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Increased Anxiety During Anticipation of Unpredictable But Not Predictable Aversive Stimuli as a Psychophysiologic Marker of Panic Disorder

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Abstract

Objective—Predictability is a fundamental modulator of anxiety in that the ability to predict aversive events mitigates anxious responses. In panic disorder, persistent symptoms of anxiety are caused by anticipation of the next uncued (unpredictable) panic attack. The authors tested the hypothesis that elevated anxious reactivity, specifically toward unpredictable aversive events, is a psychophysiological correlate of panic disorder.

Method—Participants were exposed to one condition in which predictable aversive stimuli were signaled by a cue, a second condition in which aversive stimuli were administered unpredictably, and a third condition in which no aversive stimuli were anticipated. Startle was used to assess anxious responses to cues and contexts.

Results—Relative to healthy comparison subjects, patients with panic disorder displayed equivalent levels of fear-potentiated startle to the threat cue but elevated startle potentiation in the context of the unpredictable condition.

Conclusions—Patients with panic disorder are overly sensitive to unpredictable aversive events. This vulnerability could be either a premorbid trait marker of the disorder or an acquired condition caused by the experience of uncued panic attacks. As a premorbid trait, vulnerability to unpredictability could be etiologically related to panic disorder by sensitizing an individual to danger, ultimately leading to intense fear/alarm responses to mild threats. As an acquired characteristic, such vulnerability could contribute to the maintenance and worsening of panic disorder symptoms by increasing anticipatory anxiety.

Panic disorder involves two cardinal features: panic attacks, defined as acute surges of fear (1), and anticipatory anxiety (2), defined as persistent apprehension about future panic attacks (3). Only a subset of the many individuals who experience panic attacks develop panic disorder. The transition from panic attacks to panic disorder is thought to involve a process whereby anxiety in anticipation of subsequent panic attacks (4) increases the likelihood of additional attacks (5) and leads to full-blown panic disorder (3). According to this assessment, marked anticipatory anxiety about the uncertain recurrence of panic attacks leads to chronic anxiety (2).

Interestingly, most research on the physiology of panic disorder focuses specifically on panic attacks as opposed to anticipatory anxiety in panic disorder. Understanding the correlates of

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anticipatory anxiety in the disorder may be very important. Because panic attacks typically are irregular and uncertain (2) and are perceived as arising 'out of the blue,' heightened sensitivity to unpredictable aversive events among individuals who experience spontaneous panic attacks may, over time, lead to persistent anticipatory anxiety, facilitating the transition from panic attacks to full-blown panic disorder. Consistent with this prediction, the absence of predictability is a key variable in the origin and maintenance of chronic anxiety states (6-8), both in human and animal models (8,9).

Identifying vulnerability to unpredictable danger may clarify the psychophysiology of panic disorder while also delineating dysfunction in specific neural circuits. Using the startle reflex to index fear and anxiety in rodents, Walker et al. dissociated neural systems that mediate phasic fear to a cued threat from those that mediate more persistent anxiety to temporally unpredictable danger (10). Thus, the demonstration that panic disorder is associated with increased anxiety to an unpredictable but not predictable stressor would implicate in the disorder specific neural systems involved in persistent anxiety among rodents.

Previous studies have generated mixed evidence concerning sensitivity to unpredictability in panic disorder. For example, some studies have shown that providing specific and detailed information about the effects of a panicogenic challenge reduces susceptibility to panic in the disorder (11), whereas other findings have demonstrated no such effects (11,12). Nevertheless, these findings remain of unclear relevance to research on temporal predictability in animal models of anxiety, i.e., these studies relied on paradigms relatively far removed from models used with rodents. Somewhat surprisingly, in studies that used a more translational approach with humans, we (13) as well as other investigators (14) found that patients with panic disorder displayed normal fear, as indexed by fear-potentiated startle, when anticipating predictable threat. The present study tests the hypothesis that panic disorder involves abnormal response specific to unpredictable threat, despite normal response to predictable threat. We tested this hypothesis using a well-validated startle paradigm (15). Anxiety was assessed across the following three conditions: 1) a predictable condition in which unpleasant events could occur only during a discrete 'threat' cue, 2) an unpredictable condition during which unpleasant events could occur at any time, and 3) a neutral condition during which no unpleasant event was delivered. We hypothesized that panic disorder would be associated with normal startle in response to threat (predictable) cues but enhanced startle in response to unpredictable contexts.

Method

Participants

Twenty-four medication-free patients (18 women and six men; mean age=34.0 [SD=10.5] years) with panic disorder and 24 (18 women) age- and sex-matched healthy comparison subjects (mean age=29.4 [SD=7.2] years) participated in the study. The patients met DSM-IV criteria for panic disorder based on the Structured Clinical Interview for DSM-IV axis I disorders (SCID) (16). Five patients had a comorbid diagnosis of social anxiety disorder. Patients with a comorbid past or current major depressive disorder were excluded because depression may reduce fear-potentiated startle (14). Healthy comparison subjects had no current or past psychiatric diagnosis according to the SCID. All subjects were free of drugs as per a urine screen. Patients with panic disorder had significantly higher scores on the Beck Depression Inventory (17) (8.7 [SD=7.1] versus 1.8 [SD= 2.7]; $t=4.4$, $df=46$, $p<0.0009$), Beck Anxiety Inventory (12.5 [SD= 7.3] versus 1.7 [SD=2.0]; $t=6.9$, $df=46$, $p<0.0009$), and Anxiety Sensitivity Index (18) (31.9 [SD=10.9] versus 16.4 [SD=8.9]; $t=4.8$, $df=46$, $p<0.0009$) relative to comparison subjects. After complete description of the study to the subjects, written informed consent was obtained.

Stimuli and Physiological Responses

Stimulation and recording were controlled by a commercial system (Contact Precision Instruments, London). The eye-blink reflex was recorded with electrodes under the left eye. Amplifier bandwidth was set to 30-500 Hz. Startle was elicited with an airpuff to the forehead, which gives similar results as a white noise (19), using a 40-msec,7-psi puff delivered through a polyethylene tube (length: 2.0 ft; diameter: 1/8 inch) (19). Unpleasant stimuli consisted of the following four different 3-second duration, 95-dB aversive sounds: 1) a white noise, 2) a 2-kHz tone, 3) a smoke alarm, and 4) a human female scream (the human scream was accompanied by a briefly presented picture of a fearful woman).

Procedure

The procedure was similar to that of a recent study, which tested the effect of alprazolam and citalopram on cued fear and contextual anxiety (20,21). After attachment of the eye-blink electrodes, participants were given explicit instructions regarding the conditions under which unpleasant stimuli would be administered. The threat experiment consisted of the following three 150-second conditions: no aversive event, predictable aversive event, and unpredictable aversive event. In each 150-second condition, a 10-second cue was presented four times. The cues were geometric shapes of different colors for each of the different conditions (e.g., blue square for the neutral condition; red circle for the predictable condition). The cues signaled the possibility of receiving an aversive stimulus in the predictable condition only but had no signal value in the neutral and unpredictable conditions. During the experiment, instructions were continuously displayed showing the following: ‘no aversive stimuli (N),’ ‘aversive stimuli only during shape (P),’ or ‘aversive stimuli at any time (U).”

In each condition, six tactile startle stimuli were delivered, three during cue-free periods (i.e., intertrial intervals) and one during three of the four cues, 5 to 7 seconds following cue onset. The test started with the delivery of six startle stimuli (pretest startle) and consisted of three neutral, two predictable, and two unpredicable conditions in one of the following two orders: P N U N U N P or U N P N P N U. One-half of the participants in each group were given the former order, and the other half were given the latter order. Two aversive events were administered in each individual predictable and unpredictable condition for a total of eight aversive stimuli. The aversive events were delivered 7 seconds following cue onset in the predictable condition and in the absence of a cue in the unpredictable condition. The mean inter-startle interval during the experiment was 21 seconds (range=18-25 seconds). In addition, no startle stimulus was delivered less than 8 seconds after an aversive stimulus in order 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 on a Likert scale ranging from 0 (not at all anxious) to 10 (extremely anxious). They also indicated their estimate of the probability (ranging from 0% to 100%) that an aversive event would be administered in each condition.

Data Analysis

Peak blink amplitude was determined in the 20- to 100-msec time frame following stimulus onset relative to baseline (average baseline electromyograph level for the 50 msec immediately preceding stimulus onset). Eye-blink magnitudes were standardized using within-subjects T scores ([z scores × 10] + 50) (see the data supplement accompanying the online version of this article for the results with raw scores). The startle magnitude and subjective ratings were averaged across conditions (separately for cues and cue-free periods). Because of our a priori hypothesis, we conducted two separate analyses of variance (ANOVAs), one for the threat cue and the other for the cue-free period, which was also done in our prior studies (20,21). Responses to the cues were calculated as the difference in startle magnitude or subjective

ratings between cue and cue-free periods in each condition. These difference scores were entered in a group (comparison subjects, panic disorder patients)-by-condition (neutral, predictable, unpredictable)-by-sex ANOVA. We predicted a main effect of condition because of greater startle, subjective anxiety, and expectancy of aversive events in the predictable condition relative to the neutral and unpredictable conditions. We did not expect a significant group-by-condition interaction, since we hypothesized no difference in response to the cue in the two groups. The cue-free period data were entered in a group (comparison subjects, panic disorder patients)-by-condition (neutral, predictable, unpredictable)-by-sex ANOVA. We predicted significant condition main effects because of greater startle, subjective rating of anxiety, and expectancy of the aversive stimuli in the predictable and unpredictable conditions relative to the neutral condition. We also predicted that patients would show greater responses in the unpredictable condition compared with the predictable condition, resulting in a linear tendency across the neutral, predictable, and unpredictable conditions. As a result, we expected a significant linear group-by-condition interaction.

Alpha was set at 0.05 for all statistical tests. Greenhouse-Geisser corrections were used for main effects and interactions involving factors with more than two levels.

Results

Startle Magnitude

Startle magnitudes in each condition and in each group are presented in Table 1.

Cued Fear-Potentiated Startle

Fear-potentiated startle to the cues differed significantly among conditions (condition: $F=8.1$, $df=2, 88$, $p=0.001$; Greenhouse-Geisser correction epsilon=0.91) as a result of larger potentiated startle in the predictable and unpredictable conditions relative to the N condition ($t=4.6$, $df= 47$, $p<0.0009$ and $t=3.1$, $df=47$, $p<0.0001$, respectively). Fear-potentiated startle also tended to be larger in the predictable condition relative to the unpredictable condition ($t=1.7$, $df=47$, $p=0.09$).

As hypothesized, the magnitude of fear-potentiated startle did not differ between groups, even when the analysis was restricted to the predictable condition. There was no sex difference in any effects.

Because some data suggest that depression may moderate fear-potentiated startle in panic disorder (14), we excluded subjects with major depression in the present study. Nevertheless, we also considered associations with subthreshold major depressive disorder by calculating the correlation between Beck Depression Inventory scores and fear-potentiated startle in the P condition. The results showed no significant correlation in either healthy comparison subjects ($r=-0.02$) or panic disorder patients ($r=-0.32$).

Context-Potentiated Startle

Contextual anxiety was evaluated using startle magnitudes during cue-free periods (Table 1). As shown in Figure 1, startle reactivity across conditions differed between the two groups (condition-by-group: $F=3.9$, $df=2, 88$, $p<0.02$; Greenhouse-Geisser correction epsilon=0.96). In panic disorder patients, startle magnitudes during cue-free periods increased progressively from the neutral to the predictable to the unpredictable condition (linear tendency: $F=7.0$, $df=1, 23$, $p<0.01$), whereas in healthy comparison subjects, startle was not significantly larger in the predictable condition relative to the two other conditions. This pattern reflected the hypothesized group-by-condition linear tendency ($F=6.1$, $df=1, 44$, $p<0.02$). This effect was because of a greater increase in startle from the neutral to the unpredictable condition in patients

relative to comparison subjects (F=6.0, df=1, 44, p<0.02), with startle magnitude significantly increasing in the unpredictable condition versus the neutral condition in panic disorder patients (F=7.0, df=1, 23, p<0.01) but not in comparison subjects. The two groups did not differ in the predictable condition. Sex did not influence any result.

Retrospective Subjective Ratings of Anxiety

Anxiety during the cue—Subjective anxiety to cues differed significantly across conditions (F=26.0, df=2, 88, p<0.0009; Greenhouse-Geisser correction epsilon=0.92) because of greater anxiety in the predictable condition relative to the neutral (F=38.5, df=1, 44, p<0.0009) and unpredictable (F=36.9, df=1, 44, p<0.0009) conditions, with no cue-by-group interaction.

Contextual anxiety—Subjective anxiety during intertrial intervals increased linearly from the neutral to the predictable to the unpredictable contexts (F=48.9. df=1, 44, p<0.0009). Patients tended to be more anxious across all contexts (F=2.6, df=1, 44, p<0.10), with no group-by-context interaction. Sex, once again, did not influence any result.

Retrospective Subjective Probability Rating

Probability during the cue—Subjective probability of an aversive event during the cues (relative to cue-free periods) differed significantly across conditions (condition: F=39.5, df=2, 88, p<0.0009; Greenhouse-Geisser correction epsilon=0.74) as a result of greater anticipation of an aversive event in the predictable condition relative to the neutral (F=60.7, df=1, 44, p<0.0009) and unpredictable (F=43.5, df=1, 44, p<0.0009) conditions. Subjective probability during the cues did not differ between the two groups.

Contextual probability—Patients had an overall greater expectancy of unpleasant events during cue-free periods relative to comparison subjects (F=5.0, df=1, 44, p<0.03). Overall subjective probability of aversive stimuli increased linearly from the neutral to the predictable to the unpredictable conditions (F=52.9, df=1, 44, p<0.0009), with no group-by-context interaction. There was no sex difference in any of the effects.

Discussion

As predicted, patients with panic disorder exhibited greater anxiety in the unpredictable condition relative to healthy comparison subjects. Startle was substantially potentiated by the threat cue signaling an aversive event, but the magnitude of this effect did not vary by diagnosis. In contrast, startle in the context of the unpredictable condition differentiated patients with panic disorder from healthy comparison subjects, reflecting increased anxiety from the neutral to the unpredictable conditions in patients but not comparison subjects.

Both the large fear-potentiated startle response to the threat cue (15,20,21) and the similar degree of potentiation across groups replicate previous findings (13,14). Contrary to recent suggestions (14), symptoms of depression did not appear to mask elevated fear-potentiated startle in panic disorder patients. Subclinical symptoms on the Beck Depression Inventory did not predict startle.

While anxious anticipation of signaled aversive stimuli did not differentiate among comparison subjects and patients, unsignaled presentations of the same stimuli elicited robust anxiety response only in patients. Specifically, startle in the unpredictable condition during the cue-free period provides a measure of persistent anxiety to the experimental context. This measure was significantly potentiated relative to the neutral condition in the panic disorder but not healthy comparison group. The absence of startle potentiation to the unpredictable condition in healthy subjects replicates prior reports (15,22). Interestingly, prior reports have also

suggested that more aversive stimuli (e.g., shock) than those used in the the present study do potentiate startle to the unpredictable condition (15). The results of these studies indicate that in healthy participants, unpredictability increases anxiety only when sufficiently aversive stimuli are used. The finding that less aversive stimuli are sufficient to elicit startle potentiation in the unpredictable condition among patients with panic disorder raises the possibility that the threshold for anxious responding to aversive stimuli was lower in patients relative to comparison subjects. This is unlikely because one would have expected panic disorder patients to also display greater fear-potentiated startle to signaled threat relative to healthy comparison subjects. The alternative and more probable explanation is that the panic disorder patients were abnormally sensitive to unpredictability. Predictability is a key factor in various experimental models of anxiety (6-8,23). In panic disorder, anticipation of unpredictable and irregular panic attacks may contribute to the etiology and maintenance of chronic anxiety and subsequent avoidance by causing high levels of persistent anxious apprehension about the recurrence of panic attacks (2,24) which in turn, may increase the likelihood of panic attacks (5). This is consistent with theories that posit a causal relationship between panic attacks and interpanic anxiety and agoraphobia (2).

The present study documents a proneness to react with enhanced anxiety to an unpredictable, nonspecific stressor. This raises the question of the link between unpredictability and panic disorder. One possibility is that panic disorder patients develop a persistent fear of unpredictable danger following repeated uncued panic attacks and any aversive stimulus can generate physiological arousal that can be misinterpreted as the onset of a panic attack. According to this view, vulnerability to unpredictability is an acquired deficit that may contribute to the maintenance and worsening of panic disorder because it enhances anticipatory anxiety, which can promote panic symptoms (5). Alternatively, heightened sensitivity to unpredictable aversive events may be a pre-existing vulnerability factor for panic disorder. Consistent with this view, a recent study found that nonaffected children and adolescents of parents with panic disorder exhibit increased anticipatory anxiety during a 10-minute period, during which they breathed room air via a breathing mask while waiting for an uncued panicogenic CO_2 challenge (25). At the same time, they showed normal responses to the acute challenge (25). Thus, unpredictable stressors experienced by at-risk individuals may elicit persistent anxiety symptoms that, following the first uncued panic attacks, trigger attacks with increasing frequency over time through a progressive sensitization process. For example, in rodents, unpredictable shocks increase noradrenergic activity in various brain areas involved in fear responses such as the amygdala, hypothalamus, thalamus, and locus coeruleus (26). Sensitization of regions such as the locus coeruleus over time may lead to a hyper-reactive fear or alarm response to mild stressors, which could escalate into a panic attack. This interpretation is consistent with findings pointing to noradrenergic dysregulation in panic disorder (27,28).

The present findings are consistent with animal data suggesting a system model of anxiety in which phasic fear to discrete threat cues and sustained aversive anxiety to unpredictable danger represent functionally distinct states mediated by different structures (29). Walker et al. have convincingly shown that the amygdala and the bed nucleus of the stria terminalis are involved in short- and long-duration aversive responses, respectively (10). Other investigators, using measures other than the startle reflex, have confirmed the role of the bed nucleus of the stria terminalis in sustained aversive states (30-34). We recently reported that the benzodiazepine alprazolam reduced context-potentiated startle to unpredictable shocks with-out affecting fear-potentiated startle to a threat cue (20). The present findings of heightened anxiety among panic disorder patients exclusively to unpredictable aversive events are consistent with these observations. The fact that this abnormally elevated response in panic disorder is also alleviated by alprazolam, a drug used to treat anticipatory anxiety, when tested in healthy subjects gives validation to our experimental model.

This study must be considered in light of several limitations. Subjective anxiety and expectancy rating reports did not replicate the startle data. Similar dissociation between self-reports and physiology (21,35,36) are frequently reported. One complicating factor in the current study pertains to the fact that startle was used to probe anxiety online, whereas subjective anxiety measures were retrospectively assessed, possibly obscuring group differences. We chose to only assess anxiety retrospectively for concerns that online assessment may have influenced group differences through demand features. Alternatively, startle and subjective ratings may reflect distinct aspects of anxiety, with startle assessing primitive-defensive-reflex systems and verbal report assessing elaborative cognitive systems. It is nevertheless noteworthy that the patients overestimated the probability of receiving an aversive event in the cue-free periods compared to the comparison subjects. This is consistent both with prior clinical research on the prediction of panic-attack probability (37) and with prior theory on panic disorder pathophysiology (38). Finally, it is unclear whether vulnerability to unpredictability is specific to panic disorder. Unpredictability may also play a role in anxiety disorders characterized by persistent signs of anticipatory anxiety, including generalized anxiety disorder and posttraumatic stress disorder (PTSD) (6-8). It is possible that unpredictability plays less of a role in disorders associated with clearly identifiable stressors (e.g., phobias) than in anxiety disorders characterized by generalized, high, negative affect (panic disorder, PTSD, generalized anxiety disorder) (39).

The present study found increased anxiety to unpredictable aversive events in panic disorder. This vulnerability may be a premorbid risk factor for panic disorder, or it may contribute to the maintenance and exacerbation of panic symptoms. Longitudinal studies in individuals at risk for panic disorder will help to clarify the role this deficit plays in panic disorder. These findings may also implicate brain structures relevant to panic disorder given evidence pointing to distinct neural systems mediating short- and long-duration anxious responses (10). Using functional magnetic resonance imaging, we have identified a separate network of neural structures during anticipation of predictable and unpredictable aversive stimuli (40). The bed nucleus of the stria terminalis was not a part of these neural networks, but this is likely a result of current limitations of brain imaging techniques, which do not have the spatial resolution to unambiguously detect activation of this structure (41). Nevertheless, the current experimental paradigm represents a valuable tool with which to study panic disorder in the laboratory setting and, as such, will likely facilitate future efforts to elucidate the neurobiology of the disorder.

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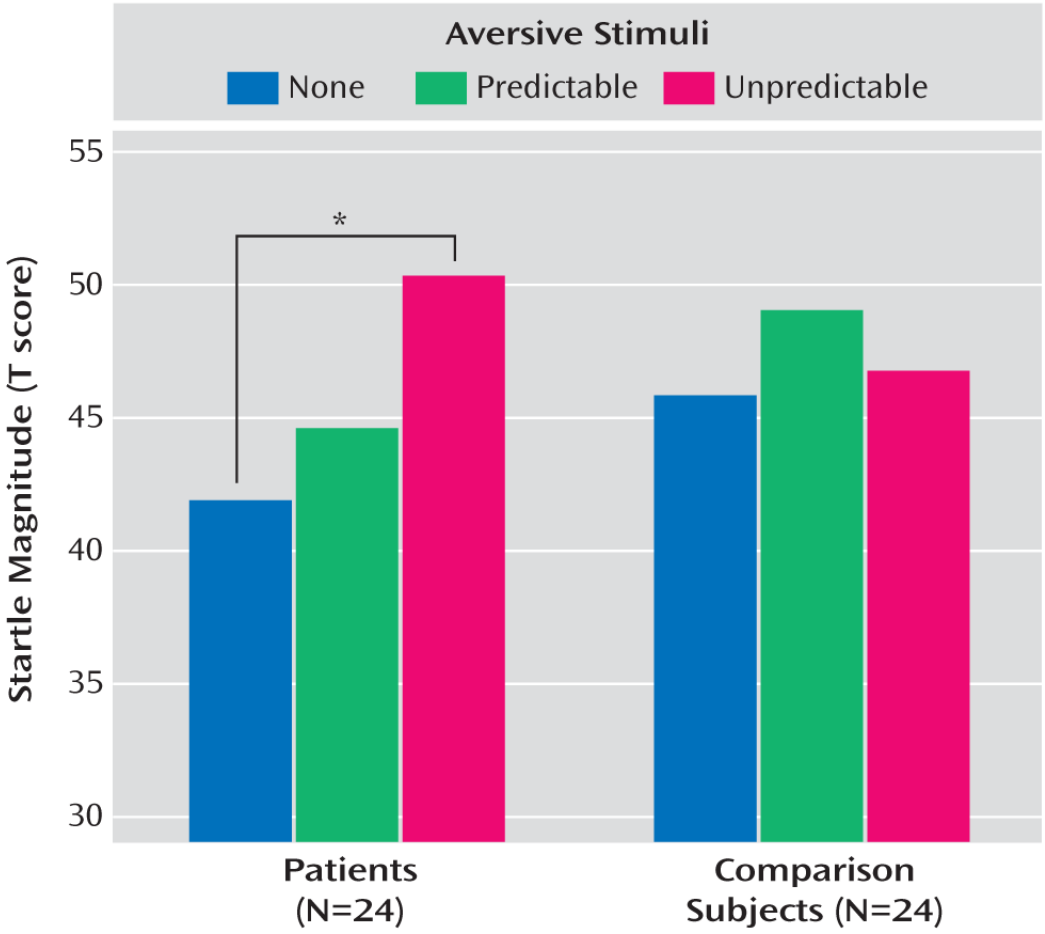

FIGURE 1. Startle Magnitudes in Cue-Free Periods in the No-Aversive-Event, Predictable, and Unpredictable Conditions Across Healthy Comparison Subjects and Patients With Panic Disorder[a]

[a]Startle reactivity across conditions differed between the two groups ($p<0.02$).

*$p<0.01$

TABLE 1

Startle Magnitude, Retrospective Rating of Anxiety, and Retrospective Rating of Shock Expectancy in Neutral, Predictable, and Unpredictable Conditions in Comparison and Panic Disorder Subjects

	Condition											
	Neutral				Predictable				Unpredictable			
	Cue		Intertrial Interval		Cue		Intertrial Interval		Cue		Intertrial Interval	
Anxiety Rating and Subject Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Startle magnitude[a]												
Comparison subjects	44.1	1.4	45.8	1.5	61.5	2.2	49.0	1.5	52.7	2.0	46.7	1.6
Panic disorder patients	48.9	1.4	41.9	1.4	56.5	2.2	44.6	1.5	57.4	2.0	50.3	1.6
Retrospective rating of anxiety[b]												
Comparison subjects	1.5	0.4	1.7	0.5	4.8	0.6	3.3	0.6	3.8	0.6	4.6	0.6
Panic disorder patients	2.2	0.4	2.9	0.4	5.9	0.6	4.0	0.6	4.6	0.6	6.0	0.6
Retrospective rating of shock expectancy[c]												
Comparison subjects	6.3	7.5	3.3	5.5	89.5	5.5	18.0	8.0	42.6	7.9	45.4	7.1
Panic disorder patients	22.3	7.5	21.2	5.2	86.8	5.5	31.3	8.0	46.9	7.9	63.4	7.1

[a] Mean values are T scores.

[b] Likert scale range of 1-10.

[c] Ratings represent probability of shock (0%-100%).