Error-Related Hyperactivity of the Anterior Cingulate Cortex in Obsessive-Compulsive Disorder

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Background: *Hyperactivity of the anterior cingulate cortex (ACC) in patients with obsessive-compulsive disorder (OCD) has been shown to increase with symptom provocation and to normalize with treatment-induced symptom reduction. Although the functional significance of anterior cingulate involvement in OCD remains unknown, electrophysiological evidence has linked this region to error-processing abnormalities in patients with OCD. In this functional magnetic resonance imaging (fMRI) study, we sought to further localize error-processing differences within the ACC of OCD patients compared with healthy subjects.*

Methods: *Event-related fMRI data were collected for eight OCD patients and seven healthy subjects during the performance of a simple cognitive task designed to elicit errors but not OCD symptoms.*

Results: *Both OCD patients and healthy subjects demonstrated dorsal ACC activation during error commission. The OCD patients exhibited significantly greater error-related activation of the rostral ACC than comparison subjects. Activity in this region was positively correlated with symptom severity in the patients.*

Conclusions: *Error-processing abnormalities within the rostral anterior cingulate occur in the absence of symptom expression in patients with OCD.*

Key Words: Obsessive-compulsive disorder, anterior cingulate, error-processing, response conflict, functional magnetic resonance imaging, error-related negativity

Several lines of evidence suggest anterior cingulate cortex (ACC) dysfunction in patients with obsessive-compulsive disorder (OCD). Neuroimaging studies demonstrate excessive baseline activity in limbic elements of cortico-striatal-pallidal-thalamic (CSPT) circuitry in OCD patients, like the anterior cingulate cortex (Machlin et al 1991; Perani et al 1995; Rauch et al 1998; Swedo et al 1989). Anterior cingulate cortex hyperactivity further increases with symptom provocation (Adler et al 2000; Breiter et al 1996; McGuire et al 1994; Rauch et al 1994) and normalizes after successful treatment of OCD (Perani et al 1995). In otherwise refractory patients, surgical ablation of the ACC can reduce OCD symptoms (Kim et al 2003). An association between enlarged ACC volumes and symptom severity in pediatric OCD patients implicates this region early in the disease course (Rosenberg and Keshavan 1998). Though involvement of the ACC in OCD is now well documented, the exact role of this region in the pathophysiology of this disorder remains unclear.

Recent functional imaging and electrophysiological studies in healthy individuals suggest that the ACC may be involved in the detection of errors (Gehring et al 1995; Kiehl et al 2000; Menon et al 2001). Several authors have suggested that OCD involves overactivity of a system designed to detect errors, leading to a preoccupation with correcting perceived mistakes (Pitman 1987; Schwartz et al 1996). Error detection can now be tracked electrophysiologically, using the "error-related negativity" (ERN) peak, which occurs as a large, negative polarity peak that begins at the moment of an error and reaches a maximum about 100 milliseconds later (Falkenstein et al 1991; Gehring et al 1995). Subjects with OCD (Gehring et al 2000; Johannes et al 2001) and undergraduates with subclinical obsessive-compulsive (OC) symptoms exhibited increased amplitude of the ERN (Hajcak and Simons 2002). Gehring et al (2000) found a positive correlation of ERN magnitude and OC symptom severity, a finding supported by the findings of an functional magnetic resonance imaging (fMRI) blood oxygenation level dependent (BOLD) study of Ursu et al (2003). These findings are consistent with the hypothesis that ACC involvement in OCD may be related to functional abnormalities in the processing of errors or perceived errors.

Preliminary findings regarding the role of the ACC in OCD have raised several questions. Uncertainty exists as to whether the neural systems that monitor errors also monitor conflicting response tendencies (Carter et al 1998) or whether separate and distinct neural circuitry subserves these two functions. It has been suggested that errors may represent a form of response conflict such that error processing and conflict detection may be one and the same process (Carter et al 1998). In line with this interpretation, the study by Ursu et al (2003) found that both errors and high-conflict conditions in OCD patients elicited hyperactivity in the same ACC subregion. Furthermore, while data suggest that the ERN originates in the ACC, other work has demonstrated that the ERN also involves areas outside the ACC, as well as different subregions within it (Kiehl et al 2000; Luu et al 2003; Menon et al 2001).

Thus, to better localize the source of error-detection and conflict processing differences between OCD and comparison subjects, we used an interference paradigm, similar to the error-eliciting tasks employed in the ERN work, but now coupling it with the fMRI BOLD technique. Although fMRI BOLD lacks the temporal resolution necessary to measure the ERN, it does have the advantage of superior anatomical localization. Based on the ERN data and functional neuroimaging evidence for hyperactivity of the ACC in OCD, we hypothesized that ACC activation during error commission would be greater in OCD patients compared with normal subjects. The interference task, which elicited errors and conflict between competing response tendencies, also permitted us to test whether conflict processing alone elicited hyperactivity of the ACC.

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Received May 11, 2004; revised September 24, 2004; accepted October 29, 2004.

0006-3223/05/$30.00
doi:10.1016/j.biopsych.2004.10.038

Methods and Materials

Subjects

Eight OCD patients (two female patients; age: 27.4 ± 8.5 years; education: 15.5 ± 2.4 years) and seven healthy control subjects (two female control subjects; age: 30.0 ± 8.6 years; education: 16.9 ± 1.7 years) were evaluated using the Structured Clinical Interview for DSM-IV (SCID) (First et al 1996), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al 1989), and the Hamilton Depression Scale (HAM-D). Among the patients, there were no current comorbid diagnoses. Patients with a past history of major depression ($n = 3$) or dysthymia ($n = 2$) were included. Three patients had OCD as their only lifetime diagnosis. Five of the patients were taking antiobsessional medications (two fluoxetine, one fluoxetine plus clonazepam, one fluoxetine plus risperidone, one sertraline), and three were unmedicated. A variety of symptom clusters were endorsed, including contamination obsessions and cleaning compulsions ($n = 5$), intrusive aggressive images or thoughts with accompanied checking or "corrective" mental rituals ($n = 5$), and symmetry and ordering ($n = 3$). Most patients endorsed other, miscellaneous OCD symptoms as well, such as repeated seeking of reassurance ($n = 3$), ritualistic blinking or staring ($n = 2$), counting ($n = 1$), or checking locks/stoves ($n = 1$). Mean Y-BOCS score was 18.0 ± 3.9, and all patients were experiencing significant illness at the time of the study. Two patients had HAM-D scores of 12, one had a score of 5, and the rest had scores <1. Comparison subjects were excluded if they had any personal history of psychiatric illness, including tic disorders, or exposure to psychotropic medications. All subjects received verbal and written explanation of the purpose and risks of the study and gave informed consent to participate, as approved by the institutional review board of the University of Michigan Medical School.

Task

Subjects performed a "flanker interference" task (Eriksen and Eriksen 1974), which required them to focus on a central target letter to make a response (right button press when target is H or C, left button press when target is S or K) while ignoring peripheral, potentially distracting letters flanking the target. The task was designed to discern increasing levels of interference by including three conditions: 1) high interference, when the flanking letters prompt a response incompatible with the target response, e.g. HHKHH (INCOMP); 2) low interference, when flanking letters are different at the stimulus level but compatible at the response level, e.g. HHCHH (response compatible [RCOMP]); and 3) no interference, when flanking letters are compatible at the stimulus and response level, e.g., KKKKK (stimulus compatible [SCOMP]). While the original report by Eriksen and Eriksen (1974) used SCOMP-type stimuli, more recent work suggests that the RCOMP control isolates differences to the level of response, where the interference effect is greatest in terms of both overall difficulty (i.e., longer response times, increased error commission) and dorsal anterior cingulate cortex (dACC) activation (Cohen and Shoup 1997). Subjects practiced before being scanned to ensure familiarity with the task. The three trial types were presented in equal numbers and in pseudorandom order, occurring every 2 seconds (stimulus duration 1.5 seconds, intertrial interval [ITI] .5 second) in an event-related fMRI experiment. Five sessions of 144 trials each were presented and responses recorded using a computer running E-prime with IFIS (MRI Devices, Inc., Milwaukee, Wisconsin) interfaced to project stimuli onto a screen located within the head coil.

Functional MRI Acquisition

Magnetic resonance imaging scanning occurred on a GE 3T Signa scanner (LX [8.3] release, Neuro-optimized gradients; General Electric, Milwaukee, Wisconsin). Scanning began with structural acquisition of a standard T1 image (T1-overlay) for anatomic normalization and alignment. A T2*-weighted, reverse spiral acquisition sequence (gradient echo [GRE], repetition time [TR] = 2000, echo time [TE] = 30, flip angle [FA] = 90, field of view [FOV] = 20, 40 slice, 3.0/0, matrix diameter 71–equivalent to 64 x 64) occurred in the same prescription as the T1-overlay, and 144 volumes were acquired for a session, after discarding 4 initial volumes to permit thermal equilibration of the MRI signal. Five sessions were obtained. This T2* sensitive acquisition sequence was specifically designed to enable good signal recovery in ventral medial frontal regions, where susceptibility artifact often impairs the T2* signal (Noll et al 1998; Yang et al 2002). After acquisition of functional volumes, a high-resolution T1 scan was obtained for anatomic normalization (three-dimensional [3-D] spoiled-gradient echo [SPGR], 1.5 mm sl, 0 skip).

Data Analysis

Scans were reconstructed, slice-time corrected, realigned to the first scan in the experiment, and co-registered with the high-resolution SPGR T1 image. This high-resolution image was then anatomically normalized to the MNI152 template brain, as implemented in the SPM99 package (Wellcome Institute of Cognitive Neurology, London, United Kingdom). The resulting transformation parameters were applied to the time series of co-registered, normalized functional volumes, which were resliced and smoothed with a 6-mm isotropic Gaussian smoothing kernel. Each normalized image set was then high-pass filtered (HPF = 100 seconds) and analyzed in a two-step process. The first step involved the construction of a fixed effects model. For each subject, error trials were modeled by an event-related regressor, plus the first temporal derivative, plus regressors for the five sessions. We tested for the effect of errors by testing the error regressor for a beta greater than zero, i.e., against an implicit baseline. Since errors were relatively infrequent, the model was designed to identify activity occurring in response to the commission of an error, against the background of all other activity, including correct responses, stimulus identification, intertrial interval, etc. Because subjects performed the task correctly on most trials with very short ITIs, there was no baseline against which to contrast correct performance on the task

For the second step, subjects were treated as a random effect, and contrast images were derived for each subject and smoothed with a 6-mm Gaussian kernal to stabilize variance properties. The smoothed contrasts were then entered into a second level analysis to examine effects of error processing within (one sample t test) and between (two sample t test) groups. For all analyses, we set an initial threshold of $p < .005$ ($Z > 2.58$), with a minimum cluster size >4 voxels. We defined a search region in the midline frontal cortex, implicated in error processing (volume of 202 cm^3; x = −18 to +18, y = 0 to 70, z = −30 to 50), corrected for the false discovery rate (FDR; $p < .01$) (Genovese et al 2002). To provide additional information about the localization of error processing, we thought it important to not omit error-related activity outside the midline frontal region. Therefore, we also identified any activation focus with a cluster size probability, $p < .05$ uncorrected, outside our a priori region of

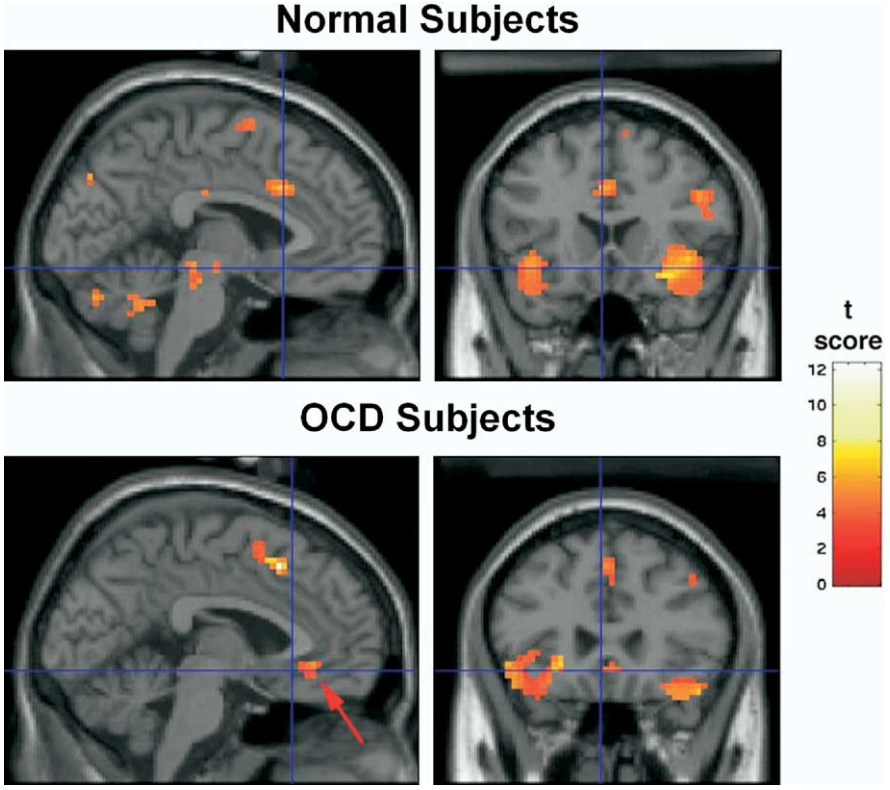

Figure 1. Both obsessive-compulsive disorder (OCD) patients and normal subjects exhibit similar patterns of dACC and pre-SMA/SMA activation during error commission. Error-related activation of the rACC is seen in OCD patients only (arrow). Activated voxels are derived from the random effects analysis for the whole brain and are superimposed on an atlas brain in stereotactic space ($p < .005$). OCD, obsessive-compulsive disorder; dACC, dorsal anterior cingulated cortex; SMA, supplementary motor area; rACC, rostral anterior cingulated cortex.

interest. In addition to the primary analysis of errors, we also examined interference effects, i.e., the effects of stimulus and response incompatibility, in this region of interest. Separate regressors for SCOMP, RCOMP, and INCOMP were entered into a new model, which excluded trials in which subjects made errors, followed by a second-level, random effects analysis to identify within-group activation and between-group differences in activation in our region of interest.

Results

Behavioral Results

Accuracy rates (mean proportion correct ± SD) were relatively high for both the comparison subjects (SCOMP: .98 ± .02; RCOMP: .99 ± .01; INCOMP: .94 ± .04) and the OCD patients (SCOMP: .93 ± .09; RCOMP: .93 ± .09; INCOMP: .86 ± .14). There was a significant effect of condition [$F(2,26) = 12.7$, $p = .0001$] on accuracy but no effect of subject type ($p = .16$) and no interaction ($p = .41$). Response latencies (mean ± SD) were similar for the groups, with patients nominally faster (OCD: SCOMP: 553 ± 101 milliseconds; RCOMP: 564 ± 106 milliseconds; INCOMP: 610 ± 105 milliseconds; Normal subjects: SCOMP: 590 ± 146 milliseconds; RCOMP: 593 ± 143 milliseconds; INCOMP: 643 ± 141 milliseconds). Again, we found a significant effect of condition [$F(2,26) = 117$, $p < .0001$] and no effect of subject type ($p = .61$) and no interaction ($p = .54$). No correlations between accuracy and response latency were found in either group ($r = .06$ for OCD patients, $r = .06$ for control subjects as well) or for all subjects combined ($r = .1$), suggesting the absence of any speed-accuracy trade-off. We also analyzed posterror response time (RT), and found that the OCD patients exhibited significantly greater slowing after making an error, although this significant group difference may have derived from the control subjects exhibiting a slight increase in RT after errors (OCD: 37 ± 44 milliseconds, Normal subjects: −42 ± 83 milliseconds; $t[13] = 2.38$, $p = .03$).

fMRI Results

The random effects analysis of the response to errors showed robust signals for both groups in medial frontal areas, bilateral insula, and some posterior regions. Figure 1 shows the medial frontal region, which was our principal region of interest. As predicted, greater ACC activation was found in OCD patients compared with normal subjects, but this difference localized to the rostral ACC (rACC). Frontal midline activation occurred in the dACC and supplementary motor area (SMA) for normal subjects and in the pre-SMA for the patients (Table 1; Figure 1). At a lower threshold ($p < .01$), the whole brain analysis revealed activated foci in the dACC and SMA/pre-SMA in both groups. However, even with lower thresholding, only the OCD patients activated an anterior focus in the rACC. In the group comparison analyses for both the whole brain and the small volume corrected search region, OCD patients exhibited a significantly greater activation in this rACC focus ([−3, 30, −6], $Z = 3.89$, $p < .01$ corrected; Figure 2). There were no other significant anterior foci ($y > 0$) where the groups differed in activation in either the search volume or whole brain analyses. We used a volume of interest to extract individual values from the rACC focus and found a significant correlation between higher Y-BOCS scores and activity in this region ($r = .62$, $df = 6$, $p < .05$ [one-tailed]; see Figure 3). Consistent with the ERN work (Gehring et al 2000), patients with greater symptom severity showed a larger error-related signal in this region.

In the analysis of interference effects (INCOMP-SCOMP, INCOMP-RCOMP), the control subjects showed significantly greater activation than the OCD patients for the INCOMP-RCOMP contrast in the pre-SMA ([3, 9, 48], $Z = 3.05$), which survived correction for multiple comparisons in the search

Table 1. Activation Foci for OCD Patients and Healthy Control Subjects During Error Trials

	Patients			Control Subjects		
Region (Brodmann Area)	Cluster Size[a]	(x, y, z)[b]	Z-Score[c]	Cluster Size[a]	(x, y, z)[b]	Z-Score[c]
Rostral ACC	36	−3, 36, −6	3.21[d]			
		3, 24, −9	3.16[d]			
		9, 30, −9	2.96[d]			
Dorsal ACC (32/24)				35	−3, 18, 33	3.30[d]
				16	9, 33, 36	2.91[d]
Presupplementary Motor Area (32/8)	145	−3, 18, 48	4.55[d]	7	9, 12, 45	2.92[d]
					6, 9, 48	2.74[d]
L Superior Frontal Gyrus (4/6)		−21, 6, 57	4.07			
		−15, 3, 63	3.52			
Supplementary Motor Area (6)				29	15,3,69	3.07
					−6, 0, 66	3.03
					6, 0, 66	2.62
R Inferior Frontal Gyrus (6/44)	68	51, 3, 39	3.93	42	48, 18, 30	3.34
		48, 21, 39	3.53		45, 27, 33	3.29
		57, 15, 30	3.48			
R Anterior Insula	155	48, 21, −21	3.73	546	48, 9, −24	3.96
		57, 18,−15	3.43		36, 15,−12	3.92
		36, 20,−21	3.22			
R Superior Temporal Gyrus (BA)					36, −9, −18	3.79
L Anterior Insula	332	−27, 27, −6	3.69	34	−42, 24, −9	3.16
		−45, 12, 46	3.53			
		−51, 24, −6	3.44			
R Medial Temporal Gyrus (37)	59	60, −45, −6	3.39			
		51, −54, 3	3.27			
Midbrain						
Cerebellum						

OCD, obsessive-compulsive disorder; ACC, anterior cingulate cortex; L, left; R, right.
[a]Number of voxels (exceeding height threshold, $p < .005$, uncorrected) per cluster; clusters listed which exceeded a size, $p < .05$, uncorrected.
[b]Stereotactic coordinates according to MNI atlas, right/left, anterior/posterior, and superior/inferior, respectively.
[c]Z-score for peak magnitude(*s*) within a cluster.
[d]Small volume corrected, $p < .01$.

volume analysis ($p_{\text{FDR-corr}} < .01$). Control subjects had activation foci just outside our search area: SMA/pre-SMA (INCOMP-SCOMP: [0, 0, 54], $Z = 3.40$; INCOMP-RCOMP: [−6, −3, 57], $Z = 3.32$; Figure 4), which contributed to the significant group difference demonstrated in the search volume analysis. Although not a primary interest of this study, the caudate nuclei fell within the a priori search area, and these subcortical nuclei have been implicated in the pathophysiology of OCD (Baxter et al 1987, 1988; Benkelfat et al 1990; Saxena et al 2002, 2003). In the interference analysis, we noted bilateral activation of the caudate nuclei for both contrasts in the OCD patients (INCOMP-SCOMP: [−15, 9, 12], $Z = 3.26$; [12, 12, 9], $Z = 3.07$; INCOMP-RCOMP: [0, 0, 15], $Z = 4.22$; [−3, 15, 12], $Z = 3.10$; [12, 18, 9], $Z = 3.30$; Figure 4). Group contrasts showed significantly greater activation for the patients, compared with the control subjects, in clusters that extended along the body of the caudate, possibly including nearby thalamus (INCOMP-SCOMP: [−6, 0, 12], $Z = 4.38$; [9, 0, 12], $Z = 3.92$; [12, 12, 6], $Z = 3.02$; INCOMP -RCOMP: [3, −3, 15], $Z = 4.60$). There were no other activation foci in the frontal midline region at the threshold of $p < .005$ for either group.

Discussion

Obsessive-compulsive disorder patients and healthy comparison subjects performed a simple cognitive task in which fMRI BOLD signal localized neural responses to errors. In line with predictions that OCD involves overactive error processing, significantly greater error-related activity occurred in the ACC (specifically, the rACC) in the OCD group. These results are consistent with event-related electrophysiological studies in this patient population (Gehring et al 2000; Hajcak and Simons 2002; Johannes et al 2001) and provide new information about the anatomical localization of error processing abnormalities within the ACC in patients with OCD. As with the ERN work, the performance of the patients did not differ from the comparison group. Limited experimental power precludes definitive statements about the absence of any particular effect; however, the results suggest that group differences in neural activity may not be attributable to performance differences on the interference processing task employed. Also consistent with the ERN work, greater error-related rACC activation in the patients was correlated with greater Y-BOC scores, suggesting a relationship between error processing abnormalities in the rACC and OCD symptom severity.

Several plausible interpretations of the role of a hyperactive rACC in OCD can be offered. Although we found a correlation between error-related activation and OC symptoms, the simple error-eliciting, cognitive task we employed was not designed to provoke characteristic OC symptoms and no patient reported the exacerbation of OCD after the study. Thus, the differences in ACC activation between patients and healthy participants could represent a stable vulnerability factor for the development of OCD. At a general level, patients with OCD might have a greater sensitivity to errors, manifest as a larger BOLD signal. This

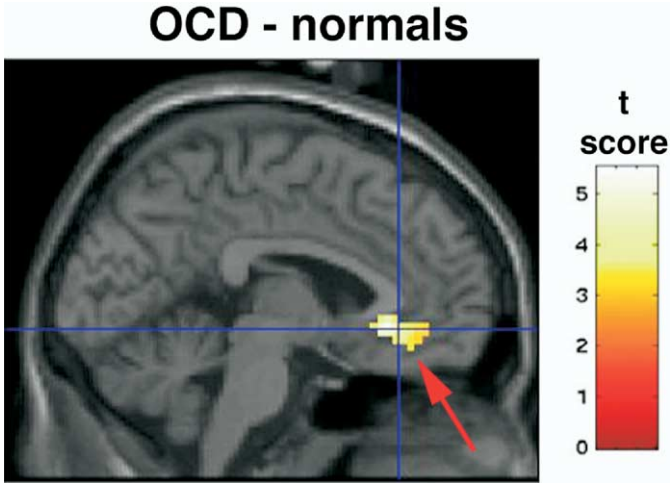

Figure 2. Obsessive-compulsive disorder (OCD) patients exhibited a significantly greater activation in the rACC compared with normal subjects in both the whole brain and the small volume corrected, random effects analysis. Activated voxels are derived from the random effects analysis for the whole brain and are superimposed on an atlas brain in stereotactic space ($p < .005$). OCD, obsessive-compulsive disorder; rACC, rostral anterior cingulated cortex.

greater sensitivity could also lead to a greater tendency to perceive errors, even where behavior was correctly executed, although our experiment did not directly test that possibility. One might expect that with greater awareness of potential errors, patients would try to avoid errors and exhibit higher accuracy and possibly speed-accuracy trade-offs. However, we did not find any evidence that our patients performed more accurately or engaged in a speed-accuracy trade-off to reduce errors. We did find a larger posterror slowing in the OCD patients, suggesting that they made a greater adjustment to perform trials following an error more accurately, but the absence of any posterror slowing in the control subjects makes this finding somewhat problematic.

Another possible interpretation of the greater rACC activity is that patients may notice errors with equal sensitivity as healthy individuals, but they may generate a greater affective response to an error. Support for this interpretation comes from work on the functional anatomy of the ERN. The ERN and related, midline frontal negativities may represent a learning signal elicited by a worse than expected outcome (Holroyd and Coles 2002), a signal indicating the presence of cognitive conflict (Carter et al 1998), or an affective reaction to loss (Luu et al 2000). Evidence that the evoked related potential (ERP) response to errors includes an affective component comes from a recent electrophysiological study in healthy subjects that demonstrated a negative polarity ERP, termed the medial frontal negativity (MFN). The MFN occurs in a gambling task in which subjects choose between two options that could lead to losing or gaining money. It is larger for choices in which the subject loses money, even when the alternative would have resulted in losing more money (Gehring and Willoughby 2002). The results from this study suggest that the MFN reflects the affective response to loss and not the mere recognition of an incorrect choice, i.e., error. The MFN resembles the ERN in latency and source localization, leading Gehring and Willoughby (2004) to suggest that there may be a source of neural activity common to the MFN and the ERN that reflects the affective response to the error.

The particular focus of group difference in the rostral part of the ACC is consistent with the abnormal engagement of affective circuitry during error commission, based on the known functional anatomy of this region. In contrast to the dACC, often referred to as the "cognitive division" of the ACC, the rACC appears to process affect and motivation (Bush et al 2000; Devinsky et al 1995; Whalen et al 1998). The rACC, often termed the "affective division" of the ACC, exhibits strong connectivity with limbic structures, such as the amygdala, ventral striatum, and orbitofronal cortex (Alexander et al 1986; Cummings 1993), areas that have also been implicated in OCD (see review by Fitzgerald et al 1999). A recent meta-analysis of neuroimaging studies of emotion showed a focus in the rACC for responses to aversive stimuli (Wager et al 2003), and fMRI studies of cognitive tasks suggest that the rACC mediates the affective response to errors (Kiehl et al 2000; Luu et al 2000, 2003). If activation in this region does subserve an error-related affective response, it is possible that the phenomenon generalizes to other psychiatric disorders. For instance, larger ERNs have been reported in patients with generalized anxiety disorder (Hajcak et al 2003) and depression (Tucker et al 2003). Although there were no active comorbid anxiety or depressive diagnoses in our patient sample, it is possible that subclinical anxiety and/or depressive symptoms could have contributed to our findings. Indeed, hyperactive response to error may occur across anxiety and depressive disorders, and it will be important to trace out the mechanisms which connect the anatomy and physiology with clinical presentation.

While error-related rACC activation was found only among patients, both patients and control subjects activated the dACC and pre-SMA/SMA during error processing. However, our study did not find support for the hypothesis put forth by Ursu et al (2003) that OCD patients should exhibit hyperactivity of the ACC during interference conditions, when response conflict is high and subjects perform correctly. Response conflict occurs when competing responses are simultaneously active, as was the case

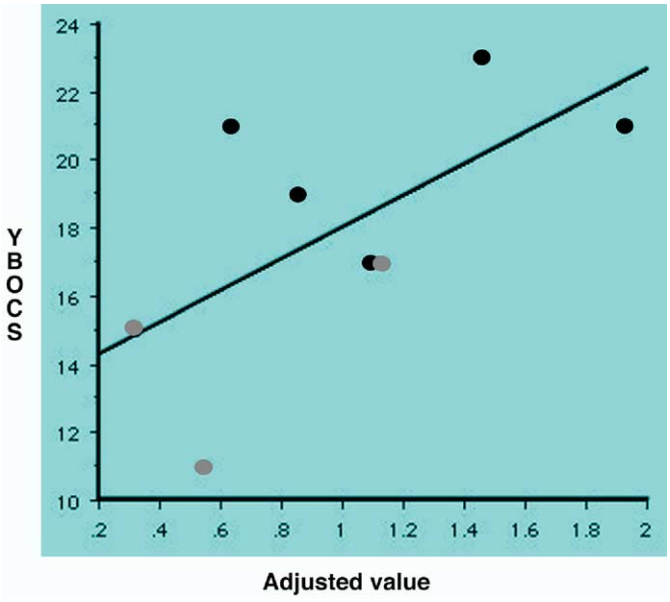

Figure 3. Positive correlation of obsessive-compulsive disorder (OCD) symptom severity with rostral anterior cingulate activation in OCD patients ($r = .62$, $df = 6$, $p < .05$ [one-tailed]). Gray circles indicate unmedicated OCD patients. Adjusted values were derived from the estimated beta values in the rACC region. OCD, obsessive-compulsive disorder; rACC, rostral anterior cingulated cortex.

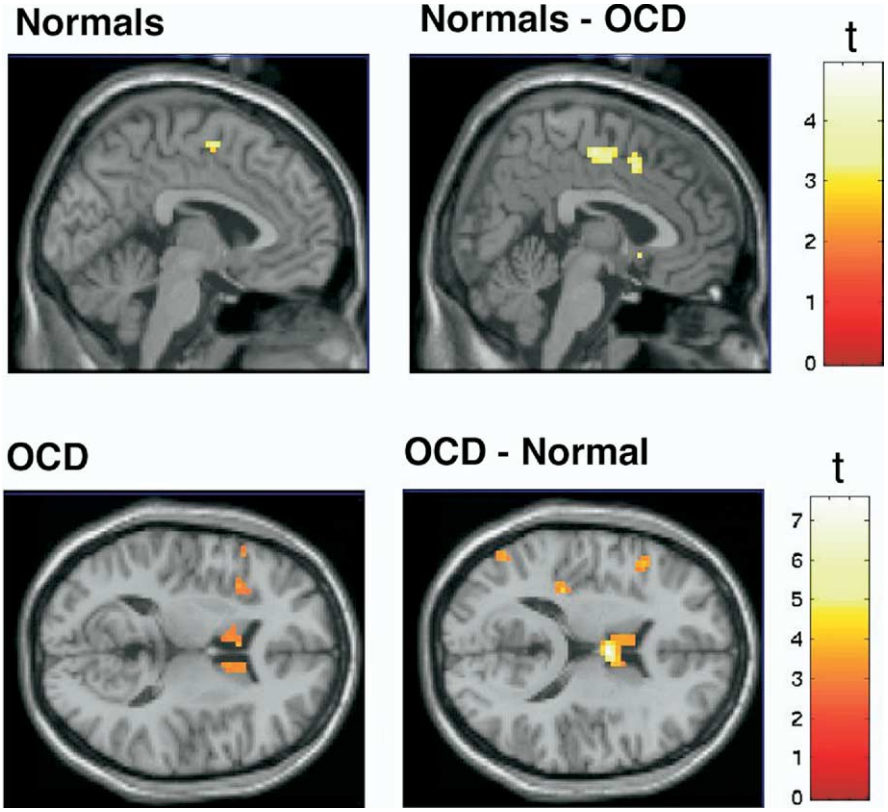

Figure 4. Conflict-related activation of the pre-SMA/SMA occurred in normal control subjects but not obsessive-compulsive disorder (OCD) patients. Control subjects also exhibited significantly greater activity in this region in the group comparision (top panel). Caudate activation occurred during the high-conflict condition in OCD patients but not normal subjects (bottom panel). Voxels are superimposed on an atlas brain in stereotactic space ($p < .005$). SMA, supplementary motor area; OCD, obsessive-compulsive disorder.

for the INCOMP condition in our flanker task, and it typically activates the dorsal region of the ACC (Botvinick et al 1999; Carter et al 1998; van Veen et al 2001). We did not find dACC activation in either group at our chosen statistical threshold, although we did find weak activation of the dACC among control subjects at more liberal thresholding. Hence, the weak dACC signal makes it difficult to interpret these negative results. One possible explanation for the absence of strong conflict-related, dACC activation in this study is that the flanker task employed here may evoke less response conflict than the continuous performance task used by Ursu et al (2003). Several features of their task may have enhanced their ability to detect conflict-related activity, such as the fact that the task required maintenance of contextual information over several seconds or the fact that they manipulated stimuli to strengthen prepotent responses. The OCD subjects in the Ursu et al (2003) study were significantly slower overall than the control subjects, in contrast to our OCD subjects, who were nominally faster than the control subjects. The performance differences between the groups in that study raise the possibility that OCD patients may have experienced greater response selection demands, also processed in this region (Badgaiyan and Posner 1998; Taylor et al 1994).

We did find conflict-related activation for control subjects, but not OCD, in the SMA/pre-SMA, which is approximately 25 mm posterior of the dACC and might also reflect the processing of response conflict, as suggested by studies using both flanker-type, interference tasks (Ullsperger and von Cramon 2001) and response inhibition tasks (Garavan et al 2003). Interestingly, of the two high-conflict conditions examined by Ursu et al (2003), the OCD patients only exhibited greater dACC activation in one, whereas the control subjects exhibited greater activation in the other. In our study, analysis of high-conflict correct trials (INCOMP-RCOMP; INCOMP-SCOMP) revealed greater pre-SMA/SMA activation in control subjects than OCD patients. Because the finding of greater activity for control subjects was not predicted, it is difficult to interpret. We also observed greater activation of the caudate nucleus (CN) in the OCD patients during conflict processing. Some work suggests CN hyperactivity in OCD (Baxter et al 1987, 1988; Benkelfat et al 1990), and the pre-SMA/SMA region sends excitatory projections to the CN. It is certainly possible that abnormalities of cognitive processing distinguish OCD subjects from healthy subjects through different neural circuitry. For instance, lateral frontal activity interacts with midline frontal negativities during error processing (Gehring and Knight 2000), and OCD patients may employ extra cognitive control attributed to lateral prefrontal regions (Ursu et al 2003). Although Ursu et al (2003) endorse the interpretation that conflict detection forms the essential process of both error processing and conflict monitoring, other works suggest that these processes have distinct but overlapping neural circuits (Garavan et al 2003; Gehring and Willoughby 2004; Kiehl et al 2000; Luu et al 2003; Menon et al 2001; Ullsperger and von Cramon 2001). Future investigations will have to pursue the possibility that in conflict processing, without errors, OCD patients use different strategies and different circuits.

Medication (selective serotonin reuptake inhibitor [SSRI]) use was a potential confound in our data. High levels of serotonergic "traffic" to and within the ACC (Chugani et al 1998; Lidov et al 1980; Mantere et al 2002; Rubenstein 1998) suggest that SSRIs could affect ACC activity, contributing to the rACC activation we detected. It is also not clear how baseline elevations in resting metabolism of the ACC, observed in OCD (Machlin et al 1991; Perani et al 1995; Rauch et al 1998; Swedo et al 1989), would affect the fMRI BOLD signal. However, because SSRI treatment generally reduces activity in the corticostriatal circuits involved in OCD, one would not expect to see greater activation as a result

of SSRI treatment. Nevertheless, replication with a larger medication-free sample is clearly needed.

In conclusion, the data presented here provide clues about ACC dysfunction and its possible role in the pathophysiology of OCD. The results from a small sample are necessarily preliminary, although they fall in line with several other similar studies with functional imaging and ERP. Taken together, these results provide evidence that a fundamental process, involved when subjects commit errors, may be associated with the symptomatology of OCD. Importantly, this processing abnormality appears to occur in the absence of overt symptoms but still exhibits associations with symptom severity. Obviously, additional work is needed to identify the processes and neural systems that lead to the generation of specific symptoms. The interpretation suggested here, that rACC activity represents an affective response to errors, rests on certain assumptions about segregated affective and cognitive functions of the ACC. Experiments that focus on rACC function, as well as adjacent orbitofrontal cortex, could expand on the hyperactive error response in OCD by testing paradigms that elicit loss, aversive outcome, and other types of affective response.

This work was supported financially by the University of Michigan fMRI Center. We thank Keith Newnham and Laura Decker for assistance with workup and acquisition of the data.

The data were previously presented at the Organization for Human Brain Mapping, New York City, June 2003.

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