

Brain Serotonin 5-HT_{1A} Receptor Binding in Schizophrenia Measured by Positron Emission Tomography and [¹¹C]WAY-100635

Johannes Tauscher, MD; Shitij Kapur, MD, PhD, FRCPC; N. Paul L. G. Verhoeff, MD, PhD, FRCPC; Douglas F. Hussey, BSc; Zafiris J. Daskalakis, MD, FRCPC; Sitra Tauscher-Wisniewski, MD; Alan A. Wilson, PhD; Sylvain Houle, MD, PhD, FRCPC; Siegfried Kasper, MD; Robert B. Zipursky, MD, FRCPC

Background: Results of postmortem studies show an elevation in serotonin-1A (5-hydroxytryptamine-1A [5-HT_{1A}]) receptor density in the prefrontal and temporal cortices of patients with schizophrenia. This study examined 5-HT_{1A} receptors in vivo in patients with schizophrenia using positron emission tomography and [carbonyl-¹¹C]-N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide ([¹¹C]WAY-100635).

Methods: The 5-HT_{1A} binding potential of 14 antipsychotic drug-naïve patients with a DSM-IV diagnosis of schizophrenia was compared with that of 14 age-matched healthy controls. Positron emission tomography data were analyzed using 9 cortical regions of interest, which were delineated on a coregistered magnetic resonance image and transferred to the positron emission tomographic image, with the cerebellum as the reference region for a simplified reference tissue model. We also performed a voxel-wise comparison using statistical parametric mapping.

Results: The region of interest-based analysis revealed a significant mean ± SD cortical 5-HT_{1A} receptor binding potential increase of 7.1% ± 6.4% in patients with schizophrenia (F = 2.975; P = .02); local differences were +20% in the left medial temporal cortex (F = 9.339; P = .005) and +13% in the right mediotemporal cortex (F = 4.453; P = .045). There were no significant differences in regional tracer delivery or cerebellar [¹¹C]WAY-100635 uptake. The voxel-based analysis also confirmed a group difference in the left medial temporal cortex.

Conclusions: The biological significance of elevated 5-HT_{1A} receptor density in schizophrenia remains unclear. Given the location of 5-HT_{1A} receptors on pyramidal cells, this elevation may reflect an abnormal glutamatergic network. Our finding needs to be viewed in light of preclinical evidence supporting a role for 5-HT_{1A} receptors in mediating antipsychotic action and extrapyramidal adverse effects of drugs.

Arch Gen Psychiatry. 2002;59:514-520

From the PET Centre (Drs Tauscher, Kapur, Verhoeff, Wilson, and Houle and Mr Hussey) and the Schizophrenia and Continuing Care Program (Drs Daskalakis, Tauscher-Wisniewski, and Zipursky), Centre for Addiction and Mental Health and the Department of Psychiatry, University of Toronto (Drs Kapur, Verhoeff, Daskalakis, Tauscher-Wisniewski, Wilson, Houle and Zipursky), Toronto Ontario; and the Department of General Psychiatry, University of Vienna, Vienna, Austria (Drs Tauscher and Kasper).

THERE IS CONSIDERABLE evidence for a role of the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) in the pathophysiologic characteristics of schizophrenia.¹⁻³ Recent interest in 5-HT has been fueled by the fact that novel antipsychotic drugs such as clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone hydrochloride are potent 5-HT_{2A} receptor antagonists and relatively weaker dopamine D₂ antagonists.⁴ In addition, 5-HT_{1A} and 5-HT_{2C} receptors seem to contribute to the clinical effects of some novel antipsychotic drugs.⁵

Results of most postmortem studies⁶⁻¹⁴ show a pronounced elevation of 20% to 79% in cortical 5-HT_{1A} receptor density in schizophrenia using [³H]-8-OH-DPAT or [³H]WAY-100635 as ligands. Human au-

toradiographic findings¹³ revealed the highest density of 5-HT_{1A} receptors in the temporolimbic cortex, followed by brainstem raphe nuclei, the frontal cortex, and other neocortical regions, with very low or undetectable levels in the cerebellum. The brainstem receptors are somatodendritic autoreceptors, whereas the cortical receptors are mainly postsynaptic. Cortical 5-HT_{1A} receptors exert inhibitory control over striatal glutamate release, and 5-HT_{1A} antagonists increase glutamate release in the striatum via corticostriatal efferents.¹⁵ In addition, 5-HT_{1A} agonists increase the outflow of dopamine in the prefrontal cortex, without a similar change in striatal dopamine release.¹⁶ Stimulation of 5-HT_{1A} receptors seems to produce many of the same effects as antagonism of 5-HT_{2A} receptors.⁵

PARTICIPANTS AND METHODS

PARTICIPANTS

Fourteen right-handed patients (6 women and 8 men; mean age, 26 years; age range, 22-37 years) with a *DSM-IV* diagnosis of schizophrenia were included in the study. Each patient experienced a first psychotic episode, had not received any psychotropic medication except for benzodiazepines within 1 month of the PET scan, and had never been treated with an antipsychotic agent. Patients were recruited from the Schizophrenia and Continuing Care Program of the Centre for Addiction and Mental Health, where they had been evaluated as either inpatients or outpatients. The diagnosis of schizophrenia was ascertained using a Structured Clinical Interview for *DSM-IV*,²⁷ which was performed by an experienced psychiatrist (J.T., N.P.L.G.V., Z.J.D., or S.T.-W.).

Fourteen age-matched individuals (8 women and 6 men; mean age, 28 years; age range, 19-36 years) comprised the control group. These 14 controls were recruited from the community by advertisements and were part of a bigger pool of healthy individuals described in an earlier [¹¹C]WAY-100635 PET study.²³

Patients were excluded from the study if they experienced a serious medical or neurologic illness, had a significant head injury, or were pregnant. Furthermore, exclusion criteria for control subjects were any Axis I psychiatric diagnosis as confirmed by the Structured Clinical Interview for *DSM-IV*, nonpatient edition,²⁸ or treatment with psychotropic medications within 3 months of the study.

All patients gave written consent after the procedure had been fully explained. The study and recruitment procedures were approved by the research ethics board of the Centre for Addiction and Mental Health and the Department of Psychiatry, University of Toronto.

IMAGE ACQUISITION AND ANALYSES

The selective 5-HT_{1A} receptor antagonist [¹¹C]WAY-100635 was synthesized according to modifications of

the McCarron method²⁹ using a short fluorocarbon resin tube loosely packed with polypropylene wool as a substitute for the narrow polypropylene tubing originally used.³⁰ This procedure yielded syntheses with high purity (>95%) and average specific activity of 47 GBq/μM (1270 mCi/μM) at the time of injection.

Positron emission tomographic images were obtained during 60 minutes using a GEMS PC2048-15B camera (General Electric Medical Systems, Milwaukee, Wis) in 15 one-minute frames followed by another 9 five-minute frames after bolus injection of a mean ± SD of 9.8 ± 0.6 mCi (363 ± 22 MBq) of [¹¹C]WAY-100635. The images were corrected for attenuation with a ⁶⁸Ge transmission scan and were reconstructed using filtered back projection (Hanning filter, 5 mm full-width at half maximum), and 15 axial slices, each 6.5-mm thick, were obtained.

For the quantification of 5-HT_{1A} receptor binding in human brain, 2 approaches were used: one based on predefined regions of interest (ROIs) and the other a voxel-wise analysis.

Each participant underwent magnetic resonance imaging (MRI) (GE Signa 1.5-T scanner; spin-echo sequence T1- and proton density-weighted images; and x, y, and z voxel dimensions 0.78, 0.78, and 3.00 mm, respectively). The MRIs were coregistered to each PET image by using RView8/mp software.³¹ For ROI analysis, brain regions were delineated on the coregistered MRI using previously defined landmarks.³² Anatomic ROIs were drawn bilaterally in the dorsolateral prefrontal (DLPFC), anterior cingulate (ACC), medial temporal (MTC), lateral temporal (LTC), and parietal cortices and in the cerebellum by an operator masked to the condition. The gray matter of the cerebellum was delineated on consecutive slices where the middle cerebellar peduncle was clearly visible. The DLPFC was delineated on axial MRI slices in which the caudate, putamen, and globus pallidus were all clearly visualized. The ACC was delineated on the same slices and identified as a gray matter structure on both sides of the interhemispheric fissure extending posterior to the anterior

Continued on next page

Earlier efforts to quantitatively analyze 5-HT_{1A} receptors using the agonist ligand 8-OH-DPAT were hampered by the fact that it labels 5-HT_{1A} receptors only in their high-affinity state. This problem has recently been overcome by the discovery of WAY-100635, a selective high-affinity (K_d < 1 nM) 5-HT_{1A} antagonist, which labels both low- and high-affinity receptors.¹⁷ WAY-100635 has been labeled at the [carbonyl-¹¹C] position¹⁸ and can be used for the quantitative analysis of binding to 5-HT_{1A} receptors in humans.¹⁹ Using [carbonyl-¹¹C]-N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl) cyclohexane carboxamide ([¹¹C]WAY-100635) and positron emission tomography (PET), cortical 5-HT_{1A} binding can be quantitatively analyzed using the cerebellum as an input function of a simplified reference tissue model (SRTM).^{20,21} Using this method, an age-dependent decline in cortical 5-HT_{1A} receptor binding potential²² (BP) in healthy volunteers was recently demonstrated,²³ consistent with findings from postmor-

tem studies,²⁴⁻²⁶ which showed a decline in 5-HT_{1A} receptor numbers with age.

We present a PET study in 14 neuroleptic drug-naïve patients with a *DSM-IV* diagnosis of schizophrenia who experienced a first psychotic episode. On the basis of human postmortem studies, we hypothesized that in vivo 5-HT_{1A} receptor BP as measured with [carbonyl-¹¹C]WAY-100635 and PET is higher in the frontal and temporal cortices of patients with schizophrenia compared with an age-matched control group.

RESULTS

The mean ± SD age of patients and controls was 26 ± 5 years and 28 ± 5 years, respectively. There was no significant difference in age between groups (*t*₂₆ = 1.071; *P* = .29).

The ROI-based analysis revealed a mean ± SD 5-HT_{1A} receptor BP increase of 7.1% ± 6.4% in patients with schizo-

genu of the corpus callosum. The MTC was delineated as a mediotemporal gray matter region corresponding to the hippocampus, amygdaloid nucleus, and parahippocampal gyrus. The LTC included temporal gray matter located laterally starting with the same slice, where the MTC was delineated, and extending superior to slices in which the caudate, putamen, and globus pallidus were clearly visualized. The parietal cortex was delineated on 3 slices corresponding to the inferior parietal lobule extending anterior to the postcentral sulcus.

Decay-corrected time-activity curves (TACs) were obtained for each ROI using the 60 minutes of the data acquisition period because 60-minute TACs in the SRTM yielded test-retest agreement comparable to 90-minute TACs.^{23,33} Because we were scanning acutely psychotic patients, we tried to keep the scanning time as brief as possible.

Regional BP²² values were calculated as an estimate of 5-HT_{1A} receptor number in each ROI using the kinetic modeling tool of PMOD Medical Imaging Software (version 2.20).³⁴ To obtain BP values, the cerebellum was used as the reference region for an SRTM.²⁰

For the voxel-wise analysis, parametric 5-HT_{1A} receptor BP images were generated using the SRTM with PMOD. Parametric images were then spatially normalized within the standard Montreal Neurologic Institute brain space using Statistical Parametric Mapping version 99 (SPM99)³⁵ and a ligand-specific template.³⁶

STATISTICAL ANALYSIS

Statistical analyses of the ROI data were performed using SPSS for Windows 10.0.0 (SPSS Inc, Chicago, Ill). Parametric statistical analyses were applied after it had been assured that skewness, kurtosis, outliers, and homogeneity of variance of our data met the criteria for a normal distribution.³⁷ In a first step, all regions were pooled together to estimate the mean cortical 5-HT_{1A} receptor BP of each group. To test the hypothesis that 5-HT_{1A} receptor BP is elevated in the frontal and temporal cortices of patients with schizophrenia, regional BP values of patients and controls were compared using

multivariate analysis of covariance, with all regional BP values as dependent variables, group (patients vs controls) as a fixed factor, and age as a covariate. Multiplying the area of each ROI by the number of slices and their respective thickness of 6.5 mm provided an approximation for the actual volume of interest (VOI). Additional separate multivariate analyses of variance were performed to compare the VOI and R₁ values between groups. R₁ is the ratio of tracer delivery to the tissue of interest (K) relative to the reference tissue (K'), and it can be described by the following equation: $R_1 = K/K'$. To compare the uptake in the cerebellum between patients and controls, an analysis of variance was performed, with the area under the curve of the cerebellar TAC as the dependent variable. For the ROI analysis, an α level of $P < .05$ was considered significant, and all tests were 2-tailed. For the post hoc tests, a Bonferroni correction for multiple comparisons was performed using 9 as the denominator because we compared [¹¹C]WAY-100635 binding indices between patients and controls in 9 different cortical regions.

Potential correlations between age and the measured activity in the cerebellar ROI, between age and ROI size or regional BP values, and between each ROI BP value and its respective area were examined using 2-tailed Pearson product moment correlation coefficients. In addition, Pearson product moment correlation coefficients were calculated to reveal possible correlations between 5-HT_{1A} receptor BP in patients and duration of untreated psychosis or severity of illness as measured using the Positive and Negative Syndrome Scale for schizophrenia.³⁸

For the voxel-by-voxel analysis, statistical parametric maps were generated using SPM99. To test whether the measured 5-HT_{1A} receptor BP differed between patients and controls in any given voxel, 2-tailed *t* tests were applied. Results were displayed as statistical parametric maps using an uncorrected height threshold of $P < .01$ (*t* test, > 2.48). We applied 2 contrasts (patient 5-HT_{1A} BP higher than that of controls and vice versa) to a search volume of 93,209 voxels, each with a size of $2 \times 2 \times 2$ mm.

phrenia across all 9 cortical ROIs (**Figure 1** and **Figure 2**). A multivariate analysis of covariance revealed a significant group effect (patients vs controls) on the BP values measured in 9 cortical ROIs ($F_{9,17} = 2.975$; $P = .02$), but neither a significant effect of age ($F_{9,17} = 0.814$; $P = .61$) nor a significant age \times group interaction ($F_{18,36} = 1.716$; $P = .08$) was found. Post hoc tests of between-subject effects revealed that 5-HT_{1A} receptor BP values of patients were significantly higher in the left MTC ($F_1 = 9.339$; $P = .005$) and the right MTC ($F_1 = 4.453$; $P = .045$) (**Table**). There were no significant differences in BP values in any other ROI. Only the result in the left MTC survived a Bonferroni correction for multiple comparisons (corrected $P = .045$).

A multivariate analysis of variance revealed no significant group differences in regional tracer delivery (R₁) between patients and controls ($F_{9,18} = 1.427$; $P = .25$). Mean VOI values were 23 mL for the cerebellum, 21 mL for the left PFC, 22 mL for the right PFC,

15 mL for the ACC, 12 mL for the left temporal cortex, 12 mL for the right temporal cortex, 4 mL for the left MTC, 4 mL for the right MTC, 26 mL for the left parietal cortex, and 27 mL for the right parietal cortex. There was no significant difference in VOIs between patients and controls ($F_{10,17} = 0.882$; $P = .57$). Furthermore, there was no significant difference in the area under the curve of the cerebellar TAC between groups ($F_1 = 0.194$; $P = .66$) (**Figure 3**).

Pearson correlation coefficients (*r*) did not reveal any significant correlation between age and the area under the curve of the cerebellum or BP in any cortical ROI, between age and VOI, or between regional BP values and their respective VOIs. Furthermore, there was no significant correlation between MTC 5-HT_{1A} receptor BP and duration of untreated psychosis in patients (left MTC: $r = 0.06$; $P = .84$; right MTC: $r = -0.18$; $P = .57$). Binding potential values were not significantly correlated to severity of illness as measured using the Posi-

tive and Negative Syndrome Scale for schizophrenia sum, positive, negative, and general scores, with $r=0.05$ to 0.37 and the corresponding $P=.41$ to $.92$.

The voxel-wise analysis produced no robust evidence for a pronounced elevation in [^{11}C]WAY-100635 uptake in the prefrontal or temporal cortex in schizophrenia. Statistical parametric mapping showed only one activity cluster denoting higher [^{11}C]WAY-100635 uptake in patients with schizophrenia, consisting of 86 voxels extending laterally from the Montreal Neurologic Institute brain space coordinates -16 , -6 , and -40 mm (x , y , and z , respectively), with $z=2.99$ and $P_{26}=.001$. Plotting this activity cluster on an averaged composite MRI of all patients, which had been normalized to the Montreal Neurologic Institute brain space, revealed a region in the left MTC similar to the one in which we found the most pronounced difference between patients and controls with the ROI-based approach (**Figure 4**).

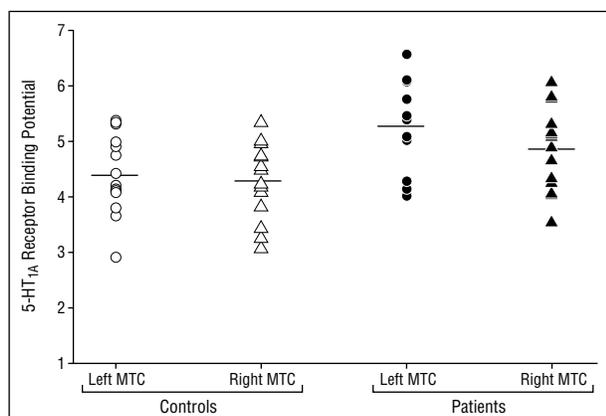


Figure 1. Serotonin-1A (5-hydroxytryptamine [5-HT_{1A}]) receptor binding potential values in 14 patients with schizophrenia and 14 healthy controls in the mediotemporal cortex (MTC). Horizontal lines indicate means.

The main finding of this in vivo PET study was an increase in cortical 5-HT_{1A} receptor BP in schizophrenia. The most pronounced difference between patients and controls was a 20% increase in [^{11}C]WAY-100635 binding in the left MTC of patients with schizophrenia found by ROI-based PET analysis, which was confirmed by an additional voxel-wise analysis using SPM99.

This in vivo PET study of 5-HT_{1A} receptors in schizophrenia did not detect a significant elevation in [^{11}C]WAY-100635 binding in the prefrontal cortex of patients, which is in contrast to results of postmortem studies⁶⁻¹³ showing a 20% to 79% elevation in 5-HT_{1A} receptor number in that region.

Postmortem studies have several limitations. All patients in the postmortem studies had received several years of antipsychotic drug treatment, and all patients except 5 in the study by Hashimoto et al⁶ were receiving antipsychotic agents at the time of death. In contrast, all patients in our study were antipsychotic drug naive. Hence, the more pronounced increase in postmortem 5-HT_{1A} receptors could be an effect of long-term drug treatment.

In contrast to the postmortem studies with an average illness duration of approximately 20 years, our sample consisted of first-episode patients with a mean \pm SD duration of untreated psychosis of 21 ± 18 months (range, 7 months to 5 years). Owing to this relatively restricted range, we were not able to systematically investigate the effects of disease progression.

For tracer kinetic modeling, we used the cerebellum as the reference region for an SRTM because the cerebellum is relatively devoid of 5-HT_{1A} receptors.¹³ Furthermore, the SRTM proved to be more reliable than kinetic modeling using arterial data²¹ and provided excellent test-retest reproducibility with [^{11}C]WAY-

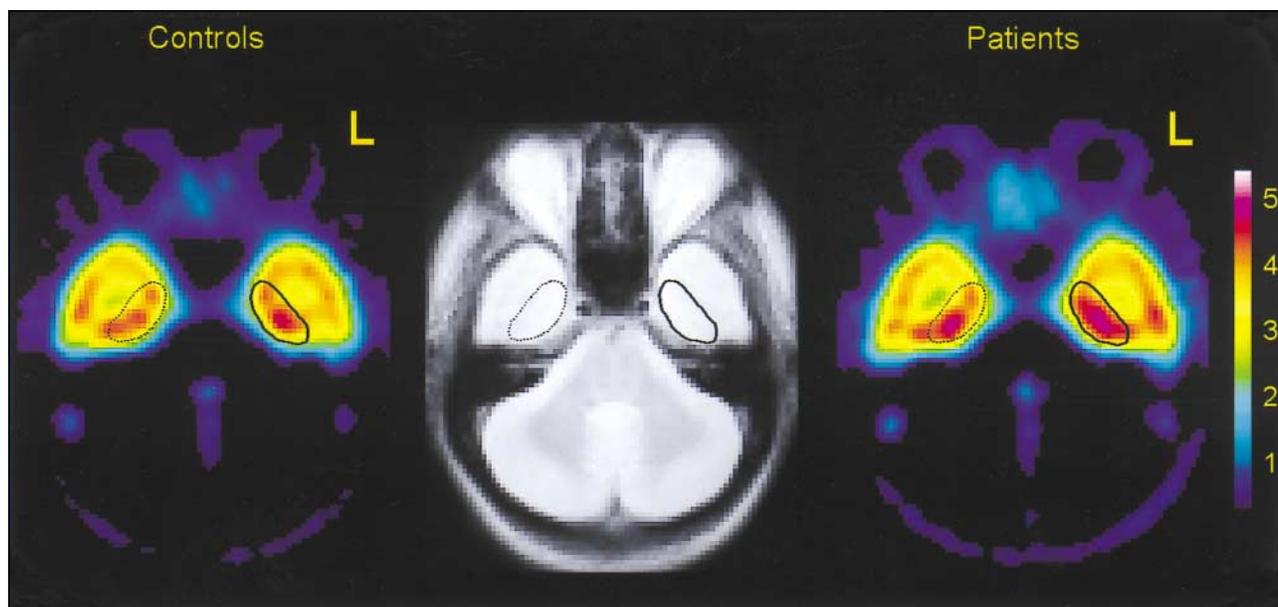


Figure 2. Composite mean serotonin-1A (5-hydroxytryptamine) receptor binding potential images of 14 healthy controls and 14 age-matched patients with schizophrenia indicating higher binding potential values in the left and right mediotemporal regions of interest. Mean binding potential images and magnetic resonance images had been spatially normalized to the Montreal Neurologic Institute brain space. The axial slice is 40 mm below the anterior commissure–posterior commissure line, in the plane where Statistical Parametric Mapping version 99 indicated the most pronounced group difference.

5-HT_{1A} Receptor Binding Potentials for the 9 Regions of Interest*

Region	5-HT _{1A} Binding Potential, Mean ± SD		Difference, %†	MANOVA	
	Controls	Patients		F Test	P Value‡
Left prefrontal cortex	3.20 ± 0.43	3.34 ± 0.50	4	0.651	.43
Right prefrontal cortex	3.18 ± 0.42	3.33 ± 0.58	5	0.639	.43
Anterior cingulate cortex	3.91 ± 0.47	4.15 ± 0.65	6	1.197	.28
Left lateral temporal cortex	4.04 ± 0.53	4.14 ± 0.68	2	0.153	.70
Right lateral temporal cortex	4.16 ± 0.61	4.10 ± 0.66	-2	0.072	.79
Left medial temporal cortex	4.39 ± 0.68	5.26 ± 0.83	20	9.339	.005
Right medial temporal cortex	4.28 ± 0.69	4.86 ± 0.75	13	4.453	.04
Left parietal cortex	3.12 ± 0.48	3.35 ± 0.47	7	1.624	.21
Right parietal cortex	3.12 ± 0.44	3.25 ± 0.59	4	0.445	.51

*5-HT_{1A} indicates serotonin 5-hydroxytryptamine 1A; MANOVA, multivariate analysis of variance.

†(Patients – Controls)/Controls.

‡df = 1.

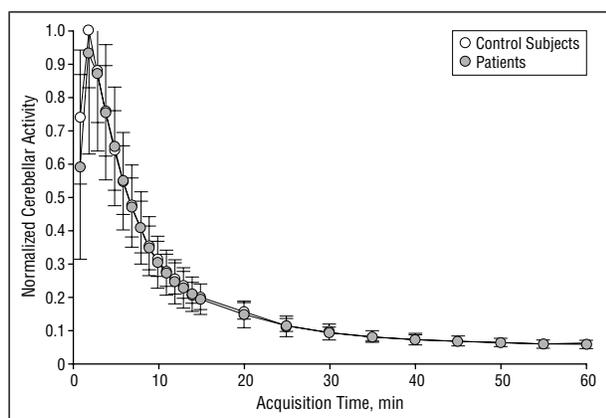


Figure 3. Decay-corrected cerebellar time-activity curves normalized to their peak values for 14 healthy control subjects and 14 patients with schizophrenia. Error bars represent 1 SD.

100635.^{21,23} A test-retest study in 6 control subjects provided strong evidence that we would be able to correctly identify a group difference of 20% to 79% with acceptable sensitivity.²³ Sixty- and 90-minute TACs gave comparable results. With 60-minute TACs, the magnitude of the mean error between 2 [carbonyl-¹¹C]WAY-100635 PET scans of the same individual ranged from 2% to 7% in cortical ROIs.²³

Most postmortem studies selected limited and often arbitrary brain regions to study. Only 2 groups^{6,7,12} studied samples from all cortical regions. All others investigated only the prefrontal cortex^{9-11,13} or the prefrontal and temporal cortices.⁸ Although all of the postmortem studies report “prefrontal” increases, the data came from Brodmann areas (BAs) 9⁸; 10⁶; 11 and 12⁹; 24, 9a, and 44¹²; or 46.^{10,13} To avoid an unjustified restriction to frontal brain areas, we analyzed 5-HT_{1A} receptor BP in cortical ROIs drawn in the DLPFC, ACC, MTC, LTC, and parietal cortex. However, we are aware of several limitations inherent to the ROI approach. The intrinsic spatial resolution of our PET camera is 4.5 to 5.5 mm in the transaxial plane. Therefore, we chose to delineate rather large areas comprising several BAs. In the case of the DLPFC, this ROI roughly corresponds to portions of BAs 9, 10, and 46, whereas in case of the ACC,

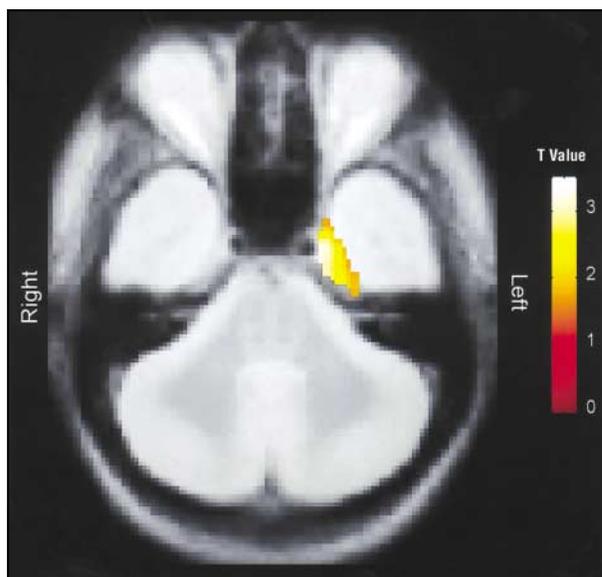


Figure 4. Activity cluster where Statistical Parametric Mapping version 99 displayed a statistically significant ($P < .01$) higher [carbonyl-¹¹C]-N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide uptake in patients with schizophrenia plotted on a composite magnetic resonance image that had been normalized to the Montreal Neurologic Institute brain space.

we tried to confine this ROI to BA 32 and frontal parts of BA 24.

The process of coregistering introduces another source of error, which also contributes to the anatomic inaccuracy of the ROI approach. Moreover, if any given pathologic condition afflicts only parts of an ROI, a possible BP increase or decrease will be diluted, and, therefore, the chance to miss a group difference is high. On these grounds we chose to corroborate the results of the ROI analysis by applying an additional voxel-wise SPM99 analysis. Because of the restricted field of view of our PET camera (15 slices of 6.5 mm each, which translates into 9.75 cm with regard to the z-axis), even the voxel-wise approach cannot be considered to cover the entire brain. Nevertheless, SPM99 revealed an elevated 5-HT_{1A} receptor BP in the left MTC of patients, confirming the strongest result of the ROI-based approach.

We matched our control group for age but not for sex because it had been shown post mortem and in vivo using PET and [¹¹C]WAY-100635 that 5-HT_{1A} density declines with age, whereas in both studies sex did not significantly affect 5-HT_{1A} receptor BP.^{23,24}

Based on the results of postmortem studies, we expected at least a 25% BP elevation in the frontal cortices of patients in vivo. Using values from controls (mean ± SD frontal BP, 3.2 ± 0.4), we estimated that our study had a power of 0.98 (1 - β) to detect a 25% elevation in frontal 5-HT_{1A} receptor BP in patients at α < .05. However, this study did not reveal such an elevation in frontal brain regions. On the other hand, to decide whether the 4% to 5% "nonsignificant" difference reported in the DLPFC is truly within chance or due to a type II error, we would have to increase our sample size 10-fold, which is not feasible because of practical limitations.

There is preclinical evidence^{39,40} to support a role for 5-HT_{1A} agonism in the antipsychotic action and extrapyramidal adverse effects of drugs. The 5-HT_{1A} agonist 8-OH-DPAT enhanced the antipsychotic-like effect of the D₂/D₃ antagonists raclopride⁴¹ and haloperidol⁴² and antagonized the catalepsy induced by the D₁ agonist SCH23390 in rats.⁴³ Several atypical antipsychotic drugs are partial agonists at the 5-HT_{1A} receptor, including clozapine, ziprasidone, quetiapine, and tiopirone hydrochloride. Clinical studies of adding 5-HT_{1A} partial agonists may help to clarify the possible importance of 5-HT_{1A} agonism in the treatment of schizophrenia.

The biological significance of elevated 5-HT_{1A} receptor numbers in schizophrenia as indicated by several postmortem studies and this in vivo PET study remains unclear. It has been suggested that given the location of most of the 5-HT_{1A} receptors on pyramidal cells, it may reflect an abnormal glutamatergic network.⁴⁴ Although we did not confirm a pronounced 5-HT_{1A} receptor elevation in frontal cortices of patients, the ROI-based approach demonstrated a 20% higher 5-HT_{1A} receptor BP in the left MTC and a 13% elevation in the right MTC. Underlining the robustness of the result in the left MTC was the fact that it survived a correction for multiple comparisons in 9 cortical ROIs and was confirmed using a voxel-wise analysis with SPM99. The left temporal cortex is an anatomic region known to be afflicted in schizophrenia,⁴⁵ but the significance and functional relevance of our finding of locally elevated [¹¹C]WAY-100635 uptake in patients with schizophrenia remains unclear and warrants replication in the future.

Submitted for publication February 26, 2001; final revision received August 16, 2001; accepted September 11, 2001.

This research was supported by the EJLB Foundation (Montreal, Quebec) and the Austrian Research Fund (Vienna).

We thank all patients and healthy volunteers for their participation; Corey Jones, BSc, Kevin Cheung, Alex Kecojevic, HBSc, Li Jin, and Armando Garcia for technical assistance; and Barb Brownlee, MSc, for proofreading.

Corresponding author and reprints: Johannes Tauscher, MD, Department of General Psychiatry, University of

Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria (e-mail: johannes.tauscher@akh-wien.ac.at).

REFERENCES

- Breier A. Serotonin, schizophrenia and antipsychotic drug action. *Schizophr Res*. 1995;14:187-202.
- Huttunen M. The evolution of the serotonin-dopamine antagonist concept. *J Clin Psychopharmacol*. 1995;15(suppl 1):4S-10S.
- Iqbal N, van Praag HM. The role of serotonin in schizophrenia. *Eur Neuropsychopharmacol*. 1995;5(suppl):11-23.
- Schotte A, Janssen PF, Gommeren W, Luyten WH, Van Gompel P, Lesage AS, De Loore K, Leysen JE. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. *Psychopharmacology (Berl)*. 1996;124:57-73.
- Meltzer HY. The role of serotonin in antipsychotic drug action. *Neuropsychopharmacology*. 1999;21(suppl 2):106S-115S.
- Hashimoto T, Nishino N, Nakai H, Tanaka C. Increase in serotonin 5-HT_{1A} receptors in prefrontal and temporal cortices of brains from patients with chronic schizophrenia. *Life Sci*. 1991;48:355-363.
- Hashimoto T, Kitamura N, Kajimoto Y, Shirai Y, Shirakawa O, Mita T, Nishino N, Tanaka C. Differential changes in serotonin 5-HT_{1A} and 5-HT₂ receptor binding in patients with chronic schizophrenia. *Psychopharmacology (Berl)*. 1993;112(suppl):S35-S39.
- Joyce JN, Shane A, Lexow N, Winokur A, Casanova MF, Kleinman JE. Serotonin uptake sites and serotonin receptors are altered in the limbic system of schizophrenics. *Neuropsychopharmacology*. 1993;8:315-336.
- Simpson MD, Lubman DI, Slater P, Deakin JF. Autoradiography with [³H]8-OH-DPAT reveals increases in 5-HT(1A) receptors in ventral prefrontal cortex in schizophrenia. *Biol Psychiatry*. 1996;39:919-928.
- Burnet PW, Eastwood SL, Harrison PJ. 5-HT_{1A} and 5-HT_{2A} receptor mRNAs and binding site densities are differentially altered in schizophrenia. *Neuropsychopharmacology*. 1996;15:442-455.
- Sumiyoshi T, Stockmeier CA, Overholser JC, Dilley GE, Meltzer HY. Serotonin_{1A} receptors are increased in postmortem prefrontal cortex in schizophrenia. *Brain Res*. 1996;708:209-214.
- Gurevich EV, Joyce JN. Alterations in the cortical serotonergic system in schizophrenia: a postmortem study. *Biol Psychiatry*. 1997;42:529-545.
- Burnet PW, Eastwood SL, Harrison PJ. [³H]WAY-100635 for 5-HT_{1A} receptor autoradiography in human brain: a comparison with [³H]8-OH-DPAT and demonstration of increased binding in the frontal cortex in schizophrenia. *Neurochem Int*. 1997;30:565-574.
- Dean B, Tomaskovic-Crook E, Opekin K, Keks N, Copolov D. No change in the density of the serotonin_{1A} receptor, the serotonin₄ receptor or the serotonin transporter in the dorsolateral prefrontal cortex from subjects with schizophrenia. *Neurochem Int*. 1999;34:109-115.
- Dijk SN, Francis PT, Stratmann GC, Bowen DM. NMDA-induced glutamate and aspartate release from rat cortical pyramidal neurones: evidence for modulation by a 5-HT_{1A} antagonist. *Br J Pharmacol*. 1995;115:1169-1174.
- Wedzony K, Mackowiak M, Fijal K, Golembiowska K. Ipsipirone enhances the dopamine outflow via 5-HT_{1A} receptors in the rat prefrontal cortex. *Eur J Pharmacol*. 1996;305:73-78.
- Fletcher A, Cliffe IA, Dourish CT. Silent 5-HT_{1A} receptor antagonists: utility as research tools and therapeutic agents. *Trends Pharmacol Sci*. 1993;14:41-48.
- Farde L, Ginovart N, Ito H, Lundkvist C, Pike VW, McCarron JA, Halldin C. PET-characterization of [carbonyl-¹¹C]WAY-100635 binding to 5-HT_{1A} receptors in the primate brain. *Psychopharmacology (Berl)*. 1997;133:196-202.
- Farde L, Ito H, Swahn CG, Pike VW, Halldin C. Quantitative analyses of carbonyl-carbon-11-WAY-100635 binding to central 5-hydroxytryptamine-1A receptors in man. *J Nucl Med*. 1998;39:1965-1971.
- Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. *Neuroimage*. 1996;4:153-158.
- Gunn RN, Sargent PA, Bench CJ, Rabiner EA, Osman S, Pike VW, Hume SP, Grasby PM, Lammertsma AA. Tracer kinetic modeling of the 5-HT_{1A} receptor ligand [carbonyl-¹¹C]WAY-100635 for PET. *Neuroimage*. 1998;8:426-440.
- Mintun MA, Raichle ME, Kilbourn MR, Wooten GF, Welch MJ. A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann Neurol*. 1984;15:217-227.
- Tauscher J, Verhoeff NPLG, Christensen BK, Hussey D, Meyer JH, Kecojevic A, Javanmard M, Kasper S, Kapur S. Serotonin 5-HT_{1A} receptor binding potential declines with age as measured by [¹¹C]WAY-100635 and PET. *Neuropsychopharmacology*. 2001;24:522-530.
- Dillon KA, Gross-Isseroff R, Israeli M, Biegon A. Autoradiographic analysis of

- serotonin 5-HT_{1A} receptor binding in the human brain postmortem: effects of age and alcohol. *Brain Res.* 1991;554:56-64.
25. Lowther S, De Paermentier F, Cheetham SC, Crompton MR, Katona CL, Horton RW. 5-HT_{1A} receptor binding sites in post-mortem brain samples from depressed suicides and controls. *J Affect Disord.* 1997;42:199-207.
 26. Matsubara S, Arora RC, Meltzer HY. Serotonergic measures in suicide brain: 5-HT_{1A} binding sites in frontal cortex of suicide victims. *J Neural Transm Gen Sect.* 1991; 85:181-194.
 27. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition, SCID-I/P, Version 2.0 Ed.* New York: Biometric Research Department, New York State Psychiatric Institute; 1996.
 28. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders—Non-Patient Edition, SCID-I/NP, Version 2.0-4/97 Revision Ed.* Biometric Research Department, New York: New York State Psychiatric Institute; 1997.
 29. McCarron JA, Turton DR, Pike VW, Poole KG. Remotely controlled production of the 5-HT_{1A} receptor radioligand, [carbonyl-¹¹C]WAY-100635, via ¹¹C-carboxylation of an immobilized Gringard reagent. *J Label Compounds Radiopharm.* 1996;38:941-953.
 30. Houle S, DaSilva JN, Wilson AA. Imaging the 5-HT(1A) receptors with PET: WAY-100635 and analogues. *Nucl Med Biol.* 2000;27:463-466.
 31. Studholme C, Hill DL, Hawkes DJ. Automated three-dimensional registration of magnetic resonance and positron emission tomography brain images by multiresolution optimization of voxel similarity measures. *Med Phys.* 1997;24:25-35.
 32. Bremner JD, Bronen RA, De Erasquin G, Vermetten E, Staib LH, Ng CK, Soufer R, Charney DS, Innis RB. Development and reliability of a method for using magnetic resonance imaging for the definition of regions of interest for positron emission tomography. *Clin Positron Imaging.* 1998;1:145-159.
 33. Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage.* 1997;6:279-287.
 34. Mikolajczyk K, Szabatin M, Rudnicki P, Grodzki M, Burger C. A JAVA environment for medical image data analysis: initial application for brain PET quantitation. *Med Inform (Lond).* 1998;23:207-214.
 35. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiack RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp.* 1995;2:189-210.
 36. Meyer JH, Gunn RN, Myers R, Grasby PM. Assessment of spatial normalization of PET ligand images using ligand-specific templates. *Neuroimage.* 1999;9:545-553.
 37. Tabachnick BG, Fidell LS. *Using Multivariate Statistics.* 3rd ed. Northridge, Calif: Harper Collins College Publishers; 1996:57-126.
 38. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13:261-276.
 39. Ichikawa J, Meltzer HY. The effect of serotonin(1A) receptor agonism on antipsychotic drug-induced dopamine release in rat striatum and nucleus accumbens. *Brain Res.* 2000;858:252-263.
 40. Ahlenius S. Antipsychotic-like properties of the 5-HT_{1A} agonist 8-OH-DPAT in the rat. *Pharmacol Toxicol.* 1989;64:3-5.
 41. Wadenberg ML, Ahlenius S. Antipsychotic-like profile of combined treatment with raclopride and 8-OH-DPAT in the rat: enhancement of antipsychotic-like effects without catalepsy. *J Neural Transm Gen Sect.* 1991;83:43-53.
 42. Prinssen EP, Kleven MS, Koek W. Effects of dopamine antagonists in a two-way active avoidance procedure in rats: interactions with 8-OH-DPAT, ritanserin, and prazosin. *Psychopharmacology (Berl).* 1996;128:191-197.
 43. Wadenberg ML. Antagonism by 8-OH-DPAT, but not ritanserin, of catalepsy induced by SCH 23390 in the rat. *J Neural Transm Gen Sect.* 1992;89:49-59.
 44. Bantick RA, Deakin JF, Grasby PM. The 5-HT_{1A} receptor in schizophrenia: a promising target for novel atypical neuroleptics? *J Psychopharmacol.* 2001; 15:37-46.
 45. Hirayasu Y, McCarley RW, Salisbury DF, Tanaka S, Kwon JS, Frumin M, Snyderman D, Yurgelun-Todd D, Kikinis R, Jolesz FA, Shenton ME. Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. *Arch Gen Psychiatry.* 2000;57: 692-699.