Startle Reflex Abnormalities in Women With Sexual Assault-Related Posttraumatic Stress Disorder

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Objective: *This investigation was designed to assess the acoustic startle response in treatment-seeking women with sexual assault-related posttraumatic stress disorder (PTSD).* *Method:* *Thirteen patients with sexual assault-related PTSD and 16 healthy female comparison subjects were recruited for participation in the study. Each patient met the full criteria for PTSD according to the Structured Clinical Interview for DSM-III-R. All subjects in the study were right-handed. The acoustic stimuli were bursts of white noise (92 dB and 102 dB) with a nearly instantaneous onset delivered binaurally through headphones.* *Results:* *The magnitude of the startle response (eye blink) to the first stimulus was asymmetrically distributed in the PTSD patients but not in the comparison subjects: it was greater for the left eye than the right eye in the PTSD patients only. There was a differential asymmetry of startle response in the two subgroups of patients (recent PTSD and long-standing PTSD): the startle reflex was larger for the left eye than the right in the subgroup with recent PTSD but not in the group with long-standing PTSD.* *Conclusions:* *This study provides the first objective evidence of startle abnormalities in women with PTSD. The significantly greater startle responses for the left eye compared with the right in the PTSD subjects suggest a laterality effect. As suggested by the preclinical model of shock sensitization, it is possible that in a subgroup of individuals with PTSD, trauma may sensitize the startle reflex. This model may hold true in humans and is supported by the findings of greater startle response in the patients with recent-onset PTSD.*
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It has been estimated that the prevalence of rape among women ranges between 14% and 25% (1–5). Furthermore, there is evidence to suggest that rape is more likely to induce posttraumatic stress disorder (PTSD) than other kinds of traumatic events affecting civilians, such as robbery and natural disasters (6). Rothbaum et al. (7) reported that 94% of rape victims met most PTSD symptom criteria an average of 12 days after the assault and that 46% continued to meet full PTSD symptom criteria 3 months after the trauma. Thus, it appears that a substantial number of female victims of sexual assault suffer from PTSD.

One of the preclinical methods used to understand more clearly neuronal reactivity in response to severe stress has been assessment of the startle reflex. The startle reflex is a cross-species response to intense stimuli with abrupt onset; it is characterized by considerable plasticity as well as behavioral flexibility that can be exploited to assess various cognitive, attentional, and sensory processes (8). Furthermore, the abundant preclinical data on the neurobiological and pharmacological substrates of stress-altered startle reflex in animals are a potentially rich and invaluable source of information for understanding CNS dysregulation in individuals with PTSD (9, 10).

In the past few years, a growing number of studies have reported on the eye-blink component of the startle response in combat veterans with PTSD (11–16). While there have been contradictory findings as to whether startle magnitude and startle modulation (prepulse inhibition) are abnormal, there remains a consensus that startle abnormalities do exist in male combat veterans with PTSD. However, at this time it is not known to what extent such neurobiological alterations described in veterans with PTSD can be extended to other populations.

The present investigation was designed to assess the acoustic startle response in treatment-seeking women with sexual assault-related PTSD. Previous studies have investigated the startle reflex with the use of unilateral recordings. In this study the eye-blink response of both eyes was recorded, because there is evidence that lateralized deficits may exist in subjects with PTSD (17, 18).

One of the models of exaggerated startle response in PTSD is known as "shock sensitization of startle." In preclinical studies, shock sensitization of startle refers to the prolonged increase in the acoustic startle response that

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TABLE 1. Magnitude of the Startle Response (Eye Blink) in Women With PTSD and in Healthy Comparison Women

	Response Magnitude (μV)									
	First Stimulus (92-dB Noise)		Block 1 Trials				Block 2 Trials			
			92-dB Noise		102-dB Noise		92-dB Noise		102-dB Noise	
Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Comparison subjects (N=16)										
Left eye	210.6	154.0	64.9	85.6	103.2	114.4	49.9	16.6	93.5	23.3
Right eye	214.4	171.2	68.6	95.2	115.2	132.4	53.9	98.0	93.0	71.6
Subjects with PTSD (N=13)										
Left eye	229.8	126.4	134.4	97.0	227.6	124.0	77.9	76.0	177.4	134.2
Right eye	178.7	120.0	103.2	68.4	166.3	92.2	58.2	44.2	147.9	113.0

occurs in rats after the administration of one or several shocks (19, 20). According to this model, startle would be increased shortly after exposure to trauma but would tend to normalize with the passage of time. At present there is indirect evidence that a startle response pattern similar to that seen in shock sensitization experiments may also occur in humans. We have reported an exaggerated startle reflex in Gulf War veterans with recent-onset PTSD (less than 3 years) but not in Vietnam veterans with long-standing PTSD (more than 23 years) (13, 16). The group of patients in the present study showed a wide variability in the time elapsed since exposure to the trauma of sexual assault, which provided us the opportunity to investigate further the effect of the time since trauma on the human acoustic startle response.

METHOD

Thirteen right-handed, female, civilian treatment-seeking subjects with sexual assault-related PTSD (mean age=38.1 years, SD=7.5) and 16 right-handed, female, civilian healthy comparison subjects (mean age=37.6 years, SD=10.5) were recruited for participation in the study. The subjects with PTSD were recruited from our outpatient women's trauma program at the Yale Psychiatric Institute. Each subject with PTSD met the full symptom criteria for PTSD according to the Structured Clinical Interview for DSM-III-R (SCID) (21). The mean time since sexual assault trauma in the PTSD group was 8.5 years (SD=7.2, range=1–27). Six of the 13 PTSD patients had a comorbid diagnosis of panic disorder with agoraphobia, and 11 patients had a history of major depression. The PTSD patients were administered a modified version of the Mississippi Scale for Combat-Related PTSD for civilian trauma (22). The Mississippi scale (range of scores=35–175) is a self-report inventory consisting of 35 items derived from DSM-III-based PTSD symptoms as well as associated features. It measures both symptom severity and the effects of those symptoms on an individual's life. All subjects completed the Spielberger State-Trait Anxiety Inventory (23), a self-report assessment that evaluates state and trait qualities of anxiety.

The healthy comparison subjects were recruited through advertisements from the Biological Studies Division of the National Center for PTSD. None of the comparison subjects met criteria for any psychiatric or substance abuse disorders according to the non-patient edition of the SCID. None of the PTSD or comparison subjects reported a history of serious medical illness.

All subjects participating in the study were free of illicit substance use as determined by urine toxicology screens. None of the subjects took medication while participating in the study. All subjects gave written informed consent to participate.

The acoustic stimuli were bursts of white noise with a nearly instantaneous onset produced by a Coulbourn S81-02 noise generator, gated through a Coulbourn S82-24 amplifier, and delivered binaurally through headphones. There were three types of trials: two pulse-alone trials—40-msec-duration bursts of white noise at 92 dB(A) and 102 dB(A)—and a prepulse plus pulse trial—a 30-msec-duration burst of 70-dB(A) white noise delivered 120 msec before the onset of a 40-msec-duration 102-dB(A) pulse. The order of stimulus presentation was as follows: an initial 92-dB pulse (the "first startle stimulus") followed by two blocks of trials during which each of the three types of trials was presented three times in random fashion. Hence, there was a total of 19 trials (one plus nine plus nine). The interstimulus interval varied from 17 to 23 seconds.

Subjects were seated in a comfortable chair that was kept in an upright position. Audioscopic assessments tested hearing levels at 500, 1000, 2000, and 4000 Hz. No hearing loss was noted in any of the subjects.

Orbicularis oculi electromyographic (EMG) activity was recorded with two disk electrodes (silver/silver chloride) placed below each eye. The ground electrode was placed on the left upper arm. Impedance was kept below 5 kΩ. EMG activity was amplified by a factor of 20,000 with a 90- to 1000-Hz band-pass filter, rectified and integrated by means of a 5-msec time constant, and digitized at 1000 Hz/second. The magnitude of the startle response was determined off-line, as the magnitude scores were reduced by averaging the data within trial types for each block. Prepulse inhibition was calculated as the percent reduction from the magnitude of the startle response to the 102-dB pulse-alone trial to the magnitude of the response to the prepulse plus 102-dB pulse trial.

The magnitude scores were analyzed with repeated measures analysis of variance (ANOVA). The eye-blink response to the first pulse (92 dB) was analyzed with a two-way ANOVA with group (patients, comparison subjects) and eye of the recording (left, right) as the two factors. The magnitudes of eye blinks in response to the subsequent pulse-alone trials (two blocks of trials) were entered into a four-way ANOVA with group (patients, comparison subjects), eye of recording (left, right), block (block 1, block 2), and stimulus intensity (92 dB, 102 dB) as the factors. The prepulse inhibition scores were analyzed with a two-way ANOVA with group (patients, comparison subjects) and block (block 1, block 2) as the factors.

RESULTS

Overall Analysis

Table 1 presents the startle response magnitude data for the two groups of women. The magnitude of the startle response to the *first* stimulus was asymmetrically distributed in the PTSD subjects but not in the comparison subjects. This was reflected by a significant group-by-eye interaction ($F=4.3$, $df=1, 27$, $p<0.04$), which was due to the greater startle response for the left eye than the right eye in the PTSD subjects only (PTSD subjects: $F=6.0$, $df=1, 12$, $p<0.03$; comparison subjects: $F=0.05$, $df=1, 15$, n.s.).

Table 2 shows the results of the four-way ANOVA of

TABLE 2. Results of the Four-Way Analysis of Variance[a] of the Data on Magnitude of the Startle Response in Women With PTSD and in Healthy Comparison Women

Effect	F (df=1, 27)	p
Group	2.8	n.s.
Group by eye	7.7	0.01
Group by block	6.0	0.02
Group by intensity	6.7	0.01
Group by eye by block	8.5	0.007
Group by eye by intensity	3.7	0.06
Group by block by intensity	0.5	n.s.
Group by eye by block by intensity	6.6	0.01

[a]Group (subjects with PTSD, healthy comparison subjects), eye (right, left), trial block (block 1, block 2), and stimulus intensity (92-dB noise, 102-dB noise).

the data on startle response magnitude. Although the overall startle response was not significantly greater in the PTSD subjects than in the comparison subjects, there were a number of significant differences between the groups, as reflected by several significant interactions with group, including a four-way interaction.

These interactions were due to the fact that the magnitude of the startle response was lateralized (left greater than right) in the PTSD subjects ($F=7.8$, $df=1, 12$, $p<0.01$) but not in the comparison subjects ($F=0.002$, $df=1, 16$, n.s.). As a result, the startle response was greater in the PTSD group than in the comparison group for the left eye but not the right eye. This laterality effect was affected by the intensity of the startle stimulus and by the block of stimulus delivery. It tended to be greater for the more intense startle stimulus and in block 1. Post hoc group comparisons for each trial in each block indicated that startle magnitude was greater in the PTSD patients than in the comparison subjects only for the left eye in response to the 102-dB startle stimuli in block 1 ($t=2.8$, $df=27$, $p<0.009$) and block 2 ($t=2.0$, $df=27$, $p<0.05$) and in response to the 92-dB startle stimuli in block 1 ($t=2.0$, $df=27$, $p<0.05$).

The prepulse inhibition effect was not lateralized and did not significantly differ between the two groups. In the comparison subjects, the prepulse stimulus reduced the startle response to the 102-dB startle stimuli by 54.6% (SD=33.6%) and 50.1% (SD=38.0%) for the left and right eye (averaged over two trial blocks), respectively. In the PTSD subjects, the reduction effect was 65.1% (SD=30.6%) and 62.3% (SD=37.8%) for the left and right eye, respectively.

Pearson correlations between trait and state anxiety ratings and the Mississippi scale scores (for the PTSD subjects only) and startle response magnitude (averaged over blocks and intensities) were calculated separately for the left and the right eye. There were no significant correlations between startle magnitude and state or trait anxiety scores in the healthy subject group. In the PTSD group, there were significant positive correlations between trait anxiety and the magnitude of the startle response for the left eye ($r=0.64$, $N=13$, $p<0.01$) and the right eye ($r=0.60$, $N=13$, $p<0.02$). The total Mississippi scale score was positively correlated with the magnitude of startle for the right eye ($r=0.61$, $N=13$, $p<0.02$).

Effects of Time Since the Trauma

Within the patient group there was a bimodal distribution in the time elapsed since the index trauma (range=2–6 years and range=10–27 years). Those individuals whose index trauma occurred within the past 6 years (mean=3.7 years, SD=2.0) were identified as the "recent" trauma subgroup (N=6). They were compared with the "long-standing" trauma subgroup, whose index trauma occurred more than 10 years (mean=16.2 years, SD=6.2) before testing (N=7). The two subgroups did not differ significantly in age (recent PTSD: mean=38.8 years, SD=8.3; long-standing PTSD: mean=37.6 years, SD=7.3).

The same ANOVAs described above were used to compare the two subgroups with PTSD. There was a differential asymmetry in the magnitude of the startle response to the first pulse-alone trial in the long-standing PTSD subgroup compared to the recent-PTSD subgroup and the non-PTSD group (group by eye of recording: $F=5.6$, $df=1, 11$, $p<0.03$, and $F=8.7$, $df=1, 21$, $p<0.008$, respectively). The eye blink response was larger for the left eye (mean=272.4 μV, SD=126.3) than the right eye (mean=182.0 μV, SD=118.0) in the recent-PTSD subgroup but not in the long-standing PTSD subgroup (mean=180.1 μV, SD=118.2, versus mean=174.9 μV, SD=133.1) or in the non-PTSD group. Although similar results were obtained for the magnitude of the eye-blink response recorded during the two blocks of pulse-alone trials, the group-by-eye-of-recording interaction was significant for the comparison between the long-standing PTSD subgroup and the non-PTSD group ($F=10.8$, $df=1, 21$, $p<0.003$) but not the comparison between the two PTSD subgroups ($F=3.0$, $df=1, 11$, $p=0.11$). The overall eye-blink magnitude was greater for the left eye (mean=175.2 μV, SD=133.9) than for the right eye (mean=120.2 μV, SD=143.3) in the recent-PTSD subgroup ($t=2.5$, $df=6$, $p<0.04$) but not in the long-standing PTSD subgroup (left eye: mean=129.9 μV, SD=75.6; right eye: mean=117.4 μV, SD=68.5). Significantly greater left eye-blink magnitude was found in the recent-PTSD subgroup compared with the non-PTSD group ($t=2.1$, $df=21$, $p<0.04$).

Subgroup analysis of the PTSD patients with comorbid panic disorder and/or a history of major depression did not reveal any significant group differences compared to those PTSD patients who did not have comorbid panic or a history of major depressive disorder.

DISCUSSION

This study provides the first objective evidence of acoustic startle abnormalities in treatment-seeking women with sexual assault-related PTSD. There were significant differences in eye-blink magnitude for the left eye between the non-PTSD and PTSD groups. It should be emphasized that although the startle reflex in the PTSD subjects was lateralized and significantly elevated for the left eye, it was also larger—though not

significantly—for the right eye as well. While previous reports have shown little evidence of lateralization of the startle reflex, there is evidence from several studies (24–27) that its modulation by negative emotion is lateralized. However, the nature of this lateralization is still not well understood, as indicated by conflicting results in those studies. The implications of lateralization in PTSD are not clear and must be interpreted with caution. Nevertheless, the data of this study add to the growing body of evidence supporting the existence of an exaggerated startle response in individuals with PTSD and suggest that some similarities in pathophysiology may exist in women and men with the disorder.

The presence of an exaggerated startle response to the 102-dB stimuli is consistent with the findings of startle studies in combat veterans, which have reported increased startle response to intermediate and loud tones (95–114 dB) (12, 14, 16). Our finding of normal prepulse inhibition and normal habituation in treatment-seeking women with sexual assault-related PTSD is also consistent with the findings of previous startle studies conducted with veterans suffering from PTSD (11, 28). By contrast, the finding of an exaggerated startle response to the 92-dB stimulus in the women with PTSD differs from startle studies in male subjects, which have not reported an exaggerated startle response to soft tones (90–95 dB) (11–13, 16). Whether this difference in the startle response is more influenced by gender, age, or recency of trauma remains to be investigated in future studies. However, taken together, these data provide additional evidence that there is heightened unconditioned responding in individuals with PTSD and that such responding may diminish with time.

The significantly greater startle responses for the left eye compared to the right in the PTSD subjects suggest a laterality effect. This was an unexpected finding given the extensive body of literature on laterality and emotional processing, which suggests that the female brain may be functionally less asymmetrical than the male brain (29, 30). No previous investigations in our laboratory have detected such a lateralized startle response in male subjects. However, there are a few studies that have described differentially lateralized abnormalities in male and female subjects with PTSD. Bremner et al. (17, 18) reported finding decreased *right* hippocampal volume in male veterans with PTSD and decreased *left* hippocampal volume in civilian women with PTSD.

While it remains unclear whether these hippocampal abnormalities existed prior to, or were the result of, exposure to trauma, there is preclinical evidence that the findings of Bremner et al. may be relevant to our data. Coover and Levine (31) reported that lesions of the rat hippocampus may lead to an increase in startle response. Thus, it is conceivable that the exaggerated startle response recorded for the *left* eye in the women with PTSD may be due to *left*-sided hippocampal abnormalities, the effects of which on the startle response are exhibited through the ipsilaterally innervated (cranial nerve VII) *left* orbicularis oculi muscle. Clearly, the issue of laterality remains to be investigated further.

Positive correlations were noted between startle response and total Mississippi scale score and between startle response and trait anxiety. Taken together, these findings suggest that heightened unconditioned responding may play a substantial role in the overall severity of clinical symptoms experienced by patients with PTSD. Indeed, these data are consistent with the findings of previous investigations and with historical perspectives suggesting that startle and anxiety are core clinical features of the human psychological response to traumatic experiences (32–34).

Clinical studies have provided evidence of learned physiological activation that becomes inappropriately displayed in stressful environments (35–37). These observations have led to the hypothesis that exaggerated startle response in PTSD is part of a conditioned response to stressful situations or stimuli reminiscent of trauma (38). However, nonassociative or unconditioned learning processes may also underlie some of the symptoms of PTSD. Recent investigations in both Israeli and American combat veterans have provided evidence for heightened unconditioned responding in individuals with PTSD (12, 14, 16). In the present study, the positive correlations between the trait (and not state) anxiety scores, the Mississippi scale scores, and the magnitude of the startle response in the PTSD subjects are compatible with this hypothesis of heightened unconditioned, or nonassociative, responding. Exaggerated startle could be viewed as a heightened unconditioned response in individuals who are considered to be in an abnormally prolonged state of anxiety or alarm.

A relevant animal model of the unconditioned response is the shock sensitization of startle. The increase in the startle response of the rat following the administration of electric shocks can be observed for a long period of time after shock administration (39). Shock sensitization of startle is critically dependent on the integrity of the amygdala (40). However, the hippocampus might also be associated with this effect, because shock sensitization of startle could be viewed as a form of contextual fear conditioning (41, 42), which itself relies on hippocampal activity (43, 44).

It is possible that in a subgroup of individuals with PTSD, repeated exposure to trauma or a single intense trauma may sensitize the startle response. Startle sensitization, however, would be expected to dissipate with the passage of time since the traumatic event. This hypothesis is supported by preclinical studies of the behavioral and neuronal transient and long-term changes to aversive stimuli. In the mollusk Aplysia, short-term sensitization generally fades within 1 hour, but severe or repeated intense stress has led to more durable increases in reactivity (45). This model may hold true in humans and is supported by our findings of greater startle response in the PTSD subjects in the recent-trauma subgroup compared with the long-standing trauma subgroup.

The findings of this study are consistent with the preclinical startle literature and are further supported by recent startle studies in our laboratory. Although we have found, in a nonstressful environment, that the startle re-

sponse was markedly elevated in Gulf War veterans with relatively recent-onset PTSD (less than 3 years), we have not found it to be increased, under similar circumstances, in Vietnam veterans with long-standing PTSD (more than 23 years) (13, 16). Hence, we suggest that individuals with recent-onset PTSD exhibit an exaggerated, sensitized, baseline startle response that tends to diminish with time.

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