

# **Supplementary Material**

Letter to the Editor

**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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## Supplementary Methods

### Participants

Eight centers throughout Germany participated in the clinical trial (Aachen, Berlin-Adlershof, Berlin-Charité, Bremen, Dresden, Greifswald, Münster, Würzburg). Four centers (Aachen, Berlin-Charité, Dresden, Münster) additionally conducted a fMRI study. From the entire sample of 369 patients enrolled in the clinical trial, 242 complete datasets were available for the present analysis. For details regarding the study protocol (including a CONSORT flowchart), in- and exclusion criteria as well as measures of fMRI data quality control see the corresponding publications [1, 2]. Only currently medication-free patients (i.e. 4-week washout period) with a primary diagnosis of PD/AG according to DSM-IV-TR criteria were included. Diagnostic criteria were assessed by means of a standardized interview (Composite International Diagnostic Interview (CIDI-2.1; DIA-X-CIDI version; [3])) validated by clinical experts, a Hamilton Anxiety Scale Score (HAM-A; [4])  $\geq 18$  and a Clinical Global Impression Score (CGI; [5])  $\geq 4$ . Patients were aged between 18 and 65 years. Clinically significant suicidal intent, inability to comply with the study schedule, meeting diagnostic criteria for any psychotic or borderline personality disorder, bipolar disorder or current alcohol dependence, medical conditions explaining anxiety symptoms and MRI-related contraindications led to exclusion. Patients meeting the criteria for other current comorbid diagnoses, including major depression, dysthymia and other anxiety disorders were included, as long as they were not the primary diagnosis. Therefore, the sample can be considered as representative of patients seen in clinical practice. At those centers participating in the fMRI study, 194 patients were recruited for the trial and 89 of these patients consented to participate in the fMRI study. Forty-two quality controlled data sets including pre- and posttreatment fMRI assessments and clinical outcome data were available (for details on data quality control in this multicenter study please refer to [2]). This study has been conducted in accordance

with the Declaration of Helsinki and has been approved by the ethics committees of all eight participating centers. The participants provided written informed consent.

For the present analysis, PD/AG patients were grouped according to the presence of comorbid SAD (DSM-IV-TR 12-month diagnosis of SAD). In the clinical sample 100 patients (41.3 %) exhibited a comorbid SAD (PD/AG+SAD), while in the fMRI subsample 14 patients (33.3 %) were in the PD/AG+SAD group. Sociodemographic and clinical characteristics between groups were tested using  $\chi^2$ - and t-tests. Within (baseline vs. after therapy) and between group (PD/AG+SAD vs. PD/AG-SAD) differences in treatment outcomes were analysed using linear regressions while adjusting for baseline values. Two robust alternatives were fitted to consider potential violations in model assumptions: robust estimation of standard errors (with the sandwich matrix, accounting for non-normal distributions and different variances in residuals) and robust linear regression (accounting also for observations that might otherwise have a strong influence on results) [6]. The significance threshold was set to two-sided alpha = .05. Clinical data were analysed using Stata, version 14.2 (StataCorp., 2016) and SPSS, version 24 (IBM, Armonk, N.Y.).

#### Exposure-based cognitive behavioral therapy

All patients (PD/AG+SAD and PD/AG-SAD) received the same manualized 12-session CBT treatment which was conducted by trained therapists targeting the primary diagnosis of PD/AG. The protocol was carried out over six weeks and was followed by two booster sessions [1]. The manualized therapy comprised psychoeducation, functional analysis of symptoms and related coping behaviors, rationale for exposure, interoceptive exposure, standardized exposure in situ (forest, shopping mall, bus), anticipatory anxiety, individualized in situ exposure (e.g. the patients' most feared situation) and relapse prevention. The aim of the original trial was to compare the effects of therapist-guided exposure vs. patient-guided

exposure. Both treatment conditions proved to be highly effective [1] with some benefits for the therapist-guided treatment arm targeting agoraphobic behaviors. As patients with and without comorbid SAD were equally distributed across treatment arms (Tables S1 & S2), they were merged for the current analysis.

### Clinical assessments

The Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; total score) [4], was used as the primary outcome measure. Clinical response was defined as a reduction of at least 50 % from baseline to post-treatment scores. The Brief Symptom Inventory subscale Interpersonal Sensitivity [7, 8] served as a proxy self-report measure of social anxiety symptomatology. It has been shown to correlate significantly with widely used measures of social anxiety like the Social Interaction Anxiety Scale (SIAS;  $r = .72$ ) or the Social Phobia Scale (SPS;  $r = .63$ ) [9].

### Fear conditioning task

As neurofunctional probe of interest we applied a previously validated [10, 11] differential fear conditioning task using colored geometric stimuli as CSs (presentation time: 2000 ms with a variable inter-trial interval (ITI) of 4.785 to 7.250 sec). An aversive white noise (100 ms; individually adapted prior to baseline MRI between 70-110 dB) represented the US (50 % partial reinforcement rate, CS counterbalanced across subjects; total task duration: approx. 17 min). While fear learning is induced by the reinforced CS+, the CS- (which is never followed by the US) acquires characteristics of a safety signal. The task comprised three phases (familiarization (F) with 16 trials; acquisition (A) with 32 trials and extinction (E) with 16 trials of each CS). During the acquisition phase, we only analysed those trials in which no US was delivered (CS+unpaired). After each phase the patients were asked to rate valence and arousal of the CSs on a five-point Likert-type scale (1, “very unpleasant” / “not arousing” to

5, “very pleasant” / “very arousing”) using the self-assessment Manikin (SAM; [12]). For results concerning the behavioral ratings as indicators of contingency knowledge see [2]. For stimulus presentation we used Presentation 11 (Neurobehavioral Systems; [www.neurobs.com](http://www.neurobs.com)) accompanied by MR-compatible LCD goggles or back-projection systems and standard headphones.

#### fMRI data acquisition and analysis

As described previously [2], MRI images were acquired using 3-T Philips Achieva (Aachen, Münster), 3-T Siemens Trio (Dresden), and 3-T General Electric Healthcare (Berlin) scanners. A total of 505 axial functional images (matrix = 64 x 64; 30 slices interleaved; field of view = 230; voxel size = 3.6 x 3.6 x 3.8 mm; TE = 30 ms; TR = 2 seconds), covering the whole brain and positioned parallel to the intercommissural line (anterior commissure-posterior commissure) were recorded. The first five volumes were discarded to reduce T1 saturation effects. All images were preprocessed using SPM5 ([www.fil.ion.ucl.ac.uk](http://www.fil.ion.ucl.ac.uk)) implemented in MATLAB, version 7.1 (MathWorks, Natick, Mass.), applying a high-pass filter (cutoff period, 128 seconds) to remove low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal. After slice time correction, functional images were temporally and spatially aligned and normalized into the stereotactic Montreal Neurological Institute template (2 x 2 x 2 mm). An iterative smoothness equalization procedure [13] was performed using a 12-mm full width at half-maximum Gaussian isotropic kernel (comparable to a kernel of 8 mm in a standard smoothing procedure). At first level, realignment parameters were included as regressors of no interest. The BOLD response was modelled for each event type (CS+ paired, CS+ unpaired, CS- and US) and phase (familiarization, acquisition, and extinction) convolved with the canonical hemodynamic response function used in SPM5 within the framework of the general linear model. Each phase was divided by half into an early and a late part to account for temporal aspects and habituation, resulting in 16 regressors

(familiarization: early CS+, late CS+; early CS-, late CS-; US; acquisition: early CS-, late CS-, early CS+ presented with the US (CS+paired); early CS+ without US (CS+unpaired), late CS+paired; late CS+unpaired; US; extinction: early CS-, late CS-; early CS+, late CS+; behavioral assessment). Parameter estimates (beta values) and t-statistic images were calculated for each subject.

The group analysis was performed in SPM8 ([www.fil.ion.ucl.ac.uk](http://www.fil.ion.ucl.ac.uk)) implemented in MATLAB, R2012b (MathWorks, Natick, Mass.), by including contrast images into a flexible factorial analysis where subjects are treated as random variables. As previously [2, 10, 14], we included a fMRI center variable to account for scanner differences between sites. Age, ASI, CGI and BDI scores were additionally entered as covariates to control for group differences between PD/AG+/-SAD (see Table S2). Two separate models were set up to test for baseline differences only (model 1: including data only from prior to therapy) and longitudinal data from baseline to post (model 2). In the first model, F-contrasts were computed separately for acquisition and extinction phases for the main effect of group and group x CS interaction; for the second model, the group x time interaction and group x time x CS interaction, followed by post-hoc t-contrasts to specify the direction of the effect (PD/AG+SAD > PD/AG-SAD, PD/AG-SAD > PD/AG+SAD, PD/AG+SAD (CS+ > CS-) > PD/AG-SAD (CS+ > CS-), PD/AG-SAD (CS+ > CS-) > PD/AG+SAD (CS+ > CS-), PD/AG+SAD (T1 > T2) > PD/AG-SAD (T1 > T2), PD/AG-SAD (T1 > T2) > PD/AG+SAD (T1 > T2), PD/AG+SAD: T1 > T2 (CS+ > CS-) > PD/AG-SAD: T1 > T2 (CS+ > CS-), PD/AG-SAD: T1 > T2 (CS+ > CS-) > PD/AG+SAD: T1 > T2 (CS+ > CS-)). As in previous studies [2], a Monte Carlo simulation of the brain volume was conducted to establish an appropriate voxel contiguity threshold [15]. Assuming an individual voxel type I error at  $p < 0.005$ , a cluster extent of 142 contiguous resampled voxels was indicated as sufficient to correct for multiple voxel comparisons at  $P < 0.05$ . Since this correction algorithm could bias findings toward larger brain regions, a region-of-interest analysis of the amygdala was

conducted using the Automated anatomical labeling atlas (AAL;[16])( $p = 0.05$ , familywise-error corrected based on a clusterforming threshold of  $p < 0.001$ ). Monte-Carlo simulations, like the one established for the “Panic-Net” studies, have recently been criticized as they may facilitate false-positive results [17]. Due to reasons of comparability between all “Panic-Net” studies we decided to maintain the correction method for multiple comparisons for the present investigation. With respect to Eklund et al. (2016) [17], our results have to be treated as preliminary results and need further replication in a larger sample. Beta values were extracted using a 5mm sphere for visualisation and used for repeated measures ANOVA as well as post-hoc t-contrasts from the corresponding main and interaction effects. In case of a violation of the sphericity assumption Greenhouse-Geisser corrected values were reported.

## **Supplementary Results**

### Clinical effects

Sample characteristics of the clinical completer sample ( $n = 242$ ) and the fMRI sample are given in Table S1 and Table S2, respectively.

In the clinical completer sample (Table S3) as well as in the fMRI sample (Table S4), both groups showed a significant reduction in all primary outcomes as well as in the BSI interpersonal sensitivity subscale. Of note, the effect size of symptom reduction in PD/AG symptomatology did not differ as a function of comorbidity, indicating that all patients benefited equally well from exposure-based CBT for primary PD/AG.

### Neurofunctional effects

Full results of the baseline effects prior to CBT are given in Table S5. Full results concerning neuroplastic effects following CBT as a function of comorbidity are given in Table S6.

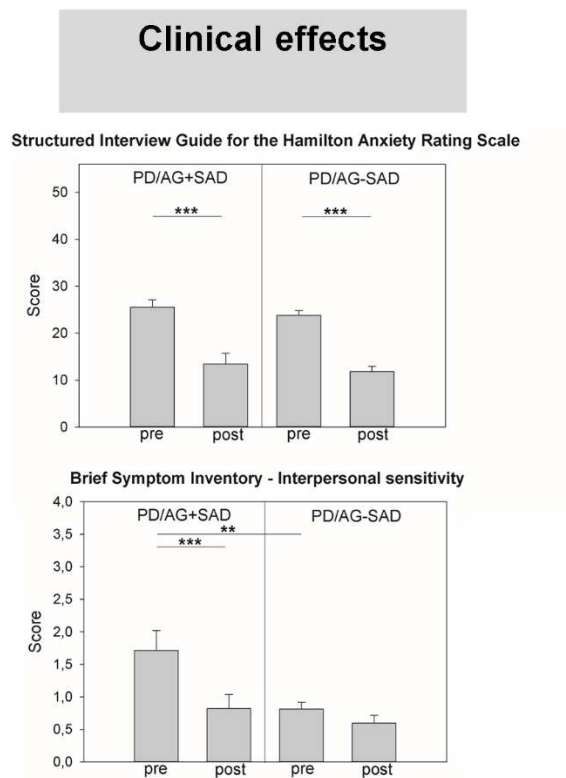
## Behavioral ratings during fear conditioning and extinction

The behavioral results of the entire fMRI sample have been published previously [18].

Behavioral data were analysed concerning potential differences between PD/AG+SAD and PD/AG-SAD groups. No significant group differences were observed regarding the valence as well as arousal ratings of CS+ and CS- (Valence: main effect of group,  $F(1,39) = 0.430$ ,  $p = 0.516$ , main effect of CS,  $F(1,39) = 4.626$ ,  $p < 0.05$ , group\*CS interaction,  $F(1,39) = 0.154$ ,  $p = 0.697$ ; Arousal: main effect of group,  $F(1,39) = 1.869$ ,  $p = 0.179$ , main effect of CS,  $F(1,39) = 4.152$ ,  $p < 0.05$ , group\*CS interaction,  $F(1,39) = 1.437$ ,  $p = 0.238$ ).



## Supplementary Figure S1



Bar graphs show group differences and changes following CBT (pre/post) in the clinical completer sample ( $n = 242$ ) for the Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A) as the primary outcome and the Brief Symptom Inventory – interpersonal sensitivity subscale (BSI-Sens) as a proxy for symptoms of social anxiety. Error bars indicate the standard error of mean. BSI-Sens: main effect of time,  $F(1,40) = 29.660$ ,  $p < 0.001$ , and group\*time interaction,  $F(1,40) = 11.142$ ,  $p < 0.01$ ; SIGH-A: main effect of time,  $F(1,40) = 113.316$ ,  $p < 0.001$ , and group\*time interaction,  $F(1,40) = 0.006$ ,  $p = 0.938$ . \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

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**Supplemental Table S1.** Demographic and clinical characteristics of the clinical completer sample. Means (SD), except where noted.

	All patients (n = 242)		PD/AG-SAD (n = 142)		PD/AG+SAD (n = 100)		Chi <sup>2</sup> or t (df)	p
<i>Demographic and clinical characteristics</i>								
Female gender [n (%)]	182	(75.21)	108	(76.06)	74	(74.00)	0.133 (1)	0.715
Years of education [n (%)]							4.474 (3)	0.215
8	23	(9.50)	12	(8.45)	11	(11.00)		
10	104	(42.98)	55	(38.73)	49	(49.00)		
12-13	109	(45.04)	72	(50.70)	37	(37.00)		
no formal degree	6	(2.48)	3	(2.11)	3	(3.00)		
Age (years)	35.16	(10.74)	35.70	(10.70)	34.37	(34.37)	0.962 (240)	0.337
Age of onset PD/AG (years) <sup>1</sup>	27.01	(9.85)	27.39	(9.53)	26.50	(10.28)	0.681 (233)	0.497
Age of onset SAD (years) <sup>2</sup>	-	-	-	-	22.61	(10.12)	-	-
Number of patients in therapist-guided treatment arm [n (%)]	129	(53.31)	74	(52.11)	55	(55.00)	0.197 (1)	0.658
Number of treatment responders [n (%)]*	134	(55.37)	82	(57.75)	52	(52.00)	0.784 (1)	0.376
<i>Symptom severity at baseline</i>								
CGI	5.26	(0.71)	5.17	(0.71)	5.39	(0.68)	-2.417 (240)	0.016
BSI – interpersonal sensitivity	1.07	(0.84)	0.92	(0.77)	1.29	(0.90)	-3.350 (240)	0.001
SIGH-A total	24.17	(5.17)	23.75	(5.12)	24.77	(5.21)	-1.508 (240)	0.133
PAS total	27.64	(9.78)	25.67	(9.31)	30.43	(9.80)	-3.826 (240)	< 0.001
ASI total	31.57	(11.30)	29.66	(11.04)	34.27	(11.17)	-3.185 (240)	0.002
BDI II total	16.46	(8.66)	14.88	(8.61)	18.71	(8.26)	-3.464 (240)	0.001

PD/AG+SAD: patients with primary panic disorder and agoraphobia with secondary social anxiety disorder; PD/AG-SAD: patients with primary panic disorder and agoraphobia without secondary social anxiety disorder; CGI: Clinical Global Impressions Scale; BSI: Brief Symptom Inventory; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Rating Scale; PAS: Panic and Agoraphobia Scale; ASI: Anxiety Sensitivity Index; BDI II: Beck Depression Inventory II; <sup>1</sup> available for n = 235 patients (n = 135 in PD/AG-SAD group); <sup>2</sup> available for n = 97 patients; \*treatment response was defined as a reduction in SIGH-A scores of at least 50% from baseline to post.

**Supplemental Table S2.** Demographic and clinical characteristics of the fMRI sample. Means (SD), except where noted.

	All patients (n = 42)		PD/AG-SAD (n = 28)		PD/AG+SAD (n = 14)		Chi <sup>2</sup> or t (df)	p
<i>Demographic and clinical characteristics</i>								
Female gender [n (%)]	29	(69.05)	20	(71.43)	9	(64.29)	0.223 (1)	0.637
Years of education [n (%)]							7.150 (2)	0.028
8	4	(9.52)	3	(10.71)	1	(7.14)		
10	18	(42.85)	8	(28.57)	10	(71.43)		
12-13	20	(47.62)	17	(60.71)	3	(21.43)		
Age (years)	35.42	(10.17)	37.73	(9.95)	30.79	(9.28)	2.178 (40)	0.035
Comorbid SAD [n(%)]	14	(33.33)	-	-	14	(100.00)	-	-
Age of onset PD/AG (years) <sup>1</sup>	27.16	(10.61)	28.92	(10.29)	23.86	(10.79)	1.461 (38)	0.152
Age of onset SAD (years) <sup>2</sup>	-	-	-	-	22.36	(9.18)	-	-
Number of patients in therapist-guided treatment arm [n (%)]	22	(52.38)	15	(53.57)	7	(50.00)	0.048 (1)	0.827
Number of treatment responders [n (%)]*	25	(59.52)	17	(60.71)	8	(57.41)	0.049 (1)	0.824
<i>Symptom severity at baseline</i>								
CGI	5.36	(0.62)	5.21	(0.63)	5.64	(0.50)	-2.219 (40)	0.032
BSI – interpersonal sensitivity	1.11	(0.90)	0.81	(0.55)	1.71	(1.15)	-3.463 (40)	0.001
SIGH-A total	24.38	(5.41)	23.79	(5.22)	25.57	(5.77)	-1.010 (40)	0.319
PAS total	25.97	(8.69)	24.45	(8.85)	29.02	(7.78)	-1.637 (40)	0.109
ASI total	31.10	(9.37)	28.86	(7.23)	35.57	(11.65)	-2.302 (40)	0.027
BDI II total	17.26	(9.28)	15.35	(7.59)	21.07	(11.34)	-1.994 (40)	0.059

PD/AG+SAD: patients with primary panic disorder and agoraphobia with secondary social anxiety disorder; PD/AG-SAD: patients with primary panic disorder and agoraphobia without secondary social anxiety disorder; CGI: Clinical Global Impressions Scale; BSI: Brief Symptom Inventory; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Rating Scale; PAS: Panic and Agoraphobia Scale; ASI: Anxiety Sensitivity Index; BDI II: Beck Depression Inventory II; <sup>1</sup>available for n = 40 patients; <sup>2</sup>available for n = 11 patients; \* treatment response was defined as a reduction in SIGH-A scores of at least 50% from baseline to post.

**Supplemental Table S3.** CBT outcomes by baseline social anxiety disorder comorbidity in the clinical completer sample (n = 242).

Outcome	SAD	n	Baseline		Post		Effect size*			Effect size difference**				
			Mean	SD	Mean	SD	point estimate	95% CI	p-value	point estimate	95% CI	p-value		
SIGH-A total	no	142	23.75	5.12	11.80	7.09	-2.28	-2.50	-2.05	0.000	<i>Ref.</i>			
	yes	99	24.71	5.20	13.53	7.59	-2.13	-2.42	-1.84	0.000	0.24	-0.10	0.58	0.164
CGI total	no	142	5.17	0.71	3.37	1.07	-2.60	-2.86	-2.34	0.000				
	yes	99	5.38	0.68	3.63	1.05	-2.54	-2.85	-2.23	0.000	0.22	-0.16	0.61	0.247
PAS total	no	141	25.63	9.32	12.88	8.55	-1.31	-1.46	-1.15	0.000				
	yes	97	30.57	9.76	16.44	9.25	-1.45	-1.65	-1.25	0.000	0.14	-0.07	0.36	0.191
Number of panic attacks	no	142	2.35	2.28	0.99	1.53	-0.58	-0.74	-0.42	0.000				
	yes	100	2.86	2.43	1.29	1.75	-0.67	-0.88	-0.46	0.000	0.08	-0.09	0.25	0.364
Mobility Inventory	no	126	2.78	0.78	1.77	0.71	-1.21	-1.35	-1.06	0.000				
	yes	89	3.22	0.80	2.19	0.94	-1.22	-1.41	-1.03	0.000	0.20	-0.03	0.42	0.085
BSI – interpersonal sensitivity	no	142	0.92	0.77	0.60	0.70	-0.37	-0.49	-0.25	0.000				
	yes	100	1.29	0.90	0.73	0.78	-0.64	-0.83	-0.44	0.000	-0.06	-0.25	0.12	0.498

CBT: Cognitive behavioral therapy; SIGHA: Structured Interview Guide for the Hamilton Anxiety Rating Scale; CGI: Clinical Global Impressions Scale; PAS: Panic and Agoraphobia Scale; BSI: Brief Symptom Inventory; \* Cohens d = post minus baseline difference divided by the standard deviation at baseline of the total sample (n = 369). Confidence intervals and p-values based on linear regression; \*\* Based on linear regression, adjusted for an outcome's baseline values.

**Supplemental Table S4.** CBT outcomes by baseline social anxiety disorder comorbidity in the fMRI sample (n = 42).

Outcome	SAD	n	Baseline		Post		Effect size*			Effect size difference**			
			Mean	SD	Mean	SD	point estimate	95% CI	p-value	point estimate	95% CI	p-value	
SIGH-A total	no	28	23.79	5.22	11.82	6.02	-2.28	-2.79	-1.77	0.000			
	yes	14	25.57	5.77	13.43	8.55	-2.31	-3.07	-1.56	0.000	0.13	-0.69	0.96
CGI total	no	28	5.21	0.63	3.61	1.03	-2.32	-2.94	-1.71	0.000			
	yes	14	5.64	0.50	3.43	1.09	-3.20	-4.14	-2.26	0.000	-0.46	-1.52	0.60
PAS total	no	28	24.45	8.85	13.62	8.31	-1.11	-1.42	-0.81	0.000			
	yes	14	29.02	7.78	14.62	9.37	-1.48	-1.79	-1.16	0.000	-0.21	-0.67	0.24
Number of panic attacks	no	28	2.82	2.21	1.36	1.87	-0.62	-1.00	-0.25	0.002			
	yes	14	2.57	1.45	1.14	1.75	-0.61	-1.24	0.02	0.057	-0.07	-0.58	0.44
Mobility Inventory	no	25	2.48	0.92	1.65	0.62	-0.99	-1.35	-0.63	0.000			
	yes	14	3.13	0.41	2.06	0.78	-1.28	-1.75	-0.80	0.000	0.13	-0.38	0.64
BSI – interpersonal sensitivity	no	28	0.81	0.55	0.60	0.64	-0.25	-0.47	-0.02	0.031			
	yes	14	1.71	1.15	0.82	0.81	-1.03	-1.58	-0.49	0.001	-0.34	-0.81	0.12

CBT: Cognitive behavioral therapy; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Rating Scale; CGI: Clinical Global Impressions Scale; PAS: Panic and Agoraphobia Scale; BSI: Brief Symptom Inventory; \* Cohens d = post minus baseline difference divided by the standard deviation at baseline of the total sample (n = 369). Confidence intervals and p-values based on linear regression; \*\* Based on linear regression, adjusted for an outcome's baseline values.

**Supplemental Table S5.** Brain activation clusters 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) at baseline (prior to CBT).

Contrast/Region	Side	Voxels	x	y	z	F or t	p uncorr.
<b>Main effect Group</b>							
<b>Overall</b>							
Superior temporal pole	L	672	-50	8	-18	18.65	< 0.001
Superior temporal pole	R	281	52	10	-20	17.77	< 0.001
Middle temporal gyrus	R	216	68	-24	-8	11.40	0.001
Post-hoc t-contrast:							
PD/AG+SAD > PD/AG-SAD							
Superior temporal pole	L	969	-50	8	-18	4.32	< 0.001
Superior temporal pole	R	997	52	10	-20	4.22	< 0.001
Middle temporal gyrus	L	221	-52	-52	14	3.42	< 0.001
Inferior frontal operculum	L	196	-46	18	14	3.42	< 0.001
Insula	L	145	-24	-32	20	3.35	< 0.001
Anterior cingulate gyrus	R	191	16	26	16	3.31	< 0.001
Middle temporal gyrus	L	159	-54	-48	-6	2.95	0.002
Post-hoc t-contrast:							
PD/AG-SAD > PD/AG+SAD							
No differential activation							
<b>Acquisition</b>							
Superior temporal pole	L	688	-52	4	-16	22.15	< 0.001
Postcentral gyrus	L	326	-26	-30	40	16.91	< 0.001
Inferior frontal operculum	R	655	30	20	30	14.09	< 0.001
Superior temporal pole	R	194	50	10	-20	13.78	< 0.001
Inferior frontal operculum	L	221	-34	10	28	12.93	< 0.001
Post-hoc t-contrast:							
PD/AG+SAD > PD/AG-SAD							
Superior temporal pole	L	1014	-52	4	-16	4.71	< 0.001
Cerebellum	L	497	-16	-54	20	4.29	< 0.001
Postcentral gyrus	L	764	-26	-30	40	4.11	< 0.001
Inferior frontal operculum	R	1205	30	20	30	3.75	< 0.001
Superior temporal pole	R	712	50	10	-20	3.71	< 0.001
Inferior frontal operculum	L	614	-34	10	28	3.60	< 0.001
Post-hoc t-contrast:							
PD/AG-SAD > PD/AG+SAD							
No differential activation							
<b>Extinction<sup>1</sup></b>							
Anterior cingulate gyrus	R	192	16	26	16	12.09	0.001
Post-hoc t-contrast:							
PD/AG+SAD > PD/AG-SAD							
Superior temporal pole	R	193	52	12	-22	3.73	< 0.001
Inferior frontal operculum	L	184	-48	18	12	3.65	< 0.001
Anterior cingulate cortex	R	299	16	26	16	3.48	< 0.001
Post-hoc t-contrast:							
PD/AG-SAD > PD/AG+SAD							
No differential activation							



**Interaction effect Group x CS**

**Acquisition<sup>2</sup>**

Middle temporal gyrus	L	4454	-40	-54	16	21.55	< 0.001
Superior occipital gyrus	L	357	-18	-76	32	16.04	< 0.001
Precentral gyrus	L	274	-52	-2	42	15.83	< 0.001
Middle temporal gyrus	L	985	-50	0	-22	15.33	< 0.001
Caudate nucleus	R	809	24	-22	22	14.28	< 0.001
Middle temporal gyrus	R	975	56	-58	2	12.98	< 0.001
Calcarine	R	1759	12	-64	10	12.82	< 0.001
Middle cingulate gyrus	L	237	-14	-30	28	12.43	< 0.001
Superior parietal gyrus	L	207	-26	-52	68	12.02	0.001
Superior parietal gyrus	R	211	28	-52	66	11.40	0.001
Insula	L	198	-28	-24	16	10.30	0.001

Post-hoc t-contrast:

PD/AG+SAD > PD/AG-SAD

CS+>CS-

Middle temporal gyrus	L	13823	-40	-54	16	4.64	< 0.001
Middle temporal gyrus	L	1747	-50	0	-22	3.91	< 0.001
Caudate nucleus	R	1488	24	-22	22	3.78	< 0.001
Angular gyrus	R	1830	64	-50	32	3.77	< 0.001
Cerebellum	R	209	34	-40	-26	3.59	< 0.001
Superior parietal gyrus	R	355	28	-52	66	3.38	< 0.001
Hippocampus	R	208	38	-14	-20	3.27	0.001
Middle temporal gyrus	L	224	-60	-30	0	3.21	0.001

Post-hoc t-contrast:

PD/AG+SAD > PD/AG-SAD

CS->CS+

No differential activation

**Extinction**

Superior parietal gyrus	R	252	24	-54	58	11.44	0.001
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Post-hoc t-contrast:

PD/AG+SAD > PD/AG-SAD

CS+>CS-

Superior parietal gyrus	R	511	24	-54	58	3.38	< 0.001
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Post-hoc t-contrast:

PD/AG+SAD > PD/AG-SAD

CS->CS+

No differential activation

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CBT: Cognitive behavioral therapy; L: left; R: right; CS+: stimulus associated with the unconditioned stimulus; CS-: CS not associated with the unconditioned stimulus; voxel: number of voxels per cluster; x, y, z: MNI coordinates; p < 0.005 (uncorr.) with a minimum cluster size of 142 contiguous voxels, indicating to correct for multiple comparisons at p < 0.05; Overall: Clusters differentially activated regardless of phase. We don't report overall effects for interactions including the CS due to the CS being specific for the experimental phase

<sup>1</sup> refers to early extinction phase

<sup>2</sup> refers to early acquisition phase

**Supplemental Table S6.** Brain activation clusters 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 behavioural therapy

Contrast/Region	Side	Voxels	x	y	z	F or t	p uncorr.
<b>Interaction effect Group x Time</b>							
<b>Overall</b>							
Superior temporal pole	L	385	-48	10	-18	15.87	< 0.001
Superior temporal gyrus	L	163	-54	-46	14	13.42	< 0.001
Superior temporal gyrus	R	400	52	-28	0	11.22	0.001
Inferior frontal operculum	R	365	52	20	14	11.19	0.001
Post-hoc t-contrast:							
PD/AG+SAD > PD/AG-SAD (T1 > T2)							
Superior temporal pole	L	972	-48	10	-18	3.98	< 0.001
Cerebellum	R	175	10	-44	-14	3.66	< 0.001
Superior temporal gyrus	L	368	-54	-46	14	3.66	< 0.001
Superior temporal pole	R	199	50	10	-18	3.54	< 0.001
Superior temporal gyrus	R	782	52	-28	0	3.35	< 0.001
Inferior frontal operculum	R	939	52	20	14	3.35	< 0.001
Inferior temporal gyrus	L	178	-50	-28	-18	3.32	< 0.001
Superior temporal gyrus	L	154	-48	-28	4	2.93	0.002
Post-hoc t-contrast:							
PD/AG-SAD > PD/AG+SAD (T1 > T2)							
No differential activation							
<b>Acquisition</b>							
Superior temporal pole	L	168	-52	6	-18	16.18	< 0.001
Vermis		159	6	-42	-16	14.45	< 0.001
Post-hoc t-contrast:							
PD/AG+SAD > PD/AG-SAD (T1 > T2)							
Superior temporal pole	L	245	-52	6	-18	4.02	< 0.001
Vermis		250	6	-42	-16	3.80	< 0.001
Postcentral gyrus	L	254	-26	-28	42	3.40	< 0.001
Middle temporal gyrus	R	189	60	-38	-8	3.25	0.001
Superior frontal gyrus	R	393	18	10	48	3.13	0.001
Superior frontal gyrus, orbital	R	147	22	16	-16	3.09	0.001
Post-hoc t-contrast:							
PD/AG-SAD > PD/AG+SAD (T1 > T2)							
No differential activation							
<b>Extinction</b>							
Inferior frontal operculum	R	210	54	18	12	14.12	< 0.001
Inferior frontal operculum	L	192	-46	18	14	13.93	< 0.001
Post-hoc t-contrast:							
PD/AG+SAD > PD/AG-SAD (T1 > T2)							
Inferior frontal operculum	R	478	54	18	12	3.76	< 0.001
Inferior frontal operculum	L	319	-46	18	14	3.73	< 0.001
Superior temporal gyrus	L	234	-54	-46	16	3.63	< 0.001
Superior temporal pole	L	248	-46	14	-16	3.40	< 0.001
Superior temporal gyrus	R	248	50	-28	0	3.35	< 0.001
Amygdala	L	151	-20	-2	-10	3.01	0.001
Post-hoc t-contrast:							
PD/AG-SAD > PD/AG+SAD (T1 > T2)							
No differential activation							

## Interaction effect Group x Time x CS

### Acquisition<sup>1</sup>

Middle temporal gyrus	L	240	-42	-52	12	13.90	< 0.001
Cerebellum <sup>2</sup>	L	819	-12	-76	-18	13.63	< 0.001
Cerebellum	R	195	10	-70	-18	12.53	< 0.001
Lingual gyrus	R	181	22	-50	-2	12.44	< 0.001
Lingual gyrus	R	431	10	-64	8	12.20	0.001
Middle temporal gyrus	L	228	-44	-30	2	12.12	0.001
Precentral gyrus	L	342	-22	-18	60	11.70	0.001
Middle temporal gyrus	L	227	-52	-72	4	10.70	0.001

Post-hoc t-contrast:

PD/AG+SAD > PD/AG-SAD: T1 > T2 (CS+ > CS-)

Middle temporal gyrus	L	5012	-42	-52	12	3.73	< 0.001
Middle temporal gyrus	R	257	64	-12	-12	3.70	< 0.001
Middle temporal gyrus	R	267	44	-64	8	3.46	< 0.001
Precentral gyrus	L	830	-22	-18	60	3.42	< 0.001
Hippocampus	R	405	38	-10	-18	3.33	< 0.001
Paracentral lobule	R	149	14	-34	56	3.21	0.001
Middle temporal gyrus	R	168	64	-42	6	3.19	0.001
Middle frontal gyrus	R	143	26	36	42	3.18	0.001

Post-hoc t-contrast:

PD/AG-SAD > PD/AG+SAD: T1 > T2 (CS+ > CS-) No differential activation

### Full Extinction

Precentral gyrus	R	591	30	-20	46	19.41	< 0.001
Middle cingulate gyrus	L	252	-18	-44	52	12.76	< 0.001
Superior parietal gyrus	R	142	32	-60	56	11.00	0.001

Post-hoc t-contrast:

PD/AG+SAD > PD/AG-SAD: T1 > T2 (CS+ > CS-)

Precentral gyrus	R	1620	30	-20	46	4.41	< 0.001
Superior parietal gyrus	R	259	32	-60	56	3.32	< 0.001

Post-hoc t-contrast:

PD/AG-SAD > PD/AG+SAD: T1 > T2 (CS+ > CS-) No differential activation

L: left; R: right; CS+: stimulus associated with the unconditioned stimulus; CS-: CS not associated with the unconditioned stimulus; voxel: number of voxels per cluster; x, y, z: MNI coordinates; p < 0.005 (uncorr.) with a minimum cluster size of 142 contiguous voxels, indicating to correct for multiple comparisons at p < 0.05; Overall: Clusters differentially activated regardless of phase. We don't report overall effects for interactions including the CS due to the CS being specific for the experimental phase.

<sup>1</sup> refers to early acquisition phase

<sup>2</sup> cluster encompassing the left fusiform face area