ELSEVIER

Psychiatry Research 64 (1996) 169–178

PSYCHIATRY RESEARCH

Baseline startle amplitude and prepulse inhibition in Vietnam veterans with posttraumatic stress disorder

Christian Grillon*[a,b], Charles A. Morgan[a,b], Steve M. Southwick[a,b], Michael Davis[b], Dennis S. Charney[a,b]

[a] *National Center for Posttraumatic Stress Disorder, Department of Veterans Affairs Medical Center, 950 Campbell Avenue, West Haven, CT 06516, USA*

[b] *Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06519, USA*

Received 6 November 1995; revised 9 March 1996; accepted 5 May 1996

Abstract

Although an exaggerated startle response is a symptom of posttraumatic stress disorder (PTSD), empirical support for elevated baseline startle in PTSD has been weak. The present study investigated the eyeblink component of the acoustic startle reflex and prepulse inhibition (PPI) in 21 unmedicated Vietnam veterans with PTSD and in 17 civilian and 10 combat veteran comparison subjects. Patients with PTSD exhibited normal acoustic startle amplitude, but showed a significant reduction in PPI relative to the civilian subjects. There was only a trend toward a reduction in PPI in the PTSD group compared with the combat control group. The study does not support the hypothesis of exaggerated baseline startle in Vietnam veterans with PTSD but suggests abnormal startle modulation by a prepulse (i.e., PPI). Discrepancies between studies concerning the amplitude of startle in PTSD are discussed.

Keywords: Psychophysiology; Arousal; Acoustic startle reflex; Eyeblink reflex; Anxiety disorder

1. Introduction

Posttraumatic stress disorder (PTSD) presents a wide array of symptoms such as hyperarousal, dissociation, avoidance, and reexperiencing of the traumatic event (*DSM-IV*; American Psychiatric Association, 1994). One important symptom of PTSD is an exaggerated startle reflex. In fact, according to *DSM-IV*, PTSD is now the only anxiety disorder in which hyperstartle is listed as a core symptom. Because a great deal is known about the neurobiological substrates of stress-induced alterations in the startle reflex in animals (Davis, 1992), an analysis of the causes of exaggerated startle in PTSD could provide an important avenue of research to increase our understanding of central nervous system dysregulation in this disorder.

There are a number of ways in which PTSD might be associated with exaggerated startle. In

* Corresponding author, Yale University, 40 Temple St., GERU, New Haven, CT 06510, USA. Tel: +1 203 764-9744; Fax: +1 203 764-9739.

0165-1781/96/$15.00 © 1996 Elsevier Science Ireland Ltd. All rights reserved.
PII S0165-1781(96)02942-3

healthy subjects, startle shows very large variability across individuals but considerable consistency within subjects across time. It is conceivable, therefore, that patients who eventually develop PTSD might be those that had generally high levels of startle before trauma. In this case, heightened startle would be associated with PTSD instead of being caused by prior trauma and, because it was actually a reflection of a relatively stable trait variable, should be measurable at any point during the disease. To our knowledge, measurement of startle in people before and after trauma sufficient to produce PTSD has not been carried out to evaluate this possibility.

A second possibility is that exaggerated startle in PTSD results from a persistent sensitization of the startle reflex caused by severe and prolonged trauma-induced stress. Although this is a very real possibility, there are very few preclinical data that would support long-term sensitization of the startle reflex. In fact, as reviewed elsewhere (Davis, 1989), the relationship between stress and startle has not been consistent. In rats, prior stress either has little effect on startle or sometimes decreases subsequent startle. On the other hand, a brief period of electric footshock can cause a pronounced increase in startle amplitude in rats (Davis, 1989; Krase et al., 1994) and in humans (Hamm et al., 1993; Hamm and Stark, 1993), although this effect only seems to last for an hour or so. Stronger, more prolonged footshock can increase startle for longer periods of time, but again the time course is still relatively short, lasting for 4 but not 10 days (Servatius et al., 1994). Thus far, therefore, persistent sensitization of startle has been difficult to demonstrate, although this phenomenon could theoretically explain exaggerated startle in PTSD. Persistent sensitization, if present, would also predict that elevated startle should be generally measurable in PTSD versus control subjects.

A third possibility would be that exaggerated startle in PTSD reflected an acute state of conditioned fear or anxiety rather than a persistent trait variable associated with a proclivity to the disease or long-term sensitization caused by prior trauma. It is well known that startle can be elevated when presented in association with emotionally significant stimuli (Lang et al., 1990). It is possible, therefore, that a startle-eliciting stimulus (e.g., a slamming door or a ringing phone) occurring during remembrance of prior trauma (e.g., in discussion with a clinician) might be elevated during such a state, leading to the dominant clinical impression of heightened startle in PTSD. In this case, however, exaggerated startle in PTSD might only be observed under stressful test conditions.

In fact, studies that have measured acoustic startle responses in individuals with PTSD have produced conflicting results. Normal (Cuthbert et al., 1994; Orr et al., 1996), reduced (Ornitz and Pynoos, 1989), and increased baseline startle (Orr et al., 1995) responses have been reported. Two additional studies produced mixed findings. PTSD was associated with a nonsignificant ($P < 0.11$) elevation of startle in a study conducted by Shalev et al. (1992). Butler et al. (1990) also found exaggerated startle in PTSD subjects, but 35% of their subjects were eliminated from the analysis because they were considered to be startle 'nonresponders'. It is unlikely that methodological differences are the main source of the discrepancies because three studies used the same paradigm and found three different results (Shalev et al., 1992; Orr et al., 1995, 1996). More likely is the possibility that differences in startle reactivity across studies reflect interactions between specific types of symptomatologies in conjunction with the amount of stress experienced during testing. For example, the withdrawal and emotional numbing characteristics of PTSD could be a behavioral strategy to counteract the excessive arousal of this disorder. As suggested by Ornitz and Pynoos (1989), the diminished startle response reported in some individuals with PTSD could be related to the cognitive and behavioral shutting-down characteristics of some subjects with PTSD. On the other hand, the degree to which the experimental test conditions are perceived as stressful or reminiscent of prior trauma may lead to a state of heightened startle during testing.

We have examined startle in Vietnam veterans with PTSD in two studies (Morgan et al., 1995a, 1995b). In one study, startle was investigated during periods of shock anticipation (threat condi-

tion) and during periods when no shocks were anticipated (safe condition) (Morgan et al., 1995a). In the other investigation, subjects were administered placebo and yohimbine on alternative days (Morgan et al., 1995b). In both studies, startle was elevated in the PTSD patients throughout the experiments. Because startle was elevated in the safe condition of the shock experiment and in the placebo condition of the pharmacological challenges, it could be argued that baseline startle is exaggerated in individuals with PTSD. It could also be argued that the stress of the experimental context was responsible for the elevated startle response in the PTSD patients. Any interpretation of startle data in experiments that use stressful procedures is critically dependent upon the status of baseline startle in patients with PTSD. One of the aims of the present study was to assess baseline startle in the absence of any obvious experimental stress in Vietnam veterans with PTSD.

The second aim of this investigation was to explore prepulse inhibition in individuals with PTSD. Prepulse inhibition (PPI) refers to the ability of a weak prepulse to reduce the startle response to a subsequent startle-eliciting stimulus. Animal studies indicate that PPI can be affected by stress. For example, PPI is reduced in the rat following immersion in cold water (Leitner, 1986). In humans, PPI deficits have been associated with perceptual abnormalities and deficiencies in gating irrelevant thoughts (Braff and Geyer, 1990). Patients with PTSD are also characterized by perceptual deficits and by an inability to gate intrusive thoughts. Both normal PPI (Butler et al., 1990) and reduced PPI (Ornitz and Pynoos, 1989) have been reported in PTSD.

2. Method

2.1. Subjects

Subjects were 21 unmedicated Vietnam combat veterans with PTSD who were hospitalized on a specialized PTSD ward. The veterans participated in the experiment within a week of their hospitalization. The comparison subjects consisted of 11 Vietnam combat veterans without PTSD (combat controls) and 17 civilians. The patients and the control subjects did not differ significantly in age (Table 1). Combat and civilian control subjects were recruited and screened for medical and psychiatric illnesses by the Neurobiology Study Unit of the National Center for PTSD. All subjects gave written and informed consent to participate in the study. None of the subjects had previously participated in a startle experiment.

All patients met criteria for PTSD according to the Structured Clinical Interview for *DSM-III-R* (SCID; Spitzer et al., 1990). Patients with major medical illness, organic brain syndrome, schizophrenia, current bipolar disorder, major depressive disorder, or current substance abuse were excluded from the study. Patients with obsessive-compulsive disorder were also excluded because loss of prepulse inhibition has been documented in such patients (Swerdlow et al., 1993). None of the patients met criteria for generalized anxiety disorder; however, four patients met criteria for panic disorder, and 10 patients had a history of alcohol dependence. The control subjects had no major medical problems or psychiatric disorders as defined by SCID (nonpatient) criteria. Combat status of the PTSD and control veterans was screened on the basis of military discharge forms.

Table 1
Age and scores on the State-Trait Anxiety Inventory, the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder (PTSD), and the Combat Exposure Scale (CES)

	Age		State anxiety		Trait anxiety		Mississippi		Scale CES	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PTSD	41.8	1.7	55.7	12.3	62.4	8.1	127.7	20.6	28.7	7.7
Combat controls	43.2	6.4	32.2	8.0	35.8	12.2	70.7	11.6	20.6	11.6
Civilian controls	38.9	6.8	29.9	6.9	32.0	5.4				

Toxicological screening confirmed that all subjects were free of psychotropic drugs or illicit substances for at least 3 months. Audiologic screening with a Welsh Allen Audioscope indicated that all subjects could hear 40 dB (HL) pure tones in the 1000- to 4000-Hz span.

Subjects were given the state and trait portions of the State-Trait Anxiety Inventory (Spielberger, 1983) (Table 2). Veterans with PTSD had significantly higher state and trait anxiety scores, compared with scores in each of the comparison groups. One-way analyses of variance with group (PTSD, civilian controls, combat controls) as the factor revealed a main effect of group for state ($F = 32.1$, $df = 2,42$, $P < 0.0009$) and trait ($F = 53.7$, $df = 2,42$, $P < 0.0009$) anxiety scores that was due to the fact that state and trait anxiety were higher in the PTSD group, compared with the civilian (state anxiety: $t = 7.1$, $df = 33$, $P < 0.0009$; trait anxiety: $t = 12.1$, $df = 33$, $P < 0.0009$) and combat (state anxiety: $t = 5.2$, $df = 27$, $P < 0.0009$; trait anxiety: $t = 6.4$, $df = 27$, $P < 0.0009$) control groups, whose scores did not significantly differ from each other. Each veteran subject (PTSD and combat control) was also given the Mississippi Scale for Combat-Related PTSD to assess the intensity of the PTSD symptoms (Keane et al., 1988) and the Combat Exposure Scale (CES) to evaluate the level of combat exposure (Lund et al., 1984) (Table 1). The scores on the Mississippi Scale and on the CES were significantly greater in the veterans with PTSD, than in the combat controls ($t = 6.9$, $df = 27$, $P < 0.0009$ and $t = 2.2$, $df = 27$, $P < 0.03$, respectively).

2.2. Stimuli and apparatus

The recording took place in a sound-proofed chamber. The startle reflex was recorded with a commercial startle system (SR-Lab, San Diego Inst.). The acoustic startle consisted of 40-ms duration bursts of white noises with a 0-ms rise time at intensities of 98 and 103 dB(A). These stimuli were delivered alone (pulse-alone) or preceded by a 30-ms 70 dB(A) (0-ms rise time) white noise prepulse (prepulse + pulse). The prepulse was presented 120 ms before the startle stimulus (onset to onset). Thus, four different types of trials were used: (1) 98 dB(A), (2) 103 dB(A), (3) 70 dB(A) prepulse followed by 98 dB pulse, and (4) 70 dB(A) prepulse followed by 103 dB(A) pulse. The stimulus sequence consisted of an initial presentation of a 98-dB(A) and a 103-dB(A) pulse-alone stimulus in that order. These two stimuli were followed by two blocks of stimuli with each block containing the four types of trials presented twice each in a random order. Thus, a total of 18 (2 + 8 + 8) trials were delivered. The intertrial interval varied between 18 and 22 s. The stimuli were delivered binaurally through headphones (Qualitone). No background noise was presented.

The eyeblink component of the startle reflex was measured by recording activity from the orbicularis oculi muscle below the left eye with two disk electrodes (Ag-AgCl). The ground electrode was placed on the left arm. Impedance was kept below 5 kΩ. The electromyographic (EMG) activity was filtered (1–500 Hz), digitized at 1 kHz for 250 ms 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.

2.3. Data reduction and analysis

The method of analysis of the blink reflex has been presented in detail elsewhere (Morgan et al., 1995a). Briefly, the eyeblink data were analyzed after smoothing with a moving average of the digital EMG signal. Peak amplitude of the blink reflex was determined in the 21–100 ms following stimulus onset. Peak amplitude was determined relative to baseline level activity in the 20-ms poststartle stimulation. To be considered as a potential startle reflex, a response needed to be no less than 25 μV. Trials that indicated increased EMG activity during the first 20 ms or failure to reach peak within 95 ms of onset latency were rejected. The number of rejected trials was < 2% in each group.

Initial startle reactivity was defined as the eyeblink responses to the initial two startle stimuli. Startle responsiveness was defined as the eyeblink responses to the pulse-alone stimuli that followed the two initial stimuli. Except for the two initial startle responses, the magnitude of the startle

response for each trial type (two pulse-alone and two prepulse + pulse trials) was first averaged within each block. The magnitude scores were then log-transformed (adding 1 to the raw scores) to reduce the effect of skewness of their distribution. Because there were no significant differences in startle magnitude across the three groups, prepulse inhibition was calculated as a difference between eyeblink magnitude on pulse-alone trials minus eyeblink magnitude on prepulse-pulse trials. Given that the difference between the log-transformed scores is equivalent to the logarithm of the ratio of the two responses, this analysis evaluated PPI by proportional changes in startle magnitude (Ornitz et al., 1986, 1990).

Startle reactivity was analyzed with a mixed two-way analysis of variance (ANOVA) with group (PTSD, combat controls, civilian controls) as the between-subjects factor and stimulus intensity (98 dB, 103 dB) as the within-subjects factor. Startle responsiveness was analyzed with a mixed three-way ANOVA with group (3) as the between-subjects factor and with block (2) and stimulus intensity (2) as the within-subjects factors. The PPI scores were entered into a similar three-way ANOVA (group × block × stimulus intensity).

Pearson correlations were performed between the Mississippi Scale and the CES scores, and the startle magnitude and PPI measures. In addition, to assess whether startle responsivity and PPI were related to specific symptoms, subsets of questions from the Mississippi Scale were selected to calculate scores for intrusive memories (questions 4, 7, 11, 13, 14, 18, and 30), emotional numbing (questions 6, 9, 16, 17, 22, 26, and 35), arousal (questions 3, 5, 20, 24, 25, 27, and 31), and avoidance (questions 1, 22, and 33). Correlations between these symptoms and startle magnitude and PPI were also performed.

For all the statistical analyses, two-tailed tests were used. The α level was set at 0.05.

3. Results

3.1. Startle magnitude

Two patients with PTSD, one combat control, and one civilian control were considered nonresponders based on our criterion of two successive no-measurable eyeblinks in the first two blocks. These subjects were excluded from the analysis.

Table 2 presents the results of the startle response to the pulse-alone stimuli. Neither initial startle reactivity (response to the first two startle stimuli) ($F = 0.40$, $df = 2,42$, $P > 0.1$) nor startle responsiveness (startle response in the following blocks) differed among the groups ($F = 0.13$, $df = 2,42$, $P > 0.1$). Startle habituated across blocks

Table 2
Magnitude of startle response (log μV)

	PTSD (n = 19)		Combat controls (n = 10)		Civilian controls (n = 16)	
	Mean	SD	Mean	SD	Mean	SD
Startle reactivity						
98 dB(A)	4.56	0.98	4.95	0.49	4.56	0.84
103 dB(A)	4.86	0.94	5.13	0.68	5.06	1.00
Startle responsivity						
Block 1						
98 dB(A)	4.04	1.03	4.37	0.74	4.27	0.88
103 dB(A)	4.44	0.94	4.61	0.83	4.46	0.88
Block 2						
98 dB(A)	3.57	0.93	3.74	0.93	3.62	0.96
103 dB(A)	3.95	1.07	4.17	0.77	3.74	1.12

Note. PTSD, posttraumatic stress disorder.

($F = 55.6$, $df = 1,42$, $p < 0.0009$) and was larger for the 103-dB(A) than for the 98-dB(A) startle stimuli ($F = 27.0$, $df = 1,42$, $P < 0.0009$). However, these effects did not significantly differ among the three groups (no significant interactions with group).

We attempted to assess whether there was a subgroup of PTSD veterans with abnormal startle responses by comparing individual startle measures to the results obtained in the controls. No PTSD patients exhibited startle responses that differed by > 1 SD from the mean of the control subjects. Hence, the present study did not identify a subgroup of patients with either exaggerated or abnormally low startle responses.

3.2. Prepulse inhibition

Fig. 1 shows that PPI was smaller in the veterans with PTSD compared with the control subjects. The statistical analysis revealed a significant main effect of group ($F = 3.7$, $df = 2,41$, $P < 0.03$) which reflected the fact that PPI was significantly reduced in the veterans with PTSD compared with the civilian controls ($F = 7.3$, $df = 1,33$, $P < 0.01$). Although PPI was smaller in the veterans with PTSD compared with the combat controls, the difference did not reach significance ($F = 2.4$, $df = 1,27$, $P = 0.13$). PPI did not significantly differ between the two control groups ($P > 0.5$).

3.3. Correlational analysis

Table 3 presents the results of the correlational analysis in the veterans with PTSD. The magnitude of startle did not correlate with the total score on the Mississippi Scale, but it did correlate negatively with the emotional numbness score. Hence, increased emotional numbness was associated with smaller startle responses. There were also significant negative correlations between PPI and Mississippi Scale scores. Increased Mississippi Scale scores were associated with smaller

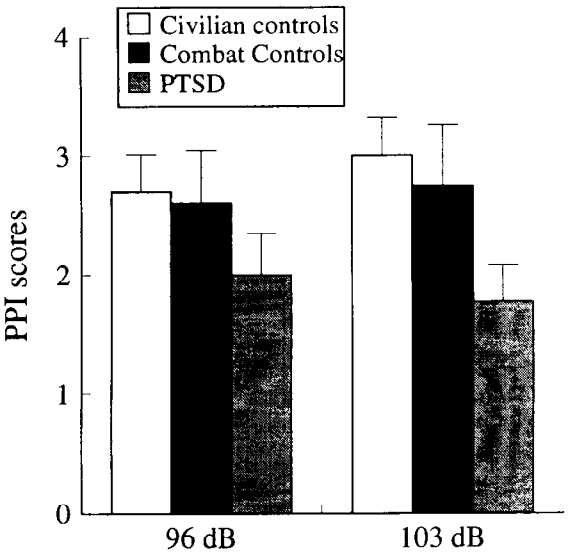

Fig. 1. Prepulse inhibition (PPI) in the Vietnam veterans with posttraumatic stress disorder (PTSD), and in the combat veteran and civilian control subjects. Greater PPI scores are associated with greater reduction of the amplitude of startle by the prepulse. A score of 0 means that the prepulse has no effect on the amplitude of startle.

Table 3
Correlational analysis in veterans with posttraumatic stress disorder

	Startle magnitude $r(P)$	Prepulse inhibition $r(P)$
Mississippi Scale for Combat-Related PTSD (total score)	NS	−0.61*[a]
Emotional numbness	−0.60*	NS
Intrusive memories	NS	−0.59*[a]
Arousal	NS	−0.66*[a]
Avoidance	NS	NS
Combat Exposure Scale	NS	NS
State anxiety	NS	NS
Trait anxiety	NS	NS

* For $P < 0.01$; [a] Negative correlation means less prepulse inhibition with increased score.

PPI. PPI was also negatively correlated with the intrusive memories and arousal subscales.

4. Discussion

The present study did not provide evidence of exaggerated startle responses in Vietnam veterans with PTSD considered either as a group or on an individual basis. This result is consistent with data reported by Orr et al. (1996), Cuthbert et al. (1994), and Ornitz and Pynoos (1989). The lack of documentation of exaggerated startle in PTSD in the present study is in contrast to clinical impressions and to empirical findings reported by Butler et al. (1990) and Orr et al. (1995). It may be that exaggerated startle is restricted to some circumstances or/and to some individuals.

It is possible that in a subgroup of veterans repeated exposure to trauma or a single intense trauma sensitizes startle. Startle sensitization, however, would be expected to dissipate with the passage of time. According to this model, increased baseline startle would be more likely to be found after a recent than after a distant trauma. In support of this hypothesis is the finding that verbal complaints of exaggerated startle were one of the first symptoms to appear in veterans from the recent Persian Gulf War (Southwick et al., 1993). In addition, Morgan et al. (1996) have documented exaggerated acoustic startle reflex in veterans with PTSD from the Persian Gulf War.

The finding of normal startle response in Vietnam veterans with PTSD in the present study, together with results from two separate studies with PTSD veterans from the same cohort indicating increased startle in stressful situations (i.e., threat of aversive shock [Morgan et al., 1995a] and yohimbine injection [Morgan et al., 1995b]), suggests that the fear-potentiated startle reflex effect is a relevant model for the symptom of exaggerated startle in Vietnam veterans with PTSD. We have suggested elsewhere that exaggerated startle in Vietnam veterans with PTSD is a reflection of their increased sensitivity to an unfamiliar and/or threatening environment and may involve deficits at the level of the hippocampus (Caine et al., 1992; Morgan et al., 1995a) because this structure has been shown to be involved in contextual fear in animals (Kim and Fanselow, 1992; Phillips and Ledoux, 1992). However, recent findings indicate that the bed nucleus of the stria terminalis is involved in fear-potentiated startle to contextual fear-eliciting stimuli (Davis et al., 1995), suggesting that this structure might also be associated with exaggerated startle in Vietnam veterans with PTSD.

The negative correlation found between emotional numbness and the magnitude of startle further suggests that startle is sensitive to individual differences in symptomatology. This hypothesis is consistent with Ornitz and Pynoos' (1989) proposal that reduced magnitude of startle in children with PTSD might be related to a cognitive and behavioral shutting down. Reduced responsivity to nonstartling stimuli in PTSD has also been reported in evoked-potential studies (Paige et al., 1990; McFarlane et al., 1993). Paige et al. (1990) noted reduced evoked potentials to intense stimuli in PTSD subjects and suggested that these individuals entered a state of protective inhibition to reduce the impact of intense stimulation. It could be argued that in some individuals with PTSD there is a general shutting down of sensory processes. This raises the possibility that behavioral withdrawal leads to reduced sensory processing through attentional deficits.

Butler et al. (1990) found exaggerated startle in Vietnam veterans with PTSD, but they discarded 35% of the patients from the analysis because they were nonresponders. In their study, eyeblink nonresponders were individuals with an eyeblink response of < 120 μV in their 116-dB(A) condition. An eyeblink of 120 μV is a response of substantial amplitude. Fig. 1 in the study of Butler et al. shows that the 100-dB startle sound elicited an eyeblink response of 75 μV in the responder control groups. This suggests that the criterion used to include subjects in the study was too restrictive. There is no agreement about what constitutes a startle nonresponder at the present time. Two patients with PTSD were designated as nonresponders in the present study on the basis of a criterion that was less restrictive than the one used by Butler et al. It should be noted that in the present study and in the study of Butler et al. the number of nonresponders did not differ between the control and patient groups, suggest-

ing that nonresponding is not a specific characteristic of a subgroup of patients with PTSD. The exclusion of subjects with substantial startle responses in the study of Butler et al. might have contributed to their findings of exaggerated startle in PTSD.

Although there are some methodological differences between studies of startle in PTSD, they do not seem to be sources of discrepancies in the results. The site (left or right) of the recording of the eyeblink does not seem to have influenced the results since exaggerated startle has been shown with recordings from both the right (Butler et al., 1990) and the left (Orr et al., 1995) eye. To the best of our knowledge, no published studies have assessed the startle/eyeblink from both eyes in patients with PTSD, but we have recently found a significant asymmetry in the magnitude of the eyeblink (left > right) in women with PTSD of recent onset (Morgan et al., submitted).

Unlike most other startle studies in PTSD, the PTSD veterans in the present study were not taking psychoactive medication. The impact of medication on startle is difficult to evaluate. Butler et al. (1990) did not report the medication status of their subjects and Shalev et al. (1992) performed no separate analyses of subjects based on medication status. Orr et al. (1995) found exaggerated startle responses in both medicated and unmedicated PTSD subjects.

PPI was impaired in patients with PTSD compared with civilian controls but not combat controls. This effect was not secondary to differences in baseline startle because the magnitude of startle responses did not differ significantly between groups. The lack of a PPI difference between the two veteran groups could be due to the fact that the present study did not have enough statistical power to detect an effect of moderate size. Alternatively, it is possible that exposure to trauma, rather than PTSD itself, affects PPI. This would be consistent with findings of reduced PPI in PTSD patients versus subjects who have not been exposed to trauma (Ornitz and Pynoos, 1989), but normal PPI compared to subjects who have been exposed to trauma (Butler et al., 1990). It is also possible that the discrepancies between studies concerning PPI deficits reflect methodological differences or differences in symptomatology or severity of illness. Based on the correlation analysis in the present study (i.e., negative correlation between PPI and total score on the Mississippi Scale), the most severely ill individuals had the least PPI. Given that the subjects of Butler et al. (1990) were recruited through advertisements, it is possible that these individuals were less ill than the veterans in the present study who were actively seeking treatment. Medication status could also have affected the PPI data in the study of Butler et al. For example, treatment with dopamine agonists could be expected to increase or normalize PPI (Swerdlow et al., 1992).

The functional significance of the reduced PPI in the veterans with PTSD is unclear. PPI has been hypothesized to reflect a gating mechanism — that is, an index of a centrally mediated inhibitory mechanism regulating sensory as well as motor and cognitive operations (Braff and Geyer, 1990). PPI deficits in schizophrenic patients (Braff et al., 1978, 1992; Grillon et al., 1992), obsessive-compulsive patients (Swerdlow et al., 1993), and individuals at-risk for schizophrenia (Simons and Giardina, 1992) have been interpreted according to this view. Thus, some of the symptoms of PTSD such as the intrusion of unwanted thoughts (e.g., flashback) could be hypothesized to result from a gating deficit. This would be consistent with the correlational analysis that showed reduced PPI correlating with increase in the score of intrusive memories. Alternatively, reduced PPI in the PTSD group could reflect an attentional deficit. PPI is increased in concert with increased attention to the prepulse (Hackley and Graham, 1987; Filion et al., 1993). Reduced PPI in the PTSD veterans would suggest less processing of the prepulse, perhaps because of distraction by internal stimuli (e.g., thoughts). Further studies should control for attention. For example, it could be investigated whether asking veterans with PTSD to pay attention to the prepulse would normalize PPI.

As indicated above, reduced PPI has been associated with several psychiatric disorders, raising the possibility that PPI impairment in the present study was not due to PTSD or combat exposure, but to a comorbid condition or to underlying

55

psychopathologic characteristics. Patients with a comorbid diagnosis that is known to be associated with PPI deficits (e.g., obsessive-compulsive disorder [Swerdlow et al., 1993]) were excluded from the study. A number of patients, however, had a history of alcohol dependence. The effects of ethanol on PPI are unclear, but it possibly could reduce PPI because PPI is affected by attention to the prepulse (Filion et al., 1993) and ethanol has a dampening effect on attention. It is unlikely that the comorbid diagnosis of alcohol dependence accounted for the present findings because the subjects had been alcohol-free for a period of at least 3 months, as verified by weekly breathalizer and urine screens. In addition, results of subjects who had a comorbid diagnosis of alcohol dependence did not significantly differ from those of subjects without such a diagnosis. Furthermore, a PPI deficit was found in children with PTSD (Ornitz and Pynoos, 1989) for whom alcohol dependence was not an issue.

Several cautions should be pointed out regarding the present findings. First, the PTSD patients had greater CES scores than did the combat controls. Although the CES score was not correlated with PPI, this difference in exposure to combat remains a potentially confounding factor. Second, it is possible that subjects exposed to gunfire experienced subtle hearing loss of a few decibels that could have affected the efficiency of the prepulse in reducing startle. This effect could account for the lack of statistical difference in PPI between the two veteran groups since both groups were exposed to gunfire. Subtle hearing loss would not have been detected by our procedure, which did not determine individual hearing thresholds but examined whether subjects were able to hear predetermined normal levels of pure tones. Future PPI studies in PTSD should carefully assess the hearing levels of their subjects.

In summary, the present study found that the acoustic startle reflex was in the normal range in Vietnam veterans with PTSD, suggesting that our previous findings of elevated startle in veterans with PTSD (Morgan et al., 1995a) may have been due to the stress induced by their participation in an experiment in which electric shocks were administered. PPI was reduced in the patients. Because it is unclear whether PPI differed in the combat controls and in veterans with PTSD, however, it is possible that exposure to trauma rather than PTSD itself is associated with PPI deficits.

Acknowledgements

The research reported was supported by National Institute of Mental Health grant 1 R29 MH-50720 to C.G., by a VA RAG to C.A.M., and by the National Center for Posttraumatic Stress Disorder.

References

American Psychiatric Association. (1994) *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*. 4th edn. American Psychiatric Press, Washington, DC.

Braff, D.L. and Geyer, M.A. (1990) Sensorimotor gating and schizophrenia: Human and animal model studies. *Arch Gen Psychiatry* 47, 181–188.

Braff, D.L., Grillon, C. and Geyer, M.A. (1992) Gating and habituation of the startle reflex in schizophrenic patients. *Arch Gen Psychiatry* 49, 206–215.

Braff, D.L., Stone, C., Callaway, E., Geyer, M., Glick, I. and Bali, L. (1978) Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology* 15, 339–343.

Butler, R.W., Braff, D.L., Rausch, J.L., Jenkins, M.A., Sprock, J. and Geyer, M.A. (1990) Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. *Am J Psychiatry* 147, 1308–1312.

Caine, S.B., Geyer, M.A. and Swerdlow, N.R. (1992) Hippocampal modulation of acoustic startle and prepulse inhibition in the rat. *Pharmacol Biochem Behav* 43, 1201–1208.

Cuthbert, B.N., Drobes, D.J., Patrick, C.J. and Lang, P.J. (1994) Autonomic and startle responding during affective imagery among anxious patients (abstract). *Psychophysiology* 31, S35.

Davis, M. (1989) Sensitization of the acoustic startle reflex by footshock. *Behav Neurosci* 103, 495–503.

Davis, M. (1992) The role of the amygdala in conditioned fear. In: Aggleton, J. (Ed.), *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*. Wiley-Liss, Inc., New York, pp. 255–305.

Davis, M., Gewirtz, J.C., McNish, K.A. and Kim, M. (1995) The role of the amygdala and bed nucleus of the stria terminalis (BNST) in the acquisition of fear potentiated startle using both explicit and contextual cues. *Soc Neurosci Abst* 21, 1224.

Filion, D.L., Dawson, M.E. and Schell, A.M. (1993) Modification of the acoustic startle-reflex eyeblink: A tool for investigating early and late attentional processes. *Biol Psychol* 35, 185–200.

Grillon, C., Ameli, R., Charney, D.S., Krystal, J. and Braff, D. (1992) Startle gating deficits occur across prepulse intensities in schizophrenic patients. *Biol Psychiatry* 32, 939–943.

Hackley, S.A. and Graham, F.K. (1987) Effects of attending selectively to the spatial position of reflex-eliciting and reflex-modulating stimuli. *J Exp Psychol* 13, 411–424.

Hamm, A.O., Greenwald, M.K., Bradley, M.M. and Lang, P.J. (1993) Emotional learning, hedonic changes, and the startle probe. *J Abnorm Psychol* 102, 453–465.

Hamm, A.O. and Stark, R. (1993) Sensitization and aversive conditioning: Effects on the startle reflex and electrodermal responding. *Int Physiol Behav Sci* 28, 171–176.

Keane, T.M., Caddell, J.M. and Taylor, K.L. (1988) Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: Three studies in reliability and validity. *J Consult Clin Psychol* 56, 85–90.

Kim, J.J. and Fanselow, M.S. (1992) Modality-specific retrograde amnesia of fear. *Science* 256, 675–677.

Krase, W., Koch, M. and Schnitzler, H.-U. (1994) Substance P is involved in the sensitization of the acoustic startle response by footshocks in rats. *Behav Brain Res* 63, 81–88.

Lang, P.J., Bradley, M.M. and Cuthbert, B.N. (1990) Emotion, attention, and the startle reflex. *Psychol Rev* 97, 1–19.

Leitner, D.S. (1986) Alterations in other sensory modalities accompanying stress analgesia as measured by startle reflex modification. *Ann N Y Acad Sci* 467, 82–92.

Lund, M., Foy, D., Sipprelle, C. and Strachan, A. (1984) The Combat Exposure Scale: A systematic assessment of trauma in the Vietnam War. *J Clin Psychol* 40, 1323–1328.

McFarlane, A.C., Weber, D.L. and Clark, C.R. (1993) Abnormal stimulus processing in posttraumatic stress disorder. *Biol Psychiatry* 34, 311–320.

Morgan, C.A. III, Grillon, C., Southwick, S.M. and Charney, D.S. (1996) Exaggerated acoustic startle in Gulf War veterans with PTSD. *Am J Psychiatry* 153, 64–68.

Morgan, C.A. III, Grillon, C., Southwick, S.M., Davis, M. and Charney, D.S. (1995a) Fear-potentiated startle in posttraumatic stress disorder. *Biol Psychiatry* 38, 378–385.

Morgan, C.A. III, Grillon, C., Southwick, S.M., Nagy, L.M., Davis, M., Krystal, J.H. and Charney, D.S. (1995b) Yohimbine facilitated acoustic startle in combat veterans with post-traumatic stress disorder. *Psychopharmacology* 117, 466–471.

Ornitz, E.M. and Pynoos, R.S. (1989). Startle modulation in children with posttraumatic stress disorder. *Am J Psychiatry* 146, 866–870.

Ornitz, E.M., Guthrie, D., Kaplan, A.R., Lane, S.J. and Norman, R.J. (1986) Maturation of startle modulation. *Psychophysiology* 23, 624–634.

Ornitz, E.M., Guthrie, D., Lane, S.J. and Sugiyama, T. (1990) Maturation of startle facilitation by sustained prestimulation. *Psychophysiology* 27, 298–312.

Orr, S.P., Lasko, N.B., Shalev, A.Y. and Pitman, R.K. (1995) Physiological responses to loud tones in Vietnam veterans with posttraumatic stress disorder. *J Abnorm Psychol* 104, 75–82.

Orr, S.P., Solomon, Z., Peri, T., Pitman, R.K. and Shalev, A.Y. (1996) Physiologic responses to loud tones in Israeli veterans of the 1973 Yom Kippur War. *Biol Psychiatry*, in press.

Paige, S.R., Reid, G.M., Allen, M.G. and Newton, J.E.O. (1990) Psychophysiological correlates of postraumatic stress disorder in Vietnam veterans. *Biol Psychiatry* 27, 419–430.

Phillips, R.G and Ledoux, J.E. (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav Neurosci* 102, 274–285.

Servatius, R.J., Ottenweller, J.E., Bergen, M.T., Soldan, S. and Natelson, B.J. (1994) Persistent stress-induced sensitization of adrenocortical and startle responses. *Physiol Behav* 56, 945–954.

Shalev, A.Y., Orr, S.P., Peri, T., Schreiber, S. and Pitman, R.K. (1992) Physiologic response to loud tones in israeli patients with postraumatic stress disorder. *Arch Gen Psychiatry* 49, 870–875.

Simons, R.F. and Giardina, B.D. (1992) Reflex modification in psychosis-prone young adults. *Psychophysiology* 29, 8–16.

Southwick, S.M., Morgan, A., Nagy, L.M., Bremner, D., Nicolaou, A., Johnson, D.R., Rosenheck, R. and Charney, D.S. (1993) Trauma-related symptoms in veterans of Operation Desert Storm: An interim report. *Am J Psychiatry* 150, 1525–1528.

Spielberger, C.D. (1983) *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologist Press, Palo Alto, CA.

Spitzer, R.L., Williams, J.B., Gibbon, M. and First, M.B. (1990) *Structured Clinical Interview for* DSM-III-R. American Psychiatric Press, Washington, DC.

Swerdlow, N.R., Benbow, C.H., Zisook, S., Geyer, M.A. and Braff, D.L. (1993) A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder. *Biol Psychiatry* 33, 298–301.

Swerdlow, N.R., Caine, S.B., Braff, D.L. and Geyer, M.A. (1992) The neural substrates of sensorimotor gating of the startle reflex: A review of recent findings and their implications. *J Psychopharmacol* 6, 176–190.