

Psychother Psychosom 2019;88:48–51
DOI: 10.1159/000493756

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

Fabian Seeger^a Yunbo Yang^b Benjamin Straube^b Tilo Kircher^b
Michael Höfler^c Hans-Ulrich Wittchen^{c,d} Andreas Ströhle^e
André Wittmann^e Alexander L. Gerlach^f Bettina Pfleiderer^g
Volker Arolt^h Alfons Hammⁱ Thomas Lang^{j,k} Georg W. Alpers^l
Thomas Fydrich^m Ulrike Lueken^{a,m}

^aCenter of Mental Health, Department of Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Würzburg, Würzburg, Germany; ^bDepartment of Psychiatry and Psychotherapy, Philipps-Universität Marburg, Marburg, Germany; ^cInstitute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany; ^dDepartment of Psychiatry and Psychotherapy, Ludwig-Maximilians-Universität München, Munich, Germany; ^eDepartment of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany; ^fDepartment of Clinical Psychology and Psychotherapy, University of Cologne, Cologne, Germany; ^gDepartment of Clinical Radiology, Medical Faculty, University of Münster and University Hospital of Münster, Münster, Germany; ^hDepartment of Psychiatry and Psychotherapy, University of Münster, Münster, Germany; ⁱDepartment of Physiological and Clinical Psychology and Psychotherapy, Ernst-Moritz-Arndt-Universität Greifswald, Greifswald, Germany; ^jChristoph Dornier Foundation for Clinical Psychology, Bremen, Germany; ^kDepartment of Clinical Psychology and Psychotherapy, University of Hamburg, Hamburg, Germany; ^lDepartment of Clinical and Biological Psychology and Psychotherapy, University of Mannheim, Mannheim, Germany; ^mDepartment of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany

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.

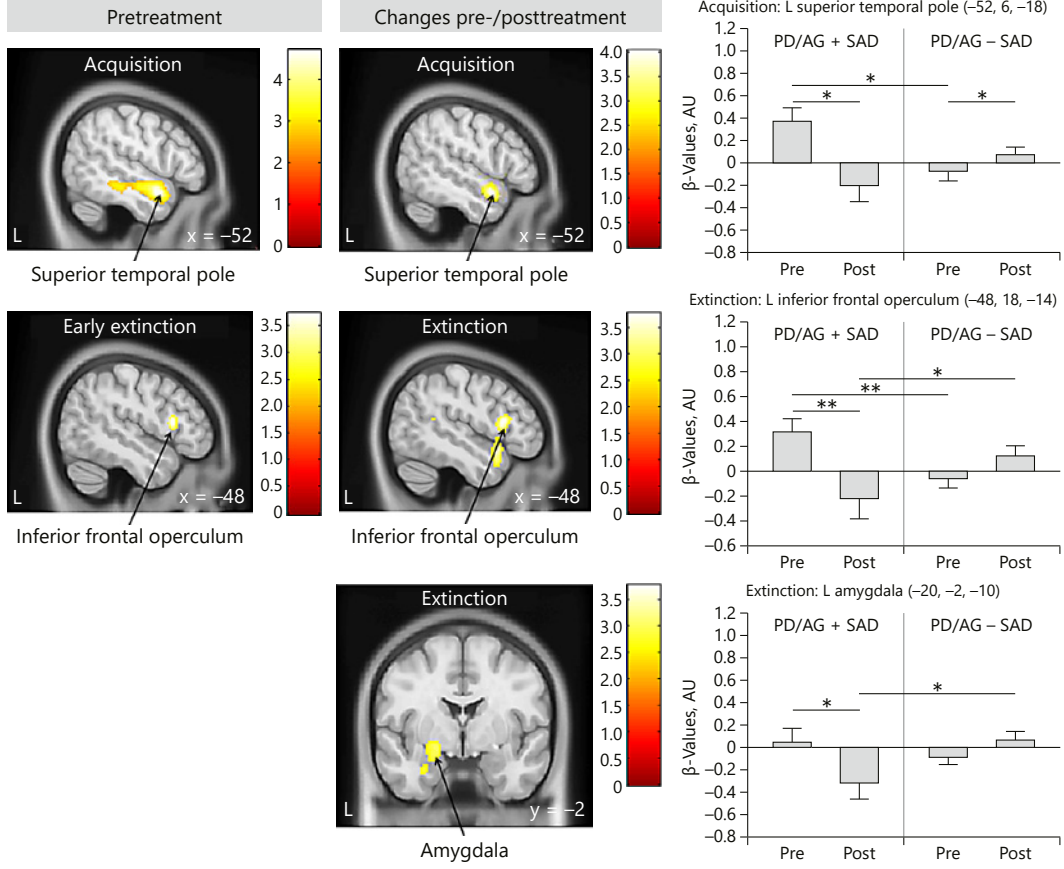
The aim of this analysis was to investigate whether CBT specifically tailored to primary PD/AG also targets clinical and neurofunctional correlates of secondary SAD.

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/10.1159/000493756, for all online suppl. material). We applied a previously validated [6] dif-

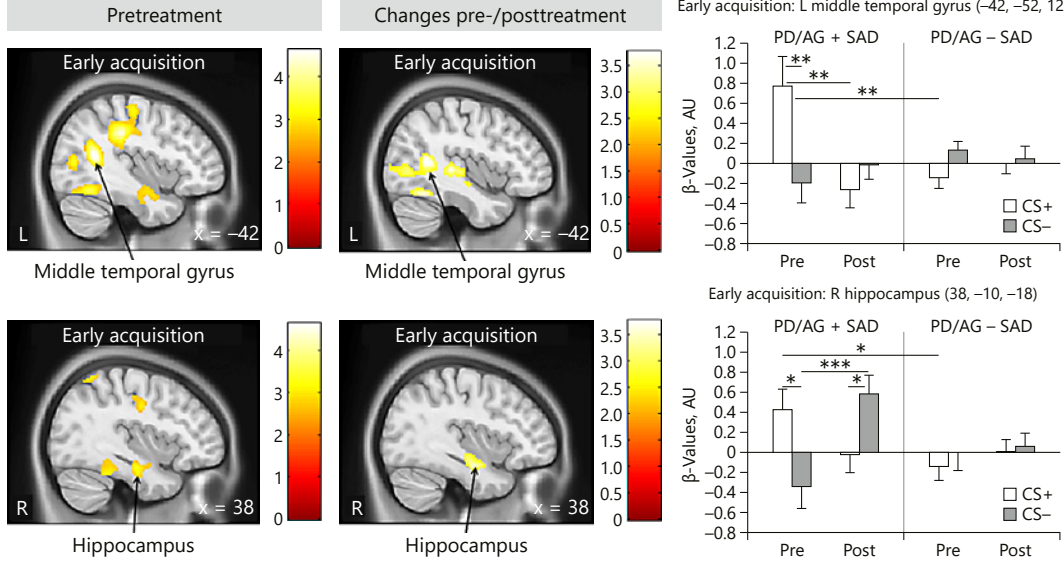
Fig. 1. Brain activation clusters differentially activated during fear conditioning and extinction in patients with panic disorder and agoraphobia with (PD/AG+SAD) or without comorbid social anxiety disorder (PD/AG-SAD) prior to and after exposure-based cognitive-behavioral therapy. The corresponding 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.)

Main group effect at baseline and group × time interaction



Interaction effect group × CS at baseline and group × CS × time interaction



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 \times time \times 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.

Acknowledgement

This work is part of the German multicenter trial Mechanisms of Action in CBT (MAC). The MAC study is funded by the German Federal Ministry of Education and Research (BMBF; project No. 01GV0615; neuroimaging study: project No. 01GV0611) as part of the BMBF Psychotherapy Research Funding Initiative. Fabian Seeger is supported by the German Research Foundation (Collaborative Research Center SFB-TRR 58 “Fear, Anxiety, Anxiety Disorders”; PI: Ulrike Lueken). Benjamin Straube is supported by the German Research Foundation (project No. STR 1146/8-1).

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-Westfälische 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.

Staff Members by Site

Greifswald (coordinating site for psychophysiology): Christiane Melzig, Jan Richter, Susan Richter, Matthias von Rad; Berlin-Charité (coordinating center for experimental pharmacology): Harald Bruhn, Anja Siegmund, Meline Stoy, André Wittmann; Berlin-Adlershof: Irene Schulz; Münster (overall MAC program coordination, genetics and functional neuroimaging): Andreas Behnken, Katharina Domschke, Adrianna Ewert, Carsten Konrad, Bettina Pfeleiderer, Christina Uhlmann, Peter Zwanzger; Münster (coordinating site for psychophysiology and subtyping): Judith Eidecker, Swantje Koller, Fred Rist, Anna Vossbeck-Elsebusch; Marburg/Aachen (coordinating center for functional neuroimaging): Barbara Drüke, Sonja Eskens, Thomas Forkmann, Siegfried Gaugel, Susan Gruber, Andreas Jansen, Thilo Kellermann, Isabelle Reinhardt, Nina Vercamer-Fabri; Dresden (coordinating site for data collection, analysis and the RCT): Franziska Einsle, Christine Froehlich, Andrew T. Gloster, Christina Hauke, Simone Heinze, Michael Hoefler, Ulrike Lueken, Peter Neudeck, Stephanie Preiß, Dorte Westphal; Würzburg Psychiatry Department (coordinating

center for genetics): Andreas Reif, Caro Gagel; Würzburg Psychology Department: Julia Duerner, Hedwig Eisenbarth, Antje B.M. Gerdes, Harald Krebs, Paul Pauli, Silvia Schad, Nina Steinhäuser; Bremen: Veronika Bamann, Sylvia Helbig-Lang, Anne Kordt, Pia Ley, Franz Petermann, Eva-Maria Schroeder. Additional support was provided by the coordinating center for clinical studies in Dresden (KKS Dresden): Xina Graehlert and Marko Käppler.

References

- 1 Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2006 Apr; 63(4):415–24.
- 2 Gilbert CD: The constructive nature of visual processing. In: Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ, editors. Principles of neural science. New York: McGraw-Hill; 2013. p. 556–576.
- 3 Kim YK, Yoon HK. Common and distinct brain networks underlying panic and social anxiety disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018 Jan 3;80(pt B):115–22.
- 4 Fullana MA, Harrison BJ, Soriano-Mas C, Vervliet B, Cardoner N, Avila-Parcet A, et al. Neural signatures of human fear conditioning: an updated and extended meta-analysis of fMRI studies. *Mol Psychiatry*. 2016 Apr;21(4):500–8.
- 5 Dresler T, Guhn A, Tupak SV, Ehlis AC, Herrmann MJ, Fallgatter AJ, et al. Revise the revised? New dimensions of the neuroanatomical hypothesis of panic disorder. *J Neural Transm (Vienna)*. 2013 Jan;120(1):3–29.
- 6 Kircher T, Arolt V, Jansen A, Pyka M, Reinhardt I, Kellermann T, et al. Effect of cognitive-behavioral therapy on neural correlates of fear conditioning in panic disorder. *Biol Psychiatry*. 2013 Jan;73(1):93–101.
- 7 Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, et al. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depress Anxiety*. 2001;13(4):166–78.
- 8 Franke GH. BSI. Brief Symptom Inventory von L.R. Derogatis (Kurzform der SCL-90-R). Deutsche Version. Göttingen: Beltz Test; 2000.
- 9 Slotnick SD, Moo LR, Segal JB, Hart J Jr. Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. *Brain Res Cogn Brain Res*. 2003 Jun;17(1):75–82.
- 10 Kozak MJ, Cuthbert BN. The NIMH research domain criteria initiative: background, issues, and pragmatics. *Psychophysiology*. 2016 Mar;53(3): 286–97.