Published in final edited form as:

Biol Psychiatry. 2011 March 15; 69(6): 583–591. doi:10.1016/j.biopsych.2010.09.048.

Hyperactive error responses and altered connectivity in ventromedial and fronto-insular cortices in obsessive-compulsive disorder

Emily R. Stern, Ph.D.¹, Robert C. Welsh^{1,2}, Kate D. Fitzgerald, M.D.¹, William J. Gehring, Ph.D.³, Jamey J. Lister, M.S.W.¹, Joseph A. Himle, Ph.D.¹, James L. Abelson, M.D.¹, and Stephan F. Taylor, M.D.¹

¹ Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

² Department of Radiology, University of Michigan, Ann Arbor, MI, USA

³ Department of Psychology, University of Michigan, Ann Arbor, MI, USA

Abstract

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 as compared to controls. 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—OCD 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.

Corresponding author: Emily R. Stern, Ph.D., University of Michigan Department of Psychiatry, 4250 Plymouth Rd, 2506 Rachel Upjohn Building, Ann Arbor, MI 48109, emistern@med.umich.edu, Phone: 734-936-1323, Fax: 734-936-7868.

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

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

fMRI; performance monitoring; anxiety; default mode; salience network; functional coupling

Introduction

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder (lifetime prevalence 1-3%, ref 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 (dACC) often extending into rostral ACC, 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.

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, regions of the “default-mode” network (DMN) including VMPFC and posterior cingulate cortex deactivate with increases in externally-directed cognition (31-33) including that associated with error detection (34,35). Although the meaning of DMN deactivation is under debate, VMPFC plays a role in internal mentation and automatic value judgments (36-38), in contrast to lateral OFC, which may be associated with externally-triggered valuation (39). 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 (33,38,40). Increased 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.

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). Recently, an electrophysiological

index of error detection that is reliably increased in OCD, the error-related negativity (ERN) (8,10,11,13), was found to differ between OCD patients and controls based on whether errors were associated with a monetary loss versus no loss (41). However, ERN data cannot provide precise circuitry information (42), 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 (fMRI) 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 controls 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 controls. 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 the Supplement for exclusion criteria). The control group included 20 unmedicated healthy controls (uHC) without psychiatric diagnoses and 18 medicated patient controls (mPC) who were on SRIs for major depression (in remission). As the majority of OCD patients had a history of major depression (see Methods and Materials in the Supplement), a comparison of OCD and controls 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 the Supplement lists medications).

Subjects provided written informed consent and were evaluated by a trained clinician using the Structured Clinical Interview for Diagnosis (43). Generalized depression and anxiety were assessed using Hamilton Ratings Scales for Depression (HDRS) and Anxiety (HARS). Obsessive-compulsive (OC) symptom severity was quantified using the Yale-Brown Obsessive-Compulsive Scale (YBOCS, see ref 44). As shown in Table S2 (see Supplement), 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 (45). 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, C). Subjects were pre-trained 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 0.8-1.5 times the mean reaction time (RT) 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 dollars, 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?”, 3) “When you made a mistake, were you flustered and find it hard to get back on track?”

Data acquisition

MRI 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 coregistration. Functional images were acquired with a T2*-weighted, reverse spiral acquisition sequence (GRE, TR = 2000, TE = 30, FA = 90, FOV = 20, 40 slices, 3.0/0, matrix diameter of 71 - equivalent to 64 × 64) sensitive to signal in ventral frontal regions (46). Subjects underwent 8 runs with 176 volumes plus 4 initial discarded volumes. After acquisition of functional volumes, a high resolution T1 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) × 2 (Medication: unmedicated, medicated) ANOVAs. RTs 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 BOLD processing and analysis, see Methods and Materials in the Supplement. Briefly, functional images were slice-time corrected, realigned, coregistered to the T1 SPGR image, normalized to the Montreal Neurological Institute template, and smoothed. Two general linear models (GLMs) 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 regressors 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 vs. corrects*, *null errors vs. null corrects*, *loss error vs. null error*, and *fail-to-gain error vs. null error*. In a separate interference model, low and high interference corrects were modeled separately at the time of target presentation, and a contrast examining *high vs. 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 GLM that included all the same regressors as the error model, yielding a residual timecourse 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 the Supplement) in a separate model that again included all error model event regressors (see ref 47), in order 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 (47, 48).

Primary analyses focused on activity in a frontal-striatal-thalamic (FST) search area (Methods and Materials in the Supplement). One- and two-sample t-tests were thresholded with an alpha of .05, cluster-level corrected for multiple comparisons within the FST search

area using Monte-Carlo simulations as implemented by AlphaSim in AFNI (49, 50). 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 the Supplement), using an alpha of .05, cluster-level corrected within the aI/fO 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 the Supplement).

In order to examine the relationship between evoked activity and intrinsic connectivity, Pearson's correlations were performed (separately for OCD and control groups) between regions 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, OC symptom severity, and SRI dosage on neural activity in regions exhibiting group differences (see Supplemental Methods and Materials, Tables S5 and S6 in the Supplement).

Results

Behavioral

Error rates and RTs are shown in Supplemental Results and Table S3 (see Supplement). 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 vs. corrects—Control and OCD groups exhibited similar patterns of activations for errors > corrects, averaged across incentive value, within the FST area (Figure 2A and Table 1; see Supplemental Results and Table S5 in the Supplement for whole-brain results). While both groups showed VMPFC deactivation in response to errors, the extent of this deactivation was larger for controls (Figure 2A and Table 1), leading to a significant OCD > control difference for errors > corrects (Figure 2B). No other group difference 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 controls (Figure 2B). There were no regions where controls 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 vs. null errors—To investigate activations for errors carrying greater incentive value, we compared loss errors to null errors and fail-to-gain errors to null errors (see Table S4 in the Supplement 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 as compared to 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 controls 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 vs. null errors—OCD patients showed significantly more activity for errors when they failed to gain money as compared to 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 vs. low interference corrects—Cognitive conflict on high vs. low interference trials elicited activations in pMFC and bilateral aI/fO and deactivations in VMPFC for both OCD patients and controls (Table 2). For controls, 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 timecourse and other areas of DMN including subgenual cingulate, anterior MFC, and dorsomedial prefrontal cortex (Table 3). VMPFC was also positively coupled with bilateral aI/fO and adjacent lateral OFC (BAs 11/13/47), caudate head, and posterior thalamus. Extent of positive coupling between VMPFC and aI/fO was greater in OCD patients than controls, and overlapped with aI/fO regions that were activated in the errors > corrects and loss > null errors contrasts in patients (see Figure S1 in the Supplement). Whereas controls exhibited negative connectivity between VMPFC and pMFC as well as a region of left aI/fO located superior and posterior to aI/fO areas showing positive connectivity with VMPFC, no negative coupling was found in OCD patients. Group comparisons revealed significantly more positive coupling of VMPFC with right aI/fO in OCD (Figure 4A). OCD patients also exhibited more positive connectivity between VMPFC and left aI/fO as well as VMPFC and right thalamus, although this may be due to differences in generalized depression and anxiety (see Methods and Materials in the Supplement).

Post-hoc ANOVAs performed on parameter estimates extracted from these regions revealed a medication-by-diagnosis interaction in right aI/fO ($p = .04$, see 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.

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

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 controls.

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 controls, 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/dACC, 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 (51) and intolerance of uncertainty (52). 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 OCD patients appraise the motivational salience of errors as greater than controls, with loss errors in particular eliciting activity in right aI/fO associated with arousal and negative emotion, consistent with our behavioral evidence indicating that OCD patients experienced errors as more frustrating than controls.

OCD 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 (45,53-55), self-referential processing (56), and risky decision-making (57,58). Unlike pMFC and aI/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 (33,38,40). 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 (38,59). Recently, however, it has been suggested that more posterior ventral regions of DMN are associated with projections of the self into the future (60), 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 (61), yet has also been applied to connectivity analyses during task performance when variance associated with task events has been regressed out (47). Using this latter method, we found that OCD was associated with greater positive coupling between VMPFC and right aI/fO than controls. Recent data suggests that aI/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 aI/fO and VMPFC in OCD patients suggests that, in this disorder, activation of aI/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 (or “spontaneous”) and linearly superimposed on event-related activations (48), 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 aI/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 mentation 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 over-valued than others, it may be evolutionarily adaptive to focus on safety-related items (62).

Reduced VMPFC deactivation may not be specific to OCD (see ref 63 for review), having also been noted in major depression (64), autism spectrum disorder (65), and schizophrenia (66), 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 (67), there have been inconsistent results regarding the location of medial frontal increases in OCD, with one fMRI study finding differences only in VMPFC (12), another only in pMFC (7), and others in both regions (9,35). 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support for this research has been provided by National Institute of Mental Health (NIMH) R01 MH071821 awarded to SFT, K23MH082176 awarded to KDF, and a NARSAD Young Investigator Award and NIMH F32 MH082573 awarded to ERS. We would like to thank Keith Newnham for help with data collection and Ben Johnides for help with data analysis.

References

1. Friedlander L, Desrocher M. Neuroimaging studies of obsessive-compulsive disorder in adults and children. *Clin Psychol Rev.* 2006; 26:32–49. [PubMed: 16242823]
2. Pitman RK. A cybernetic model of obsessive-compulsive psychopathology. *Compr Psychiatry.* 1987; 28:334–343. [PubMed: 3608467]
3. Taylor SF, Stern ER, Gehring WJ. Neural systems for error monitoring: recent findings and theoretical perspectives. *Neuroscientist.* 2007; 13:160–172. [PubMed: 17404376]
4. Whiteside SP, Port JD, Abramowitz JS. A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. *Psychiatry Res.* 2004; 132:69–79. [PubMed: 15546704]
5. Rotge JY, Guehl D, Dilharreguy B, Cuny E, Tignol J, Bioulac B, et al. Provocation of obsessive-compulsive symptoms: a quantitative voxel-based meta-analysis of functional neuroimaging studies. *J Psychiatry Neurosci.* 2008; 33:405–412. [PubMed: 18787662]
6. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev.* 2008; 32:525–549. [PubMed: 18061263]
7. Ursu S, Stenger VA, Shear MK, Jones MR, Carter CS. Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. *Psychol Sci.* 2003; 14:347–353. [PubMed: 12807408]
8. Stern ER, Liu Y, Gehring WJ, Lister JJ, Yin G, Zhang J, et al. Chronic medication does not affect hyperactive error responses in obsessive-compulsive disorder. *Psychophysiology.* epub ahead of print.
9. Maltby N, Tolin DF, Worhunsky P, O'Keefe TM, Kiehl KA. Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: an event-related fMRI study. *Neuroimage.* 2005; 24:495–503. [PubMed: 15627591]
10. Hajcak G, Simons RF. Error-related brain activity in obsessive-compulsive undergraduates. *Psychiatry Research.* 2002; 110:63–72. [PubMed: 12007594]
11. Gehring WJ, Himle J, Nisenson LG. Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science.* 2000; 11:1–6. [PubMed: 11228836]
12. Fitzgerald KD, Welsh RC, Gehring WJ, Abelson JL, Himle JA, Liberzon I, et al. Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biol Psychiatry.* 2005; 57:287–294. [PubMed: 15691530]
13. Endrass T, Klawohn J, Schuster F, Kathmann N. Overactive performance monitoring in obsessive-compulsive disorder: ERP evidence from correct and erroneous reactions. *Neuropsychologia.* 2008; 46:1877–1887. [PubMed: 18514679]

14. Page LA, Rubia K, Deeley Q, Daly E, Toal F, Mataix-Cols D, et al. A functional magnetic resonance imaging study of inhibitory control in obsessive-compulsive disorder. *Psychiatry Res.* 2009; 174:202–209. [PubMed: 19906516]
15. Roth RM, Saykin AJ, Flashman LA, Pixley HS, West JD, Mamourian AC. Event-related functional magnetic resonance imaging of response inhibition in obsessive-compulsive disorder. *Biol Psychiatry.* 2007; 62:901–909. [PubMed: 17511967]
16. Woolley J, Heyman I, Brammer M, Frampton I, McGuire PK, Rubia K. Brain activation in paediatric obsessive compulsive disorder during tasks of inhibitory control. *Br J Psychiatry.* 2008; 192:25–31. [PubMed: 18174505]
17. Rauch SL, Savage CR, Alpert NM, Dougherty D, Kendrick A, Curran T, et al. Probing striatal function in obsessive-compulsive disorder: a PET study of implicit sequence learning. *J Neuropsychiatry Clin Neurosci.* 1997; 9:568–573. [PubMed: 9447498]
18. Sridharan D, Levitin DJ, Menon V. 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.* 2008; 105:12569–12574. [PubMed: 18723676]
19. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci.* 2007; 27:2349–2356. [PubMed: 17329432]
20. Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, et al. A core system for the implementation of task sets. *Neuron.* 2006; 50:799–812. [PubMed: 16731517]
21. Mohr PN, Biele G, Heekeren HR. Neural processing of risk. *J Neurosci.* 2010; 30:6613–6619. [PubMed: 20463224]
22. Gu X, Liu X, Guise KG, Naidich TP, Hof PR, Fan J. Functional dissociation of the fronto-insular and anterior cingulate cortices in empathy for pain. *J Neurosci.* 30:3739–3744. [PubMed: 20220007]
23. Craig AD. How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci.* 2009; 10:59–70. [PubMed: 19096369]
24. Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science.* 1998; 280:747–749. [PubMed: 9563953]
25. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. *Psychological Review.* 2001; 108:624–652. [PubMed: 11488380]
26. Simmons A, Matthews SC, Stein MB, Paulus MP. Anticipation of emotionally aversive visual stimuli activates right insula. *Neuroreport.* 2004; 15:2261–2265. [PubMed: 15371746]
27. Paulus MP, Stein MB. An insular view of anxiety. *Biol Psychiatry.* 2006; 60:383–387. [PubMed: 16780813]
28. Critchley HD. Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol.* 2005; 493:154–166. [PubMed: 16254997]
29. Cechetto DF, Shoemaker JK. Functional neuroanatomy of autonomic regulation. *Neuroimage.* 2009; 47:795–803. [PubMed: 19446637]
30. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in Neurobiology.* 2004; 72:341–372. [PubMed: 15157726]
31. Simpson JR Jr, Snyder AZ, Gusnard DA, Raichle ME. Emotion-induced changes in human medial prefrontal cortex: I. During cognitive task performance. *Proc Natl Acad Sci U S A.* 2001; 98:683–687. [PubMed: 11209065]
32. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, et al. Common blood flow changes across visual cortex: II. Decreases in cerebral cortex. *Journal of Cognitive Neuroscience.* 1997; 9:648–663.
33. Drevets WC, Raichle ME. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: Implications for interactions between emotion and cognition. *Cognition and Emotion.* 1998; 12:353–385.
34. Stern ER, Fitzgerald KD, Taylor SF (2006): unpublished data.

35. Fitzgerald KD, Stern ER, Angstadt M, Nicholson-Muth K, Maynor M, Welsh RC, et al. Altered function and connectivity of the medial frontal cortex in pediatric obsessive compulsive disorder. *Biological Psychiatry*. in press.
36. Lebreton M, Jorge S, Michel V, Thirion B, Pessiglione M. An automatic valuation system in the human brain: evidence from functional neuroimaging. *Neuron*. 2009; 64:431–439. [PubMed: 19914190]
37. Hare TA, Camerer CF, Rangel A. Self-control in decision-making involves modulation of the vmPFC valuation system. *Science*. 2009; 324:646–648. [PubMed: 19407204]
38. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008; 1124:1–38. [PubMed: 18400922]
39. Bouret S, Richmond BJ. Ventromedial and orbital prefrontal neurons differentially encode internally and externally driven motivational values in monkeys. *J Neurosci*. 2010; 30:8591–8601. [PubMed: 20573905]
40. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A*. 2001; 98:4259–4264. [PubMed: 11259662]
41. Endrass T, Schuermann B, Kaufmann C, Spielberg R, Kniesche R, Kathmann N. Performance monitoring and error significance in patients with obsessive-compulsive disorder. *Biol Psychol*. 84:257–263. [PubMed: 20152879]
42. Luck, SJ. An introduction to the event-related potential technique. 1. Cambridge, MA: MIT Press; 2005.
43. First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV Axis Disorders (SCID), Clinician Version: User's Guide. Washington, D.C.: American Psychiatric Press; 1996.
44. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry*. 1989; 46:1006–1011. [PubMed: 2684084]
45. Taylor SF, Martis B, Fitzgerald KD, Welsh RC, Abelson JL, Liberzon I, et al. Medial frontal cortex activity and loss-related responses to errors. *J Neurosci*. 2006; 26:4063–4070. [PubMed: 16611823]
46. Yang Y, Gu H, Zhan W, Xu S, Silbersweig DA, Stern E. Simultaneous perfusion and BOLD imaging using reverse spiral scanning at 3T: characterization of functional contrast and susceptibility artifacts. *Magn Reson Med*. 2002; 48:278–289. [PubMed: 12210936]
47. Fair DA, Schlaggar BL, Cohen AL, Miezin FM, Dosenbach NU, Wenger KK, et al. A method for using blocked and event-related fMRI data to study “resting state” functional connectivity. *Neuroimage*. 2007; 35:396–405. [PubMed: 17239622]
48. Fox MD, Snyder AZ, Zacks JM, Raichle ME. Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat Neurosci*. 2006; 9:23–25. [PubMed: 16341210]
49. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996; 29:162–173. [PubMed: 8812068]
50. Ward BD. Simultaneous inference for fMRI data. 2000
51. Preuschoff K, Quartz SR, Bossaerts P. Human insula activation reflects risk prediction errors as well as risk. *Journal of Neuroscience*. 2008; 28:2745–2752. [PubMed: 18337404]
52. Simmons A, Matthews SC, Paulus MP, Stein MB. Intolerance of uncertainty correlates with insula activation during affective ambiguity. *Neuroscience Letters*. 2008; 430:92–97. [PubMed: 18079060]
53. Sommer T, Peters J, Glascher J, Buchel C. Structure-function relationships in the processing of regret in the orbitofrontal cortex. *Brain Struct Funct*. 2009; 213:535–551. [PubMed: 19760243]
54. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage*. 2002; 16:331–348. [PubMed: 12030820]

55. O'Doherty J, Critchley H, Deichmann R, Dolan RJ. Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *J Neurosci.* 2003; 23:7931–7939. [PubMed: 12944524]
56. Phan KL, Taylor SF, Welsh RC, Ho SH, Britton JC, Liberzon I. Neural correlates of individual ratings of emotional salience: a trial-related fMRI study. *Neuroimage.* 2004; 21:768–780. [PubMed: 14980580]
57. Clark L, Bechara A, Damasio H, Aitken MRF, Sahakian BJ, Robbins TW. Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain.* 2008; 131:1311–1322. [PubMed: 18390562]
58. Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex.* 2000; 10:295–307. [PubMed: 10731224]
59. Beckmann M, Johansen-Berg H, Rushworth MF. Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J Neurosci.* 2009; 29:1175–1190. [PubMed: 19176826]
60. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. *Neuron.* 2010; 65:550–562. [PubMed: 20188659]
61. Bressler SL, Menon V. Large-scale brain networks in cognition: emerging methods and principles. *Trends Cogn Sci.* 2010; 14:277–290. [PubMed: 20493761]
62. Szechtman H, Woody E. Obsessive-compulsive disorder as a disturbance of security motivation. *Psychol Rev.* 2004; 111:111–127. [PubMed: 14756589]
63. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev.* 2009; 33:279–296. [PubMed: 18824195]
64. Grimm S, Boesiger P, Beck J, Schuepbach D, Bermpohl F, Walter M, et al. Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. *Neuropsychopharmacology.* 2009; 34:932–843. [PubMed: 18536699]
65. Kennedy DP, Redcay E, Courchesne E. Failing to deactivate: resting functional abnormalities in autism. *Proc Natl Acad Sci U S A.* 2006; 103:8275–8280. [PubMed: 16702548]
66. Pomarol-Clotet E, Salvador R, Sarro S, Gomar J, Vila F, Martinez A, et al. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychol Med.* 2008; 38:1185–1193. [PubMed: 18507885]
67. Gehring, WJ.; Liu, Y.; Orr, JM.; Carp, J. The error-related negativity (ERN/Ne). In: Luck, SJ.; Kappenman, E., editors. *Oxford handbook of event-related potential components.* New York: Oxford University Press; in press

Figure 1. Diagram of incentive flanker task

Prior to 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 (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 ms, 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 RT such that total time between presentation of letter stimuli and end of feedback was 1500 ms. Feedback was followed by a 2000 ms blank inter-trial interval (ITI). Prior to 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). In order to be able to decouple the BOLD signal associated with the response/feedback from that elicited by cues, cues were jittered between 1500 and 9500 ms in increments of 500 ms.

Figure 2. Errors > correct trials in 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 controls; B) Activity in VMPFC ($x = 0, y = 51, z = -15, k = 51, z = 3.35$) and left aI/fO ($x = -33, y = 30, z = -3, k = 20, z = 3.2$) was greater in OCD patients than control subjects; C) Post-hoc ANOVAs examining effects of medication status on activity in regions showing group difference 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

Figure 3. Loss > null errors in OCD patients and control subjects

A) Whole-brain activations (displayed at $p < .005$ with 20 contiguous voxels) for OCD patients and controls, showing activity in VMPFC ($x = -9, y = 36, z = -24, k = 73, z = 3.91$) and right 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 controls; 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 controls showed more activations than OCD patients; C) Post-hoc ANOVAs examining effects of medication status on activity in regions showing group differences found no main effects of medication (VMPFC: $p = 0.81$, aI/fO: $p = 0.94$) and no interactions between medication and diagnosis (VMPFC: $p = 0.49$, aI/fO: $p = 0.83$). Color bars represent t scores.

Figure 4.

Functional connectivity with VMPFC. A) OCD patients showed greater positive connectivity than controls between VMPFC seed and right aI/fO ($x = 39, y = 9, z = 3, k = 134, z = 3.63$), left aI/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 ANOVAs 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 aI/fO ($F(1,73) = 4.4, p = .04$), and no interactions in left aI/fO or right thalamus. Values on y-axes represent parameter estimates; C) Positive correlations between VMPFC-right aI/fO connectivity values and evoked activity in VMPFC for errors > corrects contrast ($r = 0.32, p = .05$) and right aI/fO for loss > null errors contrast ($r = 0.42, p = .007$). There was also a correlation (not shown) between VMPFC-right thalamus connectivity and right aI/fO activity for loss > null error contrast ($r = 0.31, p = .05$). Values represent parameter estimates.

Table 1
Errors > corrects (all incentive types) for control subjects and OCD patients in FST search area

BA = Brodmann's areas; k = number of voxels; Z = maximum z-score; L = left; R = right; B = bilateral; pMFC = posterior medial frontal cortex; aI/fO = anterior insula/frontal operculum; VMPFC = ventromedial prefrontal cortex; OFC = orbitofrontal cortex; coordinates are in MNI space. Regions shown in bold font exhibited significant group differences.

Region	CONTROL										OCD			
	BA	k	x	y	z	Z	k	x	y	z	x	y	z	Z
<i>Activation</i>														
pMFC (B)	6,8,9,24, 32, 10	1436	6	21	45	7.53	1607	3	27	36	6.96			
aI/fO (L)	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)	N/A	148	-9	-24	0	4.79	126	-9	-18	6	5.12			
Thalamus (R)	N/A	126	9	-24	0	5.21	153	9	-12	6	5.15			
<i>Deactivation</i>														
VMPFC (B)	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								

Table 2
High > low interference corrects for control subjects and OCD patients in FST search area

BA = Brodmann's areas; k = number of voxels; Z = maximum z-score; L = left; R = right; pMFC = posterior medial frontal cortex; aI/fO = anterior insula/frontal operculum; VMPPFC = ventromedial prefrontal cortex; coordinates are in MNI space. No significant group differences were found between OCD patients and controls.

Region	CONTROL						OCD					
	BA	k	x	y	z	Z	k	x	y	z	Z	
<i>Activation</i>												
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)	n/a	47	-9	3	6	3.43						
<i>Deactivation</i>												
VMPPFC (B)	10, 11	62	0	60	-18	3.59	237	3	60	12	4.23	

Table 3
Functional connectivity with timecourse in VMPFC for control subjects and OCD patients in FST search area

BA = Brodmann's areas; k = number of voxels; Z = maximum z-score; L = left; R = right; B = bilateral; VMPFC = ventromedial prefrontal cortex; aI/FO = anterior insula/frontal operculum; OFC = orbitofrontal cortex; pMFC = posterior medial frontal cortex; coordinates are in MNI space. Region shown in bold font exhibited significant group differences.

Region	BA	CONTROL						OCD					
		k	x	y	z	Z	k	x	y	z	Z		
<i>Positive connectivity</i>													
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)	11, 13, 47	673	-24	33	-15	> 7.5	865	-24	33	-15	> 7.6		
aI/FO/OFC (R)	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)	n/a	38	21	-27	9	3.94	284	6	-15	0	5.56		
<i>Negative connectivity</i>													
pMFC (B)	6, 24, 32	298	0	9	39	4.24							
aI/FO (L)	13	96	-30	24	15	4.73							