

Attention mechanisms during predictable and unpredictable threat – A steady-state visual evoked potential approach



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ABSTRACT

Fear is elicited by imminent threat and leads to phasic fear responses with selective attention, whereas anxiety is characterized by a sustained state of heightened vigilance due to uncertain danger. In the present study, we investigated attention mechanisms in fear and anxiety by adapting the NPU-threat test to measure steady-state visual evoked potentials (ssVEPs). We investigated ssVEPs across no aversive events (N), predictable aversive events (P), and unpredictable aversive events (U), signaled by four-object arrays (30 s). In addition, central cues were presented during all conditions but predictably signaled imminent threat only during the P condition. Importantly, cues and context events were flickered at different frequencies (15 Hz vs. 20 Hz) in order to disentangle respective electrocortical responses. The onset of the context elicited larger electrocortical responses for U compared to P context. Conversely, P cues elicited larger electrocortical responses compared to N cues. Interestingly, during the presence of the P cue, visuocortical processing of the concurrent context was also enhanced. The results support the notion of enhanced initial hypervigilance to unpredictable compared to predictable threat contexts, while predictable cues show electrocortical enhancement of the cues themselves but additionally a boost of context processing.

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Introduction

Based on animal models (Barlow et al., 1996; Davis et al., 2010), fear (phasic) and anxiety (tonic) seem to be different affective states (Sylvers et al., 2011). Accordingly, anxiety is defined as a future-oriented affective state with sustained tonic responses to possibly impending aversive events, while fear is defined as an immediate phasic alarm reaction to the perception of present specific and predictable threat and characterized by impulses to escape, typically associated with surge of sympathetic arousal (Barlow, 2002). Thus, fear may be characterized as an aversive reaction to a specific threat stimulus, whereas anxiety may be characterized as a prolonged vigilance to a diffuse, unspecific threat (Davis et al., 2010; Lang et al., 2000; MacLeod and Rutherford, 1992). In behavioral terms, fear mobilizes the organism to take action (fight/flight response), whereas anxiety leads to increased environmental and somatic scanning that facilitates sensory perception. In this terminology, predictability of upcoming aversive events during

anticipation is considered a key feature for the distinction between transient phasic fear and sustained tonic anxiety (Davis et al., 2010).

Differences in defensive behavior and attention as a result of fear and anxiety are best described in the threat imminence model (Blanchard et al., 1997; Blanchard et al., 1993; Fanselow, 1994; Lang et al., 1997; Lang et al., 2000). According to this model, the proximity of the threat determines different stages of defensive behavior: the pre-encounter phase, the post-encounter phase, and the circa-strike phase (Lang et al., 1997; Lang et al., 2000). At the pre-encounter stage when a threat has been encountered previously but has not yet been detected, threat-nonspecific vigilance is engaged. As soon as the threat is detected (post-encounter phase), the organism shows freezing behavior and an orienting response with increased selective attention allocation to the potential threat. When the threat is imminent (circa-strike phase), the organisms show strong autonomic arousal, culminating in a fight-or-flight response (Blanchard et al., 2001). While anxiety is linked to the pre- and post-encounter stage of the defense cascade model, fear is associated with the circa-strike zone in which the organism is directly threatened by the predator (Blanchard et al., 1993). These three stages of defensive behavior are presumably associated with quantitatively and qualitatively different physiological responses and mechanisms of attention allocation, with hypervigilance during pre-encounter and

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selective attention to the source of threat during post-encounter (Hamm et al., 2014).

Recently, an experimental paradigm has been developed which allows comparing phasic fear and sustained anxiety and their physiological correlates in humans (NPU-threat test; Schmitz and Grillon, 2012). This paradigm is based on the aforementioned idea of fear and anxiety developing due to a different extent of predictability of a threatening event. In this vein, a cue, which reliably predicts an upcoming aversive event, leads to a phasic fear response. In contrast, unpredictable aversive events are thought to be associated with the embedding context and create a state of sustained anxiety and anxious apprehension due to the chronic expectation of threat. In the NPU-threat test three different conditions are realized: a neutral condition without any aversive event (N), a predictable condition (P), in which an aversive event (electric shock) is reliably predicted by a cue, and an unpredictable condition (U), in which the aversive event is presented independently of any predicting cue. Each condition comprises a specific context and a corresponding cue. While the N-condition serves as a control condition, in which the participants experience safety, the P-condition elicits a phasic fear response to the cue, while in the U-condition a sustained anxiety response is observed (Grillon, 2008; Grillon et al., 2006b; Grillon et al., 2004). While most studies so far used simple geometric shapes as cues and verbal instructions for the N, P, or U context, some studies employed virtual reality technology as a possibility to create environments of high external validity (Alvarez et al., 2011; Baas, 2013; Grillon et al., 2006a; Haaker et al., 2013; Lonsdorf et al., 2014). In this case, three virtual rooms serve as contextual stimuli (constituting the N, P, and U condition), while predictable cues appear in each room and either predict the occurrence of the aversive event (P) or are presented without any informative character about the aversive event. Participants are informed about the nature of the three conditions beforehand. As a psychophysiological marker of fear and anxiety, the startle response has been most frequently used during predictable and unpredictable threat. According to Schmitz and Grillon (2012), a fear-potentiated startle is the difference in the startle magnitude elicited during the cue presentation compared to the context-only presentation within the predictable condition. In contrast, an anxiety-potentiated startle is defined as the difference between startle magnitudes elicited in the context of the unpredictable condition compared to the context of the neutral condition, both of which have repeatedly been reported (Grillon, 2008; Grillon et al., 2004).

Animal and human neuroimaging studies also showed support for distinct neural circuits for predictable and unpredictable threat, with differential involvement of the amygdala vs. the extended part of the amygdala (BNST) during fear and anxiety conditioning (Davis and Shi, 1999; Davis et al., 2010). While the central nucleus of the amygdala (CeA) plays a key role for short termed fear responses, the BNST mediates the sustained responses seen during contextual anxiety (Alvarez et al., 2011). In addition, a broad network of brain areas is reported to be activated in unpredictable compared to predictable threat (Alvarez et al., 2011; Carlson et al., 2011; Hasler et al., 2007; Somerville et al., 2013) including the hippocampus, the insula, and the fronto-parietal attention network. Especially the sustained engagement of the attention network supports the view that sustained anxiety may be associated with enhanced vigilance for threat, which is also supported by frequently reported activations in visual sensory and parietal attentional areas in fMRI studies on context conditioning (Alvarez et al., 2011; Andreatta et al., 2015; Lang et al., 2009; Marschner et al., 2008; Pohlack et al., 2012).

The aim of the present study was to quantify attention allocation and its electrocortical correlates during predictable and unpredictable threat in an adapted NPU-threat paradigm by using steady-state visual evoked responses as a continuous index of electrocortical facilitation. This measure has been proven to be highly suitable for investigating attention allocation to different stimuli in the visual field competing for attentional resources at the same time (Wieser and Keil, 2011), which is not easily

accomplished by other neural measures such as ERPs and fMRI. Based on the theory of imminent threat and empirical findings from neuroimaging, we assumed that the onset of contexts signaling unpredictable threat would elicit larger electrocortical responses (i.e. hypervigilant attention allocation) than predictable threat contexts. Conversely, cues indicating the potential threat (P) were assumed to elicit stronger electrocortical responses compared to cues in the N and U conditions, where they did not have any predictive value. We also exploratory investigated context processing during the presence of the cues to see if attentional allocation to the central cue would either result in a reduced processing of the context at the same time (competition) or even enhance parallel processing of the context (attentional boost). With regard to affective and threat ratings we assumed to replicate previous findings in which unpredictable contexts were rated as most threatening, while predictable cues were rated as more threatening than cues in the other two conditions.

Material and methods

Participants

Twenty-seven participants were recruited at the University of Würzburg and received course credit or 8 € for participation. Due to hardware failure, data from one participant had to be excluded from the analysis, resulting in a final sample of 26 participants (18–30 years old, $M = 23.31$, $SD = 2.94$; 17 females). All of the participants had no family history of photic epilepsy, and reported normal or corrected-to-normal vision. Written consent was obtained from all participants. Prior to testing, participants completed several questionnaires (German version): Pain Sensitivity Questionnaire (PSQ; Meyer et al., 2008), $M = 3.59$, $SD = 1.06$; State-Trait-Anxiety Inventory (STAI; Laux et al., 1981), $M = 35.19$, $SD = 7.82$, $M = 33.84$, $SD = 7.74$; and Anxiety Sensitivity Index (ASI; Reiss et al., 1986), $M = 15.15$, $SD = 9.65$. All procedures were approved by the institutional review board of the German Society for Psychology (Deutsche Gesellschaft für Psychologie, DGPs).

Design and procedure

The visual stimuli serving as cues were black-and-white Gabor patches (Miskovic and Keil, 2014), which consisted of black-and-white sinusoidal gratings (Gaussian-windowed with maximal contrast at center) subtending horizontal and vertical visual angles of 7° , with a spatial frequency of 1.4 cycles per degree. The compound stimuli which were used to indicate the context conditions (N = neutral, P = predictable threat, U = unpredictable threat) were four peripherally presented geometrical shapes (triangles, squares, circles). Peripheral cues were located ca. 1.7° of visual angle from the central grating stimuli and subtended visual angles of 1.5° (see Fig. 1).

A 2 ms electric pulse stimulation served as aversive unconditioned stimulus (US). These electric stimuli were applied to the left calf via surface bar electrodes consisting of two gold-plated steel disks (9 mm diameter, 30 mm spacing). The electric stimulation was generated by a constant-current stimulator (Digitimer DS7A, Digitimer Ltd., Welwyn Garden City, UK). The intensity of the electric shock was adjusted individually in a threshold procedure prior to the actual experiment. The pain threshold procedure consisted of two ascending and descending series, starting from 0 mA with increasing or decreasing stimulus intensity in steps of 0.5 mA steps (see Andreatta et al., 2012; Andreatta et al., 2015). Participants were asked to evaluate US intensities on a scale ranging from 0 (no pain at all) to 10 (unbearable pain). The individual US intensity was determined by calculating the mean value of the four stimulus intensities (two from the ascending series, and two from the descending series) rated as “just noticeable pain” (i.e., 4) and then adding 1 mA to avoid habituation ($M = 5.11$, $SD = 1.99$ mA; mean of the subjective painfulness before conditioning started: $M = 5.13$, $SD = 1.23$).

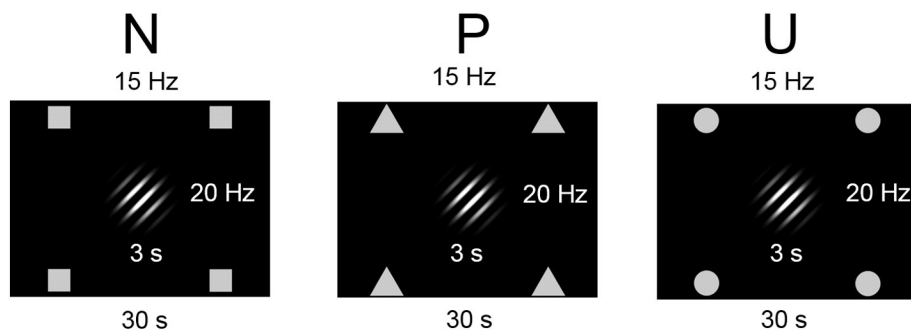


Fig. 1. Stimulus layouts for the three conditions. The 4-object arrays indicated the context condition (N, P, U) and were flickered for the whole duration of the trial (30 s) at a frequency of 15 Hz. The central cues (Gabor patches) were shown up to three times during a trial (3 s) and flickered at a frequency of 20 Hz. Participants were instructed before about the meaning of the peripheral cues. In contrast to the original paradigm (Schmitz and Grillon, 2012), no verbal instructions were shown during the actual experiment.

After providing written informed consent and initial screening to rule out photic epilepsy/seizures, participants were seated in a dimly lit testing room where the electroencephalogram (EEG) sensor net was applied and participants were given instructions to fixate, avoid eye movements and blinks. To facilitate learning the CS–US contingencies and context conditions, participants were instructed about the different conditions (NPU) as recommended in the NPU paradigm protocol (Schmitz and Grillon, 2012). To this end, one of each 4-object arrays was introduced as indicating either the neutral, predictable or unpredictable block, in which either no aversive electric stimuli would appear (N), electric stimuli would always immediately follow the presentation of central Gabor patches at a 100% reinforcement rate (P), or electric stimuli could appear anytime. In the unpredictable condition, at least one US was presented, at least 1250 ms after context array onset, but maximally 3 times at random time intervals between 1250 ms and 28,000 ms after context onsets unpredictably during the whole block (U). The minimum temporal lag between two consecutive electric stimuli was set to 4000 ms. Each block lasted for 30 s in which the 4-object arrays (contexts) were flickered at a frequency of 15 Hz. During each block, 1–3 Gabor patches were presented as central cues for 3000 ms (randomly between 1250 ms and 25,000 ms after context-array onset with a minimum temporal lag of 3000 ms between offset and onset of two consecutive visual cues) with a flicker frequency of 20 Hz. Overall, 54 blocks (18 per N, P, or U condition) were realized with 6 blocks per condition containing 1 cue, 6 blocks containing 2 cues and 6 blocks per condition containing 3 cues. Blocks were separated by presentation of gray screens (ITI) of random durations between 2500 and 3500 ms.

Tagging the peripheral contexts and the central cues with different driving frequencies ensured the later disentanglement of electrocortical responses associated with the transient cues from the responses to the ongoing contexts (Wieser and Keil, 2014). Using presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA), stimuli were displayed on a 19-inch computer monitor (resolution = 1280 × 1024 pixel) with a vertical refresh rate of 60 Hz, located approximately 80 cm in front of the participant.

After the EEG recording, participants were asked to rate each of the context compound stimuli and the compound stimuli together with the central Gabor cue with regard to affective arousal (1 = not arousing at all – 9 = very arousing) and affective valence (–4 = very negative – +4 very pleasant). Furthermore, they were asked about the threat (1 not threatening at all – 9 very threatening) and the likelihood of receiving a shock when the respective stimuli were present during the experiment (VAS, ranging from 1 to 100%).

EEG recording and data analysis

The EEG was continuously recorded from 129 electrodes using an Electrical Geodesics System (EGI, Eugene, OR, USA), referenced to Cz, digitized at a rate of 250 Hz, and on-line band-pass filtered between

0.1 and 100 Hz. Electrode impedances were kept below 50 k Ω , as recommended for the Electrical Geodesics high-impedance amplifiers.

Using EMEGS (Peyk et al., 2011), a low-pass filter of 40 Hz (45 dB/octave, 16th order Butterworth) was applied off-line. Epochs of 600 ms pre-stimulus (context onset, cue onset) and 2900 ms post-stimulus onset were extracted off-line. Artifact rejection was also performed off-line, following the procedure proposed by Jungthöfer et al. (2000). Using this approach, trials with artifacts were identified based on the distribution of statistical parameters of the EEG epochs extracted (absolute value, standard deviation, maximum of the differences) across time points, for each channel, and - in a subsequent step - across channels. Sensors contaminated with artifacts were replaced by statistically weighted, spherical spline interpolated values. The maximum number of approximated channels in a given trial was set to 20. Such strict rejection criteria also allowed us to exclude trials contaminated by vertical and horizontal eye movements, but also trials in which the electric shock appeared during the cue presentation in the unpredictable condition. Due to the long epochs and these stringent rejection criteria, the mean rejection rate across all conditions was 34.7%. The number of remaining trials did not differ between experimental conditions, contexts $F(2,50) = 0.69$, $p = 0.505$, $\eta_p^2 = 0.03$, and cues, $F(2,50) = 0.01$, $p = 0.978$, $\eta_p^2 < 0.01$. For interpolation and all subsequent analyses, data were arithmetically transformed to the average reference. On average, 9.8 electrodes were interpolated (range 1–16). Most of these interpolated electrodes were outside of the analyzed electrodes of interest: On average, 1.2 electrodes had to be interpolated for the electrodes used in the statistical analyses. Artifact-free epochs were averaged separately for the three context conditions of peripheral stimuli and the three cue conditions within respective contexts. To ensure that the ssVEP signal in this study represented robust phase-locked driving of cortical networks at the flicker frequencies, time-domain averaging was performed before frequency-domain analysis. Reliability of the ssVEP at both driving frequencies was then quantified by means of the circular T-square statistic (Mast and Victor, 1991), which formally tests the stability of the evoked signal at a given driving frequency. To this end, the whole ssVEP viewing period for context arrays and cues in each condition was segmented in separate non-overlapping epochs containing four cycles each, and then submitted to the circular T-square algorithm. This algorithm can be used to test for the presence of an evoked signal at the frequency of interest, taking both phase and amplitude information into account. All participants included in this study showed reliable (defined as $p < 0.05$ for the Chi-square distributed circular T-square at site Oz and its nearest neighbors) evoked oscillations at the driving frequency. This suggests satisfactory signal-to-noise ratios with the trial counts available in this experiment.

The raw ssVEP for a segment when both contexts and central cues were present for a representative electrode (Oz, EGI sensor #75), the Fast Fourier Transformation on this ssVEP, and the spatial topography of the two driving frequencies averaged across all subjects and conditions are shown in Fig. 2.

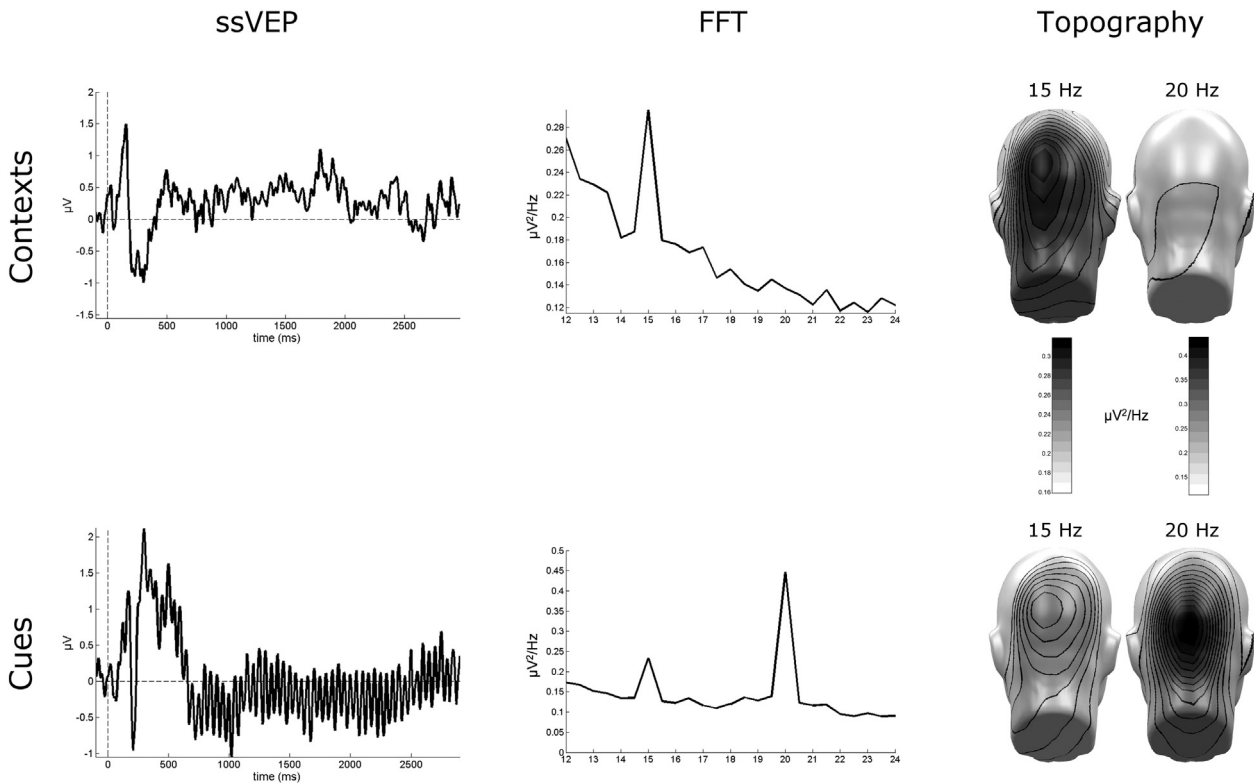


Fig. 2. Grand mean steady-state visual evoked potentials (ssVEP) evoked by context 4-object arrays (15 Hz) and central cues (20 Hz) averaged across all participants and conditions, recorded from an occipital electrode (approximately corresponding to Oz of the 10–20 system). Note that the ssVEP evoked by central cues contains a superposition of the two driving frequencies (15 and 20 Hz) due to the concurrent presence of the context flicker stream, as shown by the frequency domain representation of the same signal (Fast Fourier Transformation of the ssVEP in a time segment between 500 and 2500 ms) in the upper panel. The mean scalp topography of the central cue frequency (20 Hz) in response to the cues shows clear medial posterior activity over visual cortical areas (lower panel). In contrast, the peripheral context frequency (15 Hz) shows a more distributed topography (upper panel).

As in previous research (Miskovic and Keil, 2013b; Wieser et al., 2014a; Wieser and Keil, 2014), the time-varying amplitude of the ssVEP signal was extracted by means of Hilbert transformation on the time-domain averaged ssVEP data. To this end, data were first bandpass-filtered with a 12th order Butterworth filter having a width of 0.5-Hz (48 dB/octave), around the target frequencies of 15 and 20 Hz. Then a phase-shifted version (the analytic signal) of the empirical signal was generated using the native Hilbert function implemented in MATLAB, and the time-varying amplitude was extracted as the modulus of the empirical and analytic signal.

For context onsets, the target frequency of 15 Hz was extracted. For cue onsets, the target frequency of 20 Hz was extracted to obtain a measure of cue processing, while for the same segment the frequency of 15 Hz was extracted to obtain a measure of context processing at the same time. In order to examine the attentional engagement for context and cue processing, ssVEP amplitudes were averaged across time points in two time regions, between 100 and 1000 ms for context onsets (to include only phases in which no electric stimulation appeared), and 100–2900 ms after cue onset. The relatively early starting point (100 ms after picture onset), was chosen to ensure maximal possible SNR of the ssVEP. As was seen in previous work (e.g., Müller et al., 2008; Wieser and Keil, 2011), amplitudes of the ssVEPs in response to the central Gabor patches were most pronounced at electrode locations near Oz. For the 4-object array due to its more peripheral coverage of the visual field, the activation was more wide-spread across parieto-occipital areas. Thus, for contexts we averaged all signals spatially across an occipital cluster comprising Oz and its 19 surrounding sensors (EGI sensors 64, 65, 66, 68, 69, 70, 71, 73, 74, 75, 76, 81, 82, 83, 84, 88, 89, 90, 94, 95; see Fig. 3), whereas all signals for the Gabor patch were averaged

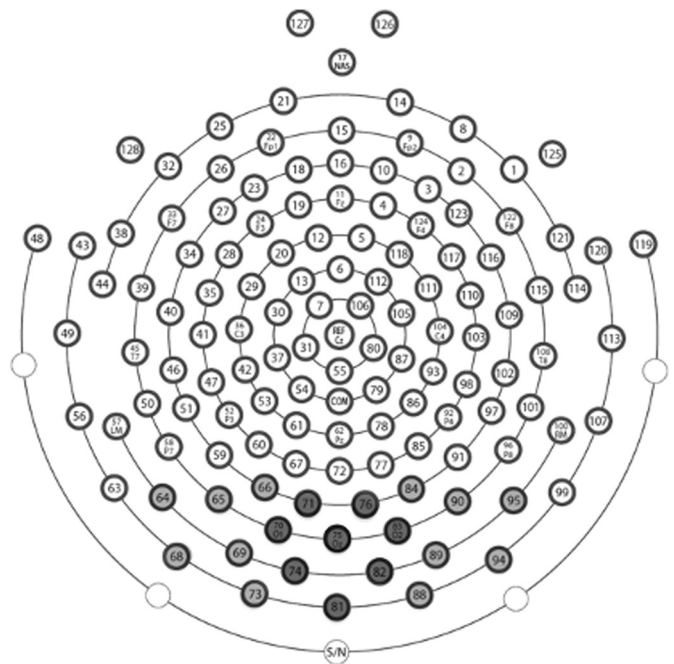


Fig. 3. Electrode layout. Bright gray indicates the 19 electrodes which were used for the analysis of the context-evoked ssVEPs, whereas dark gray shows the 9 electrodes which were used for the analysis of the cue-evoked ssVEPs. Note: dark gray electrodes were also included in the analysis of the context-evoked brain activity.

spatially across a medial-occipital cluster comprising Oz and its 8 nearest neighbors (EGI sensors 70, 71, 72, 74, 75, 76, 81, 82, 83, see Fig. 3).

Statistical analysis

Context onset

Mean ssVEP amplitudes in response to context onset (without any central cue present) were analyzed between 100 and 1000 ms with repeated-measures ANOVAs (PASW Statistics 18, Version 18.0.2, Chicago, IL, USA) containing the within-subjects factor context (N, P, U). Significant effects were followed up by *t*-tests. In order to exploratory test if the contexts were also differently processed immediately before the onset of cues, the same analysis was run for the activity 600 ms before cue onset in the respective conditions.

Cue onset

Mean ssVEP amplitudes in response to central threat cues were analyzed in between 100 and 2900 ms by repeated-measures ANOVAs (PASW Statistics 18, Version 18.0.2, Chicago, IL, USA) containing the within-subjects factor context (N, P, U). To also analyze how contexts were processed when a cue was present at the same time, the context-evoked ssVEP activity was analyzed cue-locked in the same time interval (100–2900 ms).

Ratings were averaged per condition and submitted to separate ANOVAs for valence and arousal, threat and likelihood ratings, containing the within-subject factor context (N, P, U). Ratings for contexts alone and contexts together with central cues were analyzed separately. If necessary, Greenhouse-Geisser correction of degrees of freedom (GG- ϵ) was applied. A significance level of 0.05 (two-tailed) was used for all analyses. Throughout this manuscript, the uncorrected degrees of freedom, the corrected *p* values, the Greenhouse-Geisser (GG) ϵ , and the partial η^2 (η_p^2) are reported (Picton et al., 2000).

Results

Steady-state visual evoked potentials

Context onset

The mean ssVEP amplitudes in response to the three different context conditions are given in Fig. 4A (upper row). The analysis of the context-evoked ssVEP amplitudes (100–1000 ms) revealed a significant main effect of Context, $F(2,50) = 3.31$, $p = 0.045$, $\eta_p^2 = 0.12$. As post-hoc pairwise *t*-tests show, unpredictable threat elicited larger electrocortical facilitation compared to predictable contexts, $U > P$; $t(25) = 2.50$, $p = 0.019$, Cohen's $d = 0.44$, while no significant differences emerged between predictable and unpredictable and neutral contexts, all *t*'s, < 1.71 , $p > 0.10$ (see Fig. 4A and B).

The analysis of the 600 ms immediately before cue onset did not reveal a significant difference between conditions, $F(2,50) = 1.79$, $p = 0.187$, $\eta_p^2 = 0.07$.

Cue onset

The topographies of the mean ssVEP amplitudes in response to the centrally presented cues within the three context conditions are given in Fig. 4A (lower row). The analysis of the cue-elicited ssVEP amplitude (100–2900 ms) showed a significant main effect of condition, $F(2, 50) = 6.15$, GG- $\epsilon = 0.80$, $p = 0.008$, $\eta_p^2 = 0.20$. This was due to larger ssVEP amplitudes in response to predictable threat cues compared to neutral cues, while only marginally higher amplitudes were found for predictable compared to unpredictable threats, $P > N$, $t(25) = 2.91$, $p = 0.008$, Cohen's $d = 0.37$, and $P > U$, $t(25) = 2.39$, $p = 0.063$, Cohen's $d = 0.31$, respectively. Interestingly, the cue in the unpredictable condition also elicited higher ssVEP amplitudes compared to the neutral condition, $U > N$, $t(25) = 2.09$, $p = 0.047$, Cohen's $d = 0.18$ (see Fig. 4A and B).

Interestingly, the context-evoked electrocortical activity during the presentation of the central cues was also differentially expressed in

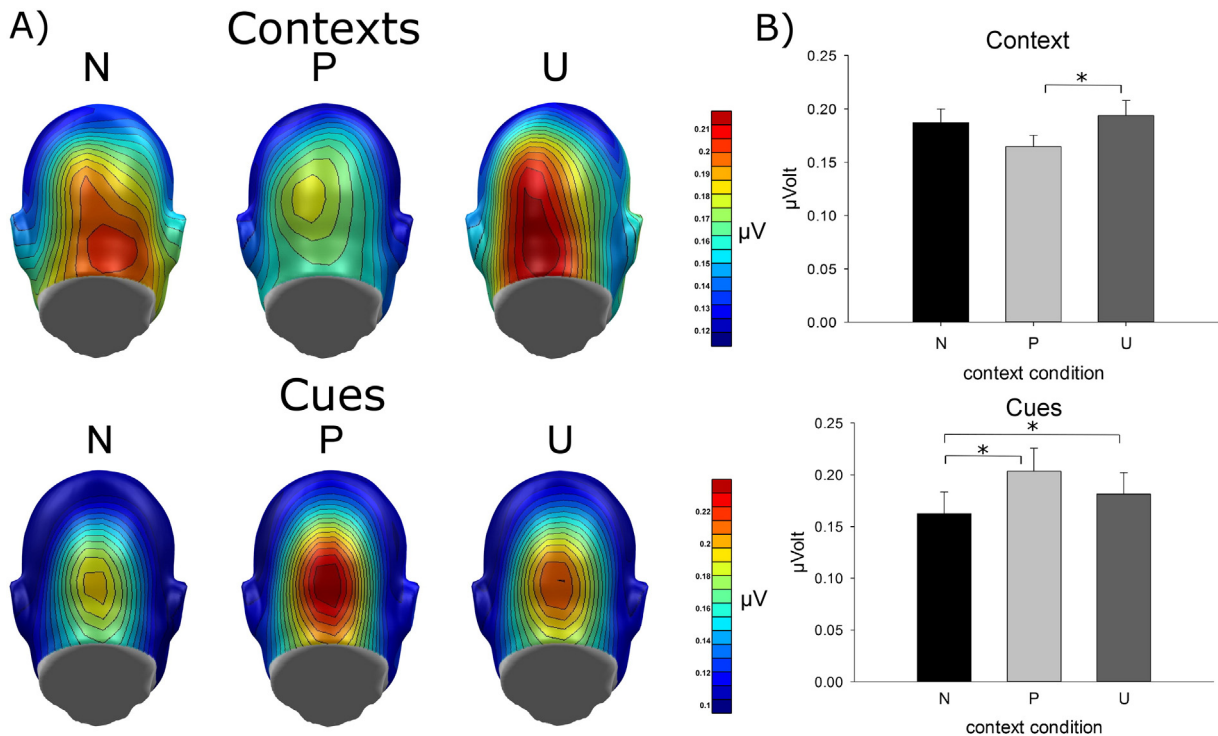


Fig. 4. A) Grand mean topographical distribution of the ssVEP amplitudes (mapping based on spherical spline interpolation) in response to the 4-object arrays stream (upper row) and cues within context conditions (lower row). Grand means are averaged across a time window between 100 and 1000 ms after stimulus onset for the contexts, and between 100 and 2900 ms after stimulus onset for the cues. Note that scales used for contexts and cues are different. B) Mean ssVEP amplitudes for the respective time windows and SEM elicited by contexts and cues. Asterisks indicate *p*-levels of < 0.05 in post-hoc comparisons.

the three conditions, $F(2, 50) = 3.29$, $p = 0.045$, $\eta_p^2 = 0.12$. In contrast to the context-related activity at the beginning of each trial, here the context when a predictable cue was present at the same time elicited marginally larger electrocortical responses compared to unpredictable contexts, $P > U$, $t(25) = 2.02$, $p = 0.054$, Cohen's $d = 0.56$. No difference emerged between N and P, and N and U conditions (Fig. 5).

Ratings

Context

The mean ratings for contexts and contexts together with cues are given in Fig. 6. For valence, the main effect of condition was highly significant, $F(2.50) = 9.08$, $p < 0.001$, $\eta_p^2 = 0.27$. Unpredictable contexts were rated as more unpleasant compared to neutral as well as predictable contexts, $t(25) = 4.50$, $p < 0.001$, Cohen's $d = 1.20$, and $t(25) = 2.73$, $p = 0.012$, Cohen's $d = 0.69$, respectively. The analysis of arousal ratings of the three context conditions revealed a trend effect for conditions, $F(2.50) = 3.05$, $p = 0.056$, $\eta_p^2 = 0.11$. This was due to higher arousal ratings for unpredictable compared to predictable contexts, $t(25) = 2.81$, $p = 0.010$, Cohen's $d = 0.50$. No differences were found in other comparisons.

Contexts were also rated differently with regard to perceived threat, $F(2.50) = 24.97$, $p < 0.001$, $\eta_p^2 = 0.50$. Unpredictable contexts were rated as more threatening than neutral as well as predictable contexts, $t(25) = 6.38$, $p < 0.001$, Cohen's $d = 1.64$, and $t(25) = 4.78$, $p < 0.001$,

Cohen's $d = 0.73$. Moreover, predictable contexts were also rated as more threatening compared to neutral contexts, $t(25) = 3.06$, $p < 0.001$, Cohen's $d = 0.96$. Expectancy of electric shock ratings also differed as expected between conditions, $F(2.50) = 220.19$, $p < 0.001$, $\eta_p^2 = 0.90$. Predictable as well as unpredictable contexts were associated with higher expected shock probabilities than neutral contexts, $t(25) = 16.89$, $p < 0.001$, Cohen's $d = 4.89$, and $t(25) = 25.73$, $p < 0.001$, Cohen's $d = 7.93$. However, no differences in expected shock probability were found between P and U conditions, $t(25) = 0.96$, $p = 0.348$, Cohen's $d = 0.23$.

Contexts with central cues

Similar to the ratings for the context arrays alone, the arrays together with the central cue were rated differentially with regards to affective valence, $F(2.50) = 15.89$, $p < 0.001$, $\eta_p^2 = 0.39$, and $F(2.50) = 20.65$, $p < 0.001$, $\eta_p^2 = 0.45$. The cues together with predictable and unpredictable contexts were rated as more negatively compared to cues within neutral contexts, $t(25) = 4.43$, $p < 0.001$, Cohen's $d = 1.34$, and $t(25) = 4.30$, $p < 0.001$, Cohen's $d = 1.25$, respectively. No differences were observed between P and U conditions, $t(25) = 1.11$, $p = 0.278$, Cohen's $d = 0.24$. Similarly, the cues within predictable and unpredictable contexts were rated as more arousing compared to cues within neutral contexts, $t(25) = 5.45$, $p < 0.001$, Cohen's $d = 0.93$, and $t(25) = 4.43$, $p < 0.001$, Cohen's $d = 0.75$. In addition, the P condition

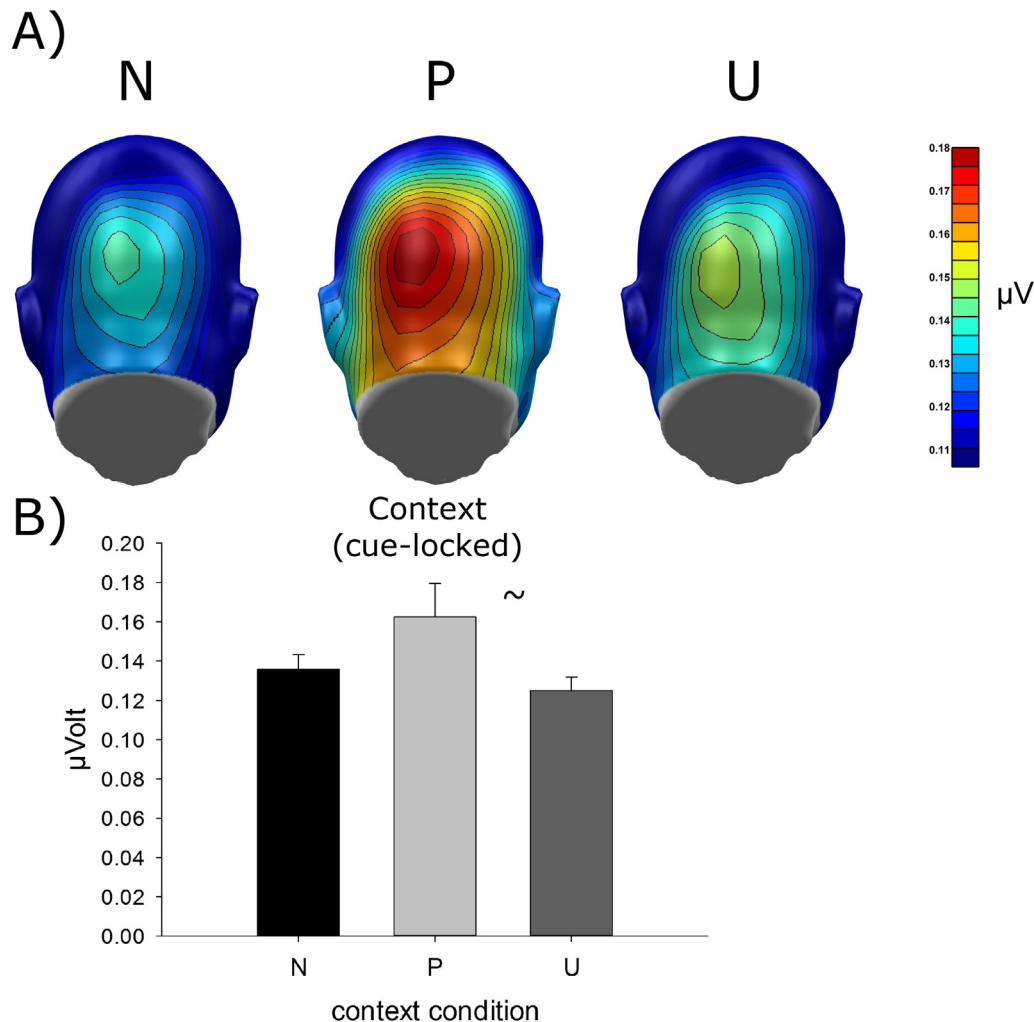


Fig. 5. A) Grand mean topographical distribution of the ssVEP amplitudes (mapping based on spherical spline interpolation) in response to context arrays when simultaneously the cues were presented (cue-locked). Grand means are averaged across a time window between 100 and 2900 ms after cue stimulus onset. B) Mean ssVEP amplitudes for the respective time windows and SEM elicited by contexts during cue presentation (cue-locked). ~ indicates marginally significant p-level of $p = 0.054$ in post-hoc comparisons.

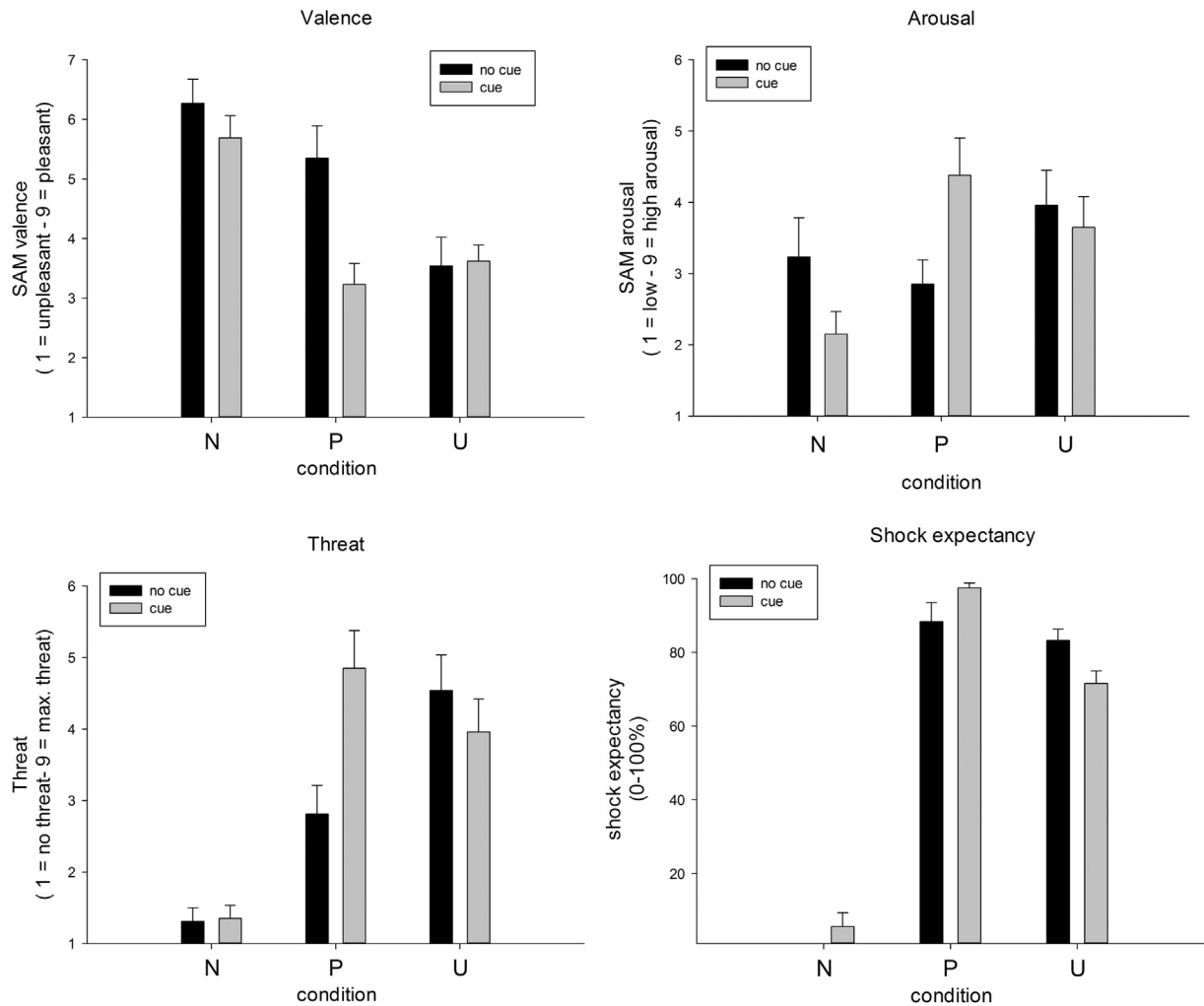


Fig. 6. Means and SEM for the ratings of affective ratings with and without cues present. Given are mean arousal (left upper panel), valence (right upper panel), threat (left lower panel), and shock expectancy (right lower panel).

was rated to be more arousing than the U condition, $t(25) = 2.38$, $p = 0.025$, Cohen's $d = 0.29$.

The contexts plus cues were also rated differentially with regard to their threat value, $F(2.50) = 31.87$, $p < 0.001$, $\eta_p^2 = 0.56$. As expected, both predictable and unpredictable contexts with central cues were rated as more threatening than the neutral condition, $t(25) = 6.64$, $p < 0.001$, Cohen's $d = 1.67$, and $t(25) = 5.71$, $p < 0.001$, Cohen's $d = 1.40$. Also, the predictable condition was rated as more threatening than the unpredictable condition, $t(25) = 2.40$, $p = 0.024$, Cohen's $d = 0.35$, which is in line with the assumption that the central cue in the predictable condition adds threat value. Also in line with our predictions, shock expectancy ratings differed between conditions, $F(2.50) = 31.87$, $p < 0.001$, $\eta_p^2 = 0.56$, such that high shock probabilities were estimated for the predictable and the unpredictable compared to the neutral condition, $t(25) = 24.09$, $p < 0.001$, Cohen's $d = 6.35$, and $t(25) = 15.09$, $p < 0.001$, Cohen's $d = 3.63$. As expected, shock probability was estimated higher for the P compared to the U condition, $t(25) = 15.08$, $p < 0.001$, Cohen's $d = 1.91$ (see Fig. 6).

Correlational analysis

In order to identify potential associations between anxiety and pain-related personality traits and enhanced responding to cued or contextual fear, bi-variate (Pearson) correlations were calculated for

questionnaire scores (STAI state and trait version, ASI, PSQ) and ssVEP amplitudes. However, no significant correlations were observed (Table 1).

Discussion

How do phasic threat and ongoing sustained anxiety affect the attention and the concomitant visuocortical processing of respective cues? To answer this research question, we adapted the NPU-threat paradigm (Schmitz and Grillon, 2012) to investigate electrocortical correlates of stimulus processing by means of ssVEPs together with frequency-tagging. To this end, the three context conditions (N = neutral, P = predictable threat, U = unpredictable threat) were indicated by three different arrays of four peripherally presented geometric shapes (triangles, squares, circles) in a 30 s continuous flicker stream of 15 Hz, while Gabor patches were centrally presented for 3 s at a different flicker frequency (20 Hz). These central cues indicated either predictably (100% reinforcement rate) the occurrence of an electric shock at cue offset (P condition) or were not associated with the occurrence of a shock (U condition). Cues were also presented in the neutral phase, which did not indicate any shock. ssVEPs at the target frequencies were analyzed for the context array onsets and for the cue onsets within the three conditions (N, P, U). Here, the context-evoked ssVEPs were also analyzed time-locked to the occurrence of the cues to obtain

Table 1
Correlation coefficients between questionnaires and ssVEP amplitudes.

	Mean ssVEP amplitude											
	Context N		Context P		Context U		Cue N		Cue P		Cue U	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
STAI state	−0.21	0.30	−0.13	0.54	−0.28	0.17	0.16	0.45	0.03	0.89	0.08	0.69
STAI trait	−0.19	0.36	−0.19	0.35	−0.25	0.21	0.18	0.39	−0.02	0.91	0.12	0.56
ASI III	−0.28	0.17	−0.26	0.20	−0.31	0.13	0.21	0.29	0.09	0.65	0.20	0.33
PSQ	−0.29	0.15	−0.32	0.11	−0.31	0.12	−0.03	0.90	−0.13	0.53	−0.06	0.76

a measure of context processing while central targets competed for attentional resources. Context arrays and context arrays together with central cues compounds were also rated with regard to affective valence and arousal, threat, and shock expectancy.

The ratings confirmed our assumptions and previous results (Davis et al., 2010; Schmitz and Grillon, 2012). Both contexts in which shocks were delivered (P and U) were rated as more negative, more threatening, and with higher expectancies for shock occurrence. Also, unpredictable contexts were rated as to be more arousing than predictable contexts, but no differences were found compared to neutral contexts here. No differences emerged between P and U except for higher threat ratings for the unpredictable compared to the predictable contexts, which indicates enhanced sustained anticipatory anxiety due to the unpredictability of shock in line with earlier findings (Grillon, 2008). The ratings of the compound of context array and central cue support the findings from the context arrays ratings, however, some interesting differences were also observed: the predictable condition was rated as much more threatening and with higher probability of shock occurrence than the unpredictable condition. This is in line with the assumption that the central cue has only predictive value in the P condition, as it reliably indicated the predictable occurrence of a shock. Hence, these differences show that the central cue adds threat value only in the predictable condition.

The ssVEPs revealed two interesting findings: First, contexts in which threat was unpredictable initially elicited facilitated electrocortical processing, which indicates heightened attention towards the unpredictable contexts (initial hypervigilance). This however was only the case in the first second and not sustained. Also, the difference to neutral contexts was not large, probably indicating that neutral contexts also receive more attention allocation initially as the participants need to make sure that it is indeed the safe N condition. The findings are in line with a recent study, in which we were able to show enhanced processing of unpredictable contexts in an ssVEP paradigm (Kastner et al., 2015), in which screenshots from two virtual offices were used as context stimuli, similar to previous context conditioning studies (Ewald et al., 2014; Glotzbach-Schoon et al., 2013a; Glotzbach-Schoon et al., 2013b). In the conditioning phase, the context stimuli flickered for 30 s and during the threat context (CTX+), the US (a 95 dB noise burst) was randomly presented once between 1000 and 12,000 ms after context onset. ssVEP amplitudes were found to be increased for the CTX+ compared to the CTX− during the conditioning phase for the whole presentation time of the context (30 s), which extends previous findings of cue conditioning studies which demonstrated increased ssVEP amplitudes to threat conditioned cues (Ahrens et al., 2015; Miskovic and Keil, 2013a, 2013b; Moratti and Keil, 2005; Moratti and Keil, 2009; Wieser et al., 2014a; Wieser et al., 2014b). Heightened ssVEP amplitudes indicate cortical facilitation and are also seen during cued shifts of spatial attention (Morgan et al., 1996; Müller et al., 1998), possibly reflecting attention mechanisms facilitating discriminative processing of stimuli (Müller and Hillyard, 2000). In contrast, however, the effects of the context array in the unpredictable condition in the present study were not long lasting, but restricted to the very onset of the condition. Although we had expected

longer hypervigilance, one has to note that in contrast to the original NPU-threat paradigm we did not instruct context significance (either N, P, U) before each block, instead participants had to keep the meaning of each context in mind. This may have caused some sort of memory interference because participants had to remember all contexts throughout the experiment. However, as the threat expectancy ratings show participants were able to distinguish predictable and unpredictable contexts after the experiment, this explanation seems questionable. Another possible explanation may be a shift of attention from the visual context array to the site of electric stimulation in the unpredictable condition only, which would possibly interfere with processing of the visual context.

The analysis of the cues showed as expected enhanced activity for the predictable threat cue compared to the cue in the neutral condition, which is in line with findings of enhanced startle responses for the cues in the predictable condition (Grillon, 2008; Schmitz and Grillon, 2012). Interestingly, no difference was observed in the electrocortical responses to the predictable threat cue compared to the cue in the unpredictable condition (albeit near significance) while cues during the unpredictable condition also elicited enhanced electrocortical activity compared to cues in the neutral condition. Most interestingly, contexts during presentation of the threat cue in the P condition showed also enhanced electrocortical activity, which indicated that the visual system in the face of threat also enhanced attentional resource allocations to peripheral cues. This is in line with recent findings showing that centrally presented fear faces enhance the processing of peripheral threatening scenes (Wieser and Keil, 2014). However, it has to be acknowledged that this enhanced processing might also be caused by a methodological issue in our current design. In contrast to the original NPU-threat test, we used the same cues in all three conditions (Gabor patch). Thus, in the predictable condition, the combination of the context and the cue gave the information about imminent threat. Consequently, it may well be that participants widened their attentional focus both to the cue and the context to identify in which conditions they were.

No associations between measures of state and trait anxiety and of anxiety sensitivity and pain sensitivity and electrocortical responses were observed. The main reason may be low statistical power, as associations between anxiety sensitivity and attentional processes were found in a recent sample of >130 participants (Nelson et al., 2015). In order to further understand possible associations between anxiety-related traits and attentional mechanisms during predictable and unpredictable threat, studies including larger samples with possibly pre-screened participants seem warranted.

Taken together, the present findings offer a first glimpse into attention mechanisms during context and cue processing in an NPU-threat test. Indicators of sustained unpredictable (context) and about predictable threat showed enhanced electrocortical processing and attentional capture. Further research is needed to quantify the amount of learning in this adapted NPU-threat test, the modulation of the attention deployment in anxious participants, and finally, this paradigm may also be used to investigate the time-course of cue and context conditioning and extinctions mechanisms by using single-trial ssVEP estimates (Wieser et al., 2014b).

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