Reduced Orbitofrontal-Striatal Activity on a Reversal Learning Task in Obsessive-Compulsive Disorder

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Context: The orbitofrontal cortex (OFC)—striatal circuit, which is important for motivational behavior, is assumed to be involved in the pathophysiology of obsessive-compulsive disorder (OCD) according to current neurobiological models of this disorder. However, the engagement of this neural loop in OCD has not been tested directly in a cognitive activation imaging paradigm so far.

Objective: To determine whether the OFC and the ventral striatum show abnormal neural activity in OCD during cognitive challenge.

Design: A reversal learning task was employed in 20 patients with OCD who were not receiving medication and 27 healthy controls during an event-related functional magnetic resonance imaging experiment using a scanning sequence sensitive to OFC signal. This design allowed investigation of the neural correlates of reward and punishment receipt as well as of “affective switching,” i.e., altering behavior on reversing reinforcement contingencies.

Results: Patients with OCD exhibited an impaired task end result reflected by a reduced number of correct responses relative to control subjects but showed adequate behavior on receipt of punishment and with regard to affective switching. On reward outcome, patients showed decreased responsiveness in right medial and lateral OFC as well as in the right caudate nucleus (border zone ventral striatum) when compared with controls. During affective switching, patients recruited the left posterior OFC, bilateral insular cortex, bilateral dorsolateral, and bilateral anterior prefrontal cortex to a lesser extent than control subjects. No areas were found for which patients exhibited increased activity relative to controls, and no differential activations were observed for punishment in a direct group comparison.

Conclusions: These data show behavioral impairments accompanied by aberrant OFC-striatal and dorsal prefrontal activity in OCD on a reversal learning task that addresses this circuit’s function. These findings not only confirm previous reports of dorsal prefrontal dysfunction in OCD but also provide evidence for the involvement of the OFC-striatal loop in the pathophysiology of OCD.

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processing of reward and punishment stimuli, either from a sensory quality or from an abstract (monetary) nature. Moreover, neuroimaging studies using reversal learning paradigms have reported OFC activity during affective switching.

As stated earlier, the OFC is connected with the ventral sector of the caudate nucleus and these structures conjointly form a fronto-striatal circuit. Indeed, neuroimaging studies have also demonstrated the ventral striatum to be engaged in reward processing and in affective switching. Thus, the OFC and the ventral part of the striatum are presumed to be crucial in an organism’s processing of reward and punishment and in the ability to alter behavior on changing stimulus-reinforcement contingencies, i.e., in affective switching.

Recent neurobiological models of obsessive-compulsive disorder (OCD) have stressed the role of dysfunctional OFC-striatal circuitry in the pathogenesis of this disorder based on several observations. First, from a phenomenological point of view, reward and punishment perception appear to be abnormal in OCD; i.e., patients with OCD give the impressions of having an ongoing error sensation (“something is wrong”) when experiencing obsessions and of feeling insufficiently relieved by compulsive behavior that serves a rewarding goal. Moreover, the rigid behavior exhibited by patients with OCD that appears insensitive to reinforcing signals can be thought of as reflecting an inability to perform affective switching. Second, neuropsychological tasks that specifically address OFC function have shown impaired performance in patients with OCD compared with healthy controls (but see other resources). Third, structural and functional neuroimaging studies have repeatedly shown abnormalities associated with these brain areas in OCD, although these findings have not been uniform: i.e., increased or decreased OFC volumes and enlarged, normal, or diminished striatal volumes in morphometric studies in addition to either increased or decreased activity in the OFC and hypoactivity or hyperactivity in the caudate nucleus during resting-state imaging. Similarly, symptom provocation studies in OCD have demonstrated increased OFC activity next to both increased and decreased caudate activity. Finally, selective serotonin reuptake inhibitors and dopamine antagonists appear to be efficacious in OCD, and intact transmission of serotonin (5-hydroxytryptamine) and dopamine has been associated with normal OFC functioning and reward processing in the ventral striatum.

Thus, several lines of research have indicated that OFC-striatal dysfunction is a key factor in the pathogenesis of OCD and may be the neural substrate of abnormal reward, punishment, and affective switching processing in OCD. Although other parts of frontostriatal circuitry, in particular anterior cingulate cortex, have been targeted before using cognitive neuroimaging paradigms in OCD, the OFC-striatal loop has not been challenged directly so far. In the present study, we addressed this issue by employing a reversal learning task in an event-related, functional magnetic resonance imaging experiment. This paradigm enabled assessment of reward and punishment processing as well as affective switching and was shown to recruit OFC and striatal regions in healthy controls, data of which were also used in the present study. Since functional magnetic resonance imaging of the OFC is notoriously difficult because of signal dropout, we applied a scanning sequence specifically sensitive to OFC signal. Based on the previously reviewed data on OFC-striatal function together with its proposed role in the pathophysiology of OCD, we hypothesized that patients would show impaired performance during the reversal learning task compared with control subjects. Moreover, we expected that this would be accompanied by abnormal OFC-striatal activity during processing of reward, punishment, and affective switching.

METHODS

SUBJECTS

Twenty patients with OCD (14 women; mean age, 34 years; range, 19-54 years) and 27 healthy controls (19 women; mean age, 32 years; range, 22-53 years) participated in this study. Patients were recruited from the outpatient clinic for anxiety disorders and by advertisements on the internet. Diagnoses were established by experienced clinicians with the Structured Clinical Interview for DSM-IV Axis I disorders. Exclusion criteria were the presence of alcohol or substance abuse and major internal or neurological disorders. The following comorbid disorders were diagnosed with the Structured Clinical Interview for DSM-IV Axis I disorders: major depressive disorder (n=7), dysthymia (n=4), social phobia (n=3), generalized anxiety disorder (n=3), panic disorder (n=2), agoraphobia (n=1), and posttraumatic stress disorder (n=1). Moreover, comorbid Tourette disorder was clinically diagnosed in 2 patients, whereas 5 patients were diagnosed with “pure” OCD. At the time of the study, all patients and control subjects were free of psychotropic medication for at least 2 weeks and, in case of fluoxetine or antipsychotic medication, for at least 1 month. Moreover, no patients were currently involved in a cognitive behavioral therapy program. All participants gave written informed consent and the study was approved by the ethical review board of the VU University Medical Center (Amsterdam, the Netherlands).

To assess symptom characteristics and severity scores, the Yalom Brown Obsessive Compulsive Scale was administered (patients only), whereas the Padua Inventory—Revised was used to measure participants’ obsessive-compulsive characteristics (both groups). One patient with OCD had obsessions only and 1 had compulsions only, and symptoms were mainly related to the obsessions/checking (n=15) and symmetry/ordering (n=5) dimensions. To rate the presence and severity of depressive symptoms in both groups, we used the Beck Depression Inventory, the 21-item Hamilton Depression Rating Scale, and the 10-item Montgomery-Asberg Depression Rating Scale. Because of logistic problems, 3 patients failed to be interviewed with the Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale, and 2 patients did not complete the Beck Depression Inventory and Padua Inventory—Revised.

REVERSAL LEARNING TASK AND EXPERIMENTAL PROCEDURE

We used a self-paced, probabilistic reversal learning task with an affectively neutral baseline (Figure 1) that has been described in detail elsewhere. In brief, each trial in the experi-
The mental task consisted of 2 stimuli, i.e., cartoons of a bus and a tie, which were presented at either side of a screen with randomized locations for 3000 milliseconds maximally. Subjects were instructed in advance which of the 2 stimuli to select and neutral feedback was given after a subject's choice (Choice Made). After 6 to 10 correct responses, a reversal occurs without the subject's knowledge. CR indicates correct response; BL, baseline trial; PENS, probabilistic error with no shift; PRE, preceding reversal error; FRE, final reversal error.

Figure 1. The reversal learning task. This example (consecutive trials are running from top left to bottom right) shows all events of interest. Two stimuli are presented to subjects on each trial, i.e., cartoons of a bus and a tie in experimental trials and cartoons of a car and a pair of trousers on baseline trials. In experimental trials, either stimulus is correct and positive or negative feedback is given in the form of points immediately after a subject's choice as well as the total number of points accumulated up to that trial. In baseline trials, subjects were instructed in advance which of the 2 stimuli to select and neutral feedback is given after a subject's choice (Choice Made). After 6 to 10 correct responses, a reversal occurs without the subject's knowledge. CR indicates correct response; BL, baseline trial; PENS, probabilistic error with no shift; PRE, preceding reversal error; FRE, final reversal error.
Demographic and behavioral data were analyzed using SPSS software (version 11.5 for Windows; SPSS Inc, Chicago, Ill). For our behavioral analysis, the following outcome variables were assessed in both groups: the average number of CR, PENS, FRE, PRE, PES, and SE events and the average number of points accumulated by the end of the task. A 1-way analysis of variance with group (OCD vs controls) as the between-subject factor and event type as the within-subject factor was performed to assess performance differences between groups.

Imaging analysis was done using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, United Kingdom). Images were reoriented, slice-time, and realigned to the first volume. The mean image was coregistered with the whole-brain EPI volume, and images were normalized to a SPM T2* template (using 12 linear parameters and a set of nonlinear cosine basis functions). Spatial smoothing was performed using a 6-mm full-width-at-half-maximum gaussian kernel with the aim of increasing sensitivity for small activation foci, particularly in the OFC, even though larger filters may be more efficient for noise reduction. Statistical analysis was carried out in the context of the general linear model, in which each event was modeled using a δ function convolved with the canonical hemodynamic response function. The following events were modeled to the onset of the feedback presentation, as defined previously: (1) baseline events (BLs), (2) correct responses with a reward outcome (CRs), (3) probabilistic errors with no following shift (PENSs), (4) preceding reversal errors, ie, false responses after reversal not leading to a shift (PREs), and (5) final reversal errors, ie, the last false response after reversal prior to a shift (FREs). Two events were modeled as events of no interest: (6) spontaneous errors (SEs), and (7) probabilistic errors with a following shift (PESs).

Movement parameters were also included in the model as regressors of no interest. The following contrasts were computed: (1) CRs minus BLs to assess the main effect of reward, (2) PENSs plus PREs minus FREs) minus BLs to assess the main effect of all punishment events, and (3) FREs minus (PENSs plus PREs) to subtract punishment events not leading to a shift from punishment events prior to a shift, ie, to isolate affective switching.

Contrasts were first performed at single subject level. These were then entered into a second level (random effects) analysis by calculating 1-sample t tests on each individual’s contrast images for contrasts 1 through 3. Group main effects for each contrast were analyzed with 1-way analysis of variance. We performed conjunction analyses for our events of interest to identify regions showing consistent activations across groups and group interaction effects by using a statistical parametric map of the minimum t statistic over the relevant orthogonal contrasts. The P values of the ensuing regional effects were adjusted for the whole-brain search volume using the false discovery rate method implemented in SPM2. A significant effect (P < .05) suggests that one or both contrasts were significant at a corrected level against the null hypothesis of no effect in either contrast. After statistical testing, inclusive masking was used to ensure that both contrasts contributed substantially to the overall effect. In the patient group, additional correlation analyses were performed between BOLD responses on reward, punishment, and affective switching and OC and depression severity scores. Results for main effects and correlation analyses are similarly reported at P < .05 and are false discovery rate–corrected unless indicated otherwise. Localization of group results was expressed in MNI (Montreal Neurological Institute) coordinates.
Table 1. Demographic and Clinical Characteristics of OCD and Control Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With OCD (n = 29)</th>
<th>Controls (n = 27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F/M, No.</td>
<td>14/6</td>
<td>19/8</td>
<td>.97*</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>34 (10.8)</td>
<td>32 (7.7)</td>
<td>.58†</td>
</tr>
<tr>
<td>Handedness, R/L, No.</td>
<td>16/4</td>
<td>23/4</td>
<td>.64*</td>
</tr>
<tr>
<td>Education score, mean (SD)</td>
<td>7.8 (2.3)</td>
<td>8.6 (1.4)</td>
<td>.28§</td>
</tr>
<tr>
<td>(range 1-10)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness, mean (SD), y</td>
<td>20.8 (14.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication naive patients, No.</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with previous CBT, No.</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Y-BOCS severity score, mean (SD)</td>
<td>20.8 (5.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range 11-29)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Padua-IR score, mean (SD)</td>
<td>56.8 (36.6)</td>
<td>11.5 (10.4)</td>
<td></td>
</tr>
<tr>
<td>BDI score, mean (SD)</td>
<td>17.0 (8.5)</td>
<td>1.7 (2.6)</td>
<td></td>
</tr>
<tr>
<td>HDRS score, mean (SD)</td>
<td>11.7 (4.3)</td>
<td>4.0 (1.0)</td>
<td></td>
</tr>
<tr>
<td>MADRS score, mean (SD)</td>
<td>13.6 (8.0)</td>
<td>0.6 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Postscan 5-item OC questionnaire score, mean (SD) (range 0-20)</td>
<td>3.0</td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BDI, Beck Depression Inventory; CBT, cognitive behavioral therapy; HDRS, Hamilton Depression Rating Scale; L, left; MADRS, Montgomery-Asberg Depression Rating Scale; OCD, obsessive-compulsive disorder; Padua-IR, Padua Inventory-Revised; R, right; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.
*χ² Test.
†Independent samples t Test.
‡A score of 1 denotes primary school unfinished; 10 denotes university graduated.
§Mann-Whitney U test.
||Assessed in 18 patients with OCD.
†|Assessed in 17 patients with OCD.

RESULTS

DATA

Table 1 summarizes demographic and clinical characteristics for both groups. The OCD group displayed significantly higher OCD severity scores in addition to significantly increased depressive symptom ratings compared with the control group. Table 2 lists behavioral data from the reversal learning task. Patients with OCD were found to have a significantly lower average number of points accumulated by the end of the task as well as a significantly reduced number of CRs and an increased number of SEs that was borderline significant. In the patient group, no significant correlations were found between the average number of points obtained and the number of CRs on the one hand and depression severity measures (P > .30 for all), OCD severity ratings (P > .10 for all), or scores from the 5-item postscan OC questionnaire (P > .16 for both) on the other. Imaging results for main effects of reward, punishment, and affective switching in both groups as well as conjunction analyses are listed in Table 3.

REWARD

In controls, reward processing (CRs–BLs) was associated with increased activity in the right medial and lateral OFC, right DLPFC, right superior parietal cortex, bilateral occipital cortex, bilateral caudate nucleus, and left ventral pallidum/nucleus accumbens. Patients with OCD did not show activations at our a priori significance level. However, at P < .001 uncorrected, increased BOLD responses were found in the right DLPFC, right inferior parietal cortex, and bilateral occipital cortex (see Figure 2 for an example of individual results at the level of the OFC together with each subject’s mean EPI). Conjunction analyses demonstrated greater reward-associated activity in the right medial and lateral OFC, bilateral occipital cortex, and right caudate nucleus (border zone ventral striatum) in controls relative to the OCD group (Figure 3). No areas were found showing hyperactivity for patients compared with controls.

PUNISHMENT

When contrasting all punishment events with baseline events ([PRES] + [PENSs] + [FRES]–BLs), controls showed activity in the right medial and lateral OFC, right insular cortex, and bilateral occipital cortex. In contrast, patients demonstrated inferior parietal cortex activity. At an uncorrected significance level of P < .001, additional areas were found activated in the OCD group, ie, in the right anterior PFC, right DLPFC, right insular cortex, and right occipital cortex. Conjunction analyses did not reveal significant group differences for punishment-associated brain activity. An additional analysis subtracting baseline events from punishment events not leading to a shift ([PRES] + [PENSs]–BLs) showed the same main effects in both groups as the contrast ([PRES] + [PENSs] + [FRES]–BLs), albeit with the exception of right insular activity and at a slightly lower threshold (P < .001 uncorrected). Again, a conjunction
analysis did not reveal significant group \times task differences.

**AFFECTIVE SWITCHING**

To assess the main effect of affective switching, punishment events not leading to a shift were subtracted from punishment events prior to a shift (i.e., \( \text{FREs} - \left[ \text{PREs} / \text{PENSs} \right] \)). In controls, this contrast revealed activity in the left posterior OFC, bilateral anterior PFC, bilateral DLPFC, bilateral insula, and anterior cingulate cortex. No significant activations were found in the patient group at \( P < .05 \) corrected. However, at \( P < .001 \) uncorrected, activity was observed in the right lateral OFC, bilateral anterior PFC, left DLPFC, and right insular cortex. Conjunction analyses showed increased

### Table 3. Brain Regions Showing Main Effects for Reward, Punishment, and Affective Switching in Patients With OCD and Control Subjects and for the Conjunction of Main Effects and Group Interaction Effects*

<table>
<thead>
<tr>
<th>Area</th>
<th>OCD Group (n = 20)</th>
<th>Control Group (n = 27)</th>
<th>Conjunction of Main Effects and Group Interaction Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>MNI Coordinates</strong></td>
<td><strong>MNI Coordinates</strong></td>
<td><strong>MNI Coordinates</strong></td>
</tr>
<tr>
<td></td>
<td>L/R x y z z value</td>
<td>L/R x y z z value</td>
<td>L/R x y z z value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cluster Size†</td>
<td>Cluster Size†</td>
</tr>
<tr>
<td><strong>Reward (CRs – BLs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral OFC</td>
<td>R</td>
<td>36 54 –12 4.37 21</td>
<td>36 51 –12 4.35 1</td>
</tr>
<tr>
<td>Medial OFC</td>
<td>R</td>
<td>15 36 –15 4.16 13</td>
<td>15 36 –15 4.49 1</td>
</tr>
<tr>
<td>Dorsolateral PFC</td>
<td>R</td>
<td>45 42 –18 3.65§ 3</td>
<td>45 42 –21 3.70 10</td>
</tr>
<tr>
<td>Parietal superior</td>
<td>R</td>
<td>30 –63 48 3.77 17</td>
<td></td>
</tr>
<tr>
<td>Parietal inferior</td>
<td>R</td>
<td>27 –63 45 4.01§ 20</td>
<td></td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>R</td>
<td>33 –93 0 4.18§ 50</td>
<td>36 –93 –9 5.76 173</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>R</td>
<td>6 18 6 4.43 49</td>
<td>6 18 3 4.49 1</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>–6 15 6 3.73 49</td>
<td></td>
</tr>
<tr>
<td>Ventral pallidum/ nucleus accumbens</td>
<td></td>
<td>–12 6 9 3.76 3</td>
<td></td>
</tr>
<tr>
<td><strong>Punishment ([PREs + PENSs + FREs] – BLs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral OFC</td>
<td>R</td>
<td>33 54 –12 5.45 48</td>
<td></td>
</tr>
<tr>
<td>Medial OFC</td>
<td>R</td>
<td>16 42 –15 3.74 7</td>
<td></td>
</tr>
<tr>
<td>Anterior PFC</td>
<td>R</td>
<td>39 51 –3 4.31§ 20</td>
<td></td>
</tr>
<tr>
<td>Dorsolateral PFC</td>
<td>R</td>
<td>45 39 27 3.94§ 42</td>
<td></td>
</tr>
<tr>
<td>Insular cortex</td>
<td>R</td>
<td>33 21 –3 4.33§ 26</td>
<td>30 24 –12 4.04 16</td>
</tr>
<tr>
<td>Parietal inferior</td>
<td>R</td>
<td>27 –63 45 4.77 29</td>
<td></td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>R</td>
<td>36 –96 0 4.30§ 9</td>
<td>33 –93 –9 5.00 122</td>
</tr>
<tr>
<td></td>
<td>L –33 –96 –12 3.78 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affective Switching (FREs – [PREs + PENSs])</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lateral OFC</td>
<td>R</td>
<td>30 51 –15 3.61§ 4</td>
<td></td>
</tr>
<tr>
<td>Posterior OFC</td>
<td>L</td>
<td>–18 18 –15 3.70§ 8</td>
<td>–18 18 –15 4.15 1</td>
</tr>
<tr>
<td>Anterior PFC</td>
<td>R</td>
<td>30 54 15 3.38§ 4</td>
<td>36 51 9 4.71 136</td>
</tr>
<tr>
<td></td>
<td>L –30 51 6 3.31§ 3</td>
<td>–30 60 9 3.85§ 29</td>
<td>–31 60 6 4.38 2</td>
</tr>
<tr>
<td>Dorsolateral PFC</td>
<td>R</td>
<td>33 45 33 5.09 136</td>
<td>33 45 33 5.45 5</td>
</tr>
<tr>
<td></td>
<td>L –45 36 27 3.46§ 3</td>
<td>–42 33 42 4.17 9</td>
<td>–42 33 42 4.71 1</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>R</td>
<td>33 18 6 3.95§ 4</td>
<td>33 18 6 4.53 75</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>–33 21 9 4.99 70</td>
<td>–33 21 6 5.37 12</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>R</td>
<td>0 30 33 3.89§ 15</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BLs, baseline events; CRs, correct responses; FREs, final reversal errors; L; left; MNI, Montreal Neurological Institute; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PENSs, probabilistic errors with no shift; PFC, prefrontal cortex; PREs, preceding reversal errors; R, right.

*All results at \( P < .05 \) false discovery rate-corrected unless indicated otherwise.

†Number of voxels.

‡ \( z \) Values refer to the effect for the combination of main effects and group interaction effect.

§ \( P < .001 \) uncorrected.

|| \( P < .06 \) FDR corrected.
BOLD responses in the left posterior OFC, bilateral anterior PFC, bilateral DLPFC, and bilateral insular cortex (right-sided at borderline significance level \(P < .06\)) for controls vs patients with OCD (Figure 4). The opposite contrast did not reveal significant differences.

CORRELATION ANALYSES

In patients, no significant correlations were found between BOLD responses during reward, punishment, or affective switching on the one hand and symptom
Figure 4. Conjunction analysis of overall main effect for affective switching and interaction effect of controls vs patients with obsessive-compulsive disorder (OCD) for affective switching, superimposed on sagittal, coronal, and transaxial slices from a canonical (MNI [Montreal Neurological Institute] compatible) T1 image as supplied by SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, United Kingdom). Enhanced blood oxygenation level–dependent responses are shown for control subjects relative to patients with OCD in the left posterior orbitofrontal cortex (A) (encircled; x=−18, y=18, z=−15); right anterior prefrontal cortex (B) (encircled; x=36, y=54, z=−3); right dorsolateral prefrontal cortex (C) (encircled; x=33, y=45, z=33); and left anterior insular cortex (D) (encircled; x=−33, y=21, z=6). The mask is set at P=.05 for purposes of illustration. Significant effects in structures B, C, and D were found bilaterally (not shown in this figure). L indicates left; R, right.
severity ratings on the other (Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and Beck Depression Inventory for depression; Yale-Brown Obsessive Compulsive Scale and Padua Inventory—Revised for OCD). Nor did we find significant correlations between 3 contrasts of interest and performance scores.

To our knowledge, the present functional magnetic resonance imaging study is the first to investigate orbitofrontal function in OCD employing a reversal learning task. This paradigm allowed the investigation of reward and punishment processing as well as affective switching, i.e., the alteration of behavior by switching to new associations after a reversal of stimulus-reinforcement contingencies. Moreover, these effects were assessed with the aid of a scanning sequence specifically sensitive to OFC signal. As was hypothesized, patients showed impaired overall task performance reflected by a significantly lower number of accumulated points by the end of the task. This was found to be associated with a smaller number of correct responses (CRs) as well as a greater number of spontaneous errors (SEs). Our findings of impaired overall performance are in accordance with some, but not all, previous neuropsychological studies using tasks addressing OFC function in OCD. These discrepant results may be explained by major differences in task implementation (i.e., object alternation, decision-making, olfactory discrimination, and reversal learning tasks), medication status, and patient inclusion criteria. However, compared with these previous studies, the current paradigm provides direct support for the hypothesis of OFC dysfunction in patients with OCD not receiving medication by showing abnormal neural responsiveness during cognitive challenge.

Imaging results showed differential activity between groups in the OFC-striatal circuit, among other areas, during reward processing and affective switching. Specifically, patients with OCD recruited the right medial and lateral OFC as well as the right caudate nucleus (border zone ventral striatum) to a lesser extent than controls during reward processing. During affective switching, patients showed decreased activity compared with controls in the left posterior OFC in addition to the bilateral insula, bilateral anterior PFC, and bilateral DLPFC. It can be argued that comorbid depression may have confounded these between-group differences. However, we found no significant correlations between task-induced brain activity and depression severity ratings in patients. Moreover, post hoc analyses performed after excluding patients with OCD with comorbid depression revealed similar group differences for reward and affective switching (data not shown).

The finding of lower task-induced activity of the OFC-striatal circuit in the present study is remarkable because a wealth of data have demonstrated increased perfusion and glucose uptake in these regions in resting-state neuroimaging designs in OCD, although conflicting results have also been reported. Enhanced baseline activity is not likely to explain decreased task-associated activity as observed in our patients with OCD, however. First, OFC-striatal hypoactivity was found only for reward and affective switching but not for punishment; second, the contrast assessing affective switching compares 2 different punishment events and does not include baseline activity, ruling out ceiling effects as a possible explanation. It is interesting that task-induced hypoactivity in brain regions associated with resting-state hyperactivity has been reported before in OCD because Rauch and coworkers demonstrated decreased striatal responsiveness in OCD during implicit learning, in both a positron emission tomography and a functional magnetic resonance imaging design. Taken together, these findings suggest that OFC-striatal dysfunction in OCD is associated with increased resting-state activity together with decreased responsiveness on cognitive challenge. Future research may address this issue by combining resting-state and cognitive activation paradigms within a single session.

Current neurobiological models of OCD emphasize the involvement of the OFC-striatal circuit in the pathogenesis of this disorder, although the exact nature of this dysfunction is insufficiently clear. As outlined previously, this neural loop is associated with motivational behavior, in particular processing of reward and punishment, and rapid reversal of stimulus-reinforcement associations. Consequently, dysfunctional OFC-striatal circuitry in OCD may be the neural substrate of deficient modulation of emotional information with subsequent ineffective behavioral adaptation being core features of this disorder. The present findings of reward-associated activity in the right OFC and ventral caudate in healthy controls but not in patients with OCD appear to be in line with these models. With respect to affective switching, patients showed less activity in the left posterior OFC compared with control subjects. Interestingly, the posterior region of OFC has been found to be associated with reversal learning impairments in a recent study of subjects with left-lateralized OFC/ventromedial brain lesions. The posterior OFC is part of a paralimbic circuit encompassing, among other areas, insular and cingulate cortices. The functional relationship between these structures may explain functional abnormalities in anterior cingulate and insula during affective switching in OCD, although only the latter region was found to be hypoactive in our study. Although speculative, the observed OFC-striatal deficiencies in OCD on reward and affective switching may be the neural correlates of a failure of compulsive behavior to alleviate obsession-caused anxiety and cognitive-behavioral inflexibility despite changing reinforcing signals in the environment, respectively. Clearly, this hypothesis is in need of further empirical testing.

In addition to these paralimbic regions, we found decreased activation in OCD during affective switching for brain areas that are normally involved in “executive” functions, i.e., the bilateral DLPFC and anterior prefrontal cortex. In a recent article, we reported the engagement of these structures in affective switching and concluded that this may reflect cognitive set switching per se as well as inhibitory control. The involvement of these regions has been reported during decision-making in another re-
cent study, suggesting that these areas support the computational aspects not only of affective switching but also of decision-making. Our finding of diminished activations in paralimbic and executive brain structures during affective switching in OCD points to an impairment of both emotional and cognitive aspects in reversal learning in this disorder. Inadequate functioning of dorsal and ventral prefrontal-striatal loops is in agreement with pathophysiological models of OCD focusing on an altered balance between inhibitory (dorsolateral) and excitatory (ventromedial) frontal-striatal circuits.

Contrary to expectation, conjunction analyses failed to show group differences for punishment events in the present study despite clear-cut differences in group main effects because right medial and lateral OFC activity was seen in controls but not in patients, whereas the opposite was true for right inferior parietal activity. Previous cognitive activation paradigms during functional neuroimaging using response conflict tasks have associated OCD with increased anterior cingulate cortex activity both on errors and during correct responses encompassing high-conflict situations. These results corroborated the notion that OCD is characterized by a dysfunctional error recognition system that has its origin in aberrant anterior cingulate cortex and OFC activity. It is assumed that this is the neural substrate of the continual sense in patients with OCD that something is wrong. Discrepant results between these studies and the present experiment may be explained by different methods of error sensation induction, ie, external negative feedback in our reversal learning task vs internally generated error detection in response conflict tasks.

It is interesting that our finding of OFC hypoactivity for reward but not for punishment processing in OCD may be related to recent data from a tryptophan depletion study in healthy volunteers. These authors showed that lowering serotonergic transmission altered the processing of reward but not of punishment-related information during a decision-making task, implying that serotonin selectively modulates reward processing, most likely mediated by the OFC. These findings suggest that OFC hypoactivity during reward processing in subjects with OCD is due to abnormal serotonin (5-hydroxytryptamine) transmitter function, in accordance with the commonly assumed role of brain serotonergic systems in the pathophysiology of OCD.

In contrast to the presumed serotonergic regulation of OFC function, dopaminergic activity is intimately associated with normal basal ganglia function, including reward processing in the ventral striatum. In the context of our finding of reward-related ventral striatal hyporesponsiveness in OCD, it is of interest that recent single photon emission computed tomography ligand studies reported abnormal dopamine transporter density and D2 receptor binding in the basal ganglia in OCD. Further research to clarify the relationship between OCD and dopamine dysfunction is obviously warranted.

The present study is not without limitations. First, we used a new reversal learning task that, although employed successfully in a group of healthy volunteers, has not been validated before in subjects with OCD. This implies the need for a replication of the present results with a different task known to validly probe the OFC in OCD. Second, effect sizes for reward- and punishment-associated activity were only modest, in particular for interference effects. Given our fairly robust sample size, the most likely explanation is that OFC signal is difficult to capture, even with a specifically tailored sequence. Third, mean symptom severity in our OCD group was only mild to moderate (mean Yale-Brown Obsessive Compulsive Scale score, 20.8), and our sample was clinically heterogeneous, despite evidence that different neuronal mechanisms may underlie various OCD subdimensions. The current findings may therefore possibly reflect a diluted effect that is specific to one of the OCD symptom dimensions.

In conclusion, the present study has shown that abnormal OFC-striatal activity is associated with impaired performance during an OFC-sensitive reversal learning task in OCD, consistent with a proposed role for this circuit in the pathogenesis of this disorder. Future research will need to further specify the significance of aberrant activity in these structures on reward and affective switching processing in relation to OCD symptoms.

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