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ORIGINAL INVESTIGATION

Multimodal psychodynamic psychotherapy induces normalization of reward related activity in somatoform disorder

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Abstract

Objectives. Somatoform disorder patients demonstrate a disturbance in the balance between internal and external information processing, with a decreased focus on external stimulus processing. We investigated brain activity of somatoform disorder patients, during the processing of rewarding external events, paying particular attention to the effects of inpatient multimodal psychodynamic psychotherapy. *Methods.* Using fMRI, we applied a reward task that required fast reactions to a target stimulus in order to obtain monetary rewards; a control condition contained responses without the opportunity to gain rewards. Twenty acute somatoform disorder patients were compared with twenty age-matched healthy controls. In addition, 15 patients underwent a second scanning session after participation in multimodal psychodynamic psychotherapy. *Results.* Acute patients showed diminished hemodynamic differentiation between rewarding and non rewarding events in four regions, including the left postcentral gyrus and the right ventroposterior thalamus. After multimodal psychodynamic psychotherapy, both regions showed a significant normalization of neuronal differentiation. *Conclusion.* Our results suggest that diminished responsiveness of brain regions involved in the processing of external stimuli underlies the disturbed balance of internal and external processing of somatoform disorder patients. By providing new approaches to cope with distressing events, multimodal psychodynamic psychotherapy led to decreased symptoms and normalization of neuronal activity.

Key words: *fMRI, brain imaging, reward, somatoform disorder, psychotherapy*

Introduction

Somatoform disorders are a group of complex diseases consisting of medically unexplained somatic symptoms (Kirmayer et al. 1994; Stein and Muller 2008; Pedrosa Gil et al. 2009; Hiller et al. 2010). Such disorders have been shown to have the highest prevalence among all mental disorders in primary care (Toft et al. 2005). Furthermore, the economic burden on the health system is twice that of non-somatizing patients (Barsky et al. 2005), rendering somatoform disorders an important research area. Somatoform disorders result in an increase in the patient's attention towards the internal world of the body, which leads to emotional overvaluing of somatic symptoms (Hansell and Mechanic 1985; Fillingim and Fine 1986; Barsky et al. 1988; van Wijk and Kolk 1997; Eriksen and Ursin 2004; Nakao and Barsky 2007; Witthoft and Hiller 2010). This concentration on sensations that occur within the body leads to a decrease in awareness of events in the external world (Pennebaker and Lightner, 1980; van Wijk and Kolk 1997; van der Werf et al. 2002). Based on these findings, dysbalance between internal (such as bodily) and external (such as environmental) stimuli can be assumed.

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The reward system is crucially involved in the processing of stimuli from the external world (Berridge and Robinson 1998; Zink et al. 2004, 2006; Schultz 2010). One of its main functions is the emotional evaluation of external stimuli with regard to their potential signaling of reward or punishment (Berridge and Robinson 2003). Besides, the reward system plays an important role in numerous other processes including the processing of salient (Zink et al. 2004, 2006) or self-related (de Greck et al. 2008; Enzi et al. 2009) stimuli. Dysfunctions of the reward system are relevant in psychiatric diseases including schizophrenia (Heinz and Schlagenhauf 2010) and addiction (Kalivas and Volkow 2005).

Whilst recent studies in somatoform disorder showed that a central structure of the reward system, the striatum, is indeed altered in somatoform disorder patients (Hakala et al. 2002, 2004, 2006), we hypothesized that the increased focus on internal stimuli in somatoform disorder patients may lead to a disturbance in the ability to (emotionally) evaluate external stimuli, thus altering the function of the underlying neural mechanisms.

Psychodynamic concepts explain the concentration of somatic sensations in somatoform disorder by the patient's strategy to deal with emotional distress (Hurwitz 2004; Nijenhuis et al. 2004; Waller and Scheidt 2006). Psychodynamic psychotherapy aims to provide understanding of the stress-causing conflicts and to enable patients to utilize other coping strategies (Vaillant, 1977; Blagys and Hilsenroth 2002; Leichsenring, 2005; Grabe et al. 2008). Through this, psychodynamic psychotherapy aims to restore the balance between the processing and emotional valuing of internal and external stimuli (Beutel et al. 2008).

In this study, we first aimed to investigate brain responses of acute somatoform disorder patients towards rewarding external stimuli. For this, we applied a simplified version of a standard and well established reward paradigm, the Monetary-Incentive-Delay Task (Knutson et al. 2000).We expected to find diminished activation in core reward regions of somatoform patients. Since the striatum region is predominantly engaged in the processing of rewarding (Knutson et al. 2000, 2001) and significant stimuli (Zink et al. 2004, 2006), and since it has also shown structural changes (Hakala et al. 2004) as well as functional hypo-activity (Hakala et al. 2002, 2006) in somatoform disorder patients, we expected this region to be particularly sensitive to the test. In addition, we hypothesized a reduction in neural activity of regions involved in the processing of external stimuli, for instance in the postcentral gyrus and the thalamus. Secondly, we investigated the effect of psychodynamic psychotherapy on neural activity of somatoform disorder patients. We hypothesized that successful psychotherapy should lead to a balanced processing of important external and internal stimuli and to a normalization of brain activity in regions that showed altered function in the acute stage of the disorder.

Methods

Participants

We investigated 20 patients (gender: 12 females, eight males; handedness: 19 right-handed, one left-handed; age: mean = 42.5, SD = 14.0). All patients suffered from a somatoform disorder as ascertained by the Structured Clinical Interview for DSM-IV (German version: SKID (Wittchen et al. 1997)). Further, 13 of the 20 patients fulfilled criteria of an undifferentiated somatoform disorder (DSM-IV: 300.81), five of the 20 patients had a pain disorder (DSM-IV: 307.80), and two of the 20 patients had a somatization disorder (DSM-IV: 300.81). For a description of the leading symptoms described by the acute patients see Table I. All patients were recruited at the start of an inpatient psychotherapy. Patients were recruited from the Department of Psychosomatic Medicine and Psychotherapy of the Otto-von-Guericke-University Hospital in Magdeburg (11/20), from the Department of Psychotherapeutic Medicine of the Fachklinikum Uchtspringe (4/20), and from the Department of Psychosomatic Medicine and Psychotherapy of the AWO Hospital Jerichow (5/20). Six of the

Table I. Leading symptoms.

Leading symptom	*n*
Aphonia	1
Breast pain	1
Decreased appetite	1
Diarrhea	3
Dizziness	1
Dysmenorrhea	2
Ear complaints	1
Headache	5
Heart complaints	2
Hyperhydrosis	3
Intestinal complaints	7
Nausea	5
Pain in neck, shoulder, back, or extremities	5
Sexual dysfunction	4
Shortness of breath	1
Skin complaints	1
Sleep disturbances	3
Visual defects	2
Vomiting	1
Weakness	1

Leading symptoms of the acute patients (n = 20).

20 patients were on psychotropic medication with duloxetine (1/20), duloxetine and trimipramine (1/20), opipramol (1/20), opipramol and paroxetine (1/20), doxepine (1/20), and hypericum (1/20) during the time point of the fMRI session.

Fifteen of the 20 patients (gender: eight females, seven males; age: mean = 42.6, SD = 13.6; 11 undifferentiated somatoform disorder, two somatization disorder, and two pain disorder) also underwent a second fMRI session at the end of their psychotherapy. The time difference between both scanning session was 60 days on average (range: 35–80 days). During the second fMRI session, one patient continued with psychotropic medication with duloxetine and one other patient continued with duloxetine and trimipramine. Five of the 20 patients who participated in the first scanning session were not included in the second scanning session due to premature termination of psychotherapy (3/20), refusal to participate a second time (1/20), or inaccessibility after discharge (1/20).

In addition to the patient group studied, we also investigated 20 gender- and age-matched healthy control subjects (gender: 12 females, eight males; handedness: 16 right-handed, two left-handed, two both-handed; age: mean = 37.0, SD = 10.6, $t(38) = 1.387$; $p_{[\text{two-tailed}]} = 0.173$).

All subjects received financial compensation for their participation in the study. The study was ethically approved by the Institutional Review Board of the Otto-von-Guericke University of Magdeburg/ Germany. After a detailed explanation of the study, all subjects gave informed consent.

Psychodynamic psychotherapy

Standardized inpatient psychodynamic psychotherapy was conducted as recently explained (Grabe et al. 2008; Haase et al. 2008; Huber et al. 2009). The therapeutic regime included psychodynamic individual therapy, psychodynamic group therapy, and medical therapy. Psychodynamic psychotherapy involved the verbalization of emotional and interpersonal problems (Grabe et al. 2008; Leichsenring 2005); the aims were to understand the underlying intrapsychic and interpersonal conflicts and to enable the patient to utilize a broader spectrum of coping strategies. This setting was complemented by music therapy, communicative movement therapy, art therapy, social therapy, and various relaxation methods (Heuft et al. 2002). Patients participated in approximately 10 h of psychotherapy per week. (For a more detailed explanation of the different psychotherapeutic techniques, please refer to the Supplementary Material which is available online.)

Psychological measures

We applied the following psychological measurements to control for differences between the patient group and the group of age-matched healthy subjects. *Somatization:* Somatization was assessed using a German edition of the "Symptom Check List 90" (SCL-90 (Derogatis et al. 1973)). The SCL-90 is a 90-item self-report questionnaire, which contains a number of subscales such as somatization, depression, and anxiety. Here, we focused on the somatization subscale. The SCL-90 somatization score was collected from 16 control subjects, 19 acute patients, and 12 patients after psychotherapy. *Emotional abilities:* To test for emotional comprehension and awareness, we applied a German edition of the "Toronto Alexithymia Scale – 20" (TAS-20 (Bagby et al. 1994; Bressi et al. 1996)), a well established self-descriptive questionnaire. TAS-20 scores were recorded for 19 healthy subjects, 20 patients in the acute stage, and 15 patients after psychotherapy. *Mood state:* Subjective experience of depressive symptoms was assessed with a German edition of the "Beck Depression Inventory" (BDI (Beck et al. 1961)). BDI scores were obtained from 18 healthy subjects, 20 acute patients, and 15 patients after psychotherapy.

Paradigm

We applied a paradigm that contained a combination of two tasks: a reward anticipation task and an emotion perception task. The tasks were separated from each other in a block wise manner. Due to the complexity of the emotion perception task, here we report only results obtained from the reward anticipation blocks.

Experimental design. The fMRI experiment was divided into six blocks of 630 s duration each. Blocks 1, 3, and 5 were reward blocks; blocks 2, 4, and 6 were emotion perception blocks. Prior to entering the scanner each subject read detailed information about the paradigm with all the tasks and completed a couple of trial runs in order to familiarize themselves with the experiment. While lying in the scanner, the patients were shown the stimuli using the "Presentation" software package (Neurobehavioral Systems, Albany, CA); the stimuli were projected onto a matt screen via an LCD projector, visible through a mirror mounted on the head coil.

Reward blocks. The reward task was a modified version of the "Monetary Incentive Delay Task" (MID) as introduced by Knutson and colleagues (2000). Every reward block started with a 6-s presentation

of an instruction. In each reward block a total number of 60 trials were presented in a randomized manner (20 trials with reward anticipation, 20 trials with punishment anticipation, and 20 trials with the anticipation of no outcome). See Figure 1 for a detailed description of the tasks applied.

At the end of all blocks subjects were asked to rate their subjective feeling of contentedness as well as their impression of how easily they were able to overall engage in the reward paradigm.

fMRI data acquisition

The fMRI data were collected in a 1.5 T MR scanner (General Electric Sigma Horizon) via a standard circular polarized head coil. Using a midsagittal scout image, a stack of 23 slices was aligned parallel to the bicomissural plane. During each functional run 320 whole brain volumes were acquired (gradient echo EPI, TR = 2 s; TE = 35 ms; flip angle = 80°; field of View = 200 × 200 mm; slice thickness = 5 mm, inter-slice gap = 1 mm, spatial resolution = 3.125 × 3.125 × 5 mm). Additionally, a T1 weighted image of every subject was acquired.

fMRI data analysis

Image processing and statistical analyses were carried out using the software package AFNI (http://afni.nimh.nih.gov/afni/ (Cox 1996)). Preprocessing included slice-time correction, movement correction, spatial normalization, resampling and smoothing. For each subject, regressors of interest for all relevant conditions were created by the convolution of a canonical, fixed shape hemodynamic response function with the according stimulus time functions (Josephs et al. 1997). Contrast images were calculated by employing linear contrasts to the parameter estimates for the regressors of each event. The resulting contrast images

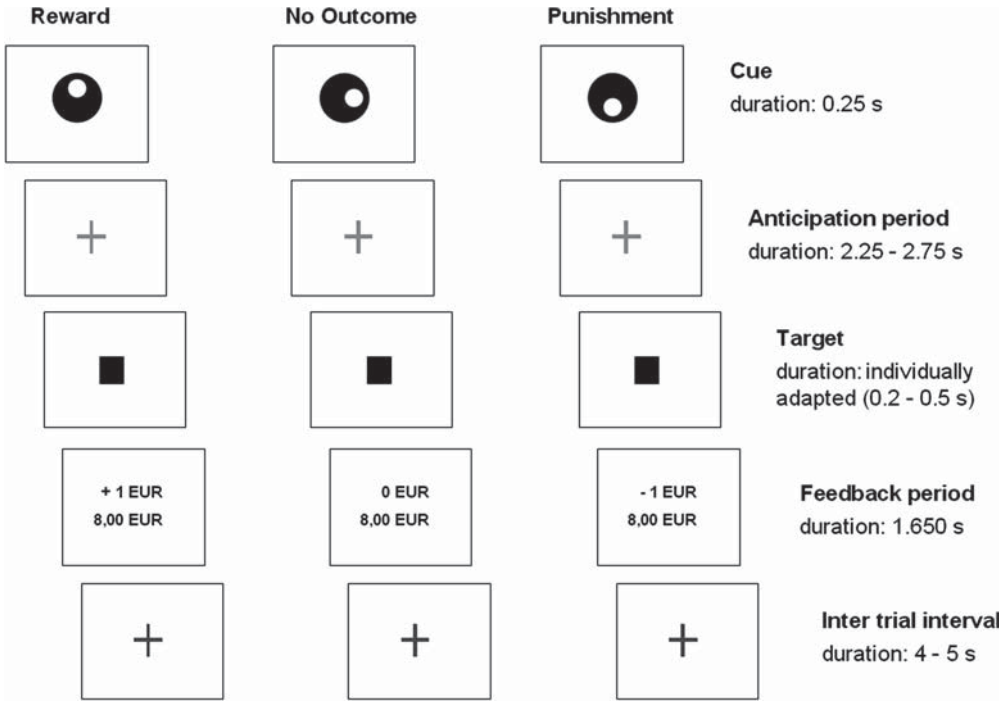

Figure 1. Paradigm of the fMRI study. At the beginning of each trial the cue, a symbol indicating what the possible outcome of the task would be (reward, punishment, or no-outcome) was shown for 0.3s, followed by a 2.25s - 2.75s anticipation period. The trial type indicator was represented by a black circle with a small white circle within it at one of the cardinal points. Each position represented a different trial type. During the anticipation period a light grey colored cross was displayed in the centre of the screen. Every trial required the subject to press a button with the index finger of their right hand, within a certain time during the presentation of the target image. The length of this time period was determined in accordance with the average reaction time obtained in the pre-scan trial run (allowing the difficulty of the task to be modulated according to the individual's ability) and varied between 0.2s and 0.5s. Furthermore, we applied an adapting algorithm to ensure that in approximately 66% of all reward and punishment trials the required response was successful. In reward trials, completing the task successfully resulted in the subject winning €1, whilst failure meant that they would neither win nor lose anything. During punishment trials, a response within the required time period resulted in the subject neither winning nor losing money, whilst an unsuccessful response resulted in €1 being deducted from their total. Finally, in no-outcome trials no money was either won or lost, regardless of whether the subject responded within the required time period or not. Subjects were, however, instructed to still respond to the cue as quickly as possible. Each trial was followed by a feedback stage during which the subject was informed of the outcome. The amount of money won or lost in the preceding trial was displayed, along with the running total for their winnings, for a period of 1.65s. Trials were separated by a 4s to 5s inter trial interval. The end amount of money won during the whole experiment was provided to the subjects as reimbursement for their participation in the experiment.

were then submitted to a second level random-effects analysis. Here, one-sample *t*-tests, independent two sample *t*-tests, and paired *t*-tests were applied (Friston et al. 1995) using corrections for multiple comparisons (Nichols and Hayasaka, 2003).

In a second step, we extracted raw fMRI signals, using sphere-shaped "regions of interest" (ROI, radius 5mm). Mean normalized fMRI signal values were included in the statistical analysis using paired *t*-tests and Spearman correlations. (For a more detailed explanation of the fMRI data analysis, please refer to the Supplementary Material available online.)

Results

Performance

We compared the 20 somatoform disorder patients with the 20 healthy control subjects and found no significant differences in reaction times during the Monetary-Incentive-Delay task. Acute patients had significantly more successful trials when compared to healthy controls (n = 20/20; healthy: mean = 53.1%; acute patients: mean = 60.5%; $t(38) = 3.537$; $p_{[\text{two-tailed}]} = 0.01^{**}$) .When comparing the behavioral results of the 15 subjects that participated in the second fMRI session after psychotherapy, we found no differences that reached statistical significance.

Intra scanner ratings

We did not find differences between healthy subject and acute somatoform patients for intra scanner ratings of engagement in the reward paradigm (n = 20/20; healthy: mean = 77; acute patients: mean = 80; $t(38) = 0.528$; $p_{[\text{two-tailed}]} = 0.600$) and general contentedness (n = 20/20; healthy: mean = 67; acute patients: mean = 71; $t(38) = 0.429$; $p_{[\text{two-tailed}]} = 0.670$). In addition, we were not able to detect differences between acute patients and patients after psychotherapy; neither scanner ratings of engagement in the reward paradigm (n = 15; acute: mean = 82; after psychotherapy: mean = 85; $t(14) = 0.792$; $p_{[\text{two-tailed}]} = 0.441$) nor the ratings of contentedness (n = 15; acute: mean = 72; after psychotherapy: mean = 77; $t(14) = 0.692$; $p_{[\text{two-tailed}]} = 0.500$) showed significant differences.

Psychological tests

In addition to the psychotherapy induced improvement of somatization, alexithymia, and depression scores (please see Figure 2), we also found a significant correlation between psychotherapy induced decreases in SCL-90 – somatization scores and decreases of BDI scores ($r_{[\text{Spearman}]} = 0.558$; $p_{[\text{one-tailed}]} = 0.030^{*}$). Further, improvement of TAS-20 scores and improvement of BDI

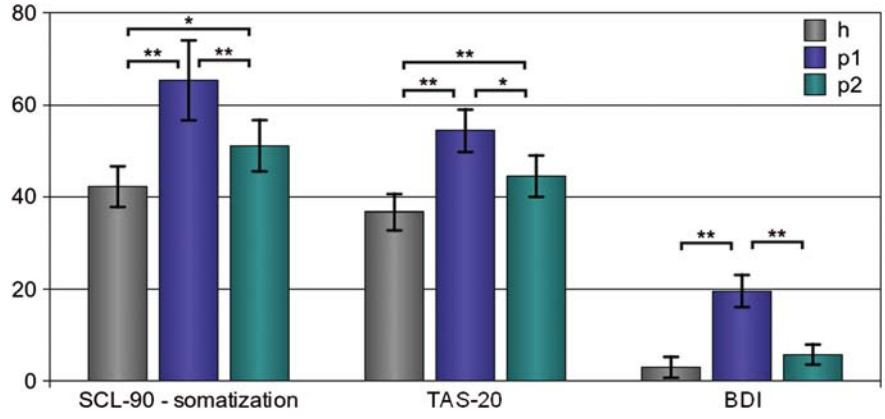

Figure 2. Therapeutic success. Mean values of the Symptom-Check-List-90 somatization scale (SCL-90 – somatization), the Toronto-Alexithymia-Scale-20 (TAS-20), and the Beck-Depression-Inventory (BDI) for healthy subjects (h), acute patients ($p1$), and patients after psychotherapy ($p2$). SCL-90 – somatization: Compared to healthy subjects, acute patients showed a significant increase in somatization scores (n = 16h/19p; mean difference = 23.13; t(33) = 4.718; $p_{[\text{one-tailed}]} < 0.001^{**}$). After psychotherapy, somatization scores decreased compared to the acute stage (n = 12; mean difference = 16.58; t(11) = 3.565; $p_{[\text{one-tailed}]} < 0.002^{**}$), but were still greater when compared to the healthy subjects (n = 16h/12p; mean difference = 8.90; t(26) = 3.247; $p_{[\text{two-tailed}]} < 0.011^{*}$). TAS-20: Acute patients showed significantly greater scores in the TAS-20 when compared to the healthy controls (n = 19h/20p; mean difference = 17.66; t(37) = 6.115; $p_{[\text{one-tailed}]} < 0.001^{**}$). After psychotherapy, the patients showed a significant decrease in TAS scores (n = 15; mean difference = 8.87, t(14) = 2.456, $p_{[\text{one-tailed}]} = 0.014^{*}$); however, their scores were still elevated compared to the group of healthy subjects (n = 19h/15p; mean difference = 7.78; t(32) = 2.788; $p_{[\text{two-tailed}]} = 0.009^{**}$). BDI: BDI scores of acute somatoform patients were increased when compared to healthy subjects (n = 18h/20p; mean difference = 16.60; t(36) = 8.217; $p_{[\text{one-tailed}]} < 0.001^{**}$). After psychotherapy, however, BDI scores of somatoform disorder patients significantly decreased (n = 15; mean difference = 15.33; t(14) = 5.660; $p_{[\text{one-tailed}]} < 0.001^{**}$) and showed no significant difference when compared to the BDI scores of the healthy control subjects (n = 18h/15p; difference = 2.40; t(31) = 1.594; $p_{[\text{two-tailed}]} = 0.121$).

scores were significantly correlated ($r_{[Spearman]} = 0.723$; $p_{[one\text{-}tailed]} = 0.001^{**}$). Correlation of SCL-90 – somatization improvement with TAS-20 improvement, however, showed no statistical significance ($r_{[Spearman]} = 0.323$; $p_{[one\text{-}tailed]} = 0.153$).

A TAS-20 score greater than 60 indicates alexithymia (Kooiman et al. 2000), whilst a BDI score greater than 18 indicates moderate (or severe) depression (Beck et al. 1961). Of the acute patients, 35% (7/20) had TAS-20 scores greater than 60 and 45% (9/20) had BDI scores above 18. After psychotherapy, none of the patients had TAS-20 or BDI scores above threshold.

fMRI results

Reward related activity of healthy subjects. The contrast of 'anticipation of reward' > 'anticipation of no outcome' of the 20 healthy subjects led to increased neural activity in several regions, including the bilateral ventral striatum, the bilateral cingulate cortex, the bilateral thalamus, and the left posterior midbrain (see Table II).

Decreased differentiation of hemodynamic responses in acute patients. The AFNI contrast revealed four regions with diminished hemodynamic differentiation between 'anticipation of reward' and 'anticipation of no outcome'. See Table III and Figure 3.

Psychotherapy induced normalization of hemodynamic differentiation. By analyzing extracted fMRI signals, we found normalization of hemodynamic differentiation between 'anticipation of reward' and 'anticipation of no outcome' in all four regions that showed diminished hemodynamic differentiation in the acute stage (see Figure 3 for details).

These results were partially confirmed by an additional analysis; we calculated voxel-based paired *t*-tests to look for clusters with enhanced activity after psychotherapy. As Table IV shows, this contrast revealed three regions, one located in the left postcentral gyrus and two in the right cingulate cortex. The left ventroposterior thalamus, however, did not appear in this contrast.

Correlation of psychotherapy induced improvement of somatoform symptoms and hemodynamic differentiation. Using Spearman correlation tests, we correlated the psychotherapy induced improvement of somatization scores with the improvement of fMRI signal differentiation from the four regions that showed diminished neural differentiation in the acute stage. We found a negative correlation of decreased somatoform symptoms and enhanced neuronal differentiation only for the left postcentral gyrus (please see Figure 4 for details).

No correlation of acute patients' hemodynamic responses and psychotherapy induced improvement of somatoform symptoms. We were curious whether hemodynamic responses of the four main regions (namely the left postcentral gyrus, the right cingulate cortex, the right occipital cortex, and the right ventroposterior thalamus) in the acute stage could predict later improvement of somatoform symptoms. Using Spearman correlations, we were, however, not able to detect any significant correlations between mean fMRI signals in the acute stage and psychotherapy induced improvement

Table II. Activated regions of healthy subjects for the contrast 'anticipation of reward' > 'anticipation of no outcome'.

Region		*x*	*y*	*z*	*T*	*n*	$p_{[FWE]}$
Left	Ventral striatum	–12	–3	–12	8.362	56	0.0011
Right	Ventral striatum	15	0	–9	7.316	88	0.0001
Right	Cingulate cortex	6	12	45	8.366	115	<0.0001
Left	Cingulate cortex	–6	12	48	6.997		
Right	Supplementary motor area	12	24	51	6.846	20	0.0491
Left	Precentral gyrus	–51	6	33	7.102	17	0.0760
Left	Postcentral gyrus	–45	24	48	7.684	236	<0.0001
Left	Postcentral gyrus	–15	36	63	7.472	16	0.0882
Right	Superior parietal gyrus	57	–3	3	7.096	16	0.0882
Left	Ventral posterior thalamus	–15	21	6	7.715	54	0.0011
Right	Ventral posterior thalamus	9	24	3	7.501	80	0.0001
Left	Posterior midbrain	–6	30	–9	7.701	28	0.0167

Active clusters of the contrast 'anticipation of reward' > 'anticipation of no outcome'; one sample *t*-test of healthy subjects ($n = 20$). The table presents all clusters with a cluster size ≥ 15 and $p_{[FDR]}$ values ≤ 0.0005. *x*, *y*, and *z* coordinates belong to the peak voxel and refer to the Talairach & Tournoux stereotactical space. *t* Values refer to the peak voxel; n represents the number of voxels in the cluster; $p_{[FWE]}$ describes the family-wise error of a cluster of the given size.

Table III. Decreased differentiation of hemodynamic responses in acute patients ('anticipation of reward' > 'anticipation of no outcome').

Region		*x*	*y*	*z*	*T*	*n*	$p_{[FWE]}$
Left	Postcentral gyrus	–45	24	48	6.120	97	0.0001
Right	Cingulate cortex	6	12	45	5.086	43	0.0265
Right	Occipital cortex	6	69	–3	5.613	34	0.0868
Right	Ventroposterior thalamus	15	21	–3	4.987	17	0.6230

Applying independent *t*-tests, we found four regions with stronger activations in healthy subjects compared to somatoform disorder patients for the contrast 'anticipation of reward' > 'anticipation of no outcome'. The table presents all clusters with a cluster size ≥ 15 and $p_{[FDR]}$ values ≤ 0.05. *x*, *y*, and *z* coordinates belong to the peak voxel and refer to the Talairach & Tournoux stereotactical space. *t* Values refer to the peak voxel; "*n*" represents the number of voxels in the cluster; "$p_{[FWE]}$" describes the family-wise error of a cluster of the given size.

of somatoform symptoms (as assessed with the SCL-90 somatization scale).

No differences in hemodynamic responses of the bilateral striatum. Structural (Hakala et al. 2004) and functional (Hakala et al. 2002, 2006) alterations of the striatum of somatoform disorder patients have been reported. Since we did not find significant differences in the striatum using the AFNI independent samples *t*-test, we also analyzed fMRI signal changes of the left and right ventral striatum by comparing acute somatoform patients and healthy controls. fMRI signals were extracted from the two regions in healthy subjects (please see Table I). As presented in Table V, we did not find significant differences of hemodynamic responses of the left and right ventral striatum, when comparing somatoform patients and healthy subjects.

Control for medication. Six of the somatoform disorder patients were on medication during either one or both scanning sessions. In order to control for potential drug related effects, we conducted both of the main comparisons, namely the comparison of healthy subjects with acute patients and the comparison of acute patients with patients after psychotherapy, again; this time, we included only the 14 unmedicated subjects. All four regions listed in Table III also appeared for the comparison of healthy control

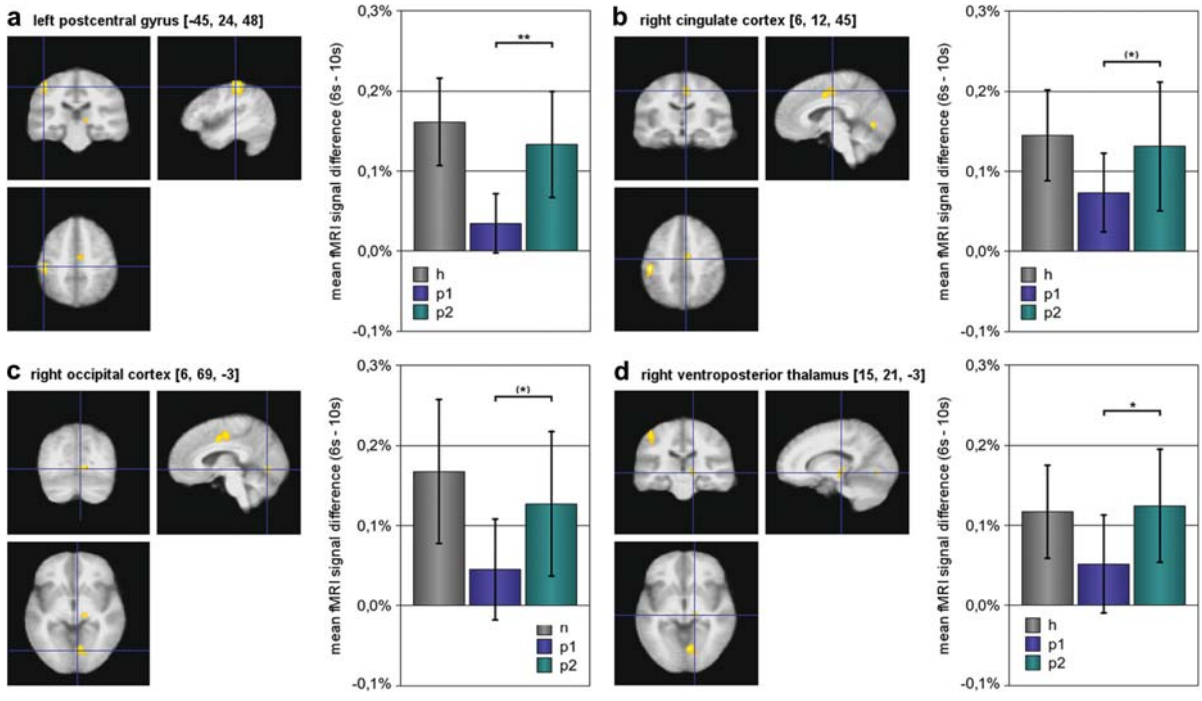

Figure 3. Psychotherapy induced normalization of hemodynamic differentiation. Four regions showed stronger hemodynamic differentiation between the conditions 'anticipation of reward' and 'anticipation of no outcome' in healthy subjects, when compared to acute somatoform disorder patients: the left postcentral gyrus (a), the right cingulate cortex (b), the right occipital cortex (c), and the right ventroposterior thalamus (d). The left column shows the locations of the regions, whereas the right column presents the mean fMRI signal difference of both conditions. After psychotherapy, differentiation of hemodynamic responses significantly increased in the left postcentral gyrus (a; t(14) = 2.854; $p_{[one\text{-}tailed]} = 0.006^{**}$), and the right ventroposterior thalamus (d; t(14) = 2.074; $p_{[one\text{-}tailed]} = 0.028^{*}$). Psychotherapy also led to normalization of hemodynamic responses of the right cingulate cortex (b; t(14) = 1.573; $p_{[one\text{-}tailed]} = 0.069^{(*)}$) and the right occipital cortex (c; t(14) = 1.642; $p_{[one\text{-}tailed]} = 0.061^{(*)}$); however, the latter results failed statistical significance and only reached a statistical trend. Activation maps are superimposed on a normalized mean image of all 40 participants (patients and healthy control subjects). The error bars in the diagrams of the right column reflect the 95% confidence interval.

Table IV. Psychodynamic psychotherapy induced normalization of hemodynamic differentiation.

Region		*x*	*y*	*z*	*T*	*n*	$p_{[FWE]}$
Left	Postcentral gyrus	–42	24	42	4.152	56	0.352
Right	Cingulate cortex	12	0	42	3.556	23	1
Right	Cingulate cortex	3	21	39	4.151	18	1

Using voxel-based paired *t*-tests, we found three regions with stronger activations in somatoform patients after psychotherapy compared to the acute stage. Again, we focused on the contrast 'anticipation of reward' > 'anticipation of no outcome'. The table presents all clusters with a cluster size ≥ 15 and $p_{[uncorrected]}$ values ≤ 0.01. *x*, *y*, and *z* coordinates belong to the peak voxel and refer to the Talairach & Tournoux stereotactical space. *t* Values refer to the peak voxel; "*n*" represents the number of voxels in the cluster; "$p_{[FWE]}$" describes the family-wise error of a cluster of the given size.

subjects with unmedicated somatoform patients. In addition, we found in all regions but one (the occipital cortex region) comparable psychotherapy-induced effects (please refer to Table VI for details).

Discussion

Acute somatoform disorder patients showed diminished neuronal differentiation between reward and no outcome in four regions: the left postcentral gyrus, the right cingulate cortex, the right ventroposterior thalamus, and the right occipital cortex. Inpatient psychodynamic psychotherapy induced normalization of SCL-90 somatization, TAS-20 and BDI scores. In addition, psychodynamic psychotherapy led to significant enhancement of neuronal differentiation of the left postcentral gyrus and the right ventroposterior thalamus. Finally, improvement of fMRI signals of the left postcentral gyrus predicted improvement of SCL-90 somatization scores.

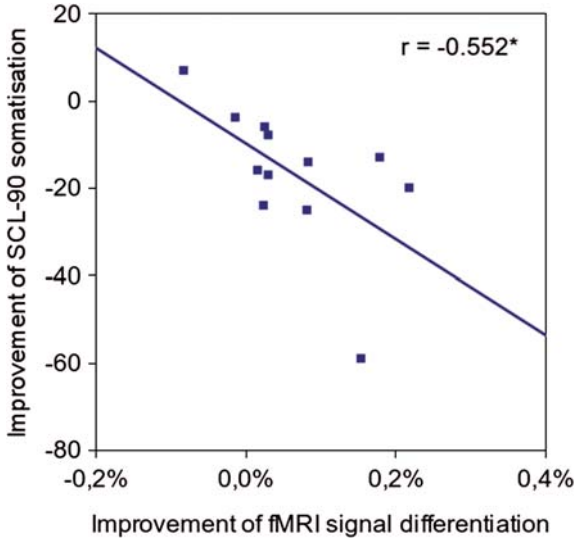

Figure 4. Psychotherapy induced normalization of hemodynamic differentiation predicts improvement of somatization scores. Improved differentiation of fMRI signals of the left postcentral gyrus predicted the improvement of somatization scores as assessed with SCL-90 somatization scale. Patients who showed high increases in their postcentral gyrus' hemodynamic differentiation between 'anticipation of reward' and 'anticipation of no outcome' also reported a high improvement of somatization complaints ($n = 12$; $r_{[Spearman]} = -0.552$; $p_{[one\text{-}tailed]} = 0.031^{*}$).

The regions activated in healthy subjects by our reward task are reliably found to be active during the anticipation of reward (Knutson et al. 2000, 2001; Knutson and Gibbs 2007). Our paradigm was hence apt to be used in the investigation of reward related activity. All of the four regions with diminished neuronal differentiation in acute somatoform patients are involved in the processing of external stimuli and support our initial hypothesis of disturbed reward processing of external stimuli in somatoform patients: The postcentral gyrus (BA 1, 2, 3) is the primary somatosensory cortex (Kurth et al. 2000; Karageorgiou et al. 2008). The cluster observed in our study probably represents the somatotopic field of the right index finger, since this finger responded to the target cue in the paradigm and the observed activation is in accordance with the somatotopic representation of the index finger as described in previous studies (Nakamura et al. 1998; Stippich et al. 1999; van Westen et al. 2004). The right ventroposterior thalamus is a relay station, which receives somatosensory information from contralateral skin (Casey and Morrow 1983; Casey et al. 1996) and muscle afferents (Andersson et al. 1966; Zhang and Davenport 2003) via corticothalamic fibers and conveys them to the ipsilateral primary somatosensory cortex (Remy et al. 1999; Kaas 2004). We found diminished neuronal differentiation in the right ventroposterior thalamus in acute somatoform patients. In contrast to healthy subjects, who showed increased activity in the right ventroposterior thalamus during the anticipation of reward, somatoform patients lacked this modulation. Regarding this, modulation of the right ventroposterior thalamus' activity might have been induced be the left somatosensory cortex activation; Li and Ebner (Li and Ebner 2006) describe that ventroposterior thalamus activity was modulated by ipsilateral as well as contralateral primary somatosensory cortex activity (in rats). The right occipital cortex (BA 18) represents the human secondary visual cortex (Kaas 1996). Acute somatoform disorder patients showed diminished differentiation in this region during the anticipation of rewarding and non-rewarding events. In a recent study (Buffalo et al. 2010), the secondary visual cortex was involved in mediating top-down controlled attention shifts. Our finding may hence be interpreted in line with our initial hypothesis: The diminished

Table V. No differences in hemodynamic responses of the bilateral striatum.

Region		x	y	z	h	$p1$	t-Test
Left	Ventral striatum	–12	–3	–12	0.11%	0.12%	$t(38) = 0.209$ $p_{[\text{two-tailed}]} = 0.836$
Right	Ventral striatum	15	0	–9	0.14%	0.10%	$t(38) = 1.266$ $p_{[\text{one-tailed}]} = 0.107$

Comparison of hemodynamic responses of the left and right ventral striatum. x, y, and z coordinates refer to the peak voxels, of the activation clusters, found in healthy subjects. "h" and "$p1$" show the mean fMRI signal difference (6–10 s) between 'anticipation of reward' and 'anticipation of no outcome'. Our results do not show any significant difference between somatoform patients and healthy controls.

neural differentiation between reward and no outcome may reflect the diminished capability to attribute salience to rewarding external stimuli. Finally, the right cingulate cortex (BA 31) plays a role in the anticipation of rewarding events (Ernst et al. 2004; Tom et al. 2007). This finding is consistent with a recent study (Fujiwara et al. 2009) that combined an fMRI reward task, in which the authors found the cingulate cortex to be active during the processing of rewarding and punishing stimuli, through a meta-analysis, in which the cingulate cortex was shown to be active during the processing of noxious skin stimulation in a number of studies. The cingulate cortex might thus play a role in the affective valuing of rewarding events. All of these regions showed a lack of modulation during the presence of external events.

Psychodynamic psychotherapy was successful as can be seen from the improvement in all applied scales, namely SCL-90 somatization, TAS-20, and BDI. Psychodynamic psychotherapy did, however, not only lead to normalization of psychological parameters, but also induced normalization of hemodynamic responses in the left postcentral gyrus and the right ventroposterior thalamus. In addition, the normalization of hemodynamic responses in left postcentral gyrus predicted psychotherapeutic success as assessed with the SCL-90 somatization scale.

In contrast to our initial expectation and to previous studies, which reported a crucial role of the striatum in somatoform disorder (Hakala et al. 2002, 2004, 2006), this region (and in particular the ventral striatum) showed no anomalies during the anticipation of reward. This finding might be interpreted to be consistent with the behavioral finding, where acute somatoform patients and patients after psychotherapy did not report significant differences in their ratings of engagement in the reward task.

Here we highlight the neural mechanisms that underlie somatoform disorders. Our data suggest that the disturbed balance of internal and external processing, present in acute somatoform disorder patients, led to decreased responsiveness of a set of brain regions crucially involved in the processing of external stimuli during the processing of external rewarding stimuli. In addition, our results contribute to our understanding of how psychodynamic psychotherapy interacts with the brain, leading to significant decrease of somatic symptom load. By providing patients understanding for the psychogenesis of their somatic symptoms and by offering new approaches to deal with underlying emotional problems (Blagys and Hilsenroth 2002; Leichsenring 2005; Grabe et al. 2008), psychodynamic psychotherapy not only reduced salient somatic symptoms, but also normalized neuronal activity during the processing of external relevant stimuli. In addition, our results further confirm that multimodal psychodynamic psychotherapy that was applied in this paper is indicated for the treatment of somatoform disorders (Beutel et al. 2008; Huber et al. 2009).

Table VI. Confirmatory analysis with unmedicated patients only.

Region		x	y	z	T	n	$p_{[\text{FWE}]}$	$p2–p1$
Left	Postcentral gyrus	–45	24	45	6.026	684	> 0.001	$t(9) = 2.606$ $p_{[\text{one-tailed}]} = 0.014^{*}$
Right	Cingulate cortex	6	12	45	6.153	684	> 0.001	$t(9) = 1.569$; $p_{[\text{one-tailed}]} = 0.076^{(*)}$
Right	Occipital cortex	6	69	–3	5.029	94	0.021	$t(9) = 0.9374$ $p_{[\text{one-tailed}]} = 0.187$
Right	Ventroposterior thalamus	15	21	–3	4.718	52	0.398	$t(9) = 2.1903$ $p_{[\text{one-tailed}]} = 0.028^{*}$

Including the 20 healthy subjects and the 14 unmedicated acute somatoform disorder patients into AFNI independent t-tests, we found the same four regions with stronger activations in healthy subjects compared to somatoform disorder patients as listed in Table II. Independent t-tests were calculated using the contrast values of the contrast 'anticipation of reward' > 'anticipation of no outcome'. The table presents clusters which consist of voxels with $p_{[\text{FDR}]}$ values ≤ 0.1 and have a similar location as the clusters described in Table III. x, y, and z coordinates refer to the Talairach & Tournoux stereotactical space. t Values refer to the peak voxel of the region; "n" represents the number of voxels in the cluster; "$p_{[\text{FWE}]}$" describes the family-wise error of a cluster of the given size. The last column, "$p2–p1$" lists the psychotherapy induced effect on hemodynamic responses of the 10 unmedicated subjects, who also participated in the second fMRI session. Please note, that the results are very similar to those of all somatoform disorder patients, as presented in Table III and Figure 3.

Moreover, one might conclude that adjunct therapies that target the disturbed balance of internal and external processing (such as communicative movement therapy) are particularly important in the treatment of somatoform disorders.

Our data also suggest that the function of the ventral striatum, one of the key structures of the reward system, is not altered in somatoform disorder. During anticipation of reward, the ventral striatum regions of somatoform disorder patients were activated as strongly as those of their healthy control subjects. Although these results are in contrast to previous studies which reported hypo metabolism in the striatum of somatoform disorder patients (Hakala et al. 2002, 2006), these results are consistent with the clinical impression of somatoform disorder patients. Unlike for instance addicted patients, who suffer from a dysfunctional ventral striatum (Volkow et al. 2006, 2007; Wrase et al. 2007; de Greck et al. 2009), somatoform disorder patients are still responsive to subtle reward signaling events. Our data suggests that it is rather the way in which somatoform disorder patients use their body to achieve and perceive rewards, which makes them different from healthy subjects.

We would also like to address a few limitations of our study. Our group of patients was rather heterogeneous, consisting of different forms of somatoform disorders. Moreover, we are aware of the criticism directed against the heterogeneous concept of somatoform disorders in general (Mayou et al. 2005). However, here we are based on an etiological approach towards somatoform disorders, which interprets somatoform disorders as a patient's strategy to deal with emotional distress (Hurwitz, 2004; Nijenhuis et al. 2004; Waller and Scheidt 2006; Beutel et al. 2008). While our patients described a variety of different symptoms (see Table I), their unconscious emotional conflicts centered around common themes. Moreover, since we focused on the processing of external rewarding stimuli and the modulatory effects of psychodynamic psychotherapy, which were independent of the individual symptoms of each patient, we decided to include any patient who fulfilled the criteria of a somatoform disorder. Further, six patients were on psychotropic medication. To control for possible effects of the medication, however, we calculated an additional analysis including only the unmedicated patients. This analysis showed similar results which make it rather improbable that our findings are solely based on drug effects. In addition, our patients not only demonstrated increased somatization scores, but also elevated scores of alexithymia and depression. Somatoform disorders, alexithymic symptoms, and mood disorders are nevertheless highly connected (Bailey and Henry 2007; Hanel et al. 2009), which makes it very difficult to conduct a somatoform disorder study which excludes any patient with an alexithymic or mood related co morbidity. One may also argue that the findings observed here are due to general anxiety effects associated with the scanning procedure, which might have been stronger in the acute patients compared to the healthy subjects. Accordingly, also the changes in hemodynamic responses after psychotherapy might have been caused by general adaptive effects, due to the fact that the patients were generally more relaxed when they entered the scanner for the second time (Beutel 2006). To control for this, future studies should compare somatoform disorder patients with equally depressed patients (that do not report somatoform symptoms). At this point, we also note, that the number of subjects that participated in the second scanning session was comparatively low. Due to the lack of a second group of somatoform disorder patients, which would not have undergone psychotherapy (but would have been tested in the same way), we can also not conclude for certain that the observed psychotherapy effects are indeed related to psychotherapy and not to spontaneous remissions of symptoms during the test-retest interval. However, since somatic symptoms of somatoform disorder patients are rather stable across time (Leiknes et al. 2008), we consider this as rather improbable. Finally, in line with recent discussions about fMRI methodology (Kriegeskorte et al. 2009; Vul et al. 2009), it may be claimed that our results of psychotherapy induced normalization in the left postcentral gyrus and the right ventroposterior thalamus are biased, since the extracted fMRI timecourse data are not completely independent from the fMRI data used during the selection of the regions of interest. In order to justify our approach (Poldrack and Mumford 2009), we would like to mention two issues. First of all, our regions of interest for the comparison of healthy controls with acute somatoform patients were obtained using a correction for multiple comparisons ($p_{[FDR]} \leq 0.05$, $p_{[FWE]}$ of the left postcentral gyrus: 0.0001, $p_{[FWE]}$ of the right ventroposterior thalamus: 0.6230). Secondly, we performed an additional voxel based analysis (see Table IV), which confirmed our results in case of the left postcentral gyrus. Taken together, we consider it rather implausible that the observed results of the postcentral gyrus are caused by a methodological bias. However, the confirmatory results concerning the right ventroposterior thalamus are much weaker, since its $p_{[FWE]}$ score is rather low and the result is not confirmed by the additional voxel based analysis. Finally, our paradigm only examined brain responses

towards external rewarding stimuli. Our paradigm however did not allow for direct investigation of the increased awareness of somatoform disorder patients towards internal stimuli. Thus future studies may attempt to further clarify the exact relationship between reward anticipation and the disturbed balance of external and internal awareness in somatoform disorders, via the application of a paradigm, which combines reward anticipation with the detection of external (such as tactile) and internal (such as heartbeat) stimuli.

Conclusion

Our findings reveal changes in brain activity during reward in acute somatoform disorder patients, which may reflect the patients' disturbed balance of internal and external stimuli processing. Moreover, our results demonstrate modulation of brain activity by psychodynamic psychotherapy. By providing new forms of conflict solution, therapeutic intervention enabled the patient to re-balance their processing of internal and external stimuli, which led to a reduction of somatic symptoms and normalization of neuronal activity in brain regions involved in the processing of external stimuli.

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Statement of interest

None to declare.

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Supplementary material available online

Description of psychotherapeutic techniques.
Detailed description of the fMRI data analysis.
References.

Supplementary Material for De Greck M, Scheidt L, Bölter A, Frommer J, Ulrich C, Stockum E, Enzi B, Tempelmann C, Hoffmann T, Northoff G. Multimodal psychodynamic psychotherapy induces normalization of reward related activity in somatoform disorder. World J Biol Psychiatry, 2010, doi: 10.3109/15622975.2010.539269.

Description of psychotherapeutic techniques

Standardized multimodal inpatient psychodynamic psychotherapy was conducted as recently explained (Grabe et al., 2008; Haase et al., 2008; Huber et al., 2009) and included the following therapeutic measures:

Psychodynamic individual psychotherapy

Psychodynamic individual psychotherapy was limited to 100 minutes per week. Aims of psychodynamic individual psychotherapy were the verbalization of emotional and interpersonal problems (Grabe et al., 2008; Leichsenring, 2005) in order to understand the underlying intrapsychic and interpersonal conflicts and to enable the patient to utilize a broader spectrum of coping strategies. Within this setting, the psychotherapist provided a space for the patient to address his problems. The psychotherapists interpreted resistances, confronted the patient with his behavior, and detected connections between the patient's actual behavior / symptoms and his biography.

Psychodynamic group psychotherapy

Psychodynamic group therapy was for between 120 and 270 minutes per week. Aims of psychodynamic group psychotherapy were the verbalization of individual and interpersonal problems. The group situation enabled a group dynamic, which brought forth actual interpersonal problems with their according emotional dynamic. Participants of the group therapy gave mutual feedback about the way they perceived the appearance and the behavior of their copatients. This setting provided the possibility for each participant to reflect about himself and his behavioral patterns in social situations.

The psychotherapists focused on the observation and interpretation of emotional dynamics, emotional atmosphere, and conflicts.

Music therapy

Music therapy was conducted for approximately 3 $\times$ 90 minutes per week. Aims of music therapy were the non-verbal communication the patients' actual emotional conflicts and moods. Music therapy was performed in a group setting. At the beginning of each session, patients were given opportunity, to speak about their current issues. This was followed by a musical improvisation part, during which patients played different instruments (for instance xylophone, drums, triangle), whilst the music therapist accompanied on the piano. The improvisation was recorded and played to the patients after the improvisation. Finally, the music therapist lead a reflection round.

Communicative movement therapy

Communicative movement therapy was conducted for approximately 1 $\times$ 60 minutes per week. It included different exercises to increase body awareness (for instance walking through warm sand, grass, etc), awareness of non-verbal social interactions (how do argue with others, how can I accomplish my aims), or awareness of emotions in the context of distance and proximity. The therapist was responsible for the thematic content of each session. He observed, gave feedback and led through a final reflection round.

Art therapy

Art therapy was conducted for approximately 2 $\times$ 90 minutes per week.

Art therapy aimed to increase the access to unconscious feelings by means of a non-verbal, creative activity. The art therapist provided the thematic content of each session (for instance "the group and me") and led through a closing feedback- and reflection round.

Social therapy

Social therapy was conducted for approximately 1 $\times$ 60 and 1 $\times$ 90 minutes per week. Aims of social therapy were the discussion of social issues concering family, work, etc.

Relaxation methods

Patients were encouraged to learn and engage in the following relaxation techniques: autogenic training and progressive muscle relaxation.

Autogenic training. Autogenic training was practised for approximately 2 $\times$ 30 minutes per week. It was

conducted in a group setting according to the established standards.

Progressive muscle relaxation. Progressive muscle relaxation was practised for approximately 2 × 30 minutes per week. It was conducted in a group setting according to the established standard by Jacobsen.

Detailed description of the fMRI data analysis

Image processing and statistical analyses were carried out using the software package AFNI (http://afni.nimh.nih.gov/afni/, (Cox, 1996)). The first five volumes were discarded due to saturation effects. All functional images were slice-time corrected with reference to the acquisition time of the first slice and corrected for motion artifacts by realignment to the first volume. The images were spatially normalized to a standard EPI-template provided by AFNI ('TT_EPI') and resampled to 3 × 3 × 3 mm. Finally, all functional images were smoothed with an isotropic 6 mm full-width half maximum Gaussian kernel. Only runs 1, 3, and 5 were included in the statistical analysis. T1-weighted images were normalized to a standard T1-template provided by AFNI ('TT_avg152T1').

For each subject, regressors of interest were created by the convolution of a canonical, fixed shape hemodynamic response function with the according stimulus time functions (Josephs et al., 1997). At this, all relevant periods (namely all anticipation periods, all feedback periods, the inter trial interval, and the free interval at the end of each session) were included in the model. In addition, six movement parameters resulting from motion correction, as well as nine regressors for the 3rd degree polynomial model of the baseline of each block were included as regressors to account for any residual effects of head motion and baseline fluctuations respectively.

Contrast images were calculated by employing linear contrasts to the parameter estimates for the regressors of each event. The resulting contrast images were then submitted to a second level random-effects analysis. Here, one-sample t-tests (including the 20 healthy subjects), independent two sample t-tests (comparing the 20 acute patients and the 20 healthy subjects), paired t-tests (comparing the 15 patients in their acute stage and after psychotherapy) were applied (Friston et al., 1995). To control for the multiple testing problem, we performed a false discovery rate correction (Nichols and Hayasaka, 2003) and calculated family-wise error probabilities. The anatomical localization and labeling of significant activations were assessed with reference to the standard stereotactic atlas of Talairach & Tournoux (Talairach and Tournoux, 1988) and by superimposition of the group contrast images on a mean brain generated by an average of each subject's normalized T1-weighted image.

In a second step, we performed a statistical analysis of the raw fMRI signals. Using a sphere-shaped "region of interest" (ROI, radius 5mm) we extracted fMRI signals from activations found in the second level analysis. fMRI raw data timecourses were processed using the software package PERL (http://www.perl.org). The timecourses were linearly interpolated and normalized with respect to a time window ranging from −6s to 30s before and after the onset of each event. fMRI signal changes of every event were calculated with regard to the fMRI signal value of the onset of the according event. Mean normalized fMRI signal values from three following time steps (6s to 10s after onset of the according event) were included in the statistical analysis. We used paired t-tests and Spearman correlations to analyze the effect of psychodynamic psychotherapy on the fMRI signals.

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