Supplemental information

Neural correlates of procedural variants in cognitive behavioral therapy: A randomized, controlled multicentre fMRI study

Inclusion and exclusion criteria

Inclusion criteria for all patients were: (a) a current primary diagnosis of panic disorder and agoraphobia (PD/A); (b) a clinical interview score > 18 on the structured interview guide for the Hamilton anxiety scale (HAMA); (c) a score > 4 on the clinical global impressions scale (CGI); (d) an age of 18–65 years; and (e) the ability and availability to regularly attend treatment sessions (Gloster, et al., 2009). Exclusion criteria were (a) comorbid DSM-IV-TR psychotic or bipolar I disorder; (b) current alcohol dependence/current abuse or dependence on benzodiazepine and other psychoactive substances; (c) current suicidal intent; (d) borderline personality disorder; (e) concurrent ongoing psychotherapeutic or psychopharmacological treatment for PD/A or another mental disorder; (f) antidepressant or anxiolytic pharmacotherapy; and (g) physician-verified contraindications of exposure-based CBT (i.e., severe cardiovascular, renal, or neurological diseases). The control subjects were free of current or past medical, neurological or psychiatric illness, as evidenced by the Composite International Diagnostic Interview (CAPI-WHO-CIDI; DIAX-CIDI version), ASI, BDI II and HAMA. Exclusion criteria for both groups were cardiac pacemaker, ferromagnetic metal implants, tattoos or permanent make up with ferromagnetic colors.

Training and selection of therapists

Prior to beginning the study, 90 advanced-level clinical psychology graduate students and postdocs experienced in CBT of anxiety disorders took part in a 3-day training workshop. The treatment manual was explained and practiced in role-plays. Subsequent to the training and prior to seeing study patients, all therapists recorded role-plays of complicated aspects of the manual.

Twelve therapists did not pass, and five never submitted videos. Only those who passed (n = 73) were eligible to treat patients in the study. Therapists were trained to see patients in both variants of the active treatment. Weekly supervision and videotaping of all sessions was implemented to maintain therapy integrity and identify violations of the protocol.

Self-report results of the conditioning experiment

The rating of valence and arousal with regard to the stimuli (CS+ and CS-, respectively) that were acquired after the acquisition (Acq) and extinction (Ext) phase (see (Reinhardt, et al., 2010)) revealed a main effect of condition for valence (CS->CS+; $F_{1,78}$=8.134, P=0.006; partial-eta squared=0.094) and arousal (CS+>CS-; $F_{1,78}$=8.411, P=0.005; partial-eta squared=0.097) in an analysis of variance. Thus, the conditioned stimulus (CS+) was evaluated as less positive (low valence) and more arousing (high arousal) than the neutral stimulus (CS-). The effect was further influenced by phase as indicated by a significant condition (CS+/CS-) by phase (Acq/Ext) interaction for valence (Acq[CS->CS+]>Ext[CS->CS+]; $F_{1,78}$=9.124, P=0.003; partial-eta squared=0.105) and arousal (Acq[CS+>CS-]>Ext[CS+>CS-]; $F_{1,78}$=8.599, P=0.004; partial-eta squared=0.099). Thus, differences in valence and arousal ratings between CS+ and CS- decreased from the acquisition to the extinction phase. The presented objects (CS+ & CS-) were evaluated less positive (low valence) and more arousing (high arousal) in the acquisition in contrast to the extinction phase as indicated by a significant main effect of phase for valence (Acq<Ext; $F_{1,78}$=20.576, P<0.001; partial-eta squared=0.209) and arousal (Acq>Ext; $F_{1,78}$=30.989, P<0.001; partial-eta squared=0.284).

For arousal a significant main effect time (t1>t2; $F_{1,78}$=4.654, P<0.034; partial-eta squared=0.056) indicates a decrease in arousal from t1 to t2. However this effect did not interact with condition (CS+, CS-), phase (Acq, Ext) or group (HS, PD/AG).

For the valence rating significant interactions were found between time (t1, t2), phase (Acq, Ext), group (HS, PD/AG) and treatment (T+, T-) condition ($F_{1,78}$=5.835, P=0.018; partial-

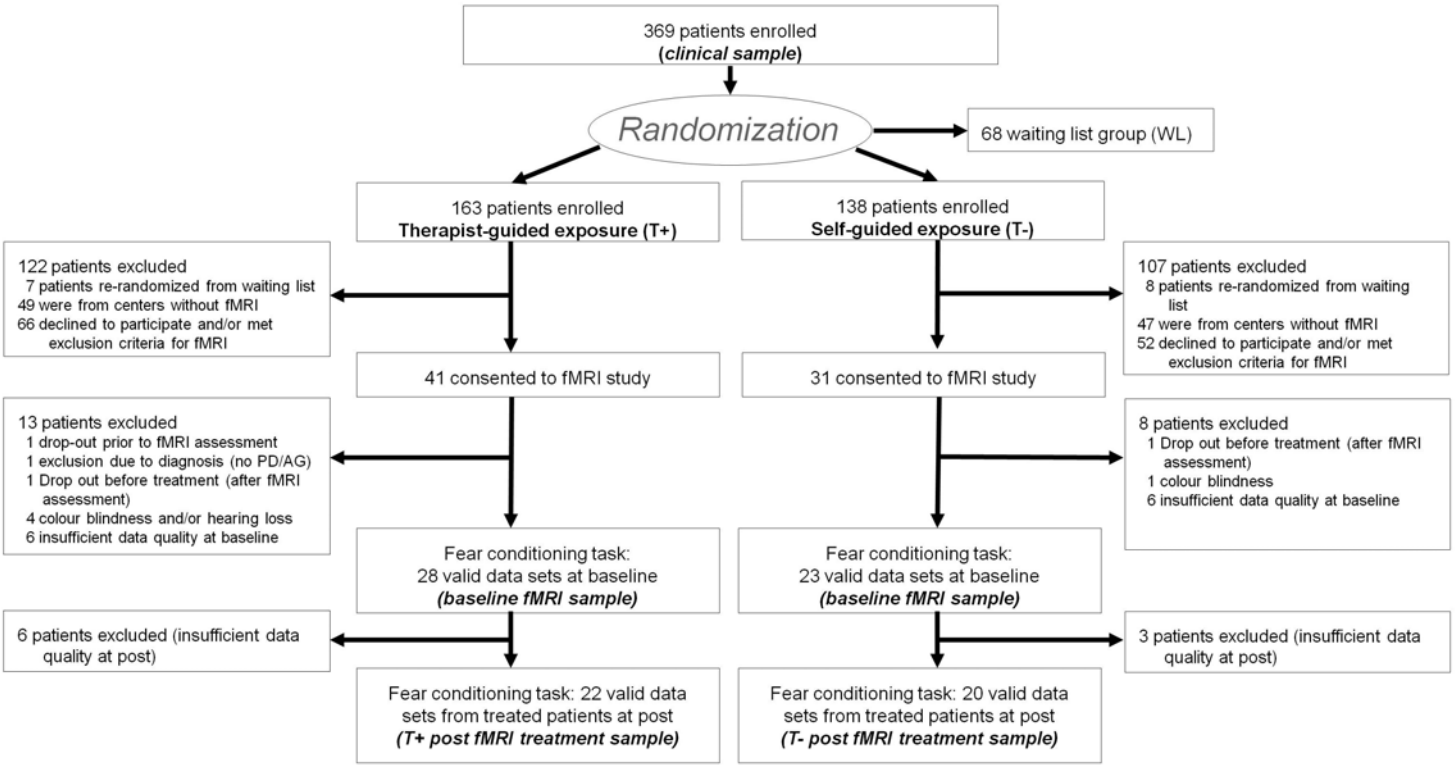
eta squared=0.070); phase, group and treatment condition ($F_{1,78}$=7.087, P=0.009; partial-eta squared=0.083); phase, group and stimulus (CS+/CS-) condition ($F_{1,78}$=5.236, P=0.025; partial-eta squared=0.063); and phase, stimulus and treatment condition ($F_{1,78}$=4.371, P=0.04; partial-eta squared=0.053) (see Supplementary Figure 2). These interactions suggest that all factors and most of their combinations are relevant for valence evaluations in a fear conditioning paradigm. The significant time point, phase, group by treatment interaction seem predominantly be based on an increased positive evaluation of the objects (CS+ & CS-) in the extinction phase after CBT in the T- group (see Supplementary Figure 2).

The significant main effect of group indicates general lower ratings of valence (P<C; $F_{1,78}$=7.860, P=0.006; partial-eta squared=0.092) and higher ratings of arousal for patients in contrast to the control group (P>C; $F_{1,78}$ = 10.026, P=0.002; partial-eta squared=0.114). However, no further interactions between group (HS, PD/AG) and treatment (T+, T-) has been found.

Exploratory analyses of the late acquisition and extinction phase

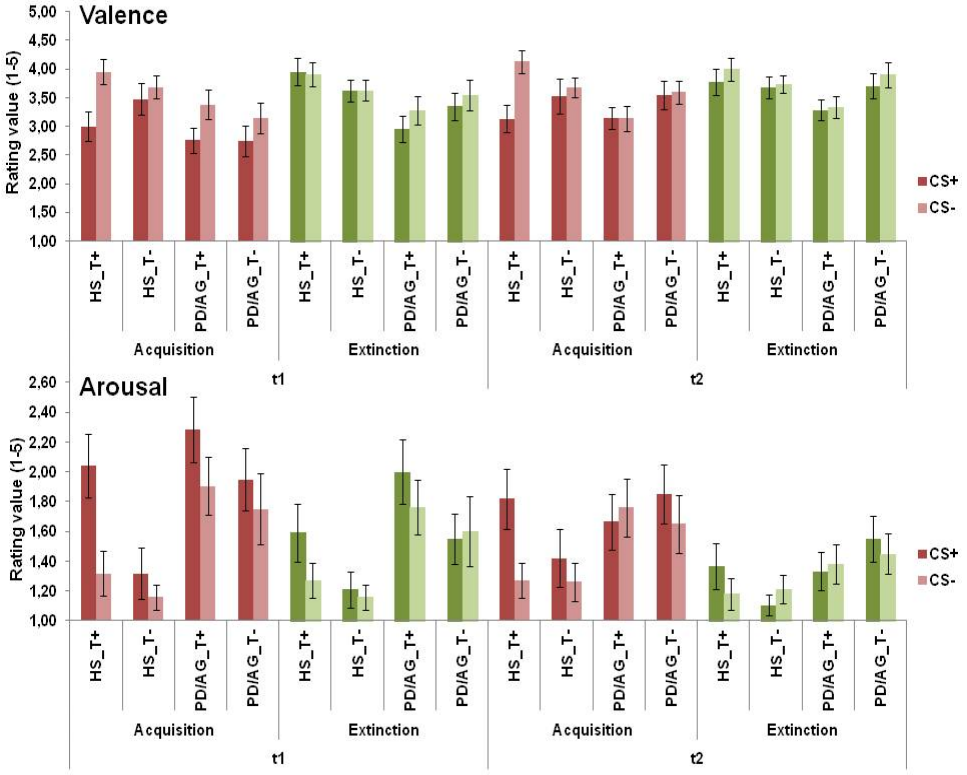
Exploratory analyses of the late acquisition end extinction phase revealed that differential effects of T+ and T- were also present in the late acquisition phase in the right occipital and inferior temporal cortex. Exploratory analyses, identical to the analyses of the acquisition phase, had been performed for the early and late extinction phase. Analyses revealed no significant interactions of treatment, time point and condition.

Supplementary Figure 1. Patient flow chart



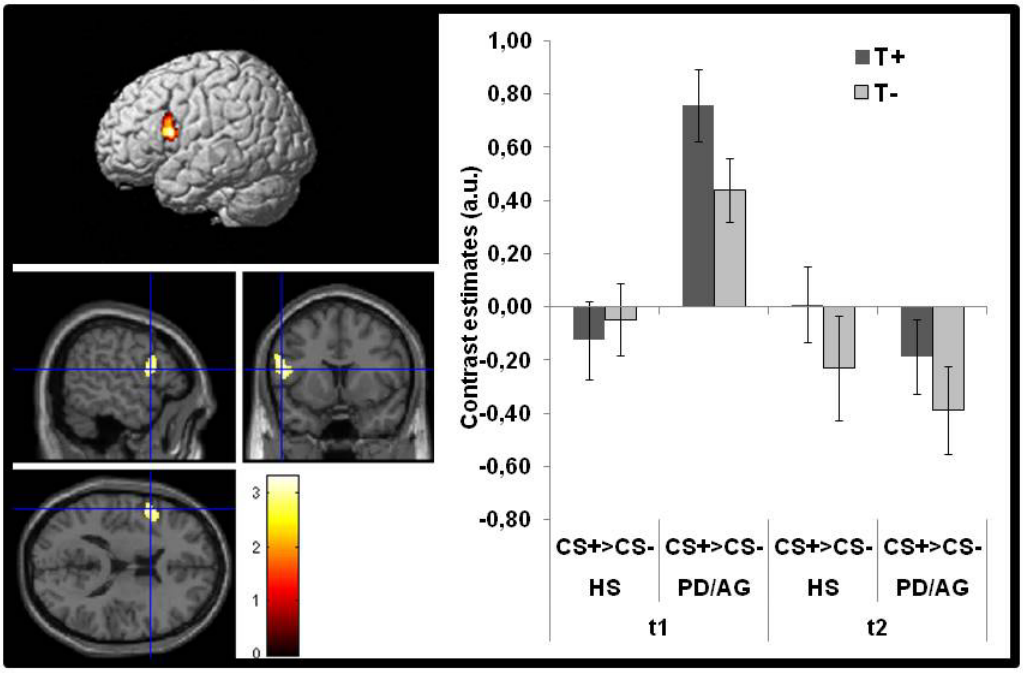
Supplementary Figure 1. Please note: healthy control subjects were matched to the respective patient samples (baseline fMRI samples and post fMRI treatment samples). Similar to the clinical sample, there were no significant differences in drop-out rates between treatment conditions in the fMRI sample (drop out at t1: T+ = 13 T- = 8; drop out at t2: T+ = 6 T- = 3; no-drop out: T+ = 22 T- = 20; Chi-square = 0.914, P = 0.633).

Supplementary Figure 2. Self-report data of the conditioning experiment



Supplementary Figure 2. Self-report data of the conditioning experiment for valence (from negative = 1 to positive = 5) and arousal ratings (from low arousal = 1 to high arousal = 5) acquired after acquisition (red) and extinction (green) phase at t1 and t2. Dark bars illustrate rating data for the CS+, light bars for CS-. Error bars represent the standard error of the mean. HS = Healthy subjects; PD/AD = Panic disorder with agoraphobia; T+ = Therapist-guided exposure; T- = Self-guided exposure.

Supplementary Figure 3: Interaction of clinical group (PD/AG>HS), time (t1>t2) and stimulus (CS+>CS-)



Supplementary Figure. 3 illustrates the activation of the left IFG for the interaction of clinical group (PD/AG>HS), time (t1>t2) and stimulus (CS+>CS-) as previously reported in (Kircher, et al., 2013). Bar graphs on the right show a similar reduction of activation from t1 to t2 for both treatment groups (T+/T-).