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Inter-individual differences in trait anxiety shape the functional connectivity between the bed nucleus of the stria terminalis and the amygdala during brief threat processing

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ABSTRACT

An influential framework suggests that the central nucleus of the amygdala (CeA) is involved in phasic responses to threat, while the bed nucleus of the stria terminalis (BNST) mediates sustained anxiety. However, this model has been questioned, proposing that the role of the BNST is not limited to sustained threat contexts. Rather, amygdala and BNST also seem to work in concert in the processing of discrete and briefly presented threat-related stimuli, likely dependent on inter-individual differences in anxiety. A direct test of this assumption with sufficient experimental power is missing in human research and the degree to which individual differences in trait anxiety moderate phasic responses and functional connectivity of amygdala and BNST during threat processing remains unclear. The current event-related functional magnetic resonance imaging (fMRI) study investigated activation and connectivity of amygdala and BNST, as well as modulating effects of trait anxiety, during processing of briefly presented threat-related relative to neutral standardized pictures in 93 psychiatrically healthy individuals. Both amygdala and BNST activation was increased during presentation of threat-related relative to neutral pictures. Furthermore, functional connectivity between BNST and amygdala in response to threat was positively associated with trait anxiety. These findings suggest that amygdala and BNST form a functional unit during phasic threat processing whereby their connectivity is shaped by inter-individual differences in trait anxiety.

Introduction

A widely accepted model by Walker et al. (2009) proposes dissociable fear and anxiety systems in the central extended amygdala, with rapid processing of imminent threat in the central nucleus of the amygdala (CeA), and a transition to sustained anxiety states during unpredictable threat via projections from the CeA to the bed nucleus of the stria terminalis (BNST) (also see Walker et al., 2003; Davis et al., 2010). Indeed, many studies report sustained responses in the BNST during uncertain threat situations (Alvarez et al., 2011; Grupe et al., 2013; Somerville et al., 2013; McMenamin et al., 2014; Herrmann et al., 2016). Others suggest that the BNST is involved not only under sustained threat, but also in processing discrete, phasic threat stimuli, indicating similar functional roles for BNST and amygdala (Gungor and Pare, 2016; Shackman and Fox, 2016). Especially research in animals provides evidence for processing of discrete threat-related stimuli in the BNST (Meloni et al., 2006; Duvarci et al., 2009; Haufler et al., 2013). CeA and BNST thus seem to constitute a tightly interconnected system that functions as a unit during processing of threat-related information and the expression of fear and anxiety (Gungor and Pare, 2016; Shackman and Fox, 2016). Although inter-individual differences in anxiety likely shape these processes, the influence of such differences on phasic responses and functional connectivity of amygdala and BNST during threat processing has not been investigated so far.

The amygdala is well known for its role in rapid threat processing (Tovote et al., 2015) and this function has been intensively studied in humans using functional magnetic resonance imaging (fMRI) (for meta-analyses and reviews see Costafreda et al., 2008; Sergerie et al., 2008; Fox et al., 2015). The BNST has received considerably less attention and much of the work has focused on sustained or uncertain threat

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(e.g. Somerville et al., 2010; Alvarez et al., 2011; Grupe et al., 2013; Herrmann et al., 2016). Despite its rather small size, the BNST is a fairly heterogeneous region with various subregions, subnuclei, receptors and functions (Bota et al., 2012; Avery et al., 2016; Gungor and Pare, 2016; Lebow and Chen, 2016), and these functions, including potential phasic responses to threat, are not well understood. Among human fMRI studies, several have provided evidence that the BNST can be recruited by more fleeting threat-related stimuli (Mobbs et al., 2010; Alvarez et al., 2011; Choi et al., 2012; Grupe et al., 2013; Klumpers et al., 2015). For example, a 4s video clip of an approaching tarantula led to increased BNST activation in healthy subjects (Mobbs et al., 2010). BNST activation was also found during 2–8s of anticipating threat-related pictures (Grupe et al., 2013). Whether the BNST also responds to very brief threat-related stimuli (i.e. <1s) is thus unknown.

There is evidence suggesting that the BNST contributes to the development or maintenance of maladaptive and chronic anxiety (Straube et al., 2007; Münsterkötter et al., 2015; Brinkmann et al., 2017a, 2017b), even though its association with inter-individual differences in anxiety is still much neglected in humans (Avery et al., 2016; Lebow and Chen, 2016). The interplay between BNST and amygdala shapes inter-individual differences in the expression of fear and anxiety in rats (Duvarci et al., 2009). In humans, a relationship between individual measures of anxiety and BNST activation or connectivity has only been shown in anticipation studies (Straube et al., 2007; Somerville et al., 2010; McMenamin et al., 2014). For example, Somerville et al. (2010) demonstrated enhanced tracking of threat proximity in the BNST for more anxious individuals. However, no study investigated anxiety-dependent modulation of the BNST or amygdala and BNST as a functional unit during brief threat processing.

The aim of this study was to investigate phasic activation and functional connectivity of amygdala and BNST as well as the modulatory influence of inter-individual differences in trait anxiety during processing of briefly presented threat-related and neutral pictures by means of event-related fMRI in a large sample of 93 healthy subjects. Trait anxiety represents a stable personality trait, and a potential predisposition for the development of pathological anxiety (Shackman et al., 2016). Based on the existing literature, two competing hypotheses regarding activation in amygdala and BNST are conceivable. In line with the model described by Walker et al. (2009) it could be hypothesized that only the amygdala shows phasic activation during presentation of threat-related relative to neutral pictures. Alternatively, as suggested by recent reviews (Gungor and Pare, 2016; Shackman and Fox, 2016), it could also be hypothesized that both amygdala and BNST show phasic activation. Furthermore, we conducted psychophysiological interaction (PPI) and correlational analyses to investigate functional connectivity patterns of amygdala and BNST and the modulation of neural responses and connectivity patterns in BNST and amygdala by inter-individual differences in trait anxiety. Since amygdala and BNST have been suggested to form a functional unit during the processing of threat-related information (Gungor and Pare, 2016; Shackman and Fox, 2016), we wanted to investigate if and in how far this unit is modulated by trait anxiety.

Materials and methods

Subjects

Ninety-eight healthy volunteers were recruited for the study through public advertisement and a local database. Five participants had to be excluded from further analyses due to excessive movement ($n = 2$), technical problems during scanning ($n = 2$) or drug intake ($n = 1$). The final sample thus consisted of 93 healthy volunteers (60 female; age: $M = 25.46$, $SD = 4.25$; years in school: $M = 12.84$, $SD = 0.93$). All participants were right-handed and had normal or corrected-to-normal vision. An experienced psychologist screened all participants with the Structured Clinical Interview for DSM-IV (German version of the SCID; Wittchen et al., 1997) to ensure that participants were free of any psychiatric disorders within the past five years. All participants completed the trait anxiety subscale of the State-Trait Anxiety Inventory (STAI-T; Spielberger et al., 1983) ($M = 30.10$, $SD = 5.64$, range: 20–50). Exclusion criteria comprised psychiatric or neurological disorders, traumatic brain injury and drug abuse or dependence within the past ten years. The study conforms to the Declaration of Helsinki and was approved by the local ethics committee. All participants gave written informed consent prior to the experiment.

Stimuli

We used a picture set consisting of 50 threat-related and 50 neutral pictures from the International Affective Picture System (IAPS; Lang et al., 2008; 48 threat pictures, 14 neutral pictures) and EmoPics (Wessa et al., 2010; 2 threat pictures, 36 neutral pictures) (for identification numbers see Supplementary Table 2). Threat-related pictures showed for example interpersonal violence, injuries, motor-vehicle accidents and threatening animals, while neutral pictures showed objects or animals. Threat-related and neutral pictures were matched for color scheme, luminance and complexity (Supplementary Table 1). Additionally, picture properties regarding the main picture component (human, object, animal, nature), the number of humans in the picture, facial expression (central to the picture, in the background, no face) and location (inside, outside) did not differ between threat-related and neutral pictures (Pearsons chi-squared test, all $p > 0.05$).

Experimental design

During scanning, pictures were presented in pseudorandomized order (<10 pictures of the same valence in a row) within an event-related experiment, using Presentation Software (v17.2, Neurobehavioral Systems, Albany, California, USA). Each picture was presented for 800 ms. Between consecutive pictures, a fixation cross was shown, with a jittered duration (1280–18 960 ms, mean = 3890 ms; determined using the Optseq algorithm [http://www.surfer.nmr.mgh.harvard.edu/optseq/]). Attention to the stimuli was ensured by instructing participants to press a button whenever a blurred picture was presented, which happened five times during the experiment. Trials with blurred pictures were excluded from analyses. After scanning, the participants rated the pictures (presentation duration: 2000 ms) with regard to valence (1 = very unpleasant, 9 = very pleasant, with 5 = neutral), anxiety (1 = not anxiety-inducing, 9 = highly anxiety-inducing) and arousal (1 = not arousing, 9 = highly arousing) on a nine-point Likert scale. Rating data were analyzed with *t*-tests using SPSS (Version 22; IBM, Armonk, New York, USA). A *p*-value of < 0.05 was considered statistically significant.

FMRI

FMRI data were collected with a 3 T magnetic resonance scanner ("Magnetom PRISMA"; 20-channel Siemens Head Matrix Coil; Siemens Medical Systems, Erlangen, Germany). First, a high resolution T1-weighted anatomical scan with 192 slices was recorded (TE = 2.28 ms, flip angle = 8°, matrix = 256 × 256, FOV = 256 mm, TR = 2130 ms, voxel size = 1.0 × 1.0 × 1.0 mm). Subsequently, one functional dataset per subject was acquired with a T2*-weighted echo-planar sequence (TE = 30 ms, flip angle = 90°, matrix = 92 × 92, FOV = 208 mm^2, TR = 2080 ms) consisting of 255 vol with 36 axial slices (thickness = 3 mm, gap = 0.3 mm, in plane resolution = 2.26 × 2.26 mm).

Functional data were preprocessed and analyzed with BrainVoyager QX (Version 2.8; Brain Innovation, Maastricht, the Netherlands). The first ten volumes were discarded from each run to ensure adequate saturation. During preprocessing, data were corrected for slice time errors and movement artifacts (participants with >3 mm in any direction were excluded from further analyses) and were resampled to a voxel size of 2 × 2 × 2 mm. Anatomical and functional data were co-registered with