



Psychophysiological correlates of anxious apprehension: Trait worry is associated with startle response to threat

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ARTICLE INFO

Keywords:

Worry
Anxiety
Psychophysiology
Startle response
Threat
Uncertainty

ABSTRACT

Worry is a form of repetitive negative thought that is closely associated with anxiety disorders. Worry has been described as anxious apprehension and conceptualized as reflecting heightened anticipation of potentially threatening future events. However, it is unclear whether people who tend to worry show heightened physiological reactivity when anticipating threat, especially if the threat is uncertain. In the current study, community participants ($n = 52$) completed a threat anticipation task featuring uncertain threat, certain threat, and safety while the startle response to auditory probes was measured. Self-reported tendency to worry was assessed using the Penn State Worry Questionnaire, and anxiety disorder status was assessed via a clinical interview. A repeated-measures general linear model showed a main effect of threat level on the startle response, as well as a significant three-way interaction among threat level, worry, and anxiety disorder status. Follow-up tests showed that higher worry was associated with blunted startle responses to threat but particularly to uncertain threat among participants with a history of anxiety disorders. Worry did not moderate startle responding in participants without a history of anxiety disorders. These results indicate that psychophysiological correlates of worry depend on clinical status and suggest that trait worry is associated with physiological blunting to threat in individuals with a history of anxiety disorders, particularly when threat is uncertain. Implications for theoretical models of worry are discussed.

Worry is a form of perseverative thinking, characterized by repetitive thoughts or concerns about future events, and is a cardinal feature of anxiety disorders (American Psychiatric Association, 2013). Worriers often mentally rehearse future dangerous or aversive events and experiences, while at the same time searching for solutions to avoid them (Matthews, 1990). Research and theory have elucidated ways in which worry may lead to further worry and the subsequent maintenance of anxiety disorders. According to these models (Borkovec et al., 2004; Newman and Llera, 2011), worry functions as an avoidance or coping mechanism for perceived threat and helps regulate affect experienced when exposed to uncertainty (Krohne, 1993). These theories posit two main avoidant functions of worry: (1) worry allows individuals to plan for and avoid potential threats, and (2) worrying just prior to facing fear-inducing stimuli may actually blunt certain physiological responses to those stimuli. Unfortunately, these methods of cognitive avoidance—though seemingly effective in the moment—preclude fear responding that may be necessary for the extinction of anxiety (e.g., Borkovec and Hu, 1990; Borkovec et al., 1993). This pattern of behavior has been

thought to lead to further maintenance of worry and anxiety.

Despite decades of research on anxiety, our understanding of how cognitive and, especially, somatic responses to threats differ among high- versus low- trait worriers and how anxiety disorder diagnosis fits into this picture is lacking. The first aim of this study was to investigate how the tendency to worry interacts with anxiety disorder diagnosis to predict physiological responses to threat anticipation. Furthermore, for individuals who worry, the uncertainty of whether a threat will occur may be particularly aversive, because it disrupts the ability to plan for, avoid, or mitigate the consequences of impending threat (Grupe and Nitschke, 2013). Therefore, the second aim of this study was to interrogate how anxiety disorder status and trait worry impact physiological responding to certain versus uncertain threats.

1. Worry, anxiety, and their physiological correlates

Given that worry has been hypothesized to serve an avoidant function in response to perceived threat, we would expect the presence of

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worry to affect all levels of anxiety responding—including the extent to which participants with anxiety react physiologically in the face of threat. Over the past two decades, many studies have been conducted to understand physiological reactivity that accompanies anxiety and worry and whether the tendency to engage in worry affects physiological responses that are associated with heightened anxiety (for a recent review see Newman et al., 2013). This literature has yielded surprisingly mixed results, emphasizing the importance of further investigating this question.

Early research demonstrated, for example, the blunting of certain biophysiological measures across different studies, including decreased heart rate variability (HRV; Thayer et al., 1996; Lyonfields et al., 1995) and respiratory sinus arrhythmia (Kollai and Kollai, 1992) in individuals with diagnosed generalized anxiety disorder (GAD) compared to non-anxious controls. Recent studies examining the effect of worry in anxiety disorders on threat responding, however, have provided different results. Some studies have found worrying in GAD to be associated with increased physiological responding to threat (e.g., Dunning and Hajcak, 2015; Gazendam and Kindt, 2012), whereas other studies have shown decreases in physiological responding to threat associated with worry (e.g., Delgado et al., 2009). Some studies show no differences at all in physiological responding to threat among high- and low-level worriers (Segerstrom et al., 1999). Unfortunately, most of these studies have not been able to parse the effects of anxiety disorder diagnosis and worry and have not examined responding to certain versus uncertain threat. Given the link between worry and uncertainty, the effect of uncertain threat may be a particularly important question to examine in understanding the relation among worry, anxiety disorders, and physiological responding to threat.

2. Uncertain vs. certain threat

Studies show that physiological responding to threat is enhanced when the degree or likelihood of threat is uncertain (e.g., Grupe and Nitschke, 2011; Sarinopoulos et al., 2010). This research has largely focused on the startle response to threat (“fear-potentiated startle”), a measure thought to reflect defensive reactivity. Potentiation of the startle response is often measured in tasks similar to that described by Bradford et al. (2014). In their version, called the Threat Probability Task (TPT), startle responding is measured while participants anticipate varying probabilities of threat: a 100% chance of electric shock (certain threat), a 50% chance of shock (uncertain threat), and a 0% chance of shock (safety; Bradford et al., 2014). The authors find that the startle response is potentiated by threat relative to safety, but that uncertain threat is associated with even greater potentiation than certain threat, suggesting that there may be a unique enhancing effect of *uncertainty* on physiological responding to threat. Indeed, enhancing effects of uncertain threat relative to certain threat on the startle response have been found across similar tasks (e.g., Bradford et al., 2017 & Hefner and Curtin, 2012).

The effect of uncertainty on the startle response appears to be particularly pronounced among those with a current or lifetime history of anxiety disorders. For example, Grillon et al. (2008) found that participants with panic disorder showed elevated startle responses when anticipating unpredictable shocks compared to healthy controls. Similar findings of greater startle potentiation by uncertain threat among those with anxiety have been found across diagnostic groups (Grillon et al., 2009; Shankman et al., 2013; Gorka et al., 2017).

Although previous research has demonstrated that physiological responding to threat is enhanced by uncertainty and that individuals with anxiety disorders show elevated responding to uncertain threat specifically, the roles of worry, anxiety disorder status, and how the two relate to one another remain unclear. If worry serves an avoidant function in anxiety, is trait worry related to differential startle responding to certain versus uncertain types of threat? Furthermore, is the relation between trait worry and responding to certain versus

uncertain threat different in participants who do not have or have a lifetime history of a diagnosed anxiety disorder? In this study, we aimed to address these questions in a sample of individuals with and without a lifetime history of anxiety disorder using the TPT (Bradford et al., 2014) to examine differences in physiological responding to uncertain and certain threat.

3. Methods

3.1. Participants

Participants were recruited from the New Haven community via electronic and printed advertisements. Prior to being invited to the laboratory, participants completed an online pre-screening battery of questionnaires to assess exclusion criteria. Participants who reported a lifetime history of psychosis based on the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995) were excluded. Those who screened positive for current problematic alcohol use on the Alcohol Use Disorders Identification Test (Babor et al., 2001), defined as a score of 20 or more on the 10 screening items (scored from 0 to 4), were excluded. Similarly, those who screened positive for current problematic substance use on the Drug Use Disorders Identification Test (Berman et al., 2005), defined as a score of 25 or more on the 11 screening items (scored from 0 to 4) and indicating significant drug-related problems, were excluded. Additionally, participants who reported a history of neurological disorder or brain injury were excluded.

The current study was part of a larger multi-session protocol, in which 100 community members participated. Participants who completed both the Threat Probability Task (TPT) and the Penn State Worry Questionnaire (PSWQ) were included in the current sample ($n = 64$). Attention checks were embedded within the PSWQ to ensure that participants were paying attention (e.g., “If you are reading this question, select 1.”). Eight participants failed attention checks and were thus excluded from subsequent analyses, and four participants were excluded for issues during the TPT, described below, resulting in a final sample of 52 participants. Of these participants, 59.6% identified as White/Caucasian, 15.4% as Black/African American/African, 15.4% as Asian, 3.8% as Latino/Latina, and 5.8% as more than one race. The mean age was 30.77 years ($SD = 12.82$), and 61.5% of the sample was female. The Yale University Human Subjects Committee approved the study, and informed consent was obtained from each participant prior to beginning the procedure. Participants were compensated \$15.00 per hour for their time.

3.2. Measures

3.2.1. Structured clinical interview for the DSM-5 (SCID-5)

Current and lifetime mood and anxiety disorders were assessed using Modules A (mood disorders) and F (anxiety disorders) of the SCID-5 (First et al., 2015), administered by a trained graduate student. All participants completed the interview.

3.2.2. Penn State Worry Questionnaire (PSWQ)

The PSWQ is a 16-item questionnaire that measures the extent to which a participant’s worry is excessive, generalized, or uncontrollable (Meyer et al., 1990). Participants rate items on a 5-point scale from 1 (*not at all typical of me*) to 5 (*very typical of me*). In the current sample, the PSWQ had excellent internal consistency ($\alpha = 0.94$).

3.3. Threat probability task

The TPT was used to measure startle responding when anticipating varying levels of threat, operationalized as low-intensity electric shocks (see below for the calibration procedure; Bradford et al., 2014). The task consisted of three conditions: an uncertain condition with a 20% probability of shock, a certain condition with a 100% probability of shock,

and a safe condition with a 0% probability of shock. In each trial, a cue denoting the condition was displayed for 5 s and followed by an inter-trial interval (ITI) with a variable duration (range = 15–20s). The cue consisted of a colored shape (yellow for uncertain, orange for certain, and green for safe) and text stating the probability of shock (20%, 100%, or 0%). In the uncertain and certain conditions, shocks lasting 200 ms were delivered 4.5 s into the cue presentation. Shocks were delivered in 20% of trials in the uncertain condition and 100% of trials in the certain condition. In total, 6 blocks of trials were presented (2 blocks of each condition type) with a total of 15 trials per condition. Between each block, text was displayed indicating what the next block type would be.

Acoustic startle probes (50 ms bursts of 105 dB white noise with near instantaneous rise time) were presented through headphones. Startle probes were delivered 4 s into the presentation of cues on a subset of trials (8 out of 15 trials in each condition). Probes were also delivered during the ITI (4 out of 15 ITIs in each condition; 13–15 s into the ITI) in order to decrease their predictability; startle responses to these probes were not analyzed. Additionally, three startle probes were delivered at the start of the task, before any of the trials began, in order to habituate the startle response before the main task; again, startle responses to the habituation probes were not analyzed. The order of blocks was counterbalanced, and the serial position of probes was matched across conditions within subjects in order to balance the effects of habituation on the startle reflex (Blumenthal et al., 2005). The task and procedure were based on recommendations by Bradford et al. (2014). The TPT was administered in MATLAB.

3.4. Baseline startle reactivity assessment

Prior to undergoing the shock calibration procedure and beginning the TPT, participants' general startle reactivity was measured using a baseline task. The task was designed to be perceptually similar to the TPT but to not include any threat or uncertainty, thereby allowing for the measurement of general reactivity of the startle reflex to acoustic probes. The baseline task consisted of 9 trials featuring the presentation of colored squares that were identical to those used in the TPT but that had not yet been associated with shock. Startle probes were administered during both the cue presentation and the ITI.

3.5. Shock calibration

Electric shocks were administered to the median nerve of the non-dominant wrist using two Ag/AgCl electrodes positioned 20 mm apart. Shocks were delivered using a Grass Instruments stimulator (Grass Instruments, Quincy, MA, USA). Because sensitivity to shocks varies across individuals, the intensity of shock was calibrated individually for each participant. Calibration was done by first delivering a shock of low intensity, 10 V, and increasing the voltage by 5 V with every subsequent shock and with the participant's permission. The voltage of shocks never exceeded 70 V. Participants were told that the goal was to reach a level that they found uncomfortable and unpleasant, but not painful. Participants rated the intensity of the shocks on a five-point scale: 1 – *not noticeable*, 2 – *hardly noticed*, 3 – *acceptable*, 4 – *unpleasant/uncomfortable*, and 5 – *painful*. The experimenter informed the participant that the target intensity was 4 – *unpleasant/uncomfortable* but reminded the participant that he/she could stop at any time and withdraw participation. No participants chose to withdraw. The calibration procedure ended when participants reported that the shocks had reached an intensity of 4 or when the maximum allowed voltage of 70 was reached. Participants then rated the intensity of the shock using the aforementioned rating scale on the computer, presented using PsychoPy (Peirce et al., 2019).

3.6. Startle response measurement and processing

Participants were asked to wash their faces and hands with soap and

water before electrodes were applied. The skin was further cleaned with alcohol swabs and exfoliated using an abrasive electrolytic gel. Two 4 mm Ag/AgCl electrodes were placed underneath the left eye to measure EMG activity of the orbicularis oculi muscle, which is associated with eyeblinks that occur in response to startling stimuli. Two 8 mm Ag/AgCl electrodes placed at the top of the forehead served as the ground and reference. Recording was done using a sampling rate of 5000 Hz using a Neuroscan system and Curry acquisition software (Compumedics, Charlotte, NC). Subsequent processing was performed using the EEGLAB and Physbox MATLAB plugins (Delorme and Makeig, 2004; Curtin, 2011).

Processing steps were based on procedures described by Kaye et al. (2016). The same steps were used for processing of both the baseline reactivity assessment and the TPT. A fourth-order 28 Hz Butterworth filter with zero phase shift was applied offline. Epochs from 150 ms before to 250 ms after the startle probe were created from the continuous data. A second-order 30 Hz Butterworth filter with zero phase shift was applied for smoothing. Trials with activity greater than $\pm 20 \mu\text{V}$ during the 50 ms before to 10 ms after the startle probe were automatically rejected, as were trials with activity less than $-10 \mu\text{V}$ during the 150 to 250 ms after the startle probe. Additionally, all trials were manually inspected to identify artifacts not detected by these parameters. The startle response was measured as the peak amplitude 20 to 100 ms following the onset of the startle probe, using the 50 ms immediately preceding the onset of the probe as a baseline. Non-response trials (when no discernible startle response was elicited) were included in the average for each condition (Blumenthal et al., 2005).

Participants who had startle reactivity under $5 \mu\text{V}$ during the baseline task were classified as non-responders ($n = 2$) and excluded from further analysis (Kaye et al., 2016). Additionally, one participant was excluded for falling asleep, and another was excluded because an electrode came off during the task. We planned to exclude participants who had more than 25% of trials within a given condition rejected but no participants exceeded this criterion.

3.7. Procedures

The study was divided into two experimental sessions. At the beginning of each session, the procedures were explained, and informed consent was obtained. Session 1 consisted of in the following order: basic neuropsychological measures, a novel threat task developed by our lab (unpublished), and a probabilistic gambling task (Charpentier et al., 2017). The SCID-5 and self-report measures, including the PSWQ, were administered at the end of this session. The second session included, in the following order: the TPT, a threat avoidance task (Collins et al., 2014), an abbreviated questionnaire battery, and debriefing. The average time between Session 1 and Session 2 was 6.35 days ($SD = 4.27$).

4. Results

4.1. Descriptive statistics for interview and self-report measures

The mean score on the PSWQ was 51.88 ($SD = 14.72$; range = 22–78; possible range = 16–80). Fifty-six percent of the sample met diagnostic criteria for a current or past mental disorder. In terms of current psychopathology, 25% of participants met criteria for an anxiety disorder; of those participants, 30.77% also met criteria for a mood disorder. The mean number of current diagnoses was 0.53 ($SD = 1.05$). Additionally, 11.5% of the sample met criteria for a past anxiety disorder that had remitted, and 32.7% met criteria for a past mood disorder that had remitted. In total, 32.7% of the sample had a lifetime history of anxiety disorders; of those participants, 52.94% also had a lifetime history of a mood disorder. Overall, the level of psychopathology in the current sample was comparable to national estimates (33.7% lifetime prevalence of anxiety disorders; Kessler et al., 2012) (Table 1).

Table 1
Descriptive statistics of clinical and self-report variables.

	With lifetime history of anxiety disorders	Without lifetime history of anxiety disorders
<i>n</i>	17	35
Gender	13 female	19 female
Age	29.65 (12.51)	31.31 (13.12)
PSWQ	60.06 (10.95)	47.91 (14.80)

Note: Standard deviations are in parentheses.

4.2. TPT analyses

A repeated-measures general linear model was performed to examine effects of and interactions among threat, anxiety disorder status, and trait worry on startle responding. Baseline startle reactivity was included as a covariate. The within-subjects threat factor consisted of three levels: uncertain threat, certain threat, and safety. The anxiety disorder status factor consisted of two levels: those with a lifetime history and those without. Finally, trait worry was included as a continuous

factor. In any analyses for which Mauchly’s test of sphericity indicated that the assumption of sphericity was violated, the reported statistics refer to Greenhouse-Geisser-corrected values.

There was a main effect of threat level on the startle response, $F(1.51, 70.95) = 11.94, p < .001, \eta_p^2 = 0.20$. Follow-up pairwise comparisons showed that uncertain trials ($M = 65.61, SE = 4.61$) were associated with a larger startle response than were certain threat ($M = 58.41, SE = 5.36$), $F(1, 47) = 6.15, p = .02, \eta_p^2 = 0.12$, and safe trials ($M = 42.75, SE = 4.64$), $F(1, 47) = 20.21, p < .001, \eta_p^2 = 0.30$. Additionally, certain threat trials were associated with larger startle responses than were safe trials, $F(1, 47) = 8.36, p = .01, \eta_p^2 = 0.15$. These results indicate that the startle response was potentiated by threat, particularly when uncertain. There were no main effects of anxiety disorder status, $F(1, 47) = 1.61, p = .21, \eta_p^2 = 0.03$, or worry, $F(1, 47) = 0.45, p = .51, \eta_p^2 = 0.01$, on startle response.

There was a significant two-way interaction between threat level and worry, $F(1.51, 70.95) = 9.53, p < .001, \eta_p^2 = 0.17$. Follow-up pairwise comparisons revealed that the effect of worry on startle response differed between the uncertain and certain threat conditions, $F(1, 47) =$

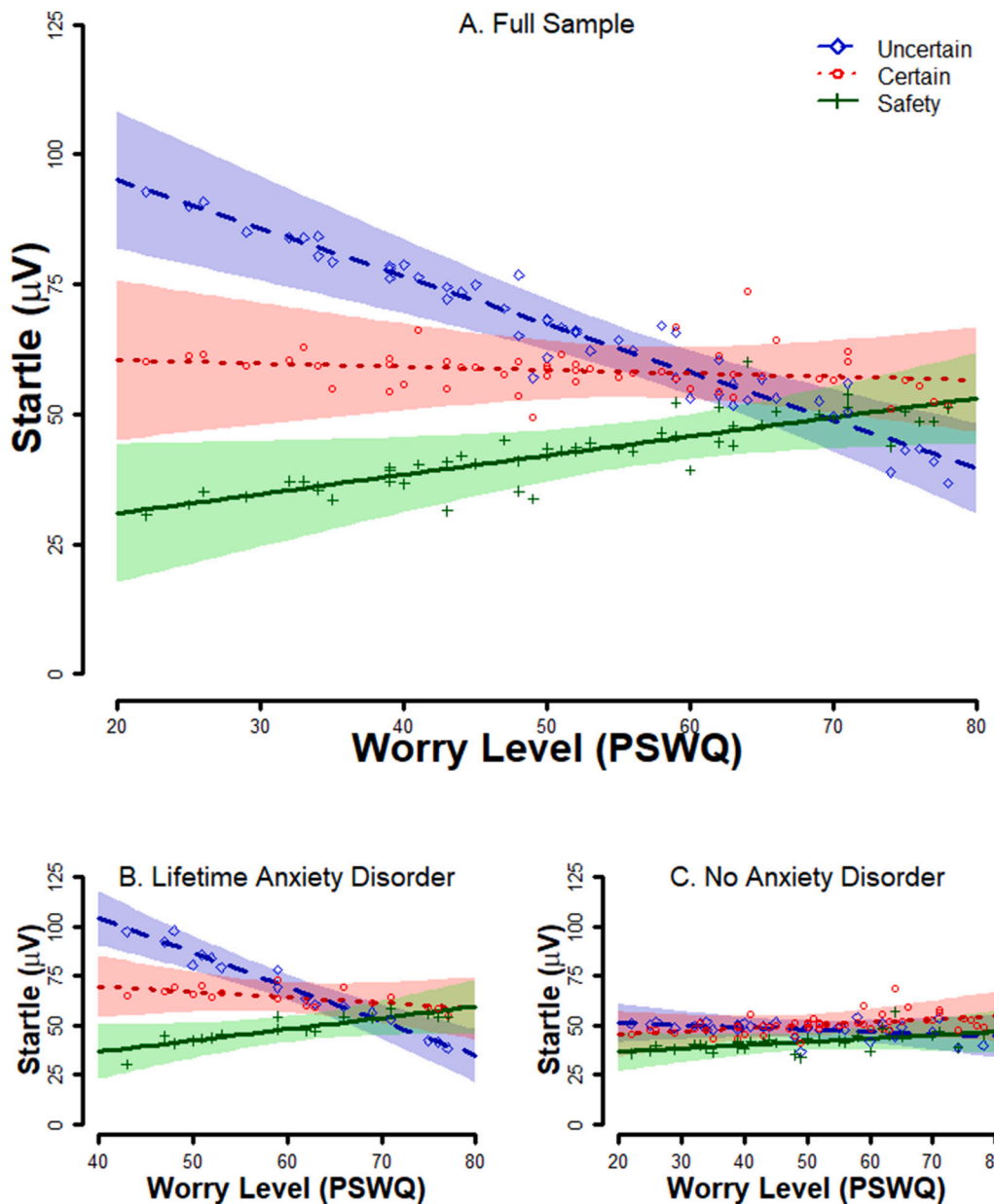


Fig. 1. Startle response as a function of PSWQ scores for uncertain threat, certain threat, and safety conditions across the entire sample (A), participants with a lifetime anxiety disorder (B), and participants without a lifetime history of anxiety disorder (C). Lines display point estimates for mean startle response by worry level and threat level from the general linear model. Translucent bands indicate confidence envelopes (± 1 SE) for these point estimates. Points represent participants’ startle residual scores relative to their predicted values and scaled by the square root of *N* to allow display on the same scale as the population mean point estimates.

5.87, $p = .02$, $\eta_p^2 = 0.11$, the uncertain and safe threat conditions, $F(1, 47) = 15.79$, $p < .001$, $\eta_p^2 = 0.25$, and the certain and safe threat conditions, $F(1, 47) = 4.611$, $p = .04$, $\eta_p^2 = 0.09$. Simple effect tests indicated that worry significantly affected startle responding during uncertain threat but not certain threat or safety in the full sample. More specifically, for every one unit increase in worry, startle responding decreased by 0.9 microvolts during uncertain threat ($b = -0.9$, $p = .01$) but not certain threat ($b = -0.1$, $p = .87$) or safety ($b = 0.4$, $p = .28$; see Fig. 1A).

There was also a significant two-way interaction between threat level and anxiety disorder status, $F(1.51, 70.95) = 7.78$, $p = .002$, $\eta_p^2 = 0.14$. Follow-up pairwise comparisons revealed that the effect of anxiety disorder history on startle response differed between the uncertain and safe threat conditions, $F(1, 47) = 13.23$, $p < .001$, $\eta_p^2 = 0.22$, and the certain and safe threat conditions, $F(1, 47) = 5.94$, $p = .02$, $\eta_p^2 = 0.11$, but not the uncertain and certain threat conditions, $F(1, 47) = 3.80$, $p = .057$, $\eta_p^2 = 0.08$. Simple effect tests indicated that startle responding was 35.8 microvolts higher for individuals with lifetime anxiety compared to those with no anxiety disorder history during uncertain threat ($b = 35.8$, $p < .001$) but not certain threat ($b = 16.0$, $p = .15$) or safety ($b = 1.4$, $p = .89$).

These interactions were qualified by a significant three-way interaction between threat level, worry, and anxiety disorder status on startle magnitude, $F(1.51, 70.95) = 5.74$, $p = .01$, $\eta_p^2 = 0.11$. Given our hypotheses about the interaction between threat level, worry, and anxiety disorders status, we further explored this significant three-way interaction by examining the interaction between threat level and worry separately for participants with and without a lifetime history of anxiety disorders. Among those with a lifetime history of anxiety disorders, there was a significant interaction between threat level and worry, $F(2, 28) = 9.96$, $p = .001$, $\eta_p^2 = 0.42$. To further characterize this interaction, pairwise comparisons of startle responses – i.e., uncertain vs. certain threat, uncertain threat vs. safety, and certain threat vs. safety – with worry as a continuous predictor were examined among participants with a lifetime history of anxiety disorders. There were significant interactions between worry and threat level on startle responding when comparing uncertain vs. certain threat, $F(1, 14) = 7.00$, $p = .02$, $\eta_p^2 = 0.33$, uncertain threat vs. safety, $F(1, 14) = 14.72$, $p = .002$, $\eta_p^2 = 0.51$, and certain threat vs. safety, $F(1, 14) = 4.68$, $p = .048$, $\eta_p^2 = 0.25$. Tests of the simple effects of worry on startle responses for each threat type for participants with a lifetime history of anxiety disorders indicated that for every one unit increase in worry, startle magnitude decreased by 1.7 microvolts during uncertain threat ($b = -1.7$, $p = .01$) but worry did not affect startle responding during certain threat ($b = -0.3$, $p = .69$) or safety ($b = 0.6$, $p = .35$; see Fig. 1B).

Among those without a history of anxiety, there was not a significant interaction between threat level and worry, $F(1.33, 42.67) = 0.44$, $p = .57$, $\eta_p^2 = 0.01$. Follow-up pairwise analyses revealed no significant interactions between worry and threat ($ps > 0.49$). Furthermore, the simple effects of worry indicated that worry did not affect startle responding for any threat type (all $ps > 0.59$) for participants without a lifetime history of anxiety disorders (see Fig. 1C). Overall, these results suggest that worry moderated the effect of threat level on the startle response only for those with a lifetime history of anxiety.

5. Discussion

The current study examined the relation between trait worry and startle responding under certain vs. uncertain threat in participants with and without a lifetime anxiety disorder diagnosis. The results show that startle responding was enhanced in response to threat broadly, relative to safety. Importantly, however, uncertain compared to certain threat trials were associated with a larger startle response. These results replicate previous work (e.g., Bradford et al., 2014; Hefner and Curtin, 2012) showing potentiated startle responding to threat, particularly when threat is uncertain. This growing body of research suggests that uncertain threat does indeed mobilize more defensive responding as

indexed by the startle response than does certain threat.

Importantly, we found an interaction among trait worry, anxiety history, and threat level on startle responding. Among participants with no lifetime history of anxiety disorders, worry was not associated with the effect of threat on startle magnitude. However, among participants with a lifetime history of anxiety, worry moderated the effect of threat on magnitude of the startle response. Specifically, startle responding to threat was decreased in high worriers, and this effect was particularly strong when threat was uncertain. These findings suggest that high levels of worry are associated with physiological dampening when responding to threat (i.e., Delgado et al., 2009; Dunning and Hajcak, 2015; Gazendam and Kindt, 2012). This research extends prior work on uncertainty and threat responding by showing that both anxiety disorder diagnosis and trait worry play key roles in understanding how threat affects magnitude of the startle response.

Our results have important implications for models of worry and anxiety (e.g., Borkovec et al., 2004; Newman and Llera, 2011), many of which have posited that worry is an immediate coping response to the anxiety that any perception of threat may generate. First, we extend previous research by showing that worry is associated with blunted physiological responding in the face of threat, as shown in some earlier studies, but that a lifetime history of anxiety matters for understanding this association. Specifically, we find a blunting association with worry only among those with a lifetime history of anxiety disorders. These findings build on recent work that point to the importance of clinical status in influencing physiological responding to threat. For example, Hyde et al. (2019) distinguish between MDD and fear-disordered participants and find that fear-disorder participants without MDD show enhanced physiological responding whereas those with MDD display reduced physiological responding. These results point to the importance of considering how clinical disorder status may influence physiological reactions to threat. Other research has highlighted that clinical disorder status may be particularly relevant in the context of worry: using an unstructured thinking task that did not involve threat, Ottaviani et al. (2014) found that the effect of instructed worry on resting state physiology differed depending on whether individuals were healthy controls or engaged in clinical levels of worry. Our results extend this work to the realm of threat and provide evidence of a moderating role of anxiety disorder status in the relation between worry and startle response to threat. Nevertheless, more research is needed to identify which aspects of having a lifetime anxiety disorder history (e.g., impairment, chronicity, clinical severity) are important in understanding the relation between worry and physiological responding.

Additionally, our findings extend previous research by highlighting the importance of uncertainty. Although we find that worry is associated with blunting of physiological responding to threat among those with a history of anxiety, this effect is strongest when the threat is uncertain. Theoretical work has suggested that uncertain situations are particularly difficult for those who worry, but little empirical work has systematically examined this question. We find evidence that, indeed, worry and uncertainty are related at the level of physiological responding, above and beyond the relation between worry and threat. These results also extend work at the self-report level showing that worry is associated with intolerance of uncertainty (IU), a trait that refers to the extent to which individuals react negatively on an emotional, cognitive and behavioral level when future events and their implications are uncertain (Buhr and Dugas, 2002; Dugas et al., 2004). We demonstrate that self-reported worry is associated with a physiological marker of uncertainty reactivity, in addition to self-reported IU.

5.1. Limitations and future directions

This study has several limitations. Firstly, the size of the sample was limited, especially within the lifetime anxiety disorder group. As a result, the study was only powered to detect very large effects. While we did find a large, significant effect, it is possible that the effect size we

report is overestimated due to the limited sample size. Furthermore, the size of the lifetime anxiety disorder group precluded more granular analyses that would be of interest. Specifically, the group included individuals with current anxiety disorders, as well as those with anxiety disorders in remission. The limited sample size made it impossible to reliably analyze differences between those with and those without a current diagnosis. Thus, we are unable to draw conclusions about whether the results we observed are related to having had an anxiety disorder overall or whether they reflect acute effects of currently having an anxiety disorder. In future work, it will be important to parse whether the effect of worry on physiological reactivity differs among those with past versus current anxiety disorders. This will be important in determining whether worry's physiological blunting effect to threat is a stable result of having had an anxiety disorder, or whether blunting by worry is driven by current distress or severity.

Similarly, due to the limited sample size of the lifetime anxiety disorder group, we are unable to examine whether the effect of worry on physiological responding to threat varies by type of disorder. Some research has demonstrated that difficulty with uncertainty is particularly elevated among some anxiety disorders (Mahoney and McEvoy, 2012), whereas other research has suggested that difficulty with uncertainty is a transdiagnostic construct comparable across disorders (Carleton et al., 2012). Recent work examining the startle response to uncertain threat has shown that individuals with social anxiety disorder and specific phobia display greater startle potentiation to uncertain threat, but not certain threat, relative to individuals with GAD, major depressive disorder, and healthy controls (Gorka et al., 2017). These findings point to the potential importance of examining whether disorder type moderates effects of worry on the startle response. As our results are preliminary, future work should address this question by including sufficient sample sizes of multiple types of anxiety disorders.

Furthermore, the current study did not examine whether the effect of anxiety disorder status is specific to anxiety disorders or common across other categories of psychopathology. For example, previous research has demonstrated that IU is elevated among those with major depressive disorder (Carleton et al., 2012) and eating disorders (Sternheim et al., 2017). Thus, in addition to examining specific types of anxiety disorders, future research should examine whether other diagnostic categories associated with IU or transdiagnostic factors (e.g., negative affect) may moderate the effect of worry on the startle response.

An additional limitation lies in our study's focus on the effects of trait worry on physiological responding to threat. Our study adds to past research examining the effects of the tendency to worry, which is an important construct that gives insight into what participants typically do. However, examining associations with the tendency to worry does not allow us to make inferences about what happens when people are actively worrying. These are two different questions, and future research should examine whether the effects of acutely worrying (i.e., state worry; perhaps assessed using a real-time measurement of worry) parallel those of the tendency to worry (i.e., trait worry) that we find here. It is also important to note that, because we did not induce worry, we can only draw correlational conclusions about the effect of worry on physiological responding to threat. Additionally, the effect of uncertainty of threat on physiological responding might be influenced by the ability to utilize active avoidance and emotion regulation strategies in the moment (e.g. Löw et al., 2015; Wendt et al., 2017), which we could not account for in this study.

Finally, it is important to note that the data reported in the current study were obtained as part of a larger experimental protocol that included other tasks and questionnaires. All of the measures were administered in the same order for all participants to standardize any potential order effects and for practical reasons, including limiting the number of electric shocks given in each experimental session. Future research could attempt to replicate the current results using fewer tasks, a counterbalanced design, and other threat contingencies (e.g., Bradford et al., 2017) to further reduce any extraneous effects of a specific task or

task sequence on the results.

Acknowledgments

The authors would like to thank Marisella Andrews and Marike Kooistra for their assistance with data collection. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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