

Enhanced Dopamine Transporter Density in Psychotropic-Naïve Patients With Obsessive-Compulsive Disorder Shown by [^{123}I] β -CIT SPECT

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Objective: The authors examine the functional anatomy of serotonergic and dopaminergic systems in obsessive-compulsive disorder in psychotropic-naïve patients without comorbidity.

Method: [^{123}I] β -CIT binding patterns for dopamine and serotonin transporters in the brain were measured in 15 psychotropic-naïve adult outpatients with OCD (no comorbidity) and in 15 pairwise-matched healthy subjects. Volumes of interest were constructed on magnetic resonance imaging scans and coregistered with single photon emission computed tomography scans. Binding ratios were compared, and possible correlations between bind-

ing patterns and obsessive-compulsive symptoms were assessed.

Results: There were significant differences between patients and healthy subjects in the [^{123}I] β -CIT binding pattern for dopamine transporter in the left caudate and left putamen. Patients had higher binding ratios than healthy subjects. No differences were found in the less specific [^{123}I] β -CIT binding pattern for serotonin transporters in the selected volumes of interest. Hemispheric within-group comparisons revealed no asymmetry effects.

Conclusions: The results of our study provide direct evidence for an involvement of the dopaminergic system in the pathophysiology of OCD.

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Obsessive-compulsive disorder (OCD) is characterized by recurrent, persistent, and intrusive thoughts or images that cause anxiety or distress (obsessions) and repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). Patients recognize that these obsessions and compulsions are unreasonable and products of their own mind. Once considered rare, recent epidemiological data suggest prevalence rates of OCD from 1.5% to 3% (1, 2). In general, OCD symptoms can best be managed with selective serotonin reuptake inhibitors (SSRIs) or behavioral therapy. The selective response of OCD patients to SSRIs has led to the hypothesis that changes in the central serotonergic systems may be the mechanism by which these compounds exert their effect (3). Direct evidence that serotonergic perturbations are implicated in the neurobiology of OCD, however, is sparse. Serotonergic pharmacological challenges and CSF metabolite studies have yielded data that are too inconsistent—or too open to different interpretations—to serve as a valid basis for dissecting the neurobiology of OCD (3–5). Growing evidence that atypical antipsychotics, such as risperidone and quetiapine, may augment the response to SSRIs in patients with refractory OCD and those with comorbidities, as well as studies showing an exacerbation of symptoms after administration of a dopamine agonist, would seem to point to an increase in dopaminergic system activity in OCD (6, 7). The role of dopamine in stereotypic

behaviors in animal models and the preclinical evidence of important interactions between serotonergic and dopaminergic systems further strengthen the putative role of dopamine in OCD (8, 9). Studies examining the concentration of the dopamine metabolite homovanillic acid and the dopaminergic regulation of the hypothalamo-pituitary-adrenal axis lend further support to a possible role of dopamine in the pathophysiology of OCD (10, 11). Neuroimaging studies have been very influential in shaping neurobiological models of OCD. Converging data have implicated a network of brain regions, including the orbitofrontal cortex, striatum, and thalamus, in the pathophysiology of OCD. Most regions of the putatively involved network in OCD are densely innervated by serotonergic or dopaminergic neurons (12). However, despite the advent of several ligands for dopaminergic and serotonergic binding sites suitable for positron emission tomography (PET) or single photon emission computed tomography (SPECT), the functional anatomy of these neurotransmitter systems in OCD has scarcely been investigated. A commonly used ligand is 123-I-labeled 2- β -carbomethoxy-3- β -(4-iodophenyl)-tropane ([^{123}I] β -CIT), a SPECT ligand enabling both serotonin (5-HT) and dopamine transporter visualization in the brain. [^{123}I] β -CIT has already been used extensively to investigate several psychiatric and neuropsychiatric disorders (13). Binding of [^{123}I] β -CIT in the striatal region has been shown to reflect mainly

binding to dopamine transporter. Binding to 5-HT transporter occurs predominantly in the thalamus, midbrain, and pons, but the binding in these regions might also reflect densities of other monoamine transporters to an unknown proportion (14, 15). Differences in [123 I] β -CIT binding characteristics for dopamine and 5-HT transporters also make temporal separation of the transporter occupancy possible (16, 17). Because of these characteristics, both dopamine and 5-HT transporter densities can be visualized in the same subject after a single administration of the ligand. The present study sought to examine possible differences in [123 I] β -CIT binding patterns between patients with OCD and healthy comparison subjects pairwise matched by age, sex, and handedness. In order to further reduce the number of potential confounders, only OCD patients who were psychotropic naive and had no comorbid diagnoses or history of any other major psychopathology were included. We hypothesized that as a result of a putative increase in dopaminergic system activity in OCD, the binding patterns of [123 I] β -CIT in OCD would reflect higher dopamine transporter density.

Method

Subjects

Psychotropic-naïve patients with OCD and no comorbid diagnoses were recruited from 375 patients with OCD as their primary diagnosis who had been referred to the anxiety research unit of the Department of Psychiatry at the University Medical Center of Utrecht from 1997 to 2001. Most patients came from direct physician referrals. Healthy subjects were enrolled through advertisements in flyers and newspapers or were obtained from an existing database. Only subjects without a lifetime history of psychosis, substance abuse, recurrent major depression, bipolar disorder, eating disorders, other anxiety disorders, tics, or stuttering were included. Furthermore, all subjects had no first-degree relative with a history of a major DSM-IV axis I disorder (except for OCD in patients) or tics. All subjects had no lifetime history of illnesses with possible central nervous system sequelae and were in good physical health, as confirmed by physical and laboratory examinations. Subjects consumed less than six cups of coffee and four units of alcohol a day and smoked less than six cigarettes a day. Screening for current and prior adult psychopathology was done by administering the Mini-International Neuropsychiatric Interview (18). Diagnoses were confirmed by an experienced clinician (H.J.v.M., N.J.v.d.W.). Handedness was determined by administering the Edinburgh Handedness Scale (19). Patients had to have a minimum score of 16 on the Yale-Brown Obsessive Compulsive Scale and a maximum score of 13 on the Hamilton Depression Rating Scale (20, 22). Subjects underwent imaging procedures within 2 weeks after the screening examination. Patients had not received any form of psychotherapy, especially cognitive behavior therapy, in the 3 months preceding the study. The protocol was approved by the ethical committee of the University Medical Center of Utrecht. After complete description of the study to the subjects, written informed consent was obtained.

Image Acquisition and Analysis

On the first day of SPECT scanning, subjects received an intravenous injection of approximately 150 MBq of [123 I] β -CIT (MAP Medical Technologies, Finland, radionuclidic purity [125 I]/ 123 I] of

at least 9.5×10^{-3} at calibration time and a radiochemical purity of at least 95%). We used a Picker Prism 3000 triple-headed gamma camera with ultra-high resolution fan beam collimators and a full-width at half-maximum of approximately 12 mm. Four hours after the injection the first scan was done to assess binding in the 5-HT transporter-rich regions. Between 22 and 24 hours after the injection, the second scan was performed to measure binding to dopamine transporter (16). Subjects refrained from coffee and nicotine in the 6–10 hours preceding each SPECT scan. Immediately after the first scan, subjects received 20 mg of paroxetine to displace the radiolabeled β -CIT from 5-HT transporters and enable more precise determination of binding to dopamine transporter (16). Several studies have already demonstrated that serotonin transporter occupation is virtually maximal at modest oral dosages (i.e., 10 mg) of paroxetine and other potent 5-HT reuptake blockers (14, 23). We chose the 20-mg paroxetine dose to control for possible differences in metabolism between subjects. Paroxetine was well tolerated by all subjects. During scanning, subjects were in supine position with eyes and ears open and with their head fixated in a head holder. We ensured that patients stayed awake and did not move. For an accurate determination of each subject's volumes of interest, all subjects also underwent structural magnetic resonance imaging (MRI) (three-dimensional fast-field echo; TE/TR=4.6/30 msec; flip angle=30°; field of view=256×256 mm; matrix=128×128 by 130 mm; slice thickness=2 mm) 2 hours before the injection of [123 I] β -CIT. MRIs were reoriented to the standardized coordinate system of the Montreal Standard brain (24). Volumes of interest were delineated manually on the reoriented MRI scans by a researcher (J.A.H.) blind to subject identity and diagnosis who used the Display software from Brain Imaging Center of the Montreal Neuroimaging Institute (25). Because previous studies have suggested possible hemispheric asymmetries of dopamine transporter density in healthy subjects and loss of this asymmetry in specific psychiatric populations, we decided upon examination of bilateral volumes of interest (26, 27). Volumes of interest for the 5-HT transporter-rich regions included the left and right thalamus, the midbrain, and the pons; for the dopamine transporter, volumes of interest included the left and right caudate nucleus and the left and right putamen. The cerebellum was used as a reference region, representing nonspecific binding of [123 I] β -CIT.

To allow for exact coregistration of MRI and SPECT scans, fiducial markers were used. Fiducial markers were cone-shaped with cross-shaped feet and placed on the nose bridge and preauricular above the mandibular joints. The position of each marker was indicated with four dots on subjects' skin to allow for repositioning of markers immediately before the SPECT scans. Vitamin A and Co^{57} were used as contrast agents for the MRI and SPECT scans, respectively. The energy peak for [123 I] β -CIT was set at 160 keV with a window of 20% and at a peak of 120 keV with a window of 15% for Co^{57} . After standard processing, brain SPECT images were resliced to isotropic voxels with dimensions of 2 mm and further treated as three-dimensional volumes to coregister within the three-dimensional orientation of the MRIs. Coregistration was performed semiautomatically based on the position of the fiducial markers, using the Register multimodality software package and additional software developed at the Brain Imaging Center of the Montreal Neurological Institute (25). The researcher performing the coregistration (N.J.v.d.W.) was blind to subject identity and diagnosis.

For each separate volume of interest, the ratio of the specific binding of [123 I] β -CIT was calculated according to methods used in previously published [123 I] β -CIT studies: the average radioactivity count per voxel per volume of interest minus the average radioactivity count per voxel in the cerebellum/average radioactivity count per voxel in the cerebellum.

Statistical Analyses

Age was compared by using Student's *t* tests. The intrarater and interrater quality for the volumes of interest procedure was assessed by calculating intraclass correlations according to the method used by Bartko and Carpenter (28). The specific [¹²³I]β-CIT binding ratios for each volume of interest were compared by using Mann-Whitney *U* tests. Within-group comparisons of hemispheric binding ratios in bilateral volumes of interest were performed by using Mann-Whitney *U* tests. Spearman rank correlations were calculated to assess correlations between specific binding ratios and Yale-Brown Obsessive Compulsive Scale total and subscale scores. Two-tailed significances are reported throughout.

Results

Of the 375 patients with OCD as their primary diagnosis referred to our specialized unit from 1997 to 2001, 104 had never received treatment with an SSRI (29). Unfamiliarity with OCD treatment guidelines as well as several patient-related factors may underlie this lack of adequate treatment. Fifty patients were psychotropic naive. Eighteen psychotropic-naive patients fulfilled the inclusion criteria and finally 15 patients participated. Healthy subjects were mainly recruited from the existing database. Six potential comparison subjects refused participation. All subjects completed the study. Patients and comparison subjects were perfectly matched for gender and did not differ significantly in age and handedness. Demographic and clinical characteristics are shown in Table 1. Almost all subjects were nonsmokers. Symptoms of the patient group were heterogeneous: five patients had predominantly obsessions of contamination and compulsions of washing, six had obsessions of doubt and compulsions of checking, two had predominantly aggressive obsessions and compulsions of counting, and two had mixed symptoms. Most patients had a juvenile onset (before the age of 18) of OCD. Although most patients had some aspects of depressive symptoms, as reflected in the average Hamilton depression scale score, none fulfilled criteria for a depressive episode or dysthymia or any other comorbid disorder at screening. Four patients had a prior single DSM-IV depressive episode not otherwise specified (two with dysthymic and two with more depressive features). One patient had a history of two DSM-IV depressive episodes not otherwise specified, one with dysthymic and one with more depressive features. One patient had received a form of supportive psychotherapy for his depressive symptoms.

Six patients had never received any form of treatment for their OCD. Six others had received a form of supportive or psychoanalytic therapy. Three patients had received a form of cognitive behavior therapy for a short period of time and without any noticeable effect. In these patients the cognitive behavior therapy was stopped at least 18 months before scanning.

In one patient the first SPECT scan (at 4 hours after injection) could not be reliably coregistered to the MRI

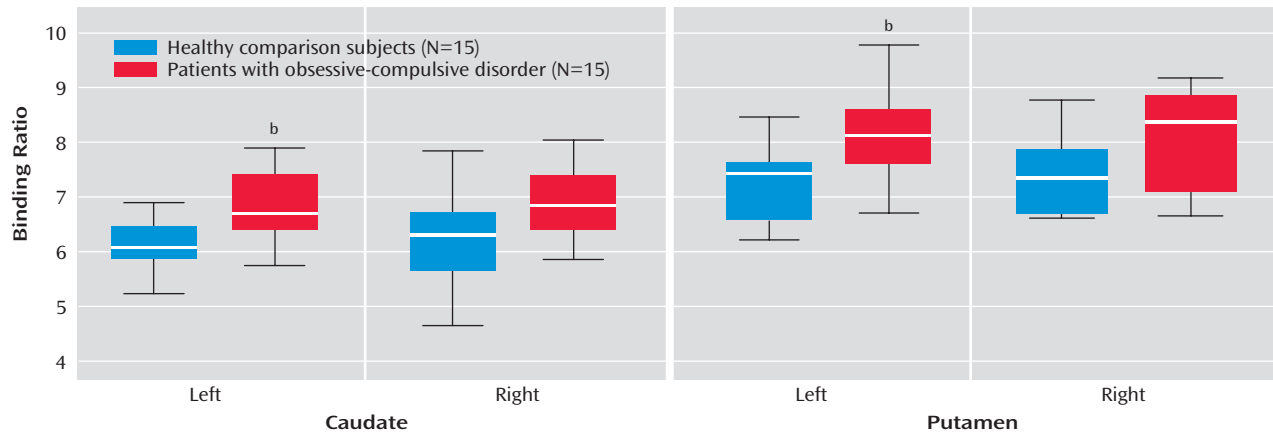
TABLE 1. Demographic and Clinical Characteristics of Psychotropic-Naive OCD Patients and Healthy Comparison Subjects Pairwise Matched by Age, Gender, and Handedness

Characteristic	OCD Patients (N=15)		Matched Comparison Subjects (N=15)	
	Mean	SD	Mean	SD
Age (years)	31.4	9.0	32.0	9.5
Handedness	0.96	0.03	0.94	0.04
Duration of illness (years)	12.2	7.2		
Yale-Brown Obsessive Compulsive scale scores				
Total	23.4	4.2		
Obsessions subscale	12.0	2.1		
Compulsions subscale	11.4	2.6		
Total Hamilton depression scale score	8.4	4.1		
	N	%	N	%
Sex				
Male	11	73.3	11	73.3
Female	4	26.7	4	26.7
Nonsmokers	12	80.0	11	73.3
Onset				
Juvenile (<18 years)	10	66.7		
Adult	5	33.3		

because of motion artifacts, so the final analysis for the binding in the 5-HT transporter-rich regions involved 14 patients and 14 pairwise-matched healthy subjects. The intraclass correlation coefficients for the intrarater and interrater reliability of the volume of interest procedure were between 0.89 and 0.98 (mean=0.94, SD=0.04) and between 0.86 and 0.99 (mean=0.95, SD=0.05), respectively.

Mann-Whitney *U* tests revealed a significantly higher average binding ratio to the dopamine transporter in the left caudate and in the left putamen of patients with OCD relative to the matched healthy subjects (Figure 1, Table 2). There were no significant differences in average binding ratios to dopamine transporter in the right caudate and right putamen. Patients with juvenile onset and patients with adult onset had similar average binding ratios to dopamine transporter. There were also no significant differences in average binding ratios between the different subtypes of OCD. Hemispheric within-group comparisons for patients and healthy subjects revealed no significant asymmetry effects. No significant correlations were found between binding ratios to dopamine transporter and duration of illness or scores on the Yale-Brown Obsessive Compulsive Scale (total or subscales).

No significant differences in binding patterns were found between patients with OCD and healthy subjects in the 5-HT transporter-rich regions, i.e., the left and right thalamus, midbrain, and pons (Table 2). Hemispheric within-group comparisons revealed no asymmetry effects. No significant correlations were found for binding ratios in the thalamus, midbrain, and pons with duration of illness or scores on the Yale-Brown Obsessive Compulsive Scale (total or subscales).

FIGURE 1. Specific Binding Ratios of [123 I] β -CIT to Dopamine Transporter in the Caudate and Putamen of Psychotropic-Naive OCD Patients and Healthy Comparison Subjects Pairwise Matched by Age, Gender, and Handedness^a

^a Horizontal lines within boxes indicate median, boxes represent 75% confidence intervals, and limit lines depict the range.

^b Significant between-group difference ($p < 0.00625$, corrected for multiple comparisons).

TABLE 2. Dopamine and 5-HT Transporter Binding Ratios in the Volumes of Interest of Psychotropic-Naive OCD Patients and Healthy Comparison Subjects Pairwise Matched by Age, Gender, and Handedness

Transporter and Volume of Interest	Binding Ratio				Analysis	
	OCD Patients (N=15)		Comparison Subjects (N=15)		Mann-Whitney U	p
	Mean	SD	Mean	SD		
Dopamine transporter						
Caudate						
Left	6.80	0.64	5.99	0.78	44.0	0.004
Right	6.78	0.67	6.16	0.85	64.0	0.04
Putamen						
Left	8.00	0.74	7.04	0.79	46.0	0.006
Right	7.97	0.89	7.16	1.23	65.0	0.05
5-HT transporter						
Thalamus						
Left	8.38	1.46	8.34	0.75	96.0	0.95
Right	8.24	1.55	8.51	0.72	88.0	0.46
Midbrain	10.74	1.90	11.04	1.31	95.0	0.69
Pons	8.34	1.77	8.74	0.63	99.0	0.82

Discussion

We found significantly higher [123 I] β -CIT binding ratios, an index of dopamine transporter density, in the left basal ganglia of psychotropic-naive OCD patients with no comorbid diagnoses relative to healthy comparison subjects pairwise matched by age, sex, and handedness. No abnormalities in binding ratios to the 5-HT transporter-rich regions in the midbrain, thalamus, or pons were found.

To the best of our knowledge, this is the first study examining central 5-HT and dopamine transporter densities in a carefully selected group of psychotropic-naive patients with OCD. Of interest is that in a recent [123 I] β -CIT SPECT study of Tourette's syndrome, a disorder that is purported to have also basal ganglia abnormalities, no abnormalities in 5-HT or dopamine transporter densities were found in the basal ganglia, midbrain, or thalamus (30). Results ob-

tained from functional neuroimaging studies of OCD that used other methodologies most consistently show abnormalities in the right caudate and right orbitofrontal cortex that normalize after treatment (31). Although this seems suggestive of some form of lateralized functional abnormality in OCD, this is not postulated in the prevailing neurobiological model of OCD.

We did not find hemispheric asymmetries in dopamine or 5-HT transporter binding ratios in any of the bilateral brain structures of OCD patients or healthy comparison subjects. The results of previous studies examining hemispheric asymmetry of dopamine transporter density in healthy subjects and neuropsychiatric conditions are inconsistent with these findings. Differences in radioactive ligands, neuroimaging techniques, and the number of subjects may account for these discrepancies. In a small PET study examining dopamine transporter density in patients with schizophrenia and healthy comparison subjects that used a radiolabeled form of 2-beta-carbomethoxy-3-beta-(-4-fluorophenyl)tropane ([18 F]-CFT), hemispheric asymmetry was only found in the caudate of healthy comparison subjects (26). In contrast, a SPECT study with a radiolabeled cocaine analog (99Tc TRODAT) did not reveal hemispheric asymmetry in binding ratios to the dopamine transporter in the caudate and putamen of healthy volunteers (32). However, in a very large [123 I] β -CIT SPECT study that examined age-related decline in dopamine transporter density in 126 healthy subjects, higher binding ratios in the left caudate and putamen were found (27). Although standard templates were used instead of volumes of interest defined on coregistered MRIs, these findings suggest that our study group may have been too small to detect hemispheric asymmetries within groups.

The data from our present study in psychotropic-naive patients clearly suggest a dopamine transporter role in the pathophysiology of OCD. Theoretically, the higher dopa-

mine transporter density in the left basal ganglia of psychotropic-naïve OCD patients, as measured by the [123 I] β -CIT binding ratios, may be either due to a primary abnormality at the level of the transporter or secondary to other abnormalities. Higher transporter density may result from a higher homeostatic tone of the dopaminergic system, with lower densities of D₁ and D₂ receptors (33, 34). The possible role of higher dopaminergic activity in the left basal ganglia in the pathophysiology of OCD still needs to be elucidated. Both dopamine (through D₁ and D₂ receptors) and serotonin (e.g., through 5-HT₂ receptors) are known to have a modulatory influence on the activity of excitatory (i.e., glutamate) and inhibitory (i.e., GABA) neurotransmitters in the basal ganglia and their cortico-thalamo-limbic connections. Furthermore, both the serotonergic and dopaminergic systems are known to modulate each other's activity in parts of the fronto-thalamo-basal ganglia circuitry supposedly involved in OCD (35–37). Data on the exact nature of these interactions are still inconclusive. Finally, on the basis of the results of the present study, it is not possible to dissect whether dopaminergic abnormalities are causal or epiphenomenal to OCD.

Our study has several strong points. Patients and healthy subjects were pairwise matched, and the patient group consisted of a population with no comorbidity (including tics) that had never been exposed to psychotropic drugs or, for the most part, psychotherapy. Furthermore, SPECT data were analyzed by using coregistered MRI, allowing for more precise determination of the volumes of interest.

There are also some possible limitations to this study. The patient group was heterogeneous for OCD symptoms, reducing the chance of finding abnormalities related to a particular subtype of OCD (38). We did not match female subjects for the stage of menstrual cycle, but the stage of menstrual cycle was noted at time of scanning. Four female patients were scanned in the first 2 weeks of their menstrual cycle, the remaining four (two patients and two healthy subjects) in the last 2 weeks. Although we included several important parts of the putative disturbed fronto-thalamo-cortical circuitry in OCD in our volumes of interest, other areas could not be investigated in this study. Considering the dispersion of the data, the power of our study may have been too small to detect a bilateral increase in dopamine binding potential in the basal ganglia. Such a bilateral increase in dopamine binding potential could theoretically result from differences in the frequency of the dopamine transporter SLC6A3 genotype, associated with dopamine transporter availability in previous studies (39).

We found no abnormalities in binding ratios for the 5-HT transporter-rich regions of psychotropic-naïve patients with OCD. However, [123 I] β -CIT binding in these regions probably also reflects availability of other monoamine transporters to an unknown proportion. The time point for visualization may have further limited the possibility of finding abnormalities at the level of the 5-HT

transporter, as was illustrated in the study by Willeit et al. (40) in seasonal affective disorder. In the latter study the 5-HT transporter was visualized at 4 hours and 24 hours after injection of the ligand, when a pseudoequilibrium state is reached. Differences were found only in the SPECT acquisitions 24 hours after the injection. In the present study, a 5-HT transporter inhibitor was administered after the first scan in order to displace [123 I] β -CIT from the 5-HT transporter. Hence, the 5-HT transporter could not be visualized 24 hours after injection.

Finally, it should be mentioned that although SPECT is easier to use, has a higher safety index, and is less expensive than PET, it has also relative disadvantages like the poorer anatomical resolution and the use of semiquantitative techniques.

Notwithstanding the possible limitations, our data clearly indicate a role for dopamine in the pathophysiology of OCD. This finding needs to be replicated and should be further explored in studies examining the effect of pharmacotherapy and psychotherapy on both serotonergic and dopaminergic transporter densities in OCD and in studies further dissecting the possible involvement of neurotransmitter systems in this disorder.

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