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Effects of Cognitive Behavioral Therapy on Neural Processing of Agoraphobia-Specific Stimuli in Panic Disorder and Agoraphobia

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Keywords

Agoraphobia · Anxiety · Amygdala · Ventral striatum · Functional MRI · Psychotherapy

Abstract

Background: Patients suffering from panic disorder and agoraphobia are significantly impaired in daily life due to anxiety about getting into a situation due to apprehension about experiencing a panic attack, especially if escape may be difficult. Dysfunctional beliefs and behavior can be changed with cognitive behavioral therapy; however, the neurobiological effects of such an intervention on the anticipation and observation of agoraphobia-specific stimuli are unknown. ***Methods:*** We compared changes in neural activation by measuring the blood oxygen level-dependent signal of 51 patients and 51 healthy controls between scans before and those after treatment (group by time interaction) during anticipation and observation of agoraphobia-specific compared to neutral pictures using 3-T fMRI. ***Results:*** A significant group by time interaction was observed in the ventral striatum during anticipation and in the right amygdala during observation of agoraphobia-specific pictures; the patients displayed a decrease in ventral striatal activation during anticipation from pre- to posttreatment scans, which correlated with clinical improvement measured with the Mobility Inventory. During observation, the patients displayed decreased activation in the amygdala. These activational changes were not observed in the matched healthy

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controls. ***Conclusions:*** For the first time, neural effects of cognitive behavioral therapy were shown in patients suffering from panic disorder and agoraphobia using disorder-specific stimuli. The decrease in activation in the ventral striatum indicates that cognitive behavioral therapy modifies anticipatory anxiety and may ameliorate abnormally heightened salience attribution to expected threatening stimuli. The decreased amygdala activation in response to agoraphobia-specific stimuli indicates that cognitive behavioral therapy can alter the basal processing of agoraphobia-specific stimuli in a core region of the fear network.

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Introduction

Individuals suffering from panic disorder and agoraphobia experience panic symptoms such as accelerated heart rate, shortness of breath, and dizziness. These symptoms can come about when it is difficult or embarrassing to escape a situation, when the person believes they cannot receive help, or where they perceive they have little control over the situation. Furthermore, panic symptoms can be evoked simply by being afraid of experiencing a panic attack in the future; as a consequence, those who suffer from panic attacks avoid situations such as open spaces, crowded places, public transport, and/or simply being outside of their home. During anticipatory anxiety, bodily symptoms and cognitive processes that estimate the potential threats of an upcoming situation become prominent. The development of avoidance behavior in relation to such situations may result in the manifestation of agoraphobia [1], from which more than one-third of persons afflicted by panic disorder suffer as well [2]. Despite the fact that panic disorder and agoraphobia have a high 12-month prevalence (1.8 and 2%, respectively) [3], little is known about the neural mechanisms behind these disorders.

Research on the neurocircuitry in both animals and healthy humans has been important for defining neural mechanisms in anxiety disorders. Anxiety can be defined as a persistent and general emotional state. Fear, on the other hand, is a reaction to an explicit threatening stimulus which results in escape or avoidance behaviors [4–7]. Consequently, the processing of threats has been associated with activations in fear-related brain structures such as the amygdala, insula, or cingulate cortex [8]. These brain areas have been subsequently shown to be activated during symptom provocation in anxiety disorders such as panic disorder and agoraphobia [9–11] and specific phobia [12]. Anticipation of aversive and anxiety-related stimuli has also been associated with increased activation in the amygdala [13] and insula [11, 14]. Research into animal models [15, 16], healthy subjects [17], and patients with anxiety disorders [18, 19] has underlined the role of the ventral striatum in anticipatory processes relevant to the identification and evaluation of stimuli with emotional significance [20, 21]. The ventral striatum and its neuroanatomical connections (e.g., to the insula and amygdala) have been found to be involved in psychomotor processes [22, 23] such as action planning [24]. In patients with panic disorder and agoraphobia, hyperactivation in the ventral striatum might be related to a more intense exploration of potentially threatening situations and evaluation of their individual salience. Assessing an environment as dangerous might result in increased action planning and faster motor responses. Furthermore, processes of avoidance learning following agoraphobic situations seem to be affected by those alterations [15, 25].

Currently, cognitive behavioral therapy (CBT) can be seen as the first-line treatment. The combination of psychoeducation and exposure-based therapy can lead to improvements in patients' mobility and reduce overall panic attacks, resulting in long-lasting effects [26]. Until now, studies on the neural effects of treatment on neurofunctional alterations have been sparse [27–29] and the findings have been inconsistent [30–33]. The findings include decreases in activation of the inferior, medial, and superior frontal gyrus and the hippocampus, and increases in activation of the insula, the inferior and medial frontal gyrus, and the middle and superior temporal gyrus. One study reported no change in activation over time [32]. This inconsistency may be related to the heterogeneity of the studies (Table 1).

These inconsistent findings led us to establish an fMRI paradigm containing disorder-specific stimuli that allows the delineation of anticipation and observation effects in pre-/posttreatment approaches ("Westphal-Paradigm" [11]). We administered the paradigm to a large homogeneous sample of patients with panic disorder and agoraphobia during 3-T fMRI before and after performing standardized CBT [26]. Previous data had displayed heightened neural activation in the amygdala and insula during observation and in the ventral striatum during anticipation of agoraphobia-specific stimuli in patients suffering from panic disorder with agoraphobia [11, 25]. It was hypothesized that during observation and anticipation of agoraphobia-specific stimuli, patients would show a decrease in blood oxygen level-dependent response in areas of the "classic" fear network including the amyg-

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Table 1. Former treatment studies on panic disorder and agoraphobia using an imaging technique

	Diagnosis for inclusion		Sample size per group, *n*				Treatment setting		Imaging technique			Experimental design		
	PD±A	PD+A	CBT	PD	SSRI/ SNRI	controls	individ- ual	group	PET	fMRI 1.5 T	fMRI 3 T	resting state	linguis- tic[1]	fear cond.[2]
Prasko et al. [30], 2004	●		6		6	0	●		●			●		
Sakai et al. [31], 2006		●	12			0	●		●			●		
Beutel et al. [32], 2010	●			9		18		●		●			●	
Kircher et al. [33], 2013		●	42			42	●				●			●

●, study meets feature; PD+A, panic disorder with agoraphobia; PD±A, panic disorder with or without agoraphobia; CBT, cognitive behavioral therapy; PD, short-term psychodynamic inpatient treatment; SSRI/SNRI, psychopharmacological treatment with selective serotonin reuptake inhibitors (SSRI) or selective serotonin-noradrenalin reuptake-inhibitors (SNRI); PET, ^{18}F-2-fluoro-deoxyglucose positron emission tomography. [1] Linguistic go/no-go task. [2] Fear conditioning.

dala and insula [9–11, 34]. In addition, a decrease in the ventral striatum during anticipation would be seen [35, 36]. Secondly, it was hypothesized that a positive relationship would be seen between subjective reports of anxiety induced by the presented stimuli and the Mobility Inventory [37] as a clinical measure of agoraphobia and neural activation. Lastly, it was expected that altered activations in these regions would be able to predict the outcome (as measured by the clinical values of the Hamilton Anxiety Rating Scale [HAM-A] [38]) of the disorder-specific psychotherapy.

Subjects and Methods

Participants

The fMRI centers in Aachen, Berlin (Charité and Adlershof), Dresden, and Münster obtained 72 data sets from 369 patients who met the diagnostic criteria for panic disorder with agoraphobia (DSM-IV-TR). Patients were recruited by 8 German centers participating in the German multicenter trial Mechanisms of Action in CBT (MAC) [39] (Aachen, Berlin-Adlershof, Berlin-Charité, Bremen, Dresden, Greifswald, Münster, and Würzburg). The results of this pretreatment comparison have been reported in a former publication [25].

In order to minimize dropouts due to scanning anxiety, we aimed to establish a comfortable atmosphere where the participants had maximum control over their insertion into the MRI scanner and knew that they could interrupt the scanning procedure in the case of an emergency. Fifty-one of the 72 patients also participated in the second scanning session and provided data for the pre-/posttreatment analysis. Although the fMRI-specific environment can be quite taxing and anxiety inducing for patients with panic disorder, none of the 51 patients ceased participation (either because of anxiety or panic or exhaustion before or during the pre- or posttreatment scanning sessions). Only in the former study [25] did 5 patients refuse to undergo fMRI scanning because of too much anxiety (compare Fig. 1) and therefore did not provide any data for the pre-/posttreatment analysis. However, also the additional 11 patients who were excluded because of bad data quality could have been in an anxious or exhausted state which could have contributed to the bad data quality. Ten further patients were randomized to a waitlist patient group. To increase the sample size of the waitlist patient group, 5 additional patients were independently recruited from the overarching German multicenter CBT trial. These patients met the same diagnostic criteria (see Table 2).

As expected, no significant changes in activation in our predefined volumes of interest (amygdala and ventral striatum) were found between pre- and posttreatment scans in this group.

Diagnostic Procedure

All patients met the DSM-IV-TR diagnostic criteria for primary panic disorder with agoraphobia. The assessment was carried out by trained professionals using a standardized computer-administered personal Composite International Diagnostic Interview (CAPI-WHO-CIDI; DIAX-CIDI version [40]). Patients who were diagnosed with having panic disorder, agoraphobia, or panic attacks exclusively were excluded.

The patients had to have a clinical interview score ≥18 on the structured interview guide for the HAM-A [38] and a score ≥4 on the Clinical Global Impression (CGI [41]) rating scale. They were aged between 18 and 65 years and were free of any psychopharmacological treatment for at least 4 weeks prior to participation. They did not undergo any other psychotherapeutic treatment. Patients who suffered from comorbid psychotic or bipolar I disorder, current alcohol dependence/current abuse of or dependence on psychoactive substances, current suicidal ideations, borderline personality disorder, or significant abnormalities in routine clinical chemistry or hematology, EEG or ECG were excluded from the study.

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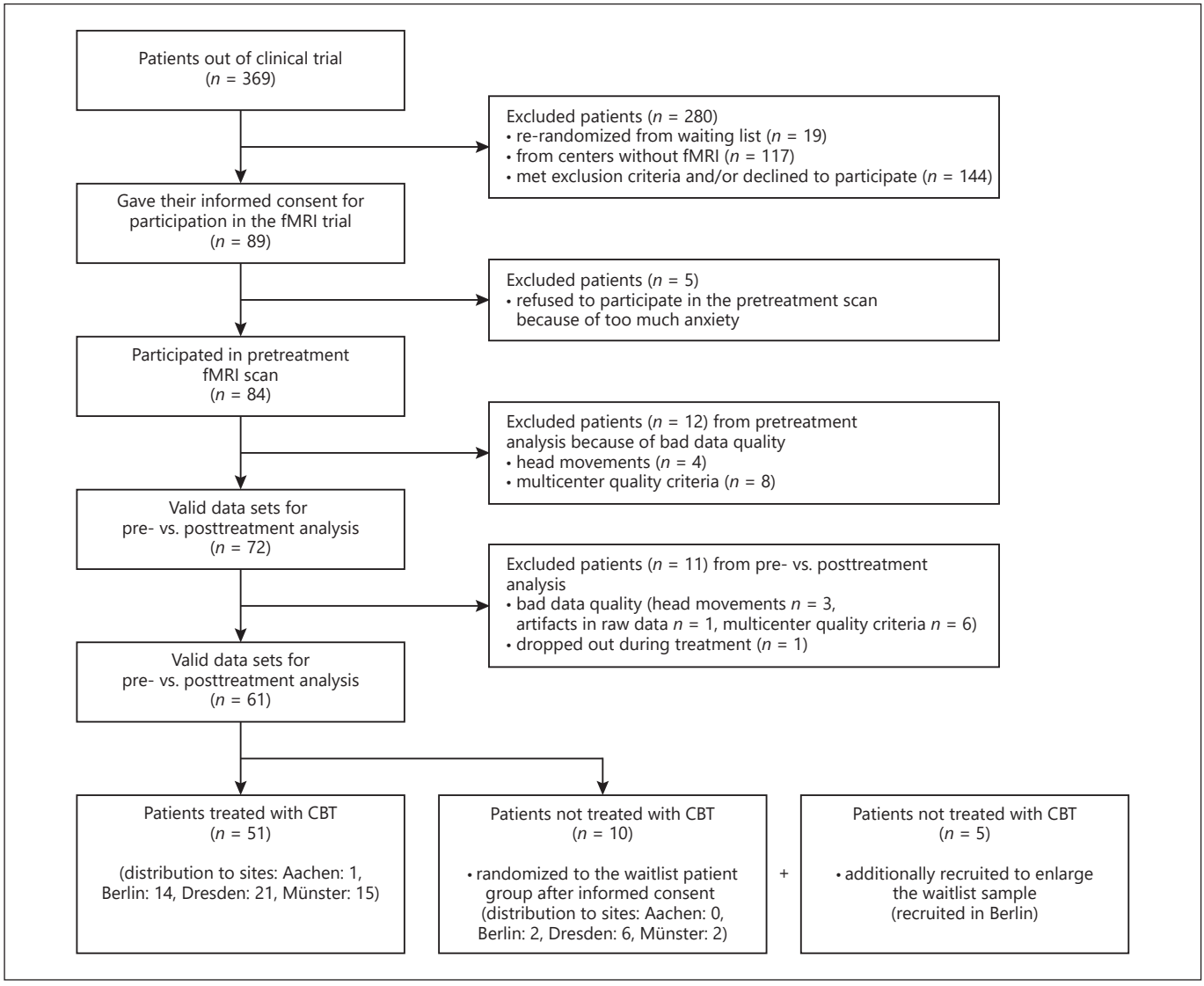


Fig. 1. Flow of participants' inclusion.

The Edinburgh Inventory [42] was used to measure handedness. Color vision was assessed with Ishihara's test for color blindness [43]. Healthy volunteers were recruited by the participating fMRI centers using advertisements on their respective websites. Those healthy volunteers who fulfilled the individual matching criteria (age, gender, handedness, smoking status, and education) of the respective patients were invited. The healthy volunteers underwent a similar DIAX-CIDI interview as the patients and would have been excluded if currently they met, or in the past had met, any criteria for mental disorder. None of the healthy volunteers who participated in the diagnostic procedure had to be excluded.

The patients were screened for contraindications to MRI, including ferromagnetic material or cardiac pacemakers, and were asked not to smoke for at least 4 h prior to the fMRI sessions. A more detailed description of data inclusion can be found in the study by Wittmann et al. [25], and an overview in Figure 1.

A total of 51 healthy controls without any mental disorders or psychotherapeutic or psychopharmacological treatment were individually matched according to gender, age, handedness, smoking status, and education (Table 2).

Data Inclusion

Of the 72 data sets, 11 were discarded due to intense head movements ($n = 2$: movement of more than twice the voxel size along the z axis and pitching the head >3°; $n = 1$: pitching the head >3°) or intense artifacts in the MRI raw data ($n = 1$) or because they did not meet the joint multicenter quality criteria ($n = 6$: >2.5 SDs) on the point spread function [44] or signal-to-fluctuation noise ratio (SFNR) [45]. One patient dropped out during CBT treat-

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Table 2. Sociodemographic and clinical data

	Patients with panic disorder and agoraphobia (n = 51)	Healthy controls (n = 51)	Patients in waitlist group (n = 15)	
Female, *n*	34	34	7	
Age, years	36.4±11.1	36.0±11.1	36.3±10.8	
Left-handed, *n*	4	5	2	
Smokers, *n*	25	19	7	
Education, *n*				
13 years	26	36	5	
10 years	21	13	9	
9–10 years	4	2	1	
HAM-A score				
T1	23.7±5.4	1.9±1.7	23.5±4.0	
T2	12.2±6.6	1.5±1.5	20.0±7.7	
T1–T2	11.5±6.7	0.5±2.1	3.4±6.1	
t/*p*/*d*	**12.35/<0.001/1.4**	1.51/0.14/0.2	**2.16/0.05**/0.1	
Mobility Inventory score				
T1	2.7±0.8	na	2.6±0.9	
T2	1.8±0.7	na	2.6±0.9	
T1–T2	1.0±0.7	na	0.1±0.6	
t/*p*/*d*	**10.04/<0.001/1.6**		0.44/0.66/0.1	
	Patients with panic disorder and agoraphobia vs. healthy controls	Patients with panic disorder and agoraphobia vs. waitlist group patients	Healthy controls vs. waitlist group patients	Group differences
				χ^2/*p*
Female				2.27/0.32
Age				85.34/0.27
Left-handed				0.43/0.81
Smokers				1.5/0.47
	χ^2/*p*	χ^2/*p*	χ^2/*p*	χ^2/*p*
Education				
13 years	4.11/**0.04**	1.45/0.23	6.84/**0.009**	**8.03/0.02**
10 years	3.63/0.06	1.66/0.2	7.12/**0.008**	**7.8/0.02**
9–10 years				1.9/0.39
	t/*p*/*d*	*t*/*p*/*d*	*t*/*p*/*d*	*F*/*p*
HAM-A				
T1	27.61/<**0.001**/1.1	0.16/0.87/–	4.48/<**0.001**/1.8	**426.5/<0.001**
T2	11.35/<**0.001**/0.4	–3.9/<**0.001**/0.1	–16.42/<**0.001**/0.4	**95.45/<0.001**
T1–T2	11.3/<**0.001**/0.4	4.21/<**0.001**/0.2	–2.95/<**0.004**/0.1	**61.51/<0.001**
		t/*p*/*d*		
Mobility Inventory				
T1		0.29//0.78/–		
T2		–3.71/<**0.001**/1.3		
T1–T2		4.48/<**0.001**/2		

Values are presented as mean ± SD unless specified otherwise. Bold values denote significance. *d*, Cohen's $d = (\text{mean}_1 - \text{mean}_2)/\text{SD}_{\text{pooled}}$; education, reported are years at school; HAM-A, Hamilton Anxiety Rating Scale; T1, before CBT/waiting period; T2, after CBT/waiting period; T1–T2, difference in values between before CBT/waiting period and after; na, value not available; CBT, cognitive behavioral therapy.

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ment. The sociodemographic and clinical data about the patients not included in the pre-/posttreatment analysis did not significantly differ from those about the patients who participated in the complete study. The patients who participated in the fMRI experiments did not differ from the whole CBT sample regarding symptom severity as assessed with the HAM-A and the Mobility Inventory (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000493146). This resulted in a sample of 51 patients (Fig. 1). In order to control for effects of "site," this was included as a covariate into the analyses, since the inclusion as an additional between-subject factor did not reveal any significant main or interaction effects.

The clinical data (HAM-A [38] and Mobility Inventory scores) for the original CBT sample (n = 369) [39] were comparable with those for the fMRI subsample (n = 51) (HAM-A fMRI sample, mean = 23.7, SD = 0.6, vs. HAM-A CBT sample, mean = 24.1, SD = 5.2; Mobility Inventory fMRI sample, mean = 2.7, SD = 0.8, vs. Mobility Inventory CBT sample, mean = 3.0, SD = 0.9).

Moreover, we computed the relative SFNR [46] for our volumes of interest (right amygdala and right ventral striatum) using a 3 × 2 × 2 (site × time × group) ANOVA to test for differences between sites, for potential interactions between site and time, and for a three-way interaction between site, time and group in separate analyses for the right amygdala and the right ventral striatum SFNR values. For both regions there was a main effect of site (right amygdala: $F(2, 94) = 49.955$, $p < 0.001$; right ventral striatum: $F(2, 94) = 47.616$, $p < 0.001$). Critically, no differences were found between groups (amygdala: $p > 0.8$; ventral striatum: $p > 0.8$) or times (amygdala: $p > 0.6$; ventral striatum: $p > 0.1$) and there was no time by group interaction (amygdala: $p > 0.1$; ventral striatum: $p > 0.9$). Additionally, we did not observe any significant interactions between site and time, nor between site, time, and group in the right amygdala (time × site: $p > 0.5$; site × time × group: $p > 0.5$) or in the right ventral striatum (time × site: $p > 0.5$; site × time × group: $p > 0.2$). This indicated that although there were differences in SFNR between scanners, these were stable over time and did not show any time by group interaction.

To probe whether the SFNR affected our results, we repeated our analyses to test for a significant group by time interaction on BOLD response during feedback (panic pictures > neutral pictures) in the right amygdala, including the individual SFNR values as a covariate. While controlling for individual SFNR values in this region, the group by time interaction remained significant ($F = 28.593$, $p < 0.001$). Similarly, the group by time interaction on BOLD activation in the right ventral striatum during anticipation (panic cue > neutral cue) remained significant ($F = 7.078$, $p = 0.008$).

In order to rule out possible effects of the interval between pre- and posttreatment scanning, we correlated beta values of the parameter estimates from each participant for the ventral striatum (anticipation) and the amygdala (picture phase) with the number of days between the pre- and the posttreatment scan. However, no significant correlation was found (ventral striatum (r)T2 vs. interval T2–T1: $r = 0.028$, $p = 0.780$; amygdala (r)T2 vs. interval T2–T1: $r = -0.024$, $p = 0.814$).

The interval between the two fMRI scans for the healthy controls was 8 weeks.

Treatment

The patients underwent standardized and manualized CBT (12 sessions over 8 weeks) [39]. Treatment included psychoeducation, interoceptive and in vivo exposure, and relapse prevention. Between-therapist variability was minimized by therapist trainings, detailed procedural descriptions, and guidance for solutions to anticipated problems. Therapy integrity was assured by reporting all treatment procedure deviations to the study coordination center and by a selected and randomized analysis of 17.2% of the video-recorded sessions. More details on the treatment and on treatment outcomes are reported elsewhere [26].

Experimental Design

We applied one of two randomly assigned sets of the Westphal-Paradigm (online suppl. Fig. 1) before and after treatment. The sets were previously evaluated in two studies [11, 25]. Each set consisted of 48 agoraphobia-specific pictures (e.g., public transport, crowds, automobiles, dense situations) as well as 48 neutral pictures as a control condition. A stimulus signaled the category of the upcoming picture (for each half of the 96 pictures, the word "Neutral," "Panic," or a random combination of characters ["DGHNTFJ"] as nonspecific stimulus).

All pictures were presented in a randomized sequence to each participant for a duration of 2,000 ms. The duration of presentation of the anticipatory cue was 250 ms. The presentation of a fixation cross (presented between 2 and 4 s) separated the anticipatory cue and the agoraphobia-specific/neutral stimuli to minimize artifacts due to eye movements. The fixation cross was also presented during the intertrial intervals, with a variable duration of between 2 and 6 s. The overall duration of the complete paradigm was approximately 15 min. We used Presentation version 11.0 (Neurobehavioral Systems, Albany, CA, USA) for stimulus presentation.

The participants were instructed to imagine themselves being in the presented situation. They were also asked to pay attention to the anticipatory cue and its predictive content with regard to the pictures. The requirement to push a button during the presentation of each picture assured that the participants were paying attention to the paradigm. The neutral pictures were taken from the International Affective Picture System [47] (compare online suppl. Fig. 1).

Comparison of Anticipation Conditions and Picture Phase

To compare the results across the anticipation conditions and picture phases, the analysis was recalculated. Thus, the picture phase was divided by the type of the preceding cue. The contrast "uncued panic pictures > uncued neutral pictures" showed a significant group by time interaction ([patients > controls] × [T1 > T2]) in the right amygdala (27/2/–29, $t = 2.52$, $p = 0.098$), whereas the contrast "cued panic pictures > cued neutral pictures" showed a similar direction but was not significant (24/2/–20, $t = 1.74$, $p = 0.361$). Formally testing a cue by group by time interaction did not reveal any significant result in the right amygdala ($p > 0.4$).

Due to the circumstance that the contrast "panic cue > neutral cue" is most appropriate in the fMRI design because uncued neutral or panic conditions do not exist during anticipation, a similar factorial design was not established for the anticipation phase. However, an examination of the noninformative cue ("uncued cue") showed no significant group by time interaction ([patients > controls] × [T1 > T2]) in any predefined region ($p > 0.3$).

Self-Report Data

After each scanning session, the pictures were rated with regard to agoraphobic anxiety using a 5-level Likert-type scale. Four pa-

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tients and 3 control subjects did not complete these ratings due to either being too stressed or having to leave immediately after the scan (online suppl. Table 2). To analyze the ratings, a 2 × 2 ANOVA for repeated measures (group[patients/controls] × time[before CBT/after CBT]) with "group" as the between-subject factor and "time" as the within-subject factor was used.

The clinical data (HAM-A and Mobility Inventory scores) on the patients and controls before and after treatment were analyzed using paired *t* tests. Associations between anxiety ratings and clinical data were calculated using Pearson's correlations.

Functional Imaging

Functional imaging was performed in Berlin (3T General Electric Healthcare), Dresden (3T Siemens Trio), and Aachen and Münster (3T Philips Achieva). EPI sequences minimized artifacts and signal loss (TE = 30 ms, TR = 2 s, flip angle = 90°, matrix = 64 × 64, voxel size = 3.6 × 3.6 × 3.8 mm). In each session, 446 volumes were acquired, with 30 slices aligned parallel to the AC-PC line. Statistical Parametric Mapping (version SPM8; http://www.fil.ion.ucl.ac.uk/spm) was applied to the data analysis.

Given our a priori hypotheses, correction for multiple comparisons was performed using SPM's small volume correction (SVC). Due to results of previous studies, treatment effects were expected in the a priori defined volumes of interest – namely, in the ventral striatum, the insula, and the amygdala during the anticipation phase and in the insula and the amygdala during the picture phase. All reported coordinates are voxelwise-corrected MNI (Montreal Neurological Institute) coordinates. The results are reported at $p < 0.05$ (family-wise error corrected) for the volumes of interest and the whole brain levels for future hypotheses (online suppl. Table 3). Pearson's correlations were calculated to test associations between picture ratings, clinical data, and neural activation patterns in the volumes of interest.

As we hypothesized that the amygdala, insula, and ventral striatum would be involved in anticipating and perceiving anxiety-related stimuli [9, 10, 24, 34–36, 48], a correction for multiple comparisons was carried out using SPM's SVC at $p < 0.05$ (family-wise error corrected). For the amygdala and insula, masks combining all voxels of interest (VOI) were generated using the automated anatomical labeling atlas [49] (WFU PickAtlas software toolbox [50]). The mask for the ventrostriatal VOI was generated with a probabilistic, literature-based SPM tool [51].

During preprocessing, correction for slice-time acquisition delay and movement (by realignment to individual mean EPI), spatial normalization to the standard EPI template, and spatial smoothing with 8 mm full width at half maximum were performed. To avoid non-steady-state effects caused by T1 saturation, the first 5 volumes of each time series were discarded. The general linear model was used for data analysis with a two-level approach.

On the single-subject level, the three anticipatory stimuli ("Panic," "Neutral," and "DGHNTFJ") and the picture onsets of the four different trial types were modeled as explanatory conditions after convolution with the hemodynamic response function: (1) "expected agoraphobia-specific picture," (2) "unexpected agoraphobia-specific picture," (3) "expected neutral picture," and (4) "unexpected neutral picture." Movement parameters were included as additional regressors. The computation of contrast images was done for the anticipation phase "agoraphobic anticipation minus neutral anticipation" and for the picture phase "all agoraphobia-specific pictures minus all neutral pictures" combining expected and unexpected pictures ([(1) + (2)] – [(3) + (4)]). On the second level (group-level statistics), separate flexible factorial 2 × 2 (group × time) ANOVAs were utilized to determine interaction effects using the appropriate contrast images for the anticipation and the picture phase. Post hoc one-sample, two-sample, and paired *t* tests were calculated to detect group differences.

Furthermore, the prediction of outcome was analyzed by correlating the neural activation in our hypothesized volumes of interest at pretreatment scanning with the difference scores of clinical values (HAM-A and Mobility Inventory) between pre- and posttreatment scanning.

Results

Self-Report Data

Clinical Data

The patients showed a significant decrease in symptom severity from pre- to posttreatment as assessed by the HAM-A ($t(50) = 12.35$, $p < 0.001$, $d = 1.4$) and Mobility Inventory ($t(48) = 10.04$, $p < 0.001$, $d = 1.6$), whereas the controls did not (HAM-A: $t(50) = 1.51$, $p = 0.137$, $d = 0.2$; Mobility Inventory scores not available) (Table 2).

Picture Rating

Before treatment, the patients rated the agoraphobia-specific pictures as more anxiety inducing than did the controls, while neutral pictures were rated similarly. The patients rated the induced anxiety as higher before than after treatment (indicated by a main effect of group [$F(1, 93) = 94.72$, $p < 0.001$; $\eta_p^2 = 0.5$], time [$F(1, 93) = 46.70$, $p < 0.001$; $\eta_p^2 = 0.3$], and group by time interaction [$F(1, 93) = 53.99$, $p < 0.001$; $\eta_p^2 = 0.4$]) for agoraphobia-specific but not for neutral pictures (online suppl. Table 2).

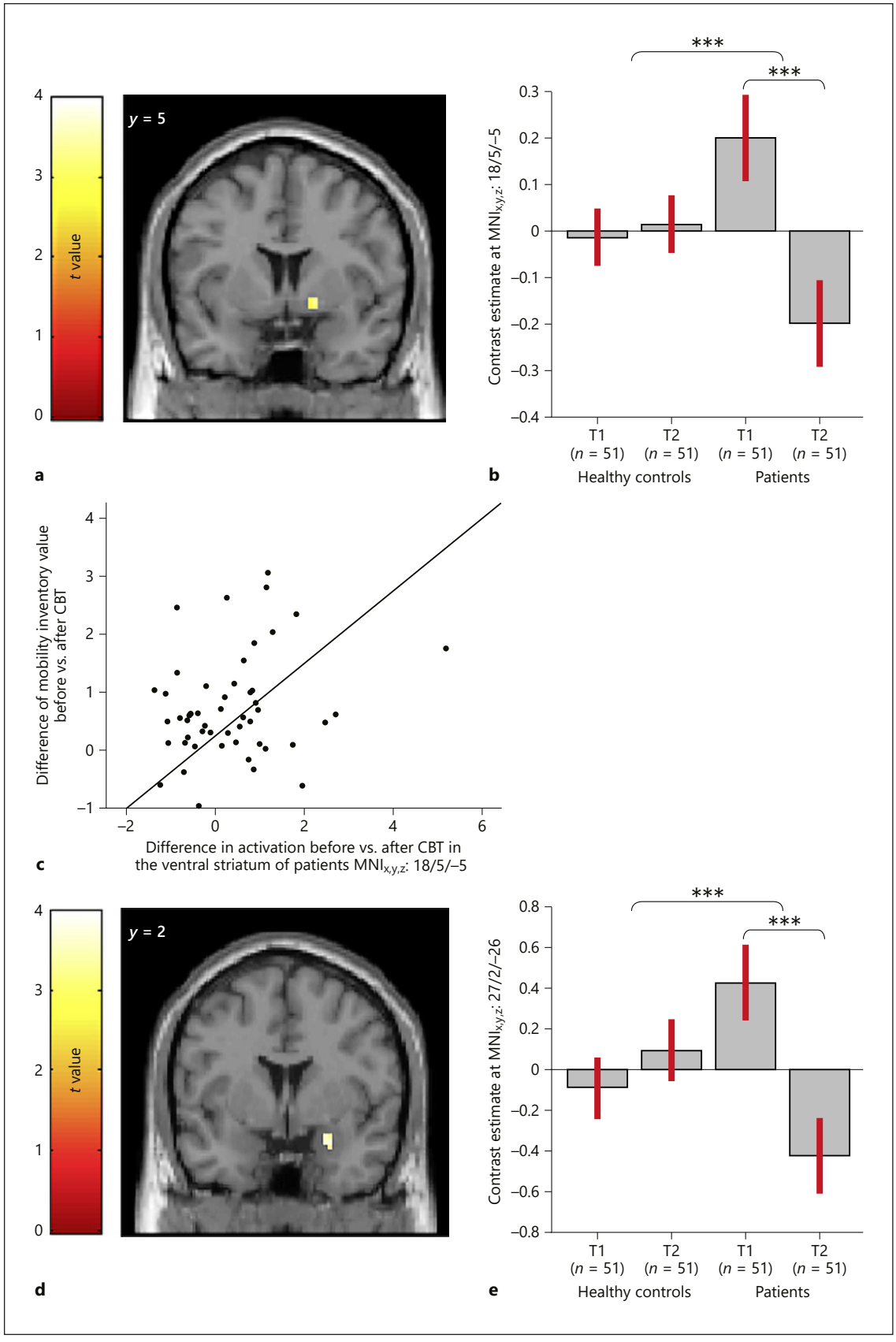
Correlation between Picture Rating and Clinical Data

A correlation was found between anxiety ratings for the agoraphobia-specific pictures and symptom severity in the patient group (HAM-A score: before CBT, $r = 0.78$,

Fig. 2. Neural activations of patients compared with controls before versus after treatment. **a** Group by time interaction in the right ventral striatum (displayed at $p < 0.001$ [uncorrected], $k > 10$, MNI slice $y = 5$). **b** Parameter estimates at $MNI_{x/y/z}$: 18/5/–5, $t = 3.56$, $p = 0.004$ (small volume corrected for ventral striatal volume of interest). **c** Correlation of differences in Mobility Inventory scores with differences in activation of the ventral striatum of patients before versus after cognitive behavioral therapy (CBT) ($r = 0.31$, $p = 0.028$). **d** Group by time interaction in the right amygdala (displayed at $p < 0.001$ [uncorrected], $k > 10$, MNI slice $y = 2$). **e** Parameter estimates at $MNI_{x/y/z}$: 27/2/–26, $t = 4.11$, $p = 0.002$ (small volume corrected for amygdala volume of interest).

(For figure see next page.)

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$p < 0.001$, and after CBT, $r = 0.56$, $p < 0.001$; Mobility Inventory score: before CBT, $r = 0.55$, $p < 0.001$, and after CBT, $r = 0.47$, $p = 0.001$). The decrease in anxiety ratings from pre- to posttreatment correlated with clinical outcome (decrease in Mobility Inventory score during treatment) ($r = 0.45$, $p = 0.001$).

Functional Imaging

Prefixed Analyses

Due to therapy dropout, poor data quality, and being randomized to a waitlist patient group (see patient flow for detailed information; Fig. 1), 21 of the 72 patients from our previous study [25] could not be included in the assessment of the treatment effect. Indeed, we did not observe a significant group difference in amygdala activation during the picture phase in the larger sample (patients vs. healthy controls: right amygdala, $p_{\text{SVC amygdala VOI}} = 0.2$, and left amygdala, $p_{\text{SVC amygdala VOI}} = 0.4$). In the current subsample ($n = 51$), we observed a significant interaction and a trendwise group difference at T1 ($p = 0.074$). Therefore, we controlled for potential group differences between the included patients and the 21 patients who were not part of the pre-/posttreatment analysis. We found that the data quality at T1, although passing the necessary quality criteria of the consortium [33], differed significantly (QA $n = 21$: 2.75 ± 0.74; QA $n = 51$: 2.24 ± 0.55; $t = 3.202$, $p = 0.002$). This might have led to the reduced sensitivity to detected group differences in the larger sample at T1.

Furthermore, in the present paper we only observed a trendwise group difference between healthy controls and patients at T1 in the amygdala, contributing to the significant group by time interaction. The interaction was further driven by a deactivation in the patient group at T2 ($t = 4.11$; $MNI_{x,y,z}$: 27, 2, –26; $p = 0.002$), which was not found in the larger sample at T1. Further, we conducted post hoc volume of interest analyses of the group by time interaction effects. This still revealed a significant group by time effect in the amygdala and a stronger activation of the amygdala in patients compared to healthy controls at T1, and contrariwise a lower activation at T2. The activation of the amygdala was significantly reduced in the patients from pre- to posttreatment, but this was not the case in the healthy controls.

To avoid the possibility that BOLD effects during the anticipation and observation phases are only particular peak voxel activations, we extracted clusters for our main findings. The data thus obtained still showed a significant group by time effect ($F = 4.367$, $p = 0.039$) in the ventral striatum during the anticipation phase. This effect is explainable by a higher activation in patients compared to healthy controls at T1 ($t = –4.211$, $p < 0.001$) and a nonsignificant difference in activation between these groups at T2 ($t = –0.871$, $p > 0.3$). The activation of the ventral striatum was significantly reduced in the patient group from pre- to posttreatment ($t = 2.293$, $p = 0.026$) but not in the healthy control group ($t = –0.453$, $p > 0.6$).

For the observation phase, a significant group by time effect was found in the amygdala after cluster extraction ($F = 13.806$, $p < 0.001$). The higher BOLD response for the observation phase is also a result of higher activations in the patient group compared to the healthy control group at T1 ($t = –2.604$, $p = 0.011$) and lower activation in T2 ($t = 2.264$, $p = 0.015$). The activation of the amygdala was significantly reduced in the patient group when comparing pre- to posttreatment activations ($t = 4.009$, $p < 0.001$) but not in the healthy control group ($t = –1.163$, $p > 0.2$).

Anticipation Phase

Treatment effects on functional activation during the anticipation phase were assessed using a group by time interaction, which was found to be significant in the right ventral striatum ($F = 10.04$; $MNI_{x,y,z}$: 18, 5, –5; $p = 0.026$; $\eta_p^2 = 0.053$ for peak voxel and $\eta_p^2 = 0.025$ for mean VOI values) (Fig. 2). This was due to a decrease in activation in the patients from pre- to posttreatment ($t = 3.56$; $MNI_{x,y,z}$: 18, 5, –5; $p = 0.004$), while the healthy controls did not show any change ($p > 0.05$). Before treatment, the patients showed more activation than the controls ($t = 4.42$; $MNI_{x,y,z}$: 15, 8, –8; $p < 0.001$). After treatment, the patients no longer displayed any difference in activation in the right ventral striatum compared to the controls ($p > 0.1$). No other significant group by time interaction was found in any other region (Table 3).

Extracting the mean parameter estimates from the right ventral striatum of the scans before and after treatment, their differences showed positive correlations with differences in Mobility Inventory scores (reported for the previous 7 days on the first and last days of CBT) for the patient group ($r = 0.31$, $p = 0.028$). This means that the reduction in ventral striatal activation correlated with clinical improvement as measured using the Mobility Inventory.

Picture Phase

The effect of treatment on functional activation during the observation phase was tested using group by time interaction, which was found to be significant for the right amygdala ($F = 12.99$; $MNI_{x,y,z}$: 27, 2, –20; $p = 0.015$; $\eta_p^2 = 0.113$ for peak voxel and $\eta_p^2 = 0.054$ for mean amygdala

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Table 3. Group by time interactions

Anticipation phase (agoraphobia-specific cues vs. neutral cues)													**Picture phase (agoraphobia-specific pictures vs. neutral pictures)**											
Group differences													*Group differences*											
Hyperactivations in patients > controls T1						Hyperactivations in patients > controls T2							Hyperactivations in patients > controls T1						Hyperactivations in patients > controls T2					
VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$
Amygdala (l)	−21	−1	−14	3.02	**0.03**	Amygdala (l)	−24	−1	−23	3.63	**0.005**	Amygdala (l)					ns	Amygdala (l)					ns
Amygdala (r)	30	2	−29	2.54	0.09	Amygdala (r)					ns	Amygdala (r)	24	2	−23	2.66	0.07	Amygdala (r)					ns
Insula (l)	−30	26	10	3.79	**0.02**	Insula (l)					ns	Insula (l)					ns	Insula (l)					ns
Insula (r)	33	20	−14	3.44	**0.05**	Insula (r)	45	20	−2	3.76	**0.02**	Insula (r)					ns	Insula (r)					ns
VS (l)	−15	2	−5	3.64	**0.003**	VS (l)	−18	5	−8	2.43	0.06												
VS (r)	15	8	−8	4.42	**<0.001**	VS (r)					ns												
Hyperactivations in controls > patients T1						Hyperactivations in controls > patients T2							Hyperactivations in controls > patients T1						Hyperactivations in controls > patients T2					
VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$
Amygdala (l)					ns	Amygdala (l)					ns	Amygdala (l)					ns	Amygdala (l)	−18	−7	−17	3.03	**0.03**
Amygdala (r)					ns	Amygdala (r)					ns	Amygdala (r)					ns	Amygdala (r)					ns
Insula (l)					ns	Insula (l)					ns	Insula (l)					ns	Insula (l)					ns
Insula (r)					ns	Insula (r)					ns	Insula (r)					ns	Insula (r)					ns
VS (l)					ns	VS (l)					ns												
VS (r)					ns	VS (r)					ns												
Changes over time													*Changes over time*											
Change over time in patients T1 > T2						Change over time in patients T1 > T2							Change over time in patients T1 > T2						Change over time in patients T1 > T2					
VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$
Amygdala (l)					ns	Amygdala (l)					ns	Amygdala (l)	−18	−7	−17	3.18	**0.02**	Amygdala (l)					ns
Amygdala (r)					ns	Amygdala (r)					ns	Amygdala (r)	27	2	−26	4.11	**0.002**	Amygdala (r)					ns
Insula (l)					ns	Insula (l)					ns	Insula (l)	−30	20	4	3.59	**0.04**	Insula (l)					ns
Insula (r)					ns	Insula (r)					ns	Insula (r)	39	17	−2	3.85	**0.02**	Insula (r)					ns
VS (l)					ns	VS (l)					ns												
VS (r)	18	5	−5	3.56	**0.004**	VS (r)					ns												
Change over time in controls T1 > T2						Change over time in controls T1 > T2							Change over time in controls T1 > T2						Change over time in controls T1 > T2					
VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$	VOI	*x*	*y*	*z*	*t*	$p_{SVC\text{-}cor}$
Amygdala (l)					ns	Amygdala (l)					ns	Amygdala (l)					ns	Amygdala (l)					ns
Amygdala (r)					ns	Amygdala (r)					ns	Amygdala (r)					ns	Amygdala (r)					ns
Insula (l)					ns	Insula (l)					ns	Insula (l)					ns	Insula (l)					ns
Insula (r)					ns	Insula (r)					ns	Insula (r)					ns	Insula (r)					ns
VS (l)					ns	VS (l)					ns												
VS (r)					ns	VS (r)					ns												

Bold type denotes significance. CBT, cognitive behavioral therapy; VOI, volume of interest; *x*, *y*, *z*, MNI coordinates; $p_{SVC\text{-}cor}$, SVC (small volume correction)-corrected $p \leq 0.05$; (l), left hemisphere; (r), right hemisphere; ns, not significant (all values >0.1); VS, ventral striatum; T1, before CBT/waiting time; T2, after CBT/waiting time.

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Table 4. Outcome prediction

Anticipation phase (agoraphobia-specific cues vs. neutral cues)

Positive correlation of HAM-A values with activations in patients before treatment

Activations in patients before treatment

VOI	*x*	*y*	*z*	*t*	*p**
Amygdala (l)					ns
Amygdala (r)	30	−1	−14	2.20	0.212
Insula (l)	−36	−16	19	3.94	**0.028**
Insula (r)	48	5	−2	2.90	0.266
Ventral striatum (l)	−18	5	−5	2.79	**0.039**
Ventral striatum (r)	18	5	−8	2.16	0.130

VOI	*x*	*y*	*z*	*t*	*p***
Fusiform gyrus	−21	−58	−8	4.39	**<0.001**
Insula	−33	−13	19	4.17	**<0.001**
Inferior temporal gyrus	−51	−10	−32	3.3	**0.001**
Inferior frontal gyrus	−42	56	1	3.24	**0.001**

Negative correlation of HAM-A values with activations in patients before treatment

Activations in patients before treatment

VOI	*x*	*y*	*z*	*t*	*p**
Amygdala (l)	−24	−1	−29	2.11	0.222
Amygdala (r)					ns
Insula (l)					ns
Insula (r)					ns
Ventral striatum (l)					ns
Ventral striatum (r)					ns

VOI	*x*	*y*	*z*	*t*	*p***
ns					

Picture phase (agoraphobia-specific pictures vs. neutral pictures)

Positive correlation of HAM-A values with activations in patients before treatment

Activations in patients before treatment

VOI	*x*	*y*	*z*	*t*	*p**
Amygdala (l)					ns
Amygdala (r)					ns
Insula (l)	−27	17	4	1.73	0.858
Insula (r)					ns
Ventral striatum (l)					ns
Ventral striatum (r)					ns

VOI	*x*	*y*	*z*	*t*	*p***
Corpus callosum	−9	−43	13	4.64	**<0.001**
Middle frontal gyrus	−54	8	46	3.61	**0.001**
Rectal gyrus	6	23	−20	3.3	**0.001**

Negative correlation of HAM-A values with activations in patients before treatment

Activations in patients before treatment

VOI	*x*	*y*	*z*	*t*	*p**
Amygdala (l)					ns
Amygdala (r)					ns
Insula (l)					ns
Insula (r)					ns
Ventral striatum (l)					ns
Ventral striatum (r)					ns

VOI	*x*	*y*	*z*	*t*	*p***
ns					

Positive correlation of Mobility Inventory values with activations in patients before treatment

Activations in patients before treatment

VOI	*x*	*y*	*z*	*t*	*p**
Amygdala (l)	−24	2	−20	2.28	0.17
Amygdala (r)					ns
Insula (l)	−36	−1	7	3.12	0.18
Insula (r)	36	−4	7	2.88	0.274
Ventral striatum (l)					ns
Ventral striatum (r)					ns

VOI	*x*	*y*	*z*	*t*	*p***
Caudate	−9	11	13	4.63	**<0.001**
Culmen	−42	−37	−23	4.25	**<0.001**
Postcentral gyrus	−60	−22	31	4.12	**<0.001**
Transverse temporal gyrus	63	−16	13	4.18	**<0.001**
Middle temporal gyrus	60	−16	−5	3.51	**0.001**
Precentral gyrus	27	−13	67	3.25	**0.001**

Negative correlation of Mobility Inventory values with activations in patients before treatment

Activations in patients before treatment

VOI	*x*	*y*	*z*	*t*	*p**
Amygdala (l)					ns
Amygdala (r)	18	−1	−17	1.73	0.384
Insula (l)					ns
Insula (r)					ns
Ventral striatum (l)					ns
Ventral striatum (r)					ns

VOI	*x*	*y*	*z*	*t*	*p***
ns					

Positive correlation of Mobility Inventory values with activations in patients before treatment

Activations in patients before treatment

VOI	*x*	*y*	*z*	*t*	*p**
Amygdala (l)					ns
Amygdala (r)					ns
Insula (l)	−33	11	13	1.94	0.776
Insula (r)					ns
Ventral striatum (l)					ns
Ventral striatum (r)					ns

VOI	*x*	*y*	*z*	*t*	*p***
ns					

Negative correlation of Mobility Inventory values with activations in patients before treatment

Activations in patients before treatment

VOI	*x*	*y*	*z*	*t*	*p**
Amygdala (l)					ns
Amygdala (r)	24	−7	−17	2.38	0.143
Insula (l)					ns
Insula (r)					ns
Ventral striatum (l)					ns
Ventral striatum (r)					ns

VOI	*x*	*y*	*z*	*t*	*p***
Superior frontal gyrus	−18	32	46	3.44	**0.001**

Positive correlation: the lower the clinical value after treatment, the higher the neurofunctional activation before treatment. Negative correlation: the higher the clinical value after treatment, the higher the neurofunctional activation before treatment. Bold type denotes significance. * $p \leq 0.05$ (small volume corrected), ** $p \leq 0.01$ (uncorrected, cluster size >10). CBT, cognitive behavioral therapy; HAM-A, Hamilton Rating Scale for Anxiety; VOI, volume of interest; *x*, *y*, *z*, MNI coordinates; (l), left hemisphere; (r), right hemisphere; ns, not significant ($p > 0.1$); T1, before CBT/waiting time; T2, after CBT/waiting time.

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VOI values) (Fig. 2). This was due to decreased activation in the patient group from pre- to posttreatment ($t = 4.11$; $MNI_{x,y,z}$: 27, 2, –26; $p = 0.002$), while the controls did not show any changes between the scans ($p > 0.7$). Before treatment, the patients showed a trendwise increased activation in the right amygdala compared to the controls ($t = 2.66$; $MNI_{x,y,z}$: 24, 2, –23; $p = 0.074$). After treatment, the patients' activation in the right amygdala did not differ from that of the controls ($p > 0.7$). No other region showed a significant group by time interaction (Table 3). Differences in mean parameter estimates from the amygdala between pre- and posttreatment scans did not correlate with the improvement measured with the Mobility Inventory.

Prediction of Outcome

For the anticipation phase, we found positive correlations between the difference in HAM-A scores and neural activation in the left insula ($t = 3.94$; $MNI_{x,y,z}$: –36, –16, 19; $p = 0.028$) and the left ventral striatum ($t = 2.79$; $MNI_{x,y,z}$: –18, 5, –5; $p = 0.039$) (Table 4), which is to say that patients with a stronger reduction in HAM-A scores (from pre- to posttreatment) had higher neurofunctional activations before treatment in these regions.

Response Prediction

For the anticipation phase, we also found that responders to CBT (patients with at least a reduction of 50% in HAM-A score or an Mobility Inventory score <1.5) had a trendwise stronger activation in the left ventral striatum ($t = 2.48$; $MNI_{x,y,z}$: –18, 5, –5; $p = 0.072$), i.e., patients who responded to treatment had a higher neurofunctional activation before treatment in the left ventral striatum.

No effects were found for the observation phase or using the Mobility Inventory as an outcome or response criterion.

Discussion

This is the first study to report neural effects of standardized CBT on anticipation and observation of agoraphobia-specific stimuli in patients suffering from panic disorder with agoraphobia. The main findings are a decrease in activation from pre- to posttreatment in the right ventral striatum of patients during anticipation and in the right amygdala during observation of agoraphobia-specific stimuli, whereas a waitlist group did not show changes over time.

The ventral striatum is involved in salience evaluation and action planning when confronted with relevant and potentially threatening stimuli, and is also associated with avoidance learning [36, 52, 53]. Previous studies have shown decreased activation to aversive stimuli after treatment with selective serotonin reuptake inhibitors [54, 55] and increased activation after tryptophan depletion [56]. Complementing these preliminary pharmacotherapy-related results, we found a normalization of ventral striatal hyperactivation after CBT, which points towards a normalized processing of disorder-specific stimuli after successful CBT. The activational decrease in the ventral striatum indicates that CBT leads to a reduction in the pathologically heightened anticipation of potentially threatening situations, which may in turn prevent a flight reaction. Indeed, this notion is supported by the significant correlation between reduced ventral striatal activation and the decrease in clinical symptoms (Mobility Inventory score before treatment vs. Mobility Inventory score after treatment).

The amygdala, conceptualized as the switching point in the neural network relevant to fear processing, modulates physiological responses to threat [57, 58] and is more likely involved in the observation and evaluation than the anticipation of anxiety-related events [8, 34, 59]. The significant decrease in activation from pre- to posttreatment in the right amygdala of patients (compared to healthy controls) during observation of agoraphobia-specific stimuli supports this notion. Our finding indicates that amygdala activation is sensitive to cognitive-behavioral interventions as shown for social phobia and specific phobia [27, 28, 60], an effect also found for pharmacological interventions in social phobia and depression [28, 61, 62]. Following Etkin and Wager [59], our finding of increased amygdala activation in patients with panic disorder and agoraphobia suggests a neurofunctional overlap with social phobia and specific phobia and altered fear-regulatory processes. Arguably, the latter are most important in panic disorder with agoraphobia when considering the increased evaluation of the environment regarding potentially agoraphobic situations. Our finding of a marginally significantly heightened activation of the amygdala in patients with panic disorder and agoraphobia in response to agoraphobia-specific pictures before CBT may be a correlate of this pathological process. Furthermore, heightened amygdala activation might be a common factor for stimulus processing in patients suffering from phobias, indicating common alterations at a basic and implicit processing level. The reduced activation could indicate changes in anxiety-specific experience and behavior due to treatment.

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In contrast to our hypothesis, we could not find consistent differences regarding insula activation when comparing patients and controls over time. Indeed, we found a stronger activation during the anticipation phase in patients before treatment, indicating altered anticipatory and introspective processes. However, the insula does not seem to be as responsive to our therapeutic intervention as the ventral striatum.

In the prediction outcome analysis, activation of the ventral striatum and insula was correlated with a reduction in clinical symptoms (HAM-A). This illustrates the fact that patients with higher activations in these regions benefit more from CBT. Successful CBT reduces avoidance behavior, which contributes to a meaningful benefit to patients' daily lives as measured by the HAM-A. Increased anticipation-related striatal activation might indicate pronounced planning and execution of flight reactions and avoidance behavior, which are approachable by CBT. No prediction effects were observed for amygdala activation, potentially due to the less specific neuronal function of this region. Future studies need to clarify this assumption by directly comparing different treatment strategies.

Taken together, studies on depression and anxiety disorders have reported that the ventral striatum and amygdala are sensitive to treatment. In contrast to former studies on panic disorder and agoraphobia [30–33], in this study we for the first time demonstrated decreased activations after CBT in patients compared to controls in the ventral striatum during anticipation and in the amygdala during observation of agoraphobia-specific stimuli (compared to neutral stimuli). We did not observe any treatment-related increase in prefrontal activations, suggesting that the neurofunctional mechanisms related to the reported subcortical activation reduction did not involve prefrontal downregulations [8]. Another reason might be that our paradigm involves passive viewing and does not include any instructions regarding active suppression or reappraisal of emotions, as reported for paradigms showing such prefrontal activations [27].

The self-report data support the validity of the stimulus material. Agoraphobia-specific pictures were rated to be more anxiety inducing than neutral pictures, and the ratings were correlated with the magnitude of clinical impairment, assessed by HAM-A and Mobility Inventory scores and their reduction after CBT.

This study has several limitations. The agoraphobia-specific and neutral pictures were not specifically tailored to each individual, and thus the anxiety-inducing effect may have varied interindividually. This concern is mitigated by the individual picture ratings, which clearly indicated that agoraphobia-specific pictures were rated to be more anxiety inducing than neutral pictures by the patients but not the controls. We did not include any group of patients with other mental disorders, for example, specific phobias [59], social phobia [63], or panic disorder without agoraphobia, which may be a target for future investigations. Analyzing changes in neuronal activation patterns needs a standardized treatment strategy. However, the multifactorial mechanisms of treatment and different combined treatment strategies – as may usually be found in representative and realistic clinical practice – should be targeted by future investigations [64]. In line with the sample characteristics, our healthy participants never fulfilled the criteria for any mental disorder, thereby probably representing an artificial group. This was necessary to clearly dissociate neural activation patterns of pathological fear processes from those of normal fear processes in this early stage of proving and establishing a disorder-specific paradigm. Although we included data from different sites, we accounted for this possible confounder using a joint multicenter quality control [33], since criteria for data inclusion and differences between study sites were not found. The variance of each site was controlled for in all analyses. Neural activity might be affected by the anxiety-inducing environment of the MRI scanner itself; however, this should be the case during the entire scanning session and ought to primarily affect baseline activation.

To summarize, we found altered neural processing of disorder-specific stimuli during anticipation in the ventral striatum and during observation in the amygdala in response to CBT. As reported previously [25], the anticipatory anxiety before being confronted with an agoraphobic situation is a greater burden to affected persons than being in the situation itself [65]. Such heightened neurofunctional processes during anticipation and observation of agoraphobia-specific stimuli followed by altered action planning and avoidance behavior might be a specific characteristic of panic disorder with agoraphobia. Our findings provide evidence that exposure-based CBT modifies neural processing as a neural correlate of clinical improvement in CBT-treated patients. After cognitive preparation, encouraging patients to try exposure therapy is often challenging, but arguably one of the most efficient active ingredients of CBT [26, 66]. In the future, further specifying the mechanisms of action of CBT and its ability to change neurofunctional brain activity will be essential for better understanding and improving treatment.

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Statement of Ethics

All participants gave written informed consent. The Ethics Committee of the Technische Universität Dresden (EK164082006) approved the clinical trial and the fMRI experiment. All approvals were made according to the Declaration of Helsinki.

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All PI take responsibility for the integrity of the respective study data and their components. All authors and co-authors had full access to all study data. Data analysis and manuscript preparation were completed by the authors and co-authors of this article, who take responsibility for its accuracy and content.

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