What happens in the brain after successful vs. non-successful CBT treatment?
A multicenter fMRI study on panic disorder with agoraphobia

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Background

- Panic disorder with agoraphobia (PD/AG) is a common and debiliating anxiety disorder characterized by recurrent and sudden attacks of intense anxiety and concerns about their potential implications[1].
- Exposure-based cognitive behavioral therapy (CBT) is an effective treatment of PD/AG. Still, not all patients benefit from this treatment.
- Fear conditioning and extinction may represent a pathogenetic pathway for the development and treatment of PD/AG[2,3].
- Neural correlates of fear conditioning could therefore provide an experimental approach to investigate outcome-rleated neuroplasticity in PD/AG.

Research question:

- To investigate neuroplastic changes following CBT in treatment responders (R) and non-responders (NR).

Methods

Sample

- Within the national research network PANIC-NET[4], n = 89 patients participated in the fMRI study. Quality-controlled pre-post data sets from n = 42 patients (R: n = 24; NR: n = 18) were used for the present analysis (Table 1).
- Treatment response: >50% reduction in HAM-A scores baseline to post assessment. R and NR groups were comparable in clinical baseline characteristics (Table 1).

Table 1. Sample characteristics

	Responder (n = 24)		Non-Responder (n = 18)		p
Female gender	17	(70.8)	12	(66.7)	ns
Age	33.2	(11.2)	37.1	(8.3)	ns
CGI	5.4	(0.7)	5.3	(0.6)	ns
HAM-A	24.2	(5.5)	24.7	(5.4)	ns
ASI	32.9	(8.3)	28.7	(10.4)	ns
BDI	17.4	(10.1)	17.1	(8.3)	ns

CGI: Clinical Global Impressions Scale; HAM-A: Hamilton Anxiety Scale; ASI: Anxiety Sensitivity Index; BDI II: Beck Depression Inventory II

Task

Differential conditioning task, reinforcement rate: 50% (Figure 1).

Data acquisition: 3 T scanners, 30 axial slices, TR=2sec, TE=30ms, voxel size 3.6x3.6x3.8mm, inter-leaved acquisition.

Data analysis: SPM5;flexible factorial design (whole brain analysis). Target contrast: Interaction effect group x time (Monte-Carlo simulation with a minimum cluster size of 142 voxels to correct for multiple comparisons with p < 0.05 corr.).

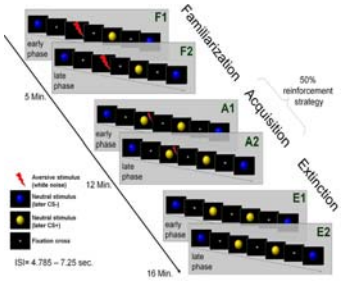


Figure 1. Differential fear conditioning task (see Kircher et al.[3] for a detailed descrition of the methods used in this multicenter study).

Results

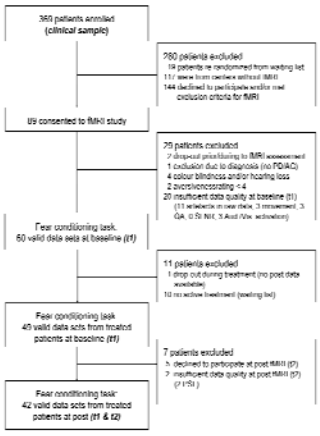
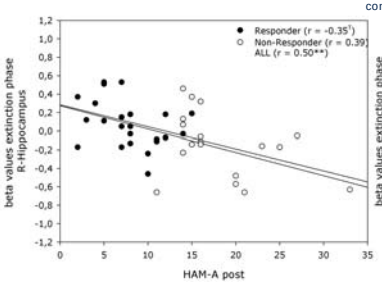


Figure 2. Patient flow chart of the multicenter fMRI study (T1: baseline assessment; T2: post assessment; PSF: percent signal fluctuation; SFNR: signal-to-fluctuation-noise-ratio).

Table 2. Brain activation during fear conditioning at baseline and at post assessment for responders and non-responders. Reported are main and interaction effects (F contrasts) including the factor "group".

Contrast/Region	Side	Voxels	x	y	z	F	p uncorr.
Acquisition phase							
ME "group"							
Lingual gyrus	L	231	-20	-86	-12	20.93	< 0.001
IE "group x CS"	No differential activation						
IE "group x time"	No differential activation						
IE "group x CS x time"							
Precentral gyrus	R	255	23	-22	68	14.48	< 0.001
Cerebellum	R	435	8	-86	-18	13.90	< 0.001
Supplementary motor area	L	720	0	-4	74	11.31	0.001
Cerebellum	R	143	16	-60	-16	10.97	0.001
Extinction phase							
ME "group"							
Superior parietal gyrus	L	343	-28	-60	44	19.63	< 0.001
Superior temporal gyrus	R	336	50	-36	10	18.52	< 0.001
Precentral gyrus	R	226	54	0	20	11.46	0.001
IE "group x CS"	No differential activation						
IE "group x time"							
Hippocampus	R	332	40	-22	-12	17.03	< 0.001
Superior temporal gyrus	R	224	42	-44	10	16.35	< 0.001
Inferior frontal gyrus pars triangularis	L	196	-42	22	12	11.73	0.001
Superior medial frontal gyrus	L	143	-8	60	22	11.26	0.001
Superior medial frontal gyrus	R	208	12	48	32	10.70	0.001
IE "group x CS x time"							
Middle temporal gyrus	L	283	-46	64	14	16.92	< 0.001
Middle temporal gyrus	L	261	-56	-34	-8	14.58	< 0.001

ME: main effect; IE: interaction effect; R: responder (n = 24); NR: non-responder (n = 18); group: factor "group" (R, NR); CS: factor "stimulus" (CS+unpaired: associated, but not paired with the US, CS-: never followed by the US); time: factor "time" (baseline, post assessement). L: left; R: right; voxel: number of voxels per cluster; x, y, z: NMI coordinates; p < 0.005 (uncorr.) with a minimum cluster size of 142 contiguous voxels, indicating to correct for multiple comparisons at p <0.05.



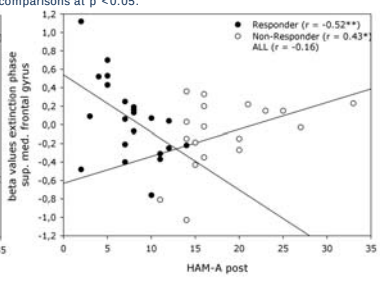
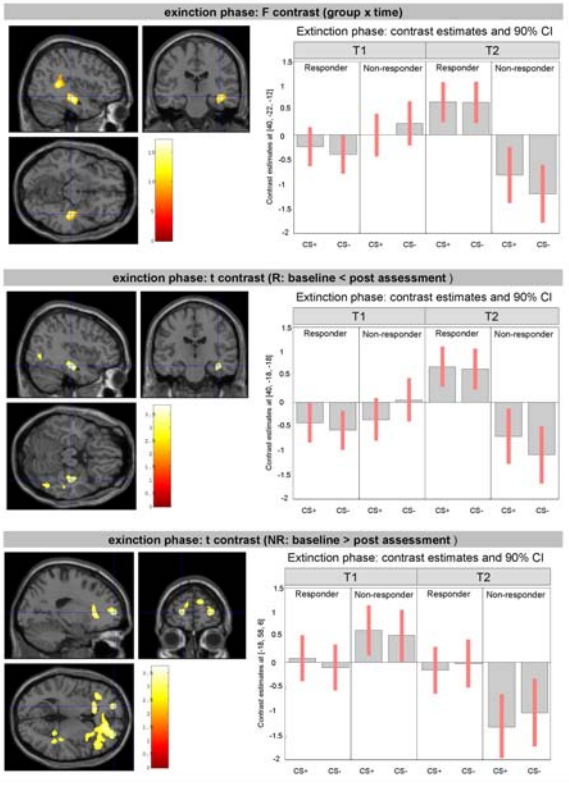


Figure 3. Upper figure: Interaction effect „group x time" during the extinction phase. Changes from baseline to post in R > NR (middle figure) and NR > R (lower figure). T1: baseline assessment; T2: post assessment: CS-: non-rein-forced stimulus; CS+unpaired: reinforced stimulus).

Figure 4. Relationship between symptom severity at post assessment and estimated beta values from the hippocampus (left figure) and sup. med. frontal gyrus (right figure) for R, NR, and the entire patient group.



Discussion

- Present results indicate differential neuroplastic changes as a function of treatment response in PD/AG.
- Treatment response was associated with enhanced hippocampal activity, a brain region well known to be involved in learning and memory.
- In contrast, neuroplastic changes in non-responders were characterized by decreased prefrontal activity, possibly indicating less cognitive appraisal of emotional-associative contingencies.
- The predictive value of neurofunctional response markers needs however to be evaluated in a second, independent sample to predict treatment response a priori.
- If replicated, these findings could contribute to the improvement of patient allocation strategies and treatment response rates.

Recommended Literature
[1] Wittchen HU et al. *Eur Neuropsychopharmacol.* 2011;15:655-679.
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