Fear-Potentiated Startle in Posttraumatic Stress Disorder

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Exaggerated startle is reputed to be one of the cardinal symptoms of posttraumatic stress disorder (PTSD); however, objective studies have given conflicting results as to whether or not startle is increased in PTSD. The present study investigated startle in PTSD during the threat of shock (fear-potentiated startle). The eyeblink component of the startle reflex was measured at various times preceding and following the anticipation of unpleasant electric shocks in 9 PTSD subjects and 10 age-matched, healthy controls. Startle amplitude was significantly greater during baseline and during shock anticipation in the PTSD subjects, compared to the controls. Habituation of the startle reflex was normal. Because other studies in the literature, as well as in our own laboratory, have failed to find exaggerated startle at baseline (i.e., absence of stress) in PTSD patients, it is unlikely that the present results reflect a chronic elevation of startle in this group. Instead, the higher levels of startle in the PTSD group probably resulted from a greater conditioned emotional response in this group, triggered by anticipation of electric shocks that generalized to the unfamiliar experimental context in which testing occurred. Hence, emotionally charged test procedures may be especially informative in distinguishing PTSD patients from other psychiatric diagnostic groups.

Key Words: Fear, startle, PTSD, anxiety disorders, stress

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Introduction

Accounts of psychopathology resulting from extraordinary trauma can be traced back over 200 years (Kolb 1984); however, it was not until 1980 that posttraumatic stress disorder (PTSD), marked by symptoms of reexperiencing, avoidance, and arousal, was officially delineated in the DSM-III (APA 1980) as a clinical diagnosis within the category of anxiety disorders. PTSD can be caused by a variety of catastrophic events, natural disasters, rape, and combat, which are outside the range of usual human experience and would be markedly distressing to anyone.

Although initial delineation and further characterization (APA 1987) of PTSD represents a major advance, the diagnostic criteria continue to emphasize factors mainly dependent on patient self-reporting. The DSM-III-R includes increased "physiological reactivity" as one diagnostic feature of PTSD. The presence of physiological alterations (including exaggerated startle) accompanying a mental disorder offers the opportunity to obtain data that may be more "objective" and more readily quantifiable than self-report data.

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Because exaggerated startle is a clinical physiological symptom of PTSD, acoustic startle may well represent an objective index of central nervous system (CNS) dysregulation in PTSD. It has been argued that the startle reflex is an ideal means of assessing sensory-motor reactivity in humans and animals. The startle reflex is a ubiquitous, cross-species response to strong exteroceptive stimuli. In human subjects, it can easily be recorded by measuring the electromyogram (EMG) of facial muscles (orbicularis oculi). There have been few published objective studies of the amplitude of the eyeblink component of the startle response in combat veterans with PTSD. Butler et al (1990) found increased acoustic startle amplitude to moderate levels of startle stimuli in a subgroup of Vietnam combat veterans with PTSD compared to combat controls. They did not find abnormal startle to high or low stimuli, nor did they find abnormal habituation of the startle reflex. In addition, 35% of the patients were eliminated from the analysis because they were considered nonresponders. At the present time there is no agreement in the field about what constitutes a nonresponse. Butler et al used criteria that eliminated startle response trials that were up to 114 microvolts (mv) in size. In light of the very few published studies of startle in patients with PTSD, this threshold may be too high; however, if these findings are indeed representative of PTSD, then it would indicate that a substantial percentage of subjects with PTSD do not have exaggerated startle.

Failure to find increased acoustic startle was also reported by Shalev et al (1992) in Israeli combat veterans with PTSD. In that study, habituation of the reflex was found to be normal. Similarly, Ross et al (1989) reported normal habituation in Vietnam veterans with PTSD.

Given the extensive historical clinical impression (Grinker and Spiegel 1945; Kardiner 1941) of exaggerated startle in this disorder, additional study is clearly needed. Numerous psychophysiology studies of Vietnam combat veterans with PTSD have suggested that exaggerated peripheral nervous system responses are seen when patients are exposed to war-related "conditioned" stimuli (Esler 1982; McFall et al 1990; Orr 1990; Pallmeyer et al 1986; Pitman et al 1987, 1990; Blanchard et al 1982). If, as Kolb has suggested, exaggerated startle in PTSD is a conditioned emotional response to stimuli reminiscent of trauma (Kolb 1984), then a reasonable model for the study of startle is the fear-potentiated startle paradigm.

Brown et al (1951) demonstrated that the amplitude of the acoustic startle reflex in the rat can be augmented by presenting the eliciting auditory startle stimulus in the presence of a cue (e.g., a light) that has previously been paired with a shock, a phenomenon termed the fear-potentiated startle effect (Brown et al 1951; Davis and Astrachan 1978). The fear-potentiated startle reflex effect is decreased by anxiolytic and increased by anxiogenic neurochemical agents (Davis 1979; Davis et al 1979; Kehne et al 1988). It is also completely blocked by destruction of the central nucleus of the amygdala (Hitchcock and Davis 1986), a structure highly implicated in conditioned and unconditioned fear responses (Davis 1992).

Fear-potentiated startle has been investigated in humans during the anticipation of adversive events (Grillon et al 1991, 1993). For example, Grillon et al (1991) reported increased startle in healthy control subjects when the subjects anticipated an electric shock. Taken together, these preclinical and clinical results suggest that fear-potentiated startle is a sensitive index of contextual fear or anxiety. The present study was designed to determine if fear-potentiated startle responses are increased in combat veterans.

Method

Subjects

The subjects were 12 male Vietnam combat veterans with posttraumatic stress disorder who were hospitalized on a specialized PTSD ward (mean age 43 ± 2 years). All patients met criteria for PTSD per DSM-III-R, Structured Clinical Interview for DSM-III-R, and consensus diagnosis team. Five of the 12 PTSD subjects had a comorbid diagnosis of panic disorder, and seven subjects a history of alcohol dependence. Subjects were interviewed by the investigating psychiatrist (CAM) and noted to have a sudden onset of diaphoresis, shortness of breath, feeling of dying, dizziness, fear of losing control, and numbness and tingling in fingertips, meeting DSM-III-R criteria for panic attack.

Three patients did not complete the testing because they reported experiencing a panic attack early in the procedure; their results were not included in the analysis. Of the three subjects who were excluded due to panic attacks during testing, only one had a diagnosis of comorbid panic disorder; two had a diagnosis of comorbid alcohol dependence. Thus, of the nine PTSD patients who completed testing, four had comorbid panic disorder, and five, comorbid alcohol dependence. (These five did not differ significantly in their startle responses and did not account for the group difference.) The mean age of the nine patients included in the data set was 42 ± 1 years.

The control subjects consisted of 10 male healthy volunteers (mean age 42 ± 4 years). They had no major medical problems or psychiatric disorders as determined by physical examination and Structured Clinical Interview for DSM-III-R, nonpatient version. All of the control subjects completed the entire experiment.

Urine drug screens confirmed that all subjects had been free of drugs or alcohol for at least 8 weeks prior to testing. Audiologic testing was performed on each subject (Welsh Allen). None of the subjects included in the study showed hearing deficits in the 1000–4000 Hz span. All participants

gave written, informed consent and were driven to the Yale campus for startle testing.

Stimuli and Apparatus

Details of the apparatus, stimuli, and procedure can be found in Grillon et al (1991). Briefly, the startle reflex was recorded with a commercial startle system (SR-Lab, San Diego Instruments). The acoustic startle stimulus was a 40 msec burst of white noise with a near instantaneous rise time presented binaurally through headphones (Amplivex). The intensity of the acoustic stimulus was 106 dB (A) and was delivered over a 70 dB (A) background of white noise. The eyeblink component of the startle reflex was measured by recording activity from the orbicularis oculi muscle underneath the right eye with two disk electrodes (Ag-AgCl). The ground electrode was placed on the right arm. Impedance level was kept below 5 Kohms. EMG activity was filtered (1–500 Hz), digitalized at 1 kHz for 250 msec from the onset of the acoustic stimuli, and stored for off-line analysis. A 60 Hz notch filter was also used to eliminate 60 Hz interference. The electric shock was delivered through two pure tin disk electrodes located on the median nerve of the left wrist by a constant current stimulator (Grass Inst. Corp. Model CCUIA, set at 1.5 mA, 5 msec).

During the experiment, subjects sat in a reclining chair. A red light, a blue light, and a digital timer were placed in front of them on a table. One of the two lights signaled that shock could be administered (Threat condition). The other light signaled that shock would definitely not be administered (No-Threat condition). Threat and No-Threat conditions lasted 50 and 60 sec, respectively.

The experiment was divided into three parts. The first part was an habituation procedure to acquaint the subjects with the startle stimuli. The second part was the fear-potentiated experiment. The third part was a recovery period.

During the habituation procedure, 18 startle stimuli were delivered every 18–22 sec (mean 20 sec) without threat of shock. The shock electrodes were not on the subject's wrist. Four minutes after the completion of the habituation procedure, the shock electrodes were taped onto the wrist and the fear-potentiated startle experiment was started. The startle reflex was then recorded under Threat and No-Threat conditions in three experimental blocks separated by 4-min rest periods. Each block started with six "within-block" habituation startle stimuli (not included in the analysis). Following these six startle stimuli, six Threat and six No-Threat conditions were alternated. For half the subjects, blocks 1 and 3 started with a Threat condition and block 2 started with a No-Threat condition. For the other half, the order was reversed. In each block, the acoustic startle stimuli were presented every 18–22 sec (mean 20 sec). The startle reflex was elicited three times during each of the following time intervals: Threat condition, 5, 15, 25, 35, and 45 sec; in the No-Threat condition, 5, 15, 25, 35, 45, and 55 sec. Thus, 39 startle stimuli were delivered during each block for a total of 153 (18+39+39+39+18) startle stimuli during the entire experiment.

For half the subjects, the Threat condition was signaled by the onset of a blue light, whereas the No-Threat condition was signaled by a red light. For the other half, the light colors were reversed. The subjects were told that electric shock *could be* delivered only in the *last 10 sec* of the Threat (Time = 40–50 sec) condition, but not in the No-Threat condition. The subjects were also informed about the duration of each condition. In the Threat condition, a digital timer counted the time from 0–50 sec. The subjects were informed that they would receive between one and three shocks and that the second and third shocks, if administered, would be more intense than the preceding shock(s). Previous work indicates that these instructions allow a relatively constant level of fear to be maintained during the threat conditions throughout the experiment (Grillon et al 1991). All subjects received an electric shock in the last 5 sec of the last Threat condition in block 2. Two of the PTSD subjects also received an additional shock in the last 5 sec of the last Threat condition following the last startle probe of the fear-potentiated startle experiment in block 3. This was to preserve the validity of the experiment, which could have been compromised by subjects who might share information about the procedure while staying on the same inpatient ward.

At the conclusion of the fear-potentiated startle experiment, the shock electrodes were removed from the subject and the habituation procedure was readministered. These data were referred to as recovery data, because they were recorded after the completion of the fear-potentiated startle testing.

Anxiety Scales

The state portion of State Trait Anxiety Inventory (STAI) (Spielberger 1983) was utilized to assess the subjects' fear of the shock. This questionnaire was given when the subjects arrived, in order to obtain a pretest assessment of the subjects' state anxiety, and at the end of each of the fear-potentiated startle experimental blocks. Subjects were asked to rate how they were feeling in the last 10 sec of the threat condition. Subjects' fear of the shock was operationally defined as the average of the STAI-state scores obtained during the three blocks.

Data Reduction

To analyze the blink reflex, the digital signal was smoothed by an averaging routine that performed a rolling average over 10 successive points. The startle data were analyzed using a program written by Balaban et al (1986). Details of

Table 1. State-Trait Anxiety Inventory Scores[a]

	Trait	State baseline	State shock anticipation
Controls	37.1 (8.7)	36.8 (9.6)	41.9 (9.6)
PTSD	58.6 (7.4)	48.7 (11.8)	61.0 (5.8)

[a] Mean (standard deviation) STAI scores.

the analysis procedure can be found in Grillon et al (1991). Briefly, peak amplitude of the blink reflex was determined in the 21–120 msec following stimulus onset. A startle reflex was considered to have occurred when EMG activity surpassed baseline activity by at least 4 analog/digital units (1.1 mV per analog/digital unit). Baseline activity was the rolling average of the minimum and maximum EMG values recorded during the first 20 msec. Trials were rejected if they indicated increased EMG activity during the first 20 msec or failure to reach peak within 95 msec of onset latency. Less than 3% of trials were rejected, and there were no significant differences in the rate of rejection between the two groups.

In the habituation procedure, the 18 eyeblinks were averaged into six blocks of three eyeblinks each. The data of the recovery period were analyzed similarly. As indicated in the previous section, during the fear-potentiated startle experiment the startle stimuli were delivered three times at each time-interval in the Threat and in the No-Threat conditions in each block. The mean of these three eyeblink reflexes was calculated.

Data Analysis

The State Trait Anxiety Inventory scores were analyzed in a two-way analysis of variance (ANOVA) with repeated measures with Group (patients, controls) and Period (pretest, threat) as the factors.

To reduce the data in the fear-potentiated startle experiments, the amplitude measures were averaged across blocks. Startle measures were analyzed with a three-way ANOVA with repeated measures using Group (patients, controls), Condition (Threat, No-Threat), and Time Interval (5, 15, 25, 35, 45) as the factors. The data of the habituation and recovery period were analyzed separately with two-way ANOVAs, using Group (patients, controls) and Block (six successive blocks of three eyeblinks) as factors. Reduced degrees of freedom (Greenhouse-Geisser) were used to minimize inflated degree of freedom (*df*) and type I error.

Results

Anxiety Scores

Table 1 shows the STAI-State scores upon the subjects' arrival in the laboratory (pretest), and at the time of shock anticipation (Threat condition). The STAI-state scores were significantly higher in the PTSD subjects compared to the controls ($F = 15.00$, $df = 1,17$; $p < .001$). As expected, the level of anxiety increased during the Threat condition ($F = 25.62$; $df = 1,17$; $p < .001$) reflecting the subjects' fear of shock. While the effect was significant in each group (control: $t(9) = 3.3$ $p \leq .009$; PTSD $t(8) = 3.8$ $p \leq .005$), the magnitude of the increase was greater in the patients than in the controls (Group × Period interaction $F = 4.31$; $df = 1,17$, $p < .05$). The STAI-Trait score was significantly more elevated in the PTSD, compared to the control subjects ($t = 5.51$; $df = 16$; $p < .001$).

Habituation

Figure 1 presents the amplitude of the startle reflex during the habituation procedure. Panel A presents the results of the first six startle stimuli, and Panel B shows the data averaged over three successive trials. Startle habituated with repeated stimulation (linear trend) (the first six trials: $F = 21.2$, $df = 1.17$, $p \leq .0009$; 18 trials $F = 20.0$, $df = 1.17$, $p \leq .0009$). Overall startle amplitude was greater in the PTSD patients compared to the control subjects (the first six trials: $F = 7.92$, $df = 1,17$, $p < .01$, 18 trials: $F = 7.13$, $df = 1.17$, $p < .01$). There was no significant Group × Time Interval interaction, indicating that the rate of habituation of startle amplitude did not differ between groups.

Previous studies have attempted to identify subjects who were startle nonresponders (Butler et al 1990; Shalev et al 1992). Shalev et al (1992) used criteria of two consecutive nonresponsive trials to classify a subject as a nonresponder. Using the same criteria during the habituation procedure, one control and no patient reached this criterion for nonresponder.

Fear-Potentiated Startle

Figure 2 shows the startle response measures in the Threat and No-Threat conditions averaged across blocks in PTSD subjects and in controls. Startle amplitude was progressively increased as the time of shock expectation approached and returned to baseline level rapidly thereafter. This resulted in a significant Condition × Time Interval interaction ($F = 3.60$; $df = 4,68$; $p < .04$). The progressive increase in the startle response in the threat condition were best fitted by a third-order polynomial ($F = 4.63$; $df = 1.17$, $p < .04$).

Overall startle was larger in the PTSD group compared to the control group ($F = 4.62$; $df = 1,17$; $p < .04$). The interactions between Group and the other factors were not significant.

Figure 2 suggests that the magnitude of fear-potentiated startle at time 45 sec (the point of greatest shock expectation) in the threat condition was greater in the PTSD veter-

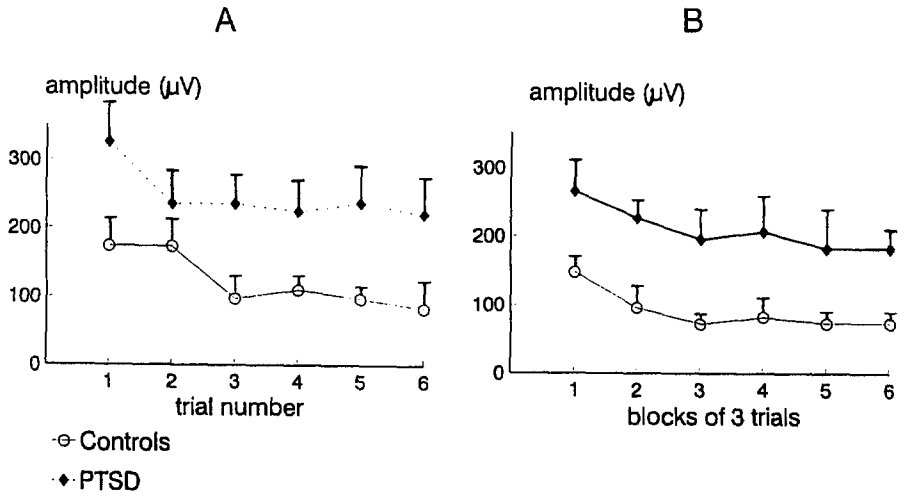

Figure 1. Habituation of the startle reflex during the first six trials (*A*) and grouped into blocks of three trials (*B*). Error bars are standard errors.

ans compared to control subjects; however, examination of the individual data indicates that this effect was due to one PTSD patient who showed an increase from baseline to time 45 sec in the threat condition of 557 μV.

Recovery

Figure 3 shows startle reflex data during recovery. Startle habituated with repeated stimulation (linear trend $F = 6.7$, $df = 1.17; p \leq .01$). Although startle amplitude seemed to be larger in patients compared to the controls, this difference was not significant ($p > .1$). The Group × Time Interval interaction for amplitude also was not significant.

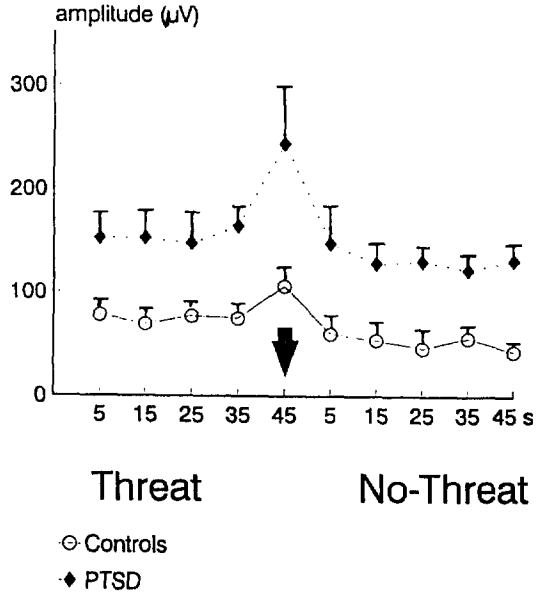

Figure 2. Fear-potentiated startle. Startle reflex in the Threat and No-Threat conditions. The dark arrow at time 45 sec in the Threat condition indicates the time of shock expectation. Error bars indicate standard errors.

Discussion

To our knowledge, this is the first fear-potentiated startle reflex study in veterans with PTSD. Startle amplitude was greater in the habituation and fear-potentiated startle periods in the PTSD patients compared to the controls. This finding of significantly greater startle in the PTSD subjects is consistent with both historical clinical reports and with the findings of Butler et al (1990); however, the findings in this study are unlike those of prior studies in several aspects—the presence of a robust and uniform exaggeration of startle in PTSD subjects and the absence of startle nonresponders in a subgroup of PTSD patients.

Habituation of the startle amplitude during the Habituation and Recovery periods was normal in the PTSD patients. This is consistent with findings in several studies (Butler et al 1990; Ross et al 1989; and Shalev et al 1992) and suggests that the exaggerated startle seen in PTSD patients in the present study was not due to a failure to habituate.

Two hypotheses might be invoked to account for the exaggerated startle in the veterans with PTSD in this study. First, startle could be chronically increased in these individ-

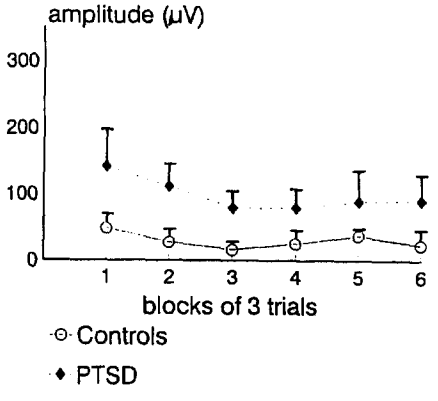

Figure 3. Startle reflex during the recovery period.

uals. This hypothesis suggests an abnormality in unconditioned responding, as generally inferred from clinical observations (Grinker and Spiegel 1945; Kardiner 1941; Esler 1982); however, objective experimental investigations have mostly failed to demonstrate exaggerated startle in PTSD (Shalev et al 1992; Ornitz and Pynoos 1989; Ross et al 1989; Pallmeyer et al 1986; Malloy et al 1983). Moreover, we have recently found that veterans with PTSD from the same cohort as the subjects who participated in the present experiment exhibit normal startle reflex amplitudes when tested in a nonstress condition (Grillon et al, submitted; Morgan et al 1990). Thus, it seems unlikely that the elevation of startle in the PTSD patients in the present study can be attributed to a chronic elevation of the startle reflex.

The alternative explanation is that exaggerated startle in the PTSD subjects in the present experiment was contextual. There were two main experimental differences between the present experiment and our recent experiment with the same cohort of Vietnam veterans with PTSD who showed normal startle response. First, the previous experiment did not involve the threat of an aversive event. Second, the present experiment was carried out in an unfamiliar setting at Yale University, whereas the first experiment took place at the VA itself. It is possible that the novelty of the environment was responsible for the present result. It is also possible that a conditioned emotional response triggered by anticipation of electric shocks generalized to the experimental context in which testing occurred. Finally, the results might also be due to a combination of a novel environment and the threat of an aversive event. We are presently designing experiments to evaluate these different possibilities.

One major characteristic of patients with PTSD is that they exhibit a conditioned emotional response to stimuli reminiscent of combat (Kolb 1984). War-related stimuli induce physiological arousal, such as increased heart rate, blood pressure, and skin conductance (McFall et al 1990; Orr 1990; Pallmeyer et al 1986; Pitman et al 1987, 1990; Blanchard et al 1982, 1986; Malloy et al 1983; Meakins and Wilson 1918). In the present study, however, there was no apparent war-related stimulus to elicit an emotional conditioned response. During post-test interviewing, subjects denied that the threat of shock was connected to pre-war, or war-related trauma. Similarly, they also denied that the startle sounds were reminiscent of gunfire. This could be considered compatible with the hypothesis of heightened unconditioned responding; however, eight of the nine PTSD subjects indicated that the feeling of waiting for the shock to be administered was reminiscent of the combat zone experience of waiting for a firefight or ambush. It is possible, therefore, that the subjects were conditioned to the state of anxious anticipation (anticipation of danger), and that this "war-conditioned" state resulted in exaggerated startle. Indeed, in animals at least two types of conditioning can be identified: conditioning to specific cues that have been associated with aversive stimuli, and conditioning to the context in which the conditioning occurred. Whereas the conditioning to specific cues is dependent on the amygdala, contextual fear is disrupted by lesions of the hippocampus (Kim and Fanselow 1992; Phillips and LeDoux 1992; Hitchcock and Davis 1986, 1991). It is conceivable that patients with PTSD suffer from a dysregulation of hippocampal activity that leads to an abnormal processing of contextual information. Such a hypothesis could account for the increased fear response and the increased startle displayed by patients in the "threatening" laboratory setting. If so, this would be compatible with a contextual hypothesis.

It is also possible that in the present experiment, the perceived threat of shock became abnormally generalized to the experimental context in the PTSD subjects because of a dysregulation of the fear-alarm system. That such dysregulation exists is supported by a recently completed challenge study (Southwick et al 1993) using yohimbine, an alpha$_2$ adrenergic receptor antagonist, as a probe of central and peripheral noradrenergic reactivity. Combat veterans with PTSD showed a significantly greater behavioral, biochemical, and cardiovascular response compared to healthy controls. When subjects in the PTSD group were exposed to intravenous yohimbine, 70% had a panic attack and 40% a flashback. In contrast, none of the healthy controls had either a panic attack or a flashback. Similarly, the PTSD group had significantly greater increases in plasma MHPG, resting systolic blood pressure, and heart rate. These results are consistent with a chronic alteration in peripheral and central presynaptic noradrenergic neuronal reactivity in PTSD patients. The exaggerated startle seen in the present investigation might be a reflection of this dysregulated noradrenergic system, which is a known alarm response.

In the present study, only one control subject reached the criteria of two successive startle nonresponses during the 18-trial habituation procedure. This compares with 7 out of 14 veterans with PTSD and 17 out of 19 in the no-trauma control group during the 15-trial session in Shalev et al (1992) study. Although this difference may be attributed, in part, to parametric variations (stimulus intensity, intertrial interval, criteria for a response, integrator time constant), it is likely that the threat of shock potentiated the startle response throughout the experiment in all subjects, and especially those with PTSD. This interpretation is supported by the finding that in our present study of startle in a nonstress condition, about 25% of veterans with PTSD are nonresponders.

Some of the PTSD subjects in this study also met DSM-III-R criteria for panic disorder. Three of the 12 PTSD subjects (27%) involved in this study experienced panic attacks during the test session; however, two of the three

who did experience a panic attack did not meet criteria for panic disorder prior to the experimental testing. Surprisingly, in a study similar to the present one in patients with panic disorder, only three of the 30 subjects (10%) reported experiencing panic attacks (Grillon et al 1994). It has been suggested that the comorbid panic disorder described in PTSD subjects may in fact be a symptom of posttraumatic stress disorder itself (Nagy et al 1993). Therefore, it is possible that the panic attacks reported in our study may be reflective of PTSD and not panic disorder.

The PTSD subjects also had a history of comorbid alcohol dependence. Although alcohol withdrawal in rats and in humans has been shown to increase startle (Pohorechy et al 1976; Krystal et al 1992), this is unlikely to account for our findings, because identical inclusion criteria and length of sobriety were used in a previous study which did not find increased startle in PTSD (Grillon et al, submitted; Morgan et al 1990). Also, all PTSD subjects were alcohol free for a minimum of 3 months prior to the study, as verified by weekly breathalizer and urine tox screens performed by the clinical treatment teams of the inpatient specialized treatment unit. None of the subjects was in a state of alcohol withdrawal. Nor did any subjects show any psychotic-like symptoms of PTSD.

In summary, the present results clearly indicate elevated levels of acoustic startle in PTSD patients under test conditions involving anticipation of electric shock. Because the previous studies are limited and have given conflicting data, a cautious interpretation is offered. The present results suggest that fear of shock or other stressful experimental procedures may be a critical variable in detecting PTSD vs. control differences in startle amplitude; however, direct studies, using matched groups of PTSD patients tested under normal or shock-threat conditions, will be required to test this hypothesis. If fear of shock or stress proves to be a critical variable, then further work looking at rates of extinction of cue-specific fear or overgeneralization to the experimental context will also have to be investigated.

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