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Anxiety sensitivity and the anticipation of predictable and unpredictable threat: Evidence from the startle response and event-related potentials

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ABSTRACT

There is growing evidence that heightened sensitivity to unpredictable threat is a core mechanism of dysfunction in anxiety disorders. However, it is unclear whether anxiety sensitivity is also associated with sensitivity to unpredictable threat. In the present study, 131 participants completed the Anxiety Sensitivity Index-3, which includes physical concerns (PC), social concerns (SC), and cognitive concerns (CC) subscales, and a predictable vs. unpredictable threat-of-shock task. Startle eyeblink and ERP responses (N100, P300) to the acoustic startle probes were measured during the task. PC and CC were associated with heightened and attenuated, respectively, startle for the unpredictable (but not predictable) condition. CC were also associated with attenuated probe N100 for the unpredictable condition only, and PC were associated with increased P300 suppression across the predictable and unpredictable conditions. This study provides novel evidence that the different anxiety sensitivity dimensions demonstrate unique relationships with the RDoC domains "acute" and "potential" threat.

1. Introduction

Anxiety sensitivity (AS) is the fear of anxiety-related sensations due to their perceived physical, psychological, or social consequences (Reiss & McNally, 1985). AS was originally conceptualized as an individual difference factor that contributed to the etiology and maintenance of panic disorder (PD) (McNally, 2002). Indeed, research has shown that AS is elevated in first-degree relatives of probands with PD relative to healthy controls (Van Beek & Griez, 2003) and prospectively predicts panic attacks (Maller & Reiss, 1992; Schmidt, Lerew, & Jackson, 1999), panic symptoms (Cox, Taylor, Clara, Roberts, & Enns, 2008), and panic response to a CO_2 challenge (Bernstein, Zvolensky, & Schmidt, 2009; Blechert, Wilhelm, Meuret, Wilhelm, & Roth, 2013). However, AS has also been linked to several other psychopathological behaviors and conditions (Deacon & Abramowitz, 2006; Taylor, Koch, Woody, & McLean, 1996), including alcohol use (Allan, Albanese, Norr, Zvolensky, & Schmidt, 2015; Schmidt, Buckner, & Keough, 2007), depression (Allan, Capron, et al., 2014; Viana & Rabian, 2009), generalized anxiety disorder (GAD; Allan, Macatee, et al., 2014), and suicide (Capron, Cougle, Ribeiro, Joiner, & Schmidt, 2012; Medley, Capron, Korte, & Schmidt, 2013). Thus, AS has more recently been considered a transdiagnostic factor of psychopathology (Boswell et al., 2013).

The National Institute of Mental Health's Research Domain Criteria (RDoC) initiative seeks to identify biobehavioral dimensions that are common across several disorders and then relate those dimensions to specific biological processes (Insel et al., 2010; Sanislow et al., 2010). AS is an ideal construct to examine using the RDoC approach given its dimensional nature (Asmundson, Weeks, Carleton, Thibodeau, & Fetzner, 2011; Broman-Fulks et al., 2008, 2010), genetic correlates (Taylor et al., 2008; Waszczuk et al., 2013), high heritability (Stein et al., 1999), and the aforementioned relationship with multiple psychopathologies (Deacon & Abramowitz, 2006; Taylor et al., 1996). In terms of physiological correlates, greater AS has been associated with a heightened baseline startle eyeblink electromyography (EMG) response (McMillan et al., 2012), decreased baseline startle habituation (Campbell et al., 2014), and heightened startle response in anticipation of interoceptive threat (Melzig et al., 2008).

Affective responses to threat, however, are not uniform. Predictability is an important feature of threat that has been suggested

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to impact defense system activation and differentiate the states of fear and anxiety (Barlow, 2000; Grillon et al., 2004; Hamm & Weike, 2005). Fear is associated with predictable threat and a more immediate fight, flight, or immobilization response. Conversely, anxiety is elicited when perceived threat is less certain (or present) and requires a sustained state of vigilance and defensive preparedness. The distinction between fear and anxiety has been well supported by animal (Davis, 1998), psychophysiological (Grillon et al., 2004; Nelson & Shankman, 2011), and pharmacological studies (Grillon et al., 2006), and is represented by separate Negative Valence System constructs ("acute" and "potential" threat, respectively) in the RDoC matrix (NIMH, 2011). Several anxiety disorders (e.g., PD, PTSD) have been associated with an increased startle response in anticipation of unpredictable threat, although the role of predictable threat has been mixed (Grillon et al., 2008, 2009; Shankman et al., 2013). Similarly, high AS has been associated with a preference for predictable relative to unpredictable CO_2 administration (Lejuez et al., 2000). However, no study has examined whether AS is associated with the startle response in anticipation of unpredictable vs. predictable threat. This is the first aim of the present study.

High levels of AS have also been associated with increased attention toward threatening stimuli (Hunt et al., 2006; Keogh et al., 2001; Lees et al., 2005). Importantly, this relationship can be examined in the context of startle methods, as the startle probe elicits event-related potential (ERP) measures of early sensory and attentional processing. Specifically, the startle probe elicited N100 is a negative deflection in the ERP signal that is maximal around frontocentral sites and occurs 100 ms after the onset of the startle probe. The probe N100 reflects early perceptual processing of auditory stimuli and is enhanced when participants are instructed to attend to the startle probe while viewing unpleasant relative to pleasant or neutral pictures (Cuthbert et al., 1998). In addition to the probe N100, the startle probe P300 is a positive deflection of the ERP signal that is maximal at centroparietal sites and occurs approximately 300 ms after the onset of the startle probe (Putnam & Roth, 1990; Roth, Dorato, & Kopell, 1984; Sugawara, Sadeghpour, Traversay, & Ornitz, 1994). The probe P300 reflects attention toward the startle probe and is reduced when viewing emotional relative to neutral pictures due to increased attention to emotional foreground stimuli (leaving less attention allocated to the probe itself) (Bradley, Codispoti, & Lang, 2006; Cuthbert, Schupp, Bradley, McManis, & Lang, 1998; Schupp, Cuthbert, Bradley, Birbaumer, & Lang, 1997). Importantly, the startle probe N100 and P300 responses do not reflect the same attentional processes and behave differently: the N100 and P300 are potentiated and reduced, respectively, in the context of threat. Thus, examining the association between AS and startle allow for the examination of both EMG and ERP responses during the same task.

In a recent investigation, Nelson et al. (in press) examined the psychometric properties of the probe N100 and P300 responses during a no, predictable, and unpredictable threat-of-shock (NPU-threat) task. The NPU-threat task contains three distinct within-subjects conditions during which participants anticipate no threat (no aversive stimulus is delivered), predictable threat (aversive stimulus is signaled by short duration cue), or unpredictable threat (aversive stimulus is not signaled). Results indicated that the probe N100 was enhanced in the unpredictable (but not predictable) condition even though participants were not specifically instructed to attend to the startle probe. These data suggest that the anticipation of unpredictable electric shock, relative to unpleasant pictures, may more readily prime early cortical processing of sensory input. In contrast, the probe P300 was attenuated during both the predictable and unpredictable conditions. In addition, the probe N100 and P300 were not correlated across threat conditions, indicating they were measuring separate attentional processes. Collectively, these results suggest that the anticipation of unpredictable threat enhances early perceptual processing and the anticipation of threat in general (irrespective of predictability) increases attention during the threatening conditions of the NPU-threat task. However, no study has examined individual differences in these ERP responses.

Utilizing data from Nelson et al. (in press), the current study examined the association between AS and startle EMG and ERP responses in anticipation of predictable and unpredictable threat. Specifically, 131 undergraduates completed the NPU-threat task and the startle eyeblink EMG response and electroencephalography (EEG) were recorded during the different threat conditions. Self-reported anxiety was also assessed at the end of the task. The current study focused on continuous variation in AS in a college student sample to (1) minimize the contribution of severe psychopathology that is more prevalent in clinical populations and (2) limit the possibility of a restricted range of AS scores in a clinical sample. Moreover, AS was not examined using a taxometric approach (Bernstein et al., 2007), because we did not expect to have a significant number of participants in the "high-risk" group to adequately examine AS as a dichotomous construct. We hypothesized that AS would be associated with increased startle EMG, probe N100, and self-reported anxiety and decreased probe P300 in anticipation of unpredictable (but not predictable) threat.

AS was originally conceptualized as a unitary construct measured with the Anxiety Sensitivity Index (ASI) (Reiss et al., 1986). However, since its inception there have been multiple revisions to the ASI and increased recognition that AS is multifaceted. In the present study, participants completed the ASI-3 (Taylor et al., 2007), the most recent version of the ASI, which consists of three factor analytically derived subscales: physical concerns (PC), cognitive concerns (CC), and social concerns (SC). The discriminant validity of these dimensions has been supported by a number of investigations that have examined the ASI-3 subscales in relation to anxiety and depression symptoms. Specifically, research has indicated that ASI-3 PC has been most consistently associated with panic, CC with depression and worry, and SC with social anxiety (Allan, Capron, et al., 2014; Kemper et al., 2012; Olthuis et al., 2014; Wheaton et al., 2012). We did not have specific hypotheses regarding which AS subscales would be associated with responding during the NPU-threat task. However, given that the aversive stimulus used in the task was a physical danger (electric shock), we hypothesized that the association between AS and these measures would be particularly strong for the PC subscale.

Finally, the ASI-3 CC subscale has been strongly associated with depression (Olthuis et al., 2014; Taylor et al., 1996). Therefore, to determine the unique association between ASI-3 CC and the anticipation of predictable and unpredictable threat, participants also completed a self-report measure of depression, and additional analyses were conducted with this measure included as a covariate. We hypothesized that the relationship between AS (and, in particular, the ASI-3 CC subscale) and startle EMG, probe ERPs, and self-reported anxiety would be independent of depression.

2. Method

2.1. Participants

The sample included 131 introduction to psychology students from the University of Illinois-Chicago who participated for course credit. Exclusion criteria were an inability to read or write English, history of head trauma with a loss of consciousness, or being left-handed (as confirmed by the Edinburgh Handedness Inventory; range of laterality quotient: +10 to +100; Oldfield, 1971). The sample was college-aged (M = 19.36, SD = 2.02), 64.9% female, and

Table 1
Descriptive statistics and correlation coefficients between the ASI-3 and QIDS-SR_{16}.

	1	2	3	4	5
1. ASI-3 PC	–	0.59	0.40	0.80	0.34
2. ASI-3 CC		–	0.50	0.85	0.49
3. ASI-3 SC			–	0.79	0.42
4. ASI-3 total				–	0.51
5. QIDS-SR_{16}					–
M	5.18	4.54	8.54	18.26	7.02
SD	4.08	4.37	4.64	10.66	4.00
Range	0–20	0–22	0–24	1–56	0–17
Cronbach's α	0.75	0.82	0.74	0.87	0.73

Note. All correlations were significant at $p < .001$. ASI-3 = Anxiety Sensitivity Index-3; CC = cognitive concerns; PC = physical concerns; SC = social concerns; QIDS-SR_{16} = Quick Inventory of Depressive Symptomatology-Self-Report 16-Item.

ethnically diverse, including 38.2% Caucasian, 28.2% Hispanic, 22.1% Asian, and 11.5% African-American. Over the preceding 6 months, 32.1% of participants reported smoking cigarettes, and over the preceding 30 days 49.6% of participants reported drinking alcohol and 14.5% reported smoking marijuana.[1] No participant reported a current medical condition that impacts central nervous system functioning. Informed consent was obtained prior to participation and the research protocol was approved by the University of Illinois-Chicago Institutional Review Board.

2.2. Measures

2.2.1. Anxiety Sensitivity Index-3

The Anxiety Sensitivity Index-3 (Taylor et al., 2007) is an 18-item self-report measure of AS. Each item is rated on a 5-point Likert scale ranging from 0 (*very little*) to 5 (*very much*), with higher scores indicating greater AS. The ASI-3 consists of three subscales that contain six items each: physical concerns (PC), cognitive concerns (CC), and social concerns (SC). Cronbach's alpha for the ASI-3 PC, CC, and SC subscales and total score were all greater than 0.73 (see Table 1).

2.2.2. Quick inventory of depressive symptomatology

The Quick Inventory of Depressive Symptomatology-Self-Report 16-Item (QIDS-SR_{16}) (Rush et al., 2003) measures the nine symptoms of depression over the last week, with higher scores indicated greater depression severity. Each item was rated on a scale ranging from 0 to 3, with the total QIDS-SR_{16} score ranging from 0 to 27. In the present study, the average QIDS-SR_{16} score indicated minimal depression severity (see Table 1). Cronbach's alpha for the QIDS-SR_{16} was 0.73.

2.3. Stimuli

Stimuli were administered using PSYLAB (Contact Precision Instruments, London, UK). Acoustic startle probes were 40-ms duration, 103-dB bursts of white noise with near-instantaneous rise time presented binaurally through headphones. Electric shocks were 400 ms in duration and administered to the wrist of the participant's left (non-dominant) hand. Shock intensity was determined ideographically using a work-up procedure for each participant (see Section 2.4).

2.4. Procedure

After electrode placement, participants were seated in an electrically shielded, sound-attenuated booth approximately 3.5 ft from a 19-in computer monitor. Participants first completed a 2.5-min baseline habituation task during which nine acoustic startle probes were administered.[2] Next, shock intensity was determined using a work-up procedure where participants received increasing levels of shock, until they reached a level they described as "highly annoying but not painful" (maximum shock level was 5 mA). The average shock level was 2.25 mA (*SD* = 1.21).

The NPU-threat task was a variant of that used by Grillon and colleagues (Schmitz & Grillon, 2012) and included three within-subjects conditions: no shock (N), predictable shock (P), and unpredictable shock (U). Text at the bottom of the screen informed participants of the current condition by displaying "no shock" (N), "shock at 1" (P), or "shock at any time" (U). Each condition lasted 90 s, during which a 6-s visual countdown (CD) was presented five times. The inter-stimulus interval (ISI; i.e., time between CDs during the 90-s condition) ranged from 7 to 17 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 received a shock every time the CD reached 1. In the U condition, shocks were administered at any time (during CD or ISI). Startle probes were presented both during the CD (1–5 s following CD onset) and ISI (5–14 s following ISI onset). Participants did not receive instructions regarding whether they should attend to or ignore the startle probes, but rather were told that, similar to the baseline condition, they would continue to hear the startle probes during the NPU-threat task. The time intervals between shocks and subsequent startle probes were always greater than 10 s to ensure that subsequent probes were not affected by prior shocks.

The task consisted of two presentations of each 90-s condition (N, P, U), during which the CD appeared five times. Participants received startle probes during four out of the five CD and ISI presentations. Conditions were presented in one of the following orders (counterbalanced): PNUPNU or UNPUNP. All participants received 20 electric shocks (10 during P, 10 during U), and 48 startle probes (16 during N, 16 during P, and 16 during U) during the CD and ISI (with an equal number of startle probes occurring during the CD and ISI).

At the end of the task, participants rated their anxiety during each threat condition (i.e., N_{ISI}, N_{CD}, P_{ISI}, P_{CD}, U_{ISI}, U_{CD}) on a scale ranging from 1 (*not at all nervous/anxious*) to 7 (*extremely nervous/anxious*).

2.5. EMG recording and processing

Startle eyeblink EMG was recorded using Neuroscan 4.4 (Compumedics, Charlotte, NC, USA) and measured from two 4-mm Ag/AgCl electrodes placed over the orbicularis oculi muscle below the right eye. EMG was recorded using a band-pass filter from DC to 200 Hz at a sampling rate of 1000 Hz. Offline, EMG data were rectified and then smoothed using a finite impulse response filter with a band-pass of 28–40 Hz. Peak amplitude of the startle response was determined in the 20–150 ms time frame following the startle probe onset relative to baseline (average baseline EMG level for the 50-ms preceding the startle probe onset). Blinks were scored as non-responses if EMG activity during the 20–150 ms post-stimulus time frame did not produce a blink peak that was visually differentiated from baseline activity. Blinks were scored as missing if the

[1] A history of substance use has been shown to impact aversive responding (Engelmann et al., 2011; Gorka et al., 2013). However, in the present study, all associations between AS and anticipatory threat responding remained significant when cigarette, alcohol, and marijuana use were included as additional covariates (all $p < .05$).

[2] The baseline data from this sample were previously examined in a study that found AS was associated with decreased startle habituation (see Campbell et al., 2014).

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 probe-elicited blink response. Startle analyses were conducted using blink magnitude (i.e., averages include values of 0 for non-response trials) as this is a more conservative estimate of blink response (Blumenthal et al., 2005).

2.6. EEG recording and data processing

EEG was recorded using Neuroscan 4.4 (Compumedics, Charlotte, NC, USA) and measured from Ag/AgCl electrodes in a 64-channel stretch-lycra electrode cap. The ground electrode was at the frontal pole (AFz) and the online reference was near the vertex (between Cz and CPz). Electrodes placed at the right supra- and infra-orbital sites were used to monitor vertical eye movements and electrodes placed at the right and left outer canthi were used to monitor horizontal eye movements. Electrode impedances were under 5000 Ω, and homologous sites (e.g., F3/F4) were within 1500 Ω of each other. EEG was recorded through a Neuroscan Synamp2 data acquisition system at a gain of 10 K (5 K for eye channels) with a band-pass of DC-200 Hz and digitized continuously at a sampling rate of 1000 Hz. Offline, EEG data were re-referenced to the average of the left and right mastoid and band-pass filtered from 0.1 to 30 Hz. Eye blink and ocular corrections were conducted using established standards (Gratton et al., 1983).

A semiautomatic procedure was employed to detect and reject artifacts. The criteria applied were a voltage step of more than 50 μV between sample points, a voltage difference of 300 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100 ms intervals. These intervals were rejected from individual channels in each trial. Visual inspection of the data was then conducted to detect and reject remaining artifacts.

2.7. Principal components analysis

A principal components analysis (PCA), an empirically based method of isolating and scoring ERP components, was conducted to better isolate the startle probe N100 and P300. For the PCA, the ERP was segmented for each trial beginning 200 ms before the startle probe and continuing for 1200 ms, and the baseline was the 200 ms prior to the onset of the startle probe. The ERP segment for each condition (N_{ISI}, N_{CD}, P_{ISI}, P_{CD}, U_{ISI}, U_{CD}), electrode location, and participant was entered into the data matrix. Using the MATLAB ERP PCA Toolbox-Version 2 (Dien, 2010b), a temporal PCA was performed first in order to capture variance across time and to maximize the initial separation of ERP components (Dien & Frishkoff, 2005), and a promax rotation was used to rotate to simple structure in the temporal domain (Dien, 2010a; Dien, Khoe, & Mangun, 2007). Following the first rotation, a parallel test (Horn, 1965) was conducted on the resulting Scree plot (Cattell, 1966), in which the Scree plot of the actual dataset is compared to that derived from a fully random dataset. The number of factors retained is based on the largest number of factors that account for a greater proportion of variance than the fully random dataset (see Dien, 2010b for more information). Based on this criterion, 39 temporal factors were extracted for rotation and the covariance matrix and Kaiser normalization were used for the PCA (Dien, Beal, & Berg, 2005). Following the temporal PCA, a spatial PCA was performed on each temporal factor retained in the previous step in order to reduce the spatial dimensions of the datasets. Infomax was used to rotate to independence in the spatial domain (Dien, 2010a; Dien et al., 2007). Based on the results of the parallel test (Horn, 1965), four spatial factors were extracted from each temporal factor for Infomax rotation, yielding a total of 156 temporospatial factor combinations. To directly assess timing and spatial voltage distributions, the factors were translated back into voltages.

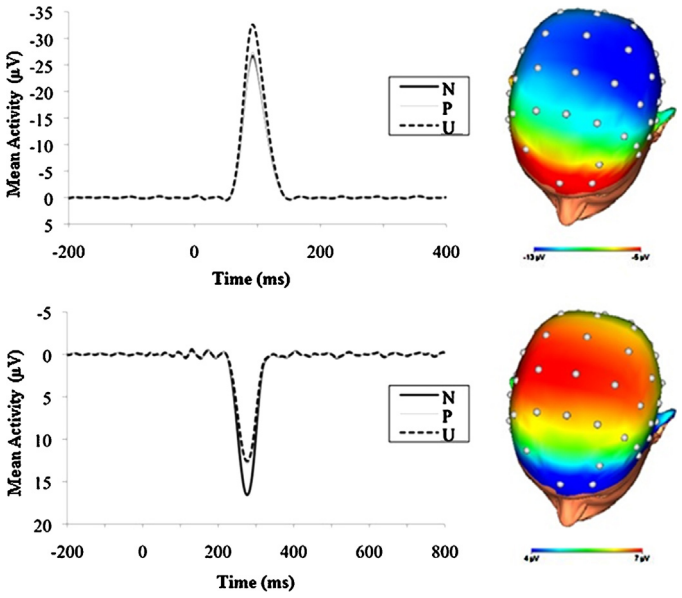

Fig. 1. Waveforms (left) and head maps (right) for the PCA-derived N100 (top) and P300 (bottom). Data were collapsed across CD and ISI phases of each threat condition. The *x*- and *y*-axes are at difference scales for the N100 and P300 figures. CD = countdown; ISI = inter-stimulus interval; ms = milliseconds; N = no threat; P = predictable threat; PCA = princal components analysis; U = unpredictable threat.

Eighteen temporospatial factor combinations accounted for more than 1% of the variance and in total accounted for 59.4% of the variance. Of the 18 factors, two resembled the temporal and spatial characteristics of the N100 and P300 (see Fig. 1). Specifically, TF4SF1 resembled the N100, was maximal approximately 100 ms after the onset of the startle probe, and accounted for 3.1% of the variance. In addition, TF5SF1 resembled the P300, was maximal approximately 300 ms after the onset of the startle probe, and accounted for 3.4% of the variance. Therefore, TF4SF1 and TF5SF1 were used as the PCA-derived N100 and P300, respectively, for subsequent analyses.[3]

2.8. Data analysis

Twelve participants were excluded from analyses due to equipment failure ($n = 5$), excessive EEG artifacts that resulted in less than 50% useable trials ($n = 2$), outlier startle values ($n = 2$) (Hoaglin, 1986; Hoaglin & Iglewicz, 1987; Tukey, 1977), or current psychotropic medication use (antidepressant, $n = 2$; stimulant, $n = 1$), leaving a final sample of 119 participants.

To examine the association between the ASI-3 and responding during the NPU-threat task, we conducted two separate ASI-3 × Condition (N, P, U) × Cue (CD vs. ISI) mixed-measures analysis of covariance (ANCOVA) models; the first model included the ASI-3 total as a mean-centered independent variable and the second had the PC, CC, and SC subscales entered as simultaneous mean-centered independent variables. NPU-threat condition order (PNUPNU vs. UNPUNP) was also included as a dichotomous

[3] Similar to the grand average ERPs reported in Nelson et al. (in press), a Condition (N, P, U) × Cue (CD vs. ISI) repeated-measures analysis of variance (ANOVA) incidated that the PCA-derived N100 differed between the threat conditions, $F(2,236) = 39.79$, $p < .001$, $\eta_p^2 = .25$, and was enhanced during the U_{CD+ISI} relative to the N_{CD+ISI} and P_{CD+ISI}, $F(1,118) = 55.64$, $p < .001$, $\eta_p^2 = .32$; $F(1,118) = 41.88$, $p < .001$, $\eta_p^2 = .26$, respectively, but did not differ between the N_{CD+ISI} and P_{CD+ISI}, $F(1,118) = 1.63$, ns, $\eta_p^2 = .01$. The PCA-derived P300 also differed between the threat conditions, $F(2,236) = 16.19$, $p < .001$, $\eta_p^2 = .12$, and was attenuated during the P_{CD+ISI} and U_{CD+ISI} relative to the N_{CD+ISI}, $F(1,118) = 27.38$, $p < .001$, $\eta_p^2 = .19$; $F(1,118) = 23.77$, $p < .001$, $\eta_p^2 = .17$, respectively, but did not differ between the P_{CD+ISI} and U_{CD+ISI}, $F(1,118) = 0.19$, *ns*, $\eta_p^2 < .01$.

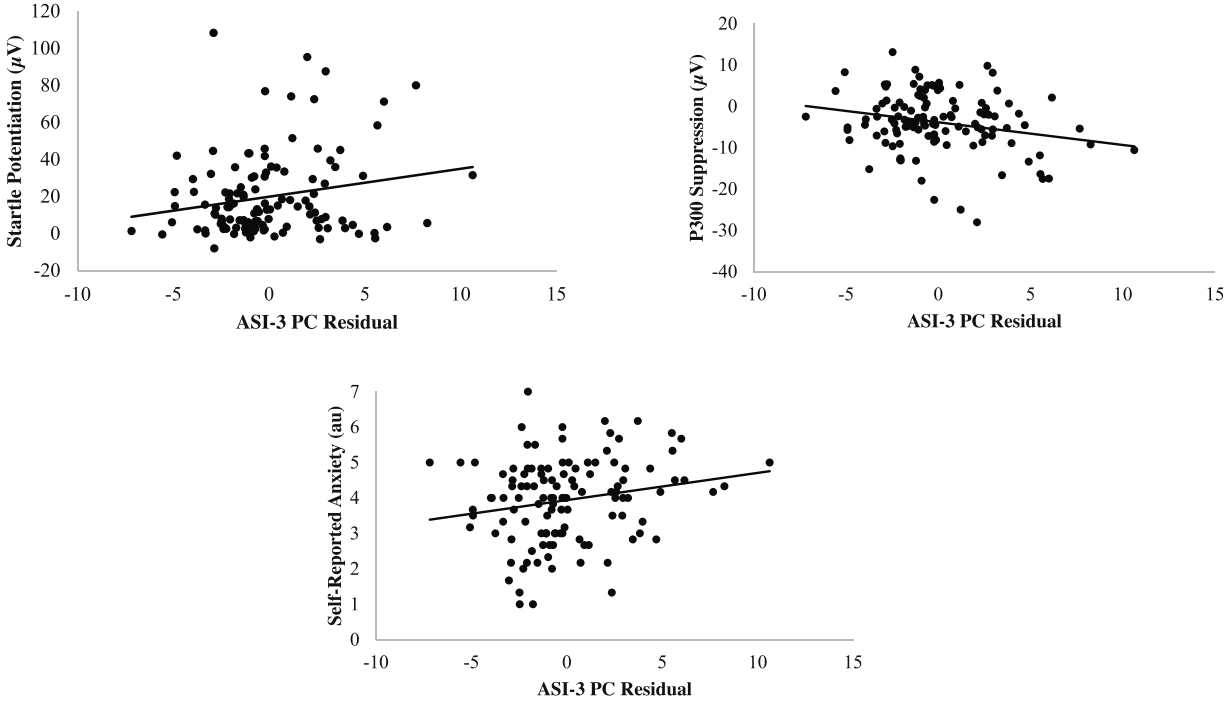

Fig. 2. Scatterplots depicting the association between ASI-3 PC residuals and startle potentiation during the U_{CD+ISI} (relative to the N_{CD+ISI}; top), P300 suppression (more negative values indicate greater suppression) during the P_{CD+ISI} and U_{CD+ISI} (relative to the N_{CD+ISI}; middle), and self-reported anxiety across all conditions. ASI-3 = Anxiety Sensitivity Index-3; au = arbitrary units; CD = countdown; ISI = inter-stimulus interval; N = no threat; P = predictable threat; PC = physical concerns; U = unpredictable threat.

covariate in both sets of analyses. Separate analyses were conducted for the startle response, N100, P300, and self-reported anxiety. One participant did not complete the self-report anxiety measure, leaving a sample of 118 participants for those analyses. All analyses were conducted in IBM SPSS Statistics, Version 22.0 (Armonk, NY, USA).

3. Results

3.1. Self-report questionnaires

Table 1 lists the descriptive statistics and correlation coefficients between the ASI-3 and QIDS-SR_{16}. As expected, all measures were moderately correlated and demonstrated moderate to excellent reliability.

3.2. Startle EMG

For startle EMG, there were no main effects or interactions involving ASI-3 total ($p > .24$). However, there were ASI-3 PC × Condition, $F(2,228) = 5.49$, $p < .05$, $\eta_p^2 = .05$, and ASI-3 CC × Condition interactions, $F(2,228) = 7.20$, $p < .01$, $\eta_p^2 = .06$. The ASI-3 PC and CC subscales were not associated with startle during the N_{CD+ISI} ($p < .68$); therefore, the interactions were followed-up by conducting separate partial correlations between the specific ASI-3 subscale and startle potentiation for the unpredictable condition (i.e., $U_{CD+ISI} - N_{CD+ISI}$), controlling for the other ASI-3 subscales and NPU-threat task order. For the ASI-3 PC × Condition interaction, follow-up analyses indicated that greater physical concerns was associated with *increased* startle potentiation during the U_{CD+ISI}, $pr(114) = .20$, $p < .05$, but not the P_{CD+ISI}, $pr(114) = -.03$, *ns* (see top of Fig. 2). In contrast, for the ASI-3 CC × Condition interaction, follow-up analyses indicated that greater cognitive concerns was associated with *decreased* startle potentiation during the U_{CD+ISI}, $pr(114) = -.25$, $p < .01$, but not the P_{CD+ISI}, $pr(114) = -.09$, *ns* (see top of Fig. 3). In other words, while the ASI-3 PC and CC subscales both exhibited unique associations with startle potentiation for the unpredictable (but not predictable) condition, they demonstrated the opposite relationship (positively and negatively correlated, respectively). There were no effects for ASI-3 SC ($p > .31$).

3.3. ERPs

3.3.1. N100

For the PCA-derived N100,[4] there were no main effects or interactions involving ASI-3 total ($p > .08$). However, ASI-3 subscale analyses[5] indicated an ASI-3 CC × Condition × Cue interaction, $F(2,228) = 4.45$, $p < .05$, $\eta_p^2 = .04$. The ASI-3 CC subscale was not associated with the N100 during the N_{CD} or N_{ISI} ($p < .66$); therefore, to follow-up the interaction separate ASI-3 CC × Cue ANCOVA models were conducted for N100 enhancement during the predictable (i.e., $P_{CD} - N_{CD}$, $P_{ISI} - N_{ISI}$) and unpredictable (i.e., $U_{CD} - N_{CD}$, $U_{ISI} - N_{ISI}$) conditions. For the predictable condition, there were no main effects or interactions involving ASI-3 CC ($p > .85$). For the unpredictable condition, results indicated an ASI-3 CC × Cue interaction, $F(1,114) = 6.66$ $p < .05$, $\eta_p^2 = .06$. This interaction was followed-up by conducting separate partial correlations between ASI-3 CC (controlling for the PC and SC subscales and the NPU-threat task order) and N100 enhancement during the U_{ISI} and U_{CD}. Results indicated

[4] The PCA-derived N100 and P300 variables for each condition were highly correlated with the analogous variables reported by Nelson et al. (in press) derived from scoring the ERP grand average (i.e., average activity; Pearson's *r* range: 0.72–0.87). Nonetheless, identical analyses for the grand average variables indicated the ASI-3 CC X Condition X Cue interaction for the N100, $F(2,228) = 1.52$, $p = .22$, $\eta_p^2 = .03$, and the ASI-3 PC X Condition interaction for the P300, $F(2,228) = 1.66$, $p = .19$, $\eta_p^2 = .01$, only (at best) approached significance. These results for grand averages further supported use of the PCA-derived ERP components as they are likely to have a better signal-to-noise ratio than grand average waveforms (Dien & Frishkoff, 2005).

[5] There were also ASI-3 PC X Condition X Cue, $F(2,228) = 3.78$, $p < .05$, $\eta_p^2 = .03$, and ASI-3 SC X Condition X Cue interactions, $F(2,228) = 4.32$, $p < .05$, $\eta_p^2 = .04$. However, follow-up analyses revealed no significant correlations between ASI-3 PC or SC and the N100 during any condition ($p > .12$).

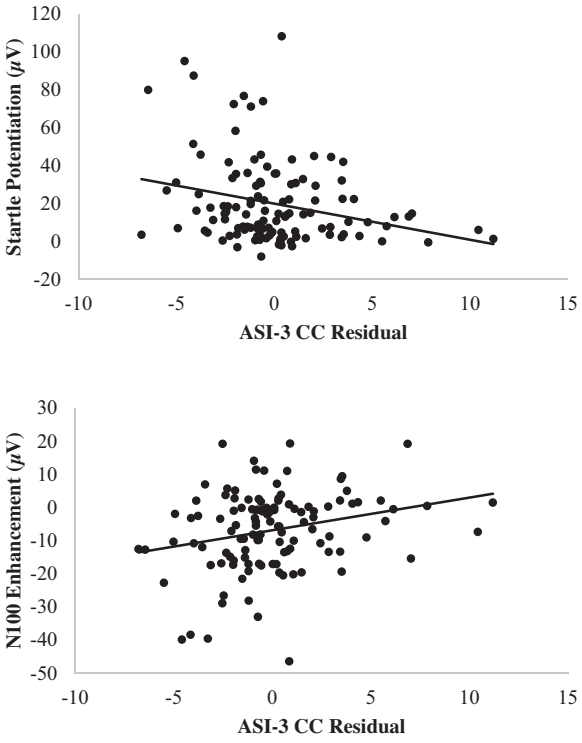

Fig. 3. Scatterplots depicting the association between ASI-3 CC residuals and startle potentiation during the U_{CD+ISI} (relative to the N_{CD+ISI}; top) and N100 enhancement (more negative values indicate greater enhancement) during the U_{CD} (relative to the N_{CD}; bottom). ASI-3 = Anxiety Sensitivity Index-3; CC = cognitive concerns; CD = countdown; ISI = inter-stimulus interval; U = unpredictable threat.

ASI-3 CC was positively associated with N100 enhancement during the U_{CD}, $pr(114) = 0.25$, $p < .01$, but not the U_{ISI}, $pr(114) = -.01$ (see bottom of Fig. 3). In other words, greater cognitive concerns were associated with a *decreased* (i.e., less negative) N100 during the U_{CD}. There were no associations between ASI-3 PC or SC and the N100 during any threat condition ($p > .12$).

3.3.2. P300

For the PCA-derived P300,[4] there was a main effect of ASI-3 total, $F(1,116) = 4.56$, $p < .05$, $\eta_p^2 = .04$, such that greater AS was associated with a smaller P300 across all conditions, $pr(116) = -.19$, $p < .05$. ASI-3 subscale analyses indicated an ASI-3 PC × Condition interaction, $F(2,228) = 3.56$, $p < .05$, $\eta_p^2 = .03$. The ASI-3 PC subscale was not associated with the P300 during the N_{CD} or N_{ISI} ($p < .61$); therefore, to follow-up the interaction separate ASI-3 PC × Cue ANCOVA models were conducted for P300 suppression during the predictable (i.e., $P_{CD} - N_{CD}$, $P_{ISI} - N_{ISI}$) and unpredictable (i.e., $U_{CD} - N_{CD}$, $U_{ISI} - N_{ISI}$) conditions. Results indicated a main effect of ASI-3 PC, $F(1,114) = 7.37$, $p < .01$, $\eta_p^2 = .06$, such that greater physical concerns were associated with increased P300 suppression during the P_{CD+ISI} and U_{CD+ISI}, $pr(114) = -.25$, $p < .01$ (see middle of Fig. 2). There were no effects for ASI-3 CC or SC ($p > .12$). These results suggest that the association between ASI-3 total and P300 suppression in anticipation of threat was due to the PC subscale and was evident across predictable and unpredictable contexts.

3.4. Self-reported anxiety

For self-reported anxiety, there was a main effect of ASI-3 total, $F(1,115) = 14.63$, $p < .001$, $\eta_p^2 = .11$, such that greater AS was associated with increased anxiety across all conditions, $pr(115) = 0.33$, $p < .001$. ASI-3 subscale analyses indicated a main effect of ASI-3 PC, $F(1,113)$, such that greater physical concerns were associated with increased anxiety across all conditions, $pr(113) = 0.22$, $p < .05$ (see bottom of Fig. 2). There were no effects for ASI-3 CC or SC ($p > .11$).[6] These results suggest that the association between ASI-3 total and self-reported anxiety was due to the PC subscale and was evident across all threat contexts.

3.5. Independence of AS and depression

Finally, we examined whether the aforementioned associations between the ASI-3 subscales and responding during the NPU-threat task were independent of depression. Specifically, we conducted identical follow-up partial correlations between the ASI-3 subscales and startle EMG, N100, P300, and self-reported anxiety but also included the QIDS-SR_{16} as a covariate.[7] Results again indicated a significant association between ASI-3 PC and CC and startle potentiation during the U_{CD+ISI}, $pr(113) = 0.20$, $p < .05$; $pr(112) = -0.25$, $p < .01$, respectively; ASI-3 CC and N100 enhancement during the U_{CD}, $pr(113) = 0.24$, $p < .05$; ASI-3 PC and P300 suppression during the P_{CD+ISI} and U_{CD+ISI}, $pr(113) = -0.24$, $p < .01$; and ASI-3 PC and self-reported anxiety across all conditions, $pr(112) = 0.22$, $p < .05$. These results suggest that the associations between the ASI-3 subscales and responding to predictable and unpredictable threat were not better accounted for by depression.[8]

4. Discussion

The present study examined the association between AS and startle EMG, probe N100 and P300, and self-reported anxiety in anticipation of predictable and unpredictable threat. ASI-3 total was associated with increased P300 suppression across predictable and unpredictable threat conditions and self-reported anxiety across all conditions, but was not associated with startle EMG or probe N100 during any threat condition. However, the ASI-3 subscale analyses revealed a more complex pattern of results. Specifically, the ASI-3 PC and CC subscales were both associated with startle potentiation for the unpredictable (but not predictable) condition; however, they demonstrated the opposite relationship. Greater physical concerns were associated with heightened startle potentiation and greater cognitive concerns were associated with attenuated startle potentiation (even when both subscales were in the same model). ASI-3 CC were associated with decreased (i.e., less negative) probe N100 enhancement for the unpredictable condition only. ASI-3 PC were associated with probe P300 suppression across both threat contexts, such that greater physical concerns was associated with increased P300 suppression. ASI-3 PC were also associated with increased self-reported anxiety across

[6] There was also a main effect of ASI-3 SC, $F(1,113) = 4.82$, $p < .05$, $\eta_p^2 = .04$, such that greater social concerns was associated with increased anxiety across all conditions, $pr(113) = .20$, $p < .05$. However, the scatterplot indicated this correlation was influenced by an outlier ASI-3 SC value (>3 standard deviations from the mean). When this participant was excluded from analyses ASI-3 PC was still associated with anxiety, $pr(112) = .21$, $p < .05$, but ASI-3 SC was no longer related, $pr(112) = .16$, ns.

[7] There were no main effects or interactions of QIDS-SR_{16} for any measure ($p > .19$).

[8] Prior research has indicated sex differences in the startle response to predictable and unpredictable threat, such that females demonstrate a larger sustained startle response across both threat conditions (Grillon, 2008). Therefore, we tested for sex differences for all significant associations between the ASI-3 and threat responding during the NPU-threat task. To this end, for startle potentiation to unpredictable threat, P300 suppression to predictable and unpredictable threat, N100 enhancement to unpredictable threat, and self-reported anxiety across all conditions, we conducted separate hierarchical linear regressions with startle block order, sex, and ASI-3 PC, CC, and SC subscales entered as block 1 independent variables, and ASI-3 PC X Sex, ASI-3 CC X Sex, and ASI-3 SC X Sex interaction terms entered as block 2 independent variables. Results indicated no significant ASI-3 X Sex interactions for any dependent measure ($p > .10$), suggesting that the associations between AS and threat responding did not differ between females and males.

all conditions. Finally, all associations between AS and responding during the threat conditions were independent of current depression symptoms. Together, these results provide novel evidence for an association between AS and affective (startle EMG, self-report anxiety) and attentional (N100, P300) indicators of threat sensitivity and suggest that the different AS dimensions demonstrate unique relationships with these measures.

The present study adds to a growing number of anxiety phenotypes that have been associated with a heightened sensitivity to unpredictable threat. Greater physical concerns, the ASI-3 dimension most closely connected with risk for panic disorder (Schmidt et al., 1999; Van Beek & Griez, 2003), was associated with heightened potentiation in anticipation of unpredictable threat only. This result is consistent with a previous investigation that found a heightened startle response in anticipation of unpredictable (but not predictable) threat was associated with a familial history (i.e., risk) of PD, independent of current anxiety (Nelson et al., 2013). However, the present study and Nelson et al. were both cross-sectional and it is unclear whether physical concerns or a heightened sensitivity to unpredictable threat predicts the development of PD, or, alternatively, whether they are concurrent risk factors. Future longitudinal studies are needed to determine the causal relationship amongst these factors.

ASI-3 CC were associated with decreased startle potentiation in anticipation of unpredictable (but not predictable) threat. There are several potential explanations for this finding. For example, experiential avoidance (i.e., the unwillingness to remain in contact with an aversive experience; Chawla & Ostafin, 2007) has been particularly associated with the ASI-3 CC subscale (Berman et al., 2010). It is therefore possible that individuals high in cognitive concerns engaged in some form of avoidance (e.g., rumination, worry) to diminish their anxiety while anticipating unpredictable threat. This interpretation is consistent with Borkovec's cognitive avoidance theory of worry, which postulates that worry is a verbal linguistic, thought-based activity that inhibits emotional reactivity (Borkovec & Inz, 1990; Borkovec et al., 2004). Interestingly, ASI-3 CC is the subscale of AS most closely linked to depression (Olthuis et al., 2014), and depression has often been associated with a decreased emotion-modulated startle response to unpleasant stimuli (Allen et al., 1999; Kaviani et al., 2004; McTeague et al., 2009). However, in the present study the association between cognitive concerns and startle potentiation remained significant after controlling for depression. This suggests that the cognitive distress elicited by the anticipation of unpredictable threat, and not depression per se, is what contributed to diminished defense system activation. The startle response results also highlight the importance of considering the heterogeneity of anxiety in relation to emotional responding and suggest that future studies are needed to delineate the neural mechanisms that contribute to these important differences (e.g., Shackman et al., 2013).

The present study also adds to a growing literature on AS and aberrations in attention to threat. Behavioral studies have indicated that high AS is associated with an increased attentional bias toward threat (Hunt et al., 2006; Keogh et al., 2001; Lees et al., 2005); however, this relationship has not been examined in the context of predictable and unpredictable threat. In the present study, ASI-3 PC were associated with increased P300 suppression across the predictable and unpredictable conditions. Probe P300 suppression purportedly reflects increased attention to foreground emotional stimuli and the resultant decreased orienting response to the probe (Bradley et al., 2012). The present results suggest that individuals with high physical concerns directed more attention toward the foreground stimuli (i.e., the threat cues) and away from the startle probe. In contrast, ASI-3 CC were associated with decreased (i.e., less negative) N100 enhancement for the unpredictable condition only. The probe N100 has been proposed to reflect the enhancement of salient sensory input (Näätänen & Picton, 1987). Thus, in addition to attenuated defense system activation, high cognitive concerns is also related to diminished early sensory processing in anticipation of unpredictable threat. It is important to note that ASI-3 CC were only associated with the cued (i.e., CD) but not contextual (i.e., ISI) phase of the unpredictable threat condition. Interestingly, both phases of the unpredictable threat condition were equally dangerous, and it is possible that, at least in participants with high cognitive concerns, the unpredictable threat cue was particularly distressing and elicited early attention disengagement.

The correlation between AS and the startle EMG and probe N100 and P300 measures ranged from 0.20 to 0.25, indicating small effect sizes. However, there was no shared method variance between these measures, which has been shown to impact the association between two measured constructs (Campbell & Fiske, 1959). The present study provides novel evidence regarding the association between AS and sensitivity to unpredictable threat, and these results are particularly useful regarding the conceptualization of AS, future research design, and hypothesis generation. It is important to highlight the relationship between AS and anticipatory threat responding was not affected by variables that have been shown to impact aversive responding (e.g., alcohol use, smoking, etc.). However, there were several other demographic and individual difference factors (e.g., diet, exercise, menstrual cycle, sleep) that were not assessed in this sample and could influence AS and anxious responding. Future studies should measure these (and other) factors to account for a greater proportion of variance in AS and sensitivity to unpredictable threat.

The ASI-3 social concerns subscale was not associated with responding during any threat condition. It is possible that the context under which threat is measured may be differentially important for the different ASI-3 dimensions. Indeed, in the present study the NPU-threat task was administered in a sound-attenuated booth with no other people present. Future studies might consider whether being observed or different types of threat (e.g., social rejection) impact the association between the social concerns dimension of the ASI-3 and emotional responding in anticipation of predictable and unpredictable threat.

Although previous studies have been successful in targeting and reducing AS (Norr, Allan, McAtee, Keough, & Schmidt, 2014; Gallagher et al., 2013; Boswell et al., 2013; MacDonald, Koerner, & Antony, 2013; Mitchell, Capron, Raines, & Schmidt, 2014), the current results may provide further insight into possible therapeutic targets for these treatment efforts. Specifically, rather than focusing treatments on reducing sensitivity to threat more generally, interventions that target predictable and (perhaps more importantly) unpredictable threat should be considered. These treatments may want to consider increasing tolerance of unpredictability (Robichaud & Dugas, 2008), which in turn may reduce prolonged anxiety. Treatments should also consider structuring goals based on the problematic AS dimension(s) (i.e., PC, CC, SC), which, may vary from tolerating the unpredictability of threat (e.g., individuals with high physical concerns) to cognitively processing anticipatory threat cues (e.g., individuals with high cognitive concerns).

The present study supports the utility of the AS construct in relation to two separate RDoC Negative Valence System constructs—acute and potential threat (i.e., "fear" and "anxiety", respectively). The NPU-threat task is particularly useful for this aim as it assesses both constructs. The predictable condition taps responses to an acute "fearful event" (i.e., the pending danger is occurring in a matter of moments) and the unpredictable condition taps responses to a prolonged stressful or "anxiety event" (i.e., the danger might occur, but no immediate threat is pending). Additionally, as shown in the present study, the startle variant of the NPU-threat task is particularly useful for RDoC studies as it

elicits both of these constructs across multiple units of analysis (i.e., startle EMG, probe ERPs, self-report) at the same time.

The present study had several limitations that warrant consideration. First, the sample consisted of introduction to psychology students and the results may not generalize to all populations (e.g., children). Indeed, the ASI-3 means were below that of clinical samples (Kemper et al., 2012); however, they were still higher than what is typically reported in undergraduates (Wheaton et al., 2012). Future studies should attempt to replicate these findings in a mixed clinical sample. Second, all measures were collected cross-sectionally and causal relationships between AS and emotional responding to threat cannot be determined. Third, the NPU-threat task used only one type of aversive stimulus (electric shocks) and it is unclear whether a similar or different pattern of results would emerge using other threatening events or stimuli (e.g., aversive noises, social rejection, unpleasant pictures). Finally, the present study focused on examining the association between AS and the temporal predictability of threat. However, controllability is another feature of threat that overlaps substantially with predictability (Chorpita & Barlow, 1998; Mineka & Kihlstrom, 1978; Seligman & Bink, 1977), and AS has been associated with increased anxiety when there is a lack of control over interoceptive threat (Zvolensky et al., 2001). Future studies should better delineate these features of threat and examine whether they have overlapping or unique relationships with AS.

In conclusion, the present study found an association between AS and multiple measures of affective and cognitive responding in anticipation of predictable and unpredictable threat. In an unselected sample of undergraduates, increased physical concerns were associated with enhanced defense system activation (e.g., startle EMG) in anticipation of unpredictable (but not predictable) threat. Conversely, increased cognitive concerns demonstrated the opposite relationship—they were associated with decreased defense system activation. Increased cognitive concerns were also associated with decreased perceptual processing (i.e., probe N100) in anticipation of unpredictable threat only, and increased physical concerns were associated with greater attention toward foreground threat stimuli (i.e., P300 suppression) across both predictable and unpredictable contexts and increased self-reported anxiety across all conditions. AS is a multi-faceted dimensional construct that cuts across several anxiety disorders and depression (Allan, Capron et al., 2014; Wheaton et al., 2012). The present study provides novel evidence indicating that facets of AS demonstrates unique relationships with different Negative Valence System constructs (i.e., “acute” and “potential” threat) that have been implicated in the etiology and maintenance of many psychopathological conditions. Future research is needed to determine the neurodevelopment (Casey et al., 2014) and predictive validity and utility of these emotional and motivational systems.

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