

Pretrauma Cognitive Ability and Risk for Posttraumatic Stress Disorder

A Twin Study

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Context: Cognitive deficits are associated with posttraumatic stress disorder (PTSD), but whether such deficits reflect sequelae or risk factors is not fully resolved.

Objective: To determine, in a representative sample, whether preexposure cognitive ability is associated with risk for PTSD, and whether that risk is genetically mediated.

Design, Setting, and Participants: The co-twin-control study involved 2386 male Vietnam-era twin veterans with a mean (SD) age of 41.9 (2.7) years, a population-based sample of men who were in military service during this era. Cognitive ability scores were obtained just before military induction at a mean (SD) age of 19.7 (1.5) years. Participants included only individuals who were exposed to potentially traumatic events and underwent preexposure cognitive testing.

Main Outcome Measures: Armed Forces Qualification Test (of cognitive ability) percentile scores and PTSD diagnosed by means of structured interviews.

Results: We found a significant dose-response relationship between preexposure cognitive ability and risk for

PTSD. After controlling for confounders, the highest cognitive ability quartile had a 48% lower risk than the lowest ability quartile ($P < .001$). Non-PTSD-concordant pairs had the highest scores; PTSD-concordant pairs had the lowest scores; and PTSD-discordant pairs had intermediate scores. Differences in Armed Forces Qualification Test scores within twin pairs were significant only in PTSD-discordant pairs ($P = .04$) and were accounted for specifically by the discordant dizygotic pairs ($P = .002$). Genetic influences on preexposure cognitive ability explained 5% of the variation in PTSD, but 100% of that relationship was explained by common genes.

Conclusions: Preexposure cognitive ability is a risk or a protective factor for PTSD. The variance in PTSD explained by preexposure cognitive ability is accounted for entirely by common genetic factors. Lower cognitive ability may be a marker of less adaptive coping against adverse mental health consequences of exposure to potentially traumatic events. Further study of the potential mechanisms through which cognitive ability confers risk is needed.

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POSTTRAUMATIC STRESS DISORDER (PTSD) is a frequent consequence of war or disaster. Estimates from the current Iraq war indicate that as many as 30% of combat veterans have significant mental health problems, including PTSD, thus making it a serious public health issue.¹ Even if this figure is an overestimate owing to its reliance on self-report measures, the data still strongly suggest that PTSD is a serious public health issue. Cognitive deficits have been frequently observed in PTSD, but this relationship has almost always been based on studies that have assessed cognition after PTSD has developed.²⁻⁵ For the most part, cognitive deficits have been assumed to be conse-

quences or sequelae of the disorder, but lower cognitive ability might be an indicator of increased risk for PTSD as well.⁶ There have been several longitudinal studies of premorbid cognitive ability in psychiatric illness; most of them have examined schizophrenia, whereas a few have examined mood disorders. As reviewed by Zammit et al,⁷ these studies provide generally consistent evidence that lower premorbid cognitive ability is associated with a greater risk for schizophrenia, whereas the evidence has been mixed for mood disorders. Premorbid cognitive ability in PTSD has been far less well studied.

We are aware of 3 reports in which preexposure cognitive ability has been assessed, each of which contained several

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Table 1. Demographic and Clinical Characteristics of 2386 Twin Veterans

Characteristic	Finding
Continuous Variables, Mean (SD)	
Age at study, y	41.9 (2.6)
Age at military induction, y	19.7 (1.5)
Education at military induction, y	12.1 (1.3)
AFQT percentile score*	55.2 (23.4)
Mother's years of education	11.7 (2.5)
Father's years of education	11.10 (3.2)
Categorical and Ordinal Variables, No. (%)	
Combat exposure index	
No SEA service	1231 (51.6)
SEA service without combat exposure	170 (7.1)
Low combat exposure	262 (11.0)
Medium combat exposure	283 (11.9)
High combat exposure	440 (18.4)
PTSD diagnosis†	
Yes	436 (18.3)
No	1950 (81.7)

Abbreviations: AFQT, Armed Forces Qualification Test; PTSD, posttraumatic stress disorder; SEA, Southeast Asia.

*The mean is slightly above average (the 50th percentile) because candidates scoring below the 10th percentile were statutorily excluded from military service.

†Includes only trauma-exposed twins; 9.6% of the entire sample was diagnosed as having PTSD.

methodological limitations. Two studies—which had relatively small sample sizes—found that lower precombat cognitive ability scores in Vietnam veterans were associated with a greater likelihood of developing PTSD.^{8,9} As noted by the authors, the first⁸ did not control for the level of combat exposure, which could by itself account for the increased risk of PTSD, and neither used representative case or control samples.^{8,9} In the more recent study by Macklin et al,⁹ the comparison group of veterans without PTSD had cognitive ability scores approximately 1 SD above average. Age and education at entry into the military and childhood socioeconomic status tend to be associated with cognitive ability and risk for PTSD,^{10,11} but these previous studies were also unable to control for those variables.

An Israeli study that used an epidemiological sample also found that individuals who developed PTSD had lower premorbid intellectual ability than those who did not; however, there was no control for exposure to combat in that study, and control participants were not necessarily exposed to trauma at all.¹² Also, clinical—rather than research-interview-based—diagnoses were used in that study,¹² and the diagnoses were based on *DSM-III-R* criteria¹³ for some individuals and *DSM-IV* criteria¹⁴ for others. Use of these different *DSM* editions may be an important issue because the *DSM-III-R* stressor criterion is more stringent and results in a much lower lifetime prevalence of PTSD than does that of *DSM-IV*. Concerns have been raised about overclassification of people as trauma survivors on the basis of *DSM-IV* criteria.¹⁵

A large and representative epidemiological sample in which such factors are taken into account is necessary to confirm lower preexposure cognitive ability as an in-

dicator of risk for PTSD and to determine the strength of this effect. We addressed this issue through our examination of a large sample of male twins who served in the US military during the Vietnam era (1965-1975). We controlled for the following potential confounders: age and education at entry into the military, combat exposure, and parental education. Use of a co-twin-control design ensured maximal similarity of the groups being compared and enabled us to make inferences about the presence of genetic influences. For example, given lower preexposure cognitive ability as a risk factor for PTSD, we hypothesized that cognitive test scores in twins with PTSD would be lower than those of their trauma-exposed co-twins without PTSD.

METHODS

PARTICIPANTS

The study was approved by the institutional review boards of the participating institutions, and all participants gave informed consent to participate. Participants were recruited from the Vietnam Era Twin Registry¹⁶ as part of the Harvard Twin Study of Drug Abuse.¹⁷ Efforts to contact all available registry members resulted in interviews of 8269 (80.3%) of 10 300 eligible men that were completed in 1992. Twins for the present report were drawn from the 3322 pairs in which both members participated.¹⁷ Interviews were conducted by trained research assistants. Registry members are demographically representative of military personnel from that era.¹⁸ Zygosity was determined on the basis of questionnaire and blood group methods, an approach that achieves approximately 95% accuracy compared with DNA analysis.¹⁹ The racial/ethnic breakdown of the sample was 90.4% non-Hispanic white, 4.9% African American, 2.7% Hispanic, 1.3% Native American/Alaskan native, and 0.7% other. One third of the sample (33.3%) were high school graduates; 38.6% were college graduates; 92.6% were employed full-time; and 1.8% were employed part-time.

Participants were excluded from the present analyses if they (1) reported no history of exposure to a traumatic event (because, by definition, they could not be at risk for PTSD); (2) had missing or invalid cognitive ability scores; or (3) reported having experienced a traumatic event before military service (ie, before their cognitive testing). The remaining sample consisted of 1328 monozygotic (MZ) and 1058 dizygotic (DZ) twins; their demographic and clinical characteristics are shown in **Table 1**.

MEASURES

Age and education at military induction were abstracted from the original military personnel file, including the DD4 and DA-20 forms. Trauma history was assessed using the Diagnostic Interview Schedule Version III-Revised.²⁰ Diagnoses were based on *DSM-III-R* criteria. The interview includes inquiries about the occurrence of a number of traumatic events. If a respondent endorses one of these events or another qualifying experience, the interviewer gathers information about age at exposure, age at the onset of symptoms, symptom type, and duration. Premilitary trauma history was recorded if a twin reported a traumatic event with an age of onset that preceded age of induction into the military. This information is collected on up to 3 traumatic events. Only a minority of registry twins reported more than 1 trauma and, of those, PTSD was almost always associated with the earliest trauma. Approximately 34.7%

of those reporting trauma exposure cited combat as their worst trauma. A total of 3065 participants, consisting of 46.1% of the sample, reported exposure to 1 or more traumatic events, of whom 649 (21.2%) received lifetime diagnoses of PTSD.²¹ Details of the interview procedure, types of traumatic events reported, and PTSD diagnostic data were reported previously.¹⁰

Combat exposure was based on the number of reported combat experiences with distinct characteristics on the Combat Exposure Index.²² Ratings on this scale were as follows: 0 (no Southeast Asia service); 1 (Southeast Asia service without combat exposure); 2 or 3 (low combat exposure); 4 to 6 (medium combat exposure); and 7 or higher (high combat exposure). Previous work has shown that the ordinal combat categories have good internal consistency ($\alpha=0.86$) and test-retest reliability ($\kappa=0.84$).²²

The preexposure cognitive ability measure was the Armed Forces Qualification Test (AFQT),²³ a group-administered screening test used to determine whether draftees and enlistment applicants met the minimal standards for military service. These scores were obtained from the DD4 and DA-20 forms. The AFQT consisted of 100 multiple-choice items with the following 4 equal components: vocabulary, arithmetic, spatial visualization, and tool identification/understanding. Total raw scores were corrected for guessing and converted to percentile scores referenced to the male population who had been mobilized for military service during World War II. Separate scores for the 4 components are not available. Individuals scoring below the 10th percentile were excluded from the military; thus, the AFQT percentile scores in this sample range from 10 to 99. The AFQT was designed to measure military trainability rather than intelligence, but it does appear to be a highly g-loaded measure (ie, an index of general cognitive ability) that correlates well with traditional IQ measures.²⁴ After correcting for restriction of range, McGrevy et al²⁵ reported a correlation of 0.84 between scores on the AFQT and the Wechsler Adult Intelligence Scale²⁶ in a sample that was demographically similar to the present sample. More recently, Orme et al²⁷ found that the correlation between the AFQT and the Multidimensional Assessment Battery (an intelligence measure very similar to the Wechsler Adult Intelligence Scale [$r=0.91$]) was 0.85 after correcting for restriction of range.

STATISTICAL ANALYSIS

Phenotypic Analysis of Preexposure Cognitive Ability and Risk for PTSD

We first conducted phenotypic analyses using logistic regression to test the relation of preexposure cognitive ability with the risk for PTSD before and after controlling for potential confounders. Twins were treated as singletons for this analysis, and the sandwich variance estimator was used to correct for nonindependence of data from twins in the same family.^{28,29} Participants were excluded from these phenotypic analyses if they (1) reported no history of exposure to a potentially traumatic event (because, by definition, they could not be at risk for PTSD; $n=3678$); (2) had missing or invalid cognitive ability scores ($n=702$); or (3) reported having experienced a potentially traumatic event before military service (ie, before their cognitive testing; $n=376$). The remaining sample for phenotypic analyses consisted of 1328 monozygotic (MZ) and 1058 dizygotic (DZ) twins. The sample was divided into quartiles based on AFQT scores, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to indicate risk for PTSD relative to the reference group, which was the lowest-scoring AFQT quartile.

Cognitive Ability in Twin Pairs Concordant and Discordant for PTSD

Our second set of analyses examined risk for PTSD in twin pairs concordant and discordant for the disorder. Eligibility for this analysis was the same as for the previous analysis except that both members of a twin pair had to meet the criteria. The final sample consisted of 616 eligible twin pairs, including 43 pairs concordant for having PTSD, 185 pairs discordant for PTSD, and 383 pairs concordant for not having PTSD. If lower preexposure cognitive ability is a risk factor for PTSD (rather than a sequela of illness), then AFQT percentiles in discordant pairs should be lower in the twins with PTSD compared with their trauma-exposed co-twins without PTSD. The discordant co-twin–control comparison is particularly useful because co-twins are far more closely matched than other individuals. Between-pair comparisons should yield higher scores in non-PTSD-concordant pairs (where neither twin had PTSD) and lower scores in PTSD-concordant pairs. Neither of the concordant-pair groups should manifest significant within-pair differences. Given the clear directional hypothesis, we used 1-tailed matched-pairs *t* tests to assess within-pair differences. We then used ordinary least squares regression, controlling for confounders, to test the association between preexposure cognitive ability and risk for PTSD within and between twin pairs.

Genetic Influences on the Association Between PTSD and Preexposure Cognitive Ability

Our third set of analyses involved testing whether there were genetic influences underlying the association between PTSD and preexposure cognitive ability by adding a term for the interaction of zygosity and the within-pair effect to the regression model. If preexposure cognitive ability is more strongly associated with PTSD within PTSD-discordant DZ pairs than within PTSD-discordant MZ pairs (ie, a significant interaction is present), it suggests that genetic mediation is likely. This logic may not be readily apparent to someone who is unfamiliar with behavioral genetics. If any trait or association between traits is due to genes, then MZ twins cannot differ because they are genetically identical. Therefore, if the aforementioned association is genetically mediated, differences would have to be accounted for by DZ twin pairs, who share on average only 50% of their genes. The interaction being tested is, thus, one in which there is a significant difference within DZ pairs, but not within MZ pairs.

We then tested whether the association of cognitive ability with PTSD was accounted for by shared genetic etiology by using maximum likelihood estimation techniques to fit different structural equations to raw data. Structural equation models were fit in Mplus version 3.11 statistical software³⁰ (estimator, weighted least squares; parameterization, theta). The full sample of twin pairs ($N=3322$ pairs) was included in this analysis. Because exposure to a potentially traumatic event is a criterion for the diagnosis of PTSD, veterans who did not report trauma exposure were coded as missing. Participants were not excluded owing to missing data; Mplus uses full information maximum likelihood estimation to retain the complete sample size for each analysis.

We first computed correlations for MZ and DZ pairs to assess the cross-twin cross-trait correlations for the AFQT score and PTSD. In the univariate twin model, the variance for the AFQT score or PTSD is partitioned into the variance due to additive genetic (A), common environmental (C), and individual-specific environmental influences (E), including error (the ACE model). In the bivariate twin analysis, MZ and DZ correlations are compared across traits, ie, one twin's AFQT score is

Table 2. Preexposure Cognitive Ability (AFQT Percentile Scores) and Risk for PTSD Compared With the Reference Group*

AFQT Group, Quartiles	AFQT Percentile Score Range	No. of Subjects	OR (95% CI)	P Value
Comparison With Reference Group				
Low (reference group)	10-33	574
Medium-low	34-55	606	0.74 (0.56-0.98)	.04
Medium-high	56-75	612	0.56 (0.42-0.75)	<.001
High	76-99	594	0.42 (0.31-0.58)	<.001
Comparison With Reference Group After Controlling for Confounders				
Low (reference group)	10-33	574
Medium-low	34-55	606	0.87 (0.64-1.17)	.35
Medium-high	56-75	612	0.69 (0.50-0.95)	.02
High	76-99	594	0.52 (0.37-0.73)	<.001

Abbreviations: AFQT, Armed Forces Qualification Test; CI, confidence interval; OR, odds ratio; PTSD, posttraumatic stress disorder; ellipses, not applicable.

*The risk of PTSD relative to the reference group is 1 minus the odds ratio. For example, an odds ratio of 0.74 indicates a 26% lower risk relative to the reference group.

correlated with the co-twin's PTSD diagnosis. If the cross-trait twin correlations are greater for MZ than for DZ twins, this implies that genetic factors contribute to the phenotypic correlation between the 2 traits. A significant path from additive genetic influences (A) on the AFQT to PTSD indicates the extent to which genetic influences on the AFQT score also influence variation in PTSD. A significant path from shared environmental (C) influences on the AFQT score to PTSD indicates the extent to which shared environmental influences on the AFQT score also influence PTSD. A significant path from nonshared environmental influences (E) on the AFQT score to PTSD indicates the extent to which nonshared or unique environmental influences on the AFQT score also influence PTSD.

We assessed model fit via 3 fit statistics. When the models are nested (ie, identical with the exception of constraints that involve setting specific parameters to 0), the difference in fit between models can be tested by $\Delta\chi^2$, using as its degrees of freedom the difference in degrees of freedom of the 2 models. If the $\Delta\chi^2$ is statistically nonsignificant, the more parsimonious nested submodel is selected because the test indicates that the model fit does not deteriorate with the additional constraints. The second model-selection statistic was the comparative fit index, for which values greater than 0.95 are indicative of good-fitting models.³¹ The third model-selection statistic was the root mean square error of approximation, which is an index of the model discrepancy, per degree of freedom, from the observed covariance structure.³² Values less than 0.05 indicate close fit, and values less than 0.08 indicate fair fit to the data.³³

RESULTS

The demographic and clinical characteristics for participants included in the phenotypic analyses are shown in Table 1. Participants included in this analysis did not differ from those excluded on zygosity (MZ, 57.7% for those included and 55.9% for those excluded; $\chi^2_1=0.02$ [$P=.88$]), maternal education of less than high school (26.0% for those included and 27.2% for those excluded; $\chi^2_1=1.19$ [$P=.28$]), or paternal education (39.0% for those included and 38.6% for those excluded; $\chi^2_1=0.09$ [$P=.77$]). The AFQT scores also did not differ when those included were compared with those excluded for reasons other than invalid or missing AFQT data ($b=-0.005$ [SE, 0.61; $P=.99$]). Because selection criteria were based on exposure to a potentially traumatic event, included par-

ticipants were more likely to have served in Southeast Asia, to have been exposed to combat, and to have been younger and have had less than a high school education on entry into the military ($P<.001$ for all). These comparisons strongly argue against any selection bias that would have influenced the results.

PHENOTYPIC ANALYSIS OF PREEXPOSURE COGNITIVE ABILITY AND RISK FOR PTSD

Table 2 indicates that lower preexposure cognitive ability was significantly associated with increased risk of PTSD in a dose-response fashion. For example, the OR of 0.42 in the highest cognitive ability group indicates that individuals in this group are at 58% lower risk of developing PTSD compared with those in the lowest cognitive ability (reference) group. We then tested whether the cognitive ability-PTSD relation was attenuated after adjusting for confounders. Several potential confounders were associated with risk for PTSD, including combat exposure (OR, 1.30 [95% CI, 1.21-1.41; $P<.001$]), age at military entry (OR, 0.88 [95% CI, 0.81-0.96; $P=.005$]), and having less than a high school education at military entry (OR, 1.54 [95% CI, 1.13-2.10; $P=.006$]). However, as can be seen in Table 2, the strength of the association between cognitive ability and risk for PTSD remained similar after adjusting for confounders. **Figure 1** illustrates the clear linear relationship between preexposure cognitive ability and PTSD prevalence.

COGNITIVE ABILITY IN TWIN PAIRS CONCORDANT AND DISCORDANT FOR PTSD

Members of discordant pairs differed significantly in preexposure cognitive ability; PTSD was associated with lower scores in twins with PTSD compared with their non-PTSD co-twins ($t_{185}=1.79$; $P=.04$, 1-tailed test). Differences within both types of concordant pairs were nonsignificant ($P>.43$ for all). As seen in **Figure 2**, the pattern of preexposure cognitive ability was such that it was also highest in non-PTSD-concordant pairs and lowest in PTSD-concordant pairs (described in the next paragraph). Results were similar if the AFQT score was stan-

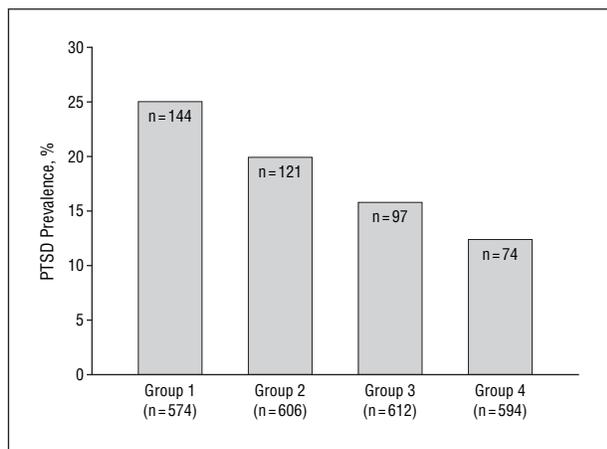


Figure 1. Prevalence of posttraumatic stress disorder (PTSD) by Armed Forces Qualification Test (AFQT) score quartile obtained before the veteran twins' exposure to trauma. Sample includes all individuals exposed to trauma after having taken the AFQT. Group 1 has low (range, 10-33 points); group 2, medium to low (range, 34-55 points); group 3, medium to high (range, 56-75 points); and group 4, high (range, 76-99 points) AFQT scores.

standardized and treated as a continuous variable in the logistic regression analysis (unadjusted OR, 0.73 [95% CI, 0.65-0.80; $P < .001$]; adjusted OR, 0.77 [95% CI, 0.69-0.88; $P < .001$]).

In the ordinary least squares regression, the within-pair components test for the association between preexposure cognitive ability and PTSD diagnosis after controlling for between-pair confounders (eg, parental education). After controlling for confounders, both the between-pair ($b = -4.96$ [SE, 2.55; $P = .05$]) and the within-pair ($b = -3.78$ [SE, 1.71; $P = .03$]) effects were significant. For the between-pair effect, PTSD-concordant pairs had AFQT scores that averaged 4.96 percentile points lower than those of non-PTSD-concordant pairs; discordant pairs had AFQT scores that were 2.48 percentile points lower than those of non-PTSD-concordant pairs. Within-pair comparisons of PTSD-discordant twins showed that twins with PTSD had AFQT scores that averaged 3.87 percentile points lower than their co-twins without PTSD. The between-pair and within-pair effects were not significantly different from one another (Wald test, $F_{1,709} = 0.15$ [$P = .70$]).

GENETIC INFLUENCES ON THE ASSOCIATION BETWEEN PTSD AND PREEXPOSURE COGNITIVE ABILITY

There was a significant interaction of zygosity and the within-pair effect in the regression model ($\beta = 10.81$ [SE, 3.43; $P = .002$]). Stratifying pairwise analyses by zygosity showed that PTSD was significantly associated with lower preexposure cognitive ability within PTSD-discordant DZ pairs (mean for non-PTSD twin, 56.64 [SD, 2.55]; mean for PTSD twin, 50.20 [SD, 2.34]; $n = 91$ pairs; mean difference, 6.44; $t_{89} = 2.42$ [$P = .02$]), but not within MZ-discordant pairs (mean for non-PTSD twin, 50.52 [SD, 2.87]; mean for PTSD twin, 50.88 [SD, 2.16]; $n = 94$ pairs; mean difference, -0.36 ; $t_{92} = -0.18$ [$P = .86$]). This pattern is shown graphically in **Figure 3**.

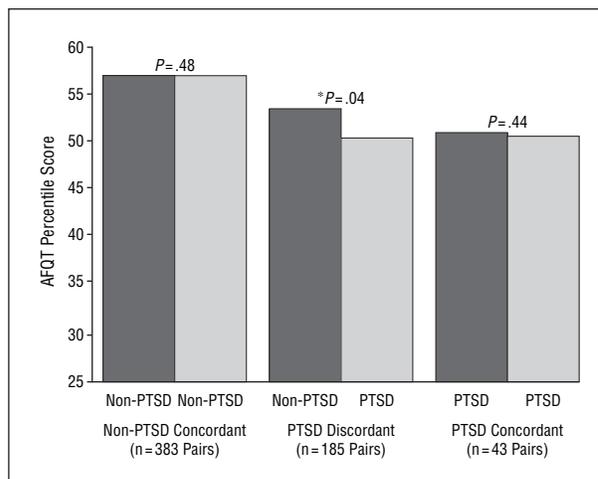


Figure 2. Mean Armed Forces Qualification Test (AFQT) scores before trauma exposure in twin pairs. Sample includes only pairs in which both twins were exposed to trauma after having taken the AFQT. PTSD indicates posttraumatic stress disorder. *Statistically significant P value.

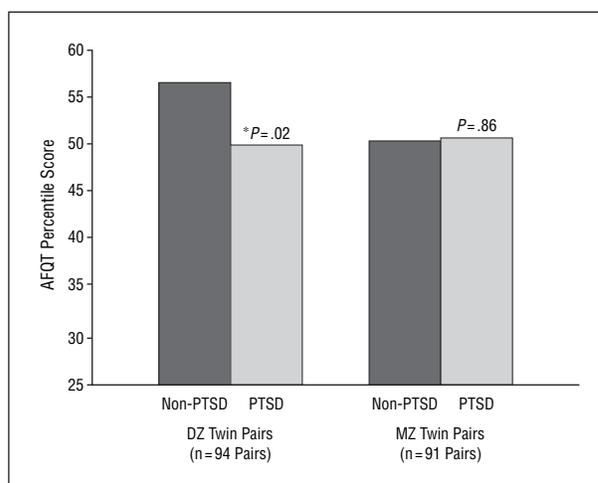


Figure 3. Mean Armed Forces Qualification Test (AFQT) scores before trauma exposure in monozygotic (MZ) vs dizygotic (DZ) twin pairs discordant for posttraumatic stress disorder (PTSD). Sample includes only pairs in which both twins were exposed to trauma after having taken the AFQT. For the interaction of zygosity and the within-pair AFQT effect, $P = .002$. *Statistically significant P value.

Table 3 presents the correlations for AFQT score and PTSD by zygosity. The higher cross-twin cross-phenotype correlations among MZ twins compared with DZ twins suggested genetic influences on the AFQT score-PTSD association. Univariate model-fitting results for AFQT score indicated that the correlation for MZ twins ($r = 0.75$ [$P < .001$]) was greater than that for DZ twins ($r = 0.51$ [$P < .001$]). The ACE model provided the best fit to the data (comparative fit index, 1.00; root mean square error of approximation, 0.001; $\chi^2_6 = 5.33$ [$P = .50$]). The proportion of variance in the AFQT score accounted for by additive genetic effects was 50% (95% CI, 42%-59%); by shared environmental factors, 25% (95% CI, 18%-33%); and by nonshared environmental factors, 25% (95% CI, 23%-26%). The univariate model-fitting results for PTSD in this sample have been published previously.^{21,34,35}

Bivariate twin modeling was used to test whether the association between the AFQT score and PTSD was accounted for by a shared genetic etiology. The cross-twin cross-trait correlations were higher for MZ than for DZ twins (MZ, -0.13 and -0.17; DZ, -0.09 and 0.01), suggesting a role for genetic influences in the AFQT score-PTSD relation. Model fit did not deteriorate significantly if the shared environmental pathway specific to PTSD and the shared and nonshared environmental pathways from the AFQT score to PTSD were fixed to zero ($\Delta\chi^2_2=1.05$ [$P=.59$]). However, model fit deteriorated significantly if additive genetic influences on the AFQT score were hypothesized to have no effect on variance in PTSD ($\Delta\chi^2_1=31.82$ [$P<.001$]). Therefore, the bivariate model that provided the best fit to the data consisted of the ACE model for the AFQT score, the AE model for PTSD, and a significant genetic pathway from the AFQT score to PTSD. This model (**Figure 4**) provided an excellent fit to the data (comparative fit index, 1.00; root mean square error of approximation, 0.008; $\chi^2_{17}=17.83$ [$P=.33$]).

Figure 4 illustrates that for the best-fitting model the only path between the AFQT score and PTSD is that from genetic influences on the AFQT score to PTSD. This indicates that 100% of the AFQT score-PTSD relationship is explained by genetic influences common to both phenotypes. When parameter estimates were standardized and calculated as proportions of the variance, ge-

netic influences on the AFQT score accounted for 5% of the variance in PTSD. The remaining variance in PTSD was accounted for by genetic (26%) and nonshared environmental (69%) influences unique to PTSD.

COMMENT

Our results indicate that preexposure cognitive ability is associated with an increased risk for PTSD in a dose-response fashion in both between-twin and within-pair analyses. After controlling for confounders, the ORs indicated that, compared with the lowest-scoring AFQT group, the risk of developing PTSD was reduced from 13% to 31% to 48% in successively higher-scoring AFQT groups (Table 2 and Figure 1). Given the significant interaction indicating that the within-pair effect of PTSD differed by zygosity (Figure 3), our findings are consistent with the notion that the association between preexposure cognitive ability and the risk for PTSD reflects some underlying genetic influences. Genetic influences on cognitive ability explained about 5% of the variance in PTSD. The overall phenotypic correlation between AFQT scores and PTSD was -0.19, and our biometrical modeling (Figure 4) indicated that this relationship was due entirely to common genetic influences.

It is a limitation of the study that our sample consisted primarily of white men; thus, we cannot be certain that the findings are generalizable to women and other racial/ethnic groups. The fact that only 35% of individuals reporting trauma exposure indicated combat as their worst trauma may be viewed as a limitation because it reduces sample homogeneity. However, the results for only those PTSD cases with combat exposure were essentially the same as the results for those who experienced other stressors (data available from the authors on request). Therefore, we see the inclusion of both combat exposure and other stressors as a strength in that it enhances generalizability. Other strengths may be noted as well. We studied a representative sample for which there is unlikely to have been any selection bias. This may be particularly important with regard to control subjects. In some previous studies,¹² controls had no mental illness, whereas in the present study controls did not undergo screening for any psychiatric diagnoses other than PTSD; this also enhances generalizability. The use of DSM-III-R criteria reduces false-positive PTSD diagnoses com-

Table 3. Correlation Matrix for AFQT and PTSD*

Twin Pairs	AFQT Twin 1	PTSD Twin 1	AFQT Twin 2	PTSD Twin 2
MZ (n = 1874)				
AFQT twin 1	1.00			
PTSD twin 1	-0.21†	1.00		
AFQT twin 2	0.75†	-0.17†	1.00	
PTSD twin 2	-0.13†	0.32†	-0.17†	1.00
DZ (n = 1498)				
AFQT twin 1	1.00			
PTSD twin 1	-0.15†	1.00		
AFQT twin 2	0.51†	0.01	1.00	
PTSD twin 2	-0.09†	0.08†	-0.18†	1.00

Abbreviations: AFQT, Armed Forces Qualifying Test; DZ, dizygotic; MZ, monozygotic; PTSD, posttraumatic stress disorder.
*Boldface text indicates cross twin with the same phenotype correlations; italic text, cross twin with cross-phenotype correlations.
† $P<.05$.

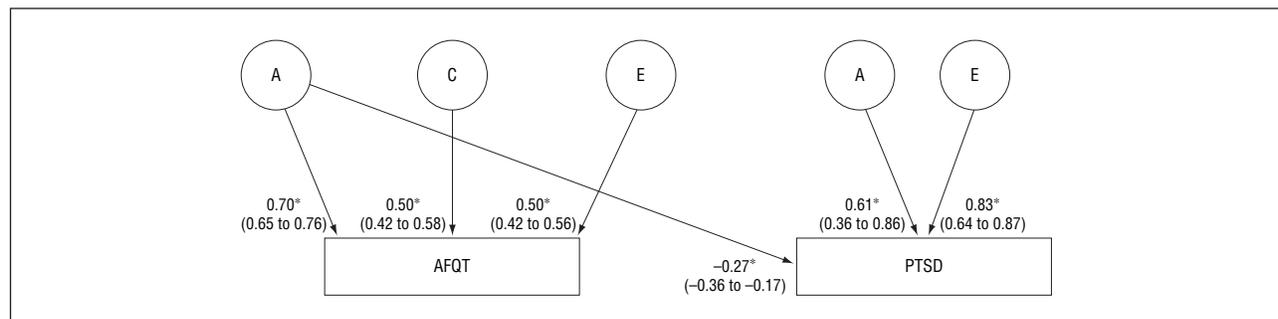


Figure 4. Bivariate twin model of association between the Armed Forces Qualification Test (AFQT) score and posttraumatic stress disorder (PTSD). Unstandardized parameter estimates (with 95% confidence intervals) are shown. A indicates additive genetic influences; C, common environmental influences; and E, individual-specific environmental influences. Note that because these parameter estimates are unstandardized, squaring them does not yield the exact proportions of variance accounted for by A, C, and E. *Statistically significant P value ($P<.05$).

pared with using *DSM-IV* criteria.¹⁵ Finally, the co-twin-control method provides the most stringent possible matching between cases and controls.

Although there may also be some cognitive deficits that are sequelae of PTSD, our premorbid data confirm that lower preexposure cognitive ability is a risk indicator (and that higher preexposure cognitive ability is protective). The twin nature of the data strengthens this conclusion and suggests that genetic influences play a significant role in the relationship between risk for PTSD and preexposure cognitive ability. A postmorbid neuroimaging study of hippocampal volumes in a small subset of PTSD-discordant twins from the Vietnam Era Twin Registry found not only that twins with PTSD had reduced volumes compared with their unaffected co-twins but also that unaffected co-twins still had reduced volumes compared with control twins.³⁶ Those results suggest that regional brain volume reductions were also indicators of increased risk for PTSD. It is not known, however, the extent to which the same or different genetic or environmental factors influence general cognitive ability and hippocampal volumes.

The specific mechanism by which higher cognitive ability confers a protective effect against PTSD remains unknown. Enhancing cognitive ability is exceedingly difficult; therefore, cognitive ability is unlikely to be an effective target of intervention for reducing the risk of PTSD. Research that elucidates the mechanism via which cognitive ability is associated with PTSD may help to inform intervention.

The personality trait of self-efficacy has been shown to mediate response to trauma in both prospective and retrospective studies.^{37,38} Although we are not aware of findings that directly address this issue, it seems likely that self-efficacy and general cognitive ability are at least modestly correlated; higher cognitive ability may tend to foster greater self-efficacy to the extent that cognitive ability fosters coping flexibility. Indeed, our findings may be consistent with that notion that higher cognitive ability is a marker of more adaptive coping mechanisms in the face of severe adversity.³⁹ However, regardless of cognitive ability, self-efficacy or mastery of trauma-related situations is amenable to training and development through a variety of approaches.³⁷

It is also possible that individuals with more cognitive resources are better able to translate their traumatic event into a narrative⁴⁰ and make meaning out of it.^{41,42} Developing programs that enhance meaning making or self-efficacy might be of substantial value for people such as military personnel and first responders to disasters who know in advance that they are going to be exposed to highly stressful experiences. On the other hand, it must be acknowledged that this discussion of potential intervention efforts is speculative. Low cognitive ability is a risk factor for other forms of psychopathology, including externalizing disorders,^{7,43} which in turn are associated with increased risk of developing PTSD.⁴⁴ Thus, the association between low cognitive ability and the risk of developing PTSD could be mediated by externalizing disorders. Before proceeding with actual intervention efforts, it will be important to gain a much more thorough understanding of the correlates of preexposure cogni-

tive ability that might suggest strong links to the risk for or protection from PTSD.

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REFERENCES

1. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med*. 2004;351:13-22.
2. Bremner JD, Scott TM, Delaney RC, Southwick SM, Mason JW, Johnson DR,

- Innis G, McCarthy G, Charney DS. Deficits in short-term memory in posttraumatic stress disorder. *Am J Psychiatry*. 1993;150:1015-1019.
3. Yehuda R, Keefe RS, Harvey PD, Levengood RA, Gerber DK, Geni J, Siever LJ. Learning and memory in combat veterans with posttraumatic stress disorder. *Am J Psychiatry*. 1995;152:137-139.
 4. Vasterling JJ, Brailey K, Constans JI, Sutker PB. Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology*. 1998;12:125-133.
 5. Golier J, Yehuda R. Neuropsychological processes in post-traumatic stress disorder. *Psychiatr Clin North Am*. 2002;25:295-315.
 6. Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *J Consult Clin Psychol*. 2000;68:748-766.
 7. Zammit S, Allebeck P, David AS, Dalman C, Hemmingsson T, Lundberg I, Lewis G. A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry*. 2004;61:354-360.
 8. Pitman RK, Orr SP, Lowerhagen MJ, Macklin ML, Altman B. Pre-Vietnam contents of PTSD veterans' service medical and personnel records. *Compr Psychiatry*. 1991;32:416-422.
 9. Macklin ML, Metzger LJ, Litz BT, McNally RJ, Lasko NB, Orr SP. Lower precombat intelligence is a risk factor for posttraumatic stress disorder. *J Consult Clin Psychol*. 1998;66:323-326.
 10. Koenen KC, Harley R, Lyons MJ, Wolfe J, Simpson JC, Goldberg J, Eisen SA, Tsuang MT. A twin registry study of familial and individual risk factors for trauma exposure and posttraumatic stress disorder. *J Nerv Ment Dis*. 2002;190:209-218.
 11. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, Weiss DS. *Trauma and the Vietnam War Generation: Report of Findings from the National Vietnam Veterans Readjustment Study*. New York, NY: Bruner/Mazel; 1990.
 12. Kaplan Z, Weiser M, Reichenberg A, Rabinowitz J, Caspi A, Bodner E, Zohar J. Motivation to serve in the military influences vulnerability to future posttraumatic stress disorder. *Psychiatry Res*. 2002;109:45-49.
 13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised*. Washington, DC: American Psychiatric Press; 1987.
 14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
 15. Breslau N, Kessler RC. The stressor criterion in *DSM-IV* posttraumatic stress disorder: an empirical investigation. *Biol Psychiatry*. 2001;50:699-704.
 16. Eisen S, True WR, Goldberg J, Henderson W, Robinette CD. The Vietnam Era Twin (VET) Registry: method of construction. *Acta Genet Med Gemellol (Roma)*. 1987;36:61-66.
 17. Tsuang MT, Bar JL, Harley RM, Lyons MJ. The Harvard Twin Study of Substance Abuse: what we have learned. *Harv Rev Psychiatry*. 2001;9:267-279.
 18. Henderson WG, Eisen SE, Goldberg J, True WR, Barnes JE, Vitek M. The Vietnam Era Twin Registry: a resource for medical research. *Public Health Rep*. 1990;105:368-373.
 19. Eisen S, Neuman R, Goldberg J, Rice J, True W. Determining zygosity in the Vietnam Era Twin Registry: an approach using questionnaires. *Clin Genet*. 1989;35:423-432.
 20. Robins L, Helzer J, Cottler L, Goldring E. *NIMH Diagnostic Interview Schedule, Version III-Revised (DIS-III-R)*. St Louis, Mo: Dept of Psychiatry, Washington University Medical School; 1989.
 21. Koenen KC, Hitsman B, Lyons MJ, Niaura R, McCaffery J, Goldberg J, Eisen SA, True W, Tsuang M. A twin registry study of the relationship between posttraumatic stress disorder and nicotine dependence in men. *Arch Gen Psychiatry*. 2005;62:1258-1265.
 22. Janes GR, Goldberg J, Eisen SA, True WR. Reliability and validity of a combat exposure index for Vietnam era veterans. *J Clin Psychol*. 1991;47:80-86.
 23. Bayroff AG, Anderson AA. *Development of Armed Forces Qualification Tests 7 and 8 (Technical Research Report 1122)*. Alexandria, Va: US Army Research Institute; 1963.
 24. Grafman J, Jonas BS, Martin A, Salazar AM, Weingartner H, Ludlow C, Smutok MA, Vance SC. Intellectual function following penetrating head injury in Vietnam veterans. *Brain*. 1988;111:169-184.
 25. McGrevey DF, Knouse SB, Thompson RA. *Relationships Among an Individual Intelligence Test and Two Air Force Screening and Selection Tests: AFHRL-TR-74-25*. Brooks Air Force Base, Texas: Personnel Research Division; 1974. Air Force Human Resources Laboratory Technical Report.
 26. Wechsler D. *Manual for the Wechsler Adult Intelligence Scale*. New York, NY: Psychological Corp; 1955.
 27. Orme DR, Brehm W, Ree MJ. Armed Forces Qualification Test as a measure of premorbid intelligence. *Mil Psychol*. 2001;13:187-197.
 28. Huber PJ. The behavior of maximum likelihood estimates under non-standard conditions. In: *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*. Vol 1. Berkeley: University of California Press; 1967: 221-233.
 29. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica*. 1980;48:817-838.
 30. Muthen LK, Muthen BO. *Mplus Version 3.11*. Los Angeles, Calif: Muthen & Muthen; 2004.
 31. Hu LT, Bentler PM. Cutoff criteria for fit indices in covariance structure analysis: conventional criteria versus new alternatives. *Struct Equation Model*. 1999;6:1-55.
 32. MacCallum RC, Browne MW, Sugawara HM. Power analysis and determination of sample size for covariance structure modeling. *Psychol Methods*. 1996;1:130-149.
 33. Browne MW, Cudeck R. Alternative ways of assessing model fit. In: Bollen KA, Long JS, eds. *Testing Structural Equation Models*. Thousand Oaks, Calif: Sage Publications; 1993.
 34. Xian H, Chantarujikpong SI, Sherrer JF, Eisen SA, Lyons MJ, Goldberg J, Tsuang M, True WR. Genetic and environmental influences on posttraumatic stress disorder, alcohol, and drug dependence in twin pairs. *Drug Alcohol Depend*. 2000;61:95-102.
 35. True WR, Rice J, Eisen SA, Heath AC, Goldberg J, Lyons MJ, Nowak J. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. *Arch Gen Psychiatry*. 1993;50:257-264.
 36. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathological vulnerability to psychological trauma. *Nat Neurosci*. 2002;5:1242-1247.
 37. Benight CC, Bandura A. Social cognitive theory of posttraumatic recovery: the role of perceived self-efficacy. *Behav Res Ther*. 2004;42:1129-1148.
 38. Heinrichs M, Wagner D, Schoch W, Soravia LM, Hellhammer DH, Ehlert U. Predicting posttraumatic stress symptoms from pretraumatic risk factors: a 2-year prospective follow-up study in firefighters. *Am J Psychiatry*. 2005;162:2276-2286.
 39. Masten AS, Hubbard JJ, Gest SD, Tellegen A, Garmezy N, Ramirez N. Competence in the context of adversity: pathways to resilience and maladaptation from childhood to late adolescence. *Dev Psychopathol*. 1999;11:143-169.
 40. Pennebaker JW. The effects of traumatic disclosure on physical and mental health: the values of writing and talking about upsetting events. *Int J Emerg Ment Health*. 1999;1:9-18.
 41. Klein I, Janoff-Bulman R. Trauma history and personal narratives: some clues to coping among survivors of child abuse. *Child Abuse Negl*. 1996;20:45-54.
 42. Gottfredson LS. Intelligence: is it the epidemiologists' elusive "fundamental cause" of social class inequalities in health? *J Pers Soc Psychol*. 2004;86:174-199.
 43. Fergusson DM, Horwood LJ, Ridder EM. Show me the child at seven, II: childhood intelligence and later outcomes in adolescence and young adulthood. *J Child Psychol Psychiatry*. 2005;46:850-858.
 44. Koenen KC, Fu QJ, Lyons MJ, Toomey R, Goldberg J, Eisen SA, True W, Tsuang MT. Juvenile conduct disorder as a risk factor for trauma exposure and posttraumatic stress disorder. *J Trauma Stress*. 2005;18:23-32.