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Event-related potentials to threat of predictable and unpredictable shock

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Abstract

Cognitive affective neuroscience tasks that are straightforward to administer, measure key constructs of interest and can be used in different lab settings and with multiple psychophysiological methods can lead to a more complete understanding of effects. The No-Threat, Predictable Threat, Unpredictable Threat (NPU-threat) task assesses constructs of interest to both clinical and basic affective science literatures, is relatively brief to administer and has been used across labs with a number of different measurements (e.g., startle eyeblink, fMRI, corrugator response and subjective ratings). ERPs provide another means of assessing neurobiological reactivity during the NPU-threat task, but to date, such measures have been underutilized. That is, no study has yet evaluated cue-elicited ERPs in the NPU-threat task. Here, cue-elicited ERPs were assessed in 78 participants who completed a version of the NPU-threat task previously shown to reliably moderate startle eyeblink amplitudes. Results showed larger P2 amplitudes for unpredictable versus predictable trials; increased P3s and late positive potentials (LPPs) for threatening versus no-threat trials as well as larger stimulus preceding negativities (SPNs) for threatening versus no-threat trials (driven primarily by predictable threat cues). In line with prior work, we observed enhanced startle eyeblink for threatening versus no-threat trials and for unpredictable compared to predictable threat inter-stimulus intervals. In addition, the probe-elicited P3 was suppressed for predictable and unpredictable compared to no-threat trials. Therefore, cue-elicited ERPs, which can be recorded alongside other measures in the NPU-threat task (e.g., startle) may provide useful indices of temporally distinct stages of predictable and unpredictable threat processing.

1. Introduction

The clinical utility and reproducibility of cognitive affective neuroscience research rests on the development of standardized batteries of tasks that have clear links to constructs of interest, are reliable and can be used to assess reactivity across multiple units of response. The No Threat, Predictable Threat, Unpredictable Threat (NPU-threat) task meets several of these criteria. For example, it assesses phasic fear and sustained anxiety (Schmitz & Grillon, 2012) – key constructs of interest within the Research Domain Criteria (RDoC) and affective science, more broadly. The task shows effects across multiple measures, and exhibits moderate to excellent reliability when used with eyeblink startle (Kaye, Bradford, & Curtin,

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2016a; Lieberman et al., 2017; Shankman et al., 2013) and ERPs elicited in response to acoustic startle probes (Nelson & Hajcak, 2017). The task has also been used with fMRI BOLD (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011) and steady state visual evoked potentials (ssVEPs; Wieser, Reicherts, Juravle, & von Leupoldt, 2016). Although cue-elicited ERPs can also be used to assess threat-processing (either alone, or in conjunction with the above), no published work to-date has documented such measures during the NPU-threat task.

The NPU-threat task consists of three different types of trials. On no-threat trials, participants view cues but no aversive stimulus is delivered. On predictable trials, an aversive stimulus (e.g., mild electric shock) is delivered at the offset of each cue. On unpredictable trials, participants also view cues and an aversive stimulus can be delivered in the middle or end of each cue or during the inter-stimulus interval (ISI). Startle probes are typically delivered during all three cues and during ISIs, with EMG amplitude providing a measure of defensive reactivity in each condition. Startle responses are typically larger for the unpredictable and predictable conditions compared to no-threat condition (Nelson & Hajcak, 2017). In addition, when used with fMRI BOLD, both predictable and unpredictable cues have been shown to increase activation in the amygdala, involved in the detection of proximal threat and fear; unpredictable cues, on the other hand, have been uniquely associated with increased activation in the bed nucleus of the stria terminalis (BNST), which is involved in anxious anticipation (Alvarez et al., 2011). Work using ssVEPs has shown that onset of the unpredictable context results in increased electrocortical response compared to the predictable context, and that predictable cues elicit greater activity than no-threat cues (Wieser et al., 2016). In regards to probe-elicited ERPs, larger (more negative) probe N1s have been observed during anticipation of unpredictable threat. In addition, the probe P3 is suppressed during predictable and unpredictable threat relative to no threat, indicating threat-related attentional capture (Nelson & Hajcak, 2017). Cue-elicited ERPs could provide an alternative measure of anticipatory threat-processing over time and would facilitate comparison with a vast body of literature that has used the same components in other threat-anticipation or processing tasks.

Other affective cue paradigms (e.g., Bublatzky & Schupp, 2012; Grant, Judah, White, & Mills, 2015), suggest that the following ERPs might be evident in the NPU-threat task: the P2, P3, late positive potential (LPP) and stimulus preceding negativity (SPN). The P2 is a positive-going, centrally maximal component that peaks approximately 200 ms after stimulus onset. It measures early selective attention, and is larger for target compared to non-target stimuli, as well as emotional compared to non-emotional pictures (Foti & Hajcak, 2008). In threat-of-shock paradigms, the P2 has been shown to be larger for threat compared to safety cues (Bublatzky & Schupp, 2012; Weymar, Bradley, Hamm, & Lang, 2013); moreover, cues that unpredictably signal an aversive stimulus may further increase the P2 (Huang, Shang, Dai, & Ma, 2017; see also Gole, Schäfer, & Schienle, 2012).

Soon after the P2, the P3 begins around 300 ms post-stimulus onset. The P3 is a positive-going ERP component with a parietally maximal distribution that manifests more occipitally in response to cues (Volosin, Grimm, & Horváth, 2016; Weymar et al., 2013). The P3 provides a measure of stimulus salience (Spencer, Dien, & Donchin, 2001) or attention

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towards stimulus categorization (Kok, 2001). For example, the P3 is larger for targets than standards (Squires, Donchin, Herning, & McCarthy, 1977) and to stimuli that are intrinsically motivating, such as negative compared to neutral pictures ("natural targets"; Hajcak, MacNamara, & Olvet, 2010). The P3 is also larger to cues predicting shock versus no shock (Baas, Kenemans, Böcker, & Verbaten, 2002; Weymar et al., 2013). In addition, the P3 has been shown to be larger for low probability and unexpected events (e.g., auditory stimuli on trials when participants predicted a visual stimulus; Sutton, Braren, Zubin, & John, 1965; Martens, Elmallah, London, & Johnson, 2006); little work, however, has examined the P3 elicited by *cues* that are associated with unpredictability (i.e., that signal the potential onset of an aversive stimulus) but are not themselves unpredictable.

The LPP is a positive-going, centroparietal ERP component that begins around 400 ms and is larger for more salient compared to less salient stimuli, such as emotional compared to neutral stimuli (e.g., Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Dillon, Cooper, Grent-'t-Jong, Woldoff, & LaBar, 2006), as well as stimuli that are denoted as salient in a more top-down manner – e.g., stimuli that are task-relevant/to which participants are asked to respond (targets) compared to those that are not task-relevant (standards; Weinberg, Hilgard, Bartholow, & Hajcak, 2012). In addition, larger occipitally maximal LPPs have been found for threat of shock compared to no shock cues (Bublatzky & Schupp, 2012). Prior work found that negative pictures that had been unpredictabily cued elicited larger LPPs (Nelson & Hajcak, 2017); however, similar to the P3, prior work has not assessed the LPP elicited by a cue that precedes unpredictable shock.

As a measure of affective anticipation, the SPN is a fronto-central, negative going slow-wave. The SPN is usually elicited in the context of S1–S2 paradigms, in which an initial stimulus (S1) reliably predicts a subsequently presented stimulus (S2). The SPN grows in magnitude as S2 approaches, and is believed to measure the allocation of attentional resources towards upcoming stimuli (Böcker & Van Boxtel, 1997). Studies using prolonged S1 durations have shown that the SPN precedes the motivationally salient S2, rather than being evoked by S1 (Regan & Howard, 1995; Rockstroh, Elbert, Canavan, Lutzenberger, & Birbaumer, 1989). In addition, the SPN is larger in anticipation of emotional compared to neutral events – e.g., aversive compared to neutral pictures (Grant et al., 2015) and electric shock (Böcker, Baas, Kenemans, & Verbaten, 2001; Rockstroh et al., 1989; but see Babiloni et al., 2007). The SPN is only evident if S2 can be anticipated (i.e., predicted in some sense), however given this, some degree of uncertainty may potentiate the SPN. For instance, when S2 is temporally predictable, the SPN is largest in anticipation of uncertain/infrequent S2s (Catena et al., 2012). By contrast, when S2 is temporally *un*predictable, the SPN is largest in anticipation of certain S2s (i.e., that reliably onset on each trial; Lin et al., 2014). Therefore, the SPN can track the anticipation of threatening stimuli and is sensitive to stimulus probability but has not yet been examined in the NPU-threat task.

To expand the range of measures known to index effects in the NPU-threat task, we assessed cue-elicited ERPs. We expected to observe the largest P2s to cues unpredictably signaling shock (Huang et al., 2017). We also hypothesized that we would observe larger P3s (Baas et al., 2002; Weymar et al., 2013) and LPPs (Bublatzky & Schupp, 2012) to both predictable and unpredictable compared to no-threat cues. In addition, we thought it likely that we

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would observe an SPN to predictable cues (Böcker et al., 2001; Rockstroh et al., 1989); if an SPN was evident for unpredictable cues, we hypothesized that it would be smaller (i.e., less negative). For comparison with prior work, we also administered startle probes and assessed probe-elicited ERPs and startle magnitude. There are many versions of the NPU-threat task (e.g., a virtual reality variation in which participants enter different locations; Alvarez et al., 2011; the "countdown" version in which the numbers 5, 4, 3, 2 and 1 appear prior to shock delivery; Nelson, Hajcak, & Shankman, 2015). We used a well-documented and previously validated version of the NPU-threat task (Kaye et al., 2016)[1] because this version (using geometric cues) is well-suited to ERP elicitation, to promote consistency and replicability in paradigm use across labs and because this version has been shown to reliably modulate startle EMG.

2. Method

2. 1 Participants

Sample size was determined by our a priori decision to run the study for a single semester, with the total *N* resulting from the number of undergraduates who signed up to complete the study during this time. Participants were 78 undergraduates who completed the experiment for course credit (46 female; age $M = 19.68$, $SD = 1.40$). 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.

Procedure and NPU-threat Task—After giving their consent to participate in the experiment, participants completed a demographics questionnaire and other questionnaires that were not analyzed here. To control for individual differences in shock sensitivity, participants' shock sensitivity tolerance was determined using standard procedures (Bradford, Magruder, Korhumel, & Curtin, 2014). In brief, participants rated a series of gradually increasing shocks, administered to the wrist, using a scale from 0 ("Can't feel shock") to 100 ("Highest you can tolerate"). When participants indicated that the shock level had reached the highest level they could tolerate, no further shocks were administered, and the shock level selected by the participant was used for the NPU-threat task.

Next, participants performed the NPU-threat task while continuous EEG was recorded. The task was adapted from and is explained thoroughly in Kaye and colleagues (Kaye et al., 2016a; Kaye, Bradford, & Curtin, 2016b). Participants viewed centrally presented colored shape "cues" (blue oval, green triangle, red square). Shape cues indicated whether the participant would definitely receive a shock ("Predictable threat" or "P"), possibly receive a shock ("Unpredictable threat" or "U") or would never receive a shock on that trial ("No threat" or "N"). Shock conditions (P, U) were presented in blocks of six trials; each block was presented twice throughout the task. Shock condition blocks were interspersed with 6-trial blocks of the no-threat condition (N) and cue-condition pairings were counterbalanced

[1]The only differences between the NPU-threat task used in the current study and that employed by Kaye and colleagues (2016) were: a) we did not probe participants' knowledge of cue-shock contingencies by inquiring (verbally), "Can you be shocked in the next five seconds?" at various timepoints during the task; b) we used a circle, a square and a triangle (each a different color) as condition cues; Kaye and colleagues used three squares of different colors.

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across participants. As in Kaye and colleagues (Kaye et al., 2016a), there were two condition block orders (PNUNUNP and UNPNPNU) that were counterbalanced across subjects. Shock cues were presented for 5 s with a variable ISI separating the cues (mean 17 s, range 14–20 s). During the cues and ISI, a white fixation cross was presented in the center of the screen. In the predictable condition, a 200-ms shock was administered 200 ms prior to every cue offset. In the unpredictable threat condition, shocks were administered pseudorandomly during cues (at 2s or 4.8s post-cue onset) or during ISIs (at 4, 8 or 12 s post-cue offset). In each predictable and unpredictable threat block, participants received a total of 12 electric shocks. No shocks were delivered in the no-threat condition.

To ensure that both the procedure and differences between the shock conditions were clearly understood by the participants, they were first informed verbally about the cue contingencies. Further, a reminder (e.g., “no shocks,” “shock at end of red square,” “shock at any time”) was displayed at the top of the computer screen for 9 s prior to the beginning of the block and throughout the entire duration of each block (Kaye et al., 2016a). In addition, the experimenter removed the shock electrode from participants’ wrists prior to the start of each no-threat block; the shock electrode was reapplied prior to the beginning of the next block.

Acoustic startle probes were presented binaurally (40 ms, 90 dB white noise with near instantaneous rise time). Three startle probes were presented at the start of each task to allow for stabilization of the startle response (Blumenthal et al., 2005); data from these initial three probes was not analyzed. Startle probes were presented.at 4.5 s post-cue onset on a random subset of eight cues and at 13, 14, or 15 s post-cue offset during four ISIs in both shock conditions (no-threat condition: 12 cues and six ISIs). Startle probes occurred a minimum of 12.5 s after another startle-eliciting event (e.g., shock or startle probe). Serial position of startle probes across the three conditions for both cues and ISIs was balanced within subjects to account for habituation. Two different orders of startle probe serial position were used and were counterbalanced between subjects.

2.2 EEG Recording and Data Reduction

Continuous EEG recordings were collected using an ActiCap and the ActiCHamp amplifier system (Brain Products GmbH, Gilching Germany). Thirty electrode sites were used based on the 10/20 system. The electrooculogram (EOG) was recorded from four facial electrodes: two that were placed approximately 1 cm above and below the right eye, forming a bipolar channel to measure vertical eye movement and blinks and two that were placed approximately 1 cm beyond the outer edges of each eye, forming a bipolar channel to measure horizontal eye movements. The EEG data were digitized at 24-bit resolution and a sampling rate of 1000 Hz.

EEG data was processed offline using Brain Vision Analyzer 2 software (Brain Products GmbH, Gilching Germany). Data were segmented for each trial beginning 200 ms prior to stimulus onset and baseline correction for each trial was performed using the 200 ms prior to cue onset. For cue-elicited ERPs, segments were 5.2 s long (i.e., lasting 5 s beyond cue onset); for probe-elicited ERPs, segments were 500 ms long (i.e., lasting 300 ms beyond probe onset). The signal from each electrode was re-referenced to the average of the left and

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right mastoids (TP9/10) and band-pass filtered with high-pass and low-pass filters of 0.01 and 30 Hz, respectively. Eye blink and ocular corrections used the method developed by Miller, Gratton and Yee (1988). Artifact analysis was used to identify a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100 ms intervals. Trials were also inspected visually for any remaining artifacts, and data from individual channels containing artifacts were rejected on a trial-to-trial basis. There were 5 participants who were excluded from EEG analyses due to messy data, leaving 73 participants for analyses. An additional 1 participant was missing from the cue P2 and cue P3 analyses, and an additional 2 participants were missing for the probe-elicited N1 and 3 participants were missing from the probe-elicited P3 analyses, due to messy data/insufficient trials (< 50%) after artifact rejection.

Based on visual inspection of grand-averaged waveforms and topographic maps, the cue P2 was scored using average amplitudes at electrode Cz between 190–250 ms after cue onset; the P3 was scored by averaging amplitudes at pooling, Pz, PO3 and PO4, between 250–350 ms post-cue onset and the LPP was scored at a pooling of PO3 and PO4, between 350–800 ms. The SPN was scored at Fz during an early (1000–2000 ms post-cue onset) and late (3500–4500 ms post-cue onset) window (Morton, Brown, Watson, El-Deredy, & Jones, 2010). The probe-elicited N1 was scored between 140–190 ms post startle probe, by averaging amplitudes at FC1 and FC2 and the probe-elicited P3 was scored at electrode Cz, between 230–300 ms after startle probe onset. ERP time windows were chosen to avoid shock delivery (which was at 2 s or 4.8 s on unpredictable trials and at 4.8 s on predictable trials) and startle probe delivery (at 4.5 s).

2.3 EMG Recording and Data Reduction

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 (Brain Products GmbH, Gilching Germany). Data were digitized at 24-bit resolution and a sampling rate of 1000 Hz. EMG activity was band-pass filtered between 28 and 499 Hz and segmented using a 250-ms window that began 50 ms prior to startle probe onset. The data was rectified, and was smoothed using a 50 Hz low-pass filter. Startle amplitude was quantified as the peak amplitude occurring between 20ms prior to startle probe onset and 150 ms after startle probe onset relative to the average baseline, defined as the average of activity in the 50 ms preceding probe onset. Each trial was examined manually and blinks were scored as nonresponses if EMG amplitude did not yield a peak that was visually differentiated from baseline activity; nonresponses were scored as 0. Blinks were determined to be missing if there was significant noise, movement artifact or if a spontaneous blink was evident in the baseline period, because such factors can interfere with the probe-elicited startle response (Blumenthal et al., 2005). Non-responders were identified as participants who had fewer than 2 visually discernable startle blinks per condition ($n = 9$) and were excluded from analyses. In addition, 7 subjects' startle data was lost due to technical problems, leaving a total of 62 participants for startle analyses.

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2.4 Data Analyses

A series of one-way repeated measures analyses of variance (ANOVAs) were performed to compare the effects of Condition (no-threat, predictable, unpredictable) on cue-elicited ERPs; a Cue (Cue, ISI) X Condition (no-threat, predictable, unpredictable) repeated measures ANOVA was used to assess effects on startle eyeblink and probe-elicited ERPs. Greenhouse-Geisser corrections were applied as necessary when the assumption of sphericity was violated. Significant effects of Condition were followed up using two orthogonal contrasts: no-threat versus threat (predictable and unpredictable) and predictable versus unpredictable. This approach helped control the false-positive rate and is theoretically meaningful because it evaluates the effect of threat vs no-threat with the first contrast and the effect of (un)predictability with the second contrast. The internal consistency of electrocortical and psychophysiological measures was assessed using even-odd reliability. That is, correlations were assessed between averages created separately for even and odd trials. A minimum of 2 trials were required for each even-odd average. The Spearman Brown formula was used to correct these correlations (Nunnally, 1978). All analyses were performed using SPSS statistical software version 22.0 (IBM, Armonk, NY).

3. Results

The study was not pre-registered. However, all data are open and available on the Open Science Framework (https://osf.io/2k4tj/) and we report all conditions, measures, manipulations, and data exclusions. Table 1 presents means and standard deviations for all dependent variables, shown separately for each condition. Table 2 presents reliability for each measure and condition, and additional reliability results are available in supplementary material.

3.1 Cue-elicited ERPs

3.1.1 P2—Grand-averaged waveforms at electrode Cz where the cue P2 was scored are depicted in Figure 1, as well as headmaps showing the voltage difference between no-threat minus predictable cues and between unpredictable minus predictable cues, from 190–250 ms after cue onset. As is suggested by the figure, a significant effect of Condition, $F(2,142) = 4.34$, $p = .01$, $\eta_p^2 = .06$ revealed that unpredictable cues elicited larger P2s compared to predictable cues, $t(71) = 2.59$, $p = .01$. The P2 elicited in response to threat cues did not differ from no-threat cues, ($p = .37$).

3.1.2. P3—Figure 2 depicts grand-averaged waveforms at the parieto-occipital pooling where the cue P3 was scored, as well as headmaps showing the voltage difference between predictable minus no-threat and unpredictable minus no-threat conditions. Results showed that there was a significant effect of Condition on the cue P3 $F(2,142) = 5.44$, $p = .005$, $\eta_p^2 = .07$ such that amplitudes were larger in the threat compared to no-threat conditions, $t(71) = 3.35$, $p = .001$. No significant differences were found between the predictable and unpredictable conditions, $p = .21$.

3.1.3. LPP—Figure 3 depicts grand-averaged waveforms at the parieto-occipital pooling where the LPP was scored, as well as headmaps showing the voltage difference between

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predictable minus no-threat and unpredictable minus no-threat conditions. As is suggested by the figure, there was a main effect of Condition on the LPP, $F(1.72,123.86) = 8.77$, $p = .001$, $\eta_p^2 = .11$. Follow-up tests showed that the LPP was larger in the threat compared to the no-threat conditions, $t(72) = 5.19$, $p < .001$; there was no significant difference between the LPP elicited by predictable and unpredictable cues ($p = .41$).

3.1.4. SPN—Figure 4 depicts grand-averaged waveforms at electrode Fz, where the SPN was scored, as well as headmaps illustrating the spatial distribution of voltage differences corresponding to predictable minus no-threat conditions. As is suggested by Fig. 4, there was a significant effect of Condition on early, $F(2,144) = 5.77$, $p = .004$, $\eta_p^2 = .07$ and late, $F(2,144) = 3.53$, $p = .04$, $\eta_p^2 = .04$ SPN amplitudes. Follow-up t-tests showed that both early and late SPNs were larger (more negative) in the threat compared to the no-threat conditions, early SPN: $t(72) = 3.15$, $p = .002$ and late SPN: $t(72) = 2.36$, $p = .02$. Differences between the unpredictable and predictable conditions did not reach significance, early SPN, $p = .11$; late SPN, $p = .28$. Nonetheless, because the grand-averaged waveforms strongly suggest that the threat versus no-threat difference might be driven by predictable (rather than unpredictable) trials, we also report here the comparison between predictable versus no-threat and unpredictable versus no-threat trials (using a more stringent threshold of p = .01). Results of these tests indicate that predictable trials elicited a larger SPN than no-threat trials, early SPN: $t(72) = 3.78$, $p < .001$ and late SPN: $t(72) = 2.81$, $p = .006$, whereas unpredictable trials did not, early SPN, $p = .10$; late SPN, $p = .17$[2].

3.2 Probe-elicited ERPs

3.2.1. Probe N1—There was a significant effect of Cue for the Probe N1, such that the N1 was larger (more negative) for cues compared to ISIs, $F(1,70) = 26.34$, $p < .001$, $\eta_p^2 = .27$. The effect of Condition and the interaction between Cue X Condition failed to reach significance, both ps > .12.

3.2.2. Probe P3—Figure 5 depicts grand-averaged waveforms corresponding to electrode Cz, where the probe P3 was scored. There was a significant main effect of Cue, indicating that the P3 was larger for cues compared to ISIs, $F(1,69) = 6.43$, $p = .01$, $\eta_p^2 = .09$. In addition, and as is suggested by the figure, condition significantly modulated the probe P3, $F(2,138) = 11.99$, $p < .001$, $\eta_p^2 = .15$, such that the P3 was suppressed for startle probes presented during threat compared to no-threat cues and ISIs, $t(69) = 4.72$, $p < .001$. There was no significant difference between the probe P3 on predictable compared to unpredictable trials, $p = .69$, and the interaction between Cue X Condition did not reach significance, $p = .17$.

[2]Because the late SPN (3500–4500 ms) on unpredictable trials might have been influenced by shock delivery when it occurred at 2 s, we re-analyzed the late SPN for unpredictable trials, leaving out these two trials. Results were unchanged: there was a significant effect of Condition, $F(2,144) = 3.69$, $p = .03$, $\eta_p^2 = .05$; follow-up t-tests showed that the SPN was larger (more negative) in the threat compared to the no-threat conditions, $t(72) = 2.63$, $p = .01$; the difference between the unpredictable and predictable conditions did not reach significance, $p = .52$. Reliability for the late SPN on U trials also remained low ($r = .09$).

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3.3 Startle eyeblink

Figure 6 depicts means and standard error of the mean for startle eyeblink in each experimental condition and in corresponding ISIs. As is suggested by the figure, there was a significant effect of Condition, $F(1.5, 91.6) = 50.64$, $p < .001$, $\eta_p^2 = .45$ that was qualified by an interaction between Cue X Condition, $F(2,122) = 31.32$, $p < .001$, $\eta_p^2 = .34$. Follow-up tests showed that the effect of Condition was significant for both Cue, $F(1.5, 91.1) = 67.74$, $p < .001$, $\eta_p^2 = .53$ and ISI, $F(1.8, 108.2) = 24.10$, $p < .001$, $\eta_p^2 = .28$ periods. During cues, startle was larger for threat compared to no-threat trials, $t(61) = 9.4$, $p < .001$ but did not differ for predictable and unpredictable trials, $p = .50$; however, during ISIs, startle was larger during both threat compared to no-threat trials, $t(61) = 4.69$, $p < .001$. and for unpredictable compared to predictable trials, $t(61) = 5.31$, $p < .001$.

4. Discussion

In recent years, the NPU-threat task has become an increasingly popular task in basic and clinical affective science. Several measures have been used to assess threat processing in the NPU-threat task, including startle eyeblink, corrugator activity, fMRI blood oxygen-level dependent (BOLD) activity, and ERPs to startle probes and to electric shock itself. Cue-elicited ERPs can also be used to assess threat processing and anticipation, yet these measures had not previously been used in the context of the NPU-threat task. Results showed larger P2s to unpredictable (compared to predictable) cues, whereas the cue P3 and the LPP were larger for threat compared to no-threat cues. The early and late SPN were enhanced for threat compared to no-threat cues, however this was driven mostly by larger SPNs for predictable cues. In line with prior work, startle magnitude was larger for threat compared to no-threat cues and ISIs, as well as for unpredictable compared to predictable ISIs. Although we failed to replicate prior evidence of enhanced N1 amplitudes for startle probes presented during unpredictable threat, the probe-elicited P3 was suppressed for predictable and unpredictable threat compared to no-threat trials, in line with prior findings (Nelson & Hajcak, 2017).

Literature on how uncertainty affects *cue*-elicited ERPs in an affective context is relatively scarce, with most work focusing on how uncertainty affects ERPs to subsequently presented (i.e., predictably or unpredictably *cued*) stimuli (e.g., emotional pictures; Dieterich, Endrass, & Kathmann, 2016). Nonetheless, we were able to identify two studies that assessed cue elicited ERPs in uncertain threat-of-shock paradigms (Huang et al., 2017; Seidel et al., 2015). Though these paradigms shared some characteristics with the NPU-threat task, they also differed in key ways, including fixed cue-condition pairings and a confound between shock uncertainty and shock probability[3] (i.e., unlike in the NPU-threat task, a different number of shocks were administered in the unpredictable versus predictable conditions). Nonetheless, one of these tasks assessed the parietal P2 and found that it was larger for unpredictable compared to predictable threat cues, in line with results observed here (Huang

[3]Other ways in which the Huang and colleagues' (2017) and Seidel and colleagues' (2014) tasks differed from the NPU-threat task are as follows: shocks were *either* always temporally predictable (even in the unpredictable condition; Huang et al., 2017) or always unpredictable (even in the predictable condition; Seidel et al., 2014); shocks were not administered during the ISI; cue-shock contingencies were fixed and did not vary across participants (e.g., an "X" was used for the no-threat condition; a checkmark was used for the predictable condition; and a question mark was used for the unpredictable condition) and trials were not blocked by condition.

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et al., 2017). Additionally, work that used cues to signal the onset of negative and neutral pictures has suggested a tendency for unpredictable and no-threat cues to elicit larger P2s than predictable cues during threat anticipation (Gole et al., 2012). However, Dietrich and colleagues (2001) observed a somewhat different set of results: predictable *and* unpredictable cues that signaled the onset of upcoming aversive pictures elicited larger P2s than cues signaling safety/no aversive picture (supplemental results, Dietrich et al., 2001). Complicating interpretation of these effects, however, cue-condition assignment was not counterbalanced in any of these prior studies, and evidence from one of these studies suggests that the cues themselves may have driven effects (supplemental results, Dietrich et al., 2001). P2 enhancement to unpredictable threat observed here might stem from the increased salience of these cues, or alternatively, because the meaning of these cues may have been less immediately apparent/may have consumed more processing resources. Here, we have chosen to interpret results in terms of P2 enhancement for unpredictable and no-shock compared to predictable cues however, another interpretation would be that the P2 is *suppressed* for predictable cues, perhaps because participants' attention throughout predictable blocks was consumed by the high likelihood of shock/affective arousal. To rectify these explanations, more work will be needed. Overall, these results indicate that the P2 measures an early, temporally distinct stage of uncertainty processing in the NPU-threat task and extend prior research to show that this effect is not dependent on cue-condition pairing or differences in shock frequency/probability.

The P3 has been studied most extensively in "oddball" paradigms, in which target stimuli elicit larger positivities (e.g., Duncan-Johnson & Donchin, 1977; e.g., Squires et al., 1977), yet it is also known to be increased for emotional stimuli (e.g., Lifshitz, 1966; Mini, Palomba, Angrilli, & Bravi, 1996). The LPP is most often investigated in emotional paradigms, however like the P3, it is also sensitive to more top-down modulations of stimulus salience, such as task instructions/target status (e.g., Weinberg et al., 2012). Therefore, the P3 and early LPP share some functional significance. In addition, the P3 and early LPP are similar in terms of their timing and spatial distribution; in fact, the P3 and early LPP might be best characterized as a series of overlapping positivities that begin approximately 200–300 ms after stimulus onset (Foti, Hajcak, & Dien, 2009). Here, we found that both the P3 and the LPP were larger for cues in threat-of-shock conditions, however there was no difference between the P3 or LPP elicited by predictable compared to unpredictable cues. These results are broadly in line with prior work showing that both the P3 and LPP are larger for cues that signal shock (Nelson, Weinberg, Pawluk, Gawlowska, & Proudfit, 2015) as well as cues signaling the onset of upcoming negative pictures (Michalowski, Pané-Farré, Löw, & Hamm, 2015). In the current design, unpredictable cues did not reliably signal shock, as shocks could be delivered either during the cue or ISI period during unpredictable blocks; nonetheless, 1/3 of all cues in the unpredictable condition did predict shock. The results observed here underscore the notion of the LPP as a measure of stimulus salience that does not rely on an emotional visual percept (MacNamara, 2018)[4]. They also suggest that by the time range of the P3/LPP, categorical processing was

[4]Of note, the P3 and the LPP observed here were maximal at parieto-occipital rather than central sites, in line prior work that used neutral cues paired with shock (Baas et al., 2002; Böcker, Baas, Kenemans, & Verbaten, 2004; Nelson, Weinberg, et al., 2015) and with other work that has elicited affective modulation of the LPP in the absence of an emotional visual percept (i.e., LPPs to imagined

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complete, with resulting positivities primarily reflecting post-perceptual processing and the increased salience of predictable and unpredictable compared to no-threat cues (as opposed to enhanced amplitudes for unpredictable compared to predictable cues observed for the P2).

In prior work, larger SPNs were found for threat-of-shock cues, however predictability was either not manipulated (Böcker et al., 2001) or the SPN was scored in atypical time windows and at unconventional sites (Seidel et al., 2015)[5]. The SPN depends on temporal predictability to induce affective anticipation (i.e., the SPN is not observed when stimuli are completely unpredictable). However, in a non-affective context, previous work had suggested that probabilistically unpredictable stimuli might elicit larger SPNs under conditions of temporal predictability (Catena et al., 2012). Here, unpredictable shocks were both probabilistically and temporally unpredictable (i.e., shocks on these trials were not always delivered and when they were, they could onset at either 2 or 4.8 s); therefore, while the SPN was larger for threat compared to no-threat trials, this enhancement appeared to be driven primarily by predictable cues. Although it is tempting to conclude that the SPN might provide a measure of phasic anxiety in the NPU-threat task, another interpretation is that the SPN observed here might reflect an entirely non-affective process, since the predictable cue was the only cue that reliably predicted the onset of another stimulus. Perhaps relatedly, reliability for the SPN was poor, in particular for unpredictable trials and the late SPN on no-threat trials – both of which failed to consistently predict the onset of a salient stimulus. Nonetheless, we note that reliability for the predictable versus no-threat SPN residuals and difference scores was substantially better than the reliability for the raw scores (see supplementary material), and emphasize that recent work has suggested that researchers report the reliability of both types of measures (Infantolino, Luking, Sauder, Curtin, & Hajcak, 2018). When selecting measurement indices of unpredictable threat processing, researchers may wish to take into account their reported reliabilities.

In addition to the ERP results described above and in line with prior work, startle eyeblink was enhanced for threat compared to no-threat cue and ISI periods, and additionally, for unpredictable compared to predictable ISIs. Also replicating prior work (Nelson & Hajcak, 2017), the probe-elicited P3 was suppressed in response to threat compared to no-threat cues. The probe P3 is a measure of attention to the startle stimulus and is reduced when viewing emotional stimuli, presumably because fewer attentional resources are available to process the startle stimulus (Bradley, Codispoti, & Lang, 2006). We did not replicate prior effects showing that the probe-elicited N1 is larger for unpredictable compared to predictable and no-threat cues (Nelson, Hajcak, et al., 2015). However, an examination of mean amplitudes suggests a trend in this direction (Table 1). Though it is difficult to say for certain why this effect did not reach significance, one possibility concerns differences in design between the task used here and that used in prior work. For instance, we followed Kaye and colleagues' (2016) design, in which shocks delivered during unpredictable cues

negative stimuli; MacNamara, 2018; Suess & Abdel Rahman, 2015). Therefore, future work may wish to determine whether internally generated stimulus salience (i.e., in the absence of a stimulus percept) elicits P3s and LPPs with different spatial topographies than externally generated stimulus salience (e.g., negative pictures).

[5]In addition, work by Huang and colleagues (2017) reported that a frontal LPP was larger (more positive) for no-threat ("safe") cues compared to predictable and unpredictable threat cues; however, examination of the waveforms in this study suggests that results might alternatively be interpreted as evidence of a larger SPN to predictable and (to a lesser extent) unpredictable threat cues.

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onset at either 2 or 4.8 seconds; by contrast, in the Nelson and colleagues' (2015) study, shocks in the unpredictable condition could be delivered at any time (whereas in the predictable condition, a visual "countdown" indicated precisely when predictable shocks would be delivered). Therefore, unpredictable trials in the current study may have been relatively more predictable/similar to predictable trials than in prior work, which may have weakened our ability to detect an effect on the probe N1.

In sum, the current study is the first to document cue-elicited ERPs in the context of the NPU-threat task. Results suggests that cue-elicited ERPs may provide useful measures of the temporally distinct stages of unpredictable and predictable threat on stimulus processing and attention. Nonetheless, there may be some constraints inherent in using ERPs to assess threat-anticipation in the NPU-threat task. For example, we used geometric shapes instead of the stimulus countdown version of the NPU-threat task (Nelson, Hajcak, et al., 2015), in part because the former design is better suited to ERP measures of threat-anticipation. However, as a result, shock delivery in the predictable condition may have been somewhat less predictable than in the countdown version of the task. In addition, reliability was lower for cue-elicited ERPs than for startle and probe-elicited ERPs. This may be in part because there were fewer trials per condition than is typical for visual-stimulus ERP research. Therefore, future work may wish to increase the number of trials in an effort to achieve higher levels of reliability for ERPs (Nelson, Hajcak, et al., 2015). Nonetheless, there are trade-offs to increasing the number of trials in the NPU-threat task, including human subject concerns with increasing number of shocks and habituation of startle response to increasing number of probes; as such, the balanced between these competing priorities must be considered in future work. In prior work, ssVEPs have been used to assess brain activity during both context and cue in the NPU-threat task. Because of their superior temporal resolution, ERPs can better assess the distinct stages of predictable and unpredictable threat processing, although ssVEPs may be better-suited to measuring contextual effects on electrocortical response. Startle eyeblink and ERPs to startle probes provide discrete measures of defensive reactivity in the context of predictable and unpredictable threat, but do not directly measure neural response to threat cue or context. Therefore, future work might benefit from using multiple measures – including ssVEPs, cue-elicited ERPs and startle eyeblink – in the same dataset (e.g., Hajcak, MacNamara, Foti, Ferri, & Keil, 2013), in order to best measure predictable and unpredictable threat anticipation in the NPU-threat task.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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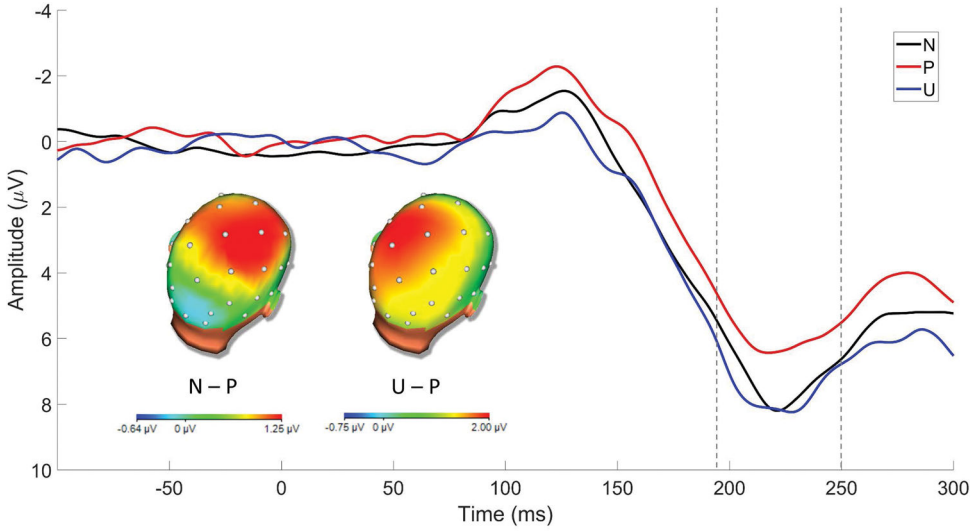

Figure 1.

Grand-averaged waveforms depict amplitudes at electrode Cz and dashed lines indicate the time window in which the cue-elicited P2 was scored. Headmaps illustrate the difference between no-threat minus predictable (left) and unpredictable minus predictable (right) trials, between 190–250 ms after cue onset.

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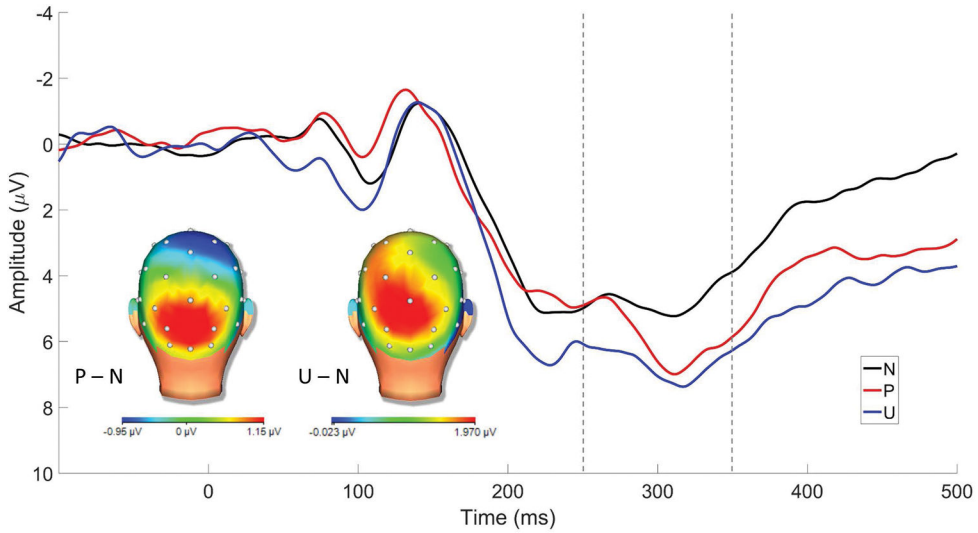

Figure 2.

Grand-averaged waveforms depict amplitudes at a pooling of Pz, PO3 and PO4 and dashed lines indicate the time window in which the cue-elicited P3 was scored. Headmaps illustrate the difference between predictable minus no-threat (left) and unpredictable minus no-threat (right) conditions, between 250–350 ms after cue onset.

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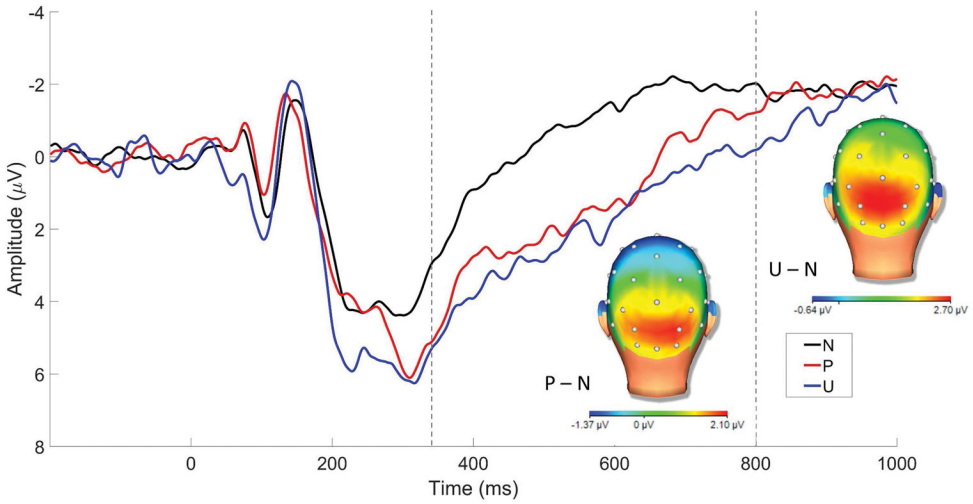

Figure 3.

Grand-averaged waveforms depict amplitudes at a pooling of PO3 and PO4 and dashed lines indicate the time window in which the cue-elicited LPP was scored. Headmaps illustrate the difference between predictable minus no-threat (left) and unpredictable minus no-threat (right) conditions, between 350–1000 ms after cue onset.

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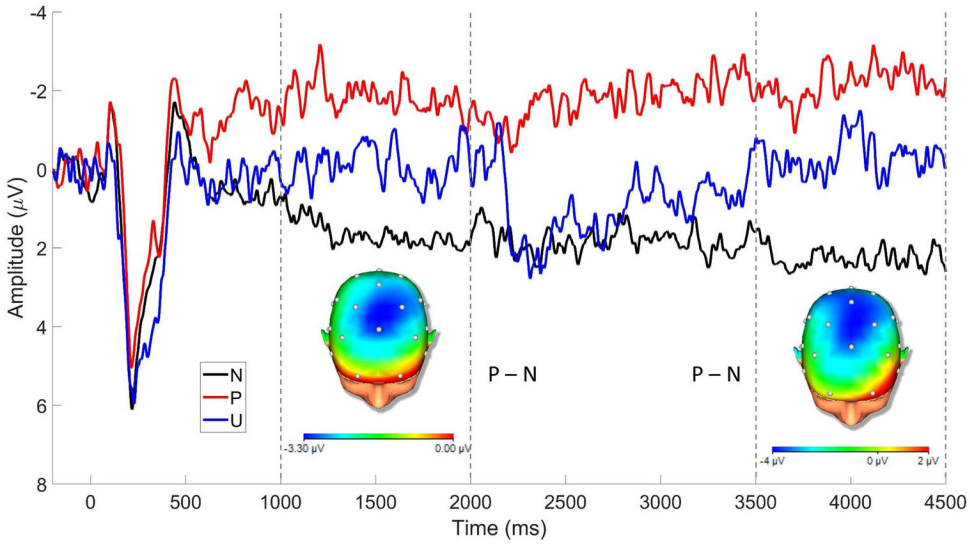

Figure 4.

Grand-averaged waveforms depict amplitudes at electrode Fz and dashed lines indicate the time windows in which the early and late SPN were scored. Headmaps illustrate the difference between predictable minus no-threat conditions, between 1000–2000 ms (left) and 3500–4500 ms (right) after cue onset.

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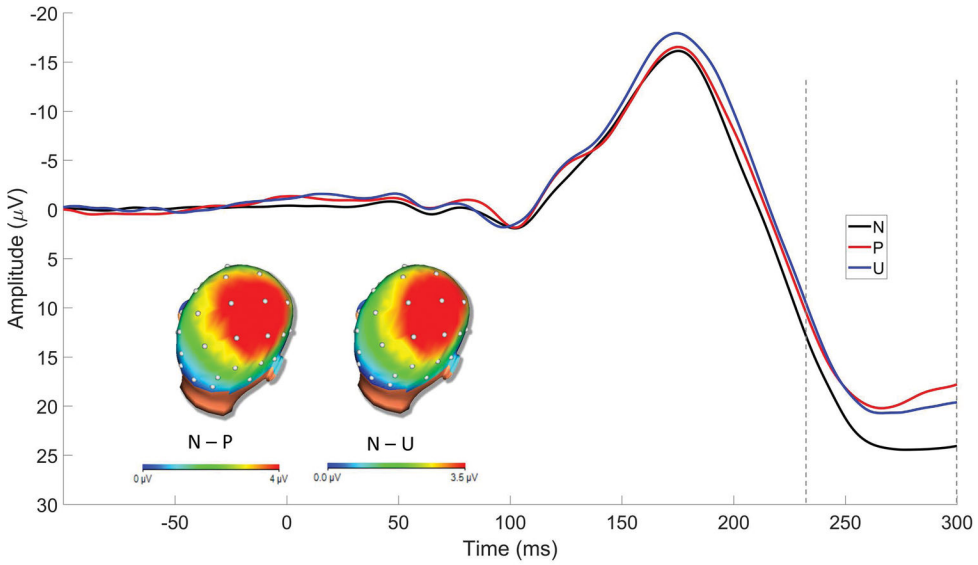

Figure 5.

Grand-averaged waveforms depict amplitudes at electrode Cz and dashed lines indicate the time window in which the probe-elicited P3 (averaged across cue and ISI periods) was scored. Headmaps depict the difference between no-threat minus predictable (left) and no-threat minus unpredictable (right) conditions, between 230–300 ms after startle probe onset.

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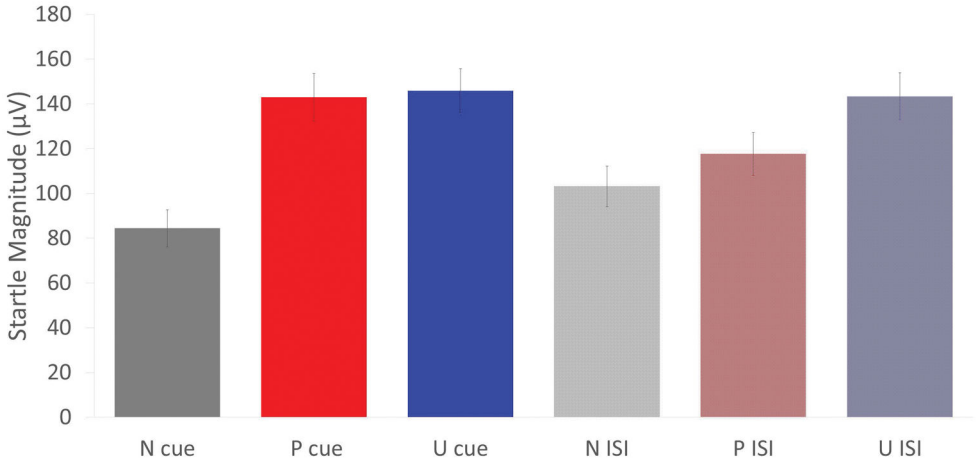

Figure 6.

Bar graphs depicting mean startle magnitude, shown separately for each cue type (left) and for startle probes delivered during ISIs in each block (right). Error bars indicate standard error of the mean.

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Table 1

Mean values (and standard deviations) in each condition, shown separately for cue and ISI periods.

	No-threat Cue (μV)	Predictable Cue (μV)	Unpredictable Cue (μV)
Cue-locked			
P2	7.18 (5.16)	5.84 (6.99)	7.63 (6.14)
P3	4.84 (4.48)	5.93 (5.72)	6.71 (5.69)
LPP	−.82 (3.22)	1.22 (5.09)	1.86 (5.83)
Early SPN	1.64 (4.21)	−1.83 (7.29)	−.10 (8.07)
Late SPN	2.25 (5.63)	−2.18 (12.47)	−.31 (14.66)
Probe-locked			
N1	−14.15 (11.21)	−13.49 (12.72)	−15.16 (14.63)
P3	23.66 (12.83)	18.48 (12.96)	19.59 (14.19)
Startle	84.40 (65.61)	143.08 (83.20)	145.83 (78.68)
	No-threat ISI (μV)	Predictable ISI (μV)	Unpredictable ISI (μV)
N1	−8.55 (10.23)	−8.87 (10.05)	−10.00 (12.22)
P3	20.04 (15.44)	17.38 (16.45)	16.96 (18.63)
Startle	103.24 (71.16)	117.68 (75.60)	143.38 (82.35)

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Table 2

Split-half reliability (95% confidence intervals) for each measure and condition.

	No-threat Cue (*r*)	**Predictable Cue (*r*)**	**Unpredictable Cue (*r*)**
Cue-locked			
P2	.68 (.53–.79)	.63 (.47–.75)	.56 (.38–.70)
P3	.67 (.52–.78)	.78 (.67–.86)	.72 (.59–.82)
LPP	.35 (.13–.54)	.64 (.48–.76)	.60 (.43–.73)
Early SPN	.39 (.18–.57)	.38 (.16–.56)	−.07 (−.30–.16)
Late SPN	−.06 (−.29–.17)	.47 (.27–.63)	.17 (−.06–.39)
Probe-locked			
N1	.91 (.86–.94)	.91 (.86–.94)	.82 (.73–.88)
P3	.90 (.84–.94)	.88 (.81–.92)	.69 (.54–.80)
Startle	.97 (.95–.98)	.93 (.89–.96)	.92 (.87–.95)
	No-threat ISI (*r*)	Predictable ISI (*r*)	Unpredictable ISI (*r*)
N1	.74 (.61–.83)	.70 (.56–.80)	.76 (.64–.84)
P3	.87 (.80–.92)	.82 (.72–.88)	.83 (.74–.89)
Startle	.91 (.85–.94)	.94 (.90–.96)	.90 (.84–.94)