



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

Manfred E. Beutel<sup>a</sup>, Rudolf Stark<sup>b</sup>, Hong Pan<sup>c</sup>, David Silbersweig<sup>d</sup>, Sylvia Dietrich<sup>a,\*</sup>

<sup>a</sup>Clinic for Psychosomatic Medicine and Psychotherapy, University Medicine, Mainz, Germany

<sup>b</sup>BION, University of Giessen, Giessen, Germany

<sup>c</sup>Department of Radiology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

<sup>d</sup>Department of Psychiatry, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

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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.

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### 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 (Pražko et al., 2004) found similar changes of brain metabolism

\* Corresponding author. Klinik für Psychosomatische Medizin und Psychotherapie, Universitätsmedizin Mainz, Untere Zahlbacher Str. 8, D-55131 Mainz, Germany. Tel.: +49 6131 17 4039; fax: +49 6131 17 6212.

E-mail address: [sylvia.dietrich@unimedizin-mainz.de](mailto:sylvia.dietrich@unimedizin-mainz.de) (S. Dietrich).

(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-/tetracyclic 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 popula-

tion 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).

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