



## Commonalities and differences in the neural substrates of threat predictability in panic disorder and specific phobia



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### ABSTRACT

Different degrees of threat predictability are thought to induce either phasic fear or sustained anxiety. Maladaptive, sustained anxious apprehension is thought to result in overgeneralization of anxiety and thereby to contribute to the development of anxiety disorders. Therefore, differences in threat predictability have been associated with pathological states of anxiety with specific phobia (SP) representing phasic fear as heightened response to predictable threat, while panic disorder (PD) is characterized by sustained anxiety (unpredictable threat) and, as a consequence, overgeneralization of fear. The present study aimed to delineate commonalities and differences in the neural substrates of the impact of threat predictability on affective processing in these two anxiety disorders. Twenty PD patients, 20 SP patients and 20 non-anxious control subjects were investigated with an adapted NPU-design (no, predictable, unpredictable threat) using whole-head magnetoencephalography (MEG). Group independent neural activity in the right dlPFC increased with decreasing threat predictability. PD patients showed a sustained hyperactivation of the vmPFC under threat and safety conditions. The magnitude of hyperactivation was inversely correlated with PDs subjective arousal and anxiety sensitivity. Both PD and SP patients revealed decreased parietal processing of affective stimuli. Findings indicate overgeneralization between threat and safety conditions and increased need for emotion regulation via the vmPFC in PD, but not SP patients. Both anxiety disorders showed decreased activation in parietal networks possibly indicating attentional avoidance of affective stimuli. Present results complement findings from fear conditioning studies and underline overgeneralization of fear, particularly in PD.

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### 1. Introduction

The predictability of threat is thought to modulate the discrimination between potential threat, imminent threat and safety conditions (Grillon et al., 2006). According to the concept of phasic fear and sustained anxiety, phasic fear is the response to an explicit, predictable threat, while sustained anxiety is defined as anxious apprehension anticipating an unpredictable, distant threat (Grillon et al., 2004). The NPU (no threat, predictable, and unpredictable threat) threat test has been used as common experimental method to investigate the impact of threat predictability (Grillon et al., 2004; Schmitz and Grillon, 2012). On a clinical level, phasic fear and sustained anxiety have been

linked to different anxiety phenotypes, e.g. specific phobia (SP) as a model disorder of phasic fear and panic disorder (PD) as a model for sustained anxiety (McNaughton and Corr, 2004). The specific neural signature of threat predictability in these anxiety disorders possibly representing two extrema on the fear and anxiety continuum are, however, poorly understood.

There is growing evidence that phasic fear and sustained anxiety evoke activity in overlapping but also different neurofunctional systems (Alvarez et al., 2011; Davis et al., 1997; McNaughton and Corr, 2004). While phasic fear has been linked to activity of the central amygdala, sustained anxiety predominately activated the bed nucleus of the stria terminalis (BNST), anterior cingulate cortex (ACC), and insula (Herrmann et al., 2016; Muensterkoetter et al., 2015). Using a novel paradigm based on the NPU design (Klahn et al., 2016; Klinkenberg et al., 2016) in an MEG study focusing on cortical activation patterns, we recently showed that the dorsolateral prefrontal cortex (dlPFC) modulated threat predictability while parietal cortex activation dissociated

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between threat and safety conditions. Individuals with specific phobia were characterized by reduced overall parietal processing compared to non-anxious controls (Klahn et al., 2016).

Anxiety disorders have been linked to heightened threat sensitivity and dysfunctional prefrontal emotion regulation mechanisms resulting in exaggerated fearful defensive responses and prolonged anxiety (Grillon, 2008; Shankman et al., 2013). As one example for dysfunctional emotion regulation (Bouton et al., 2001; Lissek et al., 2010), PD patients showed deficient safety signal processing during fear conditioning resulting in overgeneralization of fear and, as a putative consequence, sustained anxiety (Lissek et al., 2009, 2010). The inability to differentiate between threatening and safe environments and to inhibit aversive responding under safety conditions which in turn results in a failure to relax under safety conditions is considered as a core dysfunction in PD (Gorka et al., 2014; Lieberman et al., 2015; Lissek, 2012). Regarding the regulation of defensive and negative affective responding, neural circuitry models propose the ventromedial (vm) PFC to down-regulate negative affect and fearful arousal by inhibiting the amygdala and other brain regions involved in the processing of negative emotions (Myers-Schulz and Koenigs, 2012; Schiller and Delgado, 2010). In fact, pathological anxiety is thought to partly result from such deficient vmPFC emotion regulation ability (Ball et al., 2013; Banks et al., 2007; Motzkin et al., 2016). In PD patients, increased activity in an anterior cingulate cortex (ACC)-medial prefrontal-limbic network during safety signal processing has been associated with enhanced defensive responding under safety conditions (Tuescher et al., 2011). Furthermore, activity in this network predicted the response to exposure-based cognitive behavioral therapy, potentially by enhanced emotion regulation capacities via fear extinction (Lueken et al., 2013). While passively viewing emotional faces, reduced vmPFC activity along with greater amygdala responsiveness was reported in PD as well as in SP compared to controls (Killgore et al., 2014). In SP, anticipating phobia-relevant stimuli led to greater vmPFC activity under controllable compared to uncontrollable conditions (Kerr et al., 2012). Although the role of this vmPFC-limbic circuit has been investigated in other forms of emotion regulation, only little is known in relation to threat predictability in anxiety disorders.

The aim of this study was to compare the neural signature of threat predictability and overgeneralization between two anxiety phenotypes as model disorders for phasic fear (SP) and sustained anxiety (PD). As PD has been associated with prefrontal emotion regulation deficits and based on previous evidence on safety signal processing, we assumed PD patients to show altered vmPFC activity during both threat and safety conditions, but predominately during unpredictable threat. We expected them to fail at discriminating these conditions due to the phenomenon of overgeneralization. Considering SP as phasic fear related disorder, altered vmPFC activity in SP should particularly occur under conditions of predictable threat. On a subjective level, we expected PD patients to report higher subjective distress and arousal than SP and non-anxious controls. Symptom severity and subjective arousal as reaction to a threat should be related to mid-latency to late neural activity in emotion-regulating circuits e.g. the vmPFC. Based on previous findings in SP (Klahn et al., 2016), we additionally hypothesized to find a disorder unspecific effect of decreased mid-latency parietal processing.

## 2. Methods and materials

### 2.1.1. Participants

We included 22 patients diagnosed with PD (of which 2 dropped out due to anxiety before scanning), 20 patients diagnosed with SP (both according to DSM-IV-TR-criteria), and 20 non-anxious controls (for detailed characteristics of the sample, see Table 1). Parts of this sample have been published addressing a different research question (Klahn et al., 2016); the sample was enriched by the PD group for the present analysis. All participants were right-handed and fulfilled general MEG-related requirements. Exclusion criteria were any current or lifetime

psychosis, bipolar disorder, severe Major Depression, Posttraumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), any severe somatic or neurological illness, or any complex psychopharmacological treatment. A stable treatment with SSRIs as well as psychotherapeutic treatment within the past 2 years was only tolerated if current symptoms were still clinically significant. All participants were diagnosed using the structured interview (SCID-I) for DSM-IV-TR (American Psychiatric Association, 2000; Wittchen et al., 1997) and completed the Beck Depression Inventory (BDI (Beck et al., 1996)), Beck Anxiety Inventory (BAI (Beck and Steer, 1993)), Anxiety Sensitivity Index (ASI (Taylor et al., 2007)), trait version of the State-Trait Anxiety Inventory (STAI-T (Spielberger, 1983)), Anxiety Cognitions Questionnaire (ACQ (Chambless et al., 1984)), Panic and Agoraphobia Scale (PAS (Bandelow, 1995)), Spider Phobia Questionnaire (SPQ (Watts and Sharrock, 1984)), and Fear of Spider Questionnaire (FSQ (Szymanski and O'Donohue, 1995)).

### 2.1.2. Ethics statement

All procedures were approved by the Ethics Committee of the Medical Faculty of the University of Muenster. The ethical standards of the Declaration of Helsinki were met. All participants provided written informed consent after the study procedure was fully explained and received financial compensation for their participation.

## 2.2. Material and procedure

The modified *NPU* paradigm (Klinkenberg et al., 2016) consisted of three consecutive runs presented in randomized order across subjects. In each run, a different set of 56 greyscaled male and female faces with fearful or neutral expressions (i.e. 28 faces per face expression), randomly chosen from a total compilation of 236 facial stimuli (see Klinkenberg et al., 2016 for more details regarding stimulus choice), was presented four times resulting in a total presentation of 112 facial stimuli per run and experimental condition (stimulus duration: 500 ms; jittered ITI: 825–1325 ms). In the predictable (P) and unpredictable (U) runs, a video (760 ms duration) of a rapidly appearing monster paired with an aversive scream served as threat stimulus and was presented four times per run. The threat stimulus could appear at any time in the unpredictable condition, but was cued by a warning signal in the predictable condition. No threat (N) runs were regarded as safety conditions with only facial stimuli being presented. Participants were informed about the respective threat or safety conditions before run onsets. Four additional filler faces presented between the warning signal and the aversive stimulus, as well as one filler presented after the threat stimulus were excluded from the main analysis to correct for movement artifacts. After each run, participants completed the scales agitation and mood of the multidimensional mood state questionnaire (MDSQ, German version (Steyer et al., 1997)) and were asked to rate the threat stimulus regarding perceived valence (unpleasant to pleasant) and arousal (calm to arousing) on a 9-point Likert SAM-rating scale (Bradley and Lang, 1994). Prior to and after MEG-measurement, participants completed a SAM-rating regarding valence and arousal for all fearful and neutral faces, respectively. For more details on the experimental paradigm see (Klinkenberg et al., 2016).

### 2.3. Apparatus and data analysis

MEG volume conductor modeling was based on head surface detection using polhemus 3Space® Fastrack. For later spatial coregistration of anatomy and function, landmark coils (MEG) were attached to the two auditory canals and the nasion. Visually evoked magnetic fields were acquired using a 275 MEG whole-head sensor system (VSM Medtech Ltd.) with first-order axial SQUID gradiometers. Continuous recorded MEG data were down-sampled offline to 300 Hz and filtered between 0.01 Hz and 148 Hz. Data were aligned to stimulus onset, with an averaging epoch ranging from 200 ms before to 600 ms after

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