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A controlled single case study with repeated fMRI measurements during the treatment of a patient with obsessive-compulsive disorder: Testing the nonlinear dynamics approach to psychotherapy

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LETTER TO THE EDITOR

A controlled single case study with repeated fMRI measurements during the treatment of a patient with obsessive-compulsive disorder: Testing the nonlinear dynamics approach to psychotherapy

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Abstract

There is increasing evidence that obsessive-compulsive disorder (OCD) is associated with a dysfunction of cortico-striato-thalamo-cortical neuronal circuits. In order to examine treatment-related changes in neuronal processes, a drug-naive female patient with OCD (subtype: washing/contamination fear) and an age- and gender-matched healthy control were repeatedly tested using functional magnetic resonance imaging (fMRI) during the presentation of a symptom provocation task. Patient-specific visual stimuli of symptom provoking situations were compared with disgust provoking and neutral pictures. fMRI scanning was conducted at the beginning, during and upon completion of an inpatient treatment. During the treatment period of more than eight weeks (combined behavioural and systemic couple therapy) the patient filled out a therapy process questionnaire (TPQ) which was administered daily. Results show a phase transition-like change characterized by a sudden reduction of clinical symptoms as assessed by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) in the middle of the treatment period. Before the discontinuous symptom reduction occurred, the dynamic complexity of the TPQ-time series increased which might be indicative for a critical instability of the system. The fMRI results at the beginning of the treatment suggest strong activities in various brain regions, especially in the anterior cingulate cortex. The results of the second and third acquisition revealed comparably smaller OCD-related neuronal responses. The results may indicate that important clinical changes are taking place during the psychotherapy process which correspond to changing patterns of brain activation as well as to critical instabilities and phase-transition like phenomena in the time-series of the patient's daily self-report data.

Key words: *Obsessive-compulsive disorder, functional MRI, psychotherapy process, nonlinear phase transition, anterior cingulate cortex*

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Introduction

Whereas some studies report changes in brain activities after successful psychological treatment of OCD, little is known about the dynamics of psychotherapeutic processes and their neural correlates.

Neuroimaging studies showed that the frontocortico-striatal circuitry is affected in OCD. This circuitry seems to be explicative for executive dysfunctions and impulse control disorders (Friedlander and Desrocher 2006; Schiepek et al. 2007).

Neurophysiological and brain imaging studies on washing/contamination fear reported variations in various brain regions, e.g., subcortical areas (Desarkar et al. 2007), increased rCBF in the left orbitofrontal cortex and in the anterior cingulate cortex (Rauch et al. 1998, PET-study), as well as increased activity in the ventromedial prefrontal cortex (Mataix-Cols et al. 2004, fMRI-study), in the ventrolateral prefrontal cortex, the gyrus parahippocampalis, and the right insula (Shapira et al. 2003, fMRI-

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study). Gross-Isseroff et al. (2003) reported on communalities between OCD and schizophrenia in the caudate nucleus, orbitofrontal cortex, anterior cingulate, and mediodorsal thalamic nucleus.

Evaluations of cognitive behavioural therapy (CBT) using neuroimaging methods showed reduced responses in the caudate nucleus (NCd) after treatment (right NCd: Baxter et al. 1992 (FDG-PET, nine patients CBT, nine patients fluoxetine, four healthy controls); Nakatani et al. 2003 (fMRI, 22 patients behaviour therapy (BT), 31 healthy controls); left and right NCd: Schwartz et al. 1996 (FDG-PET, nine patients CBT, nine controls)). Pre-treatment associations between orbitofrontal cortex, caudate nucleus, and putamen (Baxter et al. 1992), as well as between orbitofrontal cortex, caudate nucleus, and thalamic structures (Schwartz et al. 1996) decreased after successful CBT. Brody et al. (1998) reported on higher pre-treatment metabolic activity in the left orbitofrontal cortex predicting a better outcome after behaviour therapy, but not after treatment with fluoxetine (FDG-PET, 27 patients). Using a symptom provocation task, Nakao et al. (2005, fMRI study) found reduced activity in the orbitofrontal cortex, anterior cingulate cortex, putamen, insula, temporal and occipital cortex, and cerebellum after successful BT, as well as after successful medical treatment with fluvoxamine.

These partially heterogeneous results indicate that further research on the neurobiological effects of the psychological treatment of OCD is warranted. It is assumed that treatment including CBT may lead to a “normalization” of neurobiological processes. However, relatively little is known about the specific mechanisms of psychological or pharmacological treatment (Etkin et al. 2005) and especially about treatment-related changes. For this purpose, neuroimaging procedures should be applied not only at the beginning and upon completion of the therapy but also during the treatment process.

The aim of this study was to investigate OCD-related BOLD responses and to display variations during the therapeutic process. We assumed that reduced symptom severity should correspond to reduced activity in OCD-related brain regions. With daily ratings, phase-transition-like phenomena between patterns of emotions and cognitions were hypothesized to occur, each transition accompanied by critical instabilities manifesting transient increases in fluctuations or dynamic complexity of the time series. Similar structures of therapeutic change processes were identified in recent process-outcome studies (Haken and Schiepek 2006; Schiepek and Perlit in press). The phase-transitions observed could be associated with intensive and

widespread brain activity compared to brain responses after the transition. As ACC is thought to be connected with conflict monitoring (van Veen and Carter 2002a,b) or – in terms of synergetics – to be a symmetry monitoring system, respectively, dynamic instabilities should be correlated to ACC activity.

Methods and Materials

Subjects

A 34-year-old female patient with OCD (washing/contamination fear) (DSM IV: 300.3, APA 1994) was investigated. The patient had been unmedicated for several years and devoid of comorbid psychiatric or somatic diagnoses (clinical judgement based on ICD-10 and DSM-IV criteria and on a psychiatric interview). The father of the patient died at the age of 58 years, suffering from alcohol dependence and OCD (controlling compulsions). The younger sister of the patient met the criteria of major depression, eating disorder, and OCD. The obsessive-compulsive symptoms of the patient had begun about 4 years before admission to the psychosomatic hospital.

On a special ward for OCD the patient was treated with combined behaviour therapy and systemic therapy (couple therapy). The duration of the hospital stay was 59 days. The functional MRI data of the patient were compared to those of a healthy, female, control subject (38 years) without any history of neurological or psychiatric disorders.

A written informed consent was obtained from both participants after procedures had been fully explained according to the guidelines of the ethics committee of the University of Munich.

Real-time monitoring procedure

Upon admission, the patient was asked to fill out the Therapy Process Questionnaire (TPQ, Haken and Schiepek 2006) presented on a PC screen at the end of each day, using the internet-based Synergetic Navigation System. Daily ratings were given on seven-point Likert scales or visual analogue scales, and then transformed into time series of the clinical course. A factor analysis of the items was realized in a former study and resulted in the following seven subscales of the TPQ: (1) experience of progress, confidence, and self-efficacy during the ongoing therapy, (2) insight and development of new perspectives, (3) intensity of therapeutic work and intrinsic motivation, (4) social climate and interpersonal relations to other patients, (5) quality of the therapeutic relationship, (6) dysphoric emotions and self-relatedness, (7) symptom severity. The subscales resulted from a factor analysis which produced seven

factors with eigenvalues >1 (cumulated explained variance: 59.6%). Cronbach's alpha ranges from .82 (subscale VII) to .94 (subscale I). Reliability and validity measures of the TPQ were reported in detail in Haken and Schiepek (2006).

The real-time monitoring technology is an internet-based service which allows the continuous visualization of raw data and subscale values as time series. For further analysis the dynamic complexity of the time series was calculated and visualized. Dynamic complexity is a combined measure of the intensity of fluctuations, and the distribution of the values over the available range (Schiepek 2003). Fluctuations are calculated by summing up the ratio between the absolute difference of the measurements between two turning points (i.e. the change between ascending and descending values, or vice versa) to the duration of this change process. The fluctuation is sensitive to the frequency and amplitudes of value alternations. The distribution measure is high if the values are not concentrated within small subdivisions of the range, but follow an equal distribution over the range of possible measurement values. The multiplicative combination of both results become evident in the *dynamic complexity* of the time series which was calculated within a gliding window (window width: 7 days) (for details of the algorithm, see Haken and Schiepek 2006).

Outcome criteria

Treatment effects were measured using the Y-BOCS (Goodman et al. 1989a,b), BDI (Beck Depression Inventory, Beck and Steer 1987), SCL-90 (Symptom Check List, Derogatis 1983), and the INK (Incongruence Questionnaire, Grosse Holtforth et al. 2004). The Y-BOCS was administered weekly, the other questionnaires were completed at the beginning and at the end of the hospital stay.

fMRI scanning

The fMRI scans were carried out three times during the stay at days 9, 30, and 57. The second acquisition was done after an intensive period of critical instability of the time series, but just before the flooding treatment was started. The healthy control was also scanned three times at identical time intervals so was the patient. Both subjects were scanned with a 1.5-Tesla MRI scanner (Magnetom Sonata; Siemens, Erlangen, Germany) and a standard head coil. A high-resolution T1-weighted scan was acquired for anatomical referencing. Functional images were obtained with a gradient echo-planar imaging sequence (repetition time: 4000 ms; echo

time: 53 ms; 16 axial slices; matrix size: 64×64 ; slice thickness: 6 mm; gap: 0.3 mm).

For the processing and statistical analysis of the fMRI data, the Brain Voyager Software Package (Goebel, Maastricht) was used. The first five images were excluded from any further analysis due to inhomogeneities of the magnetic field. The preprocessing of the functional data included high-pass filtering (cutoff three cycles in time course) to low-frequency signal drift inherent in echo planar imaging, slice scan time correction, spatial smoothing (Gaussian filter with FWHM 8.0 mm) and a 3D motion correction. In addition, the functional images were transferred to a standard Talairach brain.

Significant fMRI activity was determined by cross-correlation of MR image pixel intensity with an expected hemodynamic response function. Voxel-wise *t*-tests were used to identify the brain areas in which the percent signal change associated with each contrast was significantly different between patient and control subject under different conditions, respectively (GLM analysis). BOLD responses thresholded at $P < 0.001$ uncorrected for multiple comparisons were regarded as significant. Only clusters with more than 50 activated voxels were included in the analyses.

Picture material and stimulation paradigm

The visual stimulation consisted of 30 symptom provoking, 30 disgust provoking, and 30 neutral pictures. Disgust and neutral pictures were taken from the International Affective Picture System (IAPS, Lang 1997/2001). The OCD-relevant pictures had been photographed by the patient: the pictures showed specific triggers for obsessive-compulsive behaviours. The scenes were captured with a digital camera from the patient's home context (see Schienle et al. 2005, for first using this individualized symptom provocation paradigm with OCD patients). All pictures were shown twice each for four seconds in pseudorandomized order. The same picture sequence was presented to the patient and the matched control subject. All pictures were presented to the participants prior to the first fMRI session in order to reduce primacy, surprise or habituation effects.

After the MRI session subjects were asked to rate the pictures by means of five-point scales for (a) emotional valence, (b) arousal, (c) ambiguity, and (d) self-efficacy. The ratings for valence and arousal used the visual symbols of the IAPS standard rating procedure (five steps), the ambiguity and self-efficacy ratings were done on a five-point scale (with 1 = "not at all" and 5 = "very strong").

Results

Therapy effects

The patient started with a Y-BOCS score of 14 (mild symptom severity) in the first week of treatment. Although this score corresponds to only mild symptom severity, the patient's suffering from OCD was strong, and she was obviously impaired in her daily routines and vocational activities. The score slightly increased up to 17 (moderate severity) until week 3 of treatment and then decreased to a value of 4 in week 5. Between weeks 5 and 8 the Y-BOCS scores remained stable on a low level and reached a score of one (i.e. no clinical OCD) by the end of treatment (Figure 1).

The BDI overall score was 21 at the beginning and 3 at the end of treatment. A pre-post comparison of the SCL-90 showed reduced values in all psychopathological subscales at the end of therapy. The most pronounced pre- versus post-differences were seen in the subscales of obsession/compulsion (raw score: 2.7 vs. 0; t -value: 77 vs. 37), depression (raw score: 2.8 vs. 0; t -value: 75 vs. 37), and aggression/hostility (raw score: 2.0 vs. 0; t -value: 68 vs. 39). The total score was reduced from 1.32 to 0.16 (t -value: 66 vs. 46) indicating a significant clinical improvement. The experienced incongruence between personal needs and goals on one hand and the actual fulfilment of these needs and goals on the other hand was measured by the incongruence questionnaire (INK). The incongruence of the subscale "goals to approach" was reduced from 3.54 (pre) to 1.84 (post), the incongruence of the subscale "goals to avoid" was reduced from 3.50 to 1.45, and the overall incongruence was reduced from 3.52 to 1.64.

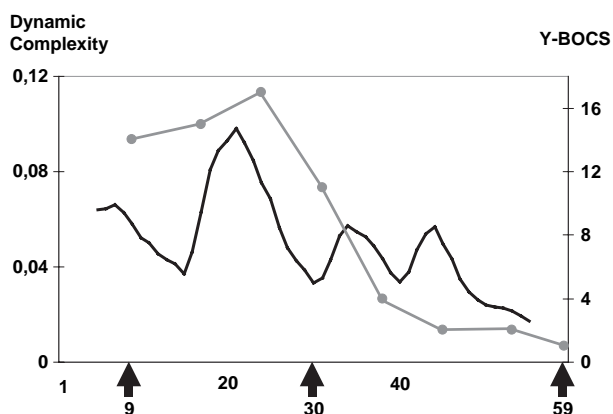


Figure 1. Grey dots and line: the course of the Y-BOCS scores (ratings once a week, scale on the right side). Black line: dynamic complexity, averaged over all 45 items of the TPQ. The dynamic complexity of each item is based on daily ratings and calculated within a gliding window of 7 days (scale on the left side). X-axis: days of hospital stay. Black arrows indicate the days where fMRI sessions were taking place.

This is a significant increase in experienced emotional congruence which is seen as an important factor of mental health (Grawe 2004).

Clinical course and time series data

The problems of the patient can be seen in a context of autonomy conflicts with her husband. Symptoms started after a dermatological infection of her husband, and the focus of her symptoms and anxieties concentrated on getting infected from her husband. Before the actual clinical stay, she visited some sessions of couple therapy together with her husband and an ambulatory individual psychotherapy, which was interrupted when a potential separation was discussed as a possible solution by the therapist.

Actual development: After the second couple therapy session the patient decided to file for divorce. This decision was accompanied by feelings of anger. The couple's therapy session took place 2 days before the second fMRI session. The period before this critical event and her decision were characterized by intensive fluctuations and increased complexity of her daily ratings of therapy-related feelings and cognitions (Figure 2). The average dynamic complexity of all items of the TPQ

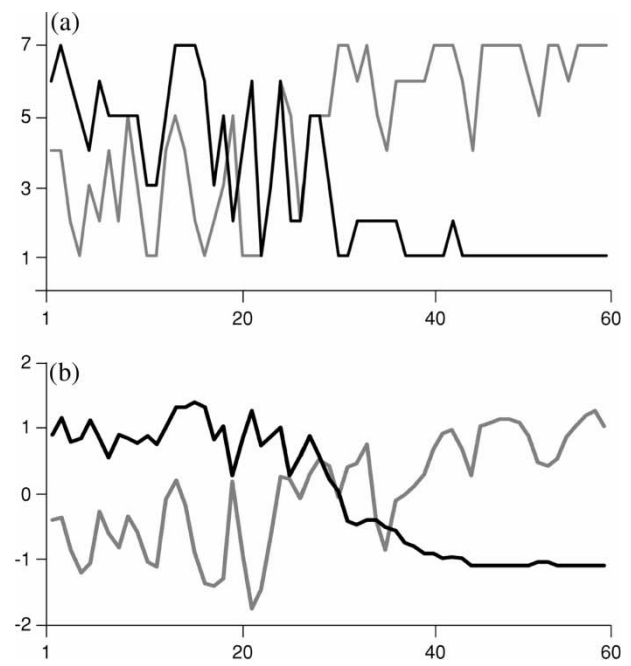


Figure 2. (a) The course of two TPQ items: Concerning my personal goals, I was successful (1 = "not at all", 7 = "very successful") (grey line); Today, I avoided situations provoking obsessions or compulsions (1 = "not at all", 7 = "very much") (black line). (b) The course of two factors (subscales) of the TPQ (items were z -transformed and averaged). Factor 1: progress of therapeutic work/confidence/self-efficacy (grey line). Factor 7: symptom severity (black line). X-axis: days of hospital stay.

manifested a significant peak between days 15 and 30 (Figure 1). Evidently the patient was destabilized and a phase transition took place, in the period before the second couple therapy session. Twenty-six out of 45 TPQ items manifested statistically increased complexity values during this period.

The flooding procedure started one day after the second fMRI session. Thus, specific psychopathological variations were demonstrated before decisive psychotherapeutic interventions took place (rapid early response Hayes et al. 2007; Lambert and Ogles 2004): alterations in brain activity (see below), increased instability of the therapy dynamics, and the beginning of an essential symptom reduction (mirrored by her daily ratings, see Figure 2) as well as by the Y-BOCS (see Figure 1) occurred before the flooding was started. The increased complexity of her daily ratings followed by changed dynamics (Figure 2) can be seen as a phase-transition in the sense of nonlinear dynamic systems theory. Clinically, the phase-transition concerned a pattern including several components like finishing an important and long-term subliminal decision process, becoming aware of one's emotions, and a clear-cut symptom reduction. Evidently, the system was destabilized before a discontinuous symptom reduction begun which was initiated before the flooding started and the second fMRI session took place.

Self-report data on the stimulus material

Figure 3 shows the results of the participants' evaluation of pictures immediately after the fMRI scans. The neutral pictures were rated more positive by the patient (Mean = 4.92) than by the control subject (Mean = 3.75, $t = 11.19$, $P = 0.000$). The patient rated the OCD-related pictures more negative than the disgust-associated pictures (1.73 vs. 2.22, $t = -3.27$, $P = 0.002$). The reverse was true in the healthy subject (OCD-related pictures: 2.57 vs. disgust pictures: 1.90, $t = 6.33$, $P = 0.000$). The OCD stimuli were rated by the patient more positive in the third fMRI session (2.06) compared to the first session (1.46) ($t = 3.84$; $P = 0.001$). Furthermore, arousal ratings differentiated clearly between OCD (4.53), disgust (2.93), and neutral pictures (1.00) (OCD vs. disgust: $t = 6.03$, $P = 0.000$; OCD vs. neutral: $t = 33.87$, $P = 0.000$; disgust vs. neutral: $t = 8.61$, $P = 0.000$). The arousal level of the patient was smallest for the neutral pictures and greatest for the individual OCD-associated pictures. Concerning

OCD-related pictures, the arousal decreased from the first session (4.53) to the second session (3.96) and from the second session to the third session (2.00). By contrast, the experienced self-efficacy increased from the second session (1.73) compared to the third session (4.23). For the control person, arousal was most intensive for disgust pictures (disgust: 3.26, OCD: 1.06, neutral: 1.73, first session). The individual scores in the ambiguity scale were not very pronounced, neither for the patient nor for the control subject. Self-efficacy related to OCD pictures differentiated clearly between patient and control. For the control subject it seemed to be easier to cope with OCD pictures (4.92) than with disgust provoking situations (3.03). For the patient her own OCD situations were the most difficult to cope with at the beginning of the therapy (session 1: OCD-pictures: 1.53, disgust pictures: 3.66, $t = 6.80$, $P = 0.000$), whereas at the end of treatment there was no more difference (session 3: OCD-pictures: 4.23, disgust-pictures: 4.26, $t = 0.11$, $P = 0.910$). Interestingly, self-efficacy during disgust provocation seemed greater for the patient than for the control person (mean over all three sessions: 3.91 vs. 3.03, $t = 4.48$, $P = 0.000$).

Functional MRI data

At the beginning of the therapy, the patient demonstrated enhanced activations during the presentation of OCD-associated pictures compared to the presentation of neutral pictures in medial frontal brain regions, including the anterior cingulate cortex (BA 32/24), supplementary motor cortex (BA 6), medial frontal gyrus (BA 9), and the medial and left lateral part of the superior frontal gyrus (BA 10). Moreover, symptom-related pictures compared to neutral pictures produced enhanced activations mainly in the following areas: superior frontal gyrus (BA 9/10), inferior frontal gyrus, insula (BA 47), inferior frontal and inferior temporal gyrus (BA 47/38), superior temporal gyrus (BA 38), precentral gyrus (BA 6), inferior parietal lobe (BA 40), thalamus (L > R), and caudate nucleus. In addition, clear differences could be observed in the (pre-) cuneus (BA 7), the fusiform gyrus (BA 37) as well as (secondary) visual-association areas in occipito-parietal brain regions (e.g. superior and inferior parietal lobe (BA 7/39), middle and inferior occipital gyrus (BA 18)). The BOLD responses in these areas were more

Figure 3. Ratings of the pictures which were presented during the fMRI sessions. Left column: patient; right column: healthy control. The diagrams represent the experienced intensities of emotional valence (5 = positive, 1 = negative), arousal (5 = very strong, 1 = no arousal), ambiguity (5 = very strong, 1 = no ambiguity), and self-efficacy (5 = I feel able to handle this situation, 1 = not at all). Results are showing the intensities of neutral, disgust provoking, and OCD provoking pictures, during the first (1), second (2), and third (3) fMRI session.

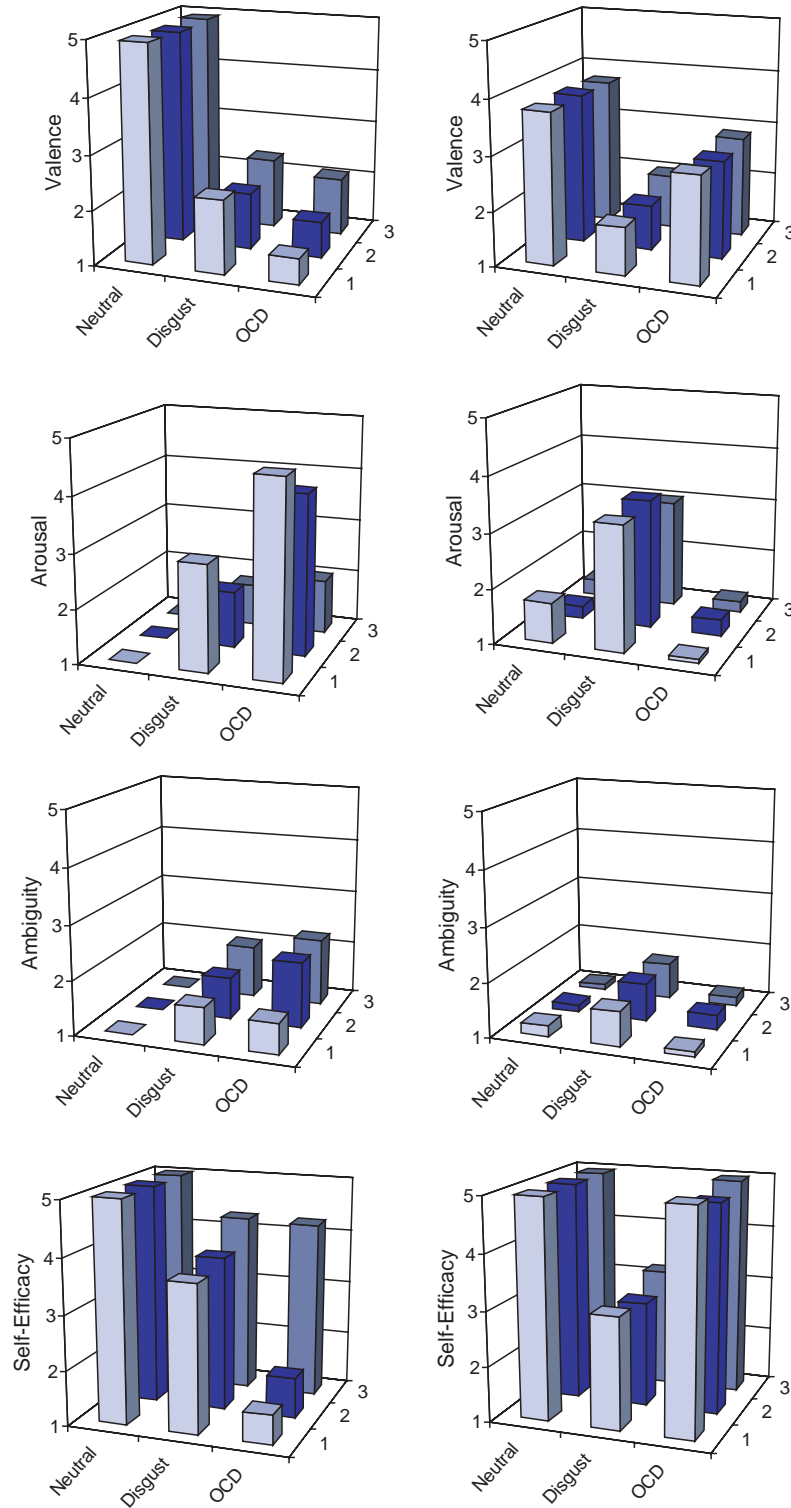


Figure 3 (Continued)

pronounced during the OCD-associated stimulation than in the control condition (Figure 4).

The comparison of OCD-specific brain responses at the beginning of the therapy and the second fMRI measurement during the therapy revealed reduced

contributions mainly of the medial frontal gyrus (BA 8/6) and anterior cingulate cortex (BA 32/24), superior and middle frontal gyrus (BA 6/10), precentral gyrus (BA 44/45), superior temporal gyrus (BA 22), cuneus (BA 19/18), the thalamus and

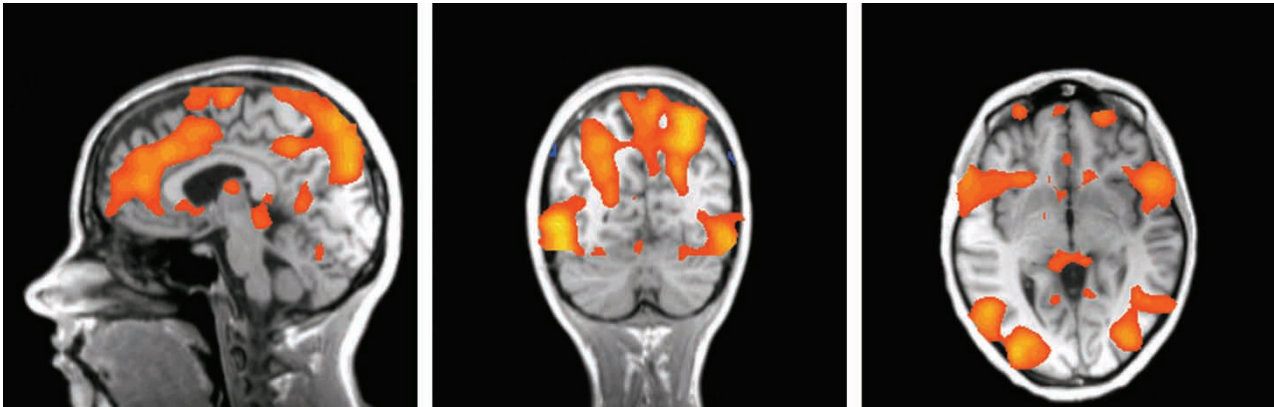


Figure 4. OCD-related functional MRI activation of the patient at the beginning of the therapy (OCD-related pictures minus neutral pictures; $x=4$, $y=-62$, $z=-3$; $P(\text{uncor}) < 0.001$).

caudate nucleus in both hemispheres as well as the right fusiform gyrus during the second session (Figure 5).

The OCD-associated BOLD responses (activations during the presentation of OCD-related pictures compared to activations during the presentation of neutral pictures) of the second and third session at the end of therapy revealed only small differences. Slightly enhanced responses were found during the second session compared to the third session in the precuneus (BA 7), and the inferior parietal lobe (BA 40). However, the middle frontal gyrus (BA 8), the left inferior parietal lobe (BA 40), the cuneus (BA 18/19) the superior and middle frontal gyrus, and the cingulate gyrus (BA 32) responded slightly stronger during the third session compared to the second session (Figure 6).

The comparison of disgust-related BOLD responses did not show any significant results. However, when the influence of BOLD responses was examined on a lower significance level ($p < .005$; uncorrected for multiple comparisons), disgust-related activities during the first session were observed

in the thalamus, the middle frontal gyrus (BA 46/8), the postcentral gyrus (BA 2), the (pre-)cuneus, the inferior frontal gyrus, the anterior cingulate gyrus (BA 32) and the fusiform gyrus. The activations in the superior frontal gyrus (BA 10), the thalamus, the postcentral gyrus (BA 3), the precuneus, the inferior parietal lobe, and the fusiform gyrus (BA 20/36) slightly decreased between the first session and the second session. A comparison of the second and the third session differences in the left middle frontal gyrus (BA 46/10), and the left inferior frontal gyrus showed that these brain areas were stronger activated during the second session. However, slightly increased brain activations in the third session compared to the second session were evident in the left thalamus, the (pre-)cuneus (BA 30/31), the right superior temporal gyrus (BA 22), the left inferior frontal gyrus (BA 20), and the left insula (BA 13).

The healthy subject showed comparable BOLD responses during the presentation of OCD-related pictures and neutral pictures. Slightly enhanced activations during the neutral condition compared to the OCD-related pictures were shown in the left

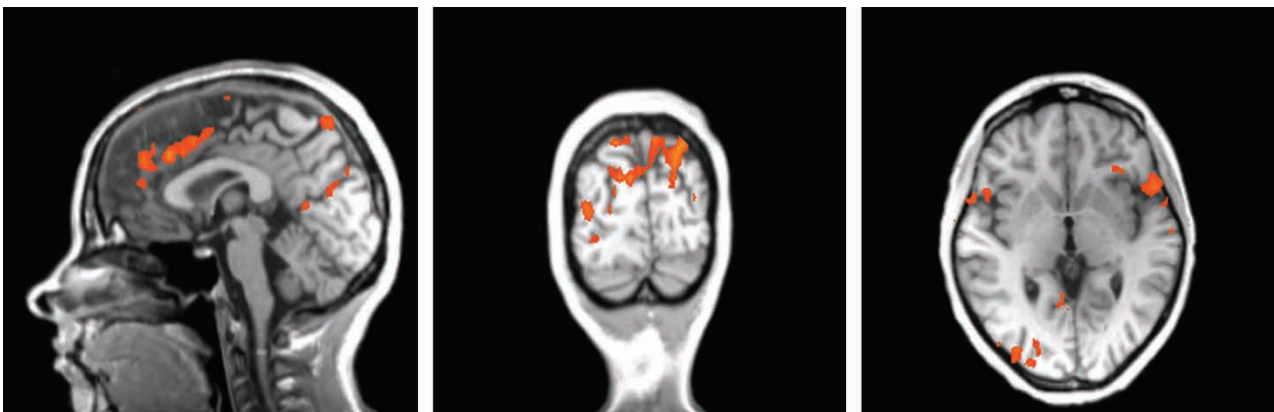


Figure 5. OCD-related BOLD responses in the patient at the beginning of the therapy compared to the BOLD responses during the second session (OCD-related pictures minus neutral pictures; $x=1$, $y=-82$, $z=1$; $P(\text{uncor}) < 0.001$).

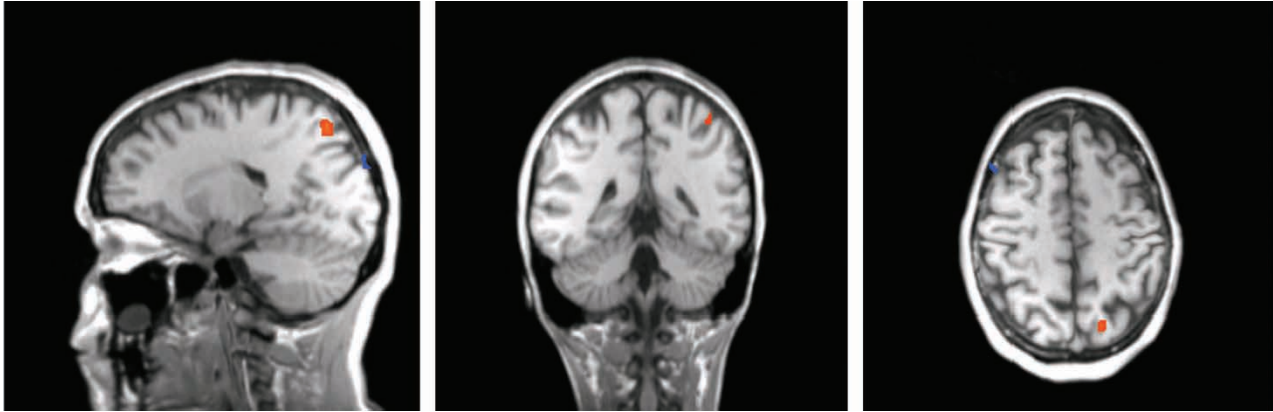


Figure 6. OCD-related BOLD responses in the patient during the second session compared to the BOLD responses at the end of therapy (OCD-related pictures minus neutral pictures; $x = -18$, $y = -37$, $z = 46$; $P(\text{uncor}) < 0.001$).

inferior occipital gyrus. In addition, the superior frontal gyrus (BA 6), the middle frontal gyrus (BA 8), the inferior frontal gyrus (BA 44/45), and the right superior temporal gyrus (BA 13) were stronger activated during the OCD condition compared to the neutral condition (Figure 7).

In order to compare the MRI activity after the presentation of disgust-related pictures to brain responses after the presentation of neutral pictures in the healthy control subject, the significance level was lowered to $P < 0.005$ (uncorrected for multiple comparisons). Disgust associated information revealed enhanced BOLD activity in the left medial and bilateral lateral part of the superior frontal gyrus (BA 8/9), medial frontal gyrus (BA 6), the precuneus (BA 7), the cuneus (BA 17), the left precentral gyrus, the right postcentral gyrus (BA 2/3), the left caudate body, and the right superior temporal gyrus.

These disgust-specific responses (disgust minus neutral condition) hardly changed even when presented several times in functional MRI sessions. Slightly enhanced responses during the first session compared to the second session were shown in the

medial frontal gyrus (BA 6), the precentral gyrus (BA 6), and the left caudate body. The disgust-specific responses of the second MRI session were somewhat enhanced in the left precuneus (BA 7) and the inferior frontal gyrus (BA 44) compared to those activations in the third MRI session.

Discussion

The aim of the study was to identify the association between brain activity and changes in the subjective experience of psychotherapy. Daily ratings of the therapy processes were done using an internet-based Real-Time Monitoring device (Synergetic Navigation System) which allowed ongoing data analyses of the resulting time series. Three repeated fMRI sessions were performed (1) before and at the end of the treatment period as well as (2) immediately after a critical instability.

Concerning functional MRI data, the most pronounced changes in brain activity occurred between the first and the second session. As these changes happened before the flooding procedure was started,

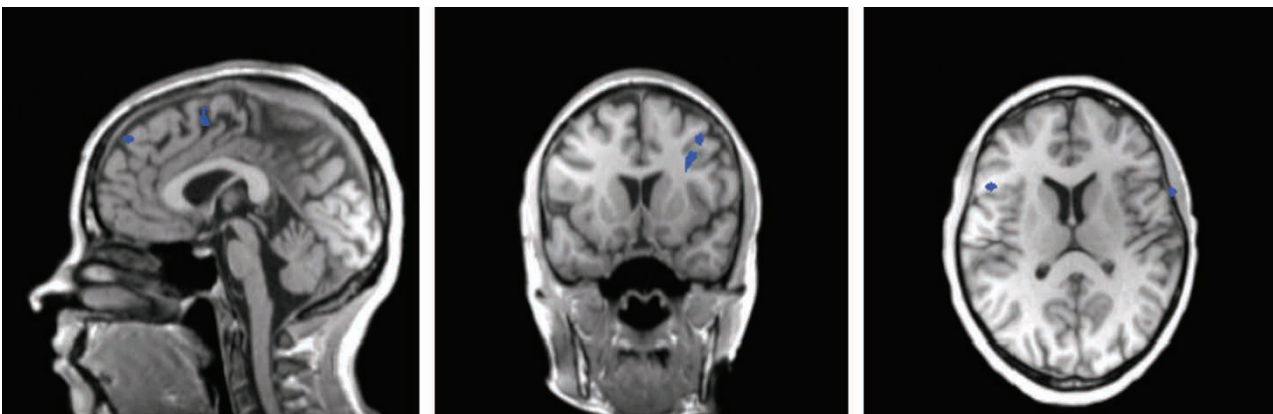


Figure 7. Functional MRI activation during the presentation of the OCD-related pictures in the healthy control subject (first session, OCD-related pictures minus neutral pictures; $x = -2$, $y = 10$, $z = 13$; $P(\text{uncor}) < 0.001$).

these variations may indicate early rapid responses in psychotherapy (Lambert and Ogles 2004; Hayes et al. 2007). They occurred after a preceding instability. Marked alterations in brain activity were to be observed before or during symptom reduction took place, not afterwards.

Alterations in brain activity involved widespread areas, e.g., the medial frontal brain regions including anterior cingulate cortex, superior and middle frontal gyrus, inferior frontal and precentral gyrus, superior temporal gyrus, superior parietal lobe, cuneus, thalamus and caudate nucleus in both hemispheres, as well as the right fusiform gyrus. Activations in parietal structures like the precuneus or gyrus supramarginalis matched the results of other studies using OCD-specific stimulation in comparison to emotion provoking material (disgust, fear) (e.g., Schienle et al. 2005, fMRI-study, 10 patients, 10 healthy controls). Any activation in the dorsolateral-caudate-striatum-thalamus circuitry has repeatedly been demonstrated to “normalize” after psychotherapeutic treatment (e.g., Baxter et al. 1992; Schwartz et al. 1996).

The function of the anterior caudate nucleus in OCD is less clear. Some studies have shown that the caudate nucleus is part of the modulatory control model of OCD and could play a role in the washing/contamination fear syndrome (e.g., Rauch et al. 1998; Saxena et al. 1998; Friedlander and Desrocher 2006; Schiepek et al. 2007 Whiteside et al. 2004). The cingulate cortex comprises various functions like somatosensory integration, mediation of affective and cognitive processes, control of attention, and processing of painful stimuli. Additionally, it plays an important role as conflict monitoring system: it is sensitive to ambiguous or conflicting information (van Veen and Carter 2002a,b; Davidson et al. 2003), is involved in decision processes (Sanfey et al. 2003; King-Casas et al. 2005), and its activation is predictive to treatment outcome in depression (e.g., Mayberg et al. 1997; Pizzagalli et al. 2001; Etkin et al. 2005; Evans et al. 2006). In terms of complexity theory, it could be an indicator of symmetry states of brain functioning, which is characterized by two or more dynamic patterns or attractors in competition. Therefore, the ACC activation at the beginning of the therapy could either be part of the pathology or it could be indicative for the critical instability of the cognitive-affective system of the patient (or both). The dynamic complexity of the TPQ data decreased from 0.066 (the days around the first fMRI session) to 0.033 (around the second session) which means a reduction by 50%. The second fMRI measurement was conducted during a local minimum of critical fluctuations. Whether the change in cingulate

activation could be attributed to an altered critical symmetry state of the neural self-organization before versus after the phase-transition or to changes in symptom severity cannot be decided within a single case study. Nevertheless, this seems to be an interesting question for further research. Since it could be an indicator for the instability hypothesis, that Y-BOCS scores were similar during fMRI sessions one and two, compared to a 50% reduction in dynamic complexity.

Limitations

There are several limitations to our results. The data were obtained from a single patient and a single control subject and can, therefore, only provide a first approach to this issue. The investigation of a single control subject can be misleading since effects and potential confounders introduced by one healthy subject are not definable or controllable. However, the brain activity of the patient in our study showed neural responses dependent on her subjective experience and independent of the results of the healthy subject. These results are in line with those of previous studies in literature. The healthy control did not show alteration between sessions concerning the evaluation of the pictures. As expected, brain responses of the healthy control were pronounced during the presentation of disgust-related pictures. Small effects were demonstrated when the pictures did not produce strong affective responses.

Although there is an increasing interest in the neuropsychology of positive emotions (e.g., Ryff and Singer 2003), their role within the psychopathology of OCD is not clear. Hence, no positive pictures were integrated in the study.

Statistical analyses of fMRI data were done without correction for multiple comparisons, but the statistical threshold is not unusual for small sample sizes. Nevertheless, the results should be considered preliminary.

Despite these limitations we were able to demonstrate a clear effect of psychotherapy on neural responses contributing to the understanding of neurobiological bases of OCD and therapy processes.

Conclusion

It seems to be worthwhile having a closer look at the neurobiology of psychotherapy processes, using combined strategies of functional brain imaging and time-series data. We were able to demonstrate marked changes in brain activation during a psychological treatment, associated with a dynamic

phase-transition followed by a pronounced symptom reduction. The results emphasize the importance of an individualized symptom provoking paradigm as well as the application of repeated assessments of functional MRI. Real-time monitoring technology can help to determine important variations in therapy processes in order to analyse symptom reduction, complexity changes or phase transitions.

The theory of a self-organizing brain undergoing cascades of cognitive-affective phase-transitions during the process of psychotherapy could be an interesting framework for the creation of hypotheses, data interpretation, and modelling brain dynamics (Friston et al. 2003; Haken 2002; Haken and Schiepek 2006).

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References

- American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th rev ed. Washington, DC: APA.
- Baxter Jr LR, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, et al. 1992. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Arch Gen Psychiatry* 49:681–689.
- Beck AT, Steer RA. 1987. Beck Depression Inventory – Manual. San Antonio, TX: The Psychological Corporation.
- Brody AL, Saxena S, Schwartz JM, Stoessel PW, Maidment K, Phelps ME, et al. 1998. FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive-compulsive disorder. *Psychiatry Res – Neuroimaging* 84:1–6.
- Davidson RJ, Pizzagalli D, Nitschke JB, Kalin NH. 2003. Parsing the subcomponents of emotion and disorders of emotion: Perspectives from affective neuroscience. In: Davidson RJ, Scherer KR, Goldsmith HH, editors. *Handbook of affective sciences*. Oxford: Oxford University Press. pp 8–24.
- Derogatis LR. 1983. SCL-90: Administration, scoring, and procedures manual for the revised version. Baltimore, MD: Clinical Psychometric Research.
- Desarkar P, Sinha VK, Jagadheesan K, Nizamie SH. 2007. Subcortical functioning in obsessive-compulsive disorder: an exploratory EEG coherence study. *World J Biol Psychiatry* 8:196–200.
- Etkin A, Pittenger C, Polan HJ, Kandel ER. 2005. Toward a neurobiology of psychotherapy: Basic science and clinical applications. *J Neuropsychiatry Clin Neurosci* 17:145–158.
- Evans KC, Dougherty DD, Pollack MH, Rauch SL. 2006. Using neuroimaging to predict treatment response in mood and anxiety disorders. *Ann Clin Psychiatry* 18:33–42.
- Friedlander L, Desrocher M. 2006. Neuroimaging studies of obsessive-compulsive disorder in adults and children. *Clin Psychol Rev* 26:32–49.
- Friston KJ, Harrison L, Penny W. 2003. Dynamic causal modelling. *Neuroimage* 19:1273–1302.
- Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. 1989a. The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 46:1006–1011.
- Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, et al. 1989b. The Yale-Brown obsessive compulsive scale. II. Validity. *Arch Gen Psychiatry* 46:1012–1016.
- Grawe K. 2004. *Neuropsychotherapie*. Göttingen: Hogrefe.
- Grosse Holtforth M, Grawe K, Tamcan Ö. 2004. Inkongruenzfragebogen (INK). Göttingen: Hogrefe.
- Gross-Isseroff R, Hermesh H, Zohar J, Weizman A. 2003. Neuroimaging communality between schizophrenia and obsessive compulsive disorder: a putative basis for schizo-obsessive disorder? *World J Biol Psychiatry* 4:129–134.
- Haken H. 2002. *Brain dynamics*. Berlin: Springer.
- Haken H, Schiepek G. 2006. *Synergetik in der Psychologie*. Göttingen: Hogrefe.
- Hayes AM, Feldman GC, Beevers CG, Laurenceau JP, Cardaciotto LA, Lewis-Smith J. 2007. Discontinuities and cognitive changes in an exposure-based cognitive therapy for depression. *J Consult Clin Psychol* 75:409–421.
- King-Casas B, Tomlin D, Anen C, Camerer CF, Quartz SR, Montague PR. 2005. Getting to know you: reputation and trust in a two-person economic exchange. *Science* 308:78–83.
- Lambert MJ, Ogles BM. 2004. The efficacy and effectiveness of psychotherapy. In: Lambert MJ, editor. *Handbook of psychotherapy and behavior change*. New York: Wiley. pp 139–193.
- Lang PJ, Bradley MM, Cuthbert BN. 1997/2001. *International Affective Picture System (IAPS): Instruction manual and affective ratings*. Gainesville, FL: Center for Research in Psychophysiology, University of Florida.
- Mataix-Cols D, Wooderson S, Lawrence N, Brammer MJ, Speckens A, Phillips ML. 2004. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Arch Gen Psychiatry* 61:564–576.
- Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, et al. 1997. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 8:1057–1061.
- Nakatani E, Nakagawa A, Ohara Y, Goto S, Uozumi N, Iwakiri M, et al. 2003. Effects of behavior therapy on regional cerebral blood flow in obsessive-compulsive disorder. *Psychiatry Res* 124:113–120.
- Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, et al. 2005. Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement. A functional magnetic resonance imaging study. *Biol Psychiatry* 57:901–910.
- Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, et al. 2001. Anterior cingulate activity as a predictor of degree of treatment response in major depression: Evidence from brain electrical tomography analysis. *Am J Psychiatry* 158:405–415.
- Rauch SL, Dougherty DD, Shin LM, Alpert NM, Manzo P, Leahy L, et al. 1998. Neural correlates of factor-analyzed OCD symptom dimensions: A PET study. *CNS Spectrum* 3:37–43.
- Ryff CD, Singer BH. 2003. The role of emotions on pathways to positive health. In: Davidson RJ, Scherer KR, Goldsmith HH, editors. *Handbook of affective sciences*. New York: Oxford University Press. pp 1083–1104.
- Sanfey AG, Rilling JK, Aronson JA, Nystrom LE, Cohen JD. 2003. The neural basis of economic decision-making in the Ultimatum Game. *Science* 300:1755–1758.

- Saxena S, Brody AL, Schwartz JM, Baxter LR. 1998. Neuroimaging und frontal-subcortical circuitry in obsessive-compulsive disorder. *Br J Psychiatry* 173(Suppl 35):26–37.
- Schienle A, Schäfer A, Stark R, Walter B, Vaitl D. 2005. Neural responses of OCD patients towards disorder relevant, generally disgust-inducing and fear-inducing pictures. *Int J Psychophysiol* 57:69–77.
- Schiepek G. 2003. A dynamic systems approach to clinical case formulation. *Eur J Psychol Assess* 19:175–184.
- Schiepek G, Tominschek I, Karch S, Mulert C, Pogarell O. 2007. Neurobiologische Korrelate der Zwangsstörungen – Aktuelle Befunde zur funktionellen Bildgebung (Neuroimaging and the neurobiology of obsessive-compulsive disorder). *Psychother Psychosom Med Psychol* 57:379–394.
- Schiepek G, Perlitz V. in press. Self-organization and clinical psychology. In: Meyer N. editor. *Encyclopedia in complexity and systems science*. New York: Springer.
- Schwartz JM, Stoessel PW, Baxter LR, Martin KM, Phelps ME. 1996. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 53:109–113.
- Shapira NA, Liu Y, He AG, Bradley MM, Lessig MC, James GA, et al. 2003. Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. *Biol Psychiatry* 54:751–756.
- van Veen V, Carter CS. 2002a. The anterior cingulate cortex as a conflict monitor: fMRI and ERP studies. *Physiol Behav* 77:477–482.
- van Veen V, Carter CS. 2002b. The timing of action-monitoring processes in the anterior cingulate cortex. *J Cogn Neurosci* 14:593–602.
- Whiteside SP, Port JD, Abramowitz JS. 2004. A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. *Psychiatry Res – Neuroimaging* 132:69–79.