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Diminished medial prefrontal cortex activity in blood-injection-injury phobia

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Abstract

We examined the effects of symptom induction on neural activation in blood-injection-injury (BII) phobia. Nine phobic and 10 non-phobic subjects participated in an fMRI study in which they were presented with disorder-relevant, generally disgust-inducing, generally fear-evoking and neutral pictures. We observed diminished medial prefrontal cortex (MPFC) activity in patients compared to controls for phobia-relevant and disgust-inducing pictures. The MPFC has been shown to be critically involved in the automatic and effortful cognitive regulation of emotions. Therefore, the results might reflect reduced cognitive control of emotions in BII phobics during the experience of phobic symptoms as well as during states of disgust. The latter response component might be a result of the elevated disgust sensitivity of BII phobics.

Keywords: Blood phobia; Fear; Disgust; Medial prefrontal cortex, MPFC; Cognitive control; Emotion regulation

1. Introduction

Blood-injection-injury (BII) phobia is an atypical specific phobia that strongly affects patients' daily lives. The sufferers often experience emotional fainting (vasovagal syncope) when exposed to phobic stimuli such as blood, injections or injuries (APA, 1994). This physiological response is at first sympathetically dominated, as seen in other specific phobias (e.g. spider phobia), but is then followed by a pronounced parasympathetic component (Page, 1994). The phobics display excessive fear reactions and avoidance behavior. Moreover, it has been shown that not only fear, but the emotion disgust, plays a major role in this disorder as well. Questionnaire studies and picture perception experiments have shown positive associations between blood-related fears and disgust reactivity (e.g. Tolin et al., 1997; deJong and Merkelbach, 1998; Schienle et al., 2003).

To our knowledge there is only one published fMRI study on BII phobia (Schienle et al., 2003). This investigation addressed the elevated disgust sensitivity of this patient group by analyzing neural responses to generally disgust-inducing pictures. The only ascertainable difference between BII phobics and healthy controls was a heightened activity in the visual association cortex. A shortcoming of this study was the lack of a phobia-relevant condition. The goal of another fMRI investigation (Wright et al., 2004) was to determine if two types of disgust-relevant stimuli, pictures depicting mutilation or contamination, were able to provoke similar or differential hemodynamic responses in healthy subjects. The findings indicated that the insula was crucial for the processing of both disgust stimuli, whereas pictures of mutilation specifically activated the superior parietal cortex. The results could not be replicated in a similar experiment (Schienle et al., 2006). In this case, a comparable activation pattern including the occipitotemporal cortex, the amygdala and the orbitofrontal cortex occurred in both disgust conditions. Mutilation scenes triggered greater activity in inferior parietal cortex regions as compared to contamination scenes.

Neuroimaging studies focusing on other anxiety disorders besides BII phobia have often found increased activity in regions involved in the automatic processing of fear stimuli such as the amygdala, the hippocampus, the thalamus, the insula, the anterior cingulate cortex (ACC) and motor-related regions, e.g. the supplementary motor area (Lorberbaum et al.,

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2004; Schienle et al., 2005; Kim and Gorman, 2005). Also, a decreased activation in prefrontal cortex regions has frequently been observed (Kim and Gorman, 2005). The latter component might reflect a deficit in cognitive control during excessive states of anxiety. This could possibly lead to reduced inhibitory regulation of limbic regions such as the amygdala. Especially, the medial prefrontal cortex (MPFC) and the ACC are assumed to have specific functions in cognitive and self-referential processing as well as in emotion modulation (Phan et al., 2004). Taking this into account, it is likely that abnormal activity in MPFC areas might be an important characteristic of anxiety disorders (LeDoux, 2002). Furthermore, neuroimaging studies on cognitive regulation of emotions in healthy subjects have shown that these prefrontal areas are involved in different kinds of cognitive control of emotions, for instance reappraisal, anticipation and attention distraction (Ochsner and Gross, 2005).

The main goal of the present study was to identify the neural correlates of phobic states in BII phobics. We hypothesized that the presentation of blood-related pictures would activate regions important for the automatic processing of emotions (e.g. the amygdala). This should apply to both patients and non-phobic control subjects due to the overall emotional relevance of this stimulus type. The activation, however, should be greater in patients than controls. Further, the smaller capacity of phobics to cognitively regulate affective responses during the exposure should be mirrored in a reduced activation of prefrontal cortex regions relative to controls. Moreover, we hypothesized that phobic compared to healthy subjects would show an elevated disgust sensitivity and stronger hemodynamic responses towards disgust-inducing disorder-irrelevant pictures (e.g. in the amygdala). A fear condition with threatening, but non-phobic pictures served as a further emotional control condition.

2. Materials and methods

The participants of this study consisted of 9 female patients with a DSM-IV diagnosis of BII phobia (mean age = 22.9 years; S.D. = 4.7) and 10 non-phobic female control subjects (mean age = 27.6 years; S.D. = 10.7), who gave written informed consent for the study after the experiment had been explained to them. All participants denied taking any medication. The control subjects received 20 Euros for their participation. The patients underwent an exposure therapy after the experiment. This study was approved by the Ethics Committee of the German Society for Psychology.

The study consisted of two separate sessions. In the first session the participants were interviewed with the short form of the clinical interview for DSM-IV (Margraf et al., 1991) to ensure the diagnosis and exclude individuals with comorbidities. A behavior test was conducted, where the subjects were asked to undergo a blood draw. All control subjects and none of the patients were able to perform this test. Afterwards, the participants completed the Mutilation Questionnaire (MQ, Klorman et al., 1974), the Blood Injection Symptom Scale (BISS, Page et al., 1997), the Questionnaire for the Assessment of Disgust Sensitivity (QADS, Schienle et al., 2002b), the trait scale of the State Trait Anxiety Inventory (STAI, Laux et al., 1981) and the Beck Depression Inventory (BDI, Hautzinger et al., 1993).

The fMRI study was conducted in the second session (approximately 1 week later). After the scanning, the subjects gave disgust, fear, valence and arousal ratings for each picture category (possible range: 1–9; '9' indicated that the subject felt disgusted, anxious, pleasant and aroused). The Self-Assessment Manikin (SAM; Bradley and Lang, 1994) was used for the valence and arousal ratings. The intensity of experienced disgust and fear was rated on 9-point Likert scales (1 = 'not at all'; 9 = 'very strong'), which had been developed by the authors.

The stimulus material consisted of four categories with 160 pictures in total: 40 phobic, 40 disgust, 40 fear and 40 neutral pictures. These stimuli were selected from the IAPS (Lang et al., 1997) and another picture set (Schienle et al., 2002a). The phobia-relevant scenes depicted, e.g. blood draws and wounds. The disgust-evoking pictures represented the domains poor hygiene (e.g. garbage piles, dirty toilets), animals (e.g. maggots, snails), body products (e.g. excrements, vomit) and unusual food (e.g. a man eating a grasshopper). Pictures showing attacks by humans (e.g. with pistols or knives) and animals (e.g. lions, sharks) formed the fear category, whereas the affectively neutral scenes consisted of, e.g. geometric figures and household articles. The pictures were presented for 1.5 s in blocks of 40 pictures of the same category. The pictures sequence in each block was randomized and each block was shown six times during the experiment. Two categories of the same type were not allowed to follow each other. Participants viewed the pictures by a mirror fixed on the head coil (visual field = 18°). The complete experiment took 24 min.

A total of 492 volumes (T2*-weighted gradient echo-planar imaging sequence with 30 slices covering the whole brain, slice thickness = 5 mm, no gap, interleaved, TA = 100 ms, TE = 60 ms, TR = 3000 ms, flip angle = 90°, field of view = 192 mm × 192 mm, matrix size = 64 × 64) were acquired with a 1.5 T whole-body tomograph (Siemens Symphony, Erlangen, Germany; standard head coil). The axial slices were oriented parallel to the AC-PC line. To control for saturation effects the first six volumes were discarded. The statistical parametric mapping software package (SPM2, Wellcome Department of Cognitive Neurology, London) implemented in Matlab (Mathworks, Inc., Natick, MA, USA, release 12) was used for the preprocessing and statistical analyses. Slice time correction, realignment and normalization to the standard space of the Montreal Neurological Institute brain and the smoothing procedure (isotropic three-dimensional Gaussian filter with a full width at half maximum of 9 mm) were carried out. Each experimental condition was modeled by a boxcar function convolved with a hemodynamic response function in the GLM. The six movement parameters of the rigid body transformation were introduced in the model as covariates. Serial correlations were controlled by an AR(1) process and the high pass filter was set at 512 s. In the first level analyses the following contrasts were calculated for each subject: Phobia > Neutral, Disgust > Neutral, Fear > Neutral, Fear > Disgust, Disgust > Fear, Phobia > Fear, Fear > Pho-Phobia, Phobia > Disgust and Disgust > Phobia. Then, the contrast images were used in second level random effects analyses. We conducted one-sample *t*-tests for each group and two-sample *t*-tests to explore differences between the phobic and the control group. We computed voxel intensity tests (intensity threshold: $p = 0.01$ uncorrected) for the whole brain volume (exploratory analyses) and for regions of interest (ROI). Error probabilities (p) were corrected for multiple comparisons using the random field theory. When exploratory analyses were conducted, p was corrected for the whole brain volume, when a ROI test was used p was corrected for the specific volume of interest according to the tested hypothesis. The significance level was always set to alpha = 0.05. The following ROIs had been selected on the basis of previous findings on anxiety disorders and the neural processing of mutilation stimuli: anterior cingulate cortex (ACC), amygdala, dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), hippocampus, insula, lateral orbital prefrontal cortex (LOFC), supplementary motor area (SMA), inferior parietal cortex, superior parietal cortex, thalamus, ventromedial prefrontal cortex (VMPFC). The ROIs had been defined by the anatomical parcellation of the normalized brain (single-subject high-resolution T1 volume of the Montreal Neurological Institute). We created masks based on this assignment between anatomical structures and voxel coordinates (Tzourio-Mazoyer et al., 2002).

3. Results

3.1. Self-report-data

Phobic subjects scored significantly higher on the Mutilation Questionnaire, the Blood Injection Symptom Scale and the Questionnaire for the Assessment of Disgust Sensitivity