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ORIGINAL PAPER

A new paradigm (Westphal-Paradigm) to study the neural correlates of panic disorder with agoraphobia

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Abstract Agoraphobia (with and without panic disorder) is a highly prevalent and disabling anxiety disorder. Its neural complexity can be characterized by specific cues in fMRI studies. Therefore, we developed a fMRI paradigm with agoraphobia-specific stimuli. Pictures of potential agoraphobic situations were generated. Twenty-six patients, suffering from panic disorder and agoraphobia, and 22 healthy controls rated the pictures with respect to arousal, valence, and agoraphobia-related anxiety. The 96 pictures, which discriminated best between groups were chosen, split into two parallel sets and supplemented with matched neutral pictures from the International Affective Picture System. Reliability, criterion, and construct validity of the picture set were determined in a second sample (44 patients, 28 controls). The resulting event-related "Westphal-Paradigm" with cued and uncued pictures was tested in a fMRI pilot study with 16 patients. Internal consistency of the sets was very high; parallelism was given. Positive correlations of picture ratings with Mobility Inventory and Hamilton anxiety scores support construct validity. FMRI data revealed activations in areas associated with the fear circuit including amygdala, insula, and hippocampal areas. Psychometric properties of the Westphal-Paradigm meet necessary quality requirements for further scientific use. The paradigm reliably produces behavioral and fMRI patterns in response to agoraphobia-specific stimuli. To our knowledge, it is the first fMRI paradigm with these properties. This paradigm can be used to further characterize the functional neuroanatomy of panic disorder and agoraphobia and might be useful to contribute data to the differentiation of panic disorder and agoraphobia as related, but conceptually different clinical disorders.

Keywords Agoraphobia · Anxiety · Panic · Parahippocampal place area · Amygdala · fMRI

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Introduction

A great number of studies have focused on the neurobiology of panic attacks, panic disorder, and panic disorder with agoraphobia. Agoraphobia though (i.e., the avoidance of certain places and situations as crowded places, shopping malls, public transport, and others) either as a symptom or a distinct disorder has only rarely been studied, although it might be much more impairing than panic attacks or panic disorder [37]. As a clinical syndrome, agoraphobia was first described by Carl Westphal [35]. Because the mechanisms of panic disorder and agoraphobia are still insufficiently studied, brain areas which are associated with this disease have not yet been consistently identified. In contrast to this fact, quite a number of imaging studies in neural correlates of other mental diseases like depression and even of therapeutical effects in treatment of these diseases already has been done [34].

Functional imaging techniques may help to elucidate the neural basis of mental disorders and mechanisms of action of either psychotherapy or psychopharmacotherapy, with the aim of further improving our treatment approaches. There are only a few studies presenting functional imaging data of patients suffering from panic disorder with or without agoraphobia [5, 18, 26, 27]. To our knowledge, there are no fMRI (functional magnetic resonance imaging) studies investigating neural mechanisms using agoraphobia-specific stimuli or cues.

Former studies used different kinds of stimuli to investigate emotional processing in anxiety disorders. Commonly used stimuli are individually tailored provocative stimuli in Obsessive Compulsive Disorder, trauma-related visual or acoustic stimuli and script-driven imagery in Posttraumatic Stress Disorder [21], social anxiety imagery scripts, speech anticipation, angry and negative faces in Social Anxiety Disorder, and spider pictures in specific phobia [10]. Whereas stimuli for specific phobias have a clear phobia-related object, which can be presented in a simple and robust way (e.g., spiders or snakes), the development of disorder-specific stimuli for the investigation into agoraphobia is more complex. However, imaging studies dealing with specific phobias—namely spider phobia—provide the best starting point to generate a theoretical basis for the neural correlates of agoraphobia. Meta-analyses point to a lack of studies on neural mechanisms of this disorder and their modification after treatment [11].

The first aim of this study was therefore to generate a picture set of agoraphobic situations differing in complexity for implementation in the "Westphal-Paradigm" which may then be employed in further neurofunctional research. To investigate agoraphobic and anticipatory anxiety separately, the paradigm involves a cued and an uncued condition.

Our hypothesis was that patients suffering from panic disorder and agoraphobia show abnormal neural activation patterns in two important main regions: (1) in the fear circuit—a neural network involving brain regions predominant in the processing of anxiety-related information, and (2) in brain structures which are involved in the anticipation of such aversive stimuli. In line with this, we expected an increase in activation in the amygdala, insula, hippocampus, anterior cingulate cortex, precuneus and a decrease in activation in the prefrontal cortex [17, 31, 33].

Considering a FDG-PET (fluor-deoxy-glucose positron emission tomography) study comparing patients with panic disorder and agoraphobia with healthy controls, neural correlates of panic disorder with agoraphobia should be characterized by higher activation especially of hippocampal areas and the thalamus plus of the amygdala in resting states [28]. Regarding the role of the hippocampus in processing of contextual situations, this seems to be important for patients suffering from agoraphobic anxiety and analyzing their environment or actual situation [25]. Because somatic sensations as main panic symptoms are contextual stimuli, the hippocampus could play an important role in the development of panic disorder and of agoraphobic avoidance [15]. Moreover, we hypothesize that patients with panic disorder and agoraphobia show an increased orientation reaction toward agoraphobic stimuli. The need to gain a precise and fast overview over an anxiety-inducing situation would be functionally represented by an increased activation of the parahippocampal place area (PPA) as suggested by Epstein et al. [9].

Methods

Subjects

Subjects were recruited by information material sent to local hospitals and local physicians, advertisements in newspapers, information events, via our outpatients' department for anxiety disorders and via the internet. A total of 120 volunteers participated in the study; 26 patients and 22 healthy control subjects rated the first collection of pictures. A second sample of 44 patients and 28 healthy control persons was recruited for the determination of psychometric properties. A subset of the second sample (16 patients) was included in the fMRI pilot study. All patients met DSM-IV-TR [1] criteria for panic disorder and agoraphobia, as determined by a standardized computer-administered personal Composite International Diagnostic Interview (CAPI-WHO-CIDI; DIAX-CIDI version [36]) had a clinical interview score ≥ 18 on the structured interview guide for the Hamilton anxiety scale (SIGH-A [30]) and a score ≥ 4 on the clinical global impressions scale (CGI [16]). They were between 18 and 65 years old, did not suffer from any other mental disease, were free of psychopharmacological treatment for at least 4 weeks (or 6 weeks in case of psychotropic drugs) before the beginning of the study and passed a test for color-blindness [19]. Other exclusion criteria were drug dependence or abuse, suicidal ideations, significant abnormalities in routine clinical chemistry or hematology, EEG or ECG. Out of those patients who meet those criteria, we included 16 patients into the fMRI pilot study who additionally did not meet MRI contraindications (e.g., ferromagnetic material or cardiac pacemakers) and who showed to be willing to participate. The study was approved by the Ethics Committee of Charité-Universitätsmedizin Berlin. Informed written consent was obtained from all participants prior to their inclusion in the study.

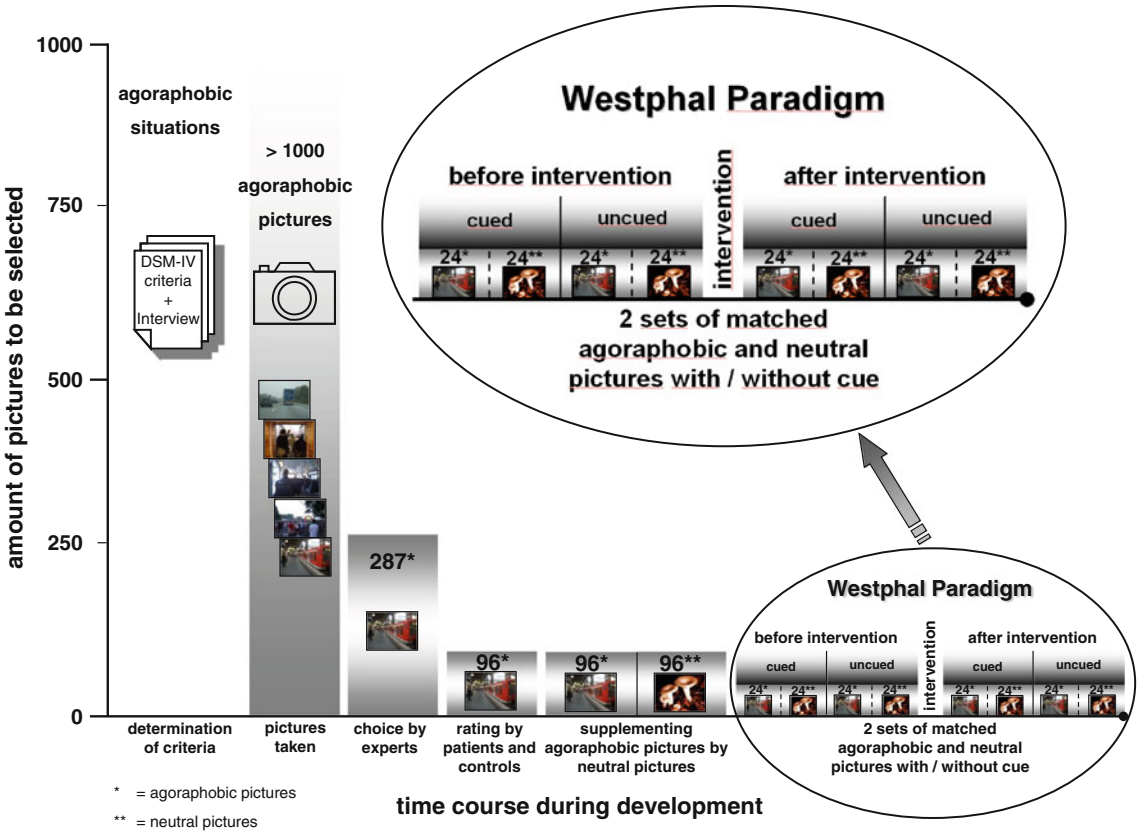

Fig. 1 Development of the Westphal-Paradigm

Development of the Westphal-Paradigm

More than 1,000 pictures which represent typical agoraphobic situations (e.g., being alone out of the house, crowds, bridges, elevators, using public transport, open, or public places) were taken in a balanced amount for each category by a digital camera. For defining these categories of agoraphobic situations, we used examples given by the DSM-IV and interviews we performed with patients (suffering from agoraphobia) of the Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité-Universitätsmedizin Berlin. Thereafter, five clinical experts with therapeutical background selected the best-suited pictures, which altogether were 287. For this selection, experts used their experience especially in therapeutic exposure of patients in relevant situations and judged whether situations on the pictures meet DSM-IV or patients' description and whether they are representative for this purpose. Twenty-six patients with panic disorder and agoraphobia (15♀; 11♂; mean age = 38.6; SD ± 11.7) and 22 healthy control subjects (12♀; 10♂; mean age = 34.5; SD ± 14.1) rated the pictures using the Self-Assessment Manikin Scale [4]. The pictures which discriminated best with respect to ratings for agoraphobic anxiety between patients and healthy controls were chosen. To do this, we used the *t* test for independent samples. Criterions were $P < .05$ and maximum group difference in agoraphobic anxiety and arousal. The thus resulting 96 agoraphobia pictures were matched to 96 neutral pictures from the International Affective Picture System (IAPS; [20]). Matching criteria were complexity, brightness, and number of living beings on the pictures. For applicability of the Westphal-Paradigm for pre-post designs (e.g., for therapy evaluation studies where memory effects would be unwanted), we divided the picture collection into two subsets using the following matching criteria: same number of pictures of agoraphobic categories, intensity of anxiety induced, complexity, brightness, and number of living beings (see Fig. 1). Finally, pictures of following agoraphobic categories were included: (1) 8 pictures of public transport INSIDE: 3 underground and 5 busses; (2) 18 pictures of public transport OUTSIDE: innercity trains: 6, intercity trains: 6, train stations: 6; (3) 22 pictures of crowds: 8 theaters, 10 crowds in general, 4 of malls and supermarkets; (4) 14 pictures of heights difficult to escape: 5 bridges and 9 towers; (5) 20 automobile: 14 pictures of drivers view to traffic jams and waiting at traffic lights, 6 highways; (6) 14 pictures of dense situations: 6 elevators, 8 tunnels. Due to the needed ability to differ between patients and healthy controls (regarding to anxiety induction), the amount of pictures in each of the categories is not equally distributed—even

though the basic set which was rated by the patient contained this distribution.

Psychometric properties of the Westphal-Paradigm

We determined criterion validity, construct validity, and reliability with a second sample of 72 persons (patients with panic disorder and agoraphobia: 31♀; 13♂; mean age = 37.5; SD ± 11.1; healthy controls: subjects 18♀; 10♂; mean age = 37.2; SD ± 13.6). Twenty-two of the 44 patients rated pictures of set 1 and 22 patients rated pictures of set 2 (due to the start of their treatments after the first rating). Controls rated the full set (set 1 and set 2).

Criterion validity and parallelism of the two sets

In order to determine the criterion validity and parallelism of the two sets, we used a 3-factorial 2 × 2 × 2 ANOVA [*Category* (agoraphobic pictures/neutral pictures) × *Group* (patients/controls) × *Set* (Set 1/Set 2)] with *Group* as between-subject factor and *Category* and *Set* as the within-subject factors.

Construct validity

Construct validity was determined by correlations of patients' picture ratings with the established clinical questionnaires Brief Symptom Inventory—BSI [7] using the subscale phobic fear, Beck Depression Inventory—BDI-II [2] using Pearson correlation coefficients and the Mobility Inventory—MI [6]. The MI-7 and MI-E [14] are adapted versions of the Mobility Inventory developed for use in the underlying psychotherapy multicenter trial "Mechanisms of Action in CBT (MAC)" [13] using value for agoraphobic avoidance of situations without attendance.

Reliability

Reliability of set 1 and set 2 were determined by the dimensions valence, arousal, and anxiety by means of internal consistency (Cronbachs α).

Design of the Westphal-Paradigm

Each of the two sets of the Westphal-Paradigm finally consists of 24 neutral pictures and 24 agoraphobia pictures which were presented in a cued manner (by the words "Neutral" and "Panic"). The remaining 48 neutral and agoraphobia pictures were presented uncued by a senseless combination of characters: "DGHNTFJ".

Picture sequence was randomized for each subject. Each picture was presented for 2,000 ms and cues for 250 ms, separated by the presentation of a fixation cross for minimizing artifacts due to eye movements. The presentation duration of the fixation cross was jittered with 1, 2, or 3 times the TR (time to repetition). The intertrial interval after each picture was jittered with 1 or 2 times the TR, while also showing the fixation cross. The complete presentation duration was approximately 15 min. During the fMRI session, participants were instructed to pay attention to the content of the pictures. Subjects were requested to experience the presented situation. Furthermore, they were asked to pay attention to the cue and its predictive content before picture presentation. Attention to the paradigm and its pictures was assured by the request to push a button each time a picture was presented.

Table 1 Sociodemographical and clinical data of subjects included in the fMRI pilot study

	Patients with panic disorder and agoraphobia	
	Women	Men
n	8	8
Age	Mean = 36.4 (SD ± 14.5)	Mean = 37.9 (SD ± 14.3)
Right-hander	8	7
Smoker	5	6
Education		
University and comparable	1	1
Years at school		
13	5	3
10	1	2
9–10	1	2
HAM-A	Mean = 24.6 (SD ± 7.6)	Mean = 23.8 (SD ± 4.0)
CGI	Mean = 5.3 (SD ± .46)	Mean = 5.3 (SD ± .886)

HAM-A Hamilton anxiety scale, *CGI* clinical global impression, *mean* mean value

Functional imaging: pilot study

The sample of 16 patients included in the fMRI pilot study (as shown in Table 1) met the same clinical criteria as the validation sample and was recruited by the same methods. Handedness was controlled by the Edinburgh Inventory [23]. All patients with exception of one male patient were right handed. Because of the behavioral data confirm the parallelism of the two picture sets, each patient was measured with one of both in a randomized manner.

FMRI data acquisition was performed on a 3-Tesla MR system (Signa, General Electric Healthcare, Milwaukee, WS, USA) with a quadrature headcoil. Functional imaging was performed with the use of an echo-planar imaging (EPI) pulse sequence at an echo-time (TE) of 30 ms. Other

imaging parameters were a repetition time (TR) of 2 s, flip angle of 90 degrees, a matrix size of 64 × 64, and a section thickness of 3.8 mm without intersection gap resulting in a voxel size of 3.6 mm × 3.6 mm × 3.8 mm. Thirty slices were collected aligned parallel to a plane through the anterior and posterior commissure (AC-PC line). The parameters and slice orientation were chosen to minimize artifacts and signal loss present especially in the amygdala regions and the orbitofrontal cortex due to magnetic susceptibility effects. The image acquisition order was interleaved, ascending. In each event-related trial, 446 volumes were acquired time-synchronized to the randomized offset of each event, which was jittered by intertrial intervals with a duration of 1 or 2 times the TR. Duration of the fixation cross presented between cue and stimulus was also jittered with 1–3 times the TR. Head movement was minimized using a foam pad and foam wedges. Using Presentation Version 11.0 (Neurobehavioral Systems, Albany, CA, USA), the stimuli were beamed by a LCD-projector (NEC GT950, resolution matrix, VGA 640*480) equipped with a 300-mm telelense (Isco Precision Optics GmbH, Göttingen, Germany) onto a mirror system (Sensomotoric Instruments [SMI], Berlin, Germany) mounted on the headcoil such that the subjects could watch the presented images in supine position.

FMRI data were processed using Statistical Parametric Mapping (Version SPM5, http://www.fil.ion.ucl.ac.uk/spm) including correction for acquisition delay and movement (by realignment to the individual mean EPI), spatial normalization to a standard EPI template provided in SPM 5 and spatial smoothing with 8-mm FWHM filter. To avoid non-steady-state effects caused by T1 saturation, the first five volumes of each time series were discarded.

On the single subject level, the BOLD (Blood Oxygen Level Dependence) response was analyzed in the context of the General Linear Model (GLM). The three cues ("Panic", "Neutral" and "DGHNTFJ") and the picture onsets were modeled as explanatory condition after convolution with the HRF (Hemodynamic Response Function). The parametric modulation function of SPM5 was used to enter the individual agoraphobia-related anxiety ratings, the cued vs. uncued condition, and the interaction between anxiety ratings and cued/uncued condition in the single subjects models during the picture phase. Movement parameters were included as additional regressors.

On the group level, one-sample-*t* tests were used with the appropriate contrast images during the picture phase (parametric modulation of agoraphobic anxiety, cue, and the interaction cue by agoraphobic anxiety) and during the anticipation phase (panic versus neutral cue). Association with psychopathology was assessed by including HAM-A and MI ratings as covariates into the second level analyses.

Correction for multiple comparisons was performed with SPM's small volume correction (SVC) in a priori defined anatomical regions according to our hypotheses based on findings in literature (e.g., [29, 32]) for the amygdala, insula, and the parahippocampal place area at $P < .05$ FWE-corrected for the respective VOI. The masks for the amygdala and the insula were generated using the wfu-pick-atlas [22]. The PPA was defined according to Epstein et al. [9] using a 10-mm sphere around the reported activation (left: $x = -28$, $y = -39$, $z = -6$ and right: $x = 20$, $y = -39$, $z = -5$). All other activations are reported at $P < .001$ with a cluster extend of 5 voxels. Association with psychopathology was assessed by including HAM-A and MI ratings as clinical covariates into the second level analyses.

Results

Psychometric properties

Criterion validity

The 2 × 2 × 2 ANOVAs revealed a significant interaction between category of pictures (agoraphobic vs. neutral) and group (patients vs. healthy) for valence ($F(1, 68) = 19.063$; $P < .001$), arousal ($F(1, 68) = 64.522$; $P < .001$) and agoraphobic anxiety ratings ($F(1, 68) = 64.592$; $P < .001$). Post hoc *t* tests showed that patients rated the agoraphobia pictures as being significantly more aversive, more arousing, and more agoraphobia-related anxiety-inducing compared to healthy controls, while there was no group difference for the neutral pictures (Fig. 2).

Parallelism of the two sets

Ratings for set 1 and set 2 of the Westphal-Paradigm did not differ in category (agoraphobic pictures/neutral pictures) or group (patients/controls) on the dimensions valence [*Set*: $F(1, 68) = .476$; $P = .493$, *Category* × *Set*: $F(1, 68) = .071$; $P = .791$; *Group* × *Set*: $F(1, 68) = .465$; $P = .497$], arousal [*Set*: $F(1, 68) = .344$; $P = .560$, *Category* × *Set*: $F(1, 68) = .578$; $P = .450$; *Group* × *Set*: $F(1, 68) = .01$; $P = .974$] and agoraphobic anxiety [*Set*: $F(1, 68) = .255$; $P = .615$, *Category* × *Set*: $F(1, 68) = .868$; $P = .355$; *Group* × *Set*: $F(1, 68) = .104$; $P = .749$].

Construct validity

Correlation of picture ratings with the clinical questionnaires MI, BSI, and BDI-II were calculated using Pearson correlation coefficient. Correlations between MI, BSI, and picture ratings were significant for the dimensions arousal and anxiety ($P < .01$), thus showing convergent validity with correlation coefficient between $r = .418$ and $r = .497$

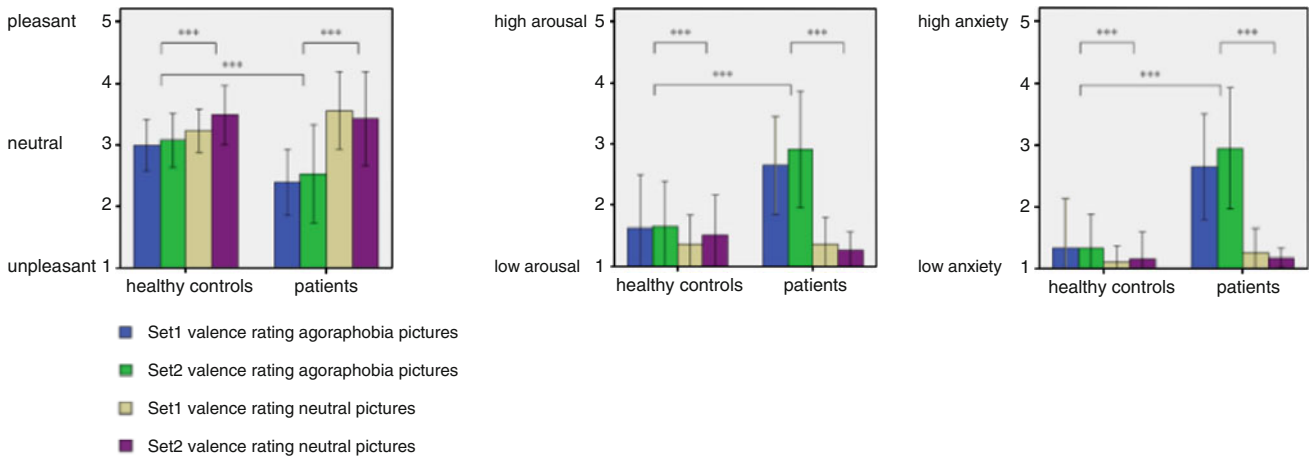

Fig. 2 Criterion validity of the Westphal-Paradigm (*$P < .05$, **$P < .01$, ***$P < .001$)

Table 2 Criterion validity of the Westphal-Paradigm (*$P < .05$, **$P < .01$, ***$P < .001$) and internal consistency of picture ratings ($n = 72$)

Pearson-correlation	Agoraphobia pictures		Neutral pictures	
	Arousal	Anxiety	Arousal	Anxiety
MI (unaccompanied)	.435**	.497**	.147	.138
BSI (phobic fear)	.447**	.418**	.237	.085
BDI	.104	.109	.002	.214
Cronbachs α	Agoraphobia pictures		Neutral pictures	
	Set 1	Set 2	Set 1	Set 2
Valence	.961	.973	.966	.973
Arousal	.986	.986	.960	.969
Anxiety	.987	.988	.969	.951

MI (unaccompanied) Mobility Inventory (unaccompanied version), *BSI (phobic fear)* brief symptom inventory, subscale "phobic fear", *BDI* beck depression inventory

** $P < .01$

as shown in Table 2. The BDI-II did not correlate with agoraphobic picture ratings, reflecting discriminant validity ($P > .104$). As expected, ratings of neutral pictures were not correlated with clinical questionnaires.

Reliability

Cronbachs α of agoraphobic and neutral pictures for set 1 and set 2 on the dimensions valence, arousal, and anxiety showed values between $\alpha = .951$ and $\alpha = .988$ (Table 2).

Functional imaging

Pictures which induce agoraphobic anxiety increased the BOLD response in the right insula, the bilateral precuneus and in a bilateral cluster posterior in the middle temporal gyrus/angular gyrus (see Table 3). Correcting for a PPA sphere [9], we also observed activation in the PPA bilaterally (left: $x = -24$, $y = -39$, $z = -18$; $t = 6.1$; $P = .001$ FWE-corrected for PPA VOI; right: $x = 27$, $y = -45$, $z = -12$; $t = 3.8$; $P = .02$ FWE-corrected for PPA VOI) (see Fig. 3).

Table 3 Brain activation in fMRI (BOLD contrast) during perception of agoraphobic pictures in patients with panic disorder and agoraphobia

k-size	Region (BA)	Side	*T*	*x*	*y*	*z*
574	Precuneus (31)	R	6.9	12	−60	21
		L	6.2	−9	−63	27
	Precuneus (7)	L	5	−9	−66	36
166	Middle occipital gyrus (39)	L	6.9	−45	−78	27
	Angular gyrus	L	4.6	−51	−63	30
	Middle temporal gyrus (39)	L	4.6	−57	−66	24
118	Fusiform gyrus (37)	L	6.1	−24	−39	−18
		L	5.8	−33	−45	−12
71	Middle temporal gyrus (19)	R	5.1	48	−78	18
	Precuneus (19)	R	4.7	42	−78	39
	Middle occipital gyrus (19)	R	4.6	36	−87	27
35	Insula/inf. front. gyrus (47)	R	4.6	33	18	−15
		R	4.5	45	30	−15
5	Angular gyrus (40)	R	4.3	48	−54	30
6	Superior occipital gyrus (19)	L	4	−33	−90	24

Located with SPMs anatomy toolbox [8]

$P < .001$ uncorrected, cluster size > 5

Pictures whose category were not indicated by a preceding cue ('uncued') revealed a stronger BOLD response compared to cued pictures in the right precuneus ($x = 12$, $y = -63$, $z = 30$; $t = 4.65$; $P < .001$ uncorrected).

The left amygdala showed a significant cue by agoraphobia-induced anxiety interaction, indicating more activation during cued compared to uncued agoraphobia-related

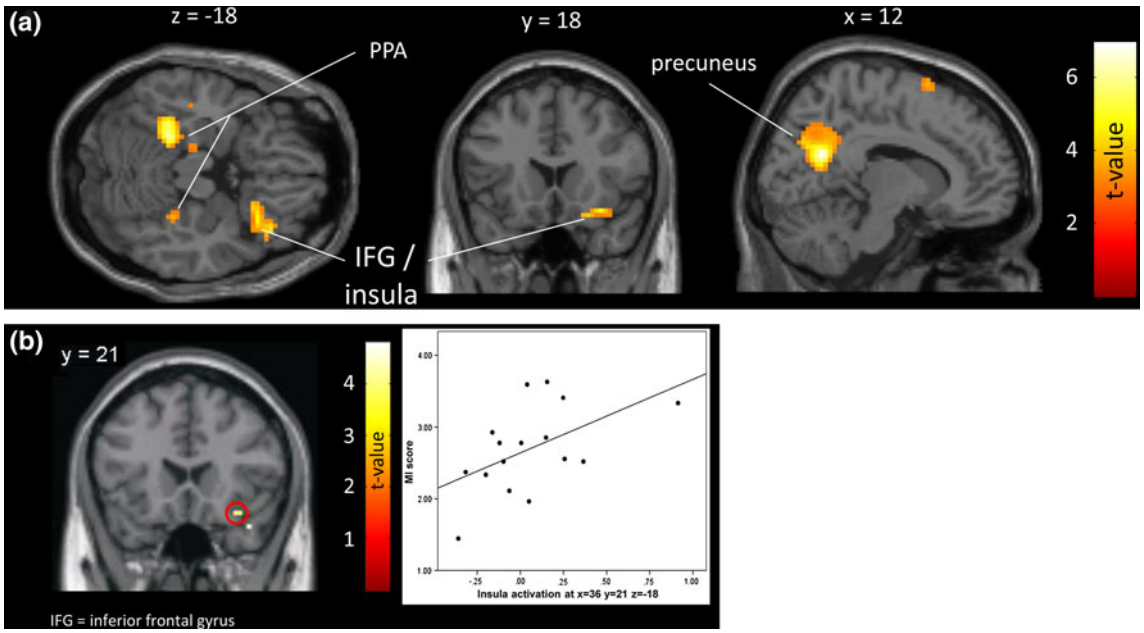

Fig. 3 **a** Brain activation (BOLD response) in the PPA, insula, and precuneus elicited by presentation of agoraphobic stimuli (displayed at *left* $x = 12$, $y = 18$, $z = -18$). **b** *Left side* association between BOLD response elicited by agoraphobic stimuli and MI in the insula (displayed at $y = 21$). *Right side* plot of parameter estimates of insula activation and MI (unaccompanied version) scores

pictures ($x = -27$, $y = 3$, $z = -18$; $t = 3.05$; $P = .004$; FWE-corrected for amygdala VOI). No activation outside the predefined VOIs was observed for the cue by agoraphobia-induced anxiety interaction.

During the anticipation phase, the agoraphobia cue compared to the neutral cue revealed significant activation in the amygdala (left: $x = -18$, $y = -3$, $z = -21$; $t = 3.31$; $P = .03$ FWE-corrected amygdala VOI) and insula (left: $x = -39$, $y = 15$, $z = -15$; $t = 4.07$; $P = .054$ FWE-corrected for insula VOI).

Clinical covariates in functional imaging

In a further step, the association between brain activation elicited by agoraphobic anxiety and clinical assessments with HAM-A and MI were investigated using the ratings as covariates. A significant correlation between HAM-A score and neural activation due to agoraphobic stimuli was found in the bilateral amygdala (left: $x = -27$, $y = -3$, $z = -27$; $t = 3.6$; $P = .026$; right: $x = 33$, $y = 3$, $z = -27$; $t = 3.6$; $P = .028$; both FWE-corrected for amygdala VOI) and parahippocampal place area (left: $x = -27$, $y = -48$, $z = -6$; $t = 3.3$; $P = .05$; right: $x = 15$, $y = -33$, $z = -12$; $t = 3.5$; $P = .03$; both FWE-corrected for PPA VOI). In addition, correlation analysis between the MI scores and activation in the insula was significant (right: $x = 36, y = 21$, $z = -18; t = 3.6; P = .013$; FWE-corrected for insula VOI, in an analysis restricted to voxels displaying a significant activation to agoraphobic stimuli at $P < .001$), displaying agoraphobia-related anxiety (Fig. 2).

Discussion

To our knowledge, this is the first study which assessed a set of agoraphobia-specific pictures (in patients with panic disorder and agoraphobia) on behavioral and neural level. The picture sets of the Westphal-Paradigm showed good psychometric properties. All agoraphobic pictures are more aversive, arousing, and anxiety-inducing for patients than for healthy volunteers. Correlations with HAM-A and MI (as typical clinical outcome values for anxiety and agoraphobia) but not BDI-II (for depression severity) support the disorder-specific relevance of the stimuli. Criterion and construct validity and reliability meet common criteria of quality. The two picture sets can be regarded to be parallel and the internal consistency proved to be high.

The pilot fMRI study in patients with panic disorder and agoraphobia revealed significant activation in the parahippocampal cortex, the precuneus, and the insula during presentation of agoraphobia-specific pictures. This is in line with Straube et al. [32] and Paquette et al. [24], who also observed precuneus and insula activation in spider phobics perceiving anxiety-inducing spider pictures. Another finding was that patients activated not only the precuneus and posterior cingulate cortex, which are involved in self-referential evaluative judgments concerning autobiographical memory [38] and in dysregulated anxiety-related thoughts in patients with social phobia [12], moreover, they also activate the parahippocampal place area [9]. We suggest that perceiving pictures that induce high agoraphobic anxiety is associated with a specific way

of processing this information, which involves higher spatial and visual processing, activation of autobiographical memory and self-referential aspects. In line with this assumption is our finding of a stronger precuneus activation in response to processing uncued pictures compared to cued pictures.

Furthermore, we observed increased activation of the amygdala in patients while watching cued agoraphobic stimuli. The increased activation of the amygdala, a central area of the fear circuit [15, 29], may activate processes related to anticipatory anxiety. Several studies [17, 31, 33] observed such activations in healthy volunteers who expected unpleasant stimuli. This may support the idea that patients who know that they will have to confront themselves with an agoraphobic situation suffer from a high anxious arousal before entering the agoraphobic event. Indeed, patients often describe this arousal as higher, more anxiety-inducing, and interfering with the daily routine than staying in the agoraphobic situation itself. Following this, the idea of a neural correlate of anticipatory anxiety is supported by our finding, i.e., the presentation of the cue itself increased activation in amygdala and insula [3]. In line with Bystritsky et al. [5], who reported hyperactivity in the inferior frontal gyrus, we also observed an increased activation in the inferior frontal cortex/insula as a typical hyperactive activation pattern in anticipatory anxiety.

Although one limitation of our pilot fMRI study is the missing control group, association between neural activation and clinical assessments (HAM-A and MI) suggest a syndrome-specific relevance of the fMRI paradigm. Positive correlations between state anxiety in the last week (HAM-A) and BOLD response to agoraphobia-specific stimuli were found in the amygdala, which is a key structure reported e.g., by Sakai et al. [28] and by van den Heuvel et al. [18] in patients with panic disorder with and without agoraphobia and in the PPA. This indicates stronger activation in patients with higher levels of anxiety in the amygdala as a key structure of the fear circuit and the PPA, which is involved in perception and processing of scenes and pictures [9] that may have specific relevance for processing of agoraphobic stimuli in patients. Perceptual areas such as the PPA may therefore be involved in the disorder-specific processes, although a comparison with a control group is warranted.

A further agoraphobia-specific quality of the used stimulus material was suggested by the association between the agoraphobia-specific Mobility Inventory (MI) and activation of the insula, which was hyperactive in anxiety-related disorders [10] and was involved in the processing of interoceptive states related to anxiety.

Encouraged by these findings, we will perform subsequent to this pilot study a study with a sufficient group of healthy controls. This work will also enable us to receive picture ratings by the same healthy controls and patients for both of the two parallel sets. Afterward, a study with patients suffering from other anxiety disorders as for instance specific phobias will be interesting and necessary. Further eye-tracking recordings and measurement of physiological signals as for instance skin conductance and its correlation with the picture ratings can be able to enrich the knowledge about attention to and processing of the agoraphobia-specific visual stimuli.

Altogether, our findings suggest that the Westphal-Paradigm is a valid and reliable tool, which is able to induce behavioral and neural activation in response to agoraphobia-specific stimuli. More than this, the paradigm is feasible, especially regarding research in patients suffering from agoraphobia and their specific needs in environments as MR-Tomographs are. Finally, the quality of the data is appropriate for further research. In particular, there are less movement artefacts and patients were able to perform the whole fMRI study procedure.

Thus, it may be applied for further research on the neurofunctional correlates of agoraphobia. Therefore, it will be necessary to investigate and differentiate neural activation patterns of patients with panic disorder without agoraphobia and patients with agoraphobia without panic disorder or panic attacks. This paradigm can be used for further characterization of the functional neuroanatomy of panic disorder and agoraphobia and might be useful to contribute data to the differentiation of panic disorder and agoraphobia as related, but conceptually different clinical disorders.

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