

Increased Anxiety During Anticipation of Unpredictable Aversive Stimuli in Posttraumatic Stress Disorder but not in Generalized Anxiety Disorder

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Background: Uncontrollability and unpredictability are key concepts related to re-experiencing, avoidance, and hypervigilance symptoms of posttraumatic stress disorder (PTSD). However, little is known about the differential sensitivity of PTSD individuals to unpredictable stressors, relative to either healthy individuals or individuals with other anxiety disorders. This study tested the hypothesis that elevated anxious reactivity, specifically for unpredictable aversive events, is a psychophysiological correlate of PTSD.

Methods: Sixteen patients with PTSD (34.5 ± 12.4 years) were compared with 18 patients with generalized anxiety disorder (GAD) (34.0 ± 10.5 years) and 34 healthy control subjects (30.2 ± 8.5 years). Participants were exposed to three conditions: one in which predictable aversive stimuli were signaled by a cue, a second in which aversive stimuli were administered unpredictably, and a third in which no aversive stimuli were anticipated. Startle magnitude was used to assess anxious responses to the threat cue and to contexts associated with each condition.

Results: Posttraumatic stress disorder and GAD patients showed normative enhancement of fear to the predictable threat cue, but the PTSD group displayed elevated anxiety during the unpredictable condition compared with participants with GAD and healthy control subjects.

Conclusions: Anxious reactivity to unpredictable aversive events was heightened in PTSD but not in GAD and healthy subjects. Prior works also found signs of increased reactivity to unpredictable threat in panic disorder (PD), suggesting that PTSD and PD may involve shared vulnerability. As such, the current results inform understandings of classification, pathophysiology, and psychopharmacology of anxiety disorders, generally, and PTSD and panic disorder specifically.

Key Words: Anticipatory anxiety, anxiety, fear-potentiated startle, generalized anxiety disorder, predictability, PTSD, startle, threat

Startle reflex studies in rodents dissociate neural systems underlying phasic responses to predictable threats from those mediating tonic responses to unpredictable threats (1,2). While the central nucleus of the amygdala is implicated in the former class of response, the bed nucleus of the stria terminalis (BNST)—and its modulation by corticotrophin-releasing hormone (CRH)—is involved in the latter. Walker *et al.* (1) labeled the phasic response to predictable threat “fear” and the tonic response to unpredictable threat “anxiety.”

This dissociation between fear and anxiety may relate to current anxiety disorder classification, linking specific anxiety disorders to dysfunction in distinct brain regions. Relating specific anxiety disorders to patterns of reactivity found in research with rodents might elucidate pathophysiological mechanisms and provide targets for psychopharmacological treatments.

We recently reported that patients with panic disorder (PD) were overly sensitive to unpredictable threats (3), while showing a normal response to predictable (signaled) threats. This suggests that PD involves normal fear but enhanced anxiety. Given that vulnerability to unpredictability is seen in several anxiety disorders

(4–6), it is possible that this profile of enhanced anxiety may occur in several conditions. The present study extends this line of research to two patient groups, posttraumatic stress disorder (PTSD) and generalized anxiety disorder (GAD). Based on converging evidence from different areas, we hypothesized that PTSD would show exaggerated responses to unpredictable threat. First, theoretical accounts of PTSD indicate that the quality of unpredictability in the aversive experience is crucial to the development and maintenance of PTSD symptoms (5). These theories are based on the observation that animals exposed to unpredictable but not to predictable threats show behaviors reminiscent of PTSD in humans (7,8). Second, empirical evidence suggests heightened reactivity to uncertainty in PTSD. We have reported a proneness of PTSD individuals to show exaggerated baseline startle in threatening contexts (9,10). For example, baseline startle in Vietnam veterans with PTSD is normal in an innocuous laboratory setting (with no explicitly threatening stimuli), but it is elevated during experiments associated with later administration of shocks (9). This contextual anxiety possibly reflects anticipatory anxiety about the upcoming stressful test. Of note, PTSD individuals do not show increased fear-potentiated startle to an imminent shock signaled by a threat cue (9,11). Interestingly, prior work in PD also demonstrates similar signs of contextually modulated threat hypersensitivity, occurring in tandem with normal responding to an imminently signaled shock (12). Finally, consistent with these psychophysiology data, PTSD and PD also share common phenomenology, including the unpredictable and uncontrollable nature of the stress and enhanced anxiety sensitivity (13). Posttraumatic stress disorder is precipitated by uncontrollable and unpredictable traumatic events, which result in intrusive recollections of the trauma with associated hyperarousal and anxiety (14). Panic disorder is also characterized by brief and intermittent unpredictable and uncontrollable aversive episodes (panic attacks) inter-

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spersed with anticipated anxiety of these aversive events. Furthermore, PD and PTSD share several biological abnormalities, including increased susceptibility to panic attacks with yohimbine administration (15,16).

Excessive and uncontrollable worry about a number of events or activities is a fundamental symptom of GAD (17,18). Because intolerance of uncertainty is key to pathological worry and GAD (19), one might also expect enhanced reactivity to unpredictable threat in GAD. However, the nature of worry and its physiological manifestations are unclear. Generalized anxiety disorder is usually associated with increased muscle tension, not autonomic arousal. Work on physiological reactivity in GAD finds minimal evidence of hyperarousal and some evidence of reduced arousal (20). Nevertheless, because this is the first study of unpredictable threat in GAD, only provisional hypotheses are possible.

The present study examined responses to predictable and unpredictable aversive events using the same well-validated startle paradigm implemented to test patients with PD (3). Startle and subjective measures of anxiety were assessed across three conditions: 1) a neutral (N) condition during which no unpleasant event was delivered; 2) a predictable (P) condition in which unpleasant events could occur only during a discrete threat cue; and 3) an unpredictable (U) condition during which unpleasant events could occur at any time. This paradigm provides measures of fear (e.g., fear-potentiated startle) associated with the threat cue in the P condition and of anxiety (e.g., context-potentiated startle) in the N, P, and U contexts (no cue periods). We hypothesized that PTSD would be associated with normal startle potentiation in response to threat cues (P) but enhanced potentiation during the U condition.

Methods and Materials

Participants

Sixteen medication-free PTSD patients (9 women and 7 men; mean \pm SD age, 34.5 ± 12.4 years), 18 GAD patients (14 women and 4 men; mean \pm SD age, 34.0 ± 10.5 years), and 34 healthy control subjects (25 women and 9 men; mean \pm SD age, 30.2 ± 8.5 years) participated in the study. Mean age did not significantly differ across groups [$F(1,62) = .9$, ns]. The patients met DSM-IV criteria for PTSD or GAD as assessed by the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (21). Participants with PTSD were included if the severity of the PTSD, as measured by the Clinician-Administered PTSD Scale (CAPS) (22), was ≥ 50 . The PTSD mean CAPS score was 72.9 (SD = 4.2). Comorbidities among PTSD patients included current major depressive disorder ($n = 4$), past major depressive disorder ($n = 2$), and past substance abuse ($n = 2$). Comorbidities among GAD patients included social anxiety disorder ($n = 3$), current major depressive disorder ($n = 1$), past substance abuse ($n = 1$), and specific phobia ($n = 1$). Healthy control subjects had no current or past psychiatric diagnosis according to the SCID-I and were physically healthy. All subjects were free of drugs as per a urine screen. After description of the study was given to subjects, written informed consent was obtained.

Stimuli and Physiological Responses

Stimulation and recording were controlled by a commercial system (Contact Precision Instruments, London, England). The eyeblink reflex was recorded with electrodes under the left eye. Amplifier bandwidth was set to 30 Hz to 500 Hz. Startle was elicited with an air puff to the forehead, which gives similar

results as a white noise (23), using a 40-msec, 7-psi puff delivered through a polyethylene tube (2-ft length, 1/8-in diameter) (see [23] for additional information). Unpleasant stimuli consisted of four different 3-sec duration, 95-dB aversive sounds: 1) white noise; 2) 2-kHz tone; 3) smoke alarm; and 4) human female scream (the human scream was accompanied by a briefly presented picture of a fearful woman).

Procedure

The procedure was the same as in a recent study in PD (3). Participants were given explicit instructions regarding the conditions under which unpleasant stimuli were administered. The threat experiment consisted of three 150-sec conditions (Figure 1): 1) no aversive event (N); 2) predictable aversive event (P); and 3) unpredictable aversive event (U). In each 150-sec condition, a 10-sec cue was presented four times. The cues were different colored geometric shapes for each of the different conditions (e.g., blue square for N, red circle for P). The cues signaled the possibility of receiving an aversive stimulus in the P condition only but had no signal value in the N and U conditions. During the experiment, instructions were continuously displayed showing: “no unpleasant event” (N), “unpleasant event only during shape” (P), or “unpleasant event at any time” (U).

The experiment started with the delivery of six pretest startle stimuli to habituate initial startle reactivity (results not shown). Fifteen seconds after the last of these startle stimuli, the fear-potentiated startle experiment started. It consisted of three N, two P, and two U conditions in one of the following two orders: P N U N U N P or U N P N P N U. Half of the participants in each group received the former order and the other half of the participants received the latter order. Two aversive events were administered in each individual P and U condition for a total of eight aversive stimuli. The aversive events were delivered at cue

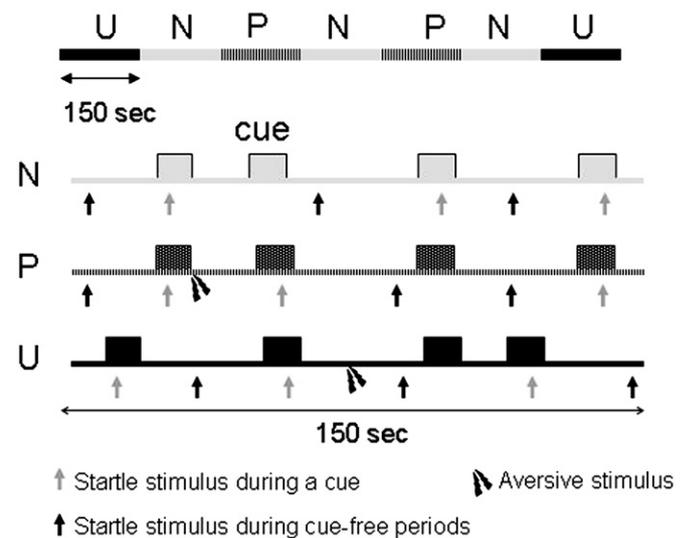


Figure 1. Schematic of the experiment. Subjects were presented with three neutral (N), two predictable (P), and two unpredictable (U) contexts (order U N P N P N U as shown or P N U N U N P). Each N, P, and U condition contained four 8-sec duration cues. In the P condition, the aversive stimulus was administered only in the presence of the cue. In the U condition, the aversive stimulus was administered randomly during cue-free periods. In the N condition, no aversive stimulus was administered. Startle stimuli were delivered during the cues (grey arrow pointing up) or during cue free-periods (black arrow pointing up). N, neutral; P, predictable; U, unpredictable.

offset in the P condition and in the absence of a cue in the U condition. In each condition (i.e., N, P, U), six tactile startle stimuli were delivered, three during cue-free periods and one during three of the four cues, 5 sec to 7 sec following cue onset. The mean interstartle interval during the experiment was 21 sec (range 18–25 sec). In addition, no startle stimulus was delivered less than 8 sec after an aversive stimulus to avoid potential short-term sensitization of startle.

After completion of the test, subjects retrospectively rated their anxiety level in the presence and absence of the cue in each condition (N, P, U) on a Likert scale ranging from 0 (not at all anxious) to 10 (extremely anxious). They also indicated which of the two aversive conditions, predictable and unpredictable, they disliked most.

Data Analysis

Peak blink amplitude was determined in the 20-msec to 100-msec time frame following stimulus onset relative to baseline taken 50 msec preceding stimulus onset. Eyeblink magnitudes were standardized using within-subjects T scores ($[Z \text{ scores} \times 10] + 50$). Results with T scores and raw scores were similar. To increase comparability of our current results with our previous study in PD (3), we present results only with the T scores, except when T scores and raw scores differed. (Mean raw scores are shown in Table 1.) Startle magnitudes and subjective ratings were averaged across conditions, separately for cues and cue-free periods. Fear was operationally defined as the increase in startle (fear-potentiated startle) or in subjective rating during the cue. Fear reactivity to the cue was calculated as the difference in startle magnitude or subjective ratings between cue and cue-free periods in each condition. Anxiety was operationally defined as the increase in startle or in subjective anxiety during the cue-free period from the N condition to the P and U conditions. Because of our a priori hypothesis, we conducted two separate analyses of variance (ANOVAs), one for the threat cue (fear) and the other for the cue-free period (anxiety), as done in our prior studies (24,25). The startle and subjective fear scores (difference scores between cue and cue-free period) were entered in separate group (control subjects, patients) \times condition (N, P, U) \times sex (men, women) ANOVAs. We predicted a main effect of condition due to greater startle and subjective rating in the P condition, compared with the N and U conditions. We did not expect a significant group \times condition interaction, as we hypothesized no difference in response to the cue among groups. The cue-free period startle and subjective rating data were entered in a group

(control subjects, patients) \times condition (N, P, U) \times sex (women, men) ANOVA. We predicted that the PTSD group, but not the control group, would show greater responses in the U compared with the P condition, resulting in a linear trend across the N, P, and U conditions in the PTSD group only and a significant linear group \times condition interaction.

Alpha was set at .05 for all statistical tests. Greenhouse-Geisser corrections (GG- ϵ) were used for main effects and interactions involving factors with more than two levels.

Results

Startle Magnitude

Startle data (raw and T scores) are presented in Table 1. Overall startle magnitudes (raw scores) appear larger in the PTSD group compared with the other groups, but this effect was not significant [omnibus ANOVA (group [3] \times condition [2] \times cue [cue, no cue]): $F(2,62) = 1.6$, ns].

Fear-Potentiated Startle. Fear-potentiated startle to the cues differed significantly among conditions [condition; $F(2,122) = 8.3$, $p = .001$, GG- $\epsilon = .89$], due to larger potentiated startle in the P and U conditions, compared with the N condition [$t(67) = 5.6$, $p < .0009$ and $t(67) = 8.2$, $p < .0001$, respectively]. Fear-potentiated startle was larger in the P condition compared with the U condition [$t(67) = 2.2$, $p = .03$]. As hypothesized, the magnitude of fear-potentiated startle did not differ between groups [group \times condition; $F(2,126) = .2$, ns], even in an analysis restricted to P [$F(2,62) = .4$, ns]. There was no sex difference in any effects.

Context-Potentiated Startle. Context-potentiated startle, reflecting the sustained change in startle associated with each condition (see Methods and Materials), was evaluated using startle magnitudes during cue-free periods (Table 1). Startle reactivity across conditions differed among the three groups [condition \times group: $F(4,122) = 2.5$, $p < .04$, GG- $\epsilon = .99$]. Both the healthy and GAD groups showed the largest response in the P condition, compared with the N and U conditions. The PTSD group, in contrast, showed the largest startle in the U condition (Figure 2). Specifically, startle magnitudes among PTSD patients during cue-free periods increased progressively from N, to P, to U [linear trend: $F(1,14) = 17.5$, $p < .001$], showing significantly larger startle magnitude in U compared with N [$F(1,14) = 8.4$, $p < .01$]. This pattern of responses was in contrast to that found in the control and GAD groups, where startle magnitude was the largest in P, though this effect reached significance only in the

Table 1. Startle Magnitude (Raw Scores and T Scores) and Subjective Rating of Anxiety

	Neutral		Predictable		Unpredictable	
	Cue	Cue-Free	Cue	Cue-Free	Cue	Cue-Free
Startle Magnitude (Raw Scores, μV)						
Control subjects	25.8 (4.7)	16.8 (4.4)	30.7 (6.0)	20.9 (5.3)	22.8 (6.2)	17.6 (5.7)
PTSD	29.8 (6.1)	26.4 (5.7)	45.4 (7.8)	30.3 (6.9)	45.2 (8.1)	38.7 (7.5)
GAD	17.2 (6.8)	17.5 (6.4)	27.9 (8.8)	23.1 (7.8)	26.3 (9.1)	18.7 (8.4)
Startle Magnitude (T Scores)						
Control subjects	46.0 (1.1)	44.3 (1.0)	58.4 (1.7)	48.2 (1.4)	50.3 (1.6)	44.6 (1.0)
PTSD	45.1 (1.4)	42.4 (1.4)	57.1 (2.1)	45.6 (1.7)	55.9 (2.1)	48.8 (1.3)
GAD	47.0 (1.6)	46.3 (1.6)	58.1 (2.4)	50.1 (2.0)	51.8 (2.4)	46.3 (1.5)
Retrospective Rating of Anxiety						
Control subjects	1.5 (.3)	1.3 (.3)	4.8 (.5)	3.1 (.5)	3.6 (.5)	4.3 (.5)
PTSD	2.2 (.3)	3.0 (.4)	6.3 (.6)	4.6 (.6)	5.3 (.6)	5.9 (.6)
GAD	2.2 (.3)	2.8 (.5)	6.0 (.8)	3.5 (.7)	4.8 (.7)	5.6 (.7)

GAD, generalized anxiety disorder; PTSD, posttraumatic stress disorder.

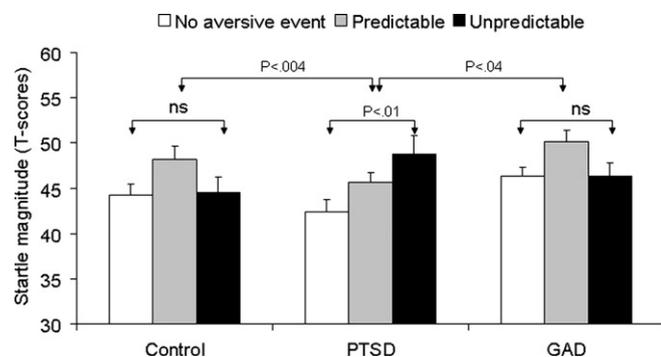


Figure 2. Startle magnitudes in the cue-free periods in the no aversive event (N), predictable (P), and unpredictable (U) conditions among the control, PTSD, and PD groups. Error bars reflect SEM. There was a significant [$F(1,14) = 8.4, p < .01$] increase in startle magnitude from N to U in PTSD only. There were also significant group differences when contrasting startle during N to startle during U. Control versus PTSD: $F(1,46) = 9.3, p < .004$; GAD versus PTSD: $F(1,30) = 4.4, p < .04$. GAD, generalized anxiety disorder; N, no aversive event; P, predictable; PD, panic disorder; PTSD, posttraumatic stress disorder; SEM, standard error of the mean; U, unpredictable.

former group [quadratic trend over N, P, U; $F(1,32) = 8.0, p < .01$]. Follow-up analyses comparing the PTSD group with the control group show significant condition \times group interactions and condition \times group linear trend [$F(2,92) = 6.9, p < .002$, GG- $\epsilon = .93$ and $F(1,46) = 9.3, p < .004$, respectively]. Similar results were found when comparing the PTSD and GAD groups [$F(2,60) = 3.5, p < .04$, GG- $\epsilon = .95$ and $F(1,30) = 4.4, p < .04$, respectively; using the raw scores, the results were $F(2,60) = 2.5, p < .11$ and $F(1,30) = 2.2, p < .14$, respectively] but not when comparing the control and GAD groups [$F(2,96) = .1, ns$, GG- $\epsilon = .98$] (see also Figure 2 legend). Sex did not influence the results.

Ratings

Subjective ratings are shown in Table 1. One subject in each patient group had missing subjective ratings.

Subjective Rating During the Cue. As expected, subjective rating to cues differed significantly across conditions [$F(2,120) = 33.3, p < .0009$, GG- $\epsilon = .86$], due to greater subjective anxiety to the cue in the P condition compared with the N condition [$t(66) = 8.2, p < .0009$] and U condition [$t(66) = 7.9, p < .0009$]. Similar to the startle data, the three groups did not differ in subjective rating to the cues [group main: $F(2,60) = .2, ns$; cue-by-group interaction: $F(4,120) = .6, ns$]. An analysis restricted to the P condition also revealed no significant difference in subjective anxiety to the threat cue.

Subjective Rating During Each Context. Overall, subjective anxiety during cue-free periods differed among groups [$F(2,60) = 4.5, p < .01$], due to greater subjective anxiety in the PTSD compared with the control group [$F(1,45) = 9.1, p < .004$]. The GAD group also tended to have higher overall ratings of subjective anxiety, but ratings in GAD differed from neither the healthy [$F(1,44) = 2.4, p = .12$] nor the PTSD [$F(1,28) = .7, ns$] groups. Overall subjective anxiety was also higher in female subjects compared with male subjects [$F(2,60) = 9.4, p < .003$], but this effect did not differ among groups. Unlike the startle data, subjective anxiety did not differ among the three groups across contexts [$F(4,110) = .4, ns$].

Condition Subjects Disliked. All three groups disliked the U condition more than the P condition and this stronger dislike for

the U condition was comparable ($\chi^2 = 1.60, ns$) across the three groups (control: 79%; PTSD: 94%; GAD: 83%).

Discussion

As hypothesized, PTSD patients compared with GAD patients and healthy control subjects displayed heightened anxiety during periods of unpredictable, but not predictable, threat. Specifically, startle potentiation during the no-cue period of the unpredictable versus neutral condition—reflecting heightened contextual anxiety—was observed only in the PTSD group. In contrast, fear-potentiated startle to the threat cue predictably signaling the aversive events was increased to the same extent in the three groups.

The results are consistent with previous startle studies showing normal fear-potentiated startle to an imminent threat in PTSD, together with heightened startle potentiation to more distal or uncertain threat (9,26). For example, Pole *et al.* (27) reported increased anxiety in police officers with PTSD under low threat after they were instructed that they would be shocked later in the study but not under high threat signaling an imminent shock. These results are consistent with the view that PTSD individuals are overly sensitive to unpredictability because distal stressors may introduce uncertainty. Alternatively, PTSD individuals may be overly sensitive to stressors in general, but greater control-patient differences emerge more readily under low threat levels (28). This latter interpretation is unlikely given the different pattern of startle potentiation to the different contexts across groups (i.e., greater contextual anxiety in P in the control subjects and in U in the PTSD patients). These results suggest that compared with healthy control subjects, PTSD individuals do not show a general increase in anxiety but a specific sensitivity to unpredictable aversive stimuli.

This sensitivity to unpredictability is only partly specific to PTSD. While the current study differentiated PTSD from GAD, prior work found heightened anxiety to unpredictability in PD (29). Posttraumatic stress disorder and PD share several common clinical features, in that both syndromes are associated with paroxysms of subjective distress and associated physiological symptoms that might be alternatively conceptualized as either flashbacks or panic attacks (30). Further, PTSD and PD frequently co-occur in clinical and general population samples (30–32).

Heightened contextual anxiety during unpredictable aversive events may be a shared clinical phenotype of subtypes of anxiety disorders characterized by intermittent, unpredictable, aversive experiences; anticipatory anxiety; and hypervigilance. If so, then why was anxiety in the U context not elevated in GAD? One possibility is that GAD patients are also sensitive to unpredictability, but their threshold for abnormal responding is higher than in the PTSD group. This hypothesis could be tested using more noxious stimuli such as shocks. Another possibility is that the nature of anxiety is qualitatively different in GAD relative to PTSD or PD. The hallmark of GAD is worry. Some suggest that worry is not synonymous with anticipatory anxiety (33) but rather reflects a verbally mediated coping mechanism that serves to distract from an impending threat (34). Generalized anxiety disorder is characterized by reduced rather than increased physiological arousal during stressors (20). In this respect and consistent with the present study, GAD differs from other anxiety disorders. Both PTSD and panic disorder are characterized by paroxysms of crescendo anxiety, which occur as part of panic attacks in panic disorder and flashbacks in PTSD. Generalized anxiety disorder, in contrast, involves no such crescendo episodes.

The lack of startle potentiation in the unpredictable condition in the control and GAD groups is in line with our previous reports (35,36). On the one hand, anticipation of aversive events signaled by a cue induces robust fear-potentiated startle regardless of whether the aversive event is a shock or less noxious stimuli such as those used in the present study (36,37). On the other hand, context-potentiated startle in an unpredictable condition is affected by the degree of stimulus aversiveness, with more noxious stimuli generating greater contextual anxiety (3,36). We have repeatedly found a linear increase in startle magnitude from N, to P, to U with shocks but not when using strong blasts of air to the neck or a collection of unpleasant sounds and visual stimuli such as those used in the present study (3,36). Thus, unpredictability increases anxiety provided sufficiently aversive stimuli are used (but see [38]), raising the possibility that PTSD patients have a reduced threshold for anxious reactivity to unpredictability.

The subjective ratings did not closely match the startle data. In work using methods similar to those employed here, dissociation between physiological measures and subjective reports is the rule rather than the exception (3,25,39,40). Two related explanations may account for this consistent trend. First, in the current study, as in many previous studies, startle probed aversive states online, whereas the subjective ratings were made retrospectively at the end of the experiment. The delay in rating may have obscured subtle differences between contexts. Second, startle and subjective ratings may measure distinct aspects of anxiety. Startle may represent a more direct index of a primitive defensive system (e.g., amygdala), whereas subjective reports may represent more elaborative cognitive processes dependent on complex, cortically based categorization. There is considerable evidence that the amygdala can be activated in the absence of subjective feelings of anxiety or conscious awareness of the threat stimulus (for a review, see [41]). For example, during aversive conditioning, startle can be increased during the conditioned stimulus in subjects unaware of the contingency between the conditioned stimulus and the unconditioned stimulus (42). Conversely, data from patients with amygdala lesions display intact subjective state rating behavior (43). This supports the distinction between amygdala-mediated processes, such as startle potentiation, and subjective state ratings. It is nevertheless noteworthy that overall subjective anxiety was the highest among the PTSD subjects. This result suggests enhanced contextual anxiety. Alternatively, the PTSD group may suffer from a general bias toward greater subjective ratings. However, this is unlikely because there was no group difference in ratings to the threat cue.

A crucial question is whether the sensitivity to unpredictability is a pre-existing vulnerability factor for PTSD or a sequel of trauma exposure. Emerging data in PTSD and in high-risk groups point to the former interpretation. In a prospective study in police officer cadets, Pole *et al.* (44) reported that contextual anxiety evoked by distal threat predicted PTSD symptom severity following a 1-year exposure to police-related trauma. The possibility that proneness to contextual anxiety is an endophenotype for anxiety disorders is also suggested by findings of heightened contextual anxiety in nonaffected children of parents with an anxiety disorder (45,46) and individuals with high levels of neuroticism (47).

The present finding may have implications for identifying underlying neural abnormalities in PTSD, as well as for pathophysiology-based psychopharmacological treatments. Rodent

studies have identified two separate neural systems for phasic fear and more sustained anxiety, the latter being mediated by the BNST in concert with CRH (1). The BNST is also involved in the long-lasting anxiety states evoked by uncontrollable stressors (48). Neuroimaging studies have begun to delineate the brain circuit involved in sustained anxiety to unpredictable stressors in humans. Unpredictable shock activates a network of regions, including the amygdala, hippocampus, and ventromedial prefrontal cortex (49,50). Bed nucleus of the stria terminalis activation has been reported during anticipation of speech in speech phobics (51). Preclinical research points to a crucial role for CRH in animal models of stress disorders, particularly PTSD (52,53). There is substantial evidence to suggest that CRH receptors mediate the sustained potentiation of startle to unpredictable threat in rodents (1). This observation has prompted the exploration of CRH receptor antagonists as novel anxiolytics in humans (52,53). Continuous sampling and single-point assessment of cerebrospinal fluid (CSF) in patients with combat-related PTSD confirm elevated CRH concentrations (54,55). Whether a CRH antagonist would also suppress enhanced context-potentiated startle in humans is currently unknown, but it is likely that CRH antagonists would be effective in treating anxiety disorders associated with heightened reactivity to contextual anxiety. Accordingly, we predict that CRH antagonists may alleviate symptoms of anxiety in PTSD and PD but not in GAD.

Results must be considered in light of study limitations. One limitation was the unequal number of male subjects compared with female subjects in each group, especially in the GAD group. However, a reanalysis of the data only in the female subjects confirmed the present findings. We found significant linear increases in startle from the N, to P, to U condition in the male subjects [43.5, 45.9, 49.0, respectively; $F(1,6) = 9.1, p < .02$] and in the female subjects [41.3, 43.3, 48.6, respectively; $F(1,8) = 10.2, p < .01$] with PTSD. A second limitation is the absence of a trauma control group. Hence, the present finding may be due to the effect of trauma rather than PTSD *per se*. However, the prospective observation that symptoms of heightened anxiety to distal threat characterize only trauma-exposed police officer cadets who later develop PTSD argues against this interpretation (44). Finally, four of the PTSD patients had current comorbid depression. It is unlikely that depression mediated the contextual effect, as depression has been associated with reduced rather than enhanced startle (56). A reanalysis excluding PTSD patients with current depression confirmed the results. There were significant linear increases in startle from the N, to P, to U condition in the remaining PTSD patients [43.0, 44.9, 49.0, respectively; $F(1,11) = 12.2, p < .005$], who showed a significantly different pattern of response compared with the control subjects [condition \times group linear trend; $F(1,42) = 6.6, p < .01$].

To summarize, unpredictable aversive events induced heightened anxiety in PTSD but not in GAD. Basic research in animals (1) and neuroimaging studies in humans (49) are helping to delineate psychopharmacological mechanisms and neural circuits involved in human fear and anxiety. The current experimental paradigm represents a valuable tool that helps translate these separate neural circuits to research in anxiety disorders. Future neuroimaging studies in patients with anxiety disorders may provide important clues as to the neural mechanisms of fear and anxiety and may help design novel pathophysiology-based psychopharmacological treatments.

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