Hyperactive Error Responses and Altered Connectivity in Ventromedial and Frontoinsular Cortices in Obsessive-Compulsive Disorder

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Background: Patients with obsessive-compulsive disorder (OCD) show abnormal functioning in ventral frontal brain regions involved in emotional/motivational processes, including anterior insula/frontal operculum (aI/fO) and ventromedial frontal cortex (VMPFC). While OCD has been associated with an increased neural response to errors, the influence of motivational factors on this effect remains poorly understood.

Methods: To investigate the contribution of motivational factors to error processing in OCD and to examine functional connectivity between regions involved in the error response, functional magnetic resonance imaging data were measured in 39 OCD patients (20 unmedicated, 19 medicated) and 38 control subjects (20 unmedicated, 18 medicated) during an error-eliciting interference task where motivational context was varied using monetary incentives (null, loss, and gain).

Results: Across all errors, OCD patients showed reduced deactivation of VMPFC and greater activation in left aI/FO compared with control subjects. For errors specifically resulting in a loss, patients further hyperactivated VMPFC, as well as right aI/FO. Independent of activity associated with task events, OCD patients showed greater functional connectivity between VMPFC and regions of bilateral aI/FO and right thalamus.

Conclusions: Obsessive-compulsive disorder patients show greater activation in neural regions associated with emotion and valuation when making errors, which could be related to altered intrinsic functional connectivity between brain networks. These results highlight the importance of emotional/motivational responses to mistakes in OCD and point to the need for further study of network interactions in the disorder.

Key Words: Anxiety, default mode, fMRI, functional coupling, performance monitoring, salience network

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder (lifetime prevalence 1% to 3% [1]) characterized by intrusive thoughts (obsessions) and/or repetitive behaviors (compulsions) frequently associated with intense fear that incorrect acts might cause serious harm to self or others. There is evidence that OCD involves an overactive error signal indicating that something is wrong (2), leading to ritualistic behaviors aimed at preventing harmful consequences of perceived mistakes. In healthy adults, error detection activates a specific neural network that includes posterior medial frontal cortex (pMFC)/dorsal anterior cingulate cortex, often extending into rostral anterior cingulate cortex, and bilateral anterior insula/frontal operculum (aI/fO) including regions of posterolateral orbitofrontal cortex (OFC) (3). Neural activity in portions of this circuit appears to be abnormal in OCD patients at rest (4), during symptom provocation (5), and when performing various cognitive tasks (6), including error detection (7–13). Although the full clinical phenotype of OCD is likely to involve additional processes, including altered response inhibition and habit formation potentially subserved by striatum and thalamus (14–17), understanding the functioning and interactions of the error detection system may shed light on a central aspect of this important disorder.

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Emerging work has begun to elucidate the functional roles of large-scale brain networks, which can inform the investigation of OCD. Both pMFC and aI/fO regions that activate with error detection are part of a broader salience network (SN) that signals the presence of important external task events requiring online adjustments in behavioral control (18,19). Though they activate simultaneously in many tasks (20), pMFC and aI/fO may have dissociable functions (21–23). While error-related activation in pMFC may signal the presence of cognitive events that require behavioral control, such as detecting mismatch between actual and intended responses (i.e., response conflict) (24,25), aI/fO and adjacent lateral OFC may be preferentially linked to the emotional/motivational salience of errors, consistent with their role in somatic-autonomic and evaluative processes (23,26–30).

While pMFC and aI/fO activate in response to errors, ventromedial frontal cortex (VMPFC) is part of the default model network (DMN) of brain regions that deactivate with increases in externally directed cognition (31–33), including that associated with error detection (ERS *et al.*, unpublished data, 2006; and [34]). Although the meaning of DMN deactivation is under debate, VMPFC plays a role in internal mentation and automatic value judgments (35–37), standing in contrast to nearby lateral OFC, which is more associated with externally triggered valuation (38). As such, deactivation in this region may represent a neural signature of disengagement from task-irrelevant, internally focused valuation when attention must be directed to external goals (33,37,39). Greater error-related VMPFC activity has been reported in OCD (12), perhaps reflecting an inability of patients to disengage from automatic evaluative processes when errors occur. Intriguingly, VMPFC deactivation in healthy adults may be modulated by saliency signals coming from aI/fO (18), suggesting that interactions between these regions may impact how errors are processed.

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Despite the fact that OCD patients show alterations in motivational brain systems, little work has investigated the impact of the emotional/motivational significance of errors in OCD, particularly relevant for a disorder where pathological levels of importance are attributed to simple behavioral errors (or perceived errors). In a recent study of the error-related negativity (ERN), an electrophysiological index of error detection that is reliably increased in OCD (8,10,11,13), Endrass *et al*. (40) found that differences between OCD patients and controls depended on whether errors were associated with a monetary loss versus no loss. However, ERN data cannot provide precise circuitry information (41), so further work is needed to understand the link between emotion/motivation, error sensitivity, and ventral frontal hyperactivity in OCD. To address this question, we used functional magnetic resonance imaging to study neural activity in OCD patients and control subjects during an incentivized flanker task containing low and high interference levels with variable monetary incentives. This paradigm allowed us to examine activity in key nodes of the error network (pMFC, aI/fO, VMPFC) based on whether errors were associated with a loss of incentives, a failure to gain incentives, or no change in incentives. We predicted that OCD patients would be more sensitive than control subjects to the motivational significance of errors, which would manifest itself as error-related hyperactivity in ventral frontal brain regions (VMPFC and aI/fO), particularly for errors carrying incentives. Furthermore, we investigated intrinsic functional connectivity that occurred during the task but was independent of event-related activity, hypothesizing that aberrant neural responses to errors may be associated with altered coupling among functional networks.

Methods and Materials

Subjects

Data were analyzed from 39 OCD patients and 38 control subjects. Twenty OCD patients were unmedicated (uOCD) and 19 were medicated (mOCD), primarily with serotonin reuptake inhibitors (SRIs). All met DSM-IV criteria for primary OCD (see Methods and Materials in Supplement 1 for exclusion criteria). The control group included 20 unmedicated healthy control (uHC) subjects without psychiatric diagnoses and 18 medicated patient control subjects (mPC) who were on SRIs for major depression (in remission). As the majority of OCD patients had a history of major depression (Methods and Materials in Supplement 1), a comparison of OCD and control groups, both including medicated patients with history of depression, allowed us to better localize group differences to the presence of OCD instead of depression or medication effects (Table S1 in Supplement 1 lists medications).

Subjects provided written informed consent and were evaluated by a trained clinician using the Structured Clinical Interview for Diagnosis (42). Generalized depression and anxiety were assessed using Hamilton Ratings Scales for Depression and Anxiety. Obsessive-compulsive symptom severity was quantified using the Yale-Brown Obsessive-Compulsive Scale (43). As shown in Table S2 in Supplement 1, the two OCD groups exhibited few demographic or clinical differences, with more treatment seeking and a trend toward longer illness duration [$t(31.7) = 1.8$, $p = .078$] in mOCD patients.

Procedure

The incentive flanker task presented target and distractor (flanker) stimuli that were preceded by cues indicating the incentive value of each trial (44). Subjects pressed one of two buttons to identify a target letter surrounded by four flankers (Figure 1). The target was a different letter than flankers, both of which were selected from a pool of four letters (S, K, H, and C). Subjects were pretrained to associate half of the letters with the left button and half with the right button (counterbalanced across subjects). On low interference trials, both target and flankers indicated the same button press, while on high interference trials, target and flankers designated opposing responses, thus eliciting errors. To maintain errors around 15%, response deadlines were individually tailored, set at .8 to 1.5 times the mean reaction time from a practice session.

Cues designated each trial's incentive condition: 1) on loss trials, subjects lost money if an error was made and avoided loss with a correct response; 2) on gain trials, subjects failed to gain money if an error was made but earned money with a correct response; 3) on null trials, no money was at stake. Subjects began with $5 and gained or lost real money. A total of 288 trials composed of 96 loss, 96 gain, and 96 null (each with 48 low and 48 high interference trials) were used.

After completion, subjects evaluated the task and their performance using five-point Likert scales (1 = none/not at all to 5 = always/very) to answer the following questions: 1) Did you make any mistakes? 2) Were you ever frustrated with your performance? and 3) When you made a mistake, were you flustered and find it hard to get back on track?

Data Acquisition

Magnetic resonance imaging scanning occurred on a GE 3T Signa scanner (LX [8.3] release). A T1-weighted image was acquired in the same prescription as functional images to facilitate co-registration. Functional images were acquired with a T2*-weighted, reverse spiral acquisition sequence (gradient echo, repetition time = 2000, echo time = 30, flip angle = 90, field of view = 20, 40 slices, 3.0/0, matrix diameter of 71–equivalent to 64 × 64) sensitive to signal in ventral frontal regions (45). Subjects underwent 8 runs with 176 volumes plus 4 initial discarded volumes. After acquisition of functional volumes, a high-resolution T1 spoiled gradient recalled echo (SPGR) scan was obtained for anatomic normalization.

Data Analysis

Commission error rates and responses to debriefing questions were examined in separate 2 (diagnosis: OCD, control subject) × 2 (medication: unmedicated, medicated) analyses of variance (ANOVAs). Reaction times on correct trials were evaluated in a 2 (diagnosis) × 2 (medication) × 3 (incentive: gain, loss, null) repeated-measures ANOVA. Omission errors were excluded.

For detailed description of blood oxygenation level-dependent (BOLD) processing and analysis, see Methods and Materials in Supplement 1. Briefly, functional images were slice-time corrected, realigned, co-registered to the T1 SPGR, normalized to the Montreal Neurological Institute template, and smoothed. Two general linear models were specified. In an error model, regressors of interest were specified for commission errors and correct trials at the time of feedback for gain, loss, and null trials separately. All egressors were convolved with the canonical hemodynamic response function (hrf) at the subject level, with four main contrasts examining magnitude of the hrf for all errors versus corrects, null errors versus null corrects, loss errors versus null errors, and fail-to-gain errors versus null errors. In a separate interference model, low and high interference corrects were modeled separately at the time of target presentation, and a contrast examining high versus low interference trials was performed.

To examine intrinsic functional connectivity, the time series from a seed region in VMPFC (chosen based on group differences, see Results) was extracted from a general linear model that included all the same regressors as the error model, yielding a resid-