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A Population-Based Study of Familial and Individual-Specific Environmental Contributions to Traumatic Event Exposure and Posttraumatic Stress Disorder Symptoms in a Norwegian Twin Sample

Ananda B. Amstadter,[1] Steven H. Aggen,[1] Gun Peggy Knudsen,[2] Ted Reichborn-Kjennerud,[2,3] and Kenneth S. Kendler[1,4]

[1]Department of Psychiatry, Virginia Institute of Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA
[2]Division of Mental Health, Norwegian Institute of Public Health, Olso, Norway
[3]Institute of Psychiatry, University of Oslo, Oslo, Norway
[4]Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA

Objective: Posttraumatic stress disorder (PTSD) is one of the only disorders in the Diagnostic and Statistical Manual of Mental Disorders that requires an environmental exposure. The relationship between liability factors for trauma exposure and those for PTSD symptoms following exposure are unclear. *Methods:* Exposure to a trauma and resulting PTSD symptoms were assessed in a sample of 2,794 members of the Norwegian Institute of Public Health Twin Panel. *Results:* In the full sample, 737 twins experienced a trauma. A modified causal, contingent, common pathway model was used to examine trauma exposure and liability for PTSD. Genetic and common environmental factors could not be distinguished, so a model that included only familial and individual specific components was fit. The best-fitting model suggested that familial factors played an important role in liability for trauma exposure and for resulting PTSD symptoms, and that there was a modest transmission between trauma exposure and subsequent PTSD symptoms. *Conclusions:* One third of the variance in liability of PTSD symptoms is due to familial factors, and of this, approximately one fifth overlaps with the familial liability for trauma exposure while the other four fifths of the variance is specific to the risk of PTSD symptoms following exposure. The hypothesis that PTSD is etiologically similar to exposures to a traumatic event is not supported, suggesting that the factors that confer risk for trauma do not overlap completely with those that confer risk for PTSD.

■ **Keywords:** twins, posttraumatic stress disorder, epidemiology

Significant Outcomes

- Familial factors are important for both traumatic event exposure and subsequent PTSD symptoms.
- The factors that account for variance in liability of PTSD symptoms overlap modestly with the factors that account for variance in liability to exposure to a traumatic event.

Limitations

- Genetic and common environmental factors were not able to be distinguished, perhaps due to low power, and therefore the model only included familial factors and individual-specific environments.

Posttraumatic stress disorder (PTSD) is unique among psychiatric disorders in that it is one of the few Diagnostic

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ADDRESS FOR CORRESPONDENCE: Ananda B. Amstadter, PhD, Department of Psychiatry, Virginia Institute of Psychiatric and Behavioral Genetics, Virginia Commonwealth University, 800 E. Leigh Street, PO Box 980126, Richmond, VA 23298-0126. E-mail: abamstadter@vcu.edu

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and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) diagnoses that requires an environmental exposure -– that is a traumatic event -– to precede the onset of the disorder. In other words, according to the DSM-IV, PTSD can only occur conditional upon trauma exposure. A key conceptual issue is the degree to which liability to traumatic event exposure overlaps with the liability of development of PTSD given exposure. Previous behavioral genetics investigations of PTSD have *not* conditioned the analyses upon trauma exposure, and therefore, it is not known, for example, if the same risk factors involved in trauma exposure also contribute to the development of PTSD posttrauma. If not examined jointly, studying only the familial and environmental influences on PTSD may result in a misleading representation of the processes involved. Furthermore, if exposure status in the population is not controlled for, then twins never exposed to trauma and having an unknown risk to PTSD and those with a trauma exposure but having never developed PTSD (and presumably having low risk for PTSD) will be combined into a single 'unaffected' category. We seek to address these issues using a genetic-epidemiology framework with a population-based Norwegian twin sample.

The epidemiological data from Western European countries suggests that a minimum of 18% of individuals will be exposed to at least one traumatic event in their lifetime (Darves-Bornoz et al., 2008; Perkonigg et al., 2000). Far fewer individuals will meet criteria for PTSD, with reported prevalence estimates for Western European countries estimated at 1.3% for lifetime PTSD, with some variation by country (Darves-Bornoz, et al., 2008; Perkonigg, et al., 2000). The extant behavioral genetics research on trauma exposure and PTSD suggests that genetic factors influence exposure to traumatic events in a noncivilian sample (the Vietnam Era Twin Registry; Lyons et al., 1993), and in a civilian sample (Jang et al., 2007; Stein et al., 2002), with heritability estimates ranging from 20% to 47%. These twin studies also suggest that genetic influences explain a proportion of vulnerability to PTSD symptoms (ranging from 30% to 38%; Jang et al., 2007; Stein et al., 2002; True et al., 1993). However, these analyses have only included twins who were concordant for trauma exposure.

To address this gap in the literature, this study sought to examine the nature of the relationship between factors that predispose to traumatic event exposure and factors that predispose to development of PTSD. However, a notable limitation of the present study is the restriction imposed by the rarity of our target outcome measures in this population-based twin sample. Apparently, insufficient power contributed to our inability to evaluate and test hypotheses that distinguish between additive genetic, shared, and unique environmental sources of variance. Therefore, a simpler model was used to analyze these twin data like a family study in which the effects of genetic and shared environmental risk are examined together.

Methods

Sample and Assessment Methods

Twins were recruited from the Norwegian Institute of Public Health Twin Panel (NIPHTP; Harris et al., 2002) having been identified through the Norwegian National Medical Birth Registry that was established on January 1, 1967, and which receives mandatory notification of all live births. Prior questionnaire studies were conducted in 1992 (twins born 1967–1974) and in 1998 (born 1967–1979). Altogether, 12,698 twins received the second questionnaire, and 8,045 (3,334 pairs and 1,377 single responders) responded after one reminder (cooperation rate 63%).

Data for this report utilize an interview study assessing DSM-IV axis I and axis II disorders, begun in 1999 (Tambs et al., 2009). Interviewers were largely senior clinical psychology students at the end of their 6-year training course (including at least 6 months of clinical practice), and psychiatric nurses with years of clinical experience. They were trained by professionals with extensive previous experience with the instruments, and for assessment of axis I disorders they received a standardized training program by teachers certified by the World Health Organization (WHO). The interviews, mostly face-to-face, were carried out between June 1999 and May 2004. For practical reasons, 231 interviews (8.3%) were done by phone. Each twin in a pair was interviewed by a different interviewer.

As outlined in detail elsewhere (Tambs et al., 2009), the 6,442 eligible participants were defined as the 3,153 complete pairs where both members completed the second questionnaire and agreed to be contacted again, as well as 68 pairs unintentionally drawn directly from the NIPHTP due to technical problems.

Altogether, 2,794 twins (44% of those eligible) were interviewed and provided data for the current study. Noncooperation was predominately the result of nonresponse to the written invitation as active refusals were rare (0.8%; Tambs et al., 2009). Approval was received from the Norwegian Data Inspectorate and the Regional Ethical Committee, and written informed consent was obtained from all participants after a complete description of the study was given. As outlined previously (Buss & Plomin, 1975), zygosity was determined by the use of questionnaire items on the entire sample (Goldsmith & Rothbart, 1991) and microsatellite markers on 676 of the like-sex pairs which, when used together in a discriminant analysis for those lacking deoxyribonucleic acid, predicted a zygosity misclassification rate of ~1% of pairs, a rate considered too low to substantially bias results (Lemery et al., 1999). Table 1 provides data on the number of twin pairs, as well as demographic data of the twins.

Axis I disorders, including PTSD, were assessed using a computerized version of the Composite International Diagnostic Interview (CIDI), developed by the WHO and used in most major psychiatric surveys all over the world in

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TABLE 1

Demographic Data and Lifetime Prevalence of Exposure to Potentially Traumatic Events

	$n = 2{,}794$	
	n	%
Twins pairs		
MZ males	221	15.8
MZ female	448	32.1
DZ males	116	8.3
DZ females	261	18.7
DZ unlike-sex	340	24.3
Individuals[a]	22	0.8
Age (*M, SD*)	28.2	3.9
Education (*M, SD*)	14.9	2.6
Any trauma	737	26.4
Combat	23	0.8
Physical threat	244	8.7
Rape	92	3.3
Child sexual abuse	92	3.3
Natural disaster	14	0.5
Accident	189	6.8
Hostage/kidnapped	21	0.8
Other event	135	4.9
Any witnessed event	138	5.0
PTSD symptoms among trauma exposed subsample (*M, SD*)	3.1	4.1

Note: [a]Only twin pairs in which both twins initially had agreed to participate were interviewed. For 22 of these pairs, one of the twins changed their minds after initial consent.

recent years. We used a Norwegian version of the computerized Munich-CIDI (Plomin et al., 1977). CIDI is a comprehensive structured diagnostic interview assessing lifetime DSM-IV axis I disorders, and has been shown to have good test-retest and inter-rater reliability (Davis et al., 2008; McBrien, 2003). This interview is strictly structured and includes skip-rules, which made it difficult to do a proper secondary rating of a taped interview. However, the CIDI is a widely used instrument, and the inter-rater reliability has previously been demonstrated to be excellent. Each participant was asked if they had personally experienced any of the following traumas: (1) a terrible experience at war, (2) serious physical threat (with a weapon), (3) rape, (4) sexual abuse as a child, (5) a natural catastrophe, (6) a serious accident, (7) being imprisoned, taken hostage, or kidnapped, or (8) another event. They were also asked if they witnessed any of the listed events happening to another person. For each event experienced in adulthood, the participant was asked if during the event they felt terrified, helpless, or frightened. For the childhood events, the participant was asked if they felt 'muddled up', or 'upset and restless'. The PTSD symptom questions were then asked in reference to this event. Finally, participants were asked specific symptom questions relating to the re-experiencing, avoidance/numbness, and hypervigilance symptom clusters.

Statistical Analysis

The causal, contingent, common pathway (CCC) twin model initially proposed for modeling the heritable components of smoking initiation and nicotine dependence (Kendler et al., 1999) was used to model trauma exposure and liability for PTSD. The CCC model is conceptually well suited to investigate PTSD, as it is assumed that (a) trauma exposure is a necessary but not sufficient condition for PTSD (causal), (b) PTSD can only be meaningfully assessed in those who have a trauma history (contingent), and (c) the familial and individual-specific environmental effects on trauma can only influence PTSD via the direct phenotype pathway from trauma liability since PTSD data is necessarily missing for those who have not been exposed to a traumatic event (common pathway). Given this twin structure for the CCC model, model estimation can be conceptualized and implemented as a missing data problem as twins who do not have a trauma history then have missing data for PTSD (Neale et al., 2006).

The phenotypic variation in the classic twin model is decomposed into additive genetic (A), common environmental (C), and individual-specific environmental (E) sources. However, due to the low prevalence of PTSD in this Norwegian population-based sample of twins (2.6%), it was determined that there was insufficient power to statistically differentiate between genetic and shared environmental sources of resemblance.

Therefore, we examine 'twin aggregation' in a similar manner to 'familial aggregation' using the Tau model (Province & Rao, 1985). We assume, as the simplest assumption, that twin resemblance for trauma exposure and PTSD is similar in monozygotic (MZ) and dizygotic (DZ) twins and thus our model for familial aggregation (τE) is identical to the classical CE model used in twin studies (see Figure 1).

In the case of trauma exposure and subsequent development of PTSD, we are missing information about the liability to PTSD among individuals who were never exposed to trauma. That is, for all those twins who never were exposed to a traumatic event, information on symptoms of PTSD is necessarily missing (Neale, et al., 2006). A path diagram of the CCC model is given in Figure 1. A modification was made to the conventional CCC model. Unreliability of the upstream dichotomous variable, trauma exposure (box labeled 'Trauma') was explicitly modeled by introducing an additional latent variable (circle) called 'Trauma Liability' with a directed arrow pointing to the observed trauma variable (*k*). Individuals with higher liability for 'Trauma' can vary in their susceptibility to developing PTSD. Based on the model, liability of PTSD can be partitioned into several sources, those that are shared (overlap) with trauma exposure (given by the transmission path, '*b*') and those unique to PTSD liability denoted by the downstream latent tau (τ) and E components with subscripts '*p*'. If *b* is 1.00, all influences contributing to exposure are shared and thus common to variation in PTSD. Conversely, if *b* is 0, variation in trauma exposure and PTSD are etiologically distinct in that risk factors do not overlap and are specific to each phenotype. Values for *b* estimated between 0 and 1 suggest varying degrees of common etiological influences.

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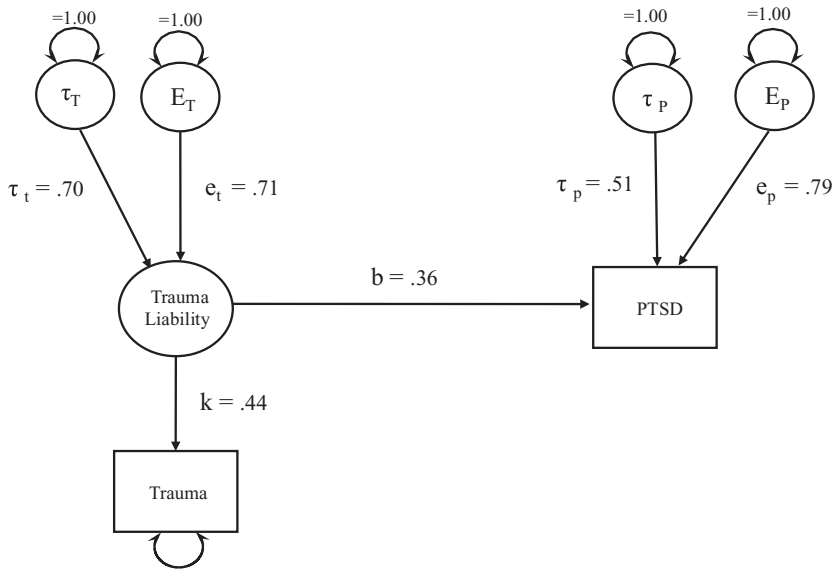

FIGURE 1

CCC model of trauma exposure and PTSD accounting for unreliability in trauma (model shown is for one member of a twin pair).

Traumatic event exposure was coded as a dichotomous variable indicating no history of exposure versus at least one type of traumatic exposure. For the PTSD phenotype, an ordinal count of the 17 binary PTSD symptoms was created. Due to the large number of categories and positive skewness of this count variable, categories were collapsed and organized into a total of five categories scored 0 through 4 that retained the ordering of the original symptom count variable. In the CCC twin model, the binary and ordered count variables are modeled using threshold locations positioned on (continuous) latent response variables. With a binary variable, there is only a single threshold to be estimated. For the trauma variable, this is the point on the underlying exposure liability variable that distinguishes between those twins who experienced a trauma (above the threshold and coded 1 in the data) from those who did not (below the threshold and coded 0). The ordered categorical PTSD variable has $m-1$ thresholds, where m is the number of categories. In this application, PTSD has four estimated thresholds that indicate increasing levels of PTSD vulnerability.

When estimating polychoric correlations based on observed ordinal variable contingency tables, it is important to determine if the assumption of bivariate normality is tenable. That is, it is appropriate to infer that an ordered continuum of liability underlies the PTSD symptom count variables. Using the MZ and DZ twin pair contingency tables for the ordinal PTSD variable, tests of bivariate normality in the population were performed using Prelis 2.8 (Joreskog & Sorbom, 2006). The likelihood ratio chi-square test is based on a comparison of observed and expected cell frequencies in the twin contingency tables. If the model holds, $2N$ times the minimum fit function is approximately distributed as χ^2.

To evaluate the fit of the CCC model, a full information maximum-likelihood approach to raw data was implemented in Classic Mx. This model calculates the expected cell frequencies, which are the product of the predicted cell proportions and the observed sample size for the group. Model fitting is done by minimizing the χ^2 for the observed and expected cell frequencies. Akaike's information criteria (AIC) can also be used as a guide to evaluating different models. AIC produces an index of goodness-of-fit which reflects a balance of explanatory power and parsimony (Akaike, 1987). In other words, AIC can be used as a 'goodness-of-fit' criteria.

Results

Table 1 presents demographic data and trauma exposure prevalence for all participants. Within the full Norwegian sample, 26.4% of twins reported exposure to at least one potentially traumatic event ($n = 737$). Test results for bivariate normality of the underlying liabilities for the ordinal MZ and DZ PTSD variables were nonsignificant for both the MZ and DZ twin data (MZ, $\chi^2 = 10.03$, $df = 15$ $p = .82$; $p = 1.00$, DZ, $\chi^2 = 13.6$, $df = 15$ $p = .82$; $p = 1.00$). Thus, the PTSD symptom count variable can be treated as a single continuum of liability.

Twin Modeling

Table 2 presents results from fitting the modified CCC model to the Norwegian twin data. The standard CCC model, in addition to including a nontransmitted error term, for reasons outlined above, we combined the A and

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TABLE 2

Parameter Estimates for CCC Model Accounting for Trauma Unreliability (Includes DZ Unlike Pairs)

Description		Model fit		Parameter estimates (95% CI)		
Model	Variables	–2lnL	AIC	*b*(top) *k*(bottom)	τ^2	E^2
τE	Trauma	5175.2 (–)	–1830.8	0.36 (.00; .99)	0.49 (.20; .99)	0.51 (.00; .79)
	PTSD			0.44 (.01; .81)	0.26 (.03; .45)	0.62 (.00; .89)
E only	Trauma	5221.2	–1788.8	0.36 (.07; .99)	= .00 (–; –)	1. 00 (–; –)
	PTSD	($\Delta\chi^2 = 46.0$; 2 *df* $p = .000$)		0.53 (.01; .99)	= .00 (–; –)	1. 00 (–; –)

C factors into a single familial component here referred to as Tau or 'τ' (see Figure 1). Dropping the familial factors resulted in significant worsening of fit compared to a model that included both τ and E (E only model: Δ–2lnL = 46.0, $df = 2$, AIC = −1788.8). The point estimate for the *b* path was +0.36. The conventional 95% confidence intervals (CIs) for the *b* and other model parameters were quite large. Given this result, empirical bootstrapping was employed to obtain empirically derived CIs (95% CI; the lower 2.5% and upper 97.5% values from the empirical bootstrapping distributions). Bootstrapped 95% CIs for traumatic event exposure were 0.23–0.99 (for τ), and 0.00–0.74 (for E); and 95% CIs for PTSD of 0.18–0.65 (for τ) and 0.16–0.94 (for E). Although these CIs are also wide, indicating that parameters are estimated imprecisely, the best-fit model predicts that approximately 32% of the variance in liability to PTSD is attributed to familial influences. Of this familial variance, 19% is shared with trauma exposure and 81% is unique to the liability to develop PTSD. The other 68% of the variance in PTSD is due to individual-specific environmental effects. Of this variance, 91% is unique to PTSD and 9% is shared with risk for trauma exposure.

Discussion

The primary goal of the present study was to examine a key etiological question in the traumatic stress field — to what degree do the etiological factors that influence trauma exposure also impact risk for PTSD? To our knowledge, this study represents the first attempt to examine this question using family data that permits the separation of familial from unique environmental influences. The results from the CCC twin modeling point to a few broad conclusions. First, the extreme hypotheses that the liability factors for trauma exposure and PTSD are entirely the same or completely independent are unlikely. The best-fit model based on negative twice the log likelihood and AIC clearly indicate that an E only model does not fit the data. Familial influences appear to be involved in trauma exposure and its transmittable relationship to risk for PTSD. Second, these model-based findings suggest that about one third of the variance in liability of PTSD symptoms is due to familial factors, and that of this, approximately one fifth overlaps with the liability for trauma exposure while the other four fifths of the variance is specific to risk levels of PTSD symptoms following exposure.

Our finding of modest overlap in liability for exposure and reaction to exposure could be due to a number of alternative possibilities. For example, it could be that this overlap in liability is operating through selection of the environment (as discussed by Stein et al., 2002). If these liability factors are related to selection into higher risk environments where traumatic event exposure is more likely, then it would follow that the likelihood of PTSD symptoms would increase as well. It is well documented that there is a dose-response relationship between the number of traumatic experiences and PTSD symptoms (e.g., Kolassa et al., in press). It is also possible that this shared familial liability that confers risk for both traumatic event exposure and stress symptoms posttrauma is due to a common mechanism, such as personality (e.g., neuroticism). Indeed, neuroticism has been shown to be moderately heritable (Eaves et al., 1998), to be related to other anxiety disorders (Hettema et al., 2006), to be related to exposure to stressful life events (Kendler et al., 2003), and the risk of developing major depression in response to stressful events (Kendler et al., 2004).

Familial factors that influence proneness to exposure and subsequent PTSD symptoms could also be mediated through a shared pathway such as neuroticism. Although the present study does not have data to directly examine this hypothesis, future studies should examine these possibilities, as elucidation of the shared mechanism will have important implications for both gene-finding efforts, as well as for informing primary prevention and secondary intervention efforts.

Finally, these findings suggest that PTSD, although a unique DSM disorder phenotype in that it is the only one that is required to be conditioned upon exposure to an environmental event, is perhaps not that unlike many other psychiatric phenotypes in its etiological roots. For example, research on major depression suggests both stressful life events and genetic influences are liability factors for depressive episodes, but moreover, that genetic factors may afford risk for depressive episodes by influencing the sensitivity of reaction to the event (Kendler et al., 1995). Future studies with data on onset of trauma and other psychiatric conditions, such as major depression and substance use disorders, could utilize modeling similar to that employed in this study to determine the degree of overlap in the influences on trauma exposure and later pathology. Additionally, modest genetic influences on measures of the

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environment have been consistently reported in the literature (for a review see Kendler & Baker, 2007); and following, the notion that individual differences in personal proneness to be exposed to a traumatic or stressful life event are well established. Two twin studies to date have examined the gene-environment correlation for traumatic events also found a modest heritability of exposure to traumatic events as well as subsequent PTSD symptoms (Lyons et al., 1993; Stein et al., 2002; True et al., 1993). However, the present study extends this literature by quantifying the degree of overlap between the liability factors for event exposure and for symptoms posttrauma. Previous twin studies were able, however, to estimate heritability for trauma exposure as well as PTSD rather than examining the familial transmission in an aggregate manner as had to be done here. Our results were also consistent with epidemiological data from Western European countries generally reporting a lower prevalence of traumatic event exposure compared to US studies (Darves-Bornoz et al., 2008; Perkonigg et al., 2000).

Limitations and Conclusions

Our results should be interpreted in the context of a number of limitations. First, due to low power and relatively infrequent endorsement of items tapping the target constructs we were unable to distinguish between genetic and common environmental effects. Therefore, we are unable to obtain separate estimates of additive genetic and share environmental contributions to the phenotypic variances of trauma exposure and PTSD symptoms in this sample. Additionally, parameters had wide CIs indicating imprecision of the estimates. Second, our data came from a native-born young adult Norwegian sample, and generalization to other ethnic or age groups should be done with caution. Third, there was substantial attrition between the original birth registry and the personal interview wave of data collection used in these analyses. As noted in previous papers from this data set (Kendler et al., 2011), prediction of nonresponse across waves indicated that sex, zygosity, age, and education, but not mental health variables (Tambs et al., 2009) were significant predictors of attrition. Fourth, an ordinal PTSD symptom count was used in analyses, rather than the diagnosis of PTSD, in order to increase statistical power. The traumatic life event assessment was brief, and did not include queries of the severity of exposure, the number of times per exposure, or age of exposure. Therefore, we were unable to create a 'total traumatic event history' variable to use as the first stage variable in our modeling, which would have been desirable. Assessing this type of information in future studies could also further this literature. Additionally, the trauma variable used in this study was quite heterogeneous. That is, we did not have the power to separate out different forms of potentially traumatic events for our modeling, and therefore qualifying events were quite broad. Future higher powered investigations of the conditional nature of various forms of trauma exposure and PTSD should be conducted to help further investigate the etiological nature of this unique psychiatric condition, especially in light of studies suggesting interpersonal events are modestly heritable, while other events (e.g., motor vehicle accidents) are not (Stein et al., 2002). A potential weakness of our CCC model is that the model requires that errors of measurement that impact on trauma in exposure to be transmitted to the risk for developing PTSD, and this limitation was overcome by adding a latent measure of trauma exposure to the model that separates out the true environmental risk and the error with only the former being transmitted.

In conclusion, the findings from the present study suggest that the pathway to PTSD may be complex, and that while the familial and environmental factors that confer risk for trauma exposure and for PTSD symptoms are correlated, they are not identical. Identification of the factors that are shared between exposure and symptoms is an important area for future clarification. As is the case with all empirical research findings, replication is needed. Plans are currently underway to apply the CCC model used in this study to an independent US twin sample.

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