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Clinical and Neurofunctional Substrates of Cognitive Behavioral Therapy on Secondary Social Anxiety Disorder in Primary Panic Disorder: A Longitudinal fMRI Study

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Clinicians frequently treat patients suffering from more than one mental disorder. As they have to choose which disorder to treat first, knowledge on generalization effects or even comorbidity-associated obstacles should guide the clinician's decision. Patients with panic disorder (PD) and agoraphobia (AG) often suffer from other mental disorders, e.g. social anxiety disorder (SAD) [1]. Nevertheless, evidence is missing whether cognitive-behavioral therapy (CBT) for PD/AG generalizes to SAD or whether comorbid SAD impedes the treatment of primary PD/AG.

Neurally, both disorders exhibit substantial neurofunctional overlap within the defensive system network. Beyond overlapping structures, PD/AG and SAD mainly differ regarding the periaqueductal grey as well as occipitotemporal and parietal regions related to the ventral object recognition pathway [2] and salience network [3]. Those networks might be crucial in SAD due to the high relevance of detecting social cues.

Fear conditioning serves as a model for the development, maintenance and treatment of anxiety disorders via CBT [4]. It involves the (pre-)motor cortex, medial prefrontal cortex/anterior cingulate cortex, anterior insula, amygdala, hippocampus and thalamus [4], which have also been partly identified as pathophysiological correlates of PD/AG [5] and SAD [3], thus indicating shared pathogenic pathways.

The aim of this analysis was to investigate whether CBT specifically tailored to primary PD/AG also targets clinical and neurofunctional correlates of secondary SAD.

We here present a secondary analysis of data originally collected by the German research network "Panic-Net" on CBT in PD/AG [6]. Two hundred and forty-two completer data sets were available (PD/AG+SAD: n = 100), including 42 with pre- and posttreatment functional magnetic resonance imaging (fMRI) assessments (PD/AG+SAD: n = 14). Adults with primary PD/AG according to DSM-IV-TR criteria were included. Patients suffering from other current comorbidities such as SAD – except for psychotic, bipolar or borderline personality disorder and alcohol dependence – were included, unless they were the primary diagnosis. Patients received a manualized 12-session CBT treatment targeting primary PD/AG [6]. The Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A) [7] was the primary outcome. The Brief Symptom Inventory subscale Interpersonal Sensitivity (BSI-Sens [8]) served as a proxy measure of SAD (see online suppl. Methods and Tables S1 and S2 for detailed information; see www.karger.com/doi/10.159/000493756, for all online suppl. material). We applied a previously validated [6] dif-

Fig. 1. Brain activation clusters differentially activated during fear conditioning and extinction in patients with panic disorder and agoraphobia with (PD/AG+SAD) or without comorbid social anxiety disorder (PD/AG-SAD) prior to and after exposure-based cognitive-behavioral therapy. The corresponding bar graphs show β-values for the peak voxels extracted from a 5-mm sphere over the time course (pre/post) as well as group differences and differences regarding the conditioned stimuli. Error bars indicate the standard error of the mean. L, left; R, right; CS+, stimulus associated with the unconditioned stimulus; CS–, CS not associated with the unconditioned stimulus; AU, arbitrary units. MNI coordinates in parentheses; $p < 0.005$ (uncorr.) with a minimum cluster size of 142 contiguous voxels, indicating to correct for multiple comparisons at $p < 0.05$ (Monte Carlo simulation). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

(For figure see next page.)

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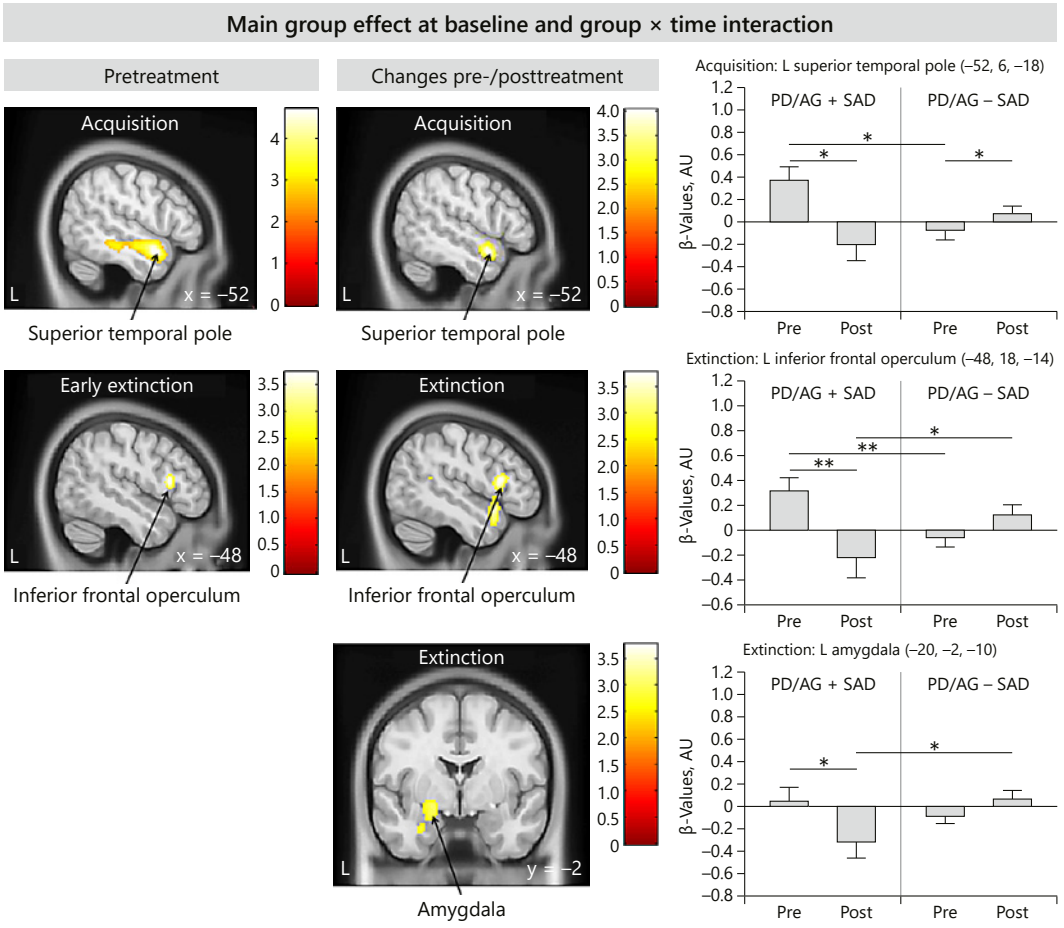
Main group effect at baseline and group × time interaction
Pretreatment
Changes pre-/posttreatment
Acquisition
Superior temporal pole
Early extinction
Extinction
Inferior frontal operculum
Amygdala
Acquisition: L superior temporal pole (–52, 6, –18)
Extinction: L inferior frontal operculum (–48, 18, –14)
Extinction: L amygdala (–20, –2, –10)
PD/AG + SAD
PD/AG – SAD
β-Values, AU
Pre
Post
Interaction effect group × CS at baseline and group × CS × time interaction
Early acquisition
Middle temporal gyrus
Hippocampus
Early acquisition: L middle temporal gyrus (–42, –52, 12)
Early acquisition: R hippocampus (38, –10, –18)
CS+
CS–

1

ferential fear conditioning task comprising familiarization, acquisition and extinction with colored geometric stimuli as conditioned stimuli (CS) and an aversive white noise (individually adapted: 70–110 dB) as unconditioned stimulus. fMRI images were acquired with 3-T scanners. Age, Anxiety Sensitivity Index, Clinical global Impression Scale and Beck Depression Inventory scores were entered as covariates (see online suppl. Table S2). In line with the primary fMRI outcome paper [6], an individual voxel type I error at $p < 0.005$ with a cluster extent of 142 contiguous resampled voxels indicated significant effects corrected for multiple comparisons at $p < 0.05$ (Monte Carlo simulation) [9]. β-Values were extracted for repeated measures ANOVA and post hoc *t* contrasts from corresponding main and interaction effects (see suppl. Methods for details on fMRI data acquisition and analysis).

In the clinical and the fMRI sample, we observed a significant reduction of SIGH-A scores within both groups (see online suppl. Tables S3, S4 and Fig. S1). Moreover, CBT effectively reduced SAD symptoms in PD/AG+SAD patients to the level of PD/AG-SAD-patients (see online suppl. Fig. S1).

On the neurofunctional level (Fig. 1 and online suppl. Tables S5 and S6), PD/AG+SAD patients exhibited enhanced activation in the bilateral superior temporal pole, left middle temporal gyrus (MTG), left inferior frontal operculum (IFO), left insula and right anterior cingulate cortex. Furthermore, PD/AG+SAD patients showed a stronger activation upon the CS+ within the left MTG and the right hippocampus compared to PD/AG-SAD patients particularly during early acquisition.

Prior to treatment, PD/AG+SAD patients showed a higher activation than PD/AG-SAD patients within the left superior temporal pole (acquisition) and left IFO (extinction), which was significantly reduced after treatment. Activations were reduced even below the level of PD/AG-SAD patients within the left IFO and left amygdala.

A significant group × time × CS interaction during early acquisition within the left MTG and right hippocampus indicated a significantly stronger activation upon the CS+ among PD/AG+SAD patients at baseline. Prior to treatment, only PD/AG+SAD patients differentiated between CS+ and CS–. After treatment, MTG activation upon the CS+ was reduced significantly in PD/AG+SAD patients to the level of PD/AG-SAD patients. Moreover, activation upon the CS– significantly increased among PD/AG+SAD patients within the hippocampus. No significant differences or activation changes within the MTG or the hippocampus were observed among PD/AG-SAD patients.

In this study, we were able to highlight the relevance of comorbidity in PD/AG. Clinically, PD/AG-specific treatment is equally effective in patients with or without SAD comorbidity. It furthermore bears potential to generalize to secondary SAD symptomatology, thus favoring the idea of a general mechanism that may foster the transfer of fear-inhibitory learning. Neurally, results demonstrate a signature associated with secondary SAD, encompassing two functional systems: first, this signature extends throughout the ventral object recognition pathway, which is related to the recognition of social cues and thus SAD symptomatology; second, comorbid SAD further amplifies the activation of defensive system structures (e.g., hippocampus and IFO) possibly indicating stronger conditionability as a function of comorbidity. Both systems were effectively targeted by CBT, resulting in attenuated activation patterns to the level of PD/AG-SAD patients.

Major limitations are a missing primary SAD group, the inclusion of other comorbidities besides SAD and the use of the BSI-Sens as proxy measure of SAD symptomatology. Monte Carlo simulations have recently been criticized as they may facilitate false-positive results. Therefore, the results are preliminary and crucially need replication in a larger sample.

Our results warrant further basic and clinical research as they indicate that exposure-based CBT is a powerful approach for treating PD/AG accompanied by SAD and leads to a symptom reduction extending to the neural level in both disorders even though only PD/AG is specifically targeted. Future studies should investigate comorbid conditions more in depth to identify common pathways of change that possibly follow overarching functional domains as laid out by the Research Domain Criteria framework [10]. Identifying these may help to develop time-efficient treatments particularly for patients suffering from more than one anxiety disorder.

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Statement of Ethics

The RCT project was approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (EK 164082006). The neuroimaging components were approved by the Ethics Committee of the Medical Faculty of the Rheinisch-Westfaehlische Hochschule University Aachen (EK 073/07) and at all local sites.

The experimental pharmacology study was approved by the Ethics Committee of the state of Berlin (EudraCT: 2006–00-4860-29). The study was registered with the ISRCTN: ISRCTN80046034.

Disclosure Statement

The following authors report no conflicts of interest concerning the content of this paper: F. Seeger, U. Lueken, Y. Yang, B. Straube, B. Pfleiderer, A. Wittmann, G.W. Alpers, T. Lang, A.L. Gerlach, M. Höfler, A. Hamm, T. Fydrich. T. Kircher received fees for educational programs from Janssen-Cilag, Aristo, Eli Lilly, Servier, Lundbeck, Bristol Myers Squibb, Pfizer and Astra-Zeneca. H.-U. Wittchen has been member of advisory boards of several pharmaceutical companies. He received travel reimbursements and research grant support from Essex Pharma, Sanofi, Pfizer, Organon, Servier, Novartis, Lundbeck, Glaxo Smith Kline. V. Arolt is member of advisory boards and/or gave presentations for the following companies: Astra-Zeneca, Janssen-Organon, Lilly, Lundbeck, Servier, Pfizer and Wyeth. He also received research grants from Astra-Zeneca, Lundbeck and Servier. He chaired the committee for the "Wyeth Research Award Depression and Anxiety". A. Ströhle received research funding from the German Federal Ministry of Education and Research (BMBF), the German Research Foundation (DFG) and the Robert-Enke-Stiftung. An educational grant was given by the Foundation Seelen Bewegt.

Author Contributions and 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 (Greifswald: PI for psychophysiology), A.L. Gerlach (Münster: PI for psychophysiology and panic subtypes), A. Ströhle (Berlin: PI for experimental pharmacology), T. Kircher (Marburg: PI for functional neuroimaging), and J. Deckert (Würzburg: PI for genetics). Additional site directors in the RCT component of the program are G.W. Alpers (Würzburg), T. Fydrich and L. Fehm (Berlin-Adlershof), and T. Lang (Bremen).

Data Access and Responsibility

All PIs 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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