Elevated Striatal Dopamine Function Linked to Prodromal Signs of Schizophrenia

Oliver D. Howes, MRCPsych, DM; Andrew J. Montgomery, MRCPsych, PhD; Marie-Claude Asselin, PhD; Robin M. Murray, FRCPsych, DSc; Isabel Valli, MBBS; Paul Tabraham, PhD; Elvira Bramon-Bosch, MRCPsych, PhD; Lucia Valmaggia, PhD; Louise Johns, PhD; Matthew Broome, MRCPsych; Philip K. McGuire, FRCPsych, PhD*; Paul M. Grasby, MRCPsych, MD*

Context: A major limitation on the development of biomarkers and novel interventions for schizophrenia is that its pathogenesis is unknown. Although elevated striatal dopamine activity is thought to be fundamental to schizophrenia, it is unclear when this neurochemical abnormality develops in relation to the onset of illness and how this relates to the symptoms and neurocognitive impairment seen in individuals with prodromal symptoms of schizophrenia.

Objectives: To determine whether striatal dopamine function is elevated in individuals with prodromal symptoms of schizophrenia before the onset of psychosis and to assess how this relates to the symptoms and neurocognitive impairment.

Design: Case-control study of in vivo striatal dopaminergic function.

Setting: Academic research.

Patients: Patients were recruited from a community mental health service. Twenty-four patients having prodromal symptoms of schizophrenia were compared with 7 patients having schizophrenia and with 12 matched healthy control subjects from the same community.

Main Outcome Measure: Striatal 6-fluoro-L-dopa F 18-dopa uptake measured using positron emission tomographic 18F-dopa imaging.

Results: Striatal 18F-dopa uptake was elevated in patients with prodromal symptoms of schizophrenia (effect size, 0.75) to an intermediate degree compared with that in patients with schizophrenia (effect size, 1.25). The elevation was localized in the associative striatum in both groups. Moreover, striatal 18F-dopa uptake in patients with prodromal symptoms of schizophrenia was correlated with the severity of prodromal psychopathologic and neuropsychological impairment but not with the severity of anxiety or depressive symptoms.

Conclusions: These findings indicate that dopamine overactivity predates the onset of schizophrenia in individuals with prodromal psychotic symptoms, is predominantly localized in the associative striatum, and is correlated with the severity of symptoms and neurocognitive dysfunction.

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CHZOPHRENIA IS A LEADING cause of disability and premature mortality. Current drug treatments are limited by poor efficacy and tolerability. Understanding the pathophysiological mechanisms of schizophrenia is fundamental to the development of new and preventive treatments.

Striatal hyperdopaminergia has been postulated to be fundamental to the generation of the psychotic symptoms that characterize schizophrenia. In recent years, neurochemical imaging techniques such as positron emission tomography (PET) have enabled the striatal dopaminergic system to be characterized in vivo in patients with schizophrenia. Studies conducted with radiotracers for which binding is sensitive to endogenous dopamine levels have found that the baseline levels of synaptic dopamine and the dopamine release in response to amphetamine sulfate are increased in patients with schizophrenia. Moreover, the magnitude is directly related to the severity of amphetamine-induced psychotic symptoms and the response to subsequent antipsychotic treatment. Further studies have investigated presynaptic striatal dopaminergic function using the PET radiotracers carbon 11-L-dopa and 6-[18F]-dopa. The accumulation of these radiotracers in the striatum reflects the functional integrity of the presynaptic dopamine system. In a review article by Howes et al., 6 of 8 studies found elevated striatal dopamine uptake in patients with schizophrenia. Elevated striatal dopamine uptake was found in
all studies involving patients who had acute psychosis at the time of imaging, with effect sizes ranging from 0.63 to 0.88. However, it is unknown whether dopaminergic dysfunction precedes the onset of schizophrenia or is secondary to its development.14

The onset of schizophrenia is usually preceded by a prodromal phase characterized by functional decline and subtle prodromal symptoms, which include attenuated psychotic phenomena and a decline in socio-occupational function.15 Individuals with these features have what has been termed an at-risk mental state (ARMS) and have a high probability of developing a psychotic illness, usually schizophrenia, within the next 1 to 2 years.16 Structured assessments and operationalized criteria for identifying individuals at high risk of psychosis have been developed.15-17 Large longitudinal studies using these operationalized criteria have found that between 22% and 31% of individuals with ARMS develop a psychotic illness within 12 months,18,19 and 35% do so after 21⁄2 years of follow-up.18 The mean times to onset of psychotic illness in these studies were 223 days19 and 276 days.18

We investigated the striatal dopaminergic system in a group of patients meeting operationalized criteria for ARMS using 18F-dopa PET imaging, comparing them with patients with schizophrenia and with healthy volunteers. We first tested the hypothesis that increased striatal dopaminergic activity would be evident in the group with prodromal symptoms of schizophrenia, although they did not yet manifest psychosis. We then tested the hypothesis that the magnitude of this increase would be associated with the severity of their prodromal symptoms and neurocognitive impairment.

### METHODS

**PATIENTS**

The study was approved by the Institute of Psychiatry, King’s College, London, England, research ethics committee. Following complete description of the study, all subjects gave written informed consent to participate. Patients with prodromal symptoms of schizophrenia meeting criteria for ARMS15 (mean [SD] age, 25.6 [4.3] years; age range, 20–33 years; 58% male [n=14], 63% white [n=13], and 38% black [n=9]) were recruited from a clinic for prodromal schizophrenia in south London. They were compared with patients meeting DSM-IV criteria for schizophrenia (mean [SD] age, 36.0 [14.7] years; age range, 19-58 years; 71% male [n=14], 43% white [n=3], and 57% black [n=4]) who were recruited from the same clinic, as well as with healthy control subjects (mean [SD] age, 24.3 [4.6] years; age range, 19-32 years; 67% male [n=8], 50% white [n=6], and 50% black [n=6]) recruited contemporaneously from the same geographic area of London. A power calculation using the effect size of the elevation in dopaminergic function from a previous study18 of schizophrenia at the same center indicated that a minimum sample size of 6 subjects per group was required. Twenty-four patients with ARMS were recruited to ensure an adequate number for the within-group analysis of the relationship between dopaminergic function and prodromal symptoms and neuropsychological performance.

All patients with ARMS met criteria of attenuated psychotic symptoms (abnormal beliefs, perceptions, or speech). Four patients (17%) also had experienced brief, spontaneously resolving psychotic episodes that always remitted within 1 week and had first occurred no longer than 5 years previously, with at least 1 episode in the past year. In addition, 4 patients (17%) had a first-degree relative with schizophrenia. Premorbid intelligence, psychoactive drug use, and prodromal, schizophrenic, depressive, and anxiety symptoms were measured using established rating scales (**Table 1**).

Exclusion criteria for all patients were pregnancy, contraindication to imaging, history of neurologic or medical illness or head injury, or alcohol or other drug abuse or dependency. In addition, all controls were required to have no personal history of psychiatric illness. All patients were not taking antipsychotic treatment for at least 8 weeks, except for 1 patient with ARMS who was taking quetiapine fumarate (100 mg/d [omitted for 24 hours before imaging]). For the statistical analysis that included this patient and is presented in the “Results” section, exclusion of the patient did not significantly alter the

### Table 1. Symptoms and Premorbid Intelligence by Study Group, With Analysis of Variance Effect of Group on These Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control Group (n=12)</th>
<th>ARMS Group (n=24)</th>
<th>Schizophrenia Group (n=7)</th>
<th>F, P Value for Effect of Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive Assessment of At-Risk Mental States score</td>
<td>2.1 (3.0)</td>
<td>37.9 (22.0)</td>
<td>49.6 (41.0)</td>
<td>13.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Positive</td>
<td>0.8 (2.0)</td>
<td>7.8 (4.0)</td>
<td>10.9 (8.0)</td>
<td>16.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Positive and Negative Symptom Scale for Schizophrenia score</td>
<td>Total 30.9 (1.9)</td>
<td>47.2 (16.0)</td>
<td>61.7 (31.0)</td>
<td>7.6</td>
<td>.002</td>
</tr>
<tr>
<td>Positive</td>
<td>7.2 (1.0)</td>
<td>12.5 (4.0)</td>
<td>17.0 (7.0)</td>
<td>12.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Negative</td>
<td>7.2 (1.0)</td>
<td>10.0 (5.0)</td>
<td>16.1 (10.0)</td>
<td>13.0</td>
<td>&lt;.007</td>
</tr>
<tr>
<td>General</td>
<td>16.5 (1.0)</td>
<td>24.7 (9.0)</td>
<td>28.6 (17.0)</td>
<td>4.0</td>
<td>.02</td>
</tr>
<tr>
<td>Hamilton scale score</td>
<td>Depression 0.7 (1.0)</td>
<td>9.0 (7.8)</td>
<td>9.3 (12.3)</td>
<td>5.4</td>
<td>.008</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.0 (1.3)</td>
<td>11.5 (11.5)</td>
<td>8.4 (12.5)</td>
<td>4.4</td>
<td>.02</td>
</tr>
<tr>
<td>National Adult Reading Test intelligence</td>
<td>102.2 (8.0)</td>
<td>99.9 (15.0)</td>
<td>103.6 (13.0)</td>
<td>0.3</td>
<td>.8</td>
</tr>
</tbody>
</table>

Abbreviation: ARMS, at-risk mental state.

a P<.05, ARMS group vs schizophrenia group.

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findings. Two patients with ARMS (8.3%) and 1 patient with schizophrenia (14.3%) met criteria for current or past mild depressive disorder, and 2 other patients with ARMS (8.3%) met criteria for current or past anxiety disorder (social phobia). All but 1 of the patients with ARMS and 3 of the patients with schizophrenia were naive to antipsychotic drugs before imaging. Two of the patients with ARMS were taking other psychotropic drugs at the time of imaging (one was taking sertraline hydrochloride [50 mg/d] and zopiclone [7.5 mg as required], and the other was taking mirtazapine [15 mg/d]). No other patients were taking or had taken any other psychotropic medication. Urinary drug testing confirmed that all subjects had not taken illicit drugs before imaging.

CLINICAL AND NEUROPSYCHOLOGICAL MEASURES

All subjects were assessed at the time of imaging using the following instruments: the Comprehensive Assessment of At-Risk Mental States (CAARMS), the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia, and the Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale. All subjects received assessment of recreational exposure to psychoactive substances by interview and by questionnaire. The Structured Clinical Interview for DSM-IV was used to assess the presence of psychiatric diagnoses, and premorbid intelligence was estimated using the National Adult Reading Test. We measured semantic and phonologic verbal fluency to index executive function in patients with ARMS using the standard method and scoring total correct words in 1 minute.

PET IMAGING

PET data acquisition was performed using an imaging system (ECAT/EXACT3D; Siemens/CTI, Knoxville, Tennessee) that has a mean (SD) spatial resolution of 4.8 (0.2) mm and a sensitivity of 69 cps/Bq/mL. High-resolution images of the whole brain were reconstructed from 95 planes with a section spacing of 2.425 mm.

All subjects received carbidopa (150 mg) and entacapone (400 mg) orally 1 hour before imaging to reduce the formation of radiolabeled metabolites, which can confound measurements by crossing the blood-brain barrier. Subjects were positioned with the orbitomeatal line parallel to the transaxial plane of the tomograph. Head position was marked and monitored via laser crosshairs and a camera. A 5-minute transmission image was obtained before radiotracer injection using a 130-MBq cesium Cs 137 rotating point source to correct for attenuation and scatter.

Approximately 150 MBq of 18F-dopa was administered by bolus intravenous injection 30 seconds after the start of the PET imaging, which lasted 95 minutes. The PET data were acquired in list mode, rebinned into 26 time frames (comprising a 30-second background frame, four 60-second frames, three 120-second frames, three 180-second frames, and finally fifteen 300-second frames), and reconstructed using the 3-dimensional reprojection algorithm. Subjects underwent structural magnetic resonance imaging to exclude intracranial abnormalities.

IMAGE ANALYSIS

Movement correction was conducted by denoising the nonattenuated dynamic image and by realigning the frames to a single frame acquired 8 minutes after 18F-dopa injection using a mutual information algorithm. The transformation parameters were then applied to the corresponding attenuation-corrected frames, and the realigned frames were combined to create a movement-corrected dynamic image for the analyses.

The region-of-interest (ROI) analysis was performed blind to group status by one of us (O.D.H.). Standardized regions in Montreal Neurologic Institute space were defined in the cerebellum (the reference region) using a probabilistic atlas and were delineated in the whole striatum using previously described criteria to create an ROI map. In addition, the 18F-dopa template used in a previous study (constructed from images acquired using the same imaging system) was normalized together with the ROI map to each individual PET summation image using statistical parametric mapping (SPM2; Wellcome Department of Cognitive Neurology, London). This procedure allowed ROIs to be placed automatically on individual 18F-dopa PET images without observer bias. Striatal subdivisions were delineated as previously described to yield limbic, associative, and sensorimotor subregions of the whole striatal ROI. These subdivisions approximate the functional organization of the striatum into 3 regions reflecting the topographic arrangement of corticostriatal projections, as well as the putative role of these striatal regions in the regulation of information flow to and from the cortex. Projections to the limbic subregion are from limbic areas such as the hippocampus and amygdala, projections to the associative subregion originate in associative areas such as the dorsolateral prefrontal cortex, and projections to the sensorimotor subregion come from motor and related areas such as primary motor cortex, premotor cortex, and supplementary motor cortex. A graphical analysis was used to calculate 18F-dopa influx rate constants (Ki values) for the whole striatal ROI and for the functional subdivisions relative to uptake in the reference region for left and right sides combined.
There was no significant effect of group on the amount of radioactivity injected (mean [SD], 147.8 [5.8] MBq for the control group, 149.1 [4.6] MBq for the ARMS group, and 149.0 [3.1] MBq for the schizophrenia group; \( F_{3,45} = 0.32, P = .7 \)). Similarly, there was no significant effect of group on the specific activity (mean [SD], 25.4 [8.4] MBq/µmol for the control group, 21.4 [9.6] MBq/µmol for the ARMS group, and 16.1 [9.2] MBq/µmol for the schizophrenia group; \( F_{3,45} = 2.2, P = .12 \)).

The mean (SD) number of cigarettes consumed per day was 2.7 (4.0) for the control group, 5.2 (6) for the ARMS group, and 4.3 (11) for the schizophrenia group. The mean (SD) alcohol consumption in units per week was 8.3 (12.0) for the control group, 6.7 (6.0) for the ARMS group, and 3.6 (6) for the schizophrenia group. The data on stimulant and cannabis use were skewed. The median (interquartile range) stimulant use was less than 0.01 (<0.01) g/mo for all groups. The median (interquartile) number of cannabis cigarettes consumed per week was less than 0.01 (0.10) for the control group, 0.02 (1.00) for the ARMS group, and less than 0.01 (0.01) for the schizophrenia group.

There was a significant effect of group on symptom ratings, as expected, but not on premorbid intelligence (Table 1). There was no significant difference in age between the control and ARMS groups (\( t_{14} = 0.8, P = .43 \)) or between the control and schizophrenia groups (\( t_{12} = 2, P = .06 \)). Similarly, there was no significant difference in cigarette consumption (\( P = .20 \) for the control group vs the ARMS group, and \( P = .34 \) for the control group vs the schizophrenia group), alcohol use (\( P = .93 \) for the control group vs the ARMS group, and \( P = .30 \) for the control group vs the schizophrenia group), stimulant use (\( P = .96 \) for the control group vs the ARMS group, and \( P = .99 \) for the control group vs the schizophrenia group), or cannabis consumption (\( P = .15 \) for the control group vs the ARMS group and \( P = .65 \) for the control group vs the schizophrenia group). There was no relationship between whole striatal Ki values and age (\( r = 0.13, P = .41 \)), and there was no significant age difference between the ARMS group and the schizophrenia group (\( t_{52} = 1, P = .32 \)). There was no significant difference in whole striatal Ki values between men and women (\( t_{41} = 1.1, P = .99 \)). Four subjects (2 in the ARMS group, 1 in the schizophrenia group, and 1 in the control group) had a history of DSM-IV substance abuse, although none met DSM-IV criteria for current substance abuse or for current or previous dependence.

### RESULTS

#### RADIOCHEMISTRY AND DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

We found a significant effect of group on Ki values for the whole striatum (\( F_{2,42} = 3.7, P = .04 \)) and for its associative subdivision (\( F_{2,42} = 6.5, P = .004 \) (Figure 2 and Table 2). There were no significant effects of group on Ki values in the limbic (\( F_{2,42} = 2.1, P = .10 \)) or sensorimotor (\( F_{2,42} = 1.0, P = .40 \)) subdivision. The significant effect of group remained for the whole striatum (\( F_{2,38} = 3.5, P = .04 \)) and for its associative subdivision (\( F_{2,38} = 6.5, P = .004 \)) after excluding the 4 patients in the ARMS group with a family history of psychosis.

In the ARMS group relative to the control group, the mean Ki value was elevated by 6.3% (effect size, 0.75) in the whole striatum (\( t_{14} = 2.2, P = .04 \)) and by 7.3% (effect size, 0.83) in the associative striatum (\( t_{14} = 2.5, P = .02 \)). In the schizophrenia group relative to the control group, the mean Ki value was elevated by 10.6% (effect size, 1.25) in the whole striatum (\( t_{16} = 2.5, P = .02 \)) and by 13.9% (effect size, 1.6) in the associative striatum (\( t_{16} = 3.4, P = .004 \)). There were no significant differences between the ARMS group and the schizophrenia group in the mean Ki values in the whole striatum or in the striatal subdivisions.

#### RELATIONSHIP BETWEEN STRIATAL DOPAMINERGIC FUNCTION, SYMPTOMS, AND NEUROPSYCHOLOGICAL PERFORMANCE

Within the ARMS group, there was a positive correlation between whole striatal Ki values and the severity of prodromal symptoms as indexed by the total CAARMS score (\( r = 0.48, P = .02 \)) (Figure 3A). A positive correlation was also evident with an independent measure of schizophrenic symptoms, the PANSS score (\( r = 0.49, P = .01 \)). This relationship between symptoms and Ki values was also evident in the associative (\( r = 0.43, P = .03 \) for the CAARMS score; and \( r = 0.45, P = .03 \) for the PANSS score) and sensorimotor (\( r = 0.54, P = .007 \) for the CAARMS score).
score; and $r = 0.57, P = .003$ for the PANSS score). In contrast, there was no relationship between striatal Ki values for the whole striatum or its subdivisions and severity of anxiety or depressive symptoms ($r = 0.09, P = .69$ for the CAARMS score; and $r = 0.09, P = .67$ for the PANSS score). In contrast, there was no relationship between whole striatal Ki values and attenuated positive symptom scores on the CAARMS. This is not surprising because patients with ARMS have a narrow range of attenuated positive symptom scores, which limits the variance in these scores.

Within the ARMS group, performance on the semantic verbal fluency task was negatively correlated with whole striatal Ki values ($r = -0.52, P = .02$): greater elevation in Ki values was associated with fewer correct responses (Figure 3B). A similar negative correlation was evident for phonologic verbal fluency, although this did not reach statistical significance ($P = .2$). The same relationship was seen between Ki values for the associative striatal subdivision and verbal fluency ($r = -0.49, P = .02$), although this association did not remain after Bonferroni correction.

We investigated the effect of extreme values on the correlations reported. After removing the high and low data points, the correlations of striatal Ki values with verbal fluency remained significant or showed trend significance ($r = -0.40, P = .08$; and $r = -0.52, P = .02$; respectively), and the same was true for the correlations with the CAARMS score ($r = 0.44, P = .04$; and $r = 0.40, P = .06$; respectively). This suggests that the correlation is not simply a function of a spurious extreme value.

Within the schizophrenia group, there was no significant relationship between whole striatal Ki values and PANSS, CAARMS, Hamilton Anxiety Rating Scale, and Hamilton Depression Rating Scale scores; these statistics were $r = -0.30, P = .51$; $r = -0.32, P = .48$; $r = -0.35, P = .45$; and $r = -0.33, P = .48$; respectively.

### COMMENT

Our first finding was that striatal $^{18}$F-dopa uptake was elevated in patients with prodromal signs of schizophrenia although they did not yet have the disorder. This el-

### Table 2. Ki Values for the Whole Striatum and for the Striatal Subdivisions by Study Group

<table>
<thead>
<tr>
<th>Region</th>
<th>Control Group</th>
<th>ARMS Group</th>
<th>Schizophrenia Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole striatum</td>
<td>0.0142 (0.0012)</td>
<td>0.0151 (0.0012)$^b$</td>
<td>0.0157 (0.0013)$^c$</td>
</tr>
<tr>
<td>Striatal subdivision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associative</td>
<td>0.0137 (0.0012)</td>
<td>0.0147 (0.0011)$^b$</td>
<td>0.0156 (0.0012)$^d$</td>
</tr>
<tr>
<td>Limbic</td>
<td>0.0140 (0.0027)</td>
<td>0.0152 (0.0013)</td>
<td>0.0143 (0.0018)</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>0.0154 (0.0018)</td>
<td>0.0162 (0.0019)</td>
<td>0.0165 (0.0020)</td>
</tr>
</tbody>
</table>

Abbreviations: ARMS, at-risk mental state; Ki value, the influx rate constant.

$^a$ There were no significant differences between the ARMS group and the schizophrenia group. There was no significant interaction between laterality and effect of group for the whole striatum ($F_{2,85} = 0.1, P = .90$) or for the associative striatum ($F_{2,85} = 0.1, P = .94$).

$^b P < .05$, control group vs ARMS group.

$^c P < .05$, control group vs schizophrenia group.

$^d P < .005$, control group vs schizophrenia group.

### Figure 3. At-risk mental state (ARMS) group. A, The positive relationship between total Comprehensive Assessment of At-Risk Mental States (CAARMS) score (higher score indicates greater severity of prodromal symptoms) and Ki value (influx rate constant) ($r = 0.48, P = .02$). B, The negative relationship between semantic verbal fluency performance (higher score indicates better performance) and Ki value ($r = -0.52, P = .02$).
Evation approached that seen in patients with established schizophrenia. Furthermore, $^{18}$F-dopa uptake in patients with ARMS was directly correlated with the severity of their prodromal symptoms and with the severity of their neuropsychological impairment. The findings remained robust after adjustment for putative factors that might affect $^{18}$F-dopa uptake. These data suggest that increased subcortical dopaminergic activity is already present before the full expression of schizophrenia, consistent with the putative role of dopamine in the pathogenesis of psychosis. However, because not all patients with ARMS go on to develop psychosis and because dopaminergic dysfunction may occur in the relatives of patients with schizophrenia, elevated dopamine activity may also be a correlate of increased vulnerability to psychosis.

A previous $^{18}$F-dopa PET study reported an association between striatal dopaminergic function and symptom domains in a sample of patients in their first episode of illness that is not evident in studies of patients with chronic illnesses. Although there have been inconsistent findings, a relationship between dopaminergic function and psychotic symptoms has also been found in studies (discussed in the review article by Howes et al) of first-episode patients using other molecular imaging techniques. These observations, taken with our finding of a relationship between symptoms and dopaminergic function in the ARMS group, suggest that striatal hyperdopaminergia may be more evident in patients who are developing or are actively experiencing psychotic symptoms than in stable remitted patients.

**METHODOLOGICAL CONSIDERATIONS**

It is unlikely that increased striatal $^{18}$F-dopa uptake is a nonspecific indicator of being unwell or is related to anxiety or depressive symptoms, as it is not elevated in patients with other psychiatric illnesses and showed no relationship to anxiety or depression in our patients. It is also unlikely that the results could be explained by an abnormality in the reference region, as previous studies in schizophrenia have reported similar findings using other reference regions. Partial volume effects could have affected our results, particularly for small ROIs such as the striatal subdivisions. However, these would tend to underestimate $^{18}$F-dopa Ki values and are unlikely to account for an elevation in Ki values. Furthermore, our groups were well matched for variables that might putatively alter dopaminergic systems such as substance use and age, and the results were significant after adjusting for these factors. In addition, all but 1 of the patients with ARMS were naive to antipsychotic drug treatment. The findings in the associative striatum rely on the application of anatomically delineated subdivisions based on animal investigations, indicating that further substantiation in humans is required.

**BIOLOGIC SIGNIFICANCE OF STRIATAL $^{18}$F-DOPA UPTAKE**

Striatal Ki values reflect the conversion of $^{18}$F-dopa by amino acid decarboxylase to $^{18}$F-fluoro-dopamine and its storage in presynaptic vesicles. Although tyrosine hydroxylase is the rate-limiting enzyme, amino acid decarboxylase is a regulated enzyme, and its activity affects the rate of dopamine synthesis. Brain metabolism of $^{18}$F-dopa parallels that of endogenous L-dopa, and striatal $^{18}$F-dopa uptake is highly correlated with striatal dopamine levels in postmortem brains. Furthermore, $^{18}$F-dopa Ki values respond to experimental manipulation of brain dopaminergic systems. Therefore, there is converging evidence that altered $^{18}$F-dopa uptake is functionally significant.

**SIGNIFICANCE OF THE LOCALIZATION OF DOPAMINERGIC ABNORMALITIES IN THE ASSOCIATIVE STRIATUM**

Our data indicate that in the ARMS and schizophrenic groups the dopaminergic abnormality was particularly evident in the associative subdivision of the striatum. This is consistent with recent evidence implicating the associative (as opposed to the limbic) subdivision of the striatum in schizophrenia. Previous $^{18}$F-dopa PET investigations have not used functional striatal subdivisions, limiting comparisons with our findings. A previous study in schizophrenia used an anatomic (as opposed to a functional) subdivision of the striatum into ventral and dorsal components and found that dopaminergic function was significantly elevated in a region that includes parts of the associative and limbic subdivisions evaluated in the present study. Furthermore, in the present study, striatal dopaminergic function in the associative subdivision was negatively related to verbal fluency performance, but this was not the case for the limbic subdivision. Because the associative striatum regulates information flow to and from the prefrontal cortex and because verbal fluency normally depends on prefrontal function, these findings provide a plausible mechanistic link between independent evidence of striatal dopaminergic dysfunction and prefrontal or executive dysfunction in schizophrenia.

**CONCLUSIONS**

Results of recent clinical trials suggest that treatment with antipsychotic medication may reduce the severity of attenuated psychotic symptoms and the risk of schizophrenia in patients with ARMS. Our finding of dopaminergic overactivity in the ARMS group indicates why drugs that act on the dopamine system may have these effects. We conclude that presynaptic striatal dopamine function may be a promising target for future drug development in the treatment of psychotic disorders.

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Correspondence: Oliver D. Howes, MRCPsych, DM, Section of Neuroimaging, Institute of Psychiatry, King's College London, Box 67, De Crespigny Park, London SE5 8AF, England (o.howes@iop.kcl.ac.uk).

Author Contributions: Drs McGuire and Grasby con-
tributed equally to this article. Dr Howes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the analysis and interpretation of the results and the preparation and approval of the manuscript.

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