Orbitofrontal Cortical Dysfunction in Akinetic Catatonia: A Functional Magnetic Resonance Imaging Study During Negative Emotional Stimulation

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Abstract

Catatonia is a psychomotor syndrome characterized by concurrent emotional, behavioral, and motor anomalies. Pathophysiological mechanisms of psychomotor disturbances may be related to abnormal emotional-motor processing in prefrontal cortical networks. We therefore investigated prefrontal cortical activation and connectivity patterns during emotional-motor stimulation using functional magnetic resonance imaging (FMRI). We investigated 10 akinetic catatonic patients in a postacute state and compared them with 10 noncatatonic postacute psychiatric controls (age-, sex-, diagnosis-, and medication-matched) and 10 healthy controls. Positive and negative pictures from the International Affective Picture System were used for emotional stimulation. FMRI measurements covered the whole frontal lobe, activation signals in various frontal cortical regions were obtained, and functional connectivity between the different prefrontal cortical regions was investigated using structural equation modeling. Catatonic patients showed alterations in the orbitofrontal cortical activation pattern and in functional connectivity to the premotor cortex in negative and positive emotions compared to psychiatric and healthy controls. Catatonic behavioral and affective symptoms correlated significantly with orbitofrontal activity, whereas catatonic motor symptoms were rather related to medial prefrontal activity. It is concluded that catatonic symptoms may be closely related to dysfunction in the orbitofrontal cortex and consequent alteration in the prefrontal cortical network during emotional processing. Because we investigated postacute patients, orbitofrontal cortical alterations may be interpreted as a trait marker predisposing for development of catatonic syndrome in schizophrenic or affective psychosis.

Keywords: Catatonia, orbitofrontal cortex, emotions, FMRI, effective connectivity.

area (SMA) and the motor cortex (MC) (Northoff et al. 1999a). Thus, unlike in Parkinson's disease (Jahanshahi et al. 1995), primary cortical motor function may be still basically intact in catatonic patients, which, clinically, could be reflected in their preserved ability to play ball even in the acute akinetic state (Northoff et al. 1995b).

Because the inability to control anxieties seems to be crucial in catatonia, motor symptoms may rather be related to abnormal emotional-motor transformation. Induction of negative emotional experience is strongly subserved by the orbitofrontal cortex (Baker et al. 1997; Beauregard et al. 1998; Drevets and Raichle 1998; Mayberg et al. 1999; Northoff et al. 2000a). The central role of the orbitofrontal cortex particularly in negative emotional experience is further underlined by findings of alterations in orbitofrontal activation in acute states of anxiety such as anticipatory anxiety (Chua et al. 1999), panic disorder (Malizia et al. 1998), and anxiety disorders (Malizia 1999). In addition to negative emotional experience, the orbitofrontal cortex has been shown to be involved in the regulation of behavior and movement (Rolls 1995, 1998; Dias et al. 1997; Nobre et al. 1999), which may be related to its connections with medial prefrontal and premotor cortical areas (Morecraft et al. 1992; Bates and Goldman-Rakic 1993; Morecraft and Hoesens 1998). Based on the orbitofrontal function and connectivity pattern, one may make the following assumptions: (1) that there are alterations in orbitofrontal cortical activity during negative emotional experience in catatonic patients that may reflect their inability to control anxieties; (2) that there is an imbalance and altered functional connectivity between the orbitofrontal cortex on the one hand and the medial prefrontal/premotor cortex on the other; and (3) that this imbalance and altered functional connectivity may be related to behavioral and motor anomalies in such patients.

To test the first assumption, that is, orbitofrontal cortical dysfunction during negative emotional experience, we investigated postacute catatonic patients and noncatatonic psychiatric and healthy controls in FMRI during an emotional-motor task with induction of negative and positive emotional experience. To test the second assumption, that is, orbitofrontal-medial prefrontal/premotor imbalance and altered connectivity, we investigated effective connectivity between these regions using structural equation modeling (SEM). To relate orbitofrontal and prefrontal cortical function with catatonic symptoms, thereby testing our third assumption, we performed correlation analyses between abnormal findings in FMRI and catatonic symptoms, expecting different correlation patterns for the three types of symptoms (affective, behavioral, motor) with regard to regions (orbitofrontal, medial prefrontal) and nature of correlation (positive, negative). Because for ethical reasons we investigated only postacute catatonic patients, it should be noted that all alterations in FMRI/SEM must be interpreted as trait markers predisposing for development of catatonic syndrome in either schizophrenic or affective psychosis.

Methods

Subjects

Catatonic patients. We investigated ten catatonic patients (five women, five men; age [mean ± standard deviation (SD)]: 41.6 ± 5.3 years) (table 1). They were selected from all incoming patients at the psychiatric university clinic in Magdeburg and psychiatric clinics in Haldensleben and Blankenburg between July 1996 and January 1998 (incidence, calculated in relation to all incoming patients: 2.6%). On admission, seven patients were neuroleptic-naive (i.e., no neuroleptics ever), two were neuroleptically untreated (i.e., no neuroleptics in the last 6 months; prior treatment with haloperidol [dose range: 5–20 mg] for an average duration of 1.1 ± 0.4 years), and one received clozapine 3 × 100 mg. No significant differences in psychopathological and FMRI measurements were found between neuroleptically medicated and unmedicated catatonic patients. In addition, three patients took antidepressants (amitriptyline 50–200 mg), two patients received lithium (serum concentration: 0.9 mmol/L), and one received carbamazepine (serum concentration 8 μg/mL). None of the patients had taken any benzodiazepines in the 6 months prior to admission (measurement of serum concentration of benzodiazepines on day 0 according to the method by Greenblatt et al. 1978); if they had, they did not enter the study. Patients with chronic neurological or other physical illness, alcohol or substance abuse, hyperkinesias or dyskinesias as assessed by the Abnormal Involuntary Movement Scale (AIMS) (> 2; Guy 1976), or neuroleptic-induced hypokinesias as assessed by the Simpson Scale for Extrapyramidal Side Effects (SEPS) (> 3; Simpson and Angus 1970) were excluded from the study.

Comorbid diagnoses were made according to DSM–IV (APA 1994) on discharge by two independent psychiatrists with a structured clinical interview. All patients were right-handed according to the Edinburgh Inventory of Handedness (Oldfield 1971). Psychopathological assessment was made with the Global Assessment Scale (GAS; Endicott et al. 1976), the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987), the Hamilton Anxiety Scale (HAM–A; Hamilton 1959), and the Hamilton Depression Scale (HAM–D; Hamilton 1960) on days 0 (the day before ini-
Table 1. Demographic and clinical data in catatonic and psychiatric control patients, mean (SD)

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Catatonics (n = 10)</th>
<th>Psychiatric controls (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.6 (5.3)</td>
<td>40.8 (4.9)</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>9.5 (1.6)</td>
<td>9.9 (1.8)</td>
</tr>
<tr>
<td>Duration of illness (yrs)</td>
<td>7.5 (5.5)</td>
<td>7.7 (5.9)</td>
</tr>
<tr>
<td>No. of hospitalizations</td>
<td>3.3 (2.1)</td>
<td>3.1 (1.9)</td>
</tr>
<tr>
<td>Age of onset</td>
<td>34.1 (12.6)</td>
<td>33.5 (8.4)</td>
</tr>
<tr>
<td>Time since acute onset (wks)</td>
<td>5.6 (1.8)</td>
<td>5.5 (1.4)</td>
</tr>
<tr>
<td>Duration of treatment (yrs)</td>
<td>5.1 (4.2)</td>
<td>5.9 (3.9)</td>
</tr>
<tr>
<td>Neuroleptics (CPZ) (mg)</td>
<td>180.2 (177.5)</td>
<td>167.0 (153.2)</td>
</tr>
<tr>
<td>Anticholinergics (n of treated patients)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Global Assessment Scale</td>
<td>14.9 (3.4)</td>
<td>20.9 (2.1)</td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale</td>
<td>85.7 (28.9)</td>
<td>83.1 (31.2)</td>
</tr>
<tr>
<td>Hamilton Anxiety Scale</td>
<td>20.9 (3.4)</td>
<td>20.1 (2.2)</td>
</tr>
<tr>
<td>Hamilton Depression Scale</td>
<td>15.9 (5.9)</td>
<td>19.9 (3.9)</td>
</tr>
<tr>
<td>No. of catatonic episodes</td>
<td>3.4 (1.9)</td>
<td>—</td>
</tr>
<tr>
<td>Days of catatonic symptoms before admission</td>
<td>14.6 (6.6)</td>
<td>—</td>
</tr>
<tr>
<td>NCS, day 0/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCSmot</td>
<td>21.3 (3.2)/1.8 (0.4)</td>
<td>—</td>
</tr>
<tr>
<td>NCSaff</td>
<td>22.9 (2.5)/3.5 (0.9)</td>
<td>—</td>
</tr>
<tr>
<td>NCSbehav</td>
<td>20.5 (8.9)/2.9 (0.6)</td>
<td>—</td>
</tr>
<tr>
<td>NCSbehav</td>
<td>64.7 (12.1)/8.2 (1.9)</td>
<td>—</td>
</tr>
<tr>
<td>Bush-Francis Catatonia Rating Scale</td>
<td>26.8 (5.7)</td>
<td>3.2 (0.8)</td>
</tr>
<tr>
<td>Diagnosis (DSM-IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catatonic schizophrenia</td>
<td>(295.20) (n = 3)</td>
<td>Paranoid schizophrenia</td>
</tr>
<tr>
<td>Bipolar I disorder</td>
<td>(296.54c) (n = 7)</td>
<td>Bipolar I disorder</td>
</tr>
</tbody>
</table>

Note.—CPZ = chlorpromazine equivalent; NCS = Northoff Catatonia Scale; SD = standard deviation.

Catatonic syndrome was diagnosed according to criteria by Lohr (Lohr and Wisniewski 1987) (3 from 11 symptoms), Rosebush et al. (1990) (4 from 12 symptoms), the Bush-Francis Catatonia Rating Scale (Bush et al. 1996a, b), and the Northoff Catatonia Scale (NCS) (Northoff et al. 1999b), with its different subscales (motor, affective, behavioral). These scales use a rather strict definition of catatonia by relying on a cluster of symptoms, as recommended by Gelenberg (1977). Catatonic symptoms had to be manifest on the day of admission in the presence of both examiners (G.N., P.D.). Furthermore, patients had to show complete akinesia (i.e., no voluntary movements at all) for at least half an hour in the presence of the examiners. All patients had to be classified as akinetic catatonic (exclusion of hyperkinetic catatonic patients because hypo- and hyperkinetic catatonia may differ in pathophysiological mechanisms [Northoff et al. 1995a, b]) according to all three criteria lists (i.e., all patients qualified as catatonic on all criteria sets) with agreement on every symptom by two independent psychiatrists (G.N., P.D.) who rated the same patients successively within 1 hour on day 0 (before initial medication with lorazepam), day 1 (24 hours after admission), and day 8 (the day of the FMRI investigation). On the day of the FMRI investigation, patients no longer had any catatonic and/or acute psychotic symptoms as measured with the above-mentioned scales.

On admission, all catatonic patients received solely lorazepam 2–4 × 1–2.5 mg (mean: 5.2 ± 1.3 mg) intravenously in the first 24 hours. According to clinical
response to lorazepam in the first 24 hours, judged by the criteria of Lohr and Rosebush, we distinguished between short-term responders (n = 10) and nonresponders (n = 3), from which only the former were included in the study, because catatonic responders and nonresponders to lorazepam might show different underlying pathophysiological mechanisms (Northoff et al. 1995b, 1998). After full resolution of catatonic syndrome on day 1, lorazepam was taken off completely and patients received antidepressants (n = 7) and/or neuroleptics (n = 6) without any further application of benzodiazepines. Serum concentration of lorazepam was measured according to the method by Greenblatt et al. (1978) on day 0, and day 8 (the day of investigation); patients who still had a measurable serum concentration of lorazepam were excluded from the study because lorazepam might modulate FMRI signals.

Ethics approval and permission were obtained from the Ethics Committee of the University of Magdeburg. After complete and detailed description of the study to the subjects, written informed consent was obtained according to the Declaration of Helsinki. The design and purpose of the study were explained to all (catatonic and non-catatonic) patients in a postacute state after remission of acute symptoms and before imaging. Because we included only those patients responding well to lorazepam within 24 hours, catatonic symptoms were no longer present and the patients' cognitive state enabled them to give informed consent.

Control groups. We investigated two control groups, psychiatric and healthy controls. The age- and sex-matched psychiatric control group (age: 40.8 ± 4.9 years; all right-handed) included 10 recently admitted postacute patients recovering from an acute episode with similar diagnosis according to DSM-IV, similar illness duration, and similar medication as catatonic patients (table 1). These patients were diagnosed according to DSM-IV with a semistructured interview by an independent psychiatrist and underwent similar psychopathological assessments as catatonic patients (see above). Subsequently, age, sex, diagnosis, illness duration, and medication were matched between the catatonic group and the psychiatric control group so that the only difference between the two was the presence or absence of catatonic syndrome. Psychiatric patients with hypo- (SEPS > 3) and hyperkinetic (AIMS > 3) neuroleptic-induced side effects, previous catatonic symptoms/episodes, alcohol/substance abuse, benzodiazepine medication in the last 6 months, and/or neurological/physical illness were excluded from the study. All psychiatric control patients received an injection of lorazepam in the same doses (no difference in dose between groups) as catatonic patients in the first 24 hours (see above), were treated with similar mediation, and were investigated with FMRI in a similar way.

In addition to psychiatric controls, ten healthy controls (25.9 ± 6.1 years, five women, five men) were investigated; for further detail concerning exclusion criteria and so on, see Northoff et al. (2000b). One may argue that the fact that healthy controls were not age-matched with both psychiatric groups may confound the present results. Although this may have occurred, the study's main conclusions remain unaffected because these rely predominantly on differences between catatonic patients and psychiatric controls, who were age-matched.

Paradigm

Affective Stimulation. Affective stimulation was performed with pictures from the International Affective Picture System (IAPS) (Lang et al. 1997), which was validated also on a German population (Hamm and Vaitl 1993). Based on the large-sample valence (positive-negative) ratings, pictures were selected as negative (e.g., a face expressing disgust or fear) or positive (e.g., smiling baby). Neutral (e.g., a book) and purely gray (with different tones of gray) pictures served as control conditions to control for potentially confounding features of the emotion-generating pictures such as emotionally irrelevant visual stimulation and attentional effects. Details of selection and presentation of pictures are described in Northoff et al. (2000a). It should be noted that slide sets were matched for contents/properties (colors, scenery, objects, people, close-ups of faces, animals) based on the method by Irwin et al. (1998), dominance (according to subjective ratings in IAPS in the norm group), and arousal (according to subjective ratings in IAPS in the norm group) (see Northoff et al. 2000a for further details). Subsequently, pictures differed in only emotional valence (positive, negative, neutral), not dominance or arousal, so that especially arousal was equated for pleasant and unpleasant pictures.

Each picture was presented for 6 seconds (based on studies by the Lang group, who used a similar duration for presentation of pictures); ten pictures of one condition were presented within one block, which accordingly lasted 1 minute. Subsequently, we induced one particular emotional (positive or negative) or nonemotional experience within each block. The duration of 1 minute per block with ten pictures of the same condition was chosen as a compromise between emotional perception (where presentation of pictures and duration of blocks would probably be much shorter) and dominance of cognitive processes (e.g., memory, which may dominate in longer presentation and duration times).

Each picture was presented only once and was projected automatically via a computer and a back-projection.
system on a biconvex lens in FMRI (see Northoff et al. 2000a for further details). Paradigm implementation and subject instruction were similar to those described in Northoff et al. (2000a). It should be noted that we focused on induction of emotional experience rather than on emotional perception because we presented each picture for 6 seconds and used experimental blocks lasting for 1 minute per emotion type (see below for further details). Subjects were asked to view the picture but not told to focus particularly on the emotionality of pictures. In addition, they were instructed to press the button (i.e., mouse click) once after the onset of each new picture without particularly speeding and concentrating on the response because the primary focus was not on the reaction time itself.

Behavioral and Psychological Monitoring. Reaction time as the time from the appearance of a new picture to the execution of the finger movement (i.e., press on the touch switch) was registered. For analysis, we calculated the means of reaction time for each condition (i.e., positive, negative, neutral, gray) and compared them statistically using Friedman tests for dependent samples. We chose reaction time as a behavioral measure of emotional valence because it is known that the time necessary for movement preparation and initiation depends on the respective functional context (other movements, concomitant visual stimuli, etc.); the more complex the content (and the movement), the longer the reaction time (Naito et al. 1998). Hence, we expected differences in reaction times between negative, positive, and neutral (i.e., more complex) pictures on the one hand and gray (i.e., less complex) pictures on the other hand.

The following analyses for reaction time were carried out: (1) paired t test for intraindividual comparison of reaction times between FMRI to account for intraindividual variability on different days; (2) analysis of variance testing for effects of group, condition, and condition by group interaction for analysis of general effects with application of post hoc t tests to test for specific effects, expecting differences between psychiatric and nonpsychiatric subjects; and (3) Spearman correlation analyses (using Bonferroni correction with a significance level of \( p = 0.042 \)) for calculation of the relation between reaction times and subjective ratings of pictures to account for the relationship between subjective emotional experience/perception and motor reaction.

To control for preexperimental psychological states, which might influence emotional induction, all subjects had to fill out the BF-s, the Befindlichkeitsskala (von Zerssen 1976), a well-validated instrument for self-evaluation of the actual psychological state, which was compared between groups by analysis of variance (ANOVA) with post hoc t tests.

Pictures from the IAPS were subjectively rated for valence, dominance, and arousal with the Self-Assessment Manikin (Lang et al. 1997). Subjective ratings of IAPS were done on day 15, that is, 1 day after FMRI investigations, in a quiet room. Subjective ratings were done for valence, dominance, and arousal for each picture, respectively, which were then compared with ratings obtained by Hamm and Vaitl (1993), who validated the IAPS for a German population. In addition, we compared subjective ratings (arousal, dominance, valence) between the three groups (catatonic, noncatatonic psychiatric controls, healthy controls) using ANOVA and post hoc analysis with t tests. It should be noted that subjective ratings were made after FMRI investigation so that they do not necessarily reflect subjective experience during scanning because subjective states may differ on different days, potentially implying different degrees of presence/absence of negative/positive emotional states. In addition, we were unable to account for the difference between emotions as state and trait marker in our patients because we measured subjective ratings in only a postacute state, not in the acute state itself. Consequently, both physiological findings obtained in FMRI during emotional experience induced by pictures and psychological findings obtained in subjective ratings of emotional pictures can reflect only trait markers. Such psychophysiological trait markers indicate predisposition for an altered physiological and/or psychological capacity for negative/positive emotions in patients suffering from catatonia and do not reflect the psychophysiological status of the acute cata
tonic state itself. Finally, it should be noted that we did not control for cognitive status, which may have influenced the ability to make subjective ratings; however, it should be taken into account that present patients were acute ones rather than chronic ones, making severe cognitive deficits rather unlikely. Because of the influence of the magnetic field, we were unfortunately unable to obtain vegetative measures of emotional responses (skin resistance, etc.) during scanning.

FMRI

Data Acquisition. The images were acquired in a Bruker Biospec 3T/60 cm head scanner equipped with a quadripolar birdcage head coil. The subjects' heads were immobilized with a vacuum cushion with attached earmuffs. An imaging session started with low-noise (sound pressure level [SPL] 62 dBA), low-contrast FLASH images in sagittal and coronal directions. The use of a FLASH sequence makes it possible to slow down the gradient switching. Together with an optimized excitation pulse and modified spoiler gradients, the final "low noise" imaging sequence, focused on a few slices, produced a
noise peak level of 58 dBA SPL at the position of the ear. Because EPI sequences are much noisier especially in a 3 Tesla scanner and may thus produce activation by themselves, we preferred a FLASH sequence (see Northoff et al. 2000a for further details concerning images and anatomical scans).

Five contiguous axial planes of the frontal lobe including the medial and lateral frontal cortex, the motor and premotor cortex, the orbitofrontal cortex, and the anterior cingulate (i.e., from upper orbitofrontal cortex and ventricles up to central sulcus) were taken for functional imaging (i.e., thickness of 8 mm, 160 mm field of view, and 64 × 64 matrix size) (figure 1).

Exactly 240 functional images for each slice were collected using a low noise conventional gradient echo sequence (SPL, 58 dBA; echo time [TE], 40 ms; repetition time [TR], 313 ms; flip angle, 8°) with medium high resolution (2.5 × 2.5 × 4 mm) within 40 minutes. For each block of visual stimuli (i.e., 10 valence-constant pictures, each presented for 6 seconds, resulting in a total duration of one block of 1 minute; see above), six images (i.e., each including all five slices) were acquired (i.e., each image lasted 10 seconds), resulting in a total acquisition time of 1 minute (i.e., 6 × 10 seconds) per block. Consequently, 60 images were acquired for each condition (i.e., 10 blocks of positive, negative, neutral, and gray pictures, respectively), resulting in a total of 240 images and an acquisition time of 40 minutes, whereas, because of a 7.5-second break between blocks, the total duration of measurement was 45 minutes. The order of blocks was counterbalanced with regard to emotional valence across subjects to control for potential order effects. All subjects tolerated the measurement quite well; only four patients (two catatonics, two psychiatric controls) complained afterward of increasing motor restlessness within the scanner, and these four subjects were among the five subjects who had to be excluded from final FMRI analyses on the basis of movement artifacts (see below).

High T1-contrast imaging (MDEFT) was used to obtain anatomical landmarks with 3D high resolution and immediately followed FMRI with the following parameters: 256 mm field of view, 2.25 mm slice thickness, 64 slices, and 256 × 256 in-plane matrix size. On the basis of these anatomical images, localization of slices/activity in FMRI and dipoles from MEG was determined.

Image and Statistical Analysis. Data were analyzed as follows: First, subject movement was monitored using the AIR package. Data were selected for further analysis on the basis of the absence of head motion artifacts in general and task-correlated head motion artifacts in particular. Based on the standard (Bandettini et al. 1993; Sanders et al. 1996; Gaschler-Markewski et al. 1997), subjects with head movements > 2 mm and/or > 1° were excluded from initial analysis. We unfortunately had to exclude two catatonic patients (means: 3.4 mm and 2.1°; both suffering from affective disorder) and three psychiatric controls (means: 3.5 mm and 2.0°; two suffering from affective disorder, one suffering from paranoid schizophrenia) (for details in healthy controls, see Northoff et al. 2000a), whose data thus did not enter into final FMRI analysis; otherwise, no significant group-related differences were found in the amount of movement correction. Based on other authors (Irwin et al. 1998; Lang et al. 1998a), all subjects entering final statistical analysis were checked for eye movements artifacts; none of the subjects entering final analysis showed any eye movement artifacts (figure 2). Finally, we excluded those scans associated with the first and last picture within each block to account for movement artifacts related to altered level of arousal/attention.

Second, activation analysis was performed by computing the correlation coefficients between voxel time response and box-car waveform representing the stimulation. Irrespective of their actual serial position in the sequence, all negative and positive blocks were modeled as “on,” whereas all neutral and gray blocks were defined as “off.” Voxels having correlation coefficients with a statistical significance p > 0.01 (corrected) were rejected. Then the functional images were superimposed on the individual anatomic reference images (Gaschler-Markewski et al. 1997).

In each slice, different anatomical regions of interest (ROIs) were outlined on the respective anatomical MRI without functional overlays for each subject separately. Each of the 11 brain regions (figure 1) was defined individually by landmarks (i.e., the respective gyri with upper orbital gyrus, inferior, middle and superior frontal gyri, cingulate gyrus and medial frontal gyrus) and manually delineated on the T1-weighted images (see Kammer et al. 1997 for a similar method). Fiducial marks were then made on the anterior commissure, the posterior commissure, and the midsagittal point, and on most anterior, posterior, superior, inferior, left, and right points of the brain that were used to standardize each participant’s anatomy in a normalized space so that the various brain regions could be identified based on the Talairach atlas (Talairach and Tournoux 1988) and characterized by the corresponding Brodman areas (BAs). The corresponding regions on adjacent slices were aggregated and then defined as upper part (exclusion of lower part) of the orbitofrontal cortex (BA upper 11 and 12), lateral prefrontal (BA 9, 45, 46, 47), medial prefrontal (BA 8, 9, 10), premotor (BA 6), and motor (BA 4) cortex on the right and left side respectively and anterior cingulate cortex (BA 24, 32) bilaterally (see Kammer et al. 1997 for a similar method). Because the orbitofrontal cortex is close to regions with a high poten-
Figure 1. Placement of slices and determination of ROIs

Note.—AC-PC = anterior commissure-posterior commissure; ROI = region of interest.

1 Midsagittal view of slice placement (T1-weighted spin-echo sequences). Five images of contiguous oblique-axial planes with slice thickness of 8 mm and 64 x 64 voxels in plane were obtained from the whole frontal lobe. Slice locations were approximately 40 degrees relative to the AC-PC line. In each slice, different anatomical ROIs were determined in orientation on the respective gyri and sulci without functional overlays. Regions were then defined in orientation on the Talairach atlas (Talairach and Tournoux 1988) covering the orbitofrontal, lateral prefrontal, medial prefrontal, cingulate, premotor, and motor areas and related to the respective Brodman areas. Numbers within the different regions show the respective Brodman areas. The two lowermost slices, as indicated by the numbers 1 and 2, are shown with their respective ROIs.
Effective connectivity in the prefrontal cortex in negative emotions in healthy controls and catatonic patients: Results from structural equation modeling for (A) healthy controls and (B) catatonic patients—(L) left and (R) right.¹

Note.—C = cingulate cortex (BA 24, 32); L = lateral prefrontal cortex (BA 9, 45, 46, 47); M = medial prefrontal cortex (BA 8, 9, 10); M1 = motor cortex (BA 4); O = orbitofrontal cortex (BA 11, 12); P = premotor cortex (BA 6).

¹ Prefrontal cortical regions are shown on a schematic of a horizontal section of the frontal lobe. Anatomical connections between regions are illustrated by arrows indicating direction of the respective connection. Path coefficients between the different prefrontal cortical regions are written as numbers on the arrows indicating the respective anatomical connection.

tial for magnetic susceptibility artifacts, we, based on Breiter et al. (1996, 1997), checked that orbitofrontal activations did not overlap regions of susceptibility artifact; if artifacts were as high as or even higher than stimulus-correlated activity, the subjects were excluded from analysis. Three subjects (two psychiatric controls, one catatonic patient) had to be excluded for susceptibility artifacts, but these three were identical with three of the five subjects who were excluded on the basis of movement artifacts (see above), so that the number of catatonics (n = 8), psychiatric controls (n = 7), and healthy controls (n = 10) entering into final analyses was not further reduced by analysis for susceptibility artifacts (see below in the discussion). Even if the determination of ROIs based on Talairach and Tournoux has considerable shortcomings (especially with regard to the ventral prefrontal cortex), we nevertheless applied it because most current imaging studies use it for anatomical determination and we wanted our localizations to be able to be compared with those of the other studies.

Activity in these ROIs in both hemispheres was analyzed by correlation analysis (Bandettini et al. 1993) to obtain a statistical parametric map. Such a map displays the spatial distribution of the z score for each of the differences or “contrasts” positive-negative, positive-neutral, positive-gray, negative-neutral, negative-gray, and neutral-gray. Then these functional t maps were thresholded (z = 3.09 or p < 0.01 corrected for multiple comparisons based on Lang et al. 1998a) and constrained to include four contiguous voxels in the final map, which effectively reduces the rate of false positives (see Lang et al. 1998a). Constraining the final maps on the basis of cluster size allows FMRI analyses to control for multiple comparisons without the concomitant loss of power that would occur with a Bonferroni correction method. Finally, t statistic maps were overlaid onto our anatomical template image to attribute each activation focus to an anatomical area. Percentages of significantly activated voxels and intensity-weighted volumes (IWVs) (product of the absolute number of voxels and average signal change in each ROI in all slices) were determined for positive (positive IWV probably reflecting activation) and negative (negative IWV probably reflecting deactivation; see below in the discussion) correlated activations (Gaschler-Markewski et
The 11 ROIs as defined above were submitted to analysis of effective connectivity using SEM as introduced by McIntosh and Gonzalez-Lima (1994) and recently applied to FMRI data (Büchel and Friston 1997; Bullmore et al. 1998). This statistical technique allows attribution of the covariances in the FMRI signal between ROIs to interactions between the corresponding cortical regions. Covariation coefficients were calculated from mean regional FMRI time series for each pair of regions, for right and left hemispheres separately, and for each condition (positive, negative, neutral, gray). Anatomical connectivity between the corresponding cortical regions was taken from CoCoMac, a relational data base of corticocortical connections in the macaque monkey (http://www.hirn.uni-duesseldorf.de/~rk/Cx/CoCoMac.htm). From this information, a path diagram was drawn linking the 11 brain regions (structural or anatomical model; figure 2).

The interregional correlations and the anatomic model were entered into AMOS (Version 5, SPSS Inc.) for SEM. Residual variances were not fixed and showed values between 0.122 and 0.525. For all calculations, we obtained quite high goodness-of-fit values between 0.804 and 0.925; solutions with a goodness of fit lower than 0.80 would have been rejected. Neither residual variances nor goodness-of-fit values differed significantly between the four conditions and the three groups. The covariances were corrected for the subject block effect, a result of the repeated measures design, using a regression procedure (McIntosh et al. 1996).

The regression procedure helps to reduce the impact of individual variability across the entire experiment while maintaining the variability attributable to the experimental manipulation. Subsequently, for each functional connection between two prefrontal cortical areas as presupposed in the underlying anatomic model, a path coefficient was determined reflecting the (statistical) strength of that particular connection.

Path coefficients were calculated separately for each hemisphere and condition as follows: (1) the forward calculation considered all existent pathways in the direction from the orbitofrontal region via the medial and lateral prefrontal cortex, anterior cingulate, and premotor cortex to the motor cortical region; (2) estimates from this step were fixed and all pathways in the reverse direction were calculated; (3) to ensure that the path coefficients were not exceedingly influenced by the order of their calculation, the order was reversed and the results compared. Order was not a confounding factor because there were no differences in path coefficients between (1) and (2). Path coefficients for feedforward and feedback connections from calculations (2) and (3) were considered for the final model (McIntosh et al. 1996; Cabezza et al. 1997). Omnibus comparisons between conditions (negative-positive, negative-positive-neutral, negative-positive-neutral-gray) as well as between groups were performed using the stacked model or multiple group approach in AMOS (McIntosh and Gonzalez-Lima 1994). Models of different conditions were combined in a single program run for statistical comparison. Path coefficients were constrained to be equal between conditions (null model) and compared with those where the coefficients were allowed to differ (alternative model). The comparison model was done by subtracting the goodness-of-fit $\chi^2$ value for the alternative model from the $\chi^2$ value for the null model.

In addition to structural modeling, we performed a multivariate analysis of covariance coefficients between ROIs with the three factors emotions, side, and group for each single connection respectively, which complements results from SEM calculating effects and differences of single connections, relying on the method described by Worsley et al. (1997).

### Statistical Analysis

#### Comparison Between Groups

Statistical analyses of the various FMRI parameters between conditions within groups (i.e., comparison of early [blocks 1–5] vs. late [blocks 5–10] conditions as well as across all conditions [blocks 1–20 vs. blocks 20–40] within each group for exclusion of habituation and attention effects) as well as between groups within conditions (comparison of conditions between groups for determination of specific alterations in catatonia) were made with Kruskal-Wallis/Friedman analysis and post hoc comparisons with Mann-Whitney U/Wilcoxon tests, applying Bonferroni correction for multiple comparisons. In addition to group comparisons between catatonics, and psychiatric and healthy controls, we performed a so-called nosological analysis (see Northoff et al. 1998, 1999a, 2000b). In this analysis, patients were no longer classified syndromatically according to the presence/absence of catatonic syndrome (table 1) independent of the respective underlying psychiatric disease (either schizophrenic or affective psychosis). Instead, they were classified according to their
underlying psychiatric disease as either schizophrenic (295.20 and 295.30) or affective (296.54) psychosis. We therefore compared schizophrenia (n = 6) and affective (n = 14) patients and healthy controls in the same way as catatonic and noncatatonic patients. Because of exclusion of movement artifacts in FMRI (see above), four patients with affective psychosis (two catatonic and two noncatatonic patients) and one patient with paranoid schizophrenia (from the psychiatric control group) had to be excluded so that five schizophrenia and ten affective patients entered into final statistical analyses for nosological analyses. Furthermore, it should be considered that unlike in the case of catatonic and noncatatonic psychiatric control patients, we were no longer able to match clinicodemographic variables between schizophrenic and affective patients in nosological analyses. Because of different criteria of classification across the same patients, the matching between catatonic and noncatatonic patients did not apply to schizophrenia and affective patients. Therefore, because of the low number of cases and the lack of matching, results from nosological analyses should be considered rather cautious and preliminary.

Correlations Between Variables. First, in an exploratory way, we correlated regional activities in FMRI with behavioral measures and clinical variables (from day 0) using Spearman correlation with Bonferroni correction for multiple comparisons. Because we correlated acute clinical symptoms from day 0 with FMRI signals obtained in a postacute state on days 8 and 14, physiological findings correlating significantly with clinical symptoms may reflect trait markers indicating predisposition for development of catatonic symptoms. Following the recommendations by Curtin and Schulz (1998), only FMRI parameters that showed significant differences between catatonics on the one hand and psychiatric and healthy controls on the other, were selected for correlational analyses, to reduce the number of comparisons. Furthermore, we performed partial correlations to control for effects of age, illness duration, and neuroleptics on those tests for which correlations were significant. If correlations turned out to be significant in both kinds of analyses, they were considered as relevant relationships between variables; only these are mentioned in the Results section.

Results

Behavioral Measures

Clinical variables. Demographic and clinical variables for both patient groups, catatonics and psychiatric controls, are presented in table 1. Catatonics and psychiatric controls showed no significant differences in any variables except the presence/absence of catatonic symptoms.

Reaction time. First, ANOVA (four conditions, three groups) revealed a significant effect of group (F = 2.8, df = 31, p = 0.028) but no significant effects in condition and group by condition interaction. Post hoc t tests showed significant differences between catatonic patients and healthy controls in negative (F = 3.4, df = 31, p = 0.026), positive (F = 2.9, df = 31, p = 0.028), and neutral (F = 3.1, df = 31, p = 0.032) conditions (table 2). In addition, significant differences were elucidated between psychiatric and healthy controls in negative (F = 2.6, df = 26, p = 0.013), positive (F = 3.0, df = 26, p = 0.011), and neutral (F = 3.4, df = 26, p = 0.019) conditions. In contrast, no significant differences in reaction times between catatonic patients and psychiatric controls were shown (table 2). Differences in reaction times between both psychiatric groups on the one hand and healthy controls on the other may have been due to psychopharmacological medication, which although there were no significant correlations between both variables (reaction times and psychopharmacological medication; see below) cannot be excluded as a causal factor within the present context.

Second, Spearman correlation analyses between reaction time and valence ratings showed no significant correlations in the four conditions and the three groups.

Third, in general, reaction times for all three groups were low in gray pictures and high in neutral, positive, and negative pictures, so that, as suggested (see

<table>
<thead>
<tr>
<th>Catatronics</th>
<th>903.3 ± 335.2 b*</th>
<th>853.5 ± 310.8 b*</th>
<th>881.3 ± 296.1 b*</th>
<th>685.9 ± 6.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric controls</td>
<td>1,071.9 ± 326.2 c*</td>
<td>1,008.4 ± 250.7 c*</td>
<td>1,016.9 ± 285.3 c*</td>
<td>722.3 ± 5.1</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>516.8 ± 161.3</td>
<td>521.4 ± 177.9</td>
<td>533.6 ± 186.3</td>
<td>452.1 ± 0.4</td>
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</table>

Note.—ANOVA = analysis of variance; SD = standard deviation.

1 ANOVA (group): p = 0.028. ANOVA (condition by group interaction): p = 0.013.

2 Post hoc t tests: a = significant difference between catatonics (n = 10) and psychiatric controls (n = 10); b = significant difference between catatonics and healthy controls (n = 10); c = significant difference between psychiatric controls and healthy controls.

*p < 0.05
Paradigm), length of reaction time was based on complexity and arousal of content of pictures rather than on emotionality of pictures (see also Bradley et al. 1992; Lang et al. 1998b; Naito et al. 1998; Nakamura et al. 1999). Matching between emotional and nonemotional (i.e., neutral) pictures with regard to arousal and dominance (see Paradigm) may have abolished differences in reaction times between both kinds of pictures (see also Whalen et al. 1998, who similar to us found no difference in reaction times between negative and neutral emotional words).

Fourth, to exclude habituation effects, we analyzed comparisons between early and late phases of the experiment (using paired t tests and a factor time in ANOVA) for each condition separately (blocks 1–5 vs. blocks 5–10) and for all conditions (blocks 1–20 vs. blocks 20–40), which revealed no significant differences in either group (see Richter 2004 for further details and Whalen et al. 1998 for similar results).

In summary, catatonic patients showed no specific abnormalities in reaction times compared to psychiatric controls, whereas both groups showed significantly longer reaction times than healthy controls.

**Psychological measures.** Preexperimental psychological states as measured with the Befindlichkeitsskala (BF-s) (see Paradigm) did not differ significantly between groups (ANOVA with post hoc t tests), although catatonic (20.00 ± 9.51) and psychiatric control (19.45 ± 8.56) patients showed higher values than healthy controls (13.33 ± 5.01), indicating increased stress and arousal.

Subjective ratings of valence, dominance, and arousal of pictures from the IAPS (see Paradigm) did differ from ratings (0–20 scale) of the already investigated healthy population (Lang et al. 1997; Northoff et al. 2000a). Furthermore, statistical analyses (ANOVA with post hoc t tests) revealed no significant differences between the three groups in any of three dimensions (valence, arousal, dominance), so that there were no psychological differences between catatonic and noncatatonic subjects with regard to emotions (mean ± SD for negative valence: 4.9 ± 0.34 [healthy controls], 4.8 ± 0.96 [psychiatric controls], 4.6 ± 0.98 [catatonics]; positive valence: 13.1 ± 0.32 [healthy controls], 12.3 ± 0.88 [psychiatric controls], 12.5 ± 0.79 [catatonics]; neutral valence: 9.9 ± 0.28 [healthy controls], 9.4 ± 0.74 [psychiatric controls], 9.5 ± 0.69 [catatonics]).

One has to take into account that subjective ratings were made in a postacute state on day 15, on which acute symptoms, either catatonic or psychotic, were no longer present. Subjective ratings do not reflect the acute catatonic state and thus a state marker but rather a postacute state reflecting a trait marker. Our results showing no difference in subjective ratings between groups do therefore suggest that catatonic patients cannot be characterized by peculiarities in psychological trait markers for emotions. This, however, does not exclude the possibility that in the acute catatonic state, psychological markers (i.e., state markers for emotions) may differ between catatonic and noncatatonic subjects.

In summary, catatonic patients showed no significant alterations in subjective ratings of emotions indicating absence of specific abnormalities in psychological trait markers for emotions.

**Cortical Activation in FMRI**

**Healthy controls.** Because details of results in healthy subjects are described extensively in Northoff et al. 2000a, we will mention here only the main results. Negative and positive emotional pictures led to different activation patterns in the orbitofrontal, the lateral prefrontal, and the premotor cortex. Negative emotional pictures induced strong activation (i.e., positive correlated IWVs) in the medial orbitofrontal cortex and marked negative correlated activity in the lateral prefrontal cortex. Positive emotional processing led to an inverse pattern with strong activation in the lateral prefrontal cortex and marked negative correlated activity in the orbitofrontal cortex (table 3, figure 3).

**Catatonic patients**

**Negative emotions.** First, catatonic patients showed significantly lower activity (positive IWV) and a significantly higher number of negative IWVs in the right orbitofrontal cortex than psychiatric (F = 4.5/4.2, p = 0.012/0.023) and healthy (F = 4.1/4.3, p = 0.032/0.028) controls, whereas neither alterations in the left orbitofrontal cortex nor in psychiatric controls compared to healthy controls were found (table 3, figures 3 and 4).

Second, catatonic patients showed significantly higher (F = 4.8–3.1, p = 0.0079–0.048) positive and negative IWV in both the right and the left medial prefrontal cortex compared to psychiatric and healthy controls (table 3).

Third, both catatonic and noncatatonic psychiatric patients showed significantly higher positive IWV in the right and left lateral prefrontal cortex than healthy controls (F = 4.0–2.8, p = 0.012–0.024).

Fourth, both catatonic and psychiatric control patients showed significantly higher positive IWV in the left premotor cortex (F = 4.1–3.3, p = 0.021/0.033) than healthy controls.

In summary, catatonic patients showed specific abnormalities in the right orbitofrontal cortex and right/left medial prefrontal cortex in negative emotions with decrease of activation (positive IWV) and increase of deactivation (negative IWV) in the former (figure 4), and an increase of activation (positive IWV) in the latter.

**Positive emotions.** First, catatonic patients showed significantly (F = 2.7/3.4, p = 0.042/0.026) higher activity
Table 3. Group means for intensity of activity with activation (positive IWV) and deactivation (negative IWV) in FMRI in different regions of interest in negative, positive, and neutral conditions

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<tr>
<td><strong>Orbitofrontal (BA 11, 12)</strong></td>
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<tr>
<td>Cat</td>
<td>107 a*,b*</td>
<td>151</td>
<td>260</td>
<td>263 a**,b**</td>
<td>424 a*,b**</td>
<td>387 a*</td>
<td>616 a*,b*</td>
<td>88</td>
<td>236 a*</td>
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<td>157</td>
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<td><strong>Cingulate (BA 24, 32)</strong></td>
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<td>Cat</td>
<td>107</td>
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<td><strong>Medial Prefrontal (BA 8, 9, 10)</strong></td>
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<td>Psych</td>
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<td>322c*</td>
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<td><strong>Lateral Prefrontal (BA 9, 45, 46, 47)</strong></td>
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<td>Cat</td>
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<td><strong>Premotor (BA 6)</strong></td>
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<td>Cat</td>
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<td><strong>Motor (BA 4)</strong></td>
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Note.—BA = Brodman area; cat = catatonic patients (n = 8); healthy = healthy controls (n = 10); IWV = intensity-weighted volume (product of percentage of activation signal and volume [μL]); psych = psychiatric controls (n = 7).

1 Post hoc t tests: a = significant difference between catatonic and psychiatric controls; b = significant difference between catatonic and healthy controls; c = significant difference between psychiatric and healthy controls.

* p < 0.05 (corrected); ** p < 0.01 (corrected)
Figure 3. Localization of FMRI activity matched into the same individual anatomical MRI image in negative emotions in (A) a healthy control and (B) a catatonic patient—(1) lowermost slice and (2) second lowermost slice.

Note.—FMRI = functional magnetic resonance imaging; MRI = magnetic resonance imaging. Black pixels = negative correlated voxels; white pixels = positive correlated voxels.
Figure 4. Means of activity in the orbitofrontal cortex during (1) negative (negative-neutral) and (2) positive (positive-neutral) emotions in catatonic patients and psychiatric and healthy controls in FMRI: (A) activation (positive IWV) and (B) deactivation (negative IWV)

(1) Negative emotions

(a) Activation (positive IWV)

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<td>catatonics (n=6)</td>
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<tr>
<td>psychiatric controls (n=7)</td>
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<td>healthy controls (n=10)</td>
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(b) Deactivation (negative IWV)

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<td>catatonics (n=6)</td>
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<tr>
<td>psychiatric controls (n=7)</td>
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<td>healthy controls (n=10)</td>
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(2) Positive emotions

(a) Activation (positive IWV)

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<tbody>
<tr>
<td>catatonics (n=6)</td>
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<td>healthy controls (n=10)</td>
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(b) Deactivation (negative IWV)

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<tbody>
<tr>
<td>catatonics (n=6)</td>
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<td>psychiatric controls (n=7)</td>
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<td>healthy controls (n=10)</td>
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Note.—FMRI = functional magnetic resonance imaging; IWV = intensity-weighted volume (product of the absolute number of voxels and average signal change in each region of interest in all slices). Positive IWV = positive correlated activity, that is, IWV (positive numbers, probably reflecting activation); negative IWV = negative correlated activity, that is, IWV (negative numbers, probably reflecting deactivation). a = significant difference between catatonic patients and psychiatric controls; b = significant difference between catatonic patients and healthy controls; c = significant difference between psychiatric and healthy controls.

* p < 0.05 (corrected) (Mann-Whitney U tests)

(positive IWV) in the right and left orbitofrontal cortex than healthy controls and significantly lower negative IWV (F = 3.2/4.3, p = 0.017/0.011) in the right orbitofrontal cortex than psychiatric and healthy controls (table 3, figure 4). Compared to negative emotions, there is a reversal in the pattern of orbitofrontal activity. Whereas in negative emotions positive IWV were lower and negative IWV were higher in catatonia compared to both control groups, this pattern is reversed in positive emotions with higher positive IWV and lower negative IWV (table 3, figure 4).

Second, we found significantly lower (F = 4.2-3.3, p = 0.013-0.032) activity in catatonic and psychiatric control patients in the right and left lateral prefrontal cortex than healthy controls. Note that unlike in negative emotions, both psychiatric groups no longer showed increased activity in the lateral prefrontal cortex but rather decreased activity.

Third, no alterations in the medial prefrontal cortex were found in positive emotions.

Fourth, catatonic patients showed significantly (F = 3.4/3.1, p = 0.013/0.036) lower activity in the left MC compared to psychiatric and healthy controls.

In summary, catatonic patients show specific abnormalities in the right orbitofrontal cortex in positive emotions with increase of activation (positive IWV) and decrease of deactivation (negative IWV) (figure 4).
Neutral condition. First, both catatonic and psychiatric control patients showed significantly (F = 3.1–2.5, p = 0.017–0.048) higher activation (positive IWV) in the right orbitofrontal cortex, anterior cingulate, left lateral prefrontal cortex, and right MC (table 3), whereas no significant differences between catatonic and psychiatric controls were found in these regions.

Second, comparison between early and late phases of the experiment (see Statistical Analysis) for each condition separately (blocks 1–5 vs. blocks 5–10) and for all conditions (blocks 1–20 vs. blocks 20–40) revealed no significant differences in either group.

In summary, analysis of the neutral condition reveals one specific difference in catatonia compared to psychiatric controls. In addition, there are specific effects in both catatonic and psychiatric controls showing increased activation in some regions compared to healthy controls, which may be related to attention effects.

Overall summary. First, catatonia can be characterized by specific alterations in the right orbitofrontal cortex in negative emotions with decreased activation and increased deactivation (figure 4).

Second, catatonia can be characterized by an abnormal pattern of activation and deactivation in the right orbitofrontal cortex in positive emotions with increased activation and decreased deactivation (figure 4).

Third, catatonia can be characterized by an almost reversed pattern of orbitofrontal cortical activity in both emotional conditions, activation (positive IWV) being low in negative and high in positive emotions, and deactivation (negative IWV) being high in negative and low in positive emotions (figure 4).

Fourth, catatonia can be characterized by specific alterations in the medial prefrontal cortex in negative emotions (table 3).

Fifth, catatonia showed minor changes in the premotor/motor cortex.

Sixth, catatonic patients showed minor changes in the neutral condition compared to psychiatric controls.

Nosological Analysis. Comparisons between catatonic and noncatatonic patients yielded the above-mentioned results. As already mentioned above (see Statistical Analysis), nosological analysis compared five schizophrenia (exclusion of one because of movement artifact in FMRI) and ten affective (exclusion of four because of movement artifacts in FMRI) patients. Nosological analysis (see above and Northoff et al. 1999c, 2000b for further details) with regard to underlying psychiatric diagnosis of either schizophrenic or affective psychosis showed significant differences in the medial prefrontal cortex, anterior cingulate cortex, and lateral prefrontal cortex compared to healthy controls. In contrast to analysis with catatonia, nosological analysis revealed no significant (or marginally significant) differences between groups in the orbitofrontal cortex. Therefore, orbitofrontal alterations must be considered as specific for catatonic syndrome itself and not its underlying disease entity. However, because of a low number of cases, results from nosological analysis should be regarded as preliminary. Nevertheless, it gives further evidence, although rather weak and indirect, for our assumption of orbitofrontal cortical dysfunction as specifically related to catatonic syndrome.

In summary, nosological comparison between affective and schizophrenia patients and healthy controls revealed no significant differences in those measures, where catatonic patients differed significantly from psychiatric and healthy controls. Hence, orbitofrontal cortical dysfunction seems related to catatonic syndrome itself rather than to underlying psychiatric disease; that is, this finding must be regarded as specific for catatonic syndrome itself.

Correlations Between MRI Signals, Behavioral Measures, and Clinical Data

Clinical symptoms—FMRI signals. To relate abnormalities in FMRI signals with clinical symptoms, we correlated both kinds of variables (see Statistical Analysis for details). Reducing the numbers of variables to be correlated, only FMRI signals specific for catatonia were entered into correlation analyses (see Statistical Analysis). In a second step, we performed the similar correlation analyses for psychiatric controls, calculating only those FMRI signals that differed significantly between psychiatric and healthy controls. Furthermore, it should be noted that, because of correlation of data obtained in different states (clinical symptoms from acute state on day 0 and FMRI signals in postacute state on days 8/14), significant relationships can be interpreted as only trait markers predisposing for development of such symptoms and do not reflect state markers and thus physiological changes potentially underlying acute catatonic symptoms themselves.

First, we found significant correlations between FMRI signals and clinical symptoms (from day 0) in only catatonic symptoms. Furthermore, catatonic symptoms correlated significantly with only FMRI signals related to negative emotions; no significant correlations were found with positive or neutral conditions. Therefore, all correlations described in the following refer to negative emotions.

Second, general catatonic symptoms (Rosebush, NCSstot) correlated significantly positively with negative IWVs in right medial/lateral prefrontal cortex (Rosebush/NCSstot: r = 0.82–0.87; p = 0.042–0.049) (i.e.,
the more symptoms, the more negative IWVs in medial/lateral prefrontal cortex) and significantly negatively with negative IWVs in right and left orbitofrontal cortex (Rosebush/NCStot: $r = -0.84$ to $-0.95$; $p = 0.008-0.044$) (i.e., the more symptoms, the less negative IWVs in the orbitofrontal cortex) (table 4).

Third, catatonic motor symptoms (NCSmot) correlated positively with positive and negative IWVs in the right and left medial/lateral prefrontal and orbitofrontal cortex ($r = 0.84-0.93$; $p = 0.008-0.048$) (i.e., the more motor symptoms, the more negative IWVs in the medial/lateral prefrontal and orbitofrontal cortex) (table 4).

Fourth, catatonic behavioral (NCSbehav) and affective (NCSaff) symptoms correlated negatively with negative IWVs in the right and left orbitofrontal cortex ($r = -0.85$ to $-0.94$; $p = 0.008-0.049$) (i.e., the more affective/behavioral symptoms, the less negative IWVs in the orbitofrontal cortex) (table 4).

Fifth, no significant correlations were obtained between FMRI signals and clinicodemographic data, including psychopharmacological treatment (i.e., neuroleptics in chlorpromazine equivalents) in both psychiatric groups.

In summary, correlation of catatonic symptoms with FMRI signals could be characterized by a differential correlation pattern between affective/behavioral and motor symptoms concerning the nature (positive vs. negative), signal (positive or negative IWV in FMRI signals), and region (orbitofrontal, medial/lateral prefrontal). In negative emotions, affective/behavioral symptoms correlated negatively with both early magnetic field strength and negative IWV in the orbitofrontal cortex, whereas motor symptoms correlated positively with negative IWVs in the medial/lateral prefrontal and orbitofrontal cortex. Such a differential correlation pattern may indicate particular alterations in different prefrontal cortical networks predisposing for development of affective/behavioral and motor symptoms.

**Reaction time—FMRI signals.** Because (1) duration of reaction time may be related to emotional processing (see Paradigm), (2) psychiatric patients showed higher reaction times than healthy controls (see Results), and (3) catatonic patients showed alterations in emotional-motor transformation (see introduction), we correlated reaction times with FMRI signals obtained during induction of emotional experience.

Both healthy controls (see Northoff et al. 2000a for further details) and catatonic patients showed no significant correlations between reaction time and FMRI signals. Psychiatric controls showed significant correlations between reaction time and positive correlated activity in negative contrasts in the right orbitofrontal ($r = -0.975$, $p = 0.008$).
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= 0.005; r = -0.900, p = 0.037) and the right medial prefrontal cortex (r = -0.975, p = 0.005) was hypothesized that in contrast to catanotics and healthy controls, psychiatric controls may recruit prefrontal cortical areas for motor function in an abnormal way that may be related to different kinds of effects of the same (both groups were matched in their medication; see Methods) psychopharmacological medication in catatonic and psychiatric control patients.

In summary, the relation between reaction time and orbitofrontal medial prefrontal cortical activity was normal in catatonic patients, while this was not the case in psychiatric controls.

Effective Connectivity in FMRI: SEM

Healthy controls. Omnibus statistical comparisons revealed the following results. We found significant differences between negative and positive emotions in the right (χ²(diff)(8) = 81.38–53.02 = 28.36) and the left (χ²(diff)(8) = 88.50–64.52 = 23.98) hemisphere. Negative, positive, and neutral emotions also differed significantly from each other in the right (χ²(diff)(16) = 130.07–89.06 = 41.01) and the left (χ²(diff)(16) = 143.27–98.53 = 44.74) hemisphere. In addition, all four conditions (negative, positive, neutral, gray) differed significantly from each other in the right (χ²(diff)(16) = 130.07–89.06 = 41.01) and the left (χ²(diff)(16) = 143.27–98.53 = 44.74) hemisphere. In addition, all four conditions (negative, positive, neutral, gray) differed significantly from each other in the right (χ²(diff)(21) = 245.03–191.81 = 53.22) hemisphere.

The following description of prefrontal cortical networks is limited to the comparison of positive and negative emotions, which is considered to be the main focus of interest. Path coefficients in negative and positive emotions are shown in figure 2 (see Schlagenhauf 2001 for further details).

Catatonic patients. Effective connectivity in catatonic patients differed significantly (χ²(diff)(16) = 41.24–45.58 = -4.34) from the one in psychiatric and healthy controls in negative and positive emotions (see Schlagenhauf 2001).

First, catatonic patients showed much stronger feedforward connections from the orbitofrontal to the anterior cingulate cortex (figure 2) in both positive and negative emotions than psychiatric and healthy controls. In addition, multiple analysis of variance (MANOVA) revealed a significant group effect (p = 0.001) for connection from the orbitofrontal to the premotor cortex, showing lower strength in catatonic than in psychiatric and healthy controls.

Second, the connection from the cingulate to the medial prefrontal cortex was stronger in catatonic patients than in psychiatric and healthy controls in both negative and positive emotions on both sides, which is further supported by MANOVA revealing a significant effect of group (p = 0.001) in this connection.

Third, the connection from the anterior cingulate to the lateral prefrontal cortex was weaker in catatonic patients than in psychiatric and healthy controls on both sides, which is further supported by MANOVA revealing a significant group effect in this connection (p = 0.001).

Fourth, the feedback connection from the medial prefrontal to the orbitofrontal cortex was much weaker in catatonic patients than in psychiatric and healthy controls in negative (figure 2) and positive emotions on both sides.

Fifth, connections between the lateral prefrontal/anterior cingulate cortex on the one hand and the premotor/motor cortex on the other were altered in catatonia with regard to either signature or strength in negative emotions (figure 2 and Schlagenhauf 2001), whereas these connections did not differ between groups in nonemootional conditions (Schlagenhauf 2001). This is further supported by MANOVA demonstrating significant group effects (p = 0.001) for connections from the lateral prefrontal/anterior cingulate cortex to the premotor/motor cortex, which showed much weaker covariation coefficients in catatonic than in psychiatric and healthy controls.

Sixth, reciprocal connections between the motor and the premotor cortex were altered in catatonia, especially in negative emotions, with differences in strength and laterality showing increased strength on the right side and rather decreased strength on the left. This is further supported by results from MANOVA demonstrating a significant group effect (p = 0.001) for the connection between the premotor and the motor cortex, with catanotics showing decreased strength relative to psychiatric and healthy controls.

In summary, catatonic patients showed alterations in orbitofrontal connectivity concerning indirect feedforward projections to the medial prefrontal cortex via the anterior cingulate and direct feedback projections from the medial prefrontal cortex. In addition, connectivity between the medial/lateral prefrontal cortex and the premotor/motor cortex was altered in catatonia.

Discussion

The main findings in the FMRI study comparing the prefrontal cortical activation pattern in negative and positive emotions between catatonic patients and psychiatric and healthy controls are the following: (1) alterations in medial orbitofrontal and medial prefrontal cortical FMRI activation in negative emotional experience in catatonic patients compared to both control groups; (2) significant correlation of catatonic behavioral and affective symptoms with orbitofrontal deactivation, whereas catatonic
motor symptoms were rather related with medial prefrontal activation; (3) significant alterations in orbitofrontal and premotor/motor cortical functional connectivity in catatonic patients compared to psychiatric and healthy controls.

Results lend support to our initial hypotheses (see introduction) of (1) orbitofrontal cortical dysfunction in negative emotional experience; (2) altered functional connectivity between orbitofrontal and medial prefrontal/premotor cortex; and (3) differential correlation pattern of affective, behavioral, and motor symptoms with FMRI signals. The only difference between our assumptions and the present results concerned behavioral symptoms, which were related to orbitofrontal dysfunction rather than to medial prefrontal and premotor/motor function, as had been predicted. Results further underline the importance of orbitofrontal cortical dysfunction in catatonic patients, which may account for not only affective symptoms but also bizarre behavioral abnormalities.

**Orbitofrontal Cortex and Emotional Processing in Catatonia.** In accordance with previous studies, we found strong activation in the orbitofrontal, lateral prefrontal, and premotor cortex during emotional stimulation in healthy controls (Pardo et al. 1993; George et al. 1995; Morris et al. 1996, 1998; Baker et al. 1997; Imaizumi et al. 1997; Lane et al. 1997; Paradiso et al. 1997; Phillips et al. 1997; Büchel et al. 1998; Irwin et al. 1998; LaBar et al. 1998; Mayberg et al. 1999; Northoff et al. 1999b). Most authors found activation of more or less similar cortical regions during negative and positive emotional stimulation, especially pointing out the central role of the orbitofrontal and ventral prefrontal cortex in emotional processing (Baker et al. 1997; Beauregard et al. 1998; Mayberg et al. 1999; Northoff et al. 2000a). The central role of orbitofrontal cortical activation in emotional processing seems to be altered specifically in catatonic patients. Orbitofrontal cortical activation was low in negative emotions and rather high in positive emotions in catatonic patients, showing an almost inverse pattern compared to psychiatric and healthy controls. Alteration in orbitofrontal cortical emotional processing may thus be considered as crucial in pathophysiology in catatonic patients, which is further supported by the following findings: (1) catatonic patients showed a higher proportion of negative correlated orbitofrontal activity in negative emotions than psychiatric and healthy controls; (2) correlation analysis revealed a significant relationship of catatonic behavioral/affective symptoms with orbitofrontal (de)activation; (3) nosological analysis revealed no alterations in orbitofrontal cortical activation in affective and schizophrenia patients, further underlining the specificity of orbitofrontal cortical dysfunction with regard to catatonic syndrome; and (4) alterations in orbitofrontal functional connectivity were found in catatonia.

However, several issues remain open. First, catatonic patients showed a tendency toward stronger deficits in the right hemisphere, which would be in accordance with previous findings (Northoff et al. 1999a). The relationship between laterality and emotional processing remains unclear, with controversial findings even in healthy subjects (see Davidson and Irwin 1999). Second, the exact physiological meaning of deactivation signals in FMRI remains unclear (Raichle et al. 2001). Because deactivation signals showed strong alterations and correlations, they may be of particular importance in catatonia. Third, distinct negative emotions—for example, sadness, anxiety, and disgust—have not been differentiated in this study.

The orbitofrontal cortex, with its reciprocal connections to the ventrolateral (medial orbitofrontal) and ventromedial (lateral orbitofrontal) parts of the basal nucleus of the amygdala (Mörcraft et al. 1992; Carmichael and Price 1995, 1996), is assumed to be strongly involved in (cognitive) control of emotional processing (Mörcraft et al. 1992; Barbas 1995; Carmichael and Price 1995; Baker et al. 1997; Drevets and Raichle 1998), especially in negative emotions (Northoff et al. 2000a). As has been shown in monkeys (Dias et al. 1997), the orbitofrontal cortex may be particularly involved in affective inhibition as a form of (cognitive) control of emotional processing. One may consequently hypothesize that, based on our finding of alterations in both the medial and the lateral orbitofrontal cortex, catatonic patients may be characterized by a lack of emotional inhibition, which is probably closely related to reduced (cognitive) control of emotional processing. Such an assumption of dysfunctional orbitofrontal cognitive inhibitory control of emotional processing in catatonia is further supported by the following findings: (1) orbitofrontal cortical activity is significantly correlated with affective alterations in catatonia (Northoff et al. 1998); (2) systematic investigation of subjective experience in catatonia has revealed an inability to control emotions so that patients have the feeling of being "overwhelmed by their strong, intense, and uncontrollable emotions" (Northoff et al. 1998; Northoff 2002); (3) lorazepam as a benzodiazepine with strong anxiolytic properties has shown an almost dramatic therapeutic efficacy in acute catatonic patients (Rosebush et al. 1990; Northoff et al. 1995a; Bush et al. 1996a, b), predominantly in those with strong emotions (Northoff et al. 1995a, 1998). However, the exact relationship between affective control and inhibition on the one hand and orbitofrontal cortical function on the other remains unclear, so additional studies are needed to further reveal pathophysiological mechanisms of lack of cognitive
inhibitory control of emotional processing in catatonic patients.

**Prefrontal Cortical Dysfunction and Psychomotor Symptoms in Catatonia.** Catatonic patients showed no major abnormalities in the premotor/motor cortex in FMRI, which is reflected in the following results: (1) no systematic alterations in premotor/motor cortical activation in FMRI during emotional-motor stimulation; and (2) no correlation of catatonic motor symptoms with premotor/motor cortical activity. Hence, cortical motor function itself seems to be basically intact in the postacute state of catatonic patients; were it not, the respective alterations would have been expected. This is further supported by an FMRI study of motor activation showing no major alterations in SMA and MC in catatonic patients (Northoff et al. 1999a) as well as by their preserved ability to play ball even in the acute catatonic state (Northoff et al. 1995b).

How, then, can we account for motor symptoms in catatonic patients? In addition to orbitofrontal cortex function alterations, we found significant alterations in medial prefrontal cortical function in catatonic patients. Catatonic patients showed increased medial prefrontal activation in negative emotions compared to psychiatric and healthy controls. In addition, we found a relationship between medial prefrontal activity and motor behavior that is reflected in the following results: (1) a significant correlation of reaction times with orbitofrontal and medial prefrontal activity in psychiatric controls but not in catatonics, and (2) a significant relationship between catatonic motor symptoms and medial prefrontal activity. The relationship between orbitofrontal/medial prefrontal cortical function and motor behavior seems to be altered in catatonia, which is further underlined by the second finding of a significant correlation of medial prefrontal activity with catatonic motor symptoms.

The orbitofrontal cortex is strongly connected with the cingulate/medial prefrontal, premotor, and parietal cortical areas, which are all involved in regulation and control of motor behavior (Morecraft et al. 1992; Bates and Goldman-Rakic 1993; Morecraft and Hoesens 1998). In addition, the orbitofrontal cortex has been shown to be closely related to shift, suppression, and alteration/flexibility of behavioral strategies (Rolls 1995, 1998; Nobre et al. 1999). Impairment in these orbitofrontal abilities leading to abnormal modulation of orbitofrontal connectivity to the above-mentioned areas may well account for catatonic behavioral and motor anomalies. It may be assumed that behavioral and motor anomalies may be accounted for by the abnormal spatial spread of activation from the orbitofrontal cortex via the prefrontal cortex to the premotor/motor cortex, which is strongly supported by the following findings: (1) specific alterations in functional connectivity between the orbitofrontal and the anterior cingulate/medial prefrontal cortex in catatonic patients; (2) specific alterations in premotor/motor cortical functional connectivity with a “functional dissociation” from medial/lateral prefrontal cortical areas in catatonic patients; (3) significant correlations between catatonic behavioral symptoms and orbitofrontal activity; (4) significant correlations between catatonic motor symptoms and medial prefrontal cortical activity; and (5) subjective reports from catatonic patients that they feel often “blocked in their movements by strong, intense, and uncontrollable emotions” (Northoff 1997, p. 25; Northoff et al. 1998).

It should, however, be mentioned that we investigated only akinetic catatonic patients responding well to lorazepam. This is important to mention because hypokinetic and hyperkinetic patients as well as responders and nonresponders to lorazepam might have different underlying pathophysiologies (Northoff et al. 1995a, 1998). It therefore remains unclear whether orbitofrontal cortical dysfunction may be as prominent in all these different groups of catatonic patients. Moreover, our findings reflect only trait markers, not state markers, because patients were investigated in a postacute state. This may account for the absence of differences in psychological rating of emotional pictures between both psychiatric groups. Even though they were postacute, catatonic patients showed orbitofrontal cortical dysfunction, which may thus predispose them to the development of catatonic syndrome.

**Conclusion**

Catatonia is a psychomotor syndrome that can be characterized by behavioral, affective, and motor anomalies. Pathophysiological mechanisms of psychomotor disturbances remain, however, unclear. We therefore investigated prefrontal cortical activation patterns during negative and positive emotional stimulation in catatonic patients, combining FMRI and analysis of functional connectivity.

Catatonic patients showed altered activation patterns and functional connectivity in the orbitofrontal and medial prefrontal cortex in negative and positive emotions compared to psychiatric and healthy controls. Catatonic behavioral and affective symptoms correlated significantly with orbitofrontal activity, whereas catatonic motor symptoms were related to medial prefrontal cortical activity. In contrast, cortical motor function as reflected in premotor/motor cortical activity showed no major abnormalities in catatonic patients.

Akinetic catatonic patients may thus be characterized by orbitofrontal cortical spatiotemporal alterations in negative and positive emotional processing. It is concluded
that psychomotor disturbances in akinetic catatonic patients may be related to abnormal negative emotional processing in the orbitofrontal cortex, with consequent alteration in the medial prefrontal and premotor/motor cortical network accounting for the unique constellation of affective, behavioral, and motor symptoms.

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