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Neural Correlates of Procedural Variants in Cognitive-Behavioral Therapy: A Randomized, Controlled Multicenter fMRI Study

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Key Words

Panic disorder · Agoraphobia · Cognitive-behavioral therapy · Hippocampus · Functional magnetic resonance imaging · Fear conditioning · Functional connectivity

Abstract

Background: Cognitive behavioral therapy (CBT) is an effective treatment for panic disorder with agoraphobia (PD/AG). It is unknown, how variants of CBT differentially modulate brain networks involved in PD/AG. This study was aimed to evaluate the effects of therapist-guided (T+) versus self-guided (T–) exposure on the neural correlates of fear conditioning in PD/AG. ***Method:*** In a randomized, controlled multicenter clinical trial in medication-free patients with PD/AG who were treated with 12 sessions of manualized CBT, functional magnetic resonance imaging (fMRI) was used during fear conditioning before (t1) and after CBT (t2). Quality-controlled fMRI data from 42 patients and 42 healthy subjects (HS) were obtained. Patients were randomized to two variants of CBT (T+, n = 22, and T–, n = 20). ***Results:*** The interaction of diagnosis (PD/AG, HS), treatment group (T+, T–), time point (t1, t2) and stimulus type (conditioned stimulus: yes, no) revealed activation in the left hippocampus and the occipitotemporal cortex. The T+ group demonstrated increased activation of the hippocampus at t2 (t2 > t1), which was positively correlated with treatment outcome, and a decreased connectivity between the left inferior frontal gyrus and the left hippocampus across time (t1 > t2). ***Conclusion:*** After T+ exposure, contingency-encoding processes related to the posterior hippocampus are augmented and more decoupled from processes of the left inferior frontal gyrus, previously shown to be dysfunctionally activated in PD/AG. Linking single procedural variants to neural substrates offers the potential to inform about the optimization of targeted psychotherapeutic interventions.

Introduction

Cognitive-behavioral therapy (CBT) has proven its efficacy for many mental disorders. More recently, neurofunctional brain changes related to psychotherapy, par-

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ticularly CBT, have been investigated [1–5]. However, the precise neural mechanisms of action by which specific psychotherapeutic intervention components lead to change are unknown.

Panic disorder (PD) is characterized by panic attacks, i.e. intermittent and sudden extreme anxiety, vegetative symptoms and concerns about the implications of these attacks [6, 7], and is frequently accompanied by agoraphobia (AG: anticipatory anxiety or avoidance of situations in which escape or help may not be available [6]).

The onset and maintenance of anxiety disorders, particularly PD, have been linked to aberrant learning (conditioning) processes [8–11]. Fear conditioning is a form of associative learning in which contingencies are established by pairing aversive stimuli (unconditioned stimulus, US) with previously neutral stimuli (conditioned stimulus, CS). Interoceptive conditioning, where the accompanying physiological symptoms during a panic attack become CS [12, 13], is linked to interoceptive symptoms in PD whereas exteroceptive conditioning is associated with agoraphobic behavior [8]. It has been assumed that a failure to inhibit the conditioned response could result in pathological overgeneralization of fear [14]. Using exteroceptive conditioning tasks, enhanced simple conditioning [9], deficient safety signal processing [15] or increased resistance to extinction learning, demonstrating more persistent recall of the conditioned response [16], have been suggested to account for learning deficits in PD [17]. However, whether specific forms of CBT are effective in normalizing dysfunctional learning processes is unknown.

There are numerous efficacious variants of CBT for PD with and without AG [18, 19]. Different theoretical frameworks have been used to explain the mechanisms of CBT in general and in PD/AG in particular (e.g. cognitive [20, 21], behavioral [22, 23]). Exposure-based interventions for anxiety are usually superior to cognitive interventions [19], and exposure is considered the crucial element of CBT for anxiety disorders [24, 25]. For PD/AG, 2 forms of exposure are of relevance, interoceptive exposure (exposure to body reactions, e.g. in response to hyperventilation) and exposure in situ (exposure to feared external situations, e.g. bus or shopping mall). In the context of exposure therapy, patients learn to broadly associate potential threatening cues with alternative or safety information [26]. Therapists can directly guide this learning process during exposure, probably leading to an increased awareness of contextual contingencies. This is especially important considering the evidence about dysfunctional safety signal processing in PD [15] or the general responding to safe conditions which is predictive to the development of PD [27]. Thus, therapist-guided exposure, where patients learn to efficiently encode feared external events and extinguish the related (internal) fear responses, should help to improve the differentiation of potential threat and safety cues. In line with the assumption that the therapist can support such relevant learning during exteroceptive exposure, we were able to show that therapist-guided exposure in vivo (T+) had somewhat superior effects compared to exposure alone (T–), especially on measures of avoidance, after treatment and a 6-month follow-up. Note, however, that both treatment arms were highly efficient in reducing symptoms across all outcome measures (d = –0.5 to –2.5) [25]. Thus, the advantage of going with the patient out into the field during exposure might be mediated by different encoding or learning strategies, possibly also leading to a better cognitive awareness of contingencies for external and internal events. The investigation of the neural correlates of learning mechanisms such as exteroceptive fear conditioning in PD/AG can help to understand CBT-related changes on the brain level [1, 28–30].

Brain imaging studies have related fear conditioning in healthy subjects to a neural network including the amygdalae, hippocampi, insulae, anterior cingulate and medial frontal cortices [1, 29, 31–37]. This network has substantial overlap with fear circuitry structures that have been reported to show dysactivation across different anxiety disorders [38, 39]. In accordance with behavioral studies on fear conditioning [15], altered neural processing of safety cues in PD has been suggested. Patients showed, for example, less activation during instructed threat and increased activity during the safe condition in the subgenual cingulate, ventral striatum and extended amygdala, and in the midbrain periaqueductal gray [40]. In line with these results, we found increased midbrain activation during safety signal processing in PD/AG patients [17]. Brain lesion and functional magnetic resonance imaging (fMRI) studies have suggested a double dissociation between the hippocampus and amygdala relative to cognitive and emotional expressions of fear learning, respectively [41, 42]. These cognitive (e.g. contingency awareness or expectancies of aversive events) and emotional (e.g. arousal, bottom-up reactivity) expressions of fear learning, which can be investigated using fear conditioning paradigms [43, 44], might play distinct roles for behavioral adaptation during exposure therapy. Using an fMRI-based fear conditioning paradigm, we showed that differential conditioning is associated with enhanced activation of the bilateral dorsal inferior frontal gyrus

whereas simple conditioning and safety signal processing are related to increased midbrain activation in PD/AG patients versus controls [17]. The results suggest aberrant top-down and bottom-up processes during fear conditioning in PD/AG [17]. Whereas the left inferior frontal gyrus during differential conditioning seemed to be generally involved in the psychopathology and treatment of PD/AG [1], successful treatment was characterized by increased right hippocampal activation when processing stimulus contingencies [30]. However, despite this evidence about treatment effects on fear conditioning, the effects of different single variants of CBT on neural correlates have not yet been investigated.

To date, only global effects of CBT on brain activation have been investigated [1–5, 45, 46]. Across anxiety and mood disorders, CBT-related changes in the hippocampus, amygdala, insula and prefrontal regions have been observed [45–47]. In a recent review, it has been suggested that pharmacotherapy particularly decreases overactivity of limbic structures (bottom-up effect) while psychotherapy tends to increase activity and recruitment of frontal areas (top-down effect [46]). However, most of the published studies were focused on experiments focusing either on resting state or on symptom provocation and not on learning mechanisms such as fear conditioning that were utilized here in both the therapy and the fMRI paradigm. Particularly in PD, two resting positron emission tomography studies demonstrated change in glucose utilization in distributed regions of predominantly the medial and lateral frontal and temporal cortices in CBT groups of 6 [2] and 11 patients [3]. Besides our own [1, 30], the only other fMRI study [48] used an emotional linguistic go/nogo design in 9 patients with PD following short-term psychodynamic inpatient treatment (4 weeks), after treatment symptoms had improved, and frontolimbic activation patterns had been normalized. Despite the small sample sizes and only partially overlapping results, these studies indicate that different forms of psychotherapy can influence processes in the brain in patients with PD. However, direct comparisons of distinct treatment variants (as opposed to comparisons between complex treatment packages) have not yet been reported neither for PD nor any other disorder.

Here we investigated the differential effects of T+ versus T– exteroceptive exposure in patients with PD/AG on the neural correlates of fear conditioning. We hypothesized that T+ versus T– exposure during CBT modifies the encoding behavior of potentially aversive events (CS+/CS–) in the acquisition phase of a conditioning experiment. Therefore we expected a differential involvement of brain regions related to contextual encoding and cognitive awareness of contingencies during fear conditioning, specifically the hippocampus [41, 42, 49], in patients using T+ versus T– exposure.

Methods

Design

The present study was part of the national research network PANIC-NET (Mechanisms of Action in CBT, MAC) [25, 50, 51] encompassing a randomized controlled clinical trial of CBT for PD/AG. Eight German centers participated in the clinical trial (Aachen, Berlin-Adlershof, Berlin-Charité, Bremen, Dresden, Greifswald, Münster, Würzburg) treating 369 patients who met DSM-IV criteria for PD/AG. Four of these centers (Aachen, Berlin-Charité, Dresden, Münster) participated in the fMRI study reported here.

Participants

In the context of the clinical multicenter study [25, 50] quality-controlled fMRI data were collected from 42 unmedicated patients diagnosed with PD/AG before and after 2 variants of CBT (see below) as well as 42 age-, gender- and handedness-matched [52] healthy control subjects (HS) 8 weeks apart (table 1) [1]. For inclusion and exclusion criteria and additional information, please see the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000359955) and Gloster et al. [50].

Randomization

The randomization list was generated at the clinical coordination center (Dresden) by personnel not associated with patient care using the randomization software RandList (http://randomisation.eu/index.shtml). The fMRI study centers were blind to the assignment of subsequent cases and were informed by the clinical coordination center after the posttreatment measurement.

Treatment Conditions

The 42 patients of the fMRI sample were randomized to 2 manual-based variants of CBT (for a patient flow chart, see online suppl. fig. 1). Both treatment groups participated in a 12-session manualized treatment protocol, implemented over 8 weeks and followed by 2 booster sessions. The treatment protocols differed in 5 of the 12 sessions, specifically in the format of implementation of in situ exposure sessions. Patients in the T+ exposure group (n = 22) completed all 5 exposures with the therapist, whereas patients in the self-guided exposure group (T–; n = 20) were instructed to complete the exposure part of the 5 treatment sessions alone. Between sessions, all patients were additionally expected to perform 2 exposure tasks between treatment sessions as a homework assignment (compare Gloster et al. [25] and Cammin-Nowak et al. [53]).

Except for the implementation of exposure in situ, the CBT variants were identical in content, structure and number of exposure sessions. Patients and therapists were blinded to the fMRI hypotheses. Neither patients nor therapists were blinded to group assignment, since blinding of condition is difficult if not impossible in a psychological intervention of this sort [25]. HS were

Table 1. Demographic, neuropsychological and clinical characteristics

	Patients with PD/AG		HS		Group differences	
	T+ (n = 22)	T– (n = 20)	T+ (n = 22)	T– (n = 20)	F/χ^2	p
Demographic characteristics						
Age, years	37.24±9.96	33.41±10.27	36.25±10.85	32.23±8.41	1.176	0.324
Females	14.00 (64%)	15.00 (75%)	14.00 (64%)	15.00 (75%)	1.266	0.737
Education	11/11	10/10	15/7	17/3	7.459	0.059
Center	8/10/4	5/8/6/1	6/10/6	5/8/6/1	3.775	0.926[a]
Neuropsychological characteristics						
Digit span total	15.36±3.24	14.70±3.36	15.36±3.00	15.85±3.45	0.420	0.739
Digit span forward	8.00±2.12	7.60±1.85	8.59±1.84	8.45±1.88	1.131	0.342
Digit span backward	7.41±1.92	7.10±2.02	6.77±1.77	7.15±2.23	0.381	0.767
Trail Making Test A, s	25.72±8.42	25.47±8.55	27.68±9.34	22.80±6.33	1.224	0.306
Trail Making Test B, s	54.44±14.39	56.45±18.19	57.59±19.55	46.95±12.47	1.729	0.168
Clinical characteristics at baseline (t1)						
Clinical Global Impression Scale	5.50±0.51	5.20±0.70			2.566	0.117
Hamilton Anxiety Scale	24.50±5.76	24.25±5.13			0.022	0.883
Panic and Agoraphobia Scale	26.49±8.64	25.40±8.94			0.161	0.690
Number of panic attacks	1.74±0.85	1.58±0.81			0.385	0.538
Mobility Inventory (7-day vers.) acc.	1.90±0.97	1.83±0.89			0.061	0.807
Mobility Inventory (7-day vers.) alone	2.40±1.12	2.37±0.99			0.008	0.931
Anxiety Sensitivity Index	33.6±8.75	31.90±10.17	8.91±8.17	7.89±5.86	5.311	<0.001*
Beck Depression Inventory II	18.18±1.39	16.25±8.04	1.45±2.04	1.26±1.85	38.189	<0.001*
Clinical characteristics after treatment (t2)						
Clinical Global Impression Scale	3.64±1.14	3.45±0.94			0.330	0.569
Hamilton Anxiety Scale	13.50±7.60	11.10±5.99			1.275	0.266
Panic and Agoraphobia Scale	15.46±10.14	12.30±6.29			1.444	0.237
Number of panic attacks	1.08±1.02	0.72±0.83			1.547	0.221
Mobility Inventory (7-day vers.) acc.	1.23±0.42	1.43±0.62			1.442	0.237
Mobility Inventory (7-day vers.) alone	1.63±0.77	1.69±0.78			0.053	0.820
Anxiety Sensitivity Index	14.73±7.62	16.30±9.71	7.41±6.83	8.35±4.74	6.515	0.001*
Beck Depression Inventory II	9.68±9.08	8.35±5.97	0.24±0.66	1.29±2.34	12.635	<0.001*

Means and standard deviations, except for gender where numbers in parentheses refer to percentages. HS T+ and HS T– refer to the two control groups matched to the T+ and T– patient groups according to age and gender. χ^2, F and p values refer to group comparisons of the respective variables. For the Beck Depression Inventory II and Anxiety Sensitivity Index, significant group differences are based on differences between PD/AG and HS. Asterisks indicate that scores did not differ between patient groups (for all $p > 0.6$) or HS groups (for all $p > 0.3$). Both patient groups demonstrated significant symptom reductions in all clinical measurements (for all $p < 0.01$) and no significant differences in symptom reduction (interaction of time × treatment group; for all $p > 0.18$). The patients who participated in the fMRI experiment did not differ in any of the sociodemographic or clinical variables from the clinical sample [1, 25]. Education: 12–13 years (left)/below 11 years (right); center: number of measurements in center 1/2/3/4 per group. [a] Exclusion of center 4 led to comparable statistics ($\chi^2 = 1.508/p = 0.959$).

matched according to age, gender, handedness and study center to the corresponding patients and were also measured twice, but received no CBT (HS T+: n = 22; HS T–: n = 20; table 1).

Treatment Intervention

Sessions 1–3 consisted of psychoeducation and an individualized behavioral analysis of the patient's symptoms and coping behaviors. Sessions 4 and 5 provided the treatment rationale for exposure and implemented interoceptive exposure exercises in the therapy room identically for both groups. Sessions 6–8 consisted of standardized in situ exposure exercises (i.e. bus, shopping mall and forest), which were implemented after the patient had agreed to enter the situation without engaging in safety behaviors and waiting for the anxiety to take its natural course. Exposures were thoroughly planned during full sessions (included mental rehearsal, anticipation of problems and instructions not to use safety behaviors) and were either later accompanied by the therapist (T+) or performed in a self-guided manner (T–). In the T+ in situ exposure, therapists provided feedback, modeled correct implementation, monitored anxiety levels and corrected any use of safety be-

haviors. Session 9 reviewed progress to date and addressed anticipatory anxiety. Sessions 10 and 11 again consisted of in situ exposures but now targeted the patients' two most significant feared situations. Session 12 repeated crucial elements of the manual and instructed patients to continue exposing themselves to feared situations. For more detailed information of the clinical and treatment aspects of the study, please see Gloster et al. [25, 50].

Functional Magnetic Resonance Imaging

The Conditioning Paradigm

Parallel versions of a previously validated differential conditioning paradigm were applied during fMRI data acquisition (details in Kircher et al. [1] and Reinhardt et al. [36]) before and after CBT. The time course of the fMRI paradigm consisted of 3 phases: familiarization, acquisition and extinction [36], each subdivided into an early and a late phase [1]. Different neutral stimuli (yellow/blue spheres and violet/green squares) were used in parallel versions to account for repeated exposure to the experiment in the pre-post design (t1, t2). Each sphere/square was visually presented for 2,000 ms with a variable intertrial interval of 4,785–7,250 s. An unpleasant white noise was used as the US and presented for 100 ms. The volume of the US was individually adapted (between 70 and 110 dB) to be unpleasant for the participant (those scoring <5 in an aversiveness rating on a scale from 1 to 10 before fMRI were excluded from analysis). During the acquisition phase, 1 sphere/square was paired pseudorandomly with the US (thus becoming CS+), while the other sphere was not (thus becoming CS–). We used a partial reinforcement strategy in which 50% of the CS+ were paired with the US and 50% were not. Only trials without the US were analyzed during acquisition to avoid overlap with neuronal activation directly related to the presentation of the US. The presentation of the US occurred 1,900 ms after the onset of the CS+; in consequence, both stimuli were coterminated. Based on previous results with the entire sample that demonstrated effects particularly in the early acquisition [1], we focused the fMRI analysis (see below) specifically on the early acquisition phase and compared the difference between CS+ and CS– across t1 and t2 to examine the therapy-related changes of the conditioning processes [1]. In this phase of the experiment exposure to potentially threatening events (CS+/CS–) and initial fear learning takes place. Therefore, the early acquisition phase is potentially most sensitive to the expected treatment-related changes.

fMRI Data Acquisition and Preprocessing

fMRI brain images were acquired using 3-tesla Philips Achieva scanners (Philips Medical Systems, Best, the Netherlands) in Münster and Aachen, a 3-tesla Siemens Trio scanner (Siemens AG, Erlangen, Germany) in Dresden, and a 3-tesla General Electric Healthcare scanner (General Electric Healthcare, Milwaukee, Wisc., USA) in Berlin. A total of 505 transaxial functional images (echo planar imaging, 64 × 64, 30 slices interleaved, field of view = 230, voxel size = 3.6 × 3.6 × 3.8 mm, echo time = 30 ms, repetition time = 2 s) that covered the whole brain and were positioned parallel to the intercommissural line were recorded.

MR images were analyzed using Statistical Parametric Mapping (SPM5; www.fil.ion.ucl.ac.uk) implemented in MATLAB 7.1 (Mathworks Inc., Sherborn, Mass., USA). The first 5 volumes of every functional run were discarded to minimize t1 saturation effects. For data preprocessing, standard slice-timing (middle slice), realignment and normalized ($2 \times 2 \times 2$ mm^3) functions of SPM5 were applied. To account for differences in intrinsic smoothness between scanners, an iterative smoothness equalization [54] procedure was performed for all data sets (12-mm full width at half maximum gaussian isotropic kernel). Thus, data from all centers have been iteratively smoothed until a smoothness of 12-mm full width at half maximum was reached, independently of scanner-specific intrinsic smoothness of the data. Finally, the data quality [55, 56] of the acquired data was carefully checked to avoid systematic differences between the patient and control groups [1].

Single-Subject fMRI Analyses

At the single-subject level, the realignment parameters of each participant were included as regressors into the model to account for the movement artifacts of the participants. The BOLD response for each event type ($CS+_{paired}$, $CS+_{unpaired}$, CS–, US) and each phase was modeled by the canonical hemodynamic response function employed by SPM5 within the framework of the general linear model to analyze brain activation differences related to the onset of the different stimuli. Each phase was separated into an early and a late part [1] to account for temporal aspects and habituation [57], resulting in 16 regressors [familiarization: early CS+, late CS+, early CS–, late CS–, US; acquisition: early CS–, late CS–, CS presented with the US ($CS+_{paired}$), US, early CS+ without US ($CS+_{unpaired}$), late $CS+_{unpaired}$; extinction: early CS–, late CS–, early CS+, late CS+; behavioral assessment]. A high-pass filter (128-second cutoff period) was applied to remove low-frequency fluctuations in the BOLD signal. Parameter estimates (β–) and t statistic images were calculated for each participant.

Group Analyses

Group analyses were performed by entering contrast images for $CS+_{unpaired}$ and CS– of the acquisition phase into flexible factorial analyses as implemented in SPM5, in which subjects are treated as random variables. fMRI centers were introduced as covariates in order to account for scanner differences. Further covariates of no interest included were age and kind of experimental set (circles vs. squares) to account for variance related to the use of parallel versions of the experiment. In line with our previous analysis, we focused specifically on the early acquisition phase of the experiment [1].

Connectivity Analyses

Connectivity analyses were used to test whether previously reported general differences between PD/AG and HS in inferior frontal gyrus activation [1] are related to brain regions demonstrating differences between treatment groups (T+/T–). For the connectivity analyses, eigenvariates adjusted for the effect of movement parameters were extracted from the inferior frontal gyrus cluster previously reported by Kircher et al. [1] on a single-subject level across the whole experiment (500 scans). The individual eigenvectors were used as regressors in new single-subject analyses that additionally included the 6 movement regressors. We obtained individual activation maps reflecting the correlation of each voxel time course with the time course of the left inferior frontal gyrus as outcomes for each time point and group. These images were used in the group analyses focusing on the main effects and interactions of treatment group (T+, T–) and time (t1, t2). An inclusive masking procedure has been used to restrict results to regions demonstrating differential effects of T+ and T– in the early acquisition phases.

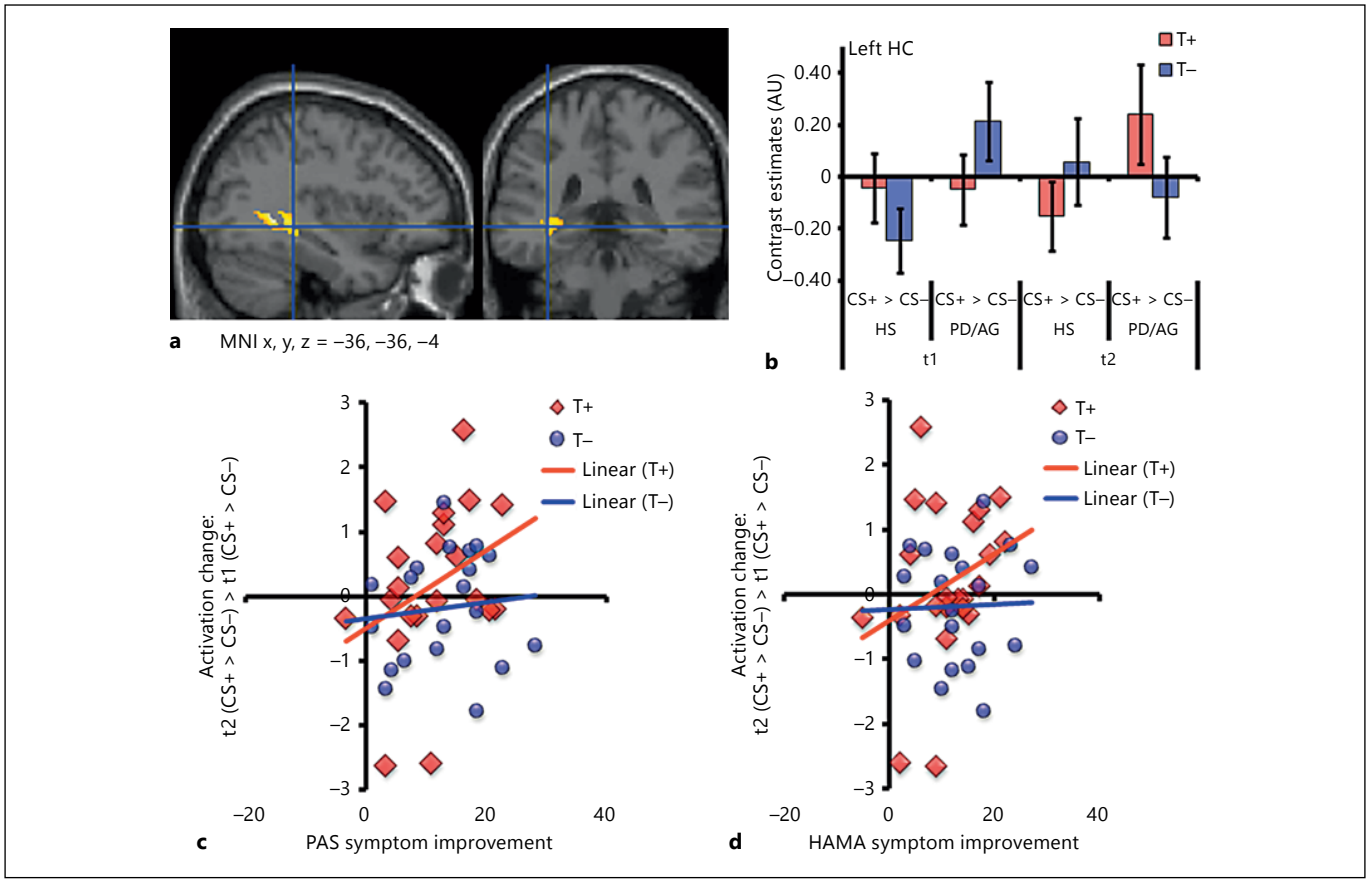

Fig. 1. Interaction of diagnosis (PD/AG, HS), treatment (T+/T–), time point (t1/t2) and stimulus condition (CS+/CS–). **a** Brain activation for the interaction of diagnosis (PD/AG, HS), treatment (T+/T–), time point (t1/t2) and stimulus ($CS+_{unpaired}$/CS–) in the early acquisition phase [1] illustrated on sagittal and coronal slices of the MNI template. **b** Bar graphs show ROI activation for the hippocampus [61] as defined by the anatomy toolbox of SPM [60]; left hippocampus, HC, peak coordinates MNI x, y, z = –36, –36, –4; probability of cornu ammonis: 50% (10–80%), volume: 312 mm^3, 75% of the cluster in cornu ammonis, 13.5% in fascia dentata; F = 12.15 at maxima. **c**, **d** Correlation of activation change with clinical improvement separate for patients of the T+ (red) and T– (blue) exposure group (colors visible in the online version only). For correlation analyses, activation has been extracted from the hippocampal ROI defined above. The y-axis represents the activation change over time (t2 > t1) of the conditioned response (CS+ > CS–). The x-axis represents symptom improvement over time (t1 > t2). The correlations in the T+ group indicate a positive relationship of a higher conditioned response in the hippocampus and clinical improvement measured using the Panic and Agoraphobia Scale (PAS; **c**) and the Hamilton Anxiety Scale (HAMA; **d**).

A Monte Carlo simulation of the brain volume was conducted for the current study to establish an appropriate voxel contiguity threshold [58]. Assuming an individual voxel type I error of $p < 0.005$, a cluster extent of 142 contiguous resampled voxels was indicated as sufficient to correct for multiple voxel comparisons at $p < 0.05$. Thus, voxels with a significance level of $p < 0.005$ uncorrected belonging to clusters with at least 142 voxels were reported for all analyses. The same threshold has been used in previous analyses of the data [1, 17, 30, 59].

Anatomical regions were defined by the anatomy toolbox of SPM [60]. For the creation of bar graphs (fig. 1, 2) and the illustration and calculation of the correlation analyses (fig. 1), we extracted the eigenvariates from a region of interest (ROI) including all subregions of the hippocampus [61].

Contrast of Interest. To test for differential effects of T+ and T– on the conditioned response during the early acquisition phase, we performed an analysis of the 4-way interaction (F contrast) of diagnostic group (PD/AG, HS), treatment group (T+, T–), time point (t1, t2) and stimulus (CS+, CS–). This analysis tests for specific activation change (t1 vs. t2) for therapist-guided exposure (T+ vs. T–) in the patient group (PD/AG vs. HS) with regard to the conditioned response (CS+ vs. CS–). To ensure that results are based on activation change in patients and not on activation change in the HS groups, we exclusively masked the 4-way interaction by a 3-way interaction analysis testing for activation changes in the HS groups [t1 ([HS T+ (CS+ > CS–) vs. HS T– (CS+ > CS–)] vs. t2 ([HS T+ (CS+ > CS–) vs. HS T– (CS+ > CS–)])] on a very liberal threshold ($p > 0.5$). Thus, brain regions showing differenc-

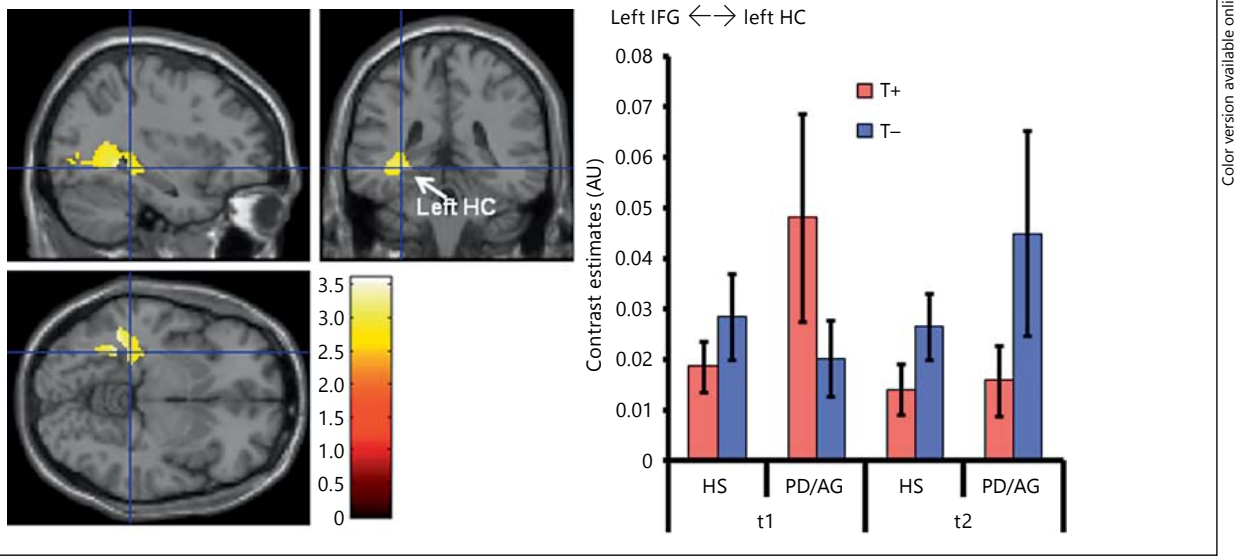

Fig. 2. Connectivity of the left inferior frontal gyrus (IFG) to regions showing treatment-related effects: interaction of treatment (T+/T–) and time point (t1/t2) in PD/AG. HC = Hippocampus. Connectivity was analyzed across the whole time course of the conditioning paradigm. The activation cluster of the left inferior frontal gyrus [1] (online suppl. fig. 3) served as the seed region. An inclusive masking procedure has been used to restrict results to regions demonstrating differential effects of T+ and T– in the early acquisition phases (fig. 1a). We found a significant interaction effect for 'treatment' (T+/T–) and 'time point' (t1/t2) in patients, indicating a reduction in functional connectivity (t1 > t2) between the left occipitotemporal activation cluster and the left inferior frontal gyrus in patients of the T+ group and an increase in the T– group [t2(T– > T+) > t1(T– > T+)]. The bar graph illustrates the contrast estimates for the connectivity with the left inferior frontal gyrus. The hippocampal aspect of the cluster (left bar graph) was defined using the anatomy toolbox of SPM [60] and a ROI including all subregions of the hippocampus [61]; left hippocampus, peak coordinates MNI x, y, z: –34, –40, –2, probability of cornu ammonis: 70% (30–90%); volume = 120 mm^3; 87.5% of the cluster in cornu ammonis; F = 10.12 at maxima. Connectivity and contrast estimates for these brain regions had also been calculated for HS to illustrate the stability in the HS group.

es between the control groups (HS T+ and HS T–) on a very liberal threshold were excluded from the analysis. Consequently, all remaining results are based on differences between patient groups and not on random differences between the control groups.

Results

Clinical Outcome

Results of the clinical trial in the large patient sample (n = 301), which demonstrated the efficiency of the CBT treatment and a small but superior effect of T+ in contrast to T–, are reported elsewhere in detail [25]. In the smaller subgroup of patients participating in our fMRI study (n = 42), we also obtained a significant reduction of symptoms after therapy for both treatment groups (table 1) which supports the efficiency of the CBT treatment in this study. In the fMRI sample (n = 42) there was no significant difference in symptom severity between treatment groups (T+, T–) neither at t1 nor at t2 (table 1). Consequently groups did not differ in responder rates or symptom reduction as indicated by absence of significant interaction effects (for all measures $p > 0.18$).

For valence and arousal ratings of the CS+ and CS– acquired in the conditioning paradigm, see online supplementary information and online supplementary figure 2.

fMRI Results

We found a significant interaction of clinical group (PD/AG, HS), treatment condition (T+, T–), time point (t1, t2) and stimulus type (CS+, CS–) in a left hemispheric cluster including occipital, temporal and hippocampal structures (peak coordinates MNI x, y, z: –32, –52, 6; F = 14.84, $p < 0.005$ uncorr., 443 voxels, $p < 0.05$ corr.; fig. 1a). Activation change within the hippocampus of this cluster [peak coordinates MNI x, y, z: –36, –36, –4; F = 12.15 at maxima; probability of cornu ammonis: 50% (10–80%); volume: 312 mm^3, 75% of the cluster in cornu ammonis, 13.5% in fascia dentata] correlated positively with clinical improvement as measured by the Panic and Agoraphobia

Scale (PAS) total score and Hamilton Anxiety Scale (HAMA) total score in the T+ group (HAMA: $r = 0.370$, $p < 0.05$; PAS: $r = 0.412$, $p < 0.05$), but not in the T– group (HAMA: $r = 0.007$, $p > 0.20$; PAS: $r = 0.267$, $p > 0.13$; all one-tailed; fig. 1c, d).

Further there was a significant interaction of clinical group (PD/AG > HS), time (t1 > t2) and stimulus (CS+ > CS–; see online suppl. fig. 3) in the left inferior frontal gyrus (as previously reported [1]) but no significant differences between treatment conditions (T+, T–) within this region ($p > 0.20$; see online suppl. fig. 3).

Connectivity Analyses

A functional connectivity analysis between the left inferior frontal gyrus cluster [1] as seed region (see online suppl. fig. 3 and Kircher et al. [1]; MNI x, y, z: –50, 10, 14; volume = 1,776 mm^3), the bilateral hippocampal and left occipitotemporal clusters (differential effects of treatment T+ vs. T– in patients; fig. 1a) was performed. In patients we obtained a significant interaction of time point and treatment condition (T+, T–) for the connectivity of the left inferior frontal gyrus and the left hemispheric cluster including occipital, temporal and hippocampal structures (fig. 2). Contrast estimates for the hippocampal subcluster (identified using ROI analyses [61]) indicated a reduction of connectivity between inferior frontal gyrus and the left hippocampus in T+ patients and an increase of connectivity in the T– group (fig. 2). In contrast to the patient groups, HS showed no significant change in connectivity with respect to time point (t1, t2) and group (HS T+, HS T–) as illustrated by bar graphs in figure 2.

Discussion

Psychotherapy integrates many diverse elements. Here, we demonstrate the effect of a single therapeutic component, i.e. T+ versus T– exposure in situ within a highly structured and controlled CBT intervention [25], on the neural correlates of fear conditioning in patients with PD/AG. As a main result, T+ versus T– in situ exposure led to differential changes of activation in the left hippocampus during fear conditioning. Patients with T+ exposure demonstrated increased involvement of the hippocampus after CBT and a decoupling of this structure from the left inferior frontal gyrus which had been shown to be overactivated in PD/AG in contrast to HS before treatment [1, 17]. The results suggest that experiences during T+ exposure treatment in situ can influence hippocampus-related learning processes and decouple it from top-down effects of the left inferior frontal gyrus.

In line with our findings, the hippocampus has been found to be relevant also for other anxiety disorders [62, 63], conditioning paradigms [35, 49, 64–69] and seems to be sensitive to exposure [70], CBT treatment [30, 71, 72], therapy response [30] or recovery in general [73]. Furthermore, the hippocampus has been discussed with regard to the potential contribution to acquisition of irregularities in PD [15] and the optimization of exposure therapy and related learning processes [26].

Clinically, both patient groups demonstrated a significant symptom reduction which did not differ between treatment conditions (T+/T–) in our MRI subsample. In the larger patient groups of the clinical trial reported previously [25], it has been shown that the T+ group (n = 163) had a slightly but significantly better clinical outcome than T– (n = 138), especially in measures of avoidance (e.g. Mobility Inventory). This finding suggests treatment-related differences in individual outcome and exposure learning. Assuming that exposure learning is most efficient when contingencies between context and the individual experiences are consciously learned (declaratively learned in terms of Bechara et al. [41]), we hypothesized that the therapist during exposure [25] will mediate patient encoding or learning strategies reflected in group differences in hippocampal activation. In line with this assumption we revealed significant differences in CBT-group-related changes in neural processing within the left posterior hippocampus and the occipitotemporal cortex. Extensive evidence from animal studies demonstrated a role of the hippocampal formation in fear conditioning [74] and specifically contextual fear learning [75–77]. In humans, fMRI and positron emission tomography studies reported hippocampal activations during the acquisition of fear [34, 66, 68, 78]. Furthermore a double dissociation between the hippocampus and amygdala activation relative to declarative and emotional expressions of fear learning has been suggested [41, 42]. Thus, activation of the posterior hippocampus in our study is in line with this evidence and may suggest differential fear learning in the sense of declarative encoding of contingencies in the T+ in contrast to the T– group after CBT. Furthermore, we found a correlation between increase in hippocampal activation and symptom improvement in the T+ group. The explicit/aware encoding of contingency-related hippocampal activation might be the reason for the slight superior clinical effect of T+ versus T– in avoidance behaviors [25]. Our fMRI sample was not sufficiently powered to detect these clinical differences

but here we could demonstrate the physiological process underlying this one specific treatment intervention.

What might be the possible differences between T+ and T– exposures during CBT which have influenced the neural processes during fear acquisition? In general, exposure is not easy for patients to perform, especially on their own. For example, avoidance behavior can interfere with necessary learning processes [79]. Similarly, it has been shown that avoidance, anxiety sensitivity and psychological flexibility are most critical during the exposure in situ phase for subsequent change in panic symptoms [80]. We suppose that the advantage of having a therapist present during in situ exposure is that the therapist ensures that the patient (a) encounters and appropriately manages the anxiety and distress during the exposure, (b) does not use safety behaviors and (c) increases the patient's overall engagement with exposure [25]. Thus, therapists' active guidance (T+) provides greater scaffolding to adequately expose [25, 26] subjects to potentially aversive situations (e.g. CS+), than simply preparing the patient for the between-session exposure exercises (T–). Consequently patients who received T+ treatment probably learned more thoroughly not to avoid potentially aversive events (adequate exposure), leading to a better contextual encoding and contingency processing. This is reflected in an increase (t2 > t1) in the conditioning response (CS+ > CS–) in the posterior hippocampus – which is positively correlated with symptom improvement. The therapist by himself might represent an important contextual factor during in vivo exposure that activates hippocampal functioning in a form of contextual conditioning. Alternatively the therapist during exposure might lead to an experience of an 'enriched environment' (due to his presence alone, but also by enforcing broad encoding behavior) for the patient. Thus, hippocampal plasticity in our study could also be a result of such an effect, parallel to hippocampal plasticity induced by enriched environments shown in animals [81–85].

A functional connectivity analysis revealed an increased connection of the inferior frontal gyrus (where we found no differences in activation change between T+ and T–; see online suppl. fig. 3) with regions of the 'fear network' in PD/AG [1], potentially indicating aversive top-down effects. By using the same seed region and analyses [1], we showed that T+ versus T– exposure led to different changes of left inferior frontal gyrus to left posterior hippocampus connectivity, indicating a stronger decoupling of inferior frontal gyrus-hippocampus activation in the T+ in contrast to the T– group. Thus, after treatment with T+ exposure in situ, neural encoding processes of the posterior hippocampus are probably less influenced (than after T– treatment) by potentially negative top-down effects of the left inferior frontal gyrus.

A limitation of this study refers to the sample size in the fMRI subgroups. However, the numbers are more than adequate for an fMRI study [86], and correlations of fMRI data with clinical improvement support the clinical relevance and internal validity of the finding. Further research along this line is necessary to support our findings, to further specify the role of the therapist and other therapy components (e.g. interoceptive exposure) and finally to translate the findings to clinical practice in new optimized treatment programs. To reach this goal it will be important to consider the patient's treatment history, too, since previous treatment attempts and experiences are relevant for the selection of the most efficient treatment for a specific patient [87].

With this study, we demonstrated the association of T+ exposure with the neural correlates of fear conditioning in patients with PD/AG. Despite comparable clinical outcomes, the differential effects of the treatment on the neural correlates of fear conditioning suggest different mechanisms related to symptom improvements in the T+ and T– groups. Contextual memory and declarative contingency encoding processes related to the posterior hippocampus seem to be increased and more decoupled from processes of the left inferior frontal gyrus after T+ exposure in situ in contrast to T– exposure in situ. On the basis of these new findings, we are convinced that further research along this line has potential to support the development and further optimization of targeted treatments.

Appendix

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The study was registered with the ISRCTN: ISRCTN80046034. The clinical trial was approved by the Ethics Committee of the Medical Faculty of the Technical University of Dresden (EK 164082006). The neuroimaging components were approved by the Ethics Committee of the Medical Faculty of the Rheinisch-Westfälische Hochschule, University of Aachen (EK 073/07).

Centers

Principal investigators (PI) with respective areas of responsibility in the MAC study are V. Arolt (Münster: overall MAC program coordination), H.U. Wittchen (Dresden: PI for the randomized clinical trial, RCT, and manual development), A. Hamm (Greif-

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Data Access and Responsibility

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.

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