

# Cortical and Subcortical 5-HT<sub>2A</sub> Receptor Binding in Neuroleptic-Naive First-Episode Schizophrenic Patients

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The serotonin 5-HT<sub>2A</sub> receptor is suspected to be involved in a number of psychiatric disorders, including schizophrenia. In particular, atypical antipsychotics have antagonistic effects on the 5-HT<sub>2A</sub> receptors, supporting a specific role of the 5-HT<sub>2A</sub> receptor in the pathophysiology of this disease. The aim of this study is to investigate cortical and subcortical 5-HT<sub>2A</sub> binding in neuroleptic-naive schizophrenic patients. Fifteen neuroleptic-naive patients diagnosed with schizophrenia (age 27.5 ± 4.5 years), 11 men and 4 women, and 15 healthy control subjects matched for age (28.5 ± 5.7 years) and gender underwent a 40 min positron emission tomography (PET) study using the 5-HT<sub>2A</sub> antagonist, [<sup>18</sup>F]altanserin, as a radioligand. PET images were co-registered to 3 T magnetic resonance images (MRIs) for each individual subject, and ROIs were applied automatically onto the individual MRIs and PET images. The cerebellum was used as a reference region. The binding potential of specific tracer binding (BP<sub>p</sub>) was used as the outcome measure. No significant difference was seen in cortical receptor distribution between patients and controls. An increase in 5-HT<sub>2A</sub> receptor binding in the caudate nucleus was detected in the group of schizophrenic patients (0.7 ± 0.1) when compared to the healthy controls (0.5 ± 0.3) (*p* = 0.02). Our results confirm other *in vivo* findings of no difference in cortical 5-HT<sub>2A</sub> receptor binding between first-episode antipsychotic-naive schizophrenic patients and age- and gender-matched healthy control subjects. However, a preliminary finding of increased 5-HT<sub>2A</sub> binding in the caudate nucleus requires further investigation to explore the relation of subcortical and cortical 5-HT<sub>2A</sub> receptor binding.

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## INTRODUCTION

A role for serotonin in the pathophysiology of schizophrenia is supported by different observations. Gaddum (1954) described that the hallucinogenic drug lysergic acid diethylamide had structural similarity to serotonin and could cause or exacerbate psychotic symptoms. These early findings led to the hypothesis that serotonin was implicated in the pathophysiology of schizophrenia. Further support for this comes from the notion that most atypical antipsychotic drugs (AAPDs) antagonize the serotonin 2A (5-HT<sub>2A</sub>) receptor. The affinity of AAPDs as determined *in vitro* (Meltzer *et al*, 1989) and *in vivo* (Zhang and

Bymaster, 1999) is often higher for 5-HT<sub>2A</sub> than D<sub>2</sub> receptors. Finally, post-mortem studies suggest a serotonergic dysfunction in cortical areas in schizophrenia. Eleven (Arora and Meltzer, 1991; Bennett, 1979; Burnet *et al*, 1996; Dean and Hayes, 1996; Dean *et al*, 1998, 1999; Gurevich and Joyce, 1997; Laruelle *et al*, 1993; Matsumoto *et al*, 2005; Mita *et al*, 1986; Pralong *et al*, 2000) out of 15 (Dean *et al*, 1996; Joyce *et al*, 1993; Reynolds *et al*, 1983; Whitaker *et al*, 1981) post-mortem studies of brains of schizophrenic patients have reported decreased 5-HT<sub>2A/C</sub> density in cortical areas, especially in the frontal cortex. Only two studies have addressed the subcortical 5-HT<sub>2A</sub> density in post-mortem material: Joyce *et al* (1993) found an increased 5-HT<sub>2A</sub> density in the ventral putamen and nucleus accumbens, whereas Matsumoto *et al* (2005) reported no significant difference in striatum between controls and patients suffering from schizophrenia.

Investigations with *in vivo* imaging techniques have not supported post-mortem findings of a cortical decrease in

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5-HT<sub>2A</sub> receptor binding in schizophrenia. Three positron emission tomography (PET) studies showed no difference in 5-HT<sub>2A/C</sub> receptor density between schizophrenic patients and controls (Lewis *et al*, 1999; Okubo *et al*, 2000; Trichard *et al*, 1998). Only one study revealed a decreased 5-HT<sub>2A</sub> binding potential in the frontal cortex of six neuroleptic-naive schizophrenic subjects when compared to healthy controls (Ngan *et al*, 2000). The latter publication was based on a voxel-based image analysis, whereas the three prior ones were based on a region-based analysis. All four previous studies were performed on a limited number of patients and only some of them were antipsychotic-naive. Three of the studies used [<sup>18</sup>F]setoperone as a 5-HT<sub>2A</sub> tracer, whereas one study used [<sup>11</sup>C] *N*-methylspiperone. Owing to a relatively poor selectivity of both radiotracers for the 5-HT<sub>2A</sub> receptor, these studies are limited to the detection of receptor binding only in cortical areas. In conjunction with the poor selectivity of the tracers, a lower ratio of 5-HT<sub>2A</sub> receptors to D<sub>2</sub> receptors in subcortical areas compared to cortical areas makes these ligands inadequate to measure subcortical binding. Today, two other specific 5-HT<sub>2A</sub> radioligands are available: [<sup>11</sup>C]MDL 100,907 and [<sup>18</sup>F]altanserin. [<sup>18</sup>F]altanserin has a 200- to 500-fold 5-HT<sub>2A</sub>/D<sub>2</sub> selectivity measured as  $1/(5\text{-HT}_{2A} K_i/D_2 K_i) = 1/(0.13\text{--}0.3/62\text{ nM}) = 1/(0.002\text{--}0.005)$  (Kristiansen *et al*, 2005; Tan *et al*, 1999), making it between 8 and 50 times more selective for the 5-HT<sub>2A</sub> receptors than [<sup>18</sup>F]setoperone ( $(1/(1/10\text{--}25\text{ nM})) = 1/(0.1\text{--}0.04) = 10\text{--}25\text{-fold}$  5-HT<sub>2A</sub>/D<sub>2</sub> selectivity (Lewis *et al*, 1999)). In addition, the affinity of [<sup>18</sup>F]altanserin for the 5-HT<sub>2A</sub> receptor is at least 20-fold higher than for other 5-HT subtypes (Tan *et al*, 1999). We have previously demonstrated that [<sup>18</sup>F]altanserin PET with a bolus infusion design is a highly reproducible method for reliable quantification of 5-HT<sub>2A</sub> receptor binding (Haugbøl *et al*, 2007).

The aim of the present PET study was to investigate cortical and subcortical 5-HT<sub>2A</sub> receptor binding in a group of first-episode antipsychotic-naive schizophrenic patients and matched healthy controls using [<sup>18</sup>F]altanserin PET.

## MATERIALS AND METHODS

### Participants

Fifteen patients (11 men and 4 women) were recruited after voluntary first-time referral to a psychiatric unit of one of the affiliated university hospitals in the Copenhagen area (Bisbebjerg Hospital, Rigshospitalet, Psychiatric University Centre Glostrup or Psychiatric University Centre Gentofte). 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.

The patients included fulfilled diagnostic criteria for schizophrenia according to both ICD-10 and DSM IV. All patients were antipsychotic-naive at the time of investigation. Diagnosis was verified by means of the structured clinical interview SCAN 2.1 (Schedules for Clinical Assessment in Neuropsychiatry). The severity of symptoms in subjects was assessed with Positive and Negative Syndrome

Scale (PANSS). All interviews were recorded on video for validation purposes.

Fifteen healthy control subjects matched for age, gender, and ethnicity were recruited from the community by advertisement. None of the healthy control subjects had either a history of present or prior psychiatric disorder or had ever used any psychotropic medication as determined by SCAN interviews.

Four patients had prior ( $n=3$ ) or present ( $n=1$ ) use of antidepressant medication (in all cases selective serotonin reuptake inhibitors). Current use of benzodiazepines was allowed, albeit not on the day of the PET scans. Except for one, none of the patients used any drugs of abuse or fulfilled ICD-10 or DSM IV criteria for either drug abuse or drug dependence by the time of inclusion. None of the healthy controls or any of the patients had a history of significant head injury or non-psychiatric disorder. Both healthy controls and patients had a normal neurological interview and examination.

### Magnetic Resonance Imaging

High-resolution 3D T1-weighted, sagittal, spoiled gradient echo scans (MPRAGE) of the head (TI/TE/TR = 800/3.93/1540 ms, flip angle 9°; matrix: 256 × 256; 192 slices) using an eight-channel head array coil were acquired in all subjects on a 3 T TRIO scanner (Siemens, Erlangen, Germany) at the MR department of the Copenhagen University Hospital, Hvidovre, Denmark.

### [<sup>18</sup>F]altanserin PET Studies

**Radiosynthesis and administration.** The radiosynthesis of [<sup>18</sup>F]altanserin was according to the method described previously by Lemaire *et al* (1991). Quality control was performed using thin-layer chromatography and high-performance liquid chromatography (HPLC). The absence of residual solvents (methanol, THF, and DMSO) in the final formulation was confirmed by <sup>1</sup>H NMR. For each PET study, 0.3–3.5 GBq of [<sup>18</sup>F]altanserin was produced with a radiochemical yield greater than 95% and a mean specific activity of  $52.4 \pm 34.0$  GBq/μmol. Catheters were inserted in both cubital veins for tracer infusion and blood sampling, respectively. [<sup>18</sup>F]altanserin was administered as a combination of a bolus injection followed by continuous infusion to obtain steady state of the tracer in blood and tissue. The bolus-infusion ratio was 1.75 h, as previously described (Pinborg *et al*, 2003). Subjects received the maximum dose of 3.7 MBq/kg body weight [<sup>18</sup>F]altanserin.

**Imaging.** PET scans were acquired in tracer steady-state conditions with an 18-ring GE-Advance scanner (GE, Milwaukee, WI, USA), operating in 3D-acquisition mode, producing 35 image slices with an interslice 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 five time points using HPLC analysis. Reconstruction, attenuation, and scatter correction procedures were conducted according to Pinborg *et al* (2003).

Ninety minutes after the bolus injection of [<sup>18</sup>F]altanserin, the subjects were placed in the scanner. Subjects were aligned in the scanner using a laser system so that the detectors were parallel to the orbitomeatal line and positioned to include the cerebellum in the field of view using a short 2 min transmission scan. An individual head holder was made to ensure relative immobility. All subjects were scanned in a resting state. A 10-min transmission scan was obtained for correction of tissue attenuation using retractable <sup>68</sup>Ge/<sup>68</sup>Ga pin sources. The transmission scans were corrected for tracer activity by a 5-min emission scan performed in 2D mode. Dynamic 3D emission scans (five frames of 8 min) were started 120 min 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 3D reprojection algorithm with a transaxial Hann filter (6 mm) and an axial ramp filter (8.5 mm) was applied. Corrections for dead-time, attenuation, and scatter were performed.

**Blood samples.** Five venous blood samples were drawn at mid-scan times 4, 12, 20, 28, and 36 min after starting 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 five blood samples drawn at 4, 20, and 36 min were also analyzed for percentage of parent compound ([<sup>18</sup>F]altanserin) using reverse-phase HPLC following the procedure described by Pinborg *et al* (2003).

In addition, the free fraction of [<sup>18</sup>F]altanserin in plasma,  $f_1$ , was estimated using equilibrium dialysis, following a modified procedure by Videbaek *et al* (1993). The dialysis was performed using Teflon-coated dialysis chambers (Harvard Bioscience, Amika, Holliston, MA, USA) with a cellulose membrane that retains proteins > 10 000 Da. A small amount of [<sup>18</sup>F]altanserin (approximately 1 MBq) was added to 10 ml plasma samples drawn from the subjects. A 500 µl portion of plasma was then dialyzed at 37°C for 3 h against an equal volume of buffer, since pilot studies had shown that 3 h equilibration time yielded stable values. The buffer consisted of 135 mM NaCl, 3.0 mM KCl, 1.2 nM CaCl<sub>2</sub>, 1.0 mM MgCl<sub>2</sub>, and 2.0 mM phosphate (pH 7.4). After the dialysis, 400 µl of plasma and buffer were counted in a well counter, and  $f_1$  of [<sup>18</sup>F]altanserin was calculated as the ratio of DPM<sub>buffer</sub>/DPM<sub>plasma</sub>.

## Data Analysis

**MR/PET co-registration.** PET images and magnetic resonance images (MRIs) were co-registered using a Matlab (Mathworks Inc., Natick, MA, USA)-based program (Willendrup *et al*, 2004), where PET images and MRIs are brought to fit through manual translation and rotation of the PET image with subsequent visual inspection in three planes (Adams *et al*, 2004).

**Volumes of interest and partial volume correction.** Volumes of interest (VOIs) were automatically delineated on each individual's transaxial MRI slices in a strictly user-independent manner (Svarer *et al*, 2005). With this approach, a template set of 10 MRIs is automatically

co-registered to a new subject's MRI. The identified transformation parameters are used to define VOIs in the new subject MRI space, and through the co-registering these VOIs are transferred onto the PET images. The investigated regions included frontal cortex (consisting of orbitofrontal, medial inferior frontal, and superior frontal subregions), anterior cingulate, posterior cingulate, insula, superior temporal cortex, medial inferior temporal cortex, sensory motor cortex, parietal cortex, occipital cortex, putamen/pallidus, thalamus, caudate nucleus, and cerebellum. For normalization purposes (see below), a global neocortical region was created for each subject. It consisted of a volume-weighted average of the binding potentials from the cortical regions listed above.

To enable partial volume correction of the PET data, MRIs, corrected for RF inhomogeneities using the N3 software (Sled *et al*, 1998), were segmented into gray matter, white matter, and cerebrospinal fluid tissue classes using SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Partial volume correction was performed according to Quarantelli *et al* (2004). The white matter value was extracted as the mean voxel value from a predominantly white matter VOI (mid-brain) in the uncorrected PET image. As the MRIs and PET images have been co-registered, it is possible to calculate the number of gray matter voxels in native subject space for each VOI, and this is reported as the gray matter volume for the VOI.

**Quantification of the 5-HT<sub>2A</sub> receptor binding.** The outcome parameter was the binding potential of specific tracer binding (BP<sub>p</sub>). The cerebellum was used as a reference region, since it represents nonspecific binding only (Pinborg *et al*, 2003). In steady state, BP<sub>p</sub> is defined as

$$BP_p = \frac{C_{ROI} - C_{Reference}}{C_{Plasma}} = f_1 \frac{B_{max}}{K_d} \text{ (ml/ml)}$$

where  $C_{ROI}$  and  $C_{Reference}$  are steady-state mean count density in the VOI and in the reference region, respectively,  $C_{Plasma}$  is the steady-state activity of non-metabolized tracer in plasma,  $f_1$  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.

## Statistics

Between-group (patients, controls) comparisons of all reported outcome measures were performed using parametric analysis after verifying that the data were normally distributed according to the Kolmogorov-Smirnov test. *P*-values from unpaired two-tailed *t*-test were reported;  $p = 0.05$  was employed as the level of significance. *Post hoc* linear regression analysis was performed with caudate 5-HT<sub>2A</sub> receptor binding as the dependent variable and PANSS scores and age as independent variables. All analyses were performed using the statistical software SAS 9.1.

## RESULTS

As shown in Table 1, no significant differences were observed in age, body mass index, injected dose, plasma free fraction, specific radioactivity of [<sup>18</sup>F]altanserin, and nonspecific binding between the two groups.

As illustrated in Table 2, two-tailed unpaired *t*-test revealed no between-group differences in 5-HT<sub>2A</sub> BP<sub>P</sub> either in any of the cortical regions or in the thalamus or putamen. However, schizophrenic patients displayed a significantly higher 5-HT<sub>2A</sub> BP<sub>P</sub> in the caudate nucleus than controls ( $0.72 \pm 0.15$  vs  $0.52 \pm 0.27$ ,  $p = 0.02$ , uncorrected). Exclusion of the subjects with prior antidepressant treatment (four patients) and illegal drug use (one patient) and their matched controls did not alter these results.

In the patient group, the positive, negative, and general symptom scores as assessed with PANSS were  $18.6 \pm 5.0$ ,  $20.6 \pm 6.6$ , and  $36.0 \pm 7.1$ , respectively. *Post hoc* linear regression analysis with adjustment for age did not reveal any significant relationship between caudate 5-HT<sub>2A</sub> receptor binding and positive, negative, or general PANSS scores. Further, there was no statistically significant group difference in the ratio between uncorrected and partial volume-corrected BP<sub>P</sub> values in the caudate ( $0.4 \pm 0.1$  vs  $0.5 \pm 0.2$  in controls,  $p = 0.57$ ).

There were no between-group differences in total gray matter volume in the caudate ( $2.3 \pm 0.3$  vs  $2.3 \pm 0.2$  ml in controls,  $p = 0.49$ ) or in any of the other regions of interest (data not shown).

## DISCUSSION

The number of antipsychotic-naïve first-episode schizophrenic patients in our study is so far the largest sample examined. Earlier studies have included 6 (Ngan *et al*, 2000), 7 (Trichard *et al*, 1998), 10 (Okubo *et al*, 2000), and 10 (Lewis *et al*, 1999) patients. Our data are in agreement with most of the previously published PET studies (Lewis *et al*, 1999; Okubo *et al*, 2000; Trichard *et al*, 1998) where no significant difference in cortical 5-HT<sub>2A</sub> receptor binding was found in schizophrenic patients as compared to healthy controls. The data of Lewis *et al* (1999) were later reanalyzed with a voxel-based approach (Verhoeff *et al*, 2000) that confirmed the outcome of the region-based analysis. In contrast, Ngan *et al* (2000) reported a decreased 5-HT<sub>2A</sub> binding in the frontal cortex of six neuroleptic-naïve schizophrenic subjects, and such a difference was also observed in a recent PET study of six subjects with elevated risk of developing schizophrenia (Hurlemann *et al*, 2005).

Despite some inconsistency in post-mortem data, the majority of post-mortem studies suggest a decreased cortical 5-HT<sub>2A</sub> receptor binding in patients with schizophrenia. This is in contrast to the outcome of most other

*in vivo* studies, including our own. This discrepancy might be caused by the influence of antipsychotic drug treatment and cause of death in the studies of post-mortem brain tissues. Suicide as a cause of death has been associated with increased post-mortem 5-HT<sub>2A</sub> receptor density, especially in younger cohorts (Oquendo *et al*, 2006). At the same time, treatment with antipsychotic drugs that antagonize the 5-HT<sub>2A</sub> receptor decreases levels of expression of the receptor (for a review, see Dean, 2003). These factors are therefore important to take into account when interpreting reports of 5-HT<sub>2A</sub> receptor levels in post-mortem tissue from schizophrenic patients. *In vivo* PET data from antipsychotic-naïve patients are spared from such confounders and might be more reliable in assessing receptor regulations in schizophrenia. On the other hand, autoradiographic post-mortem studies, in contrast to PET imaging, do allow for detection of differences in receptor binding within cortical cell layers. In conclusion, at present no firm conclusions can be made on cortical 5-HT<sub>2A</sub> receptor binding in patients with schizophrenia.

Four of the patients in the present study had prior ( $n = 3$ ) or present ( $n = 1$ ) use of antidepressant medication and one patient had illegal drug use by the time of inclusion. However, a *post hoc* analysis, performed after removing these patients and their controls from the analysis, did not change the results.

In patients with schizophrenia, we found an increased 5-HT<sub>2A</sub> receptor binding in the caudate nucleus, whereas no differences were seen in the thalamus or putamen. Owing to lack of selectivity of the radioligands employed in earlier studies, this is the first study to assess *in vivo* subcortical 5-HT<sub>2A</sub> receptor binding in schizophrenic patients. The 5-HT<sub>2A</sub> receptor density in subcortical brain regions is only modest, and accordingly for those brain regions a larger sample is required to exclude type II errors (Haugbøl *et al*, 2007). Furthermore, no relationship between severity of psychotic symptoms assessed with PANSS and caudate 5-HT<sub>2A</sub> receptor binding could be established. For the above reasons and since no corrections for multiple comparisons were made, we consider our finding of an increased 5-HT<sub>2A</sub> receptor binding in the caudate nucleus in schizophrenic patients as preliminary.

To assess any eventual regional pattern differences in further detail, we also took an additional approach. We and others have observed that cerebral 5-HT<sub>2A</sub> receptor binding displays a high degree of autocorrelation, so that a large fraction of the interindividual variability can be explained by a factor difference. To assess the subcortical binding

**Table 1** Demographic and Scan Data

Parameter	Schizophrenic patients ( $n = 15$ )	Control subjects ( $n = 15$ )	P-value
Age (years)	$27.5 \pm 4.5$	$28.5 \pm 5.7$	NS (0.60)
BMI	$23.7 \pm 2.5$	$23.4 \pm 2.2$	NS (0.77)
Injected dose (MBq)	$271 \pm 45$	$278 \pm 57$	NS (0.70)
Specific activity	$52.0 \pm 36.9$	$52.8 \pm 32.1$	NS (0.95)
Free fraction (%)	$0.36 \pm 0.19$	$0.37 \pm 0.16$	NS (0.94)
Nonspecific binding	$1.6 \pm 0.3$	$1.6 \pm 0.5$	NS (0.83)

BMI = body mass index (body weight (kg)/height<sup>2</sup> (m<sup>2</sup>)).

**Table 2** Partial Volume-Corrected Binding Potentials of the Specific [<sup>18</sup>F]altanserin Binding (BP<sub>P</sub>) in Regions of Interest of Patients and Controls

Region	Schizophrenic patients	Control subjects	P-value
Neocortex	2.8 ± 0.6	2.7 ± 0.9	NS (0.60)
Frontal cortex (total)	2.9 ± 0.6	2.7 ± 0.9	NS (0.51)
Orbitofrontal cortex	2.7 ± 0.6	2.5 ± 0.8	NS (0.44)
Medial inf. frontal cortex	3.0 ± 0.6	2.8 ± 0.9	NS (0.52)
Superior frontal cortex	3.0 ± 0.6	2.8 ± 0.9	NS (0.54)
Anterior cingulate	2.4 ± 0.5	2.2 ± 0.8	NS (0.48)
Posterior cingulate	2.6 ± 0.6	2.3 ± 0.7	NS (0.36)
Insula	2.0 ± 0.4	1.9 ± 0.6	NS (0.47)
Medial inf. temp. cortex	2.6 ± 0.6	2.5 ± 0.8	NS (0.55)
Sup. temp. cortex	2.7 ± 0.5	2.5 ± 0.8	NS (0.45)
Parietal cortex	3.3 ± 0.7	3.1 ± 1.0	NS (0.63)
Sens. mot. cortex	2.8 ± 0.6	2.6 ± 0.8	NS (0.43)
Occipital cortex	2.8 ± 0.6	2.9 ± 0.9	NS (0.75)
Thalamus	0.6 ± 0.1	0.5 ± 0.2	NS (0.15)
Putamen	0.7 ± 0.2	0.6 ± 0.3	NS (0.37)
Caudate	0.7 ± 0.1	0.5 ± 0.3	0.02

relative to the cortical binding, we normalized the subcortical regions with a volume-weighted average of cortical BP<sub>P</sub> and evaluated the within-group difference. Using these normalized values, the difference in caudate values turned out to be even more significant ( $p = 0.001$ ).

If confirmed, an increase in 5-HT<sub>2A</sub> receptor levels in schizophrenic patients could support a direct role of blockade of striatal 5-HT<sub>2A</sub> receptors in the mechanisms of action of a number of second-generation antipsychotics—in addition to the assumed indirect effects via modulation of cortical as well as striatal dopamine activity by 5-HT<sub>2A</sub> receptor blockade (Glenthøj *et al*, 1999; Meltzer *et al*, 2003; Svensson *et al*, 1995). An independent role of 5-HT<sub>2A</sub> receptor blockade in the mechanisms of action of second-generation antipsychotics is also supported by data demonstrating an association between polymorphisms in the promoter and coding regions of the 5-HT<sub>2A</sub> receptor gene and schizophrenia and/or the response to treatment with clozapine (Abdolmaleky *et al*, 2004; Arranz *et al*, 1998a, b; Masellis *et al*, 1998). Furthermore, second-generation antipsychotics are also effective as an add-on to treatment with selective serotonin reuptake inhibitors in patients with obsessive-compulsive disorder (Denys *et al*, 2007; Skapinakis *et al*, 2007), and we have previously found increased 5-HT<sub>2A</sub> receptor binding in the caudate nuclei of patients with this disease (Adams *et al*, 2005). The finding of increased 5-HT<sub>2A</sub> receptor binding in the caudate nuclei in patients with obsessive-compulsive disorder as well as in patients with schizophrenia may suggest a common pathophysiological mechanism in agreement with the frequent occurrence of obsessive-compulsive symptoms in schizophrenic patients (Kayahan *et al*, 2005a, b). If an increase in striatal 5-HT<sub>2A</sub> receptor binding is confirmed, the effects could still, however, be mediated through interactions with the dopaminergic system.

An increased 5-HT<sub>2A</sub> receptor binding in the caudate nucleus, as suggested by the preliminary data in the present

study, might alternatively result from a compensatory upregulation of 5-HT<sub>2A</sub> receptors in response to altered serotonin levels. In addition, a defect in the medial raphe-cortico-striatal serotonergic circuit has been suggested to result in disinhibition of the mesolimbic DA system, a mechanism likewise suspected to play an important role in the pathophysiology of schizophrenia (Abi-Dargham *et al*, 1997). Because of a paradoxical regulation of the serotonin 5-HT<sub>2A</sub> receptor (Gray and Roth, 2001), antagonism would lead to downregulation of the receptor, thereby normalizing its levels. The changes in striatal 5-HT<sub>2A</sub> receptor density in schizophrenia are in accordance with the post-mortem findings by Joyce *et al* (1993). By contrast, Matsumoto *et al* (2005) did not find differences in striatal 5-HT<sub>2A</sub> receptor density between schizophrenic subjects and controls; likewise, no change in striatal 5-HT<sub>2A</sub> receptor binding was seen in a smaller study of six subjects at risk of schizophrenia (Hurlemann *et al*, 2005).

## CONCLUSION

The present study is the first PET study exploring striatal as well as cortical 5-HT<sub>2A</sub> receptor binding in first-episode antipsychotic-naïve schizophrenic patients. It is also the largest *in vivo* study on 5-HT<sub>2A</sub> receptors in those patients until now. We find no difference in the cortical regions or in the thalamus or putamen between the two groups, whereas an increased 5-HT<sub>2A</sub> receptor binding is detected in the caudate nucleus in 15 first-episode antipsychotic-naïve schizophrenic patients when compared to age- and gender-matched healthy control subjects. This supports a direct or an indirect role of striatal 5-HT<sub>2A</sub> receptors in the pathophysiology of schizophrenia and in the mechanisms of action of many atypical antipsychotics. Further studies are, however, needed to explore the relation of subcortical and cortical 5-HT<sub>2A</sub> receptor activity to psychopathology, information processing, and other neurobiological measures.

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## DISCLOSURE/FINANCIAL SUPPORT FOR THE STUDY

The authors have nothing further to disclose.

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