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Healthy individuals maintain adaptive stimulus evaluation under predictable and unpredictable threat

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ABSTRACT

The anxiety inducing paradigms such as the threat-of-shock paradigm have provided ample data on the emotional processing of predictable and unpredictable threat, but little is known about the processing of aversive, threat-irrelevant stimuli in these paradigms. We investigated how the predictability of threat influences the neural visual processing of threat-irrelevant fearful and neutral faces. Thirty-two healthy individuals participated in an NPU-threat test, consisting of a safe or neutral condition (N) and a predictable (P) as well as an unpredictable (U) threat condition, using audio-visual threat stimuli. In all NPU-conditions, we registered participants' brain responses to threat-irrelevant faces via magnetoencephalography. The data showed that increasing unpredictability of threat evoked increasing emotion regulation during face processing predominantly in dorsolateral prefrontal cortex regions during an early to mid-latency time interval. Importantly, we obtained only main effects but no significant interaction of facial expression and conditions of different threat predictability, neither in behavioral nor in neural data. Healthy individuals with average trait anxiety are thus able to maintain adaptive stimulus evaluation processes under predictable and unpredictable threat conditions.

Introduction

Imagine you heard rumors about your company planning to release many employees. You would probably react with anxiety to such a situation of unpredictable threat. Further assume that coming home from work you meet a neighbor with whom you have had an argument some time ago and whose behavior since them is hostile towards you. Would your neighbor appear more threatening to you, now that you are concerned about your job? Or in general, does an aversive emotional context enhance human reaction to aversive stimuli, even when these stimuli are obviously unconnected to the appearance of the actual threats and are thus *threat-irrelevant*?

Numerous studies using functional magnetic resonance imaging (fMRI) or electro-/magnetoencephalography (EEG/MEG) showed that under innocuous passive viewing conditions, emotional stimuli are preferentially processed relative to neutral stimuli, and may attract enhanced attention (Schupp et al., 2006; Vuilleumier, 2005). Robinson et al. (2013) proposed that threatening contexts additionally sensitize for negative stimuli. Such a lowering of reaction thresholds towards negative stimuli would reduce the danger of false negative at the cost of increased false positive reactions – i.e. 'better safe than sorry'. However, changing reaction thresholds towards threat-irrelevant signals is – at least in technical systems – typically not advisable. Assume a system that measures the air temperature within a passenger airplane, which typically varies between 18 and 22 °C, and gives a warning to the pilot if the temperature rises above 25 °C. Should this system lower its reaction threshold and already warn at 22 °C if another system warns about strong winds indicating a rough landing, although the inner air temperature is definitely unrelated to the outside wind? Similarly, pilots typically learn not to modulate their learned appraisals and behaviors in case of emergency. Of course, humans do not always react in a controlled fashion. Air force pilots in World War II who were highly skilled in peacetime often crashed their planes in aerial combats owing to mental errors (Broadbent, 1971). Human and animal studies revealed that stress can in fact diminish attention regulation of the prefrontal cortex, depending on what is most relevant to the task at hand (Arnsten, 2009). However, such detrimental effects typically appear in situations of extreme or

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uncontrollable stress, while humans or animals who in fact are – or just feel – in control of the situation are typically not impaired (Glass, 1971; Minor et al., 1984). The typical processing bias for negative over neutral stimuli might thus be unaffected by threat contexts, as long as stimuli remain threat-irrelevant, and the individuals feel not overly stressed.

A proven method to experimentally induce different degrees of stress and anxiety is to vary threat predictability in an anxiety inducing paradigm such as the threat-of-shock paradigm (Grillon, 2008). The more unpredictable the threat, the stronger is the induced anxiety in the participant. Anxiety is defined as a longer-lasting state of apprehension for possibly upcoming, uncontrollable threats that goes along with a feeling of helplessness, and provokes vigilance or even hypervigilance to potentially negative events (Barlow, 2000). To advance scientific investigations of effects of varying threat predictability in humans, Grillon and colleagues proposed the NPU-threat test (Grillon et al., 2004; Schmitz and Grillon, 2012), consisting of a safe **N**eutral N-condition, a **P**redictable P-condition (threat announced by a warning cue), and an **U**npredictable U-condition (sudden threat without warning). Individuals typically react with signs of fear to both warning cue and threat, and feel safer in the P-condition than in the U-condition as long as no warning cue is presented. Meanwhile, there is ample evidence that unpredictable threat stimuli elicit more aversive responses than predictable threat stimuli in healthy individuals (Alvarez et al., 2011). It remains however less clear, how emotional, especially negative, stimuli that are threat-irrelevant are processed under threat-conditions of varying threat predictability.

Studies investigating a potential modulation of the processing bias under threat-conditions have so far shown heterogeneous results. Grillon and Charney (2011), for instance, reported specifically enhanced startle reactions to fearful relative to neutral faces, in a context of unpredictable threat (electric shocks) relative to a safe condition. Similarly, Wieser et al. (2010) reported the N170 EEG component to be larger for angry than for neutral faces, when presented during anticipated public speaking compared to a safe condition. In contrast, using EEG or MEG, Bublatzky et al. (2013) and Elling et al. (2012) observed processing of both emotional and neutral scenes to be enhanced in contexts of unpredictable threat (electric shock) or social stress (public speaking) relative to safe conditions, but found no hint for specifically enhanced processing of negative over neutral stimuli in their negative contexts.

To resolve these incompatible results, it seems relevant whether and how potentially informative value about the appearance of an upcoming threat is ascribed to the presented stimuli. For instance, illusory correlation experiments showed that people typically overestimate the covariation between phylogenetic threat stimuli and aversive events (Mineka and Sutton, 1992; Tomarken et al., 1989). This overestimation may well be explained by associative learning, as aversive events tend to follow aversive stimuli more often than neutral stimuli (e.g. an angry face starts shouting more often than a neutral face). When healthy participants are confronted with an anxiety-inducing condition – such as the unpredictable threat condition – negative stimuli, though threat-irrelevant, might falsely be estimated as having more predictive value for an upcoming threat than neutral stimuli, and might thus receive enhanced attention. Possibly convergent to this, Grillon and Charney (2011) found enhanced defensive reactions towards fearful compared to neutral faces in the first, but not in the second half of an unpredictable threat condition. This may indicate that an illusory covariation bias decreased as the participants learned about the missing predictive value (threat irrelevance) of the facial expressions during the experiment. Taken together, studies reported contradictory findings about the processing of threat-irrelevant negative stimuli under conditions of unpredictable threat, and no study yet addressed potential differences in stimulus processing during conditions of predictable threat.

In this study, we investigated in healthy participants whether the processing advantage for threat-irrelevant negative over neutral stimuli is amplified in a context of threat – operationalized by sudden onsets of short monster-videos – in comparison to a safe context. We also asked if the same processing advantage is higher in a context of unpredictable threat than in a context of predictable threat in the latter of which threat videos are preceded by a warning cue. We thus tested the hypothesis that there would be a processing advantage for threat-irrelevant negative over neutral stimuli which increased with unpredictability of threat against the alternative hypothesis that threat contexts do not sensitize for negative stimuli when participants previously knew or learned that these stimuli have no predictive value for threat appearance. We assume this independent processing of threat context and threat irrelevant stimuli as a resource-saving adaptive capacity. To investigate these issues, we presented many different fearful and neutral faces during an unpredictable (U) threat condition, a predictable (P) threat condition, and a safe neutral (N) condition, and measured neural processing of the faces using whole-head MEG. With multiple faces and detailed information about the irrelevance of faces on threat onset, we intended to prevent an illusory correlation on an implicit and explicit level. We expected a processing bias for fearful relative to neutral faces in visual sensory regions during early to mid-latency (i.e., 50–300 ms) and late time-intervals (i.e., >300 ms) in all three NPU-conditions (Pessoa and Adolphs, 2010; Steinberg et al., 2013). Effects of facial expression should reflect priority processing due to the higher intrinsic stimulus significance of emotional compared to neutral faces (Schupp et al., 2006). If a threatening context has a specific influence on the processing of threat-irrelevant negative over neutral stimuli, we expect to see an interaction of threat context and face valence. Based on findings of Wieser et al. (2010), we would expect such an interaction to occur in an early to mid-latent time frame (50–300 ms) and to mirror enhanced early perceptual processing of fearful faces in an anxiety-inducing condition. If threat-irrelevant fearful and neutral faces are processed irrespective of threat context, the two factors should exert independent influences on neural activation. Irrespective of their expression, faces should then induce increasing activity with increasing threat unpredictability (U&P > N and U > P). Based on Elling et al. (2012); Hasler et al. (2007) and Carlsson et al. (2006), we would expect this increased activity, reflecting processes of emotional attention allocation, to occur in an early to mid-latent time frame (50–300 ms) and to be located in occipito-parietal regions mediating visual attention (Pessoa and Adolphs, 2010; Schupp et al., 2003) and in the fronto-parietal attention network (Posner, 2012; Robertson and Garavan, 2004), mediating automatic attentional control of emotion. This is an emotion regulation process evoked by emotionally salient stimuli per se without conscious effort monitoring (Phillips et al., 2008) and mediated by the PFC (Blair et al., 2007; Stein et al., 2007), which is generally activated by emotion regulation (Buhle et al., 2014; Campbell-Sills et al., 2011; Lévesque et al., 2003; Ochsner and Gross, 2008; Steinberg et al., 2013). Faces presented in the safe neutral (N) condition should require least automatic attentional control, because participants know that threats will not appear. Faces presented in the safe phases of the predictable (P) threat condition should require some automatic attentional control, because participants wait for the warning cue and constantly monitor and evaluate the stream of incoming stimuli. Finally, faces presented under unpredictable (U) threat should require most automatic attentional control, as each next stimulus could be the threat.

To assess effects of threat predictability and of facial expression on a behavioral level, valence, arousal and stress ratings of threat and faces were collected. We hypothesized that participants would show higher stress levels during threatening and especially unpredictably threatening contexts. To measure these differences, participants rated their stress scores after each NPU-condition. As stress has often been shown to influence memory performance (Luethi et al., 2008; Roozendaal et al., 2009; Weymar et al., 2013), we also included a memory task in which participants were asked to recognize the faces previously

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