ORIGINAL ARTICLE

Distinct Neural Correlates of Washing, Checking, and Hoarding Symptom Dimensions in Obsessive-compulsive Disorder

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Context: Obsessive-compulsive disorder (OCD) is clinically heterogeneous, yet most previous functional neuroimaging studies grouped together patients with mixed symptoms, thus potentially reducing the power and obscuring the findings of such studies.

Objective: To investigate the neural correlates of washing, checking, and hoarding symptom dimensions in OCD.

Design: Symptom provocation paradigm, functional magnetic resonance imaging, block design, and nonparametric brain mapping analyses.

Setting: University hospital.

Participants: Sixteen patients with OCD (11 inpatients, 5 outpatients) with mixed symptoms and 17 healthy volunteers of both sexes.

Intervention: All subjects participated in 4 functional magnetic resonance imaging experiments. They were scanned while viewing alternating blocks of emotional (washing-related, checking-related, hoarding-related, or aversive, symptom-unrelated) and neutral pictures, and imagining scenarios related to the content of each picture type.

Main Outcome Measure: Blood oxygenation level–dependent response.

Results: Both patients and control subjects experienced increased subjective anxiety during symptom provocation (patients significantly more so) and activated neural regions previously linked to OCD. Analyses of covariance, controlling for depression, showed a distinct pattern of activation associated with each symptom dimension. Patients demonstrated significantly greater activation than controls in bilateral ventromedial prefrontal regions and right caudate nucleus (washing); putamen/globus pallidus, thalamus, and dorsal cortical areas (checking); left precentral gyrus and right orbitofrontal cortex (hoarding); and left occipitotemporal regions (aversive, symptom-unrelated). These results were further supported by correlation analyses within patients, which showed highly specific positive associations between subjective anxiety, questionnaire scores, and neural response in each experiment. There were no consistently significant differences between patients with (n=9) and without (n=7) comorbid diagnoses.

Conclusions: The findings suggest that different obsessive-compulsive symptom dimensions are mediated by relatively distinct components of frontostriatothalamic circuits implicated in cognitive and emotion processing. Obsessive-compulsive disorder may be best conceptualized as a spectrum of multiple, potentially overlapping syndromes rather than a unitary nosologic entity.

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OBSESSIVE-COMPULSIVE DISorder (OCD) is clinically heterogeneous. Factor-analytic studies have consistently identified at least 4 temporally stable symptom dimensions: contamination/washing, aggressive/checking, hoarding, and symmetry/ordering.[1-7] These symptom dimensions have been related to different patterns of genetic transmission,[8-10] comorbidity,[1-3,11-13] and treatment response.[3,5,14-17]

Despite this heterogeneity, most previous neuroimaging studies of OCD have grouped together patients with mixed symptoms,[18-23] thus potentially reducing their power and obscuring their findings. Few studies have examined the neural correlates of different symptom dimensions. Rauch et al[24] found that checking symptoms correlated with increased, and symmetry/ordering with reduced, regional cerebral blood flow in the striatum, while washing symptoms correlated with increased regional cerebral blood flow in bilateral anterior cingulate and left orbitofrontal cortex. Using functional magnetic resonance imaging (fMRI), Phillips et al[25] compared OCD patients with mainly washing or checking symptoms while they

viewed generally aversive or washing-related pictures. When viewing washing-related pictures, only washers demonstrated activations in regions implicated in emotion and disgust perception, ie, visual regions and the anterior insula[26-28]; checkers demonstrated activations in frontostriatal regions and the thalamus. In another fMRI study, patients with OCD with predominantly washing symptoms demonstrated greater activation than controls in the right insula, ventrolateral prefrontal cortex, and parahippocampal gyrus when viewing disgust-inducing pictures.[29] Limitations of these studies included the artificial division between washers and checkers and the exclusive use of washing-related material, but taken together, they suggest that different symptoms may be mediated by distinct neural systems and that previous discrepant findings may result from phenotypic variations in the studied samples.

Building on recent pilot work from our group,[30] we used a symptom provocation paradigm to examine, *within the same patients*, the neural correlates of washing, checking, and hoarding symptom dimensions of OCD. This dimensional approach is methodologically superior to categorically dividing patients into mutually exclusive subgroups because monosymptomatic patients are infrequent and such a division is therefore artificial. On the basis of previous studies, we hypothesized that (1) anxiety would be provoked in response to all types of emotional material both in patients and in controls but more so in patients[22,30,31]; (2) symptom provocation would activate regions previously implicated in OCD,[18-23] both in patients and in controls,[30] but more so in patients; and (3) distinct patterns of neural response would be associated with the provocation of each symptom type. Specifically, in patients compared with controls, the provocation of (*a*) washing-related anxiety would predominantly activate areas involved in emotion and disgust perception, ie, ventromedial prefrontal and paralimbic regions[24,25,29,30]; (*b*) checking-related anxiety, regions involved in attentional and motor functions, ie, dorsolateral prefrontal cortex, thalamus, and striatal regions[24,25,30]; and (*c*) hoarding-related anxiety, ventromedial prefrontal and paralimbic regions.[30] Finally, we expected that, in patients, the magnitude of activation in the predicted regions within each experiment would be significantly correlated with the corresponding subjective anxiety and/or symptom dimension scores.

METHODS

SUBJECTS

Seventeen patients with OCD (11 inpatients, 6 outpatients) who were at various stages of treatment were recruited from 2 specialized cognitive behavioral therapy clinics in London, England. This was a consecutive sample, but an effort was made to ensure that washing, checking, and hoarding symptoms were sufficiently represented. One outpatient reported having closed his eyes in the scanner and was excluded. Axis I and II diagnoses were made according to *DSM-IV*.[32,33] Patients with comorbid diagnoses were not excluded provided that OCD was the main problem for which treatment was sought. Exclusion criteria were brain injury, any neurologic condition, psychosis, and substance abuse.

The patients' mean illness duration was 14.2 years (SD, 8.3 years; range, 1.5-29 years). The OCD severity was moderate to severe (Yale-Brown Obsessive-Compulsive Scale total: mean, 24.7; SD, 7.8; obsessions: mean, 11.6; SD, 4.6; compulsions: mean, 13.1; SD, 3.6). Nine patients (56%) had 1 or more comorbid Axis I or Axis II disorders. Additional Axis I diagnoses were major depressive disorder (n=6), social phobia (n=3), specific phobia (n=2), and panic disorder, agoraphobia without panic, posttraumatic stress disorder, generalized anxiety disorder, and body dysmorphic disorder (each, n=1). Comorbid personality disorders were obsessive-compulsive (n=7), avoidant (n=6), depressive (n=5), dependent (n=3), paranoid (n=2), borderline (n=2), and narcissistic (n=1). Most patients (n=12; 75%) were taking medication at the time of the study: clomipramine hydrochloride (4 patients; 175 mg), fluoxetine hydrochloride (3 patients; 20 mg), paroxetine hydrochloride (3 patients; 40 mg), and venlafaxine hydrochloride (2 patients; 200 mg). Additional medications included buspirone hydrochloride (3 patients; 12 mg), lithium carbonate (1 patient; 800 mg), valproate sodium (1 patient; 600 mg), and chlorpromazine hydrochloride (1 patient; 25 mg).

Seventeen healthy volunteers of similar demographic characteristics were recruited among ancillary staff at the Institute of Psychiatry. They reported no history of neurologic or psychiatric disorder and were unmedicated. Data from 10 of these control subjects were partially reported elsewhere.[30] The Ethics Committee of the Maudsley Hospital/Institute of Psychiatry, London, approved the study protocol, and all subjects signed an informed consent form before their participation.

MEASURES

In the OCD group, severity and types of OCD symptoms were assessed with the Yale-Brown Obsessive-Compulsive Scale and the Symptom Checklist.[34,35]

In both groups, symptom dimension scores were obtained with the Padua Inventory–Revised (PI-R).[36] We were interested in 2 of its subscales, "washing" (10 items; score range, 0-40) and "checking" (7 items; score range, 0-28), which are particularly reliable and valid.[36-41] Hoarding symptoms were assessed with the Saving Inventory–Revised (SI-R).[42,43] The SI-R is a reliable and valid instrument consisting of 23 self-administered items requesting a response on a 0 to 4 scale (score range, 0-92). Factor analysis identified 3 robust subscales: clutter (9 items; score range, 0-36), difficulty discarding (7 items; score range, 0-28), and acquisition (7 items; score range, 0-28).[43]

Depression was assessed with the Beck Depression Inventory (BDI).[44] The state subscale of the State-Trait Anxiety Inventory[45] was administered immediately before the scan.

STIMULI

Fifty color pictures of scenes rated as aversive or disgusting by normal subjects (eg, insects, mutilated bodies, decaying food) and 50 pictures of neutral scenes (eg, furniture, nature scenes, household items) were selected from a standard set of stimuli.[46] These stimuli were carefully chosen to avoid resembling common triggers of OCD symptoms. In addition, pictures depicting contamination/washing, aggressive/checking, and hoarding material (50 of each type) were obtained with a standard digital camera. For each symptom type, 3 clinicians with experience in OCD had previously listed the most common items that were provocative of anxiety and the urge to ritualize in patients with OCD. Examples of the pictures are public telephone or toilet, money, syringe, and ashtray (washing); electric appliances, stove, open door, and purse (checking); and old newspapers or magazines, old clothes or toys, empty bottles or cans, and trash bins (hoarding).

A total of 250 scenes were selected after an independent group of 9 normal volunteers (unrelated to the study) had rated an originally larger pool of pictures according to their level of visual complexity, anxiety, and disgust on a 0 to 3 scale (0, none; 3, high). Pictures that were too simple or too complex were

excluded, and an effort was made to avoid using washing-related pictures that could be perceived as very aversive by normal individuals. The final 250 stimuli were well matched regarding visual complexity and, as intended, the normally aversive or disgusting pictures induced more anxiety and disgust than the other 3 types of pictures (data not shown).

SYMPTOM PROVOCATION PARADIGM

All subjects participated in four 6-minute experiments in which they viewed ten 20-second alternating blocks of emotional (washing, checking, or hoarding related or normally aversive) and neutral pictures. The order in which the 4 experiments were conducted was fully counterbalanced, as was the order of the emotional and neutral conditions within each experiment. More details can be found in Mataix-Cols et al.[30]

Before the presentation of each set of pictures, subjects were played a prerecorded voice file by means of high-fidelity pneumatic headphones, instructing them to imagine being in a particular situation while looking at the scenes they were about to see. Examples of these instructions are as follows: "Imagine that you must come into contact with what's shown in the following pictures without washing yourself afterwards" (washing); "Imagine that you are not sure whether you switched off or locked the following objects and it is impossible for you to go back and check" (checking); "Imagine that the following objects belong to you and that you must throw them away forever" (hoarding); "Imagine that you must touch or stand by the following objects" (aversive); "Imagine that you are completely relaxed while looking at the following scenes" (neutral).

After each set of pictures, another prerecorded sound file of the question "How anxious do you feel?" was played and the subjects rated their subjective anxiety on a 0 (no anxiety) to 8 (extreme anxiety) scale.

IMAGE ACQUISITION

Gradient-echo echoplanar images were acquired on a 1.5-T MRI system (GE Signa Neuro-optimized MR system; General Electric, Milwaukee, Wis) at the Maudsley Hospital. One hundred T2*-weighted whole-brain volumes depicting blood oxygen level–dependent contrast[47] and consisting of 16 sections oriented according to the bicomissural plane (thickness, 7 mm; 0.7-mm gap) were acquired during 6 minutes for each of the 4 experiments (repetition time, 2.0 seconds; echo time, 40 milliseconds; field of view, 24 cm; flip angle, 70; 64 × 64 matrix). This echoplanar image data set provided almost complete brain coverage.

In each 20-second stimulus presentation block, subjects viewed either 10 provocative or 10 neutral pictures. Each picture was presented for 1950 milliseconds, with an interstimulus interval of 50 milliseconds. Ten whole-brain volumes were acquired during each stimulus presentation block. Each stimulus block was followed by (1) an 8-second period of complete silence during which subjects were asked to rate their level of anxiety and (2) an additional 8-second period during which the subjects listened to a sound file containing instructions pertinent to the next stimulus block. Four "dummy volumes" were excited during this 8-second period by means of exactly the same radiofrequency envelope and gradient section selection parameter, with the same repetition time of 2 seconds to allow the magnetization to reach an equilibrium amplitude before the next period of data acquisition. The frequency-encoding gradient was turned off during this period to minimize acoustic noise and ensure that the instructions were heard clearly by the subjects.[48] The 4 dummy volumes were later discarded from the time series.

Individual brain activation maps were coregistered to a "whole head" gradient-recalled echo planar imaging scan of superior spatial resolution acquired on all subjects. This structural scan had the following acquisition parameters: echo time, 40 milliseconds; repetition time, 3000 milliseconds; field of view, 24 cm; image resolution, 128 × 128; number of sections, 43; section thickness, 3.0 mm; intersection gap, 0.3 mm; number of signal averages, 8.

STATISTICAL ANALYSES

Individual Maps

Data were analyzed with software developed at the Institute of Psychiatry, using a nonparametric approach. Data were first realigned[49] to minimize motion-related artifacts and smoothed by means of a gaussian filter (full width at half maximum, 7.2 mm). Responses to the experimental paradigms were then detected by time-series analysis using gamma variate functions (peak responses weighted between 4 and 8 seconds) convolved with the experimental design to model the blood oxygen level–dependent response. A goodness-of-fit statistic and a measure of the mean power of neural response (the sum of squares [SSQ] ratio) was computed at each voxel. This was the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). To sample the distribution of SSQ ratio under the null hypothesis that observed values of SSQ ratio were not determined by experimental design (with minimal assumptions), the time series at each voxel was permuted by a wavelet-based resampling method.[50,51] This process was repeated 10 times at each voxel to produce the distribution of SSQ ratios under the null hypothesis. Voxels activated at any desired level of type I error can then be determined by obtaining the appropriate critical value of SSQ ratio from the null distribution. Individual brain activation maps were produced for each subject for each experiment vs the neutral condition.

Group Maps

To extend inference to the group level, the observed and randomized SSQ ratio maps were transformed into standard space[52] by a 2-stage process[53] using spatial transformations computed for each subject's high-resolution structural scan. Once the statistic maps were in standard space, a generic brain activation map was produced for each experimental condition by testing the median observed SSQ ratio over all subjects at each voxel in standard space (median values were used to minimize outlier effects), against a critical value of the permutation distribution for median SSQ ratio ascertained from the spatially transformed wavelet-permuted data.[53] For greater sensitivity and to reduce the multiple comparison problem encountered in fMRI, hypothesis testing was carried out at the cluster level using methods developed by Bullmore et al.[54] This method estimates the probability of occurrence of clusters under the null hypothesis using the distribution of median SSQ ratios computed from spatially transformed data obtained from wavelet permutation of the time series at each voxel (see preceding section). Image-wise expectation of the number of false-positive clusters under the null hypothesis is set for each analysis at less than 1.

Between-Group Differences (Analysis of Covariance)

Analysis of covariance was carried out on the SSQ ratio maps in standard space by first computing the difference in mean SSQ ratio between groups at each voxel. The BDI scores were used as covariates in all analyses. Subsequent inference of the probability of this difference under the null hypothesis was made by reference to the null distribution obtained by repeated random permutation of group membership and recomputation of

Table 1. Demographic and Clinical Characteristics of 16 Patients With OCD and 17 Healthy Control Subjects*

Variable	OCD (n = 16)	Controls (n = 17)	Statistic	*P* Value
Sex, No. (%) M	8 (50)	9 (53)	$\chi^2 = 0.02$	.86
Right-handed, No. (%)	14 (88)	15 (88)	Fisher exact	>.99
Age, y	35.8 ± 9.2	30.8 ± 2.2	$t_{31} = 1.5$	.13
PI-R, total	54.2 ± 35.1	15.3 ± 19.7	$U = 41.0$; Z = –3.2	.001
PI-R, washing	15.1 ± 13.2	5.3 ± 6.5	$U = 72.5$; Z = –2.1	.03
PI-R, checking	12.0 ± 8.3	3.2 ± 5.7	$U = 38.0$; Z = –3.4	.001
SI-R, total	28.2 ± 26.6	9.1 ± 7.3	$U = 82.0$; Z = 1.9	.05
SI-R, clutter	9.4 ± 9.0	2.6 ± 3.8	$U = 81.5$; Z = –2.0	.04
SI-R, discarding	10.5 ± 9.8	2.7 ± 2.7	$U = 80.0$; Z = –2.0	.04
SI-R, acquisition	8.5 ± 8.2	3.1 ± 2.7	$U = 93.5$; Z = –1.5	.12
BDI	19.3 ± 12.6	2.6 ± 2.7	$U = 19.0$; Z = –4.1	<.001
STAI-S	35.1 ± 7.1	32.4 ± 5.1	$t_{31} = 0.14$	.22

Abbreviations: BDI, Beck Depression Inventory; OCD, obsessive-compulsive disorder; PI-R, Padua Inventory–Revised; SI-R, Saving Inventory–Revised; STAI-S, state subscale of the State Trait Anxiety Inventory.
*Values are given as mean ± SD score unless otherwise specified. For all scales, higher scores denote greater severity.

the mean difference in SSQ ratio. Cluster-level maps were then obtained as described by Bullmore et al.[54] We set a voxelwise *P* value of .025 and a clusterwise *P* value of .0001. This method ensured a total number of false positives close to zero. Correction for multiple comparisons was not required, as thresholds were set on an image-wide basis, not a voxelwise basis.

Partial Correlation Analyses

Correlation of fMRI blood oxygen level–dependent responses with behavioral measures was determined by first computing the Pearson product moment correlation coefficient at each voxel between the standardized power of the fMRI response (SSQ ratio) and the behavioral variable for each subject. The null distribution of correlation coefficients was then computed by randomly permuting group membership (see previous section) and recomputing the correlation coefficient in an analogous fashion to that used for computation of group differences. Cluster level maps of significant correlations were then computed as described by Bullmore et al.[54] The voxelwise and clusterwise *P* values were set at .05 and .0001, respectively, ensuring less than 1 false positive. For each of the significant clusters identified by the above method, we next extracted the SSQ ratio of each participant and conducted a series of partial correlation analyses with the relevant anxiety and questionnaire measures, controlling for BDI scores.

Table 2. Frequencies of Current and Past Symptom Endorsements on the Y-BOCS Symptom Checklist in 16 Patients With OCD

	No. (%) of Patients	
	Current Symptom	Past Symptom
Obsessions		
Aggressive	8 (50)	7 (44)
Contamination	12 (75)	13 (81)
Sexual	2 (13)	1 (6)
Hoarding/saving	9 (56)	9 (56)
Religious	5 (31)	3 (19)
Symmetry	9 (56)	10 (63)
Somatic	6 (38)	5 (31)
Compulsions		
Washing	12 (75)	15 (94)
Checking	13 (81)	13 (81)
Repeating	11 (70)	8 (50)
Counting	4 (25)	5 (31)
Ordering	6 (38)	7 (44)
Hoarding	8 (50)	7 (45)

Abbreviations: OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

RESULTS

There were no statistically significant differences between patients and controls on any demographic variable, but patients had more severe obsessive-compulsive (PI-R, SI-R) and depressive (BDI) symptoms (**Table 1**). Scores on the PI-R and SI-R suggested marginal levels of obsessive-compulsive symptoms in the control group. Patients and controls experienced similar moderate state anxiety levels (State-Trait Anxiety Inventory) in anticipation of having a scan. All patients endorsed more than 1 symptom type (**Table 2**).

SUBJECTIVE ANXIETY RATINGS

Mixed-model analyses of variance with group (patient vs control) as between-groups factor and experimental condition (emotional vs neutral) as within-subjects factor showed significant main group and condition effects in all 4 experiments, indicating that the paradigm was effective in provoking anxiety and that patients with OCD experienced higher anxiety levels than controls. The group × condition interaction effect was also significant for the washing and hoarding experiments, suggesting that the difference between the emotional and neutral conditions was greater in the OCD than in the control group (**Figure 1**).

A series of multiple regression analyses in the patient group showed highly specific associations between subjective anxiety scores and corresponding questionnaire measures. Thus, washing-related anxiety correlated only with PI-R washing (nonsignificant trend: $r = 0.45$, $P = .06$), checking-related anxiety correlated only with PI-R checking ($r = 0.77$, $P < .001$), and hoarding-

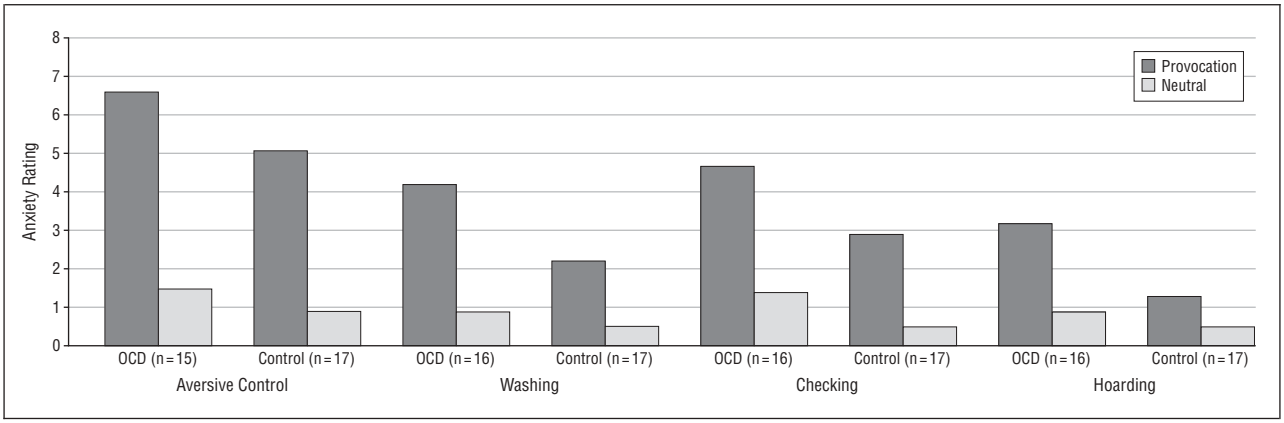

Figure 1. Subjective discomfort ratings during provoked and neutral conditions in patients with obsessive-compulsive disorder (OCD) and control subjects. For aversive control, group: $F_{1,30}=5.5$, $P=.03$; condition: Pillai $F_{1,30}=130.6$, $P<.001$; group × condition: Pillai $F_{1,30}=1.2$, $P=.27$ (not significant). For washing, group: $F_{1,31}=7.8$, $P=.009$; condition: Pillai $F_{1,31}=55.1$, $P<.001$; group × condition: Pillai $F_{1,31}=5.2$, $P=.03$. For checking, group: $F_{1,31}=7.2$, $P=.01$; condition: Pillai $F_{1,31}=29.4$, $P<.001$; group × condition: Pillai $F_{1,31}=0.6$, $P=.43$ (not significant). For hoarding, group: $F_{1,31}=6.9$, $P=.01$; condition: Pillai $F_{1,31}=24.9$, $P<.001$; group × condition: Pillai $F_{1,31}=6.1$, $P=.02$. Only 15 patients in the OCD group were available for analysis in the aversive control experiment because 1 patient had a panic attack during this experiment.

related anxiety correlated only with SI-R discarding ($r=0.80$, $P<.001$). No significant correlations emerged in the aversive control experiment.

GENERIC BRAIN ACTIVATION MAPS

In response to all types of anxiety, regions activated by both patients and controls included bilateral visual areas, cerebellum, striatum (caudate and putamen), thalamus, motor and premotor cortices, limbic and paralimbic areas (ventrolateral prefrontal and orbitofrontal gyri, insula, temporal pole, amygdala, ventral/subgenual cingulate gyrus, and hippocampus), and dorsolateral prefrontal areas (medial and middle frontal, dorsal anterior cingulate, and inferior frontal gyri).

DIFFERENCES IN NEURAL RESPONSE BETWEEN PATIENTS AND CONTROLS

Results of the analyses of covariance, covarying for BDI scores, are shown in **Table 3** and **Figure 2**.

WASHING EXPERIMENT

Patients demonstrated greater activation than controls primarily in ventromedial prefrontal regions: left medial frontal gyrus (Brodmann area [BA] 32/11), right anterior cingulate gyrus (BA32), bilateral orbitofrontal cortex (BA11), and right subgenual anterior cingulate gyrus (BA25) (extending to the ventrolateral prefrontal cortex [BA47] and the amygdala). Further differences were observed in left middle temporal gyrus (BA37), right caudate nucleus, middle frontal gyrus (BA9/46), and left dorsal anterior cingulate gyrus (BA32). Controls demonstrated greater activation than patients within left ventrolateral prefrontal (BA47) and occipital (BA17/19) cortices.

CHECKING EXPERIMENT

Patients demonstrated greater activation than controls in a large bilateral cluster including various subthalamic and brainstem nuclei, in right putamen/globus pallidus, right thalamus, various dorsal cortical regions (right inferior frontal [BA44], right anterior cingulate [BA32], left medial/superior frontal [BA6], bilateral middle and medial frontal [BA8/9], left precentral [BA4] gyri), and visual regions (precuneus/superior parietal lobule [BA7], middle occipital gyrus [BA19]). There were few differences in limbic/paralimbic regions: right hippocampus and bilateral subgenual anterior cingulate gyrus (BA25, extending to BA11). Controls demonstrated greater activation than patients in bilateral visual regions (lingual and fusiform gyri) and left inferior frontal/precentral gyrus (BA44/6).

HOARDING EXPERIMENT

Patients demonstrated greater activation than controls in left precentral/superior frontal gyrus (BA4/6), left fusiform gyrus (BA37), and right orbitofrontal cortex (BA11). Controls demonstrated greater activation than patients in bilateral visual areas (BA7/19).

AVERSIVE CONTROL EXPERIMENT

Patients demonstrated greater activation than controls in left occipitotemporal regions (BA19/37). Controls demonstrated greater activation than patients in bilateral visual areas (BA37/7), posterior cingulate gyrus (BA31), left anterior insula (extending to the ventrolateral prefrontal cortex and superior temporal gyrus), and left cerebellum.

PLANNED PARTIAL CORRELATIONS WITHIN THE OCD GROUP, CONTROLLING FOR BDI SCORES

The PI-R washing scores were positively correlated with activation in bilateral fusiform and lingual gyri and right superior temporal gyrus, ventrolateral prefrontal cortex, and anterior insula (**Figure 3**).

Checking-related anxiety was positively correlated with activation in left precentral/superior and inferior

Table 3. Differences in Neural Response Between 16 Patients and 17 Control Subjects*

Experiment	Brain Regions	Brodmann Area(s)†	Side	Talairach Coordinates x	y	z	No. of Voxels
Contamination/washing	**Patients>Controls**						
	Medial frontal gyrus	32/11	L	−18	33	−7	88
	Anterior cingulate gyrus	32/24	R	14	44	4	30
	Ventral anterior cingulate gyrus	32	L	−7	41	−2	27
		32	R	11	41	−2	23
	Orbitofrontal cortex	11	L	−14	30	−13	25
		11	R	11	48	−13	20
	Middle temporal gyrus	37	L	−43	−63	4	22
	Subgenual anterior cingulate gyrus/ventrolateral profrontal cortex/amygdala	25/47	R	14	7	−18	21
	Middle frontal gyrus	9/46	L	−25	44	26	18
	Caudate nucleus	-	R	11	22	4	18
	Dorsal anterior cingulate gyrus	32	L	−29	22	20	15
	Controls>Patients						
	Ventrolateral prefrontal cortex	47	L	−47	37	−2	17
	Lingual gyrus	17	R/L	0	−74	9	17
	Middle occipital gyrus	19	R	29	−74	20	12
Aggressive/checking	**Patients>Controls**						
	Subthalamic and brainstem nuclei	–	L/R	−4	−15	−2	48
	Putamen/globus pallidus	–	R	25	−15	−2	44
	Thalamus	–	R	7	−22	4	44
	Precuneus/superior parietal lobule	7	L	−22	−52	37	30
	Hippocampus	–	R	25	−19	−13	23
	Interior frontal gyrus	44	R	47	11	26	22
	Dorsal anterior cingulate gyrus	32	R	7	30	31	19
	Medial/superior frontal gyrus	6	L	−18	11	48	18
	Middle occipital gyrus	19	L	−32	−59	9	16
	Subgenual anterior cingulate gyrus/orbitofrontal cortex	25/11	L	−14	19	−18	16
			R	7	19	−18	13
	Middle frontal gyrus	8	L	−43	11	37	15
			R	47	11	37	12
	Medial frontal gyrus	8	R	4	30	37	15
		9	L	−7	52	26	15
	Precentral gyrus	4	L	−29	−15	59	13
	Controls>Patients						
	Lingual gyrus	18	R	4	−81	−18	58
		18	L	−4	−78	−13	14
	Fusiform gyrus	37	L	−40	−44	−18	15
		18/19	R	43	−67	−2	13
	Inferior frontal/precentral gyrus	44/6	L	−47	4	20	13
Hoarding	**Patients>Controls**						
	Precentral/superior frontal gyrus	4/6	L	−18	−22	53	22
	Fusiform gyrus	37	L	−43	−37	−18	15
	Orbitofrontal cortex	11	R	22	33	−18	11
	Controls>Patients						
	Precuneus	7	L	−7	−74	37	13
	Fusiform/inferior temporal gyrus	19	R	29	−59	−7	12
Aversive (symptom-unrelated)	**Patients>Controls**						
	Occipital gyrus	19	L	−29	−78	26	22
	Inferior temporal gyrus	37	L	−40	−67	4	11
	Controls>Patients						
	Fusiform gyrus	37	L	−47	−56	−24	15
	Precuneus	7	R	14	−59	42	14
	Posterior cingulate gyrus	31	L	−14	−52	26	11
	Insula/ventrolateral prefrontal cortex/superior temporal gyrus	47/22	L	−36	19	−2	11
			L	−43	7	−7	11
	Cerebellum	–	L	−9	−64	−35	11

Abbreviations: L, left; R, right.

*All results are covarying for Beck Depression Inventory scores. Clusterwise *P* value was conservatively set at .0001, yielding a total number of false positives close to zero. Only the cluster with the largest number of voxels within each region is reported. Talairach coordinates refer to the voxel with the maximum sum of squares ratio, a measure of power of neural response, in each cluster. Only in-phase results are reported.

†Dashes indicate that no Brodmann area numbers correspond to that region.

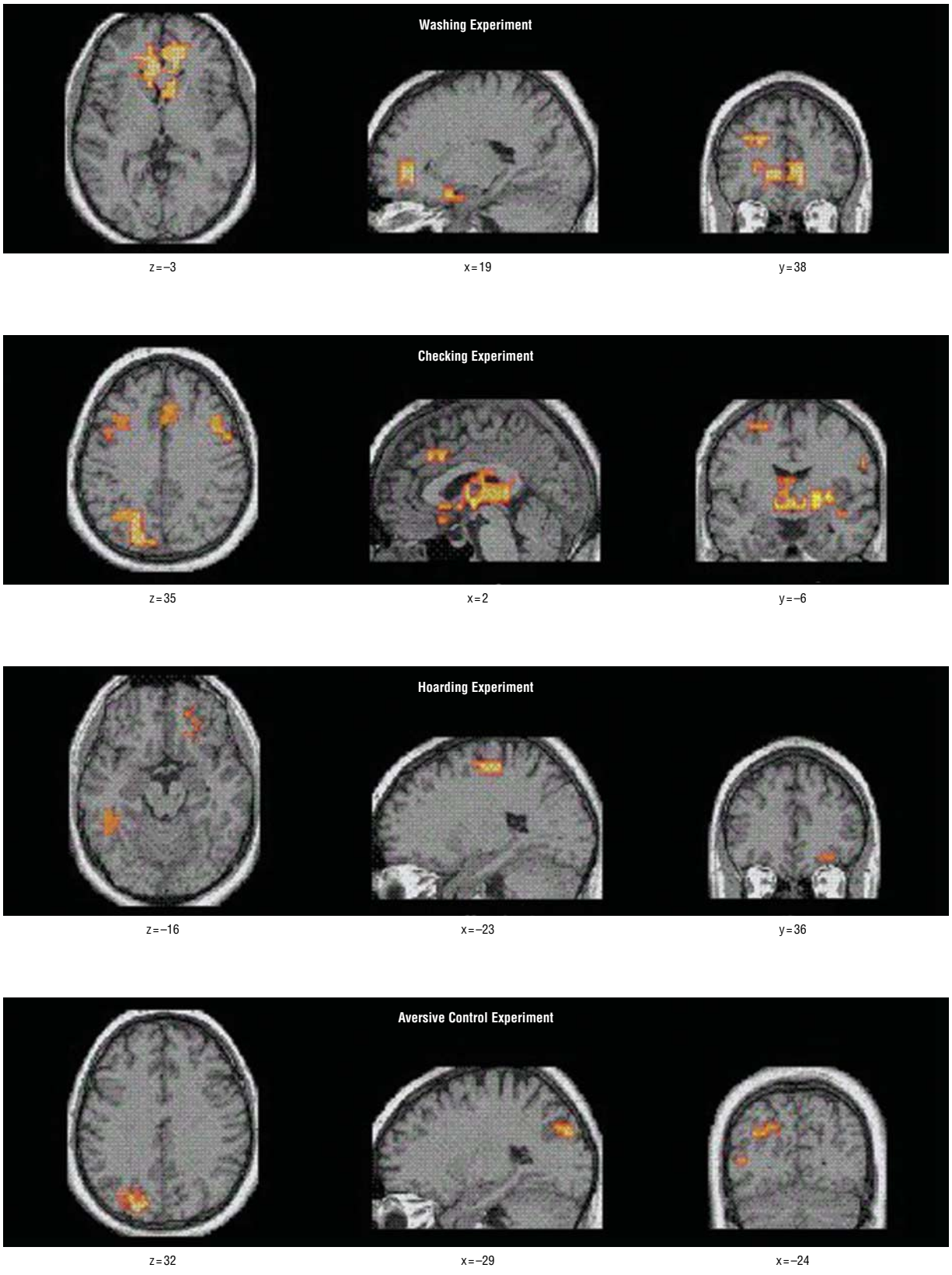

Figure 2. Regions significantly more activated in patients than control subjects. Talairach coordinates are shown in Table 3. For regions significantly more activated in controls, see "Results" section and Table 3.

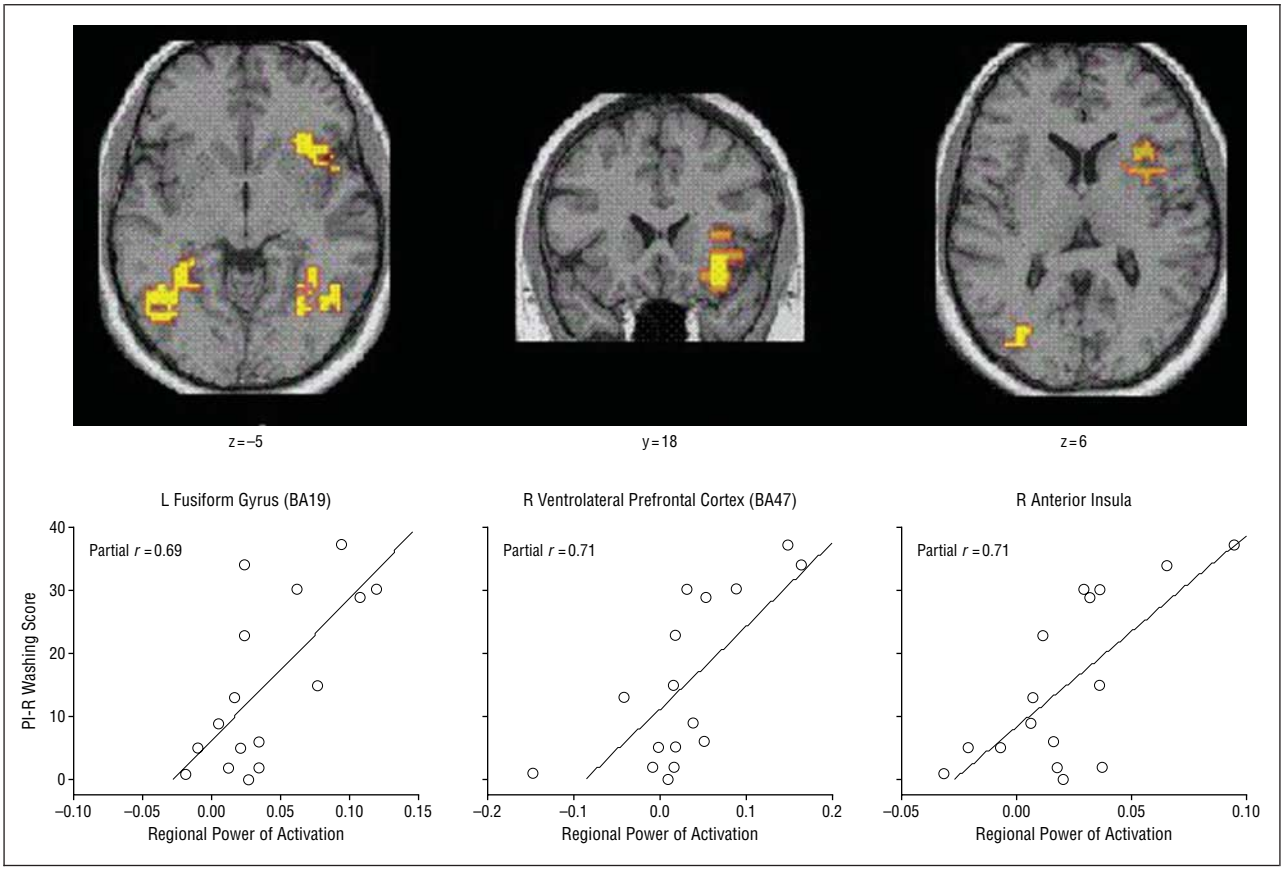

Figure 3. Significant correlations between scores on the washing subscale of the Padua Inventory–Revised (PI-R) and neural activation during the provocation of washing-related anxiety in the obsessive-compulsive disorder group. All partial correlations were controlled for Beck Depression Inventory scores. Positive correlations were found in bilateral fusiform gyrus (BA19; left: –36, –67, –7; voxels: 32; partial r=0.69; right: 29, –63, –7; voxels: 11; partial r=0.68), right superior temporal gyrus (BA38; 47, 11, –7; voxels: 16; partial r=0.75), right ventrolateral prefrontal cortex (BA47; 25, 11, –18; voxels: 15; partial r=0.71), bilateral lingual gyrus (BA19/18; left: –25, –67, –2; voxels: 14; partial r=0.61; right: 25, –74, –2; voxels: 11; partial r=0.64), and right anterior insula (32, 7, 4; voxels: 7; partial r=0.71). Figure 3 is for display purposes only and illustrates the most representative results. L indicates left; R, right.

frontal gyri, bilateral globus pallidus/putamen, and left thalamus (**Figure 4**). Similarly, PI-R checking scores were positively correlated with activation in bilateral globus pallidus/putamen (left: –14, –7, –2, corresponding to Talairach coordinates x, y, and z, respectively; voxels: 7; partial r=0.70; right: 29, –4, 4; voxels: 12; partial r=0.53) and left thalamus (–11, –4, 9; voxels: 9; partial r=0.60).

Hoarding-related anxiety was positively correlated with activation in left precentral/superior frontal gyrus (**Figure 5**).

PLANNED CORRELATIONS WITHIN THE CONTROL GROUP

Correlation analyses within the control group showed few significant associations between subjective anxiety or clinical scales and brain activation. Positive correlations were found in right occipitotemporal regions (BA19/18/37) in all experiments. Negative correlations were found in left occipital cortex (BA31/19/18; washing and checking experiments), right precentral/inferior frontal gyrus (BA6/44; washing experiment), and right middle frontal gyrus (BA46/9; checking experiment).

POST HOC ANALYSES (COMORBIDITY EFFECTS)

The "pure" (n=7) and comorbid (n=9) OCD groups had comparable sociodemographic and clinical characteristics (**Table 4**). Their generic brain activation maps were also similar, and there were few consistent differences in brain activation between the 2 groups, mainly in occipitoparietotemporal regions (**Table 5**).

COMMENT

To our knowledge, this was the first symptom-provocation study to examine the neural correlates of different symptom dimensions of OCD in a representative sample of multisymptomatic patients using a dimensional approach. The main finding was that washing, checking, and hoarding symptom dimensions of OCD were mediated by distinct but partially overlapping neural systems.

In the washing experiment, patients showed greater activations than controls predominantly in bilateral ventromedial prefrontal regions (anterior cingulate and orbitofrontal gyri). Additional regions included the left middle temporal gyrus, right subgenual anterior cingulate gyrus (extending to the ventrolateral prefrontal cor-

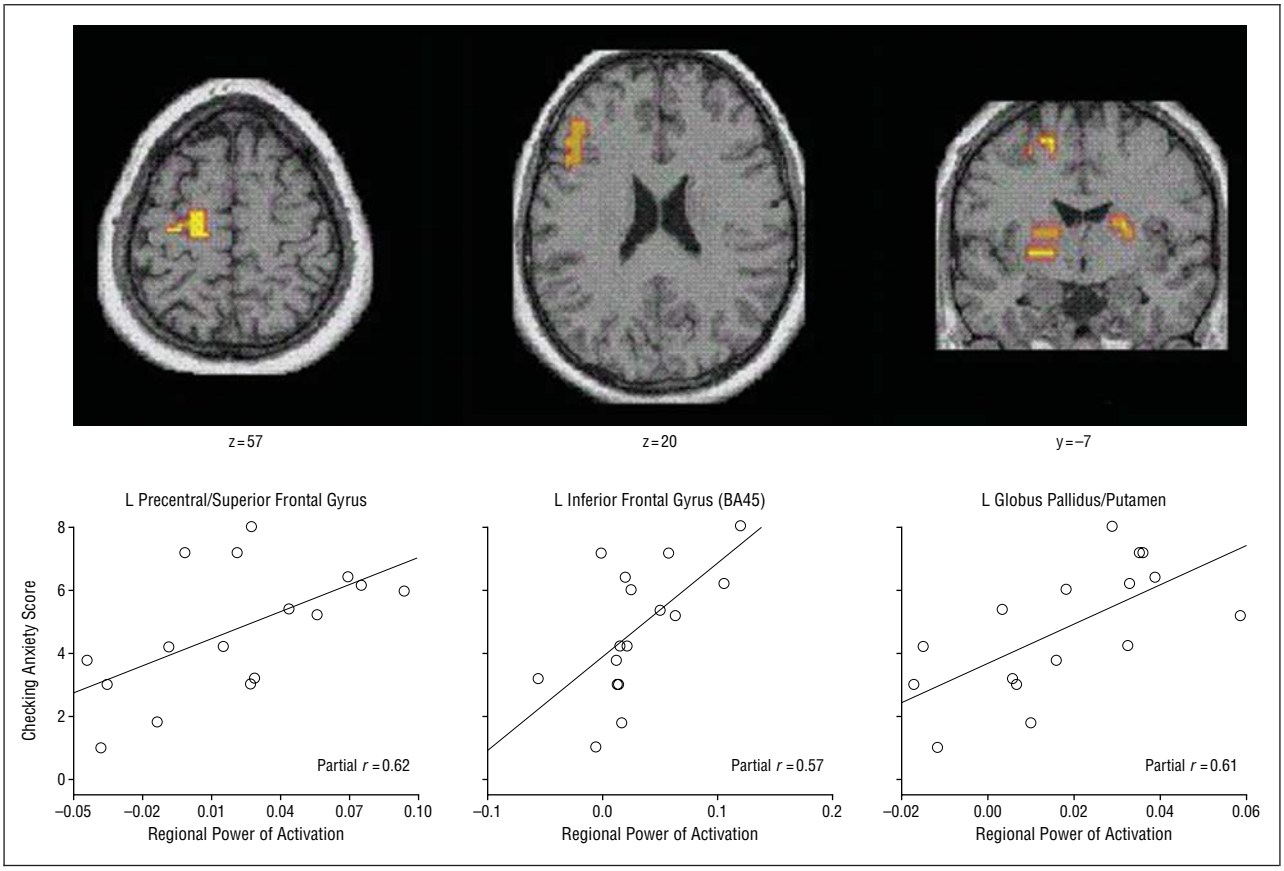

Figure 4. Activation correlating positively with subjective anxiety scores during the checking experiment in the obsessive-compulsive disorder group. All partial correlations were controlled for Beck Depression Inventory scores. Positive correlations were found in left precentral/superior frontal gyrus (BA6; –11, –15, 59; voxels: 13; partial r=0.62), left inferior frontal gyrus (BA45; –43, 19, 20; voxels: 12; partial r=0.57), bilateral globus pallidus/putamen (left: –14, –7, –2; voxels: 7; partial r=0.61; right: 25, –4, 9; voxels: 8; partial r=0.43), and left thalamus (–11, –4, 9; voxels: 6; partial r=0.64). Figure 4 is for display purposes only and illustrates the most representative results. L indicates left; R, right.

tex and amygdala), left middle frontal gyrus, right caudate nucleus, and left dorsal anterior cingulate gyrus. Correlation analyses showed significant positive correlations between scores on the PI-R washing subscale (but not subjective anxiety scores) and activations in bilateral visual regions, right temporal pole, ventrolateral prefrontal cortex, and anterior insula. These results are consistent with previous OCD symptom provocation studies that mainly recruited washers.[20-25,29,30,55] These findings also parallel those of symptom provocation studies in specific phobias,[56,57] which share elements of fear and disgust with contamination/washing symptoms.[58] Taken together, these findings suggest that washing-related anxiety is associated with regions involved in the processing of emotions,[59,60] specifically disgust.[26-28]

In the checking experiment, patients showed greater activation than controls predominantly in regions important for motor and attentional functions: a large bilateral cluster in the subthalamic region including various brainstem nuclei, right putamen/globus pallidus, right thalamus, and various dorsolateral cortical regions (inferior frontal, dorsal anterior cingulate, medial/superior frontal, middle/medial frontal, and precentral gyri). There were fewer statistically significant differences in emotion-processing regions (right hippocampus and a small bilateral cluster in the subgenual anterior cingulate gyrus, extending to the orbitofrontal cortex). Correlation analyses showed positive correlations between subjective anxiety and activation in left precentral/superior frontal (BA6), left inferior frontal gyrus (BA44), bilateral putamen/globus pallidus, and left thalamus during this experiment. Correlations with PI-R checking scores gave similar findings: positive correlations in bilateral globus pallidus/putamen and left thalamus. Thus, both state and trait checking-related anxiety correlated with activation in similar regions.

These findings are consistent with those of Rauch et al,[24] who found positive correlations between scores on a checking scale and regional cerebral blood flow in bilateral striatum, and Phillips et al,[25] who found that only checkers activated dorsal prefrontal (anterior cingulate and inferior frontal gyrus) and visual regions, thalamus, and caudate nucleus. Hypermetabolism in the putamen has been inconsistently reported in OCD.[61,62] It is possible that an excess of patients with checking symptoms were recruited for these studies but few described their samples in detail. A majority of patients (7 of 11) in the Perani et al[61] positron emission tomographic study were labeled as "checkers." These authors found increased metabolic rates in the cingulate gyrus, thalamus, and putamen/globus pallidus but no orbitofrontal or caudate involvement, findings similar to ours. We suggest that the provocation of checking-related anxiety (or the suppression of checking rituals) is associated with dysfunction in a circuit that is important for attentional and mo-

tor functions as well as the inhibition of unwanted impulses[59,63-65] rather than emotion processing per se.

In the hoarding experiment, patients showed increased activation in left precentral/superior frontal (BA4/6), fusiform (BA37), and right orbitofrontal (BA11) gyri, compared with controls. Significant correlations with hoarding-related anxiety were found in left precentral/superior frontal gyrus (BA4/6). An association between hoarding-related anxiety and activation in motor cortex was unpredicted, and its significance is uncertain. Increased activation in right orbitofrontal cortex is congruent with the intense emotional reactions these patients experience when they are asked to discard their possessions.[66] Activity in this region has been shown to be negatively correlated with response to pharmacotherapy[55,67-69] and positively correlated with response to cognitive behavioral therapy.[68] The relationship between our finding of increased activation in this region during the provocation of hoarding symptoms and the well-documented lack of treatment response of these patients[3,5,14,15,17] requires investigation.

The inclusion of an aversive, symptom-unrelated experiment allowed us to explore the neural correlates of general emotional reactivity independent of the content of the patients' symptoms. Although patients experienced more subjective anxiety than controls, they showed greater activation only in occipitotemporal regions, suggesting that the findings of the foregoing experiments were mostly symptom specific.

As in previous symptom provocation studies,[22,30,31] the presentation of OCD symptom–like material was associated with significant increases in subjective anxiety not only in patients but also in controls. Consistent with a few previous reports,[25,30,31] controls activated brain regions similar to those activated by patients. These results are not surprising, as these areas have been repeatedly associated with the induction of various emotional states in normal subjects[70-75] and patients with other anxiety disorders.[76-78] Greater activation in these regions among patients paralleled their higher anxiety, reflecting the greater salience of the provoked stimuli in the patient group.

Controls showed greater activation than patients in bilateral visual areas in all experiments. Furthermore, significant correlations with subjective anxiety and symptom rating scores were observed primarily in occipital regions. Increased activation within visual cortex was repeatedly demonstrated in response to emotive compared with neutral visual stimuli in healthy individuals.[30,79,80] It is plausible that controls directed their attentional resources to the processing of the pictures' visual details rather than their emotional salience.[25,81]

Controls showed greater activation than patients in left inferior prefrontal regions during the washing (BA47) and checking (BA44/6) experiments. Similar regions have been associated with suppression of negative emotions[82] and might reflect more successful regulation of anxiety in controls. During the aversive experiment, controls also showed greater activation than patients in the left insula (extending to the ventrolateral prefrontal and superior temporal cortices), which are emotion and disgust perception areas. This might reflect a bias toward highly aversive (but not symptom-related) material in controls and the opposite pattern in patients.

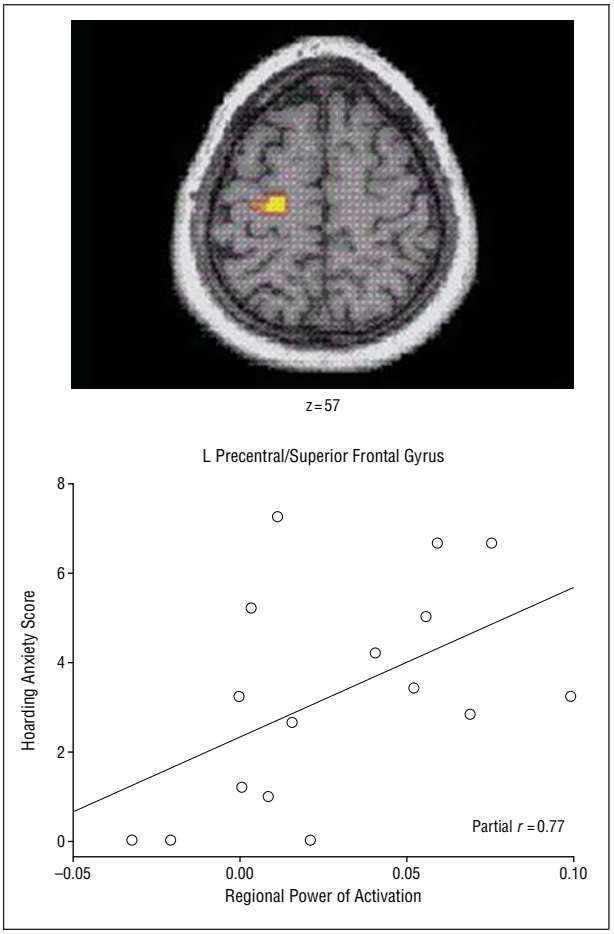

Figure 5. Activation correlating positively with subjective anxiety scores during the hoarding experiment in the obsessive-compulsive disorder group. Partial correlation controlling for Beck Depression Inventory scores was found in left precentral/superior frontal gyrus (BA4/6; –18, –15, 59; voxels: 9; partial r=0.77). Figure 5 is for display purposes only and illustrates the most representative results. L indicates left; R, right.

This study did have certain limitations. We did not exclude patients with comorbidity. Comorbid depression has been found to affect resting-state regional glucose metabolism in positron emission tomographic studies.[83-85] However, comorbidity had little impact on our results: (1) it was constant across the 4 experiments; (2) patients with (n=9) and without (n=7) comorbidity had similar sociodemographic and clinical characteristics and showed no consistent differences in brain activity; (3) BDI scores were used as covariates in all analyses; and (4) there were few consistent differences between patients and controls in the aversive control experiment.

Since most patients (n=12 [75%]) were taking medications, we could not compare medicated and unmedicated patients. However, (1) medications were constant across the 4 experiments; (2) several studies have demonstrated that drug treatment has a normalizing effect on pretreatment functional abnormalities[85,86]; medication would therefore have attenuated rather than inflated our results; (3) symptom provocation studies with[22] or without[23] medicated patients reported similar results; and (4) there were no consistent differences between patients and controls in the aversive control experiment.

Table 4. Demographic and Clinical Characteristics of Patients With OCD With and Without Comorbid Diagnoses*

Variable	Pure OCD (n = 7)	Comorbid OCD (n = 9)	Statistic	*P* Value
Sex, No. (%) M	4 (57)	4 (44)	Fisher exact	>.99
Right-handed, No. (%)	6 (86)	7 (78)	Fisher exact	>.99
Age, y	34.8 ± 10.6	36.6 ± 8.5	$F_{1,14} = 0.12$	.72
Y-BOCS total	24.1 ± 9.4	25.11 ± 6.88	$F_{1,14} = 0.05$	.81
Y-BOCS obsessions	11.2 ± 5.9	11.8 ± 3.6	$F_{1,14} = 0.06$	.80
Y-BOCS compulsions	12.8 ± 3.9	13.22 ± 3.7	$F_{1,14} = 0.03$	.85
PI-R, total	49.4 ± 39.1	58.0 ± 33.7	$F_{1,14} = 0.22$	.64
PI-R, washing	15.7 ± 13.2	14.56 ± 14.0	$F_{1,14} = 0.02$	.86
PI-R, checking	9.7 ± 7.5	13.7 ± 9.0	$F_{1,14} = 0.91$	.35
SI-R, total	25.0 ± 23.1	30.8 ± 30.3	$F_{1,14} = 0.17$	.68
SI-R, clutter	7.6 ± 7.3	9.0 ± 9.3	$F_{1,14} = 0.11$	.74
SI-R, discarding	8.8 ± 9.9	10.8 ± 10.1	$F_{1,14} = 0.14$	.71
SI-R, acquisition	6.1 ± 5.9	8.5 ± 8.6	$F_{1,14} = 0.39$	.53
BDI	13.7 ± 12.8	23.7 ± 11.2	$F_{1,14} = 2.71$	.12
STAI-S	34.0 ± 7.5	35.89 ± 7.1	$F_{1,14} = 0.26$	.61

Abbreviations: BDI, Beck Depression Inventory; OCD, obsessive-compulsive disorder; PI-R, Padua Inventory–Revised; SI-R, Saving Inventory–Revised; STAI-S, state subscale of the State Trait Anxiety Inventory; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.
*Values are given as mean ± SD score unless otherwise specified.

Table 5. Differences in Neural Response Between 9 Patients With and 7 Without Comorbid Diagnoses*

Experiment	Brain Regions	Brodmann Area(s)†	Side	Talairach Coordinates x	y	z	No. of Voxels
Contamination/washing	**Pure OCD>Comorbid OCD**						
	Inferior parietal lobule	40	L	–32	–52	26	13
	Cerebellum	–	L	–22	–44	–29	11
	Comorbid OCD>Pure OCD						
	Inferior parietal lobule	40	R	51	–44	26	12
Aggressive/checking	**Pure OCD>Comorbid OCD**						
	Precuneus	31	R/L	0	–67	15	28
	Cuneus	19	R	4	–74	31	19
	Posterior cingulate gyrus	29/30	R	4	–41	20	12
	Comorbid OCD>Pure OCD						
	Precentral gyrus	6	R	51	4	26	14
Hoarding	**Pure OCD>Comorbid OCD**						
	Inferior/superior parietal gyrus	39/7	L	–40	–63	31	34
	Middle temporal gyrus	21/37	L	–58	–44	4	31
	Precuneus	7	L	–18	–44	53	27
	Cerebellum	–	L	–11	–81	–18	25
	Lingual gyrus	17/18	L	–7	–78	–13	18
	Fusiform gyrus	18	L	–25	–78	–13	15
	Superior temporal gyrus	22	L	–51	–37	20	12
	Comorbid OCD>Pure OCD						
	Cerebellum	–	R	40	–56	–35	15
Aversive (symptom-unrelated)	**Pure OCD>Comorbid OCD**						
	Medial frontal gyrus	6	R	4	7	48	11
	Comorbid OCD>Pure OCD						
	Precuneus	7	R	18	–30	48	24
		7	L	–14	–52	37	17
	Middle temporal gyrus	39	L	–36	–63	15	15

Abbreviation: OCD, obsessive-compulsive disorder.
*Clusterwise *P* value was conservatively set at .0001, yielding a total number of false positives close to zero. Only the cluster with the largest number of voxels within each region is reported. Talairach coordinates refer to the voxel with the maximum sum of squares ratio, a measure of power of neural response, in each cluster. Only in-phase results are reported.
†Dashes indicate that no Brodmann area numbers correspond to that region.

The sample was relatively small, but this is the largest fMRI study in OCD to date. The reported effects were strong and consistent across various methods of analysis. It is possible that our hoarding experiment was underpowered, since only half of our sample had current hoarding symptoms; further research on the hoarding dimension is warranted. The neural correlates of the symmetry/ordering dimension remain to be investigated.

CONCLUSIONS

The relative inconsistency of findings from previous functional neuroimaging studies of OCD may have resulted from phenotypic variations among subject groups. Replication of our findings would suggest that discrete neural systems might mediate the expression of different symptoms. Because of the neuroanatomic proximity within the frontostriatothalamic loops,[59] it is not surprising that the different symptom dimensions often coexist in any given patient. Obsessive-compulsive disorder could be better understood as a spectrum of multiple potentially overlapping syndromes that are likely to be continuous with "normal" worries and extend beyond the traditional nosologic boundaries of OCD. Each symptom dimension might reflect the dysregulation of highly conserved complex and partially overlapping neural systems that serve to detect, appraise, and respond to potential threats.[87]

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