Exaggerated Acoustic Startle Reflex in Gulf War Veterans With Posttraumatic Stress Disorder

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Objective: Exaggerated startle reflex is reputed to be one of the cardinal symptoms of posttraumatic stress disorder (PTSD). The goal of this study was to assess the magnitude of the acoustic startle reflex in Gulf War veterans with PTSD. Method: The eye-blink component of the startle reflex was measured in response to six blocks of pseudorandomized 40-msec white noise bursts of varying intensities (90, 96, 102, 108, and 114 dB) in 10 Gulf War veterans with PTSD, seven Gulf War veterans without PTSD, and 15 civilian subjects without PTSD. Results: The magnitude of the first startle response, as well as the magnitude of startle response averaged across blocks of testing, was significantly greater in Gulf War veterans with PTSD than in veteran and civilian comparison groups. Conclusions: Consistent with some clinical studies investigating the startle response in Vietnam veterans with PTSD, this investigation provides evidence for exaggerated startle response in this disorder. Preclinical studies of shock sensitization of the startle response suggest that the higher levels of startle response seen in the PTSD subjects may reflect a sensitization of the fear/alarm response created by the stress of combat trauma.

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Accounts of psychopathology resulting from extraordinary trauma can be traced back over 200 years (1). However, it was not until 1980 (DSM-III-R) that posttraumatic stress disorder (PTSD), marked by symptoms of reexperiencing, avoidance, and arousal, was officially delineated as a clinical diagnosis within the category of anxiety disorders. A variety of catastrophic events that are outside the range of usual human experience and would be markedly distressing to anyone, including vehicular accidents, natural disasters, rape, and combat, can cause PTSD.

Although initial delineation and further characterization of PTSD represent a major advance, the diagnostic criteria continue to emphasize factors dependent mainly on patient self-reporting. DSM-III-R and DSM-IV include exaggerated startle response as one diagnostic feature of PTSD. The presence of a psychophysiological alteration, such as exaggerated startle response, accompanying a mental disorder has provided the opportunity to obtain data that are more "objective" and more readily quantifiable than self-report data.

Because acoustic startle response is a brainstem-mediated phenomenon that can be reliably and accurately measured and because exaggerated startle response is a clinical symptom that is specific to PTSD, it has been thought to represent an objective index of brain dysfunction in PTSD. In fact, five published studies have examined the eye-blink component of the startle response in traumatized humans with PTSD (2–6). These objective studies have reported conflicting results as to whether or not the startle response is abnormal in PTSD.

In a study of six traumatized children with PTSD, Ornitz and Pynoos (2) noted persistent dysregulation and a diminishing amplitude of the startle reflex up to 21 months after trauma. Their study provided evidence that trauma may have long-lasting effects on human startle response but failed to demonstrate exaggeration of startle response. Ross et al. (3) assessed the startle response in traumatized Vietnam combat veterans with PTSD. They questioned whether PTSD might involve an impaired ability to inhibit the startle reflex upon repeated presentation with a neutral stimulus. They reported that subjects with PTSD habituated normally to neutral stimuli (3). The frequency of the blink response, rather than the magnitude of the startle response, was measured. Therefore, it is possible that while subjects

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with PTSD habituated normally, they possessed an exaggerated startle response. Neurophysiologic experiments provide evidence that habituation (a decremental process) and sensitization (an incremental process) have separate and distinct neuronal substrates; therefore, normal habituation does not preclude pathologic sensitization or increased startle response (7).

Butler et al. (4) found greater acoustic startle amplitude in response to moderate levels of startle stimuli in a subgroup of Vietnam combat veterans with PTSD than in combat comparison subjects. They did not find an abnormal startle response to high or low stimuli or abnormal habituation of the startle reflex. In addition, 35% of the patients were eliminated from the analysis because they were considered "nonresponders." The criterion by which the subjects were considered nonresponders is noteworthy because subjects with substantial startle responses were removed (4). The incorporation into the study of data from those subjects might have resulted in a significantly different outcome.

Shalev et al. (5) examined the acoustic startle reflex in Israeli combat veterans with chronic PTSD and failed to find evidence for an exaggerated startle response. However, 12 of the 14 PTSD patients participating in that study were tested while they were taking psychoactive medications, which makes the results difficult to interpret. Finally, Orr et al. (6) measured the amplitude of the eye-blink component of the startle response to 500-msec tones in Vietnam veterans with PTSD, Vietnam veterans without PTSD, and civilian comparison subjects. They found the startle response to be significantly larger in the veterans with PTSD than in the combat and civilian comparison groups.

Taken together, the previously mentioned studies suggest that there is some evidence for increased startle response in PTSD. However, at this time there are not enough data to make inferences about the nature of the pathophysiology of PTSD, as measured by the startle response, from one patient population to another. Given the extensive historical clinical impression (1, 8) of exaggerated startle response in this disorder, additional study is clearly needed.

In our recent longitudinal study of Gulf War veterans, we found that exaggerated startle response was one of the most common and persistent early symptoms reported (9, 10). The present study investigated the acoustic startle reflex in Gulf War veterans with PTSD. The study of Gulf War veterans, as opposed to Israeli or Vietnam veterans, potentially offers several advantages in understanding the nature of the startle response in PTSD: 1) the recent nature of the war trauma should minimize the likelihood that issues such as chronicity and subsequent traumatic events (i.e., multiple wars) may confound interpretation of the data, 2) there is a smaller likelihood that comorbid psychiatric and substance abuse disorders would significantly influence the startle response (11–13), and 3) the fact that Gulf War veterans represent a younger age group may increase the potential for measuring elevations of the startle response following PTSD (M. Davis, personal communication).

METHOD

Ten male Gulf War veterans with PTSD, eight combat comparison subjects, and 15 civilian comparison subjects were recruited for participation in the study. One combat comparison subject had virtually no eye-blink reflex and was excluded from the analysis. Subjects with PTSD were recruited from our outpatient PTSD clinic. Each subject with PTSD met full criteria for PTSD according to the Structured Clinical Interview for DSM-III-R (14). Two of the 10 PTSD patients had a history of alcohol dependence. Combat comparison subjects were members of the same military units as the patients with PTSD and were recruited from responses to advertisements at the reserve centers. Civilian comparison subjects were recruited through responses to advertisements from the Biological Studies Division of the National Center for Post-Traumatic Stress Disorder. None of the combat or civilian comparison subjects met the criteria of the Structured Clinical Interview for DSM-III-R—Non-Patient Edition for any psychiatric or substance abuse disorders (15). All subjects gave written informed consent to participate in this study. Each of the veteran subjects was given the Combat Exposure Scale (16), which is a 5-point subjective scale that quantifies wartime stressors (1=light, 2=light to moderate, 3=moderate, 4=moderate to heavy, 5=heavy exposure to combat). The possible range of scores is from 0 to 42. Mean combat exposure scores for the PTSD and combat comparison subjects were 16 (SD=2) and 14 (SD=1), respectively, and did not differ significantly from one another. Subjects were age matched (mean ages—PTSD patients, 24 years, SD=2; combat comparison subjects, 25 years, SD=1; and civilian comparison subjects, 24 years, SD=2). The ages of subjects did not differ significantly among groups.

All subjects participating in the study were free of illicit substance use as determined by urine toxicology screens. None of the subjects was taking medication. None of the PTSD or comparison subjects reported a history of serious medical illness.

The eye-blink component of the startle reflex was recorded with a commercially available startle system in a sound-attenuated chamber. Subjects were seated in a comfortable chair that was kept in an upright position. Audioscopic assessment tested hearing at 500, 1000, 2000, and 4000 Hz. An audiologic exclusion criterion was any hearing loss greater than one frequency band in one ear. No subjects were eliminated on the basis of the audiologic assessment. No hearing loss was noted in any of the subjects.

The orbicularis oculi electromyographic (EMG) activity was recorded with two disc electrodes (silver/silver chloride) placed 1 cm below the left eye. The ground electrode was placed on the left upper arm. Impedance was kept below 5 kΩ. EMG activity was filtered (1–500 Hz), digitized for 250 msec from onset of acoustic stimuli, rectified, and stored for off-line analysis.

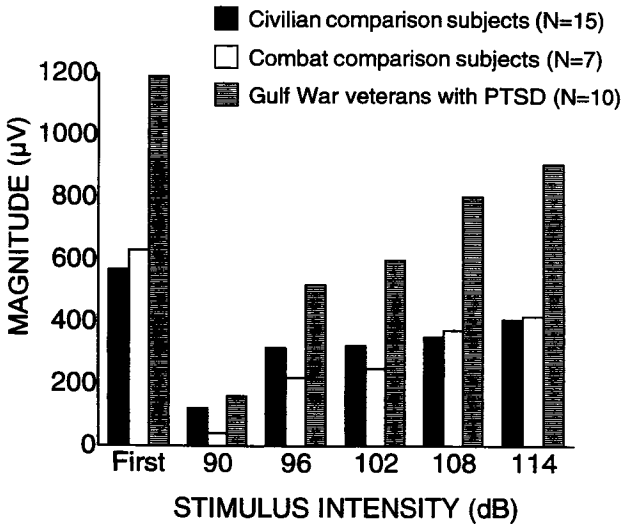
The acoustic stimulus was a 40-msec burst of white noise with a near instantaneous rise time presented binaurally through headphones. Sets of acoustic stimuli were calibrated with a sound level meter to five intensities: 90, 96, 102, 108, and 114 dB(A). These stimuli were delivered to subjects over a background of 75 dB(A) white noise. Sound was calibrated by means of a 6-cc coupler in an artificial ear and continuous noise.

Recording sessions commenced 180 seconds after the onset of background noise with an initial startle pulse (102 dB) that was analyzed separately, followed by five blocks of acoustic stimuli. Each block was composed of the five intensities presented in a pseudorandomized order every 18–22 seconds.

To analyze the blink reflex, the digital signal was smoothed by a moving average of 10 successive points. Peak amplitude of the blink reflex was determined in the 21–95 msec following stimulus onset. Peak amplitude was calculated relative to a "baseline" value. The baseline value was calculated by taking the average of the minimum and maximum values recorded during the first 20 msec. The response criterion for a peak was set at 10 μV. Trials were rejected because of unstable EMG activity during the first 20 msec or failure to reach peak within 95 msec of onset latency. Very few trials were rejected, and there was no significant difference in trial rejection among groups.

A three-way analysis of variance (ANOVA) was conducted that used group (PTSD, combat comparison subjects, and civilian comparison subjects) as between factors and block (1 to 5) and intensity

FIGURE 1. Amplitude of the Acoustic Startle Reflex in Gulf War Veterans With PTSD, Gulf War Combat Comparison Subjects, and Healthy Civilian Comparison Subjects[a]



[a]Bars show the amplitude of the first startle response, to 102 dB, as well as the startle response to the subsequent stimuli averaged over blocks of testing.

(90, 96, 102, 108, and 114 dB) as repeated factors. In addition, a one-way ANOVA with group as the factor was conducted on the first startle pulse data.

RESULTS

As shown in figure 1, the amplitude of the eye-blink reflex was larger in the Desert Storm veterans with PTSD than in the comparison groups. Analysis of the first pulse data revealed a group main effect ($F=4.21$, $df=2, 28$, $p<0.02$). The amplitude of the first startle response of PTSD subjects was significantly greater than that of the civilian comparison subjects ($t=2.6$, $df=23$, $p<0.02$) and the combat comparison subjects ($t=2.5$, $df=15$, $p<0.04$). The combat and civilian comparison groups did not differ significantly from one another.

Analysis of the eye-blink response following the initial startle stimulus revealed a significant group-by-intensity interaction ($F=5.0$, $df=8, 112$, $p<0.003$), significant linear group-by-intensity interactions ($F=6.6$, $df=2, 28$, $p<0.004$), and significant group main effect ($F=3.5$, $df=2, 28$, $p<0.04$). The same significant effects were found when the PTSD group was compared to each of the comparison groups. In the comparison of the PTSD group and combat comparison subjects, there was a significant group-by-intensity interaction ($F=4.5$, $df=4, 60$, $p<0.01$), significant linear group-by-intensity interactions ($F=6.1$, $df=1, 15$, $p<0.02$), and significant group main effect ($F=6.8$, $df=1, 15$, $p<0.02$). In the comparison of the PTSD group and civilian comparison subjects, there was a significant group-by-intensity interaction ($F=8.5$, $df=4, 92$, $p<0.002$), significant linear group-by-intensity interactions ($F=11.3$, $df=1, 23$, $p<0.003$), and significant group main effect ($F=4.7$, $df=1, 23$, $p<0.04$).

Subsequent post hoc tests indicated that the magnitude of the startle response was greater in the PTSD than in the civilian comparison group at 108 dB ($F=7.3$, $df=1, 23$, $p<0.01$) and 114 dB ($F=6.9$, $df=1, 23$, $p<0.01$). The magnitude of the startle response tended to be greater in the PTSD group at the 102-dB level of stimulation ($F=3.5$, $df=1, 23$, $p<0.07$). There were no significant differences at the 90- and 96-dB levels of stimulation. The magnitude of the startle response in the PTSD subjects was significantly greater than that in the combat comparison subjects at 96 dB ($F=5.1$, $df=1, 15$, $p<0.03$), 102 dB ($F=9.8$, $df=1, 15$, $p<0.02$), 108 dB ($F=6.4$, $df=1, 15$, $p<0.02$), and 114 dB ($F=7.6$, $df=1, 15$, $p<0.01$). The magnitude of the startle response tended to be greater in the PTSD group at 90 dB ($F=3.6$, $df=1, 15$, $p<0.07$).

Neither the group-by-block interaction nor the linear group-by-block interaction was significant, which suggests that the rate of habituation did not differ among groups. In addition, the group-by-intensity-by-block interaction was not significant.

DISCUSSION

To our knowledge, this is the first study to examine the startle response of Gulf War veterans with PTSD. Startle amplitude was greater in the PTSD patients than in the combat and civilian comparison subjects. This difference was not due to a deficit in startle habituation because the habituation of the startle reflex in the PTSD patients did not differ from that of the comparison groups and because startle response to the initial stimulus was significantly elevated. These data, like those of Butler et al. (4) and Orr et al. (6), provide evidence for the existence of an exaggerated startle response in PTSD. However, unlike Butler et al., we found a robust increase in startle response over a wide range of stimulus intensity. These results suggest that the threshold for startle elicitation may be lower for individuals with PTSD.

Several hypotheses might be invoked to account for the exaggerated startle response seen in the PTSD patients. One possibility is that the experimental situations produced higher levels of anxiety in the PTSD patients, which, therefore, served to generally elevate startle magnitude in the PTSD patients. This would account for elevated startle on the first test trial. This, coupled with the possibility that the loud startle stimuli elicited remembrance of combat situations, might account for the persistent elevation in startle response throughout testing. This would be consistent with preclinical and clinical models, which show a potentiation of the startle reflex when it is elicited in the presence of a fear-conditioned cue. However, because the acoustic stimuli were not war-related, unconditioned stimuli and because the PTSD subjects each denied that the sounds were reminiscent of war cues or war experience

in any way, it is unlikely that the increased startle reflex represents a fear-potentiated (conditioned) effect. Further studies using tactile (e.g., air puff) startling stimuli might provide additional information concerning this issue.

A second hypothesis is that the increased magnitude of startle response in the PTSD patients reflected a persistent sensitization of the reflex. Preclinical studies in the rat show that an acute elevation of the startle reflex is produced by, and persists after, stressful foot shock (17). This "shock sensitization" effect may result from activation of the amygdala and could represent a model for the increased startle response seen in the PTSD patients. Exaggerated startle response in the present study might be a reflection of a sensitization produced by the PTSD veteran's war trauma.

Because preclinical studies provide evidence that in the amygdala, noradrenaline is associated with shock sensitization of the startle reflex (18, 19), it is possible that a heightened, unconditioned response at the level of the amygdala could produce the increased startle reflex seen in the patients with PTSD. Clinical studies in our laboratory have shown that activation of the noradrenergic system with the drug yohimbine facilitates the startle reflex significantly in subjects with PTSD but not in combat comparison subjects (20). Therefore, it is possible that the alteration in central presynaptic noradrenergic neuronal reactivity that is thought to exist in PTSD (21) may be responsible for the increased startle response seen in this study. As mentioned earlier in this article, the increased startle response could be mediated by actions at the amygdala or through facilitation of the afferent volley initiated by startle at the level of the facial motor nucleus.

Two of the PTSD subjects in this study also had a history of alcohol dependence. Although alcohol withdrawal in rats has been shown to increase startle (22), this is unlikely to account for our findings. A reanalysis of the data excluding these two subjects gave the same results. In addition, both subjects had been sober for over 6 months.

The combat comparison subjects and the PTSD subjects did not differ significantly in their exposure to combat events. This finding suggests that the exaggerated startle response seen in the patients is not due simply to the experience of being in a combat zone but, rather, is a reflection of the development of PTSD and associated vulnerability factors.

The findings of this study might appear to contradict a prior investigation by Ornitz and Pynoos, which demonstrated decreased startle in children with PTSD of recent onset (2). However, because there is evidence that child and adult patterns of the startle response are not identical (23) and that age may significantly influence the startle response (24), it is premature at this time to assume a simple relationship across age between recency of trauma and startle.

The findings of this study stand in contradistinction to those of Shalev et al. (5), which did not show startle response to be significantly elevated in Israeli combat veterans with PTSD. However, it must be noted that 12 of the 14 Israeli PTSD subjects studied were taking psychoactive medications. Preclinical data indicate benzodiazepines and antidepressants may have a powerful suppressive effect on the startle reflex; therefore, it is possible that any sensitization of the startle response that may have existed was significantly inhibited. It is of note that Shalev et al. did report that there was a trend for the startle response of the PTSD veterans to be elevated (5).

Finally, the results of this study are compatible with the findings of Orr et al. (6) and suggest that a similar pathophysiology, as reflected by exaggerated startle response, may exist in PTSD veterans from different war eras.

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