

# Brain Serotonin<sub>2</sub> Receptors in Major Depression

## A Positron Emission Tomography Study

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**Background:** Postmortem and brain imaging studies that measured brain serotonin<sub>2</sub> (5-HT<sub>2</sub>) receptors in major depression reported an increase, decrease, and no change compared with controls. In this study, we assessed brain 5-HT<sub>2</sub> receptors in 20 depressed patients (mean ± SD age, 40.1 ± 9.5 years; range, 22-60 years) and 20 healthy controls similar in age (37.2 ± 12.6 years; range, 19-59 years) using positron emission tomography and setoperone labeled with fluorine 18 (<sup>18</sup>F]setoperone).

**Methods:** Patients with DSM-IV major depression and healthy controls underwent scanning with [<sup>18</sup>F]setoperone. All study subjects were drug free for at least 2 weeks. The 5-HT<sub>2</sub> binding images were created using region-to-cerebellum ratios. The differences in 5-HT<sub>2</sub> receptor binding potential between the two groups were determined with statistical parametric mapping software and region of interest analysis.

**Results:** There was a significant negative correlation between 5-HT<sub>2</sub> receptor binding potential and age in both patients and controls, and the magnitude of this correlation was similar in both groups. Both statistical parametric mapping and region of interest analyses showed that, compared with healthy controls, depressed patients had significantly lower 5-HT<sub>2</sub> receptor binding potential in frontal, temporal, parietal, and occipital cortical regions. Statistical parametric mapping analysis showed that the mean decrease in 5-HT<sub>2</sub> receptor binding potential for the entire cluster in these regions was 22%, and it ranged from 22% to 27% for local maxima within the clusters of significant voxels.

**Conclusion:** This study suggests that brain 5-HT<sub>2</sub> receptors are decreased in patients with major depression.

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**A**LTHOUGH serotonin (5-hydroxytryptamine [5-HT]) has been implicated in the pathophysiology of depression, the precise nature of alterations in the 5-HT system that underlie depressive symptoms still remains elusive. The 5-HT acts on at least 14 subtypes of 5-HT receptors (5-HT<sub>1</sub> to 5-HT<sub>7</sub> subfamilies), and, of these, 5-HT<sub>2</sub> receptors have been the most studied in suicide victims with or without a history of depression and in depressed patients who died of natural causes. Most,<sup>1-4</sup> although not all,<sup>5,6</sup> postmortem studies in suicide victims with mixed, uncertain, or no psychiatric diagnosis reported an increase in brain 5-HT<sub>2</sub> receptor binding, particularly in frontal cortex, compared with control subjects. The findings, however, are inconsistent in those with an antemortem diagnosis of depression. Although 2<sup>7,8</sup> of 3 postmortem studies<sup>7-9</sup> reported an increase in 5-HT<sub>2</sub> recep-

tors in frontal cortex of depressed patients who died of natural causes, only 1<sup>10</sup> of 5 studies<sup>10-14</sup> in suicide victims with an antemortem diagnosis of depression found an increase in 5-HT<sub>2</sub> receptors compared with control subjects. Of the other 4 studies,<sup>11-14</sup> 3<sup>11-13</sup> showed no difference in 5-HT<sub>2</sub> receptors, while 1<sup>14</sup> reported a trend for a decrease in depressed suicide victims compared with control subjects. Differences in age between patient and control groups at the time of death, cause of death, duration of drug-free periods or medication use before death, delay in brain tissue processing, and the type of ligand used may have contributed to variability in findings between postmortem studies.

Brain 5-HT<sub>2</sub> receptors have also been examined in living depressed patients in 4 studies that used either single photon emission computed tomography or positron emission tomography (PET). In the only study that used single photon emission computed

## SUBJECTS AND METHODS

### SUBJECTS

The study was approved by The University of British Columbia Human Ethics Committee. Patients who fulfilled the DSM-IV criteria<sup>24</sup> for major depression as determined by the Structured Clinical Interview for DSM-III-R, Patient Edition<sup>25</sup> were recruited from the inpatient and outpatient departments of The University of British Columbia Hospital, Vancouver. Those with other comorbid diagnoses either on Axis I or Axis II were excluded. Patients with a history of substance or alcohol abuse within the previous 6 months were also excluded. The Hamilton Rating Scale for Depression (21 items)<sup>26</sup> was used to assess the severity of depression in patients. Healthy control subjects similar in age were recruited through advertisements and screened by means of a Structured Clinical Interview for DSM-III-R, Nonpatient Edition.<sup>27</sup> They had no lifetime history of psychiatric illness and no family history of mood disorders or schizophrenia in the first-degree relatives. Both patients and control subjects were physically healthy and were free of psychotropic medications for at least 2 weeks (5 weeks in the case of fluoxetine hydrochloride) before PET scan. All study subjects gave written informed consent for participation in the study. Study subjects underwent magnetic resonance imaging to exclude cerebral abnormality and for coregistration with PET images.

### PET PROCEDURE

Subjects were scanned with a PET camera (ECAT/953B; Siemens, Knoxville, Tenn). This scanner collects 31 axial slices. The spatial resolution of PET images is about 5 mm (full width at half maximum). Setoperone labeled with <sup>18</sup>F was synthesized as previously described.<sup>28</sup> Each subject had a transmission scan for 10 minutes to correct PET images for attenuation. After this, a 15-frame emission scan was performed for 110 minutes as previously described,<sup>29</sup> after subjects were injected with 148 to 259 MBq of [<sup>18</sup>F]setoperone intravenously.

### DATA ANALYSIS

#### Determination of 5-HT<sub>2</sub> Receptor Binding

Region of interest (ROI) analyses were performed by means of a multipurpose imaging tool,<sup>30</sup> and voxel-based

analyses were performed with statistical parametric mapping (SPM 96) software.<sup>31,32</sup>

The specific binding potential of [<sup>18</sup>F]setoperone can be estimated from the measured concentration of tracer in the cerebral ROI and the estimated concentration of tracer in the blood, provided it is possible to allow for nonspecific binding of tracer in the brain. The most direct approach is to measure the time course of arterial tracer concentration and brain tracer concentration for approximately 110 minutes after tracer administration. The variation with time allows separate estimates of specific and nonspecific binding. However, arterial blood sampling is cumbersome and impractical to implement in studies involving a large number of patients. Furthermore, the timing of the arterial measurements is crucial, and errors in the estimation of the arterial input of tracer can lead to serious inaccuracy of the estimation of specific binding.

Therefore, in many circumstances, it is preferable to use an indirect method to estimate the input of tracer and nonspecific binding. One approach<sup>33</sup> is based on the observation that there is negligible specific binding of [<sup>18</sup>F]setoperone in the cerebellum for the following reasons: first, cerebellum is virtually devoid of 5-HT<sub>2</sub> receptors in humans<sup>34</sup>; second, the time course of [<sup>18</sup>F]setoperone accumulation in cerebellum is not affected by saturating doses of 5-HT<sub>2</sub> blocker ketanserin<sup>22,23</sup>; third, similar [<sup>18</sup>F]setoperone kinetics were found in cerebral cortex and cerebellum in ketanserin-pretreated subjects, indicating similar unbound radioligand in both structures.<sup>22,23</sup>

If it is assumed that nonspecific binding is identical in cortex and cerebellum, the ratio of binding in cortex ( $C_{cx}$ ) to that in cerebellum ( $C_{cb}$ ) at equilibrium, is given by the following equation:  $C_{cx}/C_{cb} = f_2 \times (B_{max}/K_d) + 1$ , where  $B_{max}$  is the total number of receptors and  $K_d$  is the equilibrium dissociation constant of the ligand-receptor complex;  $f_2 = 1/[1 + (k_5/k_6)]$ , where  $k_5$  and  $k_6$  are the transfer coefficients for association to and dissociation from nonspecific binding sites. Binding potential (BP) is defined as  $B_{max}/K_d$ , and hence region to cerebellum ratio can be used to obtain a semiquantitative measure of BP for 5-HT<sub>2</sub> receptors. Although the ratio method does not permit an independent determination of  $B_{max}$  and  $K_d$ , it provides a very reliable

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tomography to date, D'haenen et al<sup>15</sup> reported an increase in uptake of 2-ketanserin labeled with iodine 123 (<sup>123</sup>I) in parietal cortex bilaterally and right greater than left asymmetry in the inferofrontal region of depressed patients compared with control subjects, suggesting an increased 5-HT<sub>2</sub> receptor density in these regions in depressed patients. A PET study<sup>16</sup> reported a decrease in uptake of altanserin labeled with fluorine 18 (<sup>18</sup>F) in the right anterior part of insular cortex and right posterolateral orbitofrontal cortex of depressed patients compared with control subjects. Of the other 2 PET studies<sup>17,18</sup> that used setoperone labeled with fluorine 18 ([<sup>18</sup>F]setoperone) as a tracer, one<sup>17</sup> reported a slight but significant decrease in [<sup>18</sup>F]setoperone binding in the frontal cortex of depressed patients compared with control subjects, while the other<sup>18</sup> found no difference between the two groups. Therefore, the issue of whether 5-HT<sub>2</sub> receptors are altered in major depression is still unclear.

The purpose of the present study was to further examine 5-HT<sub>2</sub> receptor density in a large group of depressed patients and healthy control subjects similar in age using PET and [<sup>18</sup>F]setoperone. The [<sup>18</sup>F]setoperone has a high brain uptake, and its metabolites do not cross the blood-brain barrier in humans.<sup>19</sup> Setoperone also has a high specific-to-nonspecific binding ratio. Setoperone has a high affinity for 5-HT<sub>2</sub> receptors ( $K_d$  (equilibrium dissociation constant), 0.37 nmol/L), with relative selectivity to 5-HT<sub>2A</sub> subtype.<sup>20</sup> It also binds to dopamine-2 (D<sub>2</sub>) receptors ( $K_d$ , 10-25 nmol/L), but the density of D<sub>2</sub> receptors is very low in cortex.<sup>21</sup> Setoperone signal in the striatum is displaced by pretreatment with 5-HT<sub>2</sub> and D<sub>2</sub> antagonists, but only 5-HT<sub>2</sub> antagonists displace cortical signal.<sup>22,23</sup> Therefore, [<sup>18</sup>F]setoperone is a suitable ligand for measuring 5-HT<sub>2</sub> receptor binding in cortex in humans.

index of BP. Furthermore, the region to cerebellum ratio at pseudoequilibrium correlates with the BP estimated by using k3-to-k4 ratio with kinetic tracer modeling with a measured arterial input.<sup>35</sup>

When the time-activity curves obtained from ROIs such as frontal, parietal, temporal, and cerebellar regions were plotted, the data showed that the specific region-to-cerebellum ratio did not change significantly in the period of 70 to 110 minutes, indicating a state of pseudoequilibrium during this period. Therefore, the cortex-to-cerebellum ratio in the frames from 70 to 110 minutes after [<sup>18</sup>F]setoperone injection was used to estimate the 5-HT<sub>2</sub> receptor BP (5-HT<sub>2</sub>BP) for each study subject.

The SPM 96<sup>31,32</sup> was used for aligning and coregistering PET images to magnetic resonance images and transforming both into the standard coordinate frame used for templates in SPM 96. Then, an [<sup>18</sup>F]setoperone BP image was created for each subject by dividing each pixel in the normalized mean image with that image's average cerebellar value. A mean activity value from 2 large ROIs (one on the right and one on the left) drawn on 3 contiguous cerebellar slices was used as that image's average cerebellar value. The binding images were smoothed by means of a 12-mm gaussian filter before statistical analysis was performed.

#### SPM Analysis

The SPM 96 was used to determine the significance of differences in 5-HT<sub>2</sub>BP between patients and healthy control subjects. Gray matter threshold was determined by the multipurpose imaging tool and set at 130% of the mean image intensity, as this threshold eliminated most white matter voxels without excluding any gray matter voxels. The significance of difference in 5-HT<sub>2</sub>BP for each voxel between the 2 groups was determined with age used as a covariate. We also assessed the significance of clusters of contiguous voxels in which the difference in 5-HT<sub>2</sub>BP exceeded a threshold of  $z=2.33$  corresponding to  $P<.01$  (or  $P<.025$ , 2-tailed). The method implemented in SPM 96 as described by Worsley<sup>36</sup> calculates the significance of clusters based on extent and peak  $z$  value within the cluster and then applies a correction for

multiple comparisons performed. Cluster significance was also set at  $P<.01$ .

#### ROI Analysis

A large region was drawn on each side for each of the cortical regions (ie, frontal, parietal, and temporal) on 3 contiguous slices. The ROIs for frontal and temporal regions were drawn on transverse planes at the anterior commissure/posterior commissure (AC/PC) line, and a plane above and a plane below the AC/PC line. For parietal region, ROIs were drawn on planes that were above the level of corpus callosum. The mean activity for each region was computed by averaging the values from right and left and from all 3 planes. Region-to-cerebellum ratios were used as a semiquantitative measure of 5-HT<sub>2</sub>BP for each region. An analysis of covariance was performed to compute the difference in 5-HT<sub>2</sub>BP in frontal, parietal, and temporal cortical regions between the 2 groups, with age used as a covariate.

#### Analysis by the Method of Blin et al

A study by Blin et al<sup>37</sup> found small but significant linear increase in cerebellar nonspecific binding of setoperone with age in their study population. Therefore, in their data analysis, they used the "subtraction method (cortex-cerebellum)" instead of the ratio method (cortex-to-cerebellum) to calculate setoperone-specific binding, with the assumption that there is no differential age effect on nonspecific binding between cortex and cerebellum. They normalized for intersubject variations in the amount of radioactivity injected by expressing subtraction values as a percentage of injected dose. We have used this method as well to compare setoperone binding between patients and control subjects.

The differences in age and sex between the 2 groups were determined by means of the  $t$  and  $\chi^2$  tests. Relationships between variables were assessed by means of Pearson correlation coefficient and/or regression analysis. All tests were 2 tailed, with significance set at  $P<.05$ . The data were analyzed by means of SPSS software.<sup>38</sup> Data are given as mean ( $\pm$ SD) unless indicated otherwise.

## RESULTS

A total of 20 patients (9 men and 11 women) and 20 control subjects (8 men and 12 women) participated in the study. Patients' ages ranged from 22 to 60 years, with a mean of  $40.1 \pm 9.5$  years. Similarly, age range for healthy control subjects was 19 to 59 years, with a mean ( $\pm$ SD) of  $37.2 \pm 12.6$  years. As expected, there was no difference in age ( $t_{38}=-1.09$ ;  $P=.28$ ) or sex ( $\chi^2_1=0.10$ ;  $P=.75$ ) between the 2 groups. The number of previous depressive episodes ranged from 0 to 12, with a mean of  $2.9 \pm 3.5$  (**Table 1**). The patients' mean score on the Hamilton Rating Scale for Depression was  $27.1 \pm 5.5$ .

There was no significant difference in [<sup>18</sup>F]setoperone activity in the cerebellum between patients ( $0.077448 \pm 0.0256$ ) and control subjects ( $0.067074$

$\pm 0.0284$ ) ( $P=.23$ ). Similarly, no significant difference was found for cerebellar [<sup>18</sup>F]setoperone activity normalized for injected dose between patients ( $0.000284 \pm 0.000104$ ) and control subjects ( $0.000248 \pm 0.000102$ ) ( $P=.28$ ).

Age was a significant covariate for 5-HT<sub>2</sub>BP for both patients and healthy control subjects. **Figure 1** depicts the relationship between age and 5-HT<sub>2</sub>BP for patients and control subjects for frontal and temporal cortical regions. There was a significant negative correlation between age and the 5-HT<sub>2</sub>BP ( $P<.001$  for all regions examined), and this correlation was similar in both groups (see **Table 2** for details).

The SPM analysis demonstrated that depressed patients had a significant decrease in 5-HT<sub>2</sub>BP compared with control subjects. The analysis disclosed an extensive cluster of voxels occupying lateral and medial

**Table 1. Sociodemographic and Illness Characteristics for 20 Depressed Patients\***

Patient No./ Sex/Age, y	Previous Depressive Episodes, No.	Duration of Current Episode (wk)	Duration of Drug-Free Period	Most Recent Drug Before Washout	HAM-D 21-Item Score
1/F/49	4	78	Drug naive	None	24
2/M/46	12	50	5 wk	Sertraline hydrochloride	24
3/M/41	1	32	30 wk	Fluoxetine hydrochloride	25
4/M/29	0	12	Drug naive	None	21
5/M/34	0	120	4 wk	Paroxetine	23
6/F/35	0	106	2 wk	Sertraline	32
7/M/50	0	20	2 wk	Sertraline	35
8/M/30	0	100	5 wk	Fluoxetine	20
9/F/60	3	24	2 wk	Trazodone hydrochloride	33
10/F/40	7	78	12 wk	Venlafaxine hydrochloride	26
11/F/47	1	20	>1 y	Paroxetine	24
12/M/47	10	70	2 wk	Sertraline	27
13/F/50	0	52	3 wk	Venlafaxine	38
14/F/40	7	26	26 wk	Paroxetine	34
15/F/36	2	12	2 wk	Imipramine hydrochloride	26
16/F/22	3	26	26 wk	Venlafaxine	31
17/M/26	3	312	2 wk	Bupropion hydrochloride	33
18/F/35	2	26	4 wk	Bupropion	20
19/M/47	0	13	2 wk	Venlafaxine	21
20/F/39	3	312	4 wk	Bupropion	25
Mean ± SD/40.1 ± 9.5	2.9 ± 3.5	74.4 ± 87.8	NA	NA	27.1 ± 5.5

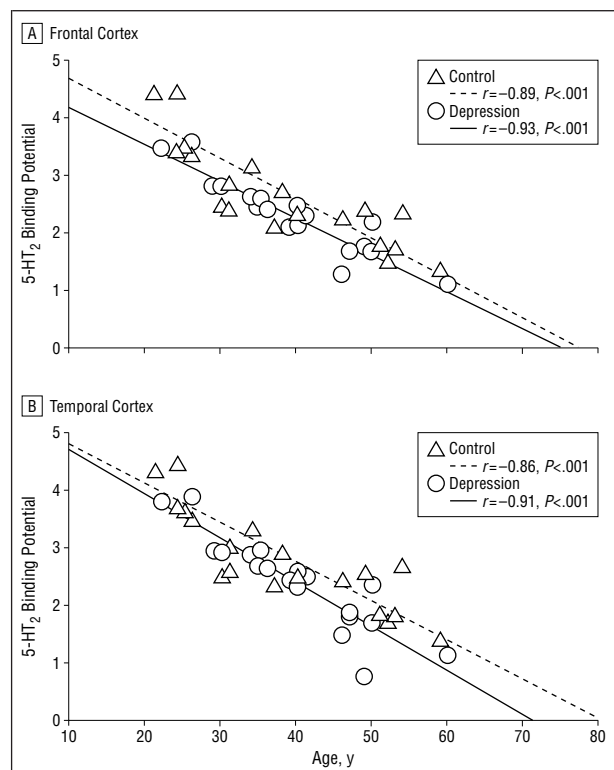
\*HAM-D indicates Hamilton Rating Scale for Depression; NA, not applicable.

frontal cortex bilaterally, extending back into insular, temporal, parietal, and occipital regions (**Figure 2**). This cluster had 37244 gray matter voxels (**Table 3**, Figure 2, and **Figure 3**). Table 3 gives the location and  $z$  value for change in 5-HT<sub>2</sub>BP at those individual voxels where  $z$  exceeded 3.45 ( $P < .025$  after stringent correction for multiple comparisons). The mean decrease in 5-HT<sub>2</sub>BP for the entire cluster was 21.7%, and it ranged from 22.1% to 27.4% for local maxima within the clusters of significant voxels (Table 3). The voxels that showed the most significant decrease in 5-HT<sub>2</sub>BP were located in the left inferior frontal gyrus, right anterior cingulate gyrus, left fusiform gyrus, right inferior temporal gyrus, right medial frontal gyrus, right cingulate gyrus, left superior frontal gyrus, and right inferior temporal gyrus (Table 3, Figures 2 and 3).

To minimize the possibility that the decrease in 5-HT<sub>2</sub>BP noted in our patients was caused by residual effects of previous antidepressant treatment, we carried out SPM analysis in a subgroup of 12 patients who had been drug free for 4 weeks or more and similar-aged control subjects. This analysis also showed a widespread decrease in 5-HT<sub>2</sub>BP in depressed patients with a peak  $z$  of 3.17.

As well, SPM analysis was done on binding images created by the method of Blin et al.<sup>37</sup> The results again showed a widespread decrease in setoperone binding in all cortical areas. The peak  $z$ , however, was somewhat lower (ie, 3.00), which was anticipated, in that this method of creating binding images introduces a greater source of variance from the use of injected dose, as the amount of radioactivity that reaches into brain varies significantly from person to person.

The 5-HT<sub>2</sub>BP values obtained with the use of ROI analysis for patients and control subjects were compared by means of analysis of covariance with age as a



**Figure 1.** Relationship between age and serotonin<sub>2</sub> (5-HT<sub>2</sub>) receptor binding potential in frontal (A) and temporal (B) cortical areas in 20 depressed patients and 20 healthy control subjects. The lines indicate significant negative correlations between age and 5-HT<sub>2</sub> receptor binding potential.

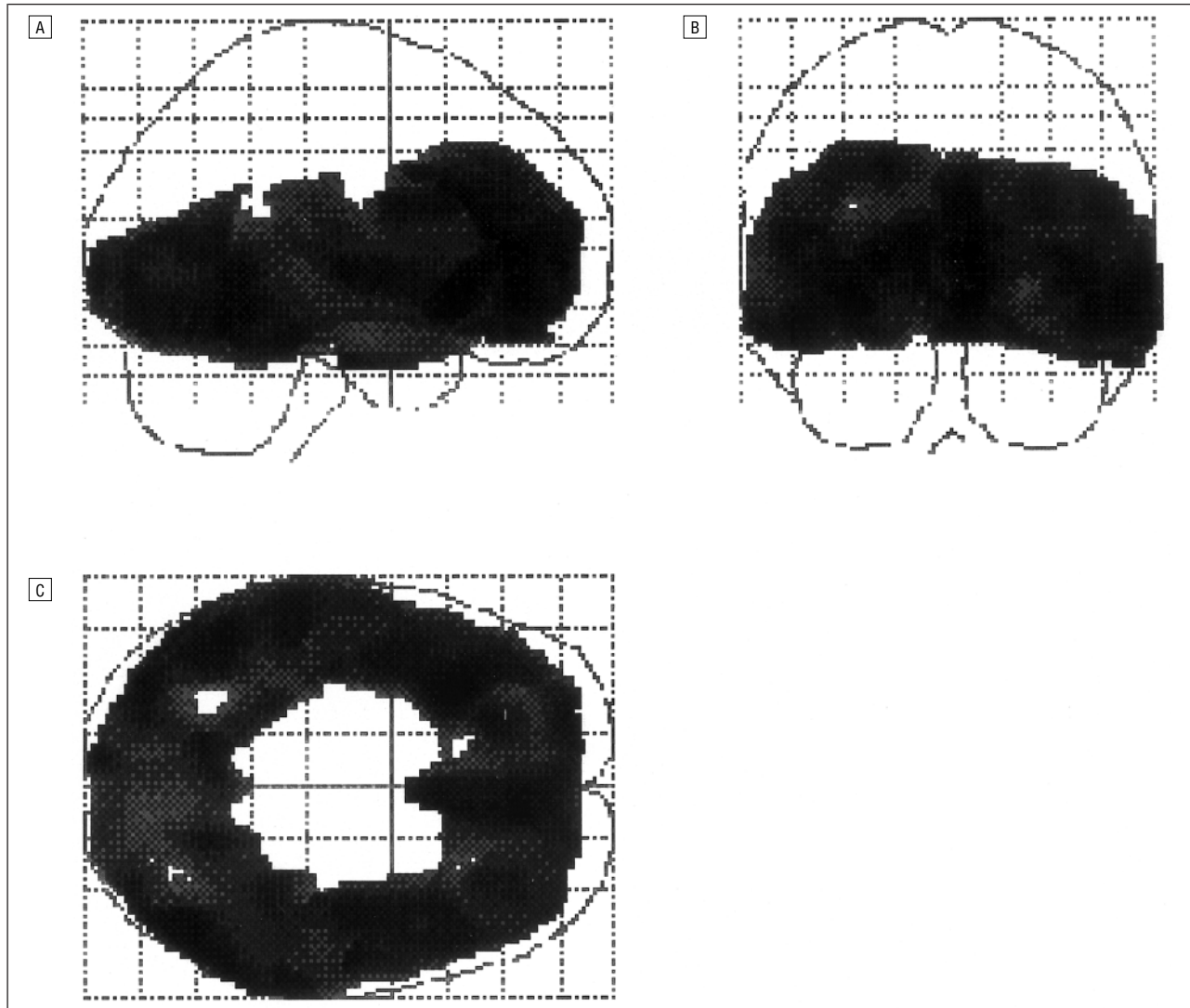
covariate. The ROI analysis confirmed the SPM analysis, indicating a significant decline in 5-HT<sub>2</sub>BP in all 3 brain regions examined in depressed patients (frontal cortex:  $F_{2,39} = 76.7$ ,  $P < .001$ ; temporal cortex:  $F_{2,39} = 72.3$ ,  $P < .001$ ; parietal cortex:  $F_{2,39} = 35.9$ ,  $P < .001$ ).



**Table 2. Correlation Coefficients and Slopes of Linear Regression Between Age and Serotonin<sub>2</sub> Receptor Binding Potential in Various Cortical Areas in 20 Depressed Patients and 20 Healthy Controls**

Brain Region	Depressed Patients			Healthy Controls		
	<i>r</i> *	Slope	95% Confidence Interval of Slope	<i>r</i> *	Slope	95% Confidence Interval of Slope
Frontal cortex	-0.93	-0.06	-0.08 to -0.05	-0.87	-0.07	-0.09 to -0.05
Temporal cortex	-0.91	-0.07	-0.08 to -0.06	-0.86	-0.07	-0.09 to -0.05
Parietal cortex	-0.75	-0.05	-0.07 to -0.03	-0.83	-0.06	-0.08 to -0.04

\*Pearson correlation coefficient.



**Figure 2.** Statistical parametric maps of *t* values displayed as projections on the sagittal (A), coronal (B), and transverse (C) renderings of the brain. These projections illustrate regions of significantly decreased serotonin<sub>2</sub> receptor binding potential in depressed patients compared with matched healthy control subjects.

The 5-HT<sub>2</sub>BP was not increased in depressed patients in any of the brain areas. There was no correlation between 5-HT<sub>2</sub>BP and scores on the 21-item Hamilton Rating Scale for Depression in depressed patients (data not shown).

#### COMMENT

To our knowledge, this is the largest study to date to assess the 5-HT<sub>2</sub> receptor binding in living depressed pa-

tients using PET. The results showed that 5-HT<sub>2</sub>BP was significantly decreased in depressed patients compared with healthy control subjects. The decrease in 5-HT<sub>2</sub>BP was widespread and included frontal, parietal, temporal, and occipital regions.

Since we found a widespread decrease in 5-HT<sub>2</sub>BP in various cortical areas, one should consider the possibility of a difference in cerebellar radioactivity between patients and control subjects because this could affect the

**Table 3. Cluster Size, P and z Values, Coordinates With P and z Values, and Serotonin<sub>2</sub> Receptor Binding Potential for Brain Regions With Highest Decreases in Binding in 20 Depressed Patients Compared With 20 Healthy Controls\***

Cluster			Voxels									Brain Region
Size	z Score	Corrected P	Serotonin <sub>2</sub> Receptor Binding Potential			Coordinates			x	y	z	
			z Score	Corrected P	Depressed Patients	Healthy Control Subjects	Difference, %					
37 244	3.63	<.001	3.63	.01	2.0658 ± 0.5559	2.6998 ± 0.9135	-23.5	-32	22	-6	Left inferior frontal gyrus	
			3.59	.02	1.9335 ± 0.5856	2.6477 ± 0.9585	-26.9	8	38	8	Right anterior cingulate	
			3.56	.02	2.2644 ± 0.6671	2.9075 ± 0.7970	-22.1	-48	-56	-14	Left fusiform gyrus	
			3.54	.02	2.0382 ± 0.5250	2.6206 ± 0.8789	-22.2	54	-14	-28	Right inferior temporal gyrus	
			3.54	.02	2.1894 ± 0.6559	2.8868 ± 0.9522	-24.1	6	40	-10	Right medial frontal gyrus	
			3.52	.02	1.9506 ± 0.6200	2.6899 ± 1.0128	-27.4	6	16	30	Right cingulate gyrus	
			3.47	.02	2.0276 ± 0.6325	2.6996 ± 0.9556	-24.8	-22	58	6	Left superior temporal gyrus	
			3.46	.02	1.9740 ± 0.5189	2.5553 ± 0.8495	-22.7	60	-54	-10	Right inferior temporal gyrus	

\*Coordinates are in millimeters from the origin at the midpoint of anterior commissure, in the coordinate frame employed in statistical parametric mapping (SPM 96).

estimate of 5-HT<sub>2</sub>BP and confound the results. There were no differences in [<sup>18</sup>F]setoperone cerebellar activity or cerebellar activity expressed as a percentage of injected dose of radioactivity between patients and control subjects. Furthermore, a decrease in setoperone binding was also detected in depressed patients by the method of Blin et al.<sup>37</sup> It is also unlikely that the observed decrease in 5-HT<sub>2</sub>BP in depressed patients could be accounted for by group differences in blood flow<sup>39,40</sup> because the values of specifically bound radioligand at equilibrium are independent of initial radioligand delivery.<sup>41</sup> Furthermore, for ligands that reach pseudoequilibrium from 30 minutes onward after injection, simulation studies have shown that the effects of cerebral blood flow on specific binding are negligible.<sup>42</sup>

The possibility exists that the decrease in 5-HT<sub>2</sub>BP observed in depressed patients in this study is caused by an increase in K<sub>d</sub> rather than a decrease in B<sub>max</sub>. This possibility is not supported by previous postmortem studies, which reported no alterations in K<sub>d</sub> in depressed patients,<sup>8,10</sup> suggesting that the decrease in 5-HT<sub>2</sub>BP found in depressed patients in this study is likely to result from a decrease in brain 5-HT<sub>2</sub> receptor density.

The results of this study confirmed previous observations that brain 5-HT<sub>2</sub> receptors decline with age.<sup>6,18,43-46</sup> The patients and control subjects in this study were similar in age. Furthermore, we also used age as a covariate in both SPM and ROI analysis to remove any age effects on 5-HT<sub>2</sub>BP. We found that the magnitude of decline in 5-HT<sub>2</sub>BP was similar for both patients and control subjects, thus making any differential age effects an unlikely explanation for the findings.

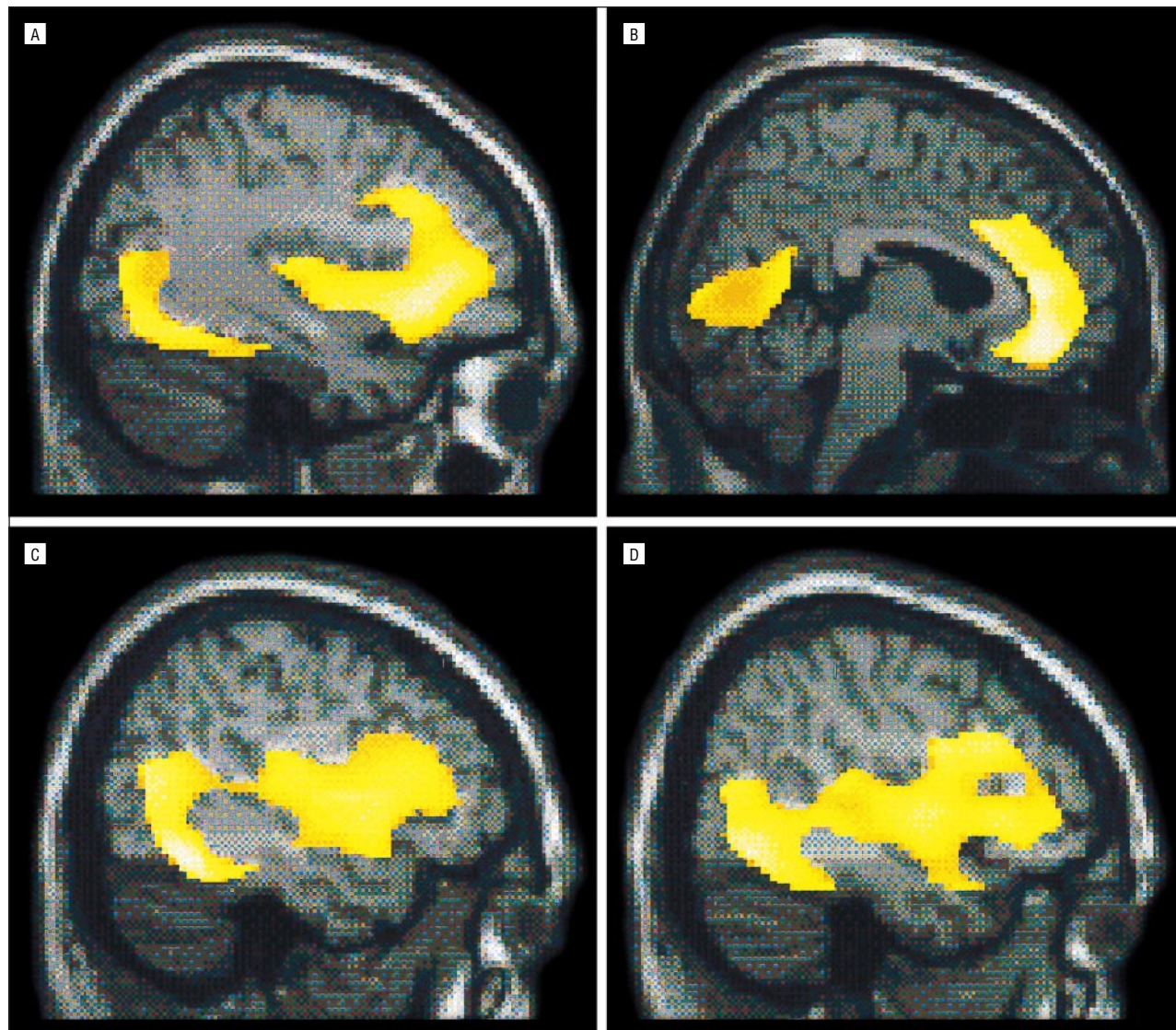
The findings of this study are in contrast to a previous single photon emission computed tomographic study<sup>15</sup> that reported an increase in uptake of 2-<sup>123</sup>I-ketanserin in parietal cortex bilaterally and right infero-frontal region of depressed patients compared with control subjects. Ketanserin is less selective than setoperone for 5-HT<sub>2</sub> receptors relative to other cortical receptors<sup>47</sup>

and it has a very high nonspecific uptake, thus making the validity of the findings of this study questionable.

The results of the present study are in partial agreement with 2 previous PET studies<sup>16,17</sup> but not the third.<sup>18</sup> The 2 previous studies with positive findings, however, unlike the present study, reported only localized significant decreases in brain 5-HT<sub>2</sub> receptor binding in depressed patients. Although Biver et al<sup>16</sup> used voxel-based analysis as in the present study, that study had only 8 patients. Similarly, Attar-Levy et al<sup>17</sup> studied only 7 patients and used ROI analysis.

Meyer et al<sup>18</sup> used a method similar to that in the present study to calculate 5-HT<sub>2</sub>BP. They, however, were unable to find any differences in 5-HT<sub>2</sub>BP between patients and control subjects by means of ROI analysis. Patients in their study were drug free for more than 6 months, whereas in our study, 8 of 20 were drug free for only 2 weeks before scanning. Therefore, one could argue that the decrease in 5-HT<sub>2</sub>BP in depressed patients in our study could result from residual effects of antidepressant medication. However, a subgroup analysis in patients who had been drug free for 4 weeks or more also showed a decrease in 5-HT<sub>2</sub>BP. Furthermore, animal studies have shown that long-term administration of antidepressants decreases brain 5-HT<sub>2</sub> receptor density.<sup>48-54</sup> The receptor density, however, returns to normal levels within 1 week to 10 days of discontinuation of antidepressants,<sup>49,50</sup> thus making the residual effects of antidepressant medication an unlikely explanation. The differences in findings between the 2 studies may also result from other sampling differences. For instance, the mean age of patients in their study was 34 years, and many underwent scanning during their first major depressive episode. In contrast, the patients in our study were slightly older (mean age, 40 years), and many had recurrent chronic depression.

Antidepressant medications such as tricyclics,<sup>48-51</sup> monoamine oxidase inhibitors,<sup>48,50,51</sup> atypical antidepressants,<sup>48,51,52</sup> and some selective serotonin reuptake



**Figure 3.** Representative areas of significant decreases in serotonin<sub>2</sub> receptor binding potential on the sagittal renderings of the brain (A,  $x=-38$ ; B,  $x=4$ ; C,  $x=-48$ ; D,  $x=48$ ) in 20 depressed patients. Coordinates are in millimeters from the origin at the midpoint of anterior commissure, in the coordinate frame used in statistical parametric mapping (SPM 96) software.

inhibitors<sup>51,53,54</sup> have been reported to down-regulate 5-HT<sub>2</sub> receptors. A recent PET study from our group<sup>29</sup> reported that desipramine hydrochloride treatment decreased 5-HT<sub>2</sub> receptor density in depressed patients. Similarly, another effective treatment, electroconvulsive therapy, also caused similar decreases in 5-HT<sub>2</sub> receptors in depressed patients.<sup>55</sup> Since effective antidepressant treatments reduce brain 5-HT<sub>2</sub> receptors, one would expect to find an increase in brain 5-HT<sub>2</sub> receptors associated with major depression. Therefore, our finding of a decrease in 5-HT<sub>2</sub> receptors in depressed patients was counterintuitive. Similar findings, however, have been reported with PET glucose and blood flow studies,<sup>39,56-61</sup> which showed a decrease in brain neuronal metabolism in frontal regions in drug-free depressed patients. Effective antidepressant treatments cause a further reduction in frontal metabolism, which is associated with recovery from depression.<sup>40,62-64</sup>

Nevertheless, one must reconcile with the fact that 5-HT<sub>2</sub> receptor density is decreased in at least some depressed patients, as shown in the present study and in 2

previous PET studies,<sup>16,17</sup> and that the effective antidepressant treatments such as desipramine and electroconvulsive therapy further down-regulate<sup>29,49</sup> rather than return 5-HT<sub>2</sub> receptor density to normal levels in depressed patients. Given this, it is tempting to hypothesize that a decrease in baseline 5-HT<sub>2</sub> receptor density might reflect a secondary compensatory response of the brain to the state of major depression. Such compensatory mechanism-induced down-regulation of 5-HT<sub>2</sub> receptors would hypothetically be sufficient in some cases to induce spontaneous remission of a depressive episode, but in many cases, treatment with effective antidepressants is needed to accelerate down-regulation of 5-HT<sub>2</sub> receptors to achieve recovery from depression.

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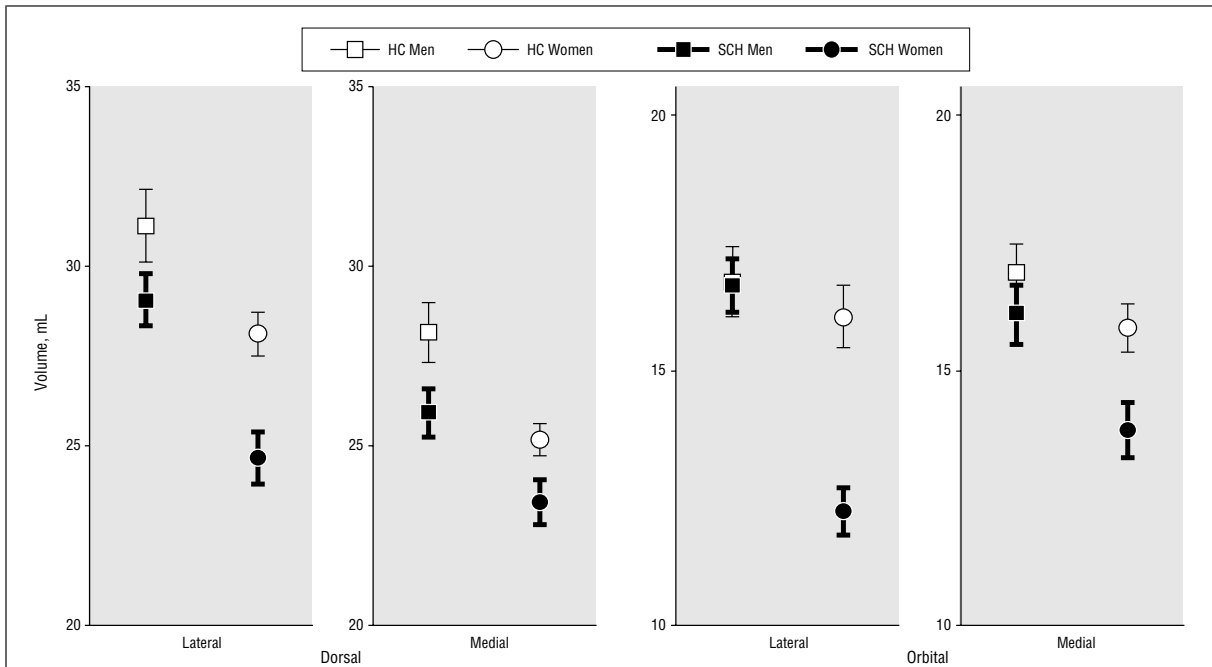
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### Correction

**Error in Figure.** In the original article by Gur et al titled "Reduced Dorsal and Orbital Prefrontal Gray Matter Volumes in Schizophrenia," published in the August issue of the ARCHIVES (2000;57:761-768), the color contents of **Figure 2** on page 766 were accidentally omitted when the figure was printed. Figure 2 is reprinted correctly here in black and white. The journal regrets the error.



**Figure 2.** Means ( $\pm$  SEM) for gray matter volume of healthy men and women and patients with schizophrenia for lateral and medial aspects of dorsal and orbital prefrontal cortex. HC indicates healthy controls (37 men and 44 women); SCH, patients with schizophrenia (40 men and 30 women).