Received: 22 March 2022 | Revised: 6 September 2022 | Accepted: 5 October 2022

DOI: 10.1111/psyp.14208

PSYCHOPHYSIOLOGY SPR WILEY

ORIGINAL ARTICLE

The effect of inherently threatening contexts on visuocortical engagement to conditioned threat

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Abstract

Fear and anxiety are crucial for adaptive responding in life-threatening situations. Whereas fear is a phasic response to an acute threat accompanied by selective attention, anxiety is characterized by a sustained feeling of apprehension and hypervigilance during situations of potential threat. In the current literature, fear and anxiety are usually considered mutually exclusive, with partially separated neural underpinnings. However, there is accumulating evidence that challenges this distinction between fear and anxiety, and simultaneous activation of fear and anxiety networks has been reported. Therefore, the current study experimentally tested potential interactions between fear and anxiety. Fifty-two healthy participants completed a differential fear conditioning paradigm followed by a test phase in which the conditioned stimuli were presented in front of threatening or neutral contextual images. To capture defense system activation, we recorded subjective (threat, US-expectancy), physiological (skin conductance, heart rate) and visuocortical (steady-state visual evoked potentials) responses to the conditioned stimuli as a function of contextual threat. Results demonstrated successful fear conditioning in all measures. In addition, threat and US-expectancy ratings, cardiac deceleration, and visuocortical activity were enhanced for fear cues presented in threatening compared with neutral contexts. These results are in line with an additive or interactive rather than an exclusive model of fear and anxiety, indicating facilitated defensive behavior to imminent danger in situations of potential threat.

KEYWORDS

anxiety, EEG, emotion, fear, heart rate, ssVEP

1 | INTRODUCTION

Adapting defensive behavior to ever-changing environments is a fundamental function for survival. A disruption of these functions lies at the heart of many mental disorders, especially anxiety disorders (Mineka & Oehlberg, 2008). Defensive mechanisms are usually finely tuned to the demands of a threatening situation, which can be arranged along a threat-imminence-continuum (Blanchard et al., 1993; Blanchard & Blanchard, 1989;

Fanselow, 2018). Entering an area where an organism has already encountered a threat in the past, but the actual threat has not yet been identified (pre-encounter stage) is usually associated with risk-assessment behavior, cardiac defensive mobilization, and hypervigilance. Once a threat is detected (post-encounter stage), the organism is preparing for an imminent fight-or-flight response accompanied by freezing behavior, fear bradycardia, and selective attention to the source of threat (Lang et al., 2000). In this framework, fear and anxiety are usually considered separate and mutually exclusive emotional states; however, different ideas exist how fear and anxiety map onto the different stages of the threat-imminence model. Most commonly, anxiety has been associated with potentially threatening situations during the pre-encounter phase, whereas the detection of an acute threat during the post-encounter phase elicits feelings of fear (Fanselow, 2018; Hamm, 2020; Lang et al., 2000). In contrast, the post-encounter phase has also been linked to anticipatory anxiety and only the circa-strike phase prompts fear (Mobbs, 2018; Mobbs et al., 2009). Accordingly, the lack of agreement about the boundaries between anxiety and fear impedes the study of defensive behavior. Various methods exist to investigate the different stages of the threat-imminence-continuum, i.e., fear and anxiety responses, in the laboratory. Aspects of the acute threat of the post-encounter stage are usually modeled with fear conditioning paradigms or brief presentations of aversive pictures (Bradley et al., 2001; Davis et al., 2010). In contrast, potentially threatening situations paralleling aspects of the uncertain and diffuse danger of the pre-encounter stage can be induced with prolonged presentations of inherently threatening pictures, threat-anticipation tasks, or context conditioning paradigms, during which aversive events occur at unpredictable timepoints (Andreatta, Glotzbach-Schoon, et al., 2015; Davis et al., 2010; Grillon et al., 2004). However, clear boundaries between paradigms that investigate acute and potential threat remain often elusive. For example, classical fear conditioning paradigms primarily elicit acute threat when reinforcement rates are high or when intervals between signaling cues and aversive events are short, while threat becomes more uncertain at lower reinforcement rates and longer intervals (Herrmann et al., 2016; Lonsdorf & Richter, 2017). Furthermore, Baas et al. (2008) could show that participants who failed to learn the association between a signaling cue and an aversive event tend to display a sustained aversive state throughout the duration of the threatening context, demonstrating the importance of individual differences in paradigms inducing acute and potential threat. To investigate the differences between fear and anxiety more rigorously, researchers commonly employ explicit manipulations of threat predictability: the so-called NPU-threat task investigates defensive responding during no threat (N), predictable threat (P), and unpredictable threat (U) conditions (Schmitz & Grillon, 2012). Each condition is indicated by a different context (e.g., different geometric symbols or verbal instructions on the screen) and contains several short presentations of centrally presented cues. However, these cues predict the presentation of aversive events only in the predictable threat condition, whereas in the unpredictable threat condition aversive events are presented independently of the central cues. Accordingly, the induction of fear and anxiety is strictly restricted to the conditions, with the central cue in the predictable threat condition inducing fear, while the whole context in the unpredictable condition induces anxiety. Measuring startle responses as an index of somato-visceral defensive mobilization, studies showed unanimous evidence for fear-potentiated startle to predictable threat cues and anxiety-potentiated startle during unpredictable threat contexts (Gorka et al., 2017; Grillon et al., 2006, 2008, 2009). In earlier work using and adapted version of the NPU-threat task, we recorded steady-state visual evoked potentials (ssVEPs) to capture electrocortical indices of selective attention and hypervigilance during fear and anxiety (Kastner-Dorn et al., 2018; Stegmann et al., 2019; Wieser, Reicherts, et al., 2016). The ssVEP is an oscillatory response to one or more periodically, e.g., luminance-modulated visual stimuli, and can be extracted from the EEG (Norcia et al., 2015). The frequency of the oscillatory response matches the driving frequency so that it can be reliably separated from background noise. Heightened ssVEP amplitudes to threatening stimuli represent increased visuocortical activation, reflecting enhanced sensory defense engagement (Miskovic & Keil, 2012). Furthermore, ssVEPs can be used to independently quantify visuocortical processing of two or more visual stimuli presented at the same time, if they flicker at different frequencies (Wieser & Keil, 2014; Wieser, Miskovic, & Keil, 2016). In our earlier studies using the NPU-threat task, context and central cues were presented at different flicker frequencies to disentangle context- and cue-related visuocortical responses by means of frequency tagging. Consistent with the concept of threat-imminence, we found stronger ssVEP amplitudes in response to the central cues in the predictable threat condition, and stronger ssVEP amplitudes evoked by the flickering contexts during the unpredictable threat relative to the neutral condition, suggesting that visuocortical processing is characterized by hypervigilance during the unpredictable threat condition, while predictable threat prompts selective attention (Kastner-Dorn et al., 2018; Stegmann et al., 2019; Wieser, Reicherts, et al., 2016). This makes ssVEPs a valuable tool to study sensory processes during fear and anxiety (Wieser, Miskovic, & Keil, 2016).

Studies capturing neural activation during acute and potential threat (Alvarez et al., 2011) indicated the involvement of partially separate neural networks during fear and anxiety, which is in close agreement with results from animal studies (Davis et al., 2010; Tovote et al., 2015). These results suggest a neural fear network with the central amygdala as the central node activated by acute threat, whereas the neural anxiety network centered around the bed nucleus of the stria terminalis (BNST) shows sustained activation during potential threat. Otherwise, the two neural networks are very similar regarding input and output regions (Davis et al., 2010; Tovote et al., 2015). Importantly, pharmacological and lesion studies in rodents revealed blunted fear but not anxiety responses when pathways of the fear network were blocked and vice versa, suggesting a double-dissociation between the central amygdala and BNST for processing acute and potential threat (Davis et al., 2010).

On the other side, there is accumulating evidence that is incompatible with a double-dissociation, and, consequently, with the notion that fear and anxiety are mutually exclusive. For example, recent human neuroimaging studies showed sustained amygdala activity during aversive context conditioning (potential threat; Andreatta, Glotzbach-Schoon, et al., 2015), whereas threat proximity (acute threat) during a dynamic threat-of-shock paradigm (Meyer et al., 2019) and a cue conditioning task (Klumpers et al., 2015) prompted BNST but no amygdala activation (note, however, that a reinforcement rate of only 33% was used). Even more compelling, results by Brinkmann et al. (2018) revealed simultaneous activation of the amygdala and the BNST during brief presentations of threatening pictures. Taken together, these findings challenge the strict segregation of the neural networks underlying acute and potential threat processing (Fox & Shackman, 2019), and it has been questioned whether fear and anxiety are distinct (see Daniel-Watanabe & Fletcher, 2021 for a review).

Another explanation for these conflicting findings is that fear and anxiety are indeed distinct but not mutually exclusive emotional states. From this perspective, an organism can be in a state of fear and anxiety simultaneously, and these states would even interact at the defense response level. However, there is a lack of studies examining possible interactions between acute and potential threat processing. Initial evidence can be extracted from a study by Somerville et al. (2013), who used a mixed-threat paradigm, in which they briefly presented neutral or threatening pictures (acute threat) either during a predictable context or during an unpredictable context (potential threat). They found enhanced transient amygdala activity to threatening compared with neutral pictures, whereas unpredictable versus predictable contexts increased sustained activity in the BNST. Most importantly, interaction analysis demonstrated potentiated amygdala responses to threatening pictures in the unpredictable compared with predictable contexts for higher levels of individual trait anxiety. Crucially, this potentiation was not evident for neutral pictures. In addition, rating analysis revealed heightened aversiveness for threatening compared with neutral pictures in the unpredictable context, suggesting that potential threat (anxiety) facilitates acute threat processing (fear).

Overall, these results suggest that fear and anxiety can occur simultaneously instead of both states being mutually exclusive. At a mechanistic level, three different models are plausible for the interplay between fear and anxiety. The results of Somerville et al. (2013) are well in line with an interactive model of fear and anxiety, which predicts that anxiety contexts specifically potentiate fear responses. An interactive model would be reflected in stronger defensive responses to fear cues but not to safety cues in the anxiety compared with the neutral context. These assumptions were tested in a study by Grillon and Charney (2011). The authors presented neutral and fearful faces during alternating blocks of threat-of-shock or safe contexts. Consistent with predictions of an interactive model of fear and anxiety, startle responses were selectively potentiated to fearful faces in the threatening but not the safe context. In a similar study, Bublatzky et al. (2013) presented pleasant, neutral, and unpleasant pictures during threat-of-shock or safe contexts to examine the effect of anticipatory anxiety on startle responses as a function of affective picture valence. In contrast to the results of Grillon and Charney (2011), the authors found increasing startle modulation with increasing picture unpleasantness, while pictures presented in threatening contexts generally elicited stronger startle responses than those presented in safe contexts. These results are more consistent with an additive model of fear and anxiety, which predicts that defensive responses to both cues are elevated in the anxiety compared with the neutral context, whereas the differentiation between fear and safety cues is similar in both context conditions. Finally, the exclusive model between fear and anxiety would be characterized by equally strong defensive responses to fear cues in the anxiety and neutral context. However, due to the lack of suitable paradigms, further evidence for an additive or interactive model of fear and anxiety remains elusive. Even in the NPU-threat task potential (U) and acute (P) threat are strictly separated by condition, obscuring potential interactions. On the other hand, cue-in-context conditioning studies suggest that contextual factors can modulate responding to conditioned fear cues (Andreatta & Pauli, 2021), by demonstrating stronger fear responses during a threatening compared with a safe context.

However, in these studies, fear cues only predict aversive events if encountered in the threatening, but not in the safe context (Andreatta et al., 2020; Baas & Heitland, 2015; de Voogd et al., 2020). Thus, there is no independent induction of fear and anxiety that would be necessary to study their interaction. Therefore, our primary goal was to implement a novel cue in context conditioning paradigm to directly study potential interactions between fear and anxiety. In particular, we tested the hypothesis that acute defensive responses as captured by visuocortical, psychophysiological (HR, SCR), and subjective indices (threat, US-expectancy ratings) are enhanced for stimuli presented during potential threatening compared with neutral contexts. We specifically compared predictions made by an additive versus an interactive model regarding potential mechanisms underlying the interplay of fear and anxiety. More precisely, a mutually exclusive model of fear and anxiety is characterized by stronger defensive responses to fear compared with safety cues, which is independent of the context in which the cues are presented. In contrast, an additive model also predicts stronger defensive responses to fear relative to safety cues, but responses are generally enhanced in threatening compared with neutral contexts. In addition, an interactive model predicts enhanced responses specifically to the fear but not to the safety cues, and thus stronger differential responding, in the threatening compared with neutral contexts (also see Figure 4).

2 | METHOD

2.1 | Subjects

A total of 52 individuals (age: $M = 22.7$, $SD = 3.6$; 41 female) recruited through a local platform completed the experiment. Participants were required to be older than 18 years old, have normal or corrected-to-normal vision, no past or present psychiatric diagnosis (self-report), and no family history of epilepsy (self-report). The sample size of $n = 50$ participants was derived from a power simulation for a 2×2 repeated measures design (see https://osf.io/p3ntc). Parallel to previous threat conditioning studies, we assumed medium effect sizes for the main effects of cue ($d = .33$) and context ($d = .30$) on ssVEP amplitudes. For simulating repeated measures data, a standard deviation of $SD = 1.4$ and a correlation between measures of $rho = 0.80$ were estimated by aggregating our previous data. A simulation of 5000 tests detects significant main effects of cue and context in at least 80% of the simulated tests for $n = 50$ participants and an alpha level of 5%. Prior to participation, written informed consent was obtained from each participant. The study was approved by the ethics review board of the University of Würzburg. All participants were paid 15€ or received course credit for participation.

2.2 | Stimuli and apparatus

Conditioned stimuli (CS) consisted of circular black-and-white sinusoidal grating stimuli (10 Hz spatial frequency) filtered with a Gaussian-envelope (i.e., Gabor-patch) with maximum contrast of 100% at center (Stegmann et al., 2021). Orientations of 30° and −30° relative to the vertical axis were selected as threat (CS+) and safety (CS−) cues for each participant. The assignment of orientation to CS+/CS− was counterbalanced between participants. The CSs were presented on a gray background at the center of a 17-inch monitor (resolution = 1280 × 1024 pixel) in a flickering mode at a frequency of 7.5 Hz to elicit ssVEPs. From a viewing distance of 80 cm the grating stimuli spanned visual angles of 7.20° horizontally and vertically.

Five threatening (CTX_t) and five neutral pictures (CTX_n) from the IAPS (Lang et al., 2008) were selected as context stimuli according to their normative ratings of valence and arousal. The picture categories contained an equal number of social and animal content (catalog numbers of the IAPS pictures used in this study are as follows: threatening, 3015, 3064, 9181, 9185, 9854; neutral, 1350, 1670, 2026, 2036, 2235) and were converted to grayscale, with luminance matched to the gray background. The background pictures were presented without flickering for 105 s, spanning visual angles of 14.18° horizontally and 10.05° vertically.

The US consisted of a 50 ms electrical pulse train (2 ms pulse width), which were delivered by a constant current stimulator (Digitimer DS7A, Digitmer Ltd., Welwyn Garden City, UK) to the left lower arm through surface bar electrodes consisting of two gold-plated stainless-steel disks of 9 mm diameter and 30 mm spacing. US intensities were adjusted to the individual pain threshold, using a staircase-procedure consisting of two ascending and descending series of electrical stimuli to achieve a perceived US unpleasantness of 6 on a scale from 0 = "not painful at all" to 10 = "very painful" (for a similar protocol, see Andreatta et al., 2010). After calibration, participants were asked to rate the US unpleasantness of the final intensity again, resulting in a mean US unpleasantness of $6.63 \pm .77$ for a mean US intensity of 2.03 ± 1.76 mA ($M \pm SD$).

2.3 | Design and procedure

After obtaining written informed consent and completing the questionnaires, sensors for recording the

electroencephalogram (EEG), electrocardiogram (ECG), and electrodermal activity (EDA) were applied to the participants, who were seated in a noise-reduced, darkened room ca. 80 cm distant to the screen. The main experiment consisted of an initial fear acquisition and subsequent test phase (Figure 1). During acquisition, 40 trials of CS (20 CS+ and 20 CS−) were presented for 5 s in 7.5 Hz flicker-mode to induce steady-state, visual-evoked potentials. The US co-terminated with the CS+ in 75% of the trials and subjects were not informed of any specific relation among the CSs and the US. Trials were pseudo-randomized so that no more than two identical CSs could occur consecutively. CS presentations were separated by an 8–9 s intertrial interval (ITI) consisting of a white fixation cross in the center of the screen. After acquisition, subjects were asked to rate perceived threat ("How threatening do you perceive this stimulus?"; from 0 = not threatening to 100 = very threatening) and US expectancy ("What is the likelihood that the currently presented stimulus is followed by an electrical stimulus?"; from 0% = not likely to 100% = very likely) for each CS via electronical visual analog scales. The test phase consisted of five blocks of threatening (CTX_t) and five blocks of neutral (CTX_n) contexts. However, each background picture was presented only once. During each block, 8 CS were presented using the same timing and reinforcement rate as during acquisition, resulting in 20 CS+ and 20 CS− per context condition. Consequently, each block lasted for ca. 105 s. Context-dependent threat and US expectancy ratings of the CS were obtained after each block while background pictures remained on screen. At the end of the experiment, subjects rated the valence (ranging from 1 - "very pleasant" to 9 - "very unpleasant") and arousal (ranging from 1 – "very calm" to 9 – "very arousing") of the background pictures using a computer-based version of the Self-Assessment Manikin Scale (Bradley & Lang, 1994) to ensure that they perceived the threatening or neutral picture as such. Results confirmed higher unpleasantness (threat vs. neutral: 8.01 vs. 4.08, $t(51) = 21.14$, $p < .001$, $d = 2.93$, $CI_{95} = [2.30; 3.56]$) and arousal (threat vs. neutral: 6.06 vs. 2.06, $t(51) = 16.83$, $p < .001$, $d = 2.33$, $CI_{95} = [1.80; 2.86]$) for threatening compared with neutral pictures.

2.4 | Physiological data processing

2.4.1 | EDA

Electrodermal activity was recorded using two Ag/AgCl electrodes filled with isotonic (0.5% NaCl) electrolyte medium placed on the thenar and hypothenar eminences of the left palmar surface. The signal was recorded with a V-Amp amplifier and Vision Recorder Software (BrainProducts Inc., Munich, Germany), using a sampling rate of 1000 Hz and an online notch-filter at 50 Hz. Analysis was then performed using Vision Analyzer 2.0 Software (BrainProducts Inc., Munich, Germany). Trough and peak values were automatically detected by an algorithm as implemented in the Vision Analyzer 2.0 software, using an onset latency (trough detection) window of 1000 ms to

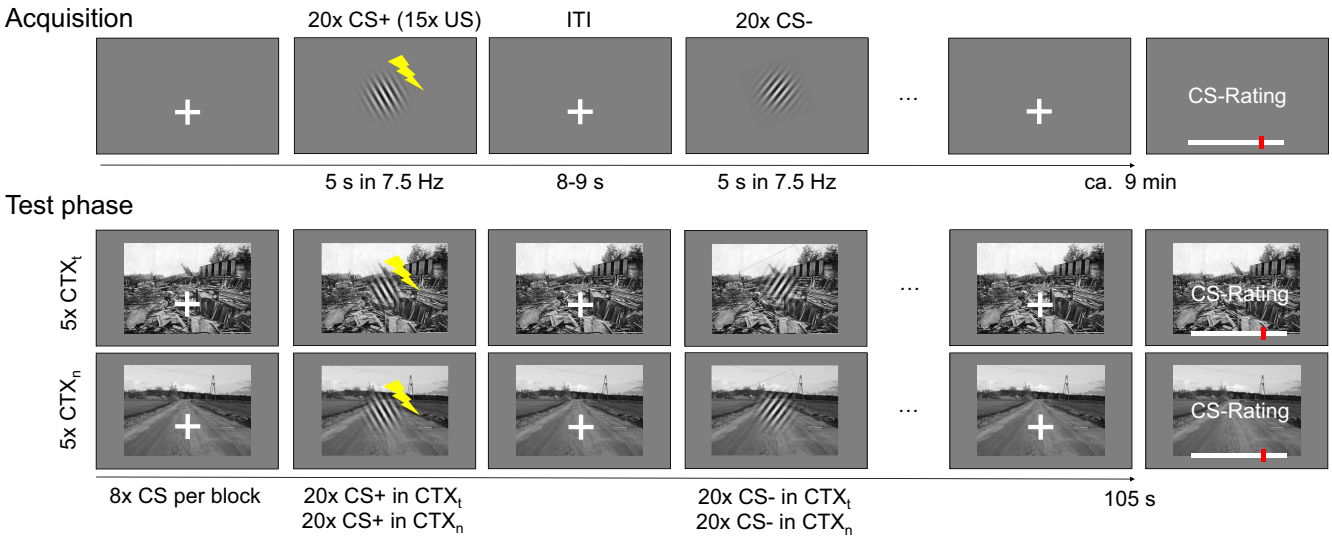

FIGURE 1 Experimental design. During acquisition, 20 CS+ and 20 CS− were randomly presented for 5 s in 7.5 Hz flicker-mode, followed by CS-rating trials. The US consisted of a 50 ms presentation of an electrical stimulus co-terminating with the CS+ in 75% of the trials. The assignment of orientation to CS+/CS− was counterbalanced between participants. The test phase consisted of five blocks of threatening (CTX_t) and neutral (CTX_n) contexts, respectively. During each block, 8 CS were presented, resulting in 20 CS+ and 20 CS− per context condition. Context-dependent ratings of the CS were obtained after each block while background pictures remained on screen. The images depicted in this figure are examples and differ from the images used in the original experiment.

4000 ms and a peak detection window of 2000 to 5000 ms after stimulus onset (Boucsein et al., 2012). All trough and peak values were then manually checked for correctness. Amplitudes of skin conductance response were defined as the difference between the peak and trough value. If multiple SCRs occurred within the analysis window, only the first response was scored. Skin conductance responses smaller than 0.02 μS were scored as zero responses. In total, eight participants did not show a single detectable skin conductance response and were consequently excluded from SCR analysis, resulting in $n = 44$ participants for SCR analysis. For the remaining participants, non-zero SCRs could be observed in 17.7% of the trials during acquisition and in 13.3% of the trials during the test phase. All SCRs were square-root-transformed to account for eventual skewedness of the underlying data.

2.4.2 | ECG

The electrocardiogram was recorded with a sampling rate of 1000 Hz from three adhesive Ag/AgCl electrodes, placed underneath the right clavicle, as well as the left and right costal arch. Processing of the heart rate was performed using the Vision Analyzer 2.0 Software (Brain Products Inc., Munich, Germany). R-waves were detected from the ECG recordings using a semi-automatic method. After visual inspection, R-R-intervals were converted to HR (in beats per minute, bpm) and then averaged across conditions. Heart rate was analyzed with baseline correction, by subtracting a baseline of 1000 ms before stimulus onset. For quantifying CS-evoked fear bradycardia, mean heart rate (changes) between 4 and 6 s after CS onset was extracted similar to other fear conditioning studies (Hamm et al., 1993; Sperl et al., 2021). Due to loss of sensor contact, one subject had to be excluded from the analysis, resulting in $n = 51$ participants for ECG analysis.

2.5 | EEG recording and analysis

The EEG was continuously recorded via 129 electrodes using an Electrical Geodesics (EGI, Eugene, OR, USA) high-density EEG System referenced to Cz, with a sampling rate of 500 Hz and online bandpass filtered with 0.1 and 100 Hz and a 50 Hz notch filter. Impedances were kept below 50 kΩ as recommended for the Electrical Geodesics high-impedance amplifiers. Epochs of 600 ms pre-stimulus and 4500 ms post-stimulus onset were extracted using the software EMEGS (Electro Magnetic Encephalography) for Matlab (Peyk et al., 2011). The last 500 ms of the cue presentation were discarded to exclude potential effects of the co-terminating US presentations. Data were then filtered with a 40 Hz low-pass filter (45 dB/octave, 23rd-order Butterworth). In a next step, we used the SCADS procedure (Junghofer et al., 2000) for artifact handling. Trials with artifacts were identified based on the distribution of statistical parameters (absolute value, standard deviation, and maximum of the differences) of the trials and sensors. Contaminated sensors were replaced by statistically weighted, spherical spline interpolated values. However, trials were rejected when more than 20 out of 129 sensors were contaminated. Artifact-free trials were then averaged separately for each subject and experimental condition. Three subjects had to be excluded because of excessive artifacts resulting in empty cells, leaving $n = 49$ participants for ssVEP analysis. To reduce topographical variability between subjects, we calculated the current source densities (CSD) of the time-averaged data, using the CSD algorithm described by Junghöfer et al. (1997). The CSD approach relies on the spatial Laplacian (the second spatial derivative) of the scalp potential to estimate the potential distribution at the cortical surface and has been used in previous fear conditioning studies (McTeague et al., 2015; Stegmann et al., 2020). The CSD time series values were then transformed into the frequency domain using a Fast Fourier Transformation on a time interval between 1000 and 4500 ms after stimulus onset. The first 1000 ms after stimulus onset were omitted to reduce the impact of initial non-stationary components of the ssVEP on the power spectrum (Miskovic & Keil, 2013; Wieser & Keil, 2014). In a next step, we extracted the spectral power for the driving frequency of 7.5 Hz. For statistical analysis, the ssVEP activity was pooled across sensor Oz and 12 neighboring electrodes (EGI sensors 66, 67, 70, 71, 72, 74, 75, 76, 77, 81, 82, 83, 84; Wieser et al., 2014; Wieser & Keil, 2014).

2.6 | Statistical analysis

Mean differences in ssVEP amplitudes, physiological responses, as well as threat and US-expectancy ratings were analyzed using repeated-measures ANOVAs with the within-subject factor Cue (2 levels: CS+, CS−) and Context (2 levels: CTX_t vs. CTX_n). Cue differences during acquisition and differences between context onsets during the test phase were tested with Student's *t*-tests. All analyses were conducted in the R software environment (version 4.0.2.; R Development Core Team, 2021), using the *afex*-package for ANOVAs (Singmann et al., 2020; version 0.28–0). Confidence intervals (95%) for Cohen's *d* and partial eta-squared (η_p^2) were calculated with the MBESS package (Kelley, 2020; version 4.8.0).

To directly compare the exclusive, additive, and interactive model of fear and anxiety, we used Bayesian

linear model analysis (Stegmann et al., 2020). To this end, we specified weight vectors for each model, which were entered into a linear regression as predictors (see Figure 4). The exclusive model was defined as an effect of cue without any modifications of context (weights: 2, 1, 2, 1, for CS+ in CTX_t, CS− in CTX_t, CS+ in CTX_n, CS− in CTX_n). For the additive model, the contrast weights reflect stronger responses to both CS in the threatening context compared with the neutral context in addition to the effect of cue (weights: 3, 2, 2, 1, for CS+ in CTX_t, CS− in CTX_t, CS+ in CTX_n, CS− in CTX_n). Moreover, the interactive model expresses that the potentiation effect of the threatening context is even stronger for the fear-associated CS than for the neutral CS (weights: 4, 2, 2, 1, for CS+ in CTX_t, CS− in CTX_t, CS+ in CTX_n, CS− in CTX_n). In each model, subjects were entered as random intercepts to the model. Bayes factors (BFs) were then calculated for each predictor model by comparison with the "random intercept only" model (null model, 0). Direct evidence for the exclusive, additive, and interactive models over the other models can then be obtained by dividing the respective Bayes factors. Interpretation of Bayes factors follows guidelines developed by Jeffreys (1961) and adjusted by Lee and Wagenmakers (2014). Bayesian analyses were conducted using the package "BayesFactor" (version 0.9.12–4.2) and default JZS-priors (Rouder et al., 2012).

3 | RESULTS

3.1 | Acquisition

During acquisition, the CS+ elicited stronger ssVEP amplitudes, $t(48) = 2.73$, $p = .009$, $d = 0.39$, $CI_{95} = [.10; .68]$, higher SCRs, $t(43) = 4.13$, $p < .001$, $d = .62$, $CI_{95} = [.30; .94]$, and was perceived as more threatening, $t(51) = 10.29$, $p < .001$, $d = 1.43$, $CI_{95} = [1.04; 1.81]$, as well as more associated with the US, $t(51) = 12.86$, $p < .001$, $d = 1.78$, $CI_{95} = [1.34; 2.22]$, than the CS−, confirming successful fear conditioning (see. Figure 2). However, there was no significant difference regarding heart rate responses, $t(50) = 0.99$, $p = .326$, $d = 0.14$, $CI_{95} = [-.14; .41]$.

3.2 | Test phase

3.2.1 | Steady-state visually evoked potentials

The *Cue* × *Context* ANOVA for ssVEP amplitudes revealed a significant main effect of Cue, $F(1, 48) = 4.68$, $p = .035$, $\eta_p^2 = .09$, $CI_{95} = [.00; .26]$, while the main effect of Context, $F(1, 48) = 3.16$, $p = .082$, $\eta_p^2 = .06$, $CI_{95} = [.00; .22]$, and the Cue × Context interaction, $F(1, 48) = 2.07$, $p = .157$, $\eta_p^2 = .04$, $CI_{95} = [.00; .19]$ did not reach significance (see Figure 3). Since it was our main hypothesis, we

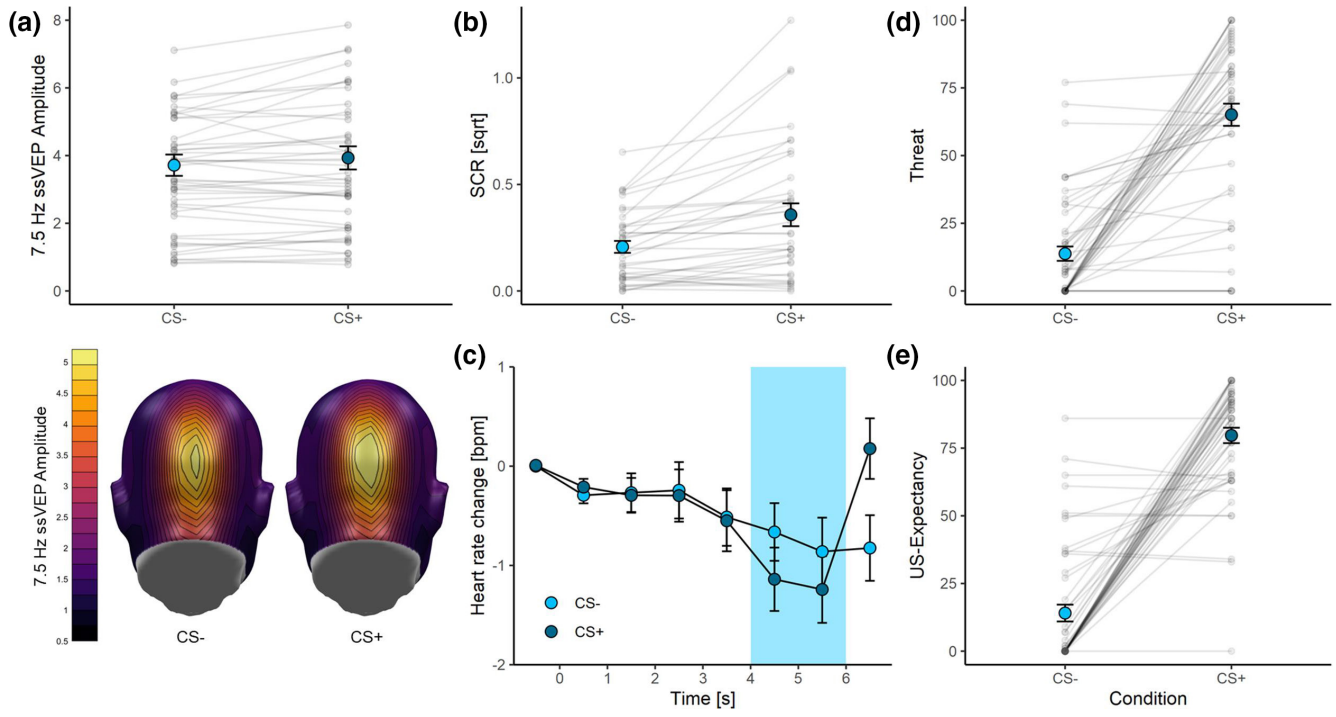

FIGURE 2 Mean 7.5 Hz power and their scalp topographies of the ssVEP (a), skin conductance responses (b), as well as heart rate responses (c) ± *SEM* to the conditioned stimuli during the acquisition phase. Note, that heart rate responses were statistically analyzed within 4 and 6 s after cue onset (blue area). Mean US-expectancy (d), and threat (e) ratings ± *SEM* of the conditioned stimuli after acquisition.

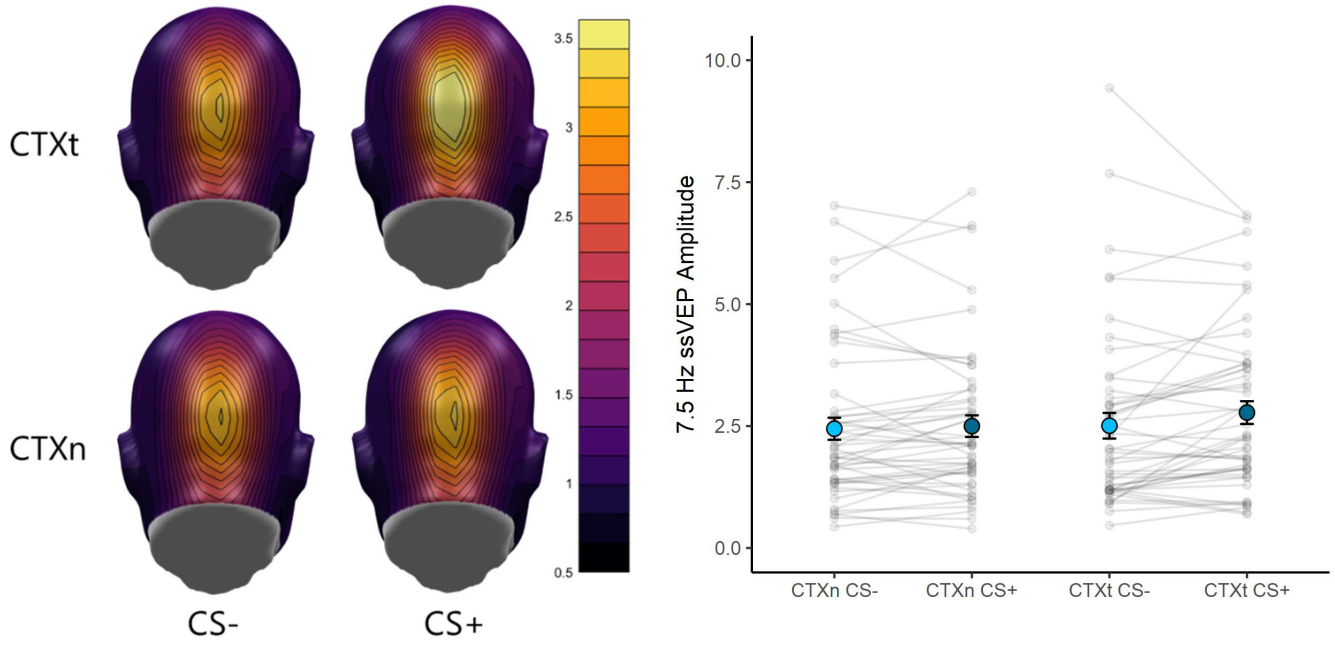

FIGURE 3 Scalp topographies of the 7.5 Hz ssVEP amplitude and mean visuocortical responses ± *SEM* in response to the central cues as a function of context during the test phase.

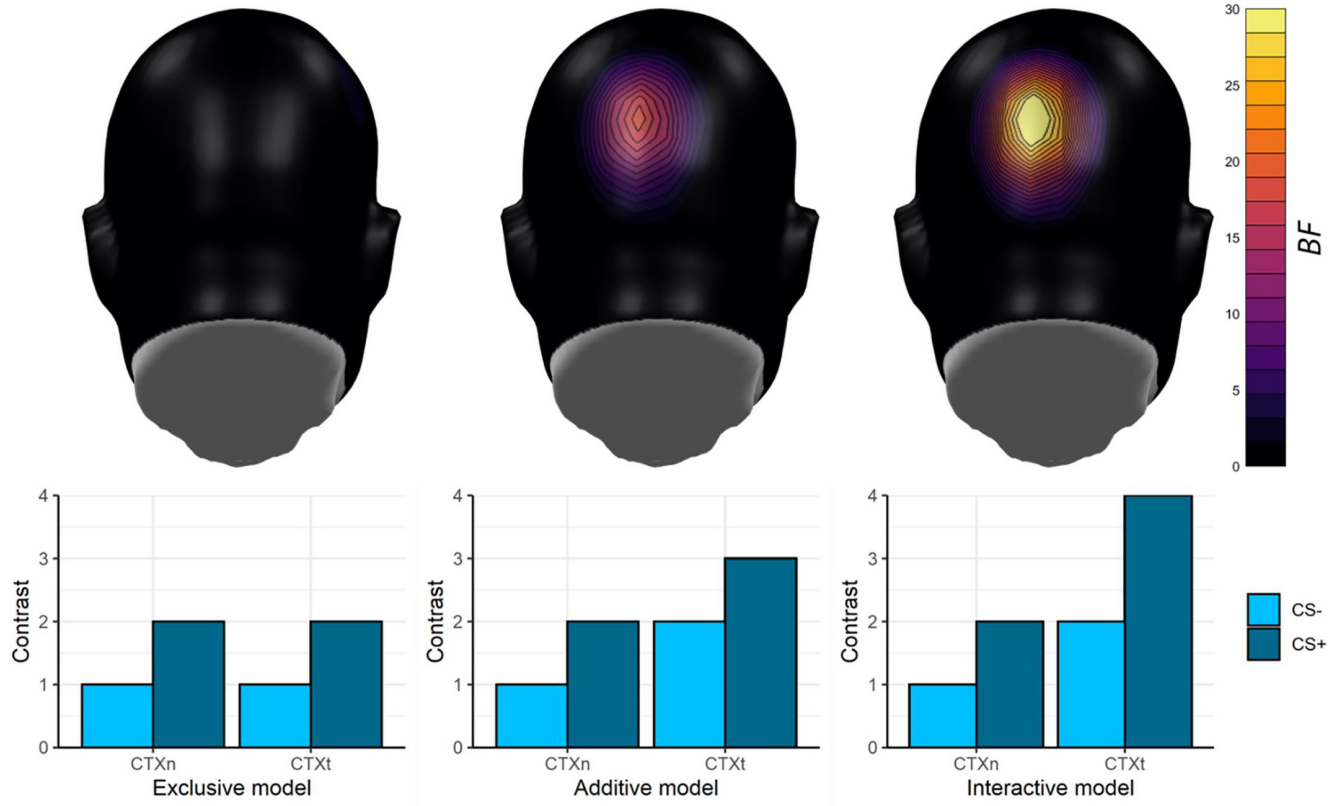

FIGURE 4 Bayesian model fit: Topographical distributions of the Bayes factor for comparing the exclusive, additive, and interactive models of fear and anxiety compared with the null model. Weights used as contrasts for the Bayesian linear mixed model analyses are displayed at the bottom row.

exploratively analyzed central cue responding with post-hoc *t*-tests, showing significant CS-differentiation in the threatening context, $t(48) = 2.26$, $p = .028$, $d = 0.32$, $CI_{95} = [.03; .61]$, but not in the neutral context, $t(48) = .59$, $p = .558$, $d = 0.08$, $CI_{95} = [-.36; .20]$, as well as stronger ssVEP amplitudes in response to the CS+ in the threatening

compared with the neutral context, $t(48) = 2.30$, $p = .026$, $d = 0.33$, $CI_{95} = [.04; .61]$, while CS− responses were not influenced by the context, $t(48) = .51$, $p = .614$, $d = 0.07$, $CI_{95} = [-.35; .21]$. Together, these results suggest stronger visuocortical responses to the CS+ during threatening compared with neutral contexts.

To confirm these findings and to directly compare different hypothetical models of fear and anxiety, we employed Bayesian linear model analysis (see Figure 4, and Table 1). In a first step, the exclusive, additive, and interactive models were each compared with the "random intercept only" model (null model, 0), resulting in moderate evidence for the additive, $BF_{Add/0} = 6.16$, and strong evidence for the interactive model, $BF_{Int/0} = 11.74$, while there was no evidence for the exclusive model, $BF_{Ex/0} = 0.87$. Moreover, the additive, $BF_{Add/Ex} = 7.09$, and interactive, $BF_{Int/Ex} = 13.50$, model received stronger support in competition to the exclusive model. However, the results yielded only anecdotal evidence for the interactive over the additive model, $BF_{Int/Add} = 1.91$. In sum, Bayesian analyses revealed further evidence for a potential influence of the context condition on central cue processing.

3.2.2 | Skin conductance responses

To confirm that threatening contexts induce defensive mobilization, we also analyzed physiological responding to the context onsets, demonstrating higher SCRs to the threatening compared with the neutral contexts, $t(43) = 2.15$, $p = .037$, $d = .32$, $CI_{95} = [.02; .63]$ (see Figure 5a). The ANOVA for SCRs to the central cues revealed a significant main effect of cue only, $F(1, 43) = 5.17$, $p = .028$, $\eta_p^2 = .11$, $CI_{95} = [.00; .29]$, without any effect of context, $F(1, 43) = 0.01$, $p = .935$, $\eta_p^2 < .01$, $CI_{95} = [.00; .04]$, or their interaction, $F(1, 43) = 0.91$, $p = .345$, $\eta_p^2 = .02$, $CI_{95} = [.00; .16]$, indicating enhanced sympathetic activation to the fear-associated cue independent of the context (see Figure 5b).

Bayesian analyses confirmed these findings by showing strong evidence for the exclusive model, $BF_{Ex/0} = 17.35$, while the additive, $BF_{Add/0} = 1.56$, and interactive models, $BF_{Int/0} = .98$, received no evidence. Moreover, the additive, $BF_{Add/Ex} = .09$, and interactive, $BF_{Int/Ex} = .06$, models received less support in competition to the exclusive model.

3.2.3 | Heart rate

The analysis of the context onset detected reduced heart rate responses for threatening compared with neutral contexts, $t(50) = 4.44$, $p < .001$, $d = .62$, $CI_{95} = [.32; .92]$, suggesting cardiac defense to the potential danger (see Figure 6a). Regarding central cue onsets, the conventional heart rate change score analysis revealed a main effect of cue, $F(1, 50) = 11.81$, $p < .001$, $\eta_p^2 = .19$, $CI_{95} = [.03; .37]$, demonstrating fear bradycardic responses to the CS+ compared with the CS− (see Figure 6b). In addition, there was an main effect of context, $F(1, 50) = 4.79$, $p = .033$, $\eta_p^2 = .09$, $CI_{95} = [.00; .25]$, indicating stronger CS−related bradycardia during the neutral context. The interaction was not significant, $F(1, 50) = 1.14$, $p = .291$, $\eta_p^2 = .02$, $CI_{95} = [.00; .15]$. However, since threatening context onsets were accompanied by a reduction in heart rate, we decided to re-run the ANOVA with uncorrected heart rate scores (without baseline-correction) to see the combined influence of context and cue processing (see Figure 6c). The main effect of cue, $F(1, 50) = 19.81$, $p < .001$, $\eta_p^2 = .28$, $CI_{95} = [.09; .45]$, and context, $F(1, 50) = 8.36$, $p = .006$, $\eta_p^2 = .14$, $CI_{95} = [.01; .32]$, remained significant, even though the total heart rate reduction is now greater for central cues presented in the threatening context compared with the neutral context. Analysis of the cue onsets revealed that this effect was due to heart rate differences between contexts already at baseline (−1000 to 0 ms relative to cue onset), $t(50) = 4.31$, $p < .001$, $d = 0.60$, $CI_{95} = [.30; .90]$, indicating that central cues are presented in the decelerative phase of the heart rate response to the threatening context. There was no interaction between cue and context, $F(1, 50) = 1.98$, $p = .166$, $\eta_p^2 = .04$, $CI_{95} = [.00; .18]$. These findings are further corroborated by the results of the Bayesian model analysis, demonstrating strong evidence for the exclusive model, $BF_{Ex/0} = 8.22$, and very strong evidence for the additive, $BF_{Add/0} = 4.1 \times 10^9$, and interactive

TABLE 1 Summary of the Bayesian linear model analysis

Model	Exclusive	Additive	Interactive	Additive vs. exclusive	Interactive vs. exclusive	Interactive vs. additive
ssVEP	.87	6.16	11.74	7.09	13.50	1.91
SCR	17.35	1.56	.98	.09	.06	.63
HR	8.22	4.1×10^9	1.4×10^8	4.9×10^8	1.6×10^7	.03

Note: Bayes factors for the exclusive (weights: 2, 1, 2, 1, for CS+ in CTX_t, CS− in CTX_t, CS+ in CTX_n, CS− in CTX_n), additive (weights: 3, 2, 2, 1) and interactive (weights: 4, 2, 2, 1) models of fear and anxiety compared with the "random intercept only" model (Null model). The last three columns display direct model comparisons between the models by dividing respective BFs.

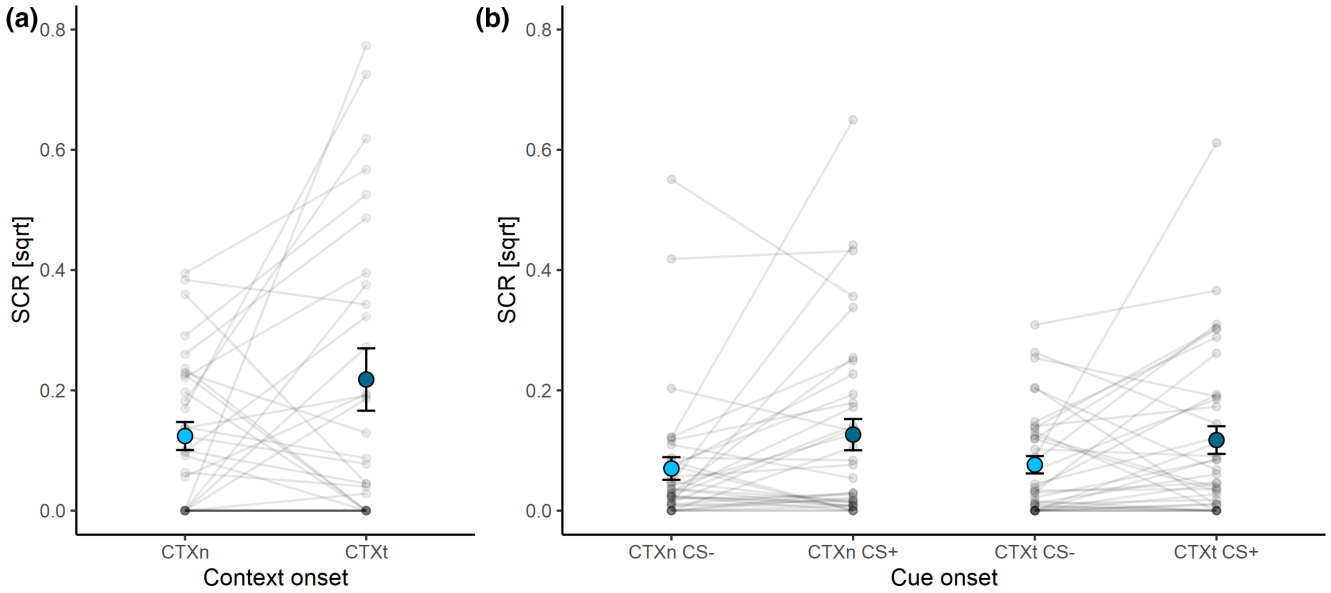

FIGURE 5 Mean skin conductance responses to the onset of the threatening and neutral context images (a), and to the onset of the central cues as a function of context (b) ± *SEM* during the test phase.

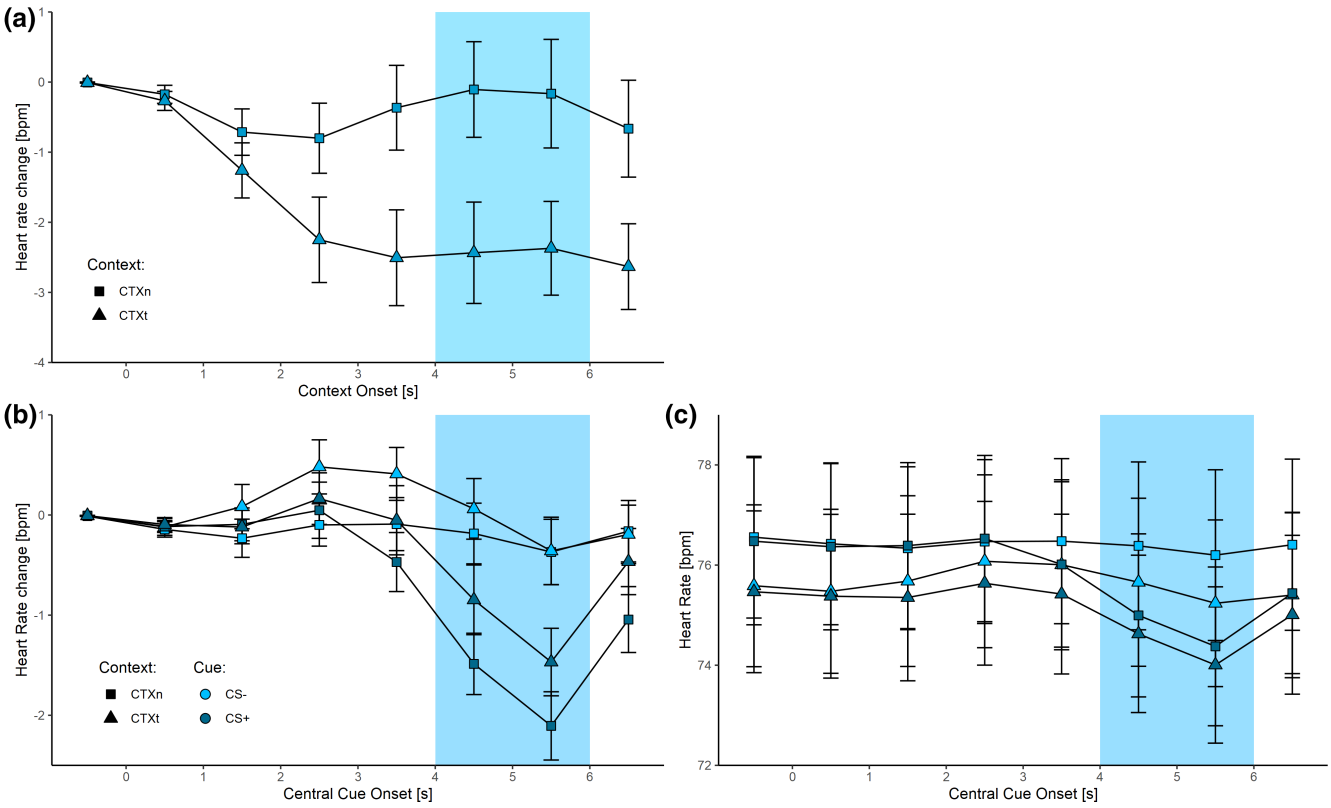

FIGURE 6 Heart rate responses to the onset of the threatening and neutral context images (a), and to the onset of the central cues as a function of context with (b), and without (c) baseline correction ± *SEM* during the test phase.

models, $BF_{\text{Int/0}} = 1.4 \times 10^{8}$, compared with the Null model. Importantly, the additive model received stronger support in competition to the exclusive, $BF_{\text{Add/Ex}} = 4.9 \times 10^{8}$, and interactive, $BF_{\text{Add/Int}} = 30.07$, models. Taken together, these results suggest a superposition of bradycardic responses to the fear cue and the threatening context, which is the main idea behind the additive model of fear and anxiety.

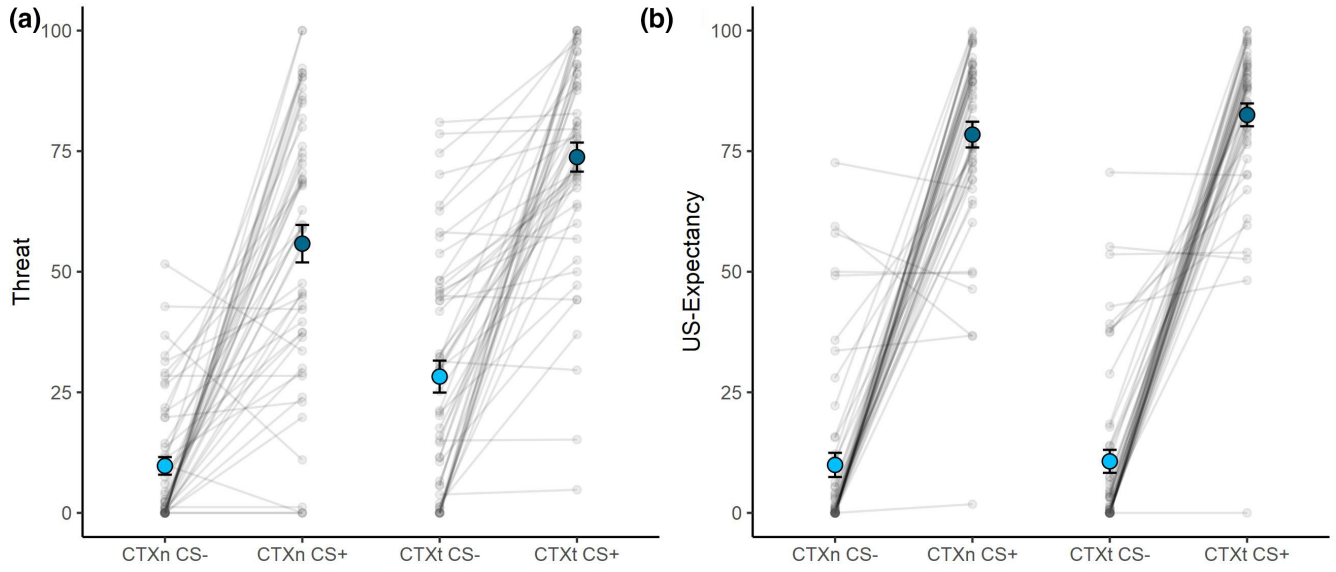

FIGURE 7 Mean threat (a) and US-expectancy (b) ratings ± *SEM* to the central cues as a function of context during the test phase.

3.2.4 | Threat and US expectancy ratings

Mean threat ratings were higher for the CS+ compared with the CS−, $F(1, 51) = 104.04$, $p < .001$, $\eta_p^2 = .67$, $CI_{95} = [.51; .76]$, while central cues were generally perceived as more threatening in the threat compared with the neutral context, $F(1, 51) = 54.37$, $p < .001$, $\eta_p^2 = .52$, $CI_{95} = [.31; .64]$. The interaction was not significant, $F(1, 51) = 0.11$, $p = .738$, $\eta_p^2 < .01$, $CI_{95} = [.00; .08]$.

US expectancy analysis revealed a main effect of cue, $F(1, 51) = 278.26$, $p < .001$, $\eta_p^2 = .85$, $CI_{95} = [.76; .89]$, and context, $F(1, 51) = 4.99$, $p = .030$, $\eta_p^2 = .09$, $CI_{95} = [.00; .25]$ which was further qualified by their interaction, $F(1, 51) = 4.91$, $p = .031$, $\eta_p^2 = .09$, $CI_{95} = [.00; .25]$, indicating that participants overestimated the likelihood of an aversive event when the fear cue was presented in a threatening context (Figure 7).

4 | DISCUSSION

The main goal of the present study was to investigate potential interplays between acute and potential threat processing. In particular, we experimentally tested exclusive, additive, and interactive models of fear and anxiety. For this purpose, differential fear conditioning was employed during neutral and threatening contexts. This orthogonal combination of acute and potential threat allowed for inferences about how defense responses to acute threat cues are modulated by potentially threatening contexts. Defense system activation was operationalized by subjective (threat, US-expectancy), physiological (skin conductance, heart rate), and visuocortical (steady-state visual evoked potentials) responses to the conditioned stimuli as a function of contextual threat. In total, we found evidence for enhanced defensive responses to fear cues presented in threatening compared with neutral contexts.

Successful fear acquisition was evident in enhanced skin conductance responses and ssVEP amplitudes, as well as higher threat and US-expectancy ratings for the CS+ compared with the CS− at the end of acquisition. These results replicate previous findings indicating that fear cues elicit enhanced electrocortical activity and physiological arousal, reflecting heightened sensory and emotional engagement (Bradley & Lang, 2000; Miskovic & Keil, 2012). Importantly, the effects of fear conditioning were stable throughout the test phase. The CS+ was generally rated as more threatening and more strongly associated with an US, elicited stronger skin conductance responses, and higher ssVEP amplitudes than the CS−, independent of the context condition. In addition, results revealed a stronger heart rate deceleration to the CS+ compared with the CS−. Consistent with other studies, fear bradycardia in response to threatening cues is often interpreted as "attentive freezing" and assumed to play an important role in facilitating defensive engagement (Bradley et al., 2001; Castegnetti et al., 2016).

Crucial for the test phase, we also found stronger skin conductance responses and a stronger heart rate deceleration to the onsets of the threatening compared with the neutral contexts, suggesting successful activation of the defense system in response to potential threat. Regarding central cue responding as function of the context, our results revealed enhanced threat and US-expectancy ratings, heart rate deceleration, and visuocortical responses to fear cues in the threatening compared with the neutral contexts. This suggests that fear responses are generally enhanced during potentially threatening contexts. Regarding

the underlying mechanism, however, results were inconsistent across different measures of defensive responding. In particular, we found higher threat ratings for the CS+ than for the CS− and higher threat ratings for central cues presented during the threatening compared with the neutral context. The absence of a Cue × Context interaction indicates that the modulating effect of the context was not specific to the CS+. Thus, the observed threat ratings are the result of a linear combination of the cue and context effect, implying a potential additive mechanism between fear and anxiety. Interestingly, these results coincide with response patterns for cardiac deceleration. Here, we found fear bradycardia to the CS+ independent of the context condition, which was superimposed on the initial heart rate reduction to the onset of the threatening context. Analysis of the baseline interval (−1000 ms – 0 ms relative to central cue onset) revealed reduced heart rates for both central cues in the threatening compared with the neutral context. While there is ample evidence for heart rate deceleration in response to threatening images (Bradley et al., 2001; Paulus et al., 2016), no study has explicitly examined the duration of this response. However, studies using affective video stimuli reported slower heart rates during the entire duration of aversive compared with neutral videos (Demaree et al., 2006; Hagenaars et al., 2014), suggesting that in our current study the baseline differences for the central cues are due to the effect of context. Then, fear bradycardia in response to the CS+ adds linearly to the context effect, resulting in the strongest heart rate reduction for fear cues presented during the threatening context. Together, this response pattern fits well with predictions made by an additive model of fear and anxiety, in which sustained anxiety responses are superimposed by phasic fear responses.

In contrast, analysis of the US-expectancy ratings revealed higher shock expectancies during threatening compared with neutral contexts specifically for the CS+. Thus, participants overestimated the likelihood that a fear cue is followed by an aversive event when it's presented during a threatening context, even though the number of CS-US pairings were equal in both contexts. This finding suggests that aversive events are more readily attributed to an acute threat when it is encountered in a potentially threatening context. This expectancy bias is well in line with studies that examined illusory correlations during various threatening situations and showed that the likelihood of aversive events are overestimated for phobic-relevant compared with phobic-irrelevant stimuli (de Jong et al., 1995; Hermann et al., 2004; Tomarken et al., 1989; Wiemer & Pauli, 2016), for unpleasant compared with neutral pictures (Pauli et al., 2002), and for stimuli associated with more aversive events compared with less aversive events (Wiemer et al., 2014). These illusory correlations are frequently discussed in the context of preparedness theories (Öhman, 1985; Öhman et al., 1975; Seligman, 1971), suggesting that selective associations receive priority processing and are more easily paired with aversive events to facilitate fear-relevant learning with the ultimate goal to optimize adaptive behavior. Applied to the current study, this could mean that CS-US associations are more readily learned in potentially threatening contexts, implying that anxiety prepares fear-relevant learning. Importantly, this finding is more consistent with an interactive rather than an additive model of fear and anxiety, as anxiety specifically modulates fear learning.

Further evidence for this notion is provided by the results of visuocortical activity. Confirmatory analyses demonstrated enhanced ssVEP amplitudes to the CS+ but not to the CS− in the threatening compared with the neutral context. These results are corroborated by direct Bayesian model comparisons, demonstrating further support for an interactive model compared with an exclusive model of fear and anxiety. Consistent with the idea of motivated attention, heightened sensory engagement to threatening cues might reflect facilitated perceptual processing as an index of selective attention (Bradley, 2009; Lang et al., 1997; Miskovic & Keil, 2012). Together with our response patterns for heart rate decelerations these results are well in line with a recent study by Echegaray and Moratti (2021), showing on the individual level that heart rate deceleration covaried with increased neural processing of visual input during passive viewing of emotional pictures. In addition, the authors could demonstrate that cardiovascular and neural sensory responses were associated with reduced beta-band desynchronization in pre-motor and motor areas, supporting the notion that depending on threat-imminence orienting is characterized by motor inhibition and neural gain in attention circuits (Roelofs, 2017).

Crucially, sensory engagement to fear cues was enhanced in potentially threatening contexts. In earlier studies, we could demonstrate that anxiety contexts prompt hypervigilance, which was characterized by enhanced perceptual processing of the contextual stimuli (Kastner et al., 2015; Kastner-Dorn et al., 2018; Stegmann et al., 2019; Wieser, Reicherts, et al., 2016). It is assumed that the function of hypervigilance during potentially threatening contexts is to monitor the environment for threats and to facilitate threat detection (Richards et al., 2014). Please note, that in these earlier studies, we also presented the contextual stimuli in flicker mode at a different flicker frequency than the central cues, allowing for a disentanglement of the ssVEPs to the context and central cues by means of frequency tagging (Wieser & Keil, 2014; Wieser, Miskovic, & Keil, 2016). In our current study, however, we could only examine the effect of the contexts on the

processing of central cues, but not the direct perceptual processing of the contextual stimuli, because only the central cues but not the contexts were presented in flicker mode to obtain an improved signal-to-noise ratio for the cue-related ssVEP. Yet, there is unequivocal evidence for enhanced ssVEP amplitudes to aversive compared with neutral images (Keil et al., 2003; Wieser & Keil, 2014). In addition, our results point to another important function of hypervigilance, namely, enhanced selective attention to fear signals in anxiety contexts, suggesting stronger attentional capture by acute threat cues when they are encountered in a potentially threatening context, which may be one of the mechanisms by which anxiety prepares and facilitates the processing of fear-relevant stimuli.

Finally, it is important to point out that our results cannot fully distinguish between an additive and an interactive models for visuocortical activity. Although the interactive model obtained the strongest support in the Bayesian analysis, it received only anecdotal evidence relative to the additive model (Lee & Wagenmakers, 2014). Since this was one of the first studies to explicitly investigate the interplay between fear and anxiety, more research is necessary to disentangle underlying additive and interactive mechanisms.

Regardless of the mechanisms involved, our results for visuocortical activity, heart rate, and aversive ratings are inconsistent with the notion that fear and anxiety are mutually exclusive. In contrast, we found stronger defensive responses to fear cues in threatening compared with neutral contexts, which opens new perspectives on how organisms could optimize defensive behaviors (Mobbs et al., 2015). Stronger fear responses are critical for survival in situations of acute threat but also come at a cost (Fanselow, 2018; LeDoux, 2012). For example, narrowing the attentional focus during selective attention to fearful stimuli also increases the chance of missing other aversive or appetitive signals in the environment. Likewise, extensive cardiac mobilization to distal threat signals might be costly in terms of energy and resources. Accordingly, organisms have learned how to use various signals of threat proximity for ecologically efficient defensive behavior (Blanchard & Blanchard, 1989; Fanselow, 2018; Mobbs et al., 2015). In this context, an additive or interactive model offers a potential mechanistic framework for defensive resource mobilization. In the first stage, anxiety triggered by potentially threatening situations leads to a slow but sustained mobilization of defensive resources to ensure a minimum of defense systema activation. Then, the detection of an acute threat prompts a rapid but short-lived fear response that instantly depletes a large amount of resources. Consequently, more defensive resources for the fear response are available when they already have been mobilized by anxiety. This model is also consistent with recent neurophysiological findings, suggesting rapid, short-lived central amygdala outputs during acute threat and more slowly recruited, sustained BNST outputs during potential threat (Davis et al., 2010; Herrmann et al., 2016; Perusini & Fanselow, 2015). However, more research is needed to elucidate the neural pathways underlying an additive or interactive model of fear and anxiety.

Several limitations should be noted when interpreting the present results. First, no context effects could be retrieved for SCRs. This is not surprising as the experiment was not primarily designed to capture SCRs. It is well known that SCR habituate quickly in fear conditioning experiments. However, many trials were needed to obtain a satisfactory signal-to-noise ratio for the ssVEP signal. In addition, presentation durations of 5 s and ITIs shorter than 10 s might have been too short to capture the entire skin conductance response and its return to baseline (Boucsein et al., 2012; Dawson et al., 2017). This is also reflected in the low number of non-zero SCR responses of 13% during the test phase. Similarly, we relied on transient SCRs to quantify defensive mobilization to the threatening context onsets, whereas recent context conditioning studies analyzed skin conductance levels throughout the context presentations to better capture the sustained component of the anxiety-induced defensive response (Andreatta, Leombruni, et al., 2015; Glotzbach-Schoon et al., 2015). In the current study, however, we were not able to analyze SCLs throughout the context presentations as these intervals were confounded by central cue and US reactions. Consequently, future studies need to adjust the experimental timing to adequately measure electrodermal activity during Fear × Anxiety paradigms. Second, the overall effects for visuocortical activity during the test phase were small. Compared with the acquisition phase, during which central cues were presented without background images, ssVEP amplitudes were generally reduced during the test phase, suggesting that attentional resources were divided between central and context stimuli. However, since background images were not presented in flicker mode, we could not quantify attention allocation and competition. Indeed, the results of a previous study by our group showed that visuocortical engagement to a flickering threatening context was enhanced during simultaneous presentations of fearful facial expressions, indicating that the interactive effect of central cue and context may not be unidirectional (Wieser & Keil, 2014). We choose to present the contexts as still images to reduce potential interferences with central cue processing. Build on our findings, future studies should now analyze perceptual processing of the context images as well.

In summary, the current study provides support for an additive or interactive model of fear and anxiety. By orthogonally combining differential fear conditioning

(acute threat) with threatening vs. neutral contexts (distal threat), we could show that defensive responses to acute threat are enhanced during potentially threatening compared with neutral contexts for multiple measures of defensive behavior. More specifically, US-expectancy ratings and indices of visuocortical threat processing were in line with an interactive model, whereas threat ratings and cardiovascular heart rate responses followed predictions of an additive model. No context-dependent effects could be obtained for skin conductance responses. Together, these findings suggest that depending on the indexed physiological system, defensive engagement is characterized by an exclusive, additive, or interactive model of fear and anxiety. However, because both an additive (Bublatzky et al., 2013) and an interactive model (Grillon & Charney, 2011) have been demonstrated for startle responses, it is also important to elucidate the methodological and contextual conditions for the adaptation of defensive behavior. Furthermore, future work may examine the role of the interplay between fear and anxiety in the maintenance and development of anxiety disorders (Grillon et al., 2019) as well as its underlying neural pathways (Fox & Shackman, 2019).

AUTHOR CONTRIBUTIONS

Yannik Stegmann: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Marta Andreatta:** Conceptualization; methodology; supervision; visualization; writing – review and editing. **Matthias Wieser:** Conceptualization; methodology; supervision; validation; visualization; writing – review and editing.

ACKNOWLEDGMENTS

We would like to thank Lara Schelske and Heike Pfister for data acquisition. This publication was supported by the Open Access Publication Fund of the University of Wuerzburg. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at https://osf.io/59tcw/.

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How to cite this article: Stegmann, Y., Andreatta, M., & Wieser, M. J. (2023). The effect of inherently threatening contexts on visuocortical engagement to conditioned threat. *Psychophysiology*, *60*, e14208. https://doi.org/10.1111/psyp.14208