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13. ABSTRACT *(Maximum 200*

This study was designed in two parts. Part one is a longitudinal descriptive study of trauma-related symptoms in veterans of Operation Desert Storm. Over the past five years we followed veterans from National Guard units in Connecticut. The natural evolution of trauma-related symptoms and the longitudinal consistency of memory for traumatic events were explored. Results indicated an increase in post traumatic stress disorder (PTSD) symptoms over the first two years after the war. Level of combat exposure was significantly associated with the Mississippi PTSD score at two years but not at one and six months. Inconsistent recall of traumatic events was also demonstrated. Thus, the data did not support the notion that traumatic memories are fixed. The current study continues the methodology for the sixth and seventh post-war years, and expands the number of participants. Part two is based on findings observed in Vietnam War veterans with PTSD who underwent memory testing and MRI scans. Veterans had an 8% decrease in right hippocampal volume relative to healthy subjects, with associated deficits in short-term memory. Thirty Desert Storm veterans with PTSD will be tested using procedures employed with the Vietnam veterans. Relationships to clinical symptoms and psychosocial functioning will be investigated.

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INTRODUCTION

The following grant application is composed of two parts: The first part is a follow-along descriptive study of trauma-related symptomatology in veterans of Operation Desert Storm. The second part is an investigation of memory funtion and hippocampal volume in veterans of Operation Desert Storm who meet criteria for post-traumatic stress disorder (PTSD).

I. LONGITUDINAL COURSE OF TRAUMA-RELATED SYMPTOMATOLOGY

Although PTSD is a common disorder, relatively little is known about its natural history. Cross sectional descriptive studies have made it clear that stress-related symptoms are often problematic even decades after a catastrophic event. For example, in a large community sample of Vietnam theater veterans nearly twenty years after the war, Kulka et al (1) found that 15% met diagnostic criteria for PTSD and another 15% for partial PTSD. Chronic trauma-related symptomatology also has been reported in survivors of the Holocaust (2-4), natural disasters (5,6), accidents (7,8), and violent crime (9,10).

While cross-sectional studies are highly informative, they are not designed to investigate the natural course of a disorder. Similarly, retrospective approaches are subject to the problem of inaccurate recall. Prospective studies, on the other hand, are ideal for collecting detailed information about the evolution and course of psychiatric symptoms and syndromes.

OBJECTIVES

1. To continue the longitudinal assessment of trauma-related symptomatology in veterans of Operation Desert Storm.

2. To evaluate the relative contribution of previously identified pre-military (child abuse, threat to life, father in the military, etc.), military (level and specific type of combat stressors), and post-military (social support, substance abuse, etc.) risk factors toward the development of trauma-related symptomatology.

3. To further investigate the manner in which memory for traumatic events in veterans of war is affected with the passage of time, and to elucidate the relationship between combat-related symptomatology and memory of wartime stressors.

HYPOTHESES

1. In the group of Desert Storm veterans as a whole, trauma-related symptomatology will continue to gradually increase with the passage of time. It is not possible to predict when level of symptomatology will plateau.

2. Subjects with known pre-military, military and post-military risk factors will have greater levels of PTSD symptomatology at future timepoints compared to subjects without risk factors.

3. Memory for traumatic events will continue to lack consistency over time. Further, there will be a direct relationship between level of trauma-related symptomatology and degree of memory inconsistency.

BACKGROUND LITERATURE

Data on the longitudinal course of PTSD are generally anecdotal or retrospective in nature and, as such, are subject to the problem of inaccurate recall. For example, proposed sub-types of PTSD based on longitudinal course include acute, chronic, delayed, intermittent, residual, and reactivated (5-7,11-18). However, there are limited empirical data to support such a classification. Furthermore, because PTSD was not yet recognized as a formal DSM psychiatric disorder until recently, there has been little systematic research in this area prior to 1980.

In the relatively few empirical longitudinal studies of trauma that have been conducted, most have included only a limited number of time points. For example, longitudinal studies of prisoners of war (POWs) have generally assessed veterans only immediately following their imprisonment and a second time many years later. In a study of WWII POWs, Speed et al (19) reported rates of 50% DSM-III PTSD at one year after the war and 29% at 40 years. Similarly, Klusnik et al (20) found that 89 of 188 WWII POWs who met criteria for PTSD shortly after the war continued to suffer from mild to moderate PTSD 40 years later, while only 36 of 188 had completely recovered. Finally, among US-Vietnam Air Force POWs, Ursano et al (21) noted that 23.4% met criteria for a psychiatric diagnosis upon repatriation and 24.9% met criteria five years later. Formal diagnoses of PTSD were not assessed in that study.

Nevertheless, several prospective studies have provided evidence for a waxing and waning of symptoms rather than a steady increase or decrease. For example, Kinsie described an ongoing sensitivity in Southeast Asian refugees who had become less symptomatic over time but who tended to experience a return of their entire PTSD syndrome under conditions of stress (22). These studies suggest that incorporating assessments at multiple intervals will lead to a more comprehensive understanding of the natural course of trauma-related symptomatology.

A variety of pre-military, military and post-military risk factors have been shown to be associated with PTSD (for review see Bremner, 1995, reference 23). Pre-military risk factors include child abuse, threat to life, father in the military, age at the time of entry into the military, years of education, minority status, socioeconomic status, substance abuse and emotional illness. Military risk factors that have been reported are degree of combat exposure, participation in or witnessing of atrocities, dissociation at the time of trauma, substance abuse, injury in combat, captivity and threat to life. Post-military risk factors include social support, substance abuse, socioeconomic status, and immediacy of discharge from the military. To date, there is little information concerning the relationship of these risk factors to the actual course of trauma-related symptomatology.

It has become increasingly clear that PTSD is a common disorder and that it frequently persists over time. Symptom development seems to vary between individuals. In some cases

PTSD develops immediately after the trauma and in other cases the onset appears to be delayed. The course may wax and wane over time or it may remain relatively steady. Further, for some the disorder appears to resolve in a short period of time, but for others it runs a chronic course. Clearly, further empirical research is necessary in order to better characterize the natural course of this debilitating disorder.

RELEVANT LONGITUDINAL COURSE-OF-ILLNESS RESEARCH CONDUCTED AT THE WEST HAVEN VAMC / YALE DEPARTMENT OF PSYCHIATRY

Over the past five years, we have been conducted longitudinal course-of-illness studies on two separate populations of traumatized war veterans: those of the Vietnam War and those of Operation Desert Storm.

1. *The Longitudinal Course of Chronic Posttraumatic Stress Disorder in Vietnam Veterans: Development, Course of Illness, and Relationship to Alcohol and Substance Abuse.*

The purpose of this study was to examine the longitudinal course of trauma-related symptoms over the 20 or more years since the Vietnam War in combat veterans with PTSD, as well as the relationship between these symptoms and substance use and stressful life events. A structured psychiatric interview (Longitudinal History for Vietnam Veterans Interview) involving retrospective reconstruction of life events was used to examine the symptom history of 61 Vietnam combat veterans with the current diagnosis of PTSD. A lifeline was used to provide anchor points for the retrospective assessment of symptoms and substance abuse at biannual intervals starting two years before the patients' combat tour.

Onset of symptomatology typically occurred at the time of exposure to combat trauma in Vietnam and increased rapidly during the first few years after the war. Sixty-two percent of patients met DSM-IIIR criteria for PTSD within the first two years following their return home. Symptoms plateaued within several years after the war, following which the disorder became chronic and unremitting. Hyperarousal symptoms (e.g., feeling on guard, feeling easily startled) developed first, followed by avoidance and then reexperiencing symptomatology. The onset of alcohol and other substance abuse typically was associated with the onset of PTSD symptoms. The findings suggests one of the following possibilities: either substance use worsens symptoms of trauma or patients with PTSD ingest these substanses in order to medicate or lessen their symptoms. All patients interviewed continued to meet criteria for PTSD once they developed the disorder, and continued to manifest high levels of symptom severity with relatively little variation.

2. *Trauma-Related Symptoms in Veterans of Operation Desert Storm: A Preliminary Report.*

This study was designed to examine prospectively the development of trauma-related symptomatology in a community sample of Desert Storm veterans. Eighty-four National Guard reservists, from one medical and one military police unit, completed questionnaires about their exposure to combat, other specific stressors, and symptom severity one month and six months after returning from the Gulf.

Mississippi combat-related PTSD scores increased significantly from one month to six months. Symptoms of hyperarousal were more severe than symptoms of reexperiencing or avoidance at both timepoints. Level of combat exposure, as reflected by the Combat Exposure Scale (CES) and the Desert Storm Trauma Questionnaire, were significantly associated with the Mississippi PTSD score.

Nearly all subjects reported one or more PTSD-specific symptoms both one month (86.9%) and six months (90.5%) after returning from the Gulf. Consistent with accounts from other wars (15,16,24,25), symptoms of hyperarousal were clearly evident early on. Although combat exposure per se was relatively limited, most soldiers spent months responding to missile attacks and anticipating the possibility of a massive ground war. While stationed in the Middle East, they recalled living in a near constant state of alert expectation. After returning home, many soldiers described feeling aroused, vigilant and often irritable, with insomnia and an increased startle response. At the six-month follow-up, this heightened state of arousal was still present in many Gulf War veterans.

Although re-experiencing and avoidance symptom clusters were significantly less severe than hyperarousal at both timepoints, the individual item of intrusive memories did increase over time to become one of the most frequently endorsed symptoms at six months. None of the avoidance symptoms, on the other hand, were among the most frequently endorsed items at either timepoint. This finding is not inconsistent with the hypothesis that avoidance develops over time in response to persistent hyperarousal and re-experiencing (24). Individuals learn to avoid situations that are reminiscent of the trauma or that cause fear. Gradually they begin to lead restricted lives. As has been shown in studies of Vietnam combat veterans, degree of traumatic exposure was significantly related to PTSD symptomatology. In this sample of Desert Storm reservists, scores on both the CES and the Desert Storm Trauma Questionnaire were significantly associated with Mississippi PTSD Scale scores at both timepoints. This finding suggests that current PTSD symptomatology is related to degree of trauma experienced.

3. *Trauma-Related Symptoms in Veterans of Operation Desert Storm: A 2-Year Follow-Up.*(see Appendix)

This report was a two-year follow up of our ongoing study designed to prospectively examine the development of trauma-related symptomatology over time in a community sample of Desert Storm veterans. Sixty-two of the original 84 National Guard reservists, from one medical and one military police unit, completed questionnaires one month, six months and two years after returning from the Gulf.

Although symptoms were relatively mild, there was an overall increase in PTSD symptomatology over the course of two years. Mississippi combat-related PTSD scores increased significantly over time. All subjects who met diagnostic criteria for PTSD according to the Mississippi PTSD Scale at one and/or six months continued to meet criteria at two years. Clinically, it appears that for the group as a whole, most PTSD-specific symptoms had already developed by six months.

Little is known about the order of PTSD symptom development. The hyperarousal symptom cluster was significantly elevated compared to the reexperiencing and avoidance clusters at one month, six months and two years after the war. This suggests that hyperarousal is

not a response to reexperiencing or avoidance, and more likely develops at or near the time of the trauma. Whether persistent hyperarousal eventually leads to reexperiencing and avoidance is a subject for further research.

Three of the four most frequently endorsed symptoms (startle, sleep disturbance and irritability) were from the hyperarousal cluster. The central importance of disturbed arousal in patients with PTSD has been described in victims of industrial accidents (25), brush fires (5) and combat (16,24). In fact, McFarlane found that symptoms of attention and arousal were far better at discriminating between brush fire victims with and without PTSD than were symptoms of reexperiencing (5).

Level of combat exposure, as reflected by the Desert Storm Trauma Questionnaire, was significantly associated with the Mississippi PTSD score at two years but not at one and six months. This suggests that it may take time for the consequences of traumatic exposure to become apparent. Retrospective studies (1) have also found a positive relationship between symptom severity and degree of traumatic exposure ten to fifteen years after trauma. The current report suggests that this association may not be present initially, but instead can develop gradually over time. Clinically, then, the presence of high combat exposure may play an important role in predicting the eventual development of symptoms. The essential question for future research is whether subjects who at early screenings present with little or no PTSD symptomatology, but high levels of traumatic exposure, can benefit from timely therapeutic intervention.

4. *Consistency of Memory For Traumatic Events.*

The nature of traumatic memories is currently the subject of intense scientific investigation. While some researchers have described traumatic memory as fixed and indelible (27-30), others have found it to be malleable and subject to substantial alteration (31-38). The current study is a prospective investigation of memory for serious combat-related traumatic events in veterans of Operation Desert Storm.

Fifty-nine National Guard reservists from two separate units completed a 19-item questionnaire about their combat experiences one month and two years after their return from the Gulf War. Responses were compared for consistency between the two timepoints, and correlated with level of PTSD symptomatology.

There were many instances of inconsistent recall for events that were objective and highly traumatic in nature (e.g., bizarre disfigurement of bodies as a result of wounds, seeing other killed/wounded, being stationed close to enemy lines, mines/booby traps). Eighty-eight percent of subjects changed their responses on at least one of the 19 items, while 61% changed two or more items. There was a significant positive correlation between the Mississippi PTSD score at two years and the number of items on the trauma questionnaire changed from "no" at one month to "yes" at two years.

These findings do not support the position that traumatic memories are fixed or indelible. Further, the data suggest that as PTSD symptomatology increases, so does amplification of memory for traumatic events. In search of a cause for their worsening symptoms, traumatized individuals may attribute their pathology to a level of combat exposure that they unknowingly have exaggerated. Alternatively, it is possible that individuals with more severe intrusive

memories, nightmares and flashbacks gradually recall traumatic events as a result of these involuntary reexperiencing symptoms. This study raises serious questions about the accuracy of traumatic events as recounted by trauma victims, as well as about the well-established but retrospectively determined relationship between level of traumatic exposure and degree of PTSD symptomatology (1,39-41).

The findings of the present study have a number of potential implications for treatment. That memory for traumatic events frequently changed over time suggests that the search for historical "truth" may be fraught with complexity. Memories described by trauma survivors in the present often appear to be inconsistent with earlier memories for the same events. Thus, efforts by therapists to uncover the real "truth" may be misguided. It may make greater psychotherapeutic sense to work with the patient's current version of the past, since the "real" version may no longer exist. Further, traumatic memories that are malleable most likely are subject to change during psychotherapy. On the one hand, such change may be beneficial to the patient if the memories become less intrusive and less distressing. On the other hand, therapists must be exquisitely sensitive to the power of suggestion and to the potential for exaggeration of memory, or even for the formation of false memories, that may serve to increase personal suffering.

Because level of combat is considered the most important determinant of PTSD, many treatment programs have focused on the reconstruction and processing of traumatic combat experiences. However, this study suggests that the relationship between PTSD development and level of combat exposure is not as clear as previously believed. Factors other than combat, such as childhood trauma and pre-existing personality, may also play an important part in symptom development. Successful treatment of combat-related PTSD requires a clear understanding of the relative etiologic contributions of both combat and non-combat factors.

WORK PROPOSED

Subject Selection.

Of the 240 members from two reserve units studied in the above-cited ongoing research, 119 completed the first questionnaire at one month following their return from the Middle East. Questionnaires were completed again at six months and two years. Arrangements will be made, given available funding, to further interview as many of the 119 subjects as possible annually over the duration of the next three years. We have stayed in contact with many of these veterans and have current addresses for nearly all of them. Additional veterans of the Gulf War will be recruited from Connecticut-based reserve and military units. Over the last four years we have been in contact with several Army National Guard Units as well as Connecticut Naval and Marine reserve units. We believe that it will be possible to recruit a large number of study subjects from these units. These subjects will include reservists and active military who did not serve in the Persian Gulf as well as those who are veterans of the Gulf War. For example, within a four month period we recently recruited 65 Desert Storm veterans for acoustic startle and psychophysiologic sensory processing research. At a minimum we expect to recruit at least 100 new subjects. Further, we have provided consultation to many reservists and their families from these units and have evaluated over one hundred Desert Storm veterans in our Outpatient PTSD Clinic. A high percentage of veterans presenting to the Clinic for evaluation have been

suffering from significant trauma-related symptomatology.

Most subjects who have been evaluated to date were confronted with multiple stressors while in the Persian Gulf. Both of the units that we have studied to date were frequently exposed to incoming SCUD missile attacks. Some members of the military police company were stationed as guards at the entrance to their compound and were prevented from taking refuge in bunkers during missile attacks. At least one missile reportedly exploded within one half mile of the compound. Members of the military police unit were particularly concerned about missile attacks because they were stationed near a U.S. munitions storage site.

In addition to SCUD missile attacks, members of the medical unit were exposed to enemy small arms fire. During an alleged ambush, many members of the unit witnessed the deaths of a physician and a nurse. The nurse was dismembered when an explosion occurred next to her. Evacuation was not possible and the nurse exsanguinated. The medical unit was then moved farther into Iraq where members reported seeing burned and charred bodies, "melted" human beings and flattened corpses. Others reported walking over body parts in the road and seeing piles of rotting or burning corpses at the side of the road. Subsequent to this, members of the medical unit reportedly suffered an accident involving an explosive device . The individual closest to the blast lost his arm and seven other unit members were seriously wounded as well.

Study Design

Subjects will be recruited from the above-mentioned military and reserve units in Connecticut. All subjects will give written informed consent for their participation in this study. They will be paid seventy -five dollars for completing the questionnaire. Subjects who agree to participate will complete the study questionnaire at the five year post-Desert Storm time point and then, if available and willing, the six and seven year time points . Seventy-five dollars will be paid for each separate year that the questionnaire is filled out. All subjects will be offered the opportunity to receive a more thorough clinical evaluation if requested.

II. MEMORY FUNCTION AND HIPPOCAMPAL VOLUME

In addition to chronic symptoms of hyperarousal, traumatized individuals with PTSD suffer from alterations in memory. These alterations include intrusive recollections, amnesia, and possible deficits in short-term memory. Intrusive recollections often remain vivid for the lifetime of the individual, and can be reawakened or triggered by a variety of stimuli. Most individuals suffering from PTSD find these memories highly distressing, and in some cases tormenting. Conversely, amnesia for important aspects of a trauma is characteristic of the disorder and has been included in the avoidance symptom cluster in DSM-IV. Additionally, patients with PTSD often complain of poor attention and memory that is generalized and interferes with daily functioning.

For the past five years, at the West Haven VAMC, we have been studying neurochemical and neuroanatomical substrates of memory function in veterans with PTSD. To date our neurochemical studies have primarily involved catecholamines and glucocorticoids while neuroanatomical investigations have focused on limbic regions including the amygdala and hippocampus.

OBJECTIVES

1. To compare memory function in Desert Storm veterans who have PTSD to memory function in National Guard Reservists who did not serve in the Gulf War.

2. To measure and compare volume of the hippocampus and comparison brain structures in Desert Storm veterans who have PTSD and in National Guard Reservists who did not serve in the Gulf War.

3. To explore the relationship between hippocampal volume and memory function in Desert Storm veterans with PTSD and in National Guard Reservists who did not serve in the Gulf War.

4. An existing data base of memory test results and hippocampal volume measurements in Vietnam veterans with PTSD will allow for comparison with results from the current study. Funding is not requested, however, for memory or MRI studies in Vietnam veterans.

HYPOTHESES

1. Memory dysfunction will be present in Desert Storm veterans with PTSD, but not in National Guard Reservists who did not serve in the Gulf.

2. Hippocampal volume will be smaller in the Desert Storm veteran group with PTSD compared to hippocampal volume in the group of National Guard Reservists.

3. Memory impairments in the Desert Storm veterans with PTSD will be significantly associated with hippocampal volume (i.e., the more memory impairment the smaller the hippocampal volume, as we have previously demonstrated in Vietnam Veterans).

BACKGROUND LITERATURE

Studies of traumatized war veterans suggest an association between the extreme stress of combat and alterations in memory function. Since the time of the First World War, military psychiatrists have treated soldiers who wander off the battlefield, having forgotten their names or other important personal information (44-49). In a study conducted during World War II, immediately after a major military campaign, about 5% of soldiers who had been combatants in that campaign had no memory for events that had just occurred (50). Further, follow-up studies of WWII veterans have found that many suffer from episodes of " blackouts " or loss of memory (16).

Disturbances of memory and concentration also have been frequent complaints in WWII and Korean prisoners of war. In one group of 321 WWII Danish concentration camp survivors who had high levels of psychiatric symptomatology and who were seeking compensation for disability, 87% had complaints of memory impairment 10 or more years after release from internment. Severe intellectual impairment was also found through formal psychological testing in 61% of cases (51). Thirty years after the war, Korean POW's were found to have impaired short-term verbal memory as measured by the Logical Memory component of the Wechsler Memory Scale in comparison to Korean veterans without a history of containment, although these findings may have been due to a decrease in body mass caused by starvation (52). Other studies have shown enhanced recall on explicit memory tasks for trauma-related words relative to neutral words in patients with PTSD compared to healthy controls (53,54).

The hippocampus and adjacent perirhinal, parahippocampal and entorhinal cortex play an important role in short-term memory (55). Damage to these regions in both animals and humans causes profound impairment in memory. Studies in humans have shown that reductions in hippocampal volume secondary to either neurosurgery (56) or the pathophysiological effects of epilepsy (57) are associated with deficits in short-term memory as measured with the Wechsler Memory Scale.

It has also been shown that stress has effects on the hippocampus that can lead to both changes in its cytoarchitecture as well as deficits in short-term memory. Twenty-one days of restraint stress has been shown to be associated with deficits in spatial memory as measured by the radial arm maze (58). Release of glucocorticoids follows exposure to stress, and the hippocampus is a major target organ for glucocorticoids in the brain (59). In addition, the hippocampus appears to play an important role in the pituitary-adrenocortical response to stress (60), including its inhibitory effect on CRF release from the hypothalamus (61). Studies of monkeys who died spontaneously following exposure to severe stress due to improper caging and overcrowding were found on autopsy to have multiple gastric ulcers, consistent with exposure to chronic stress, and hyperplastic adrenal cortices, consistent with sustained glucocorticoid release (62), as well as damage to the CA2 and CA3 subfields of the hippocampus. Follow up studies suggested that hippocampal damage was associated with direct exposure of glucocorticoids to the hippocampus (63). Studies in a variety of animal species suggest that direct glucocorticoid exposure results in a loss of neurons and a decrease in dendritic branching in the hippocampus (64,65) with associated deficits in memory function. The mechanism of glucocorticoid toxicity is probably through increasing the vulnerability of

neurons to the toxicity of excitatory amino acids (66-68). Studies utilizing computed tomography in human subjects exposed to high levels of glucocorticoids secondary to glucocorticoid steroid therapy (69,70) or affective disorders (also felt to be related to stress) (71) have shown changes in brain structure including ventricular enlargement and widening of the cortical sulci. Magnetic resonance imaging studies (MRI) in patients with affective disorders have shown a decrease in right hippocampal volume (72) and temporal lobe volume (73) in bipolar disorder, and abnormalities of the hippocampus including alterations in T1 relaxation time (74) but no change in hippocampal volume (75) in major depression. One MRI study found a relationship between deficits in short-term memory and decreased hippocampal volume, as well as increased plasma cortisol levels and decreased hippocampal volume, in patients with Cushing's Disease (76). Stress in both healthy human subjects (77) as well as soldiers undergoing random artillery bombardment (78) results in an increase in urinary cortisol, suggesting the possibility that exposure to the extreme stress of combat may be associated with damage to the hippocampus.

MEMORY STUDIES IN VETERANS WITH PTSD CONDUCTED THROUGH THE WEST HAVEN VAMC/YALE DEPARTMENT OF PSYCHIATRY

1. *Abnormal Noradrenergic Function in Posttraumatic Stress Disorder.*

To evaluate possible abnormal noradrenergic neuronal regulation in patients with PTSD, the behavioral, biochemical and cardiovascular effects of yohimbine hydrochloride was determined in 18 healthy male subjects and 20 male Vietnam combat veterans with PTSD. Yohimbine is an alpha-2 adrenergic receptor antagonist that activates noradrenergic neurons by blocking the alpha-2 adrenergic autoreceptor, thereby increasing presynaptic noradrenergic release. Although yohimbine acts on multiple neurotransmitter systems, at the dose employed, its primary effect is on the noradrenergic system.

In this double-blind, placebo-controlled study, yohimbine produced panic attacks in 70% and flashbacks in 40% of patients with PTSD. There were no yohimbine-induced panic attacks or flashbacks in the healthy non-combat control group. A more than twofold greater elevation of plasma MHPG (3-methoxy4-hydroxyphenylglycol) in the patient group following yohimbine administration suggested abnormal presynaptic noradrenergic reactivity in patients with PTSD.

In addition to flashbacks, the majority of patients reported vivid intrusive memories of traumatic combat experiences. As described by one patient, "I remember helping D.S. His arm was just about blown off, and I helped him hold onto it. I can see it all so clearly. I have forgotten a lot of it. I can remember D.S.'s face now. Haven't been able to see it clearly for 20 years. Now it's clear. I remember what town he was from. Before, I only remembered the state." The retrieval of traumatic memories in response to yohimbine infusion, is consistent with animal studies demonstrating enhanced retrieval of aversive memories through adrenergic and noradrenergic stimulation. Creating a biological context (i.e. yohimbine-induced increase in catecholamine activity) that resembles the biological state at the time of encoding (fear-induced increase in catecholamine activity) may have served to facilitate retrieval of frightening traumatic memories.

2. *Noradrenergic Contributions To Acquisition of Memory in PTSD.*

A large body of evidence suggests that arousing, fearful, or emotionally exciting events are remembered better and for a longer period of time than emotionally neutral events. Such arousing events reportedly produce what Brown and Kulik (79) have termed flashbulb memories that resemble a photographic print.

In numerous pre-clinical studies, "stress-responsive neuromodulators" such as epinephrine and norepinephrine have been shown to enhance consolidation of memory for emotionally arousing experiences. Similarly, in a recent clinical study of healthy subjects, Cahill et al (80) found that propranolol, a beta-adrenergic receptor antagonist, impaired long-term memory for an emotionally arousing story but not a neutral one. This important finding supports the hypotheses that catecholamines (i.e. beta-adrenergic systems) are involved in the enhancement of memory for emotional experiences in humans.

The purpose of the current investigation is to extend the work of Cahill et al (80) by studying the effects of augmenting rather than blocking catecholamines during acquisition of memory for arousing the neutral experiences in healthy subjects and combat veterans with PTSD. The methodology of Cahill et al is being used with the exception that yohimbine hydrochloride (an alpha-2 receptor antagonist that increases norepinephrine) rather than propranolol (a beta-receptor antagonist that blocks norepinephrine) is being compared to placebo.

Forty male combat veterans with PTSD and forty matched healthy subjects are being recruited to participate in the study. All subjects receive either placebo or yohimbine on day one. One hour following infusion they view a series of eleven slides that tell a story. Some of the slides depict neutral information while others depict arousing information. Plasma epinephrine and norepinephrine determinations are made at regular intervals during the procedure. One week later subjects receive a second infusion of IV saline. One hour after the second infusion they are asked to participate in a surprise memory test and asked to recall as much as they can concerning the slide show they viewed the previous week. There are four subject groups with twenty subjects per group: 1) Healthy placebo-placebo group 2) Healthy yohimbine-placebo group 3) PTSD placebo-placebo group 4) PTSD yohimbine-placebo group. The order of drug administration is randomized.

In this recently begun study, it is predicted that yohimbine will have the opposite effect of propranolol and will facilitate memory by increasing catecholamine activity at the time of memory encoding in both healthy subjects and in patients. Because the noradrenergic system, in many combat veterans with PTSD, hyper-responds to both stress-related stimuli and to yohimbine, it is further predicted that patients will remember the slides in greater detail than healthy subjects especially during the arousing phase after yohimbine infusion.

A more complete understanding of the role of catecholamines in information processing among both healthy subjects and patients with PTSD hopefully will lead to clinically useful interventions aimed at preventing and/or alleviating intrusive traumatic memories.

3. *Deficits in Short-term Memory in PTSD.*

The purpose of this study was to compare the memory function of patients with

posttraumatic stress disorder to that of matched comparison subjects. Vietnam veterans with combat-related PTSD (N=26) were compared to physically healthy comparison subjects (N=15) matched for age, race, sex, years of education, handedness, socioeconomic status, and alcohol abuse. Memory and intelligence were assessed with a battery of neuropsychological tests including the Russell revision of the Wechsler Memory Scale, the Selective Reminding Test, and subtests of the Wechsler Adult intelligence Scale-Revised (WAIS-R). The PTSD patients scored significantly lower than the comparison subjects on the Wechsler Memory Scale logical memory measures for immediate recall (mean=11.6, SD=3.3 versus mean =29.9, SD=6.6) and delayed recall measures for the verbal component of the Selective reminding Test and on the recall, long-term storage, long-term retrieval, and continuous long-term retieval measures for the visual component of the Selective Reminding Test. There was no significant difference between the PTSD patients and comparison subjects in prorated full-scale IQ as measured by the WAIS-R. Data from this study suggest that memory deficits in this population are relatively broad based and reflect problems at several levels of information processing, including acquisition, retention and/or retrieval.

The PTSD patients in this study displayed memory deficits comparable to those of other clinical populations with clearly documented temporal lobe damage and hippocampal involvement. The finding of 67% retention on the logical memory component of the Wechsler Memory Scale is comparable to the 53% retention in patients with left temporal lobe epilepsy and 74% in patients with right temporal lobe epilepsy that have previously been reported (56). In addition, the performance of our PTSD patients on the verbal component of the selective reminding test is similar to that of patients who have had temporal lobe and hippocampal resections for intractable epilepsy.

4. *MRI-Based Measurement of Hippocampal Volume in Patients with Combat-related Posttraumatic Stress Disorder.* (see Appendix)

Studies in non-human primates suggest that high levels of cortisol associated with stress have neurotoxic effects on the hippocampus. Further, as noted above, deficits in short-term memory have been found in combat veterans with posttraumatic stress disorder (PTSD). The purpose of this study was to compare hippocampal volume in patients with PTSD to comparison subjects and to explore the relationship between hippocampal volume and measures of short-term verbal memory. Magnetic resonance imaging (MRI) was used to measure volume of the hippocampus in Vietnam combat veterans with PTSD (N=26) and comparison subjects (N=22) who were selected to be similar to the patients in age, sex, race, years of education, socioeconomic status, body size, and years of alcohol abuse. PTSD patients had an 8% decrease in right hippocampal volume relative to the healthy subjects ($p<0.05$), with no difference in comparison regions (caudate, amygdala and temporal lobe). Deficits in short-term verbal memory as measured with the Wechsler Memory Scale were associated with decreased right hippocampal volume in the PTSD patients only ($r=0.64$; $p<0.01$). There was no significant correlation between age, years of education, years of alcohol abuse, height, or weight and left or right hippocampal volume in either the patients or the comparison subjects. These findings are consistent with a decrease in right hippocampal volume in PTSD which is associated with functional deficits in verbal memory.

There are several potential explanations for a smaller right hippocampal volume in subjects with PTSD. A small right hippocampus from the time of birth may represent a premorbid risk factor for the development of PTSD. Alternatively, extreme stress results in increased release of glucocorticoids, excitatory amino acids, serotonin, and other neurotransmitters and neuropeptides that could be associated with damage to the hippocampus

SIGNIFICANCE

PTSD is often a devastating disorder that can last for the lifetime of the individual, affecting nearly every area of psychosocial functioning. Involuntary intrusive memories can be particularly painful as the individual is forced to relive events again and again. Equally distressing are amnesia for important aspects of the trauma and deficits in short term memory. In order to appropriately treat these symptoms of altered memory, it is critical to fully deliniate the extent of deficit as well as the underlying pathophysiology. For example, if these alterations in memory are in some way related to altered hippocampal structure and function then traditional insight-oriented psychotherapy might not be the treatment of choice. Further, by studying Desert Storm veterans who have been more recently traumatized than the Vietnam veteran population, it will be possible to determine whether these abnormalities are manifest in a variety of combat populations and whether such abnormalities can be detected at earlier stages than in the previously-studied Vietnam veteran population.

WORK PROPOSED

Subject Selection.

There will be two study groups each consisting of 30 subjects each:

(1) 30 Desert Storm veterans who meet criteria for PTSD

(2) 30 National Guard Reservists who did not serve in the Gulf War and who do not meet criteria for any axis 1 DSM-IV disorder.

All subjects will be required to give informed consent for participation in the study. Exclusion criteria for all subjects include a history of psychotropic medication use within the past three weeks, meningitis, traumatic brain injury, neurological disorder, HIV positive status, current alcohol or substance abuse or lifetime schizophrenia based on the SCID, or shrapnel or other foreign bodies which would preclude MRI scanning. Further, subjects with a history of loss of consciousness for greater than 10 minutes will not be eligible.

Desert Storm veterans will be evaluated with the Structured Clinical Interview for DSM-IV (SCID) for the diagnosis of PTSD and for all other co-morbid Axis I psychiatric diagnoses. To be included in the Desert Storm PTSD group, a subject must meet DSM-IV criteria for PTSD based on the SCID, have a score of greater than 107 (consistent with the diagnosis of PTSD) on the Mississippi Scale for Combat-related PTSD (42), and be determined by consensus diagnosis of three psychiatrists to meet criteria for PTSD.

National Guard Reservists who did not serve in the Gulf War must be free of all current and lifetime DSM-IV Axis 1 disorders as determined by the SCID for normal subjects. Subjects

from the comparison group also will be carefully selected in order to be similar to the PTSD group in age, sex, race, handedness, height, weight, years of education, socioeconomic status and years of alcohol abuse.

Image Processing and Analysis.

Images will be transferred via magnetic tape to a SunSparc 10 work station for morphometric assessments. Images will be analyzed using the ANALYZE program (Mayo Clinic, Rochester, Minn.) running on the Sun Spark 10. Data is then entered into an Excel spreadsheet together with matrix and field of view information for the calculation of area.

Volumetric Measurements.

Volumetric measurements of the hippocampus will be performed independently by two investigators who will be blinded to subject diagnosis. The body of the hippocampus will be measured because it is the easiest hippocampal segment to define (85). First, corrections for head rotation will be achieved using anatomical landmarks including the internal auditory canal and the seventh and eighth cranial nerve. Then two mid-hippocampal points separated by 15 mm, and a third mid-hippocampal point in the opposite hippocampus, will be selected to define a plane parallel to the long axes of both hippocampi. A series of oblique images will be constructed perpendicular to this plane to create images orthogonal to the long axis of the hippocampus. The purpose of reslicing the MRI to create images perpendicular to the long axis of the hippocampus is for reproducibility of measurement. The outline of the hippocampus will then be traced using a mouse-driven cursor on five coronal sections (15 mm) between the superior colliculus and the bifurcation of the basilar artery, with the first slice anterior to the superior colliculus (85). The first slice in which the hippocampus will be traced is the slice anterior to the superior colliculus. Cross sectional areas will be measured in each of these five slices, summed, and multiplied by the slice thickness (3 mm) to obtain the volume of the hippocampal body segment. The mean of the two raters will be obtained for the final value of hippocampal volume.

Volumetric assessments will also be made of three other regions for purposes of comparison: the temporal lobe, amygdala and caudate. These regions have been selected because they are gray matter regions which may be used to measure the specificity of possible decreases in hippocampal volume, and because there are no theoretical reasons to suspect decreases in volume of these regions in PTSD. Volume of the temporal lobe will be obtained by measuring the cross-sectional area of all coronal slices of the temporal lobe anterior to the superior colliculus, summing, multiplying by the slice thickness, and subtracting the volume of the hippocampus (85) .

The use of methods such as brain region to whole brain ratios in order to control for

differences in brain size amongst subjects is accompanied by problems which include an increase in variability that may interfere with the detection of true differences between subject populations. We have elected to address the issue of controlling for brain size by matching patients with a comparison group of similar height and weight, since brain size is related to total body size.

Inter-rater reliability will be determined using the intraclass correlation coefficient with one-way ANOVA (with values of the coefficient approaching one representing a high level of agreement between two raters) for volumetric assessments of hippocampus with two raters and resliced MRI scans as well as for temporal lobe in a subset of 15 subjects with two raters and non-resliced MRI scans. We have previously demonstrated excellent inter-rater reliability for hipocampus, temporal lobe, caudate and amygdala.

RESOURCES

The West Haven PTSD program serves as the Clinical Neuroscience Division of the National Center for Posttraumatic Stress Disorders and consists of a fifteen bed Specialized Inpatient PTSD unit, a fifteen bed PTSD Evaluation and Brief Treatment unit, an eighteen bed PTSD Residential Rehabilitation unit, and an Outpatient PTSD clinic with over 450 patients currently enrolled. Further, as described in the Patient Selection section of the grant, we have a clinical and research relationship with multiple active Military and Reserve units in Connecticut. A substantial number of these unit members served in the Gulf War. Reservists who did not serve in the Gulf War are also present in these units and available for recruitment. To date, we have been very successful in recruiting research subjects who served in the Vietnam War and/or in Operation Desert Storm. The National Center for PTSD does not fund individual research projects, but instead funds core facilities. As a result, the imaging equipment needed to complete the present study is already on sight and fully operational. However, there currently is no specific funding to continue our descriptive follow along study of Desert Storm veterans.

There is a SunSPARC Workstation, a MicroVAX Workstation, and several Mac and PC computers in the Yale/VA PET Center. There is a SunSPARC10 Workstation, a VAX Workstation, and several MAC and PC computers connected by network in the Psychiatry Research Area at the West Haven VAMC. There are over 10 SunSPARC Workstations and four VAX Workstations connected by network in the Image Processing and Analysis Area at Yale under the direction of Dr. Staib, which are connected by computer network to the Yale/VA PET Center at the West Haven VAMC.

The MRI Center of the Yale University School of Medicine houses three whole body GE Signa imaging systems (1.5T, 100 cm bore) in approximately 20,000 sq. ft. of space. Two of the scanners are heavily committed to clinical studies, and one is dedicated to full-time research. The research device has unique options, including spectroscopy, capability for ultra-fast imaging, and shielded gradient coils to minimize eddy currents. The hardware and software of all the devices have been upgraded with improved transcriber electronics, better digital filters, and new software pulse sequences that reduce reconstruction time. A Sun graphics Workstation is available at the MRI center for image reformatting and analysis.

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