Research report

Hypervigilance during anxiety and selective attention during fear: Using steady-state visual evoked potentials (ssVEPs) to disentangle attention mechanisms during predictable and unpredictable threat

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Abstract

Anxiety is induced by unpredictable threat, and presumably characterized by enhanced vigilance. In contrast, fear is elicited by imminent threat and leads to phasic responses with selective attention. In order to investigate attention mechanisms and defensive responding during fear and anxiety, we employed an adaptation of the NPU-threat test and measured cortical (steady-state visual evoked potentials, ssVEPs), physiological (heart rate, HR), and subjective responses (ratings) to predictable (fear-related) and unpredictable (anxiety-related) threat in 42 healthy participants. An aversive unconditioned stimulus (US, loud noise) was 100% predicted by a cue (predictable P-cue) in one context (predictable P-context), but appeared unpredictably within a different context (unpredictable U-context, U-cue), while it was never delivered in a neutral safe context (N-cue, N-context). In response to predictable threat (P-cue), increased ssVEP amplitudes and accelerated HR were found. Both predictable and unpredictable contexts yielded increased ssVEP amplitudes compared to the safe context. Interestingly, in the unpredictable context participants showed longer-lasting visuocortical activation than in the predictable context, supporting the notion of heightened vigilance during anxiety. In parallel, HR decelerated to both threat contexts indicating fear bradycardia to these threatening contexts as compared to the safe context. These results support the idea of hypervigilance in anxiety-like situations reflected in a long-lasting facilitated processing of sensory information, in contrast to increased selective attention to specific imminent threat during fear. Thus, this study further supports the defense-cascade model with vigilance and orienting in the post-encounter phase of threat (anxiety), while selective attention and defensive mobilization in the circa-strike phase of threat (fear).

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1. Introduction

According to DSM-5, fear is oriented towards specific imminent threat, while anxiety is defined as the anticipation of unspecified future threat (American Psychiatric Association, 2013). In the same vein, experimental studies consider fear as a phasic response to concrete threat that dissolves quickly when the respective threat is removed, while anxiety is regarded as a sustained affective response (Davis, Walker, Miles, & Grillon, 2010; Perusini & Fanselow, 2015; Toyote, Fadok, & Luthi, 2015). In consequence, fear is expected to activate selective attention mechanisms towards a specific threat stimulus, whereas anxiety should lead to a sustained heightened vigilance, whose broadening attention aims at detecting potential but yet to be detected threat in the environment.

In experimental research, fear can be modeled using cue conditioning, where a cue becomes a reliable predictable signal of an aversive unconditioned stimulus and consequently elicits fear responses. Anxiety can be modeled using context conditioning, where the US is associated with a long-lasting stimulus, i.e., the context, in the absence of a predictable cue. As a consequence, a sustained fear response (i.e., anxiety) is elicited throughout the duration of the context (Davis et al., 2010). Thus, the predictability of the aversive event plays a crucial role during these conditioning paradigms (Bouton, 1994; Maren, Phan, & Libezron, 2013). Fear responses reflecting defensive activation such as increased startle responses, can be evoked by a cue predicting an aversive event (Andreatta & Pauli, 2015; Bradley, Moulder, & Lang, 2005). A context which is learned to be associated with aversive consequences without predicting the exact time of their occurrence elicits anxiety-related responses (Andreatta, Neudeyr, Glotzbach-Schoon, Muhlberger, & Pauli, 2017; Baas, Nugent, Lissek, Pine, & Grillon, 2004; Grillon, Baas, Lissek, Smith, & Milstein, 2004) and avoidance of this context (Glotzbach, Ewald, Andreatta, Pauli, & Muhlberger, 2012; Grillon, Baas, Cornwell, & Johnson, 2006).

The neuronal systems underlying phasic fear and tonic anxiety are seen as two overlapping, but nevertheless distinct networks (Davis et al., 2010). While the central nucleus of the amygdala plays a central role in predictable threat (Boll, Gamer, Gluth, Finsterbusch, & Buchel, 2012), the bed nucleus of the stria terminalis BNST) is involved in processing unpredictable threat (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011). In addition, several studies reported an increased and sustained activation of extended visual areas, (anterior cingulate cortex ACC), insula and parietal cortex (Alvarez et al., 2011; Andreatta et al., 2015; Hasler et al., 2007; Maren et al., 2013). These latter areas are also part of the attention network, and hence, these findings support the idea of sustained anxiety being associated with enhanced vigilance.

Fear and anxiety can also be classified according to different stages of the defense cascade model (Blanchard, Yudko, Rodgers, & Blanchard, 1993; Bradley, Codispoti, Cuthbert, & Lang, 2001; Fanselow, 1994). In this model, the proximity of the source of threat determines the type of defensive behavior. During the pre-encounter phase, where threat is looming, animals as well as humans show an orienting response with an interplay of the parasympathetic and sympathetic nervous system (Blanchard et al., 2001; Cacioppo & Berntson, 1994). Together with the post-encounter phase, when threat is identified but not close, this stage is associated with anxiety responses since the threat has not clearly been identified yet. A shrinking distance to the source of threat, however, leads to mobilization of the organism’s resources, which is regulated by activity of the sympathetic nervous system (Blanchard et al., 1993; Low, Lang, Smith, & Bradley, 2008). This transition from post-encounter to circa-strike phase is associated with the state of fear, since the organism is directly threatened by the predator. These two stages come along with different heart rate HR) response patterns, and thereby differentiate between fear and anxiety with a HR deceleration during the post-encounter stage, and an HR acceleration during imminent threat, i.e., circa-strike stage (Bradley et al., 2001; Low et al., 2008). In addition, recent studies showed that heart rate accelerates or decelerates not only as a function of threat imminence but also as a function of behavioral options. For instance, it was shown that when participants could not actively avoid the threat, stronger heart rate deceleration was observed (Low, Weymar, & Hamm, 2015; Wendt, Low, Weymar, Lotze, & Hamm, 2017). In order to directly compare anxiety and fear responses, Schmitz and Grillon developed a paradigm, which manipulates the predictability of threat, the so-called NPU-threat test (2012). The NPU-threat test includes three different conditions (neutral, predictable, and unpredictable threat). In each, a neutral or threat context is determined by an instruction presented for a long duration (>30 sec). During these periods, a cue occurs with a relatively short duration (i.e., 8 sec) repeatedly. In the (neutral condition N), no aversive stimulus (e.g., electric shock) is presented, while in the (predictable condition P) the aversive stimulus only occurs during the presentation of the respective cue. In the (unpredictable condition U), the aversive stimulus occurs unpredicatbly within the context-only parts of the trial. Startle amplitudes measured during the cue presentation revealed a fear-potentiated startle during the cue in the P-condition compared to all other conditions. For the context-only parts (i.e., periods without any cue presentations), startle amplitudes were increased during the (unpredictable context U-context) compared to the two other conditions, which is defined as anxiety-potentiated startle (Grillon et al., 2004). As indicated by this startle modulation to predictable and unpredictable threat, the motivational significance changes for the context and cue stimuli and thereby presumably facilitates sensory processing of these stimuli (Lang, Bradley, & Cuthbert, 1990). However, these results do not allow any conclusions yet whether anxiety and fear differently affect sensory processing and whether any temporal dynamics in this processing can differentiate between fear and anxiety.

The (steady-state visually evoked potential ssVEP) as an oscillatory field potential measured by (electro-encephalogram EEG), perfectly meets these requirements as
continuous measure of sensory processing (Norcia, Appelbaum, Ales, Cotterau, & Rossion, 2015; Vialatte, Maurice, Dauwels, & Cichocki, 2010; Wieser, Miskovic, & Keil, 2016a). The ssVEP signal is elicited by the driving frequency of a flickering stimulus and reflects activity of the primary and extended visual cortex as well contributions of higher order cortices (Di Russo et al., 2007; Müller, Teder, & Hillyard, 1997; Wieser & Keil, 2011). As the frequency of the ssVEP signal is known, it allows to obtain a time-frequency sensitive measure of visuocortical activity in response to the respective stimulus (Müller, Teder-Salejarvi, & Hillyard, 1998; Norcia et al., 2015). Augmented ssVEP amplitudes reveal increased attentional resources towards a stimulus (Keil, Gruber, & Müller, 2001). Furthermore, an increased motivational significance of a stimulus evokes heightened oscillatory cortical responses (e.g., Keil et al., 2010; Keil et al., 2003; Wieser, McTeague, & Keil, 2011, 2012). Similarly, a stimulus which was learned to be of significance as during fear conditioning, elicits higher ssVEP amplitudes in visual cortices (Miskovic & Keil, 2012, 2013b; Moratti, Keil, & Müller, 2006; Wieser et al., 2008, 2014a, 2014b). This does not only apply to cue-fear conditioning, but could be recently shown in context-anxiety conditioning, with sustained ssVEP amplitudes during contextual anxiety. Importantly, such higher motivational attention was maintained throughout the duration of the context (Kastner, Pauli, & Wieser, 2015). Moreover, the ssVEP approach is perfectly suited to address questions regarding the perception of social stimuli within contextual information (Wieser & Keil, 2014; Wieser et al., 2016a).

In a previous study, we successfully adapted the NPU-threat test in order to compare attention processes during predictable and unpredictable threat via ssVEPs using simple Gabor patches and surrounding arrays of geometric shapes (Wieser, Reicherts, Juravle, & Von Leupoldt, 2016b). In brief, these results showed that attention and sensory processing are selectively enhanced for the predictable cue and the onset of the unpredictable context. The present study aimed at extending these findings by using more complex, photorealistic stimuli. The continuous visuocortical changes in response to predictable and unpredictable threat were assessed in order to observe the high-resolution changes in time. It was assumed that heightened ssVEP amplitudes elicited by the context of the unpredictable condition should exceed both the activation during the neutral and predictable contexts and be maintained throughout the context. During the cue presentations, the predictable cue is expected to capture attentional resources compared to the neutral and unpredictable cue, as could be observed in previous studies on cue conditioning (Miskovic & Keil, 2012, 2013b; Moratti et al., 2006; Wieser et al., 2008, 2014a, 2014b) as well as in our previous NPU-threat study (Wieser et al., 2016b). Moreover, we expected that this differential response would be also reflected in cardiovascular responses, with HR deceleration in the unpredictable context as an index of anxiety, and HR acceleration during the cue in the predictable condition as an index of defensive mobilization (Bradley et al., 2001; Löw et al., 2008).

2. Methods

2.1. Participants

Participants were 45 female students, who were recruited via a local online platform. Exclusion criteria were any psychiatric or neurological disorders (self-report). Participants received 9 Euros as study reimbursement. Due to a failed differentiation between the three contexts, three participants had to be excluded from analysis. Resulting participants’ age ranged from 18 to 34 (M = 23.14, SD = 3.35). Mean trait and state anxiety scores as measured with the Spielberger State-Trait Anxiety Inventory were 35.19 (SD = 8.49) and 33.95 (SD = 7.52), respectively.

2.2. Stimulus materials and procedure

Three context stimuli and three cue stimuli were used. The context stimuli were screenshots from virtual offices created with the Source Engine from the Valve Corporation (Bellevue, USA), used in previous studies (Andreatta et al., 2015; Glotzbach et al., 2012). The office differed in layout and furniture, but pictures were balanced for luminance and complexity by controlling the luminance values returned by the Image Manipulation Program GIMP 2.8.14 (159, 160, 160, for the context stimuli) and a quantitative measure of entropy, calculated with the respective MATLAB function (6.68, 6.80 and 7.20, respectively). The cue stimuli were taken from the Radboud Faces database RaFD; Langner et al., 2010). Three female faces with frontal orientation and neutral expressions were chosen (RaFD090_02, RaFD090_32, RaFD090_58). As the RaFD pictures only depict faces, the facial stimuli and a neutral female body (also created with the Source Engine) were merged in order to create a more realistic situation with a person standing in an office room (see Fig. 1a). Stimuli subtended a horizontal visual angle of 33.38° and 28.61° and a vertical visual angle of 23.90° and 5.32° for context stimuli and cue stimuli, respectively. In order to evoke ssVEPs, stimuli were presented in flickering mode at either 12 or 15 Hz. If the context-stimuli flickered at 12 Hz, the cue stimuli were superimposed at the other frequency (i.e., 15 Hz), and vice versa (counterbalanced across participants). The stimuli were presented on a computer screen with a refresh rate of 60 Hz, which was positioned at a distance of 100 cm from the participants’ eyes. The combination of context and cue stimuli and the assignment to the three conditions was counterbalanced across participants. A loud startle probe (white noise), presented via headphones at 95 dB for 500 msec served as aversive unconditioned stimulus (US).

All stimuli were rated before and after the experimental session for valence, arousal, and anxiety on 9-point visual analog scales (VAS). These ranged from 1 “very unpleasant”, “very calm” and “not threatening” to 9 “very pleasant”, “very arousing” and “very threatening”, respectively. Context and cue stimuli were rated separately, as well as cue-context compounds with the cue in the foreground, similar to how they were appearing in the experimental session.
After the first ratings, participants received instructions regarding the three different conditions. Participants were explained that they were about to learn how to predict the occurrence of the aversive noise and under which condition it would not be predictable. They were informed about the three conditions called “no noise”, “predictable noise” and “unpredictable noise” and whether to expect the loud noise. Then the corresponding picture of the room and the associated person were displayed. Afterwards, participants were asked to assign each context and cue to the right condition in order to check their comprehension of instructions. A similar test was performed after the experimental session. As mentioned above, three participants had to be excluded afterwards, as they mixed up the conditions.

The design of the study followed the procedure suggested by Schmitz and Grillon (2012) for the NPU paradigm (Fig. 1b). One trial comprised the presentation of one context for 60 sec and three occurrences of the associated cue for 4 sec each, with context-only intervals of 11–13 sec. An instruction screen preceded each trial for 2,000 msec containing the information about the following condition. An inter-trial interval showing a blank screen (ITI) of 1,750–2,000 msec followed each trial. The aversive noise occurred once or twice within each trial for the predictable and unpredictable condition (50% 1x occurrence, 50% 2x occurrences within a trial), but was never presented in the neutral condition. In the predictable condition, the aversive noise was presented during the last 500 msec of cue presentation, with the cue and aversive noise co-terminating. In the unpredictable condition, the aversive noise was presented randomly in the context-only intervals. The order of trials was determined following the protocol of Schmitz and Grillon (2012) with blocks of trials with PNUNUNP or UNPNPNU order. The experimental session consisted of four of these blocks with alternating order. After half of the session, participants had a short break. Altogether, 8 predictable, 8 unpredictable and 12 neutral conditions were presented.

2.3. Data recording and analysis

2.3.1. Rating data
The ratings of valence, arousal, and anxiety for the contexts, cues, and for the cue-context compounds before and after the task were analyzed with repeated-measures ANOVAs including the within-subject factor condition (N, P, U) (Grillon et al., 2004).

2.3.2. EEG data
EEG was continuously recorded with a HydroCel Geodesic Sensor Net (Electrical Geodesics, Inc., Eugene, OR) with 128 sensors (sampling rate of 250 Hz and online band pass filter of 0.1–100 Hz). The vertex electrode (Cz) served as online-reference electrode. The impedance of each sensor was kept below 50 kΩ, as recommended for the Electrical Geodesics high-impedance amplifiers.

The raw ssVEP signal averaged across all participants and conditions for a representative electrode (sensor 75, Oz) together with the Fast Fourier Transformation and the resulting frequency topographies of this ssVEP signal are shown in Fig. 2. EEG data preprocessing was performed with the Matlab based software emeeg 2.4 (Peyk, De Cesarei, & Junghöfer, 2011) for contexts and cues separately. For the contexts, data was low-pass filtered at 40 Hz and event-related epochs were extracted from 600 msec before until 60,600 msec after context stimulus onset. Due to the unusual long segment length of 60 sec for the context stimuli, no artifact detection was performed, as it would have resulted in a rejection of more than 50% of the trials due to eye movements and eye blinks. Thus, all 8 trials per condition were used for this analysis. The raw ssVEP signal averaged across all participants and conditions for a representative electrode (sensor 75, Oz) together with the Fast Fourier Transformation and the resulting frequency topographies of this ssVEP signal are shown in Fig. 2. EEG data preprocessing was performed with the Matlab based software emeeg 2.4 (Peyk, De Cesarei, & Junghöfer, 2011) for contexts and cues separately. For the contexts, data was low-pass filtered at 40 Hz and event-related epochs were extracted from 600 msec before until 60,600 msec after context stimulus onset. Due to the unusual long segment length of 60 sec for the context stimuli, no artifact detection was performed, as it would have resulted in a rejection of more than 50% of the trials due to eye movements and eye blinks. Thus, all 8 trials per condition were used for this analysis. Due to the robustness of the ssVEP signal, this approach seems feasible and has been used in other paradigms (Rossion & Boremanse, 2011). In order to assess cortical activation during cue processing separately, data was low-pass filtered at 40 Hz and discrete epochs were extracted,
from 600 msec before to 4,600 msec after cue onset. Artifact detection on the preprocessed data was performed in a two-step method as described by Junghöfer, Elbert, Tucker, & Rockstroh, 2000. All epochs were averaged separately for every condition, and contexts and cues. A Hilbert transformation using a MATLAB script (see Miskovic & Keil, 2013a, for a detailed description) was performed on the raw signal in order to gain time varying ssVEP amplitudes in the respective stimulation frequencies.

Statistical analysis was performed using IBM SPSS Statistics 22. For context-related responses of the whole trial length (60 sec), a 3 x 5 repeated measures ANOVA including the within-subject factors condition (N, P, U) and five time windows (± 12,000 msec) was calculated, using the ssVEP signal averages across two occipito-lateral sensor clusters with 5 sensors each (Fig. 2d). The clusters were chosen according to a previous study from our lab (Kastner et al., 2015), in which context effects were found to be maximal. In a second step, four segments with equal length of 7,000 msec were cut out of the context-only interval between the cue presentations (0–7,000, 17,000–24,000, 34,000–41,000, 51,000–58,000 msec from context onset) to exclude any possible effects driven by the cue presentation. A repeated-measures ANOVA including the within-subject factors laterality (left vs right electrodes cluster), condition (N, P, U) and time (4 segments) was conducted.

For the cue-related responses, repeated-measures ANOVAs including the factors condition (N, P, U) and time window (4 time windows of 1,000 msec) were conducted for the ssVEP signal elicited by the cue and separately for the ssVEP signal elicited by the context during cue presentation. A medial-occipital sensor cluster with six sensors around Oz (Fig. 2d) was used for extracting the cue-evoked ssVEP signal (Kastner et al., 2015; Wieser et al., 2016b).

2.3.3. Heart rate (HR)
HR was assessed by recording an electrocardiogram with two adhesive Ag/AgCl electrodes. To calculate continuous heart rate, R-spikes in the electrocardiogram were counted semi-automatically using VisionAnalyzer2.0 software and the inter-beat-interval (IBI) was determined. Then, continuous HR estimates were determined per sampling point (sampling rate: 1000 Hz). Due to artifacts which made R-peak scoring impossible, only 39 participants could be included in the analysis for context effects and 36 regarding cue effects. Segments of 4 sec during cue presentation were averaged for each condition as were the segments of the first 10 sec of the trial during which only the context was presented. We decided to analyze the first 10 sec after context onset only, since this was the only time where no cue was presented across all trials. Then, change scores were calculated by subtracting a baseline of 1 sec before context or cue onset, respectively. HR response
was scored as mean activity in consecutive 1 sec bins. A repeated-measures ANOVA including the within-subject factors condition (N, P, U) and four time windows of 1 sec was conducted for the cue segments, while the analysis for the context effects included 10 time windows of 1 msec.

In all analyses, the alpha level was set at \( p < .05 \). If the assumption of sphericity was violated, Greenhouse-Geisser correction was applied and the Greenhouse-Geisser Epsilon (GG-e) is reported. Effect sizes are reported as partial eta (\( \eta^2_p \)).

### 3. Results

#### 3.1. Ratings

As the pre-ratings did not reveal any differences in valence, arousal or anxiety for the context and cue stimuli (all \( p > .482 \)). Regarding the post-ratings (Table 1), the analysis of the contexts ratings revealed a main effect of condition \([F(2, 82) = 26.05, p < .001, \eta^2_p = .39, \text{GG-e} = .84]\), with more negative valence ratings for the predictable \(t(41) = 5.88, p < .001\) and unpredictable context \(t(41) = 5.60, p < .001\) compared to the neutral context, while they did not differ from each other \(p = .348\). Similarly, a main effect of condition was found for arousal \([F(2, 82) = 37.67, p < .001, \eta^2_p = .479]\) and anxiety \([F(2, 82) = 36.47, p < .001, \eta^2_p = .47, \text{GG-e} = .87]\), revealing increased arousal and anxiety ratings for the predictable \(t(41) = 7.37, p < .001\) and unpredictable context \(t(41) = 8.13, p < .001\) and unpredictable context \(t(41) = 6.96, p < .001\); \(t(41) = 6.65, p < .001\) compared to neutral context. Again, the predictable and unpredictable context did not show differences in arousal \(p = .297\) or anxiety ratings \(p = .372\).

### Table 1 – Mean ratings (SD) Cue-Context compounds, Cues, and Contexts after the experimental session, in the three experimental conditions (N: No Shock; P: Predictable Shock; U: Unpredictable Shock).

<table>
<thead>
<tr>
<th>Cue + Context (n = 42)</th>
<th>N</th>
<th>P</th>
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<td>M</td>
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<td>Valence</td>
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<td></td>
<td>6.50</td>
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<td>Arousal</td>
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<td>Context only (n = 42)</td>
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Note: Due to saving failure, the cue ratings were only available for 35 participants.

Regarding the cues-in-contexts ratings, a similar pattern evolved. A main effect of condition for the valence ratings \([F(2, 82) = 45.90, p < .001, \eta^2_p = .53]\) showed more negative valence ratings for the predictable \(t(41) = 7.95, p < .001\) and unpredictable cue \(t(41) = 7.88, p < .001\) compared to the neutral cue but no difference between the two former \(p = .936\). Similarly, a main effect for arousal \([F(2, 82) = 38.87, p < .001, \eta^2_p = .49]\) and anxiety ratings \([F(2, 82) = 38.40, p < .001, \eta^2_p = .48]\) revealed increased arousal and anxiety for the predictable [arousal: \(t(41) = 7.33, p < .001\); anxiety: \(t(41) = 7.66, p < .001\) and unpredictable cue [arousal: \(t(41) = 7.05, p < .001\); anxiety: \(t(41) = 6.51, p < .001\) compared to the neutral cue; the predictable and the unpredictable conditions did not differ in arousal nor anxiety (all \( p > .387\)).

The cue-ratings (only available from 35 participants due to saving errors), revealed a similar pattern. A main effect of condition for the valence ratings \([F(2, 68) = 27.55, p < .001, \eta^2_p = .45]\) showed more negative valence ratings for the predictable \(t(34) = 6.05, p < .001\) and unpredictable cue \(t(34) = 5.86, p < .001\) compared to the neutral cue, but no difference between the former two \(p = .299\). Similarly, a main effect for arousal \([F(2, 68) = 27.92, p < .001, \eta^2_p = .45]\) and anxiety ratings \([F(2, 68) = 30.93, p < .001, \eta^2_p = .48]\) revealed increased arousal and anxiety for the predictable [arousal: \(t(34) = 5.90, p < .001\); anxiety: \(t(34) = 6.71, p < .001\) and unpredictable cue [arousal: \(t(34) = 5.75, p < .001\); anxiety: \(t(41) = 5.54, p < .001\) compared to the neutral cue; again, no difference was found between predictable and unpredictable cues.

#### 3.2. EEG data

##### 3.2.1. Cortical response to contexts

The analysis of the whole 60 sec context segments (including cue presentations) showed a main effect of condition \([F(2, 82) = 9.64, p < .001, \eta^2_p = .42]\) indicating increased ssVEP amplitudes during the predictable \(t(41) = 7.02, p < .001\) and unpredictable \(t(41) = 5.65, p < .001\) compared to the neutral context, while there was no significant difference between predictable and unpredictable contexts \(p = .633\) (see Fig. 3). A main effect of time \([F(4, 164) = 53.51, p < .001, \eta^2_p = .566, \text{GG-e} = .30]\) showed a significant decrease of the ssVEP signal from the first (0–12 sec) to the second time window (12–24 sec) across all three conditions \(t(41) = 7.49, p < .001\) and to all other following time windows \(t(s) > 6.62, p < .001\). As latency did not return any significant main effect nor interaction (all \( p > .520\)), this factor was disregarded in any further analyses and the two sensor clusters were combined.

The analysis of the epochs without any cue presentation revealed a main effect of condition \([F(2, 82) = 23.04, p < .001, \eta^2_p = .36]\) and phase \([F(3, 123) = 54.93, p < .001, \eta^2_p = .57, \text{GG-e} = .43]\) (Fig. 4). Furthermore, a significant interaction of condition and time was found \([F(6, 246) = 2.26, p = .039, \eta^2_p = .05, \text{GG-e} = .62]\). The conditions did not show any differential cortical activation in the first time interval (0–7 sec) \([F(2, 82) = 2.18, p = .119, \eta^2_p = .051]\), while a significant difference between conditions was found in the second (17–24 sec) \([F(2, 82) = 29.53, p < .001, \eta^2_p = .42]\) and third time interval (34–41 sec) \([F(2, 82) = 22.25, p < .001, \eta^2_p = .35]\), with increased cortical activation for the predictable [second: \(t(41) = 6.00, p < .001\)].
The main effect of condition [second: t (41) = 5.88, p < .001] and the unpredictable condition [second: t (41) = 7.41, p < .001; third: t (41) = 5.49, p < .001] compared to the neutral context. The predictable and unpredictable context did not differ from each other during these first three time intervals (all ps > .269). Interestingly, in the fourth time interval (51–58 sec) the main effect of condition \([F (2, 82) = 28.17, p < .001, \eta_p^2 = .407]\) indicated besides significant higher cortical activity during both the predictable \([t (41) = 5.26, p < .001]\) and unpredictable context \([t (41) = 6.88, p < .001]\) compared to the neutral context, a heightened ssVEP amplitude in response to the unpredictable compared to the predictable context \([t (41) = 2.73, p = .009]\).

### 3.2.2. Cortical response to cues

Analysis of the cue segments (4,000 msec) revealed marginally significant different cortical responses \([F (2, 82) = 2.86, p = .063, \eta_p^2 = .065]\). As this main effect was predicted by a main hypothesis, planned paired sampled t-tests were performed. These showed an increased ssVEP signal elicited by the predictable compared to the neutral cue \([t (41) = 2.17, p = .036]\), while neither the comparison between neutral and unpredictable cue nor between predictable and unpredictable cue returned significant (all ps > .196).

A similar analysis was performed for the ssVEP signal elicited by the contexts during cue presentation. This revealed a main effect of condition \([F (2, 82) = 3.68, p = .029, \eta_p^2 = .082]\). During cue presentation, the predictable context elicited increased ssVEP amplitudes as compared to the neutral context \([t (41) = 3.21, p = .003]\), while in the unpredictable cue condition, the context did not show any differential cortical activation compared to the neutral and the predictable context (all ps > .153) (see Fig. 5).

### 3.3. Heart rate

#### 3.3.1. Response to context

The heart rate deceleration for the predictable and unpredictable context compared to the neutral context is depicted in Fig. 6A. The repeated measures ANOVA returned a significant main effect of condition \([F (2, 76) = 5.62, GG-G = .91, p = .005, \eta_p^2 = .13]\) and time \([F (9, 342) = 14.37, GG-G = .35, p < .001, \eta_p^2 = .27]\), and a significant interaction condition x time \([F (18, 684) = 2.80, GG-G = .36, p = .010, \eta_p^2 = .07]\). Except for the first two time intervals, both predictable and unpredictable contexts elicited a significantly larger HR decrease compared to the neutral context (ts > 2.20, ps < .034). The predictable and unpredictable contexts did not elicit any differential heart rate in all time windows (all ps > .104).

#### 3.3.2. Response to cues

The repeated measures ANOVA concerning the HR changes during cue presentation returned a significant main effect of condition \([F (2, 70) = 15.01, GG-G = .78, p < .001, \eta_p^2 = .30]\) and time \([F (3, 105) = 26.07, GG-G = .52, p < .001, \eta_p^2 = .427]\), as well as a significant interaction between those factors \([F (6, 210) = 10.44, GG-G = .49, p < .001, \eta_p^2 = .23]\). As seen in Fig. 6B, the predictable cue elicited a significant HR acceleration between 1 and 4 sec compared to the neutral (ts > .251, ps < .017) and the unpredictable condition (ts > .298, ps < .005).

### 4. Discussion

The present study investigated the differential influence of predictability of threat on attention processes, with the goal to demarcate the state of fear as a phasic response with selective attention during imminent threat and the state of anxiety as a sustained response with sustained vigilance. A strength of this study is the use of steady-state visual evoked potentials within the NPU-test allowing a continuous assessment of attention-modulated electrocortical responses, thereby taking into account the temporal distinctiveness between fear and anxiety as one key characteristic differentiating between these two affective states.

As expected and in line with previous findings (e.g., Grillon et al., 2004; Wieser et al., 2016b), the contexts associated with the aversive event (i.e., P- and U-context) were rated more arousing and anxiogenic as well as more negative than the control context (N-context). Contrary to previous studies, we found no differences between predictable and unpredictable contexts (Grillon et al., 2009). A possible explanation for this lack of differentiation may be that in our paradigm, the participants actually had to learn and remember in which context they were (different office.

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**Fig. 3** — Grand average scalp topographies of ssVEP amplitudes in response to the neutral, predictable, and unpredictable contexts, averaged across the whole trial duration (60,000 msec).
rooms), whereas in the studies by Grillon and colleagues participants continuously received written information about the specific context on the screen. Possibly, the differentiation between U and P contexts in our protocol might have been more complex, which consequently led to a less clear discrimination between the two conditions. The ratings for the cues embedded in the respective context revealed a similar pattern. The cues presented in both the unpredictable and predictable condition were rated as more unpleasant, more arousing and more anxiogenic compared to the cue presented in the neutral context. The same was found for the ratings of predictable and unpredictable cues alone (Alvarez et al., 2011; Haaker, Lonsdorf, Thanellou, & Kalisch, 2013). Based on these ratings we conclude that all stimuli

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Fig. 4 – Grand average scalp topographies of ssVEP amplitudes in response to the neutral, predictable, and unpredictable contexts. The ssVEP signal was averaged and analyzed separately for four selected time intervals (7 sec) of the trial during which no cues were presented (0–7 sec, 17–24 sec, 34–41 sec, and 51–58 sec) after context onset.
associated with the US, even when not in an explicit manner, elicited strong negative affective responses.

During both the predictable and unpredictable condition, increased cortical activation in visual cortex was observed throughout the whole 60 sec of context presentation. Interestingly, when only considering time windows without cue presentation, the ssVEP amplitudes showed a differential activation in response to the unpredictable compared to the predictable threat. A facilitated sensory processing of the unpredictable context only evolved in the last window of the trial. This means that during the predictable context, sustained attentional resources were reduced as the threat of an US occurrence dissolved with the last cue presentation. In contrast, the threat was present continuously in the unpredictable context and therefore increased attentional resources were continuously maintained. This is in contrast to our previous study, which only found effects for the unpredictable context restricted to the very onset of the condition. (Wieser

Fig. 5 — Grand mean ssVEP amplitudes in response the cues, and in response to the contexts during cue presentation. The upper row shows the grand mean scalp topographies of the ssVEP amplitudes elicited by the cues within each condition, averaged across 4 sec. The lower row shows the mean ssVEP amplitudes elicited by the contexts during the cue presentation averaged across 4 sec.

Fig. 6 — Averaged heart rate responses for the neutral, predictable, and unpredictable condition. (A) Heart rate changes (from a -1 sec pre-stimulus baseline) for the first 10 sec of each trial during context presentation; Unpredictable as well as predictable threat elicited larger HR decelerations compared to the neutral condition in all but the first two time intervals. (Asterisks indicate significant effects at $p < .05$, for the post-hoc comparisons P vs N and U vs N). (B) Heart rate changes (from a -1sec pre-stimulus baseline) during the 4 sec of cue presentations. The predictable cue elicited a significant larger HR acceleration between 1 and 4 sec compared to the neutral and the unpredictable condition (Asterisks indicate significant effects at $p < .05$, for the post-hoc comparisons P vs N and P vs U).
et al., 2016b). Possibly, the more complex stimuli used here required more time to be identified and hence more attentional resources at a later time window as compared to the previous study, which only used arrays of very simple geometrical shapes as contexts. We conclude that the present findings strongly support the notion of anxiety as a state of sustained, longer lasting response with continuous heightened vigilance during unpredictable threat.

As expected, an increased cortical activation was observed in response to the predictable cue compared to the neutral cue, which corroborates findings of increased startle responses (Grillon et al., 2009) and ssVEPs (Wieser et al., 2016b) for the cues in the predictable condition. Interestingly, the context surrounding the predictable cue during its 4 sec presentation elicited also increased ssVEP amplitudes. It seems that not only the cue for the aversive event, but also the surrounding context gains motivational significance and threat value. This finding corroborates results from our previous study (Wieser et al., 2016b). Similar results were observed for visual contexts, which contained a fearful face; the aversive cues led to an amplification of the contexts, indicated by enhanced ssVEP amplitudes (Wieser & Keil, 2014). Together, these results support the notion that during specific threat, processing of surrounding contexts is also enhanced.

Our results suggest that unpredictable and predictable threat similarly draw attentional resources and lead to increased electrocortical activation when no crucial cue is present. One explanation could be that the time between cues, when only the context is present, serves for both conditions as a time of uncertainty about the occurrence of the aversive event. While in the unpredictable condition, the occurrence is not predictable in any way, even in the predictable condition the context signals some uncertainty about when the actual cue, and consequently the aversive event appear.

Both the predictable and unpredictable condition were associated with pronounced decelerations in heart rate during the first 10 sec of the trials, in which only the context was present. Such HR decelerations (often labeled fear bradycardia) are known from the animal literature to reflect an orienting response during the post-encounter phase of the defense cascade model and indicate hyper-alertness (Fanselow, 1994; Löw et al., 2008, 2015). As soon as the cue appeared, HR of the participants significantly increased in the predictable condition only compared to both the neutral and the unpredictable condition. This response resembles the circa-strike phase, in which the threat becomes proximal and physiological arousal increases as indicated by heart rate acceleration and increased skin conductance (Fanselow, 1994; Lang, Davis, & Öhman, 2000; Richter et al., 2012). As soon as the threat – that is the cue in the predictable condition – is present, heart rate significantly increases as index for sympathetic activation necessary for the defensive response.

The defense cascade model is ideally suited to explain the similarities and differences in the electrocortical and physiological activation between predictable and unpredictable threat observed in this study. During the post-encounter phase, a general facilitated sensory processing reflected by increased electrocortical activation in occipital areas (unspecific vigilance) has to be expected; as the anticipated threat is not as imminent yet, the organism needs to evaluate the situation in order to prepare any suitable responses. The observed increased cortical responses during the unpredictable condition, reflecting increased mobilization of attentional resources, are in line with this explanation. Even during the predictable condition, a preparation for the approaching cue and subsequently also for the occurrence of the aversive event has to take place, as seen with increased ssVEP amplitudes in response to the context of the predictable condition. However, a differentiation between these two conditions is observed during the cue presentation. The occurrence of the predictable cue can be classified as the circa-strike phase during defense. The proximity of the unpleasant event leads to increased physiological activations in order to prepare immediate responses together with selective attention for the threat-specific cue. These processes are reflected in our findings of increased ssVEP amplitudes as well as a heart rate acceleration in response to the cue in the predictable condition.

Some limitations of the present study should be mentioned. First, due to practical reasons we only included female participants, which naturally hampers the generalizability of our findings. Second, in order to analyze pure context time windows, we had to remove the cue periods from both the P and the U condition. This asymmetrically removes US-presentations from the P but not the U-condition. Thus, the U-condition in that set of analyses may be contaminated with time periods of presumably increased arousal due to the noise burst presentations, while these periods are removed from the P-condition. As a consequence, the comparison of N and U in those analyses does not necessarily inform about the difference between fear and anxiety. However, if arousal would be the only driving factor, we should have seen this effect also at earlier time windows.

In sum, the present study aimed at differentiating the attention mechanisms and defensive responding during fear and anxiety using ssVEP, HR, and ratings data. Increased activation in occipital areas reflecting facilitated sensory gain was found for both predictable and unpredictable threat conditions. Without the availability of a cue, unpredictable and predictable threat showed similar cortical activation, but importantly the activation was longer lasting in the unpredictable threat condition, which is in line with the predictions of the defense cascade model. Heightened vigilance during post-encounter and selective attention during circa-strike were disentangled using electrocortical measures and distinctive heart rate responses. Overall, this study confirms that anxiety and fear are indeed different affective states with distinctive patterns of attention and physiological reactivity.

In a next step, research should consider the interplay of cue and context conditioning, perhaps including extinction processes, to advance our understanding of attentional mechanisms in anxiety disorders and treatment processes. For example, it should be interesting to see if anxiety sensitivity as a potential risk factor for panic disorder is also associated with selective enhanced visuocortical responding during the unpredictable threat condition, which was observed recently (Stevens, Weinberg, Nelson, Meissel, & Shankman, 2018). In the same vein, possible plasticity of these neurocognitive mechanisms in response to treatments targeting unpredictability of threat (Gorka et al., 2017) may inform us about successful treatment components. With
regard to extinction processes, it will be important to check if participants with risk factors for anxiety disorders (e.g., enhanced trait anxiety, anxiety sensitivity or a risk allele such as of the genes coding for the 5-HT transporter [5HTT] and the NPS receptor [NPSR1] show slower extinction learning for contexts, cues, or both (Glotzbach-Schoon et al., 2013a; Glotzbach-Schoon et al., 2013b). Last but not least, in terms of the RDoC initiative it may also be important to test if this paradigm may contribute to specifically refine underlying processes contributing to the psychopathology of anxiety and stress-related disorders (Lang, McTeague, & Bradley, 2016; Lonsdorf & Richter, 2017).

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References


