Decreased Frontal Serotonin2A Receptor Binding in Antipsychotic-Naive Patients With First-Episode Schizophrenia

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Context: Postmortem investigations and the receptor affinity profile of atypical antipsychotics have implicated the participation of serotonin2A receptors in the pathophysiology of schizophrenia. Most postmortem studies point toward lower cortical serotonin2A binding in schizophrenic patients. However, in vivo studies of serotonin2A binding report conflicting results, presumably because sample sizes have been small or because schizophrenic patients who were not antipsychotic-naive were included. Furthermore, the relationships between serotonin2A binding, psychopathology, and central neurocognitive deficits in schizophrenia are unclear.

Objectives: To assess in vivo brain serotonin2A binding potentials in a large sample of antipsychotic-naive schizophrenic patients and matched healthy controls, and to examine possible associations with psychopathology, memory, attention, and executive functions.

Design: Case-control study.

Setting: University hospital, Denmark.

Participants: A sample of 30 first-episode, antipsychotic-naive schizophrenic patients, 23 males and 7 females, and 30 matched healthy control subjects.

Interventions: Positron emission tomography with the serotonin2A-specific radioligand fluorine-18-labeled alantserin and administration of a neuropsychological test battery.

Main Outcome Measures: Binding potential of specific tracer binding, scores on the Positive and Negative Syndrome Scale, and results of neuropsychological testing.

Results: Schizophrenic patients had significantly lower serotonin2A binding in the frontal cortex than did control subjects. A significant negative correlation was observed between frontal cortical serotonin2A binding and positive psychotic symptoms in the male patients. No correlations were found between cognitive functions and serotonin2A binding.

Conclusion: The results suggest that frontal cortical serotonin2A receptors are involved in the pathophysiology of schizophrenia.

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midal side effects of atypical antipsychotics and their effect on negative symptoms.20 It is unclear how serotonin$_{2A}$ activity is associated with the most commonly found clinical cognitive deficits in schizophrenia,21,22 for example, attention, executive functions, and spatial working memory. It has been proposed that working memory could be one of the central cognitive markers or endophenotypes of schizophrenia.23-25 In general, the literature suggests that serotonin$_{2A}$ receptor antagonism improves cognition in schizophrenia.26 Recent research has shown that the affinity of antipsychotic drugs to the serotonin$_{2A}$ receptor is associated with cognition in a subtle way. Spatial working memory has been suggested to improve by stimulation rather than blockade of serotonin$_{2A}$ receptors in both preclinical and clinical studies.27-29 Conversely, blockade of serotonin$_{2A}$ receptors by the serotonin$_{2A}$ antagonist ketanserin in healthy control subjects impaired memory more than combined escitalopram oxalate–ketanserin treatment.30 Atypical antipsychotic drugs with a high antagonistic action on serotonin$_{2A}$ may therefore benefit spatial working memory tasks less than low-affinity drugs.27 These studies support a linkage between impaired working memory and decreased serotonin$_{2A}$ availability or function in the human brain.

The introduction of selective serotonin$_{2A}$ receptor radioligands for positron emission tomography (PET) made it possible to examine the serotonin$_{2A}$ receptor density in the living human brain. However, few PET studies on first-episode antipsychotic-naive schizophrenic patients have been performed so far, and the results are inconsistent. Three studies found no difference in serotonin$_{2A}$ binding between schizophrenic patients and healthy control subjects,31-33 and 1 study found a decreased binding potential in the left lateral frontal cortex in 6 patients.34 These studies are limited by small sample sizes and by the use of the radioligands setoperone labeled with fluorine 18 and N-methylpiperone labeled with carbon 11, which have a relatively low serotonin$_{2A}$ receptor selectivity.35

The radioligand altanserin labeled with fluorine 18 is highly selective for the serotonin$_{2A}$ receptor and allows measurements of serotonin$_{2A}$ receptor availability in both cortical and subcortical regions.36,37 In a previous preliminary study, our group reported the use of this radioligand in 15 antipsychotic-naive schizophrenic patients.35 We were unable to confirm our hypothesis of decreased frontal serotonin$_{2A}$ binding. However, in a post hoc analysis, we found increased serotonin$_{2A}$ binding in the caudate nucleus. This result was considered a preliminary finding because of the modest receptor density of serotonin$_{2A}$ in subcortical brain regions. Larger sample sizes were deemed to be required to exclude type II errors.

The aim of the present PET study, therefore, is to use [$^{18}$F]altanserin-PET to investigate cortical and subcortical serotonin$_{2A}$ binding in an extended group of first-episode antipsychotic-naive schizophrenic patients and matched healthy control subjects. Fifteen of the patients were identical to the patients included in our previous preliminary study.35

A decrease in serotonin$_{2A}$ binding in the frontal cortex in these patients compared with matched healthy control subjects was expected a priori. We also expected to confirm our preliminary finding of serotonin$_{2A}$ receptor upregulation in the caudate nucleus. As an additional and new approach, we explored possible associations between serotonin$_{2A}$ binding, psychopathology, and central cognitive deficits, specifically spatial working memory, attention, and executive functions.

METHODS

The study was approved by the Ethics Committee of Copenhagen and Frederiksberg ([KF]11-061/03). The subjects participated after receiving a full explanation of the study and providing written informed consent according to the Declaration of Helsinki II.

PARTICIPANTS

Thirty-three patients (26 male and 7 female) were recruited after voluntary first-time referral to a psychiatric unit of one of the affiliated university hospitals in the Capital Region of Copenhagen (Bispebjerg Hospital, Rigshospitalet, Psychiatric University Center Glostrup, or Psychiatric University Center Gentofte). Thirty of the 33 patients fulfilled the diagnostic criteria for schizophrenia according to both the International Statistical Classification of Diseases, 10th Revision, and DSM-IV. Three patients proved to have a diagnosis of schizophrenic personality disorder at a later stage of the study and were therefore excluded. All included patients (mean [SD] age, 26.4 [5.5] years) were antipsychotic naive. The diagnoses of schizophrenia were verified by means of the Schedules for Clinical Assessment in Neuropsychiatry interview.36

Thirty healthy control subjects (mean [SD] age, 26.4 [5.7] years) matched for age, sex, and parental socioeconomic status were recruited from the community by advertisement. None of the healthy control subjects had present or previous psychiatric disorder or any history of psychotropic medication as determined by the Schedules for Clinical Assessment in Neuropsychiatry interviews.

Six patients were previous (n=4) or present (n=2) users of antidepressant medication (in all cases selective serotonin reuptake inhibitors [SSRIs]). Benzodiazepines were allowed, albeit not on the day of the PET scan. Eight patients fulfilled lifetime criteria for substance abuse. All abuse diagnoses were clearly secondary to the diagnosis of schizophrenia. Substance dependence was an exclusion criterion. The DSM-IV diagnoses of substance abuse were as follows: alcohol abuse, in sustained full remission (n=2); cannabis abuse, in a controlled environment (n=1); other abuse, sustained full remission (n=1); other abuse, moderate (n=1); other abuse, in a controlled environment (n=2); and other abuse, early partial remission (n=1). In 4 of the patients the diagnosis “other abuse” covered mixed cannabis and alcohol abuse, and in the remaining patient the diagnosis covered a history of amphetamine and cocaine use. Three patients had no history of abuse for the past year, and 4 patients had no abuse for the past month. All subjects had negative results of urine screening for substance intake before the PET scan.

Eighteen of the patients (60%) and 6 of the control subjects (20%) were smokers. None of the participants had smoked 2 hours before the PET investigations. Smoking status was not a matching criterion because, in a recent study on 136 healthy subjects study, our group found no effect of smoking on serotonin$_{2A}$ binding.30

No subjects had a history of significant head injury or nonpsychiatric disorder. All subjects had normal results of a neurologic interview and examination, and structural magnetic reso-
neuroradiologist.

**PSYCHOPATHOLOGICAL RATINGS**

Symptom severity was assessed by trained raters using the Positive and Negative Syndrome Scale (PANSS). All interviews were recorded on DVD for validation purposes. A subsample of 10 randomly selected PANSS ratings showed an intraclass correlation coefficient of 0.85 between the raters in a 2-way fixed-effect model.

**NEUROCOGNITIVE TESTING**

Memory, executive functions, and attention were assessed with the following subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB): Spatial Working Memory, Stockings of Cambridge, Intra-Extradimensional Set Shifting, and Rapid Visual Information Processing.

**MR IMAGING**

High-resolution 3-dimensional, T1-weighted, sagittal, magnetization-prepared rapid gradient-echo images of the whole head (inversion time, 800 milliseconds; echo time, 3.93 milliseconds; repetition time, 1540 milliseconds; flip angle, 9°; matrix, 256 × 256; 192 sections) using an 8-channel head array coil were acquired in all subjects on a 3-T imager (TRIO; Siemens, Erlangen, Germany) at the MR department of the Copenhagen University Hospital, Hvidovre, Denmark.

**[18F]ALTANSERIN RADIOSYNTHESIS AND ADMINISTRATION**

The radiosynthesis of [18F]altanserin has been described previously. Quality control was performed by means of thin-layer chromatography and high-performance liquid chromatography. The absence of residual solvents (methanol, tetrahydrofuran, and dimethyl sulfoxide) in the final formulation was confirmed by proton nuclear MR. For each PET study, 0.3 to 3.5 GBq of [18F]altanserin was produced with a radiochemical yield exceeding 95%. (To convert [18F]altanserin to curies, multiply by 2.7 × 10−3.) Catheters were inserted in both cubital veins for tracer infusion and blood sampling, respectively. The [18F]altanserin was administered as a bolus to injection followed by continuous infusion to obtain a steady state of the tracer in blood and tissue. The bolus infusion ratio was 1.75 hours, as previously described. Subjects received a maximum dose of 3.7 MBq of [18F]altanserin per kilogram of body weight.

**PET SCANNING**

The PET scans were acquired in tracer steady-state conditions with an 18-ring scanner (GE-Advance; General Electric Co, Milwaukee, Wisconsin), operating in 3-dimensional acquisition mode, producing 35 image sections with an intersection distance of 4.25 mm. The total axial field of view was 15.2 cm, with an approximate in-plane resolution down to 5 mm. During steady state, the fraction of unmetabolized tracer in venous plasma was determined at 5 time points by means of high-performance liquid chromatography analysis. Reconstruction, attenuation, and scatter correction procedures were conducted as previously described.

The subjects were placed in the scanner 90 minutes after the bolus injection of [18F]altanserin. The subjects were aligned in the scanner by means of a laser system so that the detectors were parallel to the orbitomeatal line and positioned to include the cerebellum in the field of view with the use of a short 2-minute transmission scan. An individual head holder was made to ensure relative immobility. All subjects were scanned in a resting state. A 10-minute transmission scan was obtained for correction of tissue attenuation with retractable germanium Ge 68/gallium Ga 68 pin sources. The transmission scans were corrected for tracer activity by a 3-minute emission scan performed in 2-dimensional mode. Dynamic 3-dimensional emission scans (5 frames of 8 minutes) were started 120 minutes after tracer administration.

Data were reconstructed into a sequence of 128 × 128 × 35 voxel matrices, each voxel measuring 2.0 × 2.0 × 4.25 mm, with software provided by the manufacturer. A 3-dimensional re-projection algorithm with a 6-mm transaxial Hann filter and an 8.3-mm axial ramp filter was applied. Corrections for dead time, attenuation, and scatter were performed.

**BLOOD SAMPLES**

Five venous blood samples were drawn at midscan times 4, 12, 20, 28, and 36 minutes after the start of the dynamic scanning sequence. The samples were immediately centrifuged, and 0.5 mL of plasma was counted in a well counter for determination of radioactivity. Three of the 5 blood samples drawn at 4, 20, and 36 minutes were also analyzed for percentage of parent compound ([18F]altanserin) by means of reverse-phase high-performance liquid chromatography following a previously described method.

In addition, the free fraction of [18F]altanserin in plasma, fR, was estimated by equilibrium dialysis, following a modified procedure. The dialysis was performed with Teflon-coated dialysis chambers (Amika; Harvard Bioscience, Holliston, Massachusetts) with a cellulose membrane that retains proteins larger than 10 000 Da. A small amount of [18F]altanserin (approximately 1 MBq) was added to 10-mL plasma samples drawn from the subjects. A 500-L portion of plasma was then dialyzed at 37°C for 3 hours against an equal volume of buffer because pilot studies had shown that a 3-hour equilibration time yielded stable values. The buffer consisted of 135mM sodium chloride, 3.0mM potassium chloride, 1.2nM calcium chloride, 1.0mM magnesium chloride, and 2.0mM phosphate (pH, 7.4). After the dialysis, 400 L of plasma and buffer was counted in a well counter, and the fR of [18F]altanserin was calculated as the ratio of disintegrations per minute in buffer vs plasma.

**MR/PET CO-REGISTRATION**

The PET images and 3-dimensional T1-weighted MR images were co-registered by means of a MATLAB-based program (MathWorks Inc, Natick, Massachusetts), in which PET and MR images are brought to fit through manual translation and rotation of the PET image with subsequent visual inspection in 3 planes.

**VOLUMES OF INTEREST AND PARTIAL VOLUME CORRECTION**

Volumes of interest (VOIs) were automatically delineated on each individual’s transaxial MR imaging sections in a strictly user-independent manner. This approach allowed automatic co-registration of a template set of 10 MR images to a new subject’s MR image. The identified transformation parameters were used to define VOIs in the new subject MR imaging space, and through the co-registration these VOIs were transferred onto the PET images.

A frontal cortex region was defined for each subject and served as the primary VOI. The frontal cortex VOI consisted
QUANTIFICATION OF SEROTONIN2A RECEPTOR BINDING

The outcome measure was the binding potential of specific tracer binding (BP$_R$). The cerebellum was used as a reference region, since it represents nonspecific binding only. In the steady state, BP$_R$ is defined as follows:

$$BP_R = \left[ \frac{(C_{V01} - C_{Reference})/C_{Plasma}}{f_p(B_{max}/K_d)} \right],$$

where $C_{V01}$ and $C_{Reference}$ are the steady-state mean count densities in the VOI and in the reference region, respectively; $C_{Plasma}$ is the steady-state activity of nonmetabolized tracer in plasma; $f_p$ is the free fraction of radiotracer; $B_{max}$ is the density of receptor sites available for tracer binding; and $K_d$ is the affinity constant of the radiotracer to the receptor.

Table 1. Mean Binding Potentials of Specific [18F]Altanserin Binding in Frontal Cortex and Subregions of Interest in Patients and Controls

<table>
<thead>
<tr>
<th>Region</th>
<th>Patients (n=30)</th>
<th>Controls (n=30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal cortex</td>
<td>2.91 (0.12)</td>
<td>3.37 (0.14)</td>
<td>0.07</td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>2.89 (0.13)</td>
<td>3.42 (0.15)</td>
<td>0.04</td>
</tr>
<tr>
<td>Medial inferior frontal cortex</td>
<td>3.07 (0.12)</td>
<td>3.50 (0.13)</td>
<td>0.07</td>
</tr>
<tr>
<td>Superior frontal cortex</td>
<td>3.34 (0.14)</td>
<td>3.85 (0.15)</td>
<td>0.008</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>2.34 (0.09)</td>
<td>2.68 (0.13)</td>
<td>0.02</td>
</tr>
<tr>
<td>Other regions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>0.68 (0.04)</td>
<td>0.77 (0.05)</td>
<td>0.15</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>0.60 (0.04)</td>
<td>0.65 (0.04)</td>
<td>0.34</td>
</tr>
<tr>
<td>Entorhinal cortex</td>
<td>1.11 (0.05)</td>
<td>1.21 (0.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.74 (0.04)</td>
<td>0.81 (0.05)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0.34 (0.04)</td>
<td>0.38 (0.04)</td>
<td>0.50</td>
</tr>
<tr>
<td>Insula</td>
<td>1.82 (0.08)</td>
<td>2.10 (0.09)</td>
<td>0.04</td>
</tr>
<tr>
<td>Medial inferior temporal cortex</td>
<td>2.66 (0.11)</td>
<td>3.08 (0.13)</td>
<td>0.01</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>2.56 (0.11)</td>
<td>2.97 (0.12)</td>
<td>0.01</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>3.26 (0.13)</td>
<td>3.70 (0.14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>2.57 (0.11)</td>
<td>2.93 (0.12)</td>
<td>0.03</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.41 (0.05)</td>
<td>0.48 (0.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sensorimotor cortex</td>
<td>2.72 (0.11)</td>
<td>3.13 (0.11)</td>
<td>0.01</td>
</tr>
<tr>
<td>Superior temporal cortex</td>
<td>2.68 (0.11)</td>
<td>3.03 (0.12)</td>
<td>0.04</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.48 (0.03)</td>
<td>0.52 (0.03)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Not significant.

RESULTS

The planned comparison of frontal cortical binding showed reduced serotonin2A binding in patients compared with controls ($F_{1,58}=2.54$, $P=.1$).

The ANOVA on region and group disclosed significant main effects of group ($F_{1,58}=5.58$, $P=.02$) and region ($F_{17,986}=82.19$, $P<.001$), and a significant region × group interaction effect ($F_{17,986}=5.77$, $P<.001$). Further analysis of these results indicated that serotonin2A binding in patients was significantly reduced not only in the frontal cortex but also in a number of other cortical— but not subcortical—regions (Table 1). Therefore, to test whether the frontal cortical region showed an even lower serotonin2A receptor binding than the other cortical regions, a post hoc ANOVA was performed with within-factor group (frontal cortex or other regions, Table 1) and between-factor group. This ANOVA demonstrated main effects of region ($F_{1,58}=1109$, $P<.001$) and group ($F_{1,58}=6.00$, $P=.02$) as well as a first-order interaction between region and group ($F_{17,986}=7.78$, $P=.007$), indicating a more pronounced reduction in serotonin2A receptor binding in the frontal cortical region than in the other cortical regions (Figure 1).

In the control group, the Grubbs test indicated 1 significant outlier with an increased binding in the frontal cortex. After exclusion of this outlier, the differences in serotonin2A binding remained significant. None of the results changed when the subjects with previous (n=4) or current (n=2) antidepressant treatment or cocaine and amphetamine abuse (n=1) were excluded from the analy-
ses. Data related to antidepressant medication is described in detail in Table 2. Furthermore, use of benzodiazepines did not covary significantly. The 2 groups did not differ significantly with regard to body mass index, injected radioactive dose, plasma free fraction, and specific radioactivity of [18F]altanserin (Table 3). The patients had significantly lower nonspecific binding than did the healthy control subjects.

SEROTONIN$_{2A}$ BINDING AND NEUROCognition

The cognitive data represent a subsample of a larger unpublished data set (R.A., B.O., Birgitte Fagerlund, PhD, Anders Gade, PhD, H.R., B.H.E., and B.G., unpublished data, 2009). Patients had significantly lower neuropsychological scores than healthy control subjects on the following tests: Spatial Working Memory strategy, Spatial Working Memory total errors, Spatial Working Memory between errors, Intra-Extradimensional Set Shifting total errors, and Intra-Extradimensional Set Shifting total number of trials on all stages attempted. There were no significant differences in Stockings of Cambridge or Rapid Visual Information Processing (Table 4). In the frontal cortex, no significant correlations were detected between serotonin$_{2A}$ binding and the neurocognitive measures. No significant correlations were found between the other VOIs and neurocognitive performance.

SEROTONIN$_{2A}$ BINDING AND PSYCHOPATHOLOGY

In the patients, the PANSS mean (SEM) scores were as follows: positive, 20.0 (0.93); negative, 22.0 (1.20); general, 38.5 (1.30); and total, 80.0 (2.60). A significant negative correlation ($r = -0.57$, $P < .01$) was found between serotonin$_{2A}$ binding in the frontal cortex and positive symptoms in the larger group of male patients. An explorative post hoc analysis showed significant negative correlations between frontal serotonin$_{2A}$ binding and the following subitems of the positive PANSS scale: P1 delusions ($r = -0.47$, $P = .03$) and P6 suspiciousness ($r = -0.53$, $P = .01$) (Figure 2). No significant differences were found between the other VOIs and psychopathology. There was no sex effect on symptom severity or serotonin$_{2A}$ binding.

COMMENT

In this study of serotonin$_{2A}$ binding in antipsychotic-naive, first-episode schizophrenic patients, we confirmed our hypothesis of lower frontal cortical serotonin$_{2A}$ binding in patients than in matched healthy control subjects. The serotonin$_{2A}$ binding was also reduced in a number of other cortical regions, but the reduction in the frontal cortical region was more pronounced. This is in agreement with the many postmortem studies suggesting decreased cortical serotonin$_{2A}$ receptor binding in schizophrenic patients. Moreover, the data demonstrated a significant negative correlation between frontal cortical serotonin$_{2A}$ binding and positive psychotic symptoms in male patients. We were not, however, able to confirm correlations between cognitive functions and serotonin$_{2A}$ binding, even though the patients performed significantly worse in spatial working memory and aspects of executive function than did the healthy controls.

Our results are based on what we believe to be the largest sample studied with PET, because earlier PET studies have reported results based on 6 to 15 patients. The majority of these studies, including our own, were unable to identify differences in cortical serotonin$_{2A}$ binding between schizophrenic patients and healthy control subjects. In our previous study we found increased serotonin$_{2A}$ receptor binding in the caudate nucleus. This nucleus is a region with a relatively low serotonin$_{2A}$ receptor density; hence, the post hoc analyses were more prone to type II errors. The present study does not confirm our preliminary finding of increased binding in the caudate nucleus, but it does support the study by Ngan and colleagues, who reported reduced serotonin$_{2A}$ binding in the frontal cortex of 6 neuroleptic-naive schizophrenic subjects. Similarly, Hurlemann and colleagues reported decreased cortical serotonin$_{2A}$ binding in subjects at high risk of developing schizophrenia.

Decreased frontal serotonin$_{2A}$ binding and the relationship with positive psychotic symptoms may reflect either a primary pathophysiologic disturbance in schizophrenia or a compensatory downregulation of receptors in response to altered endogenous serotonin levels. Alternatively, the finding could indicate a downregulation compensating for hyperactive second messenger systems or hyperactivity in other systems on which the serotonin$_{2A}$ receptors have a modifying effect. Finally, the finding could imply that frontal serotonin$_{2A}$ receptors are important targets for antipsychotic drugs.

The correlation between serotonin$_{2A}$ binding and symptoms was present only in the male subjects. Various aspects of schizophrenia, including age at onset, pathophysiology, symptomatology, course of illness, and treatment response, have previously been shown to be related to sex. These sex differences supply evidence for a potential role of gonadal hormones and for an interaction of these hormones with neurotransmitters (for a re-
As expected, patients showed significantly poorer performance in spatial working memory and executive functions than did healthy control subjects. This is in agreement with previous studies that have shown that spatial working memory and executive functions are centrally impaired neurocognitive domains in schizophrenia. However, we detected no correlations between the cognitive measures and serotonin2A binding in any of the VOIs. Hence, our data do not support previous findings of a correlation between D2 receptor binding and positive psychotic symptoms in male patients only.

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The interaction between serotonin and cognition is complex. Indeed, we have previously reported sex differences in drug-naive schizophrenic patients with regard to the dopamine system, namely, a correlation between D2 receptor binding in the frontal cortex and positive psychotic symptoms in male patients only.

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The interaction between serotonin and cognition is complex. Indeed, the interactions between serotonin, dopamine, norepinephrine, and the cholinergic system have been suggested to mediate cognitive behavior. Moreover, studies differ in design with regard to subjects (rodents, healthy controls, or patients), type of serotonin manipulation (global, specific depletion, or stimulation), serotonin receptor subtype (currently 15 serotonin receptor subtypes have been identified), and the cognitive tests being used. Indeed, we have previously found that [18F]altanserin binding to serotonin2A receptors is insensitive to a citalopram hydrobromide challenge increasing extracellular serotonin. Furthermore, the effect of long-term SSRI treatment on serotonin2A density is unclear because SSRIs have different effects on serotonin2A receptors. Fluoxetine hydrochloride has been reported to have no effect on serotonin2A receptor number or to actually increase receptor number. Similarly, paroxetine hydrochloride has been shown to increase or have no effect on serotonin2A receptor density. In contrast, long-term citalopram treatment has been shown to downregulate serotonin2A receptors.

For the foregoing reasons, we initially chose to include patients taking previous or current antidepressants.
sults but controlled for the potential effect in a post hoc analysis in which these patients were removed from the analyses. This did not change the results.

Similarly, 1 patient had a history of amphetamine and cocaine abuse. These substances are known to affect serotonergic innervation in the brain; however, the patient did not differ in serotonin$_{2A}$ receptor binding, and exclusion of this patient from the analyses did not alter the results.

Finally, there was a significantly lower binding in the cerebellum in patients than in control subjects. We have no explanation for this finding; the fraction of $[^{3}H]$altanserin metabolites in venous blood was the same in both groups. However, lower nonspecific cerebellar binding in the patients is not likely to bias the results because a relative underestimation of nonspecific binding in the patients would lead to an overestimation of the composite measure BP$_{S}$ (see the equation in the “Methods” section).

In conclusion, this study of serotonin$_{2A}$ receptor binding in first-episode, antipsychotic-naive schizophrenic patients shows decreased binding in the frontal cortex and a negative correlation with positive symptoms in male patients. The results suggest that frontal cortical serotonin$_{2A}$ receptors are involved in the pathophysiology of schizophrenia. Because no correlations were found between binding and cognition, this study does not support the involvement of serotonin$_{2A}$ receptors in cognitive deficits in this early stage of the disease.

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Figure 2. Correlation in male schizophrenic patients between mean frontal cortical serotonin$_{2A}$ receptor binding, positive symptoms on the Positive and Negative Syndrome Scale (PANSS), and 2 subitems. Negative correlations are evident for the PANSS positive scale ($r=-0.57$, $P=.007$) (A), as well as for subitems P1, delusions ($r=-0.47$, $P=.03$) (B), and P6, suspiciousness ($r=-0.53$, $P=.01$) (C).

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