Acoustic Startle in Individuals With Posttraumatic Stress Disorder

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Posttraumatic stress disorder (PTSD) was officially delineated in 1980 as a clinical diagnosis within the category of anxiety disorders. It was marked by symptoms of re-experiencing, avoidance, and hyperarousal that developed subsequent to exposure to one or more traumatic events. Although this definition of PTSD represents a major advance, the diagnostic criteria continue to emphasize factors mainly dependent on patient self-report and are thus susceptible to the limitations inherent in subjective data. However, both the *Diagnostic and Statistical Manual* (DSM)-III-R and DSM-IV include "exaggerated startle" as diagnostic features of PTSD. The presence of a physical alteration accompanying a mental disorder provides an opportunity to obtain data that are more "objective" and more readily quantifiable than self-reported data. The most compelling feature of the acoustic startle reflex for research on PTSD is the abundant basic research that informs its underlying anatomic functional basis. The clarity of this information represents a significant step toward understanding the biologic pathways involved in the pathophysiology of PTSD.

The primary aim of this article is to familiarize the reader with the conceptual basis, hypotheses, and results of investigations examining the acoustic startle response in traumatized individuals. Many of the underlying hypotheses and concepts are similar to those associated with psychophysiology studies of individuals with PTSD. The reader interested in a comprehensive review of the PTSD psychophysiology literature is advised to consult the extensive review by Prins and colleagues.[1] After completing this article, it is anticipated that the reader will understand why and how startle studies have been conducted, and the degree to which the results of these studies can be interpreted or applied to the clinical setting.

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THE RELEVANCE OF THE STARTLE RESPONSE TO PTSD

Historic and contemporary records provide evidence that an important symptom seen in combat veterans with combat-related psychiatric sequelae has been and continues to be an exaggerated startle reflex.[2-4] Clinical observations of exaggerated startle in distressed combat veterans were so common by mid-century that some psychiatric authorities referred to increased startle as the cardinal symptom of combat fatigue.[5] Although not considered the cardinal symptom of PTSD today, exaggerated startle remains tightly linked to trauma exposure. In fact, according to DSM-IV, PTSD is now the only anxiety disorder in which exaggerated startle is listed as a core symptom.

The startle reflex is a ubiquitous, cross-species response to intense exteroceptive stimuli with abrupt onset. Its plasticity to experimental manipulation, its short latency, and the ease with which it can be recorded make this reflex an extremely useful tool to investigate sensorimotor reactivity. The startle reflex in humans and animals shares a number of similar parametric characteristics and displays habituation, sensitization, and prepulse inhibition.[5,6] All of these characteristics indicate that

modulation of startle in humans provides an important experimental paradigm that can be closely modeled in infrahuman subjects.

There are several animal models that are relevant to the exaggerated startle response in individuals with PTSD: fear conditioning, shock sensitization, and a generalized, heightened physiologic arousal. In animals, startle can be increased by conditioned fear, exposure to highly stressful events (eg, shocks), and environments that are stressful.

Considerable evidence suggests that the startle reflex is increased by fear in animals.[7] In the rat, the startle reflex is potentiated when it is elicited in the presence of a discrete cue (for example, a light) that has been previously associated with an aversive outcome (for example, a shock). This "fear potentiation" of the startle reflex is reduced in animals by drugs known to reduce anxiety in humans (eg, diazepam)[8] and is increased by drugs that increase human anxiety (eg, yohimbine).[9]

In addition to fear-potentiated startle to discrete cues, startle is also potentiated by situations in which the environmental context is threatening. Two types of aversive contexts that have been shown to potentiate startle in the rat are sustained bright lights and placement of the animal in a cage where it has previously received electric shocks.

Animal studies suggest that different brain systems may mediate fear to explicit cues and contextual fear. Lesions of the hippocampus or the bed nucleus of the stria terminalis (BNST) block context conditioning but not explicit cue conditioning, whereas lesions of the amygdala block both.[11-13] In addition, inactivation of the BNST but not the central nucleus of the amygdala blocks the potentiation of startle by sustained bright lights.[13] These data suggest that the hippocampus and the BNST may be especially important in contextual fear or anxiety compared with explicit cue conditioning, which is dependent on the amygdala. The finding that separate brain processes mediate fear to explicit and contextual cues is significant for the study of both normal and pathologic anxiety because it suggests that different neurobiologic mechanisms may underlie aversive responses.

Fear-potentiated startle can also be measured in humans using the eye blink, which is the most persistent component of the startle reflex. Startle is potentiated by explicit threatening stimuli such as those signaling the imminent administration of unpleasant electric shocks.[14] After telling subjects that they might receive an aversive shock when a threat light is turned on, the magnitude of startle elicited in the presence of the threat signal doubles in size.

Startle is also potentiated by several types of contextual stimuli. Placing shock electrodes or returning to an experimental room where subjects previously have been shocked increase the magnitude of startle.[15] Startle is also potentiated by darkness and increases by approximately 15% to 20% when elicited in a dark room as compared with an illuminated room.[16] This effect is consistent with the facilitation of startle by sustained bright lights in the rat and suggests that animals and humans are both sensitive to contextual cues.

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Human studies also suggest that fear to explicit cues and fear to contextual cues are separate processes. Individuals with anxiety disorders, such as PTSD and panic disorder, are especially sensitive to contextual threatening stimuli but show relatively normal responses to explicit threat cues. It is possible that the differentiation between fear to explicit and contextual cues is relevant to the distinction between stimulus-specific fear elicited by a clearly identifiable source and generalized free-floating anxiety that is not stimulus-bound. One hypothesis states that explicit threat cues produce fear, whereas contextual stressful stimuli elicit anxiety. If this model is correct, anxiolytic stimuli or safety cues might be expected to act preferentially on contextual fear rather than on fear to explicit cues.

Thus, startle possesses several properties that make it an ideal tool for investigating the neuropathophysiology of PTSD: it is modulated by anxiety and fear; it undergoes a generalized increase following exposure to highly aversive stimuli; it is reflective of classic fear-conditioning to specific cues; it is increased in environments that are perceived to be stressful; and finally, its modulation under the above-described circumstances involves brain mechanisms that are distinct and that are differentially associated with these various properties.

THE ASSOCIATION BETWEEN EXAGGERATED STARTLE AND PTSD

Theoretically, there are a number of ways that exaggerated startle and PTSD might be associated. Because startle shows a large variability across individuals but high consistency within subjects over time, it is possible that exaggerated startle might be a marker in individuals with PTSD, that is, people who eventually develop PTSD might be those individuals who had high levels of startle before exposure to trauma and the development of the disorder. Rather than being caused by trauma (and/or PTSD itself) exaggerated startle might be a reflection of a stable trait. At this time, however, no controlled studies have tested this possibility because none have measured the startle response in individuals before and after exposure to intense trauma to test this possibility.

Subjects whose PTSD was of a long-standing nature (more than 10 years) showed no differences in startle compared with healthy subjects.

A second possibility, and one that is compatible with preclinical literature, is that exaggerated startle in PTSD reflects a persistent sensitization, or heightened responding, caused by exposure to trauma-induced psychologic stress. Support for this hypothesis in humans comes from a number of startle studies that have documented heightened baseline startle in individuals with PTSD. For example, Butler and Braff[17] reported exaggerated startle to brief (40 ms) white noise burst in a subgroup of Vietnam combat veterans with PTSD compared with combat veterans without PTSD. This study provided the first objective evidence for startle abnormalities in Vietnam veterans with PTSD and was thought to be compatible with the sensitization hypothesis of the startle reflex because the testing conditions were free of stressful or trauma-related stimuli. Surprisingly, the data from this study also showed that 30% of the veterans with PTSD did not show a startle response. It is possible that this finding may be the result of methodological considerations; however, these data may also be taken as evidence that some individuals with PTSD may not exhibit exaggerated startle.

Orr and colleagues[18] also investigated the eye-blink component of the startle response in Vietnam veterans with combat-related PTSD. They too found exaggerated baseline startle in veterans with chronic PTSD. Exaggerated baseline startle was interpreted as compatible with a sensitization model in which the startle reflex becomes exaggerated in response to a broad array of stimuli and not just trauma-relevant stimuli. In retrospect, the data from this study may not represent unambiguous evidence for a "trauma-induced," tonic sensitization of startle in individuals with PTSD. There is a possibility that the white noise stimuli used to elicit startle may have unintentionally sounded like gunfire (or radio static) to some veterans and thus evoked a "conditioned response."

In two separate investigations, Morgan and colleagues[19,20] examined the baseline startle reflex in Gulf War veterans with combat-related PTSD and in civilian women with sexual assault-related PTSD. In both studies, the startle reflex was noted to be significantly increased in PTSD subjects compared with subjects without PTSD. These investigations provide robust evidence for the shock-sensitization model of increased startle in PTSD because the greatest increases in startle were seen in individuals whose PTSD was of recent onset (less than 5 years). Subjects whose PTSD was of a long-standing nature (that is, longer than 10 years) showed no differences in startle compared with healthy subjects. Finally, because the women had not been exposed to gunfire, it is extremely unlikely that the exaggerated startle reflects a conditioned response to the white noise stimuli used in the experiment.

Although most studies have provided evidence of exaggerated baseline startle in individuals with PTSD, some have not. Indeed, a number of investigations have reported *normal* or *reduced* startle in individuals with PTSD. For example, Ornitz and colleagues[21] examined the startle reflex in children with PTSD and found it to be reduced when compared with children without PTSD. Similarly, Shalev and colleagues[22] and Grillon and colleagues[23] failed to find any significant differences in acoustic startle responding between combat veterans with PTSD and non-PTSD subjects. These data do not support the idea of a general, pervasive sensitization of startle in individuals with PTSD. However, they are compatible with the animal literature regarding the chronic effects of trauma on the startle response. This literature suggests that exaggerated startle responses may be phasic (or intermittent) rather than tonic (or continuous) in nature.[24]

Thus, a third possible explanation for the association between exaggerated startle and PTSD is that increased startle reflects a classically conditioned, or fear-potentiated, response. In other words, exaggerated startle may be reflective of a conditioned response to the emotional states of anxiety or fear. Increased startle may manifest itself in individuals with PTSD when they are in a state of heightened emotional arousal brought on by stress. Support for this idea comes from the observation that human startle can be elevated under conditions that are emotionally salient[25] and from four relevant studies of startle in Vietnam combat veterans with PTSD.[23,26-28]

In the first study, startle was investigated during periods of time when subjects anticipated the receipt of electric shocks (threat period) and during periods when they knew that no shocks would be administered (safe period). In the second study, each subject was administered the alpha-2 antagonist yohimbine on one day and placebo on a separate day. In both experiments, the startle response of PTSD subjects was elevated throughout all phases of the studies, whereas startle in the comparison subjects was normal. In the third study, startle was tested under neutral conditions and found to be normal for PTSD subjects, healthy subjects, and combat control subjects. Because startle was elevated in the safe condition of the shock experiment and also in the placebo condition of the pharmacologic challenge study but was not elevated when tested under neutral conditions, we

proposed that the stress of the experimental context was responsible for the exaggerated responses.

This hypothesis was tested in our fourth investigation. In this study, the startle of Vietnam veterans with combat-related PTSD was tested under neutral (baseline) conditions and then 1 week later under both neutral and stressful (threat of shock) conditions.[28] The startle of veterans with PTSD did not differ from that of comparison subjects when tested on the neutral day alone. However, significant differences were noted on the second day of testing. During the baseline startle test, in the absence of shock electrodes, startle was noted to be significantly larger in the PTSD patients. This difference in startle continued to increase as the threat-of-shock testing began. The largest differences between the startle of control subjects and PTSD veterans occurred after the placement of the shock electrodes. These data provided strong evidence that the exaggerated startle in Vietnam veterans with PTSD was context-dependent.

These data may seem to be incompatible with our reports of exaggerated startle in both Gulf War veterans with PTSD and in civilian women with sexual assault-related PTSD. However, it is likely that abnormalities of both a tonic and phasic nature may exist in PTSD and are reflections of the evolution of PTSD symptomatology over time. In our laboratory, Gulf War veterans with recent-onset PTSD (3 years) showed exaggerated baseline startle whereas Vietnam veterans with PTSD of a longstanding nature (20 years) did not. Similarly, civilian women with PTSD exhibited exaggerated baseline startle if the onset of PTSD was within 5 years of testing. Subjects whose PTSD was of an onset longer than 10 years before testing did not exhibit exaggerated startle under neutral conditions. Consistent with this hypothesis, a recent investigation of startle in adult women with PTSD from childhood sexual abuse failed to find abnormalities in baseline startle.[29] Thus, early in the development of PTSD, the tonic state of heightened arousal may be exhibited as a generally elevated startle reflex. After a number of years, however, this overall heightened responding is most likely to be seen during or after exposure to stressful contexts.

EXPLICIT AND CONTEXTUAL LEARNING IN PTSD

Finally, clinically distressing levels of fear and anxiety are prominent in cases of PTSD. It is possible these highly disruptive affective states may also reflect deficits in learning or in the modulation of the emotional states. To examine this possibility, we recently performed a conditioning experiment with Gulf War veterans suffering from PTSD.[30] In this procedure, we exposed subjects to a series of electric shocks while they viewed a series of lights. We did not tell the subjects which of the two lights would be associated with electric shock. Their startle

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responses were measured throughout the testing. We wanted to determine whether or not they would be able to discriminate (as measured by fear-potentiated startle) between threat and safety signals. On the first day of testing, startle was measured before, during, and after subjects were exposed to the lights followed by the light/shock training trials. During the training trials, only one of the two lights was paired with electric shocks (threat light). This design permitted an assessment of whether, and to what degree, startle would increase in the presence of the light that was paired with the electric shock. At the conclusion of the training trial on the first test day, subjects were exposed to the safe and threat lights. At this point, significant differences in the startle response were noted between PTSD and comparison subjects.

Although startle in PTSD subjects had not differed from that of the control subjects before the light/shock training trials, it was significantly different after the training trials. The main difference noted was that the PTSD subjects showed increased startle to both the safe and threat lights, whereas the healthy subjects only increased startle when presented with the threat light. Startle did not differ between the groups when both lights were turned off. This meant that the differences between the groups were not simply the result of a generalized increase in overall startle. The PTSD subjects did not show greater increases in conditioned fear as measured by startle to the threat light compared with healthy subjects. They did, however, exhibit fear in the presence of the safe light despite their verbalization that the safety light was not associated with shock.

One week later, subjects returned to the laboratory and repeated the same procedure. This time, baseline startle in PTSD subjects was noted to be significantly greater than that seen in comparison subjects. During exposure to the safe and threat lights, startle in PTSD subjects increased, but did not vary, consistent with the idea that they had not developed differential conditioning the week before. By contrast, healthy subjects continued to show significant increases in startle when exposed to the threat light. These data suggest that the PTSD subjects generated the same levels of conditioned fear to a threat cue as did healthy subjects. They could not, however, inhibit this fear when presented with a safety signal. The significant increase in baseline startle of PTSD subjects from day 1 to day 2 suggests that, in addition to

a fear of the lights (explicit cues), they developed a fear to the test setting itself (contextual cue).

As noted above, these findings are consistent with animal studies, which suggest that different brain systems mediate fear to explicit cues (such as a light indicating shock) and contextual fear (fear of the place where the shocks were experienced).[11-13] These results of the above-described study in Gulf War veterans point to a dysfunction of the hippocampus and/or the BNST.

CONCLUSION

The various startle investigations in PTSD have not uniformly reported exaggerated responding. The data are, however, compatible with animal models of startle abnormalities following exposure to highly aversive events. Taken together, the animal and clinical literature support the idea that shortly after exposure to a stressful or traumatic event, startle may be tonically elevated. In recent-onset PTSD, it is likely that this exaggerated startle reflects increased physiological arousal resulting from noradrenergic hypersensitivity. Although this deficit may last for a number of years, it eventually fades with the passage of time. In long-standing PTSD, this tonic physiological arousal is replaced by a sensitized response to stressful stimuli. To clarify, this sensitization is not general; it concerns only the response to stressful contexts.

Finally, there is evidence that some individuals with PTSD show deficits in aversive learning. They tend to generalize fear across stimuli and are unable to respond appropriately to safety signals. Studies of the neural mechanisms that are involved in these processes have provided evidence that CRH release may be responsible for these deficits through its influence on the BNST. Clearly, future studies examining the pharmacology of fear-potentiated startle in humans may contribute to the treatment of PTSD.

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