Is Trauma a Causal Agent of Psychopathologic Symptoms in Posttraumatic Stress Disorder? Findings From Identical Twins Discordant for Combat Exposure

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Objective: The diagnosis of posttraumatic stress disorder (PTSD) is unique in that its criteria are embedded with a presumed causal agent, viz, a traumatic event. This assumption has come under scrutiny as a number of recent studies have suggested that many symptoms of PTSD may not necessarily be the result of trauma and may merely represent general psychiatric symptoms that would have existed even in the absence of a trauma event but are subsequently misattributed to it. The current study tests this hypothesis.

Method: A case-control twin study conducted between 1996–2001 examined psychopathologic symptoms in a national convenience sample of 104 identical twin pairs discordant for combat exposure in Vietnam, with (n = 50) or without (n = 54) combat-related PTSD (*DSM-IV*–diagnosed) in the exposed twin. Psychometric measures used were the Symptom Checklist-90-Revised, the Clinician-Administered PTSD Scale, and the Mississippi Scale for Combat-Related PTSD. If a psychopathologic feature represents a factor that would have existed even without traumatic exposure, then there is a high chance that it would also be found at elevated rates in the non–trauma-exposed, identical cotwins of trauma-exposed twins with PTSD. In contrast, if a psychopathologic feature is acquired as a result of an environmental factor unique to the exposed twin, eg, the traumatic event, their cotwins should not have an increased incidence of the feature.

Results: Combat veterans with PTSD demonstrated significantly higher scores ($P < .0001$) on the Symptom Checklist-90-Revised and other psychometric measures of psychopathology than their own combat-unexposed cotwins (and than combat veterans without PTSD and their cotwins).

Conclusions: These results support the conclusion that the majority of psychiatric symptoms reported by combat veterans with PTSD would not have been present were it not for their exposure to traumatic events.

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Posttraumatic stress disorder (PTSD) following a traumatic event is the exception rather than the rule.[1,2] Accordingly, the concepts of vulnerability and resilience have entered into the vernacular of PTSD and shifted focus from the causal trauma to dispositional factors in the disorder's pathogenesis.[3–5] Some neurocognitive[6–8] and biologic[9] concomitants of PTSD appear to reflect preexisting vulnerabilities rather than posttrauma effects. The issues of causality and vulnerability extend naturally to psychopathologic symptoms themselves, and gene-environment studies have, for example, generally demonstrated PTSD symptoms to be moderately heritable.[10,11] Additionally, PTSD shares modest genetic variation with other anxiety disorders,[12] major depression,[13] and substance dependence.[14] Such findings raise the possibility that some psychiatric symptoms may exist as vulnerability markers that predate trauma exposure. Studies that have retrospectively examined putative PTSD risk factors have frequently cited premorbid psychological problems. However, 2 meta-analyses found very small effect sizes ($r = 0.11–0.17$) for the predictive power of preexisting psychopathology,[15,16] especially in combat samples ($r = 0.06$).[16]

Hypotheses regarding genetic contributions and the role of psychiatric symptoms as preexisting markers have generated controversial questions as to whether individuals with PTSD may simply possess general psychiatric susceptibilities that would have led to symptoms even in the absence of the traumatic event. The diagnosis of PTSD, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,[17] is unique in that its criteria are embedded with a presumed causal agent, viz, a traumatic event. This assumption has come under increasing scrutiny as a number of recent studies have suggested that the symptoms of PTSD may not necessarily be the result of *DSM*-defined traumatic events.[18–20] For example, in a sample of patients with current major depressive disorder, Bodkin et al[18] reported that nearly 80% met the *DSM-IV* B–F symptom criteria for PTSD regardless of whether they had ever experienced a criterion A traumatic event. (In subjects who reported no traumatic event, a proxy of "troubling thoughts" of past life events was created in order to allow for the assessment of *DSM-IV* criterion B [reexperiencing] and C 1–3 [avoidance] symptoms that could not otherwise exist.)

The issue is further complicated by the fact that PTSD is frequently comorbid with other mental disorders.[1] The

familiar Symptom Checklist-90-Revised (SCL-90-R) evaluates a broad range of psychopathologic symptoms. Virtually all of its subscales have been found to be elevated in one or another study of PTSD patients compared to normal controls,[21,22] including combat veterans.[23] It is possible that trauma-exposed individuals diagnosed with PTSD may be erroneously perceiving pathology that already existed prior to the traumatic event (or would have come to exist even without it) as a consequence of that event (misattribution).[24]

Indeed, it has been argued that PTSD may simply represent a group of nonspecific symptoms that are widely observed in psychiatric patients regardless of a trauma history.[18] The occurrence of such symptoms in the absence of a trauma event challenges the notion that traumatic events cause the psychiatric symptoms seen in trauma survivors. Bodkin et al write, "Our findings suggest caution in this regard, as the diagnosis of posttraumatic stress disorder may harbor an uncertain theory of etiology within its name."[18(p181)] From this perspective, frequently published studies demonstrating increased PTSD and other psychopathology among traumatized versus nontraumatized individuals may simply capitalize on the identification of individuals who are genetically or environmentally prone to develop psychiatric symptoms regardless of trauma exposure but are selected for study participation as PTSD patients because they attribute their symptoms to a traumatic event. It is also possible that individuals who are genetically or environmentally prone to develop psychiatric symptoms regardless of trauma exposure are also more likely to experience traumatic events, leading to a spurious causal inference. However, such criticisms must also be viewed in the context of PTSD studies that have not ascertained samples on the basis of psychiatric self-report, such as the well-known National Vietnam Veterans Readjustment Study[25] and its more recent reanalysis.[26] Even in the absence of an ascertainment bias, elevated rates of PTSD were observed in Vietnam war theater veterans relative to Vietnam era (noncombat) veterans, as was a strong dose-response relationship between objective (non–self-report) measures of combat exposure and rates of PTSD.

It should be noted that the inferences of Bodkin et al[18] are significantly limited by an ascertainment method that first selected patients with already established depressive illness and then, regardless of trauma history, sought to examine whether these patients also met PTSD symptomatic criteria. Such an approach capitalizes on symptom commonalities between the 2 disorders. The fact that a subset of PTSD symptoms may exist outside the context of trauma in some cases does not preclude the possibility that trauma caused these symptoms in other cases. Although studies of this nature may raise questions regarding the "theory of etiology" in PTSD, they are unable to adequately test a hypothesized causal relationship between trauma and PTSD.

Identical twins discordant for traumatic exposure offer an alternative strategy for investigating the cause of psychopathology in PTSD. We have employed a case-control twin design to investigate the origins of neurobiologic, cognitive, and psychophysiologic features of PTSD. If a psychopathologic feature of PTSD is genetic or due to early environmental influences, ie, if the feature represents a factor that would have existed even without traumatic exposure, then it should also be found at elevated rates in the non–trauma-exposed, identical cotwins of trauma-exposed twins with PTSD. Such cotwins are termed here *high-risk*, because they have the same genes and shared environment as their twin who developed PTSD after traumatic exposure. Cotwins of persons who were exposed to trauma but did not develop PTSD are termed *low-risk* for the inverse reason. In contrast, if a psychopathologic feature is acquired as a result of an environmental factor unique to the exposed twin, eg, the traumatic event, the PTSD that may follow it, or some sequel thereof, their cotwins should not have an increased incidence of the feature. Such a design offers an advantage not conferred by prospective studies, in that it allows measurement in the trauma-unexposed cotwin of psychopathology that may have not been present prior to the exposed twin's traumatic exposure but rather developed years afterward. Thus, the unexposed cotwin serves as a putative surrogate for what the exposed twin would have become like but for the experience of trauma.

The present study attempted to clarify the nature and origin of symptoms reported by PTSD patients by administering 3 psychometric measures to a national convenience sample of identical twins discordant for combat exposure in Vietnam. The SCL-90-R was administered as a measure of a broad range of psychopathologic symptoms. A 25-item war-zone PTSD scale previously derived from responses on the SCL-90-R that best discriminated between samples of Vietnam veterans with versus without PTSD[27] was added to the traditional 9 SCL-90-R clinical scales. The Mississippi Scale for Combat-Related PTSD (MISS) was developed as an ancillary tool for the diagnosis of PTSD.[27,28] It consists of items that are related to PTSD but do not necessarily form the formal PTSD diagnostic criteria. A modified MISS has been created for civilians.[29,30] In the present study, the combat-related version was used in the combat-exposed twins, and the civilian version, in their combat-unexposed cotwins. The Clinician-Administered PTSD Scale (CAPS) is a widely accepted structured clinical interview instrument that quantifies the severity of each of the *DSM-IV* PTSD diagnostic criteria.[31,32] In the combat-exposed twins, the CAPS was administered with regard to the most potentially traumatic combat event reported by the subject. In the combat-unexposed twins, it was administered with regard to the subject's most potentially traumatic lifetime event.

METHOD

Participants

The participants were the same 103 male monozygotic twin pairs who had participated in a previous study of heart rate responses to loud tones,[33] except that psychometric data from 1 additional twin pair, for whom psychophysiologic data had not been available, are added here. A full description of the recruitment sources and strategy, and the

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characteristics of the participant population, has already appeared in that report. Within each pair, 1 "exposed" (Ex) twin had served in combat in Vietnam, whereas his "unexposed" (Ux) cotwin had not. According to the CAPS, of the Ex twins, 50 had current, combat-related PTSD (P+), and 54 had never had combat-related PTSD (P–). Thus, there were 4 participant cells as follows: ExP+: combat-exposed veteran with current, combat-related PTSD, and UxP+: his combat-unexposed cotwin; as well as ExP–: combat-exposed veteran who never had combat-related PTSD, and UxP–: his combat-unexposed cotwin. Use of the "P+" or "P–" symbol always refers to the PTSD diagnostic status of the exposed (Ex) twin. For example, the designation "UxP+" refers to an unexposed cotwin of an exposed twin with PTSD, not to a cotwin who himself has PTSD. Exclusion criteria included (1) past but not current Vietnam-related PTSD; (2) current non–Vietnam-related PTSD; (3) past non–Vietnam-related PTSD in participants who never met criteria for Vietnam-related PTSD; and (4) current or past schizophrenic, paranoid, bipolar I, or other psychotic disorder. Demographic mean (SD) values were as follows: age, ExP+/UxP+ 50.0 (3.2) years, ExP–/UxP– 49.2 (2.5) years, NS; education (grades completed), ExP+ 12.1 (5.0), ExP– 13.8 (2.8), UxP+ 13.1 (3.3), UxP– 13.8 (3.1), NS; and combat severity (see Psychometrics), ExP+ 7.6 (2.5), ExP– 3.8 (2.7), $t_{102} = 4.7$, $P < .001$. Written informed consent was obtained from each subject after the procedures had been fully explained. Approval was obtained from the institutional review board of the Manchester VAMC (New Hampshire). The study was conducted between 1996–2001.

Psychometrics

The SCL-90-R is a 90-item self-report symptom inventory that measures current psychological symptom status with a time reference of "the past 7 days including today." The subject rated each item on a 5-point (0–4) Likert-type scale, with 0 representing "not at all" and 4 representing "extremely." The score for each of the 9 clinical scales is the average rating given to the symptoms the scale comprises. Additionally, the SCL-90-R Global Symptom Index (GSI) is the average rating given to all 90 items. The SCL-90-R War-Zone PTSD Scale is described earlier in the article.

In addition to using the CAPS to make a categorical PTSD diagnosis, a doctoral-level clinical psychologist scored each of its 17 *DSM-IV* PTSD diagnostic criteria items with regard to frequency and intensity on separate 0–4 scales, which were summed to yield item severity score. Total CAPS severity score for all 17 items, as well as CAPS cluster subscale scores for the *DSM-IV* B (reexperiencing, 5 items), C (avoidance/numbing, 7 items), and D (hyperarousal, 5 items) diagnostic criteria, were used to quantify current PTSD symptomatology.

On the MISS, the subject rated each of its 39 items on a 5-point (1–5) Likert-type scale, with 1 representing "not true at all" and 5 representing "extremely true" at the time. (To make the number of items on the 35-item combat and 39-item civilian versions equal, the last 4 items of the civilian version were added to the combat version.) A Combat Severity Scale[34] provided a measure of the intensity of combat exposure in Ex twins.

Statistical Analyses

The SCL-90 clinical, GSI, and War-Zone PTSD Scale scores; total CAPS and CAPS cluster subscale scores; and MISS score were all analyzed separately by a 2-factor mixed model that treated combat exposure (Ex vs Ux) as a within-pairs repeated measure, diagnosis (P+ vs P–) as a between-pairs measure, and twin pairs as a random effect. Due to the large number of (nonindependent) tests, $P < .01$ was required for statistical significance. Additionally, analyses were conducted separately within Ex and Ux groups, and within P+ and P– groups.

RESULTS

The SCL-90-R, CAPS, MISS, and group mean (SEM) values are displayed in Figure 1A–C. Inspection of these figures reveals the same pattern of results for each dependent measure, with ExP+ participants showing much greater scores than the remaining 3 groups. The diagnosis × exposure interaction adjusted for age, education, combat severity (in the Ex twin), current alcohol dependence, and current other substance dependence was highly significant for each of the 16 scales and subscales ($F_{1,97} \geq 21.0$, $P < .0001$). For the ExP+ versus ExP– contrast, the group difference for each of the 16 scales and subscales was highly significant ($F_{97} \geq 28.7$, $P < .0001$). For the UxP+ versus UxP– contrast, there were no significant group differences. For the ExP+ versus UxP+ contrast, the group difference for each of the 16 scales and subscales was highly significant ($F_{1,46} \geq 41.2$, $P < .0001$). For the ExP– versus UxP– contrast, the only significant group differences were for total CAPS score ($F_{1,50} = 8.9$, $P = .004$) and CAPS cluster D score ($F_{1,54} = 13.1$, $P < .001$).

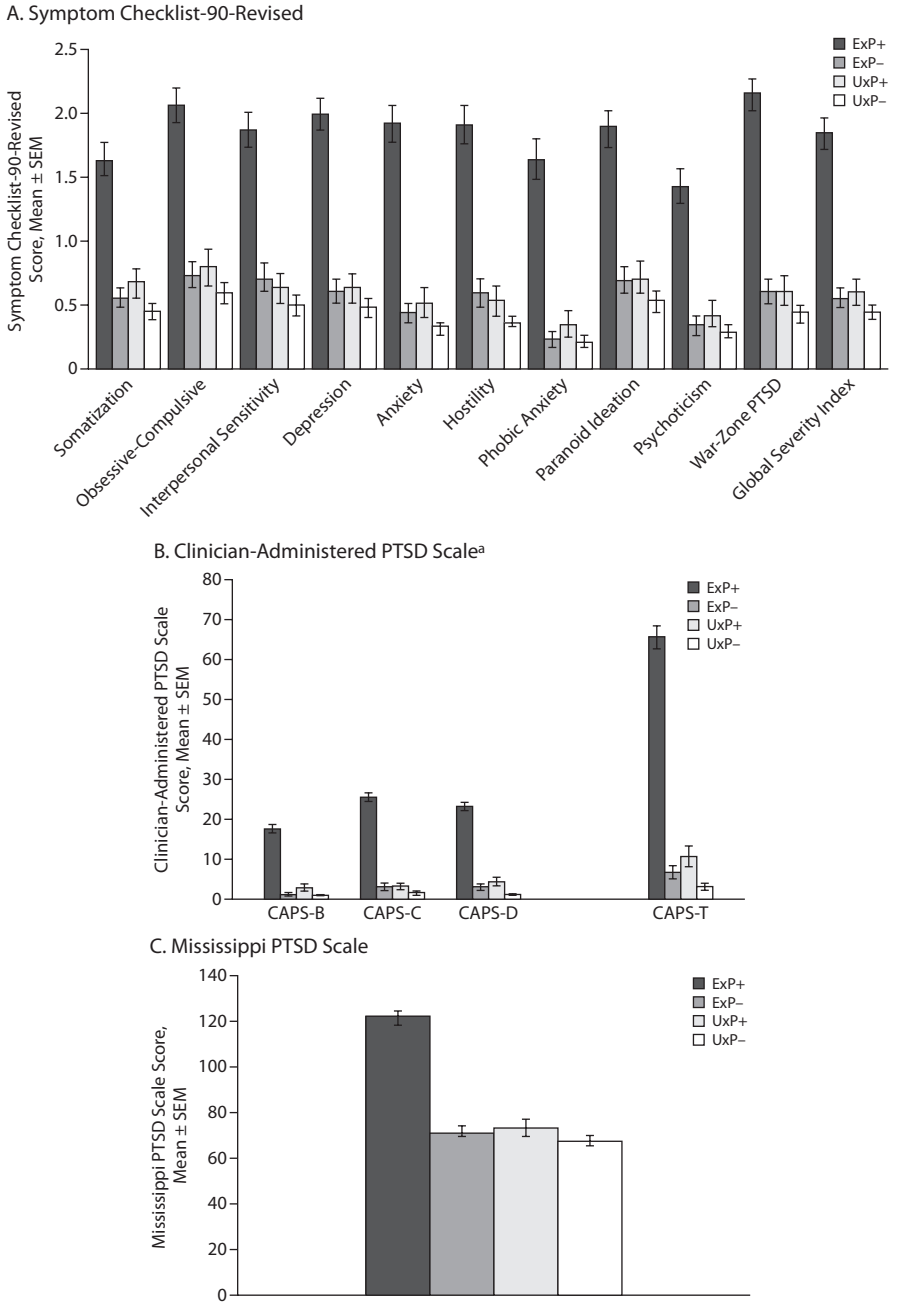
For the unadjusted ExP+ versus ExP– contrasts, the CAPS scales explained the most variance, especially total CAPS score, at 79%. (This is not surprising because the CAPS was used to make the group assignments.) MISS followed next at 62%. The SCL scale that explained the most variance was War-Zone PTSD Scale, at 47%; GSI explained 43%.

The ExP+ subjects' mean GSI score of 1.8 placed them in the 82nd percentile (T score = 60) among psychiatric outpatients. Each of the remaining 3 groups scored below the 25th percentile (T score < 44).[35] Although published normative data are unavailable, both the CAPS and MISS scores of the ExP+ subjects would commonly be recognized as well into the range for PTSD subjects, and the scores of the remaining 3 groups, far below it.[28,36]

DISCUSSION

The present design provides a rare opportunity to deepen our understanding of the origin of psychopathologic symptoms in PTSD. The mean SCL-90-R GSI score (a measure of current general psychiatric symptomatology) of the

Figure 1. Mean Values on Psychometric Measures Among Twins Discordant for Combat Exposure



[a]CAPS-B, CAPS-C, and CAPS-D indicate *DSM-IV* categories B (reexperiencing), C (avoidance/numbing), and D (hyperarousal), respectively; CAPS-T indicates total.

Abbreviations: CAPS = Clinician-Administered PTSD Scale, Ex = combat-exposed twin, P+ = exposed member of twin pair has current (combat-related) PTSD, P– = exposed member of twin pair has never had PTSD, PTSD = posttraumatic stress disorder, SEM = standard error of the mean, Ux = combat-unexposed twin.

combat-exposed PTSD twins was approximately 3 times higher than that of their own combat-unexposed cotwins and than those of the combat-exposed non-PTSD twins and their cotwins. The pattern of results was virtually the same for all 9 SCL-90-R clinical scales and the War-Zone PTSD Scale. PTSD-related symptoms as measured by the MISS and CAPS demonstrated a similar pattern. Significant differences between combat-exposed, non-PTSD twins and their cotwins were limited to total CAPS score and CAPS cluster D score. Similar to, but less pronounced than, the difference observed between combat-exposed PTSD twins and their cotwins, this finding also very likely reflects the impact of traumatic combat exposure on the genesis of PTSD symptoms, albeit in an attenuated, subthreshold manifestation. The fact that combat-exposed individuals without full-blown PTSD nevertheless reported modest elevations in such symptoms as insomnia, irritability, difficulty concentrating, hypervigilance, and startle, relative to brothers never exposed to combat, is not surprising and consistent with the present study's main finding. However, these differences were small and of little clinical significance.

To the extent that a combat veteran's non–combat-exposed identical twin is a valid surrogate for what the veteran would have become absent the experience of combat, these results support the conclusion that the great majority of the psychiatric symptoms reported by combat veterans with PTSD would not have been present were it not for their exposure to military combat in Vietnam. As such, our findings are at odds with suggestions that individuals diagnosed with PTSD display general psychopathology that would have existed even in the absence of a true traumatic event.[18–20] Bodkin et al reported that among psychiatric outpatients, nearly 80% endorsed sufficient symptoms to meet criteria for PTSD in the absence of a lifetime traumatic event. Given the symptom overlap that exists between PTSD and other anxiety/depressive disorders (eg, loss of interest, irritability, sleep disturbance, poor attention, social withdrawal), it is not surprising that depressed outpatients would at least minimally meet PTSD criteria if given an opportunity to associate this with either a de facto or "proxy" traumatic event.[18] Furthermore, criterion B (as well as a subset of criterion C avoidance symptoms) for PTSD would be met ipso facto in non–trauma-exposed depressed patients

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as an artifact of the "proxy" methodology, perhaps thereby neutralizing a cluster of symptoms within PTSD that more clearly sets it apart from depression and other psychiatric disorders. Although findings such as those published by Bodkin et al usefully illustrate the complicating commonalities that can exist between disorders and pose an appropriate warning regarding the dangers of assuming that PTSD-like symptoms are caused by trauma in all cases, they do not convincingly argue against the conceptual basis of PTSD and its embedded assumption of causal trauma, which the present results support. Similarly, if a study of major depression patients found that symptoms of sadness, social withdrawal, guilt, and loss of energy were present even in the absence of a history of a recent death in the family, that would not negate the fact that bereavement can cause depressive-like symptoms. The current study more directly assessed the potential impact of trauma in producing psychopathology (both PTSD-related and general) by employing a case-control study design in which genetic and early environmental factors were controlled by the inclusion of non–combat-exposed identical twins. Our findings support the ability of trauma to produce psychiatric symptomatology because the PTSD veterans' twins did not develop significant symptoms. They do not support the proposition that PTSD and its embedded trauma assumption represent a misattribution of symptoms that would have existed even in the absence of trauma.[24]

The results of the current study add to a growing set of data obtained in the present cohort of identical twins discordant for combat exposure that identify and differentiate preexisting vulnerabilities versus trauma-induced attributes.[7,9,33,37–42] On the basis of results obtained here, it would not appear that the comorbid psychiatric symptoms currently existing in combat veterans with PTSD are an extension of pretrauma pathology that originally served to increase their vulnerability for PTSD. That is, our findings are not consistent with the presence of predisposing psychopathologic traits (due to either genetics or environmental factors that twins are likely to share) that increase vulnerability to the development of PTSD upon exposure to a traumatic stressor. There were no significant differences between the high- and low-risk, combat-unexposed cotwins, ie, those whose combat-exposed brothers did or did not develop PTSD. As such, these results are broadly consistent with several prospective studies of combat veterans that have failed to establish a relationship between predeployment personality or psychopathology variables and posttrauma PTSD.[43–45] Some prospective studies, however, have suggested the presence of pretrauma psychological variables that may predispose to PTSD in nonveteran populations.[46–48] Although our data suggest that general psychiatric symptoms are unlikely to represent preexisting or predisposing factors for PTSD, this conclusion is weakened by the fact that we measured symptoms later in life, not prior to trauma exposure. It is possible that the combat-unexposed cotwins of the PTSD veterans at some time in the past had more symptoms, which had subsided by the time of the present study. Although we think this unlikely, our findings nonetheless argue for the fact that trauma exposure subsequently results in more durable, unremitting psychiatric symptoms. The design employed here also cannot rule out the possibility that unique (ie, nonshared) environmental factors occurring in the ExP+ twins (but not the UxP+ cotwins) prior to combat generated psychopathologic symptoms that served as risk factors for developing PTSD upon combat exposure, although we think it unlikely that such symptoms, even if present, could constitute the entirety of PTSD veterans' psychopathology. Furthermore, our design cannot rule out the possibility that, even though they do not manifest an increased rate of psychopathology, the (high-risk) non–combat-exposed cotwins of combat veterans with PTSD may share latent inherited phenotypes predisposing to these comorbidities that require traumatic exposure in order to be activated.[49]

It is worth noting that results from the current study failed to find any specific pattern of comorbid psychopathologic symptoms to be associated with a diagnosis of PTSD. That is, all clinical scales of the SCL-90-R as well as the GSI and the War-Zone PTSD Scale showed the same pattern. It is possible that the pattern of comorbid traits in PTSD is in fact best characterized by a general psychopathology factor, which is consistent with epidemiologic studies of PTSD in which comorbid disorders cover a range of clinical syndromes. It is also possible that this finding is reflective of distress associated with the functional impairment of having a chronic, unremitting PTSD syndrome.[27] Furthermore, we cannot rule out the possibility that increased SCL-90-R scores to some degree represent compensation-seeking or general symptom overreporting in the PTSD group. The literature on this, however, has been inconclusive.[50–52]

In summary, results of the current study provide support for a causal relationship between combat exposure and psychiatric symptomatology, both PTSD-related and general, in veterans diagnosed with PTSD. They suggest that even non–trauma-specific symptoms may be caused by trauma exposure, because these symptoms were not found in combat veterans' "identical surrogates" who did not have trauma histories. As such, the presence of nonspecific symptoms that are shared with other mood and anxiety disorders in PTSD does not argue for the invalidity of the embedded presumption of causality, nor does it argue for the misattribution to trauma of symptoms that would have existed even in the absence of trauma exposure. Rather, the challenge remains one of refining the symptom criteria for PTSD to better articulate the disorder's core psychopathologic features in order to allow greater differentiation of posttraumatic psychopathology from other disorders.

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