ORIGINAL ARTICLE

Subtle Neurologic Compromise as a Vulnerability Factor for Combat-Related Posttraumatic Stress Disorder

Results of a Twin Study

Tamara V. Gurvits, MD, PhD; Linda J. Metzger, PhD; Natasha B. Lasko, PhD; Paul A. Cannistraro, MD; Alexandra S. Tarhan, MD, PhD; Mark W. Gilbertson, PhD; Scott P. Orr, PhD; Anna M. Charbonneau, BA; Michelle M. Wedig, BS; Roger K. Pitman, MD

Context: Previous studies have demonstrated subtle neurologic dysfunction in chronic posttraumatic stress disorder (PTSD) manifest as increased neurologic soft signs (NSSs). The origin of this dysfunction is undetermined.

Objective: To resolve competing origins of increased NSSs in PTSD, namely, preexisting vulnerability factor vs acquired PTSD sign.

Design: Case-control study of identical twins.

Setting: A Veterans Affairs and academic medical center (ambulatory).

Participants: A convenience sample of male Vietnam veteran twins with (n=25) and without (n=24) PTSD and their combat-unexposed identical (monozygotic) co-twins.

Interventions: Neurologic examination for 45 NSSs.

Main Outcome Measure: Average scores for 45 NSSs, each scored on an ordinal scale from 0 to 3, masked to diagnosis and combat exposure status.

Results: There was a significant between-pair main effect of PTSD diagnosis (as determined in the combat-exposed twin) on average NSS score in the absence of a significant combat exposure main effect or diagnosis × exposure interaction. Combat veterans with PTSD had significantly higher NSS scores than combat veterans without PTSD. The "high-risk," unexposed co-twins of the former also had significantly higher NSS scores than the "low-risk," unexposed co-twins of the latter. This result could not be explained by age, number of potentially traumatic lifetime noncombat events, alcoholism, or the presence of a comorbid affective or anxiety disorder. The average NSS score in unexposed co-twins was not significantly associated with combat severity in combat-exposed twins.

Conclusions: These results replicate previous findings of increased NSSs in Vietnam combat veterans with PTSD. Furthermore, results from their combat-unexposed identical co-twins support the conclusion that subtle neurologic dysfunction in PTSD is not acquired along with the trauma or PTSD but rather represents an antecedent familial vulnerability factor for developing chronic PTSD on exposure to a traumatic event.

Arch Gen Psychiatry. 2006;63:571-576

Author Affiliations: Research Service, Veterans Affairs Medical Center, Manchester, NH (Drs Gurvits, Metzger, Lasko, Gilbertson, and Orr and Ms Charbonneau); Department of Psychiatry, Massachusetts General Hospital, Boston (Drs Metzger, Lasko, Cannistraro, Orr, and Pitman and Ms Wedig); Bekhterev Psychoneurological Research Institute, St Petersburg, Russia (Dr Tarhan); and Department of Psychiatry, Harvard Medical School, Boston (Drs Gurvits, Metzger, Lasko, Cannistraro, Gilbertson, Orr, and Pitman).

DOES STRESS DAMAGE THE Brain?"[1] The appearance of a review article with this title in *Biological Psychiatry*, and a review article in *Science* entitled "Why Stress Is Bad for Your Brain,"[2] illustrates how seriously this possibility is taken regarding posttraumatic stress disorder (PTSD). In experimental animals, chronic stress has been shown to cause dendritic atrophy or even cell death and to inhibit neurogenesis in the hippocampus[3] and prefrontal cortex.[4] Findings of diminished volume of these brain structures[5,6] in PTSD have led some researchers to propose that the etiologic traumatic event or the resulting chronic stress disorder damaged them.

Ongoing combat actions in Iraq and Afghanistan have recently focused attention on the substantial mental health problems posed by combat-related PTSD.[7-10] In calculating the "psychiatric cost of war,"[8] it is important to keep in mind that although PTSD is (indisputably) the result of a psychologically traumatic event, this does not mean that all abnormalities associated with PTSD are as well. If an abnormality were to antedate a traumatic event and increase the risk of developing PTSD from it, it too would be found to be associated with PTSD in cross-sectional

©2006 American Medical Association. All rights reserved.

Downloaded From: http://archpsyc.jamanetwork.com/ on 07/27/2017

studies. The best way to resolve these competing interpretations is longitudinal investigation. However, longitudinal studies require performing measurements on people before they are exposed to a traumatic event and develop PTSD. Because there are no guarantees that either will occur, such studies are difficult. A next-best strategy is to study surrogates for what trauma-exposed individuals would be like except for their trauma exposure, for example, trauma-unexposed identical twins who share their genes and familial environment but not their traumatic events. If an abnormality found to be associated with PTSD has been acquired as a result of the traumatic event or the PTSD, it should not be found in the trauma-unexposed co-twins of the individuals with PTSD. However, if it represents a familial (pretrauma) vulnerability factor, it should be found in the ("high-risk") unexposed co-twins of exposed twins with PTSD but not in the ("low-risk") unexposed co-twins of exposed twins without PTSD.

We have been studying well-replicated abnormalities associated with PTSD in a sample of identical twins discordant for combat exposure in Vietnam. In 1 study,[11] we found that increased heart rate responses to loud tones in combat veterans with PTSD were not shared by their combat-unexposed identical co-twins, consistent with their status as an acquired PTSD sign. However, in another study,[12] we found that hippocampal diminution in combat veterans with PTSD was shared by their high-risk co-twins, who had lower hippocampal volumes than the low-risk co-twins of combat veterans without PTSD. This finding is inconsistent with brain damage resulting from stress but instead suggests that hippocampal diminution is a preexisting PTSD vulnerability factor.

In previous studies of non-twins, we found that male combat veterans[13,14] and women sexually abused as children[14] (but not female military nurses[15]) with chronic PTSD are more neurologically compromised than their counterparts without PTSD, as evidenced by more neurologic soft signs (NSSs). These are various subtle indices of neurologic dysfunction that are distinct from hard signs because they are difficult to localize to a specific brain area. To resolve whether the increased NSSs found in PTSD reflect (1) subtle brain damage from the traumatic event or subsequent PTSD or (2) preexisting vulnerability factors, we measured NSSs in identical twins discordant for combat exposure in Vietnam.

METHODS

PARTICIPANTS

The participants in the present study were drawn from a pool of individuals who had participated in a previously described psychophysiologic study.[11] A full description of the recruitment sources and strategy, and the characteristics of the participant population, appeared in that article.[11] That study's sample consisted of 103 male monozygotic (identical) twin pairs; one twin served in combat in Vietnam and his co-twin did not. The participants were invited to return for further testing; the order of their return was based on scheduling convenience. The study reported herein was terminated when one of us (T.V.G.) moved to another state, at which time 49 twin pairs had been studied. Participants were excluded if they had a history of major head injury involving loss of consciousness for more than 10 minutes, tumor, epilepsy, cerebrovascular accident, or other neurologic disorders or if they had a history of dementia, amnestic disorder, mental disorder due to a general medical condition, or psychotic disorder.

In 25 pairs, the combat veteran had current combat-related PTSD; in 24 pairs, the combat veteran had never had combat-related PTSD. The proportion of PTSD pairs and the group demographic and psychometric means of the present participants closely parallel those of the original, larger sample,[11] except that participants were approximately 3 years older, reflecting the time elapsed between visits.

PSYCHODIAGNOSTICS AND PSYCHOMETRICS

This research protocol was approved by the institutional review boards of the Massachusetts General Hospital and the Manchester Veterans Affairs Medical Center. Written informed consent was obtained after the procedures had been fully explained. The Clinician-Administered PTSD Scale[16] was administered to determine the presence or absence of combat-related PTSD in the combat-exposed twins. Data from an 18-item Combat Severity Scale[17] were already available. All the participants were interviewed using the Structured Clinical Interview for *DSM-IV*[18] to determine the presence of Axis I mental disorders. The Michigan Alcoholism Screening Test[19] quantified lifetime alcoholism. A stressful life events checklist (available on request) quantified lifetime noncombat events that potentially met the *DSM-IV* PTSD "A" (stressor) criterion.

NEUROLOGIC EXAMINATION

The 45 NSSs examined are listed in **Table 1**. The rationale for their choice is described in previous publications.[13,14] The current protocol (available on request) called for a score for each NSS on an ordinal scale from 0 to 3, with specific anchors for each item. Neurologic examinations were performed by a neurologist-psychiatrist (T.V.G.), who was masked to diagnosis and combat exposure but not to twinship. As part of the NSS examination, the participant's figure copy drawings, which comprised 2 of the NSSs studied, were scored according to a published technique.[20] The figures were also independently scored in scrambled order by a trained second rater (A.M.C.), who was fully blind to diagnosis, combat exposure, and twinship. Because the second rater saw only the participant's figure drawings, her scoring could not have been affected by the participant's dress or demeanor.

STRUCTURAL NEUROIMAGING

Seventy-four of the present study's 98 participants had participated in a previous study that used structural magnetic resonance imaging.[12] Total brain gray and white matter volumes were quantified according to a published technique.[21] Those data were entered into Pearson product moment correlations, with the average NSS score for all 74 participants combined.

STATISTICAL ANALYSIS

Scores for the 45 NSSs were averaged before analysis. Scores for the 2 NSSs that involved figure copying were also averaged before analysis. The data were analyzed using a mixed model for repeated measures that treated PTSD diagnosis (ie, PTSD vs non-PTSD in the combat-exposed twin) as a between-pairs fixed effect, combat exposure as a within-pair fixed effect, and twin pairs as a random effect.[22] This analysis yields a t statistic.

©2006 American Medical Association. All rights reserved.

Downloaded From: http://archpsyc.jamanetwork.com/ on 07/27/2017

If a dependent variable represents a PTSD vulnerability factor, the model predicts a significant diagnosis main effect in the absence of a diagnosis × exposure interaction. If a dependent variable represents an acquired PTSD sign, the model predicts a significant interaction.

To decompose significant diagnosis main effects, contrasts using independent *t* tests were performed for the combat-exposed twins with PTSD vs the combat-exposed twins without PTSD and separately for the (high-risk) unexposed co-twins of combat-exposed twins with PTSD vs the (low-risk) unexposed co-twins of combat-exposed twins without PTSD. Because the predictions were unequivocally directional, that is, greater dysfunction in the former than in the latter in each case, 1-tailed *P* values are reported for these contrasts and for the correlations with total brain gray and white matter volumes.

RESULTS

DEMOGRAPHICS, PSYCHOMETRICS, AND COMORBIDITY

Demographic and psychometric data are given in **Table 2**, along with the results of the mixed-model analyses and independent *t* tests. A visual comparison of these data with those in Table 1 of our previous publication that included the full sample of 103 twin pairs[11] indicates that the mean age, combat severity, and total Clinician-Administered PTSD Scale score of the subsample studied are comparable with those of the full sample. Age and education were similar in the various participant groups in the present study. As expected, combat veterans with PTSD had higher Clinician-Administered PTSD Scale scores than combat veterans without PTSD; the former also had more severe combat experiences. Combat veterans with PTSD had higher scores on the Michigan Alcoholism Screening Test than the other 3 groups; there was no significant difference on this test between the unexposed co-twins of combat veterans with PTSD and the unexposed co-twins of combat veterans without PTSD. Combat veterans with PTSD and their unexposed co-twins reported more (non–combat-related) potentially traumatic lifetime events than did combat veterans without PTSD and their unexposed co-twins.

NSS AND COPY FIGURE SCORES

The group mean (SD) NSS scores and the results of the statistical analyses are also given in Table 2. It is impossible to report the reliability of average NSS scores based on the data in this study because except for 2 NSSs that involved figure copying (see later in this subsection), there was only 1 rater. However, we previously reported the interreliability for average NSS score as 0.74 (intraclass correlation coefficient).[14] For average NSS score, there was a significant diagnosis main effect in the absence of a significant exposure main effect or diagnosis × exposure interaction. Combat veterans with PTSD had significantly higher average NSS scores than combat veterans without PTSD. The unexposed (high-risk) co-twins of the former also had significantly higher average NSS scores than the (low-risk) unexposed co-twins of the latter. The effect size of this last key result of $d=0.50$ (Table 2) would be regarded as moderate by conventional standards[23]; the percentage of the variance accounted for was 6%. Three individual NSSs showed a significant diagnosis main effect at $P<.01$: figure copying[20] (2 NSSs) and the road map test of direction sense[24] (Table 1).

Average NSS score was significantly correlated with total gray matter volume ($r=-0.26$; $P=.01$), although the mixed model did not show any significant main effects or interaction for gray matter. Average NSS score was not significantly correlated with white matter volume ($r=-0.15$; 1-tailed $P=.10$).

Table 1. The 45 Neurologic Soft Signs Examined in This Study

Neurologic Soft Sign	*P* Value*
Copy figure No. 1	.002
Copy figure No. 2	.003
Road map test of direction sense	.004
Finger-thumb opposition (L)	.01
Pronation-supination (R)	.03
Optic agnosia No. 1	.03
Nose-finger-nose (L)	.04
Nose-finger-nose (R)	.06
Pronation-supination (both)	.07
Tongue twister	.07
Geographic agnosia	.12
Pronation-supination (L)	.13
House from matches	.14
Walking tiptoe	.15
Finger-thumb opposition (R)	.16
Fist-palm-side (L)	.21
Palmomental reflex (L)	.21
Extinction	.21
Palmomental reflex (R)	.24
Astereognosis No. 2 (R)	.28
Optic agnosia No. 2	.37
Astereognosis No. 2 (L)	.43
Graphesthesia (L)	.45
Adventitious overflow	.48
Romberg test	.50
Astereognosis No. 1 (R)	.54
Foot tapping (R)	.57
Drawing clock	.58
Gait	.59
Foot tapping (L)	.60
Standing on 1 foot (R)	.63
Mirror movements (L)	.65
Tapping rhythm	.65
Drawing house	.66
Astereognosis No. 1 (L)	.69
Draw a face	.71
Walking on heels	.77
Standing on 1 foot (L)	.77
Drawing flower	.78
Graphesthesia (R)	.81
Finger-nose (L)	.88
Mirror movements (R)	.94
Fist-palm-side (R)	.94
Tandem gait	.98
Finger-nose (R)	.99

Abbreviations: L, left; R, right.
*Diagnosis main effect, that is, the significance of the difference between combat-exposed veterans with posttraumatic stress disorder and their unexposed co-twins (averaged) vs combat-exposed veterans without posttraumatic stress disorder and their unexposed co-twins (averaged).

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 07/27/2017

Table 2. Characteristics of Combat-Exposed Vietnam Veterans With and Without PTSD and Their Combat-Unexposed Identical Co-twins[a]

	PTSD Pairs		Non-PTSD Pairs		Mixed Model						Independent *t* Tests			
					Diagnosis		Exposure		Interaction		ExP+ vs ExP–		UxP+ vs UxP–	
	Exposed (ExP+) (n = 25)	Unexposed (UxP+) (n = 25)	Exposed (ExP–) (n = 24)	Unexposed (UxP–) (n = 24)	t_{47}	*P* Value	t_{48}	*P* Value	t_{47}	*P* Value	t_{47}	*P* Value	t_{47}	*P* Value
Age, y[b]	53.6 (3.7)	53.6 (3.7)	52.5 (2.4)	52.5 (2.4)	NA	NA	1.1	.26	NA	NA	1.1	2.6	1.1	.26
Education, y	13.8 (3.2)	13.3 (2.8)	14.5 (2.4)	14.3 (2.6)	1.2	.22	0.7	.47	0.6	.58	0.9	.40	1.3	.20
CAPS score	68.8 (17.9)	NA	4.9 (5.6)	NA	NA	NA	NA	NA	NA	NA	16.7	<.001	NA	NA
Combat severity[c]	9.4 (5.8)	NA	4.1 (2.8)	NA	NA	NA	NA	NA	NA	NA	4.0	<.001	NA	NA
Traumatic events, No.[d]	12.4 (9.5)	13.4 (18.7)	7.4 (8.8)	4.2 (3.2)	3.0	.003	0.4	.66	0.9	.37	1.9	.07	2.4	.02
MAST score	13.7 (14.9)	6.7 (12.4)	2.4 (4.5)	3.1 (4.8)	3.2	.003	1.6	.12	2.1	.04	3.6	.001	1.3	.22
Average NSS score[e]	0.85 (0.38)	0.80 (0.36)	0.59 (0.33)	0.64 (0.30)	2.3[f]	.03	0.1	.96	1.2	.25	2.5[g]	.008[h]	1.7[i]	<.05[h]
Average figure-copying score[e] (examiner)	0.97 (0.75)	0.88 (0.73)	0.48 (0.52)	0.40 (0.38)	3.1[j]	.003	1.0	.34	0.1	.95	2.6[k]	.006[h]	2.9[l]	.003[h]
Average figure-copying score[e] (second rater)	1.15 (0.53)	0.97 (0.58)	0.75 (0.53)	0.65 (0.50)	2.5[m]	.02	2.2	.04	0.7	.50	2.5[n]	.007[h]	1.9[o]	.03[h]

Abbreviations: CAPS, Clinician-Administered PTSD Scale (total combat-related symptom score; range, 0-136); MAST, Michigan Alcoholism Screening Test (score range, 0-25); NA, not applicable; NSS, neurologic soft sign; PTSD, posttraumatic stress disorder.

[a]Data are given as group mean (SD).
[b]As of July 1, 2001.
[c]Eighteen-item measure (range, 0-18).
[d]Potentially traumatic lifetime noncombat events.
[e]Score range, 0-3.
[f]$d = 0.67$, partial $\eta^2 = 0.10$.
[g]$d = 0.73$, $\eta^2 = 0.12$.
[h]One-sided.
[i]$d = 0.50$, $\eta^2 = .06$.
[j]$d = 0.90$, partial $\eta^2 = 0.17$.
[k]$d = 0.76$, $\eta^2 = 0.12$.
[l]$d = 0.85$, $\eta^2 = 0.15$.
[m]$d = 0.73$, partial $\eta^2 = 0.12$.
[n]$d = 0.75$, $\eta^2 = 0.12$.
[o]$d = 0.55$, $\eta^2 = 0.07$.

Table 2 also provides the examiner's and second rater's average figure-copying scores. The intraclass correlation between the examiner's and second rater's average figure-copying scores was 0.81. The examiner's average figure-copying scores fit the same pattern as average NSS scores. The second rater's average figure-copying scores also fit this pattern, except that the exposure main effect was also significant, with combat-exposed twins showing significantly higher scores than combat-unexposed co-twins in the absence of a significant interaction with diagnosis. The effect size of the second rater's average figure-copying scores for the high-risk vs low-risk, unexposed co-twin comparison (another key result) of $d = 0.55$ (Table 2, footnote o) was also moderate; the percentage of the variance accounted for was 7%.

Pearson product moment correlations between exposed and unexposed twins across diagnosis were as follows: examiner's average NSS scores, $r = 0.69$; examiner's average figure-copying scores, $r = 0.63$; and second rater's average figure-copying scores, $r = 0.68$ ($P < .001$ for all).

ANALYSES OF POTENTIALLY CONFOUNDING THIRD VARIABLES

The higher average NSS scores in the unexposed co-twins of the combat veterans with PTSD compared with the unexposed co-twins of the combat veterans without PTSD is the key finding of this study. None of the following variables were found to be associated with average NSS scores in the unexposed co-twins at the screening level of $P < .20$: age, number of potentially traumatic lifetime noncombat events, Michigan Alcoholism Screening Test score, presence of an affective or anxiety disorder, and combat severity in the exposed twin. Therefore, these variables were not considered to have potentially confounded the key finding. However, educational level and use of 1 or more potentially confounding medications or substances (itemized in a previous publication[11]) were associated at $P < .20$ with average NSS scores in the unexposed co-twins. Repeating the contrast between unexposed co-twins of combat veterans with PTSD vs unexposed co-twins of combat veterans without PTSD as an analysis of covariance with educational level as the covariate yielded $F_{1,38} = 1.0$ (1-tailed $P = .16$). The same contrast was also repeated on medication- and substance-free high-risk vs low-risk co-twins, and the difference remained significant: 21 vs 20 co-twins; mean (SD) NSS score, 0.76 (0.26) vs 0.59 (0.25) ($t_{39} = 2.1$; 1-tailed $P = .02$).

COMPARISON WITH PUBLISHED DATA IN NON-TWINS

In a previous study,[14] the same examiner scored the same NSSs in combat-exposed, non-twin (singleton) Viet-

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 07/27/2017

nam combat veterans. Fifteen Vietnam combat veteran singletons without PTSD (mean age, 49.2 years) were found to have a mean (SD) NSS score of 0.32 (0.13).[14] An independent *t* test contrasting those data with the mean (SD) NSS score of 0.59 (0.33) in the 24 combat-exposed twins without PTSD in the present study (mean age, 52.5 years) yielded $t_{37}=3.0$ (2-tailed $P=.005$).

COMMENT

The results of the present study again replicate our previous findings[13,14,20] of subtle neurologic compromise, manifest as increased NSSs, in male Vietnam combat veterans with PTSD compared with Vietnam combat veterans without PTSD. The finding that the average NSS score was significantly correlated with total brain gray matter volume supports the validity of the NSS measurements. The unique feature of the present study is that each combat veteran had an identical twin who did not serve in combat, which allowed us to investigate the origin of subtle neurologic compromise in PTSD. The results clearly support the conclusion that subtle neurologic dysfunction in PTSD does not reflect brain damage acquired along with the PTSD but instead represents a familial vulnerability factor, which likely antedates the traumatic exposure. Especially supporting the premorbid vulnerability interpretation is the finding that the (high-risk) unexposed co-twins of the combat veterans with PTSD had significantly higher average NSS scores than the (low-risk) unexposed co-twins of the combat veterans without PTSD. This difference was not explained by several potentially confounding factors, including age, number of potentially traumatic lifetime noncombat events, alcoholism, psychiatric comorbidity, and use of medications or substances. When the analysis was adjusted for educational level, the result was no longer statistically significant. However, lower educational level is more likely to be an effect than a cause of subtle neurologic compromise, considering our previously reported finding of more self-reported neurodevelopmental problems and childhood attention-deficit/hyperactivity disorder symptoms in singleton Vietnam combat veterans with (vs without) PTSD.[14]

The fact that the average NSS score in the unexposed co-twins was not associated with combat severity in their combat-exposed twins refutes the interpretation that subtle neurologic dysfunction in this study increased the risk of PTSD by increasing the likelihood of exposure to more severe combat events. However, preexisting subtle neurologic dysfunction could plausibly confer vulnerability to developing PTSD after the occurrence of a psychologically traumatic event. Failure of cortical inhibitory control over conditioned emotional responses may play a role in the pathogenesis of PTSD.[25] Although the acquisition of fear conditioning can occur at the subcortical level,[26] retention of extinction of fear conditioning requires an intact cerebral cortex[27]; the increased NSSs found herein point to subtle cortical dysfunction in PTSD combat veterans and their combat-unexposed twins. The presence of antecedent subtle neurologic dysfunction may make it less likely that patients with PTSD will recover, thereby predisposing them to a chronic course. It is also possible to phrase these relationships inversely. That is, a healthy nervous system may, for all the previously mentioned reasons, confer resilience in the face of highly stressful life events.

In the present study, the examiner was masked to the participants' diagnosis and combat exposure, but she interacted with the participants. Therefore, the possibility cannot be ruled out that she picked up clues to these factors that might have affected her ratings. However, in our previous study,[14] a second rater who scored NSSs from videotaped examinations and who was fully masked to diagnosis confirmed the finding of higher average NSS scores in combat veterans with PTSD. A more serious potentially biasing factor in the present study was that the examiner saw members of a twin pair on the same day and obviously knew that they were twins. If this resulted in a tendency to give similar NSS scores to similarly appearing persons, it could potentially account for the comparable mean NSS scores found in exposed twins and their unexposed co-twins. Videotaped examinations scored by a masked rater were unavailable in the present study. However, as in our previous study[14] of 45 NSSs in PTSD, figure copying[20] comprised the 2 NSSs that best distinguished patients with vs without PTSD (and their co-twins) in the present study. We provided copies of all participants' figure drawings to a second rater who was fully masked to diagnosis, exposure, and twinship. This rater's results parallel the results of the NSS examinations in that the diagnosis main effect was significant, and the high-risk co-twins showed significantly more figure-copying abnormalities than the low-risk co-twins. Exposed twins and their unexposed co-twins shared 46% of the variance in the second rater's average figure-copying scores, which actually was greater than the 40% shared variance for the examiner's average figure-copying scores. Moreover, the second rater's average figure-copying scores were highly correlated with the examiner's average NSS scores. These results support the conclusion that the study's key finding is not due to examiner rating bias.

Another limitation of the present study is that its insight into the origin of increased NSSs in PTSD may not be generalizable to victims of noncombat traumatic events or women, although our group[14] found increased NSSs in such persons. Twin, or prospective, studies need to be conducted to ascertain the origin of increased NSSs in these groups.

Finally, the finding that the twin Vietnam veterans without PTSD in the present study had significantly more NSSs than the non-twin Vietnam veterans without PTSD in our previous study that used the same examinations conducted by the same examiner suggests that twins have more subtle neurologic dysfunction than singletons. To our knowledge, this finding has not previously been reported. However, this finding is not surprising considering that twins have a more tenuous in utero status, with more premature deliveries, more traumatic deliveries, and lower birth weights.[28]

Submitted for Publication: May 25, 2005; final revision received October 24, 2005; accepted October 25, 2005.

©2006 American Medical Association. All rights reserved.

Downloaded From: http://archpsyc.jamanetwork.com/ on 07/27/2017

Correspondence: Roger K. Pitman, MD, Department of Psychiatry, Massachusetts General Hospital, 13th Street, Bldg 149, Room 2616, Charlestown, MA 02129 (roger_pitman@hms.harvard.edu).

Funding/Support: This study was supported by grant MH54636 from the US Public Health Service (Dr Pitman), a grant from the US Department of Veterans Affairs Medical Research Service (Dr Gilbertson), and ongoing support from the Department of Veterans Affairs for the development and maintenance of the Vietnam Era Twin Registry.

Acknowledgment: Through their support of the Vietnam Era Twin Registry, numerous organizations provided invaluable assistance, including the Department of Defense; National Personnel Records Center, National Archives and Records Administration; Internal Revenue Service; National Institutes of Health; National Opinion Research Center; National Research Council, National Academy of Sciences; and Institute for Survey Research, Temple University. We gratefully acknowledge the continued cooperation and participation of the members of the Vietnam Era Twin Registry and their families. Without their contribution this research would not have been possible.

REFERENCES

1. Bremner JD. Does stress damage the brain? *Biol Psychiatry*. 1999;45:797-805.
2. Sapolsky RM. Why stress is bad for your brain. *Science*. 1996;273:749-750.
3. McEwen BS. Stress and hippocampal plasticity. *Annu Rev Neurosci*. 1999;22:105-122.
4. Radley JJ, Sisti HM, Hao J, Rocher AB, McCall T, Hof PR, McEwen BS, Morrison JH. Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience*. 2004;125:1-6.
5. Liberzon I, Phan KL. Brain-imaging studies of posttraumatic stress disorder. *CNS Spectr*. 2003;8:641-650.
6. Rauch SL, Shin LM, Segal E, Pitman RK, Carson MA, McMullin K, Whalen PJ, Makris N. Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport*. 2003;14:913-916.
7. 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.
8. Friedman MJ. Acknowledging the psychiatric cost of war. *N Engl J Med*. 2004;351:75-77.
9. Friedman MJ. Veterans' mental health in the wake of war. *N Engl J Med*. 2005;352:1287-1288.
10. Kang HK, Hyams KC. Mental health care needs among recent war veterans [perspective]. *N Engl J Med*. 2005;352:1289.
11. Orr SP, Metzger LJ, Lasko NB, Macklin ML, Hu FB, Shalev AY, Pitman RK. Physiologic responses to sudden, loud tones in monozygotic twins discordant for combat exposure: association with posttraumatic stress disorder. *Arch Gen Psychiatry*. 2003;60:283-288.
12. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci*. 2002;5:1242-1247.
13. Gurvits TV, Lasko NB, Schachter SC, Kuhne AA, Orr SP, Pitman RK. Neurological status of Vietnam veterans with chronic posttraumatic stress disorder. *J Neuropsychiatry Clin Neurosci*. 1993;5:183-188.
14. Gurvits TV, Gilbertson MW, Lasko NB, Tarhan AS, Simeon D, Macklin ML, Orr SP, Pitman RK. Neurologic soft signs in chronic posttraumatic stress disorder. *Arch Gen Psychiatry*. 2000;57:181-186.
15. Gurvits TV, Carson MA, Metzger LJ, Croteau HB, Lasko NB, Orr SP, Pitman RK. Absence of selected neurological soft signs in Vietnam nurses with posttraumatic stress disorder. *Psychiatry Res*. 2002;110:81-85.
16. Weathers FW, Keane TM, Davidson JR. Clinician-Administered PTSD Scale: a review of the first ten years of research. *Depress Anxiety*. 2001;13:132-156.
17. 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.
18. First MB. *User's Guide for the Structured Clinical Interview for* DSM-IV *Axis I Disorders SCID-I: Clinician Version*. Washington, DC: American Psychiatric Press; 1997.
19. Selzer ML. The Michigan Alcoholism Screening Test: the quest for a new diagnostic instrument. *Am J Psychiatry*. 1971;127:1653-1658.
20. Gurvits TV, Lasko NB, Repak AL, Metzger LJ, Orr SP, Pitman RK. Performance on visuospatial copying tasks in individuals with chronic posttraumatic stress disorder. *Psychiatry Res*. 2002;112:263-268.
21. Dickey CC, Shenton ME, Hirayasu Y, Fischer I, Voglmaier MM, Niznikiewicz MA, Seidman LJ, Fraone S, McCarley RW. Large CSF volume not attributable to ventricular volume in schizotypal personality disorder. *Am J Psychiatry*. 2000;157:48-54.
22. Little RC, Milliken GA, Stroup WW, Wolfinger RD. *SAS System for Mixed Models*. Cary, NC: SAS Institute Inc; 1996.
23. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
24. Money J, Alexander D, Walker HT. *A Standardized Road Map Test of Direction Sense*. Baltimore, Md: Johns Hopkins Press; 1965.
25. Pitman RK, Shalev AY, Orr SP. Post-traumatic stress disorder: emotion, conditioning, and memory. In: Gazzaniga MS, ed. *The New Cognitive Neurosciences*. Cambridge, Mass: MIT Press; 2000:1133-1147.
26. Romanski LM, LeDoux JE. Bilateral destruction of neocortical and perirhinal projection targets of the acoustic thalamus does not disrupt auditory fear conditioning. *Neurosci Lett*. 1992;142:228-232.
27. Quirk GJ, Russo GK, Barron JL, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *J Neurosci*. 2000;20:6225-6231.
28. Buscher U, Horstkamp B, Wessel J, Chen FC, Dudenhausen JW. Frequency and significance of preterm delivery in twin pregnancies. *Int J Gynaecol Obstet*. 2000;69:1-7.

©2006 American Medical Association. All rights reserved.

Downloaded From: http://archpsyc.jamanetwork.com/ on 07/27/2017