ORIGINAL ARTICLE

Presynaptic Dopaminergic Dysfunction in Schizophrenia

A Positron Emission Tomographic [18F]Fluorodopa Study

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Context: The dopamine overactivity hypothesis of schizophrenia remains one of the most influential theories of the pathophysiology of the illness. Radiotracer brain imaging studies are now directly testing aspects of the overactivity hypothesis.

Objective: To assess presynaptic dopaminergic function in a large cohort of patients with schizophrenia by means of [18F]fluorodopa uptake and a high-sensitivity 3-dimensional positron emission tomograph. We predicted elevations in striatal [18F]fluorodopa uptake and reductions in prefrontal cortical [18F]fluorodopa uptake in patients with schizophrenia.

Design: Case-control study.

Setting: Research institute investigation recruiting hospital outpatients.

Patients: Sixteen male medicated hospital outpatients with a *DSM-IV* diagnosis of schizophrenia (mean age, 38 years) and 12 age-matched male volunteers free of psychiatric and neurologic illness.

Intervention: [18F]fluorodopa positron emission tomographic scanning.

Main Outcome Measure: [18F]fluorodopa uptake constant K_i measured with statistical parametric mapping and region-of-interest analyses.

Results: Statistical parametric mapping ($P<.05$ corrected) and region-of-interest analyses ($P<.01$) showed increased [18F]fluorodopa uptake, confined primarily to the ventral striatum in patients with schizophrenia. No reductions in prefrontal cortical [18F]fluorodopa uptake K_i were seen in the statistical parametric mapping and region-of-interest analyses, although dorsal anterior cingulate [18F]fluorodopa K_i correlated with performance on the Stroop Color-Word Test in both groups.

Conclusions: As in studies in unmedicated patients, presynaptic striatal dopamine dysfunction is present in medicated schizophrenic patients, adding further in vivo support for dopamine overactivity in the illness.

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THE ORIGINAL DOPAMINE (DA) hyperactivity hypothesis of schizophrenia,[1] although undergoing revisions and reformulations,[2,3] remains a pivotal neurochemical hypothesis of the illness that is yet to be fully confirmed or refuted. Multiple components of dopaminergic neurotransmission may cause dopaminergic overactivity, including increased DA synthesis, release, receptor number and/or affinity, and DA-mediated postsynaptic effector mechanisms. Certain of these processes can be quantified in vivo in patients, allowing a more comprehensive test of the DA overactivity hypothesis than was previously available.

To date, most imaging studies have examined DA receptor changes in the illness, but positron emission tomography (PET) and single-photon emission computed tomographic studies of DA D_1 and D_2 receptors have produced equivocal results. Recently, prefrontal D_1 receptors have been reported to be elevated, unchanged, or lowered in the illness,[4-6] while 2 meta-analyses of striatal D_2 receptor changes[7,8] suggest that increases of D_2 receptors, if present in the illness, are of much smaller magnitude than the reported postmortem changes, where the confounding effect of neuroleptic exposure is more difficult to control. Direct in vivo evidence of enhanced DA release has been more consistently obtained in the recent studies by Laruelle et al[9-11] and Breier et al.[12] These authors used the single-photon emission computed tomographic tracer [123I]iodobenzamide and the PET radiotracer [11C]raclopride to index amphetamine-induced DA release in the striatum of patients with schizophrenia. Binding of these radiotracers to striatal DA D_2 recep-

tors is sensitive to endogenous levels of DA (see Laruelle[10] for comprehensive review) such that increases of synaptic DA decrease the radiotracer's specific binding and decreases of DA increase specific binding. Patients with schizophrenia show greater reductions of striatal [^{123}I]iodobenzamide binding or [^{11}C]raclopride after amphetamine challenge compared with healthy volunteers,[11,12] a finding compatible with enhanced DA release. Recently, these findings have been replicated in a second cohort of patients with schizophrenia.[13] Furthermore, worsening of positive symptoms in patients correlated with the degree of DA release, estimated by striatal [^{123}I]iodobenzamide displacement. Finally, after pretreatment with α-methyl-para-tyrosine (AMPT), which lowers synaptic DA levels, with the radiotracer[^{123}I]iodobenzamide, an increased "DA D_2 availability" has been observed in patients compared with control subjects,[14] implying that synaptic levels of "baseline" DA may be high in the illness.[15,16]

A complementary method of imaging presynaptic dopaminergic function under baseline conditions measures the formation and storage of DA in presynaptic terminals with [^{18}F]fluorodopa, a radioactive analogue of L-dopa, the precursor of DA. [^{18}F]fluorodopa is taken up by presynaptic monoaminergic neurons and is metabolized by aromatic acid decarboxylase (AADC) to [^{18}F]fluorodopamine ([^{18}F]DA), which is trapped and stored within vesicles in the nerve terminals. [^{18}F]fluorodopa uptake, quantified as the influx constant K_i, measures AADC activity and vesicular storage capacity.[17] High values for [^{18}F]fluorodopa K_i are observed in areas of dense DA nerve terminal innervation (eg, the striatum), and [^{18}F]fluorodopa uptake correlates with surviving nigrostriatal cell numbers in both monkey and human studies.[18,19] [^{18}F]fluorodopa has been extensively used to probe the structural and functional integrity of striatal dopaminergic neurons, particularly in Parkinson disease and other movement disorders.[20-23]

To date, 6 studies using [^{18}F]fluorodopa and 1 using dopa labeled with carbon 11 ([^{11}C]dopa) have been reported in patients with schizophrenia. Five of the 7 studies describe elevated dopa metabolism in the striatum,[24-28] whereas no difference was detected by Dao-Castellana and colleagues[29] and 1 study reported reduced [^{18}F]fluorodopa striatal uptake.[30] Elevations of [^{18}F]fluorodopa and [^{11}C]dopa in the striatum were observed in both medication-naive and medication-free patients. The total numbers of schizophrenic patients studied with [^{18}F]fluorodopa and [^{11}C]dopa to date have been limited, however (n=approximately 50), with 5 to 12 patients per study. Furthermore, quantification of cortical [^{18}F]fluorodopa uptake had not been attempted or achieved, in most studies probably because of the small signal magnitude in cortical areas and/or sensitivity of the previous generation of PET cameras.

Thus, the available in vivo imaging evidence points to alterations of presynaptic striatal dopaminergic function in schizophrenia. However, it is not clear how presynaptic striatal dopaminergic dysfunction is related, if at all, to mesocortical dopaminergic function in schizophrenia or to activity in cortical areas such as the prefrontal cortex. An inverse reciprocal relationship has been postulated between mesocortical (particularly prefrontal) DA systems and striatal DA systems,[31-33] with prefrontal DA lesions giving rise to enhanced subcortical DA activity in some animal studies. Also, prefrontal lesions modulate striatal DA function in some but not all studies (for full discussion, see Grace[34] and Carlsson et al[35]). Pertinent to these issues, the most recent [^{18}F]fluorodopa study demonstrated a negative correlation between elevated striatal [^{18}F]fluorodopa K_i and prefrontal activation in patients with schizophrenia.[28] Although small (n=6), this study provided one of the first in vivo demonstration of the hypothesized link between prefrontal dysfunction and altered subcortical DA function in the illness.

In the present study, we extend previous studies of [^{18}F]fluorodopa in schizophrenia by studying a larger sample of patients (n=16), with a highly sensitive PET camera with an optimized [^{18}F]fluorodopa scanning protocol. We determined whether elevated striatal [^{18}F]fluorodopa uptake could still be detected in medicated patients with schizophrenia, as previously reported in a number of studies of unmedicated patients. Second, we tested the hypothesis that prefrontal [^{18}F]fluorodopa uptake would be reduced in the illness. Third, we explored whether regional [^{18}F]fluorodopa uptake in striatal and cortical areas correlated with positive or negative symptoms of schizophrenia; we hypothesized that positive symptoms would correlate with striatal [^{18}F]fluorodopa uptake while negative symptoms would correlate inversely with [^{18}F]fluorodopa uptake in prefrontal regions. Finally, we examined the relationships, if any, between regional [^{18}F]fluorodopa uptake and performance on neuropsychological tests sensitive to the cognitive impairment in schizophrenia.[36]

METHODS

PARTICIPANTS

The control group comprised 12 right-handed healthy volunteers (age range, 29-49 years; mean age, 38.3 years; SD, 7.1 years) with normal results of neurologic examination. Twenty patients (age range, 25-65 years; mean age, 39.9 years; SD, 11.3 years) who met *DSM-IV* criteria for schizophrenia were recruited to the patient group from routine hospital outpatient clinics. All participants were assessed by a trained psychiatrist (S.M.), and current and past psychiatric morbidity was excluded in healthy volunteers by routine psychiatric interview (S.M.) and the General Health Questionnaire[37] with a cutoff of 5 points or less. All patients were taking neuroleptic medication. Left-handed participants were not excluded from the patient group, as this may reflect the disorder. Exclusion criteria for both groups were a history of neurologic illness, serious physical illness, or substance dependence.

All subjects gave written informed consent after a full explanation of the procedure. Permission to undertake the study was granted by the ethics committees of participating hospitals. Approval to administer radiotracers was obtained from the Administration of Radioactive Substances Advisory Committee, United Kingdom.

PET SCANNING

A 3-dimensional PET scanner (HR++/966 EXACT; CTI PET Systems, Knoxville, Tenn) was used, which reconstructs high-resolution images of the whole brain from 95 planes with a slice spacing of 2.425 mm. In brief, the physical characteristics of the scanner, which have been described in full elsewhere,[38] in-

clude a spatial resolution of 4.8±0.2 mm (full-width half-maximum–transaxial) and a sensitivity of 2.6×10^{12} cps/Ci per milliliter (69 cps/Bq per milliliter), which compares favorably with PET cameras used in previous studies (spatial resolution, 5-7 mm; sensitivity, 1.0×10^{11} to 5.3×10^{11} cps/Ci per milliliter [2.8-14.4 cps/Bq per milliliter[24-30]]). To correct for attenuation, a 5-minute transmission scan was carried out before emission scanning, with the use of a 4.05-mCi (150-MBq) cesium 137 rotating point source.

To further enhance specific signal detection, 1 hour before the start of each scan, 150 mg of carbidopa, a peripheral AADC inhibitor, and 400 mg of entacapone, a peripheral catechol-O-methyltransferase inhibitor, were given orally. These compounds minimize metabolism of [^{18}F]fluorodopa by peripheral AADC and reduce the formation of radioactively labeled metabolites of [^{18}F]fluorodopa by peripheral catechol-O-methyltransferase, which may cross the blood-brain barrier and increase the background cerebral signal.[39,40]

The radiotracer [^{18}F]fluorodopa, 2.97 mCi (110 MBq) (range, 2.76-3.65 mCi [102-135 MBq]), was administered intravenously over 30 seconds with a scan protocol of 26 time frames starting with a background frame of 30 seconds, followed by injection of [^{18}F]fluorodopa at the beginning of four 60-second frames, three 120-second frames, three 180-second frames, and, finally, fifteen 300-second frames. Participants were positioned in the scanner with the orbitomeatal line parallel to the transaxial plane of the tomograph. Head position was monitored via laser crosshairs and video camera.

MAGNETIC RESONANCE IMAGES

For each participant, a structural magnetic resonance (MR) T1 image was obtained for coregistration and comparison of any volumetric differences between groups.

EXCLUSION OF SUBJECTS

Four patients were excluded: 1 patient had bilateral perisylvian atrophy on MR imaging; in 1 patient there were technical problems with the PET scan; and 2 patients had excessive head movement during the PET scan. Data are thus reported for 16 patients and 12 controls.

NEUROPSYCHOLOGY AND SYMPTOM RATING

Premorbid IQ was assessed with the revised version of the National Adult Reading Test.[41] Participants completed the verbal fluency (FAS) task,[42] Symbol Digit Modalities Test (SDMT),[43] and the Stroop Color-Word Test.[44,45] The FAS was scored as the total number of correct words produced in 180 seconds. A second, more sensitive cluster score was also calculated, providing an index of the production of words within semantic subcategories.[46] The SDMT was scored as the number of correctly completed targets in 90 seconds. For the Stroop test, the performance measure was an interference score, calculated as the color–color-word difference score.[44] One participant did not complete the National Adult Reading Test or the FAS because English was not his first language. Symptoms during the preceding month were rated on the scan day by a trained psychiatrist (S.M.) using the Present State section of the Comprehensive Assessment of Symptoms and History.[47] The mean sum of positive symptoms was 4.2 (range, 0-14), and the mean sum of negative symptoms was 6.3 (range, 0-16), yielding overall mean total symptom scores for patients of 10.6 (range, 3-28). By means of the subcategories of symptoms in the Comprehensive Assessment of Symptoms and History, patients could be classified as follows: predominantly positive (n=1), predominantly negative (n=1), mixed high (n=1), and mixed low (n=13). In addition, the presence of any abnormal movements was assessed with the Abnormal Involuntary Movement Scale, with a mean score of 0.1 in patients (range, 0-2).[37]

DATA ANALYSIS

Two methods of image analysis of [^{18}F]fluorodopa PET scans were used: (1) statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, London, England) and (2) an automated region-of-interest (ROI) approach. One advantage of using more than one image analysis method is that results, if physiologically valid, should be independent of the image analysis performed. All data analysis was performed by one worker (S.M.) on a workstation (Sun Sparc; Sun Microsystems, Silicon Valley, Calif) using image analysis software (AnalyzeAVW 3.0 Biomedical Imaging Resource; Mayo Foundation, Rochester, Minn) and in-house software written in Matlab (version 5; The MathWorks, Inc, Natick, Mass), which, by a multiple time graphical approach,[48] generates parametric images of [^{18}F]fluorodopa influx rate constants (K_i) or values of K_i for defined ROIs. In both methods, the occipital cortex was used as a reference region to generate the input function for the Patlak analysis, the region being drawn on MR images coregistered to the PET scans.

SPM ANALYSIS

A template of [^{18}F]fluorodopa uptake was created for use within the SPM system by using combined images of [^{18}F]fluorodopa and T1 MR images (details available on request). The SPM results were thresholded using a value of $P<.05$ corrected, with the use of small volume corrections for the striatal and prefrontal regions. The anatomic mask defining striatal areas was taken from Mawlawi et al[49] and the prefrontal mask derived from the atlas of Hammers et al,[50] with an in-house modification to include regions of the prefrontal cortex.

AUTOMATED ROI ANALYSIS

The data were analyzed by means of standardized ROIs drawn with AnalyzeAVW image analysis software on the representative single participant T1 MR image available in SPM. This T1 image originated from the Montreal Neurological Institute brain database. For the striatal ROI, the volume was subdivided as follows: all planes containing striatal structures below the anterior commissure–posterior commissure plane were operationally defined as the ventral striatum ROI, and all planes above the anterior commissure–posterior commissure plane with striatal structures formed the dorsal striatum ROI. For the anterior cingulate (ACC), in the sagittal orientation, the genu of the corpus callosum was used as an anatomic landmark to divide the anterior portion of the gyrus into dorsal and ventral ROIs bilaterally. In the same sagittal orientation, an ROI was defined anterior to the cingulate ROIs for the medial prefrontal cortex. Finally, a unified cerebellar ROI was defined on both hemispheres, extending over 3 planes. In this manner, these ROIs are defined in a known orientation and a standardized space, which is important for generating ROIs where arbitrary, rather than anatomically visible, criteria are being used. The [^{18}F]fluorodopa template used in the SPM analysis was in the same standardized space as the single-subject T1 MR image. By means of SPM, the [^{18}F]fluorodopa template was normalized to each individual [^{18}F]fluorodopa summation image. The individual specific mathematical transformation parameters to accomplish this process were then applied to the ROIs defined on the single-subject T1 MR image, thereby normalizing ROIs to each individual PET scan. With this method, observer bias in defining ROIs for each individual scan is avoided. These normal-

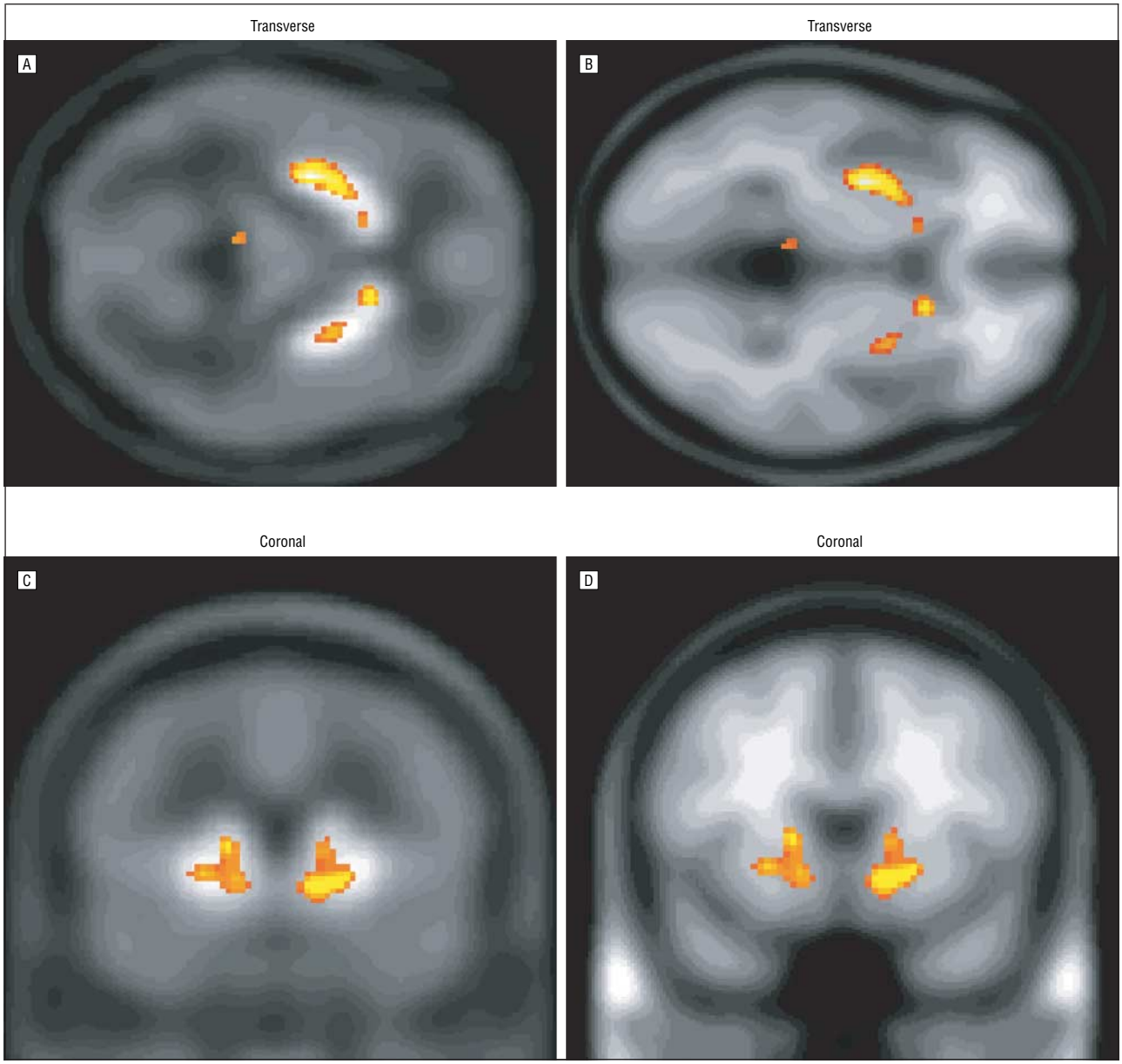

Figure 1. Ventral striatum K_i increases in patients coregistered with structural templates. Statistical parametric mapping outputs show areas of increased [^{18}F]fluorodopa K_i mapped onto [^{18}F]fluorodopa template (A and C) and T1 magnetic resonance imaging template (B and D). For clarify of display, images are thresholded at $P<.01$ uncorrected.

ized ROIs were then used to generate values of [^{18}F]fluorodopa K_i for each individual.

STATISTICAL ANALYSIS

As an a priori hypothesis existed that patients would show increases in striatal [^{18}F]fluorodopa K_i and decreases in prefrontal cortical K_i, results of the SPM analysis were thresholded at $P<.05$ corrected for the volumes (striatum and prefrontal cortex) analyzed. For the automated ROI analysis of K_i values, the 2 groups were compared by means of the 2-way *t* test comparison for 2 populations for each of the brain regions. *P* values were set at $P<.01$ to correct for the 5 principal ROIs examined (ventral striatum, dorsal striatum, ventral anterior cingulate, dorsal anterior cingulate, and medial prefrontal cortex). For the neuropsychological scores, all data were normally distributed and analyzed by independent-sample *t* tests. Pearson product-moment correlation coefficients were calculated between the cognitive test scores and [^{18}F]fluorodopa K_i values in the ROIs.

RESULTS

SPM ANALYSIS

The SPM analysis showed increases in [^{18}F]fluorodopa uptake K_i in the striatum of patients compared with controls ($P<.05$ corrected; $df=1,26$) (**Figure 1**, **Table 1**). The increase in [^{18}F]fluorodopa uptake was predominantly located in the ventral striatum. No other significant differences were seen between patients and controls.

AUTOMATED ROI ANALYSIS

With the use of standardized ROIs, only K_i values in the whole striatum and the ventral striatum were increased in patients compared with controls (striatum: $P = .001$,

Table 1. Statistical Parametric Mapping Analysis

Region of Interest	*Z* Value	Coordinates (x, y, z)
Left ventral putamen	4.58	–30, –6, 0*
Right ventral putamen	4.23	12, 10, –10*

*$P<.05$ corrected for volume analyzed.

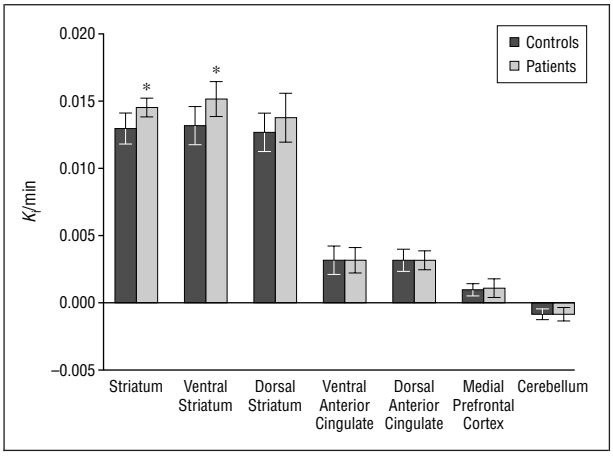

Figure 2. Automated region-of-interest analysis for striatum and cortical regions. Asterisk indicates $P<.002$, independent-sample *t* test: patients vs controls. The data given are means; the error bars represent the SD.

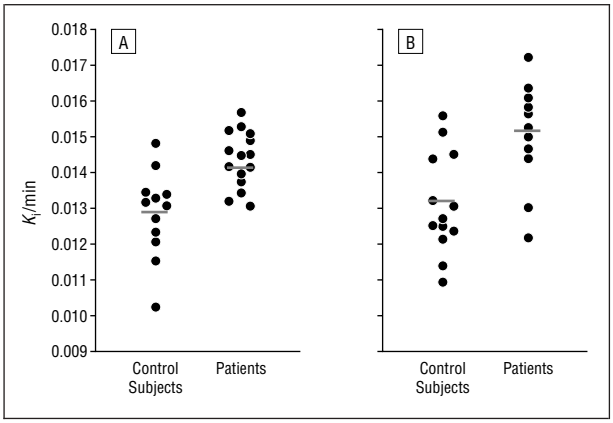

Figure 3. Striatal (A) and ventral striatum (B) influx constant K_i values from automated region-of-interest analysis. Horizontal bars indicate group mean.

$t_{26}=-3.92$; ventral striatum: $P=.001$, $t_{26}=-3.79$; dorsal striatum: $P=.09$, $t_{26}=-1.77$), corroborating the SPM analysis. No significant differences were detected in any of the other ROIs between the 2 groups (**Figure 2** and **Figure 3**).

DEMOGRAPHICS

There was no significant difference in age between the control group and the patients ($P=.86$, $t_{26}=0.18$) (**Table 2**). There was no significant difference in IQ between controls and patients, although IQ was generally lower in patients at a trend level ($P=.07$, $t_{25}=1.93$). Only one of the patients was left-handed. Of the 16 patients, 10 were taking atypical antipsychotic medication and 4 were taking typical neuroleptics. Two patients were receiving both typical and atypical antipsychotic drugs. Medication dose (expressed as chlorpromazine equivalents) did not correlate with [^{18}F]fluorodopa K_i in any of the ROIs (striatum: $r=0.06$, $P=.83$, n=15; ventral striatum: $r=0.2$, $P=.47$, n=15; dorsal striatum, $r=-0.07$, $P=.8$, n=15; 1 outlier 4 SDs from the average neuroleptic dose was excluded in this analysis). [^{18}F]fluorodopa K_i did not correlate with age among both controls and patients, and in the patient group [^{18}F]fluorodopa uptake K_i did not correlate with duration of illness or age at onset of illness (data not shown).

Table 2. Demographics

	Healthy Volunteer Participants (n = 12)	Patients With Schizophrenia (n = 16)
Age, y		
Mean ± SD	38.3 ± 7.1	37.3 ± 10.8
Range	29-49	25-65
Full IQ (range)	116 (100-124)	110 (95-124)
Duration of illness, y, mean (range)		10.9 (1-26)
Handedness, No. right/left	12/0	15/1
Medication, mg/d, mean (range)*		663 (125-3000)
Activity injected, mCi, mean (range)	3.08 (2.76-3.65)	3.03 (2.84-3.27)
Specific activity, mCi/μmol, mean (range)	0.46 (0.22-0.73)	0.46 (0.19-0.89)
Total stable 6F-dopa/μg, mean (range)†	1806 (807-3477)	1951 (738-3319)
Total stable L-dopa/μg, mean (range)	2.2 (0-5.5)	3.1 (0-18.4)

SI conversion: to convert activity to megabecquerels, multiply by 37.
*Chlorpromazine equivalents.
†Refers to the amount of nonradioactive fluorodopa generated during the synthesis of the radiotracer [^{18}F]fluorodopa.

Table 3. Striatal Volumes

	Volume, mm^3, Mean ± SD (Range)	
	Healthy Volunteer Participants (n = 12)	Patients With Schizophrenia (n = 16)
Ventral striatum	11 036 ± 1491 (13 760-8508)	10 187 ± 1230 (12 322-8097)
Dorsal striatum	7951 ± 1191 (9710-6526)	8585 ± 1475 (12 138-5470)
Striatum	18 988 ± 2269 (22 891-15 034)	18 772 ± 2119 (22 119-13 567)

STRUCTURAL MR IMAGING

Striatal volumes did not differ between patients and controls whether assessed as whole striatum or as dorsal and ventral components (**Table 3**) (independent-samples *t* test: striatum: $P=.80$, $t_{26}=0.26$; ventral striatum: $P=.11$, $t_{26}=1.65$; dorsal striatum: $P=.23$, $t_{26}=-1.22$).

SYMPTOM RATINGS

Most patients had symptoms of relatively low severity, a reflection that most were stable clinically and had been recruited from hospital outpatient clinics. [^{18}F]fluorodopa uptake K_i in the ROIs was not significantly correlated with either positive or negative symptom scores, summed from the Comprehensive Assessment of Symptoms and History (*positive:* striatum: $r=-0.03$, $P=.91$, n=16; ventral striatum: $r=0.33$, $P=.21$, n=16; dorsal striatum: $r=-0.25$, $P=.35$, n=16; *negative:* striatum: $r=0.45$, $P=.08$, n=16; ventral striatum: $r=0.22$, $P=.42$, n=16; dorsal striatum: $r=0.25$, $P=.35$, n=16). Likewise, [^{18}F]fluorodopa uptake K_i in prefrontal cortex ROIs did not correlate with symptom scores (data not shown).

NEUROPSYCHOLOGY

Schizophrenic patients were impaired on both the SDMT and FAS (total and cluster scores) but showed the same degree of Stroop interference as did controls (**Table 4**). There were significant negative correlations between Stroop interference scores and dorsal ACC K_i values in both groups ($P=.01$ for patients and trend-level $P=.08$ for controls), with greater ACC K_i values reflecting reduced interference (**Table 5**). The magnitude of this correlation did not differ between groups (Fisher r to Z transformation, $Z=0.35$, $P=.72$ [2-tailed]). The 2 groups did diverge, however, in the pattern of correlations between cognitive scores and K_i values in the ventral striatum. Thus, FAS cluster scores showed a significant positive correlation with ventral striatal K_i values in controls, but not in patients, and the 2 correlation coefficients significantly differed ($Z=2.94$, $P=.004$). For the SDMT, there was a significant negative correlation with ventral striatal K_i values in patients, but not in controls. Again, these 2 correlation coefficients were significantly different ($Z=2.04$, $P=.04$).

Table 4. Neuropsychological Data

	Mean (SD)	
	Healthy Volunteer Participants	Patients With Schizophrenia (n = 16)
SDMT	58 (8)	38 (11)*
Verbal fluency	51 (11)	39 (13)†
Verbal fluency, clusters	0.43 (0.15)	0.31 (0.13)‡
Stroop interference	34 (14)	33 (14)

Abbreviation: SDMT, Symbol-Digit Modalities Test.
*SDMT: $t=5.1$, $P<.001$.
†FAS, $t=2.57$, $P=.02$. One patient did not perform the FAS.
‡FAS clusters: $t=2.34$, $P=.03$. Stroop interference: $t=0.15$, $P=.88$.

COMMENT

The SPM analysis comparing [^{18}F]fluorodopa uptake K_i values between patients and controls on a voxel-by-voxel basis confirmed our hypothesis of striatal K_i increases among patients with schizophrenia. These changes were confined primarily to the ventral striatum. The subsequent ROI analyses using automated measures confirmed the SPM findings for the ventral striatum. Thus, 2 independent methods of image analysis demonstrated a similar finding. The elevation in striatal [^{18}F]fluorodopa uptake K_i replicates previous findings in medication-naive and medication-free patients with schizophrenia.[24-26,28] In these previous studies, no distinction was made between ventral and dorsal striatum, although even in our study with a high-performance camera, partial volume effects would dictate that up to 30% of a ventral [^{18}F]fluorodopa signal could be contributed by the dorsal striatum. However, if the increased ventral striatal [^{18}F]fluorodopa signal observed in this study had arisen from dorsal striatal changes alone, proportionately larger localized changes in dorsal striatal [^{18}F]fluorodopa signal would have been observed, which was not the case in the SPM and ROI analyses.

Although the exact relationship between striatal [^{18}F]fluorodopa uptake K_i and synaptic DA release is not known, in Parkinson disease reduced [^{18}F]fluorodopa uptake K_i correlates with blunted [^{11}C]raclopride displacement with amphetamine,[51] suggesting that under certain conditions these 2 measures can be functionally related. Whether this relationship pertains in schizophrenia is unknown, although the results of this study appear compatible with greater DA release with amphetamine challenge in patients with schizophrenia.[12] Speculatively, enhanced DA release could be a consequence of increased DA synthesis, as suggested by our results.

Using a high-sensitivity camera and a PET protocol designed to maximize [^{18}F]fluorodopa signals, we were able to obtain measures of [^{18}F]fluorodopa K_i in cortical areas in addition to the striatum. In both groups, a detectable signal was found in the anterior cingulate cortex on ROI analysis. However, no differences in cortical [^{18}F]fluorodopa uptake K_i in patients compared with controls could be detected in the ROI analyses. Cortical K_i values were about 25% of striatal values but had similar estimates of variability. Thus, although striatal K_i values and variability allowed for a detection of a 10% increase of signal with 16 participants (power, 80%; α $P<.05$, 2-tailed test), the corresponding number of participants for detecting a similar change in cortical areas was prohibitively large (eg, n=144 for dorsal anterior cingulate). Thus, without a 30% or greater change in signal, it would not have been possible to detect cortical changes in this study by ROI approaches despite an optimized scanning protocol. Despite such limitations, however, Stroop performance correlated with dorsal anterior cingulate [^{18}F]fluorodopa K_i in both groups independently, suggesting that the cortical signal, although of small magnitude and highly variable, has physiological relevance for tasks that are known to invoke anterior cingulate activity.[52]

Striatal K_i represents a measure of the uptake of [^{18}F]fluorodopa into presynaptic dopaminergic terminals in the basal ganglia and its conversion by AADC to [^{18}F]DA, which enters the vesicular compartment. As all the patients in this study were being treated with antipsychotic medication, the effect of such drugs on AADC activity and hence K_i is an important consideration in the interpretation of our findings. Although AADC is not the rate-limiting step in the synthetic pathway for DA, it has

Table 5. Correlation Analysis*

	Ventral Striatum	Dorsal Striatum	Ventral Anterior Cingulate	Dorsal Anterior Cingulate	Medial Prefrontal Cortex
			Schizophrenic Patients		
Verbal fluency, total	–0.18	0.09	–0.10	–0.36	–0.13
Verbal fluency, cluster	–0.24	–0.14	0.35	–0.18	0.23
SDMT	–0.59†	0.14	0.38	–0.33	0.37
Stroop	0.12	–0.29	–0.35	–0.62‡	–0.20
			Control Subjects		
Verbal fluency, total	0.44	0.03	–0.04	–0.03	–0.16
Verbal fluency, cluster	0.75§	0.06	–0.13	0.46	0.34
SDMT	0.19	0.40	–0.40	–0.04	–0.25
Stroop	0.08	–0.35	–0.57‖	–0.52‖	0.18

Abbreviation: SDMT, Symbol-Digit Modalities Test.
*Pearson correlation coefficients between cognitive scores and influx constant K_i values in 16 schizophrenic patients (for verbal fluency, n = 15; 1 patient did not perform the verbal fluency task) and 12 controls.
†$P<.05$ ($P = .02$ for ventral striatum and SDMT).
‡$P = .01$.
§$P = .005$.
‖$.05<P<.1$ ($P = .053$ for ventral anterior cingulate and Stroop; $P = .08$ for dorsal anterior cingulate and Stroop).

been suggested that AADC activity may influence the rate of DA synthesis.[53,54] In rats, increases in AADC activity in vitro and in vivo have been reported after acute treatment with DA antagonists,[55-58] and in anesthetized pigs (n=3), the estimated dopa decarboxylation rate was increased by short-term haloperidol infusion.[54] Conversely, short-term treatment with the DA agonist apomorphine decreases [^{11}C]dopa influx in monkeys.[59] Evidence of such effects in humans, however, is extremely limited. Thus, in the only comprehensive study to date, Grunder et al[60] recently reported a decrease in [^{18}F]fluorodopa K_3 in 9 patients with schizophrenia after 5 weeks' treatment with haloperidol,[60] suggesting that long-term neuroleptic administration will tend to decrease AADC activity and hence DA synthesis. Given that our medicated patients, like previous unmedicated cohorts, showed elevations of [^{18}F]fluorodopa K_i, our findings suggest that neuroleptic treatment has not fully normalized the elevated [^{18}F]fluorodopa K_i in the illness. The absolute magnitude of the [^{18}F]fluorodopa K_i increase in our medicated patient sample (striatum K_i, 0.0144 in patients vs 0.0128 in controls) is very similar to that reported in the study closest in design to our own involving medication-naive patients (K_i, 0.0149 in medication-naive patients vs 0.0129 in controls[25]). Finally, in the other studies reporting [^{18}F]fluorodopa K_i increases, all patients were not taking medication and the majority were drug naive. Therefore, neuroleptic medication or previous exposure does not appear to readily explain the observed increase in [^{18}F]fluorodopa K_i seen in patients with schizophrenia. However, further longitudinal studies of patients, on and off neuroleptic medication, may be necessary to fully address this issue.

Another potentially confounding variable in interpreting the elevation of [^{18}F]fluorodopa K_i is the influence of smoking on PET measures of [^{18}F]fluorodopa uptake. One recent study in healthy volunteers demonstrated increased [^{18}F]fluorodopa K_i in smokers compared with nonsmokers.[61] Psychiatric patients tend to smoke more than healthy volunteers,[61] and this was observed in our data (25% of controls and 50% of patients). However, [^{18}F]fluorodopa K_i for smokers and nonsmokers did not differ in our study (data available on request).

A further issue that should be considered when our findings are interpreted concerns possible striatal volumetric differences between patients and controls. Long-term treatment with neuroleptics has been reported to increase striatal volume in patients with schizophrenia.[62] Potentially, this might alter the [^{18}F]fluorodopa K_i signal in patients via partial volume effects. However, when striatal ROI volumes drawn on the T1 MR images by an investigator blind to diagnosis were used to compare patients against controls, no difference in striatal volume was found (Table 3) (patient vs control striatum: $P=.23$, $t_{26}=-1.22$).

Elevated [^{18}F]fluorodopa K_i values did not correlate with symptom ratings in our study. However, all the patients were relatively stable in terms of their psychopathology and the severity of their symptoms was mild for most of the group; thus, correlations may have been underpowered because of the low variance of symptom severity, perhaps induced by neuroleptic treatment. However, Hietala et al[26] demonstrated correlations of [^{18}F]fluorodopa only with depressive symptoms in their drug-naive cohort, suggesting that neuroleptic treatment is not a significant confound in the lack of correlation with symptomatology. Interestingly, Laruelle and Abi-Dargham[63] observed that the increased DA release demonstrated by [^{123}I]iodobenzamide displacement is only present in patients who are currently relapsing, suggesting that differing measures of presynaptic DA function may be dissociable at the level of symptomatology or overall clinical state (stable vs relapsing).

A number of investigators have proposed a role for dysfunction in DA systems in the core cognitive deficits thought to underlie schizophrenic symptomatology,[64-66] although theories place different emphases on the importance of cortical vs subcortical DA alterations in relation to cognitive impairment. In this study, we found a rela-

tionship between [^{18}F]fluorodopa K_i in the ACC and Stroop performance in both patients and controls. However, in contrast to some studies,[44] schizophrenic patients showed Stroop interference effects of the same magnitude as those in healthy controls. The [^{18}F]fluorodopa K_i cingulate data extend previous findings showing a correlation between Stroop performance and both blood flow[67] and metabolism[68] in the ACC in schizophrenic patients. In both of those studies, greater ACC activation was seen in patients producing more errors, which has been taken to support the influential view that the ACC is involved in detecting response conflict during task performance that might be associated with errors.[69] In our study, increased K_i values in the ACC were associated with reduced interference, which would support the idea that increased DA neurotransmission, by increasing neural signal-to-noise ratios, leads to increased processing efficiency.[65]

In contrast, the 2 groups appeared to show qualitative differences in the relationship between cognitive performance and ventral striatal [^{18}F]fluorodopa K_i values. Schizophrenic patients performed significantly less well on the SDMT and FAS tests. Furthermore, the relationship between [^{18}F]fluorodopa K_i and verbal fluency and SDMT performance in patients was significantly different from that in controls, with controls showing a positive correlation between K_i values and performance, but patients showing a negative relationship. Speculatively, our results are compatible with the hypothesized inverted U-shaped curve of dopaminergic tone (acting via D1 receptor stimulation) and cognitive performance described by a number of authors.[70,71] Thus, in a hyperdopaminergic state (evidenced as abnormally increased [^{18}F]fluorodopa K_i), ventral striatum DA function may lead to impaired performance while increases of [^{18}F]fluorodopa K_i, within normal levels, would be predicted to improve cognitive performance. A number of investigators have suggested a prominent role for ventral striatal DA dysfunction in the cognitive impairment seen in schizophrenia.[64,72,73] In particular, Gray et al[64] argued that the core cognitive deficit in schizophrenia lies in the context-dependent use of stored regularities in guiding current action. Although the precise nature of this deficit in biological terms is unclear, the current data provide evidence of a role for ventral striatal DA alterations in the cognitive impairment of schizophrenia. Both SDMT (which requires the use of regular symbol-digit mappings to guide action) and verbal fluency (which relies on the use of stored semantic regularities to guide output) would seem to require the kind of cognitive processes described by Gray and colleagues in their neuropsychological model of schizophrenia.[64]

Altogether our results add to an accumulating body of in vivo imaging data that indicate abnormal presynaptic striatal DA function in treated as well as untreated patients with schizophrenia. Whether abnormal striatal DA function is primary or, perhaps more likely, secondary to pathophysiologic changes in other neurotransmitter systems (eg, prefrontal glutamatergic or γ-aminobutyric acid–ergic systems) remains to be fully determined.

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