

## Self-relevant threat contexts enhance early processing of fear-conditioned faces<sup>☆</sup>

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### ABSTRACT

Anxiety states are characterized by attentional biases to threat and increased early brain responses to potentially threat signaling stimuli. How such stimuli are processed further depends on prior learning experiences (e.g. conditioning and extinction) and the context in which a stimulus appears. Whether context information and prior learning experiences interact with early threat processing in humans is largely unknown. Here, EEG was recorded while healthy participants (N = 20) viewed faces that were fear-conditioned and/or extinguished 24 h before. Faces were either passively viewed or presented within different contexts, which were created by describing scenarios that could either involve participants directly (self-threatening), or made them observers (other-threatening) of a potentially dangerous situation. Early brain responses (i.e., P1 amplitudes) were specifically enhanced during the self-threatening condition in response to non-extinguished versus extinguished fear-conditioned faces. This finding suggests that top-down contextual information is incorporated into early attention modulation of previously learned threat signals.

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Being able to adequately process environmental threat signals is essential for survival across species, including humans. Accordingly, we are able to detect potentially harmful stimuli rapidly. Presumably, this ability is especially pronounced in contexts associated with elevated danger. While the rapid detection of threat signals is an important adaptive mechanism, in anxiety disorders, which are associated with hypervigilance towards threat related stimuli (Mathews & MacLeod, 2005), this ability could lead to a significant interference in normal life and reduce general well being.

Most species can learn to show threat reactions to previously neutral stimuli by means of Pavlovian conditioning, where a neutral stimulus turns into a conditioned stimulus (CS) and elicits a conditioned fear response after it has been (repeatedly) paired with

an aversive unconditioned stimulus (UCS). Through the mechanism of extinction, most species can also learn to no longer show threat reactions to previously fear-associated but now no longer danger-signaling cues. Extinction occurs following repeated CS presentation in the absence of the unconditioned stimulus (UCS) (Rescorla & Wagner, 1972). While the early model of Rescorla and Wagner (1972) postulated that extinction is a reversed learning process, recent models assume that an inhibitory association between CS and UCS is learned during extinction (Quirk, 2002). This leads to co-existing associations, whereby the CS signals both the presence and absence of danger (Bouton, Westbrook, Corcoran, Maren, 2006; Brooks and Bouton, 1994). Which association triggers the final response depends on several factors, including the context where learning took place (Hermans, Craske, Mineka, Lovibond, 2006; Milad et al., 2007).

It has further been postulated that acquisition and consolidation of the extinction association underlie distinct mechanisms (Milad and Quirk, 2002; Mueller, Porter, Quirk, 2008; Mueller, Hofmann, Cherry, 2010). Accordingly, several brain imaging studies found distinct brain structures that are involved in either extinction acquisition or extinction retrieval (Hartley and Phelps, 2010;

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Milad et al., 2007; Phelps, Delgado, Nearing, LeDoux, 2004; Quirk and Mueller, 2008). Although the exact structures underlying the extinction acquisition remain unclear (Quirk & Mueller, 2008), it has been suggested that the ventral medial prefrontal cortex (vmPFC) plays a critical role in inhibitory mechanisms during long-term extinction retrieval (Hartley and Phelps, 2010; Milad et al., 2007; Phelps et al., 2004; Quirk and Mueller, 2008).

Interestingly, the vmPFC has been hypothesized to be involved in voluntary cognitive emotion regulation, which may also serve to reduce fear, for example by reappraising threat-related information to be part of a different, less threatening context (Diekhof, Geier, Falkai, Gruber, 2011). To investigate mechanisms of cognitive strategies in reducing fear, Delgado, Nearing, Ledoux, Phelps (2008) instructed participants to think of something calming while viewing previously fear conditioned stimuli in an fMRI study. Notably, participants successfully diminished their fear, and this reduction was accompanied by a higher activation of dorsolateral and ventromedial prefrontal cortex (dlPFC and vmPFC). The authors further compared these findings with another dataset containing an extinction procedure (published in Milad et al., 2005; and Phelps et al., 2004) and obtained similar activation patterns during both strategies, suggesting that fear reduction due to cognitive emotion regulation and extinction may depend on overlapping neural pathways.

An extended body of research provides evidence that cortical responses towards affective stimuli can be reliably captured with event-related potentials (ERPs). A number of studies demonstrated enlarged ERP amplitudes during early stages of processing (<300 ms after stimulus onset; e.g. P1, N1, P2, N2, EPN) elicited by fear-conditioned or other highly emotional compared to neutral pictures (Cuthbert, Schupp, Bradley, Birbaumer, Lang, 2000; Foti, Hajcak, Dien, 2009; Hajcak, Dunning, Foti, 2009; Miskovic and Keil, 2012; Schupp, Junghofer, Weike, Hamm, 2004) and face stimuli (Eimer and Holmes, 2007; Pizzagalli, Regard, Lehmann, 1999; Pizzagalli et al., 2002). Although these early latencies are consistent with a sensory-driven selective processing enhancement for emotional stimuli (Schupp, Junghofer, Weike, Hamm, 2003; Schupp et al., 2007), there is converging evidence that the overall framework or context in which emotional stimuli are presented also affects visual processing (Van den Stock, Vandenbulcke, Sinke, Goebel, de Gelder, 2014) including early processing stages (Wieser et al., 2014; de Gelder et al., 2006). Thus, early neural processing of emotional stimuli is influenced by emotion regulation strategies, such as reappraisal (Hajcak & Nieuwenhuis, 2006), in which emotional events are reframed by considering another (e.g., less threatening) context (Gross, 2002; Ochsner, Silvers, Buhle, 2012). Evidence for global context effects on rapid processing of single stimuli presented within that context also comes from Wieser, Pauli, Reicherts, & Muhlberger (2010) who reported that an overall social stress context created by anticipating to give a speech led to enhanced P1 amplitudes in response to angry human faces.

A recently used approach to investigate such context effects applies specific descriptions prior to a stimulus labeled *preappraisal* frames (Hajcak, Dunning, Foti, Weinberg, 2013). For example, a picture with a man pointing a gun to his head could be preceded either by the *preappraisal* frame “This man is about to commit suicide” or by the *preappraisal* frame “This man ends up not committing suicide”. It is assumed that depending on the *preappraisal* frame, the same pictures could provoke an increased or a decreased emotional response. Consistent with this assumption, both EEG and magnetoencephalographic (MEG) findings demonstrated that *preappraisal* frames modulate early as well as late potentials in response to unpleasant pictures (Foti and Hajcak, 2008; MacNamara, Foti, Hajcak, 2009) and faces (Wessing, Rehbein, Postert, Furniss, Junghofer, 2013). Human faces are considered as particularly evolutionary relevant, especially angry faces as they

might indicate an attack (Ohman, 1986). Based on that Wessing et al. (2013) presented angry face stimuli preceded by *preappraisal* frames that indicated either the presence or absence of personal threat. They found that *preappraisal* frames modulated MEG activity around 100 ms after stimulus onset at posterior recording sites. The impact of *preappraisal* frames on emotion processing may further be related to the self-relevance determined by the specific formulation of the frames. In this regard, Ma et al. (2014) observed enlarged ERP amplitudes around 200 ms following pictures indicating high personal danger. Moreover, Fields and Kuperberg (2012) found that higher self-relevance led to higher P1 amplitudes on frontal and occipital regions.

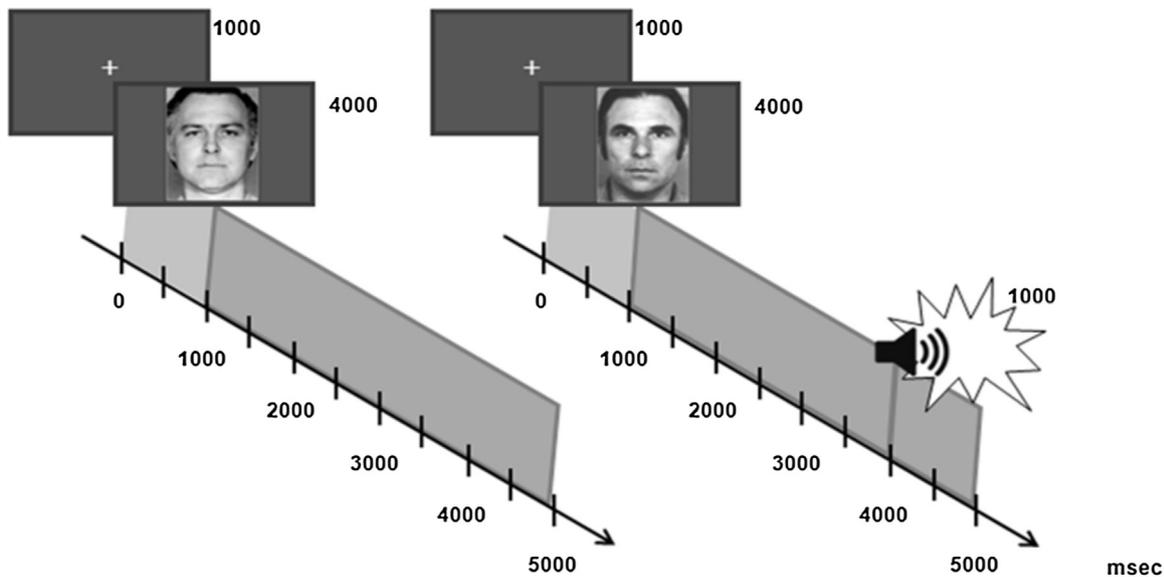
Taken together, previous findings indicate that threatening contexts – especially with high self-relevance – modulate early responses to emotional stimuli, presumably reflecting a mechanism to enhance rapid detection of relevant stimuli through higher engagement of attentional resources (indicated by enlarged early potentials such as P1) (Ma et al., 2014; Schupp et al., 2007).

The observed overlaps of brain regions involved in contextual and extinction-based modulation of threat processing are based mainly on studies using techniques with high spatial resolution like fMRI. However, the temporal sequence of these overlaps and functional mechanisms remain unclear. For this reason the aim of the present study was to investigate whether the extinction retrieval process modulates the impact of context effects on early threat processing using event related potential techniques.

In accordance with this aim, we presented *preappraisal* frames (see Appendix) followed by previously fear-conditioned ( $CS^+$ ) or non-conditioned ( $CS^-$ ) stimuli that had either been presented during an additional extinction session ( $CS^+_{ext}$  or  $CS^-_{ext}$ ) one day before or not ( $CS^+_{nonext}$  and  $CS^-_{nonext}$ ).<sup>1</sup> In earlier studies on a partially overlapping dataset we had established effects of day 1 conditioning and extinction on day 2 electrodermal, cardiovascular, electrophysiological and subjective measures when there were no *preappraisal* frames (Mueller, Panitz, Hermann, Pizzagalli, 2014; Mueller et al., 2015; Panitz, Hermann, Mueller, 2015). In the current study, the *preappraisal* frames were supposed to increase or decrease the sensation of personal threat depending on their specific formulation (self- vs. other-threatening). We focused on the P1 amplitude because the associated ERP latency has been found sensitive for emotional relevant stimuli, specifically those signaling threat or danger such as angry (Klucharev & Sams, 2004) or fearful (Pourtois et al., 2005; Vuilleumier and Pourtois, 2007) faces or fear conditioned stimuli (Brockelmann et al., 2011; Pizzagalli, Greischar, Davidson, 2003; Steinberg et al., 2013). Moreover, the P1 is highly sensitive to attentional bias as observed in anxiety (Mueller et al., 2009).

Generally, we expected an increase in threat processing in the self- rather than the other-threatening context descriptions. This increased self-relevant threat might lead to an anticipated preparation of the system in order to detect important stimuli as fast as possible. As a consequence not previously extinguished fear conditioned stimuli ( $CS^+_{nonext}$ ), which would still signal danger, might be processed with more urgency than previously extinguished stimuli ( $CS^+_{ext}$ ) for which an inhibitory association had been acquired during extinction. We expected that this would be reflected in enlarged P1 amplitudes towards the non-extinguished vs. the extinguished

<sup>1</sup> Like the  $CS^+$  we also presented one  $CS^-$  during extinction and the other one not. Because the  $CS^+_{ext}$  had been presented more often (i.e. during conditioning and extinction) than the  $CS^+_{nonext}$  (only during conditioning)  $CS^+_{ext}$  and  $CS^+_{nonext}$  may also evoke different reactions due to different levels of familiarity and not due to their different conditioning and extinction history. To have adequate control stimuli, one  $CS^-$  was presented during conditioning only ( $CS^-_{nonext}$ ) and one during both, conditioning and extinction ( $CS^-_{ext}$ ).



**Fig. 1.** Sample trials of the conditioning, extinction, and recall phase. Following a fixation cross face stimuli were presented for four sec (left). During the conditioning phase, an aversive noise was co-presented during the last sec of the face presentation (right) for half of the CS<sup>+</sup> trials.

CS<sup>+</sup>, particularly after those *preappraisal* frames that supposedly created a self-threatening context.

## 1. Methods

### 1.1. Participants

Twenty students from the University of Marburg (9 male; mean age 25.00 years  $\pm$  3.68) participated in this study. All participants reported that they are right-handed and native speakers with normal or corrected-to-normal vision. The study met the standards of the Declaration of Helsinki and was approved by the institutional review board of the psychology department of the University of Marburg. Written informed consent was obtained from each participant. All subjects received student credits for their participation.

### 1.2. Stimuli

As elaborated in the next section, the paradigm consisted of four phases: (I) day-1 conditioning, (II) day-1 extinction, (III) day-2 recall (not further considered in this article), and (IV) day-2 preappraisal (central to the present article). During the first three phases, five neutral faces from the Ekman, Friesen, Press (1975) series were used. Two of the five faces served as conditioned stimuli (CS<sup>+</sup>) and two as non-conditioned stimuli (CS<sup>-</sup>). The fifth face served as a dummy stimulus during the extinction phase. In the final experimental phase (IV), we presented faces of the same four males as in the previous experimental phases but now depicting angry rather than neutral facial expressions in order to increase the sensation of potentially threatening contexts during this phase.

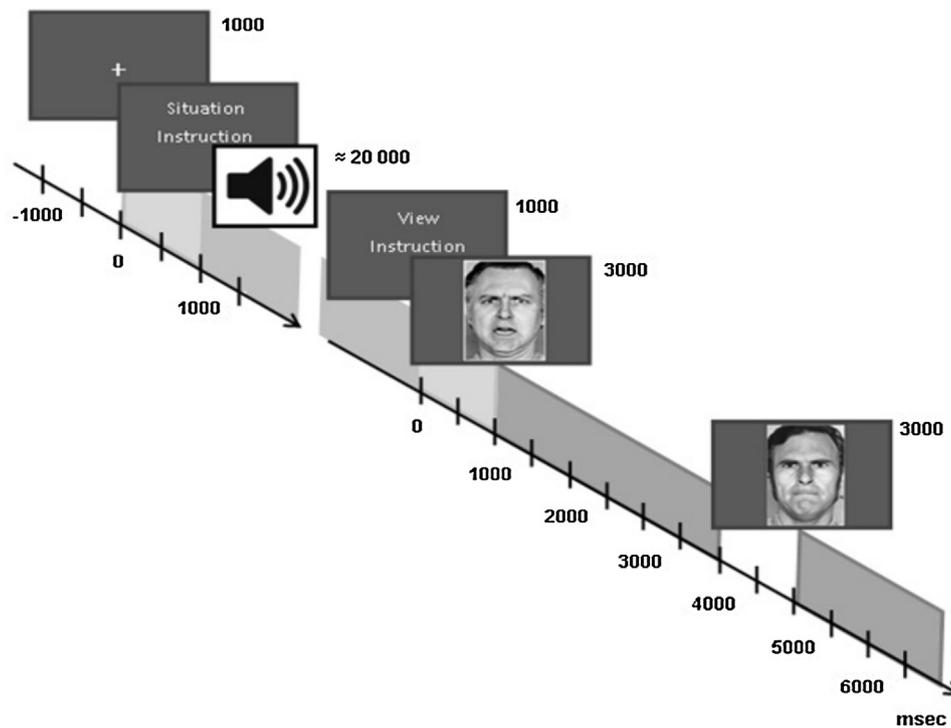
The unconditioned stimulus (UCS) which was only presented during the conditioning phase on day 1 was an aversive white noise burst (85 dB) delivered through room speakers for 1 s. We used noise bursts rather than electric shocks because we had previously shown that when many trials are used, white noise burst is better suited for aversive conditioning than electric shock (Sperl, Panitz, Hermann, & Mueller, in press).

### 1.3. Paradigm

During the conditioning phase, both CS<sup>-</sup> never co-terminated with the UCS, whereas in the CS<sup>+</sup> trials the UCS was presented 3 s after the CS onset for the duration of 1 s (see Fig. 1). To achieve a more stable and more extinction resistant CS-UCS association an intermittent conditioning protocol was used in which the CS<sup>+</sup> only co-terminated with the UCS in 50% of the trials.

During the extinction phase only one CS<sup>+</sup> and one CS<sup>-</sup> were presented<sup>1</sup>. The inter trial interval (ITI) varied between 6 and 8 s. At the end of these experimental phases, there were four distinct stimulus types that differed in their associated contingency depending on whether they had been aversively conditioned or not (CS<sup>+</sup>, CS<sup>-</sup>) and whether they had been included in the extinction procedure or not (ext, nonext). The contingency of each of the four facial stimuli serving as one particular stimulus type (CS<sup>+</sup><sub>ext</sub>, CS<sup>+</sup><sub>nonext</sub>, CS<sup>-</sup><sub>ext</sub>, CS<sup>-</sup><sub>nonext</sub>) was counterbalanced across participants. Both the conditioning and recall phase contained three blocks comprising 80 trials, each with equal numbers of each stimulus type (CS<sup>+</sup><sub>ext</sub>, CS<sup>+</sup><sub>nonext</sub>, CS<sup>-</sup><sub>ext</sub>, CS<sup>-</sup><sub>nonext</sub>) presented in random order. The extinction phase contained only one block with 100 trials of which 40 comprised one of each stimulus (CS<sup>+</sup><sub>ext</sub> and CS<sup>-</sup><sub>ext</sub>), and the remaining 20 were dummy-face trial. In order to motivate participants to maintain their attention on the screen, we included a secondary vigilance task throughout the conditioning, extinction and recall phases whereby the participants had to react by either a right or left bottom press of a computer mouse to a clockwise or counter-clockwise segmented arrow, respectively. Approximately 12.5% of the experimental trials included such a vigilance task.

The preappraisal phase consisted of three different conditions: self-threatening context, other-threatening context, and control condition. For the self- and other-threatening context, brief acoustic situation descriptions were presented through speakers. These descriptions implied that the upcoming angry face stimuli were either directed at another person or at the participant himself (see Appendix). During the listening phase with the acoustic context description the participants were instructed to picture themselves in the described situations as vivid as possible. At the end of each description participants were visually instructed that the subsequent faces belonged to the persons who were involved in the described situation. Then the faces that previously served as the



**Fig. 2.** Sample of a block of the preappraisal phase. Each block started with a *preappraisal* frame followed by the presentation of a sample of angry facial stimuli, comprised of four of each CS-type ( $CS^{+}_{ext}$ ,  $CS^{+}_{nonext}$ ,  $CS^{-}_{ext}$ ,  $CS^{-}_{nonext}$ ).

$CS^{+}_{ext}$ ,  $CS^{+}_{nonext}$ ,  $CS^{-}_{ext}$ , and  $CS^{-}_{nonext}$  were presented again, but this time with an angry facial expression to facilitate the imagination of the described threat-related scenarios. In the control condition, participants were instructed to simply view the faces. After each context description every face was presented four times in random order (16 presentations after each context description) for 3 s with an ITI of 1 s between each face presentation. The preappraisal phase contained 30 situation descriptions, 10 of each condition (Fig. 2). The presentation of each description followed a random order.

#### 1.4. Procedure

To investigate interactions of contextual information and extinction retrieval (rather than short-term extinction), the experiment was implemented on two consecutive sessions separated by approximately 24 h. In the laboratory, participants were set up for electrophysiological data recording. The conditioning and extinction phase were conducted on day 1 to create the specific stimulus types. On the following day (day 2) the preappraisal phase was implemented immediately after a recall phase that was conducted to examine the extinction retrieval after one night sleep and expected memory consolidation (results have been published elsewhere: Mueller & Pizzagalli, 2016; Mueller et al., 2014).

Within four time points during the whole experiment (comprising both test days) participants' affective ratings for each stimulus were obtained using analogue visual scales for valence and arousal. The ratings were collected before the first experimental phase started ( $T_0$ ) and again following each affective learning experimental phases ( $T_1$ : conditioning,  $T_2$ : extinction,  $T_3$ : recall). At each rating phase participants were asked to rate the valence and arousal related to each of the four faces individually on a five-point Likert Scale (results have been published elsewhere: Mueller et al., 2014). Furthermore, to determine whether the *preappraisal* frames created the intended contexts and the corresponding affective states we collected *context-related affective-state ratings* by asking the partici-

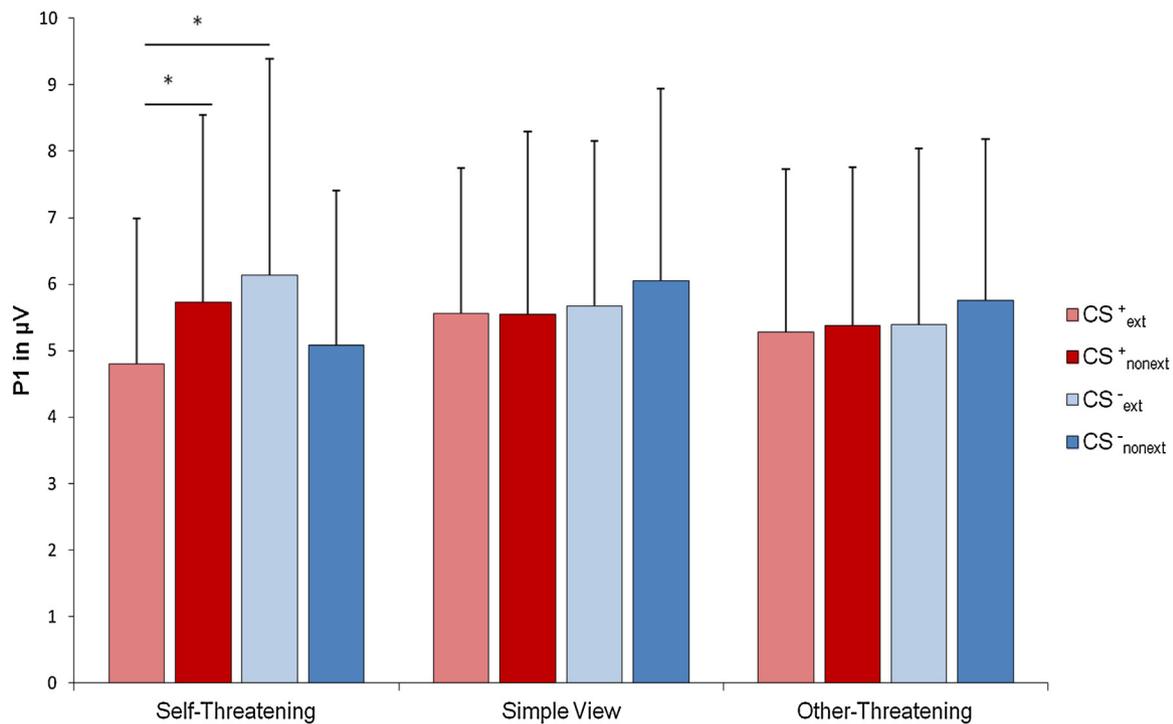
pants after each block of the preappraisal phase to rate their current overall affective state using a nine-point Likert Scale ranging from very unpleasant to very pleasant.

#### 1.5. EEG data recording

EEG recordings were obtained solely on day 2 comprising the recall phase and the preappraisal phase. Recordings were acquired with a sampling rate of 512 Hz using Active Two (BioSemi, Amsterdam, Netherlands) active electrode system referenced against common mode sense and driven right leg. EEG data were recorded with 64-Ag/AgCl-electrodes positioned according to the 10/20 system. Two further electrodes placed below and on the outer canthus of the left eye were used to record eye movements for later artifact identification.

#### 1.6. Data reduction

Only the EEG recordings during the preappraisal phase were analyzed. The signals were re-referenced off-line to the average reference and segmented for each stimulus type and condition. Each segment ranged from 500 ms before to 4000 ms after stimulus onset (−500 to 4000 ms). EEG was low- and high-pass filtered using cut-offs of 30 and 0.5 Hz, respectively, and visually screened for muscle, movement, and technical artifacts. Segments with recognized non-ocular artifacts were removed from the dataset. Artifacts based on blinks and eye movements were removed using independent component analysis. The remaining segments were baseline-corrected using the 200 ms before stimulus onset. All analyses were performed using Brain Vision Analyzer 2 software (Brain Products, Germany). Following prior studies (e.g. Mueller et al., 2009; Pourtois et al., 2004; Pourtois et al., 2005), the P1 was measured at electrode sites P7, P8, PO7 and PO8. The area under the curve within a 100–150 ms time window after stimulus onset was extracted for statistical analyses. Additionally, to test for the specificity of the reported P1 findings we also analyzed N170



**Fig. 3.** P1 amplitudes for each stimulus type (CS<sup>+</sup><sub>ext</sub>, CS<sup>+</sup><sub>nonext</sub>, CS<sup>-</sup><sub>ext</sub>, CS<sup>-</sup><sub>nonext</sub>) and condition (self-threatening, simple view, other-threatening). The P1 amplitudes were scored as the mean voltage between 100 and 150 ms after stimulus onset at posterior electrode sites (PO7, PO8). Error bars represent the standard deviation of the mean.

(150–190 ms) on electrode sites CP5/CP6 and TP7/TP8 (Pourtois et al., 2004), EPN (200–300 ms) on electrode sites P3/4 and O1/2 (Wieser et al., 2006), and the LPP component (400–1000 ms) on electrode sites Fz, Cz, and Pz (Panitz et al., 2015; Schupp et al., 2000).

### 1.7. Statistical analyses

To evaluate the intended effect of *preappraisal* frames (self-threatening, other-threatening) as well as the impact of the simple view condition on general affective state we analyzed the participant's *context-related affective-state rating* data using a univariate repeated-measures analysis of variance (ANOVA), with *context* (self-threatening/other-threatening/control) as within-subject factor. We further calculated a  $2 \times 2 \times 3 \times 2 \times 2$  repeated-measure ANOVA to analyze the amplitude of the P1 depending on prior conditioning, extinction, context, hemisphere, and electrode site. Accordingly, the within-subject factors were *hemisphere* (left vs. right), *electrode site* (P7/P8 vs. PO7/PO8) *context* (self-threatening vs. other-threatening vs. control), *CS-type* (CS<sup>+</sup> vs. CS<sup>-</sup>), and *extinction* (extinguished vs. non-extinguished). Greenhouse-Geisser correction was used where applicable. For all statistical analyses IBM SPSS Statistics Version 20 was used.

## 2. Results

### 2.1. Affective state ratings

The univariate ANOVA on the context-related affective state ratings revealed a significant main effect of *context*,  $F(2,38) = 43.59$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.70$ . Pairwise analyses indicated significantly decreased (i.e. less pleasant affective state) ratings after self-threatening context blocks ( $M = 3.11$ ,  $SD = 1.03$ ) compared to simple view ( $M = 5.08$ ,  $SD = 0.98$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.76$ ) and other-threatening context blocks ( $M = 4.91$ ,  $SD = 0.97$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.71$ ). No differences in affective ratings were found between the simple view and other-threatening condition ( $p > 0.99$ ).

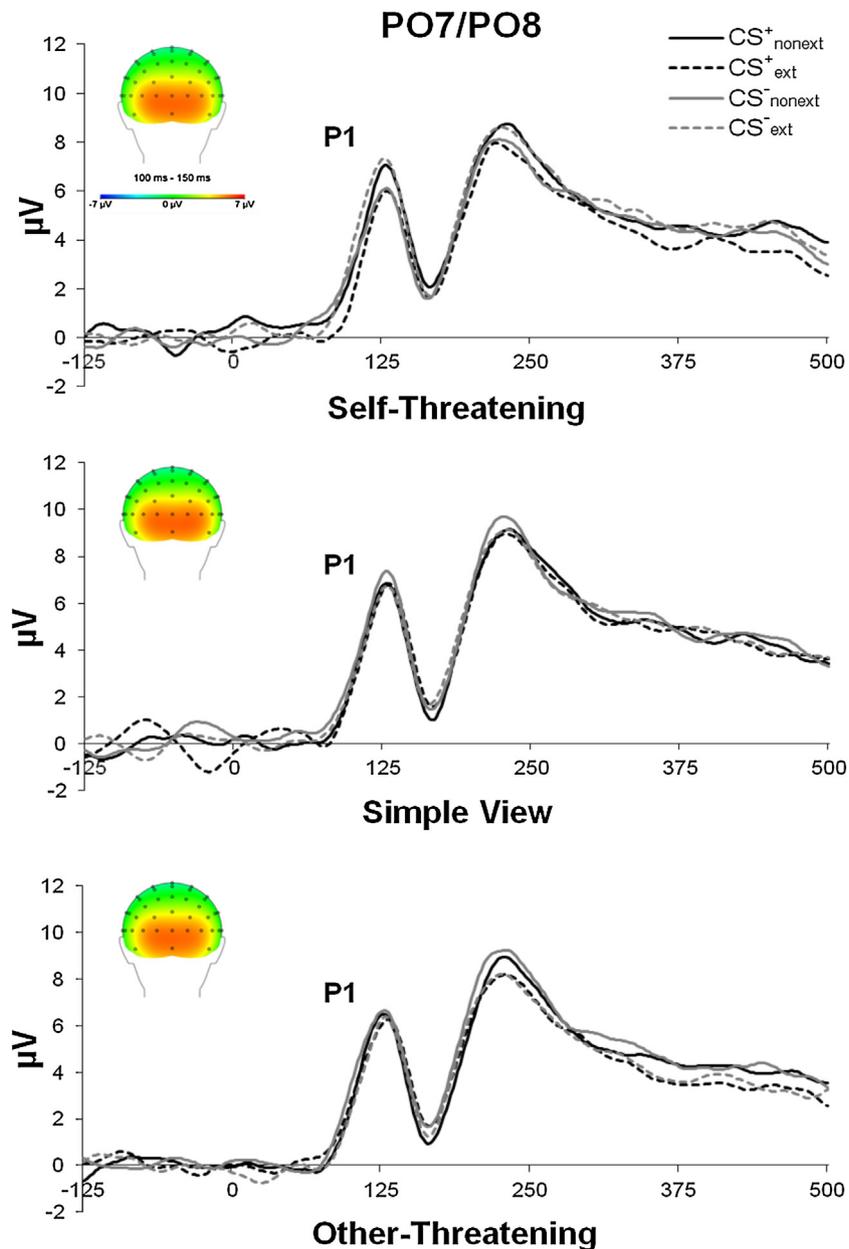
### 2.2. P1 amplitude

Analyses of the P1 amplitude revealed a significant main effect of *electrode site*,  $F(1,19) = 57.45$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.75$ , with larger P1 amplitudes over parietal-occipital (PO7 and PO8) compared to parietal (P7 and P8) electrode sites (P7/8:  $M = 3.39$ ,  $SD = 1.24$ ; PO7/8:  $M = 5.53$ ,  $SD = 2.30$ ). Furthermore, a four-way interaction of *electrode site*, *context*, *CS-type*, and *extinction*,  $F(2,38) = 3.64$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.16$  was found (Figs. 3 and 4). Most importantly, follow-up analyses revealed significantly enhanced P1 amplitudes in response to CS<sup>+</sup><sub>nonext</sub> vs. CS<sup>+</sup><sub>ext</sub> ( $F(1,19) = 4.71$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.20$ ) only within the self-threatening context that was specific for parietal-occipital electrode sites (PO7/PO8). In addition, CS<sup>-</sup><sub>ext</sub> evoked enhanced amplitudes as compared to CS<sup>+</sup><sub>ext</sub> ( $F(1,19) = 6.44$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.25$ ). No differences were found for other comparisons of stimulus types within the self-threatening context and no effects of prior conditioning or extinction were observed within the other-threatening context or the simple view condition (all  $p$ -values  $> 0.05$ ). Comparing each CS-type across the three different contexts (self-threatening/other-threatening/control) also revealed no significant results (all  $p$ -values  $> 0.05$ ).

### 2.3. Additional ERP components

The *hemisphere x electrode site x context x CS x extinction* ANOVA performed on the N170 revealed a significant main effect *electrode site*,  $F(1,19) = 24.90$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.57$ , with larger negative N170 amplitudes over central-parietal electrode sites compared to temporal-parietal electrode sites. There were no other main effects or interactions ( $p$ -values  $> 0.05$ ).

The same ANOVA performed on the EPN revealed a main effect of *electrode site*,  $F(1,19) = 10.1$ ,  $p < 0.01$ ,  $\eta_p^2 = 0.44$ , with a significantly more negative EPN amplitude over parietal compared to occipital electrode sites, and a significant interaction of the factors *hemisphere* and *electrode site*  $F(1,19) = 5.23$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.22$ , indicating that the difference between parietal and occipital electrodes was larger



**Fig. 4.** Grand average ERP waveforms elicited at posterior electrode sites by each CS-Type separated for each condition (top: self-threatening, middle: simple view, bottom: other-threatening). CS stimulus onset occurred at 0 ms. Both electrode sites were averaged. Also presented are scalp distributions during the P1 time window (100–150 ms) collapsed across all CS types for each preappraisal condition.

on the left vs. right hemisphere. Additionally, there was a significant five-way interaction between *hemisphere*, *electrode site*, *context*, *CS type*, and *extinction*,  $F(2, 38) = 3.41$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.15$ , that was due to a significantly more negative amplitude following CS<sup>-</sup><sub>ext</sub> vs. CS<sup>-</sup><sub>nonext</sub> within the simple view condition at electrode site P4,  $F(1, 19) = 4.70$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.20$ .<sup>2</sup>

To examine the LPP we performed an *electrode site*  $\times$  *context*  $\times$  *CS type*  $\times$  *extinction* ANOVA. This analysis revealed a significant main effect of *electrode site*,  $F(2, 38) = 5.64$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.23$ , with the smallest positivity over central compared to frontal and parietal

electrode sites. There were no other main effects or interactions ( $p$ -values  $> 0.05$ ).

### 3. Discussion

The present study investigated the interplay of extinction memory retrieval and contextual threat processing. We applied a paradigm that presented *preappraisal* frames preceding the presentation of previously extinguished and non-extinguished CS<sup>+</sup> and CS<sup>-</sup>. The *preappraisal* frames contained situational descriptions that induced an either self-threatening or other-threatening context. The subjective ratings on current affective states after each block of different contexts indicate that our experimental manipulation successfully increased an unpleasant affective state in the self-threatening conditions. For the central question regarding the processing of previously fear-conditioned and extinguished

<sup>2</sup> As this complex interaction of the EPN amplitude was not expected a priori and because it may reflect a chance finding due to the analysis of several ERP components we decided not to further elaborate on it.

stimuli, within specific contexts we analyzed the P1 amplitudes elicited by each stimulus type within each *preappraisal* condition. Consistent with an influence of the *preappraisal* context on the perceptual processing of previously conditioned and extinguished stimuli we found specifically enlarged P1 amplitudes in response to non-extinguished vs. extinguished CS<sup>+</sup> during the self-threatening condition only. As P1 amplitudes in general and P1 amplitudes to non-extinguished CS<sup>+</sup> in particular did not significantly differ between contexts the present findings suggest that the self-threatening context did not lead to a general enhancement of attention but rather to a specific modulation of attentional resources to previously fear-conditioned and extinguished stimuli.

In reviewing studies that investigated neural processing of affective pictures, Olofsson, Nordin, Sequeira, Polich (2008) postulate that the valence of a visual stimulus affects the P1 (amongst other early ERPs) and thus selective attention when the intrinsic relevance of the stimulus is high. Accordingly, attention towards threatening stimuli might be modulated when there is a general aim to be prepared in case of defense. Furthermore the P1 indicates reflexive attention deployment triggered by a bottom-up mechanism (Hopfinger, Luck, Hillyard, 2004). Applied to the present findings this indicates that the non-extinguished CS<sup>+</sup> may still be treated as more relevant due to the aversive conditioning procedure in which the CS<sup>+</sup> had been associated with the UCS. The extinguished CS<sup>+</sup> on the other hand elicited suppressed P1 amplitudes indicating a lower engagement of attentional resources, presumably reflecting successful extinction retrieval and a suppressed fear response. Of particular relevance, this finding was specific to the self-threatening condition, suggesting that participants showed a more refined discrimination of potentially threatening vs. non-threatening cues in their environment while anticipating context-related self-relevant threat. This might be an important survival mechanism that enables the individual to react as fast as possible to probable danger while tuning down attention to safety signals. It should further be emphasized that unlike renewal studies indicating that the presentation of previously extinguished stimuli in a context other than the extinction context leads to a renewal of conditioned fear responses (Bouton, 2004), the present findings suggest that the effect of prior extinction on early visual processing may in fact be amplified in particular threat-relevant contexts.

Given that angry faces were presented, it was also expected that P1 amplitudes would be generally enlarged in the self-threatening compared to the other-threatening condition, regardless of the previous conditioning and extinction history of presented stimuli. Although we could not find such neurophysiological differences, the results of the subjective ratings following each block of the *preappraisal* phase clearly provided evidence for a negative impact on participant's affective states throughout the self-threatening context descriptions. Consistent with prior studies (Wessing et al., 2013) such differences failed to appear between the simple view and the other-threatening condition. The lack of a down-regulation effect throughout the other-threatening vs. simple view condition may reflect a floor effect, whereby the initially low ratings after the angry faces in the simple view condition could not be further reduced after the other-threatening *preappraisal* frames.

In addition to the expected findings regarding the P1 amplitudes in response to the different CS<sup>+</sup> types we also, surprisingly, found enhanced P1 amplitudes to the CS<sup>-</sup> vs. CS<sup>+</sup> that had been presented during the extinction learning procedure (CS<sup>-</sup><sub>ext</sub> and CS<sup>+</sup><sub>ext</sub>). It is unclear why exactly the *extinguished* CS<sup>-</sup>, which was repeatedly proven not to be associated with the UCS, attracted also increased attention during the self-threatening condition, as indicated by the enlarged P1 amplitude. It could be speculated whether the extinguished CS<sup>-</sup>, as the most familiar safety signal of the stimulus set, attracted enhanced attention in a potentially threatening situation. Obviously, in conditions of social threat it would not only

be adaptive to identify potential threats but also to rapidly spot potential allies. Note, however, that this post hoc explanation of an unexpected finding is speculative and a replication of enhanced P1 amplitudes to CS<sup>-</sup><sub>ext</sub> in threatening contexts is needed until firm conclusions can be drawn.

Two special features of the present study should be acknowledged. First, the recall phase on day 2 prior to the *preappraisal* phase might have led to further unintended extinction of the CS<sup>+</sup><sub>nonext</sub> because all CS were presented in the absence of the UCS in this phase. However, the fact, that we nevertheless revealed a distinct neural response between the intendedly extinguished vs. non-extinguished CS<sup>+</sup> speaks for a strong effect of the day 1 extinction retrieval. Second, to facilitate imagination of the scenarios described in the *preappraisal* frames, the faces presented during this stage had an angry emotional expression, whereas during the associative learning phases (conditioning and extinction in particular) the faces had a neutral expression. Although the faces of the same four males were presented, the different facial expressions might have attenuated the extinction retrieval during the *preappraisal* phase. However, the observed influence of prior fear conditioning and extinction on angry face processing in self-threatening contexts indicates that prior learning may have associated threat to particular face identities that generalized across emotional expressions.

Besides these features we showed that in a context with potential danger the non-extinguished CS<sup>+</sup> elicited enlarged P1 amplitudes as compared to a previously extinguished CS<sup>+</sup>, presumably indicating relatively higher attention deployment to unambiguously threat-related cues in a threatening context. A future goal will be to investigate processing patterns of conditioned and extinguished stimuli within different contexts in highly anxious individuals who often show potentiated processing of threatening stimuli (Bar-Haim, Lamy, Glickman, 2005; Helfinstein, White, Bar-Haim, Fox, 2008; Mueller et al., 2009). It would be interesting to evaluate whether conditioned and extinguished fear reactions in phobias are characterized by reduced contextual control leading to similar conditioned fear reactions in threatening and actually harmless situations. Moreover, anxious individuals might show reduced extinction retrieval in self-threatening contexts, so that relative processing enhancements and/or attentional biases remain towards both CS<sup>+</sup> whether extinguished or not. Future studies applying the experimental design of the present study to individuals with anxiety disorders will be needed to test this clinically important question.

## Appendix A.

*Preappraisal* frames. Every description was accompanied by the visual instruction to emphasize as well as possible in the described situation and was replaced by the visual instruction to look at the response of the persons involved right prior the stimuli presentation.

Self-threatening	Other-threatening
<i>You are in a foreign city. You suddenly find yourself lost in a back alley. You then see a group of dangerous-looking men coming right up to you.</i>	<i>You are watching a movie at the cinema. In the film, you watch how a group of dangerous-looking men approach the protagonist in a back alley.</i>
<i>You are at the food court. There you stumble into the crowd and drop your tablet on a group of men.</i>	<i>You are at the food court. There you can see how someone stumbles into the crowd and drops his tablet on a group of men.</i>
<i>You are sitting in the car waiting in front of a traffic light. Because you are so busy with your cell phone, you missed the green light and now it is red again.</i>	<i>You see a car driver waiting in front of a traffic light. But because he is so busy with his cell phone he misses the green light and it turns red again</i>

You are at the supermarket. Because you're carrying all your goods you pass the waiting line and place them all on the checkout conveyor belt in front of the people who are already waiting.

You are struggling to get your car parked. Meanwhile, there is an accumulation of other cars because you are blocking the entire road.

You are waiting at the bus stop. As soon as the bus arrives you just step into the bus without letting other passengers get off the bus first.

You pass a protest march. Accidentally, you end up joining a group of protestors who are provoking the surrounding policemen.

You are visiting a soccer game. Because the home-team has lost the game, a group of fans is ill-tempered and coming right towards you.

You are sitting in a pub. There is a group of drunken men who start bullying you and other guests.

You are cycling through the rain. There you drive right through a huge puddle, so that the people standing around get completely drenched.

You are in the supermarket. There you see how someone cuts the waiting line, and places all their goods on the checkout conveyor belt in front of everyone else in line.

You are walking down the street and pass cars backed up because one single driver is struggling with getting the car parked and is blocking the entire road.

You are waiting at the bus stop. There you see how someone just steps into the bus without letting other passengers get off the bus first.

You are watching a live report. The report shows scenes of rioting during a protest march. A group of protesters seem to be provoking the surrounding policemen.

You are watching a live television broadcast of a soccer game. There you see how fans of different teams start shouting at each other.

You are walking along the street and pass by a pub. There you see some drunk guests arguing with the owner, because he is about to throw them out.

You are walking through the rain. You see a cyclist driving right through a huge puddle, thereby completely drenching the people standing nearby.

- Hajcak, G., Dunning, J. P., & Foti, D. (2009). Motivated and controlled attention to emotion: Time-course of the late positive potential. *Clinical Neurophysiology*, *120*, 505–510.
- Hajcak, G., Dunning, J., Foti, D., & Weinberg, A. (2013). Temporal dynamics of emotion regulation. In *Handbook of emotion regulation*. pp. 441–474.
- Hartley, C. A., & Phelps, E. A. (2010). Changing fear: The neurocircuitry of emotion regulation. *Neuropsychopharmacology*, *35*, 136–146.
- Helfinstein, S. M., White, L. K., Bar-Haim, Y., & Fox, N. A. (2008). Affective primes suppress attention bias to threat in socially anxious individuals. *Behaviour Research and Therapy*, *46*, 799–810.
- Hermans, D., Craske, M. G., Mineka, S., & Lovibond, P. F. (2006). Extinction in human fear conditioning. *Biological Psychiatry*, *60*, 361–368.
- Hopfinger, J. B., Luck, S. J., & Hillyard, S. A. (2004). Selective attention: Electrophysiological and neuromagnetic studies. *The Cognitive Neurosciences*, *3*, 561–574.
- Klucharev, V., & Sams, M. (2004). Interaction of gaze direction and facial expressions processing: ERP study. *Neuroreport*, *15*, 621–625.
- Ma, Q., Fu, H., Xu, T., Pei, G., Chen, X., Hu, Y., et al. (2014). The neural process of perception and evaluation for environmental hazards: Evidence from event-related potentials. *Neuroreport*, *25*, 607–611.
- MacNamara, A., Foti, D., & Hajcak, G. (2009). Tell me about it: Neural activity elicited by emotional pictures and preceding descriptions. *Emotion*, *9*, 531–543.
- Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology*, *1*, 167–195.
- Milad, M. R., & Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*, *420*, 70–74.
- Milad, M. R., Quinn, B. T., Pitman, R. K., Orr, S. P., Fischl, B., & Rauch, S. L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 10706–10711.
- Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biological Psychiatry*, *62*, 446–454.
- Miskovic, V., & Keil, A. (2012). Acquired fears reflected in cortical sensory processing: A review of electrophysiological studies of human classical conditioning. *Psychophysiology*, *49*, 1230–1241.
- Mueller, E. M., & Pizzagalli, D. A. (2016). One-year-old fear memories rapidly activate human fusiform gyrus. *Social Cognitive and Affective Neuroscience*, *11*, 308–316.
- Mueller, D., Porter, J. T., & Quirk, G. J. (2008). Noradrenergic signaling in infralimbic cortex increases cell excitability and strengthens memory for fear extinction. *Journal of Neuroscience*, *28*, 369–375.
- Mueller, E. M., Hofmann, S. G., Santesso, D. L., Meuret, A. E., Bitran, S., & Pizzagalli, D. A. (2009). Electrophysiological evidence of attentional biases in social anxiety disorder. *Psychological Medicine*, *39*, 1141–1152.
- Mueller, E. M., Hofmann, S. G., & Cherry, J. A. (2010). The type IV phosphodiesterase inhibitor rolipram disturbs expression and extinction of conditioned fear in mice. *Neuropharmacology*, *59*, 1–8.
- Mueller, E. M., Panitz, C., Hermann, C., & Pizzagalli, D. A. (2014). Prefrontal oscillations during recall of conditioned and extinguished fear in humans. *Journal of Neuroscience*, *34*, 7059–7066.
- Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, *1251*, E1–24.
- Ohman, A. (1986). Face the beast and fear the face: Animal and social fears as prototypes for evolutionary analyses of emotion. *Psychophysiology*, *23*, 123–145.
- Olofsson, J. K., Nordin, S., Sequeira, H., & Polich, J. (2008). Affective picture processing: An integrative review of ERP findings. *Biological Psychology*, *77*, 247–265.
- Panitz, C., Hermann, C., & Mueller, E. M. (2015). Conditioned and extinguished fear modulate functional corticocardiac coupling in humans. *Psychophysiology*, *52*, 1351–1360.
- Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, *43*, 897–905.
- Pizzagalli, D., Regard, M., & Lehmann, D. (1999). Rapid emotional face processing in the human right and left brain hemispheres: An ERP study. *Neuroreport*, *10*, 2691–2698.
- Pizzagalli, D. A., Lehmann, D., Hendrick, A. M., Regard, M., Pascual-Marqui, R. D., & Davidson, R. J. (2002). Affective judgments of faces modulate early activity (approximately 160 ms) within the fusiform gyri. *Neuroimage*, *16*, 663–677.
- Pizzagalli, D. A., Greischar, L. L., & Davidson, R. J. (2003). Spatio-temporal dynamics of brain mechanisms in aversive classical conditioning: High-density event-related potential and brain electrical tomography analyses. *Neuropsychologia*, *41*, 184–194.
- Pourtois, G., Grandjean, D., Sander, D., & Vuilleumier, P. (2004). Electrophysiological correlates of rapid spatial orienting towards fearful faces. *Cerebral Cortex*, *14*, 619–633.
- Pourtois, G., Dan, E. S., Grandjean, D., Sander, D., & Vuilleumier, P. (2005). Enhanced extrastriate visual response to bandpass spatial frequency filtered fearful faces: Time course and topographic evoked-potentials mapping. *Human Brain Mapping*, *26*, 65–79.
- Quirk, G. J. (2002). Memory for extinction of conditioned fear is long-lasting and persists following spontaneous recovery. *Learning and Memory*, *9*, 402–407.
- Quirk, G. J., & Mueller, D. (2008). Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology*, *33*, 56–72.

## References

- Bar-Haim, Y., Lamy, D., & Glickman, S. (2005). Attentional bias in anxiety: A behavioral and ERP study. *Brain and Cognition*, *59*, 11–22.
- Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning and Memory*, *11*, 485–494.
- Bouton, M. E., Westbrook, R. F., Corcoran, K. A., & Maren, S. (2006). Contextual and temporal modulation of extinction: Behavioral and biological mechanisms. *Biological Psychiatry*, *60*, 352–360.
- Brockelmann, A. K., Steinberg, C., Elling, L., Zwanzger, P., Pantev, C., & Junghofer, M. (2011). Emotion-associated tones attract enhanced attention at early auditory processing: Magnetoencephalographic correlates. *Journal of Neuroscience*, *31*, 7801–7810.
- Brooks, D. C., & Bouton, M. E. (1994). A retrieval cue for extinction attenuates response recovery (renewal) caused by a return to the conditioning context. *Journal of Experimental Psychology Animal Behavior Processes*, *20*, 366–379.
- Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology*, *52*, 95–111.
- de Gelder, B., Meeren, H. K., Righart, R., van den Stock, J., van de Riet, W. A., & Tamietto, M. (2006). Beyond the face: Exploring rapid influences of context on face processing. *Progress in Brain Research*, *155*, 37–48.
- Delgado, M. R., Nearing, K. I., Ledoux, J. E., & Phelps, E. A. (2008). Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron*, *59*, 829–838.
- Diekhof, E. K., Geier, K., Falkai, P., & Gruber, O. (2011). Fear is only as deep as the mind allows: A coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. *Neuroimage*, *58*, 275–285.
- Eimer, M., & Holmes, A. (2007). Event-related brain potential correlates of emotional face processing. *Neuropsychologia*, *45*, 15–31.
- Ekman, P., Friesen, W. V., Press, C. P., 1975. Pictures of facial affect. consulting psychologists press.
- Fields, E. C., & Kuperberg, G. R. (2012). It's all about you: An ERP study of emotion and self-relevance in discourse. *Neuroimage*, *62*, 562–574.
- Foti, D., & Hajcak, G. (2008). Deconstructing reappraisal: Descriptions preceding arousing pictures modulate the subsequent neural response. *Journal of Cognitive Neuroscience*, *20*, 977–988.
- Foti, D., Hajcak, G., & Dien, J. (2009). Differentiating neural responses to emotional pictures: Evidence from temporal-spatial PCA. *Psychophysiology*, *46*, 521–530.
- Gross, J. J. (2002). Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology*, *39*, 281–291.
- Hajcak, G., & Nieuwenhuis, S. (2006). Reappraisal modulates the electrocortical response to unpleasant pictures. *Cognitive, Affective and Behavioral Neuroscience*, *6*, 291–297.

- Rescorla, R. A., & Wagner, A. R. (1972). *A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. Classical Conditioning II: Current Research and Theory*, 64–99.
- Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., & Lang, P. J. (2000). Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology*, 37, 257–261.
- Schupp, H. T., Junghofer, M., Weike, A. I., & Hamm, A. O. (2003). Attention and emotion: An ERP analysis of facilitated emotional stimulus processing. *Neuroreport*, 14, 1107–1110.
- Schupp, H. T., Junghofer, M., Weike, A. I., & Hamm, A. O. (2004). The selective processing of briefly presented affective pictures: An ERP analysis. *Psychophysiology*, 41, 441–449.
- Schupp, H. T., Stockburger, J., Codispoti, M., Junghofer, M., Weike, A. I., & Hamm, A. O. (2007). Selective visual attention to emotion. *Journal of Neuroscience*, 27, 1082–1089.
- Sperl, M. F., Panitz, C., Hermann, C., & Mueller, E. M. (2016). A pragmatic comparison of noise burst and electric shock unconditioned stimuli for fear conditioning research with many trials. *Psychophysiology*, <http://dx.doi.org/10.1111/psyp.12677>
- Steinberg, C., Brockelmann, A. K., Dobel, C., Elling, L., Zwanzger, P., Pantev, C., et al. (2013). Preferential responses to extinguished face stimuli are preserved in frontal and occipito-temporal cortex at initial but not later stages of processing. *Psychophysiology*, 50, 230–239.
- Van den Stock, J., Vandenbulcke, M., Sinke, C. B., Goebel, R., & de Gelder, B. (2014). How affective information from faces and scenes interacts in the brain. *Social Cognitive and Affective Neuroscience*, 9, 1481–1488.
- Vuilleumier, P., & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. *Neuropsychologia*, 45, 174–194.
- Wessing, I., Rehbein, M. A., Postert, C., Furniss, T., & Junghofer, M. (2013). The neural basis of cognitive change: Reappraisal of emotional faces modulates neural source activity in a frontoparietal attention network. *Neuroimage*, 81C, 15–25.
- Wieser, M. J., Muhlberger, A., Alpers, G. W., Macht, M., Ellgring, H., & Pauli, P. (2006). Emotion processing in Parkinson's disease: Dissociation between early neuronal processing and explicit ratings. *Clinical Neurophysiology*, 117, 94–102.
- Wieser, M. J., Gerdes, A. B., Bungel, I., Schwarz, K. A., Muhlberger, A., & Pauli, P. (2014). Not so harmless anymore: How context impacts the perception and electrocortical processing of neutral faces. *Neuroimage*, 92, 74–82.
- Wieser, M. J., Pauli, P., Reicherts, P., & Muhlberger, A. (2010). Don't look at me in anger! Enhanced processing of angry faces in anticipation of public speaking. *Psychophysiology*, 47, 271–280.