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Anxiety Sensitivity and Intolerance of Uncertainty Facilitate Associations Between Generalized Pavlovian Fear and Maladaptive Avoidance Decisions

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Generalization of Pavlovian fear to safe stimuli resembling conditioned-danger cues (CS+) is a widely accepted conditioning correlate of clinical anxiety. Though much of the pathogenic influence of such generalization may lie in the associated avoidance, few studies have assessed maladaptive avoidance decisions associated with Pavlovian generalization. Lab-based assessments of this process, here referred to as aversive Pavlovian-instrumental covariation during generalization (APIC-G), have recently begun. The current study represents a next step in this line of work by conducting the first examination of anxiety-related dimensions of personality that may exacerbate APIC-G. Specifically, we test anxiety sensitivity (AS) and intolerance of uncertainty (IU) as moderators of relations between Pavlovian generalization and maladaptive avoidance decisions in 102 undergraduate students with wide-ranging levels of IU and AS. Results indicate a facilitative effect of AS on this APIC-G process, with AS strengthening relations between Pavlovian generalization and maladaptive generalized avoidance whether operationalizing Pavlovian generalization with psychophysiological (fear-potentiated startle) or behavioral measures. Additionally, IU was found to facilitate APIC-G when indexing Pavlovian generalization with behavioral but not fear-potentiated startle measures. Moderating effects of AS were most pronounced for stimulus classes bearing the highest resemblance to CS+, whereas effects of IU were most pronounced for the stimulus class with the highest level of threat ambiguity. Results implicate AS and IU as risk factors for the maladaptive decisional correlates of Pavlovian generalization and suggest that established associations between these traits and clinical anxiety may derive, in part, from their enhancement of maladaptive APIC-G.

General Scientific Summary

The generalization of fear from dangerous situations to resembling safe situations is a core feature of clinical anxiety, and much of the dysfunction from such generalization lies in its association with excessive avoidance. In the present study, we identify two personality-based risk factors for clinical anxiety (anxiety sensitivity [AS], intolerance of uncertainty [IU]) that facilitate the degree to which generalization of fear is associated with maladaptive avoidance decisions. Such findings implicate levels of IU and AS as cross-diagnostic indicators of the extent to which maladaptive generalized avoidance may be contributing to the symptom profile of a given anxiety patient.

Keywords: generalization of conditioned fear, behavioral avoidance, fear-potentiated startle, anxiety sensitivity, intolerance of uncertainty

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The transfer of fear from a learned danger cue to resembling safe stimuli, referred to as Pavlovian fear-generalization, is widely accepted as a pathogenic marker of anxiety pathology by clinicians and theorists alike (e.g., Craske et al., 2009; Ehlers & Clark, 2000; Foa, Steketee, & Rothbaum, 1989). Such generalization is thought to contribute to clinical anxiety by unduly increasing the number of innocuous environmental stimuli that are capable of eliciting and maintaining anxious distress. In support of this view, results across lab-based, case-control studies implicate heightened Pavlovian fear-generalization as a transdiagnostic correlate of clinical anxiety (Cha et al., 2014; Kaczkurkin et al., 2017; Lissek & Grillon, 2012; Lissek at al., 2010, 2014; Morey et al., 2015), but no such studies assess the avoidance decisions thought to accompany generalized Pavlovian fear in the anxiety disorders (e.g., Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015; Ehlers & Clark, 2000; Foa et al., 1989; Pittig, Treanor, LeBeau, & Craske, 2018). This is a significant omission, given that much of the pathogenic

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potential of Pavlovian fear-generalization may lie in its association with generalized instrumental avoidance: active decisions to withdraw from safe stimuli resembling learned danger cues. Work in clinically relevant samples is thus needed to identify moderating effects of anxious dispositions on relations between Pavlovian generalized-fear and decisions to instrumentally avoid, herein referred to as aversive Pavlovian-instrumental covariation during generalization (APIC-G). Through APIC-G, Pavlovian generalization of fear motivates decisions to avoid safe stimulus events resembling learned danger cues. APIC-G is maladaptive when it results in unnecessary avoidance of benign experiences at a cost to one's pursuit of life goals.

Despite the promise of APIC-G as a key path to the maladaptive avoidance centrally implicated in the anxiety- and trauma-related disorders (American Psychiatric Association, 2013), only five studies to date explicitly test relations between Pavlovian generalization and generalized avoidance decisions (Arnaudova, Krypotos, Effting, Kindt, & Beckers, 2017; Boyle, Roche, Dymond, & Hermans, 2016; Cameron, Schlund, & Dymond, 2015; Hunt, Cooper, Hartnell, & Lissek, 2017; van Meurs, Wiggert, Wicker, & Lissek, 2014). Furthermore, the only study testing moderating effects of clinically relevant individual differences in APIC-G identified stress-buffering personality traits that protect against APIC-G (Hunt et al., 2017). Specifically, findings from this study demonstrate that dispositions to persevere in the face of distress (distress endurance) and dispositions to cope with distress through distraction and suppression (distraction/suppression) each mitigate the extent to which generalized fear is accompanied by maladaptive avoidance decisions. Thus, whereas stress-buffering proclivities have been found to reduce APIC-G, no studies assess anxiety-related traits that may confer risk for clinical anxiety through enhanced APIC-G.

In the present study, we fill this gap by testing two transdiagnostic risk factors for clinical anxiety predicted to exacerbate APIC-G: (a) anxiety sensitivity (AS: Reiss, Peterson, Gursky, & McNally, 1986), and (b) intolerance of uncertainty (IU: Carleton, Norton, & Asmundson, 2007). The applied APIC-G paradigm is a behaviorally and psychophysiologically validated generalization task designed to analogue real-world, avoidance-related dysfunction by assessing generalized avoidance decisions that are maladaptive by virtue of an unnecessary cost to task performance incurred by participants choosing to avoid (Hunt et al., 2017; van Meurs et al., 2014). Our central goal is thus to test the extent to which AS and IU positively moderate the strength of relations between Pavlovian fear-generalization and maladaptive decisions to avoid (i.e., maladaptive APIC-G).

AS as a Moderator of Maladaptive APIC-G

AS, often characterized as fear of fear, refers to beliefs that anxiety-related sensations are physically or psychologically threatening (Reiss et al., 1986). AS has been repeatedly documented as a risk factor for anxiety pathology (Olatunji & Wolitzky-Taylor, 2009). According to Reiss et al.'s (1986) conceptualization of AS, the fear of experiencing anxiety associated with AS serves to amplify avoidance of anxiety-provoking situations. Specifically, the fear that anxious arousal constitutes—or brings about—negative outcomes, motivates those high on AS to avoid stimulus events to which anxious reactivity is experienced or anticipated. The facilitating effect of AS on avoidance is supported by studies finding positive relations between AS and avoidance of fear provoking encounters (Wilson & Hayward, 2006) and risky situations (Broman-Fulks, Urbaniak, Bondy, & Toomey, 2014).

In the current study, AS is predicted to enhance APIC-G because the anxiety provoked by safe stimuli resembling danger cues, referred to as generalization stimuli (GS), will itself be appraised as harmful among those higher on AS, leading to greater aversive motivation to unnecessarily avoid during safe GS. That is, fear of fear associated with AS is predicted to enhance initial anxious reactivity to the appearance of danger cued by safe GS, preferentially incentivizing avoidance of such stimuli among those higher on AS. This prediction of stronger fear-avoidance relations associated with AS is supported by a recent behavioral study documenting fear of spiders as a significant predictor of avoidance of spider images among those high, but not low, in AS (Lebowitz, Shic, Campbell, Basile, & Silverman, 2015).

IU as a Moderator of APIC-G

IU is the second personality factor proposed to moderate APIC-G. IU involves a proclivity to react negatively on cognitive, emotional, and behavioral levels to uncertain events (Dugas, Buhr, & Ladouceur, 2004), and has been positively associated with a variety of anxiety- and trauma related disorders (for a review, see Shihata, McEvoy, Mullan, & Carleton, 2016). Those high on IU experience uncertainty as upsetting and unacceptable, which tends to motivate avoidance of uncertain situations (e.g., Carleton et al., 2007). In the context of the present work, IU is predicted to enhance APIC-G because threat uncertainty communicated by safe stimuli bearing some resemblance to danger cues (i.e., GS) will be appraised as unacceptable by those higher on IU, increasing the likelihood of avoidance during presentations of GS.

Goals of the Present Study

In the current study, we applied a Pavlovian-instrumental generalization (PIG) paradigm to test the prediction that both AS and IU would facilitate the degree to which behavioral and psychophysiological (fear-potentiated startle) indices of Pavlovian fear generalization are accompanied by maladaptive, generalized avoidance decisions (i.e., AS and IU as moderators of APIC-G). These predictions were premised on the notion that fear reactivity to the false alarm of danger, signaled by safe stimuli exhibiting some resemblance to danger cues, would be enhanced by fear of fear and uncertainty-related distress among those high on AS and IU, respectively, augmenting aversive motivation to unnecessarily avoid during exposure to such stimuli. We also assessed whether moderating effects of AS and IU extend to a more adaptive form of aversive Pavlovian-instrumental covariation, referred to as APIC-CS+, in which Pavlovian fear of genuine danger, signaled by the conditioned-danger cue (CS+), is associated with instrumental avoidance decisions during CS+ presentations (i.e., AS and IU as moderators of APIC-CS+). All such moderating effects of AS and IU were tested while controlling for levels of both broad trait anxiety and the nontested personality factor (IU or AS) to determine whether predicted effects were attributable to the specific trait features of AS and IU. Through this work we aimed to identify cross-diagnostic, trait-based risk factors for clinical anxi-

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ety that augment relations between generalized Pavlovian fear and maladaptive avoidance decisions.

Method

Participants

A total of 115 University of Minnesota students were recruited and tested. Inclusion criteria are listed in the online supplemental materials. Of the 115 tested participants, seven were dropped due to validity concerns, as they provided invalid responses to validity items embedded in self-report questionnaires. An additional six participants were excluded from analyses because they failed to acquire the CS+/unconditioned stimulus contingency (as indicated by CS+ vs. conditioned-safety cue [CS−] risk-rating difference scores less than or equal to 0). Furthermore, psychophysiological data for nine participants were not included in analyses because either such participants were startle nonresponders, or because of technical problems with electromyography (EMG) equipment. These issues left behavioral data from 102 participants and psychophysiological data from 93 participants available for analysis. Of the 102 participants comprising the final study sample, 38 were participants tested in Hunt et al., 2017. The rationale for including these 38 overlapping participants stems from the large sample sizes needed to detect effects of continuous dimensions of personality on psychophysiological measures. Of the $N = 109$ included in Hunt et al. (2017), only 38 completed measures of AS and IU. We thus added these 38 participants to the study sample to achieve the needed statistical power.

In the current study sample of $N = 102$ (62% female; $M_{age} = 20.42$, $SD = 3.22$), average scores on the Anxiety Sensitivity Index (ASI: Reiss et al., 1986) and Intolerance of Uncertainty Short Form (IUSF: Carleton et al., 2007), were 21.78 ($SD = 11.27$) and 30.73 ($SD = 9.58$), respectively. Furthermore, this sample had wide ranging scores across quartiles (Q) on both the ASI ($M_{Q1} = 9.12$, $M_{Q2} = 16.37$, $M_{Q3} = 25.00$, $M_{Q4} = 37.07$) and IUSF ($M_{Q1} = 19.46$, $M_{Q2} = 26.48$, $M_{Q3} = 33.48$, $M_{Q4} = 43.42$), with average scores in the top quartile of each measure matching or exceeding levels of AS and IU previously documented among those with clinical anxiety (AS: Taylor, Koch, & McNally, 1992; IU: Carleton et al., 2012). All participants provided written informed consent after receiving a complete description of the study.

Questionnaires

Participants completed the ASI (Reiss et al., 1986), IUSF (Carleton et al., 2007), and Spielberger State and Trait Anxiety Inventory (STAI: Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) as part of a larger ongoing study on fear learning, avoidance, and personality. For the current study, only results from the ASI, IUSF, and trait portion of the STAI (STAI-T) were analyzed.

PIG Paradigm

The PIG paradigm is a psychophysiologically validated experimental task designed to assess generalized Pavlovian fear, maladaptive generalized instrumental avoidance, and the relation between these Pavlovian and instrumental processes (Van Meurs et al., 2014). Pavlovian responses (fear-potentiated startle, perceived risk of shock) and instrumental responses (behavioral avoidance) are assessed to five ring-shaped stimuli and one triangle-shaped stimulus embedded in the computer-based farmer game (Figure 1 and, in the online supplemental materials, Figure S1). The five rings gradually increase in size with extreme sizes serving as conditioned-danger (CS+: paired with electric shock) and conditioned-safety cues (CS−: not paired). Intermediately sized rings form three classes of GS (GS_1, GS_2, GS_3) all of which are presented in the absence of shock. These five ring sizes form a continuum of size (from CS− to GS1, to GS2, to GS3, to CS+) with which to assess continuous gradients of generalized fear and avoidance. The triangle functions as a noncircular conditioned-safety cue (ΔCS−: not paired with shock) to assess a broader form of generalization to all things circular. Pavlovian and instrumental responses are also assessed to the video game only (VGO: video game graphics in the absence of shapes), to control for contextual effects of the video game environment that are unrelated to discretely cued conditioning processes of interest.

As can be seen in Figure 1, the paradigm is embedded in a virtual farmer computer game during which the participant is a farmer whose task it is to travel between a shed and garden to successfully plant and harvest crops. Two different roads connect the shed to the garden: (a) a short road, and (b) a long road. Traveling the short road is perilous (contingently associated with shock) but allows the farmer quick travel from shed to garden, and assures a successful harvest. Conversely, traveling the long road is always safe but often prevents the farmer from arriving at the garden before wild birds eat the crop. During instrumental avoidance trials, a CS or GS is superimposed in the middle of the screen and participants are asked to choose the long road (avoidance response) or short road (nonavoidance response) following a 5-s deliberation period. That is, participants are placed in an approach-avoidance conflict that must be resolved by cognitively weighing the costs and benefits of decisions to either approach or avoid within a 5-s deliberation period. The current task thus pulls for deliberative avoidance decisions that are not mere expressions of Pavlovian fear reactivity, but are a function of how that fear is processed along with other (competing) motivational forces (e.g., a desire to win) to determine whether avoidance will best meet current needs and goals. Avoidance responses (choosing the long road) on CS+ trials are considered more adaptive, despite compromised performance, because there is a genuine possibility of shock following nonavoidance responses (choosing the short road) during CS+ trials. By contrast, avoiding during safe GS presentations is considered maladaptive because shock is not a realistic possibility, and avoiding thus unnecessarily compromises performance on the task.

During Pavlovian trials, a CS or GS is presented, but participants are automatically sent down the short path during which startle magnitudes and perceived risk of shock are recorded as measures of Pavlovian conditioning to each stimulus type. A full description of the PIG paradigm including task parameters, psychophysiological methods, procedures, and analytic strategies can be found in the online supplemental materials.

Results

Behavioral and psychophysiological results for preacquisition and acquisition of Pavlovian fear are of secondary interest and can be found in the online supplemental materials. Noncentral findings

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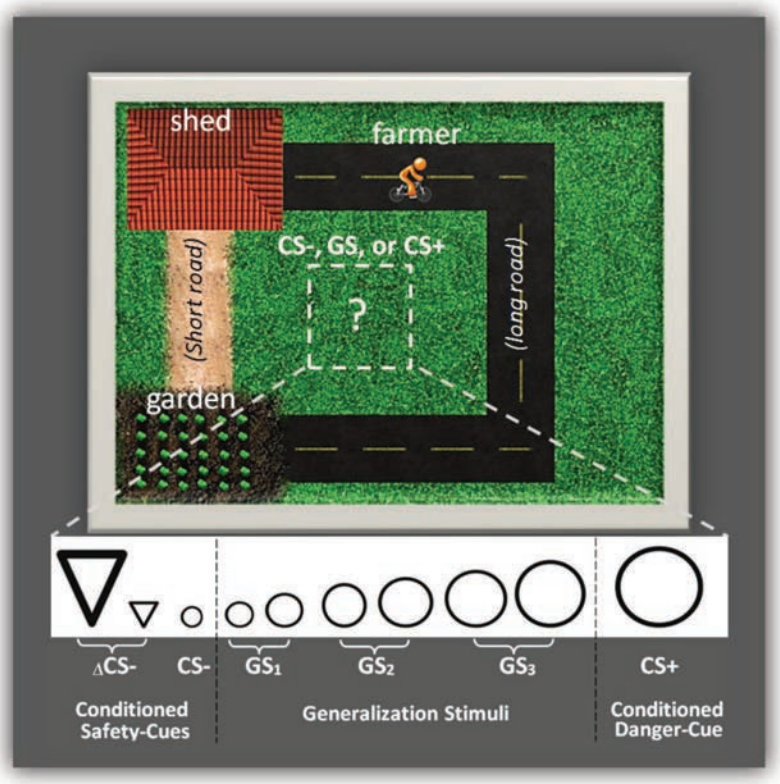

Figure 1. Picture of the Pavlovian-instrumental generalization paradigm displaying the short and long roads connecting the shed to the garden. Also pictured are the conditioned and generalization stimuli presented in the center of the screen during the task. The size of stimuli was counterbalanced across participants (see the online supplemental materials). GS = generalization stimulus; $_{\Delta}$CS− = triangular CS−; CS− = conditioned-safety cue; GS_1, GS_2, GS_3 = generalization stimulus Classes 1–3; CS+ = conditioned-danger cue. See the online article for the color version of this figure.

at generalization (i.e., manipulation checks) can also be found in the online supplemental materials.

Pavlovian Generalization

Startle EMG. Startle magnitudes formed a continuous generalization-gradient (Figure 2A) as indicated by a main effect of trial type, $F(4, 88) = 96.69$, $p < .001$, $\eta_p^2 = 0.79$, 95% CI [0.73, 0.85], that was driven by strongest startle to CS+, and gradual declines in startle as the presented stimulus differentiated from CS+, linear decrease: $F(1, 92) = 185.60$, $p < .001$, $\eta_p^2 = 0.65$, 95% CI [0.56, 0.74].

Risk ratings. As with startle EMG, risk ratings fell along a generalization gradient (Figure 2A) as evidenced by a main effect of trial type, $F(4, 97) = 304.81$, $p < .001$, $\eta_p^2 = 0.90$, 95% CI [0.90, 0.94], that was driven by highest perceived risk to CS+ and gradually declining levels as the presented stimulus differentiated from CS+, linear decrease: $F(1, 101) = 668.12$, $p < .001$, $\eta_p^2 = 0.87$, 95% CI [0.84, 0.90].

Instrumental Behavioral Avoidance

The main effect of trial type was significant for avoidance decisions, $F(4, 98) = 150.23$, $p < .001$, $\eta_p^2 = 0.58$, 95% CI [0.47, 0.68], and reflected gradients of generalization across stimuli (see Figure 2B) with highest rates of avoidance to CS+ and gradually declining rates as the presented stimulus differentiated from CS+, linear decrease: $F(1, 101) = 189.97$, $p < .001$, $\eta_p^2 = 0.64$, 95% CI [0.54, 0.74].

APIC

APIC-G. Participants displayed APIC-G as evidenced by positive relations between Pavlovian generalization and generalized avoidance when indexing Pavlovian generalization with either risk ratings, $r(102) = .34$, $p < .001$, or fear-potentiated startle, $r(93) = .18$, $p = .041$.

APIC-CS+. Pavlovian responses to CS+ were positively correlated with the more adaptive form of avoidance to CS+ when indexing Pavlovian responses with risk ratings, $r(102) = .29$, $p < .001$, but not fear-potentiated startle, $r(93) = .004$, $p = .484$.

Relations Between Personality Measures and Independent/Dependent Variables

AS was associated with IU, $r = .17$, $p = .046$, and STAI-T was associated with both AS, $r = .24$, $p = .008$, and IU, $r = .61$, $p <$

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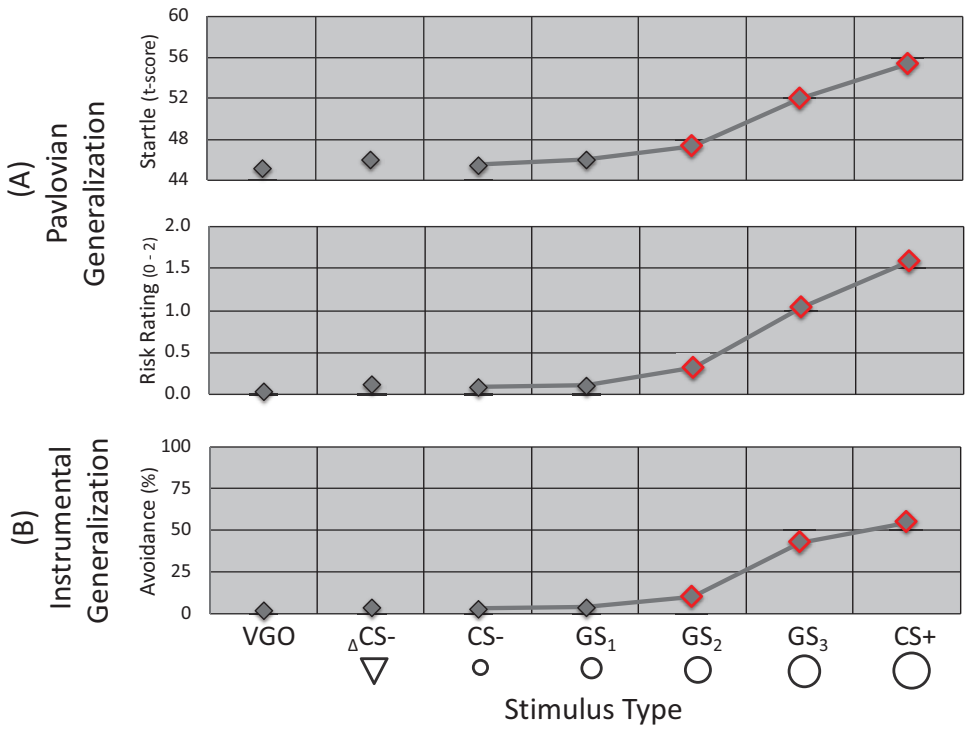

Figure 2. Pavlovian and instrumental generalization gradients across the video game only (VGO) condition, triangular conditioned-safety cue (ΔCS−), circular conditioned-safety cue (CS−), generalization stimulus Classes 1, 2, and 3 (GS_1, GS_2, GS_3), and the conditioned-danger cue (CS+). (A) Pavlovian generalization gradients for standardized fear potentiated startle magnitudes and online risk-ratings (0 = *no risk*, 1 = *some risk*, 2 = *high risk*). (B) Instrumental generalization gradients reflecting the percentage of avoidance responses across stimulus types. Data points outlined in red (gray) reflect stimulus classes eliciting significant generalization as defined by elevations relative to CS− at the Bonferroni adjusted *p* value of .0125. See the online article for the color version of this figure.

.001. Additionally, IU correlated at the trend level with levels of generalized risk, $r = .16$, $p = .054$ and generalized avoidance, $r = .16$, $p = .055$, and AS was not correlated with either generalized risk, $r = .10$, $p = .165$ or generalized avoidance, $r = .06$, $p = .289$. Finally, AS was unrelated and IU was inversely related to levels of generalized fear-potentiated startle (AS: $r = -.06$, $p = .301$; IU: $r = -.20$, $p = .030$). All other correlations between measures of personality (ASI, IUSF, STAI-T) and indices of conditioning, generalization, and reward motivation can be found in the online supplemental materials (Tables S1 and S2).

Moderating Effects of AS on APIC-G

Startle EMG. AS was found to positively moderate the relationship between Pavlovian generalized startle-potentiation and generalized avoidance as indicated by a significant interaction between generalized Pavlovian fear-potentiated startle and AS scores, $\beta = 0.30$, 95% CI [0.10, 0.50], $t(92) = 2.99$, $p = .004$, which explained an additional 8.5% of the variance in generalized avoidance, $F(5, 87) = 8.91$, $p = .004$ (see Table S3 in the online supplemental materials). These findings reflect stronger relations between Pavlovian generalized startle-potentiation and maladaptive generalized avoidance as scores on AS increase. Indeed follow-up tests of simple slopes revealed a significant relation between Pavlovian generalization of startle potentiation and generalized avoidance at high AS, $\beta = 0.54$, 95% CI [0.24, 0.84], $t(92) = 3.70$, $p < .001$, but not at moderate AS, $\beta = 0.19$, 95% CI [−0.01, 0.39], $t(92) = 1.88$, $p = .063$, or low AS, $\beta = -0.12$, 95% CI [−0.55, 0.37], $t(92) = -0.80$, $p = .424$ (Figure 3A). For post hoc tests at individual GS classes, the AS × Startle-Potentiation interaction term significantly predicted generalized avoidance in both the GS_3 model, $\beta = 0.29$, 95% CI [0.08, 0.50], $t(92) = 2.83$, $p = .006$, and GS_2 model, $\beta = 0.22$, 95% CI [0.01, 0.43], $t(92) = 2.11$, $p = .037$, which, respectively, explained an additional 8.1% of the variance, $F(5, 87) = 8.00$, $p = .006$, and 4.5% of the variance, $F(5, 87) = 4.47$, $p = .037$, in generalized avoidance. The GS_1 model did not yield a significant AS × Startle-Potentiation interaction term, $\beta = 0.18$, 95% CI [−0.03, 0.39], $t(92) = 1.70$, $p = .093$. Simple regression slopes reflecting the strength of APIC-G for GS_1, GS_2, and GS_3 across low, moderate, and high levels of AS are displayed in Figure 3B–3D.

To further examine the influence of AS on responses to stimulus types for which AS moderated APIC-G, we tested associations between AS and levels of Pavlovian and instrumental generalization to GS_3 and GS_2 (relative to VGO). AS was not correlated with either Pavlovian startle potentiation or instrumental avoidance for either GS_3 or GS_2 (all *p*s > .240), indicating that AS did not affect

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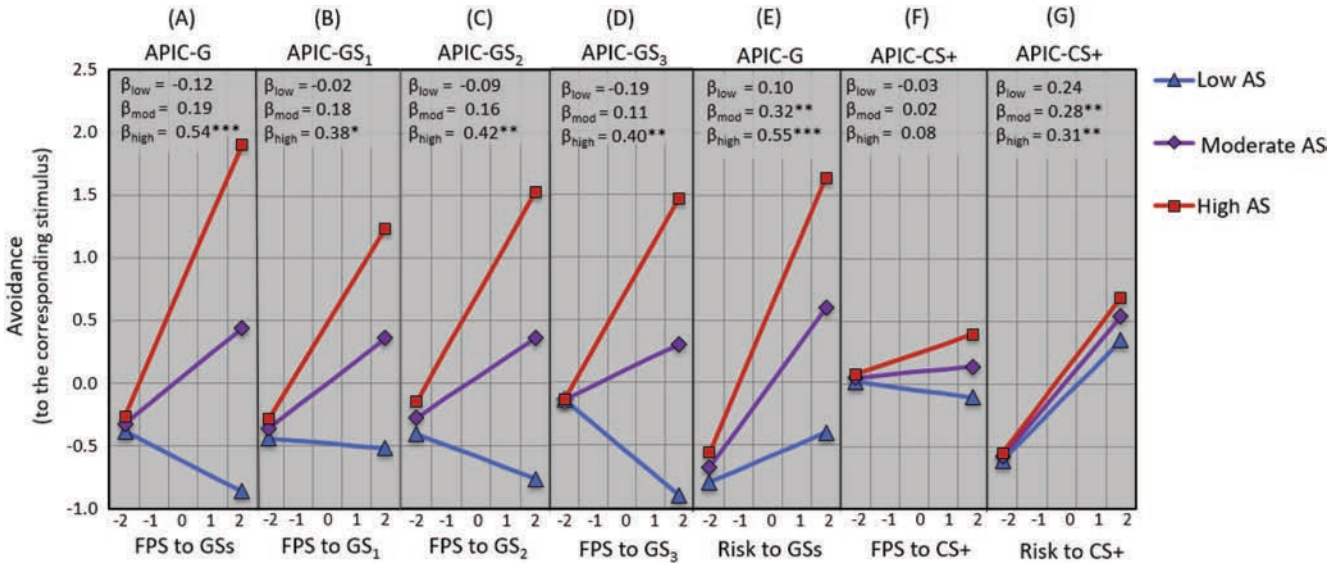

Figure 3. Simple regression slopes and associated standardized beta weights (β) depicting the moderating effect of anxiety sensitivity (AS) on aversive Pavlovian-instrumental covariation (APIC) for (A) all generalization stimuli averaged: APIC-G; (B–D) generalization stimulus Classes 1 (GS_1), 2 (GS_2), and 3 (GS_3): APIC-GS_1, APIC-GS_2, APIC-GS_3; and (F–G) the conditioned- danger cue (CS+): APIC-CS+. Relations between Pavlovian responses (*x*-axis) and levels of avoidance (*y*-axis) are displayed for low (−1 *SD* below the mean), moderate (the mean), and high (+1 *SD* above the mean) AS separately. In graphs A–D and F, Pavlovian responses are indexed by fear-potentiated startle (FPS). In graphs E and G, Pavlovian responses are indexed by risk ratings. Simple slopes for APIC-GS_1, APIC-GS_2, and APIC-GS_3 are not shown for risk ratings, given no significant moderating effects for AS with individual GS classes were found. All responses (FPS, risk ratings, avoidance) were converted to *Z* scores expressing average responding to the stimulus class of interest minus average responding to the video game only condition. * $p \leq .050$. ** $p \leq .010$. *** $p \leq .001$. See the online article for the color version of this figure.

the strength of either Pavlovian or instrumental generalization to these two stimulus types. Thus, AS moderated the strength of the relation between generalized fear and generalized avoidance at both GS_3 and GS_2 without influencing the actual magnitudes of generalized fear or avoidance to such stimuli.

Risk ratings. AS was also found to positively moderate the link between Pavlovian generalized risk ratings and generalized avoidance as evidenced by a significant interaction between generalization of risk ratings during Pavlovian trials and scores on AS, β = 0.25, 95% CI [0.06, 0.44], $t(101) = 2.56$, $p = .012$, which explained an additional 5.6% of the variance in generalized avoidance, $F(5, 96) = 6.57$, $p = .012$ (see Table S3 in the online supplemental materials). Simple slope analyses indicated that generalization of risk ratings during Pavlovian trials did not significantly predict generalized avoidance at low AS, β = 0.10, 95% CI [−0.13, 0.33], $t(101) = 0.82$, $p = .414$, but did at moderate AS, β = 0.32, 95% CI [0.15, 0.49], $t(101) = 3.62$, $p < .001$, and high AS, β = 0.55, 95% CI [0.29, 0.81], $t(101) = 4.17$, $p < .001$ (see Figure 3E). Unlike startle results, however, post hoc analyses of individual GS classes yielded nonsignificant interactions between AS and generalized risk on generalized avoidance at each individual GS (*p*s ≥.250). Thus, when indexing Pavlovian responses with risk ratings, the moderating effect of AS on overall APIC-G (all GSs averaged together) was not driven by results at a specific GS but was generated cumulatively by results across GSs.

Moderating Effects of AS on APIC-CS+

In contrast to APIC-G findings, AS did not moderate the relation between Pavlovian responses to CS+ (both startle potentiation and risk ratings) and instrumental avoidance to CS+ (*p*s >.600). Thus the degree to which fear reactivity to the genuine threat of CS + elicited avoidance during CS + did not depend on levels of AS. Simple slopes for the null moderating effects of AS on APIC-CS+ with Pavlovian responses indexed by fear-potentiated startle and risk ratings are displayed in Figure 3F and 3G alongside the significant simple-slope findings for the corresponding APIC-G analyses (Figure 3A–3E). Taken together, the moderating function of AS across corresponding analyses appears to be specific to maladaptive APIC-G and unrelated to the more adaptive APIC-CS+.

Moderating Effects of IU on APIC-G

Startle EMG. IU did not moderate the link between generalization of Pavlovian fear-potentiated startle and generalized avoidance, as shown by a nonsignificant contribution to generalized avoidance from the interaction between generalization of Pavlovian startle potentiation and scores on IU, β = 0.09, 95% CI [−0.13, 0.31], $t(92) = 0.72$, $p = .445$.

Risk ratings. IU was found to moderate the relation between generalization of perceived risk during Pavlovian trials and generalized avoidance, as indicated by a significant inter-

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action between generalized risk ratings and scores on IU, β = 0.27, 95% CI [0.08, 0.46], $t(101) = 2.78$, $p = .007$, which explained an additional 6.5% of the variance in generalized avoidance, $F(5, 96) = 7.72$, $p = .007$ (see Table S4 in the online supplemental materials). Results from simple-slope analyses revealed that generalization of risk ratings during Pavlovian trials did not significantly predict generalized avoidance at low IU, β = 0.08, 95% CI [−0.15, 0.31], $t(101) = .60$, $p = .552$, but did at moderate IU, β = 0.29, 95% CI [0.11, 0.47], $t(101) = 3.10$, $p = .003$, and high IU, β = 0.52, 95% CI [0.29, 0.75], $t(101) = 4.39$, $p < .001$ (Figure 4A). Furthermore, results of post hoc tests indicate that IU did not moderate APIC-G for GS_1 or GS_3 ($ps \geq .320$: see Figure 4B and 4D), but did moderate APIC-G for GS_2, β = .21, 95% CI [0.001, 0.42], $t(101) = 2.03$, $p = .045$, explaining an additional 3.7% of the variance in generalized avoidance during GS_2, $F(5, 96) = 4.13$, $p = .045$ (see Figure 4C). Thus, the moderation effect of IU on APIC-G was driven by responses to the middlemost ring size, GS_2, which can be thought of as having the most ambiguous signal value by virtue of being equally similar to CS+ and CS−.

To further examine the influence of IU on responses to GS_2, we tested associations between IU and both Pavlovian risk ratings and instrumental responses for GS_2. We also tested the same associations for all other stimulus types to determine whether any found relations were specific to GS_2. Of all these associations, only the positive relation between IU and risk ratings to GS_2 (vs. VGO) was significant, $r(102) = .22$, $p = .013$, showing that increases in IU were exclusively related to increased perceived risk during GS_2 presentations. A closer look at risk-rating values to GS_2 across participants in the bottom and top quartiles of IU scores (where 0 = *no risk*, 1 = *some risk*, and 2 = *a lot of risk*) indicate little to no perceived risk of shock among those in the bottom IU quartile ($M = .23$), but midway between no risk and some risk among those in the top IU quartile ($M = .53$). In other words, low IU participants were fairly certain of safety during the middlemost rings whereas those higher on IU were less certain of safety.

Moderating Effects of IU on APIC-CS+

Like AS, IU did not moderate relations between Pavlovian responses to CS+ (both startle-potentiation and risk ratings) and instrumental avoidance to CS+ ($ps \geq .190$). Thus, when looking at results across APIC-G and APIC-CS+, IU moderated neither APIC-G nor APIC-CS+ when indexing Pavlovian responses with startle potentiation, but moderated APIC-G and not APIC-CS+ with Pavlovian responses indexed by risk ratings (see Figure 4A and 4E). Accordingly, only IU findings with Pavlovian responses

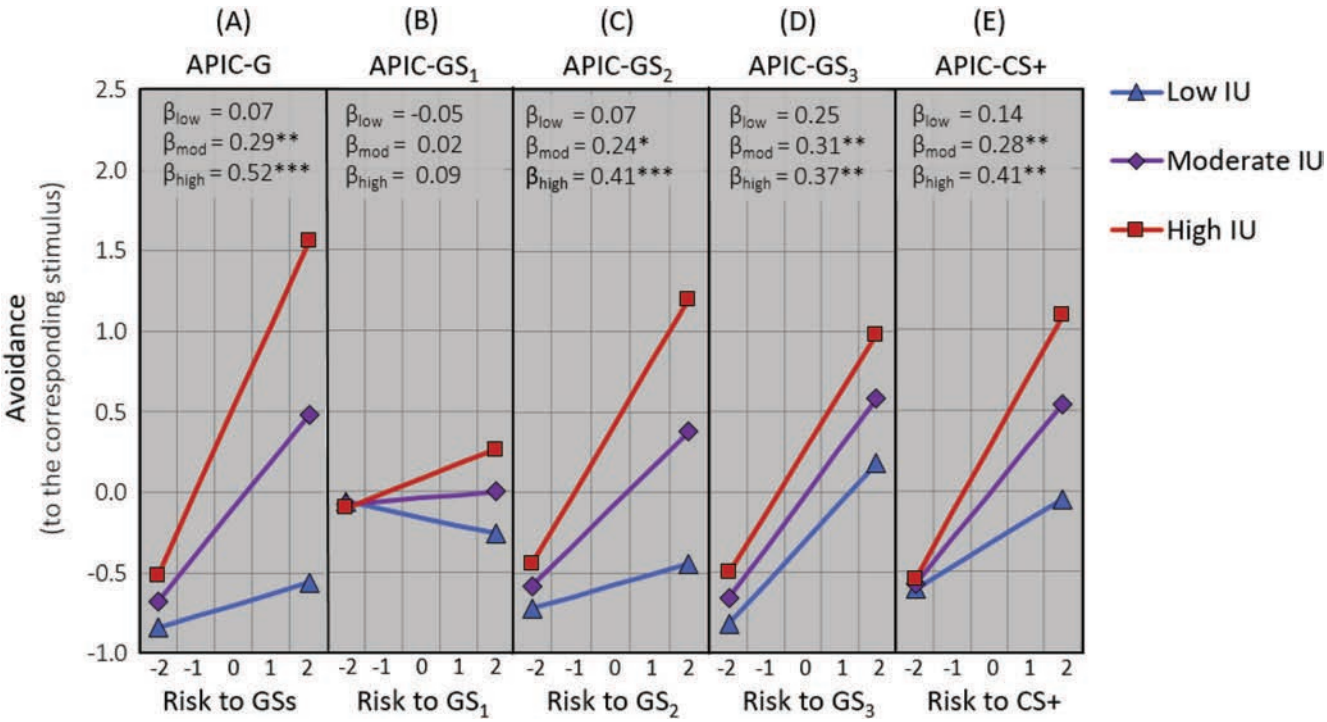

Figure 4. Simple regression slopes and associated standardized beta weights (β) depicting the moderating effect of intolerance of uncertainty (IU) on aversive Pavlovian-instrumental covariation (APIC), with Pavlovian responses indexed by risk ratings, for (A) all generalization stimuli averaged; (B–D) generalization stimulus Classes 1 (GS_1), 2 (GS_2), and 3 (GS_3); and (E) the conditioned-danger cue (CS+). Relations between Pavlovian responses (*x*-axis) and levels of avoidance (*y*-axis) are displayed for low (−1 *SD* below the mean), moderate (the mean), and high (+1 *SD* above the mean) IU separately. Both risk ratings and avoidance are Z scores expressing the average responding to the relevant stimulus class of interest minus the average response during the video game only condition. * $p \leq .050$. ** $p \leq .010$. *** $p \leq .001$. See the online article for the color version of this figure.

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indexed by risk ratings supported the prediction that IU would moderate maladaptive APIC-G without modifying the strength of more adaptive APIC-CS+.

Moderating Effects of IU Subscales on APIC-G and APIC-CS+

All moderating effects of prospective and inhibitory IU subscales were identical to those of overall IU (see the online supplemental materials).

Effects of Reward-Related Motivation to Win the Farmer Game

None of the significant moderating effects of AS or IU on APIC-G were driven by effects of appetitive motivation to win the farmer game. Full results of such analyses can be found in the online supplemental materials.

Moderation Effects of AS and IU at the Individual Stimulus Level

To identify the pattern of main findings across all stimulus types, *t* values reflecting the strength of APIC-G/CS+ moderation by AS and IU at CS−, GS_1, GS_2, GS_3, and CS+ are plotted in Figure 5. Only results of analyses for which Pavlovian-instrumental relations were moderated by AS or IU at one or more stimulus types are plotted (i.e., moderation effects of AS and IU with Pavlovian responses indexed by startle and risk ratings, respectively). As can be seen, moderation of Pavlovian-instrumental relations by AS emerged for stimulus classes bearing the highest resemblance to CS+ (GS_2, GS_3), whereas corresponding effects of IU were specific to GS_2, the middlemost ring size with the most ambiguous signal value (i.e., GS_2 is equally similar to CS− and CS+). Additionally, neither AS nor IU moderated Pavlovian-instrumental relations for stimuli signaling more certain safety (CS−) or danger (CS+).

Discussion

The current study represents the first effort to test the degree to which AS and IU, two trait-based markers of clinical anxiety, facilitate relations between generalized Pavlovian fear and generalized instrumental avoidance: APIC-G. APIC-G, as presently operationalized, assesses maladaptive fear-avoidance relations, whereby generalized fear to safe stimuli resembling a danger cue is accompanied by decisions to avoid such stimuli that are considered maladaptive by virtue of being unnecessary and costly. Such APIC-G thus reflects a lab-based analogue of real-world impairment from excessive fear and avoidance expressed widely in clinical anxiety (American Psychiatric Association, 2013). Importantly, AS and IU scores in the tested sample ranged widely, with the top quartile of scores falling well within the clinical range of each scale.

Results show that AS facilitated fear-avoidance relations during generalization (i.e., APIC-G), with stronger associations between generalized fear and maladaptive generalized avoidance as levels of AS increased, whether operationalizing generalized fear behaviorally (risk ratings) or psychophysiologically (fear-potentiated

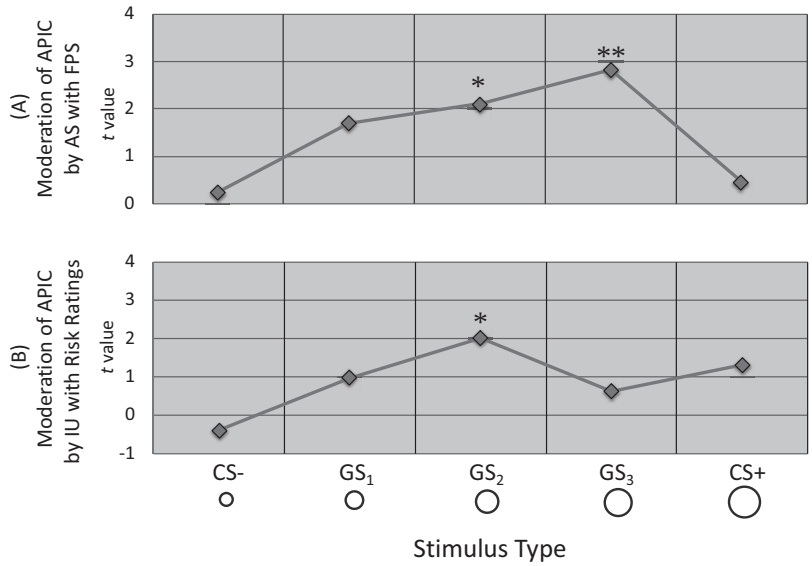

Figure 5. Moderating effects of: (A) anxiety sensitivity (AS), and (B) intolerance of uncertainty (IU) on aversive Pavlovian-instrumental covariation (APIC) separately for conditioned-safety cue (CS−), generalization stimulus (GS) Classes 1, 2, and 3 (GS_1, GS_2, and GS_3), and conditioned-danger cue (CS+). Pavlovian generalization is indexed by fear-potentiated startle (FPS) and risk ratings for effects of AS and IU, respectively, because effects from these analyses alone yielded significant findings at one or more stimulus types. On the *y*-axis are *t* values reflecting the degree to which interactions between AS or IU and their respective measures of Pavlovian generalization contributed to variance in the corresponding avoidance measure during hierarchical regression analyses. Higher *t* values reflect greater facilitation of relations between Pavlovian fear and instrumental avoidance with increasing levels of AS or IU. * $p \leq .050$. ** $p \leq .001$.

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startle). Thus safe stimuli resembling a learned danger cue, referred to as GS, elicit generalized fear responses that are more often accompanied by maladaptive avoidance decisions among those higher on AS. IU and its facets (prospective anxiety, inhibitory anxiety) were similarly found to positively moderate maladaptive fear-avoidance relations during generalization with fear generalization indexed by risk ratings, implying that perceived threat to GS communicating uncertain danger are more strongly associated with maladaptive avoidance decisions among those disposed to fear uncertainty (prospective IU) or avoid uncertainty (inhibitory IU). Unexpectedly, IU and its facets had no moderating effect on generalized fear-avoidance relations when fear-potentiated startle was used to measure generalized fear.

Each significant moderating effect of AS and IU on fear-avoidance relations during generalization was found while controlling for levels of both broad trait anxiety and the nontested personality factor (IU or AS), suggesting that moderation findings were attributable to the specific trait features of IU and AS. Additionally, neither AS nor IU moderated the degree to which reward-related motivation (i.e., motivation to win) led to nonavoidance decisions during GS, and central moderation results for AS and IU were found after controlling for potential AS/IU × Motivation to Win interaction effects on levels of generalized avoidance. Thus AS and IU influenced the aversive but not appetitive motivational correlates of generalized avoidance.

AS and IU Moderate Maladaptive, but Not More Adaptive, Fear-Avoidance Relations

Whereas AS and IU were found to augment maladaptive fear-avoidance relations elicited by safe stimuli resembling the danger cue, more adaptive associations between fear of veridical danger cues and decisions to avoid prompted by such cues (CS+), referred to as aversive Pavlovian-instrumental covariation during CS+ (APIC-CS+), were not moderated by AS, IU, or IU facets whether indexing fear responses behaviorally or psychophysiologically. Thus, the facilitative influence of AS and IU on links between learned fear and avoidance decisions was specific to maladaptive fear-avoidance coupling during generalization and did not extend to more adaptive forms of fear-avoidance correspondence.

This pattern of findings is consistent with the strong threat situation perspective (Lissek, Pine, & Grillon, 2006) according to which cues of certain, unambiguous, imminent, and potent danger, referred to as strong threats, invariably elicit adaptive, normative fear-related emotion and behavior across individuals. In contrast, weakening the threat situation, by reducing the certainty, imminence, or potency of danger, facilitates the emergence of individual differences in fear-related responding because less clear and objective threat information is available, and reactions are guided by more idiosyncratic threat appraisals and responses. In the current context, fear-avoidance associations elicited by the genuine danger cue may not have been facilitated by such individual differences as AS or IU because the danger cue is a stronger threat that was more likely to evoke normative patterns of fear and avoidance to the threat of electric shock in all participants. On the other hand, AS and IU may have augmented fear-avoidance relations elicited by stimuli bearing a degree of resemblance to the danger cue (i.e., GS) because such stimuli reflect weaker threats with increased likelihood of eliciting individual differences in patterns of fear and avoidance. This interpretation of findings for AS and IU, two correlates of anxiety pathology, is consistent with the phenomenology of clinical anxiety whereby fear-related aberrancies lie predominantly in overreactions to more minor (i.e., weaker) threats (e.g., Eysenck, 1992).

Interpreting Moderating Effects of AS on the Strength of Fear-Avoidance Relations

Whereas AS consistently enhanced the degree to which fear-generalization was accompanied by generalized avoidance decisions, AS was unrelated to levels of fear generalization whether measured behaviorally or psychophysiologically. This finding is consistent with Lebowitz and colleagues (2015), who found a moderating effect of AS on relations between fear and avoidance but no direct relation between AS and fear reactivity. That AS did not increase anxious reactivity to GS in the present study raises the possibility that facilitative effects of AS on generalized fear-avoidance relations occurred after initial anxious reactivity to GS in a way that facilitated generalized avoidance decisions. Given that AS is defined as fear of anxiety-related sensations, what likely occurred following initial anxious reactivity to GS among those high, but not low, on AS was additional fear about being anxious. The added fear experienced by those high on AS may have then served to increase their motivation to avoid during GS, contributing to the positive moderation of fear-avoidance relations during generalization by AS. That is, AS may have strengthened the link between generalized fear and maladaptive avoidance decisions by supplementing initial fear reactivity to GS with the ensuing fear of fear, resulting in greater overall aversive motivation to avoid in the presence of such stimuli among those higher on AS. This interpretation suggests that fear of fear among those higher on AS enhances anxious reactivity to safe situations resembling dangerous encounters and thereby confers risk for unnecessary avoidance of benign events.

Moderating Effects of AS at the Individual Stimulus Level

Follow-up tests for individual stimulus types revealed that the moderating influence of AS on fear-avoidance relations, when indexing fear psychophysiologically, was driven by effects for stimuli most closely resembling the danger cue (i.e., GS_3, GS_2) but not for stimuli with the least resemblance (CS−, GS_1). Additionally, as described above, fear-avoidance relations elicited by the danger cue (CS+) were not found to depend on levels of AS. Taken together, such findings indicate that AS strengthened the extent to which fear was accompanied by avoidance for target stimuli communicating moderate levels of threat uncertainty (i.e., GS_3, GS_2), but not for target stimuli signaling more certain threat (CS+) or more certain safety (CS−). This pattern of findings may be driven by differential degrees to which fear of fear influenced decisions to avoid across different stimulus types among those higher on AS. Specifically, AS may not have influenced fear-avoidance relations for stimuli bearing little resemblance to the danger cue (CS−, GS_1) because such stimuli were not sufficiently anxiety provoking to elicit fear of fear in those higher on AS. Additionally, the more certain threat signaled by the genuine

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danger cue may have elicited sufficient fear to elicit avoidance decisions without the need for fear of fear to further enhance levels of avoidance, thus blocking the influence of AS on fear-avoidance coupling elicited by the danger cue. Finally, safe GS most closely resembling the danger cue (GS_3, GS_2) may have elicited moderate levels of fear that were too weak to sufficiently motivate avoidance decisions in the absence of fear of fear, but the presence of fear of fear in those higher on AS may have served to enhance this moderate level of fear to levels sufficient to elicit decisions to avoid. Whether or not these interpretations are correct, facilitative effects of AS on relations between Pavlovian fear and unnecessary avoidance seem to require evoking stimuli, signaling threat uncertainty rather than stimuli communicating more certain threat or more certain safety.

Interpreting Moderating Effects of IU on Fear-Avoidance Relations During Generalization

IU was found to increase the extent to which generalized fear was accompanied by maladaptive avoidance decisions when indexing fear generalization with risk ratings, and this moderating role of IU was driven by effects at the middlemost ring size (GS_2): the stimulus class with the most ambiguous signal value by virtue of being equivalently similar to the safety and danger cue. Given that those high on IU find ambiguity stressful and upsetting (Buhr & Dugas, 2006), it is not surprising that IU exerted the most influence on fear-avoidance relations for the stimulus class with the highest safe-threat ambiguity. More specifically, the middlemost class of rings may have elicited the strongest ambiguity-related unpleasantness among those higher on IU resulting in the strongest differential motivation to choose avoidance among those higher versus lower on IU. This pattern of findings suggests that individuals high on IU may be at increased risk for maladaptive avoidance decisions, prompted by perceived danger, specifically when the evoking situation is of high threat ambiguity.

In addition to increasing the degree to which perceived risk to the middlemost class of rings was accompanied by avoidance, high IU was positively related to levels of perceived risk of shock to the middlemost class, a finding consistent with past work linking IU to heightened tendencies to interpret ambiguous information as negative or threatening (e.g., Koerner & Dugas, 2008). More specifically, the ambiguous signal value of the middlemost class of rings was appraised as presenting little to no risk of shock among those low on IU, but midway between no risk and some risk for those high on IU. This pattern of findings suggests that those high versus low on IU were less certain of safety during presentations of the middlemost ring class.

Taken together, the association between IU and responses to the highly ambiguous threat of the middlemost rings may occur in two stages. First, high IU is associated with reduced certainty of safety during exposure to ambiguous threat. Second, IU may strengthen relations between perceived risk of ambiguous threat and decisions to avoid by increasing the experienced unpleasantness of uncertain safety, which may then amplify the degree to which perceptions of uncertain safety are accompanied by avoidant choices.

The Null Moderation Effect of IU With Fear Generalization Indexed by Fear-Potentiated Startle

Contrary to predictions, no moderating effect of IU on fear-avoidance relations during generalization was found when indexing generalized fear with fear-potentiated startle: the reliable enhancement of the startle reflex when an organism is in a state of fear (Grillon, Ameli, Woods, Merikangas, & Davis, 1991). This null effect was accompanied by an inverse relation between IU and levels of generalized startle potentiation, suggesting that those higher on IU were actually less anxiously reactive to the threat uncertainty signaled by GS. Though this is a perplexing finding, it is quite consistent with findings from one of the few past startle studies assessing IU (Nelson & Shankman, 2011) in which startle potentiation to uncertain threat was found to be negatively associated with IU.

One possible explanation for this negative correlation between IU and startle potentiation stems from the strong association between IU and dispositions to worry (e.g., Dugas et al., 2004). Specifically, worry has been shown to dampen fear-related psychophysiological responding to aversive stimuli, despite enhanced subjective anxiety (e.g., Borkovec & Hu, 1990). This raises the possibility that participants higher on IU engaged in more worry during the uncertain threat signaled by GS, suppressing startle potentiation to such stimuli and generating the inverse relation between IU and generalized startle potentiation. Whether or not the proposed explanation is correct, the unexpected inverse relation between IU and generalized startle potentiation may have thwarted efforts to identify moderating effects of IU on relations between generalized startle potentiation and avoidance decisions, as this hypothesized moderating effect of IU depends on increased anxious reactivity (e.g., startle potentiation) to threat uncertainty cued by GS among those higher on IU.

Clinical Implications of Findings

Because AS and IU are linked to a variety of anxiety and trauma-related disorders, present findings implicate levels of IU and AS as transdiagnostic indicators of the extent to which heightened relations between generalized fear and maladaptive avoidance decisions may be contributing to the symptom profile of a given anxiety patient. The presence of such indicators might thus cue clinicians to consider interventions designed to reduce avoidance prompted by generalized fear. One such intervention would aim to reduce fear-generalization using discrimination training to enhance abilities to identify subtle stimulus features that differentiate dangerous situations from resembling, safe situations. The initial stages of developing this kind of intervention for clinical anxiety is underway, and two recent studies have demonstrated the efficacy of perceptual discrimination training for reducing levels of generalized perceptions of threat (Ginat-Frolich, Klein, Katz, & Shechner, 2017) and generalized avoidance decisions (Lommen et al., 2017) in nonclinical samples. Applying this kind of discrimination training to those high on AS or IU may reduce the likelihood of fear of fear and anxiety-related uncertainty, respectively, to benign stimuli resembling danger cues, thereby preventing the enhancement of maladaptive fear-avoidance relations by AS or IU. Additionally, pharmacologically enhanced discrimination training could be developed for those unresponsive to the standard proce-

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dure using medications thought to enhance discrimination of conditioned stimuli from its approximations (e.g., D-cycloserine: Thompson & Disterhoft, 1997; anticholinergic agents: Thiel, Bentley, & Dolan, 2002).

Current results may also prescribe therapeutic strategies shown to reduce AS or IU in anxiety patients high on one or both traits who display pronounced symptoms of avoidance. For example, AS amelioration training (Schmidt et al., 2007) and IU therapy (Dugas & Ladouceur, 2000) may effectively treat symptoms of generalized avoidance among those high on AS and IU by facilitating a reduction in fear of fear and increasing acceptance of uncertainty, respectively, in the presence of safe stimuli resembling danger cues.

Finally, the link between Pavlovian generalization and maladaptive avoidance decisions may warrant the application of exposure treatments with a focus on exposure to benign stimulus events that resemble feared stimuli, in addition to feared stimuli themselves, for patients exhibiting excessive avoidance. This could be done through in vivo exposure therapy using a hierarchy of feared stimuli, with exposures to stimuli resembling the feared stimulus added at each level of the fear hierarchy. Furthermore, given that distress intolerance is an important precipitant of avoidance (e.g., Leyro, Zvolensky, & Bernstein, 2010), the efficacy of this kind of generalized exposure therapy for treating excessive avoidance may strengthen with the inclusion of methods for increasing toleration of fear, as done in inhibitory learning approaches to exposure therapy (Craske et al., 2008). Exposure with a focus on fear toleration may be particularly valuable when treating patients high on AS, for whom avoidance often stems from beliefs that the experience of fear is itself harmful.

Conclusions

Both AS and IU were found to exacerbate the degree to which fear generalization is accompanied by maladaptive avoidance decisions. Such findings implicate levels of IU and AS as transdiagnostic indicators of the extent to which generalized avoidance may be contributing to the symptom profile of a given anxiety patient. Present results also suggest that established associations between clinical anxiety and both AS and IU may derive, in part, from their enhancement of the maladaptive behavioral correlates of fear generalization. Specifically, AS and IU may enhance anxiety-related dysfunction by increasing the extent to which generalization of fear to safe situations resembling threatening past experiences is accompanied by unnecessary decisions to avoid, and result in missed opportunities critical to meeting one's needs and life goals. Furthermore, the increased likelihood of excessive avoidance during fear generalization among those high on AS and IU may preserve such fear by preventing disconfirmation of erroneous threat appraisals of safe events with inconsequential resemblance to dangerous encounters.

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