Archival Report

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Error Processing and Inhibitory Control in Obsessive-Compulsive Disorder: A Meta-analysis Using Statistical Parametric Maps

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ABSTRACT

BACKGROUND: Error processing and inhibitory control enable the adjustment of behaviors to meet task demands. Functional magnetic resonance imaging studies report brain activation abnormalities in patients with obsessive-compulsive disorder (OCD) during both processes. However, conclusions are limited by inconsistencies in the literature and small sample sizes. Therefore, the aim here was to perform a meta-analysis of the existing literature using unthresholded statistical maps from previous studies.

METHODS: A voxelwise seed-based *d* mapping meta-analysis was performed using t-maps from studies comparing patients with OCD and healthy control subjects (HCs) during error processing and inhibitory control. For the error processing analysis, 239 patients with OCD (120 male; 79 medicated) and 229 HCs (129 male) were included, while the inhibitory control analysis included 245 patients with OCD (120 male; 91 medicated) and 239 HCs (135 male).

RESULTS: Patients with OCD, relative to HCs, showed longer inhibitory control reaction time (standardized mean difference = 0.20, $p = .03$, 95% confidence interval = 0.016, 0.393) and more inhibitory control errors (standardized mean difference = 0.22, $p = .02$, 95% confidence interval = 0.039, 0.399). In the brain, patients showed hyperactivation in the bilateral dorsal anterior cingulate cortex, supplementary motor area, and pre-supplementary motor area as well as right anterior insula/frontal operculum and anterior lateral prefrontal cortex during error processing but showed hypoactivation during inhibitory control in the rostral and ventral anterior cingulate cortices and bilateral thalamus/caudate, as well as the right anterior insula/frontal operculum, supramarginal gyrus, and medial orbitofrontal cortex (all seed-based *d* mapping z value >2, $p < .001$).

CONCLUSIONS: A hyperactive error processing mechanism in conjunction with impairments in implementing inhibitory control may underlie deficits in stopping unwanted compulsive behaviors in the disorder.

Keywords: Error processing, fMRI, Inhibitory control, Meta-analysis, OCD, Performance monitoring

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Obsessive-compulsive disorder (OCD) has a lifetime prevalence of 2% to 3% (1). The disorder is characterized by recurrent and intrusive obsessive thoughts as well as by time-consuming, ego-dystonic behavioral and mental compulsions (2).

Patients with OCD often show altered brain activation during erroneous and correct responses on inhibitory control tasks (3,4). Relevant tasks include go/no-go and stop tasks, which measure the ability to inhibit responses to no-go stimuli among prepotent go stimuli and to withdraw already triggered motor responses following stop signals, respectively, as well as tasks of interference inhibition such as antisaccade, flanker, Simon, Stroop, and multisource interference tasks, which require participants to ignore interfering stimulus features and override prepotent responses in order to process relevant information and perform goal-directed actions (3,5,6). Impairments in the functioning of error processing and inhibitory control brain networks may, in part, underlie poor control over obsessions and compulsions in OCD, with many patients showing good insight into their symptoms but nonetheless continuing to carry out compulsive behaviors (3,6–8).

Successful task performance involves the capacity to monitor for errors and to adjust behavioral responding accordingly (9). Error processing is widely held to depend on the posterior medial frontal cortex (pMFC), incorporating dorsal anterior cingulate cortex (dACC), supplementary motor area (SMA), and posterior portions of pre-supplementary motor area (pre-SMA) (10). The pMFC, together with the anterior insula/frontal operculum (al/fO) and rostral anterior cingulate (rACC), forms the cingulo-opercular network (4,10,11). During error processing and inhibitory control, this cingulo-opercular

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network detects the demand for behavioral or attentional control and initiates recruitment of lateral frontoparietal and frontostriatal networks responsible for enacting top-down executive control (9,10,12–14).

Heightened error processing, as indicated by an increased amplitude of a midline frontal electrophysiological potential, the error-related negativity, is arguably the most reliable neurocognitive biomarker of OCD (15–17). Consistent with this, several functional magnetic resonance imaging (fMRI) studies of OCD report cingulo-opercular hyperactivation during error processing (4,18–24). In contrast, during correct inhibitory control, patients with OCD often show decreased pMFC/rACC activation (21,25–37) and altered striatal functioning (18,19,25,28–31,33–36,38), as confirmed in recent meta-analyses (3, 5), although some studies report increased pMFC activation in patients relative to healthy control subjects (HCs) (19,20,26,35).

Given the reliability of heightened error-related negativity findings in OCD, numerous theoretical accounts emphasize a role for cingulo-opercular hyperactivation as a key mechanism underlying OCD symptoms (11,16,39). However, most studies of error processing in OCD have employed small samples or focused on cingulo-opercular regions of interest, thereby limiting knowledge of potential group differences in other brain networks (4,19–21). Moreover, some previous work has reported decreased activation or no differences in these regions in patients with OCD relative to HCs during error processing (28,40,41). Existing meta-analyses of inhibitory control in OCD did not consider error processing and used coordinates from significant clusters rather than unthresholded group maps, meaning that true group differences may have been lost (3,5).

Therefore, the primary aim of the current study was to provide the first fMRI meta-analysis of error processing in patients with OCD relative to HCs based on whole-brain unthresholded statistical maps where possible (42). A second aim was to examine group differences in the same set of studies during inhibitory control. We anticipated heightened cingulo-opercular activation during error processing, but decreased cingulo-opercular and altered striatal activation during inhibitory control, in patients with OCD relative to HCs.

METHODS AND MATERIALS

Search and Inclusion of Studies

The meta-analysis was conducted in line with Meta-analysis of Observational Studies in Epidemiology group guidelines (43). The study protocol was registered with PROSPERO (No. CRD42017062495) and is accessible from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017062495.

A comprehensive literature search was performed using the PubMed, ScienceDirect, Web of Knowledge, and Scopus research databases through August 1, 2017. Reference lists of retrieved studies and recent meta-analyses (3,5) were also hand searched. Search syntax is provided in the Supplement. Included studies provided whole-brain pairwise voxel-based comparisons of the OCD group against the HC group using fMRI during errors on inhibitory control tasks (e.g., stop, go/no-go, Stroop, Simon, flanker, anti-saccade, multisource interference). Studies were excluded if they provided no case-control comparisons, were unable to provide findings from whole-brain analyses, had very high accuracy rates that precluded fMRI analysis of error processing (see Supplement), or used subject data that overlapped with another already included study. If the same patient group was used in multiple studies/tasks, then the study/task with the largest sample was included. For studies that used longitudinal/treatment designs, only baseline data were included. The meta-analysis examined both pediatric and adult patients with OCD diagnoses regardless of medication status, gender, symptom subtype, or comorbidities. Details of current comorbid diagnoses were extracted for each included dataset and are provided in Supplemental Table S1.

Authors of relevant papers were contacted and asked to provide whole-brain unthresholded t-maps for the pairwise comparison of OCD versus HC groups for the error contrast included in the original paper, as well as t-maps for the within-group error contrast separately for the HC and OCD groups. Authors who did not report error contrasts in their original publications were contacted to ask for unpublished whole-brain data in the form of unthresholded t-maps or in the form of coordinates from a whole-brain analysis. For studies providing error contrast maps/coordinates, data were also requested for the inhibitory control contrast.

Meta-analyses

A random-effects meta-analysis of the standardized mean differences (SMDs) (Hedges' *g*) between the OCD and HC groups in task performance (reaction time [RT] measures of inhibitory control; inhibitory control errors; congruent/go errors) was performed in the Esc (44) and metafor (45) packages for R (http://www.r-project.org). Details on the included measures and studies are provided in the Supplement.

Voxelwise meta-analyses of regional brain differences were conducted using the anisotropic effect size version of the seed-based *d* mapping (AES-SDM) software package (http://www.sdmproject.com). This method has been described in detail elsewhere (42,46,47) and is also described in the Supplement. In brief, AES-SDM allows for a combination of peak coordinates and t-maps to create whole-brain effect size and variance maps, which are then used in voxelwise random-effects meta-analyses (42,46,47). The SDM method has been empirically validated by comparing its results with a mega-analysis (47). While the control over the false positive rate is not formal but rather based on an empirical validation, this validation showed AES-SDM to have a good overlap with the mega-analysis, with adequate sensitivity and excellent control of false positives.

Assessment of statistical significance was performed using standard permutation testing, against the null hypothesis that blood oxygen level–dependent response/group differences are the same throughout the brain (47). We used the default voxel p value threshold of $p < .005$ (uncorrected), which was shown to be equivalent to $p < .05$ familywise error corrected (47). In addition, a cluster extent threshold of 80 voxels and a peak SDM z value threshold of >2 were used to reduce the false positive rate. We first examined the brain regions showing activation or deactivation in the errors and inhibitory control contrasts separately within each group using the within-group

maps (Supplemental Tables S2–S5). We then performed a separate analysis using the between-group maps to examine regions showing reliable differences between groups. Voxelwise meta-regressions were used to examine the effects of age, gender, symptom severity, comorbid diagnosed anxiety and mood disorders, medication status, and error rates on brain activation differences between groups as well as on activation within the OCD and HC groups (46). Mood disorders were combined into a single category for this analysis owing to the limited details available from the original studies on the specific disorder subtypes. The relationship between group differences in task performance (as SMD) and group differences in brain activation was also examined.

Jackknife sensitivity analyses were performed to assess robustness of between-group findings (Supplemental Tables S6–S9) (47). To illustrate the influence of each dataset on significant between-group clusters, cluster effect sizes for each dataset were extracted using the extract function in AES-SDM and plotted in forest plots (see Supplement). Sensitivity analyses examined whether between-group differences remained when including only the adult datasets (see Supplement) (3). There were too few datasets for a pediatric sensitivity analysis to be performed.

The Egger test was used to examine potential publication bias in between-group findings (48), corrected for multiple comparisons using the Benjamini–Hochberg method (49). Heterogeneity was assessed using the Q statistic (47,50).

RESULTS

Included Studies and Characteristics

Nine datasets were available to be included as whole-brain t-maps in the current meta-analysis (4,18,23,26,35,37,41,51,52). One study was originally included as a conference abstract (51) but has been published subsequently as a full journal article (24). Peak coordinate data from a whole-brain analysis were available for a 10th dataset for the between-group error contrast (40). Yücel *et al.* provided a new unpublished dataset that partially overlapped with data included in their published study (35) and for the error contrast included only participants who made at least five errors. Details of each dataset are given in Table 1. See the Supplement for details on excluded studies. Details on comorbidities are given in Supplemental Table S1.

Data from 239 patients with OCD (120 male; 79 medicated) and 229 HCs (129 male) were included for the error contrast. Patient and control datasets did not differ on sample size weighted mean age ($t_{1,18} = 0.06$, $p = .95$) or percentage of male and female subjects ($t_{1,18} = 0.68$, $p = .51$) (3). Seven datasets included adult patients and HCs ($n = 286$), while three datasets focused on adolescent/child samples ($n = 182$).

For the inhibitory control contrast, data from 245 patients with OCD (120 male; 91 medicated) and 239 HCs (135 male) were included. These included six adult datasets ($n = 263$) and three adolescent/child datasets ($n = 221$). Groups did not differ on age ($t_{1,16} = 0.06$, $p = .95$) or gender ($t_{1,16} = 1.04$, $p = .31$).

All studies reported event-related designs except for the study by Yücel *et al.* (35), which used a block design. However, for inclusion in the error contrast in the current meta-analysis, this dataset was reanalyzed as an event-related design with separate regressors for correct incongruent, erroneous incongruent, correct congruent, and erroneous congruent trials.

Task Performance

Patients showed impaired inhibitory control relative to HCs, as determined by RT measures (SMD = 0.20, $p = .03$, 95% confidence interval = 0.016, 0.393) (Supplemental Figure S2). Tests for heterogeneity ($Q_7 = 4.64$, $p = .70$, $I^2 = 0\%$) and publication bias ($z = 0.52$, $p = .60$) were nonsignificant.

Patients also made significantly more inhibitory control errors (SMD = 0.22, $p = .02$, 95% confidence interval = 0.039, 0.399), but groups did not differ on the number of congruent/go errors (SMD = 0.02, $p = .90$, 95% confidence interval = −0.21, 0.24) (Supplemental Figures S3 and S4). Tests for heterogeneity (incongruent: $Q_8 = 6$, $p = .65$, $I^2 = 0\%$; congruent: $Q_5 = 2.36$, $p = .80$, $I^2 = 0\%$) and publication bias (incongruent: $z = 0.38$, $p = .70$; congruent: $z = 0.71$, $p = .48$) were also nonsignificant.

Within-Group Brain Findings

A summary of within-group findings can be found in the Supplement and Figures 1 and 2.

Between-Group Brain Findings

OCD Versus HC Group Errors. Patients with OCD showed greater activation than HCs during error processing in the bilateral dACC/SMA and pre-SMA as well as the right aI/fO and anterior lateral prefrontal cortex (aLPFC). Patients with OCD showed decreased activation relative to HCs in the bilateral occipital lobe and right middle temporal lobe (Table 2, Figure 1A, and Supplemental Figures S5–S10).

OCD Versus HC Group Inhibitory Control. Patients with OCD showed greater activation than HCs during inhibitory control in the bilateral premotor cortex and right inferior temporal lobe/occipital lobe and superior parietal lobule. Patients with OCD showed decreased activation relative to HCs in the bilateral rACC/ventral anterior cingulate cortex (vACC) and thalamus/caudate and right supramarginal gyrus (SMG)/angular gyrus, aI/fO/superior temporal lobe, medial orbitofrontal cortex (mOFC), and occipital lobe/cerebellum (Table 2, Figure 1B, and Supplemental Figures S10–S22).

Adult Subgroup Analysis

See Supplement.

Meta-regressions

There were no significant effects of age, gender, symptom severity, comorbid diagnosed anxiety and mood disorders, medication status, and error-rates or group performance differences on brain activation during errors or inhibitory control except that comorbid specific phobia was associated with greater occipital lobe activation (left: Montreal Neurological Institute x, y, z = −16, −66, −24, $p < .001$, voxels = 681; right: Montreal Neurological Institute x, y, z = 18, −64, 4, $p < .001$, voxels = 88) within patients with OCD during errors.

Publication Bias and Heterogeneity Tests

The results of the Egger tests were nonsignificant ($p > .05$, corrected), suggesting that there was no publication bias. No regions from the between-group analysis showed significant heterogeneity in the voxelwise analysis.

Table 1. Demographic and Clinical Characteristics of 10 OCD fMRI Datasets

				Patients					Healthy Control Subjects		
Study	Task	Adults/ Pediatric	Contrasts	*N* (% Male)	Mean Age, Years (SD)	Mean (C)Y-BOCS (SD)	*N* Medication[a] (%)	Mean Performance (SD)	*N* (% Male)	Mean Age, Years (SD)	Mean Performance (SD)
Agam *et al.*, (41)[b]	Antisaccade	Adults	Errors > correct Correct > fixation	19 (42)	33 (10)	23 (5)	6 (32)	Antisaccade errors: 14% Antisaccade RT: 267 ms	15 (60)	35 (12)	Antisaccade errors: 12% Antisaccade RT: 283 ms
de Wit *et al.*, (26)	Stop	Adults	Failed stop > successful stop Successful stop > go	41 (51)	38.6 (9.8)	21.9 (6.1)	0 (0)	Stop errors: 45% (4) Go errors: 1% (1) SSRT: 204.9 ms (45)	37 (57)	39.7 (11.6)	Stop errors: 44% (4) Go errors: 1% (1) SSRT: 184.2 ms (43.2)
Fitzgerald *et al.*, (24,51)											
Errors	MSIT	Pediatric	Incongruent errors > incongruent correct	51 (47)	14.2 (2.8)	17.8 (7.4)	23 (45)	Incongruent errors: 13% (7) Congruent errors: 1% (2) Conflict RT: 324.33 ms (120.12)	51 (55)	14.1 (3.2)	Incongruent errors: 12% (7) Congruent errors: 2% (2) Conflict RT: 322.78 ms (111.17)
Inhibitory	MSIT	Pediatric	Incongruent correct > congruent correct	69 (45)	13.9 (2.8)	18.6 (7.7)	34 (49)	Incongruent errors: 11% (7) Congruent errors: 1% (2) Conflict RT: 325.50 ms (118.08)	72 (54)	14 (3.5)	Incongruent errors: 9% (7) Congruent errors: 1% (2) Conflict RT: 306.63 ms (93.16)
Fitzgerald *et al.*, (18)	Flanker	Adults	Errors > correct Incongruent correct > congruent correct	8 (75)	27.4 (8.5)	18 (3.9)	5 (63)	Incongruent errors: 10% (11%) Congruent errors: 7% (9) Conflict RT: 27.78 ms (14.95)	7 (86)	30 (8.6)	Incongruent errors: 3% (3) Congruent errors: 2% (2) Conflict RT: 25.85 ms (12.72)
Grutzmann *et al.*, (40)[c]	Flanker	Adults	Incongruent errors > all correct	20 (55)	32.3 (8.6)	19.8 (5.6)	4 (20)	All errors: 15% (10)	22 (50)	30.8 (8.1)	All errors: 20% (10)
Hough *et al.*, (52)	Go/No-go	Adults	No-go > go No-go errors > fixation	17 (47)	36.1 (10.4)	27 (6.7)	11 (65)	No-go errors: 27% (18)	22 (41)	46.77 (16.77)	No-go errors: 21% (15)
Huyser *et al.*, (23)	Flanker	Pediatric	Errors > correct Incongruent correct > congruent correct	25 (36)	13.95 (2.52)	24.92 (5.08)	0 (0)	Incongruent errors: 21% (12.31) Congruent errors: 8% (6) Conflict RT: 57.85 ms (22.47)	25 (36)	13.71 (2.85)	Incongruent errors: 25% (17) Congruent errors: 8% (10) Conflict RT: 54.51 ms (14.19)
Rubia *et al.*, (37)	Stop	Pediatric	Failed stop > go Successful stop > go	10 (100)	14.3 (1.7)	11	8 (80)	Stop errors: 52% (11) SSRT: 283 ms (193)	20 (100)	14.5 (1.1)	Stop errors: 51% (7) SSRT: 256 ms (165)
Stern *et al.*, (4)	Flanker	Adults	Errors > correct Incongruent correct > congruent correct	39 (43)	27.73 (8.68)	25.27 (3.84)	19 (49)	Incongruent errors: 26% (13) Congruent errors: 11% (11) Conflict RT: 38.66 ms (19.29)	20 (50)	25.5 (7.7)	Incongruent errors: 26% (11) Congruent errors: 13% (8) Conflict RT: 31.25 ms (16.51)

Table 1. Continued

Study	Task	Adults/ Pediatric	Contrasts	Patients					Healthy Control Subjects		
				N (% Male)	Mean Age, Years (SD)	Mean (C)Y-BOCS (SD)	*N* Medication[a] (%)	Mean Performance (SD)	*N* (% Male)	Mean Age, Years (SD)	Mean Performance (SD)
Yücel *et al.*, (35)											
Errors	MSIT	Adults	Errors > correct	9 (67)	35.22 (12.08)	17.44 (5.50)	3 (33)	Incongruent errors: 12% (7) Congruent errors: 3% (3) Conflict RT: 407.91 ms (100.90)	10 (60)	34.2 (8.83)	Incongruent errors: 10% (6) Congruent errors: 1% (1) Conflict RT: 384.83 ms (90.67)
Inhibitory	MSIT	Adults	Incongruent > congruent	17 (59)	33.65 (10.59)	17.35 (5.12)	8 (47)	Incongruent errors: 8% (8) Congruent errors: 2% (6) Conflict RT: 359.27 ms (102.03)	21 (57)	32.95 (8.73)	Incongruent errors: 6% (6) Congruent errors: 1% (8) Conflict RT: 342.12 ms (89.88)

(C)Y-BOCS, (Children's) Yale–Brown Obsessive Compulsive Scale; fMRI, functional magnetic resonance imaging; MSIT, Multisource Interference Task; OCD, obsessive-compulsive disorder; RT, reaction time; SSRT, stop signal reaction time.

[a]Number receiving antidepressant medication at time of scan.

[b]Performance and Y-BOCS data were available only for a larger sample of $n = 21$ patients with OCD and $n = 20$ healthy control subjects, some of whom were excluded from the final analysis.

[c]Performance data were available only for a subset of subjects ($n = 16$ patients with OCD and $n = 16$ healthy control subjects) who completed both the fMRI and electroencephalographic tasks.

DISCUSSION

Error processing and inhibitory control enable adaptive behavioral regulation and are hypothesized to be abnormal in OCD (3,53). In this meta-analysis, patients with OCD showed impaired task performance relative to HCs during tasks of inhibitory control. In addition, patients showed hyperactivation relative to HCs during error processing in cingulo-opercular regions, including the dACC/SMA, pre-SMA, and right aI/fO, as well as in the right aLPFC. In contrast, patients primarily showed hypoactivation relative to HCs both within the cingulo-opercular network (in the rACC/vACC and right aI/fO) and outside this network in the caudate, thalamus, SMG, mOFC, and cerebellum during inhibitory control.

Some smaller studies have reported cingulo-opercular hyperactivation in patients with OCD during error processing (4,18–24). We confirm here in a meta-analytic sample that patients with OCD showed increased activation in key dACC, SMA, pre-SMA, and aI/fO cingulo-opercular regions relative to HCs during error processing. Such findings are in line with previously reported robust differences in error-related negativity in OCD (16,17) as well as with theoretical accounts proposing important roles for error-related hyperactivation in driving OCD symptoms (11,16,39).

Outside of cingulo-opercular regions, we also found that a cluster in the aLPFC was more activated in patients with OCD relative to HCs. To investigate this unexpected cluster, we extracted the SDM *z* values for the cluster peak from the within-group error contrast maps, finding that while HCs deactivated the aLPFC in response to errors (SDM $z = -2.33$), patients with OCD had a positive SDM *z* value (SDM $z = 1.68$), suggesting relatively greater activation during errors compared with during correct trials. While not typically emphasized in OCD, previous research has found altered activity in anterior prefrontal regions during resting-state (54), decision-making (55), and symptom provocation (56) studies. Moreover, treatment with cognitive behavioral therapy (57), antidepressants (58), and repetitive transcranial magnetic stimulation (59) modulates aLPFC cortex activity in OCD, and targeting this region with neurofeedback training decreases OCD symptoms (60,61). In patients with OCD, activation to errors might represent additional neural resources that are assigned to error processing outside of the cingulo-opercular network owing to compensatory efforts at engaging corrective behavioral adjustments.

In addition to finding cingulo-opercular hyperactivation during errors relative to HCs, we found cingulo-opercular hypoactivation in patients with OCD during inhibitory control within the rACC/vACC and right aI/fO. Hypoactivation was also observed in patients during inhibitory control within the thalamus, caudate, SMG, mOFC, and cerebellum, while hyperactivation was found in the bilateral premotor cortex and right inferior temporal lobe/occipital lobe and superior parietal lobule. Hypoactivation within the rACC/vACC and caudate and hyperactivation in the premotor cortex replicate our previous meta-analyses in OCD (3,5). Novel findings may result from the inclusion of t-maps in the current analysis (47).

It is interesting to note that the rACC/vACC cluster overlaps with an area of deactivation in the OCD group during inhibitory control, indicating that group differences in this region are

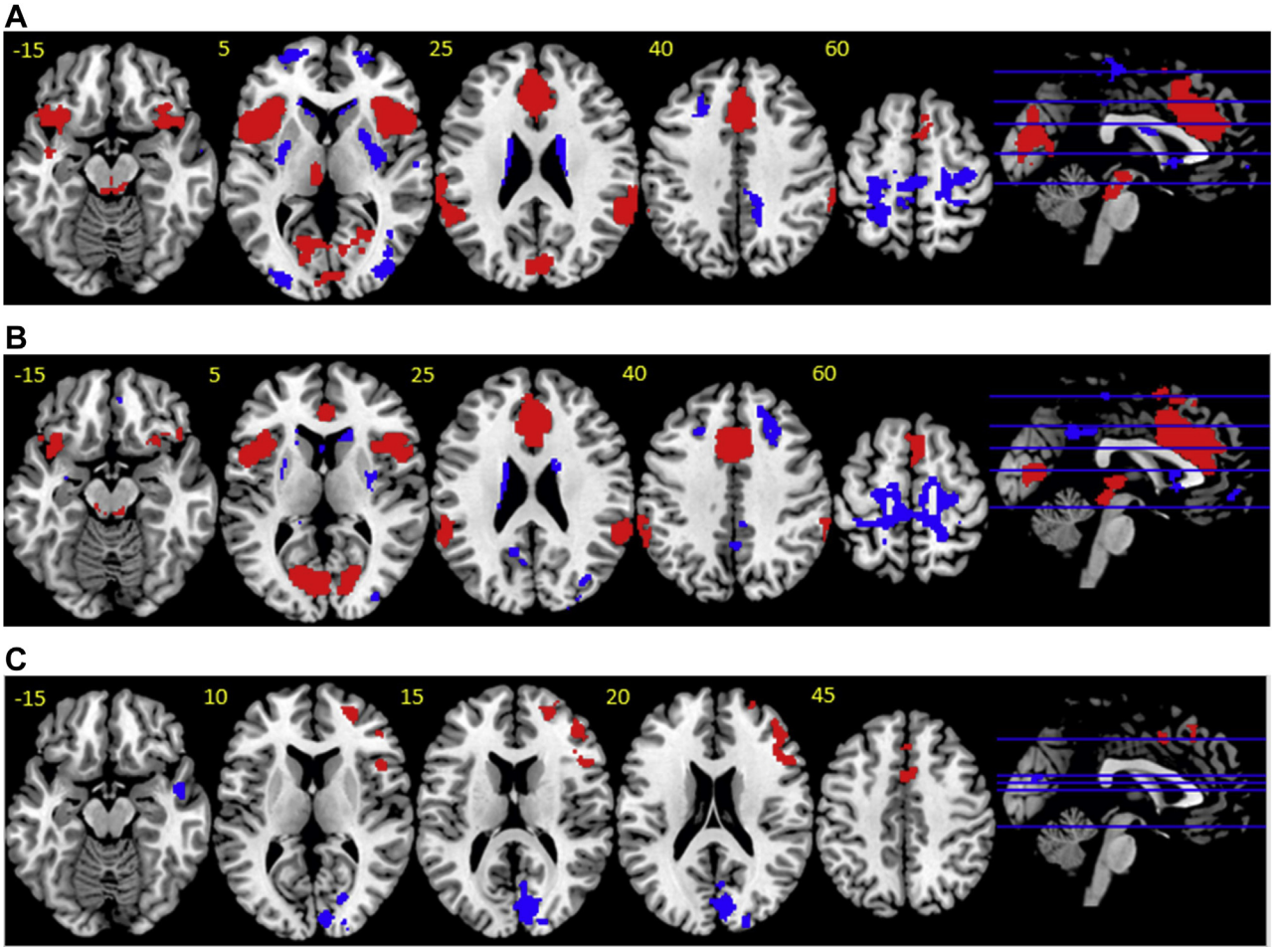

Figure 1. Findings from a meta-analysis of differences in brain activation during error processing in patients with obsessive-compulsive disorder (OCD) and healthy control subjects (HCs). **(A)** Error processing in HCs. Red indicates regions showing activation. Blue indicates regions showing deactivation. **(B)** Error processing in patients with OCD. Red indicates regions showing activation. Blue indicates regions showing deactivation. **(C)** Group differences during error processing. Red indicates regions where OCD > HC. Blue indicates regions where HC > OCD. Thresholded at $p < .005$, seed-based d mapping z value >2, >80 voxels.

driven by greater deactivation in patients with OCD, as reported elsewhere (29,35). Importantly, this shows that the previous findings of reduced rACC/vACC deactivation in patients with OCD during tasks of hot executive functions, such as emotional Stroop, emotion regulation, and decision-making tasks (62–64), do not extend to tasks of cool executive functions, such as those measuring inhibitory control. Nonetheless, the current findings are consistent with the notion that patients with OCD show perturbations in the pattern of rACC activations/deactivations.

During inhibitory control, patients with OCD also showed bilateral dorsal premotor cortex hyperactivation relative to HCs. Findings of decreased right aI/fO, but increased premotor cortex activation, in patients with OCD during inhibitory control are in line with a previous report using a stop task (included in the meta-analysis), which reported that premotor cortex hyperactivation was shared with unaffected siblings and predicted better task performance (26). Similar findings were also reported during an *n*-back task in the same sample, where the premotor cortex was also more activated in unaffected siblings than in patients (65). Together, this evidence suggests that increased dorsal premotor cortex activation may be compensatory in OCD and also may be protective in unaffected siblings (26,65).

Overall, activation abnormalities within cingulo-opercular and orbito-striato-thalamic regions are consistent with previous findings of alterations in these regions at rest (54,66,67), in gray matter structure (3,5,68–70), during symptom provocation (64,71,72), and across multiple cognitive and decision-making tasks in OCD (3–5,73,74). Moreover, many resting-state, structural, and functional abnormalities within these regions are shared with unaffected relatives of patients with OCD (26,65,66,69,72,75,76) and are OCD specific relative to disorders such as attention-deficit/hyperactivity disorder, autism spectrum disorder, and anxiety disorders (3,42,55,73,74,77). The current findings provide further evidence of cross-modal abnormalities in cingulo-opercular and orbito-striato-thalamic brain networks in OCD (3,5), which may be endophenotypes for the disorder (69,78).

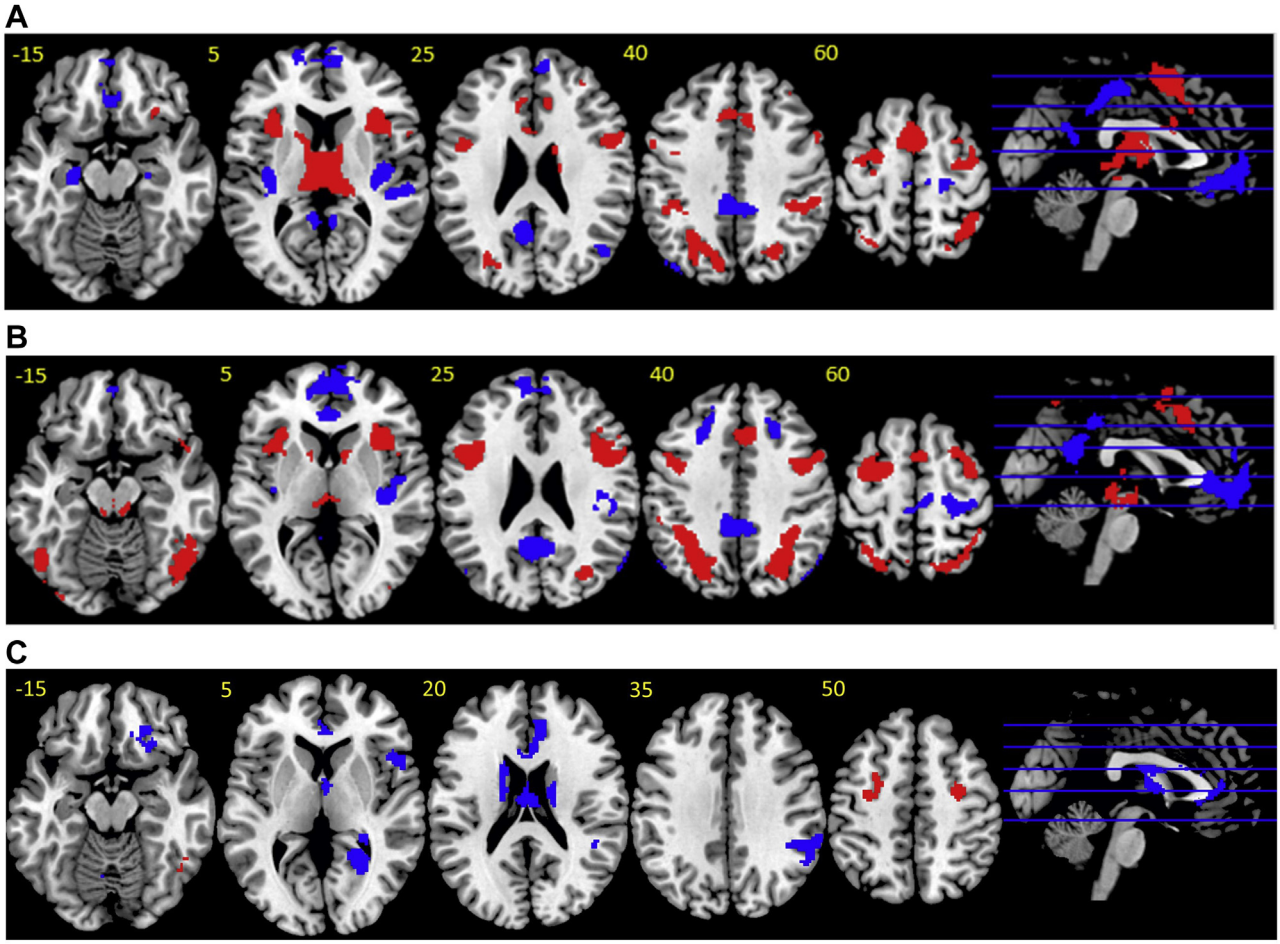

Figure 2. Findings from a meta-analysis of differences in brain activation during inhibitory control in patients with obsessive-compulsive disorder (OCD) and healthy control subjects (HCs). **(A)** Inhibitory control in HCs. Red indicates regions showing activation. Blue indicates regions showing deactivation. **(B)** Inhibitory control in patients with OCD. Red indicates regions showing activation. Blue indicates regions showing deactivation. **(C)** Group differences during error processing. Red indicates regions where OCD > HC. Blue indicates regions where HC > OCD. Thresholded at $p < .005$, seed-based d mapping z value >2, >80 voxels.

The current results are also interesting when considering that existing neurosurgical treatments for severe refractory OCD target cingulo-opercular and orbito-striato-thalamic networks (79–81). For instance, dorsal anterior cingulotomy involves making small stereotactic lesions to a region of the pMFC similar to the one found to be hyperactive to errors in the current meta-analysis, and treatment response following this surgery is predicted by pMFC gray matter volume and pMFC-striatal structural connectivity (80). In subcortical regions, anterior capsulotomy (stereotactic lesioning of the white matter between the caudate and putamen, targeting thalamocortical projections) normalizes heightened resting-state pMFC-striatal connectivity (81), while deep brain stimulation of the ventral striatum or subthalamic nucleus normalizes heightened rACC-striatal connectivity and pMFC, rACC, mOFC, and striatum hyperactivation at rest (54,82,83) while also normalizing hypoactivation in the right AI/fO and striatum during inhibitory control (79). The current meta-analytic findings provide further support for these network regions as potential targets for surgical treatments in the disorder. However, findings of cingulo-opercular hyperactivation during error processing but cingulo-opercular and orbito-striato-thalamic hypoactivation during inhibitory control demonstrate that future developments of such treatments must be guided by theoretical accounts that recognize the context specificity of neurofunctional abnormalities in OCD.

Historically, heightened error processing in OCD has been interpreted as generating context-inappropriate feelings that "something is wrong," which trigger hypercorrective OCD behaviors (39), although this account does not explain the hypoactivation observed in the al/fO, caudate, thalamus, and SMG during inhibitory control. In healthy participants, error processing is hypothesized to be an adaptive process associated with subsequent changes in behavioral strategies and neural functioning that improve ongoing task performance (9,10,13,84), and the magnitude of cingulo-opercular activation during error processing has been found to predict the degree of post-error adjustment (14,85). These post-error adjustments include behavioral adjustments such as correcting the original incorrect response, recalibrating speed–accuracy trade-offs

Table 2. Meta-analysis Results for fMRI Studies of Error Processing and Inhibitory Control in Patients With OCD and HCs

Contrast	MNI x, y, z Coordinates	Peak SDM *z*	Peak SMD	Mean SMD	*p* Value	Number of Voxels	Brodmann Area(s)
Errors OCD > HC							
Right al/fO	44, 42, 18	2.80	0.27	0.22	.0005	302	45, 44
Right aLPFC	24, 50, 12	3.714	0.35	0.24	.000005	123	10, 46
Left and right pre-SMA, right premotor cortex	20, 12, 48	2.797	0.26	0.21	.0005	126	8
Left and right dACC/SMA	4, 10, 46	2.527	0.25	0.21	.001	111	32, 24, 6
Errors HC > OCD							
Left and right occipital lobe	10, −82, 16	−2.630	−0.25	−0.17	.00005	545	18, 17, 19
Right MTL	50, −4, −20	−2.224	−0.21	−0.17	.0005	97	21
Inhibitory Control OCD > HC							
Left premotor cortex	−26, 0, 60	2.50	0.23	0.16	.00005	283	6
Right premotor cortex	30, −6, 52	2.349	0.22	0.15	.00005	134	6
Right ITL/occipital lobe	48, −54, −10	2.237	0.21	0.15	.0001	102	37, 19, 20
Right SPL	28, −52, 56	2.096	0.19	0.14	.0005	100	7
Inhibitory Control HC > OCD							
Left and right thalamus, left caudate	−16, 6, 22	−3.68	−0.34	−0.27	.00005	437	
Left and right dACC/rACC/vACC	14, 42, 12	−3.789	−0.35	−0.27	.00005	410	32, 24, 11, 25
Right occipital lobe	26, −54, 2	−4.205	−0.4	−0.31	.000005	310	19, 17
Right SMG/angular gyrus	56, −44, 30	−3.483	−0.32	−0.25	.0001	347	40, 39
Left occipital lobe/cerebellum	−28, −46, −8	−2.813	−0.26	−0.24	.005	135	37, 18, 19
Right mOFC	20, 36, −18	−3.514	−0.33	−0.26	.0001	101	11
Right caudate	18, −12, 22	−3.399	−0.32	−0.27	.0005	90	
Right al/fO/STL	48, 18, 4	−3.131	−0.29	−0.25	.0005	88	45, 44, 38

al, anterior insula; aLPFC, anterior lateral prefrontal cortex; dACC, dorsal anterior cingulate cortex; fO, frontal operculum; HCs, healthy control subjects; ITL, inferior temporal lobe; IPL, inferior parietal lobe; mOFC, medial orbitofrontal cortex; MNI, Montreal Neurological Institute; MTL, middle temporal lobe; pre-SMA, pre-supplementary motor area; OCD, obsessive-compulsive disorder; rACC, rostral anterior cingulate cortex; SDM, seed-based *d* mapping; SMD, standardized mean difference (Hedges' *g*); SMA, supplementary motor area; SMG, supramarginal gyrus; SPL, superior parietal lobe; STL, superior temporal lobe; vACC, ventral anterior cingulate cortex.

(e.g., post-error slowing), and enhancing task-focused attention and interference resolution as well as neural adaptations including the upregulation of task-relevant brain activation on subsequent trials (9,14,85,86). However, patients with OCD typically show either no performance differences relative to control subjects or poorer performance and impaired post-error adjustments (41,87,88), perhaps suggesting that the mechanism linking cingulo-opercular activation during errors and subsequent corrective recruitment of inhibitory control brain networks may be inefficient in OCD or else suggesting that cingulo-opercular hyperactivation to errors during error processing is unable to correct preexisting deficits in inhibitory control–related brain activation in the disorder.

As with inhibitory control errors, OCD compulsions likely result, in part, from impaired top-down control over bottom-up stimulus-driven actions (3,6,8,89). We propose that impairments in implementing corrective inhibitory control following the detection of goal-incongruent behaviors is a key mechanism in OCD that leads to patients' becoming stuck in compulsive loops. While existing research in OCD has concentrated on inhibitory control tasks, the wider literature shows that cingulo-opercular regions respond strongly when participants detect or regulate behaviors resulting from urges (90), supporting a broader role outside of standard cognitive tasks. Moreover, error processing is aversive and anxiety provoking (91,92) and is potentially heightened and continuously reactivated in patients with OCD as compulsive behaviors persist. Detecting that performed actions do not align with beliefs and goals leads to the aversive state of cognitive dissonance, which others have proposed to drive or worsen some instances of obsessions (89,93) [but see (94) for an excellent critique] and found to be associated with cingulo-opercular activation (95,96). In other words, the unease caused by prolonged and heightened error processing during compulsions may motivate rationalizations of OCD behaviors (e.g., "I continue to check the stove; therefore, it must be important that the stove is checked and rechecked."). In addition, the resultant anxiety may further bias behavior toward bottom-up stimulus-generated responses (e.g., compulsions). An overview of our proposed model is given in Figure 3. To test aspects of this model, future studies should use paradigms specially designed to examine trial-to-trial modulations in task-related activation following error processing (14,97), with the hypothesis that cingulo-opercular activation to errors is less efficient in patients with OCD than in HCs at bringing about post-error adjustments in brain activation.

It is also important to note that the effect sizes for between-group differences in performance and brain activation were small, indicating substantial overlap between patients and HCs on these measures. Crucially, even large reliable differences between groups would not have necessarily indicated a causal mechanistic relationship. For instance, it is also plausible that observed neurocognitive abnormalities in OCD are secondary to the OCD-specific symptoms of the disorder, and it has been

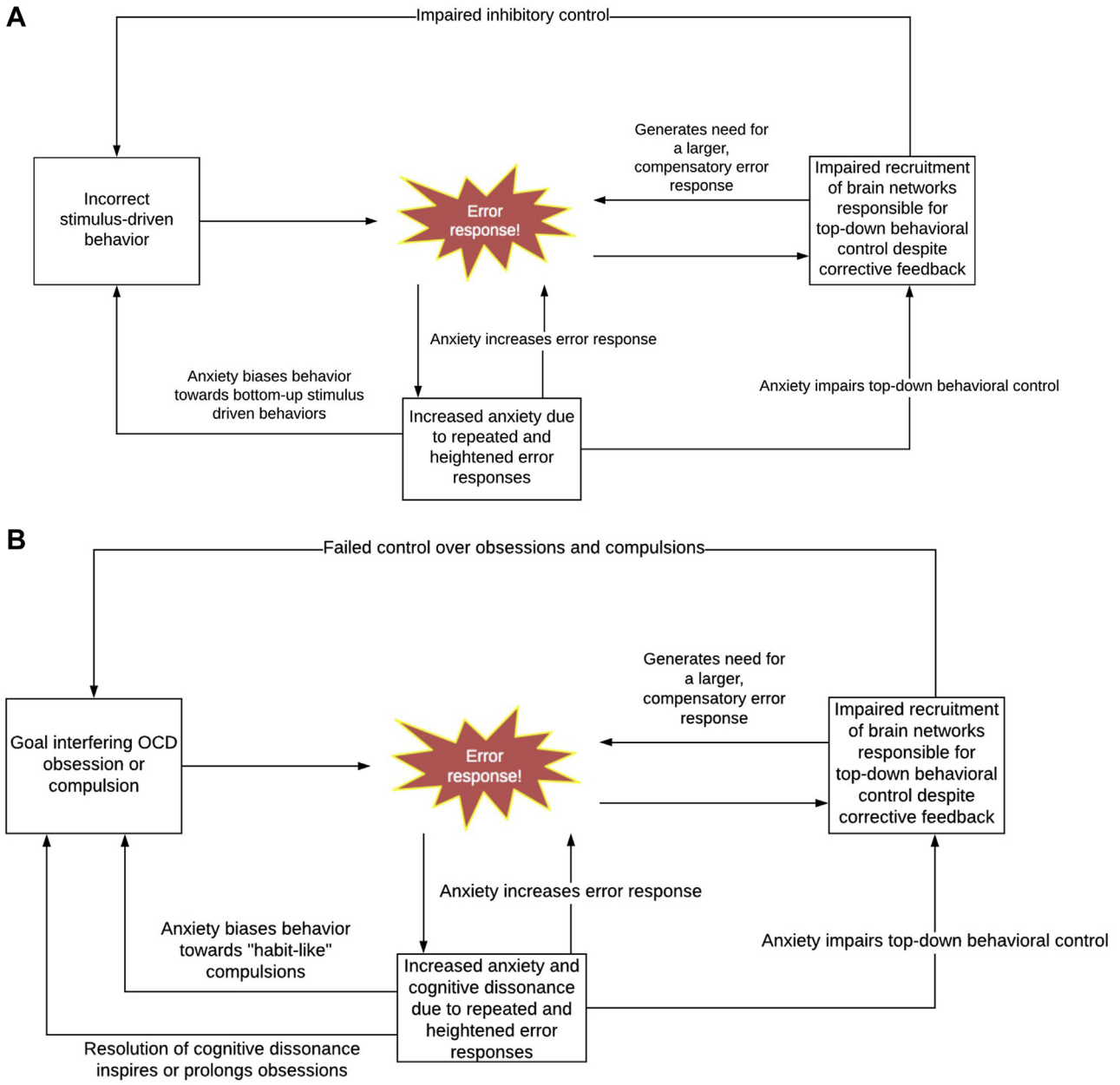

Figure 3. Error processing and inhibitory control in obsessive-compulsive disorder (OCD). **(A)** During errors on inhibitory control tasks, error responses in the cingulo-opercular network signal a need for behavioral correction. In patients with OCD, this error signal does not efficiently increase activation within underactive brain networks responsible for inhibitory control. Owing to continued underrecruitment of these brain networks, error processing signals are increased as a compensatory attempt at correction. Heightened and repeated error signaling increases anxiety in the disorder, which further interferes with top-down behavioral control, biases behavior toward bottom-up stimulus-driven responses (errors), and feeds back to further increase error signaling. **(B)** During obsessions and compulsions, error responses are generated to signal the need to stop goal-incongruent or goal-irrelevant behaviors. This error signal does not appropriately recruit activation in brain networks responsible for behavioral control in OCD. This means that patients with OCD continue to experience obsessive and compulsive symptoms, with these generating repeated error signals, and these signals are increased in the disorder as a compensatory attempt at generating behavioral control. Heightened, repeated, and aversive error signaling increases anxiety, which further interferes with top-down behavioral control in the disorder and biases behavior toward bottom-up stimulus-driven responses (compulsions). Anxiety caused by continued performance and poor perceived control over interfering OCD compulsions also further increases cingulo-opercular activation and creates a feeling of cognitive dissonance that is resolved through rationalization of compulsive behaviors (e.g., through reinforcement of obsessions).

proposed that obsessive or worrying thoughts in patients with OCD may occur at the expense of task engagement/attention, resulting in nonoptimal performance and altered brain activation during cognitive tasks (i.e., the overload model of neuropsychological impairment in OCD) (98). Alternatively, observed neurocognitive abnormalities may be driven by

transdiagnostic phenotypes that are closely associated with OCD such as heightened anxiety, which has also been associated with heightened error processing and impaired inhibitory control (17). Finally, heightened error processing and impaired inhibitory control may share genetic risk and co-occur with OCD without there being a direct causal relationship between these phenotypes. With a few exceptions (23,26), most fMRI studies on the topic have focused on simple case-control comparisons. Now that reliable differences between the OCD and HC groups have been determined, future work should use sophisticated imaging genetics and longitudinal and treatment designs to further elucidate whether heightened error processing and impaired inhibitory control do indeed have mechanistic roles in the etiology and treatment of OCD or whether they are instead secondary to OCD symptoms or otherwise linked in a noncausal way to the disorder.

Limitations of the meta-analysis include a reliance on meta-regressions to test for relationships between brain activation and age, gender, symptom severity, comorbid anxiety and mood disorders, medication status, and error rates. In particular, many patients were medicated with antidepressants, and this may have exacerbated between-group findings (24,99). A more sensitive approach would be to test for relationships between these variables using large samples and subject-level individual differences. In addition, we combined data from different inhibitory control tasks with varying levels of difficulty and error rates. Degree of error-related brain activation varies according to task error rates, and these rates varied widely in the current meta-analysis (100,101). Moreover, while there is substantial overlap in the neural underpinnings observed across different inhibitory control tasks (102), the specific cognitive demands and underlying neural bases of each task also vary between tasks (103). The aim here was to investigate the most consistent abnormalities in OCD regardless of task type. As the field grows, future meta-analyses will be better placed to test for task-specific effects. Finally, we combined data from both pediatric and adult samples, and although the primary between-group findings were also present in the adult sensitivity analysis, there are likely developmental changes in brain activation that we were unable to investigate here (24,97).

To summarize, in a large meta-analytic sample, patients with OCD relative to HCs showed impaired task performance as well as hyperactivation in the dACC/SMA, pre-SMA, right aI/fO, and right aLPFC during error processing and showed hypoactivation in the rACC/vACC, right aI/fO, striatum, thalamus, SMG, mOFC, and cerebellum during inhibitory control. These findings may support a model in which patients become stuck in compulsive loops because detected erroneous OCD behaviors remain uncorrected by hypoactive inhibitory control networks. However, more work is needed to further our understanding of how these performance and brain function abnormalities relate to OCD symptoms.

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