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

Emily R. Stern, Robert C. Welsh, Kate D. Fitzgerald, William J. Gehring, Jamey J. Lister, Joseph A. Himle, James L. Abelson, and Stephan F. Taylor

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.

From the Departments of Psychiatry (ERS, RCW, KDF, JJL, JAH, JLA, SFT), Radiology (RCW), and Psychology (WJG), University of Michigan, Ann Arbor, Michigan.

Address correspondence to Emily R. Stern, Ph.D., University of Michigan, Department of Psychiatry, 4250 Plymouth Road, 2506 Rachel Upjohn Building, Ann Arbor, MI 48109; E-mail: emistern@med.umich.edu.

Received Jun 24, 2010; revised Sep 25, 2010; accepted Sep 28, 2010.

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.

0006-3223/$36.00
doi:10.1016/j.biopsych.2010.09.048

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-

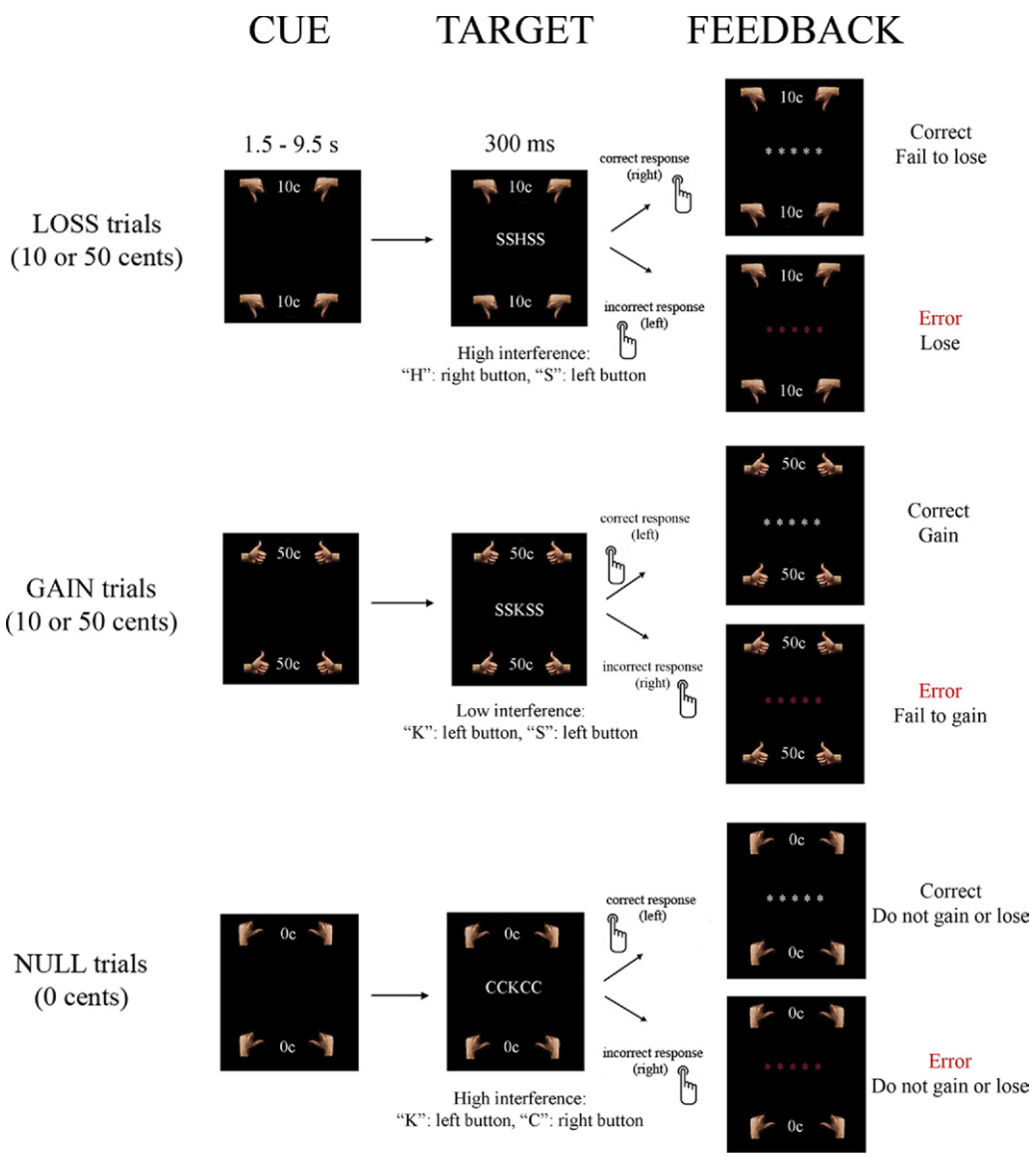

Figure 1. Diagram of incentive flanker task. Before participation, subjects learned to associate two letters with a left button press (in this example, S and K) and two different letters with a right button press (in this example, H and C). During the task, subjects pressed the left or right button based on the identity of a target letter placed in the second, third, or fourth position in a string of five letters (all examples in figure show target in third position). The target letter was always different from flanking letters; low interference trials were those where target and flankers designated the same button press (example shown in middle row), while high interference trials were those where target and flankers designated opposite button presses (examples shown in top and bottom rows). Letter stimuli were presented on screen for 300 msec, followed by a blank screen until a response was made or until response deadline was achieved. Feedback was presented immediately following response, indicating to the subject whether they made a correct response, an error of commission, or were not within the response deadline (i.e., omission error). Duration of feedback was varied based on the individual subject's reaction time such that total time between presentation of letter stimuli and end of feedback was 1500 msec. Feedback was followed by a 2000-msec blank intertrial interval. Before letter stimuli, subjects received cues on each trial indicating whether an error (correct response) would result in a loss of money (failure to lose money) (LOSS trials), a failure to gain money (gain of money) (GAIN trials), or no change in money (NULL trials). The amount of money each trial was worth was real and presented on screen (10 or 50 cents for loss or gain trials, 0 cents for null trials). To be able to decouple the blood oxygenation level-dependent signal associated with the response/feedback from that elicited by cues, cues were jittered between 1500 msec and 9500 msec in increments of 500 msec.

ual time course that did not include variance associated with task events. This residual time series was then used as a covariate (as well as movement parameters, see Methods and Materials in Supplement 1) in a separate model that again included all error model event regressors (46), to examine positive and negative correlations between residual VMPFC activity and other voxels in the brain. These correlations are described as intrinsic because this method identifies interregional coupling that is independent of and linearly superimposed upon event-related activity (46,47).

Primary analyses focused on activity in a frontal-striatal-thalamic (FST) search area (Methods and Materials in Supplement 1). One-sample and two-sample *t* tests were thresholded with an alpha of .05 and cluster-level corrected for multiple comparisons within the FST search area using Monte Carlo simulations as implemented by AlphaSim in AFNI (48,49). Given purported interactions between aI/fO and default mode networks (18), we also tested for effects in bilateral aI/fO specifically (Methods and Materials in Supplement 1), using an alpha of .05, cluster-level corrected within aI/fO regions of

Figure 2. Errors > correct trials in obsessive-compulsive disorder (OCD) patients and control subjects. **(A)** Whole-brain activations and deactivations (warm colors: activations, cool colors: deactivations; displayed at $p < .005$ with 20 contiguous voxels) for OCD patients and control subjects. **(B)** Activity in ventromedial frontal cortex (VMPFC) (x = 0, y = 51, z = −15, k = 51, $z = 3.35$) and left anterior insula/frontal operculum (aI/fO) (x = −33, y = 30, z = −3, k = 20, $z = 3.2$) was greater in OCD patients than control subjects. **(C)** Post hoc analyses of variance examining effects of medication status on activity in regions showing group differences revealed a trend toward an interaction between diagnosis and medication in VMPFC [$F(1,73) = 3.5$, $p = .067$]. For aI/fO, there was a main effect of medication [$F(1,73) = 6.5$, $p = .01$]. Color bars represent *t* scores. mOCD, medicated OCD patients; mPC, medicated patient control subjects; uHC, unmedicated healthy control subjects; uOCD, unmedicated OCD patients.

interest (ROIs) using AlphaSim. Finally, whole-brain analyses, cluster-level corrected using AlphaSim at $p < .05$ across all gray matter, were explored for all contrasts (Results in Supplement 1).

To examine the relationship between activity evoked by task events and intrinsic connectivity, Pearson correlations were performed (separately for OCD and control groups) between activity in areas exhibiting group differences in response to task events (i.e., errors) and those showing altered functional connectivity. Multiple regression analyses probed for effects of generalized depression and anxiety, obsessive-compulsive symptom severity, and SRI dosage on neural activity in regions exhibiting group differences (Methods and Materials and Tables S5 and S6 in Supplement 1).

Results

Behavioral

Error rates and reaction times are shown in Results and Table S3 in Supplement 1. Groups did not differ in number of errors or perception of error frequency ($p > .1$ for all effects), but OCD patients were more flustered by mistakes [$F(1,73) = 5.8$, $p = .02$] and marginally more frustrated with their performance [$F(1,73) = 3.3$, $p = .075$].

Event-Related Activity

Errors Versus Corrects. Control and OCD groups exhibited similar patterns of activations for errors > corrects, averaged across

Table 1. Errors > Corrects (All Incentive Types) for Control Subjects and OCD Patients in FST Search Area

		CONTROL					OCD				
Region	BA	k	x	y	z	*Z*	k	x	y	z	*Z*
Activation											
pMFC (B)	6, 8, 9, 24, 32, 10	1436	6	21	45	7.53	1607	3	27	36	6.96
aI/fO (L)[a]	13, 47	417	−42	15	−3	6.22	400	−33	27	0	7.35
aI/fO (R)	13, 47	453	48	21	−3	6.10	461	39	27	0	6.85
Thalamus (L)	NA	148	−9	−24	0	4.79	126	−9	−18	6	5.12
Thalamus (R)	NA	126	9	−24	0	5.21	153	9	−12	6	5.15
Deactivation											
VMPFC (B)[a]	10, 11	415	0	54	−12	7.02	54	−3	54	−9	4.14
OFC (L)	11	59	−15	54	−15	4.09					
Subgenual cingulate/ caudate head (B)	25	163	−6	15	−9	5.06					

Coordinates are in Montreal Neurological Institute space.

aI/fO, anterior insula/frontal operculum; B, bilateral; BA, Brodmann area; FST, frontal-striatal-thalamic; k, number of voxels; L, left; NA, not applicable; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; pMFC, posterior medial frontal cortex; R, right; VMPFC, ventromedial prefrontal cortex; Z, maximum *Z* score.

[a]Significant group differences.

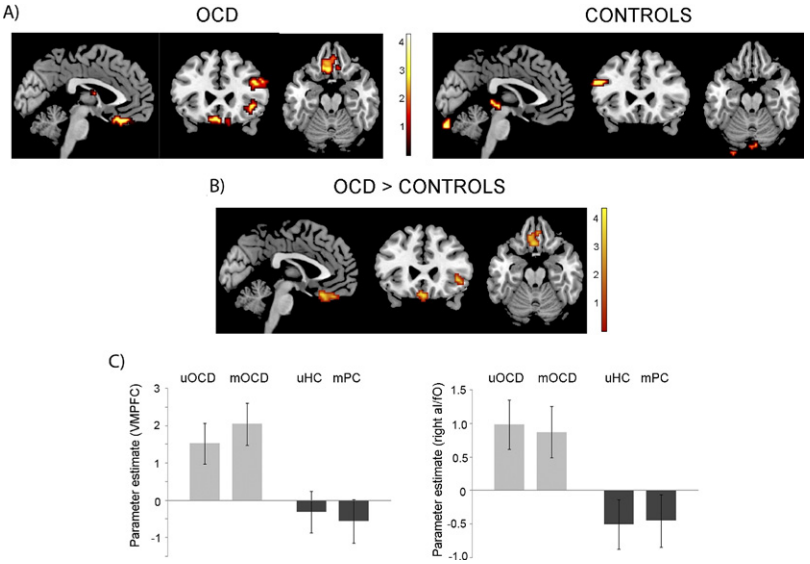

Figure 3. Loss > null errors in obsessive-compulsive disorder (OCD) patients and control subjects. **(A)** Whole-brain activations (displayed at $p < .005$ with 20 contiguous voxels) for OCD patients and control subjects, showing activity in ventromedial frontal cortex (VMPFC) (x = −9, y = 36, z = −24, k = 73, z = 3.91) and right anterior insula/frontal operculum (aI/fO) (x = 45, y = 24, z = −3, k = 34, z = 3.21) for the loss > null error contrast in OCD patients but not in control subjects. **(B)** Group comparisons revealed greater activity in VMPFC (x = 0, y = 27, z = −21, k = 52, z = 3.65) and right aI/fO (x = 45, y = 24, z = −3, k = 21, z = 3.4) in OCD patients. There were no areas of deactivation for either group and no regions where control subjects showed more activations than OCD patients. **(C)** Post hoc analyses of variance examining effects of medication status on activity in regions showing group differences found no main effects of medication (VMPFC: $p = .81$, aI/fO: $p = .94$) and no interactions between medication and diagnosis (VMPFC: $p = .49$, aI/fO: $p = .83$). Color bars represent t scores. mOCD, medicated OCD patients; mPC, medicated patient control subjects; uHC, unmedicated healthy control subjects; uOCD, unmedicated OCD patients.

incentive value, within the FST area (Figure 2A, Table 1; see Results and Table S5 in Supplement 1 for whole-brain results). While both groups showed VMPFC deactivation in response to errors, the extent of this deactivation was larger for control subjects (Figure 2A, Table 1), leading to a significant OCD > control group difference for errors > corrects (Figure 2B). No other group differences were identified at the current threshold; however, results from a targeted analysis of aI/fO showed significantly greater activation in left aI/fO in OCD patients than control subjects (Figure 2B). There were no regions where control subjects showed greater activity than patients.

Parameter estimates extracted from the VMPFC focus of group difference demonstrated a negative signal relative to implicit baseline for both errors and corrects in all four groups (uOCD, mOCD, uHC, mPC). Post hoc ANOVAs on contrast estimates (errors > corrects) revealed no effect of incentive ($p = .11$) or incentive-by-diagnosis interaction ($p = .35$), suggesting a relative failure of VMPFC deactivation in OCD for all three errors types (null, fail-to-gain, and loss). While there was no effect of medication ($p = .25$), VMPFC deactivation was smallest in mOCD and greatest in mPC subjects (trend medication-by-diagnosis interaction, $p = .067$; Figure 2C). Examination of parameter estimates from left aI/fO revealed a positive signal relative to implicit baseline for both errors and corrects in all groups, with a post hoc ANOVA on contrast estimates (errors > corrects) revealing no effect of incentive ($p = .54$) and no interaction between incentive and diagnosis ($p = .11$). There was a main effect of medication in left aI/fO ($p = .01$; Figure 2C), with greater error signal for unmedicated than medicated patients.

Loss Versus Null Errors. To investigate activations for errors carrying greater incentive value, we compared loss errors with null errors and fail-to-gain errors with null errors (see Table S4 in Supplement 1 for null errors vs. null corrects). Whereas control subjects showed no differences between loss and null errors, OCD patients exhibited more activity in VMPFC for loss than for null errors (Figure 3A). Results from targeted analyses of aI/fO also showed greater right aI/fO activity in loss compared with null errors in OCD patients. No significant deactivations were found for either group. Group comparisons yielded significant differences in VMPFC (Figure 3B), with no other regions surviving correction; however, OCD patients also showed greater activity than control subjects in right aI/fO when correcting within aI/fO ROIs.

Parameter estimates from VMPFC revealed negative signals relative to implicit baseline for null errors in all four groups and for loss errors in both control groups. Both OCD groups showed a positive signal in this region for loss errors. For the right aI/fO cluster, loss and null errors both showed positive signals in all groups. Post hoc ANOVAs on contrast estimates (loss > null errors) revealed no effects of medication and no medication-by-diagnosis interactions in either region (Figure 3C).

Fail-To-Gain Versus Null Errors. Patients with OCD showed significantly more activity for errors when they failed to gain money compared with null errors in right aI/fO (x = 51, y = 27, z = −12, k = 43, z = 4.02), with no deactivations. Control subjects showed no differences (activations or deactivations) between fail-to-gain and null errors. No significant group differences were found within the FST search area or when using small volume correction within aI/fO ROIs.[1]

High Versus Low Interference Corrects. Cognitive conflict on high versus low interference trials elicited activations in pMFC and bilateral aI/fO and deactivations in VMPFC for both OCD patients and control subjects (Table 2). For control subjects, left caudate head was also activated. No significant group differences were found in either the FST search area or when correcting within aI/fO.

Intrinsic Functional Connectivity

Both groups showed considerable positive connectivity between the residual VMPFC time course and other areas of the DMN, including subgenual cingulate, anterior medial frontal cortex, and dorsomedial prefrontal cortex (Table 3). VMPFC was also positively coupled with bilateral aI/fO and adjacent lateral OFC (Brodmann areas 11/13/47), caudate head, and posterior thalamus. Extent of positive coupling between VMPFC and aI/fO was greater in OCD patients than control subjects and overlapped with aI/fO regions that were activated in the errors > corrects and loss > null errors contrasts in patients (Figure S1 in Supplement 1). Control subjects exhibited negative connectivity between VMPFC and pMFC, as well as a region of left aI/fO located superior and posterior to those aI/fO areas showing positive connectivity with VMPFC, yet no negative

[1]For the fail-to-gain > null error contrast, a small cluster of hyperactivity was observed for OCD patients compared with control subjects in right aI/fO, but significance reached only trend level within aI/fO ROIs (x = 48, y = 27, z = −12, k = 11, $p = .09$).

Table 2. High > Low Interference Corrects for Control Subjects and OCD Patients in FST Search Area

		CONTROL					OCD				
Region	BA	k	x	y	z	*Z*	k	x	y	z	*Z*
Activation											
pMFC (B)	6, 8, 32	258	3	12	51	5.23	175	3	21	54	4.58
aI/fO (L)	13, 47	160	−33	30	−6	4.98	121	−33	30	−6	4.86
aI/fO (R)	13, 47	78	45	18	3	4.29	97	36	27	−6	3.89
Caudate head (L)	NA	47	−9	3	6	3.43					
Deactivation											
VMPFC (B)	10, 11	62	0	60	−18	3.59	237	3	60	12	4.23

Coordinates are in Montreal Neurological Institute space. No significant group differences were found between OCD patients and control subjects.

aI/fO, anterior insula/frontal operculum; B, bilateral; BA, Brodmann area; FST, frontal-striatal-thalamic; k, number of voxels; L, left; NA, not applicable; OCD, obsessive-compulsive disorder; pMFC, posterior medial frontal cortex; R, right; VMPFC, ventromedial prefrontal cortex; *Z*, maximum *Z* score.

coupling was found in OCD patients. Group comparisons revealed significantly more positive coupling of VMPFC with right aI/fO in OCD (Figure 4A). Patients with OCD also exhibited more positive connectivity between VMPFC and left aI/fO, as well as VMPFC and right thalamus, although these differences may be due to effects of generalized depression and anxiety (Results in Supplement 1).

Post hoc ANOVAs performed on parameter estimates extracted from regions showing group differences revealed a medication-by-diagnosis interaction in right aI/fO ($p = .04$; Figure 4B), indicating that mOCD patients showed the most positive connectivity with VMPFC, while mPCs showed the least. No interactions were found for left aI/fO and thalamus, and no main effects of medication were found in any regions.

In the OCD group only, intrinsic coupling between VMPFC and right aI/fO was positively correlated with event-related activity in VMPFC for errors > corrects and right aI/fO for loss > null errors, indicating that patients with more positive coupling independent of task events also showed greater evoked responses in VMPFC and right aI/fO during errors (Figure 4C). In addition, VMPFC-thalamic connectivity was positively correlated with right aI/fO activity for loss > null error contrast, again only in the OCD group. No significant correlations were found among control subjects.

Discussion

Using a task that varied the monetary consequences of mistakes to examine how motivational factors modulate error-related neural processing, we have shown that OCD patients exhibit greater activity in VMPFC due to a failure to deactivate this DMN region to the same extent as control subjects, both across all error types and specifically for errors associated with loss. Patients also showed more activation in aI/fO and altered functional connectivity between aI/fO and VMPFC, independent of event-related activation. By contrast, no differences were found between groups in pMFC regions associated with detection of cognitive conflict. We thus demonstrate alterations of function and connectivity in emotional/motivational brain systems in OCD, with evidence that these effects are not due to medication or history of depression. These data suggest that the enhanced error response in OCD may be due to an overvaluation of error significance potentially related to altered intrinsic connectivity between regions involved in valuation and emotion.

Previous research suggests that aI/fO, along with pMFC/dorsal anterior cingulate cortex, is part of a network responding to salient external events (18,19). Despite significant coactivation, these regions may have distinguishable functions (22,23), with aI/fO being preferentially active in tasks involving autonomic-somatic responses and integration of bodily signals with feeling states (27,29), such as risk (50) and intolerance of uncertainty (51). In the context of salience detection, then, aI/fO may respond to the perceived value of external events, in contrast to pMFC, which may be more engaged in processing cognitive information (21) or the initiation of volitional behaviors when responding to salient events (23). Right aI/fO, in particular, has been associated with sympathetic arousal (29) and anticipation of aversive stimuli (26). Our results suggest that errors may be more motivationally salient for OCD patients than control subjects, with loss errors, in particular, eliciting greater activity in right aI/fO associated with arousal and negative emotion,

Table 3. Functional Connectivity with VMPFC Time Course for Control Subjects and OCD Patients in FST Search Area

		CONTROL					OCD				
Region	BA	k	x	y	z	*Z*	k	x	y	z	*Z*
Positive Connectivity											
VMPFC/caudate head (B)	8, 9, 10, 11, 25, 32	2166	0	51	−12	>7.5	2382	0	51	−12	>7.6
aI/fO/OFC (L)[a]	11, 13, 47	673	−24	33	−15	>7.5	865	−24	33	−15	>7.6
aI/fO/OFC (R)[a]	11, 13, 47	712	18	45	−18	7.50	926	30	33	−12	7.62
Thalamus (L)							220	−9	−9	0	5.14
Thalamus (R)[a]	NA	38	21	−27	9	3.94	284	6	−15	0	5.56
Negative Connectivity											
pMFC (B)	6, 24, 32	298	0	9	39	4.24					
aI/fO (L)	13	96	−30	24	15	4.73					

Coordinates are in Montreal Neurological Institute space. Region shown in bold font exhibited significant group differences.

aI/fO, anterior insula/frontal operculum; B, bilateral; BA, Brodmann area; FST, frontal-striatal-thalamic; k, number of voxels; L, left; NA, not applicable; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; pMFC, posterior medial frontal cortex; R, right; VMPFC, ventromedial prefrontal cortex; *Z*, maximum *Z* score.

[a]Significant group differences.

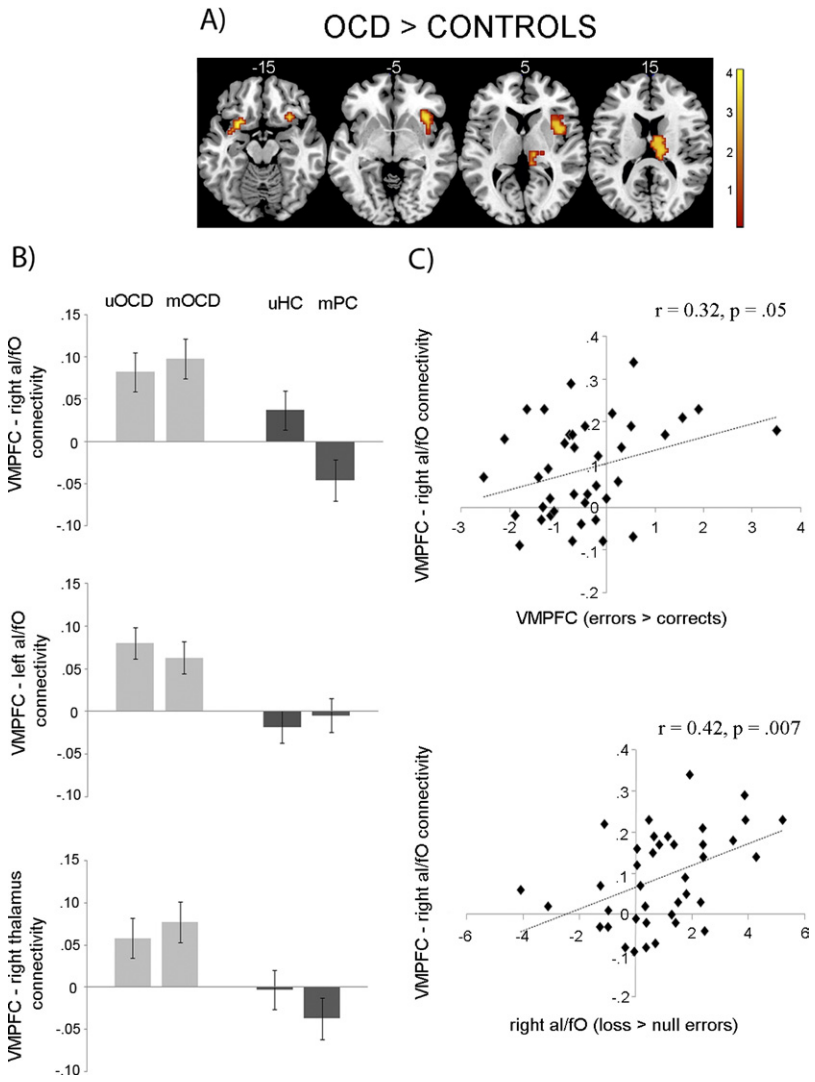

Figure 4. Functional connectivity with ventromedial frontal cortex (VMPFC). **(A)** Obsessive-compulsive disorder (OCD) patients showed greater positive connectivity than control subjects between VMPFC seed and right anterior insula/frontal operculum (al/fO) (x = 39, y = 9, z = 3, k = 134, $z = 3.63$), left al/fO (x = −27, y = 12, z = −15, k = 38, $z = 4.09$), and right thalamus (x = 15, y = −18, z = 18, k = 95, $z = 3.27$). Numbers above axial slices represent z coordinates. Color bar represents *t* scores. **(B)** Post hoc analyses of variance examining effects of medication status on activity in regions showing group differences found no main effects of medication. There was a significant medication-by-diagnosis interaction in right al/fO [$F(1,73) = 4.4$, $p = .04$] and no interactions in left al/fO or right thalamus. Values on y axes represent parameter estimates. **(C)** Positive correlations between VMPFC-right al/fO connectivity values and evoked activity in VMPFC for errors > corrects contrast ($r = .32$, $p = .05$) and right al/fO for loss > null errors contrast ($r = .42$, $p = .007$). There was also a correlation (not shown) between VMPFC-right thalamus connectivity and right al/fO activity for loss > null error contrast ($r = .31$, $p = .05$). Values represent parameter estimates. mOCD, medicated OCD patients; mPC, medicated patient control subjects; OCD, obsessive-compulsive disorder; uHC, unmedicated healthy control subjects; uOCD, unmedicated OCD patients.

consistent with our behavioral evidence indicating that OCD patients experienced errors as more frustrating than control subjects.

Obsessive-compulsive disorder patients also showed greater activity in VMPFC, a region of DMN that has been associated with a variety of motivational behaviors, including the experience of positive and negative emotions (44,52–54), self-referential processing (55), and risky decision making (56,57). Unlike pMFC and al/fO, VMPFC tends to deactivate when attention is directed to external stimuli in cognitive tasks (31,32), perhaps reflecting disengagement from or suppression of automatic internal emotional-evaluative processes (33,37,39). Thus, OCD patients' reduced deactivation of VMPFC to errors may be due to an inability to properly disengage internal-evaluative processes when mistakes are detected.

This relative failure for OCD patients to deactivate VMPFC was seen not only across all errors but also for errors involving a loss in excess of what was found for errors without consequences. Although the region of VMPFC found for loss > null errors was located posterior and ventral to the region emerging for all errors > corrects, areas within VMPFC are densely interconnected and strongly positively correlated (37,58). Recently, however, it has been suggested that more posterior ventral regions of DMN are associated with projections of the self into the future (59), suggesting that the posterior VMPFC activation found for loss errors in OCD may be related to greater concern for the future consequences of loss.

The notion of intrinsic functional connectivity has its roots in studies examining low-frequency BOLD fluctuations during resting state (60), yet has also been applied to connectivity analyses during task performance when variance associated with task events has been regressed out (46). Using this latter method, we found that OCD patients showed greater positive coupling between VMPFC and right al/fO than did control subjects. Recent data suggest that al/fO may be a central "hub" that initiates switching between central executive and default modes of processing (18). If so, the significantly more positive relationship between al/fO and VMPFC in OCD patients suggests that, in this disorder, activation of al/fO is more likely to "switch on" internal-evaluative processes subserved by VMPFC, independent of task events. Although such interregional connectivity is independent of task events (i.e., spontaneous) and linearly superimposed on event-related activations (47), intrinsic coupling patterns may ultimately influence event-related responses, perhaps by maintaining the structural integrity and functional strength of network connections. Indeed, the fact that the amount of connectivity between VMPFC and right al/fO in OCD patients was correlated with evoked responses in these areas during errors suggests that positive coupling within these regions is associated with an enhanced error-related response in OCD.

Although speculative, it is conceivable that altered activity in a system subserving salience detection and internal-emotional men-

tation could contribute to the OCD phenotype in several ways. In the simple case of a patient experiencing harm obsessions with checking compulsions, hyperactivity in neural regions detecting salience could lead to a greater attribution of the importance of various stimuli and associated safety behaviors (e.g., locking the door), while a concomitant inability to dampen internal-emotional responding may trigger fearful obsessions about negative outcomes resulting from mistakes in safety behaviors (e.g., an intruder entering through an unlocked door). Although it is unclear why certain stimuli appear to be more consistently overvalued than others, it may be evolutionarily adaptive to focus on safety-related items (61).

Reduced VMPFC deactivation may not be specific to OCD (see [62] for review), having also been noted in major depression (63), autism spectrum disorder (64), and schizophrenia (65), suggesting that an inability to disengage from evaluative and self-referential functions may be a general process that contributes to the pathophysiology of many disorders. It is perhaps the interaction of a VMPFC-based vulnerability with other brain regions, as well as the context in which VMPFC impairment is found (e.g., reduced VMPFC deactivation to errors in OCD vs. emotional faces in depression), that determines the clinical manifestation of VMPFC dysfunction.

While both OCD and control subjects showed error-related activation of pMFC, there were no group differences in this region. Although OCD patients exhibit an increased ERN, which has a source in pMFC (66), the functional magnetic resonance imaging literature is inconsistent with regard to the location of medial frontal increases in OCD, with one study finding differences only in VMPFC (12), another only in pMFC (7), and others in both regions (9,34). The cause for these differences is unclear, but variability in sample sizes, tasks employed, and patient characteristics may be contributing to inconsistencies.

Limitations of the current study should be the focus of future research. Performance feedback provided on each trial was used to increase motivation, but made it impossible to disentangle neural activity to responses versus feedback. Although current interpretations are not dependent on distinguishing these events, future work may wish to examine OCD error responses in the absence of feedback to determine the generality of these findings. In addition, examination of resting state functional connectivity in OCD would complement the current findings of altered intrinsic connectivity during task and help us further understand connectivity disturbances in the disorder. Despite these limitations, our results highlight the role of motivational brain systems in OCD, pointing to an overvaluation of errors related to alteration in functional relationships between networks processing external salience and emotional-evaluative internal thought.

Support for this research has been provided by National Institute of Mental Health R01 MH071821 awarded to SFT, K23MH082176 awarded to KDF, and a National Alliance for Research on Schizophrenia and Depression Young Investigator Award and National Institute of Mental Health F32 MH082573 awarded to ERS.

We thank Keith Newnham for help with data collection and Ben Johnides for help with data analysis.

All authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

1. Friedlander L, Desrocher M (2006): Neuroimaging studies of obsessive-compulsive disorder in adults and children. *Clin Psychol Rev* 26:32–49.
2. Pitman RK (1987): A cybernetic model of obsessive-compulsive psychopathology. *Compr Psychiatry* 28:334–343.
3. Taylor SF, Stern ER, Gehring WJ (2007): Neural systems for error monitoring: Recent findings and theoretical perspectives. *Neuroscientist* 13: 160–172.
4. Whiteside SP, Port JD, Abramowitz JS (2004): A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. *Psychiatry Res* 132:69–79.
5. Rotge JY, Guehl D, Dilharreguy B, Cuny E, Tignol J, Bioulac B, *et al.* (2008): Provocation of obsessive-compulsive symptoms: A quantitative voxel-based meta-analysis of functional neuroimaging studies. *J Psychiatry Neurosci* 33:405–412.
6. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET (2008): Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofronto-striatal model revisited. *Neurosci Biobehav Rev* 32:525–549.
7. Ursu S, Stenger VA, Shear MK, Jones MR, Carter CS (2003): Overactive action monitoring in obsessive-compulsive disorder: Evidence from functional magnetic resonance imaging. *Psychol Sci* 14:347–353.
8. Stern ER, Liu Y, Gehring WJ, Lister JJ, Yin G, Zhang J, *et al.* (2010): Chronic medication does not affect hyperactive error responses in obsessive-compulsive disorder. *Psychophysiology* 47:913–920.
9. Maltby N, Tolin DF, Worhunsky P, O'Keefe TM, Kiehl KA (2005): Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: An event-related fMRI study. *Neuroimage* 24: 495–503.
10. Hajcak G, Simons RF (2002): Error-related brain activity in obsessive-compulsive undergraduates. *Psychiatry Res* 110:63–72.
11. Gehring WJ, Himle J, Nisenson LG (2000): Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychol Sci* 11:1–6.
12. Fitzgerald KD, Welsh RC, Gehring WJ, Abelson JL, Himle JA, Liberzon I, Taylor SF (2005): Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biol Psychiatry* 57:287–294.
13. Endrass T, Klawohn J, Schuster F, Kathmann N (2008): Overactive performance monitoring in obsessive-compulsive disorder: ERP evidence from correct and erroneous reactions. *Neuropsychologia* 46:1877–1887.
14. Page LA, Rubia K, Deeley Q, Daly E, Toal F, Mataix-Cols D, *et al.* (2009): A functional magnetic resonance imaging study of inhibitory control in obsessive-compulsive disorder. *Psychiatry Res* 174:202–209.
15. Roth RM, Saykin AJ, Flashman LA, Pixley HS, West JD, Mamourian AC (2007): Event-related functional magnetic resonance imaging of response inhibition in obsessive-compulsive disorder. *Biol Psychiatry* 62: 901–909.
16. Woolley J, Heyman I, Brammer M, Frampton I, McGuire PK, Rubia K (2008): Brain activation in paediatric obsessive compulsive disorder during tasks of inhibitory control. *Br J Psychiatry* 192:25–31.
17. Rauch SL, Savage CR, Alpert NM, Dougherty D, Kendrick A, Curran T, *et al.* (1997): Probing striatal function in obsessive-compulsive disorder: A PET study of implicit sequence learning. *J Neuropsychiatry Clin Neurosci* 9:568–573.
18. Sridharan D, Levitin DJ, Menon V (2008): A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A* 105:12569–12574.
19. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27:2349–2356.
20. Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, *et al.* (2006): A core system for the implementation of task sets. *Neuron* 50:799–812.
21. Mohr PN, Biele G, Heekeren HR (2010): Neural processing of risk. *J Neurosci* 30:6613–6619.
22. Gu X, Liu X, Guise KG, Naidich TP, Hof PR, Fan J (2010): Functional dissociation of the frontoinsular and anterior cingulate cortices in empathy for pain. *J Neurosci* 30:3739–3744.
23. Craig AD (2009): How do you feel—now? The anterior insula and human awareness. *Nat Rev Neurosci* 10:59–70.
24. Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998): Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.
25. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD (2001): Conflict monitoring and cognitive control. *Psychol Review* 108:624–652.

26. Simmons A, Matthews SC, Stein MB, Paulus MP (2004): Anticipation of emotionally aversive visual stimuli activates right insula. *Neuroreport* 15:2261–2265.
27. Paulus MP, Stein MB (2006): An insular view of anxiety. *Biol Psychiatry* 60:383–387.
28. Critchley HD (2005): Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol* 493:154–166.
29. Cechetto DF, Shoemaker JK (2009): Functional neuroanatomy of autonomic regulation. *Neuroimage* 47:795–803.
30. Kringelbach ML, Rolls ET (2004): The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. *Prog Neurobiol* 72:341–372.
31. Simpson JR Jr, Snyder AZ, Gusnard DA, Raichle ME (2001): Emotion-induced changes in human medial prefrontal cortex. I. During cognitive task performance. *Proc Natl Acad Sci U S A* 98:683–687.
32. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, Petersen SE (1997): Common blood flow changes across visual cortex. II. Decreases in cerebral cortex. *J Cogn Neurosci* 9:648–663.
33. Drevets WC, Raichle ME (1998): Suppression of regional cerebral blood during emotional versus higher cognitive implications for interactions between emotion and cognition. *Cogn Emot* 12:353–385.
34. Fitzgerald KD, Stern ER, Angstadt M, Nicholson-Muth K, Maynor M, Welsh RC, *et al.* (2010): Altered function and connectivity of the medial frontal cortex in pediatric obsessive compulsive disorder [published online ahead of print October 13]. *Biol Psychiatry*.
35. Lebreton M, Jorge S, Michel V, Thirion B, Pessiglione M (2009): An automatic valuation system in the human brain: Evidence from functional neuroimaging. *Neuron* 64:431–439.
36. Hare TA, Camerer CF, Rangel A (2009): Self-control in decision-making involves modulation of the vmPFC valuation system. *Science* 324:646–648.
37. Buckner RL, Andrews-Hanna JR, Schacter DL (2008): The brain's default network: Anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 1124:1–38.
38. Bouret S, Richmond BJ (2010): Ventromedial and orbital prefrontal neurons differentially encode internally and externally driven motivational values in monkeys. *J Neurosci* 30:8591–8601.
39. Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001): Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proc Natl Acad Sci U S A* 98:4259–4264.
40. Endrass T, Schuermann B, Kaufmann C, Spielberg R, Kniesche R, Kathmann N (2010): Performance monitoring and error significance in patients with obsessive-compulsive disorder. *Biol Psychol* 84:257–263.
41. Luck SJ (2005): *An Introduction to the Event-Related Potential Technique*, *1st ed.* Cambridge, MA: MIT Press.
42. First M, Spitzer R, Gibbon M, Williams J (1996): *Structured Clinical Interview For DSM-IV Axis Disorders (SCID), Clinician Version: User's Guide*. Washington, DC: American Psychiatric Publishing.
43. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, *et al.* (1989): The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 46:1006–1011.
44. Taylor SF, Martis B, Fitzgerald KD, Welsh RC, Abelson JL, Liberzon I, *et al.* (2006): Medial frontal cortex activity and loss-related responses to errors. *J Neurosci* 26:4063–4070.
45. Yang Y, Gu H, Zhan W, Xu S, Silbersweig DA, Stern E (2002): Simultaneous perfusion and BOLD imaging using reverse spiral scanning at 3T: Characterization of functional contrast and susceptibility artifacts. *Magn Reson Med* 48:278–289.
46. Fair DA, Schlaggar BL, Cohen AL, Miezin FM, Dosenbach NU, Wenger KK, *et al.* (2007): A method for using blocked and event-related fMRI data to study "resting state" functional connectivity. *Neuroimage* 35:396–405.
47. Fox MD, Snyder AZ, Zacks JM, Raichle ME (2006): Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat Neurosci* 9:23–25.
48. Cox RW (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29:162–173.
49. Ward BD (2000): Simultaneous inference for fMRI data. Available at: http://homepage.usask.ca/~ges125/fMRI/AFNIdoc/AlphaSim.pdf. Accessed February 1, 2010.
50. Preuschoff K, Quartz SR, Bossaerts P (2008): Human insula activation reflects risk prediction errors as well as risk. *J Neurosci* 28:2745–2752.
51. Simmons A, Matthews SC, Paulus MP, Stein MB (2008): Intolerance of uncertainty correlates with insula activation during affective ambiguity. *Neurosci Lett* 430:92–97.
52. Sommer T, Peters J, Glascher J, Buchel C (2009): Structure-function relationships in the processing of regret in the orbitofrontal cortex. *Brain Struct Funct* 213:535–551.
53. Phan KL, Wager T, Taylor SF, Liberzon I (2002): Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16:331–348.
54. O'Doherty J, Critchley H, Deichmann R, Dolan RJ (2003): Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *J Neurosci* 23:7931–7939.
55. Phan KL, Taylor SF, Welsh RC, Ho SH, Britton JC, Liberzon I (2004): Neural correlates of individual ratings of emotional salience: A trial-related fMRI study. *Neuroimage* 21:768–780.
56. Clark L, Bechara A, Damasio H, Aitken MRF, Sahakian BJ, Robbins TW (2008): Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain* 131:1311–1322.
57. Bechara A, Damasio H, Damasio AR (2000): Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex* 10:295–307.
58. Beckmann M, Johansen-Berg H, Rushworth MF (2009): Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J Neurosci* 29:1175–1190.
59. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL (2010): Functional-anatomic fractionation of the brain's default network. *Neuron* 65:550–562.
60. Bressler SL, Menon V (2010): Large-scale brain networks in cognition: Emerging methods and principles. *Trends Cogn Sci* 14:277–290.
61. Szechtman H, Woody E (2004): Obsessive-compulsive disorder as a disturbance of security motivation. *Psychol Rev* 111:111–127.
62. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ (2009): Default-mode brain dysfunction in mental disorders: A systematic review. *Neurosci Biobehav Rev* 33:279–296.
63. Grimm S, Boesiger P, Beck J, Schuepbach D, Bermpohl F, Walter M, *et al.* (2009): Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. *Neuropsychopharmacology* 34:932–943.
64. Kennedy DP, Redcay E, Courchesne E (2006): Failing to deactivate: Resting functional abnormalities in autism. *Proc Natl Acad Sci U S A* 103:8275–8280.
65. Pomarol-Clotet E, Salvador R, Sarro S, Gomar J, Vila F, Martinez A, *et al.* (2008): Failure to deactivate in the prefrontal cortex in schizophrenia: Dysfunction of the default mode network? *Psychol Med* 38:1185–1193.
66. Gehring WJ, Liu Y, Orr JM, Carp J (in press): The error-related negativity (ERN/Ne). In: Luck SJ, Kappenman E, editors. *Oxford Handbook of Event-Related Potential Components*. New York: Oxford University Press.