



STARTLE RESPONSE IN INDIVIDUALS WITH PTSD

C. A. Morgan III, M.D., M.A.



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Post traumatic Stress Disorder (PTSD), marked by symptoms of reexperiencing, avoidance, and arousal, was officially delineated in 1980 as a clinical diagnosis within the category of anxiety disorders. Although initial delineation and characterization of PTSD represents a major advance, the diagnostic criteria continue to emphasize factors mainly dependent on patient self-reporting. The DSM-III-R includes physiologic reactivity and exaggerated startle as diagnostic

features of PTSD. The presence of psychophysiological alterations accompanying a mental disorder has provided the opportunity to obtain data that is more objective and more readily quantifiable than self-report data. While this article will focus primarily on investigations of the startle response, a few words are in order about psychophysiological investigations.

Psychophysiology studies have attempted to assess the symptoms of physiologic reactivity in individuals with PTSD by measuring the heart rate (HR), electrodermal, and blood pressure responses of veterans with PTSD and control subjects when said subjects are exposed to recorded sights and sounds of combat in the laboratory. In most of these studies, the veterans with PTSD have shown greater autonomic arousal when exposed to the combat stimuli than the comparison subjects. The ability to discriminate PTSD from control subjects using these physiologic measures has been thought impressive and has ranged from 80%-95% (1-3). While these studies have contained design flaws (such as group discrepancies in age, educational level, and combat exposure; comparisons of medicated and unmedicated subjects; differences in baseline physiologic arousal), taken together, they have been perceived by biological investigators as providing convincing evidence of physiologic hyperreactivity to combat-related stimuli in

veteran subjects with PTSD. Yet some investigators felt that the presentation of identical stimuli to all subjects did not permit an accurate assessment of what was uniquely stressful about a particular individual traumatic experience. It was thought that without the possibility of eliciting an individual's unique response to a stressful event, the sensitivity and specificity of psychophysiological testing could not improve.

As a result, several researchers have used script-driven mental imagery as a means of provoking a more personalized physiologic response in the laboratory. The scripts are recorded narratives taken from a detailed description of the most traumatic event experienced by the participant, then played back to the participant in the laboratory. Each participant is asked to listen to the recording and to imagine the events portrayed. While the participant does this, heart rate, skin conductance and electromyogram activity of the left frontalis are recorded. This technique has successfully demonstrated significantly larger physiological responses during personal

The idea of an objective test for PTSD remains extraordinarily appealing to many clinicians and forensic specialists.

combat imagery compared with mentally healthy Vietnam veterans (4), and Vietnam veterans with non-PTSD anxiety disorders (5). Discriminant analyses of the physiologic measures indicated that skin conductance successfully classified 73%, EMG 67%, and HR 64% of the PTSD subjects (4). The convergent elevation of these measures in the PTSD group is noteworthy considering that concordance between physiologic measures in research of this nature has generally been found to be low.

However promising, the above described psychophysiology studies examined peripheral autonomic reactivity and behavioral changes in order to make inferences about brain function in PTSD. A number of investigators felt

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FROM THE EDITOR

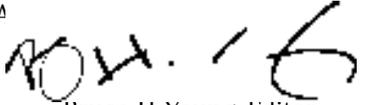
In a recent overview of the biological themes in PTSD, Pitman (1) noted that when PTSD first appeared as a diagnosis, many people, lay and professional alike, thought it was a device to appease forsaken and angry Vietnam veterans. In the early 1980's, clinicians who believed in the validity of a post-traumatic stress syndrome, founded their belief primarily on the collective self-report of patients' psychological symptoms. The validity of a post-traumatic stress disorder has since become irrefutable as several studies have indicated that neurobiological changes (e.g., changes in the central nervous system) occur in individuals who meet the diagnostic criteria for PTSD. These findings are referenced in this issue of the Quarterly. This edition also presents an update on pharmacotherapy as neurobiological research is correspondingly broadening the possibilities for pharmacological prevention and treatment. An article providing an overview of the physiologic reactivity associated with PTSD, a commentary on assessing and treating somatic symptoms related to PTSD, and the third installment in a series addressing specialized care for chronic complex PTSD round out this issue. In addition to informing clinicians, we hope the articles serve to help clinicians better educate their patients and clients about the impact of having experienced or witnessed life threatening events.

Julian Ford, Ph.D., Deputy to the Executive Director for Clinical Networking and Education has accepted an offer to become the Director of Behavioral Healthcare Outcomes Research and Associate Professor in the University of Connecticut Medical School Department of Psychiatry. Dr. Ford will be developing clinical research initiatives in mental health

primary care and mental health services research, with a special focus on trauma and PTSD. A prodigious worker, Dr. Ford has worked on several important projects since joining the National Center in 1994, including clinical evaluation projects providing early assessment and treatment for Persian Gulf veterans, assessment and treatment of complex PTSD with veterans of all eras, and education projects for VA clinicians in disaster mental health and mental health primary care. In addition, Dr. Ford has been a regular contributor to the Clinical Quarterly, authoring the Practitioner Network column. We wish him continued success and look forward to new collaborative ventures.

In closing, we apologize for the delay in getting this issue to you. We have addressed the problems resulting in the delay and, as is typical of setbacks, used the opportunity to generate new possibilities including making plans for the Clinical Quarterly to be available on the Web. As always, your comments, suggestions, or questions are appreciated and serve to guide future issues. I can be reached via the following:

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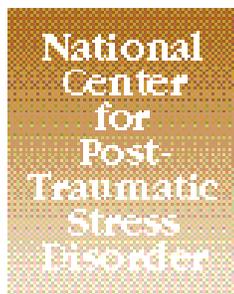
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that a clearer understanding of central nervous system reactivity and functioning might be afforded by using a more direct probe of brain function that is sensitive to noradrenergic neuronal reactivity, fear and alarm states. It was not without reason that many believed that the acoustic startle reflex could fulfill such a need.

Historical and contemporary records provide evidence that an important symptom seen in combat veterans diagnosed with Shell Shock, Combat Fatigue or Post Traumatic Stress Disorder has been, and continues to be, an exaggerated startle reflex (6-9). Clinical observations of exaggerated startle in distressed combat veterans were so common by mid-century, some psychiatric authorities argued that increased startle was cardinal symptom of combat fatigue (10). While not considered the cardinal symptom of PTSD today, exaggerated startle remains tightly linked to trauma related psychological illness. In fact, according to DSM-IV, PTSD is now the only anxiety disorder in which hyperstartle is listed as a core symptom.

Investigators have had various motivations for studying the acoustic startle reflex in humans and especially in those suffering from PTSD. Some have been interested in finding out whether or not exaggerated startle is a marker (or sign) indicating, or helping to provide a reliable diagnosis of PTSD. The idea of an objective test for PTSD remains extraordinarily

There is a great deal of evidence that startle varies according to stimulus intensity, frequency, and duration.

appealing to many clinicians and forensic specialists. It is felt that such a test would enhance discrimination between individuals who do and who do not have PTSD.

For other investigators, startle has been less interesting as test for PTSD, and more interesting as a probe in examining central nervous system reactivity in individuals with PTSD. Because so much is known about the neuroanatomical pathways of, and neurotransmitters involved in the startle reflex, several studies have used startle to gain an understanding of neurohormonal functioning in PTSD. Finally, several investigators have used startle as an objective measure of the emotional states of anxiety and fear and have used startle as a tool to elucidate the neural mechanisms involved in the learning and extinction of fear and anxiety.

The startle reflex is one that is shared by very nearly all animals. In basic terms, it is the rapid motor twitch or jump that occurs when an animal or human is exposed to a sudden stimulus (such as a touch, a noise, or a visual image or light). The term acoustic startle reflex refers to the startle response to loud or sudden sounds. In humans, the most consistent and easy way to measure the acoustic startle reflex is to record the speed and intensity of the eye-blink that occurs after someone hears the noise. Technically this is done by recording the electromyographic (EMG) activity of the orbicularis oculi muscle. This method provides information about the intensity (amplitude and the speed (latency) of the eye-blink in response to the sound stimulus.

Because the components of the basic startle response are relatively small in number, the time it takes for a sound stimulus to enter the ear and produce a corresponding eye-blink is rather short (21-75 milliseconds). This means that the optimal time to measure the blink component of the startle response is after 21 milliseconds and before 75 milliseconds. Startle responses recorded before 21 milliseconds are considered to be unrelated to the sound stimulus, while those occurring after 75 are considered as potentially random or consciously produced. Thus, it is possible to minimize the likelihood of random and voluntary blink responses. While many investigators have employed the methodology described above (assessment of EMG activity of the orbicularis oculi muscle in response to a sudden burst of white noise) they have not used identical sound stimuli. Some investigations have used sound stimuli of many different intensities and of very short duration (30-40 milliseconds), whereas others have used a single sound stimulus of a much longer duration (500 milliseconds). These distinctions are important to notice when reading the literature about startle for two main reasons: First, it makes it difficult to directly compare studies conducted in one laboratory to those from another; second, there is a great deal of evidence that startle varies according to stimulus intensity, frequency and duration. That the startle response may be directly enhanced by the type and characteristics of the acoustic stimulus is important and relevant to the issue of whether or not exaggerated startle can be used as a marker for PTSD.

One final comment is in order regarding methodology: Some authors have used different definitions than those described here when referring to the startle response (such as the heart rate response to a startling sound) while others have used a tactile stimulus (a puff of air). These distinctions are not minor in that the neuroanatomical pathways invoked in the responses are not entirely overlapping

Theoretically, there are a number of ways that exaggerated startle and PTSD might be associated. Investigators interested in whether or not hyperstartle might be a marker in individuals with PTSD know that in healthy subjects, startle shows large variability across individuals, but high consistency within subjects over time. Therefore, it is conceivable, that people who eventually develop PTSD might be those who had high levels of startle prior to the development the disorder. Rather than being caused by exposure to trauma (and/or the development of PTSD) exaggerated startle might be a reflection of a stable trait. At this present time, no studies have measured the startle response in individuals prior to, and after exposure to intense trauma to test out this possibility.

A second possibility is that exaggerated startle in PTSD reflects a persistent sensitization (or heightened responding) of the startle reflex caused by exposure to trauma induced psychological stress. While there is some evidence from animal studies that do support the idea that intense stress may increase the overall startle response, the increased responding tends to be fairly brief in duration and is not thought to be directly related to the reports of chronic and exaggerated startle in humans with PTSD. Nevertheless, there are a number of startle studies in humans with PTSD documenting heightened startle which

have invoked the stress sensitization hypothesis (or increased unconditioned responding) to explain the finding (11-15). Importantly, there are a number of studies which have not found exaggerated, but normal (16-18) or reduced startle in individuals with PTSD (19). Some authors reviewing the startle literature have wondered whether or not exaggerated startle in individuals with PTSD might be reflective of a classically conditioned response. It is reasoned that the sudden bursts of noise might be reminiscent of the sounds of the battlefield or of gun fire and thereby produce an exaggerated (fear-conditioned) startle response. This idea however, has lost considerable explanatory power given the evidence for exaggerated startle in victims of non-combat, non-firearm related trauma who suffer from PTSD.

An alternative way of viewing exaggerated startle in PTSD is to consider the increased startle as an acute state of conditioned fear or anxiety rather than as a conditioned response unique to a specific sound or object. It is possible that exaggerated startle is seen in individuals with PTSD when they are in a state of heightened emotional arousal produced by stress or reminders of their traumatic experiences. Support for this idea comes from several sources.

First, it is well known that startle can be elevated under conditions that are emotionally salient (20). Second, we have examined startle in Vietnam veterans with PTSD in three studies (17, 21-22). In one study, startle was investigated during periods of shock anticipation (threat condition) and during periods when no shocks were administered (safe condition) (21). In the second investigation, subjects were administered placebo and yohimbine on alternative days (22). Startle was elevated in the PTSD patients throughout both experiments. Because startle was elevated in the safe condition of the shock experiment and in the placebo condition of the pharmacological challenge study, we argued that the stress of the experimental context was responsible for the elevated startle. Additional support for this idea came from our third investigation in Vietnam veteran subjects who, when tested under non-stressful conditions did not show exaggerated startle compared to healthy and combat control subjects (17). What these data suggest is that the laboratory conditions affect the emotional state of the subjects participating in startle testing and that anxious or fearful states produce an increase in the startle response.

Support for the idea that exaggerated startle in PTSD is associated with a particular emotional state, rather than a trait (or marker), can also be found in studies which have used the startle response as a measure of central nervous system neuronal reactivity. Because the startle reflex is sensitive to fear/alarm responses, and modulated by CNN noradrenergic neurotransmission, it is an ideal means of assessing these elements in PTSD. In a pharmacological challenge study involving the administration of yohimbine and placebo on alternative days, Vietnam veterans with PTSD demonstrated significantly greater startle responses to yohimbine compared to placebo and compared to combat controls (22). Startle frequency and startle threshold were respectively increased and reduced by yohimbine. Taken together, the data from this

investigation provided evidence that the exaggerated startle seen in individuals with PTSD is, in part, a manifestation of heightened noradrenergic responding.

Finally, startle has been used as a tool to study the learning and extinction of conditioned fear in healthy subjects and in individuals with PTSD. Using a laboratory procedure that involves exposing subjects to stressful electric shocks while they view a series of lights, we have recently completed a 2-day study of conditioned fear in Gulf War Veterans with PTSD (23). On the first day startle was measured before, during and after subjects were exposed to light/shock training trials. During the training trials, only one of the two lights was paired with electric shocks to the subject wrists. This procedure permitted an assessment of whether, and to what degree, startle would increase in the presence of the light that was paired with the electric shocks, an indication that the subjects had learned that the bluelight was linked with an unpleasant shock. At the conclusion of the first day, we disconnected the shock electrodes and measured startle in the presence of each light. We repeated the same procedures on the second test day one week later. Several things happened: First, on the initial day of testing, the PTSD patients showed exaggerated startle to the threat light and the safe light, but not the dark; Second, overall startle responses were noted to be increased prior when the subjects came into the lab on the second day. These data suggest that Gulf War veterans with PTSD learn what to be fearful of, but cannot make use of their intellectual knowledge about the safe light to inhibit their fear. Second, they exhibit increased fear to the context, or room where the testing occurred.

These findings are important because animal studies suggest that different brain systems mediate fear to explicit cues—such as a light indicating shock—and contextual fear—fear of place where the shocks were experienced (24-27). Lesions of a areas of the brain called the hippocampus (25-26) or the BNST (24) block context conditioning, but not explicit cue conditioning, whereas lesions of the amygdala block both. In addition, inactivation of the BNST, but not the central nucleus of the amygdala, blocks the potentiation of startle by another type of contextual stimulus (such as sustained bright lights (28)). These data suggest that the hippocampus and the BNST may be especially important in contextual fear or anxiety, compared to explicit cue fear which is dependent upon the amygdala. The results of the above described study point to a dysfunction of the hippocampus and/or the BNST.

So, what have we actually learned about the startle response in PTSD? Within recent years, a growing number of studies have reported on the startle response in individuals with PTSD. The majority of these studies have been conducted on male combat veterans, however, there are a few studies involving children and civilian women with PTSD. The startle studies that have been conducted under relatively non-stressful conditions have provided contradictory evidence as to whether startle is increased, decreased, or normal in persons with PTSD. By contrast, the studies that have included threat of shock or an I.V. have consistently demonstrated exaggerated startle. Also, it is clear that a person's age, the length of time since trauma, and testing conditions all affect the startle response.

Startle Response In Individuals with PTSD

Startle provides a means of studying fear and anxiety states, as well as the learning of fear and anxiety states in individuals with and without PTSD. Since the neural pathways of the startle reflex are well understood, the findings of such studies of the human startle response in individuals with PTSD have provided information that may be of benefit to both patients and clinicians. First, the evidence supports the idea that exaggerated startle can be a long-lasting symptom in some individuals with PTSD. Clinicians might educate patients about this possibility so that both parties in the treatment setting might have realistic appraisal of the severity of the condition. Second, it may be helpful for clinicians to remember that increased startle may occur even in the absence of reminders of the traumatic events. For example, studies show quite clearly that startle may be increased by background noise. This may provide a clue as to why some patients find that their startle is increased in a mall, or a grocery store, even when they are unable to find anything that is "setting" them off. Related to this, patients will often complain that in addition to increased startle they feel rattled, agitated and restless. Third, threatening situations or fearful experiences have a powerful augmenting influence on the startle response. The research has clearly shown that the very best way to detect exaggerated startle is to test for it under stressful test conditions. Within the clinical realm, this stress may take the form of anxiously anticipating an unwanted event such as a bill, compensation & pension examination, or after discussing PTSD-related traumatic events. Clinicians and patients can explore together ways of reducing exposure (when possible) to environments that are likely to produce increases in startle. While there are no well controlled studies examining the effects of medication on the startle response in individuals with PTSD, the animal literature suggests that medications such as buspirone or clonidine may provide some relief.

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NEUROIMAGING STUDIES IN PTSD

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J. Douglas Bremner, M.D.

With the growing appreciation for the biological basis of posttraumatic stress disorder (PTSD) there has been an increase in interest in neuroimaging studies of patients with PTSD. Neuroimaging studies include all studies which take advantage of radiological techniques to provide information about the structure and function of the brain. The first radiologic studies in trauma patients used pneumoencephalography, which involves the injection of air into the cerebrospinal space, and imaging with the use of simple X-rays. This technique was applied to concentration camp survivors from World War II seeking compensation for disability. The authors reported “[cerebral] atrophy of varying degrees and “diffuse encephalopathy” in up to 81% of cases, based on their visual interpretation, although no quantitative measures of atrophy were performed (1).

Magnetic resonance imaging (MRI) is a technologically more advanced method of imaging than X-ray based techniques such as pneumoencephalography. MRI uses a powerful magnetic to throw the electrons and protons which make up brain tissue out of their normal patterns, and measures the time it takes for them to return to their normal resting state. This relaxation time says something about the content of the tissue, which can be used to create an image of the brain. MRI images are obtained of successive slices which move through the entire volume of the brain a few millimeters at a time. With specialized image processing software on the computer, the outline of individual brain regions in successive slices can be traced using a mouse driven cursor, and the volume within the outlines quantitated and converted to real brain volume. These techniques have been shown to be highly reliable in the hands of well trained operators, and have provided a wealth of information about brain structure in psychiatric disorders in general, and more recently in the field of PTSD.

Studies using MRI in PTSD have measured volume of the hippocampus, a brain structure involved in learning and memory. This line of research was prompted by studies in animals showing that high levels of cortisol seen in stress are associated with damage to the hippocampus. We compared hippocampal volume measured with MRI in Vietnam combat veterans with PTSD and healthy subjects matched for factors which could affect hippocampal volume, including age, sex, race, years of education, height, weight, handedness, and years of alcohol abuse. Patients with combat-related PTSD had an 8% decrease in right hippocampal volume in comparison to controls ($p < 0.05$), but no significant decrease in volume of comparison structures including temporal lobe, amygdala or caudate. Deficits in free verbal recall (explicit memory) as

measured by the Wechsler Memory Scale-Logical Component, percent retention, were associated with decreased right hippocampal volume in the PTSD patients ($r = 0.64$; $p < 0.05$) (2). Multivariate analyses performed to control for differences in alcohol abuse and education not completely controlled for by the matching strategy showed significant differences after controlling for these variables. Gurvits et al (3) found a significant reduction in hippocampal volume bilaterally in males with combat-related PTSD. Our group found a statistically significant 12% decrease in left hippocampal volume in 17 patients with a history of PTSD related to severe childhood physical and sexual abuse, in relationship to 17 controls matched on a case-by-case basis with the patients (4). Stein et al (5) found a reduction in left hippocampal volume in women with childhood sexual abuse compared to women without childhood sexual abuse. Reduced hippocampal volume correlated with dissociative symptomatology in this study ($r = -0.73$).

Positron emission tomography (PET) can be used to provide a measure of brain function, measured with brain blood flow and metabolism. Glucose is the primary energy source of the brain, and when there is an increase in firing of the neurons in a specific brain region, there is an increase in glucose uptake in that region to meet the demand. Similarly, with increased glucose demand there is an increase of brain blood flow to that region. With a regional increase in neuronal activity (for instance, in the visual cortex following exposure to a bright light), there is a shunting of blood flow with accompanying drop in glucose toward that region which can be measured with PET as a “real time” measure of brain function.

The radioactive substances used in PET can be prepared in an on site cyclotron and injected immediately into the patient for imaging. Brain blood flow is measured with radioactive water $H_2[O-15]$, and brain metabolism with radioactive glucose ($[^{18}F]2$ fluoro-2-deoxyglucose, or FDG). These substances emit positrons in the course of radioactive decay, which collide with electrons in the brain, creating two beams of light which travel away from each other and are “detected” by the camera. Computers then use this information to reconstruct an image of the brain’s metabolism or blood flow patterns.

We used PET and FDG in the measurement of cerebral glucose metabolic rate following administration of yohimbine and placebo in Vietnam combat veterans with PTSD and healthy controls. Increased noradrenergic function has been hypothesized to underlie many of the symptoms of PTSD, and administration of the alpha-2 antagonist, yohimbine, which stimulates brain norepinephrine release, to patients with PTSD results in increased PTSD symptoms and anxiety. Norepinephrine has a U-shaped curve type of effect on brain function, with lower levels of release causing an increase in metabolism, while very high levels of release actually cause a decrease in metabolism. We hypothesized that yohimbine would cause a relative decrease in metabolism in patients with PTSD in cortical brain areas which receive noradrenergic innervation.

Consistent with this hypothesis, yohimbine resulted in a relative decrease in metabolism in orbitofrontal, temporal, parietal, and prefrontal cortex in PTSD patients relative to controls (6). These findings are consistent with an increased release of norepinephrine in the brain following yohimbine in PTSD.

Studies have begun to use PET to identify brain regions which mediate traumatic remembrance and physiological reactivity to traumatic cues. These studies have typically started from the hypothesis that an increase in activity of limbic brain regions involved in emotion following exposure to traumatic cues is characteristic of PTSD. Three studies to date have used varying behavioral protocols, consequently the results are slightly different. Rauch et al (7) used PET and H₂O[¹⁵O] to look at blood flow during exposure to traumatic and neutral scripts in a group of PTSD patients. Exposure to traumatic scripts resulted in an increase in brain blood flow in limbic regions (right amygdala, insula, orbitofrontal cortex, and anterior cingulate) and decreased blood flow in middle temporal and left inferior frontal cortex. Our group studied Vietnam veterans with and without PTSD during exposure to combat-related and neutral slides and sounds. Vietnam veterans with combat-related PTSD demonstrated a relative failure of activation of orbitofrontal cortex with combat-related slides and sounds in comparison to Vietnam combat veterans without PTSD. Exposure to combat slides resulted in a relative increase in blood flow in two limbic regions, lingual gyrus (posterior parahippocampus) and mid-cingulate. There were also activations in several nonhypothesized regions, including parietal and motor cortex, and dorsal pons. Shin et al (8) used PET and H₂O[¹⁵O] during induction of combat trauma-related and neutral mental imagery in patients with PTSD and healthy controls. This study found a relative failure of orbitofrontal cortex activation, increased blood flow in two hypothesized limbic regions, right amygdala and anterior cingulate, as well as decreased blood flow in middle temporal and left inferior frontal cortex in PTSD patients (but not controls) during exposure to mental imagery (8).

A failure of extinction to fear is an important part of the presentation of PTSD. The neural mechanism of extinction to fear involves orbitofrontal cortex inhibition of amygdala function. Reexposure to the unconditioned-conditioned stimulus pairing results in a rapid return of the conditioned fear response, which suggests that the information was present in the amygdala but merely inhibited by orbitofrontal cortex inhibition. Exposure of PTSD patients to trauma-related material, or traumatic imagery, results in an increase in fearfulness in response to stimuli which were not truly life threatening, possibly due to a failure of orbitofrontal function. In our study, combat veterans without PTSD (unlike the PTSD patients) were able to view combat slides and not have an increase in fearfulness, which we hypothesized is due to active orbitofrontal inhibition of amygdala function. Shin et al (8) also found a relative failure of orbitofrontal activation with traumatic imagery. Our prior PET yohimbine study (6) showed a failure of orbitofrontal cortex with pharmacologic stress in PTSD. Rauch et al (7) found increased orbitofrontal activation with traumatic scripts with their PTSD patients, although this study

did not involve a control group, so it is not possible to determine whether a greater increase in orbitofrontal blood flow would be seen in subjects without PTSD. All of these PET studies found a relative decrease in middle temporal blood flow with combat slides and sounds in PTSD patients. The middle temporal cortex also plays a role in the extinction to fear through inhibition of amygdala function.

The parahippocampus was also found to activate with traumatic reminders across groups. In our study, it involved a posterior portion of the parahippocampus, the lingual gyrus, which has been specifically implicated in visual processing. The cingulate was found to activate in all studies, an area of mid-cingulate in our subjects, and anterior cingulate in the other groups. Cingulate is a limbic region involved in memory, emotion, and attention in the service of selection for action. The fact that some brain regions did not show activation in all of the studies reviewed above is not surprising, considering the differences in tasks involved in each study. Future research may show that traumatic exposure involves specific regions, regardless of the task, while other regions are task specific. For instance, other groups (but not our group) found activation in amygdala and a decrease in left inferior frontal gyrus activity with traumatic exposure. These findings were seen only with traumatic imagery, however, and not with presentation of traumatic pictures (8). It may be that a decrease in activity in this area (as well as activation of the amygdala) is specific to the generation of mental images of the traumatic event, and is not seen during presentation of pictures of traumatic events or with exposure to the combination of traumatic pictures and sounds.

Several studies are ongoing in the rapidly expanding area of functional imaging in PTSD. Semple and colleagues at Case Western Reserve are studying brain correlates of attention in patients with PTSD and comorbid substance abuse. Engdahl and colleagues at the University of Minnesota are using single photon emission computed tomography (SPECT) to study brain correlates of script driven imagery in PTSD. Liebowitz and colleagues at the University of Michigan are looking at brain activation with SPECT following exposure to combat-related sounds in PTSD patients and controls. Results of some of these studies have been presented at scientific meetings.

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Specialized Care for Chronic Complex PTSD, Part III: Extended Care Options

Post-traumatic psychosocial impairment (PTPI) is not limited to post-traumatic stress disorder (PTSD). It is also associated with comorbid psychiatric disorders, affect and identity dysregulation (1) and conflictual or isolative interpersonal relationships, vocational and financial stressors, physical health complaints and illnesses, addiction, and homelessness (2).

Therapeutic and rehabilitative care for PTPI requires a continuum of coordinated multidisciplinary services ranging from preventive screening, counseling, and referral to intensive outpatient and inpatient PTSD treatment. Moreover, intensive psychosocial case management can be utilized to prevent chronic deterioration by providing a framework for facilitating community reintegration.

The Madison model of intensive community-based psychiatric case management (3) has been adapted and refined in VA's Intensive Psychiatric Community Care (IPCC) program to assist severely mentally ill VA patients to use outpatient and community resources rather than inpatient crisis services (4). Several elements from the IPCC model are applicable to PTPI rehabilitation:

- Frequent regular contact with the client in situ, rather than only by sparsely scheduled visits to a medical center clinic or inpatient hospital treatment. Provider visits to home, work, school, employment office, or neighborhood milieus makes possible clinical observation of the physical and social environments that make up a client's "real life." Clinician modeling and coaching of "real-time" social problem solving can help the client to incorporate symptom-management skills related to anticipating and coping with anniversary periods, symbolic trauma cues, or flareups of interpersonal conflict and hypervigilance. In addition, community visits enable the clinician to assess and monitor a client's skills.

- Individualized constructive life planning and fulfillment of responsibilities: An empathic therapeutic relationship and therapeutic narrative reconstruction of trauma and its sequelae are twin cornerstones of posttraumatic treatment, but they do not guarantee that the client has the requisite commitment, skills, and resources to actively take responsibility for her or his life. Posttraumatic avoidance, isolation, hypervigilance, and fear of loss of control become retraumatizing replications of the original traumatic helplessness, terror, and hopelessness if not counterbalanced by present-day fulfillment of personally significant responsibilities. Thus, frequent in situ problem solving can be conceptualized as an essential in vivo component of posttraumatic therapy. Case management is an opportunity not just for practical problem solving and symptom management, but for exploration of the spiritual and moral

dilemmas catalyzed by trauma and PTSD (e.g., loss of purpose or goals). Case management can help the veteran with linkage to resources that can assist him or her in regaining a sense of purpose and productivity in day-to-day life (e.g., religious advisors, vocational counselors).

- Development of a stable safe dwelling, (e.g., transitional community residences) to reduce the severe strain of homelessness. As many as one in twelve Vietnam veterans are homeless or sufficiently itinerant to have no real home (5). Homelessness among veterans is associated with war traumatization, and can profoundly exacerbate chronic PTSD via social isolation, comorbid psychiatric disorders, and addiction (5). Being homeless exposes the individual to high risk for additional traumatization (e.g., assault, robbery, accidents), to stressors that exacerbate trauma and PTSD (e.g., malnutrition, malevolent environments, social rejection), and to many direct and symbolic reminders of past trauma (e.g., lack of access to safety). Even the risk of homelessness—which may be a nagging worry for veterans with compromised work, financial, and family situations—is a debilitating stressor that can catalyze and intensify PTSD. Case management makes residential security and stability a primary focus as a preventive and therapeutic intervention in its own right.

Granted the potential value of case management, where can PTSD providers and programs find the resources to provide such time-intensive care? Innovative inpatient and outpatient VA PTSD programs across the country are developing models for retaining their traditional clinic or hospital services while adding a complementary case management component. Pilot community outreach programs are being developed as VA programs ally with one another and with community programs specializing in social assistance and advocacy. For example, demonstration projects providing community outreach to severely disabled veterans with chronic PTSD are being jointly funded and staffed by the former Psychiatry, Psychology, and Social Work services in reorganized mental health product lines. Personnel dollars, although always scarce, have been targeted to fund several BA or MA level case manager positions supervised by experienced staff clinicians. Alliances have been forged between specialized PTSD programs, specialized Substance Abuse programs, and homeless Domiciliaries to establish case management services for veterans with chronic PTSD who are graduating from Domiciliary to community transitional living placements. Supplemental sponsorship of part or all of these case management programs has been undertaken by Veterans Service Organizations. Although no simple answer exists to the administrative and fiscal challenges of developing case management services for veterans with chronic PTSD, the clinical and fiscal viability of this model make it an idea whose time rapidly appears to be coming.

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CLINICAL TRAINING PROGRAM POST TRAUMATIC STRESS DISORDER

The Education and Clinical Laboratory Education Division for the National Center for Post Traumatic Stress Disorder at the Palo Alto CA VAMC, in collaboration with the VA Employee Education System offers an on-site clinical training program in the treatment of Post Traumatic Stress. The training program is approved for category 1 continuing medical education credit.

Psychiatrists, psychologists, social workers, nurses, readjustment counselors, clinical nurse specialists, occupational and recreational therapists combine to provide a comprehensive treatment program and an education experience for the mental health professional seeking to expand his or her understanding of psychic trauma and its treatment. The Clinical Training Program offers a broad range of educational activities including:

- * Lectures
- * Clinical research observation
- * Supervised clinical activities
- * Use of multimedia materials
- * Group discussions facilitated by staff

Specific training activities include warzone trauma group treatment, treatment of women veterans, treatment of sexual assault related PTSD, relapse prevention, cross cultural treatment issues, assessment and treatment of families, disaster mental health services, cognition and PTSD, assessment of PTSD, and observation of psychiatric assessment.

Training programs are scheduled for a minimum of one week, though longer programs are available if the applicant can justify an extended stay. Programs are scheduled nine times per year, generally on the third week of the month.

At present time, funding for attendance is not available from the National Center. There is no fee for the training program itself, but participants are responsible for providing their own transportation, lodging, and meals. Interested applicants are encouraged to explore funding options through their local medical centers or VA Employee Education System. For further information, please call FTS 700-463-2673 or commercial number 650-493-5000, extension 22673.

Somatic Symptoms Associated with PTSD: Assessment and Intervention

Recently, I received a request for consultation regarding a 28-year-old woman seeking mental health treatment following a serious procedural error during gynecological surgery. During the course of the operation, the surgeon sprayed an acidic rather than saline solution on her cervix. The patient sustained second degree burns and was hospitalized for several days. In the ensuing months, she experienced intermittent pelvic pain and burning sensations in her vagina. Moreover, she lost interest in sex and no longer wanted her husband to see her undressed because she felt deformed. The therapist assigned to the case was bewildered by these symptoms. He thought the patient might be suffering from a delusional disorder related to her beliefs about being deformed and what he viewed as tactile hallucinations. A colleague with whom he discussed the case suggested referring the patient to our trauma clinic.

Additional inquiry determined that the woman was experiencing nightmares about the burns, preoccupation about whether she could function sexually and whether she could have a successful pregnancy. These and other symptoms confirmed a diagnosis of PTSD. The initial difficulty in providing an accurate diagnosis reflects the ongoing struggle within general psychiatric settings to educate mental health providers about PTSD and its pertinence following physical trauma. While general practitioners are beginning to link assault victimization (e.g., child abuse, rape, muggings, etc.) to PTSD, there seems to be less consideration of traumatic induced stress when physical injury occurs, especially those occurring in a medical setting. This may be because, as an interpersonal event, there is no intention to do wrong. In this particular case, the referring therapist viewed the patient as having an unusual reaction to an event that lacked malice, an event he believed was mildly distressful. Minimizing the patient's injury and being unable to recognize her reactions, he missed PTSD Criteria A through D, concluding erroneously that she was delusional.

Fortunately, the woman was re-diagnosed and treated accordingly. Admittedly, accurate diagnoses can be a problem when the most salient symptom is somatic re-experiencing of the trauma, particularly when the patient has not yet achieved a full or the maximum physical recovery. The vital question in this case was whether or not the woman's chronic pain had a partial or substantial organic source.

Both therapist and client need to determine as best as possible the extent to which somatic symptoms derive from physical injuries (e.g., pain related scar tissue). Identifying the source of a physical problem is a prerequisite to identifying effective treatment for physical recovery. Furthermore, identifying that some pain is not "just in her head," may help

the traumatized woman regain a sense of control via an appropriate health plan. It also reduces uncertainty about her subjective experiences and delimits the domains of problems targeted for psychological intervention.

Women who have been traumatized in a medical setting are typically anxious about returning to a doctor and will need encouragement and support to do so. Ideally, therapists will have a referral network of reliable and sensitive physicians, some of whom may specialize in working with traumatized individuals. Encouraging the client to bring a friend to the doctor's office or having a friend be present during the evaluation and exam may help reduce the client's anxiety. The friend can be an additional "information processor" as the client's anxiety may not allow her to assimilate the medical information being presented. In the case of the burn patient, the traumatized woman wanted information about the risks her injuries presented to future pregnancy, but was too upset to find a doctor to whom she could make these inquiries.

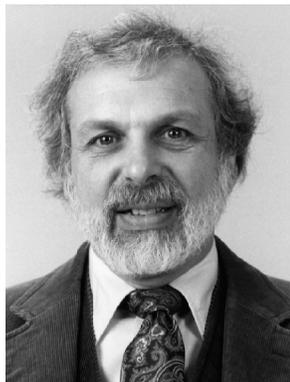
Once accurate information about the client's physical condition has been obtained, client and therapist can realistically assess potential problems and plan ways for coping with the physical sequelae of the injuries. Coping strategies should aim to speed physical recovery and enhance the client's sense of physical integrity (e.g., exercising regularly, taking prescribed medications) as well as to increase client's sense of predictability and control over her injuries. Interventions related to the psychological sequelae of the physical trauma should be considered in tandem with the plan for physical recovery.

It may be difficult for the client and the therapist to discriminate somatic symptoms directly related to the injury from psychosomatic symptoms related to the re-experiencing phenomenon. However, standard PTSD interventions such as the emotional processing of the trauma can be implemented with the expectation that such work will reduce re-experiencing as well as other symptoms, such as nightmares and intrusive thoughts. In addition, these treatments tend to reduce generalized anxiety and depression. Thus, there may be a complementary process in which increased psychological well-being facilitates physical recovery and physical recovery reinforces the psychotherapeutic aims of treatment. Lastly, the therapist should encourage the client to work collaboratively in an ongoing fashion with the physician. This will help keep the client and therapist up-to-date with the changing physical health picture and help the client re-establish a positive working relationship with physicians.

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PHARMACOTHERAPY FOR PTSD: A STATUS REPORT

Matthew J. Friedman, M.D., Ph.D.



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The majority of the initial randomized trials were published between 1987-1991 after which there was a hiatus in research on drug therapy for PTSD. These early investigations focused primarily on tricyclic anti-depressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Despite some very promising leads from these early trials, results were inconsistent and too modest to stimulate further research until selective serotonin reuptake inhibitors (SSRIs) became available in recent years.

Antiadrenergic agents: Propranolol, Clonidine and Guanfacine

Although it is well established that adrenergic dysregulation is associated with chronic PTSD (see 1, 2 for details and references), there has been little research and no randomized clinical trials with either the beta adrenergic antagonist, propranolol, or with the alpha-2 agonist, clonidine despite the fact that positive findings with both drugs were

In general, investigators have been impressed by the capacity of SSRIs to reduce the numbing symptoms of PTSD since other drugs tested thus far, do not seem to have this property.

reported as early as 1984 (3). It should be noted that positive reports of open trials with both drugs continue to be published. In addition, preliminary success has been achieved with the adrenergic alpha-2 agonist, guanfacine which has a longer half-life (18-22 hours) than clonidine.

Selective Serotonin Reuptake Inhibitors

SSRIs have revolutionized pharmacotherapy and are beginning to emerge as the first choice of clinicians treating PTSD patients. In the only published randomized clinical trial of an SSRI, fluoxetine produced a marked reduction in overall PTSD symptoms, especially with respect to numbing and arousal symptoms (4).

In addition, a number of open trials and case reports have appeared concerning fluoxetine, sertraline, and fluvoxamine (see 5 for references). In general, investigators have been impressed by the capacity of SSRIs to reduce the numbing symptoms of PTSD since other drugs tested thus far, do not seem to have this property.

Trazadone and Nefazadone

Trazadone and nefazadone are serotonergic antidepressants with both SSRI and 5-HT₂ blockade properties. They also exert alpha-adrenergic blockade and strong sedative effects. Trazadone has received renewed attention, recently, because of its capacity to reverse the insomnia caused by SSRI agents such as fluoxetine and sertraline. A recent open trial (6) indicated that trazadone may be an effective drug in its own right. Nefazadone is closely related to trazadone with respect to mechanism of action but appears to have greater potency. Multi-site trials with nefazadone are currently in progress.

Monoamine Oxidase Inhibitors (MAOIs)

Phenelzine produced excellent reduction of PTSD symptoms during an eight week randomized clinical trial, in two open trials, and in several case reports. It was less effective than placebo in a four week crossover study and one recent negative open trial with phenelzine (see 8 for references).

Southwick et al. (9) reviewed all published findings (randomized trials, open trials and case reports) concerning MAOI (phenelzine) treatment for PTSD. They found that MAOIs produced moderate to good global improvement in 82% of all patients, primarily due to reduction in reexperiencing symptoms such as intrusive recollections, traumatic nightmares and PTSD flashbacks. Insomnia also improved. No improvement was found, however, in PTSD avoidant/numbing, PTSD hyperarousal, depressive or anxiety/panic symptoms.

In summary, most published reports show that MAOIs effectively reduce PTSD symptoms. In practice, however, most clinicians appear reluctant to prescribe these agents because of concerns about the risk of administering these drugs to patients who may ingest alcohol or certain illicit drugs or who may not adhere to necessary dietary restrictions.

Tricyclic Antidepressants (TCAs)

There have been three randomized clinical trials with tricyclic antidepressants involving 124 patients as well as numerous case reports and open trials (see 10 for references). Results have been mixed and generally modest in magnitude. In their analysis of fifteen randomized trials, open trials and case reports involving TCA treatment for PTSD, Southwick and associates (9) found that 45% of patients showed moderate to good global improvement following treatment whereas MAOIs produced global improvement in 82% of patients who received them. As with MAOIs, most improvement was due to reductions in re-experiencing rather than avoidant/numbing or arousal symptoms. It also appeared that a minimum of 8 weeks of treatment with either TCAs or MAOIs was necessary to achieve positive clinical results. Because of their relative lack of potency, their side effects and their failure to reduce avoidant/numbing symptoms, TCAs have been replaced by SSRIs as first-line drugs in PTSD treatment.

Benzodiazepines

Because of their proven anxiolytic potency, benzodiazepines have been prescribed widely for PTSD patients in some clinical settings. There are only four publications on benzodiazepine treatment for PTSD. In a randomized clinical trial (11) and two open label studies, alprazolam and clonazepam were no better than placebo in reducing core PTSD symptoms although modest reductions in generalized anxiety were observed.

Anticonvulsants

It has been proposed that following exposure to traumatic events, limbic nuclei become kindled or sensitized so that, henceforth, they exhibit excessive responsiveness to less intense trauma-related stimuli (12). Arguing from this theoretical perspective, there have been several open trials of anticonvulsant/antikindling agents. In five studies carbamazepine produced reductions in reexperiencing and arousal symptoms, while in three studies, valproate produced reductions in avoidant/numbing and arousal (but not reexperiencing) symptoms (see 13 for references).

The time has come to develop and test drugs that have been developed specifically for PTSD rather than to recycle pharmacological agents that have been developed to treat affective or other anxiety disorders.

Narcotic Antagonists

There is growing evidence that the endogenous opioid system is dysregulated in PTSD patients. Spurred by the hypothesis that emotional numbing in PTSD might result from excessive endogenous opioid activity, an open trial of the narcotic antagonist, nalmefene, was conducted (14) in which some Vietnam veterans with PTSD exhibited reduced numbing whereas the others showed either no improvement or a worsening of anxiety, panic and hyperarousal symptoms.

Antipsychotics

Before the empirical and conceptual advances achieved during the past 15 years, PTSD patients were often considered to have psychotic disorder by treating physicians. Indeed the intense agitation, hypervigilance (that sometimes appeared to be paranoid delusions), impulsivity, and dissociative states seemed to call for neuroleptic treatment. It now appears that

most of these symptoms will respond to anti-adrenergic or antidepressant drugs and that antipsychotic medications should only be prescribed for the rare PTSD patient who exhibits frank paranoid behavior, overwhelming anger, aggressivity, psychotic symptoms, fragmented ego boundaries, self-destructive behavior and frequent flashback experiences marked by auditory or visual hallucinations of traumatic episodes (15).

Conclusions

Most drugs tested in PTSD were developed as antidepressants and later shown to have efficacy against panic and other anxiety disorders. Given high comorbidity rates between PTSD and such disorders and given the symptomatic overlap between PTSD, major depression, panic disorder and generalized anxiety disorder (16), it seems reasonable to have tested such drugs in PTSD. On the other hand, PTSD appears to be distinctive in a number of ways. First, it seems to be more complex than affective or other anxiety disorders; and second, its underlying pathophysiology appears to be qualitatively different. For example, abnormalities in the hypothalamic-pituitary-adrenocortical axis (HPA) system are markedly different than those present in major depressive disorder despite similarities in clinical phenomenology. In short, the time has come to develop and test drugs that have been developed specifically for PTSD rather than to recycle pharmacological agents that have been developed to treat affective or other anxiety disorders.

From this perspective, promising future directions might be to test drugs that antagonize the actions of Corticotropin Releasing Factor (CRF), the substance that appears to play such a central role in the stress response (17). Another promising direction for future research might be to design drugs that can reverse the dissociative and amnesic symptoms associated with PTSD (18).

Finally, there is certainly a need for further research on adrenergic alpha-2 agonists such as clonidine and guanfacine, on SSRIs and other serotonergic agents, and on anticonvulsants with anti-kindling/sensitization properties. It appears that we have barely begun to explore a variety of exciting pharmacotherapeutic approaches for PTSD. We can all look forward to important research findings in the coming years.

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Matthew J. Friedman is a pharmacologist turned psychiatrist who has been actively concerned about PTSD since 1974. His current positions are Executive Director of the National Center for PTSD and Professor of Psychiatry and Pharmacology at Dartmouth Medical School. Throughout his professional career, he has tried to combine strong concerns about psychiatric care with a scientific commitment to understand the etiology, diagnosis, and treatment of clinical phenomena. As a result, his publications and presentations span a variety of topics (in addition to PTSD) such as biological psychiatry, psychopharmacology, and clinical outcome research. Dr. Friedman was one of the first to publicize research on the biological alterations associated with PTSD and to clarify the implication of such research for rational pharmacotherapy for this disorder. Lastly, Dr. Friedman was President of the International Society of Traumatic Stress Studies, 1995-96.

SITUATIONS OF THREAT

Steve M. Southwick, M.D., and Rachel Yehuda, Ph.D.

During situations of life threat animals and humans mobilize multiple internal neurobiologic resources so as to maximize their chances of survival. Numerous brain regions and neurotransmitter systems become activated in parallel when the organism attempts to deal with danger. One of the most important systems to become activated during stress and threat is the sympathetic or autonomic nervous system. This system plays a central role in the organism's ability to fight a danger or to flee from that danger — the classic fight/flight response. In threatening situations the sympathetic nervous system tends to discharge as a unit. Coordinated sympathetic discharge accelerates heart rate and increases blood pressure allowing for greater perfusion of muscles and blood loss; and mobilizes blood glucose and oxidation of various food products for the purpose of increasing energy supply to skeletal musculature (1).



Steve M. Southwick, M.D.

Epinephrine (adrenalin) and norepinephrine (noradrenalin) are two important sympathetic nervous system neurotransmitters that have been studied extensively in traumatized animals and humans. In addition to their involvement in the above sympathetic nervous system functions, these neurotransmitters play a central role in the development of fear as well as the organism's ability to turn its attention toward a feared stimulus, selectively focus on it, and then respond to it. Further, they appear to facilitate the encoding and consolidation of memory for events that occur during states of arousal and fear (2,3).

Heightened sympathetic nervous system arousal repeatedly has been documented in combat veterans suffering from chronic PTSD (4-6). When exposed to visual and auditory reminders of combat (such as war movies or the sounds of gun fire), veterans with PTSD, as a group, react with higher increases in heart rate and blood pressure than non-exposed controls and combat veterans who have anxiety disorders other than PTSD (4). These physiologic responses occur in response to stimuli that remind the veteran of his own traumatic experiences but not in response to stimuli related to traumas that have not been experienced personally. Thus, combat veterans with PTSD show increased physiological responses to films of combat but normal responses to films of automobile accidents. These findings are consistent with a model of PTSD stimuli present at the time of the trauma become conditioned to fear so that even previously neutral stimuli now elicit exaggerated behavioral and psychophysiological responses (5,6). To investigate the neurochemical correlates of these psychophysiological reactions, a number of investigators have studied EPI, NE and alpha adrenergic receptors in patients with PTSD. Kosten et al. (7) was the first to observe increased levels



Rachel Yehuda, Ph.D.

of epinephrine and norepinephrine in the urine of combat veterans with PTSD compared to individuals with other psychiatric diagnoses and with normal controls, veterans with PTSD excreted significantly more adrenaline and noradrenaline. Twenty years after combat, levels of excreted epinephrine and norepinephrine were still high. Similar findings have been reported in most but not all studies involving urine catecholamines and traumatized populations. In the first study to investigate the relationship between psychophysiological hyper-reactivity and adrenergic function, McFall et al. (8) found a parallel rise in blood pressure, heart rate, subjective distress and plasma epinephrine during and after the viewing of a combat film suggesting that hyperreactive physiologic responses were indeed related to elevations of circulating epinephrine.

For epinephrine or norepinephrine to have a physiological effect they must first attach to adrenergic receptors. Once attached, a cascade of biochemical events is initiated, ultimately leading to a specific reaction. In essence, adrenergic receptors translate the biochemical message of adrenalin. Perry et al. (9), in a study of adrenergic receptors on the surface of platelets (circulating blood elements), found a 40% decrease in receptor number on the platelets of combat veterans with PTSD compared to healthy controls. This decrease was most likely a response to chronic elevation of circulating epinephrine and norepinephrine.

To directly assess adrenergic responsivity of the central nervous system, Southwick et al. (10) administered IV yohimbine to 20 Vietnam combat veterans and 18 healthy controls. Yohimbine is an alpha-2 adrenergic receptor antagonist that activates noradrenergic neurons by blocking the alpha-2-adrenergic autoreceptor, thereby increasing the release of norepinephrine. Yohimbine caused full blown panic attacks in 70% and flashbacks in 40% of combat veterans with PTSD. In contrast, none of the control subjects experienced either a panic attack or a flashback. Additionally, subjects with PTSD had greater increases in heart rate and a greater than two-fold increase in MHPG, the breakdown product of norepinephrine. These findings suggest that at least a subgroup of patients with PTSD have increased sensitivity of the noradrenergic system. The fact that equivalent doses of yohimbine caused significantly greater increases in anxiety, vigilance, arousal, intrusive traumatic memories, heart rate and MHPG among the combat-traumatized subjects compared to healthy controls is consistent with a behavioral sensitization model of PTSD. Behavioral sensitization refers to an enhancement of response magnitude following repeated presentations of stress-related stimuli. In a sensitized system

one would expect that the same stimulus, over time, would produce responses of increasing magnitude or that lower grade stimuli would sustain the system in a state of heightened responsivity.

In summary, a relatively large number of physiologic and biochemical studies now support the notion that a subgroup of traumatized individuals with PTSD have increased responsivity of the sympathetic nervous system that is most easily detected when the individual is stressed. In other words, for some individuals with PTSD the sympathetic nervous system appears to over respond to a variety of stimuli even many years after having experienced an overwhelming trauma. The individual continues to act psychologically and biologically as if the danger is still present even though the event may have occurred in the distant past. It has been hypothesized that a sensitized sympathetic nervous system may contribute to a number of core PTSD symptoms including hypervigilance, poor concentration, insomnia, irritability, exaggerated startle, and perhaps even intrusive memories. Being irritable and on edge makes it difficult to interact with family members, friends, coworkers and employers. To quiet these symptoms of hyperarousal, PTSD patients often withdraw emotionally and some use substances, particularly central nervous system depressants that suppress peripheral and central catecholamine function. In addition to the sympathetic nervous system, the hypothalamic-pituitary-adrenal axis (HPA) is a critical component of the neurobiologic response to stress. However, unlike epinephrine and norepinephrine which prepare the organism for action, cortisol appears to serve a catabolic restorative function. When the individual is stressed, corticotrophin releasing factor (CRF) is secreted from the hypothalamus. CRF then stimulates the release of adrenocorticotrophic hormone from the pituitary gland and cortisol from the adrenal gland. Cortisol's primary function is to terminate the neural defensive reaction (e.g., including those turned on by the catecholamines) that has been initiated by stress (14).

Most animals and human paradigms of stress have demonstrated increased levels of cortisol in response to increased magnitude of stress. However, studies in traumatized humans with PTSD have found low cortisol levels and other HPA abnormalities suggestive of a heightened sensitivity of this axis to stressful stimuli. Because these abnormalities typically are absent in trauma survivors without PTSD, it appears that PTSD may be a specific reaction to stress that differs from classic or normal stress reactions.

The first HPA-axis studies in PTSD showed that the amount of cortisol excreted in the urine over a 24-hour period was lower in combat veterans with PTSD than in normal controls or psychiatric patients with major depression, schizoaffective disorder, bipolar disorder, or schizophrenia (15). These 24-hour urine findings have been replicated in all but two studies. Urine cortisol has been found to be low in combat veterans regardless of comorbid diagnoses such as substance abuse or major depression (16). Circulating cortisol levels in the blood also has been reported as lower than normal in trauma victims with PTSD. In an epidemiological study of over 2000 Vietnam veterans, the 293 with PTSD had lower morning plasma cortisol levels than the remainder without PTSD (17). In a 24-hour circadian study of plasma cortisol levels, Yehuda et al. (18)

recently reported significantly lower cortisol levels particularly in the very early morning and late evening hours in combat veterans with PTSD compared to depressed patients and normal controls.

Like norepinephrine, cortisol must bind to receptors in order to exert a physiological effect. Three studies of combat veterans and one study of adult survivors of severe childhood sexual abuse have found larger numbers of glucocorticoid receptors in traumatized subjects than in non-traumatized normal controls (18). Having a larger number of glucocorticoid receptors allows more cortisol to bind to the receptor, least hypothetically, and increases the sensitivity of the system. Indeed, this possibility has been confirmed using the low-dose dexamethasone suppression test. Dexamethasone is a synthetic hormone that mimics the effects of cortisol. When dexamethasone is administered, it binds to cortisol receptors, and activates the negative feedback system. As a result, the body's own cortisol levels become lower. In trauma survivors with and without PTSD, cortisol levels following dexamethasone have been reported as lower than normals and other psychiatric diagnostic groups (19, 20). This lower cortisol response reflects a more sensitive system where cortisol has an exaggerated inhibitory effect on HPA-axis function. Thus, HPA axis alterations in PTSD resemble catecholamine alterations in that both systems appear to be sensitized (18).

For some individuals with PTSD the sympathetic nervous system appears to over respond to a variety of stimuli even many years after having experienced an overwhelming trauma. The individual continues to act psychologically and biologically as if the danger is still present even though the event may have occurred in the distant past.

It is important to point out that the sensitivity of a system cannot be measured simply by knowing whether ambient hormone or neurotransmitter levels are high or low. This is true of both the HPA and catecholamine systems. It is only by provoking the system through experimental, environmental or pharmacologic manipulations that one can truly know whether a system is more sensitive or less sensitive. In almost every such test that has been performed in PTSD, an increased sensitivity has been observed. Thus, sensitization may involve more neurochemical systems than those that have been mentioned in this review.

There has been an intriguing observation in recent years suggesting that the cortisol response in the acute aftermath of trauma is actually lower — not higher — in the subset of trauma survivors who go on to develop PTSD, or who are at greater risk for the subsequent development of PTSD. McFarlane et al. (20) demonstrated that motor vehicle accident victims who had PTSD at 6 months following a trauma actually had lower cortisol levels in the immediate aftermath of the accident compared to those who did not develop psychiatric disorders

and those who developed a major depression at 6 months. Resnick et al. (21) reported that women with a prior assault history who were at greater risk for the subsequent development of PTSD also showed an attenuated rather than an exaggerated response to the rape. This means that the behavioral sensitization that appears in chronic PTSD seems to develop very early on, and may even be a predisposing risk factor for those who subsequently develop a chronic disorder in response to trauma.

It is of interest to speculate how the low cortisol levels in the immediate aftermath of a traumatic event may affect the catecholamine system. Quite simply, if cortisol's function is to shut down biological responses, but for some reason does not do so immediately after the trauma then catecholamine levels may remain elevated for too long during a critical time and go on to affect memory, mood, and other psychological and physiological processes. This is an exciting area of investigation which should yield fruitful information in the years to come. In this review of neuroendocrine alterations in PTSD we have focused on catecholamines and the HPA-axis. It is important to note that multiple other neuroendocrine systems also may be affected by trauma. For example, in trauma victims with PTSD there is some evidence for abnormalities in the endogenous opiate, serotonin and thyroid systems. From a neurobiological perspective PTSD appears to be a multisystem disorder that effects numerous aspects of the organism's complex response to trauma (11, 12). As advances in biomedical technology are made, more sophisticated investigations of the biology of PTSD will be possible. Further, with a better understanding of the neuroendocrine underpinnings of PTSD, it may be possible to develop more effective and specific treatments for this often devastating disorder.

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- assess the impact of disaster/critical incidents on individuals, workers, organizations, communities;
- assess the factors associated with adaptation to disaster and critical incident-related trauma;
- identify at-risk groups and individuals in the wake of disaster and critical incidents;
- target phase-specific interventions to match needs of specific at-risk groups and individuals;
- identify essential operational guidelines for applying DMH/critical incident interventions;
- identify essential operational guidelines for DMH/critical incident provider stress management;
- apply an overview knowledge of the federal response plan to team or practitioner liaisons to other disaster response organizations.

Participants have been VA Medical Center, Clinic, or Vet Center mental health professionals within a VISN who are or plan to be actively involved in acute mental health response to critical incidents or disasters. Ideally, participants have experience in critical incident response (e.g., hospital or community post-trauma debriefings) and a familiarity with basic concepts of trauma, critical incident stress, and PTSD.

Course enrollment: Minimum 25, maximum 50 participants.

FOR FURTHER INFORMATION PLEASE CONTACT:

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