

# Deficits in Conditioned Fear Extinction in Obsessive-Compulsive Disorder and Neurobiological Changes in the Fear Circuit

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**Importance:** Obsessive-compulsive disorder (OCD) may be characterized by impaired self-regulation and behavioral inhibition. Elevated fear and anxiety are common characteristics of this disorder. The neurobiology of fear regulation and consolidation of safety memories have not been examined in this patient population.

**Objective:** To examine the psychophysiological and neurobiological correlates of conditioned fear extinction in patients with OCD.

**Design:** Cross-sectional, case-control, functional magnetic resonance imaging study.

**Setting:** Academic medical center.

**Participants:** Twenty-one patients with OCD and 21 healthy participants.

**Main Outcomes and Measures:** Skin conductance responses and blood oxygenation level–dependent responses.

**Results:** The between-group difference noted in our psychophysiological measure (skin conductance responses) was during extinction recall: patients with OCD showed impaired extinction recall relative to control subjects. Regarding the functional magnetic resonance imaging data, patients with OCD showed significantly reduced activation in the ventromedial prefrontal cortex

across training phases. Moreover, reduced activation in the patients with OCD was noted in the caudate and hippocampus during fear conditioning, as well as in the cerebellum, posterior cingulate cortex, and putamen during extinction recall. Contrary to our prediction, OCD symptom severity was positively correlated with the magnitude of extinction memory recall. Also contrary to our prediction, functional responses of the ventromedial prefrontal cortex were positively correlated with symptom severity, and functional responses of the dorsal anterior cingulate cortex were inversely correlated with symptom severity.

**Conclusions and Relevance:** As expected, our study showed that fear extinction and its neural substrates are impaired in patients with OCD. However, this study also yielded some surprising and unexpected results regarding the correlates between extinction capacity and its neural substrates and the severity of symptoms expressed in this disorder. Thus, our data report neural correlates of deficient fear extinction in patients with OCD. The negative correlations between fear extinction deficits and Yale-Brown Obsessive-Compulsive Scale symptoms in OCD suggest that there may be other factors, in addition to fear extinction deficiency, that contribute to the psychopathology of OCD.

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**I**NDIVIDUALS DIAGNOSED AS HAVING obsessive-compulsive disorder (OCD) are unable to control or regulate intrusive thoughts, doubts, or concerns about matters in their daily lives, such as safety, cleanliness, violence, or symmetry. These obsessions tend to generate, or be accompanied by, anxiety and fear. Consequently, patients with OCD engage in compulsive repetitive, stereotyped, or ritualized behaviors aimed to neutralize the anxiety and fear associated with their obsessions. Therefore, OCD can be viewed as a disorder of self-regulation and behavioral inhibition.<sup>1</sup>

Pavlovian fear conditioning and extinction is an experimental paradigm commonly used to study the regulation and inhibition of fear memories.<sup>2,3</sup> Results from

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animal and human studies using this paradigm converge to implicate a brain network, including the ventromedial prefrontal cortex (vmPFC), amygdala, and dorsal anterior cingulate cortex (dACC), in the acquisition and expression of the fear extinction memory.<sup>2,4</sup> For example, in-

## PARTICIPANTS

creased activation within the amygdala, insula, and dACC has been observed during fear conditioning and has been associated with the expression of conditioned responses.<sup>5-9</sup> During extinction training, the vmPFC and the amygdala have been shown to exhibit increased reactivity to conditioned stimuli.<sup>10,11</sup> When the extinction memory is then recalled, the hippocampus along with the vmPFC have been found to be involved in signaling the recall of extinction memory.<sup>10,12</sup> Pavlovian conditioning paradigms have been used to explore the psychopathology of several anxiety disorders, such as post-traumatic stress disorder (PTSD) and panic disorder, as well as schizophrenia.<sup>13-19</sup>

While fear conditioning as a model may not best explain the clinical phenomenology of OCD, understanding the neural circuits of fear extinction in OCD could be clinically relevant for several reasons. First, such studies may clarify how anxiety and distress associated with OCD are sustained and may elucidate the mechanisms by which exposure therapies confer their therapeutic effects in this disorder.<sup>1</sup> Second, cognitive behavioral therapies used to treat OCD are extinction-based therapies,<sup>20</sup> therefore, understanding the neural correlates of extinction may further our understanding of how these therapies help treat patients with OCD and how they can perhaps be augmented. Third, there seems to be overlap between brain regions involved in the psychopathology of OCD and those involved in the acquisition and extinction of conditioned fear. Data using neuroimaging techniques have begun to link the psychopathology of OCD with dysfunctional activation in a network of brain regions, many of which overlap with those involved in fear extinction.<sup>1,21</sup> Increased amygdala responses in OCD have been noted in response to emotional faces<sup>22</sup> and symptom-provoking stimuli.<sup>23</sup> Lesions of the dACC alleviate OCD symptoms<sup>24</sup> and pharmacologic treatments have been shown to normalize the activity of this region.<sup>25</sup> Hypoactive vmPFC has been observed in patients with OCD, and studies have reported inverse correlations between OCD symptom severity and vmPFC/medial orbitofrontal cortex function (reviewed in an article by Milad and Rauch<sup>1</sup>). Collectively, these data suggest that fear extinction and its underlying brain network may be altered in patients with OCD and that examining fear extinction in OCD may be useful in understanding how exposure therapies treat patients with OCD.

In this study, we hypothesized that patients with OCD exhibit aberrant fear extinction recall and that these deficits are associated with a dysfunctional fear extinction network. Patients with OCD and healthy control (HC) subjects underwent a validated 2-day fear conditioning and extinction paradigm.<sup>26-28</sup> On day 1, participants were fear conditioned and subsequently extinguished their fear to visual cues. On day 2, subjects underwent the fear extinction recall test to examine the recall of the safety memory formed during extinction learning. The study was conducted in a functional magnetic resonance imaging (fMRI) scanner, and skin conductance responses (SCRs) were collected throughout the study and used as an index of conditioned responding.

Twenty-one right-handed healthy volunteers (10 males) between 20 and 41 years of age (mean [SD], 26.4 [5.2] years) were recruited from the local community. Twenty-one right-handed subjects (7 male) between 20 and 58 years of age (mean [SD], 33.8 [11.3] years) who met the *DSM-IV* diagnosis criteria for OCD were recruited from the Obsessive-Compulsive and Related Disorders Program at Massachusetts General Hospital. Patients were eligible for participation in the study if they were medication free or taking a stable medication regimen for 8 weeks or more prior to study participation (benzodiazepine free for  $\geq 2$  weeks). After a complete study description, including all procedures, written informed consent was obtained in accordance with the Partners Healthcare System Human Research Committee requirements.

## MEASURES

The screening visit included a diagnostic interview for Axis I disorders (Structured Clinical Interview for *DSM-IV* [Patient Edition]). The Yale-Brown Obsessive-Compulsive Scale (YBOCS), a 10-item semistructured clinician-administered measure with demonstrated validity and reliability, was used to assess OCD symptom severity.<sup>29,30</sup>

## FEAR CONDITIONING TASK

The experimental protocol used in this study has been described previously.<sup>15,26,31</sup> Briefly, fear conditioning and extinction took place on day 1 and the extinction recall test occurred on day 2. The conditioned stimuli (CS) were pictures of different colored lamps and the unconditioned stimulus was an aversive electrical stimulation to the subject's fingers that coterminated with the CS during conditioning but was never presented during any of the subsequent experimental phases (see eAppendix and eFigure 1A for additional details; <http://www.jamapsych.com>). Two CS+s were followed by the electric shock during conditioning, but only 1 was presented during the extinction training phase (CS+ extinguished [CS+E]). On day 2, subjects underwent extinction recall, during which the CS+E, as well as the CS+ that was conditioned but not extinguished (CS+NE), were presented. Skin conductance was measured simultaneously with fMRI acquisition, as previously described (eAppendix). Details about the way SCR was calculated and how the extinction retention index (ERI) scores were measured are described in the eAppendix. The ERI scores were entered into a linear regression model with the fMRI data during extinction recall (contrast: early CS+E vs early CS+NE) to compute correlations at each voxel. The ERI score of 1 patient with OCD was conservatively changed from -108 to 0 to avoid overestimation of the OCD group deficit.

## FUNCTIONAL MAGNETIC RESONANCE IMAGING DATA ACQUISITION AND ANALYSIS

Our acquisition and analysis parameters were comparable with those previously published<sup>5,28,32</sup> and are further detailed in the eAppendix. Statistical Parametric Mapping (SPM8; The Wellcome Trust; [www.fil.ion.ucl.ac.uk](http://www.fil.ion.ucl.ac.uk)) was used within a MATLAB (MathWorks) environment on a Linux 64-bit system. Functional images were corrected for slice timing, realigned, coregistered with the structural image, segmented, normalized into the Montreal Neurological Institute template space, and

**Table 1. Demographics and Comorbidities of OCD in Study Cohort**

	No. (%)		P Value
	OCD	Healthy	
<b>Demographic</b>			
Age, mean (SD), y	33.8 (2.5)	26.4 (1.1)	<.01
Education, mean (SD), y	15.9 (0.4)	15.9 (0.1)	>.99
<b>Sex, No.</b>			
Male	7	10	
Female	14	11	
<b>YBOCS score</b>			
Obsessions	10.6 (0.5)		
Compulsions	12.0 (0.6)		
Total	22.6 (0.8)		
<b>Frequency of OCD subtypes</b>			
Checking	3 (14.3)		
Ordering	2 (9.5)		
Neutralizing	1 (4.8)		
Washing	8 (38.1)		
Obsessing	6 (28.6)		
Hoarding	1 (4.8)		
Age at onset, mean (SD), y	13.5 (1.8)		
<b>Current SCID-I comorbidities<sup>a</sup></b>			
Dysthymia	2 (9.5)		
Panic disorder	1 (4.8)		
Social phobia	4 (19.0)		
Specific phobia	9 (42.9)		
PTSD	1 (4.8)		
GAD	1 (4.8)		
<b>Medication status<sup>b</sup></b>			
No medication	10 (47.6)		
Antidepressant	9 (42.8)		
Antipsychotic	0		
Benzodiazepine	0		
Antidepressant + anticonvulsant	1 (4.8)		
Antidepressant + NMDA receptor antagonist	1 (4.8)		

Abbreviations: GAD, generalized anxiety disorder; NMDA, *N*-methyl-D-aspartate; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SCID-I, Structured Clinical Interview for *DSM-IV* Axis I disorders; YBOCS, Yale-Brown Obsessive-Compulsive Scale.

<sup>a</sup>Data only reported for disorders with which at least 1 participant was diagnosed as having.

<sup>b</sup>Antidepressants included clomipramine, fluoxetine, escitalopram, citalopram, duloxetine, sertraline, and bupropion; the anticonvulsant included gabapentin; and the NMDA receptor antagonist included was memantine.

smoothed (8 mm full-width at half maximum). Preprocessed functional time series data were modeled using a general linear model with regressors signifying the stimulus onsets using stick functions.

First-level contrast images were obtained for each subject and then modeled at the second level to examine significant (de)activations both within and between HC and patient groups. To analyze neurocorrelates of fear acquisition, all CS+ trials were contrasted to all CS− trials. Extinction training processes were assessed by contrasting early CS+E trials (first 8 during extinction) to late CS+E (last 8 extinction trials), as previously defined. To examine neurocorrelates of extinction recall, early CS+E trials (first 4) were contrasted to early CS+NE (first 4) trials. As a control, a secondary analysis added age as a nuisance covariate to second-level models of conditioning, extinction, and recall. Overall results were retained except where

noted. Two additional analyses used multiple regression to examine whether brain (de)activation during extinction recall correlated with ERI or YBOCS<sup>29,30</sup> scores during the contrast of CS+E vs CS+NE.

## STATISTICAL ANALYSIS

Given our prior studies in fear extinction of healthy and patient populations, we had strong unidirectional a priori hypotheses regarding the functional (de)activations of several regions. These regions included the insular cortex (during conditioning), dACC (all phases), vmPFC (during extinction training and recall), amygdala (all phases), and hippocampus (all phases).<sup>10,28</sup> Additional a priori structures included neurocircuitry implicated in OCD, namely, the striatum (including the caudate nucleus and putamen), posterior cingulate cortex (PCC), orbital frontal cortex (OFC), and cerebellum.<sup>33</sup> Within these a priori regions, clusters surviving small-volume correction (5-mm radius sphere) at  $P < .05$  familywise error were considered significant. Outside of these regions, clusters that exceeded 10 voxels and were significant at familywise error-corrected  $P < .05$  were considered significant. The descriptions of other analyses related to demographic and psychophysiological measures are detailed in the eAppendix. Two additional multiple regressions were conducted using stepwise regression methods (see eAppendix for details).

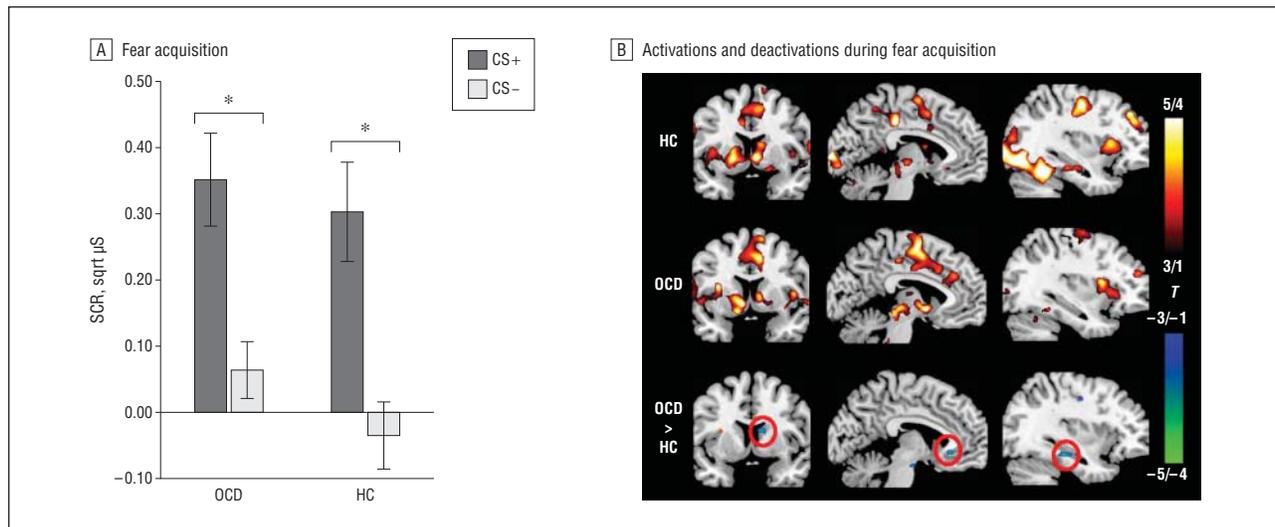
## RESULTS

The demographics for both groups, as well as all clinical data related to the OCD group, including comorbidities and medications, and OCD subtypes are described in **Table 1**. Owing to the significant between-group age difference, additional analyses were conducted to examine the effect of age on neural correlates of the conditioning and extinction paradigm listed here. The results were largely unchanged.

## FEAR ACQUISITION

Both the OCD and HC groups displayed stimulus-specific conditioning indicative of learning. Skin conductance responses were significantly different between the CS+ and CS− trials during fear acquisition in both groups ( $F_{1,35} = 28.83$ ,  $P < .001$ ; **Figure 1A**). There were no significant group differences ( $F_{1,35} = 0.99$ ,  $P > .05$ ) or interactions between the stimulus type and group ( $F_{1,35} = 0.15$ ,  $P > .05$ ), indicating equal levels of fear conditioning between the OCD and HC groups. Regarding the neuroimaging data, Figure 1B shows whole-brain activation for the contrast CS+ vs CS− presentations. Both HC and OCD groups displayed significant activation in the dACC, periaqueductal gray region of the brainstem, and insula (Figure 1B and **Table 2**).

Between-group analysis revealed that the OCD group failed to engage several regions compared with the HC group (Figure 1B, bottom row). These regions consisted of the right caudate, a region of subgenual cortex, and the hippocampus (Table 2). Brain regions that showed significant (de)activations outside of our a priori regions of interest (ROI) are listed in eTable 1.



**Figure 1.** Psychophysiological responses and blood oxygenation level–dependent reactivity during fear acquisition. A, Mean skin conductance responses (SCRs) during conditioning to the conditioned stimulus paired with the shock (CS+) and to that not paired (CS–). Both the obsessive-compulsive disorder (OCD) and healthy control (HC) groups significantly discriminated between the CS+ and CS– (asterisk denotes  $P < .05$ ) during the fear conditioning phase. B, Blood oxygenation level–dependent responses to CS+ presentations contrasted with responses to CS– presentations across all conditioning trials within and between groups. Group differences, denoted by the red circle (bottom row), were found in the right caudate nucleus, subgenual cortex, and the hippocampus. Activation maps are illustrated with a threshold of  $t > \pm 3.0$  ( $P < .01$ , uncorrected) within group and a threshold of  $t > \pm 1.0$  ( $P < .01$ , uncorrected) between groups. Results are overlaid on a template structural magnetic resonance image. The scale bar is  $\pm 3$ -5 for within-group contrasts and  $\pm 1$ -4 for between-group contrasts.

**Table 2. Activations and Deactivations for Within-Group and Between-Group Analyses Across All Experimental Phases**

Area of Activation	MNI Coordinates	T	Size, Voxels	P Value		Region
				Cluster, FWE	Voxel, FWE <sup>a</sup>	
<b>Conditioning</b>						
CS+ > CS–						
HC	–10, 8, 34	4.43	65	.02	.004	dACC
	–2, –26, –8	5.07	74	.02	.001	Periaqueductal gray
	–32, 20, 8	4.88	81	.02	.002	Insula
OCD	–4, 0, 54	5.09	81	.02	.001	dACC
	–2, –24, –6	5.71	81	.02	<.001	Periaqueductal gray
	–32, 8, 14	5.41	68	.02	.001	Insula
Between group (OCD > HC)	12, 8, 16	–2.96	28	.04	.03	Right caudate
	–4, 28, –6	–3.21	11	.05	.02	Subgenual cortex
	–34, –28, –14	–3.54	33	.04	.009	Hippocampus
<b>Extinction Training</b>						
Late CS+E < early CS+E						
HC	0, 14, 28	3.76	57	.03	.01	dACC
OCD	–4, 14, 48	4.75	81	.02	<.001	dACC
Late CS+E > early CS+E						
HC	–10, 52, –4	3.01	37	.03	.04	vmPFC
Between group (OCD > HC)	6, 52, –14	–2.98	19	.04	.03	vmPFC
<b>Extinction Recall</b>						
Early CS+E > early CS+NE						
HC	–4, 58, –8	4.53	46	.03	.003	vmPFC
	4, –12, 42	4.02	81	.02	.007	Posterior cingulate
Between group (OCD > HC)	–10, 58, –8	–3.28	23	.04	.02	vmPFC
	10, –14, 44	–3.21	47	.03	.02	Posterior cingulate
	–2, –70, –30	–3.86	64	.02	.004	Cerebellum
	32, –4, 6	–3.38	35	.03	.01	Putamen

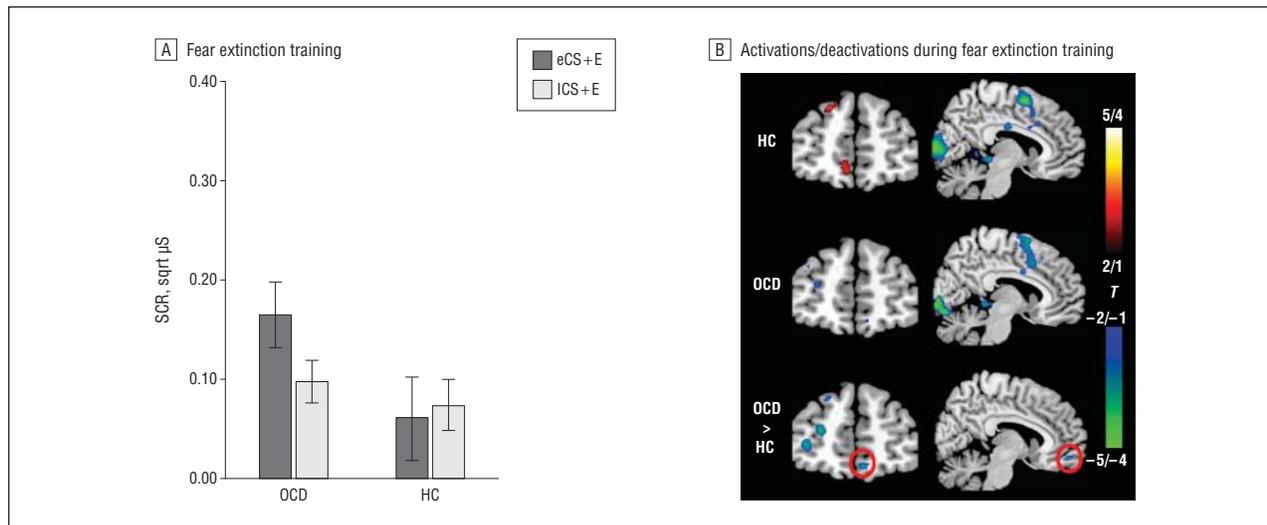
Abbreviations: CS–, nonreinforced conditioned stimulus; CS+, reinforced conditioned stimulus; dACC, dorsal anterior cingulate cortex; E, extinguished; FWE, familywise error; HC, healthy control; MNI, Montreal Neurological Institute; NE, nonextinguished; OCD, obsessive-compulsive disorder; vmPFC, ventromedial prefrontal cortex.

<sup>a</sup>Clusters surviving small-volume correction (5-mm radius sphere) corrected at  $P < .05$ , FWE.

## EXTINCTION TRAINING

To assess learning during extinction training, the first 4 trials (eCS+E) were compared with the last 4 trials

(ICS+E). A 2-way analysis of variance compared the level of SCRs (late vs early extinction training) between groups (OCD and HC). There was no significant main effect of SCR (late vs early extinction training,  $F_{1,35} = 0.77$ ,  $P = .39$ )



**Figure 2.** Psychophysiological responses and blood oxygenation level–dependent reactivity during extinction training. A, Skin conductance response (SCR) in both the obsessive-compulsive disorder (OCD) and healthy control (HC) groups did not differ at the beginning (first 4 trials, extinguished reinforced conditioned stimulus [eCS+E]) or end of extinction training (last 4 trials; ICS+E) to the CS+E. B, Blood oxygenation level–dependent responses during extinction training are displayed within and between groups. Results display responses to last 4 CS+E presentations contrasted with responses to first 4 CS+E presentations. In this contrast, both the OCD and HC groups displayed deactivation of the dorsal anterior cingulate (top 2 rows), indicating the dorsal anterior cingulate was less activated at the end of extinction training compared with at the beginning. The OCD group showed significantly less activation than the HC group in the right ventromedial prefrontal cortex, denoted by the red circle. Activation maps are illustrated with a threshold of  $t > \pm 3.0$  ( $P < .01$ ) within group and a threshold of  $t > \pm 1.0$  ( $P < .01$ ) between groups, then overlaid on a template structural magnetic resonance image. The scale bar is  $\pm 3$ -5 for within-group contrasts and  $\pm 1$ -4 for between-group contrasts.

or group ( $F_{1,35} = 2.79$ ,  $P = .10$ ). There also was no significant interaction between variables ( $F_{1,35} = 1.89$ ,  $P = .18$ ). The results indicated that the OCD group extinguished to a level comparable with the HC group (**Figure 2A**). Regarding the fMRI data, we observed significant dACC deactivation in both the HC and OCD groups late in extinction to the CS+E as compared with early trials (ICS+E vs eCS+E; Figure 2B and Table 2). These findings are consistent with previous studies suggesting that dACC activation is correlated with fear expression, where both fear expression and dACC activity decrease as extinction training occurs.<sup>9</sup> Also consistent with previous studies,<sup>10,11,34</sup> the HC group displayed an activation of vmPFC late in extinction training as compared with early extinction (Figure 2B and Table 2), consistent with a role of vmPFC in the development of the extinction memory. Despite apparent extinction as indexed by the SCR data in the OCD group, vmPFC activation was not evident in the OCD group, resulting in a significant group difference (Figure 2B, bottom row; and Table 2). Brain regions that showed significant (de)activations outside of our a priori ROI are listed in eTable 1.

#### EXTINCTION RECALL

A 2-way analysis of variance conducted on SCRs to the extinguished and nonextinguished stimuli revealed no significant group by stimulus interactions ( $F_{3,105} = 0.81$ ,  $P = .45$ ). There was no significant main effect of stimulus ( $F_{2,105} = 2.11$ ,  $P = .13$ ). However, there was a significant main effect of group ( $F_{1,105} = 7.66$ ,  $P < .01$ ; **Figure 3A**). The mean SCR collapsed across all stimuli was significantly higher in the OCD group than the HC group. A 1-way analysis of variance was conducted to test whether responses to the stimuli differed within the OCD

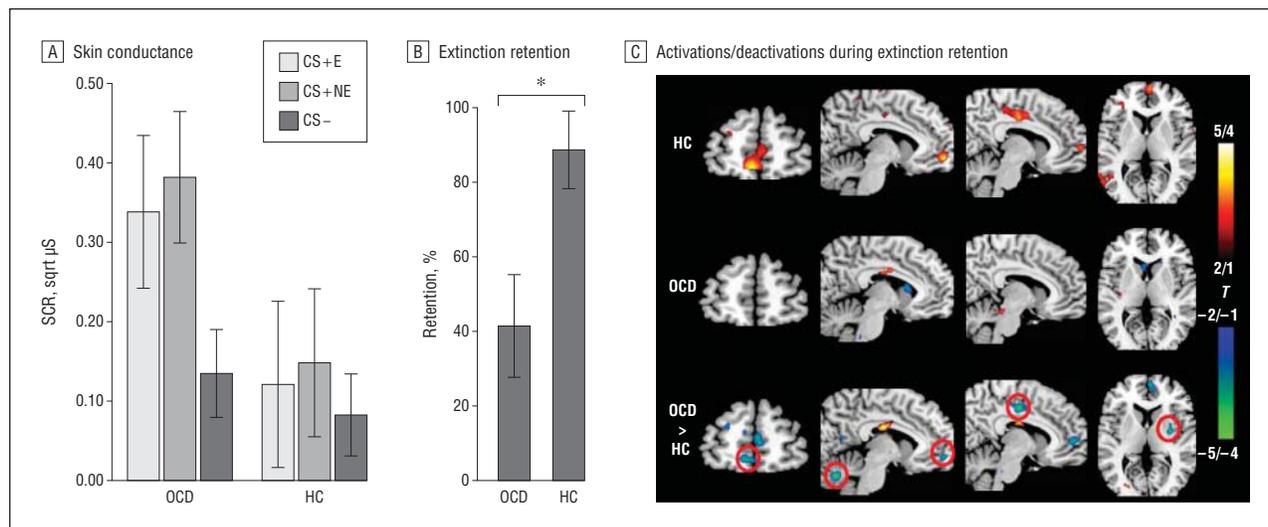
group. The results displayed a trend to this effect ( $P = .07$ ). The results obtained from the ERI analysis were clearer. Here, an independent  $t$  test resulted in a significant group difference ( $t_{34} = -2.63$ ,  $P < .05$ ; Figure 3B).

Regarding the fMRI results for this phase, the HC group displayed significant activation of the vmPFC to the CS+E as compared with the CS+NE (Table 2), consistent with our findings and other previous findings.<sup>10,28</sup> This was not observed in the OCD group, resulting in a significant difference between the groups (Table 2). We also observed a region of PCC that was significantly activated in the HC group that was not evident in the OCD group (Table 2). There was a significant group difference in the activation of PCC (Figure 3C, bottom left; and Table 2). Additional differences between the groups were observed in the cerebellum and putamen (Table 2). There were no significant differences within brain regions outside of our a priori ROI.

#### CORRELATES OF SYMPTOM SEVERITY AND FEAR EXTINCTION

##### Yale-Brown Obsessive-Compulsive Scale Correlates With Extinction-Induced Activations During Extinction Recall

This and all subsequent analyses were limited to the OCD group. Neural activation in several brain regions in the OCD group correlated with symptom severity as measured by the YBOCS during extinction recall. Four patients with OCD were removed from this analysis owing to either excessive movement ( $>3$  mm, 1 patient) or insufficient SCRs (3 patients), leaving a total of 17 patients with OCD analyzed. A number of our a priori regions exhibited significant activation in the contrast



**Figure 3.** Psychophysiological responses and blood oxygenation level-dependent activations during extinction recall. A, Mean skin conductance responses (SCRs) during recall to the extinguished reinforced conditioned stimulus (CS+E), the nonextinguished CS+ (CS+NE), and the nonreinforced CS (CS-). B, The ability to recall extinction was also assessed by an extinction retention index measure (see the Methods section). There was a significant group difference ( $* P < .05$ ) in the extinction retention index percentage, indicating that the healthy control (HC) group was better able to recall extinction training compared with the obsessive-compulsive disorder (OCD) group. C, Blood oxygenation level-dependent responses during extinction recall are displayed within and between groups. The OCD group showed significantly less activation than the HC group in the left ventromedial prefrontal cortex, cerebellum, posterior cingulate cortex, and putamen (bottom row, red circles). Results represent responses to the first 4 CS+NE presentations contrasted with responses to the first 4 CS+E presentations during recall. Activation maps are illustrated with a threshold of  $t > \pm 3.0$  ( $P < .01$ , uncorrected) within group and a threshold of  $t > \pm 1.0$  ( $P < .01$ , uncorrected) between groups, then overlaid on a template structural magnetic resonance image. The scale bar is  $\pm 3$ -5 for within-group contrasts and  $\pm 1$ -4 for between-group contrasts.

eCS+E > eCS+NE that was positively correlated with YBOCS scores. These regions included the vmPFC, cerebellum, and PCC (Figure 4A and Table 3). Additionally, activations in several other regions were negatively correlated with YBOCS scores, namely, the dACC and the insular cortex (Figure 4A and Table 3). No significant activations or deactivations were found outside of our a priori ROI. Regression plots for all the previously mentioned regions are shown in eFigure 2A.

#### Extinction Retention Index Correlates With Extinction-Induced Activation During Extinction Recall

We also examined whether neural activation in patients during recall (eCS+E > eCS+NE) was correlated with the ability to recall extinction in the OCD group (ie, ERI scores). The pattern of significantly correlated activation in these analyses revealed similar patterns or results to that of the YBOCS: ERI was positively correlated with activations in the vmPFC, cerebellum, and PCC (Figure 5A and Table 3) and negatively correlated with the dACC and the insula (Figure 5A and Table 3). No significant correlations outside of our a priori ROI were found. Regression plots for all the previously mentioned regions are shown in eFigure 2B.

#### Network Contributions to Symptom Severity and Extinction Retention Index

While a distinct pattern of correlations between the YBOCS and ERI and extinction-induced activations was noted, the correlations between these 2 measures and extinction-induced activations overlapped in 5 brain re-

gions, namely, the vmPFC, cerebellum, PCC, dACC, and insula cortex (eTable 2). Given the high correlations observed, we sought to examine the potential influence/contribution of each of these 5 brain regions to both YBOCS and ERI values using a stepwise regression analysis.

The first stepwise regression examined the additional value of these 5 brain regions (independent variables = vmPFC, cerebellum, PCC, dACC, and insula) in the ability to predict OCD symptom severity (dependent variable = YBOCS). In step 1, cerebellum was entered into the equation as an independent variable ( $r^2 = 0.69$ ;  $F_{1,15} = 32.67$ ;  $P < .001$ ) with an intercept value of 22.29 and a  $\beta$  of 0.83. In step 2, insula was added to the equation as an independent variable, significantly increasing and contributing to the ability to predict symptom severity ( $r^2 = 0.85$ ;  $F_{2,14} = 40.99$ ;  $P < .001$ ), with an intercept of 22.30 and  $\beta$  values of 0.60 (cerebellum) and  $-0.47$  (insula; Figure 4B). Addition of vmPFC, PCC, and dACC did not significantly improve the  $R^2$  value, suggesting that while all the activations during recall in all 5 brain regions are highly correlated with the YBOCS, the most significant contributors to the symptom severity were activations in the cerebellum and insular cortex. The robustness of these results was tested with forward and backward regressions. Forward regression methods confirmed the same results, while backward regression (which can lack power and result in large standard errors if substantial multicollinearity exists), resulted in the inclusion of the cerebellum, dACC, and PCC as independent variables.

The second stepwise regression examined the additional value of the same brain regions in the ability to predict extinction retention. In step 1, the cerebellum

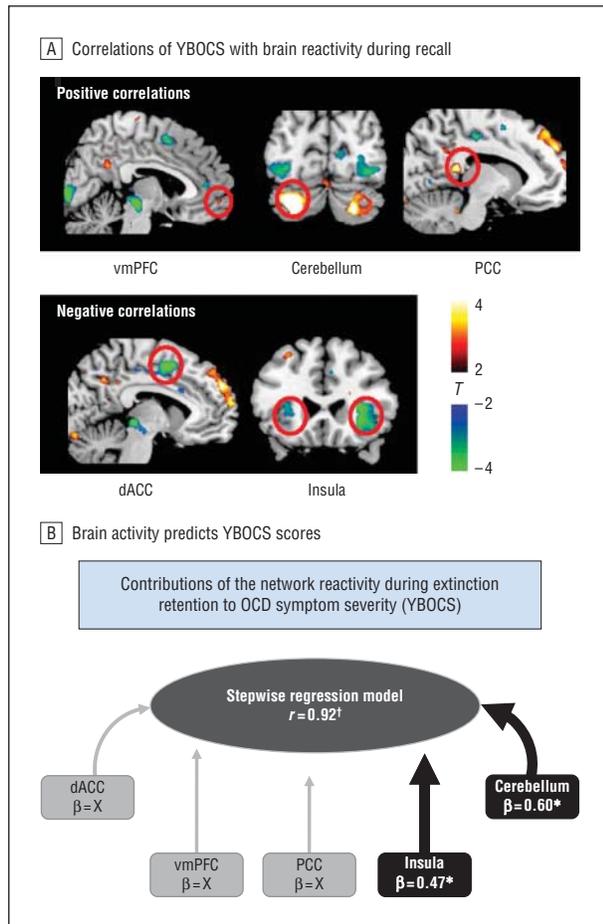
## EXTINCTION RETENTION INDEX AS A PREDICTOR OF OBSESSIVE-COMPULSIVE DISORDER SYMPTOM SEVERITY

We examined the relationship between ERI and OCD symptom severity. This analysis revealed that the higher the ERI, the worse the OCD symptoms ( $r = 0.56, P < .05, n = 18$ ; **Figure 6**). These results are consistent with the counterintuitive results previously stated, in which the higher the activations in brain regions involved in fear extinction, the worse the OCD symptom severity.

### DISCUSSION

In this study, we demonstrated that while the expression of conditioned fear and its subsequent extinction is intact (as measured by SCR), the recall of the extinction memory is impaired in patients with OCD. We observed decreased activation of the vmPFC across all experimental phases in patients with OCD relative to control subjects. In addition, blunted responses within the hippocampus and caudate were observed during the fear conditioning phase, as well as within the cerebellum, PCC, and putamen during the extinction recall phase in the patients with OCD. Stepwise regression analysis showed that the activations of the cerebellum and insular cortex during extinction recall were the most significant predictors of the variance observed in symptom severity in patients with OCD. Lastly, our data showed a paradoxical relationship between ERI, vmPFC, and dACC activations during extinction recall and OCD symptom severity. That is, the higher extinction retention values, and hence increased vmPFC and decreased dACC activations during extinction recall, the more severe the OCD symptoms. A number of studies have highlighted the role of the amygdala in fear acquisition and extinction and as a brain region that contributes to the psychopathology of anxiety disorders. However, we did not observe abnormal amygdala responses at any phase of the experiment in patients with OCD, further suggesting that this brain region may not be a key contributor to OCD pathophysiology within the context of fear conditioning and extinction.

The hippocampus and caudate have been previously implicated in the acquisition of conditioned fear in rodents and in humans.<sup>35</sup> Striatal functioning has been shown to track fear conditioning and reversal of conditioned fear responses in healthy humans.<sup>36</sup> Lesions of the dorsal striatum in rodents have been shown to impair auditory fear conditioning,<sup>37</sup> and hippocampal function is critical for contextual fear conditioning and for the expression of context-specific fear extinction memories.<sup>38,39</sup> Aberrant functional activation of the caudate is one of the most consistent findings in the neuroimaging literature of OCD (reviewed in the article by Milad and Rauch<sup>1</sup>). Structural and functional abnormalities in the hippocampus have also been previously reported in OCD.<sup>40,41</sup> Therefore, the blunted responses of these brain regions during fear conditioning (in the absence of psychophysiological differences) in the OCD group may represent abnormal encoding of the associative learning



**Figure 4.** Correlations of the Yale-Brown Obsessive-Compulsive Scale (YBOCS) with brain reactivity during recall. **A**, A voxelwise regression analysis of total YBOCS scores during extinction recall indicated a significant correlation of brain activity with symptom severity in 5 brain regions (red circles). The top row displays regions found to have a positive correlation with YBOCS scores, while the bottom row displays regions found to have a negative correlation with YBOCS scores. Activation maps are illustrated with a threshold of  $t > \pm 2.0$  ( $P < .01$ , uncorrected), then overlaid on a template structural magnetic resonance image. **B**, Model of brain activation prediction of YBOCS scores. Results based on stepwise regression analysis found that insular cortex and cerebellum activation are the most predictive contributors of the 5 brain regions correlated with YBOCS scores. X indicates the region had no role in regression or no contribution to significance in the linear regression model. dACC indicates dorsal anterior cingulate cortex; OCD, obsessive-compulsive disorder; PCC, posterior cingulate cortex; vmPFC, ventromedial prefrontal cortex. \*  $P < .05$ ; †  $P < .001$ .

was entered into the equation as an independent variable ( $r^2 = 0.72$ ;  $F_{1, 15} = 39.69$ ;  $P < .001$ ) with an intercept of 37.47 and a  $\beta$  of 0.85. In step 2, the dACC was added to the equation as an independent variable, significantly increasing and contributing to the ability to predict ERI ( $r^2 = 0.84$ ;  $F_{2, 14} = 38.74$ ;  $P < .001$ ) with an intercept of 42.23 and  $\beta$  values of 0.69 (cerebellum) and  $-0.38$  (dACC; **Figure 5B**). Addition of the vmPFC, PCC, and insula cortex did not significantly improve the  $R^2$ , suggesting again that the most significant contributors to ERI are activations in the dACC and cerebellum. Forward and backward regression methods confirmed the final model obtained using stepwise selection.

**Table 3. Correlates of Symptom Severity (YBOCS) and ERI With Brain Activations During Extinction Recall in the Obsessive-Compulsive Disorder Group**

Area of Activation	MNI Coordinates	T	Size, Voxels	P Value		Region
				Cluster, FWE	Voxel, FWE <sup>a</sup>	
<b>YBOCS</b>						
Early CS+E>early CS+NE	4, 54, -6	3.05	17	.05	.05	vmPFC
	-24, -80, -32	5.94	81	.02	<.001	Cerebellum
	-14, -40, 16	5.03	77	.02	.002	PCC
Early CS+E<early CS+NE	-8, 2, 50	4.78	73	.02	.003	dACC
	32, 26, -2	4.63	81	.02	.002	Insula
<b>ERI</b>						
Early CS+E>early CS+NE	-4, 54, -10	3.32	43	.03	.03	vmPFC
	-10, -52, -14	6.23	75	.02	<.001	Cerebellum
	-4, -38, 16	4.09	50	.03	.009	PCC
Early CS+E<early CS+NE	6, 18, 30	3.51	60	.02	.02	dACC
	-24, 24, -4	4.60	62	.02	.004	Insula

Abbreviations: CS+, reinforced conditioned stimulus; dACC, dorsal anterior cingulate cortex; E, extinguished; ERI, extinction retention index; FWE, familywise error; MNI, Montreal Neurological Institute; NE, nonextinguished; PCC, posterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; YBOCS, Yale-Brown Obsessive-Compulsive Scale.

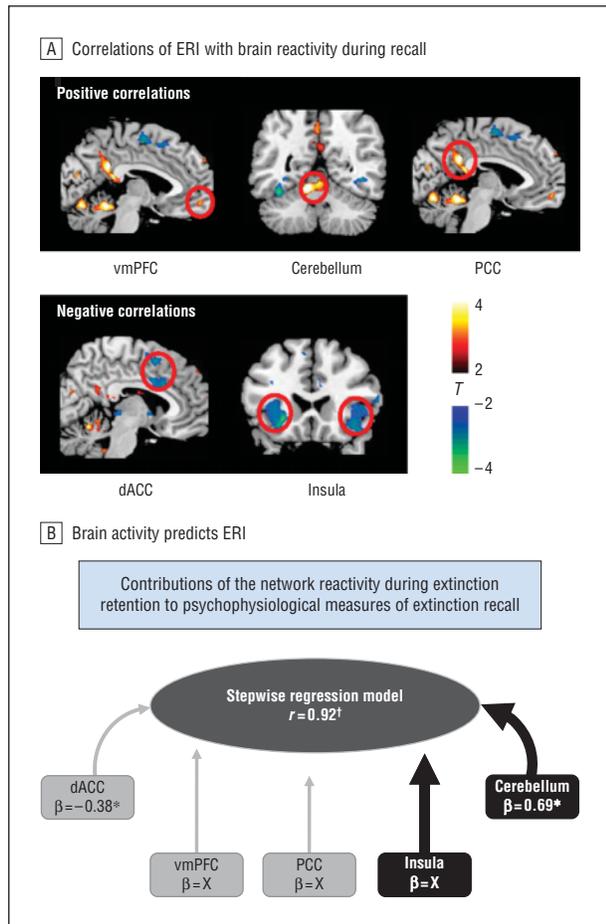
<sup>a</sup>Clusters surviving small-volume correction (5-mm radius sphere) corrected at  $P < .05$ , FWE.

needed to form fear memories in OCD, which may be related to the inflexibility to switch between fear and safety learning. Our data suggest that there may be differences in the neural networks expressing the peripheral measures of the conditioned fear and those involving the encoding of the fear memory per se. For example, it has been shown that the dACC, insular cortex, and other brainstem regions are key areas involved in the expression of conditioned responses in humans.<sup>6,42,43</sup> In the present study, we observed comparable activations in these brain regions in the 2 groups studied, supporting the lack of between-group differences at the psychophysiological level. Thus, the abnormal function within the caudate and hippocampus in OCD during the fear conditioning phase may be related to abnormal consolidation of the associative fear memory and not so much in its expression. However, an alternative explanation is that our skin conductance measure was not as sensitive as our imaging indices in detecting between-group differences in this task.

During fear extinction, we observed extinction-associated deficits in patients with OCD in a locus within the prefrontal cortex observed in this study that is distinct from the commonly reported hyperactivation of more lateral orbitofrontal cortical regions in OCD. The abnormal function of this vmPFC region in OCD has been previously reported when subjects with OCD undergo a different behavioral paradigm (error detection).<sup>44</sup> The impaired fear extinction recall and blunted vmPFC activation during extinction recall in the OCD group examined is comparable to data in patients with PTSD and schizophrenia.<sup>13,45,46</sup> Another common element between the 2 disorders is the aberrant putamen activation. The functional abnormality we observed in the putamen during extinction recall in OCD is consistent with the involvement of this brain region in fear conditioning and emotion regulation and has also been previously implicated in the pathophysiology of OCD.<sup>1</sup> We have shown that the putamen exhibits increased activation to conditioned and uncon-

ditioned cues to fear acquisition and has been shown to exhibit dysfunctional responses in patients with PTSD undergoing fear conditioning.<sup>5</sup> The abnormal responses of the putamen, together with that observed in the PCC, also distinguish the functional deficits during extinction recall in OCD from PTSD, the latter exhibiting deficits in the dACC and hippocampus instead. Thus, while there are common dysfunctions between OCD and PTSD, there are many differences in abnormal responsivity within the context of fear learning and extinction that highlight the distinct neural correlates associated with the 2 disorders.

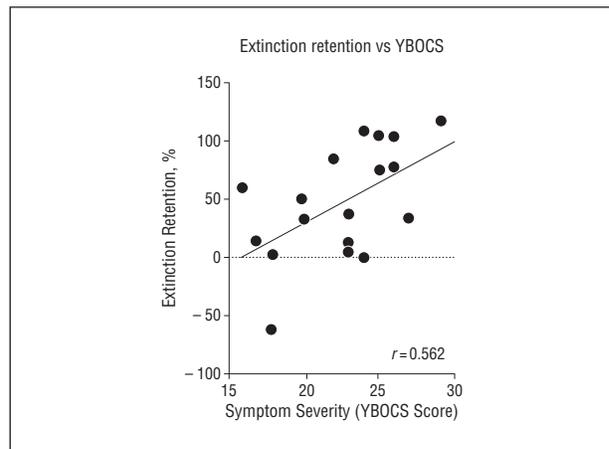
Within the vmPFC, we observed reduced activation in the patients with OCD during extinction recall. However, others have reported error-related hyperactivation of the vmPFC in patients with OCD.<sup>47,48</sup> Previous positron emission tomography studies have shown increased resting metabolic activity within the adjacent OFC (more ventral and lateral regions) that was associated with symptom provocation and severity in patients with OCD.<sup>49,50</sup> One factor that may be contributing to differences in vmPFC activation observed in our study and those observed by others is that fMRI is the use of different behavioral tasks. For example, Fitzgerald et al<sup>48</sup> used error-related monitoring task, which is arguably a more cognitive task when compared with the experimental task used in our study. Another factor is that in measuring activation (ie, relative activity), fMRI does not account for differences in baseline activity. Thus, the diminished regional activation in OCD observed in this study could be a consequence of higher baseline activity. This is especially germane, as resting state studies of OCD using positron emission tomography with <sup>18</sup>fluorodeoxyglucose have typically found elevated activity in the OFC, striatum, and ACC. Although there may be an apparent inconsistency as to whether the vmPFC/OFC is hypoactive or hyperactive in patients with OCD, our results, together with those from positron emission tomography and previous fMRI studies, suggest that lat-



**Figure 5.** Correlations of the extinction retention index (ERI) score with brain reactivity during recall. **A**, A voxelwise regression analysis of ERI scores during extinction recall indicated a significant correlation of brain activity with psychophysiological measurements of the ability to recall extinction memory in 5 brain regions (red circles). The top row displays regions found to have a positive correlation with ERI scores, while the bottom row displays regions found to have a negative correlation with ERI scores. Activation maps are illustrated with a threshold of  $t > \pm 2.0$  ( $P < .01$ , uncorrected), then overlaid on a template structural magnetic resonance image. **B**, Model of brain activation prediction of ERI scores based on a stepwise regression analysis. Results found that dorsal anterior cingulate cortex (dACC) and cerebellum activation are the most predictive contributors of the 5 brain regions correlated with ERI scores. X indicates region did not have any significant contributions to the statistical model tested in the multilinear regression model. PCC indicates posterior cingulate cortex; vmPFC, ventromedial prefrontal cortex. \*  $P < .05$ ; †  $P < .001$ .

eral and medial portions of the OFC are dysfunctional in OCD.

The cerebellum plays a role in processing fear memories<sup>51</sup> and has been implicated in the extinction of eye-blink conditioning.<sup>52</sup> We have previously reported significant increase in cerebellum activation during extinction recall in healthy humans.<sup>10,28</sup> In OCD, both structural and functional abnormalities in this brain region have been previously reported and have been linked to symptom severity. For example, reduced cerebellar functional responsivity in a Stroop task has been reported in OCD, and that cognitive behavioral therapy resulted in the normalization of this impairment.<sup>53</sup> Structural and functional abnormalities within the cerebellum have been reported in OCD and Tourette syndrome and have been associated with increased severity in tic and OCD symp-



**Figure 6.** Ability to recall extinction training correlates with symptom severity. Symptom severity, as measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS) score, was found to positively correlate with the individual's extinction retention index, a measure indicative of the ability to recall extinction training. The worse the individual's obsessive-compulsive disorder symptoms, the better that ability to recall extinction memory.

toms as well as motor disinhibition.<sup>54,55</sup> In the present study, the blunted response in the cerebellum observed in patients with OCD is consistent with its potential role in the psychopathology of OCD. Additional studies are needed to further explore the role of the cerebellum in this disorder.

While we did not observe any between-group differences in the functional activation of the insular cortex or the dACC, activation of both structures during extinction recall, along with the vmPFC, PCC, and cerebellum, was correlated with both magnitude of extinction recall and symptom severity in patients with OCD. One unanticipated result from our stepwise regression analysis was that functional responses within the vmPFC during recall was not one of the key predictors of OCD symptoms or extinction retention. Instead, our results showed that the insular cortex and cerebellum were key predictors of OCD symptom severity, and the dACC and cerebellum were significant predictors of the extinction memory recall in patients with OCD. As just noted, these analyses further highlight the potential role of the cerebellum in the pathophysiology of OCD. The involvement of the insular cortex and dACC as significant predictors of YBOCS and extinction scores may be related to the expression of fear and arousal associated/indexed by these measures. For example, the role of the insular cortex in interoceptive processing is well documented.<sup>56</sup> Thus, the significant contribution of the insular cortex to variance in YBOCS and extinction retention scores may be related to differences in interoceptive processing.<sup>57</sup>

We predicted that deficient extinction in patients with OCD would be inversely correlated with the YBOCS scores. We also predicted that vmPFC dysfunction would be inversely correlated with symptom severity. Our data showed that the better the extinction retention, the worse the OCD symptom severity. Moreover, more activation of the vmPFC (and less dACC) correlated with worse OCD symptoms. We conducted the same correlations with the

subscales of OCD (obsessions alone and compulsions alone) and again the same finding was observed (data not shown). One possible paradoxical data, is that patients with worse, or more elevated OCD symptoms, could have developed coping/avoidance mechanisms when facing aversive or unwanted stimuli. If the patients are able to avoid, fear toward the aversive stimuli is reduced.

Studies have now shown that OCD treatment with D-cycloserine enhances the efficacy of cognitive behavioral therapy in patients with OCD,<sup>58,59</sup> although some investigators did not observe this effect.<sup>60</sup> D-cycloserine has been shown to facilitate fear extinction in rodents via its effects on N-methyl-D-aspartate receptors.<sup>61</sup> It has been suggested that the clinical improvement observed with D-cycloserine use in OCD may be owing to enhancing extinction mechanisms,<sup>59</sup> but deficits in extinction in this clinical population have not been previously noted. Our data showed that extinction retention is deficient in patients with OCD, yet the correlation between OCD symptom severity and the magnitude of fear extinction was not in the expected direction. This raises an important point, which is that there may be additional factors or variables in patients with OCD that may contribute to or correlate with deficient fear extinction. Additional studies investigating different subtypes of OCD with larger sample sizes may help elucidate some of these factors and begin to examine how D-cycloserine may modulate de novo extinction capacity in patients with OCD.

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