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Research report

# Prepare for scare—Impact of threat predictability on affective visual processing in spider phobia

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## HIGHLIGHTS

- Threat predictability influences prefrontal cortical face processing.
- Unpredictability of threat leads to increased prefrontal emotion regulation.
- Phobic patients reveal decreased parietal emotional processing.

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## ABSTRACT

The visual processing of emotional faces is influenced by individual's level of stress and anxiety. Valence unspecific affective processing is expected to be influenced by predictability of threat. Using a design of phasic fear (predictable threat), sustained anxiety (unpredictable threat) and safety (no threat), we investigated the magnetoencephalographic correlates and temporal dynamics of emotional face processing in a sample of phobic patients. Compared to non-anxious controls, phobic individuals revealed decreased parietal emotional attention processes during affective processing at mid-latency and late processing stages. While control subjects showed increasing parietal processing of the facial stimuli in line with decreasing threat predictability, phobic subjects revealed the opposite pattern. Decreasing threat predictability also led to increasing neural activity in the orbitofrontal and dorsolateral prefrontal cortex at mid-latency stages. Additionally, unpredictability of threat lead to higher subjective discomfort compared to predictability of threat and no threat safety condition. Our findings indicate that visual processing of emotional information is influenced by both stress induction and pathologic anxiety.



## 1. Introduction

Visual perception and processing of emotional stimuli are influenced by individual's stress level and anxious states [1,2]. The induction of stress and anxiety may lead to enhanced attention toward emotionally salient information [3]. The detection and avoidance of potential threat are one central aspect of the human defensive system in order to secure survival [4,5]. Exaggerated reaction to threat and excessive anxious anticipation might, though, account for the development and maintenance of anxiety disorders [6,7]. Anxious expectation of a potential threat might be triggered by an external sensory cue, but also by cognitive network processes and verbal announcements. Verbal instructions have been shown to induce significant arousal and elicit a defensive reaction, even if the announced threat stimulus (e.g. electric shock or white noise) was not presented at all [2,3,8,9]. In contrast, a strong and specific stimulus is required to provoke an actual phobic fear reaction. In general, two processes are discriminated: fear, as a fast and automatic response towards an actual threat and accompanied by autonomic arousal and specific neural network activity, and anxiety, a prolonged apprehension towards a potential, unpredictable threat which may be either induced by contextual cues or cognitive processes [8,10].

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In line with this view on the dissociation of fear and anxiety [11–13] and assuming that stimulus probability has an influence on threat appraisal [14], Grillon and colleagues [9,15] established the concept of phasic fear and sustained anxiety. Phasic fear is defined as response to an explicit and predictable threat cue, while sustained anxiety describes a lasting state of anxious apprehension while anticipating an imminent and unpredictable threat. There is growing evidence for phasic fear and sustained anxiety to be related to different neural activity sources, processing intensity and temporal dynamics [16–18]. In a threat-of-shock design, induced anticipatory anxiety led to increased BOLD activity in the amygdala, insula and in prefrontal areas [19,20]. Recently, we have been able to replicate and extend current findings by revealing phasic fear responses to be related to activity of the central amygdala, while sustained anticipatory anxiety was associated with activation of the insula and the bed nucleus of stria terminalis [17,18,21,22]. However, regarding the temporal dynamics and the time course of cortical processes, only little is known on the discrimination of phasic fear and sustained anxiety.

Exploration of event-related potentials or magnetic fields (ERP, ERF) allows investigation of the temporal dynamics of affective processing. Thereby, findings from ERP/ERF studies complement findings from fMRI studies due to higher temporal resolution. The emotional valence of visual stimuli modulates emotion-specific components such as the early posterior negativity (EPN, 120–300 ms) and the late positive potential (LPP, >300 ms) and thereby allows conclusions about the motivational relevance of these stimuli: e.g. a potential threat will lead to an automatic shift of attentional resources towards the visual information [23–26]. Based on the motivated attention theory [27], these effects underline that emotional perception and processing are directed by the motivational importance of the stimuli, especially regarding approach and avoidance behavior. Emotion-specific components occur mainly at mid-latency stages of the processing stream in temporal and parietal areas. Emotionally arousing pictures have been revealed to evoke enhanced BOLD responses in occipital, parietal and inferior temporal areas [10,25,28]. Regarding event-related fields (ERF), emotion-specific components, such as the EPN, the N170 and the LPP have been shown to differentiate among emotional and neutral stimuli and often were enhanced for negative affective pictures [24,29]. In sum, we know that emotional visual stimuli modulate ERP/ERF components such as the EPN, N170 or LPP. Consistently, emotionally arousing faces evoked higher EPN compared to neutral stimuli.

So far, only little is known about the influence of pathologic anxiety on emotion-specific components evoked by emotionally salient visual stimuli. In general, anxiety disorders have been associated with a prefrontal emotion regulation deficit in the dorsomedial and dorsolateral prefrontal cortex (dmPFC/dlPFC) [26,30]. As shown recently, modulation of the dlPFC by transcranial magnetic stimulation altered affective processing [31]. In fMRI studies, the impact of threat induction on functional connectivity revealed connections of the amygdala and prefrontal areas such as the dmPFC or the mOFC [32–34]. Furthermore, high levels of trait anxiety led to decreased amygdala-vmPFC connectivity [32]. During periods of threat anticipation, connectivity of the amygdala with the dmPFC, OFC, ACC and insula had been found [35]. Therefore, we may assume that prefrontal emotion control processes should be enhanced under conditions of decreased threat predictability. However, in phobic disorders, decreased prefrontal emotional control has been revealed underlining the idea of automatic emotion regulation deficits involved in pathological anxiety [36]. During an active emotion regulation task, phobic individuals showed an activation decline in the right dmPFC [37]. Investigation of prefrontal neural activity in social phobia and generalized anxiety disorder revealed that patients suffering from anxiety disorders in general possess attenuated capacity for recruiting frontal regions in top-down emotion control processes [38]. In PTSD patients, early prefrontal neural activity in response to affective stimuli was shown, possibly based on excitatory bottom-up influence of the amygdala on the PFC [39,40]. According to a general vigilance-avoidance pattern, patients with anxiety disorders can be expected to reveal an early and transient prefrontal activation followed up by decreased prefrontal activity at later stages of emotion processing and regulation. In PTSD patients, smaller affective modulations in response to aversive visual stimuli have been shown in occipital and parietal regions [41–43] compared to controls. Furthermore, patients revealed reduced posterior activity towards emotional faces [44]. In spider phobic individuals, greater selective attention to emotional pictures has been revealed being reflected by an increased EPN [45]. However, results regarding emotion-specific components evoked by specific or general affective stimuli in anxiety disorders still are inconsistent.

Based on our knowledge about how emotional visual stimuli modulate ERP/ERF components such as the EPN and the LPP, we were interested in the influence of a threatening environment on emotional face perception. As predictability is a core factor in the sustained and phasic fear concept, the NPU-threat test is a common experimental method for investigating the impact of threat predictability [46,47]. In line with this concept, we created an experimental paradigm to investigate the processing of emotional faces under conditions of either predictable (P) or unpredictable (U), or the absence of threat (N). Recently, we have been able to show that decreased threat predictability lead to enhanced mid-latency activation in dorsolateral prefrontal areas presumably reflecting amplified top-down emotion regulation processes. Furthermore, the parietal cortex has been shown to dissociate between emotional faces presented either under conditions of potential threat or safety [48]. As the parietal cortex has been associated with emotional attention processes and revealed connections to limbic and prefrontal areas, we expected to also find effects of reduced emotional attention under threat conditions [49]. Continuing we were then interested in the effect of pathologic anxiety on the emotional processing under conditions of predictable and unpredictable threat. We further aim at exploring potential dissociations between phasic fear related and sustained anxiety related anxiety disorders. We assumed that specific phobia is characterized by a strong phobic fear reaction towards aversive material while patients suffering from panic disorder or generalized anxiety disorder experience mainly anxious anticipation. Therefore, we decided to investigate, initially, patients with spider phobia and non-phobic controls using our experimental *NPU* paradigm. As anxiety disorders in general have been associated with a prefrontal emotion regulation deficit, we assumed, firstly, phobic individuals to reveal decreased activity in frontal areas, especially when anticipating an unpredictable threat. Contrariwise, in non-anxious controls, we expected decreased threat predictability leading to enhanced top-down prefrontal emotional control, especially in the dlPFC. Secondly and according to the vigilance-avoidance hypothesis, we hypothesized phobic individuals to be less engaged in cortical parietal affective processing being reflected in decreased emotion-specific mid-latency components (EPN), especially under conditions of predictable and unpredictable threat. Additionally, we expected to replicate findings about negative compared to neutral emotional stimuli leading to increased mid-latency activation and, more specifically, enhanced EPN. Furthermore, we expected participants to be more influenced regarding subjective mood and agitation as a function to decreased threat predictability. Specifically, we expected phobic individuals to report higher subjective distress.