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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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