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ORIGINAL ARTICLE

Transdiagnostic brain responses to disorder-related threat across four psychiatric disorders

K. Feldker[1]*†, C. Y. Heitmann[1]†, P. Neumeister[1], S. V. Tupak[1], E. Schrammen[1], R. Moeck[1], P. Zwitserlood[2], M. Bruchmann[1] and T. Straube[1]

[1] *University Hospital Muenster, Institute of Medical Psychology and Systems Neuroscience, Muenster, Germany*
[2] *University of Muenster, Muenster, Germany*

Background. There is an ongoing debate whether transdiagnostic neural mechanisms are shared by different anxiety-related disorders or whether different disorders show distinct neural correlates. To investigate this issue, studies controlling for design and stimuli across multiple anxiety-related disorders are needed.

Method. The present functional magnetic resonance imaging study investigated neural correlates of visual disorder-related threat processing across unmedicated patients suffering from panic disorder ($n = 20$), social anxiety disorder ($n = 20$), dental phobia ($n = 16$) and post-traumatic stress disorder ($n = 11$) relative to healthy controls (HC; $n = 67$). Each patient group and the corresponding HC group saw a tailor-made picture set with 50 disorder-related and 50 neutral scenes.

Results. Across all patients, increased activation to disorder-related *v.* neutral scenes was found in subregions of the bilateral amygdala. In addition, activation of the lateral amygdala to disorder-related *v.* neutral scenes correlated positively with subjective anxiety ratings of scenes across patients. Furthermore, whole-brain analysis revealed increased responses to disorder-related threat across the four disorders in middle, medial and superior frontal regions, (para-)limbic regions, such as the insula and thalamus, as well as in the brainstem and occipital lobe. We found no disorder-specific brain responses.

Conclusions. The results suggest that pathologically heightened lateral amygdala activation is linked to experienced anxiety across anxiety disorders and trauma- and stressor-related disorders. Furthermore, the transdiagnostically shared activation network points to a common neural basis of abnormal responses to disorder-related threat stimuli across the four investigated disorders.

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Key words: Amygdala, functional magnetic resonance imaging, panic disorder, social anxiety disorder, specific phobia.

Introduction

The current prevalence of anxiety disorders adds up to 10.4% in Western cultures. Anxiety disorders are among the 10 leading causes of disability worldwide, and among the three most expensive mental disorders in Europe (Olesen *et al.* 2012; Baxter *et al.* 2013). Features shared by anxiety disorders, such as panic disorder (PD), social anxiety disorder (SAD), or specific phobia, are excessive fear and anticipatory anxiety, physical symptoms, escape and avoidance behaviour, thoughts of current threat, and mental apprehension (Craske *et al.* 2009). Cues triggering this initial fear response depend on the disorder and are thus disorder-related (American Psychiatric Association, 2000). In the recently published Diagnostic and Statistical Manual of Mental Disorders, 5th revision (DSM-5; American Psychiatric Association, 2013), post-traumatic stress disorder (PTSD) has been classified as a trauma- and stressor-related disorder, distinguishing PTSD from anxiety disorders. As the symptoms for anxiety disorders and trauma- and stressor-related disorders overlap, the classification change of PTSD fuelled intensive discussion (Friedman *et al.* 2011; Zoellner *et al.* 2011).

Shared behavioural features suggest a dimensional view of anxiety and trauma- and stressor-related disorders. Keeping with recent dimensional approaches such as the Research Domain Criteria (RDoC) project (Cuthbert, 2015), studies examining potential transdiagnostic neurobiological alterations that cut across anxiety, and trauma- and stressor-related disorders are needed.

Since the amygdala is linked to fear mechanisms in healthy subjects and in pathological anxiety, it could potentially represent a target structure in a

* Address for correspondence: K. Feldker, Institute of Medical Psychology and Systems Neuroscience, Von-Esmarch-Straße 52, D-48149 Muenster, Germany.
(Email: katharina.feldker@uni-muenster.de)
† Both authors contributed equally to this work.

dimensional approach (Rauch *et al.* 2003; Zald, 2003; Phelps, 2006; Forster *et al.* 2012). The amygdala is a central processing hub for emotional information. It receives input from sensory processing structures (e.g. thalamus) and higher-order regions (e.g. prefrontal cortex; PFC), and is essential for the detection of relevant emotional information (Phelps & LeDoux, 2005; Sergerie *et al.* 2008; Forster *et al.* 2012). The amygdala can be divided into lateral, basal and central components, with the lateral part functioning mainly as an entrance region for sensory information while the central region mediates behavioural and autonomous reactions via various output pathways (LeDoux, 2007; Janak & Tye, 2015).

Reviews and meta-analyses have drawn an inconsistent picture with regard to amygdala involvement across anxiety disorders during emotional processing (Rauch *et al.* 2003; Etkin & Wager, 2007; Craske *et al.* 2009; Shin & Liberzon, 2010; Holzschneider & Mulert, 2011; Fredrikson & Faria, 2013; Duval *et al.* 2015; Taylor & Whalen, 2015). This variable involvement of the amygdala in different anxiety disorders is not well understood. In general, more consistent amygdala activations are reported for SAD and specific phobia and partially PTSD as compared with PD, for example (Etkin & Wager, 2007; Shin & Liberzon, 2010; Duval *et al.* 2015). However, since designs are only partially comparable, findings are difficult to interpret. Meta-analyses have not yet included PD (Etkin & Wager, 2007; Fredrikson & Faria, 2013). Furthermore, it is unknown whether subregions of the amygdala are differentially involved when comparing effects across anxiety disorders.

Besides the amygdala, altered activation in anxiety disorders has been observed in the insula, thalamus, anterior cingulate cortex (ACC) and medial PFC (mPFC) (Etkin & Wager, 2007; Shin & Liberzon, 2010; Duval *et al.* 2015). While reviews and meta-analyses propose a set of brain regions involved in anxiety disorders, findings within each brain region vary between studies. Further, conclusions are limited since they include studies with different tasks, designs, sample characteristics and stimuli that are only partially disorder-relevant. This calls for studies across multiple anxiety disorders that use comparable stimuli, tasks and designs, while controlling for sampling confounds (Etkin & Wager, 2007; Craske *et al.* 2009; Duval *et al.* 2015).

Some studies related to this research question directly compared the neural correlates across different anxiety disorders, using facial expressions (Blair *et al.* 2008; Killgore *et al.* 2014; Pantazatos *et al.* 2014; Fonzo *et al.* 2015). Both differential amygdala activation [Blair *et al.* 2008: generalized anxiety disorder (GAD), SAD] and similar amygdala activation across groups (Killgore *et al.* 2014: PTSD, PD and specific phobia; Fonzo *et al.* 2015: GAD, SAD and PD) have been found. General threat-processing studies implementing emotional pictures have not yet compared more than two anxiety disorders. SAD patients and healthy controls (HC) have been found to show greater amygdala responses than GAD patients when confronted with negative pictures (Blair *et al.* 2012). No differential amygdala activation to negative pictures was found in GAD *v.* PD patients (Ball *et al.* 2013). Only one study used disorder-related stimuli (words) with three different anxiety disorders (van den Heuvel *et al.* 2005). Processing disorder-related words resulted in heightened activation in the right amygdala in obsessive–compulsive disorder and PD patients compared with HC.

Taken together, there are no studies that directly compared neural responses to ecologically valid disorder-specific triggers of anxiety across anxiety disorders. By means of event-related functional magnetic resonance imaging (fMRI), we investigated common and distinct neural correlates of disorder-related scene processing in PD, SAD, dental phobia (DP) and PTSD patients. We used separate, tailor-made stimulus sets displaying situations specifically relating to the core fears of each disorder.

The present study should be able to detect transdiagnostic neurobiological alterations that may cut across anxiety, and trauma- and stressor-related disorders due to high statistical power. Statistical power was increased by a large patient sample, which makes the detection of true effects across diagnoses more likely (Rauch *et al.* 2003; Button *et al.* 2013). To additionally increase internal validity, all patients were free of psychiatric medication, and patients with any of the other three disorders as a co-morbid condition were excluded. Based on this methodological stringency we expected to better understand common and diverging brain responses in the amygdala and other brain regions across the four disorders.

Method

Subjects

Patients suffering from PD, SAD, DP or PTSD were recruited via public notices, local paper advertisements and a collaborating out-patient clinic. All PTSD patients suffered from psychopathology after interpersonal violence. HC were drawn from a larger number of screened healthy controls ascertained within the framework of the Collaborative Research Center 'Fear, Anxiety, Anxiety Disorders' (TRR SFB 58; http://sfbtrr58.uni-muenster.de/) or were recruited by means of flyers and newspaper advertisements.

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Prior to participation, all patients and HC were interviewed by a psychologist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; German version, Wittchen *et al.* 1997). Patients fulfilled the criteria of PD, SAD, DP or PTSD according to DSM-IV as main diagnosis and were excluded if they had any of the other investigated disorders as a co-morbid condition (for other co-morbid conditions, see online Supplementary Table S1). HC were free of any psychiatric diagnosis. Further exclusion criteria for patients and HC were psychotropic medication, presence or history of neurological, psychotic or bipolar disorders, drug dependence or abuse within the last 10 years, suicidal ideations, and fMRI contraindications. All participants had normal or corrected-to-normal vision and were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971).

The final patient sample comprised 20 PD patients (16 female), 20 SAD patients (13 female), 16 DP patients (13 female) and 11 PTSD patients (all females). All patients were part of larger disorder-specific studies, with less restrictive sample requirements (Feldker *et al.* 2016; Heitmann *et al.* 2016; Neumeister *et al.* in press). In the present study, a same-size HC group, matched for age, gender and education was assigned to each patient group (see Table 1 for sample characteristics), resulting in a specific control group for each patient group. All subjects gave written informed consent. The study conforms to the Declaration of Helsinki and was approved by the ethics committee of the University of Muenster.

Stimuli

A tailor-made set of 50 disorder-related and 50 neutral scenes was presented to each patient group and the respective HC group, resulting in four different picture sets. Disorder-related scenes tailored to the particular disorders depicted disorder-related feared situations or cues as well as persons suffering from disorder-related symptoms (e.g. close-up of dental treatment procedure for DP). Detailed descriptions of the sets can be found elsewhere: Social Anxiety Picture Set Muenster (SAPS-M; Heitmann *et al.* 2016); Panic-related Picture Set Muenster (PAPS-M; Feldker *et al.* 2016); Trauma-related Affective Picture Set Muenster (TRAPS-M; Neumeister *et al.* in press). Similarly, the Dental Phobia Picture Set Muenster (DEPS-M) was developed (for further details, see online Supplementary Table S2). Each patient group and the respective HC group rated all 100 scenes of the respective disorder-related picture set in a separate post-scanning rating session. Each picture was presented for 2 s on a computer screen. A nine-point Likert scale was used to assess valence (1 = very unpleasant, 5 = neutral to 9 = very pleasant), arousal (1 = not arousing to 9 = very arousing) and anxiety (1 = not anxiety inducing to 9 = very anxiety inducing). Each patient group in the current sample rated the disorder-related *v.* neutral scenes as more anxiety-inducing than the respective HC group. Patient groups did not differ from each other regarding scores in anxiety rating (see Fig. 1 and online Supplementary Table S3), indicating a comparable degree of experienced threat.

Experimental task

All subjects participated in the same fMRI experiment, but, as described before, the presented stimulus set depended on the specific disorder. One patient group (e.g. PD) and their respective HC group saw the same stimulus set (here PAPS-M). Another patient group (e.g. SAD) and their respective HC group saw another stimulus set relevant for the disorder (here SAPS-M). During the 8 min 19 s functional run, each of the 50 disorder-related and 50 neutral pictures was presented once in an event-related design. Neutral and disorder-related pictures were presented in a random sequence, optimized and counterbalanced using the Optseq algorithm (http://www.surfer.nmr.mgh.harvard.edu/optseq/), which also provides temporal jitter to increase signal discriminability (Dale *et al.* 1999). Each picture was presented for 800 ms. A white fixation cross was presented between two stimuli, for a jittered time window of 1280–15 320 ms (mean = 3915 ms). To keep participants' attention and gaze towards the stimulus, they were instructed to press a button with their right index finger whenever a blurred picture occurred. Five pictures [originally EmoPicS (Wessa *et al.* 2010), blurred with Adobe Photoshop CS6 (version 13.0.1, Adobe Sytems Inc., USA)] were randomly presented over the course of the experiment. These five trials were modelled as nuisance regressors in the fMRI analysis.

fMRI acquisition and analysis

Blood oxygenation level-dependent (BOLD) responses and structural brain information were recorded using a 3 Tesla magnetic resonance scanner ('Magnetom PRISMA'; Siemens, Germany) and a 20-channel Siemens Head Matrix Coil. A high-resolution T1-weighted MPRAGE anatomical volume with 192 slices was recorded for anatomical localization. For functional data a run of 255 volumes was conducted using a T2*-weighted echo-planar sequence (echo time = 30 ms, flip angle = 90°, matrix = 92 × 92 voxels, field of view = 208 mm^2, repetition time = 2080 ms). Each volume consisted of 36 axial slices (thickness =

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Table 1. *Sample characteristics of patient groups and their respective HC groups regarding gender ratio, age, educational attainment and scores in clinical questionnaires*[a]

	Total sample		PD		SAD		DP		PTSD		
	PAT	HC	PD	HC_{PD}	SAD	HC_{SAD}	DP	HC_{DP}	PTSD	HC_{PTSD}	Comparisons
Participants, *n*	67	67	20	20	20	20	16	16	11	11	PAT = HC; PD = HC_{PD}; SAD = HC_{SAD}; DP = HC_{DP}.
Female	53	49	16	14	13	13	13	11	11	11	PTSD = HC_{PTSD}; PD = SAD = DP
Male	14	18	4	6	7	7	3	5	0	0	
Age, years	27.67 (8.53)	25.39 (5.35)	25.35 (6.83)	24.25 (3.52)	28.65 (8.86)	26.70 (5.94)	30.75 (11.15)	24.88 (5.50)	25.64 (4.82)	25.82 (6.82)	PAT = HC; PD = HC_{PD}; SAD = HC_{SAD}; DP = HC_{DP}; PTSD = HC_{PTSD}; PD = SAD = DP = PTSD
Education, years	12.72 (1.12)	12.75 (0.73)	12.50 (1.05)	12.42 (0.96)	12.95 (1.15)	13.05 (0.51)	12.80 (1.21)	12.80 (0.56)	12.56 (1.13)	12.73 (0.65)	PAT = HC; PD = HC_{PD}: SAD = HC_{SAD}; DP = HC_{DP}; PTSD = HC_{PTSD}; PD = SAD = DP = PTSD
PAS			20.95 (6.97)	0.15 (0.37)							PD > HC_{PD}
LSAS					67.90 (15.46)	10.75 (6.82)					SAD > HC_{SAD}
DAS							15.93 (2.17)	6.07 (0.89)			DP > HC_{DP}
PDS									21.82 (9.09)	0.55 (0.69)	PTSD > HC_{PTSD}
STAI-T	46.40 (11.94)	30.49 (5.68)	49.25 (9.62)	29.25 (4.25)	49.65 (10.97)	29.45 (4.92)	35.94 (10.23)	33.53 (8.18)	50.55 (12.16)	30.46 (4.03)	PAT > HC; PD > HC_{PD}; SAD > HC_{SAD}; DP = HC_{DP}; PTSD > HC_{PTSD}; (PD = SAD = PTSD) > DP
BDI	10.90 (8.56)	1.77 (2.81)	12.20 (6.73)	0.70 (0.70)	10.20 (8.23)	1.75 (3.21)	5.44 (4.34)	3.20 (3.84)	17.73 (11.71)	1.82 (1.33)	PAT > HC; PD > HC_{PD}; SAD > HC_{SAD}; DP = HC_{DP}; PTSD > HC_{PTSD}; PD = SAD = PTSD; PD > DP

Data are given as mean (standard deviation) unless otherwise indicated.

HC, Healthy controls; PD, panic disorder patients; SAD, social anxiety disorder patients; DP, dental phobia patients; PTSD, post-traumatic stress disorder patients; PAT, all patients; PAS, Panic and Agoraphobic Scale (Bandelow, 1997); LSAS, Liebowitz Social Anxiety Scale (Stangier & Heidenreich, 2005); DAS, Dental Anxiety Scale (Corah, 1969); PDS, Post-traumatic Diagnostic Scale (Foa *et al.* 1997); STAI-T, State-Trait-Anxiety-Inventory – Trait version (Laux *et al.* 1981); BDI, Beck Depression Inventory (Hautzinger *et al.* 1995).

[a] PAS, BDI and DAS scores were missing of one HC_{DP}: the clinical interview and screening procedure did not reveal any clinical symptoms. Comparisons: gender differences were calculated by χ^2 tests. Other differences were tested with *t* tests. For demographic data, $p < 0.05$, no Bonferroni correction was applied in order not to miss possible differences between groups. For questionnaire data, $p < 0.05$, Bonferroni corrected at $p < 0.005$. As expected, symptom severity scores of each patient group differed significantly from scores in the respective HC group. Average symptom severity in each patient group was mild to severe as categorized in questionnaires' manuals (Corah, 1969; Bandelow, 1997; Foa *et al.* 1997; Heimberg *et al.* 1999).

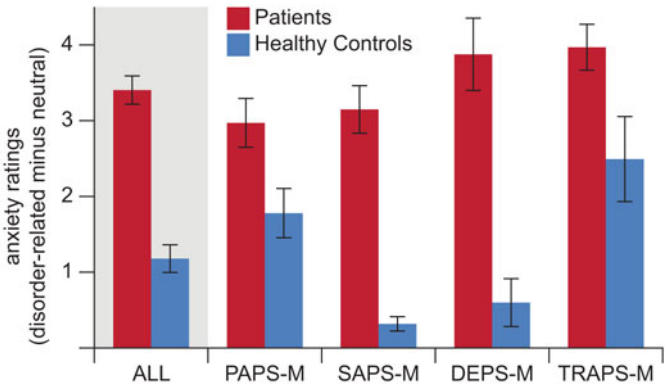

Fig. 1. Anxiety ratings (disorder-related minus neutral) for patients and healthy controls across picture sets (ALL) and for each set: Panic-related Picture Set Muenster (PAPS-M); Social Anxiety Picture Set Muenster (SAPS-M); Dental Phobia Picture Set Muenster (DEPS-M); Trauma-related Affective Picture Set Muenster (TRAPS-M). Values are means, with standard errors represented by vertical bars. For a colour figure, see the online version.

3 mm, gap = 0.3 mm, in plane resolution = 2.26 mm × 2.26 mm). To minimize susceptibility artifacts in inferior parts of anterior brain areas, the volumes were tilted approximately 20° from the anterior commissure/posterior commissure line. A shimming field was applied before functional imaging to further reduce external magnetic field inhomogeneities. fMRI data were pre-processed and analysed with BrainVoyager QX software (version 2.4; Brain Innovation, The Netherlands) and Matlab (version 8.2, The MathWorks Inc., USA). The first 10 volumes of each run were discarded from analysis to ensure steady-state tissue magnetization. First, all volumes were realigned to the first volume, to minimize artifacts due to head movements. No participant showed excessive head movement (>1 voxel). Further data pre-processing steps comprised spatial (6 mm full-width half-maximum isotropic Gaussian kernel) as well as temporal smoothing (high-pass filter: 10 cycles in time course; low-pass filter: 2.8 s; linear trend removal). The anatomical and functional images were co-registered and normalized to Talairach space (Talairach & Tournoux, 1988). Volumes were resampled to a voxel size of 2 × 2 × 2 mm, and slice-time correction was applied. Multiple linear regressions modelling the signal time course at each voxel were calculated with adjustment for autocorrelation. The expected BOLD signal change for each predictor was modelled with a canonical double γ haemodynamic response function. Predictors of interest were the two stimulus types: disorder-related and neutral scene. In the first step, voxelwise statistical maps were generated and the relevant planned contrasts of predictor estimates (β weights) were computed for each individual. β Maps for differential activation (disorder-related minus neutral) per person were then exported to Matlab. In the latter step, a group analysis of these individual contrasts was performed.

The region of interest was the bilateral amygdala (1 mm dilated), for which local information was derived from the Automated Anatomical Labeling atlas included in the Wake Forest University pick atlas (Tzourio-Mazoyer *et al.* 2002; Maldjian *et al.* 2003). The obtained Montreal Neurological Institute (MNI) coordinates were converted to Talairach space in Matlab using the ICBM-152 routine proposed by Lancaster *et al.* (2007). Obtained peak coordinates were verified with the Mai atlas (Mai *et al.* 2004). An *a priori*-defined whole-brain mask was used to mask out non-brain tissue. The watershed algorithm of Neuroelf (v0.9c; http://neuroelf.net/; i.e. the splitclustercoords function) was used to assess local maxima of clusters.

For statistical analyses, a cluster-based permutation (CBP) approach was used, as often suggested (Bullmore *et al.* 1999; Hayasaka & Nichols, 2004; Maris & Oostenveld, 2007; Kriegeskorte *et al.* 2009; Eklund *et al.* 2016). CBP approaches require no assumptions about the test statistic distribution and have recently been shown to be more valid than classical parametric fMRI analyses, and offer precise control of the false discovery rate (Eklund *et al.* 2016). In the first step, we investigated the group effect (all patients *v.* all HC) across disorders using the differential β values (disorder-related *v.* neutral pictures). In the second step, differential effects were investigated by pairwise group (patients, HC) x stimulus set (PAPS-M, SAPS-M, DEPS-M, TRAPS-M) interactions. The cluster-level α was Bonferroni-corrected to adjust for repeated comparisons.

All permutation tests were performed with 1000 permutations (Bullmore *et al.* 1999; Maris & Oostenveld,

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2007). For each permutation, the individual β maps (including the emotion effect: disorder-related minus neutral) were randomly assigned without replacement to one of the eight experimental groups. Voxel threshold was set at $p_{voxel} < 0.005$ to balance between type I and type II error type (Lieberman & Cunningham, 2009). Cluster mass was calculated by adding all F values in neighbouring significant voxels. The cluster mass observed in the contrast of interests was compared with the distribution of the maximal cluster mass observed in each of the 1000 permutations. Clusters masses larger or equal to the 95th percentile of the permutation distribution were considered as statistically significant clusters (i.e. $p_{cluster} < 0.05$).

Correlational analyses were conducted to account for dimensional effects between amygdala activation clusters of the emotion effect (disorder-related minus neutral) and scene-induced anxiety, depressive symptoms and trait anxiety across all patients. β Weights of the emotion effect for each patient were normalized relative to the β weights of the respective HC group. The mean β weight of the emotion effect of the respective HC group was subtracted from each patient's β value and this difference was divided by the standard deviation of β weights in the respective HC group. The resulting normalized β weights were then correlated with the anxiety-rating scores (disorder-related minus neutral) across all patients, and with Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory – trait version (STAI-T) scores. Bonferroni correction was applied considering the number of significant clusters.

Results

Analysis of the main effect of group showed that all patients compared with all HC showed a stronger emotion effect (disorder-related > neutral) in the left central amygdala (peak voxel Talairach coordinates: $x = -23$, $y = -7$, $z = -10$, k: 10 voxels, average F: 9.112, maximal F: 10.03, $p < 0.05$ corrected), right central amygdala (peak voxel Talairach coordinates: $x = 15$, $y = -5$, $z = -6$, k: 16 voxels, average F: 9.763, maximal F: 12.213, $p < 0.05$ corrected) and right lateral amygdala (peak voxel Talairach coordinates: $x = 31$, $y = -1$, $z = -16$, k: 14 voxels, average F: 9.62, maximal F: 13.42, $p < 0.05$ corrected). There were neither significant effects for the reversed comparison (HC > patients), nor any differential effects between patient groups in the bilateral amygdala. The size of the emotion effect in the right lateral amygdala cluster correlated significantly with anxiety ratings (disorder-related minus neutral) across all patients ($r = 0.349$, $p = 0.002$, see Fig. 2). No cluster in the amygdala correlated with BDI and STAI-T. Correlations were considered as statistically significant if $p < 0.016$ (Bonferroni-corrected for the three significant clusters in the amygdala).

Additionally, whole-brain analyses of the main effect of group yielded significant clusters in middle, medial and superior frontal regions, dorsal and pregenual ACC, midcingulate cortex, thalamus, insula, brainstem and occipital lobe (see Table 2 and Fig. 3). There were no significant effects for the reversed comparison (HC > patients) nor any differential effects between patient groups in the whole-brain analysis. Three whole-brain clusters correlated significantly with scene-induced anxiety across all patients (cluster 1: $r = 0.389$, $p = 0.001$; cluster 3: $r = 0.419$, $p < 0.001$; cluster 5: $r = 0.294$, $p = 0.008$) and two clusters correlated with BDI scores (cluster 4: $r = 0.338$, $p = 0.003$; cluster 5: $r = 0.455$, $p < 0.001$). Correlations were considered as statistically significant if $p < 0.01$ (Bonferroni-corrected for the five significant clusters).

Discussion

The aim of the present study was to investigate neural correlates of disorder-related threat processing across PD, SAD, DP and PTSD, with all patients free of psychiatric medication. To trigger disorder-related visual processing, we presented ecologically valid stimuli tailor-made for each disorder. Compared with HC, enhanced neural correlates of disorder-related processing across PD, SAD, DP and PTSD were found in distinct clusters in the bilateral amygdala. Emotion effects (always referring to disorder-related > neutral) in the lateral amygdala correlated significantly with subjective level of stimulus-induced anxiety across all patients. Whole-brain analysis yielded further common neural correlates in middle, medial, superior frontal and (para-)limbic regions, in the brainstem and in the occipital lobe, encompassing the most prominent circuits associated with anxiety (Davidson, 2002; Etkin, 2010; Sylvester *et al.* 2012; Duval *et al.* 2015; Tovote *et al.* 2015). The present analyses yielded no differential effects between patient groups.

The strong emotion effect in the bilateral central and right lateral amygdala across all patients *v.* HC suggests an involvement of the amygdala in disorder-related threat processing common to all disorders tested here. The amygdala is considered a key element in the human alarm system and has been linked to concepts of salience, attention and vigilance (Davis & Whalen, 2001; Phelps & LeDoux, 2005). Facilitating attention to, and perception of, incoming emotional information, the amygdala can be considered a relevance detector (Phelps & LeDoux, 2005; Sergerie *et al.* 2008; Janak & Tye, 2015). The lateral amygdala, described as the interface of sensory input from the

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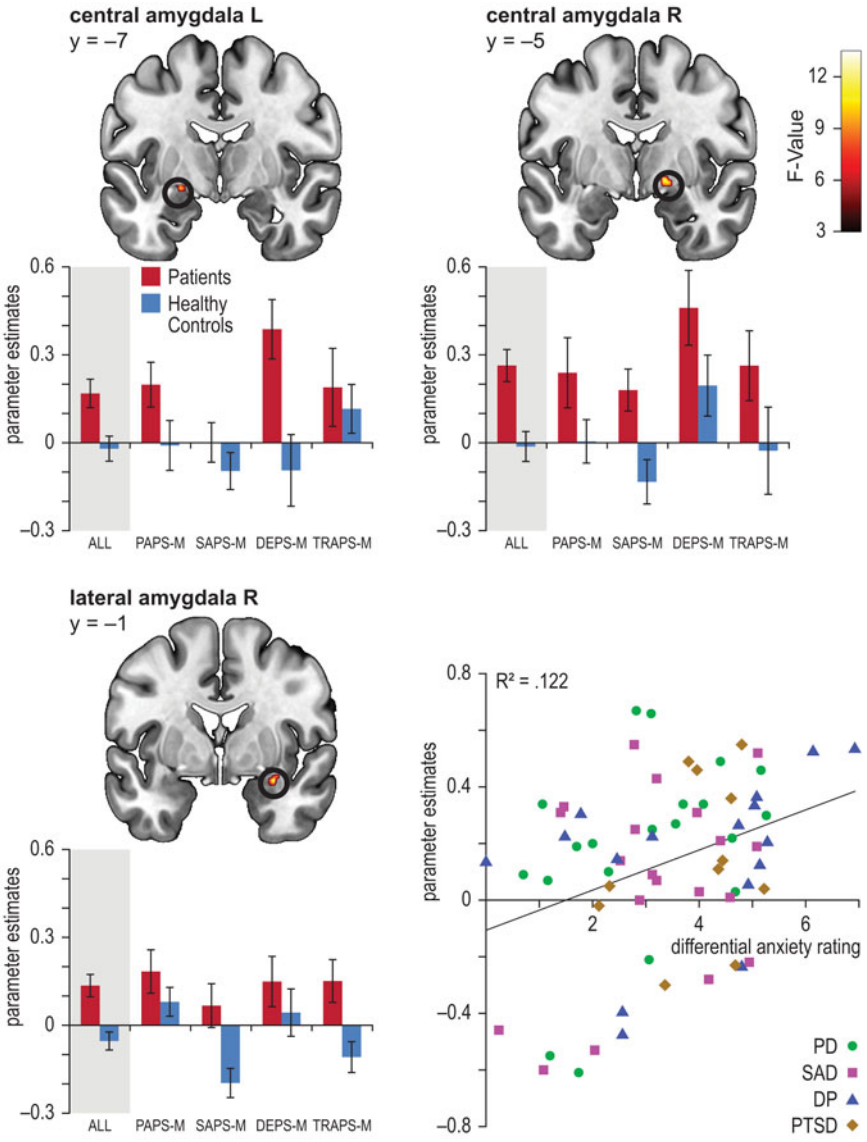

Fig. 2. Shared brain activation (disorder-related minus neutral) in the bilateral amygdala. Bar graphs are shown for patients and healthy controls across picture sets (ALL) and for each set: Panic-related Picture Set Muenster (PAPS-M); Social Anxiety Picture Set Muenster (SAPS-M); Dental Phobia Picture Set Muenster (DEPS-M); Trauma-related Affective Picture Set Muenster (TRAPS-M). Scatterplot displays correlation of activation in the right lateral amygdala and anxiety ratings (disorder-related minus neutral). L, Left; R, right; PD, panic disorder; SAD, social anxiety disorder; DP, dental phobia; PTSD, post-traumatic stress disorder. Values are means, with standard errors represented by vertical bars. All values displayed at $p < 0.05$ (corrected).

cortex and thalamus, functions as a 'gatekeeper of the amygdala' (LeDoux, 2007, p. R869), assigning emotional value to stimuli and relaying information to the central nucleus of the amygdala via direct and indirect interconnections (Pitkänen *et al.* 1997; Ball *et al.* 2007; LeDoux, 2007; Fujieda *et al.* 2015). The central nucleus is considered important for vigilance potentiation in response to relevant stimuli and control of bodily reactions. The latter is, for example, based on its projections to the brainstem, which in turn evokes autonomic threat responses and initiates the release of stress hormones (Kim *et al.* 2011; Shin, 2012). Furthermore, the emotion effect in the lateral amygdala correlated with the subjective level of stimuli-induced anxiety across all patients, which fits with the lateral amygdala's function as a gateway for salient sensory information, initiating further processes that result in behavioural and autonomic fear expression. Emotion effects in the amygdala were correlated with scene-induced anxiety but correlated neither with symptoms of depression nor with trait anxiety. This underlines the amygdala's specific role in the

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Table 2. *Significant hyperactivations for disorder-related* v. *neutral scenes across all patients relative to healthy controls revealed by whole-brain analysis in five clusters ($p \leqslant 0.05$ corrected)*[a]

Region	Lateralization	Talairach coordinates of peak voxel			*F* value maximum	*F* value average	*k*
		x	y	z			
Cluster 1	R	29	−1	48	19.969	10.798	515
Middle frontal gyrus	R	29	−1	48	19.969	11.047	271
Precentral gyrus	R	51	−7	42	18.618	10.783	85
Superior frontal gyrus	R	21	3	54	16.781	11.376	34
Middle frontal gyrus	R	37	11	46	14.624	10.019	57
Precentral gyrus	R	35	11	30	14.323	10.468	50
Middle frontal gyrus	R	51	5	32	11.939	9.401	18
Cluster 2	L	−33	−75	26	14.779	9.992	257
Superior occipital gyrus	L	−33	−75	26	14.779	9.656	186
Middle temporal gyrus	L	−41	−75	22	14.263	11.239	40
Precuneus	L	−27	−73	34	14.224	10.400	31
Cluster 3	L/R	−43	11	46	24.711	11.612	2833
Middle frontal gyrus	L	−43	11	46	24.711	11.351	594
Middle frontal gyrus	L	−29	27	46	23.892	13.118	482
Superior frontal gyrus	L	−23	33	46	23.126	19.150	20
Middle frontal gyrus	L	−27	21	38	22.287	15.592	41
Middle frontal gyrus	L	−23	3	54	22.124	11.126	272
Middle frontal gyrus	L	−41	21	44	22.076	19.064	21
Superior frontal gyrus	L	−5	19	58	19.460	11.464	513
Middle frontal gyrus	L	−37	1	54	18.717	14.587	54
Midcingulate gyrus	R	1	9	36	18.026	10.199	211
Anterior cingulate gyrus	R	3	21	18	17.733	11.064	45
Anterior cingulate gyrus	L	−3	29	22	17.347	10.617	67
Midcingulate gyrus	L	−5	19	38	16.674	12.318	34
Superior frontal gyrus	R	9	23	62	15.502	9.905	79
Superior frontal gyrus	L	−9	55	34	14.798	10.129	98
Medial frontal gyrus	L	−1	1	62	13.757	10.351	73
Medial frontal gyrus	L	−5	45	40	13.187	10.667	26
Superior frontal gyrus	L	−3	33	50	13.148	10.103	29
Cluster 4	L	−9	43	10	27.031	11.671	587
Anterior cingulate gyrus	L	−9	43	10	27.031	11.731	392
Middle frontal gyrus	L	−29	49	0	23.114	11.249	106
Medial frontal gyrus	L	−3	59	20	16.578	13.359	44
Medial frontal gyrus	L	−13	51	2	14.713	10.873	27
Anterior cingulate gyrus	L	−5	35	−4	13.064	9.954	17
Cluster 5	L/R	−3	−31	0	27.248	11.085	1570
Midbrain	L	−3	−31	0	27.248	11.481	231
Brainstem	L	−9	−27	−24	23.549	11.245	138
Thalamus	L	−7	−5	16	21.219	10.918	295
Putamen	L	−23	1	−2	20.174	10.810	147
Caudate	L	−17	15	12	20.000	11.126	135
Insula	L	−33	9	−6	19.512	10.693	120
Insula	L	−35	5	0	18.341	13.534	23
Caudate	R	15	3	12	17.789	10.512	136
Brainstem	R	1	−31	−20	17.634	12.936	32
Caudate	L	−9	3	2	17.491	12.447	41
Parahippocampal gyrus	L	−15	−31	−8	17.321	11.349	65
Inferior frontal gyrus	L	−31	27	−6	16.382	10.908	93

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Table 2 (*cont.*)

Region	Lateralization	Talairach coordinates of peak voxel			*F* value maximum	*F* value average	*k*
		x	y	z			
Inferior frontal gyrus	L	−23	9	−16	15.181	10.586	29
Thalamus	R	5	−9	14	14.516	10.518	25
Brainstem	L	−9	−11	−8	12.398	10.175	38

k, Number of voxels; R, right; L, left.

[a] The watershed algorithm of Neuroelf (v0.9c; http://neuroelf.net/, i.e. the splitclustercoords function) was used to assess local maxima of clusters.

weighting of disorder-related information and suggests scene-induced anxiety to be most closely related to emotion effects in the amygdala. The present amygdala findings might also underline the high emotional value of the disorder-related tailor-made stimuli for each disorder and thereby be the neural signature of stimulus threat relevance. Of note, neural correlates of emotion effects are based on implicit stimulus processing while post-scanning rating data rely on explicit emotional processing. Thus, correlational data reveal a relationship of implicit and explicit processing.

Altered amygdala activation has not been consistently reported in studies that focus on one disorder only (Etkin & Wager, 2007 for PD; Shin & Liberzon, 2010 for PTSD; Del Casale *et al.* 2012 for specific phobia; Schienle *et al.* 2012 for specific phobia; Ipser *et al.* 2013 for specific phobia; Brühl *et al.* 2014 for SAD). These inconsistencies have been attributed to a wide range of study features: block- *v*. even-related designs (Caseras *et al.* 2010), task properties (Straube *et al.* 2006), possible habituation effects (Taylor *et al.* 1998; Fischer *et al.* 2003), use of psychiatric medication (Brühl *et al.* 2014) or fine differences in characteristics of emotional stimuli (Zald, 2003; Carlson *et al.* 2011). Furthermore, differences between disorders have been suggested, with less frequent amygdala and insula hyperactivation in PD and GAD than in PTSD, SAD and specific phobia (Etkin & Wager, 2007; Shin & Liberzon, 2010; Duval *et al.* 2015). However, to investigate true differences between disorders, it is necessary to control for variables such as task, stimulation procedure, imaging modality and sample characteristics. The present study used this approach and revealed a threat effect across disorders in the amygdala in response to highly relevant disorder-related pictures.

Besides amygdala findings, whole-brain analysis yielded large emotion effects in middle, medial and superior frontal regions and in the pregenual and dorsal ACC and midcingulate cortex when comparing all patients with HC. This common activation in patients fits with earlier studies that reported co-activation of the mPFC and ACC, and might mirror the shared and altered mechanism of generation, evaluation and regulation of emotion across PD, SAD, DP and PTSD (Ochsner & Gross, 2005; Kober *et al.* 2008; Etkin *et al.* 2011). It could also constitute a neural correlate of shared phenomenological features among patients such as misinterpretation of ambiguous stimuli, overinterpretation of threat signals, and conscious pathological threat appraisal (Raczka *et al.* 2010; Maier *et al.* 2012; Kalisch & Gerlicher, 2014).

(Para-)limbic emotion effects in whole-brain analysis were for example revealed in the thalamus and insula. As the thalamus is associated with initial processing and relaying sensory information, the increased emotion effect across patients in the present study might reflect elevated visual processing of disorder-related scenes, and thus indicate alterations in early phases of fear processing (Jones, 2003; LeDoux, 2003). The insula is assumed to mediate alertness and awareness to salient multimodal sensory signals (Critchley *et al.* 2004; Paulus & Stein, 2006; Nagai *et al.* 2007; Craig, 2009; Sterzer & Kleinschmidt, 2010). The integration of these signals goes hand in hand with interoceptive processing, which provides the basis for the subjective experience of feelings representing a crucial process in anxiety disorders (Critchley *et al.* 2004; Nagai *et al.* 2007; Menon & Uddin, 2010). In line with this, the reported elevated emotion effect during disorder-related processing in the insula might be a correlate of increased interoceptive processing, a mechanism shared across PD, SAD, DP and PTSD, although specific differences with respect to interoception may still exist between these disorders.

Whole-brain analysis also yielded emotion effects in the brainstem, suggesting alterations in this structure to be a correlate of disorder-related processing across PD, SAD, DP and PTSD. The brainstem, considered the heart of the 'stress circuitry' and part of the

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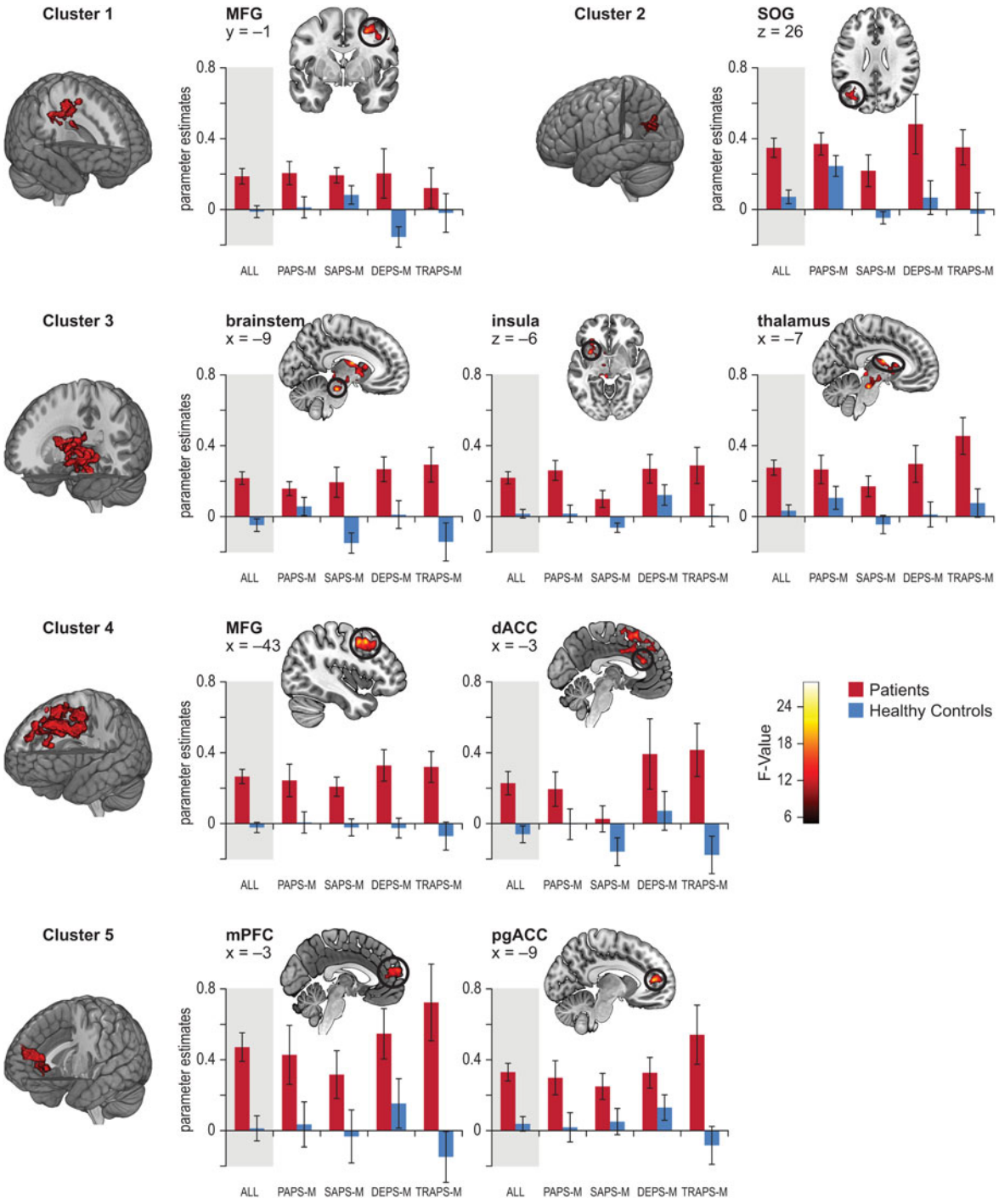

Fig. 3. Shared brain activation (disorder-related minus neutral) across disorders as revealed in whole-brain analysis. Each row presents results for one cluster (whole cluster presented in three dimensions). Selected local maxima (two dimensions) are presented with corresponding bar graphs. Bar graphs are shown for patients and healthy controls across picture sets (ALL) and for each set: Panic-related Picture Set Muenster (PAPS-M); Social Anxiety Picture Set Muenster (SAPS-M); Dental Phobia Picture Set Muenster (DEPS-M); Trauma-related Affective Picture Set Muenster (TRAPS-M). MFG, Middle frontal gyrus; SOG, superior occipital gyrus; dACC, dorsal anterior cingulate cortex; mPFC, medial prefrontal cortex; pgACC, pregenual anterior cingulate cortex. Values are means, with standard errors represented by vertical bars. All values displayed at $p < 0.05$ (corrected). For illustration purposes MRIcroGL was used (http://www.mccauslandcenter.sc.edu/mricrogl/).

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neuroendocrine stress axis, is thought to play a major role in emotional stress responses (Itoi & Sugimoto, 2010). Brainstem activation is often addressed in PD literature, since PD is particularly characterized by an exaggerated bodily fear reaction during panic attacks. However, bodily fear symptoms evoked by altered autonomic activity and neuroendocrine functioning play a role in all the investigated anxiety disorders (e.g. during a performance situation in SAD) (Sullivan *et al.* 1999). It is not yet fully understood how brainstem structures modify the perception and processing of stressful and emotional events. Our finding suggests that disorder-related stimulus processing targets a shared mechanism based on brainstem functioning most probably related to changes in the homeostatic alarm system.

The finding of increased activation to threat across disorders in the occipital lobe supports the idea of alterations in sensory processing areas (Sehlmeyer *et al.* 2009; de Carvalho *et al.* 2010; Del Casale *et al.* 2012; Ipser *et al.* 2013; Brühl *et al.* 2014), and the notion that basic, initial disorder-related processing is a dysfunctional mechanism shared across anxiety disorders in response to visual threat.

Remarkably, our study which used tailor-made disorder-related stimuli for each disorder and the same task across all disorders revealed no differential effects between disorders. We interpret the absence of statistically significant differential effects and the presence of shared effects as neuronal correlates of phenomenological aspects common to PD, SAD, DP and PTSD, rather than as correlates of disorder-specific aspects, such as the content of concerns (e.g. fear of negative evaluation in SAD *v.* the fear of bodily symptoms in PD) or feared situations (e.g. trauma-related situations in PTSD *v.* dental treatment in DP). Speaking in terms of RDoC, disorder-related visual processing might thus be regarded an intermediate phenotype across the four disorders (Cuthbert, 2014).

There are no previous studies that investigated responses to disorder-related visual threat across multiple anxiety disorders. Reviews and meta-analyses have drawn an inconsistent picture regarding neural circuitries in anxiety-related disorders (Rauch *et al.* 2003; Etkin & Wager, 2007; Craske *et al.* 2009; Shin & Liberzon, 2010; Holzschneider & Mulert, 2011; Fredrikson & Faria, 2013; Duval *et al.* 2015; Taylor & Whalen, 2015). Meta-analyses including SAD, specific phobia and PTSD studies suggested a potentially shared neural basis of disorders, but also noted differences between disorders (Etkin & Wager, 2007; Fredrikson & Faria, 2013). Taking large heterogeneity between included studies into account, caution is warranted when drawing comparative conclusions across disorders. As meta-analyses have not included PD patients (Etkin & Wager, 2007; Fredrikson & Faria, 2013), the present study contributes substantially to the knowledge about neural correlates of emotional processing across multiple psychiatric disorders.

Our study controls for task, design, procedure and operationalization of disorder-related processing. Due to its large sample size ($n = 134$) of matched patients and HC, our study has high statistical power, which makes the detection of reliable neural effects more likely than in studies with smaller sample sizes. However, caution is warranted since patient samples differ in size, with the DP ($n = 16$) and PTSD ($n = 11$) patient samples being rather small. The small size of the PTSD sample is due to the difficulty in recruiting unmedicated PTSD patients. Thus, to increase sensitivity for differential effects, future studies should implement larger samples within each disorder. Furthermore, our PTSD sample comprised only women suffering from one specific (but frequent) type of trauma. The present study uses four novel disorder-related stimulus sets, which we deem a fruitful approach also for further studies to target more disorder-relevant psychological processes (e.g. tasks related to automatic processing, interference, attentional bias).

In conclusion, using disorder-related stimuli high in ecological validity, the same procedures and task, implementing CBP statistics and comparing a large sample of medication-free PD, SAD, DP and PTSD patients with matched HC, we found evidence for shared neural correlates, including the bilateral amygdala, wide frontal and (para-)limbic regions as well as the brainstem and occipital lobe. Most strikingly, the elevated emotion effect in the lateral amygdala correlated with subjective levels of anxiety, underlining the central role of the amygdala in the pathology of all four disorders. Our findings suggest that basic mechanisms are shared across disorders, despite their different diagnostic profiles.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291716002634

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Declaration of Interest

None.

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