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Emotion Regulation in Obsessive-Compulsive Disorder, Unaffected Siblings, and Unrelated Healthy Control Participants

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ABSTRACT

BACKGROUND: Functional neuroimaging endophenotypes of obsessive-compulsive disorder (OCD) have been suggested during executive tasks. The purpose of this study was to investigate whether behavioral and neural responses during emotion processing and regulation also represent an endophenotype of OCD.

METHODS: Forty-three unmedicated adult OCD patients, 19 of their unaffected siblings, and 38 healthy control participants underwent 3T functional magnetic resonance imaging during an emotion regulation task including neutral, fear-inducing, and OCD-related visual stimuli. Stimuli were processed during natural appraisal and during cognitive reappraisal, and distress ratings were collected after each picture. We performed between-group comparisons on task behavior and brain activation in regions of interest during emotion provocation and regulation.

RESULTS: Siblings reported similar distress as healthy control participants during provocation, and significantly less than patients. There was no significant three-group difference in activation during fear provocation or regulation. Three-group comparisons showed that patients had higher amygdala and dorsomedial prefrontal cortex activation during OCD-related emotion provocation and regulation, respectively, while siblings were intermediate between patients and control participants but not significantly different from either. Siblings showed higher left temporo-occipital activation (compared with both healthy control participants and patients) and higher frontolimbic connectivity (compared with patients) during OCD-related regulation.

CONCLUSIONS: Unaffected siblings do not show the same distress and amygdala activation during emotional provocation as OCD patients. Siblings show distinct activation in a temporo-occipital region, possibly related to compensatory cognitive control. This suggests that emotion regulation is not a strong endophenotype for OCD. When replicated, this contributes to our understanding of familial risk and resilience for OCD.

Keywords: Emotion regulation, Emotional provocation, Endophenotype, Familial risk, fMRI, Obsessive-compulsive disorder

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Obsessive-compulsive disorder (OCD) is characterized by distressing obsessive thoughts, urges, or images that patients try to manage or neutralize through compulsive behaviors (1). The disorder affects 1% to 3% of the population (1) and has a large impact on social and personal impairment (2,3). OCD is a highly familial disorder (4), with first-degree family members of OCD patients having a nearly fivefold increase in the odds of developing the disorder compared with family members of non-OCD participants (5). Although genetic factors may explain as much as 47% of the variance of the risk for developing OCD (5), the underlying genetic factors are not well known (4).

An endophenotype is defined as a measurable trait along the path between the phenotype of the disorder and the distal genotype (6). Because of the considerable heterogeneity in the symptoms, etiology, and genetic risk markers of OCD, the diagnosis itself is hard to robustly relate to genetic variation (4,7,8). Endophenotypes may provide simpler clues to the genetic basis of a disorder than the disorder itself and contribute to bridging clinical heterogeneity and genetic vulnerability (6). In this context, functional neuroimaging studies on endophenotypes allow for investigating shared behavioral and neural characteristics between OCD patients and their first-degree unaffected family members, in comparison with unrelated healthy control participants (9). Previous functional neuroimaging studies showed that OCD patients and their unaffected relatives show similarities in neural responses during response inhibition (10,11), working memory (12), reversal learning (13), and error monitoring (14). For example, in previous reports on response inhibition and working memory involving the same participants as in the

current study, OCD patients and their unaffected siblings shared compensatory higher task-related activation in the left presupplementary motor area, as well as altered frontolimbic connectivity, compared with unrelated healthy control participants (10,12,15).

Neural responses during paradigms using emotion provocation with disorder-specific stimuli may provide a more disorder-specific endophenotype for OCD, as deficits in executive functioning are not specific to this disorder (16). When confronted with disorder-specific objects, situations, or thoughts, OCD patients often react with negative emotions such as anxiety, fear, guilt, or disgust, and they often experience an increased urge to ritualize (17,18). In a recent meta-analysis of 25 whole-brain studies contrasting aversive and neutral stimuli, OCD patients showed higher activation than control participants during emotion provocation in the bilateral amygdala, right putamen, orbitofrontal cortex (extending into the subgenual anterior cingulate cortex and ventromedial prefrontal cortex [PFC]), middle temporal cortex, and left inferior occipital cortex (19).

Emotion regulation involves changing emotional responses through active processes such as altering attentional deployment, cognitive reappraisal (reinterpreting the meaning and one's connection to a stimulus), or suppression of the expression or experience of an emotion, and over time these active processes are learned and become more automatic (20). Functional magnetic resonance imaging (fMRI) studies have shown that cognitive reappraisal is associated with higher activation in the dorsomedial and lateral frontal cortices, dorsal anterior cingulate cortex, and parietal and temporal regions (21,22).

Cognitive behavioral models suggest that the catastrophic interpretations of obsessions and the use of compulsions as dysfunctional methods of emotion regulation maintain the disorder (23). Maladaptive emotion regulation strategies, such as suppression, have also been related to increased distress in response to obsessions over time, while acceptance decreases distress (24). In addition, suppression has been related to increased severity of OC symptoms (25). In a previous study we investigated whether unmedicated OCD patients and healthy control participants differed in how successfully they used cognitive reappraisal to regulate distress provoked by fear- and OCD-related pictures, and whether OCD patients show altered activation of emotion regulation–related circuitry using fMRI (26). We showed that distress ratings were higher in OCD patients than in control participants, but that patients were well able to downregulate distress while viewing fear- and OCD-related pictures within the experimental setting. However, this was accompanied by aberrant brain activation in patients versus control participants. OCD patients showed greater emotion provocation-induced amygdala activation and altered timing, while emotion regulation–related activation was lower in the left dorsolateral PFC (dlPFC) and parietal cortex while viewing fear-related pictures, and higher in the dorsomedial PFC (dmPFC) while viewing OCD-related pictures. In addition, patients also showed less functional connectivity between the dmPFC and bilateral amygdala during regulation of fear-related pictures (26). This suggests that OCD patients show frontolimbic and frontoparietal dysfunction during emotion processing, but whether this dysfunction represents a consequence of the disorder or an underlying vulnerability factor remains unanswered.

The aim of the present study was to explore the neural correlates of disorder-specific emotion provocation and regulation as a potential endophenotype of OCD. Extending our previous findings on emotion regulation in OCD, we compared distress ratings and brain activation during emotion provocation and regulation in a group of unaffected siblings, with those of the previously studied OCD patients and healthy control participants (26). Using group comparisons of task-related activation in a priori regions of interest (ROIs), as well as frontolimbic functional connectivity analyses, shared and nonshared activation patterns during emotion provocation and regulation of general fear– and OCD-related stimuli were probed. Based on the previous endophenotype findings in this sample using executive paradigms (10,12,15), we hypothesized that siblings would resemble healthy control participants on the behavioral level (i.e., normal levels of provoked distress) and also show similar amygdala activation during emotion provocation (i.e., less activation compared with OCD patients). During regulation we expected that siblings would resemble OCD patients on the neural level (i.e., decreased activation in dlPFC during fear regulation, increased dmPFC activation during OCD-related regulation, and reduced frontolimbic connectivity compared with healthy control participants).

METHODS AND MATERIALS

Participants

Forty-three patients with a primary diagnosis of OCD, 19 of their unaffected siblings, and 38 healthy control participants were included in the study (see the Supplement for recruitment information). All participants were assessed using the Structured Clinical Interview for DSM-IV (27). The Yale-Brown Obsessive Compulsive Scale (28) and the Obsessive-Compulsive Inventory–Revised (29) were used to assess the severity of OC symptoms. Depressive symptoms were measured using the Montgomery–Åsberg Depression Rating Scale (30). The Emotion Regulation Questionnaire (31) was used to measure reappraisal and suppression as emotion regulation strategies in daily life. Handedness was assessed using the Edinburgh Handedness Inventory (32).

All participants had not used psychotropic medication for at least 4 weeks before inclusion, and had no psychotic symptoms, major physical or neurological illness, or any MRI contraindications. All patients had a primary diagnosis of OCD according to DSM-IV criteria and did not meet criteria for hoarding disorder. Patients experiencing other comorbidities were included as long as OCD was the primary diagnosis. Control participants were excluded if they met criteria for any current DSM-IV diagnosis, while siblings were excluded if they had a lifetime history of OCD. The study was in full compliance with the ethical standards of the local medical ethical review board of VU University Medical Center and with the Helsinki Declaration of 1975, revised in 2008, and all participants provided written informed consent.

The results of the comparison between OCD patients and healthy control participants have been presented previously (26). All subjects also participated in previous endophenotype analyses on response inhibition (10) and working memory (12).

The data for these reports were all collected during the same experiment.

Experimental Task

All participants performed an emotion regulation task [see de Wit *et al.* (26) and the Supplement for detailed procedures] and were presented with neutral, fearful, and OCD-related pictures. The OCD stimuli included those pertinent to washing, checking, and symmetry symptom dimensions, and all the participants watched the same stimuli to capture the symptom heterogeneity of OCD. The participants were instructed to either simply attend to the presented stimulus ("attend" instruction) or use cognitive reappraisal techniques to downregulate negative emotions and cognitions provoked by the stimulus ("regulate" instruction). Stimuli were presented in attend or regulate blocks for each picture type, and each stimulus was followed by having the participants indicate their current level of distress by moving a cursor to either the left (marked "not distressed") or the right ("maximally distressed") along a visual analog scale. Neutral stimuli were presented in the attend condition only.

Statistical Analysis of Behavioral and Clinical Measures

Group comparisons of clinical and demographical variables were analyzed using one-way analyses of variance (ANOVAs), and followed up by post hoc two-sample *t* tests. Categorical variables were analyzed using χ^2 tests. Distress scores during the attend and regulate conditions were analyzed separately for fear- and OCD-related pictures using repeated-measures mixed ANOVAs, with group (OCD patients, siblings, control participants) as the between-subjects factor followed by post hoc *t* tests if the main effects were significant. Within-group tests of changes in distress during provocation and regulation were analyzed with paired-sample *t* tests. Analyses were performed using SPSS statistics version 23 (IBM Corp., Armonk, NY). The statistical threshold was set at $p < .05$, with Tukey or Games-Howell corrections being used for post hoc tests of one-way and repeated-measures ANOVAs.

MRI Acquisition, Processing, and Analysis

Functional gradient echo-planar and structural T1-weighted imaging was performed on a GE Signa HDxt 3.0T MRI scanner (GE Healthcare, Chicago, IL). Functional data were preprocessed and analyzed in SPM8 (Wellcome Trust Centre for Imaging, London, United Kingdom) (see the Supplement for acquisition parameters and preprocessing steps). Intrasubject first-level analyses included nine regressors of interest consisting of the neutral (attend only), general fear, contamination, checking, and symmetry OCD-related pictures during attend and regulate instruction. Regressors of no interest included the time windows where the participants rated their distress (boxcars of 5 seconds), instruction periods (boxcars of 3 seconds), and the participant's six movement parameters. The first-level analyses were different for emotion provocation and emotion regulation to capture the different timings of these respective processes [as we described previously in de Wit *et al.* (26)]. In the emotion provocation analysis, regressors of interest were modeled as 0-second delta functions and convolved with the canonical hemodynamic response function (HRF), and its temporal and dispersion derivatives to model the amplitude of the blood oxygen level–dependent response and variation in its timing and shape. Fear > neutral and OCD > neutral contrast images (collapsed over the attend and regulate instructions) were then computed per participant. In the emotion regulation analysis, activation during emotion regulation was modeled as boxcars of the first 5 seconds of fear and the OCD-related stimuli, and were convolved with the canonical HRF. Contrast images were then computed for fear regulate > attend and OCD regulate > attend. A high-pass filter with a 128-second cutoff was used to remove low-frequency noise. See the Supplement for all additional information on MRI acquisition and modeling.

To test whether unaffected siblings also showed altered functional connectivity between the bilateral amygdala and dmPFC during emotion regulation, which was previously reported for patients versus control participants (26), we used the Generalized Psychophysiological Interaction toolbox (33) (see the Supplement). The dmPFC seed region was set at Montreal Neurological Institute x/y/z of −9/8/64, with a 10-mm sphere, based on the patient-control comparison (26). The WFU PickAtlas (http://fmri.wfubmc.edu/software/pickatlas) was used to determine the bilateral amygdala ROIs for functional connectivity.

Planned group comparisons were performed by entering the first-level contrast images into general linear models using SPM12. Between-group comparisons for emotion provocation were performed using separate 3 × 3 ANOVAs with group (OCD patients, siblings, control participants) as a between-subject factor and HRF (canonical, temporal, dispersion) as a within-subjects factor. A 3 × 2 × 3 ANOVA (group by HRF by picture type [fear- and OCD-related]) was used to test the group by picture type interactions. Group comparisons of emotion regulation and functional connectivity were performed using separate one-way ANOVAs for the two picture types (fear- and OCD-related stimuli), with group as the between-subjects factor. For all group comparisons we first used an *F* contrast to estimate the main effect of group, and the group by instruction interaction where appropriate. Post hoc two-group comparisons were then performed to follow-up significant effects (two-group ANOVAs for the emotion provocation analysis and *t* tests for the emotion regulation analysis).

We used an ROI approach, which was derived from the largest meta-analyses of emotion provocation in OCD compared with healthy control participants (five ROIs) (19), and emotion regulation in healthy control participants (eight ROIs) (21,22), as no published meta-analysis of emotion regulation comparing OCD patients and healthy control participants was available (see Supplemental Table S2 for all ROIs, and the Supplement for more information on ROI definitions, placement, and extraction). The ROIs were placed at the relevant effects of task after initial image thresholding of uncorrected $p < .001$. Statistical significance was set at $p < .05$ familywise error corrected with small volume correction (*p*FWE-SVC) with a 10-mm sphere (*p*FWE-SVC < .05; trends $p < .10$) (34). Results were corrected for the number of ROIs for each contrast using a SISA-Bonferroni correction (see http://www.quantitativeskills.com/sisa/calculations/bonhlp.htm) (35). Separate SISA-Bonferroni corrected *p* values were calculated

per analysis because of differences in provocation related distress and regulation-related reductions in distress between the picture types (see the Supplement for more information).

RESULTS

Demographic and Clinical Characteristics

The groups were demographically matched. Patients scored significantly higher on every clinical measure compared with both siblings and control participants, while siblings and control participants did not significantly differ (see Supplemental Table S1 for all results). For the Emotion Regulation Questionnaire, there was a main effect of group for the use of reappraisal. Post hoc tests showed that patients scored lower than control participants, and siblings scored intermediate (not significantly different from either). Twenty-one OCD patients (49%) had a comorbid DSM-IV diagnosis (details in Supplemental Table S1). One sibling met criteria for specific phobia, which did not interfere with scanning, while no control participants met criteria for any current mental disorder.

Distress Ratings During Emotion Provocation and Regulation

Fear- and OCD-related pictures elicited more distress than neutral pictures for all three groups, regardless of the task instruction (all $p < .05$) (see Table 1 for all behavioral results). There was a significant main effect of group (F contrast: fear, $p < .001$; OCD, $p < .001$), with post hoc tests showing that OCD patients reported more distress in general during both fear- and OCD-related pictures than healthy control participants and siblings, whereas siblings were not significantly different from control participants (t test: fear related, $p = .97$; OCD related, $p = .86$). There was a main effect of regulation across the three groups (F contrast: fear related, $p = .02$; OCD related, $p < .01$). For fear stimuli there was no significant group by instruction interaction ($p = .06$), whereas the interaction analysis was significant for OCD stimuli ($p < .01$). Post hoc two-sample t tests showed that OCD patients reported significantly larger distress reductions during OCD-related regulation compared with both siblings ($t_{43.29} = -3.79$, $p < .01$) and control participants ($t_{75.16} = -2.59$, $p = .01$), whereas siblings were not different from control participants ($t_{55} = 0.57$, $p = .57$).

Within-group paired-sample t tests revealed a regulation effect (higher distress ratings during attend instruction compared with regulation instruction) for OCD patients while viewing both picture types and in healthy control participants for fear-related pictures (all $p \leq .05$). In siblings, there was no regulation effect for fear-related ($p = .43$) or OCD-related ($p = .06$; trend) pictures.

Neural Response During Emotion Provocation in ROIs

The three-group comparison for fear provocation showed no significant differences between the groups (Supplemental Table S3). During OCD-related provocation there was a significant main effect of group in the right amygdala extending into the hippocampus, driven by alterations in the timing and shape of the blood oxygen level–dependent response in OCD patients compared with healthy control participants, whereas siblings were intermediate and not significantly different from either group (Table 2). The group by picture type interaction analysis was trend significant ($p = .02$) (Table 2). This was driven by higher responses in the right amygdala during OCD-related rather than fear-related provocation in patients compared with healthy control participants, as we previously showed (26), whereas the siblings were an intermediate group not different from either group.

Neural Response During Emotion Regulation in ROIs

Three-group comparison showed no significant group differences in activation in any of the ROIs during fear-related emotion regulation. For OCD-related regulation a significant main effect of group was found in the dmPFC and the left temporo-occipital cortex (see Table 3 and Figure 1). On post hoc tests, siblings showed significantly higher activation in the left temporo-occipital cortex compared with healthy control participants and patients. Higher dmPFC activation, as previously found in patients compared with healthy control participants, was also present in siblings compared with control participants, albeit at a trend level.

Functional Connectivity During Emotion Regulation in ROIs

The comparisons of frontolimbic connectivity during fear- and OCD-related regulation did not reveal any significant differences between the three groups (Supplemental Table S6). Exploratory post hoc analyses showed that the previously reported decreased frontolimbic connectivity in patients compared with healthy control participants during fear-related regulation was present for the left (Z score = 3.36, pFWE-SVC = .016) and right amygdala (Z score = 3.30, pFWE-SVC = .019) but that siblings were an intermediate group not significantly different from either group (see Supplemental Figure S1 for group-specific parameter estimates). Specifically, pairwise comparisons of connectivity during OCD-related regulation showed higher dmPFC-amygdala connectivity in siblings compared with patients (Z score = 3.22, pFWE-SVC = .023) and right amygdala (Z score = 3.30, pFWE-SVC = .019), while there were no other significant between-group differences.

DISCUSSION

The present study assessed whether the neural correlates of disorder-specific emotion processing and regulation can serve as a potential endophenotype of OCD. To this aim, we investigated emotion processing during fMRI scanning in unaffected siblings of a large sample of unmedicated OCD patients and in unrelated healthy control participants. We found that siblings resembled control participants in self-reported distress and clinical profile. When assessing brain activation patterns in ROIs during emotion provocation and regulation, we mostly observed that siblings were an intermediate group between patients and control participants. We also found that siblings showed slightly higher dmPFC activation during OCD-related regulation compared with OCD patients and healthy control participants, but this difference was not statistically significant.

Table 1. Group Comparisons of Behavioral Response: Distress During Provocation and Regulation

	OCD Patients (n = 43)			Siblings (n = 19)			HC Participants (n = 38)		
Neural Pictures	Mean	SD		Mean	SD		Mean	SD	
Provocation	2.04	5.24		0	0		0.74	2.78	
Fear-Related Pictures	Mean	SD		Mean	SD		Mean	SD	
Provocation	41.44	31.15		16.42	14.58		20.74	26.53	
Regulation	33.74	28.29		14.68	14.20		13.21	15.57	
	t	*df*	*p*	*t*	*df*	*p*	*t*	*df*	*p*
Provocation vs. regulation	2.02	42	.05[a]	0.80	18	.43	2.12	37	.04[a]
	F			*df*			*p*		
Main effect of group	11.28			1, 97			<.01[a]		
Main effect of instruction	5.98			1, 97			.02[a]		
Group × instruction interaction	0.57			2, 97			.57		
	t			*df*			*p*		
Post hoc tests (provocation)									
Siblings vs. OCD	−4.31			59.72			<.01[a]		
Siblings vs. HC participants	−0.66			55			.84		
Post hoc tests (regulation)									
Siblings vs. OCD	−3.53			58.89			<.01[a]		
Siblings vs. HC participants	0.39			55			.97		
OCD-Related Pictures	Mean	SD		Mean	SD		Mean	SD	
Provocation	22.30	17.95		2.75	4.56		4.88	11.93	
Regulation	14.36	9.82		2.26	4.51		3.21	7.05	
	t	*df*	*p*	*t*	*df*	*p*	*t*	*df*	*p*
Provocation vs. regulation	4.08	42	<.001[a]	2.02	18	.06	1.15	37	.26
	F			*df*			*p*		
Main effect of group	25.52			1, 97			<.01[a]		
Main effect of instruction	9.86			1, 97			<.01[a]		
Group × instruction interaction	5.47			2, 97			<.01[a]		
	t			*df*			*p*		
Post hoc tests (provocation)									
Siblings vs. OCD	−6.67			52.56			<.01[a]		
Siblings vs. HC participants	−0.75			55			.84		
Post hoc tests (regulation)									
Siblings vs. OCD	−6.64			59.85			<.01[a]		
Siblings vs. HC participants	−0.62			55			.91		

Responses were rated on a scale of 1 to 100.
HC, healthy control; OCD, obsessive-compulsive disorder.
[a]Significant within- or between-group effect.

We previously compared the same group of patients and control participants directly (26) and observed in OCD patients amygdala hyper-responsiveness during OCD-related emotion provocation, dlPFC hypoactivation and lower dmPFC-amygdala connectivity during fear regulation, and dmPFC hyperactivation during OCD-related emotion regulation. Here, we found that prefrontal and amygdala activation were not significantly different in siblings compared with either OCD patients or control participants during either OCD-related emotion provocation (amygdala) and regulation (dmPFC) or emotion regulation of fear stimuli (dlPFC activation and dmPFC-amygdala connectivity). A sibling-specific finding was increased activation in the temporo-occipital cortex, bordering on the angular gyrus, during OCD-related emotion regulation, in siblings compared with both control participants and patients. Siblings also showed higher dmPFC-amygdala connectivity compared with patients during OCD-related emotion regulation. The difference between the findings in the present report and the earlier report is likely due to methodological differences: 1) the present use of a priori defined ROIs based on meta-analyses, compared with the earlier use of functionally defined ROIs (26), and 2) due to performing a three-group ANOVA in which the dlPFC response in the sibling group is intermediate between patients and control participants. This is also reflected in the Supplemental whole-brain results, showing the same hypoactivation of the dlPFC during fear-related regulation in OCD patients compared with healthy control participants.

Table 2. Group Comparisons of Brain Activation During Emotion Provocation

	BA	Side	K_e	MNI Coordinates x	y	z	*Z*	*p*FWE-SVC
Fear Provocation: Main Effect of Group (ANOVA) (no significant voxels)								
OCD-Related Provocation: Main Effect of Group (ANOVA)								
Amygdala	N/A	R	12	27	−7	−17	3.58	.013[a]
Fear-Related vs. OCD-Related Provocation: Group by Picture Type Interaction (ANOVA)								
Amygdala	N/A	R	5	27	−7	−17	3.45	.020[b]
		K_e		*Z* Score		*p*FWE-SVC		
OCD-Related Provocation: Post Hoc Pairwise Comparisons in Right Amygdala								
Siblings vs. HC participants		NS		NS		NS		
Siblings vs. OCD		NS		NS		NS		
OCD patients vs. HC participants		21		4.22		.001[a]		
Fear-Related vs. OCD-Related Provocation: Post Hoc Pairwise Comparisons in Right Amygdala								
Siblings vs. HC participants		NS		NS		NS		
Siblings vs. OCD patients		NS		NS		NS		
OCD patients vs. HC participants		19		4.12		.001[a]		

ANOVA, analysis of variance; BA, Brodmann area; FWE, familywise error; HC, healthy control; K_e, voxel extent of cluster; MNI, Montreal Neurological Institute; N/A, not applicable; NS, not significant; OCD, obsessive-compulsive disorder; R, right; SVC, small volume correction.
[a]Significant between-group findings.
[b]Trend significant.

One explanation for the current findings is that in OCD, altered emotion processing is more state dependent than the previously reported traitlike cognitive endophenotypes, which were found to be related to altered frontoparietal recruitment, and likely related to a shared genetic vulnerability to the disorder (10,12,15). Previous task-related fMRI studies in first-degree relatives of OCD patients showed altered recruitment of frontal and parietal regions including the presupplementary motor area (10,12), dlPFC (12,13), inferior frontal gyrus (13), parietal cortex (12,13), and precuneus (12) during reversal learning, response inhibition, working memory, and error processing. During resting state, this sample of unaffected siblings (compared with healthy control participants) also showed higher connectivity between the frontoparietal control networks and the rostral anterior cingulate cortex and dmPFC, whereas only patients showed alterations in the frontolimbic circuit (36). Similarly, in this same sample of siblings, frontal-amygdala coupling during executive task we observed to have small or trend-significant aberrations, whereas findings in patients compared with control participants were more robust (12,15). In the present study, exploratory post hoc tests showed that siblings exhibited greater dmPFC-amygdala connectivity during disorder-specific emotion regulation than OCD patients. The increased frontolimbic connectivity in

Table 3. Group Comparisons of Brain Activation During OCD-Related Emotion Regulation

	BA	Side	K_e	MNI Coordinates x	y	z	*Z*	*p*FWE-SVC
Fear Regulation: Main Effect of Group (ANOVA) (no significant voxels)								
OCD-Related Regulation: Main Effect of Group (ANOVA)								
dmPFC	32	Midline	5	0	29	40	3.75	.005[a]
Temporo-occipital cortex	37	L	4	−39	−61	13	3.43	.013[a]
		K_e		*Z* Score		*p*FWE-SVC		
OCD-Related Regulation: Post Hoc Pairwise Comparisons in dmPFC								
Siblings > HC participants		1		3.22		.022[b]		
OCD patients > siblings		–		–		NS		
OCD patients > HC participants		10		3.82		.003[a]		
Post Hoc Pairwise Comparisons in Left Temporo-occipital Cortex								
Siblings > HC participants		18		3.67		.006[a]		
Siblings > OCD patients		2		3.22		.020[a]		
OCD patients > HC participants		–		–		NS		

ANOVA, analysis of variance; BA, Brodmann area; dmPFC, dorsomedial prefrontal cortex; FWE, familywise error; HC, healthy control; K_e, voxel extent of cluster; L, left; MNI, Montreal Neurological Institute; NS, not significant; OCD, obsessive-compulsive disorder; SVC, small volume correction.
[a]Significant between-group findings.
[b]Trend significant.

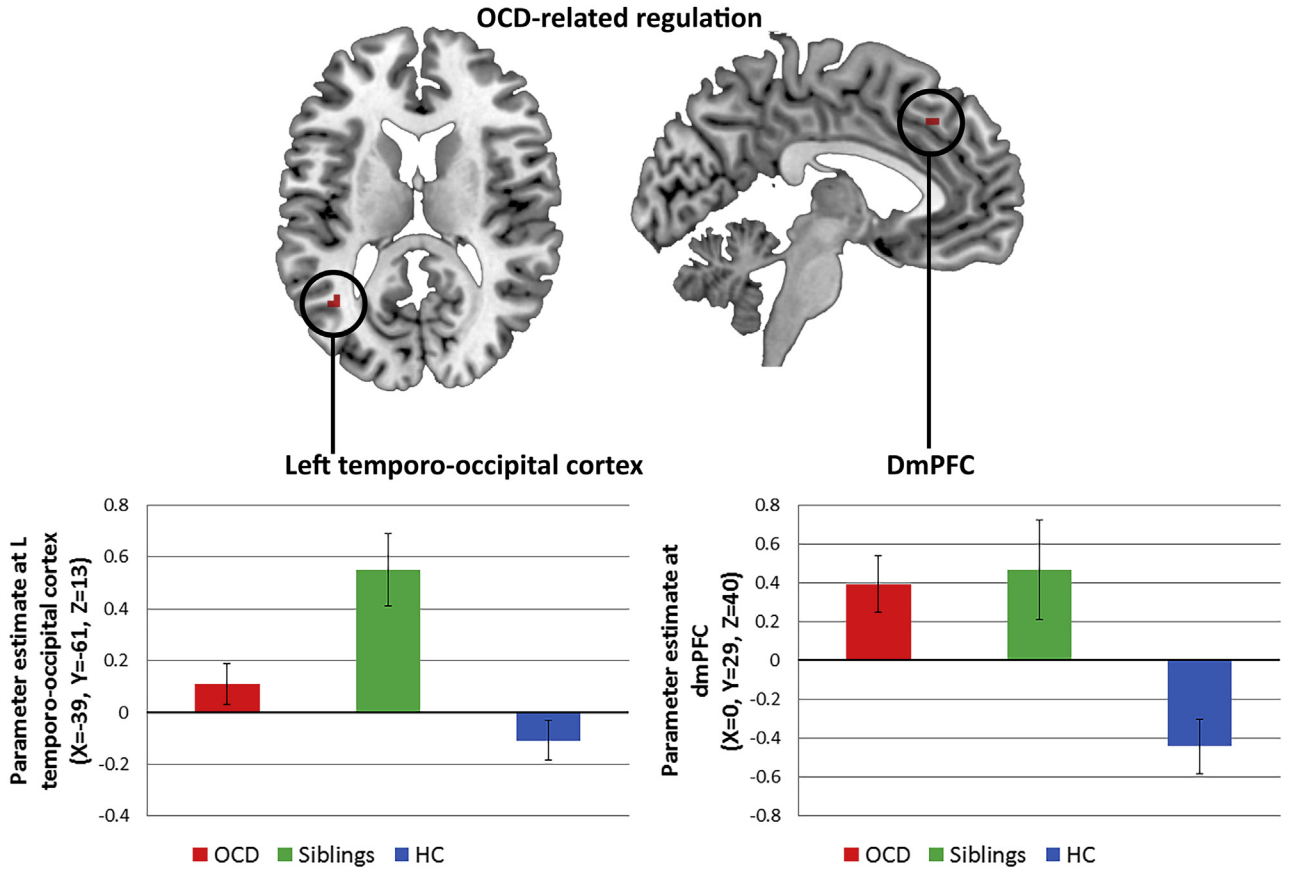

Figure 1. Group comparisons of activation during obsessive-compulsive disorder (OCD)–related emotion regulation. Top left: higher activation of the left temporo-occipital cortex in unaffected siblings compared with healthy control (HC) participants during OCD-related emotion regulation. Top right: higher activation of the dorsomedial prefrontal cortex (dmPFC) in OCD patients and siblings (trend) over HC participants during OCD-related emotion regulation. Bottom left and bottom right: parameter estimates of the blood oxygen level–dependent signal for each group during OCD-related regulation in the left temporo-occipital cortex and dmPFC, respectively. Parameter estimates are in arbitrary units, with standard errors. L, left.

siblings may represent a compensatory mechanism. Larger samples are needed, however, to better investigate this speculation.

It could also be that blood oxygen level–dependent responses in emotional paradigms in siblings are more variable than during executive functioning. This potential variability together with the relatively small sibling group size could have reduced the power to detect differences, resulting in the intermediate activation patterns in the siblings group. This is in contrast with findings in the same sibling group during inhibition and working memory where frontoparietal responses were more robust and/or extensive in the siblings compared with patients (10,12). Alternatively, a more robust provocation of distress in siblings and control participants might be needed to avoid floor effects during symptom provocation paradigms. Future research could consider how to evoke distress in healthy participants that resembles the response typically found in OCD patients.

One criterion for a candidate endophenotype is that the trait is more commonly found in unaffected family members of patients than in unrelated healthy control participants (6). Because we did not find that patients and their siblings showed the same degree of amygdala hyper-responsiveness during OCD-related emotion provocation, dlPFC hypoactivation during fear regulation, dmPFC hyperactivation during OCD regulation, or decreased frontolimbic connectivity during emotion regulation, we conclude that the neural correlates of emotion regulation are likely not a strong endophenotype of OCD.

The siblings showed increased temporo-parieto-occipital activation during regulation of disorder-specific stimuli compared with patients and control participants. The temporo-parieto-occipital brain regions are part of the larger cross-modal association cortex involved in attentional control and visuospatial representation during emotion processing (37). Taken together with the siblings' higher frontal-parietal network (36), our results suggest that siblings draw on additional resources compared with OCD patients and healthy control participants. This region has previously been reported as being especially recruited when distancing oneself from a stimulus to regulate one's emotions, while prefrontal dorsomedial and anterior cingulate activation is recruited more during reappraisal (20,38). We therefore speculate that siblings redirect their attention and distance themselves from aversive

stimuli before they elicit an emotional response, while the patients rely more on reinterpreting stimuli that are already aversively laden. This distinct recruitment of the temporo-occipital cortex in unaffected siblings could be interpreted as a compensatory response to an underlying vulnerability as seen in their afflicted siblings, possibly protecting them from developing the stronger emotional responses seen in their afflicted siblings. Structural abnormalities of nearby brain regions have been reported in siblings, including reduced fractional anisotropy in the right parietal lobule (39), and increased cortical thickness in the right precuneus (40).

Our findings of trend-significant increased dmPFC activation in siblings suggest that the OCD-related stimuli were somewhat more relevant for them than for the healthy control participants at a neural level, although this did not result in higher self-reported distress scores than in healthy control participants. Altered dmPFC activation may be related to the shared genetic vulnerability factors (increased threat sensitivity), or it might be part of a compensatory mechanism: OCD patients with lower Yale-Brown Obsessive Compulsive Scale scores reported more use of reappraisal in daily life, and also showed greater dmPFC activation during OCD-related regulation (26). In combination with the greater dmPFC activation in siblings, this suggests that dmPFC activation is compensatory, and not necessarily a vulnerability factor for OCD. Studying neural correlates of emotion processing using a longitudinal design (e.g., pre- and posttreatment) may help disentangle the neural correlates of genetic vulnerability and environmental risk (6) and the correlates of plasticity that result from disorder chronicity and successful treatment (41).

Limitations of the present study include the small number of siblings, which probably contributed to lower statistical power for this group, which could be especially relevant in the case of heterogeneity. The lower distress ratings and regulation effects in siblings and control participants suggest that the task was not as relevant for them, limiting the generalization of the findings to emotion regulation processes for more distressful situations. Finally, psychophysiological measures could have provided another view of data. Strengths include the large sample of unmedicated patients, the ability to differentiate between general fear and disorder-specific provocation and regulation-related brain activation and connectivity, and the use of rigorous meta-analyses to define a priori ROIs and adequate corrections for multiple comparisons.

Conclusions

Altered frontal and amygdala recruitment during emotion processing and regulation, although present in patients, is not a strong endophenotype of OCD. Siblings show distinct activation of the temporo-occipital cortex and frontolimbic connectivity during OCD-related emotion regulation, which may be a compensatory mechanism.

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