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ORIGINAL ARTICLE

Directed threat imagery in generalized anxiety disorder

C. Buff*, C. Schmidt, L. Brinkmann, B. Gathmann, S. Tupak and T. Straube

Institute of Medical Psychology and Systems Neuroscience, University of Muenster, Von-Esmarch-Str. 52, 48149 Muenster, Germany

Background. Worrying has been suggested to prevent emotional and elaborative processing of fears. In cognitive-behavioral therapy (CBT), generalized anxiety disorder (GAD) patients are exposed to their fears during the method of directed threat imagery by inducing emotional reactivity. However, studies investigating neural correlates of directed threat imagery and emotional reactivity in GAD patients are lacking. The present functional magnetic resonance imaging (fMRI) study aimed at delineating neural correlates of directed threat imagery in GAD patients.

Method. Nineteen GAD patients and 19 healthy controls (HC) were exposed to narrative scripts of either disorder-related or neutral content and were encouraged to imagine it as vividly as possible.

Results. Rating results showed that GAD patients experienced disorder-related scripts as more anxiety inducing and arousing than HC. These results were also reflected in fMRI data: Disorder-related *v.* neutral scripts elicited elevated activity in the amygdala, dorsomedial prefrontal cortex, ventrolateral prefrontal cortex and the thalamus as well as reduced activity in the ventromedial prefrontal cortex/subgenual anterior cingulate cortex in GAD patients relative to HC.

Conclusion. The present study presents the first behavioral and neural evidence for emotional reactivity during directed threat imagery in GAD. The brain activity pattern suggests an involvement of a fear processing network as a neural correlate of initial exposure during directed imagery in CBT in GAD.

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Key words: Amygdala, CBT, directed imagery, exposure therapy, fear network, fMRI.

Introduction

Generalized anxiety disorder (GAD) patients are characterized by excessive and uncontrollable worry and anxiety and assumed to be hyper-reactive to threat (American Psychiatric Association, 2000; Hayes & Hirsch, 2007; Newman *et al.* 2013; Mochcovitch *et al.* 2014; Duval *et al.* 2015). According to cognitive models of GAD, patients have brief images of their fears and respond to them by thinking about their worries in verbal form (Hirsch & Holmes, 2007). Verbal thinking prevents full emotional and elaborative processing of fears, resulting in prolonged bouts of distress (Hirsch & Holmes, 2007). Cognitive-behavioral therapy (CBT) aims at preventing GAD patients from thinking about their fears in verbal form by confronting them with their worries through the method of directed imagery (Becker & Margraf, 2016). During directed imagery, GAD patients imagine feared situation as vividly as possible. Facing their fears through exposure triggers emotional reactivity and thereby allows for elaborative and emotional processing, resulting in habituation and extinction (Foa & Kozak, 1986). To date, directed imagery is incorporated in established treatments of fear and anxiety in various psychiatric disorders and has also been shown to be a productive tool in research (Hoyer *et al.* 2009; McTeague & Lang, 2012).

A number of studies have applied the method of directed imagery to delineate the psychophysiology of various anxiety/stress disorders, such as post-traumatic stress disorder, panic disorder, or social anxiety disorder (Bystritsky *et al.* 2001; McTeague *et al.* 2009; McTeague *et al.* 2010; McTeague *et al.* 2011). It proved to be a productive means of eliciting emotions and to evoke disorder-related symptoms both in clinical practice and in research (Frewen *et al.* 2011; McTeague & Lang, 2012). During directed imagery, participants typically listen to an affectively laden narrative script and imagine the engaging role of the protagonist. Guided by the bio-informational view of affective imagery (McTeague & Lang, 2012), narrative scripts typically include information on stimulus events (who, what, where), reported feelings, interpretations, and responses, such as expressive physiology and actions coded in fear (Cuthbert *et al.* 2003). It appears that mental imagery elicits stronger emotions as compared to verbal processing of the same content (Pearson *et al.* 2015). Findings suggest that directed threat imagery parallels reactions to *in vivo* threat

* Address for correspondence: C. Buff, MSc, Institute of Medical Psychology and Systems Neuroscience, University of Muenster, Von-Esmarch-Str. 52; 48149 Muenster, Germany.
(E-mail: christine.buff@uni-muenster.de)

and results in potentiation of startle responses, increased autonomic arousal (heart rate, skin conductance) and the recruitment of a fear-related brain circuitry including elevated activity in the amygdala, insula, cingulate cortex, prefrontal cortex (PFC) and the hippocampus, as well as reduced activity in the thalamus and the ventromedial PFC (vmPFC) in patients (Rauch *et al.* 1996; Shin *et al.* 1997; Liberzon *et al.* 1999; Bystritsky *et al.* 2001; Lanius *et al.* 2002; Lanius *et al.* 2003; Shin *et al.* 2004; Britton *et al.* 2005; Rauch *et al.* 2006; Etkin & Wager, 2007; Shin & Liberzon, 2010; Ji *et al.* 2016). The amygdala plays a pivotal role in attention-vigilance aspects of threat-related processing and hypersensitive responding is one of the most common findings in symptom provocation studies in anxiety/stress disorder patients (Etkin, 2010; Holzschneider & Mulert, 2011; Feldker *et al.* 2017). Amygdala-driven fear expression is proposed to be regulated through PFC inhibitory mechanisms, for which both lateral and medial PFC (mPFC) appear essential (Hartley & Phelps, 2010). Lateral PFC is implicated in attention control, as well as in emotion modulation processes (Duval *et al.* 2015). VmPFC is implicated in emotion modulation through inhibiting the amygdala and reduced vmPFC activity in anxiety/stress disorder patients is one of the most widely reported findings during symptom provocation studies (Frewen & Lanius, 2010; Motzkin *et al.* 2015). Dorsomedial PFC (dmPFC) and anterior cingulate cortex (ACC) are related to threat-related appraisal, monitoring and expression (Etkin, 2010; Etkin *et al.* 2011; Kalisch & Gerlicher, 2014). The experience of negative affect, cognitive control and memory processes are related to mid-cingulate and posterior cingulate cortex (Shackman *et al.* 2011; Leech & Sharp, 2014). The insula is involved in interoceptive processing and the generation of subjective feelings (Lindquist & Barrett, 2012; Gasquoine, 2014). The hippocampus is primarily involved in processing of contextual information and fear generalization (Deckersbach *et al.* 2006; Duval *et al.* 2015). An important relay between peripheral and cortical sensory signaling is the thalamus that is linked to arousal (Duval *et al.* 2015). One directed-threat imagery study detected reduced thalamus activity (Lanius *et al.* 2003), which is in contrast to the majority of symptom provocation studies revealing increased thalamus activity in patients (Duval *et al.* 2015; Feldker *et al.* 2017). Overall, these brain regions constitute key components during fear generation and modulation in healthy subjects (HC) and patients with anxiety/stress disorders (Duval *et al.* 2015).

Surprisingly, to date, no study implemented directed threat imagery to explore neural correlates of threat-related processing in GAD. Previous functional magnetic resonance imaging (fMRI) studies have investigated brain activity patterns in GAD patients in response to several classes of aversive stimuli (e.g. facial expressions, verbal stimuli, pictures or sounds) (Newman *et al.* 2013; Hilbert *et al.* 2014; Mochcovitch *et al.* 2014) and results appear inconclusive: Amygdala activity in GAD patients tended to be elevated when anticipating aversive or neutral stimuli (Nitschke *et al.* 2009) and in response to ambiguous stimuli (Hölzel *et al.* 2013), but not or to a lesser degree during picture processing (Blair *et al.* 2008; Whalen *et al.* 2008; Etkin *et al.* 2010; Palm *et al.* 2011; Fonzo *et al.* 2015; Buff *et al.* 2016). Decreased ACC/mPFC activity in GAD patients was observed in emotion regulation tasks or in response to affective facial expressions (Etkin & Schatzberg, 2011; Palm *et al.* 2011; Ball *et al.* 2013; Duval *et al.* 2015), while increased ACC/mPFC activity was reported for worry induction tasks and in response to aversive pictures (Hoehn-Saric *et al.* 2004; Paulesu *et al.* 2010; Buff *et al.* 2016). Notably, accumulating evidence from treatment studies and a recent transdiagnostic study suggests that ACC/mPFC may play an essential role in the pathophysiology of GAD (Hoehn-Saric *et al.* 2004; Whalen *et al.* 2008; Nitschke *et al.* 2009; Buff *et al.* 2016). Furthermore, increased lateral PFC activity to aversive pictures was detected in GAD patients in a recent transdiagnostic study (Buff *et al.* 2016). Hyperactive lateral PFC activity is speculated to serve as a compensatory response to regulate abnormal function in GAD patients (Hölzel *et al.* 2013). Other studies detected hyper- and hypoactivity of lateral PFC in GAD patients in response to affective stimuli (Blair *et al.* 2008; Palm *et al.* 2011; Moon & Jeong, 2015; Moon *et al.* 2015; Moon *et al.* 2016; Park *et al.* 2016). In sum, the neural correlates of threat-related processing in GAD remain inconclusive, but tend to concentrate around dysfunctions within the amygdala–PFC circuitry (Newman *et al.* 2013; Hilbert *et al.* 2014; Mochcovitch *et al.* 2014).

A possible explanation for these mixed findings may be that most GAD patients report to fear hypothetical threatening situations rather than specifically anxiety-provoking stimuli (Hoyer *et al.* 2009). Along these lines, stimulus material used in previous studies may have been limited in terms of meaning and not deemed personally relevant by GAD patients. Another important aspect to consider is that GAD patients tend to avoid emotional experience (Mennin *et al.* 2009). Thus, in order to investigate neural correlates of threat-related processing in GAD patients, a powerful tool is required to elicit emotional experience. As described above, directed threat imagery proved a productive means to elicit disorder-related symptoms in patients and may be suitable to trigger threat-related processing in GAD patients, since it allows to present hypothetical threatening situations in form of narrative

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scripts. Overall, directed threat imagery allows us to investigate threat-related processing in GAD patients and to resolve whether directed threat imagery actually results in emotional reactivity, which is a prerequisite for elaborative processing, habituation and extinction during imagery in CBT (Foa & Kozak, 1986).

The goal of the present study was to elucidate brain activity patterns underlying fear processing during directed threat imagery in GAD patients. Since as yet, no study has used the method of directed imagery in GAD patients, we focused on brain regions that constitute key components of the circuitry involved in (altered) processing of threat-related stimuli, including the amygdala, insula, PFC, cingulate cortex, thalamus and the hippocampus (Duval *et al.* 2015). We expected increased activity in all regions except in the vmPFC to disorder-related *v.* neutral scripts in GAD patients *v.* HC, since this is commonly detected in anxiety/stress disorder patients during symptom provocation studies (Duval *et al.* 2015). With regard to behavioral results, disorder-related scripts were expected to be experienced as more anxiety-inducing by GAD patients relative to HC, while no group differences were expected for neutral scripts.

Methods and materials

Subjects

Nineteen GAD patients and 19 HC matched for age, years of education, school-leaving certificate and gender were recruited through public advertisements and an outpatient clinic (Table 1). An experienced clinical psychologist diagnosed participants by means of the Structured Clinical Interview for DSM-IV axis-I Disorders (Wittchen *et al.* 1997). GAD patients met criteria for GAD as primary diagnosis. GAD patients showed mild depressive symptoms (see Table 1). The following axis I comorbidities were further identified in patients: Recurrent major depressive disorder ($n = 3$), posttraumatic stress disorder ($n = 1$), specific phobia ($n = 1$), eating disorder ($n = 1$). Seven GAD patients took long-term medication (antidepressant medication, one GAD patient used Pregabalin). All subjects had normal or corrected-to-normal vision and gave written informed consent. Exclusion criteria were neurological disorders, presence or history of psychotic or bipolar disorders, current drug abuse or dependence and fMRI contraindications. The study was approved by the ethics committee of the University of Muenster and conformed to the latest declaration of Helsinki.

Measures

The self-report measure Beck-Depression inventory-II (BDI) was used to assess level of depressive symptoms (Beck *et al.* 1996). The BDI demonstrated good internal consistency ($\alpha = 0.84$), sensitivity (81%), specificity (92%) and test–retest reliability ($r = 0.75$) (Dozois *et al.* 1998; Kühner *et al.* 2007; Herzberg & Goldschmidt, 2008). The Penn State Worry Questionnaire (PSWQ) is one of the most commonly used measures of worry severity in GAD patients (Meyer *et al.* 1990) with good internal consistency ($\alpha = 0.90$), test–retest reliability ($r = 0.75$–93), good sensitivity (99%) and specificity (98%) (Behar *et al.* 2003; Hoyer & Margraf, 2013). The Meta-Cognition-Questionnaire (MCQ) is a trait measure assessing beliefs about worry and intrusive thoughts and showed good internal consistency ($\alpha = 0.72$–89) for subscales and test–retest reliability ($r = 0.94$) (Cartwright-Hatton & Wells, 1997; Wells & Cartwright-Hatton, 2004; Hoyer & Margraf, 2013). The Generalized Anxiety Disorder Questionnaire-IV (GAD-Q-IV) is a self-report measure, capturing both primary and associated symptoms of GAD and demonstrated to have good internal consistency ($\alpha = 0.84$), test–retest reliability ($r = 0.81$), sensitivity (69%) and specificity (97%) (Newman *et al.* 2002; Hoyer & Margraf, 2013). Compared with the PSWQ and MCQ, the GAD-Q-IV is the only self-report measure that endeavors to assess the entire clinical syndrome of GAD. The PSWQ, GAD-Q-IV and MCQ supported the diagnosis of GAD in the current patient sample.

Stimuli

Stimulus material consisted of standardized disorder-related ($n = 5$) and neutral ($n = 5$) scripts, matched for number of words ($t_{[8]} = 1.25$, $p = 0.248$), and number of sentences ($t_{[8]} = 0.89$, $p = 0.397$). All scripts were written in third person and present tense to reflect active participation and lasted exactly 30 s. The scripts included details of stimulus events (who, what, where), meaning, and response information, based on the bio-informational theory of emotional imagery (McTeague & Lang, 2012). The disorder-related scripts involved threatening themes, such as the wellbeing of a relative or partner, one's own health, but also about miscellaneous topics (Olatunji *et al.* 2010), such as being late for an appointment or a talk with the superior. Neutral scripts described various daily routines (e.g. reading a book, crossing a street). Scripts were tape-recorded and read by a female voice in a neutral tone, with the reader blind to the study's hypotheses.

Experimental design

The scanning session lasted approximately 9 min. Scripts were presented to the participants via headphones and in pseudo-randomized order by means of Presentation Software (v17.2, Neurobehavioral

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Table 1. *Demographic and clinical characterization of GAD patients and HC*

	GAD patients	HC	Statistics
Age	M = 28.26, S.D. = 8.92	M = 27.63, S.D. = 8.38	$F_{[1,36]} = 0.05$, $p = 0.823$
Gender	Male $n = 5$	Male $n = 5$	Fisher's exact test: $p = 0.643$
Education	M = 12.63, S.D. = 1.51	M = 12.68, S.D. = 0.82	$F_{[1,36]} = 0.05$, $p = 0.90$
BDI	M = 18.00, S.D. = 12.67	M = 2.53, S.D. = 3.42	
PSWQ	M = 65.58, S.D. = 8.29	M = 38.84, S.D. = 12.50	
MCQ	M = 155.58, S.D. = 23.59	M = 103.37, S.D. = 18.76	
GAD-Q-IV	M = 9.93, S.D. = 4.00	M= 1.27, S.D. = 1.24	
School leaving certificate (high school degree/secondary school certificate)	$n = 18/1$	$n = 18/1$	Fisher's exact test: $p = 0.757$

GAD, generalized anxiety disorder; HC, healthy controls; BDI, Beck-Depression Inventory (Beck *et al.* 1996); PSWQ, Penn State Worry Questionnaire (Meyer *et al.* 1990); MCQ, Metacognition questionnaire (Cartwright-Hatton & Wells, 1997); GAD-Q-IV, Generalized Anxiety Disorder Questionnaire-IV (Newman *et al.* 2002)

Systems, Albany, California, USA). Participants received instructions at the beginning in written form on a black screen and after practice trials via headphones. They were instructed to listen to the scripts with their eyes closed and to vividly imagine the described scene as being actively involved. A brief sound was played before and after each script to indicate the beginning and end (400 Hz, 500 ms). Participants were instructed to stop imagining the scripted scene as soon as they heard the sound at the end of each script, to keep their eyes closed and to pay attention to the surrounding sounds of the scanner during the 20 s inter-stimulus intervals.

Participants received standardized instructions and training both outside and inside the scanner. Practice trials consisted of two neutral scripts that were not presented in the actual experiment. The experimenter asked participants after each script how well they felt they had been able to imagine the scene and encouraged them to pay attention to auditory, tactile, olfactory, gustatory and visual aspects of the imagined scene. If participants were able to vividly imagine on the practice trials, the scanning procedure was started.

Following fMRI scanning, participants were re-exposed to the scripts. Participants listened to the first 10 s of each script minimum and could terminate the presentation through a button press if they remembered the script. If they experienced difficulties remembering, they could listen to the full script. Participants were asked to rate their emotional responses to each script in terms of valence (1 = *very unpleasant* to 9 = *very pleasant*), emotional arousal (1 = *not arousing* to 9 = *very arousing*) and experienced anxiety (1 = *not anxiety inducing* to 9 = *very anxiety inducing*) using a nine-point Self-Assessment Manekin scale (Bradley & Lang, 1994). Participants also rated their ability to imagine each script (measured in percent).

Analysis of sociodemographic clinical questionnaire and rating data

Sociodemographic clinical questionnaire and rating data were analyzed using IBM SPSS software (v22, Armonk, New York, USA). Rating data for anxiety, valence, arousal and ability to imagine each script were subjected to separate 2 (*script valence*: disorder-related, neutral) by 2 (*group*: GAD, HC) mixed model analyses of variance (ANOVA). A probability level of $p \leqslant 0.05$ was considered as statistically significant. Bonferroni-corrected t tests were applied to resolve interaction effects (corrected significance level $p \leqslant 0.008$). We report Cohen's d (Cohen, 1988) as a measure of effect size for rating data.

fMRI acquisition and analysis

Anatomical and functional data were acquired with a 3 T magnetic resonance scanner ('Magnetom PRISMA', Siemens, Erlangen, Germany) using a 20 channel head–neck coil. After acquiring a high-resolution T1-weighted anatomical scan with 192 slices, functional data were recorded with a T2*-weighted echo-planar sequence (TE = 30 ms, flip angle = 90°, matrix = 92 × 92 voxels, FOV = 208 mm^2, TR = 2080 ms); and 260 volumes consisting of 36 axial slices (thickness = 3 mm, 0.3 mm gap, in plane resolution = 2.26 × 2.26 mm^2) were acquired.

FMRI data were preprocessed and analyzed using BrainVoyager QX (BVQX, v2.8, Brain Innovation, Maastricht, Netherlands). To ensure steady-state tissue magnetization, the first four volumes were discarded. Data were corrected for slice time errors. Anatomical and functional data were co-registered and normalized to Talairach space (Talairach & Tournoux, 1988). Subsequently, data were smoothed spatially [6 mm FWHM (full-width at half-maximum) Gaussian kernel]

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and temporally (high-pass filter: 10 cycles per run; low-pass filter: 2.8 s; linear trend removal). Volumes were resampled $2 \times 2 \times 2$ mm^3 voxel size.

A canonical double-gamma HRF (hemodynamic response function) modeled the expected BOLD (blood oxygen level-dependent) signal for each predictor. Predictors of interest were disorder-related and neutral scripts, while sounds and six movement parameters were defined as predictors of no interest. Predictor estimates based on *z*-standardized time course data were calculated, with adjustment for autocorrelation following a global AR(1) model.

Analysis was conducted for a priori defined regions of interest (ROIs) that constitute key components during (altered) processing of fear-related stimuli, including the amygdala, insula, PFC, cingulate cortex, thalamus and the hippocampus (Duval *et al.* 2015). ROIs were defined based on the AAL (Automated Anatomical Labeling) atlas (Tzourio-Mazoyer *et al.* 2002; Maldjian *et al.* 2003; Maldjian *et al.* 2004). These were transformed into Talairach space (Lancaster *et al.* 2007) using ICBM2TAL in Matlab (v8.2, The MathWorks Inc, Natick, Massachusetts, USA).

Statistical parametric maps derived from voxel-wise analyses were considered significant for clusters that survived cluster-based correction for multiple comparisons. The voxel-level threshold was set to an uncorrected statistical threshold of $p \leqslant 0.005$ (Lieberman & Cunningham, 2009). Using the cluster-level statistical threshold estimator plugin for BVQX (Goebel *et al.* 2006), a mask consisting of all ROIs was applied to the thresholded maps. ROI-specific correction criteria were based on the estimates of the maps' spatial smoothness and on an iterative procedure (Monte Carlo simulation) applied to estimate cluster-level false-positive rates (Forman *et al.* 1995). After 1000 iterations, this procedure yielded a minimum cluster size ($k = 11$ resampled voxel size) to generate a map-wise corrected false positive rate of $p \leqslant 0.05$. We report effect sizes (Cohen's *d*; Cohen, 1988) for each significant outcome based on average *t* values.

To examine the relationship between differential brain responses (disorder-related *v.* neutral scripts) and behavioral measures, we correlated subjective ratings (arousal, valence, anxiety) and BDI level of patients with mean parameter estimates (disorder-related *v.* neutral scripts) of significant activation clusters resulting from ROI analysis (Bonferroni-corrected significance level: $p \leqslant 0.0125$). The influence of medication intake was tested by performing a *t* test (medicated *v.* non-medicated patients) on parameter estimates (disorder-related *v.* neutral scripts) of significant activation clusters resulting from ROI analysis ($p \leqslant 0.05$ was considered as statistically significant).

Results

Rating data

Mean ratings are provided in Table 2. Analyses of arousal, valence and anxiety ratings each revealed significant main effects of *group* (arousal: $F_{[1,36]} = 9.86$, $p = 0.003$, $d = 1.05$; valence: $F_{[1,36]} = 8.30$, $p = 0.007$, $d = 0.96$; anxiety: $F_{[1,36]} = 21.33$, $p < 0.001$, $d = 1.56$) and *script valence* (arousal: $F_{[1,36]} = 163.11$, $p < 0.001$, $d = 4.26$; valence: $F_{[1,36]} = 170.73$, $p < 0.001$, $d = 4.36$; anxiety: $F_{[1,36]} = 113.33$, $p < 0.001$, $d = 3.55$), and significant *group by script valence* interactions (anxiety: $F_{[1,36]} = 13.20$, $p = 0.001$, $d = 1.21$; arousal $F_{[1,36]} = 6.96$, $p = 0.012$, $d = 0.88$) (see Fig. 1). Disorder-related scripts were rated as more negative, more arousing and more anxiety inducing than neutral scripts and GAD patients generally rated stimuli as more negative, more arousing and more anxiety inducing than HC. Resolving the interaction effects for anxiety and arousal ratings showed that disorder-related scripts were rated as more arousing ($t_{[36]} = 3.46$, $p = 0.001$, $d = 1.12$) and more anxiety inducing ($t_{[36]} = 4.65$, $p < 0.001$, $d = 1.51$) by GAD patients *v.* HC. Analysis of the participants' ability to imagine each script yielded no significant effects (all $p > 0.184$).

ROI analysis

ROI analysis revealed that GAD patients relative to HC responded to disorder-related *v.* neutral scripts with increased activity in several areas (Fig. 2): lateral amygdala (LA), extending to central amygdala (CeA) (right: peak voxel Talairach coordinates: $x = 18$, $y = -19$, $z = -10$; size: 232 mm^3; average *t* value: 3.01; maximal *t* value: 3.76; $p \leqslant 0.005$ uncorrected, $p \leqslant 0.05$ corrected; $d = 0.98$), ventrolateral PFC (vlPFC) [(1) left: peak voxel Talairach coordinates: $x = -47$, $y = 35$, $z = 17$; size: 232 mm^3; average *t* value: 2.90; maximal *t* value: 3.04; $p \leqslant 0.005$ uncorrected, $p \leqslant 0.05$ corrected; $d = 0.94$; (2) left: peak voxel Talairach coordinates: $x = -36$, $y = 32$, $z = -1$; size: 88 mm^3; average *t* value: 2.90; maximal *t* value: 3.12; $p \leqslant 0.005$ uncorrected, $p \leqslant 0.05$ corrected; $d = 0.94$], dmPFC (left: peak voxel Talairach coordinates: $x = -10$, $y = 37$, $z = 31$; size: 96 mm^3; average *t* value: 2.93; maximal *t* value: 3.29; $p \leqslant 0.005$ uncorrected, $p \leqslant 0.05$ corrected; $d = 0.95$), and thalamus (right: peak voxel Talairach coordinates: $x = 5$, $y = -13$, $z = 11$; size: 136 mm^3; average *t* value: 2.89; maximal *t* value: 3.18; $p \leqslant 0.005$ uncorrected, $p \leqslant 0.05$ corrected; $d = 0.94$).

In addition to increased activity, GAD patients relative to HC showed reduced activity in the vmPFC/subgenual ACC (sgACC) (right/left: peak voxel Talairach coordinates: $x = 2$, $y = 20$, $z = -6$; size: 192 mm^3; average

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Table 2. *Mean ratings per script valence on the dimensions of arousal, anxiety, valence and ability to imagine the scripts*

Group	Script valence	Arousal[a]	Anxiety[a]	Valence[a]	Ability to imagine the scripts[b]
GAD patients	Disorder-related	M = 5.98, S.D. = 1.37	M = 5.53, S.D. = 1.62	M = 2.79, S.D. = 0.72	M = 82.66, S.D. = 10.36
	Neutral	M = 2.72, S.D. = 1.43	M = 1.99, S.D. = 1.26	M = 5.29, S.D. = 0.91	M = 79.18, S.D. = 16.55
HC	Disorder-related	M = 4.02, S.D. = 2.05	M = 2.86, S.D. = 1.90	M = 3.76, S.D. = 1.30	M = 74.32, S.D. = 15.98
	Neutral	M = 1.87, S.D. = 1.05	M = 1.13, S.D. = 0.26	M = 5.97, S.D. = 1.13	M = 76.23, S.D. = 16.44
Overall	Disorder-related	M = 5.00, S.D. = 1.99	M = 4.19, S.D. = 2.20	M = 3.27, S.D. = 1,15	M = 78.49, S.D. = 13.94
	Neutral	M = 2.29, S.D. = 1.31	M = 1.56, S.D. = 1.00	M = 5.63, S.D. = 1.07	M = 77.71, S.D. = 16.34
GAD patients	Across valence	M = 4.35, S.D. = 1.28	M = 3.76, S.D. = 1.32	M = 4.04, S.D. = 0.64	M = 80.92, S.D. = 11.88
HC	Across valence	M = 2.95, S.D. = 1.46	M = 2.00, S.D. = 1.01	M = 4.86, S.D. = 1.06	M = 75.27, S.D. = 15.38

GAD, generalized anxiety disorder; HC, healthy controls.
[a] Raw data drawn from a nine-point Self-Assessment Manekin Scale.
[b] In percent.

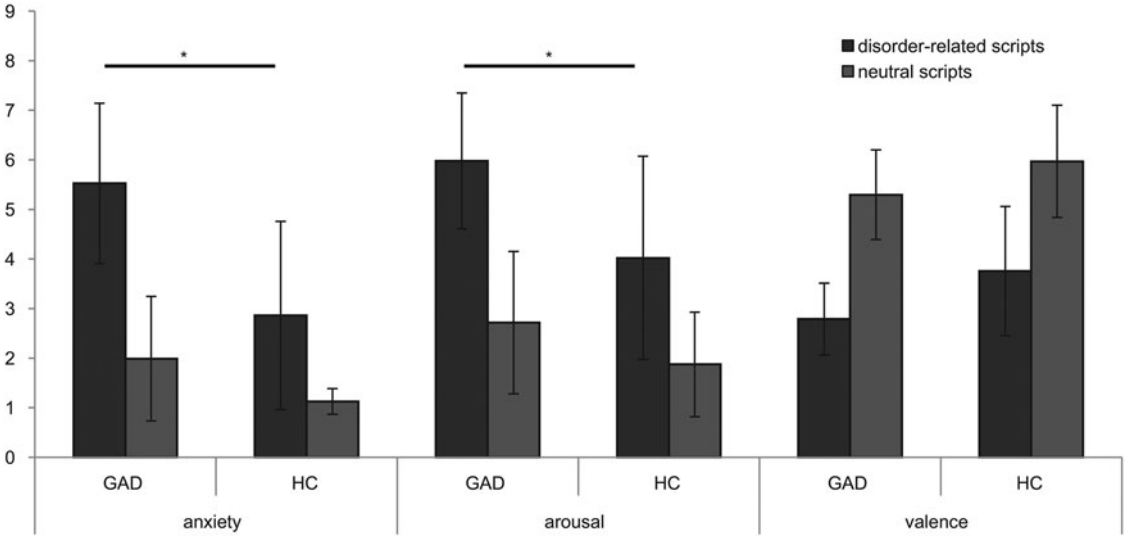

Fig. 1. Mean ratings for disorder-related and neutral scripts on a nine-point Self-Assessment Manekin Scale. The 2 (*script valence*) by 2 (*group*) mixed model analysis of variance revealed interaction effects for anxiety and arousal ratings. Generalized anxiety disorder (GAD) patients relative to healthy controls (HC) rated disorder-related scripts as more anxiety inducing and more arousing.

t value: 3.38; maximal *t* value: 4.25; $p \leqslant 0.005$ uncorrected, $p \leqslant 0.05$ corrected; $d = 1.10$) (Fig. 2).

There were no differential brain responses in GAD patients *v.* HC in the insula or the hippocampus. We conducted exploratory analysis using a voxelwise threshold of $p \leqslant 0.05$ and detected increased hippocampus and insula activity in GAD as compared to HC to disorder-related *v.* neutral scripts. It appears that the sensitivity of our study was not high enough to detected effects in these regions. There were no significant correlations between differential activations detected in ROI analysis and BDI level or subjective ratings as well as no effects regarding medication intake.

Discussion

To the best of our knowledge, the current study is the first to investigate brain responses during the well-established method of directed threat imagery in GAD patients using disorder-related and neutral scripts. Notably, the present findings show that directed threat imagery is effective in eliciting emotional reactivity related to fear processing in GAD patients on both behavioral and neural levels. While disorder-related scripts were rated as more negative, arousing and anxiety-inducing than neutral scripts by all participants, crucially, disorder-related scripts were experienced as more anxiety-inducing and more arousing

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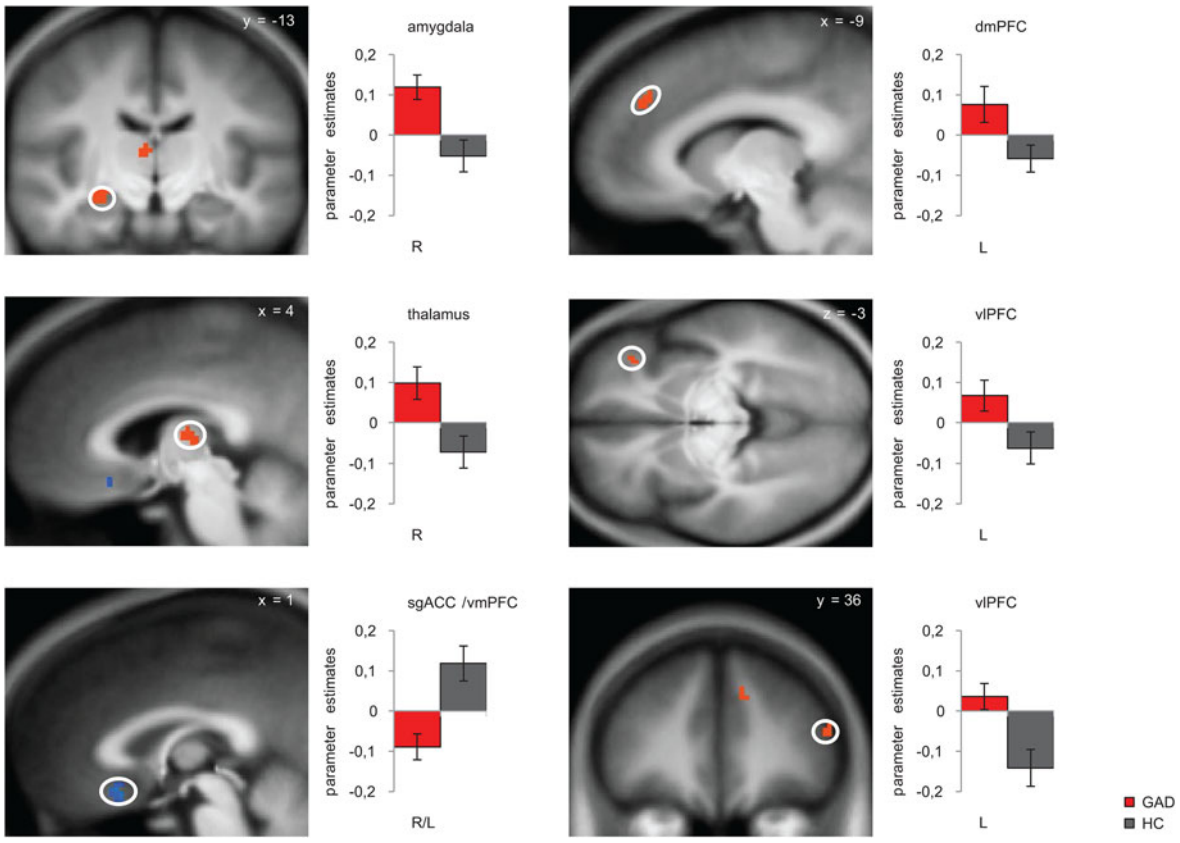

Fig. 2. Brain responses to disorder-related *v.* neutral scripts. The region of interest analysis revealed for the contrast disorder-related > neutral scripts for generalized anxiety disorder (GAD) patients relative to healthy controls (HC) increased activity in the amygdala, thalamus, dorsomedial prefrontal cortex (dmPFC) and the ventrolateral prefrontal cortex (vlPFC) and reduced activity in the subgenual anterior cingulate cortex (sgACC)/ventromedial prefrontal cortex (vmPFC). Statistical parametric maps are overlaid on an averaged T1 scan (radiological convention: left = right). Graphs display contrasts of parameter estimates [disorder-related > neutral scripts (mean ± S.E. for activation cluster)] per group.

by GAD patients relative to HC. fMRI results yielded a brain activity pattern in GAD patients in response to disorder-related scripts that parallels activations previously reported for fear processing (Shin & Liberzon, 2010; Holzschneider & Mulert, 2011; Duval *et al.* 2015). First, GAD patients responded to disorder-related scripts with elevated activity in the amygdala, thalamus and the dmPFC, possibly reflecting hyper-reactive emotional responding (Wilensky *et al.* 2006; Etkin, 2010; Etkin *et al.* 2011; Kalisch & Gerlicher, 2014; Duval *et al.* 2015). Second, GAD patients also responded with reduced vmPFC/sgACC and elevated vlPFC activity, which might reflect deficient emotion regulation (Wager *et al.* 2008; Holzschneider & Mulert, 2011; Cohen *et al.* 2013; Greenberg *et al.* 2013; Hölzel *et al.* 2013; Tupak *et al.* 2014; Motzkin *et al.* 2015).

Hyper-reactive emotional responding to disorder-related scripts in GAD patients may be associated with increased amygdala activity, which was detected in a cluster consisting of LA extending to CeA. LA encodes threat value of a stimulus and CeA is linked to the expression of conditioned fear response (Wilensky *et al.* 2006). LA and CeA appear to play an essential role in attention-vigilance aspects of threat-related processing and abnormalities in these regions have been linked to hyperarousal and/or hypervigilance to threat in anxiety/stress disorders (Etkin, 2010; Holzschneider & Mulert, 2011; Feldker *et al.* 2017). It seems that while imagining disorder-related scripts, GAD patients experienced, as part of their increased anxiety, ongoing, exaggerated arousal and vigilance towards imagined possible threat (Milad *et al.* 2009; Holzschneider & Mulert, 2011), possibly associated with exaggerated threat detection and expectancies (Grupe & Nitschke, 2013). Our findings are of particular importance in the research of the amygdala involvement in GAD, because findings are inconclusive: Some studies have reported both increased and decreased amygdala responding to affective stimuli (Blair *et al.* 2008, 2012; Fonzo *et al.* 2014; Nitschke *et al.* 2009; Park *et al.* 2016; Yassa

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et al. 2012), whereas others have failed to reveal alterations in amygdala activity altogether (Etkin et al. 2010; Fonzo et al. 2015; Whalen et al. 2008). The present results are relevant for the ongoing discussion of the amygdala involvement in GAD and imply that amygdala functioning is altered in patients.

Apart from increased amygdala activity, disorder-related scripts induced heightened thalamus activity in GAD patients. Similarly, another study showed that listening to worry statements induced elevated thalamus activity in GAD patients (Hoehn-Saric et al. 2004). The thalamus has been linked to the integration of sensory information and signals such information to the amygdala (Duval et al. 2015). Increased thalamic activation to disorder-related stimuli in anxiety/stress disorder patients has been described in previous studies (Straube et al. 2006; Duval et al. 2015; Feldker et al. 2017), except of in one directed threat imagery study in post-traumatic stress disorder patients (Lanius et al. 2003). The thalamic activation in the current study might indicate an arousal response in GAD patients when imagining disorder-related scripts (Vertes et al. 2015).

Furthermore, GAD-related emotional reactivity in response to disorder-related scripts was reflected in elevated dmPFC activity. This is in accordance with an earlier study reporting increased dmPFC activity in GAD patients during worry induction (Paulesu et al. 2010). DmPFC activity has been implicated in monitoring, evaluation and appraisal of stimuli as well as in anxiety expression (Etkin, 2010; Etkin et al. 2011; Kalisch & Gerlicher, 2014) or in the relay of information to vmPFC for regulatory purposes (Etkin, 2010). Given these findings, dmPFC hyper-activation to disorder-related scripts in the present study may indicate that scripts were more negatively appraised by GAD patients, possibly resulting in fear and anxiety expression (Etkin, 2010).

Parallel to hyper-reactive emotional responding reflected in increased activation in the amygdala, thalamus and the dmPFC, GAD patients were also marked by reduced activity in the vmPFC/sgACC and increased activity in the vlPFC. In view of findings that associate decreased vmPFC/sgACC with attenuation of fear responses (Hartley & Phelps, 2010; Greenberg et al. 2013; Frewen & Lanius, 2010; Motzkin et al. 2010), this particular result pattern may point to deficient emotion regulation in patients, with reduced vmPFC/sgACC activity reflecting difficulty in dampening fear responses. This interpretation draws upon neurocircuitry-based models of anxiety disorders in which deficient vmPFC activity together with increased amygdala activity in response to threat is assumed to mediate inadequate regulation of fear responses (Hartley & Phelps, 2010; Holzschneider & Mulert, 2011; Greenberg et al. 2013; Motzkin et al. 2015). Altered emotion regulation linked to deficient vmPFC/sgACC recruitment in GAD patients has been emphasized in previous investigations (Etkin et al. 2009; Etkin et al. 2010; Etkin & Schatzberg, 2011; Greenberg et al. 2013; Wang et al. 2016). Difficulty in dampening amygdala activity may also be reflected by increased vlPFC activity in response to disorder-related scripts in GAD patients. Functionally, vlPFC has been linked to inhibitory control or implicit emotion regulation and modulation of amygdala activity, based on findings of vlPFC recruitment during voluntary downregulation of unpleasant emotions in HC (Wager et al. 2008; Cohen et al. 2013; Tupak et al. 2014). It is speculated that increased activation of the PFC, including the vlPFC, may reflect a compensatory regulation mechanisms in GAD patients (Hölzel et al. 2013). Elevated PFC together with altered amygdala activity hints toward deficient signal transformation that may lead to unsuccessful emotion regulation (Etkin et al. 2009). Disturbed vlPFC functioning in GAD patients was detected in previous studies revealing either elevated (Blair et al. 2008; Hölzel et al. 2013; Moon et al. 2015; Park et al. 2016) or reduced vlPFC activity (Palm et al. 2011). Both vmPFC/sgACC and vlPFC possibly failed to regulate emotional reactivity, resulting in prolonged hypervigilance and hyperarousal, both of which are core symptoms of GAD (American Psychiatric Association, 2000).

Exploratory analyses revealed increased activity in the hippocampus and the insula to disorder-related scripts in GAD patients. This is in line with former investigations showing aberrant hippocampus and insula involvement during threat-related processing in GAD (Hoehn-Saric et al. 2004; Hilbert et al. 2014; Buff et al. 2016), as well as previous symptom provocation studies in anxiety/stress disorder patients (McTeague & Lang, 2012; Duval et al. 2015). It is to be assumed that future directed threat imagery studies in GAD patients with larger samples may detect hippocampus and insula activity alterations.

While not all predicted areas showed increased activation, we suggest that with regard to the aim of the present study, findings confirm that directed threat imagery triggers neural emotional reactivity related to fear processing in GAD patients. Disorder-related scripts appeared to induce heightened registration/reactivity (associated with amygdala activity), arousal (linked to thalamus activity) and negative appraisal (associated with dmPFC activity) in GAD patients. In turn, decreased activation in the vmPFC/sgACC and elevated activation in the vlPFC could be interpreted to reflect deficient downregulation of such emotional reactivity in GAD patients, possibly resulting in prolonged hyperarousal and vigilance. Both hyperarousal

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and vigilance are DSM-IV-associated symptoms of GAD (American Psychiatric Association, 2000). Consequently, the present results provide tentative evidence for emotional reactivity during directed imagery in GAD, which is a prerequisite for elaborative processing and ultimately habituation and extinction during successful CBT (Foa & Kozak, 1986). We infer from our findings that directed threat imagery is a promising tool for exposing patients to their fears and that brain activity patterns arising during directed imagery in CBT may be similar to the activation pattern of the present study.

Of course, this postulation is preliminary and somewhat tentative, given that participants in the present study were exposed to standardized rather than autobiographical scripts and given that the effect of repeated directed threat imagery exposure was not assessed. Autobiographical scripts capturing individual worries as well as effects of repeated exposure may represent two interesting and important avenues for future research. With regard to other limitations, medication needs to be mentioned. Seven GAD patients were medicated at time of testing. However, analyses showed that medication intake showed no effect on the observed results. According to a review psychotropic medication intake seems to have no influence or a normalizing influence on neuroimaging findings (Hafeman *et al.* 2012). Second, patients had comorbidities. Comorbidities constitute a challenge for patient studies and the interpretation of the results. Therefore, we carefully ensured that GAD was the main diagnosis for all patients through diagnosing patients by an experienced clinical psychologist. Furthermore, the exclusion of patients with comorbid diagnoses may have limited the representativeness and generalizability of the current findings, especially because comorbidities frequently occur in GAD (Newman *et al.* 2013). Nevertheless, it would be beneficial to investigate patients without medication or comorbidities in future studies, possibly also accounting for other variables such as personality or genotypes. Third, although we matched for school leaving certificate and years of education, there was no additional measure of intelligence. Future studies should control for level of intelligence.

To conclude, the present study investigated whether directed threat imagery resulted in emotional reactivity in GAD patients, paralleling the method used in CBT. Findings yielded a brain activity pattern in GAD patients marked by elevated amygdala, dmPFC, thalamus, vlPFC and reduced vmPFC/sgACC activity. This pattern may be indicative of hyper-reactive emotional responding together with deficient emotion regulation during imagination of disorder-related scenarios in GAD patients. We suggest that directed threat imagery is a powerful tool both for the investigation of fear processing in GAD patients and for the induction of emotional reactivity in CBT.

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Declaration of Interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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