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Aversive Responding to Safety Signals in Panic Disorder: The Moderating Role of Intolerance of Uncertainty

Stephanie M. Gorka, Lynne Lieberman, Brady D. Nelson, Casey Sarapas, and Stewart A. Shankman

University of Illinois at Chicago, Department of Psychology, 1007 West Harrison St. (M/C 285), Chicago, IL 60657

Abstract

An inability to inhibit aversive responding during conditions that signal safety may be a core dysfunction associated with anxiety disorders. However, there has been inconsistent evidence as to whether individuals with panic disorder (PD) exhibit aversive responding during safety signals. It is therefore possible that only certain subgroups of PD patients, particularly those with high levels of intolerance of uncertainty (IU), evidence this type of abnormal responding. The aim of the current study was to examine whether IU moderates the association between PD and startle potentiation during a) safety and b) threat periods during a threat-of-shock task. Participants included 172 adults, 74 of which had current diagnoses of PD. Results indicated that at high levels of IU, PD was associated with greater startle potentiation during safety. At low levels of IU, PD was not associated with startle potentiation during safety. IU did not moderate the effect of PD on threat responding. These results suggest that PD patients with high levels of IU fail to inhibit aversive responding during safety, possibly due to a tendency to interpret distal threat as distressing.

Keywords

panic disorder; uncertainty; safety signals; startle

1. Introduction

Evidence and theory suggest that anxiety disorders are characterized by heightened sensitivity to threat (Barlow, 2000; Craske et al., 2009; Stein & Nesse, 2012). Studies have shown that individuals with anxiety disorders are more likely to interpret ambiguous information as threatening (Kanai, Sasagawa, Chen, Shimada, & Sakano, 2010; Rosmarin, Bourque, Antony, & McCabem, 2009), and display elevated psychophysiological responses to threat cues (Blechert, Wilhelm, Meuret, & Roth, 2010; Robinson, Charney, Overstreet,

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Correspondence concerning this article should be addressed to Stewart A. Shankman, University of Illinois at Chicago, 1007 W. Harrison St. (M/C 285), Chicago, IL, 60657. Phone: (312)-355-3812; stewarts@uic.edu.

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Vytal, & Grillon, 2012). These maladaptive responses are considered key factors in the onset and maintenance of anxiety disorders (Beck, 1985; Dalglish et al., 2003), and are important targets of treatment (Hakamata et al., 2010).

Studies suggest that an inability to inhibit aversive responding during conditions that signal safety may also be a core dysfunction of anxiety disorders. Individuals with anxiety disorders have repeatedly been shown to exhibit elevated aversive responding during safety signals (Craske et al., 2008a; Lissek et al., 2010; Grillon, Dierker, & Merikangas, 1998). Moreover, individuals at risk for anxiety disorders have also been shown to display this pattern, suggesting that a failure to inhibit responses to safety signals may precipitate disorder onset (Craske et al., 2009; Reeb-Sutherland et al., 2009). Indeed, a recent prospective study by Craske and colleagues (2012) showed that elevated startle potentiation during safety conditions predicted anxiety disorder, but not depressive disorder, onset in a sample of older adolescents.

Several theories have been proposed to explain a lack of inhibition of aversive responding during safety in anxiety disorders. Recently, it has been suggested that safety conditions that occur in the context of threat tasks may not be interpreted as signals of safety, as the safety condition is short in duration and explicit threat conditions often immediately precede and follow safety conditions (Craske et al., 2012). In other words, aversive responding during safety conditions may index anticipatory anxiety to threat conditions that will occur in the future.

Given that heightened anticipatory anxiety between unpredictable panic attacks is a hallmark feature of panic disorder (PD; American Psychiatric Association [APA], 2013; Bouton, Mineka, & Barlow, 2001), one might speculate that PD would be associated with elevated aversive responding during safety conditions. However, prior conditioning and non-conditioning studies on this have yielded mixed results (see Grillon et al. 1994; Lissek et al., 2009; Lissek et al., 2010; but also Grillon et al., 2008; Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007; Shankman et al., 2013). In light of these discrepant findings, it is possible that there are key moderators influencing the association between PD and aversive responding during safety.

Intolerance of uncertainty (IU) may be one individual difference factor that influences the relation between PD and aversive responding during safety conditions. IU is a trait characterized by beliefs that uncertain, ambiguous, or uncontrollable situations are unacceptable and threatening (Birrell, Meares, Wilkinson, & Freeston, 2011; Carleton et al., 2012; Carleton, Norton, & Asmundson, 2007; Carleton, Sharpe, & Asmundson, 2007; McEvoy & Mahoney, 2011). IU was initially thought to be associated with worry and generalized anxiety disorder (Dugas, Schwartz, & Francis, 2004); however, more recent evidence suggests that IU is a transdiagnostic construct that is relevant to individuals with a wide range of internalizing disorders including both anxiety and depressive disorders (Barlow et al., 2014; Carleton, 2012; Jacoby, Fabricant, Leonard, Riemann, & Abramowitz, 2013). The maladaptive responses to uncertainty that are characteristic of those with high IU have been shown to exacerbate negative affect and physiological arousal (Greco & Roger, 2003), and potentially contribute to chronic anxiety and avoidance (Barlow, 2002). As such,

high IU has been conceptualized as a phenotypic core of internalizing disorders (Barlow et al., 2014).

Since the duration of safety is unknown (and thus uncertain) during within-subjects threat paradigms, it is possible that individuals with high IU are likely to interpret this ambiguity as distressing and fail to inhibit their aversive responding during safety. This may be especially likely for individuals with PD and high IU. As was previously noted, individuals with PD exhibit heightened anticipatory anxiety in between temporally unpredictable panic attacks (APA, 2013). It has been theorized that high IU may exacerbate and maintain these hallmark features of PD (Carleton, 2012). Indeed, one study recently demonstrated that within individuals that have experienced panic attacks, IU was significantly associated with severity of PD symptoms (Carleton et al., 2013). This emerging literature indicates that PD and IU may interact such that at high levels of IU, individuals with PD are intolerant of uncertain situations, which can lead to chronically high levels of anticipatory anxiety (even during safety) or a tendency to perceive even distal threat as distressing. On the other hand, at low levels of IU, individuals with PD may be less sensitive to uncertainty and can consequently inhibit their aversive responding during safety signals.

Given this literature, the current study tested whether IU moderated the association between PD and startle potentiation during the safety conditions of a threat-of-shock task. A previous analysis of this dataset indicated that PD was associated with heightened startle potentiation during explicit threat conditions, but not during safety conditions (Shankman et al., 2013). The current study sought to examine whether these null findings for safety were due to the heterogeneity within PD and, specifically, whether IU moderated effects of PD on startle during safety. We hypothesized that among PD participants, those with high IU, but not low IU, would demonstrate elevated startle responding.

For the threat-of shock task, a paradigm was used that assesses two kinds of threat - unpredictable and predictable threat - in addition to responses to safety (Schmitz & Grillon, 2012). This is important because there is growing recognition that responses to unpredictable and predictable threat are qualitatively different types of aversive responding (Davis, 2006; Grillon et al., 2004). The use of this task also allowed us to examine the specificity of the hypothesized effect to safety. That is, given that individuals with high IU find uncertainty distressing, it is possible that PD participants with high IU would also exhibit greater startle responding to an unpredictable threat compared with PD participants with low IU. We did not have a specific hypothesis about the moderating effect of IU on PD during predictable threat and therefore considered this question exploratory.

2. Methods

2.1 Participants

The study protocol has been described in detail elsewhere (see Shankman et al., 2013). In brief, sensitivity to predictable and unpredictable threat was examined in four groups of individuals: those with current (1) PD without a lifetime history of MDD ($n = 22$), (2) MDD without a lifetime history of an anxiety disorder ($n = 30$), (3) comorbid PD and MDD ($n = 52$), and (4) healthy controls with no lifetime history of Axis I psychopathology ($n = 68$).

Diagnoses were made via the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1996). Participants in the PD-only and comorbid groups were allowed to have additional current or past anxiety disorders. Participants in the MDD-only group were required to have no current or past anxiety disorder. Individuals were recruited from the community and were excluded if they had a lifetime diagnosis of a psychotic disorder, bipolar disorder, or dementia; were unable to read or write in English; had a history of head trauma with loss of consciousness; or were left-handed (as confirmed by the Edinburgh Handedness Inventory; range of laterality quotient: 20 to 100; Oldfield, 1971). It is important to highlight that Shankman et al. (2013) found that MDD was not related to startle potentiation to threat or safety. Therefore, the primary group variable in this study is current PD (yes/no). However, MDD was included as a covariate in all analyses. See Table 1 for demographic and clinical characteristics of the sample.

2.2 Procedure and NPU-Threat Task

After providing written informed consent, participants were seated in an electrically shielded, sound-attenuated booth for the duration of the session. To prevent early exaggerated startle responding, participants completed a 2.5-min habituation task during which 9 acoustic startle probes were administered. Next, a shock work-up procedure was completed in which participants received increasing levels of shock intensity until they reached a level that they described as feeling “highly annoying but not painful.” Idiosyncratic shock levels were used to ensure equality in perceived shock aversiveness (Rollman & Harris, 1987) and to be consistent with prior studies (e.g., Grillon et al., 2008). The maximum shock level a participant could achieve was 5 mA. The mean shock level was 2.2 mA ($SD = 1.3$).

Startle reactivity was assessed using the No Shock-Predictable Threat-Unpredictable Threat task (i.e., NPU-threat task, Schmitz & Grillon, 2012). Text at the bottom of the computer monitor informed participants of the current threat condition by displaying: “no shock” (N), “shock possible during square” (P), or “shock possible at any time” (U). Each condition lasted 90-s, during which an 8-s geometric cue (blue circle for N, red square for P, and green star for U) was presented four times. Different shapes were used for each condition to ensure that participants were aware of the current condition. Interstimulus intervals (ISIs) ranged from 7 to 17-s ($M = 12.4$ -s), during which only the text describing the condition was on the screen. In the N condition, no shocks were delivered. In the P condition, participants could only receive a shock when the cue (red square) was on the screen. In the U condition, shocks were administered at any time (i.e., during the cue or ISI). Startle probes were presented during the cue (2–7-s following cue onset) and ISI (4–12-s following ISI onset). Only one startle probe was delivered during each presentation of the cue or each ISI. Of note, startle responding during the PISI conditions was used to indicate safety responding. This is because the PISI was a safety condition interleaved between threat conditions (i.e., PCue) and participants were safe from shock during this time period.

The task was divided into two recording blocks, separated by a 5-minute rest period. Each block consisted of two presentations of each 90-s condition, during which the respective cue appeared four times, in the following orders (counterbalanced): PNUNPU or UPNUNP. All

participants received 12 electric shocks (6 during P and 6 during U) and 72 startle probes (24 during N, 24 during P, and 24 during U). The time interval between a shock and a subsequent startle probe was always greater than 10-s to ensure that startle responses were not affected by an immediately preceding shock. Participants rated their level of 'nervousness/anxiety' during the cues and ISIs for each condition after each block of trials on a scale ranging from 1 (Not at all) to 7 (Extremely). Participants also rated how intense, annoying, and anxiety provoking the shocks were on a scale ranging from 1 (Not at all) to 7 (Extremely), and the degree to which they would avoid the shocks on a scale ranging from 1 (Would definitely not avoid) to 7 (Would definitely avoid).

2.3 Startle Data Collection and Processing

Stimuli were administered using PSYLAB (Contact Precision Instruments, London, UK) and psychophysiological data were acquired using NeuroScan 4.4 (Compumedics, Charlotte, NC). Acoustic startle probes were 40-ms duration, 103-dB bursts of white noise with near-instantaneous rise time presented binaurally through headphones. Electric shocks lasted 400-ms and were administered to the wrist of the participants' left hand. Startle response was recorded from two 4-mm Ag/AgCl electrodes placed over the orbicularis oculi muscle below the right eye and the ground electrode was at the frontal pole (AFZ). Consistent with published guidelines (Blumenthal et al., 2005), one electrode was 1-cm below the pupil and the other was 1-cm lateral of that electrode. Data were collected using a bandpass filter of DC-200 Hz at a sampling rate of 1,000 Hz. Although the upper end of this frequency band is below the Blumenthal et al. recommendation of 500 Hz, the missing bandwidth (200–500 Hz) was not likely to effect the experimental manipulation or the reliability of the results (A. Van Boxtel and T. Blumenthal, personal communications, December 14, 2009).

Startle blinks were scored according to published guidelines (Blumenthal et al., 2005). Data were first rectified and then smoothed using a FIR filter with a band pass of 28–40 Hz. Blink response was defined as the peak amplitude of electromyography (EMG) activity within the 20–150-ms period following startle probe onset relative to baseline. Each peak was identified by software but examined by hand to ensure acceptability. Blinks were scored as non-responses if EMG activity during the 20–150-ms post-stimulus timeframe did not produce a blink peak that was visually differentiated from baseline activity. Blinks were scored as missing if the baseline period was contaminated with noise, movement artifact, or if a spontaneous or voluntary blink began before minimal onset latency and thus interfered with the startle probe-elicited blink response. Analyses were conducted using blink amplitude (i.e., condition averages do not include non-responses). The below pattern of results was identical when blink magnitudes were used (i.e., condition averaged that include 0s for non-responses).

2.4 Intolerance of Uncertainty

Participants completed the Intolerance of Uncertainty Scale (IUS; Freeston et al., 1994), a 27-item questionnaire assessing the trait-like belief that uncertainty is unacceptable, reflects poorly on a person, and leads to frustration, stress, and the inability to take action. Responses are rated on a five-point Likert scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me), with higher scores indicating greater intolerance of

uncertainty. Prior studies indicate that there is significant redundancy in the IUS-27 items (i.e., 50%+) and that several items are either worry- or GAD-specific (Gentes & Ruscio, 2011; Khawaja & Yu, 2010). Furthermore, factor analyses on the 27-item IUS have found a 12-item version that comparably measures the IU construct with less items and better psychometric properties (Carleton et al., 2007; Khawaja & Yu, 2010). Thus, the present study used the total scores of the 12-item version of the IUS scale. Reliability of 12-item IUS total scores was excellent ($\alpha = 0.96$).

2.5 Data Analysis Plan

Consistent with prior studies using the NPU-threat paradigm (Gorka et al., 2013; Shankman et al., 2013), we first examined whether there were unique or interactive effects of PD or IUS on the control conditions (i.e., NCue and NISI). There were no significant main effects or two-way interactions (all $ps > 0.22$). This allowed us to create startle potentiation scores to the PISI, PCue, UISI, and UCue conditions, which were used as the dependent variables in this study. Potentiation scores account for individual differences in baseline startle responding by subtracting startle amplitude during the control condition (i.e., PCue – NCue, PISI – NISI, UCue – NCue, and UISI – NISI).

To test our hypotheses, we conducted a series of hierarchical linear regression analyses. Continuous variables were mean centered. Covariates including age, gender, current diagnosis of MDD (yes/no), condition order of the startle task (i.e., PNUNPU or UPNUNP), and self-reported levels of neuroticism were entered in Step 1. Neuroticism, assessed using the negative temperament subscale of the General Temperament Survey (GTS; Clark & Watson, 1990), was included as a covariate to determine whether the effects were specific to IU or were better accounted for by broad, higher order trait levels of negative affectivity (i.e., neuroticism). The main effects of PD (yes/no) and IU was entered in Step 2, and the PD by IU interaction term was entered in Step 3. Significant interactions were followed up using the simple slopes approach (Aiken & West, 1991; Holmbeck, 2002). Given that IUS-12 is a continuous variable (Carleton et al., 2012), rather than dichotomize it for follow-up analyses (which would reduce power), IU was re-centered at 1 *SD* above the mean for “high IU” and 1 *SD* below the mean for “low IU.” Thus, two separate continuous, conditional moderators were created and two new interaction terms were created from these conditional moderators. *Post-hoc* two additional follow-up linear regression models were run incorporating the aforementioned covariates, PD, the conditional moderator (i.e., high or low IU), and the interaction term – one at high IU and one at low IU.

In order to assess whether the pattern of results was specific to startle, we also conducted a series of hierarchical linear regression analyses with average self-reported anxiety during PISI, PCue, UISI, and UCue as the dependent variables. Similar to the startle variables, potentiation scores were first created by subtracting self-reported anxiety during the control condition (i.e., N) from the P and U conditions (e.g., PCue – NCue, UISI – NISI). All of the variables entered into the models were identical to those described above.

3. Results

3.1 Clinical Characteristics

Demographic and clinical differences between the groups have been previously reported (see Shankman et al., 2013; also see Table 1). As expected, PD participants reported greater IU relative to non-PD participants. Participants rated the shocks as moderately to extremely intense ($M = 4.94$, $SD = 1.15$), annoying ($M = 5.18$, $SD = 1.30$), and anxiety provoking ($M = 4.91$, $SD = 1.55$). Participants reported that they would avoid receiving the shocks again to a high degree ($M = 5.51$, $SD = 1.47$). PD status was not associated with any of the shock ratings (all $ps > .09$).

3.2 Moderating Effect of IU on PD and PISI Startle Potentiation

Results are presented in Table 2 for the safety phase of the P condition (i.e., PISI). There were no main effects of PD or IU. However, there was a significant PD by IU interaction.¹ Follow-up analyses indicated that at low IU scores, PD and non-PD individuals had comparable startle potentiation to PISI, $\beta = -0.10$, $t(164) = -0.77$, $p = 0.44$. In contrast, at high IU scores, PD participants exhibited greater startle potentiation during PISI than non-PD participants, $\beta = .26$, $t(164) = 2.19$, $p = .03$.^{2,3}

3.3 Moderating Effect of IU on PD and Threat Startle Potentiation

As reported in Shankman et al. (2013), there was a main effect of PD on all three threat potentiation scores (PCue, UISI, and UCue). However, there were no PD x IU interactions in any of the models (all $ps > .74$). The PD by IU interaction on startle potentiation to safety (PISI) and threat (PCue) is displayed in Figure 1.

3.4 Moderating Effect of IU on Self-Reported Anxiety

There were no main effects of PD or IU on self-reported anxiety during the task. There was also no PD by IU interactions for the PISI, PCue, or UISI models (all $ps > 0.33$). The PD by IU interaction on self-reported anxiety during UCue was at trend level, $\beta = -0.20$, $t(164) = -1.75$, $p = 0.08$.

4. Discussion

Although heightened aversive responding during safety signals may be a core deficit of anxiety disorders, studies with PD individuals have been mixed. The current study therefore examined whether a key anxiety-related trait – IU – moderated the association between PD and startle potentiation during safety conditions during a threat-of-shock paradigm. Results

¹In addition to IUS total scores, we examined the moderating effect of the inhibitory anxiety (IA) and prospective anxiety (PA) subscales of IUS (Carleton et al., 2007) on the relation between PD and startle potentiation to PISI. Results were consistent across total scores and both subscales. At high levels of IUS-IA and IUS-PA, PD was associated with greater startle potentiation (IA: $\beta = 0.23$, $t = 2.03$, $p = 0.04$; PA: $\beta = 0.23$, $t = 2.14$, $p = 0.03$); however, at low levels of IUS-IA and IUS-PA, there was no relation between PD and startle potentiation.

²Of note, we confirmed that there were no significant MDD x IUS ($p = 0.37$) or PD x MDD x IUS interactions ($p = 0.38$) and therefore removed these interaction terms from the final model.

³The pattern of results is identical whether GTS-NE scores were included or excluded from our analyses. When GTS-NE was excluded, PD was associated with greater startle potentiation during PISI at high levels of IUS total scores ($\beta = .23$, $t(164) = 2.16$, $p = .03$), but not low levels ($\beta = -.11$, $t(164) = -0.92$, $p = .36$).

indicated that IU did moderate this association during the safety condition, but not the threat conditions. At high levels of IU, PD was associated with greater startle potentiation during safety. At low levels of IU, PD was not associated with startle potentiation during safety. Notably, this pattern of results was not due to baseline differences in startle as there was no PD by IU interaction on startle potentiation during the control conditions (i.e., N condition).

Several studies have demonstrated that individuals high in IU are more likely to interpret ambiguous situations as negative or threatening (Anderson et al., 2012; Dugas et al., 2005; Koerner & Dugas, 2008). This interpretive bias may explain the present results. In the NPU task, the PISI is ambiguous as it signals both safety (shock is not possible right now) and *pending* threat (shock will be possible in an uncertain but relatively short amount of time). As hypothesized, high IU participants with PD may have been more likely to interpret the PISI as signaling distal threat, resulting in potentiated startle, whereas low IU participants were more likely to interpret the PISI as signaling safety. In other words, the two subgroups of PD participants may have appraised the condition differently. This explanation is supported by the fact that IU did *not* moderate effects of PD on responding during explicit threat conditions. Because these conditions are less ambiguous, they left little room for differing interpretations. Instead, they were likely interpreted as threatening by all PD participants. Given this pattern of results, future studies should test whether interpretive biases mediate associations between IU and heightened responding during safety among individuals with anxiety disorders.

Closely related to these points, it is possible that individuals with high versus low IU differ in their requirements for safety responding. As noted above, in order to inhibit aversive responding, participants must appraise the situation as safe. It is possible that among individuals with PD, those with high IU require proximal *and* distal safety to inhibit aversive responding whereas those with low IU only require proximal safety. Although future research is needed to confirm these mechanisms, this explanation would have important implications. Explicit distal safety cues are extremely rare and a potentially unobtainable requirement for safety responding (Craske et al., 2012). In everyday life, there is always the possibility of future threat and expecting otherwise would be considered irrational. If individuals with PD and high IU are consistently interpreting ambiguous information as threatening and seeking proximal and distal safety, it is unlikely that they would ever appraise their present situation as safe (Degnan, Almas, & Fox, 2010). Consequently, individuals with PD and high IU may exhibit chronic defensive responding, which has substantial cognitive and physical adverse consequences.

More broadly, extant theory and research indicate that individuals with PD perceive innocuous interoceptive and exteroceptive stimuli as threatening, which maintains their disorder and generates anticipatory anxiety (Bouton, Mineka, & Barlow, 2001). In light of the current findings, PD patients with high IU may be especially vulnerable to these interpretative biases and consequently have a worse disorder prognosis. Indeed, emerging research suggests that levels of IU are positively correlated with PD symptoms (Carleton et al., 2013). Therefore, among PD patients, those with high IU may represent an important population for targeted interventions. Exposure-based interventions that directly address safety and inhibitory learning (Craske et al., 2008b) or cognitive-behavioral therapies that

incorporate intolerance of uncertainty training (Ladouceur et al., 2000) may improve treatment efficacy among this subgroup of individuals.

Although the present findings address important gaps within the literature, the study had several limitations. First, PD patients were allowed to meet criteria for other current and lifetime anxiety disorders and thus, the effects may have been due to anxiety disorders in general, rather than panic disorder specifically. Second, approximately 38% of the PD patients were taking psychiatric medications, which may have impacted psychophysiological responding. However, it is of note that when current psychiatric medication status (yes/no) was included as a covariate, the PD by IU interaction on PISI startle potentiation remained significant. Relatedly, detailed information on recreational substance use was not collected and it is unknown whether these substances may have influenced the pattern of results. Lastly, the safety conditions (and threat conditions) of the current task were short in duration and future studies are needed to examine the time course of aversive responding during safety signals to explore whether the moderating effect of IU is specific to short term safety or is a chronic issue.

Another possible limitation is that the present pattern of results did not generalize to self-report measures of aversive responding, as IU did not moderate the association between PD and self-reported anxiety during any of the task conditions. It is important to highlight that prior studies using this paradigm have similarly reported a discrepancy in findings between self-report and psychophysiological measures (e.g., Gorka et al., 2013; Shankman et al., 2013). While there are numerous factors which could contribute to this lack of convergence, a likely explanation is that startle potentiation and self-report capture slightly different constructs. For the self-report measure, participants were asked to rate their “anxiety/nervousness,” which may have assessed arousal rather than valence. Although subtle, this distinction is important given that startle has been shown to be sensitive to valence and not arousal (Lang, Greenwald, Bradley, & Hamm, 1993). In order to clarify this issue, future work should incorporate multiple measures of aversive responding including self-report, behavioral, and psychophysiological indices.

Despite these limitations, the results have several important implications. Most notably, PD patients with high levels of IU failed to inhibit aversive responding in the presence of safety information, possibly due to a tendency to interpret ambiguous information as threatening. This subgroup of PD patients may therefore fail to recognize proximal safety, instead focusing on the fact that aversive events (such as panic attacks) are likely to occur unpredictably in the future. This psychophysiological propensity to diminish aversive responding during safety cues likely has numerous negative consequences including maintaining chronic anxiety and defensive responding.

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Figure 1. Mean PCue and PISI startle potentiation at high and low intolerance of uncertainty for individuals with and without panic disorder. Values were estimated at high and low (± 1 SD) IU and adjusted for covariates.

Table 1
Participant Demographics and Study Variables by Panic Disorder Diagnosis Status

Variable	Yes PD (<i>n</i> = 74)	No PD (<i>n</i> = 98)
Age (years; <i>SD</i>)	34.7 (11.6) _a	31.1 (12.8) _b
Gender (% Female)	68.1 _a	60.5 _a
Race (% Caucasian)	51.1 _a	47.6 _a
Education (%)		
Did not graduate high school	4.3 _a	0.0 _a
Graduated high school or equivalent	4.3 _a	4.0 _a
Part college or 2-year college	39.4 _a	41.1 _a
Graduated 4-year college	30.8 _a	32.3 _a
Greater than college degree	21.2 _a	22.6 _a
Global Assessment of Functioning (<i>SD</i>)	54.8 (7.6) _a	76.2 (18.1) _b
Hamilton Rating Scale of Depression (<i>SD</i>)	20.1 (11.5) _a	10.1 (11.6) _b
Beck Anxiety Inventory (<i>SD</i>)	18.6 (13.1) _a	6.8 (8.7) _b
Current Psychiatric Medications %	38.3% _a	11.8% _b

Note. PD = Panic Disorder; Means or percentages with different subscripts across rows were significantly different in pairwise comparisons ($p < .05$, chi-square test for categorical variables and Tukey's honestly significant difference test for continuous variables).

Table 2
Hierarchical Linear Regression Analyses Examining Unique and Interactive Effects of PD and IU on Startle Potentiation During PISI Condition

	β	t	R^2	R^2
Step 1			0.03	0.01
MDD	-0.03	-0.28		
Age	-0.11	-1.47		
Gender	0.06	0.71		
GTS-NT	0.05	0.55		
Task Condition Order	-0.12	-1.56		
Step 2			0.02	0.02
PD	0.10	1.06		
IUS	0.18	1.72		
Step 3			0.03*	0.04
PD x IUS	0.24*	2.19		

Note. PD = Panic Disorder; MDD = major depressive disorder; IUS = intolerance of uncertainty scale; GTS-NT = General Temperament Survey – Negative Temperament Subscale