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Changes of brain activation pre- post short-term psychodynamic inpatient psychotherapy: An fMRI study of panic disorder patients

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ABSTRACT

Cognitive–behavioural interventions have been shown to change brain functioning. We used an emotional linguistic go/nogo functional magnetic resonance imaging (fMRI) design to determine changes of brain activation patterns of panic disorder (PD) patients following short-term psychodynamic inpatient treatment. Nine PD patients underwent fMRI before and after treatment; 18 healthy controls were scanned twice at the same interval (4 weeks). In the go/nogo design, responses to panic-specific negative words were compared with linguistically matched positive and neutral words. According to hypotheses, patients rated affective words more strongly than controls and selectively recalled negative vs. positive/neutral words. Before treatment, high limbic (hippocampus and amygdala) activation was accompanied by low prefrontal activation to negative words. Inhibition-related activation patterns indicated difficulties of behavioural regulation in emotional context. At treatment termination, panic-related symptoms had improved significantly, and fronto-limbic activation patterns were normalized. Our results indicate that short-term psychodynamic treatment leads to changes in fronto-limbic circuitry not dissimilar to previous findings on cognitive–behavioural treatments.

1. Introduction

In recent years, a growing number of functional neuroimaging studies have demonstrated the impact of cognitive–behavioural treatments on brain functioning (Linden, 2006). Thus, it seems also plausible to expect psychodynamic treatments to normalize fronto-limbic circuitry (Beutel et al., 2003; Leichsenring et al., 2004). In a controlled functional magnetic resonance imaging (fMRI) study, we therefore aimed to determine the effects of psychodynamic short-term treatment (based on Milrod et al., 1997) on brain functioning in patients with panic disorder.

Panic disorder (PD), a prevalent and debilitating disease (Jacobi et al., 2004), is characterised by recurrent, unexpected panic attacks, followed by persistent concern about future attacks, their implications for mental or general health, and avoidance of situations related to the occurrence of panic. A panic attack is defined by intense fear or discomfort accompanied by rapidly evolving symptoms of palpitations, accelerated heart beat, sweating, etc. (American Psychiatric Association, 2000).

The *fear network* consists of the amygdala and its projections to the hypothalamus and brain stem areas, the ventromedial prefrontal cortex and the hippocampus (LeDoux, 1998; Isenberg et al., 1999; Büchel and Dolan, 2000; Davis and Whalen, 2001; Critchley et al., 2002; Etkin and Wager, 2007). An amygdala hypersensitivity to subtle or unconscious sensory and visceral stimuli has been hypothesized to trigger fear responses in PD patients without sufficient top-down regulation by the prefrontal cortex (PFC) (Sakai et al., 2005). Yet, amygdala hyperactivation has rarely been found in panic patients. In a positron emission tomography (PET) study (Bisaga et al., 1998), a heightened level of glucose metabolism of panic patients was found in the left hippocampus and parahippocampus under resting conditions. Confronting fear-inducing stimuli (Bystritsky et al., 2001), PD patients showed increased activation in hippocampal, prefrontal areas (inferior frontal cortex, anterior (ACC), and posterior cingulate cortex (PCC)) and the orbitofrontal cortex (OFC) compared with healthy controls. Similar to Bisaga et al. (1998), Bystritsky et al. (2001) postulated an increased functional connectivity between cingulate, OFC, hippocampus and amygdala, promoting quick and robust associations between emotionally salient experience and later recall. The PET-fluorodeoxyglucose (FDG) study Sakai et al. (2005) reported higher glucose utilization in the bilateral amygdala, along with hippocampus, thalamus, midbrain (periaqueductal gray (PAG)), brainstem areas, and cerebellum among PD patients vs. controls.

To date, neuroimaging studies probing differential functional pre- and post-treatment effects have been rare in PD patients. A PET study (Praško et al., 2004) found similar changes of brain metabolism

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(increases in left prefrontal, temporoparietal, occipital regions; and decreases in the right hemisphere) after treatment with cognitive behavior therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs), but FDG uptake in limbic areas remained unchanged. After 10 sessions of CBT, Sakai et al. (2006) found that glucose utilization decreased in the right hippocampus, left ACC, left cerebellum, and pons, and increased in the bilateral medial PFC among successfully treated PD patients.

In the present study, we used an emotional linguistic go/nogo task to investigate the interaction of cognitive and emotional processes, which plays an important role in emotion regulation. The design consisted of a go/nogo task (cognitive process) to be performed within the context of neutral, negative, and positive words as stimuli (emotional processes). With the same design, we recently found shortest RTs for positive and longest RTs for negative context in healthy subjects (Dietrich et al., personal communication). Inhibition-related activity for the three context types was observed in different areas of the lateral PFC. Additionally, deactivations were found in limbic (neutral context) and striatal (positive and negative context) areas, indicating a concurrent pattern of activation in control-related prefrontal areas with deactivation in emotion-related areas as postulated in the reciprocal suppression system (Drevets and Raichle, 1998).

We investigated the interaction of cognitive and emotional processes in three emotional contexts in PD patients before and after psychodynamic treatment in order to determine 1) how PD patients differed from normal controls regarding cerebral activation and behaviour, and 2) how processing of affective word stimuli changed following psychotherapy. We hypothesized that inhibition-related activity would differ in PD patients before treatment compared with activity in controls, reflecting a disturbance in the reciprocal suppression of the lateral PFC and emotion-related limbic areas (amygdala, hippocampus, anterior insula, and striatal areas). Given panic patients' hypersensitivity to threat (Williams et al., 1996), we expected that patients would rate negative valences of stimulus words more intensely and have a better recall of negative vs. neutral/positive words. We anticipated increased limbic (amygdala) and reduced prefrontal activation related to emotional (esp. threat) processing. We further expected reduction of these differences after improvement of panic symptoms.

2. Methods

2.1. Subjects

Out of 12 consecutive PD patients from the University clinic for psychosomatic medicine in Gießen (Germany), who had completed scanning at intake, nine patients were rescanned after treatment (mean age 32 years; range: 20–45; 6 females). All patients were diagnosed as panic disorders (ICD-10, F41.0), and two were additionally diagnosed with agoraphobia (F40.01). Dropouts did not differ significantly ($P<0.05$) from study completers regarding sex, age, education, and anxiety scores (ASQ, BSQ) before and after treatment**.** Five patients were free of psychotropic medication, and four continued their previous medication with antidepressants (2 SSRI; 2 tri-/tetracyclical antidepressants). One patient currently on benzodiazepines was excluded. Eighteen healthy subjects (mean age 29 years; range: 21–40; 9 females) without psychiatric disorders (screening of the Structured Clinical Interview for DSM IV (Wittchen et al., 1996)) were recruited through advertisements and paid for participation. One subject was on an antidepressant as migraine prophylaxis. All participants were right-handed and gave informed consent prior to participation. Controls and patients did not differ regarding age (two-sample t-test, $P=0.27$), gender (Chi^2, $P=0.41$) and education (Chi^2, $P=0.42$). Patients' trait anxiety (State Trait Anxiety Inventory, STAI-T) mean score was in the pathological range ($M=54.6$, S.D. = 14), 2 S.D.'s above the population norm (Laux et al., 1981), and significantly higher than controls' score ($M=37.06$, S.D. = 6.99; $t=-3.54$, $df=10.1$, $P=0.005$).

2.2. Psychodynamic inpatient treatment

The focus of the intensive 4-week inpatient treatment programme (Beutel et al., 2005) was on the patient's experience of panic and agoraphobic and underlying unconscious conflicts. Treatment was conceptualised according to panic-focused psychodynamic psychotherapy, a manualised short-term treatment with established efficacy (Milrod et al., 1997; 2007), consisting of the following three phases: (a) treatment of acute panic (evaluation, psychodynamic conflicts), (b) treatment of panic/vulnerability (working through conflicts in the transference; conflictual relationship patterns), and (c) termination working through central separation and anger themes in the transference. In the multimodal setting, psychodynamic individual therapy, group therapy, body-oriented therapy, and art therapy were combined.

2.3. Study procedure

2.3.1. Measures

At intake, patients were diagnosed for PD according to the ICD-10 Diagnosis Checklist (Hiller et al., 1995) by trained raters. Main outcome measures were the Agoraphobic Cognitions Questionnaire (ACQ) assessing the frequency of panic-related cognitions (e.g., fear of heart attack), and the Body Sensations Questionnaire (BSQ) measuring the extent of anxiety in regard to bodily sensations (e.g., sweating and palpitations) (Chambless et al., 1984) at intake and discharge. Anxiety was further assessed in patients and controls by the State-Trait Anxiety Inventory (STAI; Laux et al., 1981) as trait (pre-treatment) and state (before and after each scan).

2.3.2. Activation paradigm

Patients were scanned during performance of an emotional linguistic go/nogo task based on Goldstein et al. (2007) before and after treatment; correspondingly, controls were scanned 4 weeks apart.

Behavioural response was cued orthographically: Subjects were instructed to perform a right index finger button press immediately after reading a word appearing in normal font (go trial) and to inhibit this response after reading a word in italicized font (nogo trial).

We used two linguistically matched and carefully pretested wordlists with words of neutral, negative, and positive valence. Negative words from a large pool of anxiety-related words from the literature (DSM IV research criteria (American Psychiatric Association, 2000), Dresden anxiety dictionary (Berth, 1998)) were rated by experts for suitability and valence. Negative words reflected salient concerns of PD patients (e.g., dying, infarction, and helpless). Positive and neutral words were matched to the negative words according to part of speech (noun vs. verb/adjective), word length (number of syllables), and relative frequency of usage in German speech (Institute for German Language, Mannheim). Each of the two wordlists consisted of 60 words per valence (48 for presentation, 12 distractors each for use in a recognition task). In a pilot study with PD patients and healthy controls, the two lists did not differ regarding reaction time, valence, and recognition rate.

At each scan one of the two wordlists was used for each participant. The order of the two wordlists was alternately assigned to the first and second scan for each participant, counterbalanced across group (controls and patients) and sex.

The task consisted of six main conditions (NeutralGo, NeutralNogo, NegativeGo, NegativeNogo, PositiveGo, and PositiveNogo), presented as blocks in a pseudo-random order in four runs (total of 24 blocks), in order to control for order and time effects. Each block consisted of 12 different words of the same valence in order to manipulate the emotional context (Fig. 1).

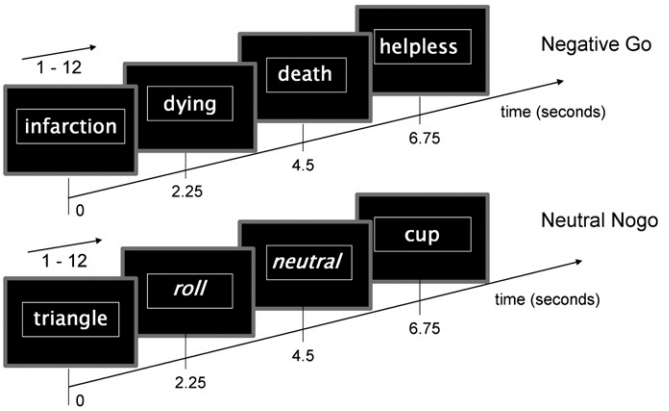

Fig. 1. Word presentation in the emotional go/nogo design illustrated by the examples of NegativeGo and NeutralNogo. Each block consisted of 12 different words of the same valence. Each word was presented in white letters on black background in a white frame for 1.5 s followed by a 0.75 s inter-stimulus interval. A resting period of 10 s followed each block.

In go blocks all the words were presented in normal font (100% go trials) in order to induce a pre-potent motor response. Nogo blocks contained 50% nogo trials (words in italicized font) and 50% go trials, requiring the inhibition of the motor response.

Stimulus presentation and response acquisition (button press) were performed with the software "Presentation" (Neurobehavioural Systems, Inc., Albany, CA). Stimuli were projected on a screen at the head side of the scanner, where subjects could see them on a mirror mounted on the head coil. Task instructions (to respond as fast as possible with a button press at the appearance of a word unless it was in italicized font) were given to the subjects individually before entering the scanner room and at the beginning of the experiment via the projection screen. Subjects were not informed about the existence of separate blocks (go/nogo and emotional). A practice run (NeutralNogo) preceded the experiment in order to ensure comprehension of the task instructions and engagement in the task.

After each imaging session, half of the consecutive subjects were instructed to complete a word recognition task. Based on the respective wordlist (144 presented and 36 distractor words), they were asked to decide for each word if they had seen it in the experiment or not. One half of the subjects completed the recognition task after the first, the other half after the second scan. This procedure was used in order to avoid confounding the task with memorizing effects at the second scan (subjects who completed the task at first scan were told that they would not be asked this again immediately before the second scan). Then all subjects rated the valence of each word on a 7-point Likert scale, followed by a short debriefing.

2.3.3. Image acquisition

Imaging data were acquired with the 1.5-T Siemens Magnetom Symphony (Erlangen, Germany) at the Bender Institute of Neuroimaging (BION), Gießen, Germany. A high-resolution T1 weighted anatomical MRI scan (160 slices; 1 mm × 1 mm × 1 mm; no gap; FOV: 250 mm, 256 × 256 matrix; TR: 1900 ms; TE: 4.18 ms; flip angle = 15°) was acquired prior to the functional measure. T2 weighted echo planar imaging (EPI) was used to obtain blood oxygen level dependent (BOLD) contrasts (TE: 60 ms; flip angle = 90°; FOV: 190 mm, 64 × 64 matrix), and each volume contained 30 transversal slices (5 mm thick, no gap), covering the whole brain. A total of 306 volumes (TR: 3000 ms) were acquired over 15 min.

2.3.4. Image processing and data analysis

The MRI data were analyzed using customized SPM software (Wellcome Dept. of Imaging Neuroscience, London, UK) implemented within MatLab (Mathworks, Inc., Sherborn, MA, USA).

2.3.4.1. Image processing. The anatomical T1 images were reoriented to the AC-PC line, subsequently deskulled using BET 1.1 (Brain Extraction Tool implemented in FSL 3.2; http://www.fmrib.ox.ac.uk/fsl) and inhomogeneity corrected. The EPI images were 1) corrected for sequential slice timing, 2) reoriented to the AC-PC line, 3) realigned to the first image of the first session of the corresponding subject to correct for slight head movements between scans, 4) coregistered to the individual anatomical T1 image subject, and 5) spatially normalized to the Montreal Neurologic Institute (MNI average 152 T1 brain) version of the standardized coordinate space (Talairach and Tournoux, 1988) based on the preprocessed T1 image of the subject, and spatially smoothed with a 9 mm full width at half maximum isotropic Gaussian kernel to increase the signal to noise ratio.

2.3.4.2. Data analysis. Statistical analysis of the fMRI data was performed using the general linear model in SPM (Friston et al., 1995). At single subject level responses were modeled for each of the two sessions (in one analysis) for the six main conditions using a boxcar function convolved with a prototypic hemodynamic response function. As regressors of no interest, realignment parameters, first-order derivatives of the regressors for the main conditions and global signal (adjusted proportional scaling) were implemented (Andersson et al., 2001; Desjardins et al., 2001).

Effects at each brain voxel were estimated by a least squares algorithm, and regionally specific effects were then compared using linear contrasts. For each subject, contrast images were generated for condition effects at both scanning times and the differential before/after effects between the two scanning sessions (S1–S2) as interaction terms. To investigate the reciprocal suppression system, contrasts for inhibition-related activity were generated comparing nogo and go conditions within each context type (e.g.: NegativeNogo–NegativeGo). To investigate emotional processing, contrasts were generated comparing emotional (positive and negative) with neutral conditions only within go, the condition with lowest behavioural demand load in this design (e.g.: NegativeGo–NeutralGo). Resulting contrast images were entered into group analyses using random-effects models (Worsley et al., 2002). For the group analysis, two-sample *t*-tests comparing patients and controls were performed, generating statistical parametric maps (SPMs) of the *t* statistic (SPM{t}), which were transformed to a unit normal distribution (SPM{z}).

Table 1
Comparison of panic-related anxiety at pre- and post-treatment in panic disorder patients ($n = 9$).

	S1	S2	*t*-value	*P*	Effect size *d*
	Mean (S.D.)	Mean (S.D.)			
ACQ-score	2.04 (0.67)	1.62 (0.57)	3.07	.015	0.68
BSQ-score	3.00 (0.83)	2.20 (0.72)	2.27	.053	1.03

ACQ: Agoraphobic Cognitions Questionnaire; BSQ: Bodily Sensations Questionnaire; S1: pre-treatment measure; S2: post-treatment measure; S.D.: standard deviation.

Table 2
State anxiety (STAI-S) at pre- and post-treatment before and after each scan: panic disorder patients (PD) vs. controls (C).

	S1		S2	
	Before scan	After scan	Before scan	After scan
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
PD ($n = 9$)	49.33 (14.15)	42.33 (8.82)	41.44 (12.97)	34.60 (8.43)
C ($n = 18$)	34.28 (5.86)	35.17 (8.02)	34.06 (5.03)	33.11 (4.20)

PD: panic disorder patients; C: controls; S1: pre-treatment measure; S2: post-treatment measure; S.D.: standard deviation.

Table 3
Valence ratings of positive, neutral, and negative words at pre- and post-treatment: panic disorder patients (PD) vs. controls (C).

	S1			S2		
	Positive	Neutral	Negative	Positive	Neutral	Negative
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
PD ($n=9$)	6.21 (0.42)	4.22 (0.18)	1.98 (0.69)	5.93 (0.47)	4.31 (0.26)	2.00 (0.55)
C ($n=18$)	5.73 (0.41)	4.25 (0.20)	2.44 (0.53)	5.53 (0.43)	4.16 (0.17)	2.58 (0.42)

Valence rating: 1 — very unpleasant; 4 — neutral; 7 — very pleasant; PD: panic disorder patients; C: controls; S1: pre-treatment measure; S2: post-treatment measure; S.D.: standard deviation.

The statistical significance for the group-level comparisons was assessed based on Gaussian random field theory. In order to correct for multiple comparisons, small volume corrections (SVCs) were performed for a priori defined regions of interest. Regarding comparisons at S1, SVCs were performed using anatomical masks (based on automated anatomical labeling structures, AAL; Tzourio-Mazoyer et al., 2002) of a priori regions of interest: ventral and dorsal lateral PFC (VLPFC: opercular and triangular part of the inferior frontal gyrus and DLPFC: dorsolateral part of the medial frontal gyrus), medial and lateral OFC (medOFC: gyrus rectus and the orbital part of the superior frontal gyrus and latOFC: orbital parts of the middle and inferior frontal gyrus), supplementary motor area (SMA), ventral and dorsal anterior cingulate cortex (the border between dorsal and ventral ACC was set at a line between $x=0-\pm16$, $y=28$, $z=14$ and $x=0-\pm16$, $y=46$, $z=32$ following Steele and Lawrie (2004)), anterior insula ($y>0$), caudate ncl., putamen, amygdala, hippocampus, and parahippocampus. Regarding the analyses at S2 and the interactions with time (S1–S2), we used a priori regions based on significant activations in the pre-treatment analysis (sphere of 9 mm radius, centered at the peak activation in S1) in order to investigate if initial differences in activation persisted at S2. For unspecified regions, *P*-value corrections based on false discovery rate were used. Activations were considered significant at $P\leq0.05$ and as trend at $P\leq0.08$ (corrected). MNI coordinates were transformed into Talairach coordinates using the nonlinear Yale MNI to Talairach conversion algorithm (http://www.biomagesuite.org/). Figures display activations with a threshold of $P<0.01$ (uncorrected) to show the spatial extent of activations.

Behavioural data and anxiety scores were analyzed with SPSS 12 (repeated measures ANOVAs; paired *t*-tests, two-tailed) setting the level of significance at $P<0.05$ with Greenhouse-Geisser adjustment for *F*-statistics and Bonferroni corrections for multiple comparisons in post hoc analyses.

3. Results

3.1. Treatment effects

Panic-related anxiety scores of patients declined from intake to discharge as shown in Table 1. The frequency of panic-related cognitions (ACQ score) declined significantly from intake to discharge from the pathological to normal range (Chambless et al., 1984). A similar decline in anxiety in regard to bodily sensations (BSQ score) barely missed significance ($P=0.053$). Effect sizes were moderate to high (ACQ: $d=0.68$; BSQ: $d=1.03$).

State anxiety scores before and after each scan are shown in Table 2. State anxiety was significantly higher for patients vs. controls (main effect of Group: $F=11.22$; $df=1, 25$; $P=0.003$). Patients' state anxiety declined from an increased level at S1 to the level of controls at S2, while controls' anxiety scores did not change over time (interaction of Scan × Group: $F=5.81$; $df=1, 25$; $P=0.024$).

3.2. Behavioural data

Valence ratings revealed highly significant differences between the three emotional categories in the anticipated directions for the whole group of participants (main effect of Valence: $F=432.78$; $df=1.15$, 28. 74; $P<0.001$). Patients rated negative words as more unpleasant and positive words as more pleasant than controls (interaction of Valence × Group: $F=7.79$; $df=1.15$, 28.74; $P=0.007$) (Table 3). These differences were comparable at both times (interaction of Scan × Valence × Group: $F=1.74$; $df=1.56$, 38.96; $P=0.194$).

The relative *recognition rates* (Table 4) of the words presented during the scans were highest for negative and lowest for neutral words (main effect of Valence: $F=60.74$; $df=1.83$, 45.65; $P<0.001$). Patients recognized negative words better and neutral words worse than controls (interaction of Valence × Group: $F=4.99$; $df=1.82$, 45.65; $P=0.013$)[1].

Reaction times (RTs) were significantly longer within nogo blocks (512.2 ms) compared with go blocks (480.7 ms) at both scans ($F=35.02$; $df=1, 24$; $P<0.001$). The overall valence effect on reaction time (RT) was significant ($F=3.933$; $df=1.68$, 40.27; $P=0.034$): RTs were shorter for positive (497.3 ms) and neutral (497.7 ms) than for negative words (506.5 ms). However, RT differences for the three valences were observed only in go blocks (Valence × Inhibition: $F=3.25$; $df=1.89$, 45.46; $P=0.051$). Patients did not differ from controls regarding valence-related RT (Valence × Group: $F=1.31$; $df=1.68$, 40.27; $P=0.276$). Patients' RTs tended to decrease from S1 to S2 compared with controls' RTs (Scan × Group: $F=3.06$; $df=1, 24$; $P=0.093$).

Mean *error rates* for the discrete conditions were low (omission: 0 to 1.5%; commission: 2.8 to 6.0%). Only the relative omission error rate was higher in the nogo compared with the go condition ($F=5.63$; $df=1, 24$; $P=0.026$). There were no significant Group or Scan (treatment) effects for both error types.

3.3. fMRI data

Differences between patients and controls in emotion- and inhibition-related brain activity at intake and discharge are shown in Table 5.

3.3.1. Emotional context related activation

Compared with controls, patients showed stronger activation in the SMA and less in lateral prefrontal areas (negative: VLPFC; positive: DLPFC) at S1 for *both emotional contexts* (NegativeGo–NeutralGo and PositiveGo–NeutralGo). *Negative context related activation* was further increased for patients in the left hippocampus reaching into the amygdala (cf. Fig. 2a) and decreased as a trend in the right putamen. At discharge (S2), no more significant differences between patients and

[1] Note: In order to prevent subjects from actively memorizing the words instead of focussing on the go/nogo task, each subject only performed the recognition task once (either after the first or after the 2nd scan), thereby ensuring the comparability of the conditions of task execution at the two measurement times. Therefore we could not analyze these data meaningfully with regard to Scan (treatment) effects.

Table 4
Recognition rates of positive, neutral, and negative words: panic disorder patients (PD) vs. controls (C).

	Positive	Neutral	Negative
	Mean [%], (S.D.)	Mean [%], (S.D.)	Mean [%], (S.D.)
PD ($n=9$)	58.33 (19.82)	37.96 (17.27)	75.00 (22.02)
C ($n=18$)	58.33 (21.35)	45.00 (20.92)	65.51 (20.98)

PD: panic disorder patients; C: controls; S.D.: standard deviation.

controls could be found in these areas; there remained only a trend ($P=0.085$) for a decreased activation in the VLPFC related to negative context. We found an additional increased activation for patients in the left middle temporal gyrus (MTG) at S2. No significant interaction effects between S1 and S2 for patients vs. controls were found.

3.3.2. Inhibition-related activation

Inhibition-related activation in neutral context (NeutralNogo>NeutralGo) was increased for patients compared with controls in the left amygdala and the hippocampus at S1 (Fig. 2b, left). There were additional trends ($P\leq0.08$) toward an increase in the SMA and a decrease in the right VLPFC (Table. 5, Fig 2b, right). Patients' activation pattern was reversed compared with the pattern in controls (Fig. 3). In the VLPFC patients showed decreased activation in the go condition, and controls showed increased activation in the nogo vs. go condition. In the SMA and the amygdala/hippocampus patients showed increased and controls a decreased inhibition-related activation (comparing nogo vs. go). At S2 patients and controls did not differ in these or other brain areas, and we could not find a significant interaction effect.

In negative context (NegativeNogo>NegativeGo) we found a marginal increase ($P=0.069$) in the right hippocampus (patients>controls, Fig. 2c), without any differences in prefrontal areas, specifically the DLPFC, where we previously found an activation for controls (controls only analysis ($n=18$), comparison of NegativeNogo vs. NegativeGo: right DLPFC at 33 8 42, $Z=4.09$, $P_c=0.054$ and left DLPFC at −33 44 28, $Z=4.26$, $P_c=0.034$). Results depicted in Fig. 4 indicate that in these DLPFC areas both groups showed increased inhibition-related activations (nogo vs. go) and a different pattern in the hippocampus with a relative increase (lesser deactivation) in patients and a decrease in controls for nogo vs. go. No difference in hippocampal activity was found at S2, and the interaction revealed that activation in this area tended ($P=0.072$) to decline from S1 to S2 for patients vs. controls. Additionally we found an increased activity in the left caudate nucleus at S2 for patients.

Inhibition-related activation in positive context (PositiveNogo>PositiveGo). Patients showed decreased activations in the left VLPFC and lateral OFC and a trend for an increased activity in the right amygdala compared with controls (Fig. 2d). As indicated in Fig. 5, activation patterns were reversed for patients and controls in the VLPFC and the amygdala, with controls showing increased and patients showing decreased inhibition-related activation (nogo vs. go) in VLPFC, and patients showing increased and controls showing decreased inhibition-related activations in the amygdala. In the lateral OFC inhibition-related activation was increased for both groups but greater in controls. No differences in the activations between patients and controls were observed at S2. Differences in the change of activation were not found in interaction terms, although left VLPFC activation only marginally failed the threshold for a trend toward an increase for patients vs. controls ($P=0.099$).

In summary, at S1, patients showed a reversed pattern of inhibition-related activation compared with controls in neutral and positive context with a decrease in lateral prefrontal areas and an increase in amygdala/hippocampal areas. Within the negative context also, an increase in the hippocampus could be observed, but not accompanied by a decrease in a lateral prefrontal area, especially the DLPFC, where we previously found an activation in controls (Fig. 2b, c, d). At S2 those differences could no longer be observed.

In order to ascertain potential effects of psychotropic medication on brain activation patterns, additional analyses compared patients with and without medication at S1. These analyses revealed no differences between medicated and unmedicated patients regarding the areas in which differences were found between patients and controls.

Table 5
Emotion-related and inhibition-related activations of PD patients ($n=9$) vs. controls ($n=18$) at first scan (S1), second scan (S2) and for the change over time (S1–S2).

Comparison	Region		Coordinates			S1		S2		S1–S2	
			x	*y*	*z*	*z*-value	P_c^a	*z*-value	P_c^b	*z*-value	P_c^b
Emotion-related activity within Go											
Negative-Neutral (PD>C)	**SMA**	**R**	**3**	**−1**	**59**	**4.00**	**0.017**				
	Hippocampus	**L**	**−23**	**−17**	**−9**	**3.73**	**0.034**				
	Amygdala	*L*	*−23*	*−11*	*−9*	*2.88*	*0.075*				
	MTG	**L**	**−60**	**−54**	**2**			**4.78**	**0.050***		
Negative-Neutral (C>PD)	**VLPFC**	**R**	**51**	**16**	**12**	**−4.33**	**0.007**				
			46	14	17			−3.07	0.085		
	Putamen	R	*29*	*−15*	*14*	*−3.45*	*0.080*				
Positive-Neutral (PD>C)	SMA	R	*3*	*−2*	*57*	*3.54*	*0.067*				
Positive-Neutral (C>PD)	DLPFC	R	*32*	*48*	*6*	*−3.98*	*0.067*				
Inhibition-related activity (Nogo–Go)											
Neutral (PD>C)	SMA	L	*−8*	*−5*	*57*	*3.51*	*0.053*				
	Amygdala	**L**	**−20**	**−11**	**−9**	**3.18**	**0.035**				
	Hippocampus	**L**	**−20**	**−14**	**−11**	**3.80**	**0.027**				
Neutral (C>PD)	VLPFC	R	*51*	*16*	*12*	*−3.71*	*0.052*				
Negative (PD>C)	Hippocampus	R	*23*	*−19*	*−6*	*3.48*	*0.069*				
			26	*−19*	*−6*					*3.14*	*0.072*
	Caudate	**L**	**−14**	**−15**	**23**			**4.80**	**0.039***		
Positive (PD>C)	Amygdala	R	*20*	*−8*	*−9*	*3.04*	*0.058*				
Positive (C>PD)	**VLPFC**	**L**	**−43**	**1**	**24**	**−4.38**	**0.004**				
			−43	0	26					−3.01	0.099
	lat OFC	**L**	**−41**	**41**	**−6**	**−3.73**	**0.031**				

PD = PD patients, C = controls; R = right, L = left; *x y z* indicate Talairach coordinates; P_c = small volume corrected *P*-value based on a) predefined anatomical (AAL) regions of interest and b) spheres of 9-mm radius, centered at the peak activation in S1 for regions of interest; *Indicating FDR for unspecified regions. Bold: significant activations ($P_c\leq0.05$); italics: trend for significant activation ($P_c\leq0.08$).

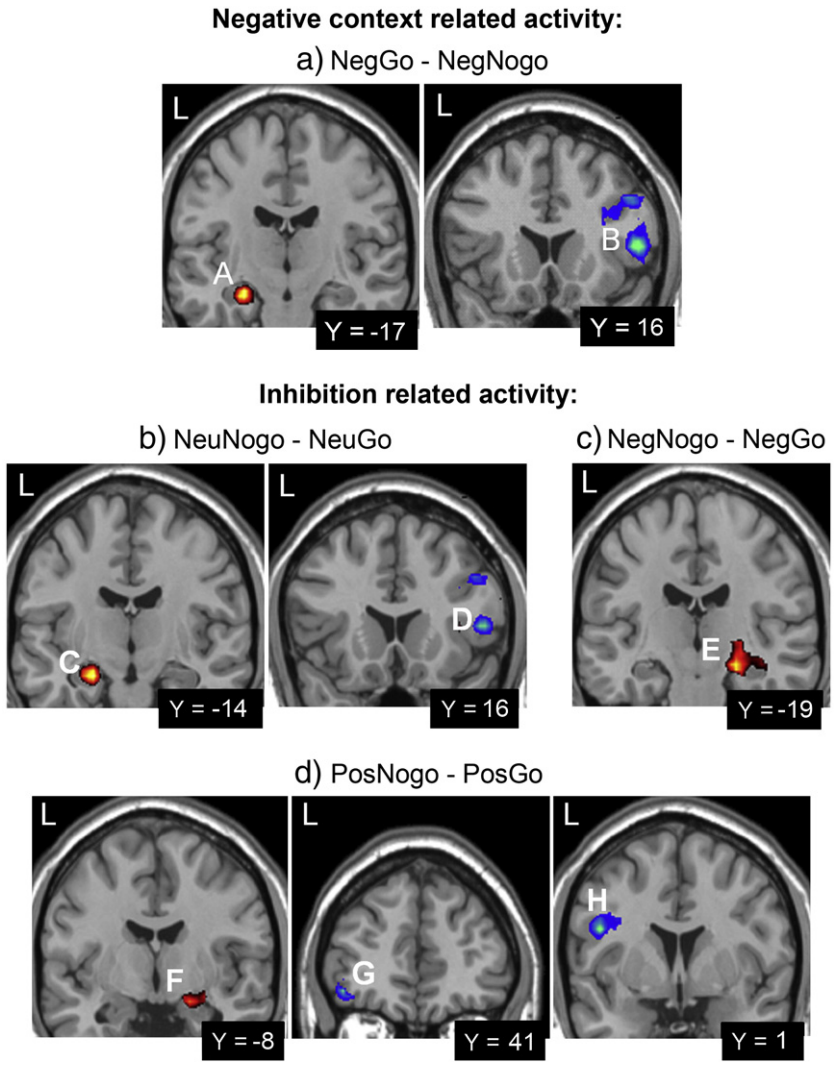

Fig. 2. Main results for negative context- and inhibition-related activation for patients compared with controls regarding the reciprocal limbic-prefrontal suppression system at pre-treatment scan. Red/yellow: increased activation for patients vs. controls; blue: decreased activation for patients vs. controls, L = left; a) increased amygdala/hippocampal (A) and decreased VLPFC (B) activation related to negative context for patients. Inhibition-related activation under b) neutral, c) negative and c) positive context. Increased amygdala/hippocampal (C, E, and F) and decreased lateral prefrontal (D, G, and H) inhibition-related activations for patients vs. controls.

4. Discussion

To our knowledge this is the first controlled fMRI study of the effects of psychodynamic psychotherapy on brain functioning. Short-term inpatient treatment of panic disorder patients was conceptualised based on a manual with established efficacy (Milrod et al., 2007) embedded in an intensive inpatient treatment setting. Panic patients were scanned before and after treatment; healthy controls were scanned at comparable intervals. We used an emotional linguistic go/nogo task to investigate the neural systems interaction of cognitive and emotional processes in negative, neutral, and positive contexts taking care to select negative words specific for PD patients and to linguistically match them to neutral and positive words.

Limitations of the study reside in the brevity of the psychodynamic treatment which — even though effective — has not been a strict replication of PFPP; it was rather implemented in an intensive, multimodal inpatient treatment setting with a psychodynamic orientation. Therefore, our results cannot be solely ascribed to the effects of outpatient PFPP, but its implementation in a psychodynamic psycho-therapy treatment setting. It was not possible to recruit medication-free patients; however, we maintained medication throughout the trial and excluded a patient on benzodiazepines. Medicated and unmedicated patients did not differ regarding the central behavioural and brain activation patterns. Nevertheless, an influence of medication cannot totally be ruled out. The patient sample was small, and the study should be replicated with more subjects.

As expected (Beutel et al., 2005), panic patients improved significantly in an intensive psychodynamic treatment of 4 weeks' duration; average scores of our main outcome measures of panic-related anxiety (cognitions, body symptoms) significantly decreased from the pathological to the normal range with moderate to large effect sizes. Initially high state anxiety scores before and after the first scan declined to the level of normal controls by the second scan.

Furthermore patients' RTs tended to decrease from pre- to post-treatment as compared with controls, which might reflect a lesser distraction after treatment due to a reduced load by symptomatology.

For all subjects, the inhibitory demand of nogo trials was reflected in increased RTs compared with go trials. According to our hypotheses, patients rated negative and positive words more strongly than controls. As expected, patients specifically recalled negative words better and neutral words worse than controls, reflecting their hypervigilance to threat.

As we had further expected, PD patients, as compared with normal controls, showed a decreased activation in lateral prefrontal areas related to negative context, accompanied by increased limbic

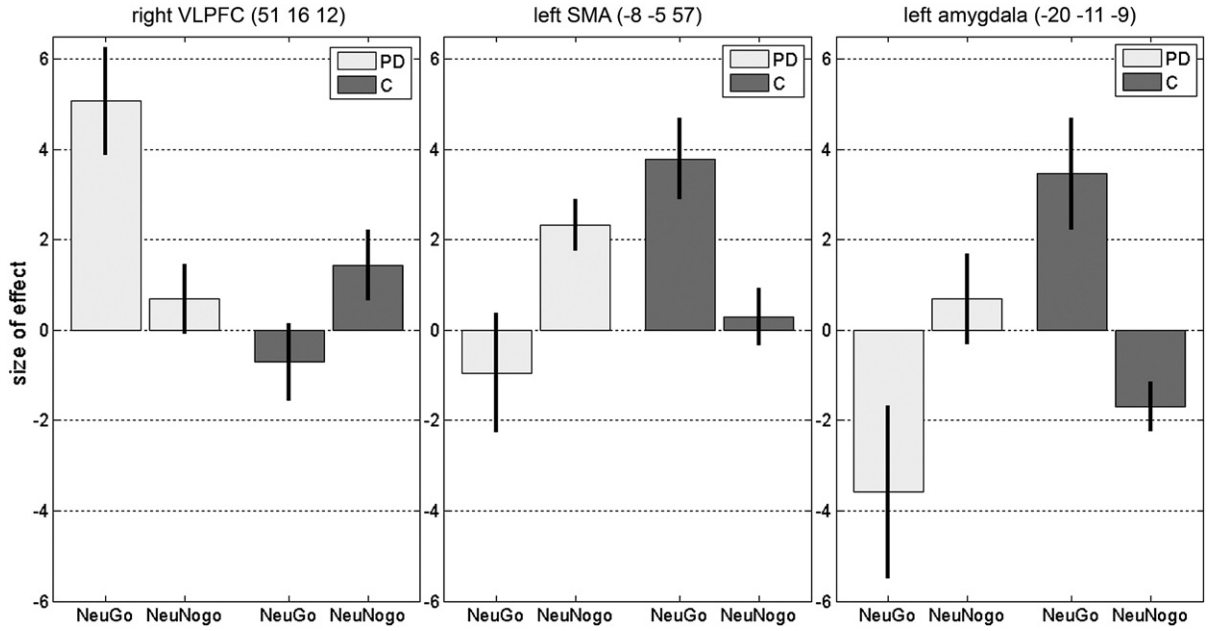

Fig. 3. Inhibition-related activation patterns in neutral context for PD and C at pre-treatment scan. Displayed are the parameter estimates for the single conditions NeutralGo (NeuGo) and Neutral Nogo (NeuNogo) for patients (PD) and controls (C) vs. baseline in prefrontal areas and the amygdala at voxels with significantly different inhibition-related activation for patients vs. controls.

activation before treatment. Increased hippocampus/amygdala activity may be associated with patients' preferential recall of threat words. These findings support the hypothesis of a disturbed fronto-limbic neural circuit underlying behavioural and emotional regulation under threat conditions. As we had further assumed, these differences were no longer found after psychodynamic treatment. It cannot be ruled out that a lack of differences in the medial orbitofrontal cortex could be due to signal loss.

Additionally, inhibition-related activation was reversed compared with controls in the neutral and positive contexts before therapy. Patients did not show the *normal* activation pattern of frontal activation and limbic/striatal deactivation as controls did. Inhibition-related activation as measured with go/nogo designs can serve as an indicator for the behavioural regulation system, as response inhibition is a basic process of behavioural control. Lateral prefrontal activations have often been reported and seem to play a crucial role for the inhibition process (e.g. Garavan et al., 1999; Aron and Poldrack, 2005). Deactivations in limbic/striatal areas may be associated with the suppression of motivational/emotional processing due to a higher cognitive load in normal controls. Thus, our findings are likely to indicate a disturbance of the emotional behavioural regulation, manifested also under neutral and positive contexts. For inhibition within a negative context, patients also showed stronger emotion-related activity in the ventral hippocampus. As dorsolateral prefrontal

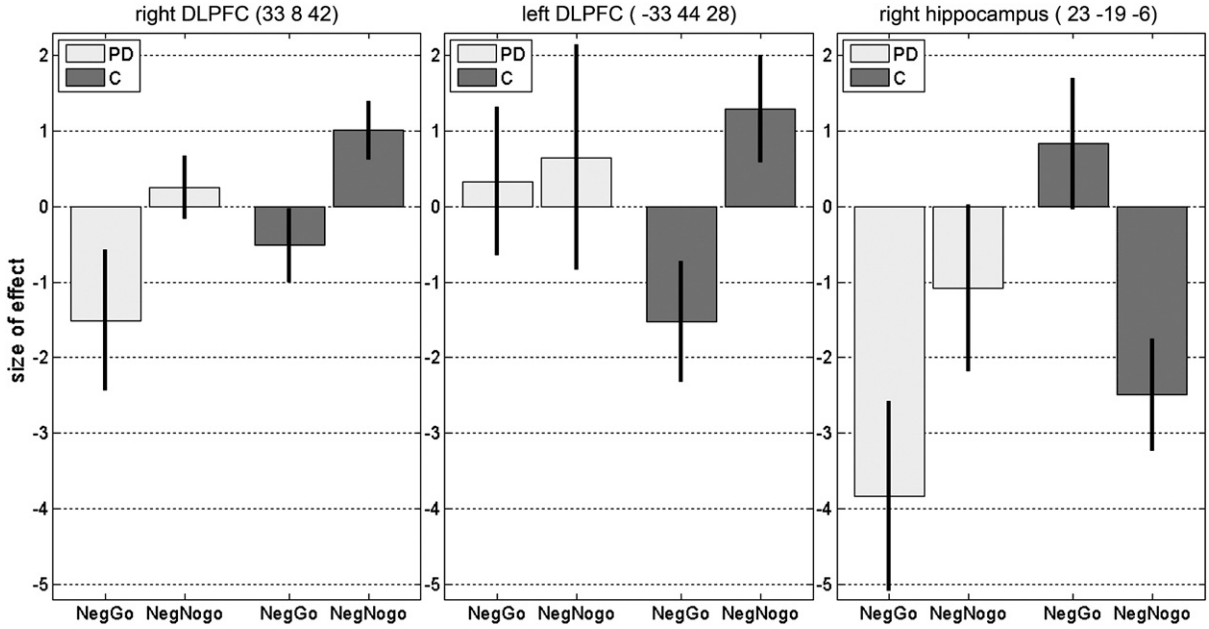

Fig. 4. Inhibition-related activation patterns in negative context for PD and C at pre-treatment scan. Displayed are the parameter estimates for the single conditions NegativeGo (NegGo) and Negative Nogo (NegNogo) for patients (PD) and controls (C) vs. baseline in the DLPFC at voxels with significant inhibition-related activations for controls and the hippocampus at the voxel with significantly different inhibition-related activation for patients vs. controls.

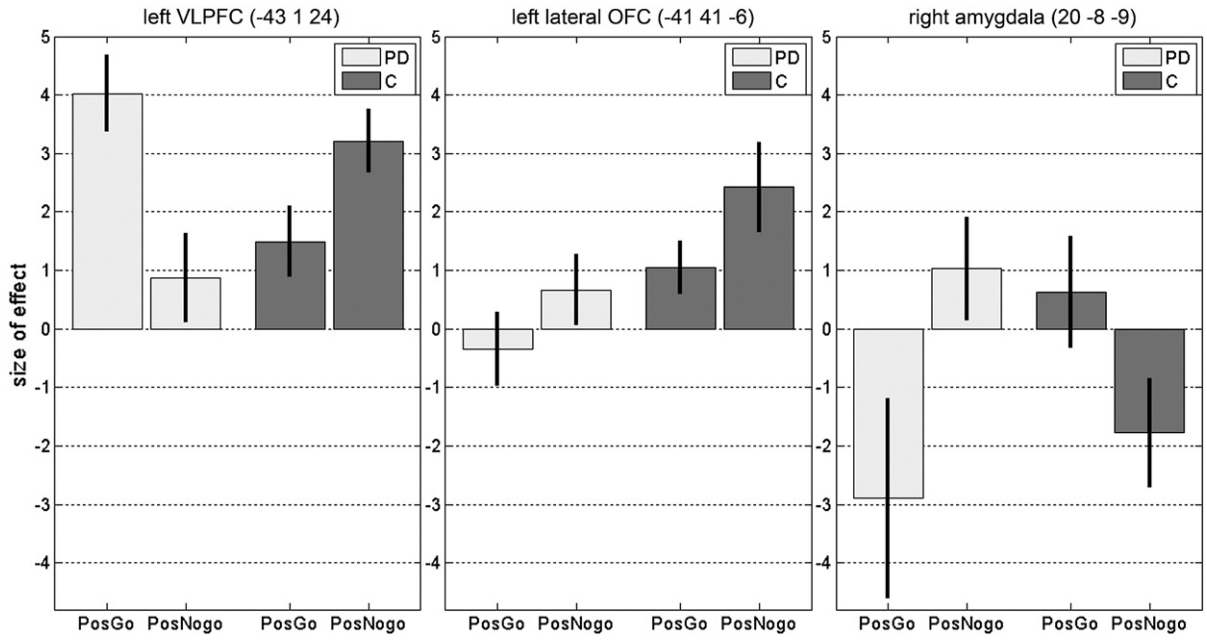

Fig. 5. Inhibition-related activation patterns in positive context for PD and C at pre-treatment scan. Displayed are the parameter estimates for the single conditions PositiveGo (PosGo) and Positive Nogo (PosNogo) for patients (PD) and controls (C) vs. baseline in prefrontal areas and the amygdala at voxels with significantly different inhibition-related activations for patients vs. controls.

activity was not reduced compared with controls, this disturbance of emotion regulation may be due either to a reduced functionality of the DLPFC or a hypersensitivity of the hippocampus to negative words or both. Increased activations in the SMA for patients under inhibitory demands in neutral and emotional (vs. neutral) conditions point to altered patterns of planning and preparation of motor behaviour, possibly associated with increased affect. It is also possible that neural activity in cognitive-processing areas is suppressed by intense emotional states, which has been discussed as a potential mechanism by which anxiety or depression may interfere with cognitive performance. Determining the causal relationships remains an important issue for future studies (Drevets and Raichle, 1998).

Following treatment, differences between patients and controls in the prefrontal-limbic circuit were no longer found. Normalization of limbic function was supported by a significant reduction of hippocampus activity from first to second scan for inhibition in a negative context. On the other hand, in this contrast, a new difference in activation occurred at discharge with the caudate nucleus showing increased activity for patients, a structure which has also been reported as related to behavioural and emotional processing. Perhaps increased subcortical activation may be related to increased automatic, unconscious control. Other significant interactions between scan and group were not found. However, it has to be considered that interaction analysis reduces statistical power in a study with a relatively small sample size. The lack of differences at S2 can be considered as an indicator of normalization of function, given the considerable clinical improvement of patients. Follow-up data on the stability of changes are expected to identify neurobiological predictors of long-term outcome.

One of the major hypotheses on the effect of CBT on brain functioning concerns a more effective ("top-down") regulation of hyperexcitable limbic structures by prefrontal control systems (Gorman et al., 2000; Kennedy et al., 2007). Our results concur with these hypotheses demonstrating both a frontal deactivation and an amygdala/hippocampal hyperactivation in symptomatic panic patients which were normalized when panic symptoms and anxiety levels were reduced following treatment. At this point it seems premature to speculate about specific neurobiological effects of psychodynamic vs. cognitive–behavioural psychotherapy (Beutel et al., 2003).

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