Presynaptic Dopaminergic Dysfunction in Schizophrenia

A Positron Emission Tomographic [18F]Fluorodopa Study

Stephen McGowan, MRCPsych; Andrew D. Lawrence, PhD; Tim Sales, MRCPsych; Digby Quested, MRCPsych; Paul Grasby, MD, MRCPsych

**Context:** The dopamine overactivity hypothesis of schizophrenia remains one of the most influential theories of the pathophysiology of the illness. Radiotracers 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 investigating 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 Measures:** [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.

Arch Gen Psychiatry. 2004;61:134-142
Copyright 2004 American Medical Association. All rights reserved.

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 × 10^4 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 × 10^4 to 5.3 × 10^4 cps/Ci per milliliter
[2.8-14.4 cps/Bq per milliliter]). To correct for attenuation,
a 5-minute transmission scan was carried out before emis-
sion scanning, with the use of a 0.45-mCi (150-MBq) cesium
137 rotating point source.

To further enhance specific signal detection, 1 hour be-
fore the start of each scan, 130 mg of carbidopa, a peripheral
AADC inhibitor, and 400 mg of entacapone, a peripheral cat-
echol-O-methyltransferase inhibitor, were given orally. These
compounds minimize metabolism of [18F]fluorodopa by per-
ripheral AADC and reduce the formation of radioactively la-
beled metabolites of [18F]fluorodopa by peripheral catechol-
O-methyltransferase, which may cross the blood-brain barrier
and increase the background cerebral signal.39,40

The radiotracer [18F]fluorodopa, 2.97 mCi (110 MBq)
(range, 2.76-3.65 mCi [102-135 MBq]), was administered in-
travenously over 30 seconds with a scan protocol of 26 time
frames starting with a background frame of 30 seconds, fol-
lowed by injection of [18F]fluorodopa at the beginning of four
60-second frames, three 120-second frames, three 180-second
frames, and, finally, 160-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 perisyl-
vian 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 Na-
tonal Adult Reading Test.33 Participants completed the verbal
fluency (FAS) task,35 Symbol Digit Modalities Test (SDMT),43
and the Stroop Color-Word Test.45,46 The FAS was scored as
the total number of correct words produced in 180 seconds. A
second, more sensitive cluster score was also calculated, pro-
viding an index of the production of words within semantic
subcategories.46 The SDMT was scored as the number of cor-
crrectly completed targets in 90 seconds. For the Stroop test, the
performance measure was an interference score, calculated as
the color–color-word difference score.46 One participant did
not complete the National Adult Reading Test or the FAS be-
cause English was not his first language. Symptoms during the
preceding month were rated on the scan day by a trained psy-
chiatrist (S.M.) using the Present State section of the Compre-
hensive 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 Compre-
hensive Assessment of Symptoms and History, patients could
be classified as follows: predominantly positive (n=1), pre-
dominantly negative (n=1), mixed high (n=1), and mixed low
(n=13). In addition, the presence of any abnormal move-
ments was assessed with the Abnormal Involuntary Move-
ment Scale, with a mean score of 0.1 in patients (range, 0-2).37

DATA ANALYSIS

Two methods of image analysis of [18F]fluorodopa PET scans
were used: (1) statistical parametric mapping (SPM99; Well-
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 Micro-
systems, Silicon Valley, Calif) using image analysis software
(AnalyzeAVW 3.0 Biomedical Imaging Resource; Mayo Foun-
dation, Rochester, Minn) and in-house software written in Mat-
lab (version 5; The MathWorks, Inc, Natick, Mass), which, by
a multiple time graphical approach, provides parametric im-
ages of [18F]fluorodopa influx rate constants (Ki) or values of
K 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 coreg-
istered to the PET scans.

SPM ANALYSIS

A template of [18F]fluorodopa uptake was created for use within
the SPM system by using combined images of [18F]fluorodopa
and T1 MR images (details available on request). The SPM re-
sults were thresholded using a value of P<.05 corrected, with
the use of small volume corrections for the striatal and pre-
frontal regions. The anatomic mask defining striatal areas was
taken from Mawlawi et al49 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 representa-
tive 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 an-
terior commissure–posterior commissure plane were opera-
tionally defined as the ventral striatum ROI, and all planes above
the anterior commissure–posterior commissure plane with stra-
tial structures formed the dorsal striatum ROI. For the anterior
cingulate (ACC), in the sagittal orientation, the genu of the cor-
pus callosum was used as an anatomic landmark to divide the
anterior portion of the gyrus into dorsal and ventral ROIs bi-
laterally. In the same sagittal orientation, an ROI was defined
anterior to the cingulate ROIs for the medial prefrontal cor-
x. Finally, a unified cerebellar ROI was defined on both hemi-
spheres, 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 [18F]flu-
rodopan template used in the SPM analysis was in the same stan-
dardized space as the single-subject T1 MR image. By means of
SPM, the [18F]fluorodopa template was normalized to each individual
[18F]fluorodopa summation image. The individual specific mathematical transformation parameters to accom-
plish 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 de-
fining ROIs for each individual scan is avoided. These normal-
IZED ROIs were then used to generate values of [18F]fluorodopa Ki for each individual.

STATISTICAL ANALYSIS
As an a priori hypothesis existed that patients would show increases in striatal [18F]fluorodopa Ki and decreases in prefrontal cortical Ki, 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 Ki 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 [18F]fluorodopa Ki values in the ROIs.

RESULTS

SPM ANALYSIS
The SPM analysis showed increases in [18F]fluorodopa uptake Ki in the striatum of patients compared with controls (P<.05 corrected; df = 1,26) (Figure 1, Table 1). The increase in [18F]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 Ki values in the whole striatum and the ventral striatum were increased in patients compared with controls (striatum: P = .001,
t_{26} = -3.92; ventral striatum: \( t_{26} = -3.79 \); dorsal striatum: \( t_{26} = -1.77 \), 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 \( (P = .86, t_{20} = 0.18) \) (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).

**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: \( P = .8, t_{25} = 0.26 \); ventral striatum: \( P = .11, t_{26} = 1.65 \); dorsal striatum: \( P = .23, t_{26} = -1.22 \)).

---

**Table 1. Statistical Parametric Mapping Analysis**

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Z Value</th>
<th>Coordinates (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventral putamen</td>
<td>4.58</td>
<td>-30, -6, 0*</td>
</tr>
<tr>
<td>Right ventral putamen</td>
<td>4.23</td>
<td>12, 10, -10*</td>
</tr>
</tbody>
</table>

* \( P < .05 \) corrected for volume analyzed.

---

**Table 2. Demographics**

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

* Chlorpromazine equivalents.
† Refers to the amount of nonradioactive fluorodopa generated during the synthesis of the radiotracer \([^{18}F]\)fluorodopa.

---

**Table 3. Striatal Volumes**

<table>
<thead>
<tr>
<th></th>
<th>Healthy Volunteer Participants (n = 12)</th>
<th>Patients With Schizophrenia (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral striatum</td>
<td>11 036 ± 1491</td>
<td>10 187 ± 1230</td>
</tr>
<tr>
<td>(13 760-8508)</td>
<td>(12 322-8097)</td>
<td></td>
</tr>
<tr>
<td>Dorsal striatum</td>
<td>7951 ± 1191</td>
<td>8585 ± 1475</td>
</tr>
<tr>
<td>(9710-6526)</td>
<td>(12 138-5470)</td>
<td></td>
</tr>
<tr>
<td>Striatum</td>
<td>18 988 ± 2269</td>
<td>18 772 ± 2119</td>
</tr>
<tr>
<td>(22 891-15 034)</td>
<td>(22 119-13 567)</td>
<td></td>
</tr>
</tbody>
</table>

SI conversion: to convert activity to megabecquerels, multiply by 37.
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 ($Z = 2.04$, $P = .04$).

### 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 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,32 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.33 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 with signal with 16 participants (power, 80%; $\alpha = .05$, 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.32

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...
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.53-56 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 [13C]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 al60 recently reported a decrease in [18F]fluorodopa Kᵢ in 9 patients with schizophrenia after 5 weeks’ treatment with haloperidol, 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 [18F]fluorodopa Kᵢ, our findings suggest that neuroleptic treatment has not fully normalized the elevated [18F]fluorodopa Kᵢ in the illness. The absolute magnitude of the [18F]fluorodopa Kᵢ increase in our medicated patient sample (striatum Kᵢ, 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 (Kᵢ, 0.0149 in medication-naive patients vs 0.0129 in controls).58 Finally, in the other studies reporting [18F]fluorodopa Kᵢ increases, all patients were not taking medication and the majority were drug naïve. Therefore, neuroleptic medication or previous exposure does not appear to readily explain the observed increase in [18F]fluorodopa Kᵢ 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 [18F]fluorodopa Kᵢ is the influence of smoking on PET measures of [18F]fluorodopa uptake. One recent study in healthy volunteers demonstrated increased [18F]fluorodopa Kᵢ in smokers compared with nonsmokers.51 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, [18F]fluorodopa Kᵢ 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 [18F]fluorodopa Kᵢ 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, t₂₉₅ = −1.22).

Elevated [18F]fluorodopa Kᵢ 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 al69 demonstrated correlations of [18F]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-Dargham53 observed that the increased DA release demonstrated by [123I]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,69-70 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 $^{[18F]}$Fluorodopa $K_i$ in the ACC and Stroop performance in both patients and controls. However, in contrast to some studies, $^{[18F]}$Fluorodopa $K_i$ cingulate data extend previous findings showing a correlation between Stroop performance and both blood flow $^{67}$ and metabolism $^{86}$ 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. $^{86}$ 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. $^{15}$

In contrast, the 2 groups appeared to show qualitative differences in the relationship between cognitive performance and ventral striatal $^{[18F]}$Fluorodopa $K_i$ values. Schizophrenic patients performed significantly less well on the SDMT and FAS tests. Furthermore, the relationship between $^{[18F]}$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 $^{[18F]}$Fluorodopa $K_i$), ventral striatum DA function may lead to impaired performance while increases in a hyperdopaminergic state (evidenced as abnormally decreased $^{[18F]}$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. $^{84}$

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 $\gamma$-aminobutyric acid–ergic systems) remains to be fully determined.

Submitted for publication January 24, 2003; final revision received June 18, 2003; accepted July 10, 2003.

This study was supported by the Medical Research Council, London, England.

Corresponding author and reprints: Paul Grasby, MD, MRCPsych, Cyclotron Unit, MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College, Du Cane Road, London, W12 0NN England (e-mail: paul.grasby@csc.mrc.ac.uk).

REFERENCES


41. Nelson HE, Willison JR.


Downloaded From: by a Non-Human Traffic (NHT) User on 11/01/2018