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Transdiagnostic fear and anxiety: prospective prediction using the NPU threat task

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Abstract

Background: Fear and anxiety are distinct dimensions of psychopathology that may be characterized by differences in dimensional threat reactivity. Heightened response to predictable threat is hypothesized to underlie fear symptomatology, whereas increased response to unpredictable threat may underlie anxiety. Despite widespread acceptance of this model, these purported associations have rarely been tested, and the prognostic value of predictable and unpredictable threat responding is unclear. Here, we examined multi-level indicators of predictable and unpredictable threat response as cross-sectional correlates and prospective predictors of transdiagnostic fear and anxiety.

Methods: 52 individuals with varying levels of internalizing psychopathology (31 female) performed the NPU (no-threat, predictable threat, and unpredictable threat) task. Transdiagnostic fear and anxiety were assessed at baseline (Time 1) and approximately 1.5 years later (Time 2). We used event-related potential, the stimulus-preceding negativity (SPN) as a measure of threat anticipation, and startle eyeblink as a measure of defensive reactivity during the NPU task. These probes were assessed as cross-sectional correlates and prospective predictors of fear and anxiety.

Results: Participants with larger Time 1 SPNs to predictable threat were characterized by greater Time 1 fear. Larger Time 1 SPNs to unpredictable threat were associated with greater increases in Time 2 anxiety. Heightened Time 1 startle to predictable threat predicted larger increases in Time 2 fear.

Conclusions: Results validate predictable and unpredictable threat responding as dimensional correlates of transdiagnostic fear versus anxiety, and suggest that psychophysiological measures of predictable and unpredictable threat response hold promise as prospective predictors for trajectories of fear and anxiety.

Keywords: predictable threat, unpredictable threat, event-related potential (ERP), startle, internalizing psychopathology, shock
Introduction

Animal work has suggested that defensive behaviors can be organized into phasic fear versus sustained anxiety. For example, cues that predictably signal an upcoming aversive stimulus elicit short-term fear behaviors in rodents, whereas uncertain threat cues activate a sustained, anxiety-like state (1). Theoretical distinctions between fear and anxiety have been adapted into a transdiagnostic model for conceptualizing anxiety disorders (2–5). These distinctions are also reflected in the Research Domain Criteria (RDoC; 5), which includes constructs of acute/predictable threat and potential/unpredictable threat. Here, we tested this framework by assessing associations between neurobiological response to predictable and unpredictable threat and transdiagnostic dimensions of fear and anxiety in a mixed, internalizing sample. To determine whether these constructs represent liabilities for the development of future psychopathology, we assessed whether predictable and unpredictable threat reactivity prospectively predict transdiagnostic fear and anxiety.

The NPU task was designed to probe predictable and unpredictable threat reactivity. Originally designed for use with eyeblink startle, the task involves three different trial types: no-threat (no aversive stimulus delivered), predictable threat (cues predict aversive stimulus delivery) and unpredictable threat (aversive stimulus might be delivered). Increased startle response to predictable and unpredictable threat in this task have been hypothesized to underlie fear-based psychopathology versus anxiety, respectively (7). Despite the popularity of the NPU task (8–11) and widespread acceptance of distinctions between fear versus anxiety in internalizing disorders (11–13), few studies have tested associations with these constructs transdiagnostically. Results to-date using the NPU task can be conceptualized within a fear versus anxiety framework when considering genetic and epidemiological data that has divided internalizing disorders into those characterized by: a) anxious misery/distress – i.e., generalized anxiety disorder (GAD), panic disorder (PD), agoraphobia, and post-traumatic stress disorder (PTSD); b) fear – i.e., the specific phobias (SP); and c) somewhere in between – i.e., social anxiety disorder (SAD; 14–16).
Most work using the NPU task in clinical samples has focused on PD, which, although dominated by worry about uncertain threat (e.g., future panic attacks; 17), is also characterized by phasic fear (e.g., during panic attacks; 3,4). Results support that individuals with PD are characterized by heightened startle response to unpredictable threat (8,18–20). A few studies have found that individuals with PD/elevated panic symptoms are characterized by increased startle potentiation to both unpredictable and predictable threat, in line with the notion that PD may be characterized by both sustained anxiety and phasic fear (21,22). Neuroimaging work suggests PD is associated with hyperactivation in the ventromedial prefrontal cortex to all cues in the NPU task, suggesting overgeneralization and excessive regulation of response to both threat and safety cues (23). Panic symptoms have also been associated with increased reactivity to unpredictable threat cues in the dorsal anterior cingulate cortex (20), brainstem (11), and bed nucleus of the stria terminalis (BNST; 24), a brain region involved in mediating response to uncertain threat (25, for review, see 26). Few studies have examined PTSD, which has typically been conceptualized as an anxiety (not fear) disorder (14,27), as evidenced by associations with increased startle response to unpredictable threat cues (13,28), as well as sustained BNST activation to anticipation of unpredictable aversive stimuli (29). GAD has also been associated with greater BNST activation to unpredictable threat cues (30). Therefore, prior findings from categorical studies suggest that anxiety symptomatology is characterized by increased peripheral response to unpredictable threat and greater engagement of brain regions involved in mediating these responses.

Fewer studies have examined predictable and unpredictable threat reactivity in the fear disorders. SP has been associated with greater startle reactivity to unpredictable threat cues (19,31), which is not in keeping with the hypothesized fear-predictable threat and anxiety-unpredictable threat associations. Results have also shown mixed findings in individuals with SAD: some studies demonstrated an association with increased startle response to predictable threat (8), whereas others found increased startle to unpredictable threat cues (19). Neuroimaging work has found that SAD is associated with decreased
BNST-amygdala connectivity to unpredictable threat cues, suggesting less coordinated response to unpredictable threat (32).

Prospective and longitudinal examination of predictable and unpredictable threat responding is rare. One study found that increased startle reactivity to both unpredictable and predictable threat cues predicted worse functional impairment approximately one year later in individuals with current and past internalizing disorders (33). Another study found that cognitive behavioral therapy reduced startle reactivity to unpredictable threat in individuals with PD, SAD, and PTSD (12). While limited, this work suggests that predictable and unpredictable threat reactivity might account for variance in outcomes beyond what can be explained by categorical diagnoses alone, and could play a causal role in internalizing psychopathology.

Given the substantial heterogeneity characterizing the current diagnostic categories (6), it would be ambitious to expect that hypothesized associations between disorders categorized as “fear” versus “anxiety” would consistently show expected associations with predictable and unpredictable threat reactivity. That is, PD, SAD and SP may be characterized to some degree by both elevated fear and anxiety. Substantial comorbidity between categorical disorders means that participants often meet criteria for multiple diagnoses, or may be characterized by heightened, but subthreshold, fear/anxiety psychopathology. In sum, transdiagnostic fear and anxiety are potentially more homogeneous constructs than the current categorical diagnoses, and might more closely track variation in neurobiological response to predictable and unpredictable threat.

Here, we used the NPU task to assess predictable and unpredictable threat responding as cross-sectional correlates and prospective predictors of fear versus anxiety symptomatology, in a mixed, internalizing sample. While the majority of work using the NPU task has used startle potentiation to probe defensive response during predictable and unpredictable threat, an event-related potential (ERP), the stimulus-preceding negativity (SPN), provides a central autonomic measure of threat anticipation (34).
The SPN is a negative-going, frontally distributed ERP component that grows larger as threatening stimuli approach (35) and is sensitive to stimulus probability (36,37), making it an ideal measure for the NPU task (10). Here, we measured the SPN to threat cues, as well as startle eyeblink, to provide a link with prior work. We expected that individuals higher in transdiagnostic fear would show increased SPNs and heightened startle potentiation to predictable threat, and that individuals higher in transdiagnostic anxiety would show increased SPNs and heighted startle potentiation in response to unpredictable threat (1,2). We also expected to observe these associations prospectively – i.e., increased SPNs and startle to predictable threat cues at baseline would predict greater self-reported fear at follow-up approximately 1.5 years later, and increased SPNs and startle to unpredictable threat cues at baseline would predict greater self-reported anxiety at follow-up (2,4). If confirmed, these hypotheses would support neurobiological distinctions between fear versus anxiety and would suggest predictable and unpredictable threat responding might represent unique liabilities for the development and worsening of fear versus anxiety psychopathology, respectively.

**Methods and Materials**

**Participants**

Fifty-six individuals who were part of a larger study participated in data collection at baseline (Time 1) and returned at follow-up approximately 1.5 years later (Time 2). From this initial sample, four participants were excluded for having poor quality data recordings at Time 1, leaving a final sample size of n = 52 (31 female; $M_{age} = 24.46$ years, $SD = 9.33$). There were two outliers excluded for the late SPN leaving 50 participants for late SPN analyses (30 female; $M_{age} = 24.60$ years, $SD = 9.48$). One outlier was excluded for startle, and six participants did not have a sufficient number of startle trials for analyses, leaving 45 participants (26 female; $M_{age} = 23.49$ years, $SD = 7.78$) for startle analyses. Details concerning sample size determinations, bad data exclusion criteria, and outliers are presented in the Supplemental Information.
Clinical characteristics of the sample are presented in Table 1. Participants were initially recruited as part of a larger study, for which they were selected to fall into a psychiatrically healthy group (no current or prior psychiatric diagnoses; \( n = 20 \)) or an anxiety group. Although participant recruitment was structured this way to ensure variability in the sample, planned analyses (both in the parent study and in the current study) were dimensional. Participants in the anxiety group were required to meet criteria for a focal fear diagnosis at Time 1 (specific phobia \( [n = 16] \) or performance-only social anxiety \( [n = 20] \)), but were permitted to vary in levels of additional, comorbid internalizing psychopathology (e.g., major/persistent depressive disorder [MDD/PDD], GAD, generalized SAD). Exclusionary criteria are included in the Supplemental Information. Participants were not engaged in psychiatric treatment of any kind. Diagnoses were made at Time 1 according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, DSM-5 (SCID; 30). Study procedures were in compliance with the Helsinki Declaration of 1975 (as revised in 1983), and were approved by the Texas A&M University institutional review board.

**Materials**

Dimensional psychopathology and internalizing symptoms were assessed using the Positive and Negative Affect Schedule-Expanded Form (PANAS-X; 31), the Penn State Worry Questionnaire (PSWQ; 32), the State Trait Anxiety Inventory, trait version (STAI; 33), and the Social Phobia Inventory (SPIN; 34). Details on each of these measures are provided in Supplemental Information.

We used the PANAS-X Fear subscale as a continuous measure of transdiagnostic fear, computed separately at each timepoint (Time 1 Fear, Time 2 Fear). Transdiagnostic anxiety was operationalized as a composite of averaged \( z \)-scored STAI, PSWQ, and SPIN scores, computed separately at each timepoint. This provided a broad measure of anxiety (Time 1 Anxiety, Time 2 Anxiety) that was not specific to a particular diagnosis, in keeping with the characteristics of our mixed, internalizing sample (43).

**Procedure**
Time 1

Participants’ shock levels were set using standard procedures, in order to control for individual differences in shock sensitivity (10,44). While EEG was recorded, participants performed the NPU task used in our prior work (10) and adapted from Kaye and colleagues (9). Participants were asked to view colored shape “cues” (blue circle, red square, green triangle). Each shape cue indicated whether the participant would definitely receive a shock (predictable), possibly receive a shock (unpredictable) or would never receive a shock (no-threat). Additional task parameters are detailed in the Supplemental Information.

Acoustic startle probes were delivered binaurally (40 ms, 90 dB white noise with near instantaneous rise time) during cues and interstimulus intervals (ISIs). Three initial startle probes were presented before the task to allow for stabilization of the startle response (45); this data was not analyzed. Startle probes were presented a minimum of 12500 ms after shock or other startle probes, with the serial position of startle probes across each condition balanced within subjects. Two different, counterbalanced orders of startle probe serial position were used. See Supplemental Information for additional task details.

Time 2

Approximately 1.5 years following their initial visit ($M = 1.68$ years; $SD = 0.68$), participants completed the same set of questionnaires completed at Time 1; due to the COVID-19 pandemic, questionnaires were completed online and participants did not complete the SCID or receive an EEG again at this time.

Electroencephalographic (EEG) Data Acquisition - Time 1

Continuous EEG recordings were collected using an ActiCap and the ActiCHamp amplifier system (Brain Products GmbH, Gilching Germany) at Time 1. Thirty-two electrode sites were used based on the 10/20 system. The electrooculogram (EOG) was recorded from four facial electrodes (see
Supplemental Information). The EEG data were digitized at 24-bit resolution and a sampling rate of 1000 Hz. EEG data reduction is described in the Supplemental Information.

Based on visual inspection of grand-averaged waveforms and topographic maps, the SPN was scored at Fz as the mean activity during an early window (1000-2000 ms post-cue onset) and a late window (3500-4500 ms post-cue onset; 39); as in our prior work (10), time windows were chosen to avoid shock delivery (which was at 2000 ms or 4800 ms on U trials and at 4800 ms on P trials) and startle probe delivery (at 4500 ms).

**Electromyographic (EMG) Data Acquisition - Time 1**

Startle eyeblink EMG activity was recorded from two 4-mm diameter electrodes placed over the orbicularis oculi muscle under the left eye and using the ActiCHamp amplifier system. Data were digitized at 24-bit resolution and a sampling rate of 1000 Hz. EMG data reduction is described in the Supplemental Information.

**Data Analyses**

To assess condition effects and group differences, cue-locked SPN amplitudes were submitted to separate 2 (group: control, anxious) X 3 (condition: no-threat, predictable threat, unpredictable threat) between-within analyses of variance (ANOVAs) and startle amplitudes were submitted to a 2 (group: control, anxious) X 2 (cue, ISI) X 3 (condition: no-threat, predictable threat, unpredictable threat) between-within ANOVA. Greenhouse-Geisser corrections were applied as necessary when the assumption of sphericity was violated. Significant effects were followed up using dependent and independent samples t-tests, as appropriate.

To examine associations between psychophysiological measures and fear and anxiety at Time 1, we conducted separate linear regressions for each of the SPN and startle as predictors of Time 1 Fear and Time 1 Anxiety. For each regression, SPN/startle response to no-threat, predictable threat and
unpredictable threat were entered as simultaneous predictors, along with the other Time 1 dimension (i.e., Fear or Anxiety).

To examine associations between psychophysiological measures and Time 2 symptoms, we conducted separate linear regressions for each of the SPN and startle elicited during no-threat, predictable threat and unpredictable threat, as predictors of Time 2 Fear and Time 2 Anxiety, controlling for Time 1 Fear and Time 1 Anxiety and the other experimental conditions (i.e., SPN/startle response to no-threat, predictable threat and/or unpredictable threat). In addition, because the time between Time 1 and Time 2 visits varied somewhat across participants, we also controlled for time passed between visits.

We used bootstrapped regression analyses (using 2000 bootstraps) which yielded bootstrapped $p$ values and 95% confidence intervals (47). Bootstrapping is a non-parametric resampling method that can produce more accurate Type 1 error rate and higher statistical power than the single sample parametric method (e.g., testing mediation effects; 48). Beta weights were considered significant when both the bootstrapped $p < 0.05$ and the confidence interval did not include zero (49). Analyses of categorical diagnosis, analyses that included outliers, and tests of condition specificity within each regression are presented in the Supplemental Information. Supplemental analyses demonstrated that startle findings were robust to inclusion of outliers, however, the late SPN findings were not. Analyses were performed using SPSS statistical software version 26.0 (IBM, Armonk, NY).

**Results**

Table 2 presents means and standard deviations for all psychophysiological measures, shown separately for each condition (no-threat, predictable threat, unpredictable threat). Table 3 presents regression results for both Time 1 and Time 2.

**Time 1**

*Electrocortical activity*
Early SPN. There was a significant effect of condition, $F(2, 100) = 4.45, p = .01$, $\eta_p^2 = .08$:
predictable cues elicited larger (more negative) SPNs compared to no-threat cues, $t(51) = 2.64, p = .01$
and compared to unpredictable cues, $t(51) = 3.73, p < .001$. The early SPN to unpredictable and no-threat
cues did not differ significantly, $p = .75$. The effect of group and the interaction between group X
condition failed to reach significance, $ps > .20$. Dimensional analyses showed no significant associations
between the early SPN to no-threat, predictable threat, or unpredictable threat and Time 1 Fear ($ps > .58$)
or Time 1 Anxiety ($ps > .69$).

Late SPN. There was a significant effect of condition, $F(2, 96) = 3.56, p = .03$, $\eta_p^2 = .07$:
predictable cues elicited larger (more negative) SPNs compared to no-threat cues, $t(49) = 2.90, p = .01$,
and compared to unpredictable cues, $t(49) = 2.73, p = .01$. The late SPN to unpredictable and no-threat
cues did not differ, $p = .91$. The effect of group and the interaction between group X condition failed to
reach significance, $ps > .06$.

Dimensional analyses showed that larger late SPNs to predictable threat cues were associated
with increased Time 1 Fear, $B = -.120$, CI: -.216, -.033, $p = .03$ (Figures 1 & 2). The late SPN to no-threat
and unpredictable threat cues was not associated with Time 1 Fear, $ps > .49$. The other regression model,
which aimed to predict Time 1 Anxiety found no association with the SPN to no-threat, predictable threat
or unpredictable threat cues, $ps > .62$.

Startle

There was a significant effect of condition, $F(2, 78) = 24.02, p < .001$, $\eta_p^2 = .38$: predictable
threat (averaged across cue and ISI) elicited larger startle responses compared to no-threat, $t(44) = 5.46, p$
< .001. Additionally, unpredictable threat elicited larger startle responses compared to no-threat, $t(44) =
6.33, p < .001$, and predictable threat, $t(44) = 2.68, p = .01$. No other effects reached significance at the
omnibus level, $ps > .13$. Dimensional analyses showed no significant associations between startle to no-
threat, predictable threat, or unpredictable threat and continuous symptoms of Time 1 Fear ($ps > .38$) or
Prospective Prediction of Fear and Anxiety

Time 1 Anxiety ($ps > .83$).

Time 2

**Electrocortical activity**

*Early SPN.* Larger early SPNs to unpredictable threat cues predicted increased Time 2 Anxiety, $B = -.032$, CI: -.054, -.011, $p = .01$ (Figures 3 & 4). Early SPNs to no-threat and predictable threat cues were not associated with Time 2 Anxiety, $ps > .06$. The other regression model, which aimed to predict Time 2 Fear found no association with the SPN to no-threat, predictable threat or unpredictable threat cues, $ps > .054$.

*Late SPN.* Larger late SPNs to unpredictable threat cues predicted increased Time 2 Anxiety, $B = -.016$, CI: -.030, -.002, $p = .04$ (Figures 3 & 5). Late SPNs to no-threat and predictable threat cues were not associated with Time 2 Anxiety, $ps > .15$. The other regression model, which aimed to predict Time 2 Fear found no association with the SPN to no-threat, predictable threat, or unpredictable threat cues, $ps > .41$.

**Startle**

Larger startle responses to predictable threat predicted increased Time 2 Fear, $B = .056$, CI: .007, .098, $p = .039$ (Figure 6). Startle to no-threat and unpredictable threat was not associated with Time 2 Fear, $ps > .054$. The other regression model, which aimed to predict Time 2 Anxiety found no association with startle to no-threat, predictable threat or unpredictable threat, $ps > .051$.

**Discussion**

Heightened predictable and unpredictable threat reactivity have been hypothesized to underlie transdiagnostic fear and anxiety in internalizing disorders, but these associations had not been tested. Here, we found that individuals with greater fear symptomatology at baseline were characterized by increased anticipation of predictable threat (SPN). Moreover, participants who showed greater defensive
reactivity to predictable threat at baseline (startle) went on to show greater increases in fear symptomatology approximately 1.5 years later. On the other hand, greater anticipation of unpredictable threat (SPN) at baseline uniquely and prospectively predicted increased anxiety. Results suggest mechanistic distinctions between transdiagnostic fear versus anxiety, implicating predictable and unpredictable threat reactivity as risk factors for the development of fear and anxiety psychopathology, respectively.

Prior work failed to find evidence of an association between predictable threat reactivity and diagnosis of a quintessential fear disorder - SP (e.g., 18, 26). All else being equal, dimensional analyses offer more power than categorical analyses (40, 41); moreover, transdiagnostic fear is likely a more cohesive construct than categorical diagnosis of SP. Therefore, dimensional assessment of fear – as in the current study - might more accurately “carve nature at its joints”, and could explain why we observed an association between anticipation of predictable threat and transdiagnostic fear, where prior work had not.

When examining prospective associations, greater defensive reactivity (i.e., startle eye blink) to predictable threat cues predicted larger increases in fear symptoms over time. Proximal threat is associated with sudden increases in autonomic arousal (i.e., fight or flight response), thoughts of immediate danger (e.g., upcoming shock), and escape behaviors (3,4). Startle eye blink may track the neurobiological pre-disposition to respond excessively to proximal threat, putting individuals at risk for greater fear symptomatology over time. As such, our results suggest that increased startle reactivity to certain threat might be a viable target for early intervention or prevention efforts aimed at reducing transdiagnostic fear.

Greater sustained anticipation (SPN) of unpredictable threat predicted larger increases in anxiety symptoms over time. These results are broadly in line with prior work, which had found evidence of cross-sectional associations between anxiety and increased defensive responding to uncertain threat (8,13,18–20,28). Results observed here suggest that heightened anticipation of uncertain threat may be
present before the development and/or worsening of anxiety symptoms. Excessive anticipation of uncertain threat could underlie the development of behaviors such as avoidance, which can lead to increases in anxiety (52). Early intervention or prevention efforts targeting anticipation of uncertain threat could be useful in combatting the development or worsening of transdiagnostic anxiety.

The unique associations we observed involving threat anticipation (SPN) versus defensive responding (startle) indicate that these measures may provide different information about prospective fear versus anxiety psychopathology, with future fear predicted by startle (to predictive threat) and future anxiety predicted by the SPN (to unpredictable threat). The SPN provides a measure of protracted and cognitively-mediated threat anticipation (35). Our prospective results could be interpreted as indicating that sustained, future-oriented attention to unpredictable threat is a risk factor for increased anxiety. This aligns with the notion that anxiety is characterized by heightened assessment of the probability and extent of threatening events (52), and with prior work, which found that for individuals at risk for future anxiety, excessive attention to threat over a period lasting several seconds was uniquely predictive of increased anxiety one year later (53).

On the other hand, startle is a subcortically-mediated measure of reflexive responding to threat (54). Therefore, our finding that increases in Time 2 Fear were predicted by heightened startle response at Time 1 suggests that increased “bottom up” response to fear-provoking stimuli and/or failure to inhibit bottom-up responding might serve as a risk factor for the development of fear-based psychopathology (55,56). Our cross-sectional results suggest, however, that after acquiring fear symptomatology, it might manifest in greater elaborated anticipation of predictable threat in the seconds prior to its delivery, as indicated by the association between the SPN to predictable threat and Time 1 Fear (57). In sum, different neurobiological markers may be best suited to tracking cross-sectional versus prospective risk for fear and anxiety. In the context of the NPU task, ERPs and startle appear to work well-together to provide insight into multiple processes that may uniquely portend risk for or covary with current fear versus anxiety. Nonetheless, more work is needed to increase confidence in the specificity of these findings.
Our results also provide initial support for distinct associations between response to predictable and unpredictable threat and transdiagnostic fear and anxiety. Continued investigation mapping neurobiological response to transdiagnostic fear and anxiety – constructs that may be more homogeneous and more closely tied to mechanism than the categorical disorders – may lead to improved classification and treatment of internalizing disorders. For example, targeting interventions at unpredictable or predictable threat responding might prove more effective than interventions that focus more generally on overall threat reactivity. Along these lines, prior work has shown that two weeks of selective serotonin reuptake inhibitors (SSRIs) modulates startle response to unpredictable threat cues in healthy adults (58), suggesting why SSRIs might be more beneficial for individuals with sustained anxiety versus phasic fear. Given that most patients will manifest with symptoms of both fear and anxiety, accurate mapping of the relative contribution of abnormalities in predictable versus unpredictable threat responding to these dimensions may facilitate personalized treatment protocols. Greater specification of both treatment targets and their intended effects (i.e., more homogeneous dimensions of psychopathology) may help ensure that viable treatments are not discarded because they are targeted at more general operationalizations of threat reactivity and/or effects are measured in terms of heterogeneous diagnostic categories.

Together, the current results provide support at multiple neurobiological levels for the theoretical distinction between fear and anxiety symptomatology, and link these dimensions to exaggerated predictable and unpredictable threat reactivity, respectively. Results support consideration of predictable and unpredictable threat reactivity as potential prognostic indicators of fear and anxiety symptomatology, which could lead to earlier and more targeted clinical care.
Acknowledgements

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Disclosures

K. Wilson and A. MacNamara report no biomedical financial interests or potential conflicts of interest.
References


### Table 1

*Clinical characteristics of participants at Time 1 and Time 2*

<table>
<thead>
<tr>
<th></th>
<th>Time 1</th>
<th>Time 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td><strong>PANAS-X Fear</strong></td>
<td>11.02 (4.26)</td>
<td>10.81 (4.59)</td>
</tr>
<tr>
<td><strong>STAI trait</strong></td>
<td>43.10 (12.76)</td>
<td>45.55 (11.39)</td>
</tr>
<tr>
<td><strong>PSWQ</strong></td>
<td>47.98 (16.24)</td>
<td>49.00 (14.23)</td>
</tr>
<tr>
<td><strong>SPIN</strong></td>
<td>18.98 (17.28)</td>
<td>20.10 (14.80)</td>
</tr>
<tr>
<td><strong># of current diagnoses</strong></td>
<td>2.27 (1.93)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Current Diagnosis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (% )</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal fear</td>
<td>36 (68)</td>
<td>-</td>
</tr>
<tr>
<td>SAD (Generalized)</td>
<td>19 (37)</td>
<td>-</td>
</tr>
<tr>
<td>GAD</td>
<td>11 (21)</td>
<td>-</td>
</tr>
<tr>
<td>MDD/PDD</td>
<td>6 (12)</td>
<td>-</td>
</tr>
<tr>
<td>PTSD</td>
<td>4 (8)</td>
<td>-</td>
</tr>
<tr>
<td>PMDD</td>
<td>3 (6)</td>
<td>-</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>2 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>2 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>1 (2)</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: PANAS-X, Positive and Negative Affect Schedule – Expanded Form; STAI, State Trait Anxiety Inventory; PSWQ, Penn State Worry Questionnaire; SPIN, Social Phobia Inventory; SAD, social anxiety disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; PDD, persistent depressive disorder; PTSD, posttraumatic stress disorder; PMDD, premenstrual dysphoric disorder. Focal fear included specific phobia ($n = 16$) and performance-only social anxiety ($n = 20$).
Table 2

*ERP and startle means (standard deviations) for each condition*

<table>
<thead>
<tr>
<th></th>
<th>No-threat (µV)</th>
<th>Predictable threat (µV)</th>
<th>Unpredictable threat (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early SPN</td>
<td>1.59 (5.93)</td>
<td>-1.63 (6.77)</td>
<td>2.00 (7.27)</td>
</tr>
<tr>
<td>Late SPN</td>
<td>1.87 (8.10)</td>
<td>-2.33 (9.22)</td>
<td>1.65 (11.29)</td>
</tr>
<tr>
<td>Cue Startle</td>
<td>49.86 (51.69)</td>
<td>82.08 (62.78)</td>
<td>89.06 (65.93)</td>
</tr>
<tr>
<td>ISI Startle</td>
<td>53.32 (55.84)</td>
<td>76.78 (71.22)</td>
<td>85.60 (74.85)</td>
</tr>
</tbody>
</table>

Note: ISI, interstimulus interval.
Table 3

*Regression results.*

<table>
<thead>
<tr>
<th></th>
<th>Outcome: Time 1 Fear</th>
<th>Outcome: Time 1 Anxiety</th>
<th>Outcome: Time 2 Fear</th>
<th>Outcome: Time 2 Anxiety</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Early SPN</td>
<td>Late SPN</td>
<td>Startle</td>
<td>Time Passed (years)</td>
</tr>
<tr>
<td>N</td>
<td>0.011</td>
<td>0.040</td>
<td>-0.018</td>
<td>0.004</td>
</tr>
<tr>
<td>P</td>
<td>-0.004</td>
<td>-0.120*</td>
<td>0.009</td>
<td>0.053</td>
</tr>
<tr>
<td>U</td>
<td>-0.028</td>
<td>0.025</td>
<td>0.007</td>
<td>0.003</td>
</tr>
<tr>
<td>Time 1 Anxiety</td>
<td>3.490*</td>
<td>3.278*</td>
<td>3.542*</td>
<td>0.163</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time Passed (years)</td>
</tr>
<tr>
<td></td>
<td>0.070</td>
<td>-0.022</td>
<td>-0.008</td>
<td>-0.009</td>
</tr>
<tr>
<td>P</td>
<td>0.033</td>
<td>0.008</td>
<td>0.056*</td>
<td>0.023</td>
</tr>
<tr>
<td>U</td>
<td>-0.129</td>
<td>-0.035</td>
<td>-0.039</td>
<td>-0.032*</td>
</tr>
<tr>
<td>Time 1 Fear</td>
<td>0.700*</td>
<td>0.698*</td>
<td>0.830*</td>
<td>0.040</td>
</tr>
<tr>
<td>Time 1 Anxiety</td>
<td>0.163</td>
<td>0.315</td>
<td>-0.438</td>
<td>0.044</td>
</tr>
<tr>
<td>Time Passed (years)</td>
<td>0.004</td>
<td>0.003</td>
<td>0.003</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Note: Columns represent separate regression models with analogous ERPs or startle entered as predictors of fear or anxiety. Regression coefficients are presented as bootstrapped, unstandardized beta weights. The SPN is a negative-going ERP component; therefore, negative beta-weights indicate that larger SPNs were associated with increased fear and/or anxiety.

*bootstrapped $p < .05$
Figure Captions

1. Time 1 late SPN to predictable threat and Time 1 Fear. Time 1 grand-averaged waveforms at Fz where the late SPN was scored, shown separately for no-threat (top), predictable threat (middle), and unpredictable threat (bottom), and for participants with high Time 1 Fear and low Time 1 Fear; positive is plotted downwards. Headmaps depict the voltage distributions for predictable threat cues, shown separately for participants with high Time 1 Fear and low Time 1 Fear. Note: high Time 1 Fear (upper third) and low Time 1 Fear (lower third) groups were created for illustrative purposes only, all analyses were continuous.

2. Scatterplot depicting the association (as unstandardized residuals after controlling for covariates) between Time 1 late SPN to predictable threat and Time 1 Fear.

3. Time 1 early and late SPN to unpredictable threat and Time 2 Anxiety. Time 1 grand-averaged waveforms at Fz where the early SPN and late SPN were scored, shown separately for no-threat (top), predictable threat (middle), and unpredictable threat (bottom) for participants with high ΔAnxiety and low ΔAnxiety; positive is plotted downwards. Headmaps depict the voltage distributions for unpredictable threat cues, shown separately for participants with high ΔAnxiety and low ΔAnxiety for both the early and late time windows. Note: ΔAnxiety = Time 2 Anxiety – Time 1 Anxiety; high ΔAnxiety (upper third) and low ΔAnxiety (lower third) groups were created for illustrative purposes only, all analyses were continuous.

4. Scatterplot depicting the association (as unstandardized residuals after controlling for covariates) between Time 1 early SPN to unpredictable threat cues and Time 2 Anxiety.

5. Scatterplot depicting the association (as unstandardized residuals after controlling for covariates) between Time 1 late SPN to unpredictable threat cues and Time 2 Anxiety.

6. Scatterplot depicting the association (as unstandardized residuals after controlling for covariates) between Time 1 startle to predictable threat cues and Time 2 Fear.