ORIGINAL ARTICLE

Differential Cerebral Metabolic Changes With Paroxetine Treatment of Obsessive-Compulsive Disorder vs Major Depression

Sanjaya Saxena, MD; Arthur L. Brody, MD; Matthew L. Ho, BS; Shervin Alborzian, BS; Karron M. Maidment, RN; Narineh Zohrabi, BS; Mai K. Ho, BS; Sung-Cheng Huang, PhD; Hsiao-Ming Wu, PhD; Lewis R. Baxter, Jr, MD

Background: Serotonin reuptake inhibitors (SRIs) effectively treat both major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). We compared and contrasted the functional neuroanatomical effects of SRIs in OCD and MDD as these 2 disorders occurred separately and concurrently by measuring pretreatment to posttreatment cerebral glucose metabolic changes in OCD vs MDD vs concurrent OCD+MDD.

Methods: We obtained [^{18}F]fluorodeoxyglucose positron emission tomography (PET) brain scans on 25 subjects with OCD, 25 with MDD, and 16 with concurrent OCD+MDD before and after 8 to 12 weeks of treatment with paroxetine hydrochloride. Controls (n=16) were scanned 10 to 12 weeks apart without treatment. Treatment response was defined as a more than 25% decline in OCD symptom severity, a more than 50% decline in MDD severity, and "much improved" clinical global impression.

Results: Although all patient groups received the same paroxetine dose for the same duration, regional metabolic changes differed significantly among diagnostic groups. Subjects with OCD alone showed significant metabolic decreases in the right caudate nucleus, right ventrolateral prefrontal cortex (VLPFC), bilateral orbitofrontal cortex, and thalamus that were not seen in any other group. Both the MDD and concurrent OCD+MDD groups showed metabolic decreases in the left VLPFC and increases in the right striatum. Treatment response was associated with a decrease in striatal metabolism in nondepressed OCD patients but with an increase in striatal activity in patients with OCD+MDD.

Conclusions: Brain metabolic responses to SRIs are both disorder-specific and response-specific. They vary according to the underlying pathophysiology of the patient and the degree of symptomatic improvement.

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From the Departments of Psychiatry and Biobehavioral Sciences (Drs Saxena, Brody, and Baxter, Messrs M. L. Ho and Alborzian, and Mss Maidment, Zohrabi, and M. K. Ho) and Molecular and Medical Pharmacology (Drs Huang, Wu, and Baxter), School of Medicine, University of California, Los Angeles; and the Department of Psychiatry and Behavioral Neurobiology, School of Medicine, University of Alabama, Birmingham (Dr Baxter).

SEROTONIN reuptake inhibitors (SRIs) are effective treatments for several psychiatric disorders, including major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). However, it is not known whether improvements in different clinical syndromes are mediated by the same effects of SRIs on brain function. This study was intended to determine whether the functional neuroanatomical effects of SRI treatment in OCD and MDD depend on the underlying pathophysiology of the clinical syndrome, the degree of symptomatic improvement, or a combination of both factors.

Positron emission tomography (PET) studies of untreated, nondepressed subjects with OCD have found elevated glucose metabolism or cerebral blood flow in the orbitofrontal cortex (OFC), anterior cingulate gyrus, caudate nuclei, and thalamus.[1-5] Activity in these structures decreases with response to a variety of SRIs.[5-10] Consequently, SRIs are thought to ameliorate OCD symptoms by decreasing functional activity along orbitofrontal–basal ganglia–thalamo–cortical circuits.[8,10,11]

The functional neuroanatomy of MDD is less well established. The dorsolateral prefrontal cortex (DLPFC) and basal ganglia have shown diminished activity,[12-17] whereas the ventrolateral prefrontal cortex (VLPFC) has shown elevated activity in MDD.[18-20] Metabolism in the DLPFC has been found to increase after treatment with fluoxetine hydrochloride,[21] sertraline hydrochloride,[22] and naturalistic treatment with tricyclic antidepressants, lithium carbonate, and trazodone hydrochloride.[12,13] Metabolism in the caudate nucleus also increased in patients with MDD who responded to tricyclic antidepressants.[19,23] In contrast, decreases in VLPFC metabolism were seen after treatment with

SUBJECTS AND METHODS

SUBJECTS

Subjects were recruited from the Los Angeles area through local physicians and advertisements in flyers, newspapers, and Web sites. Written informed consent was obtained from all subjects (n=88) after study procedures were fully explained. Of the 88 subjects enrolled, 27 had OCD alone, 27 had MDD alone, 17 had concurrent OCD+MDD, and 17 were age-matched, sex-matched, healthy controls. Diagnostic classifications were made by clinical interview using *DSM-IV*[32] criteria and confirmed with the Schedule for Affective Disorders and Schizophrenia–Lifetime Version.[33] Symptom severity and level of functioning were rated with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS),[34] Hamilton Depressive Rating Scale (HDRS),[35] Hamilton Anxiety Scale (HAS),[36] the Global Assessment Scale,[37] and the Clinical Global Impressions/Improvement Scale[38] for all subjects and controls at the time of each PET scan. All assessments were performed by a study psychiatrist with training in standardized assessment (S.S. or A.L.B.).

To be enrolled in the study, subjects with OCD alone had to meet *DSM-IV* criteria for OCD but not MDD, have pretreatment Y-BOCS scores of 16 or more, and a 17-item HDRS (HDRS-17) score of less than 15. Subjects with MDD alone had to meet *DSM-IV* criteria for unipolar MDD but not OCD, have HDRS-17 scores of 16 or more, and Y-BOCS scores of less than 10. Subjects with concurrent OCD+MDD had to meet full *DSM-IV* criteria for both disorders occurring simultaneously and have Y-BOCS scores of more than 16 and HDRS-17 scores of 16 or more. These criteria were chosen based on prior usage in several studies of OCD[7,8,39,40] and MDD.[41,42] Control subjects had scores of less than 6 on all symptom-rating scales and no self-reported history of any psychiatric disorder or substance abuse. All subjects were in good physical health. Two subjects with OCD alone and 3 subjects with comorbid OCD+MDD met *DSM-IV* criteria for Tourette syndrome. Subjects with other concurrent Axis I *DSM-IV* diagnoses, including bipolar disorder, psychotic disorders, other anxiety disorders, substance abuse, or concurrent medical conditions affecting brain function (ie, Parkinson disease, diabetes mellitus, etc) were excluded. All subjects had not taken psychoactive medications for at least 4 weeks or fluoxetine for at least 5 weeks prior to entering the study. Only 6 subjects had received any psychotropic medication within 12 weeks of entering the study. Results did not change when these subjects were excluded from the analyses. Of 88 subjects, 21 (9 with OCD alone, 6 with MDD alone, and 6 with concurrent OCD+MDD) had never before been treated with psychotropic medications.

TREATMENT

The 3 patient groups were treated openly with paroxetine titrated to a target dose of 40 mg/d, as tolerated, for the first 8 weeks. Thereafter, paroxetine doses were increased as tolerated to a maximum of 60 mg/d for up to 4 more weeks, in the absence of a satisfactory response at lower doses. Compliance was monitored by patient report during weekly medication visits. For the OCD group, responders to treatment were defined a priori as those who had a 25% or more drop in Y-BOCS score and a Clinical Global Impressions/Improvement rating of "much improved" or "very much improved" (as defined in our previous reports).[8,10] For the MDD group, responders were defined as those who had a 50% or more drop in HDRS score and a Clinical Global Impressions/Improvement rating of "much improved" or "very much improved." These criteria were chosen because these response cutoffs were used in several prior studies of OCD[8,39,40] and MDD.[42,43] Patients who did not meet these response criteria were labeled nonresponders. No psychoactive medications except paroxetine were allowed during the study period. Subjects received no formal psychotherapy during the treatment period. Controls received no treatment.

IMAGE ACQUISITION AND ANALYSIS

Cerebral glucose metabolism was measured with [^{18}F]fluorodeoxyglucose (FDG)–PET scans in all subjects, first at baseline (baseline results reported previously)[44] and again after 8 to 12 weeks of paroxetine treatment. Normal controls received their second scans after 10 to 12 weeks without medication. Six subjects (2 with OCD, 2 with MDD, 1 with concurrent OCD+MDD, and 1 control) either dropped out of the study before receiving their second PET scans or had unusable second scans because of technical problems. Therefore, their data were not included in this report.

The PET scanning methods were as described in our previous reports.[10,25,45] In brief, each subject received 5 to 10 mCi of FDG while in a supine position with eyes and ears open. Subjects were closely monitored to make sure they stayed awake and lay still without moving or talking during the 40-minute FDG uptake period. No cognitive task was given. Each subject's head was fixed in a head holder to allow accurate positioning in the tomograph. "Arterialized" venous blood was obtained from the subject's hand while it was heated with a water-based hand warmer. Scanning was performed with Seimens-CTI Inc (Knoxville, Tenn) PET tomographs: the ECAT III 831 (15 transverse sections spaced 6.75 mm apart, with 6-mm in-plane spatial resolution acquired at an angle parallel to the cantho-meatal plane) for the first 38 subjects and the EXACT HR1 961 (47 transverse sections spaced 4.0 mm apart, with 3.6-mm in-plane spatial resolution) for the next 50 subjects.

We used a double-echo sequence (proton density and T2 images; TR, 2000 to 2500 milliseconds; TE, 25 to 30 milliseconds and 90 to 110 milliseconds; 24-cm field of view; 3-mm slices with 0-mm separation) to perform magnetic resonance imaging (MRI) scans of each subject's brain during the treatment period between the 2 PET scans. All MRI scans were reviewed by a neuroradiologist. Two prospective subjects with MRI evidence of structural central nervous system lesions (1 with extensive white matter lesions and 1 with frontal encephalomalacia due to head trauma) were excluded from the study.

We used 2 methods of image analysis to assess significant regional metabolic changes from the first to the second FDG-PET scans: (1) MRI-based region of interest (ROI) analysis and (2) statistical parametric mapping (SPM).[46] Results from both methods were compared, given the limitations of each.[46,47] For 2 reasons, PET data were subjected to SPM analysis. First, the drawn ROIs were relatively large, and SPM allowed examination of smaller regions that might have significant changes. Second, selection of ROIs for analysis was based on previous studies, and SPM could screen the rest of the brain for unhypothesized changes.

Continued on next page

Each subject's pretreatment and posttreatment FDG-PET scans were coregistered with his or her MRI scan. Then, ROIs were identified and outlined on the horizontal planes of each MRI scan (**Figure 1**). This technique took intersubject neuroanatomical variability into account and allowed for measurement of glucose metabolism in each subject's specific regional volumes. The technique also partially corrected for regional atrophy because cerebrospinal fluid and white matter were excluded from the outlines of all gray matter structures and ensured that pretreatment and posttreatment metabolic rates for a given ROI were calculated in exactly the same neuroanatomical volume. Subjects' pretreatment and posttreatment PET images were resliced to coregister within the 3-dimensional orientation of their MRI images.[48] Technicians blind to subject identity and diagnosis (S.A., M.L.H., and M.K.H.) drew ROIs, and ROIs were reviewed by S.S. and A.L.B to ensure interrater reliability.[49]

Ten bilateral ROIs were selected a priori, based on previous findings: DLPFC, VLPFC, OFC, dorsal anterior cingulate gyrus, ventral anterior cingulate gyrus, caudate nucleus, putamen, thalamus, amygdala, and hippocampus (Figure 1). The dorsal half of the middle frontal gyrus made up the DLPFC, while the VLPFC consisted of the ventral half of the middle frontal gyrus.[50] The OFC ROI included the medial and lateral orbital gyri, the orbital part of the inferior frontal gyrus (IFG), and the most inferior part of the frontal pole, but excluded the gyrus rectus. The anterior cingulate gyrus was divided evenly into dorsal and ventral portions. The superior boundary of the dorsal anterior cingulate gyrus was the base of the body of the gyrus cinguli, whereas the inferior boundary was parallel to the middle of the body of the caudate nucleus. The caudate ROI included the entire head but excluded the body and tail of the caudate nucleus. Amygdala and hippocampal ROIs excluded mesial temporal cortex and parahippocampal gyrus. Both supratentorial hemispheres were also drawn.

The ROIs drawn on subjects' MRIs were transferred onto their coregistered pretreatment and posttreatment PET scans. Mean activity in each ROI volume and the ratios of each ROI normalized to ipsilateral hemispheric glucose metabolism (ROI/Hem) were calculated as previously described.[8] Absolute glucose metabolic rates could not be calculated accurately or reliably for many PET scans in this study because of errors in γ counter calibration and blood glucose measurement. Therefore, only regional metabolic data normalized to each subject's ipsilateral hemisphere were used for the MRI-based ROI analysis. This made the ROI and SPM analyses more congruent, as SPM data were also normalized and proportionally scaled to group means.

The SPM analysis of PET data employed the software package SPM96.[51] Each subject's pretreatment and posttreatment images were realigned and coregistered,[52] and all study images were reoriented to the standardized coordinate system of Tailarach and Tournoux.[53] Global normalization by proportional scaling was used. A 16-mm full-width at half-maximum, 3-dimensional Gaussian smoothing filter was applied to all images.[52] To determine the location of SPM findings, MRIs of all study subjects were transformed into Tailarach space, and clusters with significant changes were mapped onto the group-averaged MRI. Voxel coordinates were also located in the standard atlas.[53]

Subgroups of our subject sample have been described in our preliminary reports, which examined metabolic changesin a few selected brain regions within our first 20 subjects with OCD alone[10] and our first 15 subjects with MDD alone.[25] Another report[45] described cerebral metabolic changes in 10 of our paroxetine-treated MDD subjects compared with subjects treated with interpersonal therapy and controls. Those preliminary analyses did not include any subjects with concurrent OCD+MDD, comparisons between OCD and MDD, or examinations of the entire brain.

STATISTICAL ANALYSES

The data were first screened for distributional properties, outliers, and missing values. No variables were rejected during this process. Pretreatment to posttreatment changes in symptom severity (measured with the Y-BOCS, HDRS, HAS, and Global Assessment Scale) were compared among the 4 groups (OCD, MDD, concurrent OCD+MDD, and controls) with univariate analysis of variance (ANOVA) (SPSS 6.1.2; Statistical Product and Service Solutions Inc, Chicago, Ill), with post hoc least significant difference (LSD) tests to determine which diagnostic groups accounted for significant between-groups differences ($P<.05$).

Our primary PET image analysis was the directed ROI approach targeting specific regions we believed might be implicated. The primary analysis was supplemented by a series of SPM analyses looking for particular effects identified in the ROI analysis over the entire brain. This allowed us to identify brain regions not included in the ROI analysis and characterize more precisely any diagnosis-specific or response-specific effects of paroxetine on cerebral metabolism.

For the MRI-based ROI analysis, ROI/Hem change scores were compared among the 4 groups with an omnibus multivariate ANOVA (MANOVA) (SPSS 6.1.2) using diagnosis and response as between-subject factors and the selected ROIs as the dependent variables, with age, gender, and scanner type as covariates. Univariate ANOVAs were then performed for only those ROIs found to have significant effects of diagnosis, response, or diagnosis by response interaction on the omnibus MANOVA, followed by post hoc LSD tests to determine which diagnostic and response subgroups accounted for significant between-groups differences ($P<.05$). Post hoc tests were performed on main effects when no significant interaction effect was present for the region in question.

For SPM analysis, cerebral metabolic changes with paroxetine treatment in each patient group and between the 2 scans in normal controls were assessed with the paired *t* test on a voxel-by-voxel basis to identify the profile of voxels that differed significantly between first and second scans. Responders and nonresponders within each diagnostic group were analyzed separately. Age, gender, and scanner type were controlled for as nuisance covariates. Voxel size was 2.0 × 2.0 × 2.0 mm. The size of the region (whole brain) being searched varied slightly among groups, ranging from 168 000 to 218 000 voxels. Significance thresholds of $P<.01$ at the uncorrected voxel level for hypothesized regions and $P<.001$ at the uncorrected voxel level and $P<.01$ at the uncorrected cluster level for unhypothesized regions were used. These thresholds are similar to other published PET studies of mood and anxiety disorders.[20,54] Results are presented using the voxel of peak significance.

This study was carried out under guidelines established by the University of California, Los Angeles, Institutional Review Board.

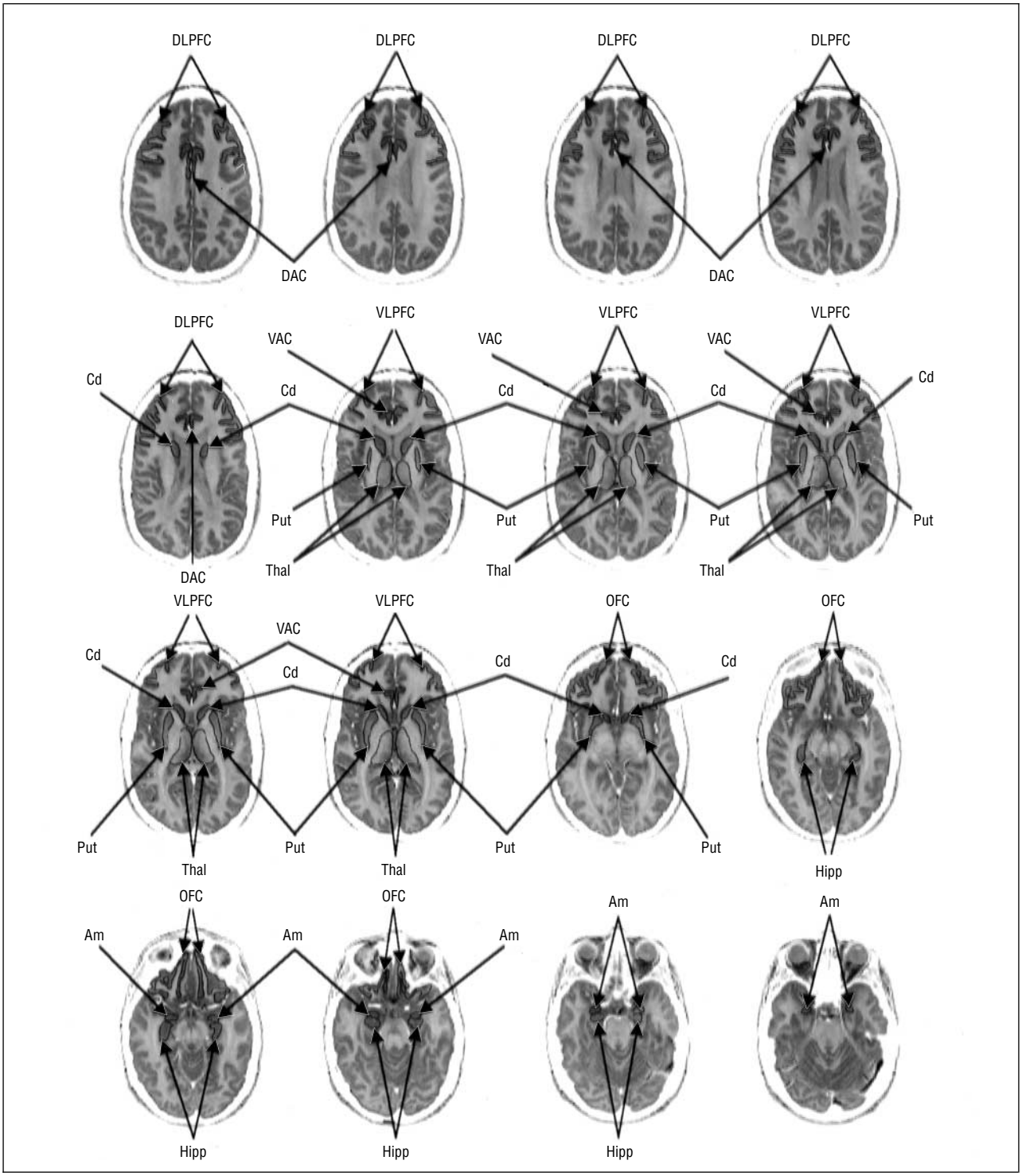

Figure 1. Regions of interest drawn on magnetic resonance images, which were then transferred onto coregistered [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) scans. After transfer, these regions were linked to give a summed value for the region, which was then normalized to the linked value for the supratentorial ipsilateral hemisphere (region not shown). DLPFC indicates dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; DAC, dorsal anterior cingulate gyrus; VAC, ventral anterior cingulate gyrus; Cd, head of the caudate nucleus; Put, putamen; Thal, thalamus; OFC, orbitofrontal cortex; Hipp, hippocampus; and Am, amygdala.

desipramine hydrochloride,[19] fluoxetine,[21] sertraline,[24] paroxetine,[25] and electroconvulsive therapy.[26]

Of all patients with OCD, 60% to 80% will have at least 1 major depressive episode in their lifetime, and approximately one third have concurrent MDD at the time of evaluation.[27,28] Conversely, obsessive-compulsive symptoms are found in 22% to 38% of all patients diagnosed with primary MDD.[29,30] Comorbid OCD can influence the response to specific classes of medications in depressed patients. The SRI sertraline was found to be significantly more effective than the tricyclic antidepressant desipramine for reducing MDD symptoms in patients with concurrent OCD+MDD.[31]

Table 1. Clinical Variables of Subjects Before and After Paroxetine Treatment*

Clinical Variable	Controls (n = 16)	OCD Group (n = 25)	MDD Group (n = 25)	OCD + MDD Group (n = 16)	Effect of Diagnosis	
					$F_{3,78}$	*P* Value
Gender, % F	50	54	50	57	1.1	.36
Age, y	32.5 ± 11.8	37.5 ± 12.6	38.1 ± 11.3	34.1 ± 9.2	1.5	.23
Treatment duration, d	79.1 ± 21.3	69.2 ± 14.8	68.1 ± 19.3	76.9 ± 17.5	1.3	.30
Paroxetine hydrochloride dose, mg	. . .	40.0 ± 10.6	36.8 ± 9.9	44.0 ± 9.9	2.41	.10
Y-BOCS						
Pretreatment	. . .	25.8 ± 5.1	2.3 ± 5.2	28.3 ± 4.6	15.1†‡	<.001
Posttreatment	. . .	20.2 ± 7.4	1.3 ± 3.2	18.8 ± 8.2		
HDRS-17						
Pretreatment	0.8 ± 1.3	9.8 ± 3.5	20.3 ± 5.0	20.5 ± 5.3	20.6‡§‖	<.001
Posttreatment	1.3 ± 1.2	8.3 ± 5.00	9.2 ± 6.5	11.7 ± 7.1		
HDRS-28						
Pretreatment	1.0 ± 1.6	16.4 ± 5.0	31.4 ± 6.5	30.3 ± 6.1	18.0‡§‖	<.001
Posttreatment	1.8 ± 1.3	14.2 ± 8.8	14.0 ± 9.3	17.9 ± 11.4		
HAS						
Pretreatment	1.4 ± 1.5	10.8 ± 4.2	20.0 ± 9.8	23.7 ± 10.2	10.3‡§	<.001
Posttreatment	1.9 ± 1.4	9.6 ± 6.7	11.0 ± 8.6	10.4 ± 10.4		
GAS						
Pretreatment	91.1 ± 3.1	50.3 ± 7.9	48.2 ± 5.9	44.4 ± 6.5	18.8†‡§	<.001
Posttreatment	88.2 ± 3.6	55.8 ± 11.8	67.7 ± 11.6	59.8 ± 9.5		

*Data are given as mean ± SD unless otherwise indicated. OCD indicates obsessive-compulsive disorder; MDD, major depressive disorder; OCD + MDD, concurrent OCD and MDD; HDRS-17, 17-item Hamilton Depression Rating Scale[35]; HDRS-28, 28-item Hamilton Depression Rating Scale[35]; HAS, Hamilton Anxiety Rating Scale[36]; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale[34]; GAS, Global Assessment Scale[37]; and ellipses, not applicable.
†OCD vs controls.
‡OCD + MDD vs controls.
§MDD vs controls and OCD.
‖OCD + MDD vs OCD.

Only 2 prior PET studies have examined patients with concurrent OCD+MDD. Baxter et al[12] found that patients with comorbid OCD+MDD had lower left DLPFC metabolism than nondepressed patients with OCD. After successful treatment of depression with non-SRI medications, left DLPFC metabolism increased. In another study, patients with concurrent OCD+MDD who responded to non-SRI antidepressants showed increases in normalized caudate nucleus metabolism with treatment,[1] in contrast to subsequent findings of decreases in caudate nucleus metabolism in nondepressed OCD patients who responded to either fluoxetine or cognitive-behavioral therapy.[8]

We sought to determine whether the cerebral metabolic effects of SRI treatment were the same or different for OCD and MDD. We compared regional cerebral metabolic changes in subjects with OCD alone, subjects with MDD alone, and subjects with concurrent OCD+MDD. All were treated with paroxetine, an SRI shown to be effective for both disorders. We hypothesized that glucose metabolism in the OFC, caudate nucleus, and thalamus would decrease in subjects with OCD alone who responded to treatment. We also predicted that VLPFC metabolism would decrease but DLPFC metabolism would increase in subjects with MDD alone who responded. Finally, we hypothesized that responders with concurrent OCD+MDD would show pretreatment to posttreatment changes that overlapped with those seen in OCD and MDD responders, with decreased metabolism in the OFC and VLPFC but increased metabolism in the DLPFC.

RESULTS

TREATMENT RESPONSE

The groups did not differ significantly in age, male-female ratio, duration of treatment, or final paroxetine dose (**Table 1**). Of the 66 treated subjects who completed the study, 40 took 40 mg/d of paroxetine. Seven took 20 mg/d because of inability to tolerate any higher dose, 8 took 30 mg/d, 4 reached a maximum dose of 50 mg/d, and 7 reached 60 mg/d for the final 4 weeks of treatment.

Univariate ANOVA revealed significant effects of diagnosis on change in Y-BOCS, HDRS-17, HAS, and Global Assessment Scale scores (Table 1). Post hoc LSD analyses showed that the OCD group had significant pretreatment to posttreatment decreases in Y-BOCS scores compared with controls but did not have significant changes in HDRS-17 or HAS scores. Twelve of the 25 OCD subjects were classified as responders and had robust decreases in Y-BOCS scores (mean±SD, 25.3±5.4 to 15.5±4.8). The MDD group had significant, pretreatment to posttreatment decreases in HDRS and HAS scores compared with controls but did not have significant changes in Y-BOCS scores. Of the 25 MDD subjects, 18 were classified as responders and had robust decreases in HDRS-17 (mean±SD, 19.7±4.5 to 5.9±2.6) and HAS (mean±SD, 20.7±9.3 to 9.4±7.1) scores. The OCD+MDD group had significant decreases in Y-BOCS, HDRS, and HAS scores compared with controls. Of the 16 OCD+MDD subjects, 9 were classified as responders and had large declines in Y-BOCS (mean±SD, 28.9±4.5 to 13.9±6.3), HDRS-17 (mean±SD, 20.0±4.8 to 6.4±3.8), and HAS (mean±SD, 21.7±9.1 to 8.6±8.7) scores. Global Assessment Scale scores improved significantly in all 3 treated groups compared with controls. Controls showed no significant changes on any clinical measures (Table 1).

MRI-BASED ROI ANALYSES

The omnibus MANOVA revealed a significant overall effect of diagnosis on pretreatment to posttreatment ROI/Hem change scores (Hotelling $F_{60}=1.75$, $P=.003$). Univariate

Table 2. Region of Interest/Hemisphere Glucose Metabolic Ratios Before and After Paroxetine Treatment*

Region of Interest	Controls (n = 16)		OCD Group (n = 25)		MDD Group (n = 25)		OCD + MDD Group (n = 16)		Analysis of Variance: Diagnosis		Response		Interaction	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	$F_{3,71}$	*P* Value	$F_{1,71}$	*P* Value	$F_{2,71}$	*P* Value
Left														
Am	0.84 ± .07	0.86 ± .05	0.81 ± .07	0.81 ± .07	0.80 ± .06	0.81 ± .06	0.78 ± .04	0.81 ± .06	...	...	...	...	...	...
Caudate	1.19 ± .06	1.17 ± .06	1.21 ± .07	1.19 ± .07	1.21 ± .08	1.22 ± .10	1.20 ± .07	1.19 ± .09	...	...	...	...	...	...
DAC	1.11 ± .07	1.10 ± .06	1.12 ± .07	1.10 ± .06	1.15 ± .08	1.15 ± .06	1.12 ± .07	1.12 ± .08	...	...	...	...	...	...
DLPFC	1.22 ± .07	1.21 ± .06	1.25 ± .07	1.23 ± .08	1.24 ± .07	1.24 ± .07	1.26 ± .06	1.26 ± .04	...	...	...	...	...	...
Hipp	0.88 ± .06	0.87 ± .06	0.87 ± .06	0.87 ± .07	0.82 ± .05	0.84 ± .06	0.84 ± .05	0.84 ± .04	...	...	...	...	...	...
OFC	1.09 ± .04	1.09 ± .06	1.07 ± .07	1.05 ± .09	1.08 ± .05	1.08 ± .05	1.07 ± .04	1.07 ± .06	**3.84**	**.01**	...	...	...	...
Putamen	1.35 ± .09	1.34 ± .07	1.33 ± .09	1.32 ± .09	1.35 ± .06	1.37 ± .09	1.28 ± .08	1.30 ± .08	...	...	...	...	...	...
Thalamus	1.03 ± .07	1.02 ± .06	1.09 ± .08	1.07 ± .10	1.14 ± .08	1.12 ± .09	1.05 ± .06	1.02 ± .07	...	...		...	...	...
VAC	1.05 ± .10	1.08 ± .11	1.07 ± .10	1.05 ± .08	1.09 ± .11	1.09 ± .11	1.09 ± .10	1.06 ± .09	...	...	...	...	...	...
VLPFC	1.14 ± .07	1.16 ± .09	1.16 ± .07	1.15 ± .08	1.17 ± .08	1.15 ± .09	1.17 ± .08	1.16 ± .09	...	...	**4.52**	**.04**	...	...
Right														
Am	0.84 ± .05	0.84 ± .07	0.82 ± .08	0.82 ± .06	0.81 ± .06	0.80 ± .07	0.79 ± .05	0.79 ± .05	...	...	...	...	...	...
Caudate	1.16 ± .06	1.18 ± .07	1.20 ± .06	1.18 ± .07	1.20 ± .07	1.20 ± .08	1.16 ± .07	1.18 ± .08	**5.29**	**.002**	...	...	**4.47**	**.02**
DAC	1.11 ± .06	1.11 ± .05	1.11 ± .07	1.10 ± .07	1.15 ± .06	1.15 ± .05	1.12 ± .07	1.14 ± .08	...	...	...	...	...	...
DLPFC	1.21 ± .06	1.21 ± .05	1.23 ± .06	1.22 ± .07	1.25 ± .07	1.24 ± .07	1.26 ± .06	1.24 ± .04	...	...	...	...	...	...
Hipp	0.87 ± .06	0.88 ± .09	0.86 ± .08	0.86 ± .08	0.83 ± .05	0.83 ± .05	0.83 ± .04	0.83 ± .06	...	...	...	...	...	...
OFC	1.08 ± .04	1.08 ± .04	1.07 ± .07	1.05 ± .08	1.07 ± .06	1.07 ± .06	1.08 ± .04	1.08 ± .04	**2.85**	**.04**	...	...	...	...
Putamen	1.32 ± .08	1.32 ± .06	1.32 ± .09	1.31 ± .08	1.33 ± .08	1.36 ± .09	1.28 ± .07	1.29 ± .09	**3.21**	**.03**	...	...	**3.22**	**.05**
Thalamus	1.05 ± .07	1.03 ± .05	1.10 ± .07	1.08 ± .08	1.12 ± .07	1.11 ± .08	1.05 ± .05	1.03 ± .07	...	...	...	...	...	...
VAC	1.09 ± .08	1.07 ± .09	1.04 ± .09	1.02 ± .10	1.07 ± .10	1.06 ± .09	1.07 ± .10	1.05 ± .09	...	...	...	...	...	...
VLPFC	1.15 ± .08	1.16 ± .07	1.19 ± .07	1.16 ± .08	1.18 ± .09	1.17 ± .11	1.19 ± .07	1.17 ± .07	**2.75**	**.05**	...	...	...	...

*Data are given as mean ± SD. OCD indicates obsessive-compulsive disorder; MDD, major depressive disorder; OCD + MDD, concurrent OCD and MDD; Pre, pretreatment; Post, posttreatment; Am, amygdala; DAC, dorsal anterior cingulate; DLPFC, dorsolateral prefrontal cortex; Hipp, hippocampus; OFC, orbitofrontal cortex; VAC, ventral anterior cingulate; and VLPFC, ventrolateral prefrontal cortex. Boldface type indicates statistically significant values; ellipses, not applicable.

ANOVA found significant effects of diagnosis on change in right caudate/Hem, right putamen/Hem, right VLPFC/Hem, right OFC/Hem, and left OFC/Hem (**Table 2**). Significant response × diagnosis interaction effects were found for changes in right caudate/Hem and right putamen/Hem (Table 2). Post hoc LSD tests revealed that pretreatment to posttreatment metabolic decreases in bilateral OFC in the OCD group were significantly different from metabolic changes in controls, the MDD group, or the OCD+MDD group ($P<.05$). The OCD group also had significantly greater decreases in right VLPFC/Hem than controls (Table 2). Post hoc LSD tests revealed that pretreatment to posttreatment metabolic decreases in the right caudate and right putamen occurring in treatment responders with OCD were significantly different from metabolic changes in all other subgroups ($P<.05$). Only OCD responders showed significant decreases in right caudate/Hem (mean±SD, 1.22±.07 to 1.15±.07), while responders in the OCD+MDD group showed a significant increase (mean±SD, 1.17±.09 to 1.21±.09) compared with the other subgroups, who showed no changes. Only OCD responders had significant decreases in right putamen/Hem (mean±SD, 1.34±.09 to 1.30±.07) compared with the other subgroups, who showed no significant changes (**Figure 2** and **Figure 3**).

A significant effect of response was found for change in left VLPFC/Hem (Table 2), indicating that responders in all 3 patient groups showed significant metabolic

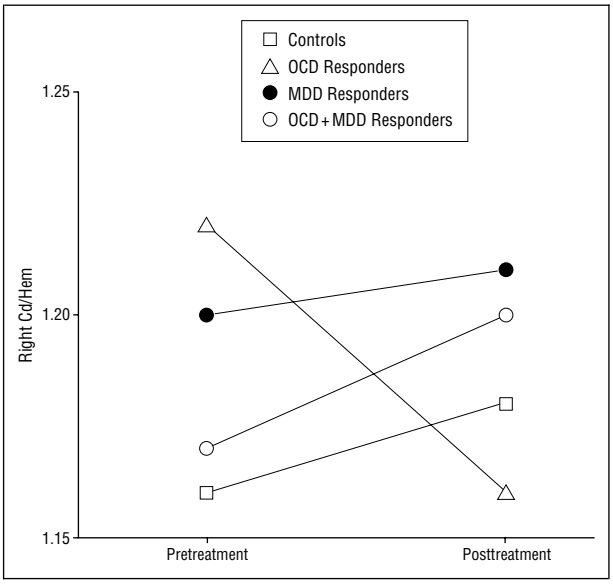

Figure 2. Pretreatment and posttreatment right caudate nucleus/hemisphere (Cd/Hem) glucose metabolic ratios in subjects with obsessive-compulsive disorder (OCD) alone who responded to paroxetine hydrochloride (n=12), subjects with major depressive disorder (MDD) alone who responded to paroxetine (n=18), subjects with concurrent OCD+MDD who responded to paroxetine (n=9), and controls (n=16). Responders in the OCD group showed a decrease in right Cd/Hem (mean±SD, 1.22±.07 to 1.15±.07) that was significantly different from changes seen in the other groups (analysis of variance, response × diagnosis interaction effect, $F_{2,71}=4.47$, $P=.02$).

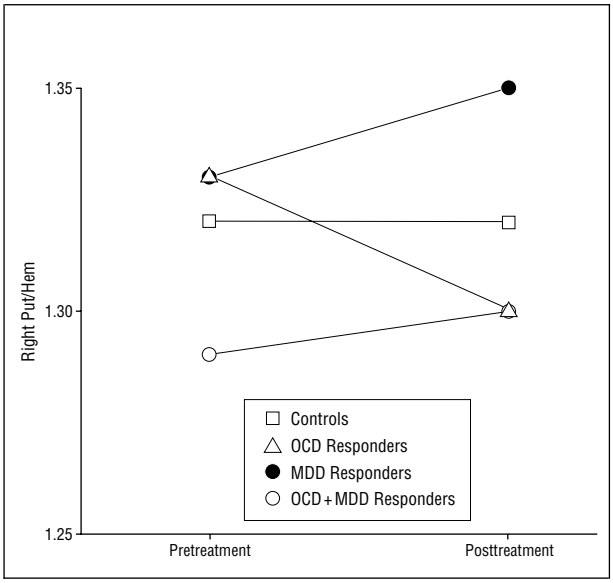

Figure 3. Pretreatment and posttreatment right putamen/hemisphere (Put/Hem) glucose metabolic ratios in subjects with obsessive-compulsive disorder (OCD) alone who responded to paroxetine hydrochloride (n=12), subjects with major depressive disorder (MDD) alone who responded to paroxetine (n=18), subjects with concurrent OCD+MDD who responded to paroxetine (n=9), and controls (n=16). Responders in the OCD group showed a decrease in right Put/Hem (mean±SD, 1.34±.09 to 1.30±.07) that was significantly different from changes seen in the other groups of subjects and controls (analysis of variance, response × diagnosis interaction effect, $F_{2,71}$=3.22, P=.05).

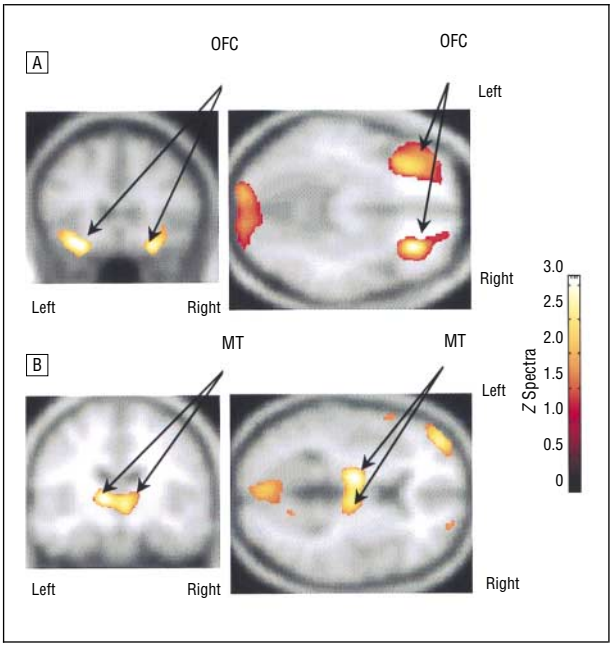

Figure 4. Statistical parametric mapping analysis showing significant pretreatment to posttreatment glucose metabolic decreases in the right orbitofrontal cortex (OFC) (Z=5.75; x=30, y=32, z=−12; P<.001) and left OFC (Z=5.00; x=−28, y=26, z=−18; P<.001) (A) and the right medial thalamus (MT) (Z=4.10; x=4, y=−16, z=2; P<.001) and left MT (Z=4.40; x=−12, y=−14, z=6; P<.001) (B) in subjects with obsessive-compulsive disorder alone treated with paroxetine hydrochloride.

Table 3. Statistical Parametric Mapping Analysis Showing Significant Regional Changes in Treatment Groups*

Region of Interest	OCD Group (n = 25)					MDD Group (n = 25)					OCD + MDD Group (n = 16)				
		Coordinates					Coordinates					Coordinates			
	Z	x	y	z	P Value	Z	x	y	z	P Value	Z	x	y	z	P Value
OFC															
Left	4.83	−28	26	−18	<.001	...	...	...	...	...	...	...	...	...	...
Right	5.56	30	32	−12	<.001	...	...	...	...	...	...	...	...	...	...
VLPFC															
Left	3.73	−38	50	2	<.001	3.92	−24	58	−8	<.001	3.34	−56	38	0	<.001
Right	2.59	26	58	4	.005	...	...	...	...	...	...	...	...	...	...
IFG															
Left	...	...	...	...	...	3.26	−56	20	4	.001	2.86	−64	6	10	.002
Right	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Thalamus															
Left	4.21	−12	−14	6	<.001	...	...	...	...	...	...	...	...	...	...
Right	3.98	4	−16	2	<.001	...	...	...	...	...	...	...	...	...	...
Occipital cortex															
Left	...	...	...	...	...	4.75	−4	−90	2	<.001	...	...	...	...	...
Right	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

*OCD indicates obsessive-compulsive disorder; MDD, major depressive disorder; OCD + MDD, concurrent OCD and MDD; OFC, orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex; IFG, inferior frontal gyrus; and ellipses, nonsignificant findings. Significance threshold was P<.01 at the uncorrected voxel level for hypothesized regions and P<.001 at the uncorrected voxel level and P<.01 at the uncorrected cluster level for unhypothesized areas. Coordinates are given for voxels of peak significance in each group. Control group showed no significant regional changes.

decreases in the left VLPFC compared with nonresponders and controls, who had no change.

SPM ANALYSES

The SPM analyses (**Table 3**) showed that subjects with OCD alone had robust pretreatment to posttreatment decreases in relative glucose metabolism in several hypothesized regions: (1) a large region extending from the right OFC to the right frontal pole and anterior VLPFC, (2) an area extending from the left OFC to the left VLPFC, (3) the left thalamus, and (4) the right thalamus (**Figure 4**). The OCD group showed no sig-

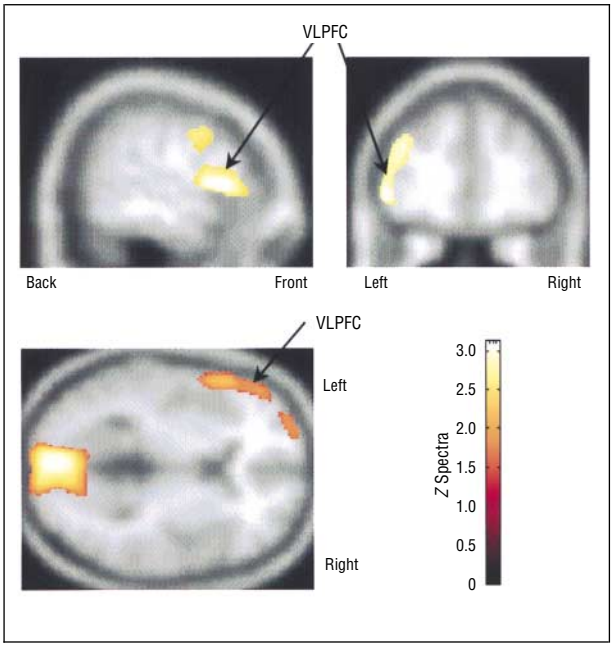

Figure 5. Statistical parametric mapping analysis showing significant pretreatment to posttreatment glucose metabolic decreases in the left ventrolateral prefrontal cortex (VLPFC) in subjects with major depressive disorder alone treated with paroxetine hydrochloride (Z=3.92; x=−24, y=58, z=−8; P<.001).

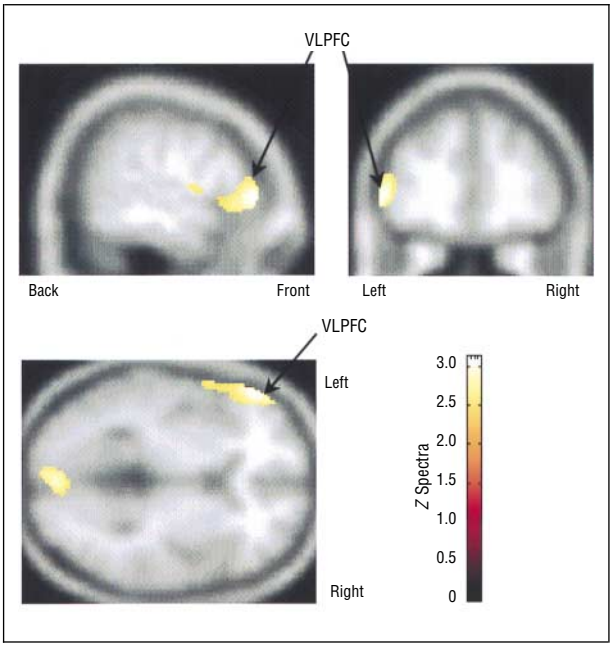

Figure 6. Statistical parametric mapping analysis showing significant pretreatment to posttreatment glucose metabolic decreases in the left ventrolateral prefrontal cortex (VLPFC) in subjects with concurrent obsessive-compulsive and major depressive disorders treated with paroxetine hydrochloride (Z=3.34; x=−56, y=38, z=0; P<.001).

nificant metabolic increases with paroxetine treatment. Subjects with MDD showed significant pretreatment to posttreatment metabolic decreases in the left VLPFC and left IFG (**Figure 5**). Significant, unhypothesized decreases were also found in the left medial occipital cortex (Table 3). The MDD group showed no significant metabolic increases with treatment. Subjects with OCD+MDD also showed significant pretreatment to posttreatment metabolic decreases in the left VLPFC and left IFG (**Figure 6**) but no significant increases. Control subjects showed no significant metabolic changes between their first and second FDG-PET scans.

In OCD responders, SPM analyses of pretreatment to posttreatment metabolic changes showed significant decreases in the bilateral OFC, bilateral thalamus, and left VLPFC (**Table 4**) with no significant increases. Nonresponders with OCD showed significant metabolic decreases in bilateral OFC and right inferior anterior temporal pole (Table 4). Responders with MDD showed significant pretreatment to posttreatment decreases in (1) a large region encompassing the left VLPFC, left frontal pole, left IFG, left DLPFC, bilateral medial prefrontal cortex, right frontal pole, and right VLPFC; (2) the right dorsal superior frontal gyrus; and (3) the left medial occipital cortex. Nonresponders with MDD showed a significant decrease only in the left anterior putamen. Neither MDD subgroup showed any significant increases. Responders in the OCD+MDD group, however, showed a significant metabolic increase in the right superior temporal cortex but no significant decreases, whereas OCD+MDD nonresponders showed significant metabolic decreases in the right VLPFC (Table 4) but no significant increases.

COMMENT

The major finding of this study was that although all patient groups were treated with the same dose of paroxetine for the same duration, pretreatment to posttreatment cerebral metabolic changes differed significantly among diagnostic and response groups. This indicates that SRIs do not have the same functional neuroanatomical effect in every clinical syndrome they ameliorate. Rather, brain metabolic responses to SRI pharmacotherapy depend on the underlying pathophysiology of the treated patient, which differs among disorders, and vary with the degree of symptomatic improvement.

Our results indicate that subjects with OCD have a unique cerebral response to SRI treatment that is not seen in subjects with MDD. Subjects with OCD alone showed significant metabolic decreases in the right caudate, right putamen, right VLPFC, bilateral OFC, and bilateral thalamus that were not seen in any other group. Decreases in the right caudate, putamen, and thalamus were seen only in OCD responders. These results were in agreement with previous findings of decreased metabolism in the OFC, caudate, and thalamus after successful treatment of OCD with SRIs[6-8] and add further evidence to the theory that OCD symptoms are mediated by the functional activity of orbitofrontal–basal ganglia–thalamo–cortical circuits, particularly in the right hemisphere.[8,11,55]

In contrast, both the MDD and OCD+MDD groups showed significant pretreatment to posttreatment decreases in the left VLPFC and left IFG but not in the OFC, striatum, or thalamus. Decreases in left VLPFC metabolism were significantly greater in responders than in non-

Table 4. Statistical Parametric Mapping Analysis Showing Significant Regional Changes in Responders and Nonresponders to Treatment*

Region of Interest	OCD Group: Responders (n = 12) Z	Coordinates x	y	z	P Value	OCD Group: Nonresponders (n = 13) Z	Coordinates x	y	z	P Value	MDD Group: Responders (n = 18) Z	Coordinates x	y	z	P Value
OFC															
Left	3.13	−28	24	−18	.001	4.06	−30	28	−16	<.001	...	...	...	...	...
Right	3.96	30	30	−16	<.001	5.05	28	32	10	<.001	...	...	...	...	...
VLPFC															
Left	3.13	−32	46	−8	.001	...	...	...	...	...	3.94	−20	60	−6	<.001
Right	...	...	...	...	...	...	...	...	...	...	3.58	20	62	−4	<.001
IFG															
Left	...	...	...	...	...	...	...	...	...	...	3.23	−50	26	2	.001
Right	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
DLPFC															
Left	...	...	...	...	...	...	...	...	...	...	3.18	−56	2	44	.001
Right	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
SFG															
Left	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Right	...	...	...	...	...	...	...	...	...	...	4.83	16	42	46	<.001
Putamen															
Left	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Right	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Thalamus															
Left	3.46	−10	−16	12	<.001	...	...	...	...	...	...	...	...	...	...
Right	3.28	16	−28	8	.001	...	...	...	...	...	...	...	...	...	...
Temporal cortex															
Left	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Right	...	...	...	...	...	4.06	42	−10	−34	<.001	...	...	...	...	...
Occipital cortex															
Left	...	...	...	...	...	...	...	...	...	...	3.73	−2	94	0	<.001
Right	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

*OCD indicates obsessive-compulsive disorder; MDD, major depressive disorder; OCD + MDD, concurrent OCD and MDD; OFC, orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex; IFG, inferior frontal gyrus; DLPFC, dorsolateral prefrontal cortex; SFG, superior frontal gyrus; and ellipses, nonsignificant findings. Significance threshold was $P<.01$ at the uncorrected voxel level for hypothesized regions and $P<.001$ at the uncorrected voxel level and $P<.01$ at the uncorrected cluster level for unhypothesized areas.

†The OCD + MDD responders group showed no significant changes.

responders across all 3 patient groups. Our results replicate previous findings of decreasing VLPFC activity with successful treatment of depression.[19,21,26] Activation of the left VLPFC and IFG has been produced by the induction of sadness[21,56-59] and anxiety[60-62] in several populations. Taken together, these findings imply that depression and anxiety symptoms are mediated by activity in the left VLPFC and IFG across a range of diagnoses.

One surprising finding was that subjects with concurrent OCD+MDD did not show the metabolic decreases in the OFC, caudate, and thalamus seen in subjects with OCD alone, even though both groups had significant improvement in OCD severity with treatment. In fact, responders in the concurrent OCD+MDD group showed pretreatment to posttreatment increases in the right caudate. This finding replicates earlier findings of Baxter et al that caudate metabolism increased in patients with concurrent OCD+MDD[1] but decreased in nondepressed subjects with OCD[8] after successful pharmacotherapy. This apparent paradox might be due to the effect of comorbid MDD on subcortical metabolism in OCD patients, and, thereby, on their cerebral response to treatment. Previously, we reported that subjects with concurrent OCD+MDD had significantly lower baseline metabolism in the caudate, thalamus, and hippocampus than subjects with OCD alone, and these metabolic reductions were strongly correlated with depression severity.[44]

Lower pretreatment subcortical activity may be related to the lower levels of tryptophan found in patients with concurrent OCD+MDD compared with patients with OCD alone[63] because tryptophan depletion has been found to markedly reduce regional metabolism in the caudate, thalamus, and hippocampus of depressed subjects.[64] Bellodi et al[63] found that plasma tryptophan levels rose in subjects with concurrent OCD+MDD who were treated with fluvoxamine but dropped in subjects with OCD alone given the same treatment. Their results are compatible with our finding that right striatal metabolism increased in subjects with concurrent OCD+MDD treated

					OCD + MDD Group†					
	Nonresponders (n = 7)					Nonresponders (n = 6)				
	Coordinates					Coordinates				
	Z	x	y	z	P Value	Z	x	y	z	P Value
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	4.69	32	54	0	<.001
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	4.47	−26	4	0	<.001	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
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	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	...

with paroxetine but decreased in paroxetine-treated subjects with OCD alone. Just as comorbid MDD significantly influenced the plasma tryptophan response to SRI treatment, it also appears to influence the cerebral metabolic response to SRI treatment.

Another surprising result was the failure to see the pretreatment to posttreatment increase in left DLPFC metabolism in MDD subjects that was expected, based on prior reports. One possible explanation for the discrepancy among various studies is that cerebral metabolic abnormalities in different subregions of the prefrontal cortex may mediate different clusters of depressive symptoms,[65,66] and therefore, cerebral metabolic changes with treatment will vary among subject groups that experience improvement in different predominant symptoms. Hypoactivity of the DLPFC has been strongly linked to "negative symptoms" of MDD[66] such as psychomotor retardation,[65] anhedonia, and cognitive impairment.[67] However, the severity of depressive symptoms, excluding negative symptoms, correlated with higher cerebral blood flow in the DLPFC.[66] Hence, we would expect DLPFC activity to increase only in patients who had major improvements in psychomotor retardation, suicidality, and cognitive functioning. This hypothesis was confirmed by post hoc analyses of depressive symptoms in subjects with MDD alone. These analyses revealed strong correlations between improvement in suicidality and cognitive disturbances and increased DLPFC metabolism with treatment.[68] Conversely, improvements in anxiety and tension were strongly correlated with decreasing metabolism in the left VLPFC.[68] The overall symptom severity of MDD subjects in our study, as measured by HDRS score, was similar to that reported in several previous studies.[1,12,17,19,23]

Discrepancies among the results of different PET studies of MDD could also be caused by other factors. Prior studies vary greatly in their patient compositions and methodologies. Some included patients who were receiving medications at the time of their baseline PET scan,[13,14,16] several studied hospitalized inpatients rather than ambulatory outpatients,[1,12,13,16] some included older patients with cognitive impairment[14] or patients with bipolar disorder,[22] and some had subjects take a continuous performance test during FDG uptake[16] rather than rest with their eyes and ears open, as in the present study.

The baseline metabolic state of the subject groups did not appear to determine differential pretreatment to posttreatment changes in regional glucose metabolism. As we reported previously,[44] baseline glucose metabolism in the right and left OFC was not significantly elevated in the OCD group compared with controls or the MDD group, yet it decreased significantly with treatment. Pretreatment right caudate metabolism was the same in the OCD and MDD groups but decreased with treatment only in OCD responders. Moreover, the left hippocampus, the region with significant pretreatment hypometabolism in both depressed groups,[44] did not show any metabolic changes with treatment. Hence, our data suggest that cerebral metabolic changes with SRI treatment are not always concordant with pretreatment functional abnormalities.

The present study had several methodological limitations. We analyzed only normalized metabolic rates, not absolute glucose metabolic rates, because the absolute and global metabolic rates generated by our PET methods were not felt to be reliable. Normalized and absolute rates have shown different results in prior studies[55] and may have given different results for this study. Subjects' thoughts were not monitored during the FDG uptake phase, so the extent to which cerebral metabolic changes observed in the 3 groups reflected different thoughts and emotions occurring during the second scan compared with the first could not be determined. In addition, the fact that we studied only nonsuicidal outpatients restricted the range of depressive symptoms we could investigate. This may have contributed to our having different results than previous studies and could limit the generalizability of our conclusions regarding MDD. Future studies should compare patients with a broader range of severity, psychomotor retardation, and suicidality to more fully elucidate the pathophysiology of MDD.

However, this study also had several strengths that afford confidence in its findings. To our knowledge, this

is the largest study of its kind, with the largest samples of OCD and MDD subjects imaged before and after standardized treatment with the same medication. Localization of ROIs using MRIs was employed to calculate regional metabolic rates. The SPM and ROI methods were compared and produced similar results. The 3 patient groups were well controlled for the severity of OCD and MDD symptoms. No medication but paroxetine was allowed during the study, which eliminated polypharmacy confounds.

In conclusion, this study demonstrates that brain metabolic responses to SRI pharmacotherapy are both disorder-specific and response-specific. Future studies will be required to determine why the cerebral metabolic effects of a single medication differ among patients with different disorders.

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Corresponding author and reprints: Sanjaya Saxena, MD, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, 300 UCLA Medical Plaza, Room 2229, Los Angeles, CA 90095 (e-mail: ssaxena@mednet.ucla.edu).

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