ORIGINAL ARTICLE

Neural Correlates of Moral Sensitivity in Obsessive-Compulsive Disorder

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Context: Heightened moral sensitivity seems to characterize patients with obsessive-compulsive disorder (OCD). Recent advances in social cognitive neuroscience suggest that a compelling relationship may exist between this disorder-relevant processing bias and the functional activity of brain regions implicated in OCD.

Objective: To test the hypothesis that patients with OCD demonstrate an increased response of relevant ventromedial prefrontal and orbitofrontal cortex regions in a functional magnetic resonance imaging study of difficult moral decision making.

Design: Case-control cross-sectional study.

Setting: Hospital referral OCD unit and magnetic resonance imaging facility.

Participants: Seventy-three patients with OCD (42 men and 31 women) and 73 control participants matched for age, sex, and education level.

Main Outcome Measures: Functional magnetic resonance imaging activation maps representing significant changes in blood oxygenation level–dependent signal in response to 24 hypothetical moral dilemma vs nondilemma task vignettes and additional activation maps representing significant linear associations between patients' brain responses and symptom severity ratings.

Results: In both groups, moral dilemma led to robust activation of frontal and temporoparietal brain regions. Supporting predictions, patients with OCD demonstrated significantly increased activation of the ventral frontal cortex, particularly of the medial orbitofrontal cortex. In addition, the left dorsolateral prefrontal cortex and left middle temporal gyrus were more robustly activated in patients with OCD. These results were unexplained by group differences in comorbid affective symptoms. Patients' global illness severity predicted the relative magnitude of orbitofrontal-striatal activation. The severity of "harm/checking" symptoms and "sexual/religious" obsessions predicted the magnitude of posterior temporal and amygdala-paralimbic activation, respectively.

Conclusions: The neural correlates of moral sensitivity in patients with OCD partly coincide with brain regions that are of general interest to pathophysiologic models of this disorder. In particular, these findings suggest that the orbitofrontal cortex together with the left dorsolateral prefrontal cortex may be relevant for understanding the link between neurobiological processes and certain maladaptive cognitions in OCD.

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EARLY PSYCHODYNAMIC THEORIES posited a link between obsessive-compulsive disorder (OCD) and heightened moral sensitivity that has become again relevant in contemporary cognitive behavioral models.[1,2] Moral sensitivity, for example, is intimately related to responsibility beliefs, which have been argued to be a primary cognitive bias in patients with OCD.[3,4] According to this view, an inflated sense of personal responsibility provoked by the harmful and immoral nature of common intrusive thoughts, images, or impulses leads to compulsive behaviors, such as checking, in an attempt to neutralize or prevent negative outcomes. Moral thought-action fusion is a related concept that is instead linked to misappraisals about the importance of one's thoughts, whereby the mere occurrence of intrusions is perceived as the moral equivalent of deliberately acting on them.[5] In both cases, compulsions are seen, in part, as direct attempts to reduce feelings of moral violation that arise from these maladaptive beliefs.[2,4,5]

Although cognitive behavioral models have traditionally been considered distinct from neurobiological accounts of

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OCD, with one seeking to explain obsessions and compulsions in terms of learned cognitive biases[2] and the other in terms of brain pathophysiological alterations,[6] there nevertheless exists potential for overlap.[7] We highlight recent developments in the social cognitive neuroscience of human moral cognition, which has implicated brain regions, such as the ventromedial prefrontal and orbitofrontal cortices, as being critical to the experience of moral emotions, such as guilt and shame.[8,9] In particular, functional imaging studies of healthy individuals consistently report activation of these regions, together with adjacent prefrontal, cingulate, and lateral temporoparietal regions—the so-called moral cognition network—in tasks that provoke moral emotions.[10-14] These findings have been corroborated by recent studies[15,16] of adult patients with ventromedial prefrontal and orbitofrontal cortex lesions, which show such patients to be less emotionally reactive to certain moral dilemmas and more likely to endorse moral violations despite intact moral reasoning.

Regarding OCD, there exists strong evidence[17-20] to implicate these ventral frontal cortex regions in the disorder's pathophysiology. For example, differences in orbitofrontal cortex structure and function have been consistently identified in neuroimaging studies of patients with OCD, often representing part of a broader pattern of frontostriatal brain changes. On the basis of functional neuroimaging studies in particular, orbitofrontal cortex activity seems to be increased under resting-state conditions in patients with OCD[21-25] and accentuated during symptom provocation and the urge to ritualize.[26-29] Although such findings do not generalize to all imaging study contexts,[30,31] increased orbitofrontal cortex activity seems to be most indicative of a patient's symptomatic state compared with changes in other brain regions.[18,20,32]

In this study, we used functional magnetic resonance imaging and a novel moral dilemma task to examine the putative neurobiological correlates of heightened moral sensitivity in patients with OCD. In keeping with an emerging neuroscientific view of human moral cognition, we hypothesized that the experience of moral dilemma in patients with OCD would provoke significantly increased activation of the ventromedial prefrontal and orbitofrontal cortex regions compared with healthy participants. To induce moral dilemmas that ostensibly overlap with OCD-relevant cognitive biases, such as responsibility beliefs, most task vignettes required participants to make difficult decisions about life and death tradeoffs that contrast utilitarian values of collective welfare against the emotionally aversive act of causing harm to others. Compared with nondilemma task vignettes, these moral dilemmas lead to robust activation of key regions of the moral cognition network.[10,33,34] Accordingly, in addition to the ventral frontal cortex, we sought to examine potential differences in other task-relevant regions between the 2 groups and whether direct relationships might exist between the severity of obsessive-compulsive symptoms and such brain responses. To satisfy this latter aim, we recruited a sufficiently large group of patients with OCD to support a detailed assessment of major symptom dimensions.

METHODS

PARTICIPANTS

Seventy-three outpatients with OCD were recruited from the Obsessive-Compulsive Disorders Unit of the University Hospital of Bellvitge, Barcelona, Spain. Patients were selected from a slightly larger cohort after having satisfied *DSM-IV* diagnostic criteria for OCD in the absence of relevant medical, neurologic, and other major psychiatric illness as well as neuroimaging data quality control checks (see "Image Acquistion and Preprocessing" subsection). Diagnosis of OCD was independently confirmed by 2 senior psychiatrists (P.A. and C.S.) through separate interviews conducted 1 month apart using the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[35] All the patients had experienced OCD symptoms for at least 1 year before this assessment. No patient met the criteria for Tourette syndrome, any psychotic disorder, or psychoactive drug abuse/dependence. Comorbid major depression and anxiety disorders were not considered to be exclusion criteria provided that OCD was the primary clinical diagnosis. All the patients were taking stable doses of medication during at least a 3-month period coinciding with the time of scanning, except 2 patients who were medication free for at least 1 month (**Table 1**).

Patients with OCD (42 men and 31 women; mean [SD] age, 33.1 [8.3] years; age range, 19-58 years) had a mean (SD) educational level of 12.9 (2.8) years (range, 5-19 years), and all but 9 were right handed (7 left handed and 2 ambidextrous) as assessed by the Edinburgh Inventory.[36] Seventy-three controls were matched to the patients for age, sex, and total years of education. Controls (42 men and 31 women; mean [SD] age, 32.6 [10.3] years; age range, 19-61 years) had a mean (SD) educational level of 13.1 (3.3) years (range, 8-22 years), and all but 6 were right handed (4 left handed and 2 ambidextrous). Each control underwent the Structured Clinical Interview for *DSM-IV* nonpatient version[37] to exclude any Axis I or II psychiatric disorders. None of them had a personal history of neurologic or psychiatric illness.

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[38] and the validated Spanish version of the Dimensional Y-BOCS (DY-BOCS)[39,40] were used to evaluate the presence and severity of patients' symptoms (Table 1). Given the strong positive correlation between the DY-BOCS total severity score and the Y-BOCS total score (Pearson $r=0.89$, $P<.001$), the former was used in subsequent brain behavior analyses. Comorbid depression and anxiety symptoms were measured using the Hamilton Depression Rating Scale[41] and the Hamilton Anxiety Rating Scale,[42] with missing data existing for 1 control and 1 patient with OCD. Mean (SD) scores on both scales were significantly more pronounced in patients with OCD (Hamilton Depression Rating Scale: patients, 10.0 [5.4] [range, 0-22]; controls, 1.0 [2.3] [range, 0-13]; $F_{1,142}=164.4$, $P<.001$; Hamilton Anxiety Rating Scale: patients, 12.5 [6.5] [range, 2-30]; controls, 2.1 [3.3] [range, 0-17]; $F_{1,142}=145.6$, $P<.001$). All the participants had normal or corrected-to-normal vision and provided written informed consent to participate in this study after receiving a complete description of its protocol, which was approved by the Institutional Review Board of the University Hospital of Bellvitge.

MORAL DILEMMA TASK

Task Stimuli

Twenty-four standard hypothetical moral dilemmas were adapted into short vignettes for this study. Most of the chosen dilemmas represent provocative "personal" moral dilemmas as

Table 1. Clinical Characteristics of 73 Patients With OCD

Variable	Value
Age at onset of OCD, mean (SD) [range], y	21.8 (7.9) [5-40]
Duration of illness, mean (SD) [range], y	11.5 (9.5) [1-45]
Y-BOCS-Total score, mean (SD) [range]	22.1 (6.5) [10-38]
Y-BOCS-Obsessions score, mean (SD) [range]	10.9 (3.3) [5-19]
Y-BOCS-Compulsions score, mean (SD) [range]	11.1 (3.6) [2-19]
DY-BOCS score, mean (SD) [range][a]	
1. Contamination/cleaning	4.0 (4.6) [0-15]
2. Harm/checking	5.7 (4.3) [0-12]
3. Sexual/religious	1.8 (3.5) [0-12]
4. Symmetry/ordering	3.2 (4.6) [0-15]
5. Hoarding	1.5 (2.8) [0-12]
6. Miscellaneous	2.5 (3.7) [0-12]
Total symptom severity, mean (SD) [range]	9.3 (2.3) [4-15]
Current level of impairment, mean (SD) [range]	9.3 (2.4) [6-15]
Comorbid mood/anxiety disorders, No. (%)	
Major depressive disorder	5 (7)
Dysthymic disorder	2 (3)
Bipolar disorder	1 (1)
Generalized anxiety disorder	3 (4)
Panic disorder	4 (5)
Social phobia	4 (5)
Medication at time of study, No. (%)	
Medication free (>4 wk)	2 (3)
Citalopram	2 (3)
Clomipramine	7 (10)
Clomipramine with an SSRI	29 (40)
Escitalopram	8 (11)
Fluoxetine	9 (12)
Fluoxetine with an SSRI	1 (1)
Fluvoxamine	3 (4)
Fluvoxamine with an SSRI	3 (4)
Phenelzine	1 (1)
Sertraline	1 (1)
Sertraline with an SSRI	1 (1)
With an adjunct antipsychotic agent	15 (21)

Abbreviations: DY-BOCS, Dimensional Yale-Brown Obsessive-Compulsive Scale; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale (1. contamination obsessions and cleaning compulsions; 2. obsessions about harm due to aggression/injury/violence/natural disasters, and related compulsions; 3. obsessions concerning sexual/moral/religious issues and related compulsions; 4. obsessions about symmetry/"just-right" perceptions, and compulsions to count or order/arrange; 5. obsessions and compulsions related to hoarding; and 6. obsessions and compulsions that include somatic concerns, need to know/remember, and superstitions, among other symptoms).

[a] Possible score range, 0 to 15.

described by Greene et al.[10] These dilemmas are considered the most emotionally engaging because they prompt one to endorse actions that directly imply serious bodily harm to a victim or set of victims in which utilitarian values (ie, sacrificing one to save many) violate typical moral-social (ie, deontologic) standards, for example, "do no harm to others." Each of the 24 text vignettes was accompanied by an artist-sketched illustration that depicted the core theme of each moral dilemma. Twenty-four nondilemma story vignettes were also developed as an imaging baseline condition for the moral dilemmas. **Figure 1** presents an example of each vignette type. The full set of vignettes can be downloaded from the first author's website (http://www.psychiatry.unimelb.edu.au/centres-units/mnc/research/affective_neuropsychiatry.html).

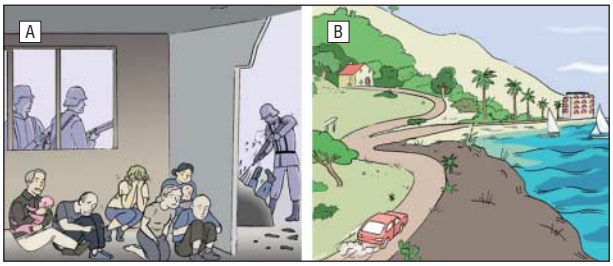

Figure 1. Examples of a moral dilemma and a nondilemma task vignette. A, The "crying baby" moral dilemma. Before scanning, participants were familiarized with the moral dilemma of Mr Jones, who is faced with either suffocating his young child to prevent his or her cries or risking his neighbor's and his own death at the hands of enemy soldiers. During scanning, the illustration was again presented, and participants were asked, "Would you remove your hand?" B, One of the nondilemma vignettes. Before scanning, participants were familiarized with the story of Mr Jones, who must decide whether to spend his weekend in a beautiful mountain town or by the seaside. They were told that he ultimately decides on the latter. During scanning, the illustration was again presented and participants were asked, "Will he go to the beach?" Participants' responses to the nonmoral dilemmas, therefore, served as a general indicator of participants' ability to recall the task vignettes on the scanning day.

Task Design

Within 1 week of scanning, participants were familiarized in detail with the moral dilemma and control vignettes. This training session lasted approximately 1 hour and ensured that participants had a clear understanding of the task and would be able to recall each vignette on the scanning day. During this session, the artist-sketched illustrations of the moral dilemma and nondilemma vignettes were presented, together with a full examiner-read description of each vignette. For this session, the moral dilemmas were described as events involving an imaginary third person ("Mr Jones"), and in no instances were participants required to provide their own moral judgment.

On the day of the experiment before scanning, participants verified that they could remember each of the individual vignettes. For the nondilemma condition, participants were told to simply recall the correct outcome of each scenario when voice prompted for a "yes/no" response by raising either their index finger (yes) or index and middle fingers (no). For the moral dilemma condition, participants were informed that during scanning they would be asked to provide their own moral judgment to each of the dilemma vignettes in response to an audio prompt, again by raising their index finger (yes) or index and middle fingers (no). Vignette-specific audio prompts were prerecorded and programmed to occur 1 second after the visual presentation of each vignette (for a written description of each prompt refer to the author's website as stated earlier). The total stimulus interval for each visual stimulus was 5 seconds. Participants' responses were made within a 4-second window using the response commands described previously herein, which were recorded by an examiner. The nondilemma and moral dilemma scenarios were presented as 4×30-second alternating blocks of 6 stimulus presentations per block, lasting 4 minutes total. The task was programmed in Presentation software (Neurobehavioral Systems Inc) and was presented using magnetic resonance imaging–compatible high-resolution goggles and headphones (VisuaStim Digital System; Resonance Technology Inc).

To confirm that participants experienced the moral dilemma condition as more emotionally provocative than the nondilemma condition, they completed postscan ratings of their overall experience of negative emotion during each task condition using a scale from 0% (not at all) to 100% (extremely): "How much did the [moral dilemma or simple] questions make

you feel negative emotions, for instance, guilt, sadness, or shame?" In addition, participants' percentage accuracy in responding to the nondilemma task vignettes and the percentage likelihood that they endorsed moral violations (ie, in accord with utilitarian values or that would be considered to violate typical moral standards) were also calculated. These data were compared between groups by either 1-way or repeated-measures analysis of variance using PASW Statistics 18.0 (SPSS Inc). Task response data were missing for 2 patients with OCD, and subjective emotion ratings were missing for 1 control and 1 patient with OCD. Pearson χ^2 analysis was used to compare group differences in yes/no responses to each of the 24 individual moral dilemmas.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Image Acquisition and Preprocessing

A 1.5-T Signa Excite system (General Electric) equipped with an 8-channel phased-array head coil and single-shot echoplanar imaging software was used. The functional sequence consisted of gradient recalled acquisition in the steady state (repetition time, 2000 milliseconds; echo time, 50 milliseconds; and pulse angle, 90°) in a 24-cm field of view, with a 64 × 64-pixel matrix and a section thickness of 4 mm (interslice gap, 1 mm). Twenty-two interleaved sections, parallel to the anterior-posterior commissure line, were acquired to generate whole-brain volumes, which corresponded to 120 volumes for the moral dilemma task, excluding 4 initial dummy volumes.

Imaging data were transferred and processed using a Microsoft Windows platform running MATLAB version 7 (The MathWorks, Inc). Preprocessing was performed using statistical parametric mapping software (SPM5; Wellcome Trust Centre for Neuroimaging) and involved motion correction, spatial normalization, and smoothing using a gaussian filter (full-width at half maximum, 8 mm). Regarding motion correction, translation and rotation estimates (x, y, z) were less than 2 mm or 2°, respectively, for all the participants. Data were normalized to the standard statistical parametric mapping–echoplanar imaging template and were resectioned to 2-mm isotropic resolution in Montreal Neurological Institute coordinate space.

Image Analysis

For each participant, a primary task regressor was created by convolving the onset of each moral dilemma block with a canonical hemodynamic response function and its temporal derivative. The nondilemma condition served as an implicit task baseline. Maximum likelihood parameter estimates were calculated at each voxel using the general linear model and an AR(1) model of serial autocorrelations. A high-pass filter was used to remove low-frequency noise (1/128 Hz).

Contrast images for each participant were carried forward to the group level using the summary statistics approach to random-effects analyses. A 2-sample *t* test design was used to estimate significant within- and between-group activation effects. Within-group statistical parametric maps were thresholded using a familywise error rate correction of $P_{FWE} < .05$ across the whole-brain volume with a minimum cluster extent of 10 contiguous voxels (K_E, ≥10 voxels). Between-group statistical comparisons proceeded in 2 stages: (1) a small volume–corrected comparison of hypothesized regions of interest and (2) a whole-brain comparison of additional task-activated regions. For the hypothesis-based comparison, between-group statistical parametric maps were thresholded at $P_{FWE} < .05$ (K_E, ≥10 voxels), corrected for a mask volume that encompassed primary moral cognition network regions, as consistently identified in functional magnetic resonance imaging studies of healthy participants.[10-14] It included the ventromedial prefrontal and medial orbitofrontal cortices, anterior and posterior cingulate cortices, and lateral temporoparietal cortex. This mask was defined bilaterally using the WFU_PickAtlas[43] (Wake Forest University School of Medicine) and had a total search volume of approximately 15 000 voxels (eFigure 1; http://www.archgenpsychiatry.com). For the whole-brain analysis, between-group statistical parametric maps were thresholded at $P < .001$ (uncorrected; K_E, ≥10 voxels).

BRAIN-BEHAVIOR ASSOCIATIONS

A 2-sample *t* test design specifying covariates and interactions was used to estimate associations between participants' overall tendency to endorse moral violations and corresponding brain activation. For patients, associations between DY-BOCS ratings of total symptom severity and current level of symptom-related impairment and brain activations were estimated in a 1-sample *t* test design. A 1-sample *t* test design was also used to test for associations between DY-BOCS severity ratings on the 6 major symptom dimensions and patients' brain activations. All of the previously mentioned associations were tested at $P < .001$ (uncorrected; K_E, ≥10 voxels) across the whole-brain volume.

RESULTS

TASK RESPONSES

The moral dilemma condition was rated as significantly more emotionally provocative (mean [SD]: patients, 60.4% [30.4%]; controls, 69.4% [28.3%]) than the nondilemma condition (mean [SD]: patients, 7.6% [14.0%]; controls, 7.6% [14.3%]), as indicated by a significant main effect of condition ($F_{1,142} = 453.0$, $P < .001$) but no main effect of group or group × condition interaction.

The frequency with which participants endorsed moral violations to the moral dilemma vignettes ranged from 7% to 95%, with 10 vignettes recording approximately 50% yes/no responses (eTable 1). No significant difference was noted between patients with OCD (mean [SD], 24.6% [9.1%]; range, 10.4%-47.9%) and controls (mean [SD], 25.9% [8.4%]; range, 10.4%-43.7%) in their overall tendency to endorse moral violations in response to the moral dilemmas ($F_{1,142} = 0.81$, $P = .37$). Both groups responded accurately to the nondilemma task vignettes (mean [SD]: patients, 80.0% [12%]; controls, 84.3% [11%]), with controls performing slightly more accurately than patients with OCD ($F_{1,142} = 4.85$, $P < .03$). The percentage of omitted responses to both task conditions was minimal (<1.0%) and did not differ between groups (eTable 1). When comparing group responses to each of the individual moral dilemma vignettes, the groups differed in their proportion of yes/no responses to only 5 of the 24 vignettes (χ^2 $P = .02$-$.005$) (eTable 1).

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Brain Activation During Moral Dilemma

Responding to the moral dilemma vs nondilemma vignettes evoked robust and overlapping activation of distributed cortical and subcortical regions in patients with

Table 2. Within-Group Activation Results Associated With the Moral Dilemma Task

Area	Peak Anatomic Coordinate			Statistics	
	x	y	z	K_E	*z* Score
Controls					
Posterior cingulate cortex	0	−58	34	12 439	>8
Dorsal prefrontal cortex	−12	54	32	12 058	>8
Inferior parietal cortex	−46	−62	24	1757	>8
Inferior temporal cortex	−64	−12	−26	1474	>8
Inferior frontal cortex	38	28	−22	299	6.95
Superior temporal cortex	64	−10	−8	181	6.09
Hippocampus	−20	−22	−20	101	5.97
Fusiform gyrus	62	−8	−32	260	5.92
Mid-cingulate cortex	0	−20	34	63	5.41
Thalamus	−2	−8	6	80	5.35
Caudate	−12	8	10	20	4.70
Patients With OCD					
Posterior cingulate cortex	0	−58	34	3163	>8
Inferior parietal cortex	−48	−62	28	29 488	>8
Inferior temporal cortex	60	−12	−34	490	7.54
Inferior frontal cortex	50	32	−16	448	7.22
Orbitofrontal cortex	−2	58	−22	122	5.80
Medial temporal cortex	68	−14	−10	118	5.63
Mid-cingulate cortex	−2	−22	36	66	5.59
Superior temporal cortex	50	−28	2	46	4.91
Caudate	−14	10	10	37	4.70

Abbreviations: K_E, cluster extent, in voxels, corresponding to a whole-brain threshold of $P_{FWE} < .05$; OCD, obsessive-compulsive disorder.

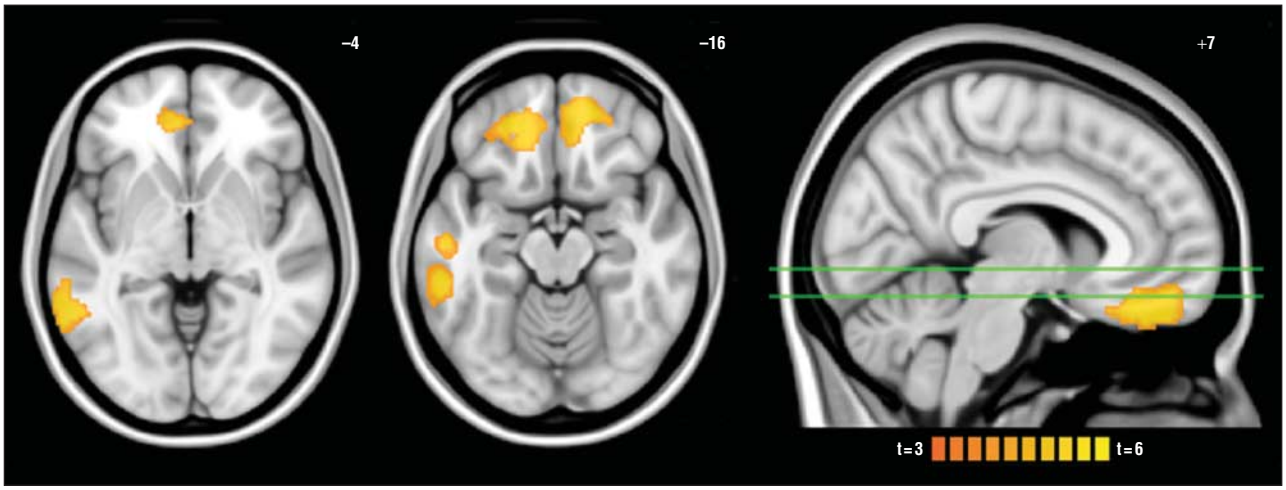

Figure 2. Regions of the ventromedial prefrontal cortex, orbitofrontal cortex, and left posterior middle temporal gyrus that were significantly increased in activation during moral dilemma in patients with obsessive-compulsive disorder. Small volume–corrected results are displayed at $P_{FWE} < .05$ (minimum cluster extent of 10 contiguous voxels). Imaging results are displayed in neurologic format (right = right).

OCD and controls that recapitulates the results of many previous studies of moral decision making.[8,9,44] Activated regions included a large expanse of the medial frontal cortex, posterior cingulate cortex, ventrolateral and dorsolateral prefrontal cortices, and lateral temporoparietal cortex, including the inferior parietal and posterior superior temporal cortices, the caudate nucleus, and the visual and visual association cortices (eFigure 2 and **Table 2**).

When comparing the groups in the hypothesis-based analysis, there were no identified regions of significantly greater activation in controls compared with patients with OCD. On the other hand, patients exhibited significantly more pronounced activation of a large region extending from the ventromedial prefrontal cortex to the orbitofrontal cortex (x, y, z = 4, 38, −20; *z* score = 3.86; K_E = 870) and the left lateral temporal cortex (x, y, z = −58, −36, −12; *z* score = 4.08; K_E = 706). The ventromedial-to-orbitofrontal cluster extended from the cingulate gyrus to the rectal and orbital gyri in both hemispheres. The lateral temporal cortex cluster extended across the posterior portions of the middle temporal gyrus and superior temporal sulcus (**Figure 2**).

Further whole-brain comparisons did not identify any regions of significantly greater activation in controls compared with patients with OCD. However, this analysis fur-

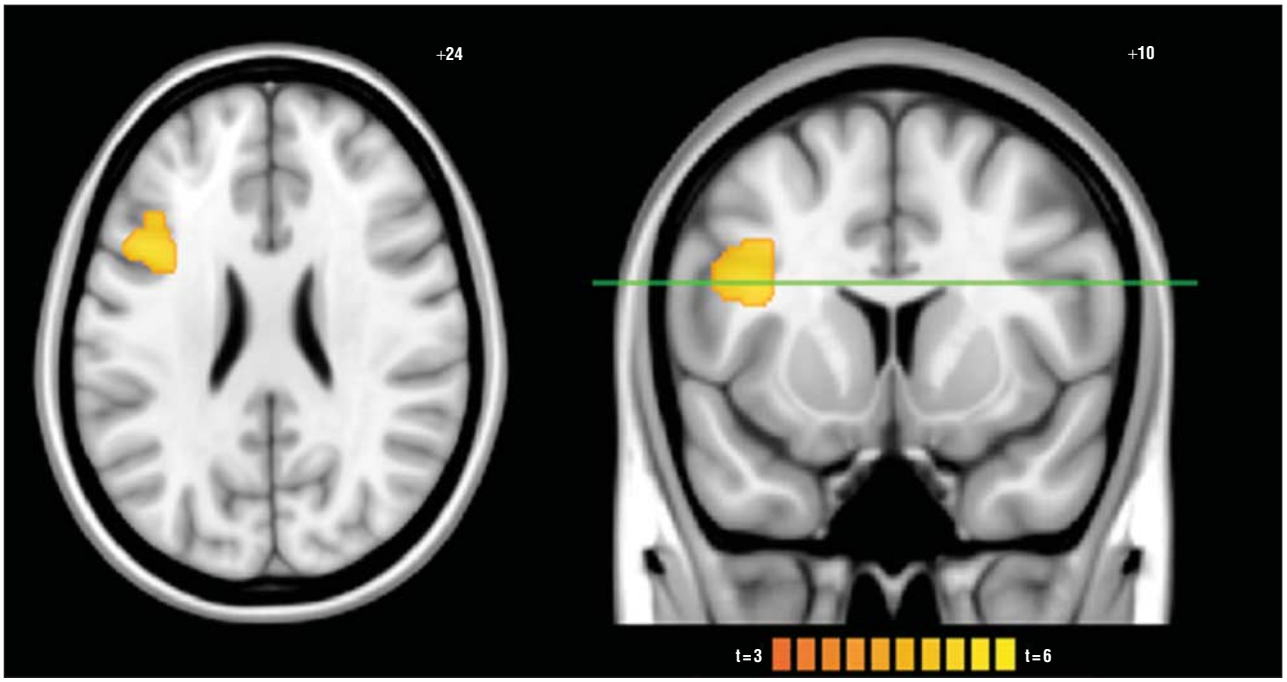

Figure 3. Region of the left posterior dorsolateral prefrontal cortex that demonstrated significantly increased activation during moral dilemma in patients with obsessive-compulsive disorder. Whole-brain uncorrected results are displayed at $P<.001$ (minimum cluster extent of 10 contiguous voxels). Imaging results are displayed in neurologic format (right=right).

ther identified a region of significantly greater activation in patients with OCD located in the left posterior dorsolateral prefrontal cortex (x, y, z=−40, 10, 24; *z* score=3.66; K_E=560) (**Figure 3**).

Because patients with OCD scored significantly higher on the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale compared with controls, we repeated the previous group analyses after covarying for these rating scores. Results shown in eFigure 3 illustrate that the brain regions identified as significantly increased in activation in patients with OCD remained when specifically controlling for group differences in comorbid affective symptoms.

Brain-Behavior Associations

Across groups, the likelihood that participants endorsed moral violations was found to be negatively associated with activation of the dorsal medial and lateral prefrontal cortices, rostral anterior cingulate cortex and posterior cingulate cortex, inferior parietal and posterior temporal cortices, caudate nucleus, medial dorsal thalamus, and globus pallidus (eTable 2 and eFigure 4). No significant differences in the strength of these associations were found to discriminate patients with OCD from controls. No significant positive associations with this behavioral measure were observed.

We observed only significant positive associations between patients' DY-BOCS ratings of total symptom severity and activation of the right caudate nucleus, midorbitofrontal cortex, hypothalamus, left posterior temporal cortex, and dorsal medial frontal cortex (eFigure 5 and eTable 3). Of the 6 major DY-BOCS symptom dimensions, severity ratings on the harm/checking and sexual/religious dimensions demonstrated significant positive associations with patients' brain activations. Greater severity of harm/checking symptoms was associated with greater activation of the right posterior temporal cortex, whereas greater severity of sexual/religious obsessions was associated with greater activation of the left anterior insular cortex, ventrolateral prefrontal cortex, left dorsolateral prefrontal cortex, right amygdala, and dorsal anterior cingulate cortex (eFigure 6 and eTable 3).

COMMENT

Although there was considerable overlap in the brain response to moral dilemma between patients with OCD and controls, there were also significant differences between the 2 groups. Overall, the nature of these differences seems to support the moral sensitivity hypothesis of OCD and suggests an intriguing putative connection between neurobiological processes and certain maladaptive cognitions in this disorder.

Consistent with predictions, the moral dilemma task provoked greater activation of the ventromedial prefrontal and orbitofrontal cortex regions in patients with OCD. This is an intuitive finding considering historical and contemporary accounts of patients with OCD being "hypermoral" and recent neuroscientific evidence linking these brain regions to the experience of moral emotions, such as guilt and shame.[15,16,45-47] One view is that the medial orbitofrontal cortex, in particular, may influence such emotions by encoding the relative value and salience of environmental stimuli in support of complex decision making and anticipation about future outcomes.[48,49] The greater engagement of these regions in patients with OCD may, therefore, represent greater perceived salience of the emotive dilemma stimuli or excessive valuation of deci-

sion outcomes. Despite rating the moral dilemmas as significantly more emotionally provocative than the nondilemma condition, patients did not rate them as more provocative than did healthy participants. Thus, although this assessment was not specific to particular moral emotions or sentiments, it nevertheless suggests some distinction between patients' increased ventral frontal cortex response and their perceived experience of emotion during moral dilemma.

With reference to the additional regions that distinguished patients with OCD from healthy participants, it is possible that the moral dilemma task provoked other disorder-relevant processes consistent with the moral sensitivity hypothesis. Recent studies[50-52] in healthy participants have shown that the explicit cognitive appraisal of emotional stimuli, including negative appraisals, consistently leads to increased activation of the left dorsolateral prefrontal cortex and posterior middle temporal gyrus, the same regions implicated in patients with OCD. For example, in one study,[52] activation of these regions was prominent when healthy participants were instructed to upregulate negative emotions by consciously reappraising visual emotional images to be more personally salient in terms of their subjective relevance. The left hemispheric predominance of this finding was attributed to the idea that such appraisals draw heavily on affective descriptors and verbal narratives to regulate emotion. In patients with OCD, it is plausible that disorder-relevant cognitive biases engaged during moral decision making, such as greater perceived responsibility, might evoke heightened activation of these same left frontotemporal regions. If true, the neural correlates of moral sensitivity in OCD would, therefore, seem to equally implicate brain regions associated with the conscious cognitive appraisal of emotional stimuli and those more directly associated with the subjective experience of moral emotions. The extent to which such processes might interact or be dissociable in patients with OCD is not presently clear.

The 2 groups were not different in their activation of other task-relevant cortical regions, including the dorsal medial frontal, inferior parietal, posterior cingulate, and rostral anterior cingulate cortices. As discussed in previous work,[34,53] each of these regions has become considered to represent part of the "default mode network," a large-scale brain system that has become associated with self-referential cognition in neuroimaging studies.[54] Thus, aside from the ventromedial prefrontal cortex, whose "default" activity has been linked principally with memory-based self-related cognition,[55] default mode regions were comparably activated in patients with OCD. Irrespective of group membership, individual differences in the willingness to endorse moral violations were found to be negatively correlated with activation of these regions. Greater difficulty in endorsing moral violations may, therefore, have been experienced as generally more self-engaging.

We recruited a large group of patients with OCD for this work, which afforded the possibility to assess relationships between brain activations and clinical symptoms. To this end, greater overall symptom severity was found to predict the activation of several task-related and task-unrelated regions as defined at the group imaging level. In the former case, this included the dorsal medial frontal cortex and left posterior temporal sulcus, and in the latter case, this included the hypothalamus, ventral caudate nucleus, and mid-orbitofrontal cortex. In previous functional imaging studies,[22,23,56,57] OCD symptom severity has been most consistently associated with elevated activity of the orbitofrontal cortex and striatum, which is, therefore, relevant to observe herein. Moreover, both of these regions remain centrally implicated in pathophysiologic models that implicate primary disturbances of orbitofrontal-striatal circuits to this disorder.[17-19,21] Therefore, as a function of illness severity, the moral dilemma task seems to have engaged regions considered, in part, to represent the primary "OCD circuit."

Regarding correlations with specific OCD symptom dimensions, these were limited to the severity of harm/checking symptoms and sexual/religious obsessions. Harm/checking symptoms, in particular, predicted greater activation of the right posterior superior temporal sulcus, which is a region typically activated by tasks of abstract visual social cognition, including moral decision making.[8,44] On the other hand, the severity of sexual/religious obsessions predicted increased activation of more distributed regions, including the amygdala, anterior insular and dorsal anterior cingulate cortices, and lateral orbitofrontal cortex. Of these regions, the amygdala was not robustly activated by the task at the group imaging level. Considering the anatomy of these limbic-paralimbic regions and their link to emotional-autonomic states,[58] it is conceivable that patients scoring high on this symptom dimension felt more challenged or provoked by the moral dilemmas. Indeed, it is generally assumed that a strong link exists between moral sensitivity in OCD and the experience of sexual and religious obsessions. Moreover, on the basis of cognitive bias models of OCD, it may be suspected that these associations were specifically mediated or modulated by common dysfunctional belief domains, such as inflated responsibility.[2,59]

There are limitations to this study. First, we attempted to maximize the emotionally provocative nature of the moral dilemmas by using a simple mode of decision making during task performance; for discussion, see the study by Harrison et al.[34] This choice came at the cost of acquiring detailed online subjective ratings of each of the dilemma vignettes and specific measurements of decision latency, as implemented in other past imaging studies of moral dilemma. However, based on accumulated evidence in other clinical cohorts and a recent behavioral study of moral reasoning in OCD, it was generally not anticipated that patients with OCD would exhibit pronounced deficits in moral decision making per se.[15,60-62] Second, this study would likely have benefited from the inclusion of additional assessments, such as the 44-item Obsessive Belief Questionnaire,[63] which is a validated measure of obsessional beliefs for use in clinical and nonclinical populations. Such a measure would have permitted direct exploration of the influence of inflated responsibility vs other belief domains on the imaging findings. Third, since all but 2 patients in this study were receiving medication at the time of as-

sessment (primarily selective serotonin reuptake inhibitor–based antidepressant treatment), we could not compare medicated and unmedicated subgroups. Although on the basis of several previous studies,[22,25,56,64-66] it can be argued that the influence of such treatments on brain activation in OCD may have been to attenuate rather than inflate this study's results; this account is not definitive. Such evidence does not address the fact that patients with OCD receiving a selective serotonin reuptake inhibitor often receive other adjunct treatments, as was the case in the present sample, and that the combined effect of such treatment on brain functional activity is mostly unexplored. The issue of medication use, therefore, represents a caveat to this study that will need to be addressed in future work. Fourth, despite the large patient cohort and evaluation of OCD symptom dimensions, comparisons with another psychiatric cohort would have enhanced the specificity of these findings.

The previous limitations considered, this study provided a novel characterization of brain regions that potentially represent an important link between neurobiological processes and certain maladaptive cognitions in patients with OCD. One broader implication of this work may be to inform more advanced models of the etiology of obsessions and compulsions with the capacity to integrate distinct measurements across cognitive and biological domains. Indeed, initial efforts to this end[67] seem to endorse a view that such "biopsychosocial" models will have the greatest potential impact for improving the future understanding and treatment of OCD.[2,6,7] However, to establish firmer links among neurobiological processes, dysfunctional beliefs, and clinical symptom dimensions, new research must endeavor to assess causality between these measurements. Such research may take the form of longitudinal studies[68,69] or specific experimental manipulations[70] capable of prospectively testing causal predictions between cognitive and neurobiological factors and the emergence of obsessive-compulsive symptoms and behaviors.

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