

Effect of Cognitive-Behavioral Therapy on Neural Correlates of Fear Conditioning in Panic Disorder

Tilo Kircher, Volker Arolt, Andreas Jansen, Martin Pyka, Isabelle Reinhardt, Thilo Kellermann, Carsten Konrad, Ulrike Lueken, Andrew T. Gloster, Alexander L. Gerlach, Andreas Ströhle, André Wittmann, Bettina Pfeiderer, Hans-Ulrich Wittchen, and Benjamin Straube

Background: Learning by conditioning is a key ability of animals and humans for acquiring novel behavior necessary for survival in a changing environment. Aberrant conditioning has been considered a crucial factor in the etiology and maintenance of panic disorder with agoraphobia (PD/A). Cognitive-behavioral therapy (CBT) is an effective treatment for PD/A. However, the neural mechanisms underlying the effects of CBT on conditioning processes in PD/A are unknown.

Methods: In a randomized, controlled, multicenter clinical trial in medication-free patients with PD/A who were treated with 12 sessions of manualized CBT, functional magnetic resonance imaging (fMRI) was used during fear conditioning before and after CBT. Quality-controlled fMRI data from 42 patients and 42 healthy subjects were obtained.

Results: After CBT, patients compared to control subjects revealed reduced activation for the conditioned response (CS+ > CS-) in the left inferior frontal gyrus (IFG). This activation reduction was correlated with reduction in agoraphobic symptoms from t1 to t2. Patients compared to control subjects also demonstrated increased connectivity between the IFG and regions of the "fear network" (amygdalae, insulae, anterior cingulate cortex) across time.

Conclusions: This study demonstrates the link between cerebral correlates of cognitive (IFG) and emotional ("fear network") processing during symptom improvement across time in PD/A. Further research along this line has promising potential to support the development and further optimization of targeted treatments.

Key Words: Agoraphobia, CBT, fear conditioning, fMRI, functional connectivity, neural plasticity, panic disorder

Panic disorder is a debilitating anxiety disorder with a lifetime prevalence of approximately 3% to 5%. It is characterized by intermittent and sudden extreme anxiety, vegetative symptoms, and concerns about the implications of the attacks. Agoraphobia, the anticipatory anxiety or avoidance of situations in which escape or help may not be available in case of panic symptoms, is a frequent consequence (1). An interaction of biological vulnerability (2,3), learning history and acute stress underlies the etiology of panic disorder with agoraphobia (PD/A) (4–6). Cognitive-behavioral therapy (CBT) and/or selective serotonin reuptake inhibitors are effective first-line treatments for PD/A (4,7).

The onset and continuation of some anxiety disorders, particularly panic disorder, has been linked to aberrant learning (conditioning) processes (5,8–10). Fear conditioning is a form of associative learning in which contingencies are established by pairing aversive stimuli (unconditioned stimulus [US]) with previously neu-

tral stimuli (conditioned stimulus [CS]). Brain imaging studies have related fear conditioning to a neural network including the amygdalae (11–14), insulae (14), anterior cingulate cortex (ACC) (14), and medial frontal gyrus ("fear network") (13,15). This network has substantial overlap with fear circuitry structures that have been reported to show aberrant activation in different anxiety disorders (16,17). Studies with functional magnetic resonance imaging (fMRI) in patients with panic disorder have implicated the amygdala, anterior insula, ACC, and medial frontal gyrus in the disorder (15), supporting the role of the "fear network" in its pathophysiology (13,15). However, with regard to fear conditioning in PD/A, to our knowledge only one imaging study has been conducted so far. Increased activity with regard to the CS- had been observed in the amygdala, subgenual cingulate, and midbrain structures using an instructed fear paradigm (18).

Whereas the neural correlates of treatment effects on patients with specific phobia (19,20) or obsessive-compulsive disorder (21) have been investigated in a number of studies (see Porto *et al.* [22] and Linden [23] for reviews), the neural mechanisms underlying PD/A and its potential changes through CBT remain largely unknown. To date, only two positron emission tomography (PET) studies have examined the modulation of brain physiology with CBT in PD using a resting state paradigm (24,25). In the first study, the CBT group (6 patients) showed decreases in regions of the right inferior temporal and superior and inferior frontal gyrus (IFG), and increases were detected in the left IFG, middle temporal gyrus, and insula (25). In the other PET study, 11 patients with PD who improved after CBT were investigated (24). Here, glucose utilization increased in the bilateral medial prefrontal cortices and decreased in the right hippocampus, left ACC, left cerebellum, and pons. Thus, these studies provide first support for CBT modulating brain activation in PD, most consistently in frontal brain regions. However, it is unknown how these changes in brain activation during rest are related to processes associated with panic disorder, such as conditioning.

From the Department of Psychiatry and Psychotherapy (TK, AJ, MP, CK, BS), Philipps-University Marburg, Marburg; Department of Psychiatry (VA, CK), University of Münster, Münster; Department of Psychiatry, Psychotherapy, and Psychosomatics (IR, TK), Medical School, Rheinisch-Westfälische Technische Hochschule (RWTH), Aachen; Institute of Clinical Psychology and Psychotherapy (UL, ATG, H-UW), Technische Universität Dresden, Dresden; Department of Psychology (ALG), University of Cologne, Cologne; Department of Psychiatry and Psychotherapy (AS, AW), Campus Charité Mitte, Charité—Universitätsmedizin Berlin, Berlin; and Department of Clinical Radiology (BP), University of Münster, Münster, Germany.

Address correspondence to Tilo Kircher, M.D., Ph.D., Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Rudolf-Bultmann-Straße 8, D-35039 Marburg, Germany; E-mail: psychiat@med.uni-marburg.de.

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Particular regions within the frontal cortex might be relevant for the psychopathology (18,26,27) and its treatment of PD/A (15). Medial and orbitofrontal brain regions are associated with emotion regulation/reduction and provide direct connections to the amygdala. The lateral prefrontal cortex and specifically the left inferior frontal gyrus/sulcus (Brodmann area 44), which is indirectly linked to the amygdala (28,29), is implicated in voluntary increase of emotions and anticipation of panic attacks (30,31). Thus, cognitions are able to increase or decrease emotional responses efficiently (32). Correspondingly, positive, negative, or bidirectional associations between frontal activity and activation of the fear network have been demonstrated (28,33–37). However, it is unknown whether patients with PD/A suffer either from a lack of cognitive control over normal emotional responses or from negative cognitions which trigger or amplify extreme emotional reactions.

In this fMRI study, we investigated the influence of CBT on the neural correlates of fear conditioning in PD/A. We hypothesized that CBT will modify activation during fear acquisition in regions of the prefrontal cortex and the “fear network”. Whereas the applied fear conditioning paradigm should probe automatic fear learning mechanisms predominantly in the “fear network” (amygdalae, hippocampi, anterior insulae, ACC), we expected that CBT will primarily act on negative cognitions triggered by conditioned stimuli in PD/A patients. The neural correlates of negative cognitions (e.g., selective attention to threat) are assumed to be related to the left lateral frontal cortex. Whereas reduction of activation in “fear network” areas as a result of symptom improvement are likely, there were two possible result patterns for regions of the prefrontal lobe: increased prefrontal activation after CBT would indicate compensation or reappraisal processes, whereas decreased activity would rather speak for a reduction of negative cognitions. Consequently two result patterns can be assumed for the connectivity between frontal regions (“cognitive processes”) activated during fear conditioning and the “fear network” (“emotional processes”) in PD/A. A negative connectivity would indicate inhibition or reappraisal processes, whereas a positive correlation would rather suggest that negative cognitions trigger emotional responses.

Methods and Materials

Participants

The present study was part of the national research network PANIC-NET (7,38,39) encompassing a randomized controlled clinical trial on CBT and experimental add-on studies on fear circuit mechanisms in PD/A. 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/A. Four of these centers (Aachen, Berlin-Charité, Dresden, Münster) also participated in the fMRI study reported here.

In the context of the fMRI part of the clinical multicenter study (38), quality controlled fMRI data (for details of the procedure, see Supplement 1) were collected 8 weeks apart from 42 unmedicated patients with PD/A before and after CBT as well as 42 healthy control subjects matched for age, gender, and handedness (40) (see Table 1 and Figure S1 in Supplement 1). For a description of the applied clinical assessments as well as inclusion and exclusion criteria, see Supplement 1 and (7,38).

After a complete description of the study protocol, written informed consent was obtained from every participant and the protocol was approved by the local ethics committees in each fMRI center according to the Declaration of Helsinki.

Procedure: Treatment and Clinical Assessment

CBT was administered in 12 twice-weekly sessions based on a highly standardized and controlled treatment protocol (see Supplement 1 Information and Gloster *et al.* [7,38]). PD/A patients were randomly assigned to two versions of CBT, which differed only in therapist-guided or non-therapist-guided exposure sessions (sessions 6–8 and 9–11). Because both groups received a comparable treatment and demonstrated significant symptom reduction after CBT (7), groups were collapsed in the current study.

In addition to those assessments of the clinical trial, cognitive abilities were assessed using Trail Making Test A and B (TMT-A/B) and digit span.

Paradigm-specific behavioral data were collected before fMRI data acquisition for the US (aversiveness rating at t1; from 0 not aversive to 10 very aversive) and during fMRI data acquisition for both conditioned stimuli (CS+ and CS–) at three time points: after the familiarization, after the acquisition and after the extinction phase using the Self-Assessment Manikin (SAM) (41), with a 5-point Likert scale (1 = very unpleasant to 5 = very pleasant and 1 = not arousing to 5 = very arousing). Behavioral data of the acquisition phase are given in the result section. The complete rating data were provided in Supplement 1 (Table S2).

fMRI

Parallel versions of a previously validated differential conditioning paradigm were applied during MRI data acquisition (Figure 1) (41) before and after CBT. All patients and control subjects were measured at the same fMRI scanner at t1 and t2. In the fMRI analysis (discussed below), we compared the difference between CS+ and CS– across t1 and t2 to examine the therapy-related changes of the conditioning processes.

fMRI Data Acquisition and Preprocessing

fMRI brain images were acquired using 3T Philips Achieva scanners (Philips Medical Systems, Best, The Netherlands) in Münster and Aachen, a 3T Siemens Trio scanner (Siemens AG, Erlangen, Germany) in Dresden, and a 3T General Electric Healthcare scanner (General Electric Healthcare, Milwaukee, Wisconsin) in Berlin. A total of 505 transaxial functional images (echo-planar images, 64×64 , 30 slices interleaved, field of view = 230, voxel size = $3.6 \times 3.6 \times 3.8$ mm, echo time = 30 msec, repetition time = 2 sec) that covered the whole brain and were positioned parallel to the intercommissural line (anterior commissure–posterior commissure) were recorded.

Magnetic resonance images were analyzed using Statistical Parametric Mapping (SPM5; www.fil.ion.ucl.ac.uk) implemented in MATLAB 7.1 (Mathworks, Sherborn, Massachusetts). The first five volumes of every functional run were discarded to minimize t1 saturation effects. For data preprocessing, standard slice-timing (middle slice), realignment and normalizing ($2 \times 2 \times 2$ mm³) functions of SPM5 were applied. To account for differences in intrinsic smoothness between scanners, an iterative smoothness equalization (42) procedure was performed for all data sets using an target smoothness of 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, independent of scanner-specific intrinsic smoothness of the data. Finally, the quality (43,44) of the acquired data was carefully checked to avoid systematic differences between the patient and control groups (Supplement 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

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