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The interactive effects of different facets of threat uncertainty and cognitive load in shaping fear and anxiety responses

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Abstract

A large body of research indicates that exaggerated response to uncertainty of a future threat is at the core of anxiety and related disorders, underscoring the need for a better understanding of the underlying mechanisms. Although behavioral and neuroimaging studies have suggested a close relationship between uncertainty responses and cognitive control, little is known about what elements of uncertainty are more or less vulnerable to cognitive modulation in shaping aversive responses. Leveraging a novel paradigm, an n-back working memory task embedded within a modified threat-of-shock paradigm, we examined how the influences of different facets of uncertainty (i.e., occurrence and timing) on psychophysiological responses were modulated by cognitive load. Psychophysiological responses were assessed using the acoustic startle reflex. Replicating prior work, the effects of cognitive load and temporal unpredictability of threat on startle responses were evident. The effect of occurrence unpredictability appears to depend on other factors. Under low cognitive load, startle response was potentiated when both the occurrence and the timing of threat were predictable. Under high cognitive load, startle response was significantly reduced, especially when a threat context involves uncertainty in both temporal and probability domains. These observations provide a framework for refining the model of fear and anxiety and for understanding the etiology of psychological disorders characterized by maladaptive uncertainty responses.

KEYWORDS

anxiety, cognitive load, fear, startle response, uncertainty

1 | INTRODUCTION

Fear and anxiety are fundamental dimensions of human emotion that serve adaptive purposes. Fear is defined as a phasic, fight-or-flight response to relatively imminent and certain threat, whereas anxiety is defined as a sustained state of heightened apprehension, arousal, and vigilance to uncertain threat (Barlow, 1991; Davis et al., 2010; Lang et al., 2000; LeDoux & Pine, 2016; Tovote et al., 2015; Wilson & MacNamara, 2022). As such, uncertainty or unpredictability of threat functions as a key determinant differentiating the two. A large body of research indicates that exaggerated response to future threat uncertainty is at the core of anxiety and related disorders (Barlow, 1991; Davies & Craske, 2015; Foa et al., 1992; Grupe & Nitschke, 2013; Mineka & Kihlstrom, 1978; Nelson et al., 2015, 2016; Nelson & Shankman, 2011), underscoring the need for a better understanding of the underlying mechanisms.[1]

To clarify the nature and mechanisms of threat processing in different contexts, theoretical models of anxiety have focused on the degree to which threat processing is influenced by bottom-up processing of emotional stimuli versus top-down cognitive control (Cisler & Koster, 2010; Curtin et al., 2001; Eysenck et al., 2007; Mathews et al., 1997). According to a resource competition account (Desimone & Duncan, 1995; Pessoa et al., 2002), the bottom-up emotion processing and top-down control mechanisms compete for a shared pool of limited processing resources, influencing each other bidirectionally. In line with this proposition, studies have demonstrated that engaging in a cognitively demanding task reduces the disruptive influence of threat-related cues or anxiety due to reliance on a shared pool (Erthal et al., 2005; Van Dillen & Koole, 2009; Vytal et al., 2012). For example, studies have found attenuated startle responses and electrophysiological markers of threat responses under cognitive load manipulations (Dvorak-Bertsch et al., 2007; Hefner & Curtin, 2012; MacNamara et al., 2011; Patel et al., 2016; Van Dillen & Derks, 2012; Vytal et al., 2012). Similarly, neuroimaging studies (Clarke & Johnstone, 2013; Loos et al., 2020; Okon-Singer et al., 2015; Pessoa et al., 2002) demonstrated that amygdala response to a task-irrelevant threat cue is hampered when cognitive control resources are taxed. These findings indicate that the degree to which threat information is processed depends on the availability of cognitive resources, highlighting the necessity to understand specific mechanisms involved in such competition.

Behavioral and neuroimaging studies have suggested a strong overlap between unpredictability and cognitive control, hinting at a potential interaction of the two in shaping fear and anxiety responses (Chin et al., 2016; Monosov, 2020; Mushtaq et al., 2011). Evidence indicates that cognitive control is involved in processing and handling uncertainty in the environment. Studies have found increased activities in the frontocortical brain regions involved in cognitive control (e.g., dorsolateral prefrontal cortex and anterior cingulate cortex) during the processing of ambiguous information, including probability and/or outcome assessment (Hsu et al., 2005; Huettel et al., 2005; Knutson et al., 2005; Shenhav et al., 2016; Wallis & Kennerley, 2011). In addition, Hur et al. (2020) found that cognitive control brain regions were more engaged during the anticipation of temporally uncertain threat ("anxiety") as opposed to certain threat ("fear"), suggesting that processing uncertain threat, compared to certain threat, requires an active involvement of top-down mechanisms. Moreover, the anxiolytic effect of benzodiazepine or alcohol was significantly larger when processing uncertain, compared to certain threat (Baas et al., 2002; Bradford et al., 2017, 2022; Grillon et al., 2006; Hefner et al., 2013; Hefner & Curtin, 2012; Moberg & Curtin, 2009). In all, it is plausible that the top-down and bottom-up resource competition is intensified when the threat context involves uncertainty, as it shares common cognitive capital compared to certain threat.

The NPU threat task (Schmitz & Grillon, 2012), a kind of threat-of-shock task (Chavanne & Robinson, 2021), is one of the most common and well-validated paradigms used to investigate emotional responses to threat uncertainty. The NPU threat task is designed to evoke anticipatory anxiety to the impending threat (e.g., most commonly mild electric shocks) and consists of three conditions: (a) a predictable threat condition ("P") where aversive stimuli (e.g., electric shock) are always signaled by a cue; (b) an unpredictable threat condition ("U") where aversive stimuli are administered with unknown probability at an unpredictable time; and (c) a neutral condition ("N") during which participants are safe from aversive stimuli. This design enables a direct comparison of psychophysiological responses to predictable and unpredictable threat, allowing researchers to examine how uncertainty influences aversive responding. One limitation of the task, however, is that most variations of the NPU have confounded effects of different facets of uncertainty. Uncertainty is not a unitary construct but rather is a multifaceted construct involving various facets of unpredictability, such as likelihood, timing, and intensity of potential events (Bennett et al., 2018; Bradford et al., 2013, 2017; Chin et al., 2016; Cornwell et al., 2008; Davies & Craske, 2015; Dunsmoor et al., 2007; Hefner et al., 2013; Hefner & Curtin, 2012; Hsu et al., 2005; Nelson & Shankman, 2011). But the unpredictable condition of the traditional NPU task (described above) contains uncertainty regarding both occurrence (i.e., likelihood) and timing, making it difficult to tease out the independent and interactive impact of different facets of uncertainty.

Acknowledging the multifaceted nature of uncertain threat and the limitations of the traditional NPU design, a few studies have attempted to investigate how different facets of threat uncertainty may have a differential impact on emotional responses (Bennett et al., 2018;

[1]Semantically, the term *uncertainty* has been used to characterize a broader construct that encompasses not only the ambiguity of a stimulus or environment but also the phenomenological experience associated with it (e.g., anticipatory anxiety), while *unpredictability* narrowly refers to the features of a stimulus that are experimentally manipulated and quantifiable (Grupe & Nitschke, 2013). Based on this distinction, in the current study, we use *unpredictability* to refer to the specific task manipulations, while using *uncertainty* when referring to the broad concept of threat uncertainty which is at the core of fear and anxiety.

Bradford et al., 2013; Davies & Craske, 2015; Monat et al., 1972; Nelson & Shankman, 2011). For instance, Bennett et al. (2018) compared eyeblink startle amplitude during the three conditions: (1) when both the timing and likelihood of threat were certain (i.e., 100% chance of shock), (2) when only the likelihood of threat was uncertain (i.e., 50% chance of shock) while its timing was certain, and (3) when only the timing of threat was uncertain while its likelihood was certain. They found that temporally uncertain threat elicits the greatest startle response overall, suggesting that one facet of threat uncertainty (i.e., temporal uncertainty) may have a more robust effect on aversive responding over another (i.e., occurrence uncertainty). In addition, Davies and Craske (2015) systematically manipulated temporal and occurrence (i.e., likelihood) unpredictability and found that greater startle response was observed when the two facets were either both predictable or unpredictable, compared to when one facet was predictable while the other was unpredictable, suggesting that uncertainty facets yield interactive effects on psychophysiological responses. In all, these studies suggest that different facets of threat uncertainty may have unique and or interactive effects on aversive responding, albeit few studies have systematically been conducted to make definitive conclusions.

Understanding the precise nature of fear and anxiety requires a consideration of the threat contexts entailing different facets of uncertainty. In particular, important gaps remain regarding the degree to which top-down control mechanisms are involved in different threat contexts, which can provide an important insight into the classification, etiology, and the treatment of fear and anxiety-related disorders. In the current study, we used a novel paradigm, an n-back working memory task embedded within a modified threat-of-shock paradigm where occurrence and temporal threat unpredictability were systematically manipulated, to examine how the influence of different facets of uncertainty on startle responses was modulated by varying levels of cognitive load. Based on prior work, we expected to observe significant startle potentiation across all threat conditions (i.e., startle responses in each threat condition greater than those in the neutral condition) and dampened startle potentiation under high cognitive load (i.e., 3-back). In addition, with a broad speculation that the effect of cognitive load would be more evident under unpredictable threat compared to predictable threat, we further explored how different facets of threat unpredictability interact with cognitive load to shape psychophysiological responses. Such investigation can clarify how malleable (rather than fixed) emotional responses are to the influence of different facets of threat uncertainty and inform our understanding of psychological disorders that are linked with maladaptive uncertainty responses.

2 | METHOD

2.1 | Participants

Sixty-three healthy participants were recruited via online advertisements on the student community website of Yonsei University. Participants were South Korean students between 19 and 30 years old and had normal or corrected-to-normal vision. Participants did not have: (a) previous experience with studies involving electric shocks; (b) severe cuts near the eyes or hands where the electrodes were to be attached; (c) cardiopulmonary issues[2]; (d) lifetime history of psychotic or bipolar disorders; and (e) a current diagnosis of mood or anxiety disorders for the past 2 months. Nine participants were excluded due to following reasons: scheduling issue ($n=1$), technical error ($n=2$), nonadherence to task instructions ($n=2$), and startle nonresponders ($n=4$, participants who had zero eyeblink startles for more than 50% of all the experimental conditions). The final sample consisted of 54 participants (75.9% female; mean age = 22.5 years; SD = 2.19 years). Using G*Power (version 3.1.9.7), a post hoc power analysis of within-factor repeated measures ANOVA was conducted with alpha of .05, using the effect size of $f=0.25$ ($N=54$, one group, two measures, correlation of 0.5, nonsphericity correction ε at 1) revealed that the current study had 95% power to detect medium-sized main effects (Cohen's $f=0.25$). A simulation-based post hoc analysis using R package *Superpower* (Lakens & Caldwell, 2021) revealed we had suboptimal power (less than 0.80) to detect medium-sized interactions. All participants provided written informed consent. The procedure was approved by the Institutional Review Board (IRB) of Yonsei University, Seoul, South Korea.

2.2 | Stimuli and apparatus

Electric shocks were generated using an isolated constant voltage/current stimulator (STIMSOLA; BIOPAC Systems) and delivered to the median nerve of participants' nonpreferred hand using two 11 mm Ag/AgCl electrodes. Shock level was calibrated for each individual at the beginning of each session. The initial voltage was set at 0 V; the experimenter increased the level by 2 V until

[2]This criterion was set to prevent possible acute respiratory or cardiac arrest caused by abrupt electric stimulation.

the participant started to feel an electric current. From there, the shock level was increased incrementally by 2.5 V where on each level participants rated the level of discomfort using a 9-point Likert scale (1: "*not at all disturbing*"; 9: "*extremely uncomfortable*; *intolerable*"). Shock calibration was terminated once participants reached a level where the shock feels "*uncomfortable but tolerable*" (mean = 7.6; *SD* = 0.8).

Presentation software® (Neurobehavioral Systems, Inc.) was used to present visual stimuli and acoustic startle probes. Acoustic startle probes were broadband white noise, the most commonly used stimuli for startle elicitation, delivered binaurally through headphones at 103 dB(A) with instantaneous signal increase and drop at 40 ms duration. White noise onset was controlled by a custom-made electronic switch. Startle amplitude in response to the white noise probes were measured using two 10 mm Ag/AgCI electrodes attached to the lower orbital portion of the orbicularis oculi muscle of the left eye.[3] The electromyographic (EMG) signals were recorded using the MP150 data acquisition system with AcqKnowledge 5.0.3 software (Biopac systems).

2.3 | Procedure

Participants visited the lab for two separate sessions that were at least one day apart, in counterbalanced order for task modality (i.e., one verbal n-back session and another spatial n-back session). The spatial n-back task is similar to a verbal n-back task except that the location of an asterisk in one of four corners of a diamond is the target, as opposed to a letter. Both tasks were included based on prior research that suggested a differential impact of threat-of-shock on verbal and spatial working memory (Vytal et al., 2013). 1-back and 3-back tasks were used for low and high cognitive load conditions, respectively. Participants indicated "same" or "different" with a keyboard button press based on the stimulus (verbal: letter, spatial: location) 1-back or 3-back from the current stimulus. N-back stimuli were surrounded by gray rectangular edges with an empty center. Each block was preceded by an instruction screen (indicating the task and threat conditions) and a fixation cross of 1000 ms. N-back stimuli were presented for 500 ms, with an interstimulus interval of 2000 ms (Figure 1B). The number of trials per block for each condition is presented in Table 1.

N-back blocks were embedded within a modified threat-of-shock paradigm of Schmitz and Grillon's (2012) NPU task adapted to systematically manipulate both occurrence unpredictability (i.e., uncertainty about whether a shock will occur) and temporal unpredictability (i.e., uncertainty about the timing of a shock) of threat (Figure 1). The threat conditions in the current paradigm consisted of a 2 (Occurrence: predictable vs. unpredictable) × 2 (Timing: predictable vs. unpredictable) within-subject design along with a neutral ("no shock") condition.

To manipulate occurrence unpredictability of threat, participants were instructed that the probability of shock will differ between runs. In the predictable occurrence condition (O_P), participants were instructed that there is a 100% probability of shock. In the unpredictable occurrence condition (O_U), participants were instructed that there is an unknown ("??%") probability of shock (i.e., it is unclear *whether* shock will be given).[4] To manipulate timing unpredictability of threat, the gray rectangular edges surrounding the n-back task stimuli changed colors (e.g., from gray to red or orange) to serve as cues that indicate the threat timing contingencies. The cues lasted for a duration of 7.5 s, during which a startle probe was presented between 2.5 and 5.0 s into the cue presentation. In the predictable timing condition (T_P), participants were instructed that shocks will be delivered only when cued (i.e., when the gray rectangular edges turn red). That is, when timing was predictable, shocks were always paired with a cue. Specifically, the shocks were delivered at the offset of the cue, occurring approximately 7.5 s into the cue presentation. The cue disappeared immediately after the shock was administered. In the unpredictable timing condition (T_U), participants were instructed that the shock may appear anytime regardless of the cue, which turned orange at times (just to make it parallel to other conditions), without being paired with the shock. In reality, undisclosed to the participants, the shocks during this block were only presented during the interstimulus interval (ISI) to prevent participants from falsely learning that shocks were more frequent during the cue. Shocks were presented at a quasi-randomized schedule during the ISI. Specifically, a shock could appear randomly between the offset of the (orange) cue and the onset of a subsequent cue, with a minimum interval of 2.5 s between the preceding startle probe and the occurrence of a shock. Past investigations have confirmed that the absence of shock

[3]Although we used electrodes that had a larger contact surface diameter than what was recommended for human startle eyeblink studies by Blumenthal et al. (2005), visual inspection of the raw data confirmed clear startle responses with minimal noise artifacts, indicating that the electrode size did not affect data quality.

[4]Participants were never explicitly informed of the minimum/maximum number of shocks. According to informal assessment after completion of the task, no participant reported being cognizant of the unbalanced number of shocks.

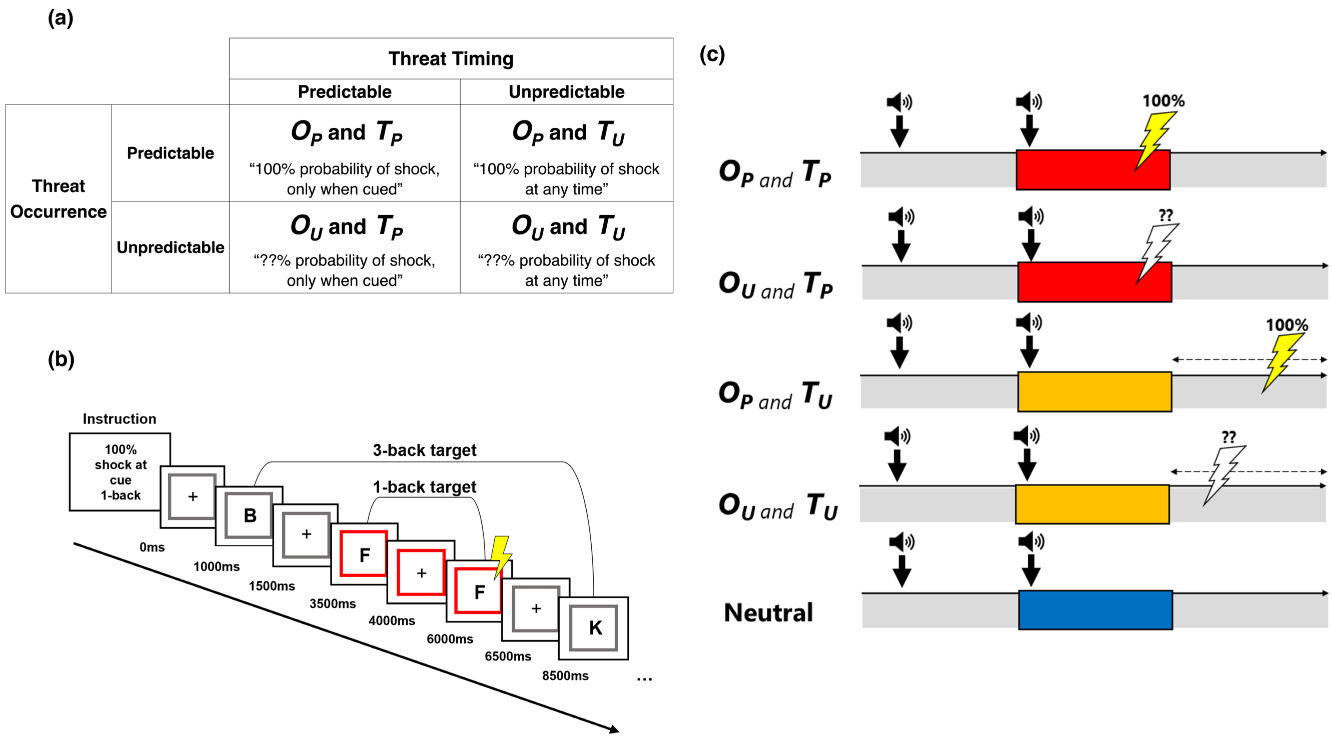

FIGURE 1 (a) Threat manipulation conditions. (b) Sample verbal N-back working memory task block. (c) Schematic of the modified threat-of-shock paradigm.

TABLE 1 Detailed paradigm features.

Condition	Blocks per condition	Trials per block	Cues per block	Shocks per block	Startle probes per block (cue + ISI)
O_P & T_P	4	72	6	6	12 (6 + 6)
O_P & T_U	4	108	6	6	12 (6 + 6)
O_U & T_P	4	84	6	2	12 (6 + 6)
O_U & T_U	4	84	6	2	12 (6 + 6)
Neutral	16	36	3	0	6 (3 + 3)

Note: These features were identical for 1-back and 3-back tasks.

during the cue under the unpredictable timing condition does not result in unintended safety learning (Schmitz & Grillon, 2012).

In combination, there were five conditions: (1) O_P and T_P ("*100% probability of shock and shock occurs only when cued*"), (2) O_U and T_P ("*unknown probability of shock and shock occurs only when cued*"), (3) O_P and T_U ("*100% probability of shock and shock occurs regardless of cue*"), (4) O_U and T_U ("*unknown probability of shock and shock occurs regardless of cue*"), and (5) Neutral ("*no shock*") conditions (Figure 1). Before initiating the actual task, the experimenter made sure that participants understood each threat condition (as well as the neutral condition). Task conditions were displayed at the periphery of the screen during the task blocks to reduce any confusion.

As presented in Table 1, threat conditions included the identical number of cues and startle probes. Meanwhile, some important details of the paradigm are worth noting as the number of n-back trials as well as the number of shocks varied by condition due to some design considerations. Firstly, although both "O_P & T_U" and "O_P & T_P" conditions included the identical number of shocks (i.e., six shocks per block), the placement of shocks was restricted by the manipulation design (i.e., shocks had to be placed during the ISI period while still having sufficient distance from each other in the T_U condition), which resulted in more trials (108 trials) in the "O_P & T_U" condition than the "O_P & T_P" condition (72 trials). Secondly, although the "O_U & T_P" and "O_U & T_U" conditions had equal numbers of trials (84 trials each), the number of shocks had to be adjusted (i.e., 2 shocks per block) in order for the occurrence unpredictability manipulation to work while controlling the number of cues (and the startle probes). For manipulation purposes, the number of shocks to be presented in each condition was not disclosed to participants. To prevent startle responses from being influenced by stimuli adjacent to the startle probes, the following rules were applied. First, the intervals between startle probes were adequately spaced (mean distance = 7000 ms, SD = 7150 ms). Second, a minimum distance of 2500 ms was maintained between a preceding startle probe and a subsequent shock. Third, there was always a minimum interval of 7.5 s between a preceding shock and a subsequent startle probe. In addition, both startle probes and shocks were separated from their closest n-back target onsets by a minimum of 500 ms.

Before initiating each session, participants practiced abbreviated versions of the 1-back and 3-back blocks. For habituation, nine startle probes were delivered before beginning the main task. For each session, there were two experimental runs, each consisting of eight alternating threat and neutral n-back blocks (Table 2). Four additional habituation probes were delivered at the start of each run. Occurrence unpredictability was counterbalanced across runs, and timing unpredictability was counterbalanced within each run, such that, in one run, predictable and unpredictable conditions alternated while having the neutral condition in-between. The order of predictable and unpredictable conditions changed their positions in the other run. The order of n-back task blocks (i.e., 1-back vs. 3-back) was also counterbalanced across runs (e.g., in the first run, four 3-back task blocks were presented after four 1-back task blocks; in the second run, four 1-back task blocks were presented after four 3-back task blocks). All threat blocks included 12 startle probes each, where 6 were presented during the cue and 6 during the ISI. Neutral blocks included six startle probes each: three during the cue and three during the ISI.

2.4 | Data reduction and analyses

2.4.1 | Working memory performance

Trial accuracy and response time (RT) were collected for behavioral measures of the n-back tasks. Trials that immediately preceded or followed shocks or startle probes were excluded from the analysis to minimize potential confounding effects. Trials where participants did not respond within 2500 ms of stimulus onset were considered inaccurate. Accuracy was computed as the percent of correct trials in each condition. For each within-subject condition, trials whose performance was below 3 *SD* of the

TABLE 2 An example block order of a modified NPU session.

		Threat condition			
Run	**Block**	**Timing**	**Occurrence**	**Cognitive load**	**Duration (s)**
1	1	Neutral		Low	91
	2	Predictable	Predictable	Low	181
	3	Neutral		Low	91
	4	Unpredictable	Predictable	Low	271
	5	Neutral		High	91
	6	Unpredictable	Predictable	High	271
	7	Neutral		High	91
	8	Predictable	Predictable	High	181
Rest					5 min
2	1	Neutral		High	91
	2	Unpredictable	Unpredictable	High	211
	3	Neutral		High	91
	4	Predictable	Unpredictable	High	211
	5	Neutral		Low	91
	6	Predictable	Unpredictable	Low	211
	7	Neutral		Low	91
	8	Unpredictable	Unpredictable	Low	211

average performance across subjects were considered outliers and excluded from the analysis.[5] Such outliers were less than 1% of the entire data. Raw accuracy data were used as a dependent variable.

2.4.2 | Startle response

Raw eyeblink startle data were sampled at 1000 Hz; filtered using a 30–300 Hz bandpass kernel; rectified; smoothed with a 20 ms time constant. Peak amplitude of the startle response was measured between 20–120 ms post-probe onset relative to baseline (i.e., 50 ms before pre-probe onset). Trials that had excessive baseline artifacts (e.g., noise; movement artifacts; spontaneous or voluntary blinks before minimal onset latency of an acoustic startle reflex) were removed, which consisted of less than 1% of trials. Trials were deemed "no blink" responses if peak eyeblink data during the 20–120 ms post-probe onset window were not differentiated from baseline EMG activity. Participants who had no significant blinks for more than 50% of all within-subject conditions ($n=4$; startle non-responders) were excluded from statistical analysis. For each participant, the peak eyeblink of each trial was T-transformed (across all within-subject conditions) and averaged per condition. For each within-subject condition, trials whose startle score exceed the upper bound of the interquartile range by a factor of 2.2 (Hoaglin & Iglewicz, 1987) are considered outliers and excluded from the analysis. Such outliers were less than 1% of the entire data. To verify results using transformed potentiation data (Bradford et al., 2015), supplemental analyses using raw (untransformed) potentiation data were performed. The results can be found in the Supplementary Materials.

The main focus of the study was to examine how the impact of different facets of threat unpredictability (i.e., occurrence and timing) on defensive physiological responding (startle responses) was modulated by cognitive load. A preliminary analysis (i.e., a repeated measures ANOVA including Modality as an additional within-subject variable) revealed that there was no effect of n-back task modality (i.e., verbal n-back vs. spatial n-back); therefore, the data were averaged across modality for the main analysis. It is also worth noting that the main analysis focused on startle responses during cued trials only to prevent potential confounding effects when aggregating data from both cued and ISI trials. Specifically, participants were instructed that shocks during the T_P condition only take place during the cued epoch (i.e., during when the rectangular edges turn red), which makes the ISI trials during the T_P condition a neutral (i.e., *no shock*) condition. Thus, in the current report, only the results from cued trials are reported (for descriptive statistics of this data, see Table S2). The dependent variable was computed by subtracting the averaged startle amplitude during the neutral (N) condition from that of each threat condition (i.e., startle potentiation).

[5]When we applied the outlier detection rule proposed by Hoaglin and Iglewicz (1987), all of our key results remained significant.

3 | RESULTS

3.1 | Working memory performance

N-back accuracy data were entered into a 2 (Occurrence: predictable vs. unpredictable) × 2 (Timing: predictable vs. unpredictable) × 2 (Cognitive Load: low vs. high) repeated measures ANOVA. The main effect of Cognitive Load was evident, $F(1,53)=69.37$, $p<.001$, $\eta_p^2=0.57$ [95% CI: 0.38, 0.68], such that accuracy was significantly reduced under high load, confirming successful task manipulation. No main effects emerged for Occurrence, $F(1,53)=0.35$, $p=.57$, $\eta_p^2=0.01$ [95% CI: 0.00, 0.10], or for Timing, $F(1,53)=0.36$, $p=.55$, $\eta_p^2=0.01$ [95% CI: 0.0, 0.11]. Results revealed a significant Occurrence × Timing interaction, $F(1,53)=6.99$, $p=.01$, $\eta_p^2=0.12$ [95% CI: 0.01, 0.28] which was further tempered by a significant Occurrence × Timing × Cognitive Load interaction, $F(1,53)=15.96$, $p<.001$, $\eta_p^2=0.23$ [95% CI: 0.06, 0.40]. The other two-way interactions were not significant (i.e., Occurrence × Load interaction, $F(1,53)=1.63$, $p=.21$, $\eta_p^2=0.03$ [95% CI: 0.00, 0.16]; Timing × Load interaction, $F(1,53)=2.11$, $p=.15$, $\eta_p^2=0.04$ [95% CI: 0.0, 0.18]). Post hoc analyses revealed that the interactive effect of occurrence and timing unpredictability of threat was only evident under high load, $F(1,53)=19.41$, $p<.001$, $\eta_p^2=0.27$ [95% CI: 0.08, 0.44] but not under low load, $F(1,53)=0.97$, $p=.33$, $\eta_p^2=0.02$ [95% CI: 0.00, 0.14] (Figure 2). Under high load, when threat timing was predictable, accuracy did not differ as a function of occurrence unpredictability, $t(53)=1.40$, $p=.17$, $d=0.19$ [95% CI: 0.08, 0.46].[6] However, when threat timing was unpredictable, accuracy was significantly higher when threat occurrence was also unpredictable, compared to when occurrence was predictable, $t(53)=-3.11$, $p<.05$, $d=0.42$ [95% CI: 0.14, 0.70].[7] Main effects for Occurrence, $F(1,53)=0.1.11$, $p=.30$, $\eta_p^2=0.02$. [95% CI: 0.00, 0.14] and Timing, $F(1,53)=1.55$, $p=.22$, $\eta_p^2=0.03$ [95% CI: 0.00, 0.16] were not significant under high load.

[6]These results are consistent when analyzing data during the cued trials only, and when averaging across cued and ISI trials (when used the same approach as for the startle analysis).

[7]This effect remained significant after we corrected for the number of pairwise comparisons conducted (Šidák $\alpha_{Critical}=.025$).

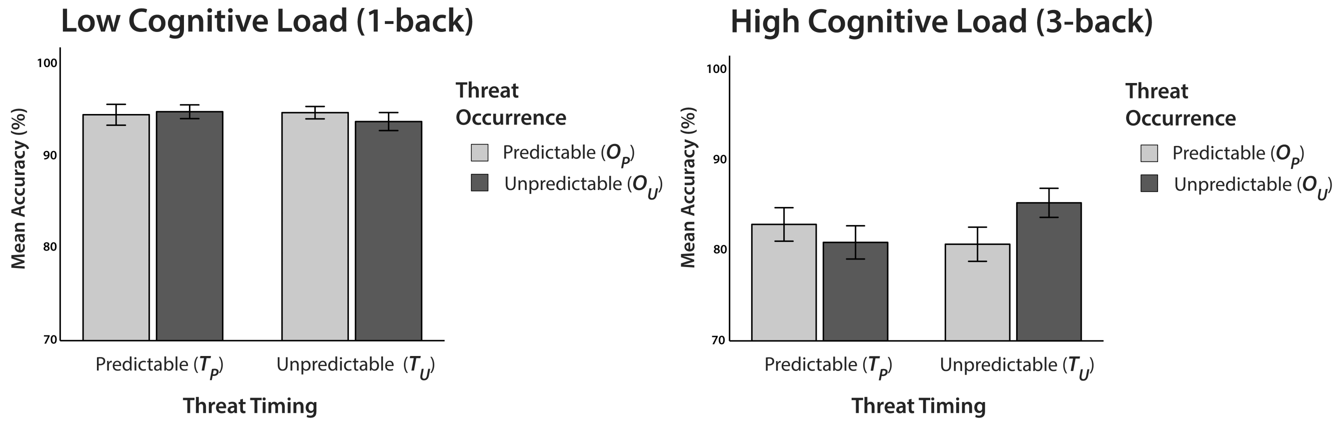

FIGURE 2 Mean performance accuracy as a function of occurrence and timing unpredictability of threat. Bars represent average performance for each threat condition. Error bars represent standard errors.

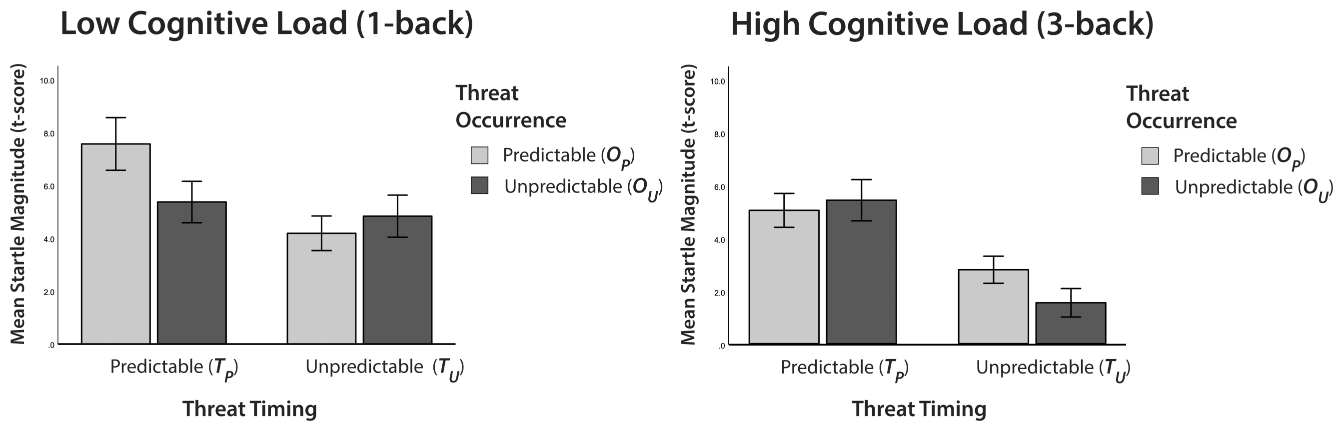

FIGURE 3 Mean startle potentiation scores (T-Scores) as a function of occurrence and timing unpredictability of threat. Error bars represent standard errors.

3.2 | Startle potentiation

One-sample *t*-test results showed that startle potentiation scores (i.e., Threat – Neutral) in all four threat conditions were statistically significantly greater than zero ($ps < .001$), validating threat manipulation. To examine the effect of occurrence and timing unpredictability of threat, and cognitive load on startle responses, startle potentiation scores were entered into a 2 (Occurrence: predictable vs. unpredictable) ×2 (Timing: predictable vs. unpredictable) ×2 (Cognitive Load: low vs. high) repeated measures ANOVA. There were significant main effects of Timing unpredictability of threat, $F(1,53) = 36.69$, $p < .001$, $\eta_p^2 = 0.41$ [95% CI: 0.20, 0.56], and Cognitive Load, $F(1,53) = 15.62$, $p < .001$, $\eta_p^2 = 0.23$ [95% CI: 0.06, 0.40]. That is, startle potentiation was greater in the predictable timing condition (T_P) compared to the unpredictable timing condition (T_U), and it was significantly lower under the high load compared to the low load condition. Neither the main effect for Occurrence nor any of the two-way interactions were significant (i.e., Occurrence, $F(1,53) = 1.06$, $p = .31$, $\eta_p^2 = 0.02$. [95% CI: 0.00, 0.14]; Occurrence × Timing, $F(1,53) = 0.88$, $p = .35$, $\eta_p^2 = 0.02$ [95% CI: 0.00, 0.13]; Occurrence × Load, $F(1,53) = 0.10$, $p = .75$, $\eta_p^2 = 0.00$ [95% CI: 0.00, 0.14]; and Timing × Load, $F(1,53) = 1.71$, $p = .20$, $\eta_p^2 = 0.03$ [95% CI: 0.00, 0.16]). Interestingly though, results revealed a significant three-way interaction of Occurrence × Timing × Cognitive Load, $F(1,53) = 12.47$, $p = .001$, $\eta_p^2 = 0.19$ [95% CI: 0.04, 0.36], such that the pattern of interaction between Occurrence and Timing unpredictability of threat differed as a function of Cognitive Load (Figure 3). Post hoc analyses revealed the following. First, under low load, startle potentiation was evident in all four threat conditions ($ps < .001$). There was a main effect of Timing, $F(1,53) = 10.46$, $p < .01$, $\eta_p^2 = 0.17$ [95% CI: 0.02, 0.34], such that startle potentiation was greater when threat timing was predictable (T_P) compared to unpredictable (T_U). No significant main effect of Occurrence was observed, $F(1,53) = 0.62$, $p = .44$, $\eta_p^2 = 0.01$ [95% CI: 0.00, 0.12]. The Occurrence x Timing interaction was significant under low load, $F(1,53) = 6.57$, $p = .01$, $\eta_p^2 = 0.11$ [95% CI: 0.00, 0.28], such that the startle potentiation was greater when threat occurrence and timing were both predictable ("O_P & T_P") compared to other conditions. Specifically, it was significantly greater when contrasted with the "O_P & T_U" condition, $t(53) = 3.76$, $p < .001$, $d = 0.51$ [95% CI: 0.22, 0.80] or the "O_U & T_U" condition, $t(53) = 2.04$, $p = .05$, $d = 0.28$ [95% CI: 0.00, 0.55] and greater than the "O_U & T_P" condition on a trend level, $t(53) = 1.74$, $p = .09$, $d = 0.24$ [95% CI: −0.04, 0.51].[8] Under high load, though to a lesser degree than the low load, startle potentiation was still evident in all four threat conditions, $ps < .005$. Consistent with low load, there was a main effect of Timing, $F(1,53) = 30.94$, $p < .001$, $\eta_p^2 = 0.37$ [95% CI: 0.17, 0.52], such that startle potentiation was stronger when the threat timing was predictable (T_P) compared to unpredictable (T_U). No significant main effect of Occurrence was observed, $F(1,53) = 0.56$, $p = .46$, $\eta_p^2 = 0.01$ [95% CI: 0.00, 0.12]. The Occurrence × Timing interaction was also significant under high load, $F(1,53) = 5.89$, $p = .02$ $\eta_p^2 = 0.10$ [95% CI: 0.00, 0.26], such that startle potentiation was significantly weaker when threat occurrence and timing were both unpredictable ("O_U & T_U") compared to other conditions, such as the "O_P & T_P" condition, $t(53) = 5.02$, $p < .001$, $d = 0.68$ [95% CI: 0.38, 0.97], the "O_U & T_P" condition, $t(53) = 5.43$, $p < .001$, $d = 0.74$ [95% CI: 0.43, 1.04], and the "O_P & T_U" condition, $t(53) = 2.00$, $p = .05$, $d = 0.27$ [95% CI: 0.01, 0.54].[9]

4 | DISCUSSION

The present study explored how the effects of two major facets of threat uncertainty, namely occurrence and temporal unpredictability of threat, on aversive responses (measured by startle response) are modulated by cognitive load. Startle was significantly potentiated for all threat conditions relative to the neutral condition, validating threat manipulation. The effects of cognitive load (Hefner & Curtin, 2012; MacNamara et al., 2011; Patel et al., 2016; Van Dillen & Derks, 2012; Vytal et al., 2012) and temporal unpredictability of threat (Bennett et al., 2018; Cornwell et al., 2008; Grillon et al., 2004; Nelson & Shankman, 2011) on startle responses were evident. The effect of occurrence unpredictability of threat, however, appears to be more nuanced and dependent on other factors (i.e., temporal unpredictability of threat, cognitive load). The implications of the main findings are discussed below.

As expected, there was a significant main effect of cognitive load, where startle response was reduced under high cognitive load (as compared to low cognitive load). These results replicate prior findings suggesting that cognitively demanding tasks lessen the effect of aversive stimuli on psychophysiological responding (Balderston et al., 2016; Clarke & Johnstone, 2013; Hefner & Curtin, 2012; Loos et al., 2020; MacNamara et al., 2011; Patel et al., 2016; Van Dillen & Derks, 2012; Vytal et al., 2012). These findings have largely been interpreted in terms of the resource competition account, whereby increased cognitive load depletes resources for emotion processing, reducing the effect of task-irrelevant aversive stimuli. In support of this account, neuroimaging studies have shown that, when engaging in a demanding cognitive task in the presence of an emotional distractor, the frontocortical region (e.g, dlPFC, vlPFC, and dACC) activities increase while amygdala activity decreases (Balderston et al., 2017; Clarke & Johnstone, 2013; Loos et al., 2020; Okon-Singer et al., 2015).

The main effect of temporal unpredictability of threat suggests that it may be a facet that has a robust effect on defensive physiological responses compared to other facets of unpredictability. This is consistent with prior findings showing that threat timing elicits the greatest startle amplitude among other facets of threat uncertainty (Bennett et al., 2018). It is worth noting that in the current study, higher startle response was observed in the predictable timing condition (as compared to unpredictable) during the cued period (on which our analysis focused), whereas greater anxiogenic effect of temporally unpredictable threat compared to temporally predictable threat was observed during the uncued (ISI) period (see Supplementary Materials). These results are consistent with prior findings using traditional NPU studies (Cornwell et al., 2008; Gorka et al., 2017; Grillon et al., 2004; Nelson & Hajcak, 2017) in which heightened startle responses were observed during both the *sustained aversive state* (i.e., during the uncued period of the temporally unpredictable condition) and the *phasic aversive state* (i.e., during the cued period of the temporally predictable condition), respectively (Schmitz & Grillon, 2012). Nonetheless, the main effect of threat timing in the current study consistently supports the robustness of threat timing over other facets of threat uncertainty, suggesting that processing temporal uncertainty is somewhat independent of top-down control processes. In support of this, the phasic response to temporally certain threat is most known to be mediated by activation of the central amygdala, particularly its medial sector (CeM), which suggests an automatic defensive response is at play in the face of impending, acute threat (Blanchard et al., 1993; Davis et al., 2010; Perusini & Fanselow, 2015).

[8]The *t*-test result comparing the "O_P & T_P" and "O_P & T_U" condition remained significant after we corrected for the number of pairwise comparisons conducted (Šidák $\alpha_{Critical} = .017$).

[9]The *t*-test results comparing the "O_U & T_U" condition with the "O_P & T_P" or "O_U & T_P" condition remained significant, after we corrected for the number of pairwise comparisons conducted (Šidák $\alpha_{Critical} = .017$).

Occurrence unpredictability functioned very differently from timing unpredictability. Its effect was dependent on other factors, namely temporal unpredictability and cognitive load. During low cognitive load, while significant startle potentiation was observed for all threat conditions, the greatest startle potentiation was observed when both the occurrence and the timing of threat were predictable. This pattern replicates Davies and Craske's (2015) findings, such that greater startle responses were observed when both the occurrence and timing of threat were predictable (compared to conditions in which only one of the facets was predictable). It seems that, when there are sufficient cognitive resources (e.g., task-free, or during 1-back task), occurrence certainty adds propulsion to defensive physiology, especially when there is impending, temporally certain threat. It is possible that a threatening context that has little to no ambiguity (i.e., occurrence and timing certainty) elicits adaptive behavior involving threat-focused narrowing of attention (Cornwell et al., 2008).

A different pattern emerged during high cognitive load, however. We found that startle response was significantly reduced under high load, especially when the threat context involved uncertainty in both temporal and probability domains. It is possible that when a threat context involves uncertainty in multiple dimensions, its complexity facilitates a more active appraisal of its ambiguous characteristics, consuming more processing resources. In fact, a sustained state involving distributed attention, vigilance, and ongoing risk assessment to navigate complex uncertainty situations closely resembles a state of anxious apprehension, or worry, which is a hallmark cognitive feature of anxiety (Barlow, 1991; Berenbaum et al., 2018; Borkovec et al., 1998; Heller et al., 1997; Hirsch & Mathews, 2012). Studies have suggested that engaging in worrisome thoughts demands working memory resources (Hayes et al., 2008; Leigh & Hirsch, 2011; Sari et al., 2017; Stefanopoulou et al., 2014; Stout et al., 2015; Toh & Vasey, 2017). In addition, induced worry resulted in dampened physiological emotional responses (Llera & Newman, 2010; Ottaviani et al., 2014; Rutherford et al., 2020), suggesting that worry prevents processing of negative emotions. Taken together, it is possible that, similar to how worry consumes working memory resources, the combination of occurrence and temporal unpredictability functions as an additional load in mind, especially when cognitive resources are sparse, making the given threat context more vulnerable to resource competition which in turn results in dampened aversive responding.

It is also possible that additional engagement of top-down control mechanisms is facilitated when coping with complex threat contexts under high load. This account is supported by our behavioral results which demonstrated enhanced 3-back performance when threat occurrence and timing were both unpredictable, compared to when only one facet of threat (i.e., threat timing) was unpredictable. In fact, there are behavioral and neural evidence supporting this account. Vytal and colleagues (2016) reported facilitated task performance in healthy participants during threat under high WM load, suggesting that participants exhibit cognitive benefits from engaging in more difficult tasks under threat. Also, Clarke and Johnstone (2013) found increased frontocortical brain (e.g., ACC and vlPFC) and decreased bilateral amygdala activities, as well as highest pupil dilation (an index of cognitive effort/top-down regulatory mechanism), when performing a cognitively demanding task under threat. The authors argued that the reduction in amygdala activity cannot be due to simply bypassing threat processing alone, but an additional cognitive control mechanism (evidenced by increased frontocortical neural activity and pupil dilation) was at play. Our findings expand this line of work by suggesting that this mechanism can be even more facilitated under threat conditions involving complex layers of uncertainty.

Developing a deeper understanding of the interplay of different facets of uncertainty and cognitive control is a matter of theoretical as well as practical importance. Since the time of Freud (1920), the dichotomy between fear and anxiety as responses to certain versus uncertain threat, respectively, has been a key feature of neuropsychiatric models of emotion (Davis et al., 2010; LeDoux & Pine, 2016; Mobbs, 2018). However, the present findings indirectly support the emerging perspective that fear and anxiety fall on a continuous dimension of defensive physiological reactions to threat (Lang et al., 2016). Specifically, the current findings suggest that a more sophisticated consideration of the nature of threat contexts, including relevant cognitive mechanisms, is required to define and classify fear and anxiety. In addition, the current findings suggest that the effectiveness of cognitive control in adapting to threatening contexts may depend on the specific nature of the threat context, especially the associated type and degree of threat uncertainties. For example, a temporally predictable threat may primarily involve a wired, automatic response, leaving little room for cognitive control to intervene. On the other hand, responses to a more complex uncertainty context, especially involving occurrence uncertainty, are likely to be more malleable to cognitive modulation. Studies have reported that working memory training improves emotion regulation and associated psychophysiological indices (e.g., increased heart rate variability), highlighting cognitive training as an augmented intervention strategy (Schweizer et al., 2013; Xiu et al., 2016, 2018). The current study expands this line of work by suggesting that the effectiveness of working memory training may vary depending on the specific nature of threat contexts involving different types of uncertainty.

Although the present study sheds light on the mechanisms underlying uncertainty responses (e.g., fear/anxiety), there are several limitations to the current study. First, the effects of other dimensions of uncertainty (e.g., intensity, imminence) need to be investigated to understand how they may have unique or combined effects with the two major facets of uncertainty investigated in the current study. Second, the current study specifically focused on startle responses during the cued period to avoid any confounding effects. The present findings await replication with a different experimental design and analytic strategy. In addition, by design, we cannot completely rule out a possibility that the imbalanced number of shocks between the occurrence unpredictable versus predictable conditions would have resulted in a confound in the current results (e.g., participants' awareness of the number of shocks given in each condition). Moreover, the current study had insufficient power to detect interaction effects from multiple tests conducted. Considering these caveats, the present findings await replication with a different experimental design and analytic strategy, and a larger sample size. Third, although startle is an excellent index for an ongoing defensive physiological response, emotion (e.g., fear/anxiety) is a multifaceted response, involving subjective feelings, expressive behaviors, and other physiological responses. In fact, studies found that responses from different emotion measures do not necessarily converge (Davies & Craske, 2015; Kuppens, 2019; Mauss & Robinson, 2009). Understanding the full complexity of human emotion would thus require cross-validation across multiple levels and units of measurement. Fourth, future investigation is needed to investigate individual differences (e.g., trait anxiety and executive functions) in emotional responses in the context of different facets of uncertainty and cognitive load. Finally, research with clinical populations is required to explicate how the interactive effects of different facets of uncertainty and cognitive control contribute to the onset and maintenance of fear and anxiety-related disorders.

In summary, the present study demonstrates that facets of threat uncertainty and cognitive load dynamically interact to shape psychophysiological responses to threat. These observations lay the groundwork for determining the etiology of and developing more effective interventions for psychological disorders characterized by maladaptive uncertainty responses.

AUTHOR CONTRIBUTIONS

Deachul Seo: Conceptualization; data curation; formal analysis; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Nicholas L. Balderston:** Data curation; methodology; software. **Howard Berenbaum:** Writing – original draft; writing – review and editing. **Juyoen Hur:** Conceptualization; funding acquisition; methodology; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest with respect to the authorship or publication of this article.

DATA AVAILABILITY STATEMENT

Data are available at the Open Science Framework website: https://osf.io/jn47b/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Data S1: Supporting Information

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