

Dysfunctional action monitoring hyperactivates frontal–striatal circuits in obsessive–compulsive disorder: an event-related fMRI study

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Converging evidence suggests that hyperactivity in frontal–striatal circuits and in action-monitoring processes characterizes obsessive–compulsive disorder (OCD). It remains unclear, however, just how these abnormalities in brain function translate into the cognitive, affective, and behavioral manifestations of OCD. One possibility is that exaggerated or false error signals generated by the anterior cingulate (ACC) underlie compulsive behaviors by triggering the feeling that things are “not just right” even when no actual error has been made. Since recurrent compulsive behavior typically follows correct completion of a behavioral task (e.g., hand washing), ACC hyperactivity should be observed during correctly completed, high-conflict trials as well as during error trials. Frontal–striatal regions would also be expected to be activated during both trial types, as these regions are robustly associated with OCD across multiple neuroimaging paradigms. To test this hypothesis, 14 OCD patients and 14 matched controls completed a speeded reaction time task during functional magnetic resonance imaging (fMRI). Only correctly rejected, high-conflict trials produced excessive activation in both action monitoring (rostral and caudal ACC, LPFC) and frontal striatal regions (lateral orbitofrontal cortex (OFC), caudate, and thalamus) among OCD patients when compared to healthy controls. Portions of the posterior cingulate were also hyperactive among OCD patients. These results suggest that correctly rejected, high-conflict trials that require response inhibition may provide a better model than error trials of compulsive behaviors in OCD.

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Introduction

Obsessive–compulsive disorder (OCD) is a chronic anxiety disorder marked by recurrent, intrusive, and distressing thoughts (obsessions) or repetitive behaviors (compulsions). OCD is the world’s fourth most common mental disorder with a 6-month prevalence of 1–2% (Myers et al., 1984) and a lifetime prevalence of 2–3% (Robins et al., 1984). Because of its high prevalence and the chronic, debilitating nature of its symptoms, the World Health Organization named OCD among the top 10 causes of years lived with illness-related disability (Murray and Lopez, 1996).

Neurobiological models suggest that OCD is characterized by excessive activity in frontal–striatal circuits of the brain, with hyperactivity observed in orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), thalamus, and caudate (Baxter, 1992; Breiter et al., 1996; Rauch et al., 1994; Saxena and Rauch, 2000). It is unclear, however, just how these abnormalities in brain function translate into the cognitive, affective, and behavioral manifestations of OCD. One theory first proposed by Pitman (1987) is that excessive error signals generated by the ACC underlie OCD patients’ subjective sense that something is wrong and that some behavior change is needed to correct the problem. In essence, these error signals convey the feeling that things are “not just right”, even when no actual error has been made. Thus, exaggerated or false error signals may explain a wide range of compulsive behaviors that involve an intense, irrational need to repeat a behavior because it was “not just right”. Dysfunctional error signals may then provide an explanatory framework for why OCD patients with checking compulsions repeatedly check the front door despite being rationally aware that the door is locked, or why OCD patients with contamination concerns continue to wash their hands despite being rationally aware that their hands are clean. This discrepancy between rational recall that a behavior was completed vs. a sense of certainty that it was completed fits with

Tulving's (Keane et al., 1985) distinction between "remembering" and "knowing", and is considered by some to be a core mechanism of OCD (Reed, 1985; Szechtman and Woody, 2004).

This hypothesis also fits well with results from experimental psychopathology research in OCD using cognitive paradigms. "Not just right" experiences are common in patients with OCD and related disorders (Leckman et al., 1994), and appear to be more strongly associated with OCD than with other anxiety disorders (Coles et al., 2003). OCD patients have also demonstrated poor confidence in "reality testing," or the ability to recall whether a behavior was actually performed or merely imagined (McNally and Kohlbeck, 1993), and progressively decreased confidence in the accuracy of their memories as they repeat trials utilizing threat-relevant stimuli (Tolin et al., 2001).

Understanding of the functional role of the ACC in monitoring errors has evolved since Pitman's original work. Current conceptions propose that caudal regions of the ACC function to prevent errors by monitoring actions for potential error-producing situations (e.g., situations high in response conflict), thus allowing top-down systems to resolve the conflict and avoid errors (Van Veen and Carter, 2002). This is more consistent with the symptom presentation of OCD than simple error monitoring models, since compulsions are not necessarily triggered by errors per se but rather by specific cues (e.g., touching a doorknob, driving over a pot hole) under circumstances that present a high degree of cognitive interference. For instance, it may be that OCD threat-relevant events, such as touching a dirty towel, create conflict as the task demands (hand washing) are processed simultaneously with anxiety-specific demands (e.g., obsessions that one will get sick). The resulting conflict may generate erroneous error signals, which are in turn interpreted by the patient as their hands being "not just right", triggering a repetition in cleaning behaviors until the "not just right" experience terminates. This conception is consistent with findings from the information-processing bias literature, which suggests that threat-relevant stimuli can interfere with task performance as both threat- and task-related stimuli are processed simultaneously (Lavy et al., 1994; McNally, 2000; Tata et al., 1996).

While the bulk of research data localizes the action-monitoring function to caudal ACC among healthy controls (e.g., Botvinick et al., 1999; Carter et al., 1998, 2000; Gehring et al., 2000), rostral ACC has also been shown to activate during errors of commission (Kiehl et al., 2000; Menon et al., 2001). Event-related brain potential (ERP) data suggest that caudal and rostral ACC may have separate time courses with caudal ACC activation consistent with the error-related negativity that occurs approximately 50 ms after the response in ERP studies and rostral ACC activation consistent with the error-related positivity that occurs approximately 300 ms after the response (Van Veen and Carter, 2002).

Studies of action monitoring in OCD have yielded mixed results. There is good support from both ERP and functional magnetic resonance (fMRI) studies that OCD patients produce exaggerated error signals following errors of commission (Johannes et al., 2001; Gehring et al., 2000; Ursu et al., 2003). Yet, dysfunctional processing of errors does not correspond to the phenomenology of OCD. False error signals during high-conflict, yet correctly performed, trials may provide a better model of compulsive behavior in OCD since this more closely matches the phenomenology of compulsive behavior. However, initial examination of action monitoring during correct, high-conflict trials among OCD patients has yielded mixed results. Ursu et al. (2003) utilized a modified continuous performance task to examine correct

trial activation among OCD patients and healthy controls during high-conflict trials. This task produced two correct trial, high-conflict comparisons. While OCD patients exhibited enhanced caudal ACC activation on one of these high-conflict trials, healthy controls trended toward greater activation on the trial with the greatest theoretical response conflict. It is possible that characteristics of OCD such as poor memory confidence (Tolin et al., 2001) may have interacted with task demands to produce these discrepant findings. For instance, a cue/probe task with a long interstimulus interval (ISI) such as the one used by Ursu et al. (2003) may uniquely increase response conflict among OCD patients during the low-conflict trials as OCD patients question their memory of the cue stimuli. In effect, OCD patients would then be less able than healthy controls to respond confidently to low conflict trials, leading to an increase in response conflict on these trials for OCD patients. This effect would be expected to be most dramatic on the lowest conflict trial and could therefore provide a possible explanation of these apparently discrepant findings.

The purpose of the present study was to explore more fully action-monitoring dysfunctions in OCD by analyzing with fMRI patterns of activation in regions of interest typically associated with action monitoring (caudal and rostral ACC, LPFC) and regions of interest typically associated with OCD (OFC, caudate, thalamus, posterior cingulate; Baxter et al., 1992; Breiter et al., 1996; Rauch et al., 1994, 2001, 2002; Saxena and Rauch, 2000). OCD patients and matched healthy controls completed a Go/No Go task during fMRI (Kiehl et al., 2000). The Go/No Go task was selected because it is a response inhibition task associated with a robust ERN and does not have a memory component. The Go/No Go task also allows for analysis of error and correctly rejected, high response conflict trials and thus may provide an analogue to actual compulsive behavior as patients respond correctly to high-conflict situations. We predicted that OCD patients, when compared to healthy controls, would exhibit increased activation in caudal ACC, posterior cingulate, left LPFC, OFC, caudate, and thalamus during both correctly rejected, high-conflict trials (false error signals) and error trials (exaggerated error signals).

Methods

Participants

Fourteen adult patients with OCD and 14 matched healthy controls participated in the study and provided written informed consent. Diagnostic status was determined using the Structured Clinical Interview for DSM-IV (First et al., 1995). Healthy controls were excluded if they met criteria for a current or past Axis I or Axis II disorder, if they had a history of neurological disorders, or were taking psychoactive medications. OCD patients were excluded if they had a history of a psychotic disorder, neurologic disorder, substance abuse, serious suicidal ideation, or if OCD was not their primary diagnosis. Severity of OCD symptoms was established using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a,b).

Using a similar Go/No Go task, Kiehl et al. (2000) reported that a minimum of five errors was needed to resolve the error response. Thus, three patients were excluded because they did not commit the minimum number of errors necessary for analysis, thus 11 patients and 11 matched controls were included in subsequent analyses. Six of the remaining 11 OCD patients (55%) met criteria

for at least one other Axis I disorder. Two met criteria for major depressive disorder and one each met criteria for generalized anxiety disorder, social phobia, and anxiety disorder NOS. All participants were right handed. Demographic and symptom severity measures are presented in Table 1.

Task

The Go/No Go task used in the present experiment has been described in detail elsewhere (Kiehl et al., 2000). Briefly, participants were presented with a series of Go stimuli (“X’s”) and No Go stimuli (“K’s”) while being scanned. Participants were instructed to respond “as quickly and accurately as possible” with a button press to Go stimuli and to inhibit responding to No Go stimuli. The proportion of Go to No Go stimuli was 5:1 causing a prepotent bias toward Go stimuli and strong response conflict when No Go stimuli were presented (Ursu et al., 2003). All stimuli were presented for 50 ms with ISIs ranging from 1000 to 3000 ms. This task thus lends itself to analysis of errors of commission (responding to No Go stimuli) as well as correct rejections (correctly inhibiting a response to No Go stimuli). All participants were trained on the task until they demonstrated that they understood the task as measured by their responding correctly to eight consecutive practice stimuli.

fMRI acquisition

Imaging

Imaging was implemented on a standard clinical GE 1.5-T scanner. The participant’s head was firmly secured using a custom head holder. Conventional spin-echo T1-weighted sagittal localizers were acquired to confirm positioning. Functional image volumes were collected with a gradient-echo sequence (TR/TE 3000/40 ms, flip angle 90°, field of view 24 × 24 cm, 64 × 64 matrix, 3.75 × 3.75 mm in-plane resolution, 5-mm slice thickness, 30 slices) covering the entire brain (145 mm). The Go/No Go task was presented twice to each participant. Each run lasted for 423 s, during which 141 images of the entire brain were collected. Before each stimulus run, four brain volumes were collected over 12 s to allow T1 effects to stabilize. These images were not included in any subsequent analyses.

Image processing

Functional images were reconstructed offline and reoriented to approximately the anterior commissure/posterior commissure (AC/PC) plane. Two functional image runs were realigned using INRIAAlign, a motion correction algorithm unbiased by local signal changes (Freire and Mangin, 2001; Freire et al., 2002). Following realignment, a mean functional image was computed for each run.

Table 1
Demographic and measures of symptom severity

| Variable | OCD | HC |
|---------------------------------|---------------|---------------|
| Age | 39.36 (13.66) | 36.55 (11.36) |
| Percent female | 64% | 64% |
| Caucasian | 11 (100%) | 11 (100%) |
| Years of education | 13.64 (1.67) | 16.00 (2.10) |
| HAM-D total | 15.70 (4.60) | 1.55 (2.34) |
| Y-BOCS total score | 24.64 (6.85) | |
| At least one comorbid diagnosis | 5 (45.5%) | |

Y-BOCS = Yale–Brown obsessive–compulsive scale. HAM-D = Hamilton depression rating scale.

Table 2

Error rates and reaction times for errors of commission and correct responses

| Variable | OCD | HC |
|-------------------------------|----------------|----------------|
| Errors rates | | |
| No Go stimuli (“K” Go) | 24.2% | 24.7% |
| Go stimuli (“X” No Go) | 0.07% | 0.08% |
| Mean reaction time | | |
| Errors of commission (“K” Go) | 321.91 (61.78) | 364.86 (70.20) |
| Correct responses (“X” Go) | 371.40 (34.50) | 373.48 (95.88) |

The mean EPI image was matched to the EPI template provided with Statistical Parametric Mapping 2. The spatial transformation into standard MNI space was determined using a tailored algorithm with both linear and nonlinear components (Friston et al., 1995). This transformation was then applied to the corresponding functional images, which were resliced into 4 × 4 × 4 mm resolution in MNI space. The normalized data were smoothed (12 mm FWHM) and a fifth-order IIR Butterworth low-pass filter of 0.16 Hz was applied to remove any high frequency noise associated with alterations in the applied radio frequency field. The data were then analyzed using a canonical hemodynamic response and temporal derivative in SPM2. Correct hits (e.g., Go trials with button press within 1000 ms post-stimulus), correct rejections (e.g., No Go trials not followed by a button press), and false alarms (e.g., No Go trials followed by a response within 1000 ms) were modeled. A high pass filter (cutoff period 116 s) was incorporated into the model to remove noise associated with low frequency confounds (e.g., respiratory artifact; scanner drift). All images were normalized to a mean of 100 (arbitrary units) for each run to compensate for any intensity variations across runs. Importantly, no within session scaling (proportional scaling) was employed to avoid the well-known artifacts that it can produce (Aguirre et al., 1998; Desjardins et al., 2001).

For both groups, contrasts were specified that evaluated the effects of (1) errors of commission to No Go stimuli relative to the baseline of correct responses to Go stimuli, and (2) correct rejections of No Go stimuli relative to the baseline of correct responses to Go stimuli. Hypotheses were that OCD patients, when compared to healthy controls, would exhibit activation in caudal ACC, posterior cingulate, left LPFC, OFC, caudate, and thalamus during both correctly rejected, high-conflict trials (false error signals) and error trials (exaggerated error signals). The images containing these amplitudes were then entered into the second level analyses (i.e., random effects analyses). A priori hypotheses were tested in the seven regions of interest associated with action monitoring or OCD mentioned above. Because the regions of interest encompassed multiple voxels, a small volume correction, as implemented in SPM2, was applied to control Type I error for the search volume examined at $P < 0.05$ (Worsley et al., 1996).

Results

Behavioral data

Table 2 presents error rates and reaction times for the OCD patients and healthy controls. The two groups did not differ in number of errors of commission or in reaction times to Go or No Go stimuli. Error rates to No Go stimuli were similar to the 23.7% of No Go trials reported in previous studies using this task (Kiehl et al., 2000).

Table 3
Summary of the significant areas of activation for errors of commission

| Region of interest | OCD | | | | HC | | | | OCD > HC | | | |
|------------------------------|-----------------------|----------|----------|----------------------------------|-----------------------|----------|----------|----------------------------------|-----------------------|----------|----------|----------------------------------|
| | Talairach coordinates | | | <i>t</i> score <i>df</i> = 10 | Talairach coordinates | | | <i>t</i> score <i>df</i> = 10 | Talairach coordinates | | | <i>t</i> score <i>df</i> = 20 |
| | <i>x</i> | <i>y</i> | <i>z</i> | | <i>x</i> | <i>y</i> | <i>z</i> | | <i>x</i> | <i>y</i> | <i>z</i> | |
| Rostral anterior cingulate | −4 | 36 | 16 | 2.73** | 8 | 32 | 24 | 4.95*** | −4 | 40 | 12 | 2.19* |
| | 4 | 32 | 16 | 2.81** | −4 | 36 | 24 | 3.12** | 4 | 40 | 12 | 2.39* |
| Caudal anterior cingulate | −4 | 20 | 36 | 4.55*** | −4 | 20 | 36 | 5.54*** | 8 | 24 | 40 | +1.68* |
| | 4 | 20 | 40 | 4.55*** | 4 | 20 | 36 | 5.78*** | | | | |
| Lateral orbitofrontal cortex | −36 | 28 | −8 | 3.58** | 48 | 20 | −4 | 6.05*** | −52 | 40 | −4 | 2.15* |
| | 44 | 28 | −8 | 2.12* | −40 | 20 | −4 | 5.79*** | | | | |
| Lateral prefrontal cortex | −36 | 40 | 16 | 2.44* | −52 | −8 | 28 | 10.54*** | 56 | 32 | 20 | 2.09* |
| | | | | | 48 | 40 | 4 | 3.94*** | | | | |
| Posterior cingulate | 4 | −44 | 20 | 2.11* | | | | ns | −4 | −44 | 20 | 2.09* |
| Caudate | | | | ns | | | | ns | 4 | −44 | 20 | 2.22* |
| Thalamus | | | | ns | | | | ns | | | | |

Coordinates are in MNI space and incorporate a small volume correction to control Type I error. Coordinates represent the highest point of activation within each ROI. HC = healthy controls, OCD = obsessive–compulsive disorder.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

+ $P = 0.053$.

Imaging results

Error-related activity

Error-related activity was first correlated (Pearson product moment correlations) with BDI scores in order to determine if symptoms of depression were systematically affecting regions of interest. BDI scores were found to be unrelated to activity in regions of interest (r range 0.08–0.42, all P 's > 0.05), thus we did not control for baseline levels of depression in subsequent analyses. Table 3 presents coordinates and t scores in regions of interest during errors of commission for healthy controls, OCD patients, and their comparisons. The hemodynamic response in regions of interest was first analyzed independently for OCD patients and healthy controls during trials in which participants made errors of commission to No Go stimuli. This analysis found activation in both caudal and rostral ACC for both healthy controls

and OCD patients. The centroid of caudal ACC activation for both groups (4, 20, 36 and −4, 20, 36) was consistent with that previously reported for errors of commission (Kiehl et al., 2000) and also for conflict-related tasks (e.g., Botvinick et al., 1999; Carter et al., 1998). Fig. 1 shows areas of ACC activation for OCD patients, healthy controls, and group comparisons for errors of commission and correctly rejected, high-conflict trials.

In addition, OCD patients and healthy controls exhibited bilateral activation in the lateral OFC. OCD patients exhibited activation in the posterior cingulate that was not observed for healthy controls. Neither group exhibited activation in caudate or thalamus during errors of commission. Thus, analysis at the group level extended previous findings by implicating lateral OFC and rostral ACC in action-monitoring processes.

The hemodynamic response of OCD patients during errors of commission was then compared to that of healthy controls (see

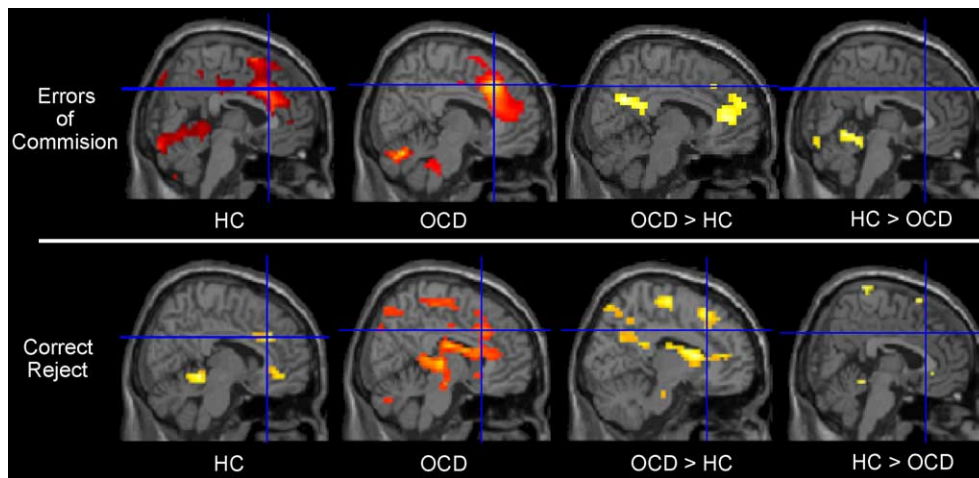


Fig. 1. Sagittal images showing anterior cingulate activation during errors of commission and correct rejects for healthy controls, OCD patients, and comparisons of OCD patients to healthy controls. Images thresholded at $P < 0.055$ to show caudal ACC activation in the OCD > HC errors of commission contrast.

Table 3 and Fig. 2). When compared to healthy controls, OCD patients exhibited excessive activation in rostral ACC and trended toward excessive activation in caudal ACC ($P = 0.053$) during errors of commission. OCD patients also exhibited excessive activation in left lateral OFC as well as bilateral LPFC and posterior cingulate relative to controls. There were no regions in which controls showed greater activation than patients.

Conflict-related activity

Conflict-related activity was first correlated (Pearson product moment correlations) with BDI scores in order to determine if symptoms of depression were systematically affecting regions of interest. BDI scores were found to be unrelated to activity in regions of interest (r range 0.03–0.25, all P 's > 0.05), thus we did not control for baseline levels of depression in subsequent analyses. Table 4 presents coordinates and t scores in regions of interest during correct, high-conflict trials for healthy controls, OCD patients, and their comparisons. The hemodynamic response

during correctly rejected, high-conflict trials requiring inhibition of a prepotent response was first analyzed separately for each group. During these trials, both OCD patients and healthy controls exhibited activation in caudal and rostral ACC as well as bilateral LPFC. The location of caudal ACC activation was also consistent with that previously associated during action-monitoring tasks for errors of commission (Kiehl et al., 2000) and also for conflict-related tasks (e.g., Botvinick et al., 1999; Carter et al., 1998). OCD patients exhibited activation bilaterally in caudate, thalamus, and lateral OFC that was not observed in healthy controls.

The hemodynamic response of OCD patients during correctly rejected, high-conflict trials was then compared to that of healthy controls (see Table 4 and Fig. 3). OCD patients, relative to controls, exhibited hyperactivity in rostral and caudal ACC, left lateral OFC, left LPFC as well as bilateral posterior cingulate, caudate, and thalamus. Thus, when OCD patients correctly inhibited a prepotent response (high response conflict), they activated regions typically associated with action monitoring as well as frontal striatal circuits

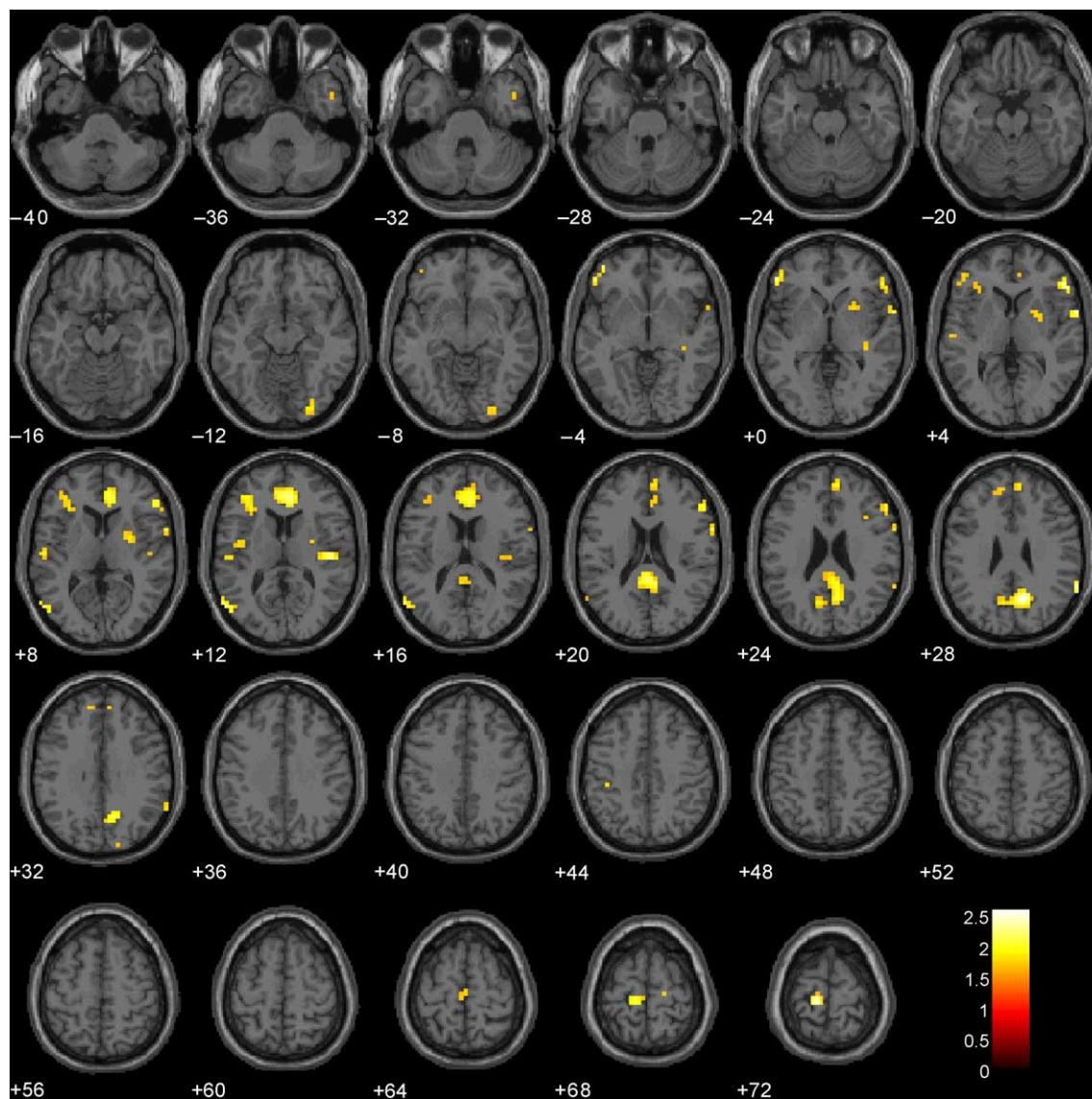


Fig. 2. Brain areas showing significantly greater activation for OCD patients than for healthy controls during errors of commission. Image is thresholded at $P < 0.05$.

Table 4
Summary of the significant areas of activation for correct rejects

| Region of interest | OCD | | | | HC | | | | OCD > HC | | | |
|------------------------------|-----------------------|----------|----------|----------------------------------|-----------------------|----------|----------|----------------------------------|-----------------------|----------|----------|----------------------------------|
| | Talairach coordinates | | | <i>t</i> score <i>df</i> = 10 | Talairach coordinates | | | <i>t</i> score <i>df</i> = 10 | Talairach coordinates | | | <i>t</i> score <i>df</i> = 20 |
| | <i>x</i> | <i>y</i> | <i>z</i> | | <i>x</i> | <i>y</i> | <i>z</i> | | <i>x</i> | <i>y</i> | <i>z</i> | |
| Rostral anterior cingulate | 4 | 32 | 8 | 3.47** | 16 | 36 | 20 | 2.62* | 4 | 32 | 12 | 2.62** |
| | −4 | 32 | 8 | 3.21** | | | | | | | | |
| Caudal anterior cingulate | 16 | 20 | 36 | 4.65*** | −4 | 20 | 36 | 1.84* | 16 | 24 | 36 | 2.73** |
| | −12 | 24 | 36 | 2.62* | 12 | 16 | 32 | 1.98* | −16 | 20 | 40 | 2.11* |
| Lateral orbitofrontal cortex | −44 | 24 | −4 | 5.00*** | | | | ns | −52 | 40 | −4 | 2.16* |
| | 44 | 16 | −8 | 4.21*** | | | | | | | | |
| Lateral prefrontal cortex | 36 | 20 | 36 | 4.65*** | 24 | 40 | 24 | 3.14** | −56 | 20 | 12 | 2.33* |
| | −40 | 28 | 32 | 2.59** | −36 | 40 | 24 | 2.44* | 64 | 0 | 24 | 2.92** |
| Posterior cingulate | | | | ns | | | | ns | 12 | −52 | 28 | 2.26* |
| | | | | | | | | | −12 | −56 | 28 | 2.36* |
| Caudate | −8 | 4 | 16 | 2.32* | | | | ns | 8 | 16 | 12 | 3.92*** |
| | 8 | 4 | 16 | 3.94*** | | | | | | | | |
| Thalamus | −8 | −16 | 4 | 2.57* | | | | ns | 8 | −20 | 0 | 2.46** |
| | 8 | −20 | 4 | 4.87*** | | | | | | | | |

Coordinates are in MNI space and incorporate a small volume correction to control Type I error. Coordinates represent the highest point of activation within each ROI. HC = healthy controls, OCD = obsessive-compulsive disorder.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

and posterior cingulate. When compared to OCD patients, healthy controls did not exhibit excessive activation in a priori regions of interest during correct, high-conflict trials.

Correlations with measures of symptom severity for OCD patients

Pearson product moment correlations were calculated for OCD symptom severity, as measured by Y-BOCS, and activation in regions of interest. During errors of commission, increased symptom severity among OCD patients was positively correlated with increased activation in the bilateral posterior cingulate ($r = 0.87$, $P < 0.001$), left lateral OFC ($r = 0.83$, $P < 0.001$), and right lateral OFC ($r = 0.68$, $P < 0.01$). No significant association was found between Y-BOCS scores and activation in the ACC, thalamus, caudate, or LPFC. During correct, high-conflict trials requiring inhibition of a prepotent response, Y-BOCS scores were positively correlated with activation in the posterior cingulate ($R = 0.62$, $P < 0.05$). No relationship was found between correct, high-conflict trials and activation in the OFC, ACC, thalamus, caudate, or LPFC.

Discussion

Results from the present study provide additional support for the hypothesis that action-monitoring processes are hyperactive in OCD. During errors of commission and correctly rejected, high-conflict trials, both rostral and caudal ACCs were hyperactive among OCD patients. The data also suggested that action-monitoring dysfunction in OCD may involve several other regions including lateral OFC, LPFC, posterior cingulate, and, for trials that involve inhibiting a prepotent response, basal ganglia and thalamus.

These latter findings suggest that high-conflict, correct trials requiring inhibition of a prepotent response may provide a better model than error trials of the “not just right” experiences that underlie compulsive behavior in OCD. During high-conflict, correct trials, OCD patients exhibited hyperactive hemodynamic

activity not only in areas typically associated with action monitoring, but also in frontal-striatal circuits typically associated with OCD. Frontal-striatal circuits were not activated for healthy controls during correct trials and, with the exception of lateral OFC, were not active for OCD patients during errors trials. This suggests that compulsive behaviors represent a failure to inhibit responding rather than a failure to properly complete a response.

Hyperactive hemodynamic responding in ACC and frontal-striatal circuits during correct, high-conflict trials would appear to reconcile differences between patterns of activation observed in OCD during action-monitoring tasks and the robust frontal-striatal activations reported during other neuroimaging paradigms of OCD. Nonetheless, if ACC plays a central role in maintaining compulsive behaviors as the action-monitoring data suggest, then caudal and rostral ACC activation as observed in action-monitoring studies should be present in OCD studies using other paradigms such as symptom provocation. Perhaps ACC activation is more apparent during tasks that elicit compulsive behaviors or their equivalent (e.g., conflict), and is less apparent during other tasks such as analysis of the resting state or pre-post treatment designs.

An alternate explanation of the observed correct trial differences may be that OCD patients differ from healthy controls on the response inhibition components of the Go/No Go task rather than on their reaction to correctly rejected, high-conflict stimuli. That is, inhibiting a prepotent response would require successful response inhibition. There is preliminary evidence suggesting that response inhibition is impaired in OCD (Bannon et al., 2002; Rosenberg et al., 1997a,b). However, deficits in response inhibition among OCD patients have typically been demonstrated through differential rates of failing to inhibit responding (e.g., making errors of commission). In the present study, however, there were no differences in error rates between OCD patients and healthy controls. This suggests that the observed group differences may not be due solely to deficits in response inhibition.

Activation patterns in the lateral OFC were asymmetrical, favoring the left side during both error and correctly rejected,

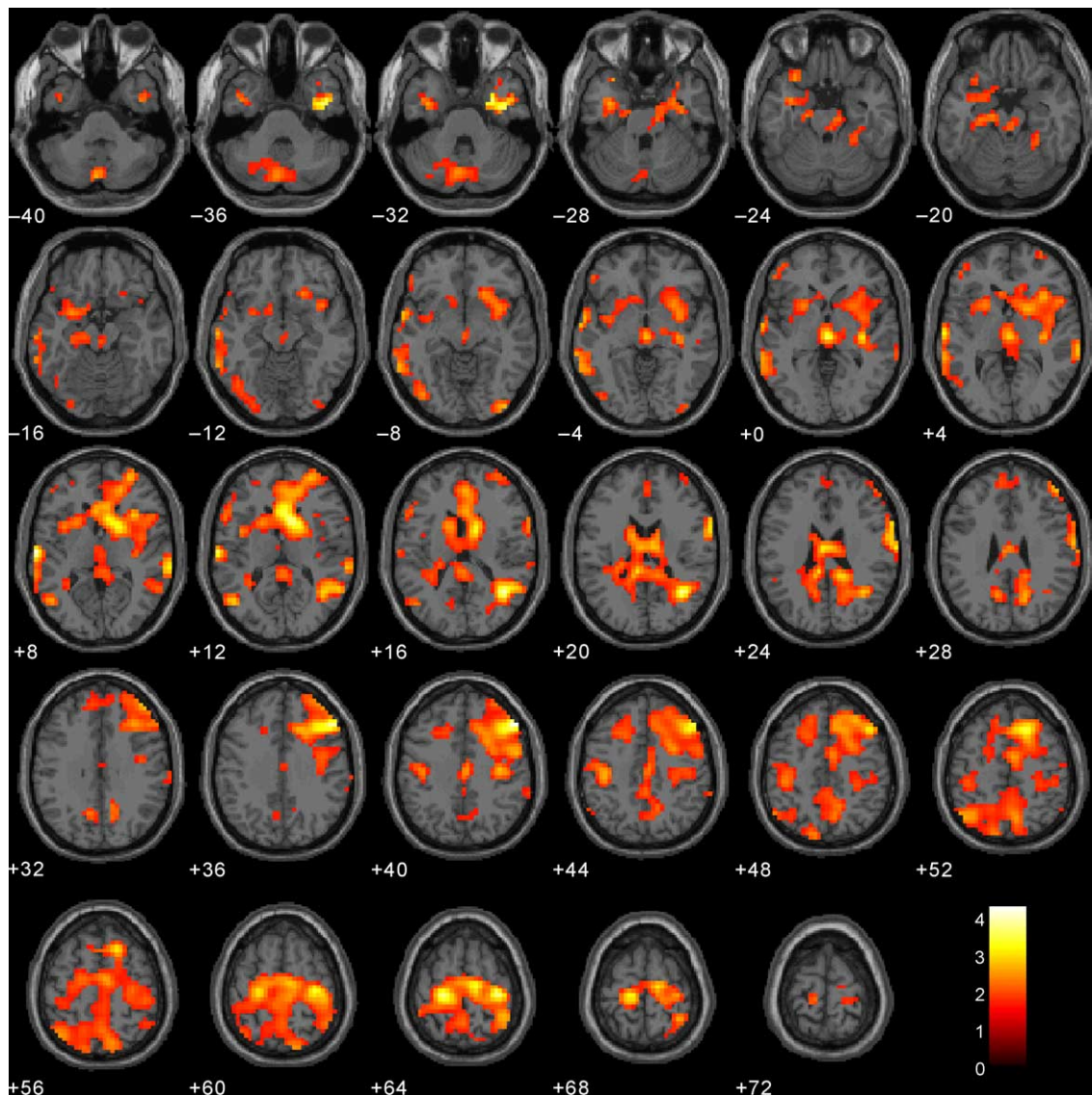


Fig. 3. Brain areas showing significantly greater activation for OCD patients than for healthy controls during correctly rejected, high-conflict trials (No Go). Image is thresholded at $P < 0.05$.

high-conflict trials. Previous studies have reported that OFC activation is typically bilateral for OCD but may trend toward increased activation on the left side (for a review, see [Baxter, 2003](#)). This is interesting in that caudate activity typically favors the right side in OCD. Models of OCD suggest that excessive tone between OFC and caudate may mediate the symptom presentation of OCD. Thus, it may be that the observed asymmetries represent excessive tone in contralateral projections between OFC and caudate. Animal models, however, suggest that the majority of projections between OFC and caudate are ipsilateral ([Baxter, 2003](#)). Thus, further studies are needed to explore this interesting finding.

The posterior cingulate was observed to be hyperactive in OCD patients, as compared to healthy controls, during both error and correctly rejected, high-conflict trials. In human and animal studies, posterior cingulate activation has been found to be associated with the evaluation of emotionally valenced but not neutral stimuli and with determining reward values ([Maddock and Buonocore, 1997](#); [Maddock et al., 2003](#); [McCoy et al., 2003](#)). Thus, it may be that

OCD patients evaluate conflict and errors as being more threatening/emotional than do healthy controls. In this sense, posterior cingulate activation may reflect early threat-identification components of information-processing biases toward threat. However, this does not explain the relative paucity of data linking posterior cingulate activation to OCD. Theoretically, information-processing biases should be present during many paradigms used in OCD neuroimaging research. In monkeys, posterior cingulate activation has been linked to reward prediction errors or the evaluation of discrepancies between expected rewards and actual outcomes ([McCoy et al., 2003](#)). While further research is needed to explore the functional role of posterior cingulate in OCD, it may be that discrepancies between expected and actual outcomes occur more frequently during high-conflict tasks than during other paradigms.

Intact LPFC has been found to be necessary for the proper functioning of action-monitoring systems. Consistent with previous studies, LPFC activity was observed for both OCD patients and healthy controls during both error and correctly rejected trials (e.g., [Bush et al., 1998](#); [Carter et al., 1998](#); [Kiehl et al., 2000](#)).

Models of LPFC interactions with ACC suggest that LPFC serves to reduce conflict by filtering responses unrelated to task demands. LPFC hyperactivity among OCD patients suggests a failure of this system; however, further research is needed to evaluate the relationship between LPFC and ACC in action monitoring.

Our finding that both rostral and caudal ACC were hyperactive in OCD may be consistent with recent models mapping the time course of action-monitoring processes (Van Veen and Carter, 2002). Caudal ACC activation may reflect the initial identification of response conflict, while rostral ACC activation may reflect subsequent affective evaluation of the response. Hyperactivity in caudal ACC may thus reflect an exaggerated response to response conflict in OCD while rostral ACC hyperactivity may reflect an exaggerated affective response to conflict-laden situations.

The Go/No Go task differed from tasks used in previous studies in that correctly rejected, high-conflict trials required response inhibition rather than replacing the prepotent response with an alternate response. In terms of OCD, the question of which is more relevant can be addressed both theoretically and empirically. Empirical data from the present study suggest that response inhibition activates a pattern of regions typically associated with OCD and may be a better model of OCD than error trials. Theoretically, it is less clear how complete response inhibition may differ functionally for patients with OCD from other tasks that require inhibiting a prepotent response and replacing it with a separate response. The phenomenology of compulsive behaviors would appear to be more consistent with failures of response inhibition (e.g., a failure to inhibit urges to wash) rather than with successful inhibition of prepotent responding. Thus far, tasks used in exploring action-monitoring dysfunctions in OCD have utilized neutral stimuli such as letters or color names. Action-monitoring studies utilizing stimuli more related to OCD, such as threat-relevant words or images, may more accurately model OCD and allow better discrimination of the role of ACC and frontal–striatal circuits in OCD and their relationship to compulsive behaviors.

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