A High Risk Twin Study of Combat-Related PTSD Comorbidity

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Combat-related posttraumatic stress disorder (PTSD) is highly comorbid with other mental disorders. However, the nature of the relationship between PTSD and other mental disorders remains unclear. A discordant high-risk twin design was used on data from a sub-sample of the male-male twin pair members of the Vietnam Era Twin Registry to examine whether patterns of comorbidity are consistent with a psychopathological response to combat exposure or reflect familial vulnerability to psychopathology. Mental disorders were assessed via the Mental Health Diagnostic Interview Schedule Version III — Revised. Discordant monozygotic within-pair comparisons revealed that PTSD probands had higher symptom counts and diagnostic prevalences of mood and anxiety disorders than their non-combat exposed co-twins. Monozygotic co-twins of PTSD probands had significantly more mood disorder symptoms than monozygotic co-twins of combat controls or dizygotic co-twins of veterans with PTSD. These findings suggest that a) major depression, generalized anxiety disorder and panic disorder are part of a post-combat response syndrome; b) a shared familial vulnerability also contributes to the association between PTSD and major depression, PTSD and dysthymia, and c) this shared vulnerability is mediated by genetic factors.

> I'm having — what do you call 'em? Flashbacks every day. It's like I'm still living in Vietnam. But I can't get help. I've been to a dozen clinics and they all say the same thing: 'stop drinking and we'll treat you for the combat. Stop drinking and we'll treat the depression'. Then they ask me 'what came first?' How the hell should I know. All I know is I was in Vietnam when I was 18 and I'm 47 now and I never left. I'm still there, fighting the war every day.
>
> **Vietnam Combat Veteran**

Posttraumatic stress disorder (PTSD) occurs following exposure to a traumatic event and is defined by three symptom clusters: re-experiencing, avoidance and numbing, and arousal. PTSD is a notable public health problem with prevalence rates among males ranging from approximately 5% in the general population to 30% among veterans who served in Southeast Asia (SEA) during the Vietnam War (Kessler et al., 1995; Kulka et al., 1990). PTSD has also been shown to have high lifetime rates of psychiatric comorbidity (Davidson et al., 1991, Helzer et al., 1987; Keane & Wolfe, 1990; Kessler et al. 1995; Kulka et al., 1990). Due to the high prevalence of PTSD in veteran samples, many studies of PTSD comorbidity have focused on Vietnam Veterans (Centers for Disease Control [CDC], 1987; Davidson et al., 1989; Faustman &White, 1989; Keane & Wolfe, 1990; Kulka et al., 1990; Orsillo et al., 1996; Resnick et al., 1989; Sierles et al., 1983). Although identifying the mechanisms underlying PTSD comorbidity is important for understanding the etiology of and developing treatment for the disorder, these mechanisms remain unclear. This paper examines the origins of comorbidity in combat-related PTSD.

There are several potential mechanisms for the observed comorbidity in combat-related PTSD. One possibility is that comorbid disorders are a part of a psychopathological combat response syndrome. That is, other disorders develop along with or following PTSD after being exposed to combat. Another possibility is that the other mental disorder would have developed anyway, without combat exposure. In this case, the other mental disorder could represent an individual or familial vulnerability to psychopathology that temporally followed combat exposure but

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was not causally related to combat exposure. Ideally, these possibilities could be investigated by using a prospective design following a large random sample of respondents from the general population. This design is, however, expensive and time consuming. In addition, there is the problem that a diagnosis of PTSD requires exposure to a traumatic stressor. It is difficult to identify representative samples in which individuals will be exposed in sufficiently large numbers to traumatic stressors (e.g., see Breslau et al., 1998). Even with military samples, researchers have limited knowledge about when and where recruits will go into battle and whether combat exposure will be of the nature and severity likely to produce PTSD.

Furthermore, previous studies have not been able to identify an adequate control group for veterans with PTSD (King & King, 1991). The ideal control group would be made of individuals who are like the veterans with PTSD in every way — except that they were not exposed to combat. Monozygotic (MZ) twins discordant for combat exposure offer a solution to this limitation of previous studies. The present study used discordant MZ twins as part of a "high-risk discordant twin design" as an alternative strategy for testing hypotheses regarding the relationship between PTSD and its comorbid disorders. This design employed two sets of twins: 1) MZ twins with combat-related PTSD and their unexposed "high-risk co-twins" and 2) MZ twins exposed to combat who did not develop PTSD and their unexposed "low-risk co-twins". The discordant high-risk co-twins are so defined because they did not serve in the Vietnam theater but share the same genes and family environment with their twin who developed PTSD following combat exposure in Vietnam. The discordant low-risk co-twins, on the other hand, also did not serve in the Vietnam theater, but they share the same genes and family environment with their twin who *did not* develop PTSD following combat exposure in Vietnam.

The high-risk design is similar to that used in other studies when combat veterans with and without PTSD are compared *across* twin pairs on rates of other mental disorders to determine whether there is an association between having PTSD and having another mental disorder. However, by allowing comparisons *within* MZ twin pairs discordant for combat exposure, the high-risk design is able to address the major limitation of previous studies — the lack of an adequate control group for veterans with combat-related PTSD. MZ twin pairs share 100% of their genes and a family environment in youth and, therefore, are matched on a number of factors that would be impossible to control for in a non-twin sample. If combat-exposed MZ twins with PTSD have higher rates of disorder than their non-combat exposed co-twins, this supports the hypotheses that comorbidity is part of a psychopathological combat response syndrome. If however, high-risk co-twins have similar prevalences to their combat-exposed co-twins, this suggests the disorder would have developed anyway, without exposure to combat or PTSD. Finally, if high-risk co-twins have higher prevalences of mental disorders than low-risk co-twins this suggests comorbidity is due, at least in part, to shared familial vulnerability between the other mental disorder and PTSD.

Materials and Methods

Participants

Participants were members of the Vietnam Era Twin (VET) Registry. The VET Registry, assembled from Department of Defense computerized military records, is a nationally distributed cohort, comprised of male-male twin pairs born between 1939 and 1957 in which both members served in the military during the Vietnam War era (Eisen et al., 1987). Demographic, socioeconomic information, and military service variables were available from military service records. A complete list of these data items is presented elsewhere (Henderson et al., 1990). Zygosity was determined using a questionnaire and blood group typing methodology that achieved 95% accuracy (Eisen et al., 1989). Of 10,300 eligible individuals (5150 pairs), 47 were deceased or incapacitated. Of the remaining cases, 8169 (79.6%) were successfully interviewed by telephone in 1993 as part of the Harvard Twin Study on Substance Abuse. Detailed interview procedures have been previously reported (Lyons et al., 1995). The mean age of respondents was 44.6 years (SD ± 2.8, range 36 to 55 years); 90.4% were non-Hispanic white, 4.9% African-American, 2.7% Hispanic, 1.3% Native American/Alaskan Native, and 0.7% "other"; 33.3% were high school graduates and 38.6% college graduates; 92.6% were employed full-time and 1.8% part-time.

Measures

Demographic and military history data were collected as part of the DIS-III-R and through military records. Age of entry into the military and years of education before the military were taken from military records.

Combat Exposure Index (Janes et al., 1991). Combat exposure was measured by asking each veteran whether he engaged in 18 specific combat activities, such as flying in an attack helicopter, being wounded, and receiving incoming fire. For each item the veteran indicated whether he had that role or experience. A global index of combat exposure was constructed by summing over all positive responses from an individual. The combat index demonstrated good internal consistency (coefficient $\alpha = 0.86$) and test–retest reliability ($k = 0.84$). A strong association between the combat exposure index and being awarded a military combat medal supports the validity of the index.

Mental Health Diagnostic Interview Schedule Version III — Revised (DIS-III-R; Robins et al., 1988). This is a structured psychiatric interview for epidemiological research that has been used in many studies of PTSD (Breslau et al., 1991; Helzer et al., 1987). The structured questions from the DIS-III-R assess mental disorders according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III-R*, American Psychiatric Association [APA], 1987). Continuous measures of symptoms were also developed from the *DSM-III-R* criteria by assigning a value of 1 to each criterion endorsed in each category. The variable childhood trauma history was created from the DIS-III-R PTSD section; the numbers of traumatic events before the age of 18 were counted.

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Design

Veterans were selected from the VET Registry for the current analysis based on the criteria outlined below. The Vietnam veterans with PTSD were designated as PTSD probands (PP) and had to meet the following criteria: 1) the co-twin did not serve in Vietnam; 2) was an MZ twin; 3) served in Vietnam with a minimum Combat Scale score of 7; 4) was diagnosed with combat-related PTSD on a lifetime basis. In order to have combat-related PTSD, the individual had to meet criteria for onset of PTSD in reference to a combat experience. There were 37 twin pairs who met these criteria. Co-twins of the PP group were designated "high-risk co-twins" (HR). The non-PTSD Vietnam veterans were designated "combat controls" (CC) and had to meet the following criteria: 1) the co-twin did not serve in Vietnam; 2) was an MZ twin; 3) served in Vietnam with a minimum Combat Scale score of 7; 4) was never diagnosed with PTSD on a lifetime basis. There were 76 subjects who met these criteria and they are included in the current report along with their co-twins. CC and PP groups were matched on level of combat exposure and there was no significant difference between the combat scale score for the PP (M = 8.59, SD = 1.14) and the CC (M = 8.48, SD = 1.60) groups.

Demographic characteristics of PP and CC groups selected for this study are presented in Table 1. PP and CC groups did not differ significantly by group on years of premilitary education, age of entry into the military, percent minority, father or mother's education level, or number of premilitary traumas.

HR versus LR groups did not significantly differ by group on years of pre-military education HR M = 11.95, SD = 1.33; LR M = 12.22, SD = 1.16; $t(111)$ = 1.13, p = .26, age of entry into the military HR M = 19.92, SD = 1.35; LR M = 20.14, SD = 1.22; $t(111)$ = 0.85, p = .40, or on the number of pre-military traumas HR M = .14, SD = .42; LR M = .08, SD = .27; $t(111)$ = 0.86, p = .40. Matched pairs t tests also indicated that PP did not differ from the HR group on years of pre-military education $t(36)$ = –0.19, p = .85, age of entry into the military $t(36)$ = 0.41, p = .68, or on the number of pre-military traumas t(36) = 0.63, p = .53; CC and the LR group also did not differ on years of pre-military education $t(75)$ = –1.32, p = .19, age of entry into the military $t(75)$ = –0.54, p = .59, or on the number of pre-military traumas t(75) = 0.28, p = .78.

For the purpose of genetic analyses only, one group of dizygotic (DZ) "medium risk co-twins" (DZMR) was selected. The DZMR group had to meet the following criteria: 1) did not serve in Vietnam; 2) had a co-twin who served in Vietnam with a minimum Combat Scale score of 7 and was diagnosed with combat related PTSD; 3) was a DZ twin. This group is named medium risk co-twins because they share 50% of their genes (as compared to 100% for the MZ high-risk co-twins) and 100% of the common family environment during youth with their co-twin who developed PTSD when exposed to combat in Vietnam. DZMR group would, therefore, be less genetically vulnerable to developing PTSD if they had been exposed to combat in Vietnam than the MZ HR group.

Statistical Analyses

Symptoms. Differences in symptom levels of mental disorders were analyzed using independent t tests for comparisons between the PP versus CC, HR versus LR, and HR versus DZMR groups. Matched pairs t tests were used for comparisons within twin pairs. When the results of the above analyses were consistent with symptoms as a familial vulnerability for PTSD, further analyses were conducted to determine if this vulnerability was inherited by comparing the number of symptoms between the HR and DZMR groups using the independent samples t test.

Diagnoses. Differences in the prevalence of each mental disorder by group were tested using the chi-square statistic. When expected cell counts are less than 5, significance is determined by Fisher's exact test for PP versus CC and HR versus LR groups. Matched pairs comparisons (to examine prevalences within twin pairs — CC versus LR group, PP versus HR group) were made using McNemar's test (Fleiss, 1981). The magnitude of association between diagnosis and group status (PP vs. CC, etc.) is estimated by using the odds ratio with 90% confidence intervals.

For disorders associated with PTSD, we tested whether the association was due to an artefact of shared diagnostic

Table 1

Demographic Characteristics of MZ Twins

	Combat Controls (n = 76)	PTSD Probands (n = 37)	Analyses
Minority (%)	6 (7.9)	2 (5.4)	$\chi^2(1)$ = 0.23, p = .63
Years of education before the military			
M	12.17	11.89	$t(111)$ = 1.00, p = .32
SD	1.23	1.59	
Age of entry into the military			
M	19.99	19.68	$t(111)$ = 1.17, p = .24
SD	1.23	1.43	
Father has less than a high school education (%)	42.10	50.00	$\chi^2(1)$ = 0.62, p = .43
Mother has less than a high school education (%)	28.80	43.20	$\chi^2(1)$ = 2.28, p = .13
Number of pre-military traumas			
M	0.08	0.09	$t(111)$ = 0.17, p = .86
SD	0.28	0.33	

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criteria. This was done by examining whether the disorder was associated with 1) higher mean scores on PTSD symptom dimensions (intrusions, avoidance, arousal) with overlapping criteria (using two-tailed *t* tests) and/or 2) increased likelihood of endorsing PTSD symptoms that overlap with the disorder (using chi-square tests).

When the results of the above analyses were consistent with a disorder functioning as vulnerability for PTSD, further analyses were conducted to determine if this vulnerability was inherited by comparing the prevalence of disorder in HR versus DZMR co-twins using the chi-square statistic (or Fisher's exact test when appropriate). To determine whether the vulnerability was associated with specific types of PTSD symptoms, those with and without the vulnerability diagnosis were compared on mean levels of symptoms for each PTSD cluster (re-experiencing, avoidance, and arousal).

Statistical significance for all tests is indicated by $p < .05$ with one-tailed tests. One-tailed tests are appropriate when two conditions are met: 1) strong a priori directional hypotheses are indicated and 2) outcomes in the wrong tail would be meaningless and could be dismissed as a chance occurrence (Abelson, 1995). Two-tailed tests are employed when a priori directional hypotheses were not outlined. Outcomes of $p > .05$ through $p < .10$ are interpreted as trends.

Power. Power analyses were conducted according to procedures described by Cohen (1977), who suggests that power be set at 1–4(α), where α is the probability of Type 1 error for a two-tailed test. In this case, given the use of one-tailed tests, power should be set at .60. For symptom scales, we have power at .60 to detect small effect sizes (.25–.33) and power of .80 or better to detect effect sizes of .50 and above for all comparisons. For diagnoses, however, power depends on the prevalence of the disorder under consideration and is poor for some comparisons. Specifically, for PP-CC and HR-LR comparisons with disorder prevalence of 5% in CC or LR groups, we have .60 power to detect a difference in prevalence of 11% or an odds ratio of 3.8 and .80 power to detect a difference in prevalence of 16% or an odds ratio of 5.3. If the prevalence is 10% in CC or LR groups, we have .60 power to detect a difference in prevalence of 13% or an odds ratio of 3 and .80 power to detect a difference in prevalence of 19% or an odds ratio of 3.7. For PP-HR matched pairs comparisons we have .60 power to detect an odds ratio of 3.5 and .80 power to detect an odds ratio of 4.5. For CC-LR comparisons, we have .60 power to detect an odds ratio of 2.5 and .80 power to detect an odds ratio of 3.1. Given greater power associated with comparisons on continuous variables, interpretation of the results will be focused on symptom scales.

Results

If PTSD and other mental disorders are part of a psychopathological post-combat response syndrome, the PP group should show higher levels of symptoms and disorder prevalences than the CC or HR groups. At the same time, no difference in symptom levels or disorder prevalences would be expected between the HR and LR or the CC and LR groups. As can be seen in Table 2, the PP group has higher means scores on symptoms of major depression, dysthymia, GAD, and Panic. In Table 3, the PP group has significantly higher prevalences on any mood disorder, major depression and shows a trend for any anxiety disorder. These results are consistent with the results for diagnoses. The PP group also showed higher prevalences than the CC or HR groups for dysthymia, GAD and Panic. Due to limited power, however, not all of these results reached the level of statistical significance.

Table 2

Pairwise Comparisons of Symptoms by Group

Symptoms	PTSD Probands ($n = 37$)	HR[a] co-twins ($n = 37$)	t[c]	Combat Controls ($n = 76$)	LR[b] co-twins ($n = 76$)	t[c]	PTSD Probands vs. Combat Controls t	HR versus LR t
Alcohol Abuse/Dependence								
M	3.57	3.37	0.19	2.31	2.62	1.13	2.29*	1.35
SD	3.01	3.03		2.57	2.69			
Major Depression								
M	5.00	3.36	2.18*	1.83	2.16	0.95	5.85***	2.97**
SD	2.93	2.82		2.18	2.39			
Dysthymia								
M	3.03	2.16	2.16*	1.14	1.30	0.71	5.07***	2.60**
SD	2.02	1.80		1.44	1.57			
GAD								
M	5.56	2.16	2.82**	1.09	1.16	0.12	4.33***	1.21
SD	5.85	4.44		3.31	3.48			
Panic								
M	2.08	0.27	2.99**	0.72	0.73	0.08	2.06*	1.21
SD	3.69	1.64		2.22	2.52			

Note: All analyses used one way tests of significance.

*$p < .05$; ** $p < .01$; ***$p < .001$.

[a]HR = High Risk co-twins; [b]LR = Low Risk co-twins; [c]Matched pairs *t* tests.

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Table 3

Lifetime Prevalence (%) and Pairwise Comparisons of Selected Mental Disorders in PTSD Probands, Combat Controls, and their Co-twins

	PTSD Probands ($n = 37$)	HR[a] co-twins ($n = 37$)	OR	p^c	Combat Controls ($n = 76$)	LR[b] co-twins ($n = 76$)	OR	p^c	PTSD Probands vs. Combat Controls			High Risk versus Low Risk		
									Odds Ratio	90% CI	$\chi^2(1)$	Odds Ratio	90% CI	$\chi^2(1)$
Alcohol abuse/ dependence	64.9	62.2	1.00	.50	57.9	57.9	1.50	.50	1.34	0.68-2.66	0.50	1.19	0.61–2.35	0.19
Any mood disorder	43.2	18.9	4.00	.04**	7.9	10.5	0.71	.36	8.89	3.66–21.59	19.83****	1.98	0.78–5.00	Fisher
Major depression	35.3	18.9	2.50	.05**	7.9	9.2	0.83	.50	6.32	2.57–15.55	13.20****	2.30	0.89–5.95	Fisher
Dysthymia	13.5	10.8	1.25	.50	3.9	2.6	1.50	.50	3.80	1.09–13.28	Fisher**	4.48	1.04–19.41	Fisher
Any anxiety disorder	18.9	5.4	6.00	.06*	2.6	1.3	2.00	.50	8.63	2.20–33.83	Fisher***	4.29	0.38–48.86	Fisher
GAD	10.8	2.7	4.00	.19	0.0	1.3	—	.50	—	—	Fisher***	2.08	0.13–34.27	Fisher
Panic disorder	10.8	2.7	—	.13	2.6	0.0	—	.25	4.48	1.04–19.41	Fisher	—	—	Fisher

Note: All analyses used one-way tests of significance. * $p < .10$ ** $p < .05$; *** $p < .01$; **** $p < .001$ [a] HR = High Risk co-twins; [b] LR = Low Risk co-twins; [c] p values are for McNemar's test.

To determine whether the association between PTSD and major depression, dysthymia, GAD, and panic disorder was an artefact of shared diagnostic criteria, we tested whether combat exposed MZ twins diagnosed with any of these disorders had 1) higher mean scores on PTSD symptom dimensions (intrusions, avoidance, arousal) with overlapping criteria (using two-tailed t tests) and 2) were more likely to endorse symptoms that overlap between disorders (using chi-square tests). Individuals diagnosed with major depression, dysthymia, GAD or panic disorder had higher mean scores on all three dimensions of PTSD than individuals who did not have these disorders including the intrusions dimension which has no overlapping symptoms with any disorder. At the symptom level, individuals diagnosed with major depression, dysthymia, GAD, or panic disorder were more likely to endorse many symptoms of PTSD including symptoms with no diagnostic overlap. Thus, the association between PTSD and these disorders does not simply appear to be an artifact of overlap in diagnostic criteria.

If comorbidity is not part of a psychopathological post-combat response syndrome but reflects disorders that would have developed anyway, the PP group should still show high levels of symptoms and disorder prevalences than the CC group. In addition, the HR group should show higher levels of symptoms and disorder prevalences than the LR group. If the HR group has higher levels of symptoms and/or disorder prevalences than the LR group this further suggests a familial relationship between the disorder and PTSD. The results in Table 2 indicate that major depression and dysthymia symptoms appear to be both part of a psychopathological post-combat response syndrome and represent a familial vulnerability for PTSD. In Table 3, due to limited power, the differences in disorder prevalences between the HR and LR groups were not significant for major depression or dysthymia; therefore, the vulnerability hypothesis was not supported. The observed prevalences, including relative large odds ratios of 2.30 and 4.48 with reasonable confidence limits are, however, consistent with the vulnerability hypothesis.

Since the pattern of results for dysthymia and major depression symptoms suggests that they operate as vulnerabilities for PTSD, analyses were conducted to determine if this vulnerability was inherited. If dysthymia or major depression symptoms are an inherited vulnerability, then the HR group should have a higher level of symptoms than the DZMR group. The HR group did not differ from the DZMR group co-twins on minority status, level of education before entering the military, age of entry into the military, parental level of education, or childhood trauma history. The t test indicated that the HR group reported significantly more dysthymia symptoms than the DZMR group $t(59.36) = 3.81$; $p < .001$. Major depression symptoms were also more frequent among the HR than the DZMR group $t(67.37) = 3.02$; $p < .01$. To test whether major depression or dysthymia was associated with a specific pattern of PTSD symptoms, we tested whether combat exposed MZ twins with and without dysthymia had 1) higher mean scores on PTSD symptom dimensions (using two-tailed t tests) and 2) were more likely to endorse

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specific symptoms (using chi-square tests). Individuals with a major depression or dysthymia diagnosis did not have higher levels of intrusions, avoidance, or arousal symptoms. At the symptom level, individuals with major depression were more likely than those without to endorse avoiding activities that reminded them of the trauma. Individuals with dysthymia were more likely than those without dysthymia to endorse feeling like the traumatic event was happening again, loss of interest in important activities, and feeling isolated or distant from other people.

Discussion

The findings of the present study use a high-risk twin design to test hypotheses about the well-established relationship between PTSD and other mental disorders in Vietnam veterans. Our findings suggest that the nature of the relationship between PTSD and other mental disorders depends on the specific disorder studied. As these results were mostly consistent at the symptom and diagnostic level, for power reasons, the focus of this discussion will be on the symptom data. Differences in symptom and diagnostic results will be addressed as well.

Overall, the results are consistent with previous research in finding high rates of association between PTSD and other mental disorders in veteran samples. Veterans with PTSD were more likely to have higher mental disorder symptoms and to meet lifetime criteria for mood disorders and anxiety disorders than veterans who had been exposed to the same level of combat but did not develop PTSD. In terms of specific symptom clusters, veterans with PTSD had more alcohol abuse/dependence, major depression, dysthymia, GAD, and panic symptoms than veterans exposed to combat who did not have PTSD. Veterans with PTSD were also more likely to meet lifetime criteria for major depression, dysthymia, and GAD than combat exposed veterans without PTSD.

The hypothesis that comorbidity is due to a psychopathological post-combat response syndrome predicts that veterans with PTSD will have higher symptom levels and disorder prevalences than either their high-risk co-twins or combat controls. The pattern of results for major depression, dysthymia, GAD, and panic symptoms supported this hypothesis. These results were consistent at the diagnostic category level. Overall, these results are consistent with epidemiological studies using community samples. Kessler and his colleagues (1995) attempted to address the issue of whether PTSD was primary or secondary with regard to other disorders (i.e., PTSD onset before versus after the onset of the comorbid disorder). They found that for men PTSD onset was likely to occur before the onset of mood disorders disorders. Moreover, in a follow-up study of a young adult sample, Breslau and colleagues (1998) found that individuals with PTSD were at increased risk of first onset of major depression and GAD. Our findings are also consistent with previous research specifically focused on Vietnam veterans (e.g., CDC, 1988; Mellman et al., 1992) and with clinical observations of individuals with PTSD (Wilson, 1988).

A unique contribution of this study is the ability to test for the role of familial vulnerability in the association between combat-related PTSD and other mental disorders. The vulnerability hypothesis predicts that PTSD probands will have higher levels of mental disorder symptoms and prevalences than combat controls as will high-risk co-twins as compared to low-risk co-twins. Results for symptom clusters indicated that major depression and dysthymia symptoms fit the pattern of the vulnerability hypothesis. At the diagnostic level, insufficient power clouds interpretation of the results. The pattern of disorder prevalences for major depression and dysthymia diagnosis fit the vulnerability hypothesis; PTSD probands have higher rates of major depression (OR = 6.32) and dysthymia (OR = 3.80) than combat controls and high-risk co-twins have higher rates of both disorders (ORs = 2.30, 4.48 respectively) than low-risk co-twins.

Major depression symptoms, therefore, appear to be both a vulnerability factor for PTSD and part of a psychopathological combat response syndrome. The familial vulnerability appears to be partially genetic. Previous work has also supported major depression as both vulnerability for (e.g., Davidson et al., 1998) and a consequence of having PTSD (Breslau et al., 1998). Our results suggest that contrasting findings from previous studies may reflect two simultaneous phenomena. First, major depression and PTSD may share a familial vulnerability such as negative affectivity or neuroticism (Clark et al., 1994). The individual's life experiences will then influence whether he or she later develops PTSD or major depression (or neither). Second, having PTSD appears to put an individual at risk for developing major depression. Future research will need to examine how the risk of developing major depression after PTSD is influenced by a family history of major depression.

In addition, previous studies examining risk factors for PTSD have most often gathered information on family psychiatric history using the family history method. One advantage of the current study is that it collected diagnostic and family psychiatric history data independently from more than one family member and is, therefore, less subject to the reporting biases present in studies that use only one informant (Kendler et al., 1991). Informants with PTSD in both this and other studies have higher rates of other anxiety disorders (Breslau et al., 1991, 1992; Kulka et al., 1990) and may therefore have a bias toward reporting these disorders in family members. Another possibility is that the relatively high rates of alcohol dependence in this sample are masking the true prevalence rates of anxiety disorders and biasing results (D. Barlow, personal communication). Variations in sample composition between the current and previous studies may also contribute to different results; the current sample is made up only of males who have served in the military and not meant to be representative of the population as a whole. In fact, the rate of PTSD in this sample (9.6%) is somewhat higher than that of males in the general population (5.0%; Kessler et al., 1995).

Limitations

These results should be interpreted in the context of six methodological limitations. First, this study focused exclusively on combat-related PTSD. The results presented here cannot be generalized to PTSD due to other traumatic

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events in the VET Registry or to civilians or females. However, combat exposure is one of the most prevalent trauma events for males in the general population (Kessler et al., 1995), since over one million men are currently in active duty in the US armed forces (Department of Defense, 2000), and active duty military personnel are at high risk of exposure. Thus, examining combat-related PTSD comorbidity remains an important goal. Second, the DIS queries about up to three traumatic events and, therefore, would not provide comprehensive information for individuals with more than three events. As a result, participants may have under reported certain traumatic events. However, only 270 veterans (4%) reported three events making the number of veterans who would have reported additional events small indeed. Still, the prevalence of traumatic exposure and PTSD in this sample may be underestimates. Such underestimates would result in undetected PTSD among the combat control group and therefore likely bias our results towards the null. Third, our assessment of PTSD has shown high specificity but low sensitivity. Thus, we may have classified some individuals as not having PTSD when they actually had the disorder. The effect of this possibility on our results is unclear. If random, misclassification would bias our results towards the null. If non-random, our results might be inflated or attenuated depending on the direction of misclassification in relation to the outcomes. Fourth, the design used in this study did not allow us to determine if certain mental disorders serve as an indirect vulnerability for PTSD by increasing risk of traumatic exposure. There is empirical evidence that preexisting mental disorders, specifically major depression and drug use disorders, serve as risk factors for traumatic exposure (Breslau et al., 1991; Breslau & Davis, 1995; Breslau et al., 1998; Bromet et al., 1998; Burnam et al., 1988; see also Kendler, 1998). By using co-twins discordant for military service, we eliminated any shared vulnerability that contributed to combat exposure. Fifth, the design tested only for familial vulnerability and not whether a preexisting disorder in an individual might increase risk for PTSD. Epidemiological studies that rigorously assess disorders before and after trauma exposure are the best way to examine the contribution of individual vulnerability to PTSD onset. Other limitations of this study include the dependence on self-report data and the retrospective report of both traumatic events and psychiatric symptoms.

Conclusions

Despite these important limitations, the results of this study make a significant contribution towards clarifying the relationship between PTSD and other mental disorders. The high-risk design contributes to the findings of previous investigators in its ability to disentangle whether comorbidity appears as a part of a psychopathological response to combat exposure or reflects disorders that would have developed without exposure. By using this design, we found that the relationship between PTSD and other mental disorders depends on the disorder being studied. Major depression, dysthymia, GAD, and panic symptoms were more prevalent in the PTSD probands than in any other groups, suggesting these symptoms appear as part of the psychopathological response to combat exposure. Dysthymia and major depression symptoms also represent a shared vulnerability for PTSD that is, in part, due to shared genes. The specific nature of this genetic vulnerability will need to be investigated by future research focused on clarifying the biological mechanisms underlying the relationships between PTSD and other mental disorders.

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