method factors (e.g., mono-method variance) and/or environmental factors (e.g., trauma exposure); we would then expect to find evidence of distinct genetic factors contributing to each construct but overlapping environmental influences. If a common genetic structure emerged across PTSD and resilience, this would provide a genetics-first, bottom-up rationale for refining the phenotype to capture a broader spectrum of vulnerability versus resilience to traumatic stress. We addressed these questions using new data from the Vietnam Era Twin Registry (VETR), a large longitudinal cohort of male–male twin pairs who served in the US military during the Vietnam era.

Methods

Participants and Procedures

Participants were male Vietnam-era twins enrolled in the VETR, a national sample of male twin pairs who served in the military between 1964–1975 (Goldberg, Curran, Vitek, Henderson, & Boyko, 2002). Participants completed an initial mailed survey in 1987 (Tsuang et al., 1996), and their physical and mental health was re-assessed via mailed survey and telephone interview in 2010–2012 (Magruder et al., 2016), from which these data were drawn. Twins provided written informed consent, and the study was reviewed by the appropriate institutional review boards. Additional details are available elsewhere (Magruder

¹All analyses were based on an index of PTSD symptom severity as opposed to PTSD diagnosis, given considerable evidence for the dimensionality of the construct (King, Leskin, King, & Weathers, 1998) and the enhanced statistical power that is associated with use of dimensional indicators. In the interest of brevity, we refer to “PTSD” throughout the paper to index PTSD symptom severity and refer explicitly to PTSD diagnosis when need be.

et al., 2016). A number of studies have reported the prevalence of PTSD and other psychiatric (Goldberg et al., 2014, 2016; Magruder et al., 2016) and physical health conditions (Vaccarino et al., 2013, 2014) in this follow-up sample and have demonstrated that the weighted lifetime prevalence of PTSD among veterans who served in the war theater was 17.6% and 8.9% among non-theater veterans (Goldberg et al., 2016). The prevalence of other psychiatric disorders varied as a function of PTSD diagnostic status (Goldberg et al., 2014).

PCL and CD-RISC scores were available for $n = 3,318$ twin pairs (1,936 monozygotic [MZ] and 1,382 dizygotic [DZ] twin pairs). Of these, 93.0% self-reported as white, 5.1% as black, 2.4% as American Indian, 0.3% as Asian, and 0.3% as Pacific Islander; 2.7% endorsed Spanish, Hispanic or Latino ethnicity. The majority (61.5%) of the sample was married or living with a partner and just over half (53.1%) completed at least a 12th grade education. Participants were born between 1939–1957.

Measures

PTSD severity was assessed with the 17-item PTSD Checklist (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993) for *DSM-IV* ($\alpha = .90$; (Magruder et al., 2015)). Items were referenced to “stressful experiences” and were not anchored to a specific event. Each item was rated on a 1–5 (*not at all* to *extremely*) scale to reflect the extent to which veterans were bothered by each *DSM-IV* criterion during the past four weeks. These items were summed to form an index of total PTSD severity. Resilience was concurrently assessed with PTSD severity using the Connor-Davidson Resilience Scale–10 Item (CD-RISC-10; Campbell-Sills & Stein, 2007), an abbreviated version of the original CD-RISC. The 10 items are rated on a 5-point scale that reflects the extent to which each item is “true” of the individual (*not true at all* to *true nearly all the time*). Examples include: “adapt to change,” “think clearly under pressure” and “handle unpleasant feelings.” Items were summed to create a total score ranging from 0–40, with higher scores reflecting higher resilience. This scale was derived through an iterative factor analytic approach that eliminated redundant and poorly performing items (Campbell-Sills & Stein, 2007). In the validation samples, items loaded together on a single factor, evidenced good internal consistency ($\alpha = .85$), and total scores showed strong association with the original CD-RISC ($r = .92$; Campbell-Sills & Stein, 2007). Coefficient alpha in this sample was .94. Zygosity was determined via questionnaire and augmented with DNA data where possible (Forsberg, Goldberg, Sporleder, & Smith, 2010).

Data Analyses

We first calculated the within and across variable cross-twin correlations for PTSD and resilience. We examined the distribution of standardized scores (*Z*-scores) on each measure separately and the co-distribution of the measures (average of PCL and CD-RISC *Z*-scores) from one randomly chosen twin in each pair. We next estimated a Cholesky decomposition biometric model using the latent variable approach to define additive genetic (A), common environmental (C), and unique environmental (E) sources of variance (see Supplementary Materials). One set of latent variables (A_1, C_1, E_1) were specified to predict both PTSD (the first phenotype in the model) and resilience, and a second set of factors (A_2, C_2, E_2) were

specific to resilience² (Supplementary Figure 1). Based on theory and initial results, we tested nested models which set specific genetic and environmental paths to 0 to determine if doing so degraded fit, per the nested χ^2 value. Analyses were based on summary scores of PTSD symptom severity and resilience, rather than on individual scale items, given our aim of modeling the biometric structure of the two constructs (rather than modeling the phenotypic structure of each construct) and given concerns about model non-convergence if additional indicators were introduced into the analysis.

Based on initial results, we evaluated biometric models for a combined phenotype spanning high PTSD severity at one end and resilience at the other (i.e., the traumatic stress spectrum). To focus on variance in common across PTSD and resilience, we first conducted a confirmatory factor analysis in which total scores on the PCL and CD-RISC were included as indicators of the latent traumatic stress spectrum. The latent variable was modeled simultaneously for each member of a twin pair, with factor loadings held equivalent across the pair. Though there were only two indicators per factor (consistent with a number of prior latent variable twin studies, see for example: Gjerdet et al., 2012; Kendler & Myers, 2015) the model was positively identified with 7 *df* because both members of a twin pair were included in the same analysis and constraints were applied to hold factor loadings equivalent across twins (as is common; see, for example: Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Kendler, Karkowski, & Prescott, 1999). We then used this latent variable in biometric models to examine its genetic and environmental architecture. All measurement (i.e., confirmatory factor) and biometric models were evaluated with Mplus 7.11 (Muthén & Muthén, 2013) using maximum likelihood estimation (see Supplementary Materials) with final models re-run with the robust maximum likelihood estimator to correct standard errors, given non-normally distributed data.

Results

Correlations and Distributions

The cross-twin correlations between PTSD and resilience for MZ and DZ twins are listed in Table 1. The within-person correlations between PTSD and resilience were $r = -.59$ within both MZ and DZ twin groups.³ The distribution of PCL *Z*-scores was positively skewed (Figure 1, Panel A) while CD-RISC *Z*-scores were negatively skewed (Figure 1, Panel B). The co-distribution of PCL and CD-RISC *Z*-scores was approximately normal (Figure 1, Panel C).

PTSD & Resilience Cholesky Decomposition Models

The first model included shared ACE factors across PTSD and resilience and separate ACE factors specific to resilience (Supplementary Figure 1).⁴ This model fit the data well (Supplementary Table 1) and yielded significant shared A_1 paths for PTSD and resilience, a

²PTSD was included as the first variable in the model because its genetic structure is arguably better established than that for resilience. In follow-up analyses detailed below we reversed the order of the variables.

³As a point of comparison, the within-twin correlations between resilience and *DSM-IV* lifetime diagnoses of PTSD, major depression, alcohol abuse or dependence, and substance abuse or dependence (as assessed via telephone interview with the Composite International Diagnostic Interview; CIDI; Kessler et al., 2004) were $r_s = -.32/- .29, -.25/- .23, -.16/- .17$, and $-.11/- .13$, respectively (MZ/DZ).

PTSD-specific C_1 path, shared E_1 paths for PTSD and resilience, and resilience-specific C_2 and E_2 paths, but notably, no A_2 path specific to resilience. A series of interim nested models were then evaluated as detailed in Supplementary Table 1 and Supplementary Results. The standardized path estimates for the best-fitting model (Model 3 in Supplementary Table 1) are shown in Figure 2, and the variance explained by each latent genetic and environmental variable listed in Table 2.⁵ This model included significant A_1 and E_1 influences on PTSD that also contributed to resilience and distinct C_2 and E_2 factors for resilience.⁶ The heritability of PTSD was 49% and of resilience was 25%, with the genetic influence on resilience fully overlapping that for PTSD. The contribution of the non-shared environment was 51% for PTSD and 60% for resilience, with 20% of the non-shared environmental influence on resilience overlapping that for PTSD. In total, 59% of the phenotypic correlation between PTSD and resilience was due to shared genetic effects, and approximately 42%⁷ was due to overlapping non-shared environment effects.

Heritability of the Traumatic Stress Spectrum

We next estimated the heritability of the broader spectrum of traumatic stress. The measurement model fit the data well (Supplementary Table 1) with large standardized loadings⁸ of PTSD ($\beta = .85$) and resilience ($\beta = -.73$, both $p < .001$).⁹ The full ACE model of the latent variable fit the data well (Supplementary Table 1) and yielded significant genetic and non-shared environmental contributions to latent traumatic stress. A series of nested models detailed in Supplementary Table 1 demonstrated that the best fitting biometric model was the AE model.¹⁰ In this model, the heritability of the latent traumatic stress spectrum was 66%, and the variance attributable to the non-shared environment was 33% (see Table 2 for variance estimates & Figure 3 for standardized parameter estimates). The 95% confidence interval for the heritability of traumatic stress did not overlap those for PTSD or resilience as estimated in the Cholesky model (Table 2).

⁴A preliminary model evaluated the genetic and environmental contributions to CD-RISC scores alone. Variance in resilience was best captured by the full ACE model. The heritability of resilience was estimated at .25, common environmental variance at .14, and unique environmental variance at .61.

⁵This model was re-run with the robust maximum likelihood estimator and results were unchanged.

⁶We conducted a parallel series of Cholesky decomposition models in which we reversed the order of the phenotypes so that resilience was the primary phenotype explained by the A_1 , C_1 , and E_1 factors while variance in PTSD severity was explained by these same factors and by PTSD-specific A_2 , C_2 , and E_2 factors. The best-fitting model from this series of nested analyses was consistent with that reported in the main text such that the heritability of resilience was estimated at .25 and the heritability of PTSD was .49, with 100% of the genetic variance in PTSD overlapping with the genetic variance in resilience. Variance attributable to the common environment was .15 for resilience and 0 for PTSD. Two non-shared environmental factors emerged. The first was shared across resilience and PTSD and captured 59% of the variance in resilience and 10% of the variance in PTSD; the second was specific to PTSD and explained an additional 41% of the variance in PTSD (so that the total variance explained in PTSD by the non-shared environment was 51%). As in the primary analysis described in the main text, the genetic factor explained 59% of the phenotypic correlation between PTSD and resilience, with the remainder of this correlation attributable to overlapping non-shared environmental effects.

⁷Percentages sum to >100% due to rounding.

⁸These loadings are from the measurement model (i.e., confirmatory factor analysis). The loadings shown in Figure 3 are from the biometric model and varied slightly (within .02 standardized units) from that reported for the measurement model.

⁹We examined correlations between traumatic stress factor scores and lifetime diagnoses of PTSD, major depression, alcohol abuse/dependence, and substance abuse/dependence. These values (MZ/DZ) were $r_s = .50/.47$, $.34/.32$, $.21/.21$, and $.16/.17$, respectively. This indicates that the traumatic stress spectrum was more highly correlated with PTSD diagnosis and symptom severity than with other psychiatric diagnoses in the cohort.

¹⁰This model was re-run using the robust maximum likelihood estimator and results were unchanged.

Discussion

The aim of this study was to clarify the nature of the relationship between PTSD and resilience by disaggregating and estimating the genetic and environmental sources of covariation between the two constructs. Consistent with prior research (Pietrzak et al., 2009), we found that scores on measures of the two constructs were strongly negatively correlated. Biometric analyses revealed a single genetic factor accounted for 59% of this correlation and explained 49% and 25% of the variance in PTSD and resilience, respectively. These results are consistent with prior studies suggesting that a common genetic factor accounts for covariation between the internalizing disorders and indices of resilience/wellbeing (Amstadter et al., 2016; Routledge et al., 2016). A single non-shared environment factor accounted for all the remaining co-variance between the measures and explained 51% of the variance in PTSD and 12% in resilience. This may reflect substantive factors, such as trauma exposure, as well as measurement factors, such as mono-method bias (e.g., covariation stemming from a shared assessment approach), that contribute to the correlation between the two measures.

Evidence for a shared genetic contribution to PTSD and resilience, in the context of no independent genetic influence on resilience, is striking and suggests the importance of aligning the phenotypic structure of traumatic stress with its genetic structure. Neither PTSD nor resilience scores were normally distributed, and this limits the magnitude of heritability estimates in twin models and may hinder the search for molecular genetic variants. In contrast, when the two measures were combined, their interlocking distribution approximated the normal distribution. Consistent with this, the heritability of the latent variable capturing common variance across PTSD and resilience exceeded that for either trait alone. This may imply the need to revise phenotypes to map a broader spectrum of traumatic stress. This genetics-first approach to phenotype refinement might involve instrument revision to combine measures of resilience and PTSD, possibly by using confirmatory factor analysis to identify items that best indicate the underlying spectrum. This bottom-up method to phenotype refinement may yield greater construct validity and true-score variance in the phenotypic scores, thereby improving the ability of molecular studies to find effects, compared to studies focusing only on the pathological end of the spectrum, defined by PTSD.

Findings of this study also showed that a considerable proportion of variance in resilience was explained by common (15%) and non-shared environment factors (48%) that were fully distinct from those involved in PTSD. This helps explain why PTSD and resilience were not perfectly correlated. Prior twin studies of resilience and related constructs have not found an effect for the common environment (Amstadter et al., 2016; Amstadter et al., 2014; Routledge et al., 2016), and in this study, the common environment did not contribute to the latent traumatic stress spectrum. Together, this suggests that the common environment influences aspects of CD-RISC scores that are distinct from adaptation to traumatic stress and may potentially be specific to the CD-RISC. Additional research is needed to further evaluate this issue.

Our estimate of the heritability of resilience was similar to that reported in prior studies (Amstadter et al., 2016; Amstadter et al., 2014), despite substantial differences in the approach to operationalizing the construct. The heritability of PTSD in this sample was also well within the range of prior published PTSD twin studies (Sartor et al., 2012; Stein et al., 2002; True et al., 1993; Wolf et al., 2014). However, this estimate was greater than the 23% heritability we previously reported using earlier VETR data (Wolf et al., 2014). The source of this discrepancy is unclear but several possibilities exist. First, it could be that the genetic contribution to PTSD increases over the lifespan (given the 20-year follow-up period), and is most relevant to chronic PTSD. This implies that the search for genetic markers of PTSD might be most successful if evaluated in samples with long-standing symptoms. Second, the difference in heritability estimates could reflect the results of intervening life traumas and stressors that serve to increase the heritability of the disorder (Wolf et al., 2014). Third, the discrepancy could be a function of historical cohort effects that altered the social acceptability of endorsing symptoms over time. Fourth, it could be an artifact of methodological differences between the two assessments including who completed the follow-up study and differences in the measurement of PTSD reflecting changing *DSM* definitions.

Limitations and Conclusion

Results should be considered in light of a number of limitations. Specifically, results pertain to the construct of resilience as measured by the CD-RISC, and other indices of resilience might yield different findings. Related to this, as we did not have multiple indicators of both PTSD severity and resilience, we were unable to model the etiological structure of residual variance not accounted for by the broader traumatic stress spectrum. The study was also limited to male veterans of a single generation and as such, results may not generalize to non-veterans, women, or veterans from other eras. This is particularly important given that for many veterans in this cohort, trauma exposure may have occurred decades prior to the PTSD assessment featured in these analyses, and PTSD may have become a chronic condition. It is unknown if results would generalize to samples assessed closer in time to trauma exposure. It is possible that with the passage of time, individuals with PTSD have a greater opportunity to develop resilience, and thus phenotypic associations between the two constructs might be stronger in this sample.

Results align with current approaches to conceptualizing psychopathology along broad underlying dimensions that relate to biology, neurocircuitry, and behavior (i.e., the National Institute of Mental Health's Research Domain Criteria; RDoC; Insel et al., 2010). The dimension of traumatic stress could potentially expand the RDoC construct of sustained threat by including adaptive responses to psychological stress. This could guide future genetic association studies, yield new insights into the neurocircuitry linking genes to behavior, and may potentially identify novel biological processes as pharmacological targets for PTSD prevention and resilience promotion. If replicated, our finding of a shared genetic liability to PTSD and resilience may help redefine the construct of traumatic stress and shape future research in ways that optimize results and improve the wellbeing of those who carry the burden of traumatic stress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A

B

C

Figure 1. shows the standardized distribution of PCL scores (Panel A), CD-RISC scores (Panel B) and their co-distribution (Panel C) as defined by the average Z -score from the two standardized variables.

Figure 2. shows the standardized parameters estimates (β) and standard errors (in parentheses) for the best-fitting Cholesky decomposition model. Paths set to 0 are omitted for simplicity. A = additive genetic; C = common environment; E = non-shared environment; PTSD = posttraumatic stress disorder; sev = severity. $^{***} p < .001$.

Figure 3. shows the standardized parameters estimates (β) and standard errors (in parentheses) for the best-fitting biometric model of the latent traumatic stress spectrum. A, C, and E paths can be squared to determine variance explained. Arrows pointing towards the indicators indicate standardized error terms. A = additive genetic; C = common environment; E = non-shared environment; PTSD = posttraumatic stress disorder; sev = severity. *** $p < .001$.

Table 1

Cross-Twin Correlations for PTSD and Resilience

Variable	<u>PTSD</u>		<u>Resilience</u>	
	MZ	DZ	MZ	DZ
PTSD	.48	.33		
Resilience	-.34	-.23	.40	.26

Note. PTSD = posttraumatic stress disorder; MZ = monozygotic; DZ = dizygotic.

Table 2

Variance Accounted for in PTSD, Resilience, and the Traumatic Stress Spectrum by the Genetic and Environmental Factors

Variable	Genetic factors			Common env. factors			Unique env. factors		
	A1	A2	Total h^2 95% CI	C1	C2	Total c^2 95% CI	E1	E2	Total e^2 95% CI
PTSD Severity	.49	–	.49 .45 to .53	0	–	0	.51	–	.51 .46 to .56
Resilience	.25	0	.25 .21 to .30	0	.15	.15 .12 to .18	.12	.48	.60 .54 to .67
Traumatic Stress Spectrum	.66	–	.66 .60 to .72	0	–	0	.33	–	.33 .27 to .40

Note. Paths that were set to 0 in the best fitting model are listed as 0. Paths that were never tested (e.g., A2 to PTSD) are indicated by dashes. PTSD = posttraumatic stress disorder; env = environmental; CI = confidence interval.