Posttraumatic stress disorder; combat exposure; and nicotine dependence, alcohol dependence, and major depression in male twins

Jeffrey F. Scherrer, Hong Xian, Michael J. Lyons, Jack Goldberg, Seth A. Eisen, William R. True, Ming Tsuang, Kathleen K. Bucholz, Karestan C. Koenen

Abstract

Combat exposure is associated with increased risk of psychiatric and substance use disorders in veterans. However, it is not known whether combat exposure independently increases risk for these disorders or whether this association is accounted for by genetic vulnerability common to posttraumatic stress disorder (PTSD). This article tests competing explanations for the association of combat exposure and PTSD with nicotine dependence (ND), alcohol dependence (AD), and major depression (MD). Data were obtained from 6099 members of the Vietnam Era Twin Registry, a national registry of male-male twin pairs who served in the military during the Vietnam era. Twin models were fit to estimate the genetic and environmental variance common and specific to Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, lifetime diagnoses of PTSD, combat trauma, and 3 comorbid conditions: ND, AD, and MD. Variance specific to ND, AD, and MD was due to genetic factors (48%, 36%, and 12%, respectively) and unique environmental factors (36%, 42%, and 58%, respectively). After accounting for variance common to PTSD, no residual genetic and environmental variance overlapped between combat and ND, combat and AD, and combat and MD. Combat exposure is not independently associated with lifetime ND, AD, and MD. The association of combat exposure with these 3 disorders is due to genetic and unique environmental contributions in common with PTSD. These findings suggest comorbid PTSD may represent a genetically mediated vulnerability to psychopathology after trauma.

1. Introduction

Combat exposure is associated with increased risk of psychiatric and substance use disorders among men in the veteran population [1,2]. This association is especially strong among Vietnam veterans [3]. According to reexamination of the National Vietnam Veterans Readjustment Study, approximately 19% of male Vietnam theater veterans developed posttraumatic stress disorder (PTSD) and 9% had PTSD a decade after the war [4]. Risk for PTSD was greater with higher levels of combat exposure [4]. Moreover, nicotine dependence (ND), alcohol dependence (AD), and major depression (MD) are frequently comorbid with PTSD in Vietnam theater veterans [3,5-10].

Posttraumatic stress disorder may account for the association between combat exposure and ND, AD, or MD. This hypothesis was tested in a sample of monozygotic
(MZ) twins discordant on the outcome of interest (eg, ND) drawn from the larger Vietnam Era Twin (VET) Registry cohort used in the present study. The authors found evidence for a direct association between combat exposure and AD, but not for ND or MD, which was entirely explained by combat-related PTSD [11]. These findings are somewhat different than those for civilians, whereby there is some evidence that trauma exposure increases risk of first onset of ND independent of PTSD [12]. However, the association between trauma and AD and MD appears to be greatest in subjects with PTSD, with the exception of AD in women, in which case trauma alone appears to increase risk [12,13]. As Breslau et al [12,13] acknowledge, this mediation could be explained by vulnerability factors common to PTSD and other disorders. The current report models genetic and environmental influences on the associations among combat exposure; PTSD; and ND, AD, and MD. Previous investigators have tested similar hypotheses in the VET Registry by controlling for genetic influences between combat-related PTSD and these other disorders using a co-twin control design [11]. This previous study can conclude that combat-related PTSD remains associated with comorbid psychopathology after controlling for genetic and unique environmental contributions. However, the co-twin design did not disentangle the magnitude of genetic, shared, and unique environmental influences that may contribute to combat-related PTSD and comorbid psychopathology. The current report extends earlier findings by explicitly modeling, rather than controlling for, these genetic and environmental influences.

Prior research studies using data from the VET Registry provide the basis for this work. There are substantial genetic influences on variation in combat exposure [14]. Prior research has also established that there are significant common genetic and nonshared environmental influences on the association of PTSD with ND [9], AD [15], and MD [16].

Our competing hypotheses make different predictions with regard to the model of genetic and environmental influences that would best explain the phenotypic association of PTSD; combat exposure; and ND, AD, and MD. If genetic or environmental contributions to combat exposure overlap with these other disorders independent of PTSD, then genetic or environmental influences specific to combat should significantly influence ND, AD, and MD after accounting for those influences common to PTSD. Alternatively, if the genetic or environmental factors between combat exposure and ND, AD, and MD are accounted for by PTSD, genetic and environmental influences specific to combat should not significantly influence the variation between these disorders and PTSD.

2. Methods

Participants were drawn from the VET Registry, a nationally distributed cohort consisting of male-male twin pairs born between 1939 and 1957 in which both siblings served on active military duty during the Vietnam War era [17]. Zygosity was determined using a questionnaire and blood group typing methodology that achieved 95% accuracy [18]. Registry members are representative of all twins who served in the military during the Vietnam War on a variety of sociodemographic and other variables [19,20]. The data used in the present study came from 6527 respondents to the 1987 Survey of Health and the 1992 Harvard Twin Study of Drug Abuse and Dependence [21]. The individual response rate to the latter study was 79.6%. The mean age of respondents was 44.6 years (SD, ±2.8; range, 36-55 years); 90.4% were non-Hispanic white, 4.9% were African American, 2.7% were Hispanic, 1.3% were Native American, and 0.7% were “other.” Eight percent of respondents had not graduated from high school, 92% were high school graduates, 22% were college graduates, and 10.2% had postcollege education; 92.6% were employed full-time, and 1.8% were employed part-time. Three quarters were married at the time of the study, and 11% were never married. Registry members lived in all 50 states of the United States.

Because this study focuses on the relationship between combat experiences and psychiatric disorders, 1215 twins who experienced noncombat trauma before entering the military and/or only after discharge from military service were excluded from the study. Thus, the present study sample consists of 5312 twins consisting of 1224 MZ pairs, 886 dizygotic (DZ) twin pairs, and 1092 singletons (singletons were not included in biometrical models).

2.1 Measures

Lifetime diagnoses of PTSD, ND, AD, and MD were obtained using the Mental Health Diagnostic Interview Schedule Version III–Revised [22]. Data obtained from the Diagnostic Interview Schedule Version III–Revised were used to derive clinical diagnoses based on Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R). Details of the interview procedure, types of traumatic events reported, and PTSD diagnostic data have been previously reported [23]. Trained, experienced staff from the Institute for Survey Research, Temple University, interviewed twins after verbal informed consent was obtained, a method approved by the Institutional Review Boards at participating institutions.

Combat exposure was measured using a Combat Exposure Index [24] that asked twins about exposure to 18 specific combat activities, such as flying in an attack helicopter, being wounded, and receiving incoming fire. A global index of combat exposure was constructed by summing all positive responses from an individual. The global index is used to classify combat exposure into 5 ordinal categories: 0 (did not serve in Southeast Asia (SEA)), 1 (served in SEA but did not experience combat), 2 (1-2 combat experiences, “low combat”), 3 (3-6 combat experiences, “medium combat”), 4 (7 or more combat experiences, “high combat”). The ordinal combat categories demonstrated good internal consistency.
(α = .86) and test-retest reliability (κ = .84). The validity of the index is supported by a strong association between the combat exposure index and being awarded a military combat medal [24].

All data collection involving members of the VET Registry was approved by human subject committees at participating institutions.

### 2.2. Statistical analysis

Analyses began by first computing descriptive statistics for the association of PTSD with ND, AD, and MD. To test if PTSD contributes to the association between combat and ND, AD, and MD, we fit logistic regression models. In each model, the dependent variable was ND, AD, or MD. We used the surveylogistic procedure in SAS version 9.1 (SAS Institute, Cary, NC) to fit regression models. The surveylogistic procedure was computed with the option to adjust for the observations clustering in twin data and correctly compute the standard errors.

Twin modeling was performed by first computing tetrachoric correlations for MZ and DZ pairs to measure the association among PTSD; combat; and ND, AD, and MD. The tetrachoric correlation assumes that a continuous, normally distributed latent liability underlies the observed dichotomous distribution of diagnosis. It estimates the correlation between the underlying liability distribution rather than the observed dichotomous variables.

We then computed 3 trivariate Cholesky decomposition models of the association between the following: (1) PTSD, combat, and ND; (2) PTSD, combat, and AD; and (3) PTSD, combat, and MD. We ordered the 3 phenotypes in the trivariate modeling to test if residual variance remained between combat and AD, combat and ND, and combat and MD after accounting for variance shared with PTSD.

In the Cholesky model, variation in phenotypes is partitioned into variance due to additive genetic influences (A), shared or common environmental influences (C), and nonshared or unique environmental influences (E). Shared environmental influences are defined as environmental influences that make twins similar. Nonshared or individual-specific environmental influences are defined as environmental influences that make twins different. Measurement error is assumed to be random, that is, uncorrelated across twins; it is therefore also included in the nonshared environmental variance. Cholesky models were fit to the tetrachoric correlation matrix using Mx [25,26].

When conducting model fitting in Mx using nested models, the difference in fit between models can be tested by the change in χ² value with the df equal to the difference in df between the 2 models. If the χ² difference is not significant, then the more parsimonious model is selected because this indicates model fit does not deteriorate with the additional constraints. When comparing 2 models that are not nested, the Akaike information criterion (AIC) [27] is used to determine the best fitting model. The smaller AIC indicates the better fit.

Fig. 1 illustrates the full model for the association between PTSD, combat exposure, and the outcome (ND, AD, or MD). Path loadings are estimated for each source of influence, and these are used to determine the contribution of A, C, and E to the variance of PTSD, combat, and the outcome and the covariance between them. These influences

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**Fig. 1.** Full Cholesky model of additive genetic (A), family environmental (C), and unique environmental (E) contributions to PTSD, combat exposure, and outcome phenotypes: ND, AD, and MD.

*nicotine dependence, alcohol dependence or major depression*
may be common to all 3 phenotypes (as is represented by the A1, C1, and E1 factors), common to only combat and the outcome (as is represented by the A2, C2, and E2 factors), or specific to the outcome (as is represented by the A3, C3, and E3 factors). Hypotheses are tested by setting specific paths to zero. For example, we can test whether combat exposure is significantly associated with ND independently of PTSD by setting the \(a_{32}^{\prime}\), \(c_{32}^{\prime}\), and/or \(e_{32}^{\prime}\) to zero. If the \(\chi^2\) is not significant, then combat exposure is not significantly associated with the outcomes independently of PTSD.

### 3. Results

Among twins in the study, 295 (5.6%) met the *DSM-III-R* criteria for PTSD, 2376 (44.7%) for ND, 1728 (32.6%) for AD, and 425 (8.0%) for MD. Of those who served in SEA, 644 (12.1%) had low combat (1 ≤ combat index ≤ 2), 692 (13%) subjects had medium combat (3 ≤ combat index ≤ 6), and 478 (9.0%) subjects had high combat (combat index ≥ 7). The remainder served elsewhere or had no combat experience in SEA.

Among subjects without PTSD, the prevalence of ND among low, medium, and high combat was 41%, 48%, and 43%; the prevalence of AD among low, medium, and high combat was 30%, 36%, and 32%; and the prevalence of MD among low, medium, and high combat was 6%, 6%, and 7%. Among subjects with PTSD, the prevalence of ND among low, medium, and high combat was 65%, 67%, and 77%; the prevalence of AD among low, medium, and high combat was 79%, 67%, and 67%; and the prevalence of MD among low, medium, and high combat was 43%, 42%, and 52%. Thus, the prevalence of ND, AD, and MD was higher among subjects with combat and PTSD as compared with those with combat only.

Posttraumatic stress disorder was strongly associated with ND, AD, and MD in regression models that included combat level and PTSD. Posttraumatic stress disorder was significantly associated with ND (odds ratio [OR] = 3.3; 95% confidence interval [CI], 2.5-4.3), with AD (OR = 3.6; 95% CI, 2.8-4.6), and with MD (OR = 7.2; 95% CI, 5.5-9.4) after adjusting for combat level.

The results for the 3 trivariate Cholesky biometrical models are shown in Tables 1A, 1B, and 1C. Based on our previous studies with the VET Registry cohort [14,15,28-31], shared environmental pathways (Fig. 1; \(c_{11}, c_{21}, c_{31}, c_{22}, c_{32}, c_{33}\)) to all phenotypes were dropped in the first reduced model (model 2), which resulted in an improvement in fit (AIC = −9.65, −11.44, and −2.78 for ND, AD, and MD, respectively). The best fitting trivariate models (model 4; Tables 1A, 1B, 1C) for ND, AD, and MD (AIC = −13.44, −15.44, and −6.78, respectively) did not allow for shared environmental pathways (Fig. 1; \(a_{32}^{\prime}\)) to combat and the outcome of interest (ie, ND, AD, MD), and did not allow for unique environmental factors common (Fig. 1; \(e_{32}^{\prime}\)) to combat and the outcome of interest.

The results for the 3 trivariate Cholesky biometrical models are shown in Tables 1A, 1B, and 1C. Based on our previous studies with the VET Registry cohort [14,15,28-31], shared environmental pathways (Fig. 1; \(c_{11}, c_{21}, c_{31}, c_{22}, c_{32}, c_{33}\)) to all phenotypes were dropped in the first reduced model (model 2), which resulted in an improvement in fit compared with the full model (AIC = −9.65, −11.44, and −2.78 for ND, AD, and MD, respectively). The best fitting trivariate models (model 4; Tables 1A, 1B, 1C) for ND, AD, and MD (AIC = −13.44, −15.44, and −6.78, respectively) did not allow for shared environmental pathways (Fig. 1; \(c_{11}, c_{21}, c_{31}, c_{22}, c_{32}, c_{33}\)), did not allow for genetic factors common (Fig. 1; \(a_{32}^{\prime}\)) to combat and the outcome of interest (ie, ND, AD, MD), and did not allow for unique environmental factors common (Fig. 1; \(e_{32}^{\prime}\)) to combat and the outcome of interest.

### Tables 1A, 1B, and 1C

**Table 1A**

<table>
<thead>
<tr>
<th>Model</th>
<th>(\chi^2)</th>
<th>df</th>
<th>(\Delta \chi^2)</th>
<th>(\Delta df)</th>
<th>(P)</th>
<th>AIC</th>
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<td>–</td>
<td>66.52</td>
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\(\Delta \chi^2 = \chi^2\) (submodel) – \(\chi^2\) (full model). \(\Delta df = df\) (submodel) – \(df\) (full model). Bold text indicates best fitting model.

**Table 1B**

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<th>(\chi^2)</th>
<th>df</th>
<th>(\Delta \chi^2)</th>
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<th>(P)</th>
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<td>58.89</td>
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\(\Delta \chi^2 = \chi^2\) (submodel) – \(\chi^2\) (full model). \(\Delta df = df\) (submodel) – \(df\) (full model). Bold text indicates best fitting model.
MD under the best fitting models. Genetic variance in risk for ND, AD, and MD that overlapped with PTSD and combat was 30%, 20%, and 21%, respectively. The unique environmental variance that overlapped with PTSD and combat was 3%, 1%, and 9%, respectively. The remaining variance in risk for ND, AD, and MD was due to disorder-specific genetic contributions to ND (48%), AD (36%), and MD (12%) and disorder-specific unique environmental contributions to ND (36%), AD (42%), and MD (58%).

4. Discussion

Our results indicate that combat exposure alone is not independently associated with DSM-III-R lifetime diagnoses of ND, AD, or MD. Rather, the association between combat and the outcomes is accounted for by genetic and environmental contributions to PTSD. After accounting for variance in common with PTSD and combat, there were no genetic or unique environmental contributions common to combat and ND, combat and AD, and combat and MD. Most of the overlapping vulnerability was genetic, although nonshared environmental influences common to PTSD were also statistically significant. Specifically, genetic influences common to PTSD explained 30% of the variance in ND, 20% of the variance in AD, and 21% of the variance in MD. Significant nonshared environmental influences common to PTSD explained 30% of the variance in ND, 20% of the variance in AD, and 21% of the variance in MD. Significant nonshared environmental influences common to PTSD explained only 1% of the variance in AD, 3% of the variance in ND, and 9% of the variance in MD. Disorder-specific genetic influences explained a substantial portion of variance for AD (36%) and ND (48%). Such influences were not significant for MD; most of the variance in MD was explained by disorder-specific nonshared environmental influences (58%). Disorder-specific nonshared environmental influences were also important components of the variance in AD (42%) and ND (36%).

Our findings are largely consistent with those of Breslau et al [12,13], who found that it is PTSD and not the traumatic event per se that increased the risk for psychiatric comorbidity. Taken together, our findings suggest that the co-occurrence of PTSD and these other disorders is partly explained by a shared diathesis. This diathesis appears to represent a genetically mediated vulnerability to developing psychopathology after exposure to life-threatening events. The presence of a significant common nonshared environmental pathway from PTSD to ND, AD, and MD is consistent with PTSD symptoms having a direct, albeit small, effect on risk of these disorders [32]. Significant common nonshared environmental influences can also reflect common unmeasured environmental risk factors or shared measurement error.

Our data do not support the position of Summerfield [33,34], who argues that PTSD is an arbitrary definition given to a range of normal responses to war trauma and should be conceptualized as a sociological phenomenon rather than a psychiatric illness. Although we have reported evidence for common vulnerability factors, interpretation of this finding must consider the evidence for specific genetic contributions to PTSD and comorbid affective and substance use disorder. The present study and previous models of illicit drug dependence (DD) and PTSD [15] and models of PTSD, generalized anxiety disorder, and panic disorder [35] include genetic variance that is specific to PTSD and genetic variance that is specific to comorbid substance use and anxiety disorders. Comorbid psychiatric disorders that are associated with combat trauma are not completely explained by genetic vulnerability shared with PTSD. Overall, our current and previous reports suggest

<table>
<thead>
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<th>Model</th>
<th>Factors common to PTSD</th>
<th>Factors common to Combat</th>
<th>Factors specific to MD</th>
<th>( \chi^2 )</th>
<th>df</th>
<th>( \Delta \chi^2 )</th>
<th>( \Delta df )</th>
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\( \Delta \chi^2 = \chi^2 (\text{submodel}) - \chi^2 (\text{full model}) \)

\( \Delta df = df (\text{submodel}) - df (\text{full model}) \)

Bold text indicates best fitting model.

Table 1C

<table>
<thead>
<tr>
<th>Cholesky model for lifetime co-occurrence of PTSD, combat, and MD</th>
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<td><strong>Model</strong></td>
</tr>
<tr>
<td>------------</td>
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<tr>
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\( \Delta \chi^2 = \chi^2 (\text{submodel}) - \chi^2 (\text{full model}) \)

\( \Delta df = df (\text{submodel}) - df (\text{full model}) \)

Bold text indicates best fitting model.
that at least 39% of the genetic variance in PTSD is not shared with these other disorders.

Xian et al [15] reported no genetic variance specific to AD in a common factor model of PTSD, AD, and DD. When compared with this previous finding, the present results suggest that there is a specific genetic factor to AD not accounted for by PTSD, which can be detected when variance is not portioned into that due to DD. Koenen et al [9] reported that 62% of the covariance in PTSD and ND is due to common genetic factors, which leaves a substantial proportion of genetic variance specific to ND as we found in the present analyses. The analysis of Fu et al [16] of conduct disorder, MD, and PTSD is consistent with the present analyses in that both allow for a common genetic factor to PTSD and MD.

Approximately 1.4 million men are in active duty in the US armed forces, and this number is likely to increase [36]. Given the continuing conflicts in Iraq and Afghanistan, active duty military personnel are at high risk of combat exposure and PTSD [37]. Combat exposure is one of the traumas with a high conditional risk of developing PTSD among men in the general population [38]. Thus, disentangling the etiology of the association among combat exposure, PTSD, and other disorders remains an important public health goal.

Our findings and those of others [12,13,39] indicate that it is not traumatic events themselves but the development of PTSD after such events that is associated with increased risk of developing other mental disorders. These findings imply that intervention efforts with demonstrated efficacy in trauma-exposed populations [40] could be focused on preventing the development and adverse secondary consequences of PTSD among the minority of trauma victims most at risk for the disorder, rather than on prevention among trauma victims more generally. Among traumatized populations, identifying those at greatest risk for subsequent substance use and affective disorders may be possible by collecting family and personal histories of psychiatric disorders that are often comorbid with PTSD.

4.1. Limitations

Our findings are subject to several limitations. First, the sample consisted entirely of male Vietnam era veterans; and results may not generalize to noncombat PTSD. The relationship between PTSD; trauma; and ND, AD, and MD may not generalize to civilians, female subjects, or other male cohorts. Our assessment of psychiatric diagnoses, trauma exposure, PTSD, and their dates of onset was undertaken retrospectively. If individuals who had PTSD were more likely to recall a history of other disorders, then our associations would be inflated. It is possible that preexisting psychopathology contributed to the ND, AD, and MD outcomes. Because minimum psychiatric health was required for service in the military, AD and MD would be less likely than ND to precede combat exposure. However, it is possible that ND onset was before combat. Our assessments are also based on DSM-III-R and not DSM, Fourth Edition; and other measures of PTSD are available. Replication with DSM, Fourth Edition, assessments and other measures of PTSD is warranted in future data collection with VET Registry members.

4.2. Conclusions

The vulnerability for substance use disorder and MD after combat trauma is accounted for by genetic factors that overlap with PTSD. Based on the present analyses, common genetic vulnerability could contribute to the incidence of substance use disorders and MD among other non–Vietnam War veterans especially among those who develop PTSD after combat exposure. Adequate health care resources should be in place to address not only PTSD but also those disorders that share common genetic vulnerability with this disorder.

Table 2B

<table>
<thead>
<tr>
<th>Factors common to</th>
<th>Factors specific to AD</th>
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<td>PTSD</td>
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<td>–</td>
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<td>E</td>
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Table 2C

<table>
<thead>
<tr>
<th>Factors common to</th>
<th>Factors specific to MD</th>
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<td>PTSD</td>
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<td>–</td>
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<tr>
<td>E</td>
<td>0.66 (0.54, 0.78)</td>
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Acknowledgment

This work was supported by National Institutes of Health grants AA12640, AA11667, AA11998, DA14363, and DA020810. Dr Koenen is supported in part by MH070627. Additional funding was provided by the National Institute on Drug Abuse and the Robert Wood Johnson Foundation. The US Department of Veterans Affairs has provided financial support for the development and maintenance of the VET Registry. Numerous organizations have provided invaluable assistance in the conduct of this study, including the Department of Defense; the National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; the National Opinion Research Center; the National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution, this research would not have been possible. Drs Scherrer and Xian had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position of the Department of Veterans Affairs.

References


