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Development of Posterior Medial Frontal Cortex Function in Pediatric Obsessive-Compulsive Disorder

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Objective: Abnormal engagement of the posterior medial frontal cortex (pMFC) occurs during performance monitoring in obsessive-compulsive disorder (OCD), including in pediatric patients. Yet, the development of pMFC function in OCD-affected youth remains poorly understood.

Method: A total of 69 patients with pediatric OCD and 72 healthy controls (HC), 8 to 19 years of age, were scanned during the Multisource Interference Task (MSIT). The effects of group, age, performance, and interactions on pMFC response to errors and interference were tested in the region of interest [ROI]) and whole-brain analyses. Secondary analyses considered bilateral anterior insula/frontal operculum (aI/fO), given the contribution of these regions with pMFC to a cingulo-opercular network (CON) for task control (e.g., error and interference processing).

Results: Error-related pMFC activity was greater for OCD patients than for HC, increased with age in OCD patients, but decreased with age in HC. Greater pMFC activation associated with better performance in HC but not OCD patients. In the patients, greater pMFC activation to errors was associated with lower OCD severity. Altered error-related activation and performance associations were also observed in the right aI/fO in OCD patients, whereas the left aI/fO response to interference was associated with lower OCD severity.

Conclusion: Atypical increase in error-related pMFC activation with age in pediatric OCD suggests altered development of pMFC function during the early course of illness. Greater pMFC activation with better performance in HC, and with age and lower symptom severity in OCD patients, suggests an adaptive function of heightened pMFC response to errors that could be further enhanced (e.g., via cognitive training) to improve outcomes in OCD from the early course of illness.

Key words: pediatric obsessive-compulsive disorder, performance monitoring, task control, cingulo-opercular network, development

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Abnormal brain response to performance monitoring in obsessive-compulsive disorder (OCD) is elicited by simple cognitive tasks not intended to provoke symptoms, suggesting a core process in the pathophysiology of illness.[1] Performance monitoring involves detection of errors and interference between competing response options to enable behavioral adjustments,[2] and abnormalities of this process could underlie the repetitive thoughts and behaviors of OCD.[1] OCD often emerges in childhood or adolescence,[3] a period in which neural networks for performance monitoring mature in healthy youth[4] and performance monitoring abnormalities can be observed in those affected by OCD.[5-7] Yet, despite important implications for early treatment, the development of performance monitoring dysfunction in OCD remains poorly understood.[1]

In healthy adults, performance monitoring engages the posterior medial frontal cortex (pMFC, encompassing the dorsal anterior cingulate and presupplementary motor area) and the bilateral anterior insula/frontal operculum (aI/fO).[8] These regions coactivate during cognitively demanding tasks and remain functionally connected at rest, defining a "cingulo-opercular network" (CON) for task control.[8] The CON is widely held to mediate the selection of salient information from internal and external inputs to guide ongoing behavior, including detection of errors and interference for performance monitoring.[8,9] In adults with OCD, several functional magnetic resonance imaging (fMRI) studies have shown pMFC hyperactivation (dorsal anterior cingulate [dACC] and/or presupplementary motor area [pre-SMA]) during performance monitoring,[10-15] and electrophysiologic research has consistently demonstrated increased error-related negativity, generated by the dACC (among other regions).[16] Hyperactivation of the aI/fO to errors also occurs in adult patients,[17] implicating broader CON function in OCD.

Neuroimaging studies of performance monitoring in pediatric OCD suggest abnormal pMFC engagement, but are inconsistent regarding the direction of the abnormality, with one study reporting increased activation[5] and another reporting the reverse in patients compared to healthy

youth.[18] Other studies report no group differences.[6,19] These inconsistencies may relate to small sample sizes (n = <25 per group), which increase variability and reduce experimental power.[20] In addition, both pediatric and adult OCD cohorts often include patients taking selective serotonin reuptake inhibitors, which have an impact on neural engagement during performance monitoring[21] and may alter neurofunctional maturation.[22]

Overall, this literature implicates atypical engagement of the CON, particularly the pMFC, during performance monitoring in OCD. However, no fMRI study has investigated whether the relation of age with CON response to performance monitoring differs between patients with pediatric OCD and healthy youth. Thus, the aim of this study was to test effects of both group and group-by-age interactions on activation of the pMFC (primary regions of interest [ROI]) and aI/fO (secondary ROIs) during performance monitoring in youth with OCD compared to matched controls. Group-by-performance interactions were assessed to test for differences in the relation of activation with behavioral output. In addition, we sought to clarify whether performance monitoring function related to symptom severity in young patients, as this has not been the case in adults.[10,11,13,17] Finally, we capitalized on our large sample of youth with OCD to explore the effects of medication status on activation.

METHOD

Participants

A total of 75 patients with pediatric OCD (13.8 ± 2.8 years) and 75 healthy controls (HC, 13.8 ± 3.4 years) were assessed by structured interview with the Kiddie–Schedule for Affective Disorders–Present and Lifetime Version[23] and, in patients, the Children's Yale–Brown Obsessive-Compulsive Scale (CY-BOCS).[24] Nine participants failed to provide useable data (Supplement 1, available online), yielding 69 patients and 72 HCs for interference analyses (i.e., correct resolution of response competition). For error analyses, at least 5 errors per subject were required,[25] leaving 51 patients and 51 HCs. OCD was the primary source of impairment; of the 69 patients, 49 had 1 to 3 fewer severe comorbid diagnoses, including anxiety (n = 27), tic (n = 18), and/or attentional (n = 9) disorders or subclinical depressive symptoms (n = 13) (Table S1, available online), consistent with previously described clinical samples.[26] Major depressive, autism spectrum, psychotic, or substance use disorders were excluded. HCs had no current or prior history of psychiatric illness and no first-degree relatives with OCD. Among patients, 34 were medicated, primarily with selective serotonin reuptake inhibitors (see Supplement 1, available online).

Task

Participants performed an event-related version of the Multisource Interference Task (MSIT)[5] (Figure S1, available online). They identified the unique number among 3 numbers, ("1," "2," and "3") by pressing a button with the first (index), second (middle), and third (ring) fingers, respectively. On incongruent trials (Inc; e.g., "331"), the unique number was positioned incongruently (i.e., "1" in the third position), flanked by distracting numbers ("33"). On congruent trials (Con; e.g., "100"), the unique number was positioned congruently ("1" in the first position), flanked by zeroes. To ensure task understanding and to minimize performance variability, participants were trained to achieve 70% to 90% accuracy on incongruent trials. During scanning, 300 trials (3,000 msec/each) were presented over 5 runs for a total of 15 minutes (120 Inc, 120 Con, 60 Fixation) in fixed order.

MRI Acquisition and Preprocessing

A 3.0 T GE Signa scanner (GE Healthcare, Waukesha, WI) was used to collect T2* reverse spiral images and a low-resolution axial T1 for coregistration.[27] A high-resolution T1-weighted SPGR was acquired for anatomic normalization.[27] Functional data were preprocessed in SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre, London, UK). Raw data were slice-time corrected and realigned to the 10th image acquired. Realignment parameters were retained for inclusion as regressors in first-level analyses and to calculate mean framewise displacement, a summary of subject motion.[28] Once coregistered, the high-resolution SPGR was segmented using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm), normalized using high dimensional DARTEL normalization,[29] and used to warp functional images into common stereotactic space (Montreal Neurological Institute [MNI]). Normalized functional data were smoothed with a 5-mm Gaussian kernel.

Analysis

Behavioral. Linear regression was used to test effects of age, group (OCD, HC), and age-by-group interactions on performance. Separate models were run for incongruent and congruent response times (RT) and accuracy.

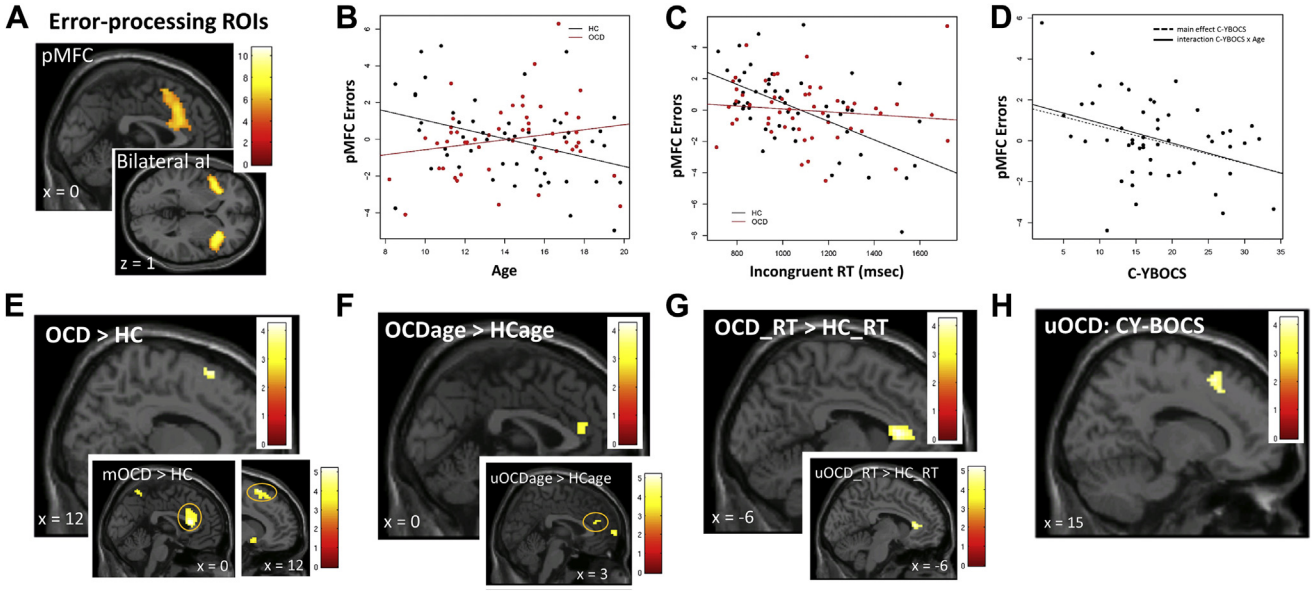
Functional MRI. Functional data were analyzed using a standard random effects analysis[30] in SPM8. At the first level, incongruent correct, congruent correct, incongruent incorrect, and congruent incorrect trials were modeled against fixation trials as implicit baseline; omission errors were regressed from the model. Six realignment parameters and their first derivatives were regressed to remove motion effects. Contrast maps were constructed of incongruent

versus congruent correct trials for interference, and incorrect versus correct incongruent trials for errors. Single-subject contrasts were entered into second-order random effects analyses[31] to test the main effects of errors and interference across subjects at a height threshold of $p < .05$, corrected for familywise error (FWE) rates (see Table S2, available online, for main effects).

Region of interest (ROI) analyses included pMFC as primary ROI, and anterior insula/frontal operculum (aI/fO) ROIs as secondary. Primary pMFC ROIs were defined by the conjunction of main effects for each contrast (errors, interference across subjects) with a meta-analysis–based medial frontal cortex ROI (Neurosynth MFC, Supplement 1, available online)[32]; secondary aI/fO ROIs were defined by contrast-specific main effects (Figures 1A, errors; 2A, interference). Secondary ROIs included pMFC subregions, preSMA and dACC, defined by conjunction of primary pMFC ROIs with Neurosynth posterior and middle MFC zones[32] (Supplement 1, Figure S2, available online). Parameter estimates were extracted from ROIs for inclusion in stepwise linear regressions, using backward elimination, to select predictor variables (group, age, performance, and interactions)—an unbiased method, as voxels of interest were orthogonal to predictors.[33] Performance variables were incongruent accuracy and response times for error analyses, and overall accuracy and response times (across conditions) for interference. Framewise displacement (FD) was regressed to control for motion effects.[28] Continuous variables were mean centered. Separate analyses tested the effects of present symptom severity, as measured by the Child Yale–Brown Obsessive-Compulsive Scale (C-YBOCS), in patients. For the primary pMFC ROI, findings were considered significant at $p < .05$; for the 4 secondary ROIS (bilateral aI/fO, dACC, preSMA), a more stringent significance threshold was used ($p < .013$) to correct for multiple comparisons. Finally, given possible medication effects,[21,22] exploratory analyses considered unmedicated OCD (uOCD), medicated OCD (mOCD), and the interactions of these patient subgroups with age and performance, relative to HC. All analyses were carried out in R, version 3.2.5. Partial residual plots were constructed to show the relationship between a given predictor and response variable, given that other predictor variables were also in the model.[34]

In addition, whole-brain analyses were conducted in SPM8, including the same regressors as ROI analyses.

FIGURE 1 Error Processing in Pediatric Obsessive-Compulsive Disorder (OCD)



Note: Error processing activated posterior medial frontal cortex (pMFC) and bilateral anterior insula (aI/fO). (A) Region of interest (ROI) analyses showed greater pMFC activation associated with younger age in healthy controls (HC), but older age in OCD patients (B); faster response time (RT) in HC, but not OCD patients (C); and lower OCD severity (C-YBOCS, Child Yale–Brown Obsessive-Compulsive Scale) in patients (D). Whole-brain analyses showed greater pMFC activation in OCD patients than in HC (E) and, as with ROI analyses, altered associations of pMFC activation with age (F) and RT (G) in OCD patients compared to HC. Exploratory analyses suggested that the effect of group on pMFC activation was driven by medicated patients (E inset, mOCD > HC), whereas unmedicated patients (uOCD) drove atypical age (F inset, uOCDage > HCage), altered RT (G inset, uOCD_RT > HC_RT), and inverse OCD severity associations (H) with pMFC activation. Color bars show t scores, reflecting the relative strength of brain activation. Montreal Neurologic Institute coordinates (x, y, z) are shown. aI/fO = anterior insula/frontal operculum; C-YBOCS = Child Yale–Brown Obsessive-compulsive Scale; FWE = familywise error; MFC = medial frontal cortex; mOCD = medicated obsessive-compulsive disorder; uOCD = unmedicated obsessive-compulsive disorder. Please note color figures are available online.

Contrasts were displayed at a peak threshold of $p < .001$ (uncorrected), and clusters were considered significant at $p < .05$, corrected for FWE across whole brain and within the pMFC and right and left aI/fO ROIs.

RESULTS

Subjects

There were no significant differences between groups on demographics, performance or in-scanner motion (FD) (Table 1). Comparison of uOCD and mOCD (Table S3, available online) showed a trend towards higher present disease severity in uOCD (p =.07); nominally but not significantly greater lifetime severity in mOCD; and, greater reduction from lifetime to present severity in mOCD (p =.007).

Behavioral Performance

There were no differences between OCD patients and healthy youth in performance (Table 1). Older age associated with faster RT on both trial types (p values $< .001$), and with higher accuracy, at trend-level, on congruent (p =.07) but not incongruent ($p = .23$) trials. There were no differences in the effect of age on RT or accuracy between groups (p values >.16).

Imaging Analyses

Error-processing. Primary pMFC ROI Analysis. ROI-based linear regression analyses showed that error-related activation of the pMFC was greater for OCD patients relative to HC ($\beta = 0.98$, $p = .02$) and decreased with age in HC, while increasing with age in OCD patients ($\beta = 0.39$, p =.03) (Figure 1B); and increased with faster RT in HC but not OCD patients ($\beta = 0.005$, $p = .03$) (Figure 1C; Table 2). Exploratory analyses showed that greater pMFC activation in patients was driven by mOCD (Table S4, available online). By contrast, altered associations of pMFC activation with age and RT were present in uOCD, but not mOCD, relative to HC (Figure S3A, B; Table S4, available online).

Secondary Left and Right aI/fO ROI Analyses. As with pMFC, the typical increase in right aI/fO activation with faster RT was attenuated in OCD patients relative to HC ($\beta = 0.006$, $p = .01$) (Table 2). Exploratory analyses showed this attenuation in uOCD but not mOCD patients relative to HC; in addition, right aI/fO activation was greater in mOCD but not uOCD patients compared to HC (Table S4, available online).

Secondary dACC and preSMA ROI Analyses. Analysis of pMFC subregions suggested several trend-level effects that did not reach significance after correction (Table S5, available online). Exploratory analyses showed greater activation in dACC ($p = .002$) and in pre-SMA at the trend level ($p = .029$) in mOCD, but not uOCD patients relative to HC, but suggested that altered age-activation (trend: p = .031) and RT-activation ($p = .011$) associations in the pMFC may have been driven by dACC voxels in uOCD (Table S6, available online).

TABLE 1 Participant Characteristics

	Error Analysis			Interference Analysis		
	OCD Patients (N = 51)	**HC (N = 51)**	**Test Statistic (*p*)**	**OCD Patients (N = 69)**	**HC (N = 72)**	**Test Statistic (*p*)**
Age	14.2 ± 2.8	14.1 ± 3.2	t(100) = −0.14 (.88)	13.9 ± 2.8	14.0 ± 3.5	t(139) = 0.11 (.91)
Sex	28 F (55%)	23 F (45%)	χ^2(102) = 0.63 (.43)	39 F (56%)	33 F (46%)	χ^2(141) = 0.34 (.56)
SES[a]	2.2 ± 0.45	2.3 ± 0.53	t(97) = 0.66 (.51)	2.2 ± .48	2.26 ± 0.53	t(136) = 0.51 (.61)
CY-BOCS, Present	17.8 ± 7.4	NA	NA	18.6 ± 7.7	NA	NA
CY-BOCS, Lifetime	27.1 ± 6.6	NA	NA	27.9 ± 6.5	NA	NA
CY-BOCS, Change	9.3 ± 7.9	NA	NA	9.3 ± 7.9	NA	NA
Illness Duration	6.4 ± 4.3	NA	NA	6.5 ± 4.0	NA	NA
AAO	7.7 ± 3.3	NA	NA	7.5 ± 3.0	NA	NA
Inc RT	1094 ± 249	1060 ± 238	t(100) = −0.71 (.48)	1114 ± 258	1071 ± 220	t(139) = −1.07 (.29)
Con RT	770 ± 176	738 ± 171	t(100) = −0.95 (.35)	789 ± 192	759 ± 162	t(139) = −0.99 (.32)
Inc Acc	0.87 ± 0.07	0.88 ± 0.07	t(100) = 1.15 (.25)	0.89 ± 0.07	0.91 ± 0.07	t(139) = 1.31 (.19)
Con Acc	0.99 ± 0.02	0.98 ± 0.02	t(100) = −0.67 (.50)	0.99 ± 0.02	0.99 ± 0.02	t(139) = −0.76 (.49)
Motion	0.20 ± 0.08	0.19 ± 0.13	t(100) = −0.11 (.91)	0.21 ± 0.11	0.19 ± 0.13	t(139) = −0.96 (.34)

Note: AAO = age of onset; Acc = accuracy; Con = congruent; CY-BOCS = Child Yale–Brown Obsessive-Compulsive Scale; F = female; HC = healthy control; Inc = incongruent, NA = not applicable; OCD = obsessive compulsive disorder; RT = response time; SES = socioeconomic status. Age, AAO, illness duration in years; RT in milliseconds. Motion denotes mean framewise displacement.[28]

[a]*SES missing for 2 HC and 1 OCD patient.*

TABLE 2 Cingulo-Opercular Network Function in Pediatric Obsessive-Compulsive Disorder (OCD) Patients Compared to Healthy Controls

	pMFC		Left aI/fO		Right aI/fO	
Errors	***B***	***p***	***B***	***p***	***B***	***p***
Intercept	**1.10 ± 0.28**	**<.001**	1.48 ± 0.25	<.001	1.42 ± 0.28	<.001
Group	**0.98 ± 0.41**	**.018**	0.50 ± 0.36	.175	0.58 ± 0.39	.139
Age	−0.25 ± 0.13	.063	---	---	−0.12 ± 0.13	.342
Inc RT	**−0.006 ± 0.002**	**.001**	---	---	−0.004 ± 0.002	.025
Inc Acc	**10.06 ± 3.07**	**.002**	1.70 ± 3.91	.665	7.1 ± 2.97	.019
Group × Age	**0.39 ± 0.18**	**.029**	---	---	0.28 ± 0.17	.098
Group × Inc RT	**0.005 ± 0.002**	**.026**	---	---	0.006 ± 0.002	.010*
Group × Inc Acc	---	---	8.13 ± 5.41	.136	---	---
Motion	---	---	−3.38 ± 1.60	.037	---	---
Adjusted R^2	0.17		0.08		0.08	
Model ANOVA	$F_{6,95} = 4.4$ ($p < .001$)		$F_{4,97} = 3.2$ ($p = .016$)		$F_{6,95} = 2.5$ ($p = .03$)	
Interference						
Intercept	**0.60 ± 0.07**	**<.001**	0.45 ± 0.08	<.001	0.52 ± 0.08	<.001
Group	−0.02 ± 0.10	.847	−0.08 ± 0.12	.492	−0.10 ± 0.12	.413
Age	---	---	---	---	---	---
Overall RT	−0.001 ± 0.0004	.055	−0.001 ± 0.0004	.053	−0.001 ± 0.0003	.001*
Overall Acc	1.41 ± 1.76	.425	4.93 ± 2.04	.017*	1.77 ± 2.06	.393
Group × Age	---	---	---	---	---	---
Group × Overall RT	**0.001 ± 0.0005**	**.028**	0.001 ± 0.0006	.100	---	---
Group × Overall Acc	**−5.17 ± 2.51**	**.042**	−7.83 ± 2.9	.008*	−4.90 ± 2.95	.099
Motion	---	---	---	---	---	---
Adjusted R^2	0.03		0.05		0.08	
Model ANOVA*	$F_{5,135} = 2.0$ ($p = .086$)		$F_{5,135} = 2.4$ ($p = .039$)		$F_{4,136} = 4.2$ ($p = .003$)	

Note: *Dashed lines represent predictor variables eliminated during backwards stepwise regression. Motion refers to framewise displacement.*[28] *Acc = accuracy; aI/fO = anterior insula/frontal operculum; ANOVA = analysis of variance; HC = healthy controls; Inc = incongruent; pMFC = posterior medial frontal cortex; RT = response time.*
Significance levels were p < .05 *for pMFC (primary region of interest, boldface type) and* p < .013 *for secondary regions of interest (*).*

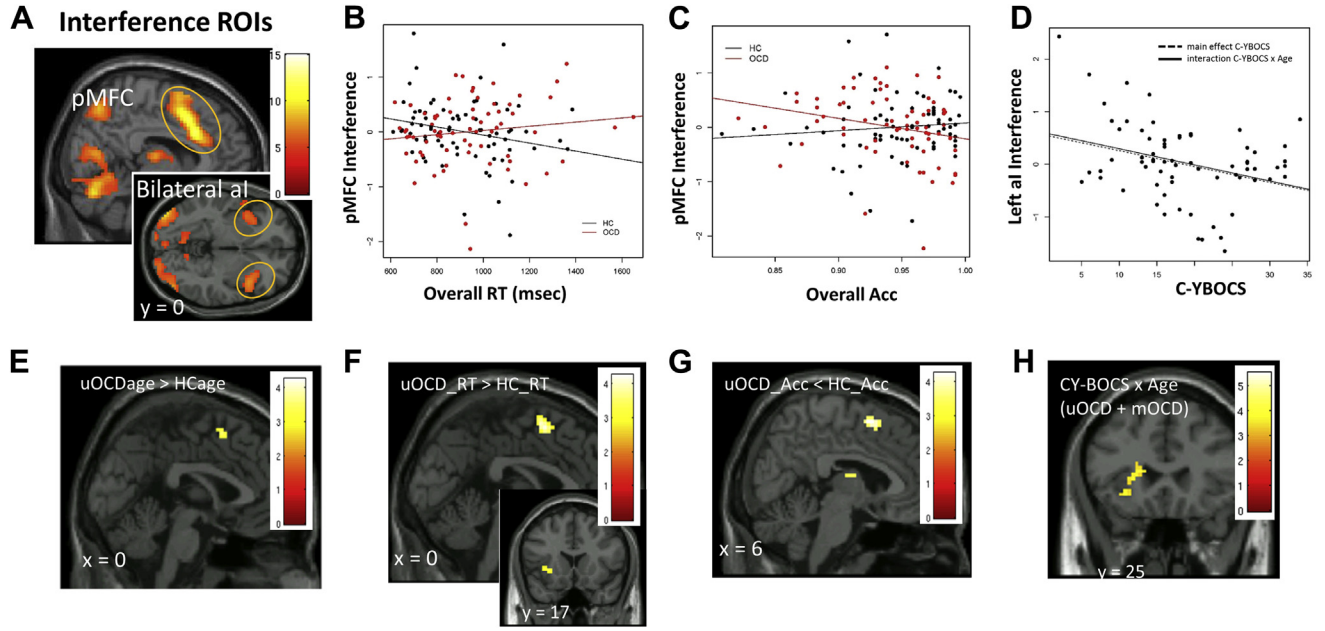
Whole-Brain Analyses. Consistent with the ROI analysis, OCD patients compared to HC showed greater error-related activation in the pMFC at the preSMA-dACC border ("preSMA-dACC") (Figure 1E); atypical increase in dACC activation with age (Figure 1F); and reversal of the typical relation of faster RT with activation in a cluster encompassing the dACC, rostral ACC, and left caudate (Figure 1G; Table S7, available online). There were no areas in which HC showed greater activation than OCD patients. Exploratory analyses comparing uOCD and mOCD patients with HC (Figure 1E–G insets; Table S8, available online) showed greater activation in the dACC and, at trend level, in the preSMA in mOCD, and atypical association of age and RT with dACC activation in uOCD.

Interference Processing. Primary pMFC ROI Analysis. There were no group differences in pMFC response to interference, but there was a reversal of the typical relation of greater interference-related pMFC activation with faster RT and greater accuracy in OCD patients relative to HC ($\beta = 0.001 \pm 0.001$, $p = .03$; $\beta = -5.17 \pm 2.51$, $p = .04$) (Figure 2B, C; Table 2). Exploratory analyses suggested that uOCD predominantly contributed to this effect (Table S4, available online).

Secondary Left and Right aI/fO ROI Analyses. The typical relation of greater left aI/fO activation with greater accuracy was attenuated in OCD ($\beta = -7.83 \pm 2.9$, $p = .008$) (Table 2). Exploratory analyses suggested that this effect may have been driven by uOCD, albeit at a level of significance that fell just below the threshold for multiple comparison correction ($p = .014$) (Table S4, available online).

Secondary dACC and preSMA ROI Analyses. Analysis of pMFC subregions suggested several trend-level effects across both dACC and pre-SMA that did not reach

FIGURE 2 Interference Processing in Left Anterior Insula/Frontal Operculum (aI/fO) and Posterior Medial Frontal Cortex (pMFC): Effects of Symptom Severity in Unmedicated Patients With Pediatric Obsessive-Compulsive Disorder (OCD)



Note: *Interference-processing–activated posterior medial frontal cortex (pMFC) and bilateral anterior insula (aI/fO) (A). Region of interest (ROI) analyses showed associations of greater pMFC activation with better performance (faster response time [RT]; higher accuracy [Acc]) in healthy controls [HC], but worse performance in OCD patients (B, C) and greater left aI/fO activation with lower OCD severity (Child Yale–Brown Obsessive-compulsive Scale [C-YBOCS]) in patients (D). Exploratory whole-brain analyses showed altered associations of pMFC activation with age (E), RT (F), and Acc (G) in unmedicated OCD patients (uOCD) compared to HC. In the patients, there was a CY-BOCs–by-age interaction driven by the association of greater left aI/fO activation with lower OCD severity at older ages across uOCD and medicated (mOCD) patients (H). Color bars show t scores, reflecting relative strength of brain activation. Montreal Neurologic Institute coordinates (x, y, z) shown. FWE = familywise error; MFC = medial frontal cortex; mOCD = medicated obsessive-compulsive disorder; uOCD = unmedicated obsessive-compulsive disorder. Please note color figures are available online.*

significance after correction (Tables S5 and S6, available online).

Whole-Brain Analyses. There were no group or interaction effects on interference-related activation; however, exploratory analyses showed attenuation of normative increase in preSMA–dACC activation with younger age, faster RT, and higher accuracy in uOCD patients compared to HC (Figure 2E–G; Table S9, available online).

OCD Severity: Correlations of Brain Activation With Errors and Interference.

ROI Analyses. Lower OCD severity predicted greater activation to errors in the pMFC ($\beta = -0.08$, $p = .02$) (Figure 1D) and interference in the left aI/fO ($\beta = -0.03$, $p = .009$) (Figure 2D; Table 3). Exploratory analyses suggested that severity associations were driven by uOCD for error-related pMFC activation (Figure S3C, available online), by both patient groups for interference-related aI/fO activation (Figure S4A, available online), and that these associations increased with age (Table S10, available online). In addition, an association between lower OCD severity and greater interference-related pMFC activation at older ages emerged across uOCD and mOCD (Figure S4B, available online; Table S10, available online). Analysis of pMFC subregions showed an association between lower OCD severity and greater error-related activation of the dACC in uOCD ($p = .012$) (Tables S11 and S12, available online). Associations of OCD severity with CON activation remained after covarying illness duration.

Whole-Brain Analyses. There were no significant effects of CYBOCS scores on activation to error or interference in primary analyses (i.e., medication status not modeled). However, when medication status was modeled, lower OCD severity was found to associate with greater error-related preSMA-dACC activation in uOCD (Figure 1H; Table S13, available online) and greater interference-related activation at older ages in left aI/fO across uOCD and mOCD (Figure 2H; Table S14, available online).

DISCUSSION

Aberrant maturation of pMFC-based performance monitoring function has been posited to underlie the early course of OCD, but pMFC development remains to be characterized in young patients. In a large sample of OCD-affected compared to healthy youth, patients exhibited

TABLE 3 Cingulo-Opercular Network Function and Obsessive-Compulsive Disorder (OCD) Severity

	pMFC		Left aI/fO		Right aI/fO	
Errors	***B***	***p***	***B***	***p***	***B***	***p***
Intercept	**1.70 ± 0.34**	**<.001**	1.91 ± 0.23	<.001	1.99 ± 0.25	<.001
CYBOCS	**−0.08 ± 0.04**	**.025**	−0.05 ± 0.03	.124	---	---
Age	0.14 ± 0.09	.139	0.12 ± 0.08	.142	0.29 ± 0.11	.013*
Inc RT	---	---	---	---	---	---
Inc Acc	**12.66 ± 3.65**	**.001***	10.09 ± 3.40	.005*	7.68 ± 3.59	.038
CY-BOCS × Age	−0.02 ± 0.01	.079	---	---	---	---
Motion	---	---	---	---	9.91 ± 3.44	.006*
Adjusted R^2	0.30		0.18		0.18	
Model ANOVA	$F_{4,46} = 6.3$ ($p < .001$)		$F_{3,47} = 4.8$ ($p = .005$)		$F_{3,47} = 4.6$ ($p = .006$)	
Interference						
Intercept	**0.57 ± 0.07**	**<.001**	0.35 ± 0.08	<.001	0.42 ± 0.09	<.001
CY-BOCS	**−0**.007 ± 0.01	.478	**−0**.03 ± 0.01	.009*	---	---
Age	0.02 ± 0.03	.504	0.01 ± 0.03	.798	0.07 ± 0.03	.043
Overall RT	---	---	---	---	---	---
Overall Acc	**−3.69 ± 1.81**	**.045**	---	---	---	---
CY-BOCS × Age	−0.006 ± 0.004	.097	−0.008 ± 0.004	.055	---	---
Motion	1.43 ± 0.76	.065	---	---	---	---
Adjusted R^2	0.09		0.15		0.05	
Model ANOVA	$F_{5,63} = 2.3$ ($p = .048$)		$F_{3,65} = 4.0$ ($p = .012$)		$F_{1,67} = 4.3$ ($p = .043$)	

Note: Dashed lines represent predictor variables eliminated during backwards stepwise regression. Motion refers to framewise displacement.[28] Acc = accuracy; aI/fO = anterior insula/frontal operculum; ANOVA = analysis of variance; CY-BOCS = Child Yale–Brown Obsessive-Compulsive Scale; Inc = incongruent; pMFC = posterior medial frontal cortex; RT = response time.
Significance levels were p < .05 for pMFC (primary region of interest, boldface type) and p < .013 for secondary regions of interest (*).

greater error-related activation of the pMFC and atypical increase of pMFC activation to errors with age. These findings provide new evidence of atypical development of pMFC-based error-processing function in pediatric OCD. Importantly, greater pMFC activation to errors was associated with better performance in HC and lower OCD severity in patients. Collectively, these findings raise the possibility that "hyperactive" pMFC response to errors may represent an adaptive response that normally facilitates task performance and, in pediatric OCD, develops with age to help patients control symptoms.

The notion that heightened error-related pMFC activation could serve a compensatory role in pediatric OCD is consistent with the function of this region in signaling for cognitive control to facilitate the flexible adjustment of behavior.[2] In the context of OCD, increased pMFC signaling could serve to improve patients' ability to detect and to dismiss obsessive thoughts and compulsive urges as irrelevant (i.e., false alarms or "thinking errors") to move on to other, more appropriate behaviors. Greater interference-related activation in pMFC correlated with better performance in HC and, in the left aI/fO, with lower OCD severity in patients, implicating more general performance monitoring function (i.e., errors and interference) of the broader CON (i.e., pMFC and aI/fO). Indeed, recent work suggests that greater engagement of the CON and related networks for task control may enhance performance on cognitive tasks in adults at familial risk for OCD and may protect against OCD expression.[35,36] Other recent models suggest that increased pMFC signaling may serve to compensate for attentional demands of anxiety during task performance, enabling patients to maintain normal performance but not necessarily reducing anxiety or OCD symptoms.[16] These possibilities represent alternatives to prior work in which increased CON response to errors in OCD was interpreted to reflect excessive emotional sensitivity to and/or detection of mistakes that could drive symptoms.[10,17]

Exploratory analyses showed greater pMFC and right aI/fO response to errors in mOCD patients than in HC or uOCD patients, raising the possibility that medication, rather than illness, may be responsible for CON hyperactivity. However, prior work in adult OCD showed no effect of SSRIs on CON hyperactivity to errors.[17] In our pediatric

sample, mOCD patients were characterized by a greater decrease from the most severe past to the less severe present CY-BOCS scores, suggesting that medication could induce CON engagement to support symptom suppression. The possibility that medication may help to resolve CON dysfunction aligns with normal association of greater error- and interference-related pMFC and right aI/fO activation with faster RT in mOCD but attenuation of this relationship in uOCD. Similarly, the normative association of greater pMFC activation to errors (and, at trend level, interference) at younger ages was observed in mOCD but reversed in uOCD. These findings raise the possibility that medication may normalize developmental trajectories in mOCD. By contrast, in uOCD, greater pMFC response to errors and interference at older ages and with lower OCD severity suggest that pMFC activation could increase naturalistically, with development, to help patients suppress symptoms.

The presence of age-related change in pMFC-based performance monitoring function in pediatric OCD suggests a still-developing system that could be modulated to improve outcomes in affected youth. Performance monitoring capabilities improve dramatically in typically developing adolescents, alongside age-related changes in brain activation to performance monitoring demands.[37] During adolescence, before CON connectivity reaches maturity,[38] the pMFC may be considered less efficient, leading to greater dynamic range in task-related activity. In this light, the association of OCD-related hyperactivity with lower OCD severity may reflect a dynamic pMFC with relevance for improving illness outcomes. Given that pMFC function appears to stabilize in adulthood,[39] adolescence may be a critical developmental window during which targeting the pMFC is most likely to be successful. Should one try to augment function of the pMFC in pediatric OCD? Findings from the present study cannot answer this question, but justify longitudinal work to determine whether increases in pMFC-based capacity for task monitoring and control are associated with reduction in OCD symptoms. In the long term, such work could pave the way for cognitive training to "exercise" the pMFC as augmentation or as an alternative to currently available treatments.

Atypical age-related increase of pMFC (and right aI/fO) response to errors has been previously reported in a smaller sample of OCD compared to healthy youth.[19] However, in contrast to our findings, the prior study showed no association of activation with OCD severity.[19] Furthermore, controls from the prior study showed no relation between activation and age,[19] contrasting with the age-related decrease in activation observed in our sample of healthy youth. These inconsistencies may relate to smaller sample size[19] or different analytic techniques. For example, the prior study assessed correlations of activation with OCD severity without covarying age or performance, which, as shown by our results, had a significant impact on CON-based performance monitoring function. On the other hand, the prior study found a pre− to post−cognitive behavioral therapy (CBT) increase in interference-related pMFC activation associated with decreasing OCD severity. Consistent is the premise that greater pMFC activation during performance monitoring may index an adaptive response in OCD.

Within the pMFC, motor-cognitive compared to cognitive-affective processes have been described as localizing along a neuroanatomical continuum from posterior-dorsal to anterior-rostral areas,[32] leading us to consider preSMA and dACC subregions in secondary ROI analyses. Many of the ROI results indicated trend-level effects that generalized across both areas, and most results from the whole-brain analysis—a more precise method for functional neuroanatomic localization—were observed in an area spanning the preSMA and dACC. These findings are consistent with a recent meta-analysis of nearly 10,000 fMRI studies showing task control processes (including errors and interference) to preferentially associate with both the preSMA and dACC.[32] Consequently, we use the term "pMFC" to link to the broader literature on overlapping task control functions in the midline frontal area that encompasses these subregions,[32] while also noting instances—specifically, altered associations of age and RT with error-related activation in uOCD—in which findings may localize to dACC and not preSMA.

Strengths of this work include the large sample size, replication of findings across ROI and whole-brain analyses, and consideration of performance and medication effects; however, several important limitations should be noted. OCD was the primary diagnosis; however, in line with the clinical presentation of OCD, some subjects had comorbid diagnoses (e.g., anxiety, attentional problems) which may have contributed variance. Due to insufficient errors (<5), 28% of subjects were excluded from error analyses; nonetheless, the percentage of excluded subjects was nearly the same across the OCD (26%) and HC (25%) groups, meaning that observed group differences should not have been biased. In addition, patient age and illness duration were correlated such that persistent illness, rather than developmental effects, may have driven greater pMFC response to errors in older OCD subjects; disentangling age and illness duration would require the recruitment of same-aged patients who vary in OCD chronicity. Finally, we acknowledge that our study was not designed to test medication-induced change in CON function and other factors, including higher rates of CBT exposure in mOCD than in uOCD, which could have contributed to effects

observed in exploratory analyses. Future longitudinal work should examine CON function in patients at different ages, before and after treatment with medication, CBT and the combination.

In summary, our study shows reversal of age-related decrease of pMFC response to errors in pediatric OCD compared to healthy youth, suggesting atypical development of neural substrate for performance monitoring during the early course of illness. In addition, error-related pMFC activity was greater in patients than controls, increased with better performance in controls and lower OCD severity in patients. Collectively, we have interpreted findings to suggest that greater pMFC engagement may serve a compensatory role in pediatric OCD. Future studies using longitudinal designs are needed to characterize maturational trajectories of pMFC and broader CON function in pediatric OCD and to determine whether increases in activation lead to reduction in illness severity after treatment and/or naturalistically over time.

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