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Serotonin 2A Receptors in Obsessive-Compulsive Disorder: a Positron Emission Tomography Study with [¹¹C]MDL 100907

H. Blair Simpson, Mark Slifstein, James Bender Jr., Xiaoyan Xu, Elizabeth Hackett, Michael J. Maher, and Anissa Abi-Dargham

Department of Psychiatry (HBS, MS, AA) at Columbia University, College of Physicians and Surgeons, and from the Anxiety Disorders Clinic in the Division of Clinical Therapeutics (HBS, JB, MM) and from the Division of Translational Imaging (MS, XX, EH, AA) at the New York State Psychiatric Institute, New York, NY.

Abstract

Background—Serotonergic abnormalities are hypothesized to contribute to obsessive-compulsive disorder (OCD). This study used positron emission tomography (PET) with the radioligand [¹¹C]MDL 100907 to examine whether the distribution of one of the serotonin receptors, the 5-HT_{2A} receptor, is altered in OCD.

Methods—Nineteen OCD subjects, free of psychiatric medications and depression, and 19 matched healthy controls underwent PET scans following injection of [¹¹C]MDL 100907. Total distribution volumes (VT) were derived by kinetic analysis using the arterial input function. Two measures of 5-HT_{2A} availability were computed (BP_{ND} and BP_P). Groups were compared using a region of interest (ROI) analysis and voxelwise analysis of spatially normalized parametric maps. ROIs included cortical regions (orbitofrontal, dorsolateral prefrontal, medial prefrontal, anterior cingulate, temporal, parietal, occipital, and insular cortex) and limbic regions (entorhinal cortex, parahippocampal gyrus, and medial temporal lobe).

Results—No significant group differences were observed in [¹¹C]MDL 100907 BP_{ND} or BP_P in the ROIs or in the voxelwise analysis of BP_{ND} maps. There was a significant correlation in the orbitofrontal cortex between [¹¹C]MDL 100907 binding and age of onset, with earlier age of onset associated with higher binding.

Conclusions—In contrast to prior reports, people with OCD (free of psychiatric medications and depression) are not characterized as a group by major changes in 5-HT_{2A} availability in cortical or limbic brain regions. Further research is warranted to examine potential differences in 5-HT_{2A} availability between early and late onset OCD and to assess 5-HT_{2A} function in relation to other neurotransmitter systems implicated in OCD.

Keywords

Obsessive-compulsive disorder; serotonin receptors; [¹¹C]MDL 100907; positron emission tomography (PET); orbitofrontal cortex; 5-HT_{2A} receptor

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Corresponding author: Dr. Simpson, Anxiety Disorders Clinic, Unit 69, 1051 Riverside Drive, New York, NY 10032; simpson@nyspi.cpmc.columbia.edu; 212-543-6532 (phone); 212-543-6515 (FAX).

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is characterized by intrusive, distressing thoughts, images, or impulses (obsessions) and repetitive mental or behavioral acts (compulsions). Brain imaging studies suggest that OCD is associated with hyperactivity in a brain circuit involving the orbitofrontal cortex (OFC), striatum, and thalamus (1), and this hyperactivity may reflect glutamatergic dysfunction in OFC-striatal pathways (2-5). Serotonergic dysfunction has also been implicated based on the efficacy of serotonin reuptake inhibitors (SRIs) for OCD symptoms; some studies also found abnormalities in peripheral measures of serotonin function and in behavioral or physiological responses following challenges with serotonergic probes in OCD patients (6, 7). However, it remains unclear whether there are serotonergic abnormalities in OFC-striatal circuits in OCD.

In vivo imaging with positron emission tomography (PET) enables a direct examination of the serotonin system in the living human brain, using radioligands to visualize multiple 5-HT receptor types and reuptake transporters (8). Two PET studies examined the distribution of the serotonin transporter in the striatum, but neither found abnormalities in OCD (9, 10). On the other hand, 5-HT_{2A} receptors in the OFC have been implicated in OCD because of their location on glutamatergic excitatory pyramidal neurons that project to the striatum and on GABAergic inhibitory interneurons that modulate these pyramidal cells (11, 12). Thus, reduced functioning or availability of 5-HT_{2A} receptors in the OFC could lead to abnormalities in glutamatergic neurotransmission, potentially explaining the OFC-striatal hyperactivity found in some OCD imaging studies. Others have suggested that SRIs work in OCD by activating OFC 5-HT_{2A} receptors, thereby reducing glutamatergic hyperactivity and decreasing OCD symptoms (2, 5, 13). If so, then baseline differences in 5-HT_{2A} availability might explain individual differences in SRI response.

Two PET studies support a link between 5-HT_{2A} receptors and OCD. Perani and colleagues (14) found small, widespread reductions in cortical 5-HT_{2A} availability in OCD subjects compared to healthy controls using the selective 5-HT_{2A} radioligand [¹¹C]MDL 100907 (15). However, the sample size was small (n=9 OCD, n=6 controls), and the groups were not matched for age. In contrast, Adams and colleagues (16) did not find significant differences in cortical 5-HT_{2A} receptor binding between OCD patients (n=15) and healthy controls (n=15). They did find increased 5-HT_{2A} binding in the caudate nucleus in OCD. However, the Adams study used [¹⁸F] altanserin, a radioligand that is less selective for 5-HT_{2A} receptors than [¹¹C]MDL 100907 and whose modeling is complicated by the fact that it has radiolabeled metabolites that enter the brain (17). Moreover, the density of 5-HT_{2A} receptors is very low in the caudate (18), such that measuring 5-HT_{2A} binding with any currently available PET radioligand is not reliable due to low signal to noise ratio.

To determine whether the distribution of OFC 5-HT_{2A} receptors is abnormal in OCD, we examined 5-HT_{2A} availability in 19 adults with OCD and 19 matched healthy controls using PET and the selective 5-HT_{2A} radioligand [¹¹C]MDL 100907. Because this is the largest OCD sample ever studied, we also examined 5-HT_{2A} availability in other cortical and limbic regions where reliable quantification is possible (19). Based on current models of OCD, we hypothesized that OCD subjects would have decreased 5-HT_{2A} availability in the OFC compared to healthy controls. We also explored whether 5-HT_{2A} availability was associated with OCD severity, OCD symptom dimensions, or age of OCD onset.

METHODS and MATERIALS

Sample selection

The institutional review board of the New York State Psychiatric Institute/Columbia University approved this study. Written informed consent was obtained from each subject after study procedures were explained. Subjects were recruited by advertisements and word-of-mouth.

Participants were between the ages of 18 and 55, had no significant medical problems, were not pregnant or nursing, had no current or past neurological disorder (other than Tic Disorder), and were free of psychoactive medications. Women who were using hormonal contraceptives or were postmenopausal were excluded. OCD subjects met OCD criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for at least one year and had no other current Axis I psychiatric disorder (except Specific Phobia in one subject). None were receiving OCD treatment (medication or cognitive-behavioral therapy [CBT]) at the time of study participation. Healthy controls had no current or past DSM-IV Axis I disorder; none had a family history of OCD as assessed by the Family History Screen (20). Groups were matched for age, sex, ethno-racial categories, and current nicotine use.

Diagnoses were made by clinical interview and confirmed with the Structured Clinical Interview for DSM-IV (21). Medical health was confirmed by physical exam, blood tests, urinalysis, urine drug screen and electrocardiogram. On the day of the PET scan, OCD and depressive severity were assessed by a trained rater using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS, scale range: 0 to 40; (22, 23)) and the Hamilton Depression Rating Scale (HAM-D, 17-item, scale range: 0 to 50; (24)). The Y-BOCS checklist was used to generate scores for each OCD patient along five different symptom dimensions (contamination and cleaning, taboo thoughts, doubt and checking, symmetry and ordering, and hoarding), using the approach recommended by Pinto and colleagues (25-27).

Radiochemistry

[¹¹C]MDL 100907 was prepared from desmethyl MDL 100907 and [¹¹C] methyl triflate according to modified procedures from Lundkvist and colleagues (28) as described elsewhere (19).

PET procedures

PET was performed with the ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN) operated in the 3D mode. Prior to the PET scan, an arterial catheter was inserted into the radial artery of each subject after completion of the Allen test and infiltration of the skin with 1% lidocaine. A venous catheter was inserted into a forearm vein on the opposite side. Head movement was minimized with a polyurethane head immobilization system (Soule Medical). Following a 10 min transmission scan, [¹¹C]MDL100907 was injected intravenously over 30 seconds. Emission data were collected for 120 minutes, as 21 frames of increasing duration. Previous analysis of [¹¹C]MDL 100907 regional uptake established that 120 minutes of data were required for stable estimates of 5-HT_{2A} availability in all cortical regions (19). Projection data were corrected for attenuation, scatter and random coincidences and reconstructed by filtered backprojection to a 128×128×63 array (Shepp filter, 0.5 cycles/ray, voxel dimensions 1.7×1.7×2.4 mm³).

Input function measurement

Following [¹¹C]MDL 100907 injection, arterial samples were collected with an automated sampling system every 10 seconds for the first two minutes, every 20 seconds for the 3rd and 4th minutes, and manually thereafter at longer intervals (total = 31 samples). Samples were

processed as described elsewhere (29). Six additional samples (collected at 2, 16, 30, 50, 70 and 90 min) were processed to measure the fraction of plasma activity representing unmetabolized parent compound (30). The metabolite-corrected input function and clearance of the parent compound (C_L , $L \cdot hr^{-1}$) were calculated following published methodology (31).

Magnetic resonance imaging (MRIs)

T1-weighted anatomical MR images for region drawing and coregistration were acquired on a GE 1.5T Signa Twin Speed Scanner. Segmentation was performed following previously published methods (30, 32). MRI scans were reviewed by a neuroradiologist and confirmed to be free of gross structural abnormalities.

Image analysis

Image analysis was performed blind to diagnosis using MEDx software (Medical-Numerics, Inc., Germantown MD) following procedures described elsewhere (33). PET data were realigned to a reference frame with the realignment tool in the SPM2 software package (34). Realigned PET data were coregistered to individual subjects' MRI image using a maximization of mutual information algorithm (35) as implemented in SPM2.

Regions of interest (ROIs) and region of reference (cerebellum; CER) boundaries were drawn on the MRI according to criteria derived from brain atlases and published reports (see 32 for original references). A segmentation-based method was used for neocortical regions, and a direct identification method was used for subcortical regions (29). Regional volumes were computed (gray matter voxels only for neocortical regions) using the statistics tool in MEDx. For bilateral regions, right and left regions were summed. The 11 ROIs were: orbitofrontal cortex (OFC, see Figure S1 in the Supplement which illustrates the derivation of this primary ROI); dorsolateral prefrontal cortex (DLPFC); medial prefrontal cortex (MPFC); anterior cingulate cortex (ACC); temporal cortex (TEM); parietal cortex (PAR); occipital cortex (OCC); insular cortex (INS); entorhinal cortex (ENT); parahippocampal gyrus (PHG); and medial temporal lobe (MTL, a spatially weighted average of 5 limbic structures: uncus, amygdala, hippocampus, ENT, and PHG). All had sufficient 5-HT_{2A} receptor density (mean BP_{ND} of 0.5, as defined below) to provide a reliable specific binding signal for analysis (36).

Derivation of Distribution Volumes

[¹¹C] MDL100907 distribution volumes (V_T , $mL \cdot cm^{-3}$), the ratio of total regional activity to arterial plasma activity at equilibrium (37), were estimated in each ROI using two-tissue compartment analysis (2TC) with metabolite-corrected arterial plasma input function. Brain activity was corrected for blood activity contribution assuming a constant 5% blood volume fraction (38). Data were fitted to the 2TC model by nonlinear least-squares regression, using in-house developed software implemented in MATLAB (The Math Works, Inc, Natick MA).

Derivation of 5-HT_{2A} receptor parameters

Derivation of 5-HT_{2A} receptor parameters was based on the assumption that human cerebellum is virtually devoid of ³H- and ¹¹C-labeled MDL100907 specific binding (39) so that cerebellum V_T ($V_{T\text{ CER}}$) was representative of equilibrium nondisplaceable binding (V_{ND}). Two measures of [¹¹C]MDL100907 equilibrium specific binding (binding potential) were calculated (40): 1) BP_p , the ratio at equilibrium of specifically bound radiotracer to unmetabolized tracer in arterial plasma, derived as the difference between V_T in the ROI and $V_{T\text{ CER}}$; and 2) BP_{ND} , the ratio at equilibrium of specifically bound radiotracer to

nondisplaceable [free plus nonspecifically bound] radiotracer in tissue, derived as the ratio of BP_P to $V_{T\text{ CER}}$. Pharmacological interpretations of these outcome measures are

$$BP_P = \frac{f_p B_{avail}}{K_D}$$

$$BP_{ND} = \frac{f_{ND} B_{avail}}{K_D}, \quad \text{Eq 1}$$

where B_{avail} is the regional density of 5-HT_{2A} receptors available to bind radioligand in vivo (nmol·L⁻¹), K_D (nmol·L⁻¹) is the in vivo affinity of the tracer for 5-HT_{2A} receptors, f_p (unitless) is the fraction of [¹¹C] MDL100907 in arterial plasma not bound to plasma proteins, and f_{ND} (unitless) is the free fraction of free plus non-specifically bound [¹¹C] MDL100907 in brain tissue (40). BP_{ND} was chosen *a priori* as the primary outcome measure.

Statistical analysis

Volumes of the 11 ROIs and the cerebellum were examined for group differences using two sample t-tests. Omnibus tests of group differences were performed with linear mixed-model analysis (LMM) for BP_{ND} and BP_P , with regions as repeated measure and diagnostic group as between subject factor. MTL was not included in the LMM analysis as it is a composite of other regions. Exploratory analyses also compared OCD subjects and controls on each parameter within each ROI using two sample t-tests. Within the OCD group, the relationship between 5-HT_{2A} availability and OCD severity (measured by the Y-BOCS), each of the five OCD symptom dimensions (i.e., contamination and cleaning, taboo thoughts, doubt and checking, symmetry and ordering, and hoarding), and age of OCD onset was examined using the Pearson's product-moment correlation, correcting for age (because 5-HT_{2A} availability decreases with age (19)). All statistical tests were 2-tailed with level of significance $\alpha = 0.05$.

Voxelwise analysis

To examine if there were small focal regions of group differences that the ROI analyses did not detect, an additional voxelwise analysis was performed. One tissue compartment analysis (1TC) was applied to each voxel, and a V_T map was generated for each subject. While the 2TC approach was considered more parsimonious for ROI analysis, the 1TC model was used for voxelwise analysis due to its greater stability in the setting of lower signal to noise ratio, and the similarity of the outcome measures between the two methods when applied to ROI data. BP_{ND} maps were generated using $V_{T\text{ CER}}$ as an estimate of V_{ND} as before. Each subject's data were nonlinearly normalized into a common template space (MNI T1-weighted single subject MRI), by first transforming their MRI images into the template space using SPM2 software, and applying the transformation parameters to the BP_{ND} images. Data were smoothed with a 12mm isotropic Gaussian filter. Analysis was restricted to voxels with BP_{ND} values exceeding 20% of the overall image mean. Comparisons of group means were performed using the False Discovery Rate correction for multiple comparisons, with corrected significance level $\alpha = 0.05$.

RESULTS

Sample characteristics

One-hundred and thirty-nine OCD subjects were evaluated. Seventy-five were ineligible: most (n=54) because of a comorbid medical or psychiatric disorder, some because they were on psychiatric medication (n=18), and the rest (n=3) for miscellaneous reasons. Of the 64 eligible OCD subjects, 40 declined participation, primarily due to concerns about the arterial line and/or radiation exposure. Twenty-four OCD subjects agreed to participate, but five did

not complete the PET scan (arterial line could not be placed, $n=3$; declined after signing consent, $n=2$).

The demographic and clinical characteristics of the 19 OCD subjects and 19 matched healthy controls who completed PET and MRI scans are shown in Table 1. There was no group difference in mean age ($t = -0.06$, $df = 36$, $p = 0.95$). Gender and ethnicity distributions were matched. There were no significant group differences in days since last menstrual period in females ($p > 0.56$). One subject in each group currently used nicotine.

OCD subjects had clinically meaningful OCD symptoms, with a mean Y-BOCS score of 26 and a range from 20 (moderate OCD) to 36 (extreme OCD). All five OCD symptom dimensions were represented (i.e., contamination and cleaning, taboo thoughts, doubt and checking, symmetry and ordering, and hoarding), and each patient had symptoms in more than one dimension with two exceptions: one had only hoarding symptoms and one had only contamination and cleaning symptoms. All but seven OCD subjects were SRI-naïve. These seven had been off SRI medication for an average of 44 weeks ($SD = 52$; range: 10-156 weeks). Only two had been exposed to other psychotropic medications (bupropion, $n=1$; olanzapine, $n=1$). All but three were CBT-naïve.

Scan Parameters

PET scan parameters are presented in Table 2. There were no significant group differences in the injected dose, specific activity at injection time, injected mass, peripheral clearance of [^{11}C] MDL100907, or fraction of [^{11}C] MDL100907 in arterial plasma not bound to plasma proteins. There was no significant difference in the volume of distribution in the cerebellum ($V_{T\text{ CER}}$), assumed to be representative of equilibrium nondisplaceable binding (V_{ND}).

Regional volumes

Volumes of ROIs are presented in Table 3. Region-wise comparisons showed no statistically significant group differences in ROI volumes, with two exceptions: OCD subjects had significantly smaller insula and parietal cortex than controls; neither remained significant after False Discovery Rate correction (41) for multiple comparisons ($n = 11$, excluding MTL).

Regional 5-HT_{2A} availability

The two measures of 5-HT_{2A} availability, BP_{ND} (the ratio at equilibrium of specifically bound radiotracer to nondisplaceable tracer) and BP_P (the ratio at equilibrium of specifically bound radiotracer to unmetabolized tracer in arterial plasma) are presented in Table 4 for each ROI. In LMM analyses, there was no significant effect of group for either outcome measure (BP_{ND} : effect of diagnosis: $F(1,36) = 0.493$, $p = 0.487$, effect of region: $F(9,36) = 120$, $p < 0.001$, region by diagnosis interaction $F(9,36) = 0.956$, $p = 0.49$; BP_P : effect of diagnosis: $F(1,36) = 0.273$, $p = 0.60$, effect of region: $F(9,36) = 87$, $p < 0.001$, region by diagnosis interaction $F(9,36) = 1.01$, $p = 0.44$). Likewise, region-wise comparisons revealed no significant differences between groups in any region. A scatter plot for OFC BP_{ND} values in OCD subjects and healthy controls is shown in Figure 1.

Clinical correlations

Neither OCD severity nor any of the five symptom dimensions (current or lifetime) were significantly correlated with [^{11}C] MDL100907 BP_{ND} or BP_P in any ROI when adjusting for age. In contrast, there was a significant association only in the OFC between age of OCD onset and both BP_{ND} and BP_P when adjusting for age (BP_{ND} : $\rho = -0.68$, $p = 0.002$; BP_P : $\rho = -0.57$, $p = 0.015$). The association with BP_{ND} survived False Discovery Rate correction (41) for multiple comparisons ($n=10$ ROIs, excluding MTL), whereas the association with BP_P

did not. The relationship between OFC BP_{ND} and age of OCD onset is illustrated in Figure 2.

Voxelwise analysis

Mean BP_{ND} maps are shown in Figure 3. 5-HT_{2A} availability was high in cortical and limbic regions and low in the striatum, in agreement with the ROI analysis and the known distribution of 5-HT_{2A} in the human brain (18). In the SPM analysis, no voxels or clusters of voxels were significantly different between the groups following False Discovery Rate correction.

DISCUSSION

This study compared 5-HT_{2A} availability in the brains of OCD and healthy subjects. Contrary to our hypothesis, we failed to detect group differences in 5-HT_{2A} availability in the OFC, in any of the other ROIs, or in the voxelwise analysis. Within the OCD group, regional 5-HT_{2A} availability was not significantly correlated with OCD severity or symptom dimensions. However, there was an association between earlier age of OCD onset and greater 5-HT_{2A} availability in the OFC when adjusting for age.

The lack of group differences in 5-HT_{2A} availability in cortical and limbic ROIs conflicts with Perani and colleagues (14). They reported small, widespread cortical decreases in 5-HT_{2A} availability in OCD using [¹¹C] MDL100907. However, their sample consisted of only 9 patients and 6 controls, and the groups were not matched for age. 5-HT_{2A} availability is known to decrease with age (19). On the other hand, the lack of group differences in cortical and limbic regions is consistent with the findings of Adams and colleagues (16) who used [¹⁸F] altanserin, a less selective 5-HT_{2A} radiotracer than [¹¹C] MDL100907, to study 15 OCD and 15 healthy control subjects. Adams and colleagues also reported increased 5-HT_{2A} binding in the caudate nucleus in OCD. In a larger sample and using [¹¹C] MDL100907, we found no caudate group differences (BP_{ND}: OCD = -0.02 ± 0.11 , healthy controls = 0.02 ± 0.07 ; $p = 0.24$, effect size = 0.39). However, given the low density of caudate 5-HT_{2A} receptors in the human brain (18), it is difficult to quantify specific binding reliably with [¹¹C] MDL100907 (caudate BP_{ND} = 0.02 observed here) or [¹⁸F] altanserin (caudate BP_{ND} = 0.13; (16)). Thus, any findings in this region should be treated with caution.

Despite the absence of group differences in 5-HT_{2A} availability, we observed a strong and significant association between earlier age of OCD onset and higher 5-HT_{2A} availability in the OFC. The voxelwise analysis showed a similar relationship (although it did not reach threshold for statistical significance) and suggested that this relationship was homogeneous across the OFC ROI. This finding should be viewed with caution given that only five subjects had early onset OCD (i.e., ≤ 10 years of age). Nevertheless, it does warrant a comment. A post-hoc review of the data suggested that those with early onset OCD had a trend toward higher 5-HT_{2A} availability than those with later onset OCD; healthy controls were in-between. This raises the intriguing possibility that the pathophysiology of OCD (including the role of the 5-HT_{2A} receptor) in early versus late-onset OCD might differ, as suggested by others (42-45). However, other factors cannot be excluded. For example, although OCD severity did not differ between those with early versus later OCD onset (mean Y-BOCS [SD]: 25.6 [1.5] versus 26.5 [4.4]), those with early onset were more likely to be SRI naïve (1 of 5 versus 6 of 13, with one subject missing age of OCD onset). Further research on potential biological differences between early and late onset OCD is warranted.

Our study has several strengths. First, it is the largest OCD study to measure 5-HT_{2A} receptor availability using PET and to conduct ROI and voxelwise analyses. The observed

difference in BP_{ND} and BP_P measures between the two groups was very small in all ROIs, with relatively narrow 95% confidence intervals that were centered typically around zero and included zero, providing confidence in our null results. The voxelwise analysis was also negative. With regards to the OFC, our hypothesized region of interest, our sample size provided 80% power to detect an effect size of 0.93 and a group difference in BP_{ND} of at least 23% if it existed. However, the empirical effect size for BP_{ND} that we observed for the OFC was 0.05. More than 6000 subjects in each group would be needed for this difference to reach significance given the within-group variability we observed.

Second, OCD subjects were well-matched to healthy controls on age, sex, and ethnicity. Moreover, none of the OCD subjects had current major depression, and only four had ever had a major depressive episode. This is important because some PET studies have found 5-HT_{2A} abnormalities in people with depression (46, 47). Additionally, the OCD sample was relatively uncontaminated by SRI treatment: 12 were SRI naïve, and the other seven had been free of SRIs for an average of 44 weeks. These factors as well as our larger sample likely explain why we had different findings than Perani and colleagues (14).

Finally, we used [¹¹C] MDL100907, the first truly selective radioligand for the 5-HT_{2A} receptor, which has excellent signal to noise properties and good test-retest reliability (19). In addition, we measured the arterial input function enabling the quantitative derivation of distribution volumes and confirmation of the lack of group differences in cerebellar distribution volume, a critical issue when calculating BP_{ND} and BP_P .

Like all PET studies, this study also had limitations. First, [¹¹C] MDL100907 provides reliable data only in cortical and limbic brain regions where 5-HT_{2A} receptor density is relatively high (19). Thus, our study cannot address whether there are differences in 5-HT_{2A} distribution in the thalamus, striatum, or midbrain. Moreover, this PET method can detect differences in 5-HT_{2A} binding (reflecting the affinity or density of 5-HT_{2A} receptors) but cannot assess 5-HT_{2A} function. Second, our results cannot exclude the possibility of 5-HT_{2A} alterations in certain homogeneous subtypes of OCD. As noted above, only five of our 19 OCD subjects had early onset OCD (i.e., 10 years of age), and only three reported OCD in a first-degree relative; this may be an inevitable trade-off of recruiting OCD adults who were free of medication and depression. Finally, although the largest OCD sample to study 5-HT_{2A} availability with PET, our sample size was still relatively small to detect associations between clinical features and 5-HT_{2A} findings. Given this, it was surprising to observe the strong association between earlier age of OCD onset and higher OFC 5-HT_{2A} availability.

In conclusion, we did not find differences in 5-HT_{2A} availability in cortical and limbic regions in OCD subjects who were free of psychiatric medication and comorbid major depression. However, earlier onset of OCD was associated with greater 5-HT_{2A} receptor availability in the OFC. Further research on potential biological differences between early and late-onset OCD is warranted. Future studies should also assess 5-HT_{2A} function in the OFC-striatal brain circuit in relation to the glutamatergic system that has been implicated in OCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. BP_{ND} in the orbitofrontal cortex in people with obsessive-compulsive disorder versus healthy controls

Scatter plots of BP_{ND} in the orbitofrontal cortex (OFC) in patients with obsessive-compulsive disorder (OCD, n=19) versus healthy controls (HC, n=19). Mean values for each group are indicated by black line.

Figure 2. The relationship between age of onset of obsessive-compulsive disorder and BP_{ND} in the orbitofrontal cortex

The relationship between age of onset (in years) of obsessive-compulsive disorder (OCD) and BP_{ND} in the orbitofrontal cortex (OFC, n=18 because one OCD subject was missing age of onset). The data are displayed with BP_{ND} corrected for age and fit the equation $BP_{ND} = -0.030 \times \text{age of OCD onset} - 0.014 \times \text{Age} + 2.722$, $F(2,15) = 12.54$, $p = 0.001$. The partial correlation between age of OCD onset and BP_{ND}, controlling for age, was significant ($\rho = -0.68$, $p = 0.002$).

Figure 3. BP_{ND} maps in people with obsessive compulsive disorder and healthy controls
Mean parametric maps of BP_{ND} in patients with obsessive-compulsive disorder (OCD, n=19; top) and healthy controls (HC, n=19; center). The MRI (bottom) is from one representative subject. For each subject, BP_{ND} was computed at each voxel with a 1TC model and spatially normalized into a common template space (see voxelwise analysis in Methods). The slice levels of the coronal (center) and transverse (right) views are represented by black lines in the sagittal view (left). Slices pass through cortex and striatum, demonstrating that BP_{ND} in striatum is very low. No voxels or clusters of voxels were significantly different between the groups in the Statistical Parametric Mapping analysis of these BP_{ND} maps (see Results).

Table 1

Demographic and Clinical Characteristics of the Sample

Parameter	OCD patients n=19	Healthy Controls n=19
Mean Age in years (SD)	30 (10)	30 (10)
Number of Males/Females	10/ 9	10/9
Ethnicity	15Cau/2His/2As	15Cau/2His/2As
History of SRI Treatment	7 of 19	-
Mean weeks (SD) since last SRI dose	44 (52)	-
Mean age of OCD onset in years (SD)	16 (7)	-
Mean Y-BOCS (SD)	26 (4)	-
Mean HAM-D (SD)	5 (5)	-
DSM-IV Axis I psychiatric comorbidity:		
No current or past comorbidity	15	19
Current Specific Phobia & History of MDD	1	-
History of MDD only	3	-
Chronic Tic Disorder/History of Isolated Tics	2/1	

Abbreviations: As, Asian; Cau, Caucasian; HAM-D, Hamilton Depression Rating Scale; His, Hispanic; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SD, standard deviation; SRI, serotonin reuptake inhibitor; Y-BOCS, Yale-Brown Obsessive Compulsive Scale

Table 2Positron Emission Tomography Scan Parameters (mean $\pm$ SD)

Scan Parameter	OCD patients n=19	Healthy Controls n=19	t-test (p)
Injected dose (mCi)	9.17 $\pm$ 4.07	9.99 $\pm$ 4.06	0.54
Specific activity (Ci/mmol)	1047 $\pm$ 501	1094 $\pm$ 482	0.77
Injected mass (μ g)	3.39 $\pm$ 0.44	3.48 $\pm$ 0.53	0.55
Peripheral clearance (L/h)	129 $\pm$ 44	147 $\pm$ 73	0.37
f_p	28.5 $\pm$ 7.3%	29.0 $\pm$ 6.8%	0.83
VND (ml*cm ⁻³)	20.99 $\pm$ 2.74	20.77 $\pm$ 3.64	0.84

Abbreviations: f_p , the fraction of [¹¹C] MDL100907 in arterial plasma not bound to plasma proteins; OCD, obsessive-compulsive disorder; SD, standard deviation; VND, equilibrium nondisplaceable binding (equivalent to the volume of distribution in the cerebellum)

Table 3Regional Brain Volumes (mm³, mean $\pm$ SD)¹

Region of interest	OCD patients n=19	Healthy Controls n=19	t-test (p)
OFC	14830 $\pm$ 4364	16735 $\pm$ 5965	0.27
DLPFC	27280 $\pm$ 5722	29280 $\pm$ 6180	0.31
MPFC	7062 $\pm$ 2810	7179 $\pm$ 2227	0.89
ACC	4197 $\pm$ 1653	4801 $\pm$ 1741	0.28
TEM	65625 $\pm$ 7855	69452 $\pm$ 15297	0.34
PAR	33294 $\pm$ 9826	39668 $\pm$ 9545	0.05
OCC	53799 $\pm$ 11978	51967 $\pm$ 9982	0.61
INS	6692 $\pm$ 826	7368 $\pm$ 1068	0.04
ENT	2383 $\pm$ 693	2143 $\pm$ 474	0.22
PHG	4373 $\pm$ 1002	4410 $\pm$ 1387	0.92
MTL	19049 $\pm$ 1657	19085 $\pm$ 2932	0.96
CER	17479 $\pm$ 4873	19408 $\pm$ 4710	0.22

Abbreviations: ACC, anterior cingulate cortex; CER, cerebellum; DLPFC, dorsolateral prefrontal cortex; ENT, entorhinal cortex; INS, insular cortex; MPFC, medial prefrontal cortex; MTL, medial temporal lobe; OCC, occipital cortex; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PHG, parahippocampal gyrus; PAR, parietal cortex; SD, standard deviation; TEM, temporal cortex

¹ Right and left sides were summed for each subject and then averaged across group.

Table 4

Regional Binding Potentials (mean BP_{ND} and BP_P [$\pm$ SD])¹

Region of Interest	BP _{ND}				BP _P			
	OCD n=19	HC n=19	t-test (p)	95% CI ²	OCD n=19	HC n=19	t-test (p)	95% CI ²
OFC	1.79 $\pm$ 0.36	1.81 $\pm$ 0.51	0.89	(-0.271, 0.312)	37.4 $\pm$ 8.4	38.0 $\pm$ 14.4	0.87	(-7.12, 8.39)
DLPFC	2.11 $\pm$ 0.44	2.21 $\pm$ 0.52	0.52	(-0.215, 0.421)	44.0 $\pm$ 10.0	46.3 $\pm$ 15.2	0.59	(-6.18, 10.79)
MPFC	2.46 $\pm$ 0.52	2.51 $\pm$ 0.58	0.77	(-0.309, 0.414)	51.6 $\pm$ 12.6	53.1 $\pm$ 18.6	0.78	(-8.99, 11.92)
ACC	2.28 $\pm$ 0.39	2.38 $\pm$ 0.59	0.52	(-0.224, 0.438)	47.8 $\pm$ 10.1	50.2 $\pm$ 17.8	0.60	(-7.05, 11.98)
TEM	1.98 $\pm$ 0.35	2.09 $\pm$ 0.53	0.49	(-0.195, 0.401)	41.7 $\pm$ 9.7	44.1 $\pm$ 16.1	0.59	(-6.38, 11.14)
PAR	2.02 $\pm$ 0.38	2.09 $\pm$ 0.51	0.63	(-0.226, 0.366)	42.3 $\pm$ 9.7	43.5 $\pm$ 14.9	0.76	(-7.04, 9.54)
OCC	1.94 $\pm$ 0.29	1.96 $\pm$ 0.45	0.88	(-0.230, 0.266)	40.6 $\pm$ 7.9	40.9 $\pm$ 13.4	0.94	(-7.00, 7.53)
INS	1.99 $\pm$ 0.30	2.05 $\pm$ 0.47	0.66	(-0.204, 0.318)	41.8 $\pm$ 8.3	43.3 $\pm$ 15.0	0.71	(-6.51, 9.42)
ENT	0.83 $\pm$ 0.37	0.99 $\pm$ 0.40	0.21	(-0.093, 0.419)	17.5 $\pm$ 8.5	21.2 $\pm$ 11.8	0.28	(-3.10, 10.48)
PHG	0.55 $\pm$ 0.21	0.66 $\pm$ 0.17	0.07	(-0.009, 0.241)	11.6 $\pm$ 4.9	13.9 $\pm$ 4.7	0.15	(-0.88, 5.43)
MTL	0.43 $\pm$ 0.14	0.51 $\pm$ 0.13	0.10	(-0.016, 0.161)	9.1 $\pm$ 3.4	10.6 $\pm$ 3.6	0.18	(-0.76, 3.80)

Abbreviations: ACC, anterior cingulate cortex; CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; ENT, entorhinal cortex; HC, healthy controls; INS, insular cortex; MPFC, medial prefrontal cortex; MTL, medial temporal lobe; OCC, occipital cortex; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PHG, parahippocampal gyrus; PAR, parietal cortex; SD, standard deviation; TEM, temporal cortex

¹ As described in the Methods, there were two measures of binding potential. BP_P is the difference between the volume of distribution (V_T) in the region of interest and the volume of distribution in the cerebellum (V_T CER). BP_{ND} is the ratio at equilibrium of specifically bound radioligand concentration to that of nondisplaceable radioligand in tissue (derived as the ratio of BP_P to V_T CER).

² The 95% CI was calculated for the difference in mean BP_{ND} and BP_P.