Initial and sustained brain responses to threat anticipation in blood-injection-injury phobia

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ABSTRACT

Blood-injection-injury (BII) phobia differs from other subtypes of specific phobia in that it is associated with elevated disgust-sensitivity as well as specific autonomic and brain responses during processing of phobia-relevant stimuli. To what extent these features play a role already during threat anticipation is unclear. In the current fMRI experiment, 16 female BII phobics and 16 female healthy controls anticipated the presentation of phobia-specific and neutral pictures. On the behavioral level, anxiety dominated the anticipatory period in BII phobics relative to controls, while both anxiety and disgust were elevated during picture presentation. By applying two different models for the analysis of brain responses to anticipation of phobia-specific versus neutral stimuli, we found initial and sustained increases of activation in anterior cingulate cortex (ACC), insula, lateral and medial prefrontal cortex (PFC), thalamus, and visual areas, as well as initial activation in the amygdala for BII phobics compared to healthy controls. These results suggest that BII phobia is characterized by activation of a typical neural defense network during threat anticipation, with anxiety as the predominant emotion.

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1. Introduction

Specific phobia is characterized by rapid, intense and uncontrollable fear in response to phobia-relevant objects and situations (American Psychiatric Association, 2000). Besides that, most phobics show anticipatory anxiety during expectation of phobia-related situations (Aue and Hoeppli, 2011) that triggers avoidance behavior which in turn prevents fear extinction (Gray and McNaughton, 2000).

A common subtype of specific phobia is blood-injection-injury (BII) phobia with an estimated prevalence of 3–4% in the general population (Wani and Ara, 2014) and a higher prevalence in women (Oosterink et al., 2009). In BII phobia, phobic fears and anxiety emerge in relation to blood withdrawal, medical interventions and the confrontation with a person’s own blood or blood of others, especially in the context of injuries. A feature that distinguishes BII phobia from other specific phobias is vasovagal syncope during exposure to phobia-specific objects or situations (Marks, 1988; Page, 1994), which affects approximately 75% of BII phobics (Marks, 1988). This reaction has been attributed to a biphasic autonomic response with a short increase followed by a marked decrease of heart rate (Page, 1994). Furthermore, besides fear and anxiety, BII phobics generally also experience strong disgust during symptom provocation (de Jong and Merckelbach, 1998; Sawchuk et al., 2002; Tolin et al., 1997). BII phobics often avoid medical treatment and even decline necessary treatment (Wani and Ara, 2014). Consequently, BII phobia can have detrimental effects and the investigation of its neural correlates could provide important insights for the development of an effective treatment.

In general, functional magnetic resonance imaging (fMRI) studies in specific phobia point towards involvement of amygdala, insula, anterior cingulate cortex (ACC) as well as prefrontal and orbitofrontal cortex during fear and anxiety, although the neural correlates of specific phobia are still not definitive and most studies were concerned with the animal subtype of specific phobia (for review see Del Casale et al., 2012; Ipsen et al., 2013; Linares et al., 2012). To date, BII phobia has received little attention in neuroscientific research (Del Casale et al., 2012). Unfortunately, results are rather inconclusive and seem to critically depend on experimental designs and procedures. Confrontation with phobia-relevant or generally disgusting images has been associated with diminished medial prefrontal cortex (PFC) activity (Hermann et al., 2007) and relatively unspecified activations in thalamus and occipital cortex in BII phobics (Caseras et al., 2010a; Schienle et al., 2003). Direct comparison between BII and animal phobics revealed that only spider phobics showed activations in key areas for emotional processing, i.e. insula and ACC, when confronted with phobia-specific pictures (Caseras et al., 2010a; Lueken et al., 2011). In contrast, another study reported...
similar activation patterns in BII and spider phobics in the amygdala, insula, ACC, thalamus and orbitofrontal cortex (OFC) (Caseras et al., 2013).

While confrontation with phobia-related stimuli is associated with strong disgust responses as well as partially different autonomic and brain responses in BII phobics as compared to other subtypes of specific phobia, it is as yet unknown to what extent these responses play a role already during anticipation of phobia-related threat. Since anticipatory anxiety includes negative affect, arousal and hypervigilance and leads to avoidance behavior and maintenance of symptoms (Gray and McNaughton, 2000), understanding its neural basis is of utmost importance. In spider phobia, anticipation of phobia-relevant in contrast to neutral pictures led to enhanced activation of ACC, insula, thalamus and visual cortex (Straube et al., 2007). Moreover, anxiety ratings during anticipation of aversive stimuli correlated with activations in dorsal and rostral ACC as well as medial PFC (Straube et al., 2007). These findings are in line with studies on anticipation of aversive stimuli in healthy subjects (e.g. Alvarezed et al., 2011; Carlson et al., 2011; Chua et al., 1999; Drabant et al., 2011; Grue et al., 2013; Kalisch et al., 2006; Nitschke et al., 2006; Shankman et al., 2014; Simmons et al., 2004; Simmons et al., 2006). Furthermore, anticipatory anxiety has been shown to lead to ACC activation in patients with panic disorder while expecting a panic attack (Boshuisen et al., 2002), to insula activation in social anxiety when anticipating public speaking (Boehme et al., 2014; Lorberbaum et al., 2004).

Aside from these brain regions, Straube et al. (2007) also reported activation in the bed nucleus of the stria terminals (BNST) during threat anticipation in spider phobics, suggesting involvement of this part of the so-called extended amygdala in anticipatory anxiety in animal phobia (also see Münsterkötter et al., 2015; but see Lueken et al., 2014). A growing body of research emphasizes a dissociation between amygdala and BNST, with the amygdala being involved in rapid processing of imminent threat and the BNST modulating sustained anxiety states in unpredictable threat contexts (Davis et al., 2010; Walker et al., 2003). In some studies with healthy subjects the anticipatory period was analyzed in such a way that it was possible to detect amygdala and BNST activation in one and the same experiment (Alvarez et al., 2011; Grue et al., 2013; Somerville et al., 2013), for example by separately modeling phasic and sustained brain responses (Grue et al., 2013).

The current fMRI study aimed to investigate neural correlates of threat anticipation in BII phobia by comparing anticipation of phobia-specific and neutral pictures. Additionally, anxiety and disgust ratings as well as changes in heart rate were examined to control for characteristic emotional and autonomic responses. Based on previous research, we were interested in brain activations in amygdala, BNST, ACC, insula, PFC, thalamus and visual areas during anticipation of phobia-specific in contrast to neutral pictures. Especially with regard to amygdala and BNST, we used an initial as well as a sustained model for BOLD responses in order to separate phasic and sustained brain activation, respectively. We hypothesized that initial amygdala activation and sustained BNST activation would be evident in phobic participants as compared to healthy controls during anticipation of phobia-specific versus neutral stimuli.

2. Material and methods

2.1. Subjects

Sixteen right-handed female subjects with BII phobia (age: 24.1 ± 3.82 years) and 16 right-handed female healthy control subjects (age: 23.7 ± 4.44 years) participated in the study. Only female participants were included since BII phobia is most common in young women (Miloyan and Eaton, 2016; Wani and Ara, 2014) and the majority of studies in specific phobia investigated female samples (for review see Del Casale et al., 2012; Ipser et al., 2013; Van Houtem et al., 2013), which makes the current study more comparable to other studies, especially to the anticipation study by Straube et al. (2007). Participants were recruited by public advertisement and received monetary reimbursement (10 €) or course credit for participation. BII-phobic subjects were selected by means of a short clinical interview (mini-DIPS, Margraf, 1994) based on DSM-IV (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1992). Patients and controls were matched with regard to age and level of education. Phobics scored significantly higher than non-phobic controls on the Mutilation Questionnaire (MQ, Klorman et al., 1974) (phobics: mean = 21.5, S.D. = 3.27; controls: mean = 5.94, S.D. = 2.29; t[30] = 15.6, p < 0.001). While confrontation with phobia-related stimuli is associated with strong disgust responses as well as partially different autonomic and brain responses in BII phobics as compared to other subtypes of specific phobia, it is as yet unknown to what extent these responses play a role already during anticipation of phobia-related threat. Since anticipatory anxiety includes negative affect, arousal and hypervigilance and leads to avoidance behavior and maintenance of symptoms (Gray and McNaughton, 2000), understanding its neural basis is of utmost importance. In spider phobia, anticipation of phobia-relevant in contrast to neutral pictures led to enhanced activation of ACC, insula, thalamus and visual cortex (Straube et al., 2007). Moreover, anxiety ratings during anticipation of aversive stimuli correlated with activations in dorsal and rostral ACC as well as medial PFC (Straube et al., 2007). These findings are in line with studies on anticipation of aversive stimuli in healthy subjects (e.g. Alvarezed et al., 2011; Carlson et al., 2011; Chua et al., 1999; Drabant et al., 2011; Grue et al., 2013; Kalisch et al., 2006; Nitschke et al., 2006; Shankman et al., 2014; Simmons et al., 2004; Simmons et al., 2006). Furthermore, anticipatory anxiety has been shown to lead to ACC activation in patients with panic disorder while expecting a panic attack (Boshuisen et al., 2002), to insula activation in social anxiety when anticipating public speaking (Boehme et al., 2014; Lorberbaum et al., 2004).

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2.2. Experimental design

In the scanner, participants anticipated the presentation of phobia-specific or neutral pictures. Pictures were selected from the International Affective Picture System (IAPS, Lang et al., 2008). Phobia-specific pictures showed bloody injuries of people and limbs as well as blood-withdrawal (# 3010, 3030, 3051, 3060, 3071, 3100, 3130, 3150, 9405, 9592). Neutral pictures showed people or objects (# 2200, 2214, 2215, 2270, 2383, 5395, 5520, 7010, 7090, 7503) and were matched to the phobia-specific pictures with regard to features, complexity, and color scheme (Adobe Photoshop, Version 13.0.1; Adobe Systems Software Ireland Limited, Ireland; see Supplementary Table 1). Phobia-specific and neutral pictures were used in previous studies on BII phobia (Buodo et al., 2006; Hamm et al., 1997). During the anticipatory period, one of two white cues (circle or square) was presented on black background, indicating whether the following picture would be phobia-specific or neutral. Assignment of the symbols to the conditions was counterbalanced across subjects, and participants were informed about cue-condition association before the session. The experiment comprised 10 phobia-specific and 10 neutral trials presented in pseudo-random order. The anticipatory period lasted 10, 12, or 14 s to ensure unpredictability of stimulus onset. The subsequent picture presentation lasted 12 s to establish a sufficiently threatening context and to be able to detect alterations in heart rate. Between trials, a fixation cross was shown for 16 s. In total, the experiment lasted 13 min.

After the scanning session, participants rated phobia-specific and neutral pictures as well as the respective anticipatory periods on the dimensions anxiety (1 = “not anxious at all” to 9 = “very anxious”) and disgust (1 = “not disgusting at all” to 9 = “very disgusting”) using a nine-point Likert-scale. Furthermore, as a measure of avoidance behavior, participants were requested to answer the question “How long did you look at the unpleasant pictures on average?” (“very briefly”, “a few seconds”, “almost the entire time”, or “I never looked away”). Behavioral data were analyzed by means of mixed-model analyses of variance (ANOVA)s using IBM SPSS software (Version 22; IBM, Armonk, New York, USA), with group (BII phobics vs. healthy controls) as between-subject factor and condition (phobia-specific vs. neutral) as within-subject factor. Post-hoc t-tests were performed to resolve interactions when appropriate. Generally, a p-value of < 0.05 was considered statistically significant. Data are presented as mean ± standard error.
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