Presynaptic Striatal Dopamine Dysfunction in People at Ultra-high Risk for Psychosis: Findings in a Second Cohort

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Background: Using positron emission tomography (PET), we previously observed increases in 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalanine (^{18}F-DOPA) uptake in the striatum of subjects at ultra-high risk (UHR) for psychosis, indicating elevated presynaptic dopamine synthesis capacity. The purpose of this study was to test if this finding would be replicated in a second UHR cohort.

Methods: ^{18}F-DOPA PET was used to estimate dopamine synthesis capacity in the striatum of an entirely new cohort of 26 individuals at UHR for psychosis (14 males, mean ± SD age = 22.7 ± 4.7 years) and 20 healthy volunteers matched for age and gender (11 males, mean ± SD age = 24.5 ± 4.5 years).

Results: Dopamine synthesis capacity was elevated in the whole [$t(44) = 2.6$; $p = .01$, effect size = .81] and associative striatum [$t(44) = 2.6$; $p = .01$, effect size = .73] of UHR compared with control subjects. When the two samples were combined to give a final sample of 32 control and 50 UHR subjects, the higher levels of dopamine synthesis capacity in the UHR group reached significance across the whole [$F(1,81) = 11.0$; $p = .001$], associative [$F(1,81) = 12.7$; $p = .001$], and sensorimotor [$F(1,81) = 4.7$; $p = .03$], but not the limbic [$F(1,81) = 2.1$; $p = .2$], striatum.

Conclusions: The findings indicate that elevated dopamine synthesis capacity in the dorsal striatum is a robust feature of individuals at UHR for psychosis and provide further evidence that dopaminergic abnormalities precede the onset of psychosis.

Key Words: Dopamine, imaging, positron emission tomography, psychosis, schizophrenia, striatum

Positive psychotic symptoms in schizophrenia are fundamentally linked to elevations in striatal dopaminergic transmission (1). In vivo positron emission tomography (PET) and single photon emission computed tomography studies in patients with schizophrenia have repeatedly shown findings consistent with elevated striatal presynaptic dopamine synthesis capacity (2–10), exaggerated striatal dopamine release following amphetamine administration (11–14), and increased baseline occupancy of striatal D2 receptors by synaptic dopamine (15,16). Meta-analysis of the published schizophrenia studies has shown that the elevation in presynaptic dopamine function is large, with an effect size of .8 (17).

The emergence of frank psychosis is usually preceded by a prodromal phase, characterized by decline in socio-occupational function and the presence of attenuated psychotic symptoms, such as perceptual abnormalities and paranoid ideas. Individuals with these symptoms, as identified by structured assessments and operationalized criteria, are described as being at ultra-high risk (UHR) for psychosis, and this UHR state is associated with a 20% to 40% increased risk of developing psychosis over the next 2 to 3 years (18–20). Characterization of the neurobiological processes that lead to psychosis may inform pharmacological strategies to prevent psychosis and also provide biomarkers to identify those most at risk.

The most replicated in vivo marker of hyperdopaminergia in schizophrenia is an increase in presynaptic striatal dopamine synthesis capacity, estimated as an increase in uptake (k_i^{cer}) of the PET radiotracer 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalanine (^{18}F-DOPA) (21). Uptake of ^{18}F-DOPA reflects conversion of ^{18}F-DOPA to ^{18}F-fluorodopamine by amino acid decarboxylase and the subsequent storage of ^{18}F-dopamine in synaptic vesicles. Although amino acid decarboxylase is not the rate-limiting step in dopamine synthesis, changes in ^{18}F-DOPA uptake correlate with striatal postmortem dopamine levels (22) and respond to experimental dopaminergic manipulations (23).

Using this approach, we have previously shown that presynaptic dopamine synthesis capacity is increased in the striatum of UHR individuals and that these elevations are directly correlated with prodromal symptom severity (5). These data provided the first evidence that subcortical dopaminergic elevations precede the onset of psychosis, in line with predictions for the prodromal phase (24). Clinical follow-up of this cohort found that the UHR subjects who had the highest level of striatal dopamine synthesis capacity at baseline subsequently developed psychosis (25) and that clinical progression to psychosis was associated with a further dopaminergic elevation (26). This indicates that elevated striatal dopamine synthesis capacity may ultimately be used as a neurobiological marker to identify those UHR individuals most likely to progress to psychosis, allowing targeting of preventative strategies.

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Replication is an important next step in assessing whether increased striatal dopamine synthesis capacity may be a biomarker of psychosis risk. As only a minority of individuals meeting UHR criteria will go on to develop a psychotic disorder, data in a large sample at intake are required to fully explore associations with longer term clinical outcome. The main purpose of this study was to confirm our finding of elevated dorsal striatal dopamine synthesis capacity in the UHR state (5) in an entirely new cohort of UHR and control subjects recruited from the same study site and to provide a larger sample for subsequent clinical follow-up by combining these datasets. A second purpose was to use the increased statistical power afforded by the combined dataset to test the anatomical specificity of the dopamine dysfunction to the dorsal over ventral striatal areas.

Methods and Materials

This study was approved by the Institute of Psychiatry, King's College London, Research Ethics Committee. After complete description of the study to the participants, written informed consent was obtained. Twenty-six UHR individuals were recruited from Outreach and Support in South London, part of the South London and Maudsley National Health Service Trust. All met criteria for attenuated psychotic symptoms (abnormal beliefs, perceptions, or speech) (27). Additionally, four (15%) UHR subjects had experienced at least one brief, spontaneously remitting psychotic episode lasting less than 1 week in the last year; six (23%) UHR subjects had a first-degree relative with schizophrenia; and two (8%) UHR subjects met DSM-IV criteria for schizotypal personality disorder. Most of the subjects were medication-free at the time of scanning. Two UHR subjects were taking antipsychotic medication (olanzapine, 7.5 mg; quetiapine, 25 mg) and four were taking an antidepressant (citalopram, 20 mg).

Twenty control subjects were recruited from the same geographic area by public advertisement. Control subjects reported no family history of psychiatric symptoms, psychotropic medication, or medical illness. For both groups, exclusion criteria included breast-feeding or pregnancy, history of head injury, and current or previous drug or alcohol dependence. Drug use and handedness were determined by self-report. None of the individuals in either the UHR or healthy comparison group were included in our previously published studies of dopamine function (5,25,26).

Clinical Measures

Psychopathology was assessed using the Comprehensive Assessment of At-Risk Mental State (CAARMS), as positive symptom score (sum of severity score on items of unusual thought content, perceptual abnormalities, and disorganized speech) and as total score (sum of severity on all items) (27); Positive and Negative Syndrome Scale (PANSS) (positive, negative, general, and total score) (28); and the Hamilton Depression and Anxiety Rating Scales (29,30). Level of global functioning was assessed using the Global Assessment of Functioning scale (31).

^{18}F-DOPA PET Imaging

Study participants were asked to fast and abstain from alcohol or other substance use for 12 hours before imaging. A urine drug screen was performed on the morning of the scan to confirm that there had been no recent use of stimulants or opiates. Subjects received carbidopa (150 mg) and entacapone (400 mg) orally 1 hour before imaging (32) to reduce the formation of radiolabeled ^{18}F-DOPA metabolites (33).

Data were acquired on an ECAT HR+ 962 PET scanner (CTI/Siemens, Knoxville, Tennessee) in three-dimensional mode, with an axial field of view of 15.5 cm. Head position was marked and monitored via laser crosshairs and a camera and minimized using a light head strap. A 10-minute transmission scan was performed before radiotracer injection to correct for attenuation and scatter.

Thirty seconds after the start of PET image acquisition, ^{18}F-DOPA was administered by bolus intravenous injection. There was no significant group difference in the amount [control: mean (SD), 182.5 (5.9) MBq; UHR: 178.2 (10.6) MBq; $t(44) = 1.6$, $p = .1$] or specific activity of radioactivity injected [control: mean (SD), 26.0 (12.9) MBq/μmol; UHR: 33.1 (20.9) MBq/μmol; $t(44) = 1.3$, $p = .2$]. Emission data were acquired in list mode for 95 minutes, rebinned into 26 time frames (comprising the 30-sec background frame, followed on ^{18}F-DOPA injection by 4 60-sec frames, 3 120-sec frames, 3 180-sec frames, and 15 300-sec frames).

To correct for head movement during the scan, nonattenuation-corrected dynamic images were denoised using a level 2, order-64 Battle-Lemarie wavelet filter (34) and individual frames were realigned to a single frame acquired 5 minutes after ^{18}F-DOPA injection using a mutual information algorithm (35). 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 analysis.

Standardized striatal volumes of interest (VOI) were delineated bilaterally on a single subject T1 magnetic resonance image in Montreal Neurologic Institute space as previously described (7). These VOI included the limbic (ventral), associative (precommissural dorsal caudate, precommissural dorsal putamen, and postcommissural caudate), and sensorimotor (postcommissural putamen) subdivisions of the striatum, as according to previously defined anatomical criteria (36,37). The cerebellar reference region was defined using a probabilistic atlas (38). An ^{18}F-DOPA template (7), also in Montreal Neurologic Institute space, was then normalized together with the VOI map to each individual PET summation (add) image using the statistical parametric mapping suite SPM5 (http://fil.ion.ucl.ac.uk/spm; Wellcome Department of Imaging Neuroscience, University College London). This procedure allows VOIs to be placed automatically on individual ^{18}F-DOPA PET images, which avoids the potential observer bias or human error associated with nonautomated, individual image VOI delineation. As such, this study did not include individual magnetic resonance imaging. Our previous ^{18}F-DOPA test-retest study shows that our automated method has good reliability, with an overall striatal intraclass correlation coefficient of .84 (39). Utilization of ^{18}F-DOPA, relative to the cerebellar reference tissue (k_i^{cer} min^{-1}, alternatively designated as K_i in some publications), was calculated for each VOI both unilaterally and bilaterally using graphical analysis, adapted for a reference tissue input function (40,41).

Combining Data from the Two Studies

A secondary objective was to combine data from the present study (20 control subjects and 26 UHR volunteers) with that from our previous investigation (12 control subjects and 24 UHR volunteers) (5) to provide a larger sample of 32 control and 50 UHR subjects to increase statistical power. Both studies used the same participant assessment methods and inclusion criteria, but data were acquired on different PET scanners (CTI/Siemens ECAT HR+ 962 in the present study and CTI/Siemens ECAT

Table 1. Group Demographics

	Control ($n = 20$)	UHR ($n = 26$)	Significance
Age, Mean (SD)	24.5 (4.5)	22.7 (4.7)	$t(44) = 1.3$; $p = .2$
Gender, Male/Female	11/9	14/12	$\chi^2 = .006$; $p = .9$
Handedness, Right/Left	14/6	23/3	Fisher's exact $p = .2$
Current Tobacco Use, No/Yes	15/5	16/10	$\chi^2 = .9$; $p = .3$
Alcohol Units per Week, Median	5.5	1.0	$U = 189.5$; $Z = 1.6$; $p = .1$
Cannabis Ever, No/Yes	11/9	12/14	$\chi^2 = .4$; $p = .6$
Ecstasy Ever, No/Yes	16/4	18/8	Fisher's exact $p = .5$
Amphetamine Ever, No/Yes	18/2	22/4	Fisher's exact $p = .8$
Cocaine Ever, No/Yes	17/3	17/9	Fisher's exact $p = .2$
Ketamine Ever, No/Yes	19/1	24/2	Fisher's exact $p = 1.0$

UHR, ultra-high risk.

HR++ 966 in the previous study). In-house phantom data show these scanners are similar in terms of spatial resolution (full width half maximum, ECAT HR+ 966: 5.3 mm; ECAT HR++ 962: 5.1 mm) but the ECAT HR++ 962 tomograph has less intrinsic sensitivity than the ECAT HR+ 966 (T. Spinks, Ph.D., GE Imanet, Hammersmith Hospital, London, United Kingdom, oral communication, 2007). All other aspects of the ^{18}F-DOPA PET scanning paradigm and analysis methods were identical.

Statistical Analysis

For data acquired in the present cohort, between-group comparisons were performed with two-tailed unpaired *t* tests for parametric variables and Mann-Whitney *U*, χ^2, or Fisher's exact test for nonparametric variables. Potentially confounding effects of recreational drug use on group differences in k_i^{cer} were investigated by univariate analysis of variance with regional k_i^{cer} as the dependent variable and group and drug use as independent variables. Each recreational drug was investigated in separate analyses. Relationships between regional k_i^{cer} values and symptoms in the UHR group were explored using Pearson product-moment correlation coefficient; as we previously observed, positive relationships between k_i^{cer} in the whole, associative, and sensorimotor striatum and the severity of prodromal or schizophrenic symptoms in the UHR group (indexed by total CAARMS and PANSS score) (5), correlation analysis was restricted to these variables. Effect sizes were estimated using Cohen's *d*, calculated using the pooled standard deviation. When combining the present and previous cohorts (5), effects of group on k_i^{cer} were determined using analysis of covariance, with PET scanner entered as a covariate, and effect sizes were estimated using partial eta squared. All analyses were performed in SPSS version 15.0 (IBM Corporation, Armonk, New York). Statistical significance was defined as $p < .05$.

Results

Demographic and Clinical Characteristics

Group demographics are presented in Table 1. The groups did not differ in age, gender, handedness, or recreational drug use. Clinical ratings are presented in Table 2. As expected, symptom ratings were significantly higher in the UHR than in the control group.

Dopaminergic Function

There was no significant effect of age or gender on whole striatal k_i^{cer} [age: $r = -.05$, $p = .85$; gender: $t(44) = .93$, $p = .36$]. In the UHR group relative to the control group, mean k_i^{cer} was elevated in the whole striatum [$t(44) = 2.6$, $p = .01$, effect size = .8] (Figure 1 and Table 3). When the analysis was restricted to functional striatal subdivisions, the elevation was significant in the associative subdivision [$t(44) = 2.6$, $p = .01$, effect size = .7]; the elevation was evident at trend level significance in the sensorimotor subdivision [$t(44) = 2.0$, $p = .05$]; and there was no significant difference in the limbic [$t(44) = .05$, $p > .99$] striatum. The elevation in the associative striatum remained significant after correction for running multiple comparisons (effect of group investigated at each of the three striatal subdivisions, giving threshold $p = .02$). After exclusion of UHR subjects who were taking antipsychotic medication ($n = 2$), k_i^{cer} was significantly higher in UHR than control subjects in the whole striatum [$t(42) = 2.5$, $p = .02$], associative [$t(42) = 2.6$, $p = .01$], and at

Table 2. Clinical Measures

	Control ($n = 20$)	UHR ($n = 26$)	Significance
CAARMS Positive	0 (.0)	8 (5.5)	$U = .5$; $Z = 5.9$; $p < .001$
CAARMS Total	0 (2.75)	44 (9.25)	$U = .0$; $Z = 5.8$; $p < .001$
PANSS Positive	7 (.0)[a]	13 (7.25)	$U = 20.0$; $Z = 5.6$; $p < .001$
PANSS Negative	7 (.0)[a]	12 (5.25)	$U = 50.0$; $Z = 5.0$; $p < .001$
PANSS General	16 (.0)[a]	30 (6.0)	$U = .0$; $Z = 6.0$; $p < .001$
PANSS Total	30 (.0)[a]	55 (12.75)	$U = .0$; $Z = 6.0$; $p < .001$
Hamilton Anxiety Rating Scale	0 (.75)	12 (16.0)	$U = 35.5$; $Z = 5.1$; $p < .001$
Hamilton Depression Rating Scale	0 (.75)	17 (16.0)	$U = 26.5$; $Z = 5.3$; $p < .001$
Global Assessment of Functioning	85 (5.0)	55 (9.5)	$U = .0$; $Z = 5.6$; $p < .001$

The table presents median (interquartile range) scores for each group. Higher scores on the CAARMS, PANSS, and Hamilton scales indicate more severe symptoms. Lower Global Assessment of Functioning scores indicate worse function.

CAARMS, Comprehensive Assessment of At Risk Mental States; PANSS, Positive and Negative Syndrome Scale.

[a]Score at floor, indicating no symptoms.

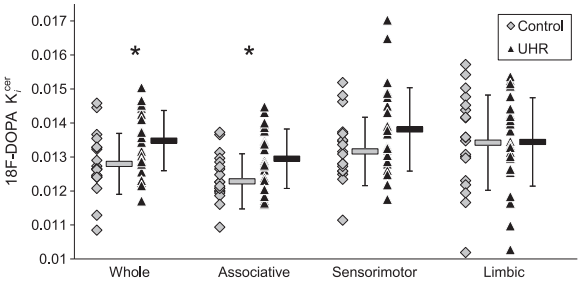

Figure 1. Individual and group mean ± SD ^{18}F-DOPA uptake (k_i^{cer}) (min−1) values (indexing presynaptic dopamine synthesis capacity) in the whole, associative, sensorimotor, and limbic striatum. Data in the healthy control group ($n = 20$) are represented by grey diamonds and data in the ultra-high risk group (UHR) ($n = 26$) by black triangles. k_i^{cer} values were significantly higher in the UHR than control group in the whole and associative striatum (*$p < .05$), indicating elevated dopamine synthesis capacity.

trend level in the sensorimotor striatum [$t(42) = 1.8$, $p = .07$], but not in the limbic striatum [$t(42) = .05$, $p = .96$]. The elevation in k_i^{cer} in the UHR group also remained significant in the whole striatum [$t(42) = 2.5$, $p = .02$] and associative striatum [$t(42) = 2.6$, $p = .01$] after removing the UHR individuals with schizotypal personality disorder ($n = 2$) from the analysis and after exclusion of both subjects on antipsychotic medication and subjects with schizotypal personality disorder [whole striatum $t(40) = 2.4$, $p = .02$; associative striatum $t(40) = 2.5$, $p = .02$].

There were no main effects of drug use or drug-by-group interactions for nicotine, cannabis, ecstasy, cocaine, or ketamine use on k_i^{cer} in any striatal region ($p > .05$). However, there was a significant main effect of amphetamine use on k_i^{cer} in the whole striatum [$F(1,45) = 5.58$, $p = .02$] and in all striatal subdivisions [associative: $F(1,45) = 5.01$, $p = .03$; sensorimotor: $F(1,45) = 4.33$, $p = .04$; limbic: $F(1,45) = 6.9$, $p = .01$]. This was due to lower k_i^{cer} values in the 6 amphetamine users (4 from the UHR group and 2 from the control group) compared with the 40 nonusers (whole striatum mean ± SD k_i^{cer} amphetamine users: .0124 ± .0005; amphetamine nonusers .0133 ± .009). There were no significant amphetamine-by-group interactions in any striatal area. The elevation in k_i^{cer} in the UHR compared with control group remained significant after excluding the six amphetamine users from the analysis [$n = 18$ control subjects, 22 UHR subjects; whole striatum: $t(38) = 3.0$, $p = .005$; associative striatum: $t(38) = 3.0$, $p = .005$; sensorimotor striatum: $t(38) = 2.3$, $p = .03$]. Furthermore, the elevation in k_i^{cer} in the UHR compared with control group remained significant after excluding volunteers reporting use of any recreational drugs except alcohol and tobacco from the sample [$n = 11$ control subjects, 12 UHR subjects; whole striatum: $t(21) = 2.8$, $p = .01$; associative striatum: $t(21) = 2.8$, $p = .01$; sensorimotor striatum: $t(21) = 2.3$, $p = .03$].

Relationships with Symptoms

Within the UHR group, there were no significant relationships between severity of prodromal symptoms (CAARMS total score) and k_i^{cer} (whole striatum: $r = -.19$, $p = .35$; associative striatum: $r = -.15$, $p = .48$; sensorimotor striatum: $r = -.07$, $p = .74$) or schizophrenic symptoms (PANSS total score) and k_i^{cer} (whole striatum: $r = -.26$, $p = .20$; associative striatum: $r = -.31$, $p = .12$; sensorimotor striatum: $r = -.14$, $p = .50$).

Replication of Previous Findings

The clinical and demographic features of the UHR samples in this and our previous study (5) were similar. Both studies found a significant elevation in k_i^{cer} in the whole and associative striatum in a UHR compared with control group (Table 3). The PET data were acquired on different scanners and, across UHR subjects and control subjects, the whole striatal k_i^{cer} values were significantly lower in the present study than in the first cohort [main effect of scanner: $F(1,81) = 43.2$, $p < .001$], reflecting known differences in the sensitivity between scanners (42).

Combining Data from Two Studies

When the analysis was repeated after the data from the two studies were combined (to maximize statistical power), after accounting for scanner effects, there was a significant overall elevation in k_i^{cer} in UHR compared with control subjects in the whole striatum [$F(1,81) = 11.0$, $p = .001$; with a partial eta squared = .12] and in the associative [$F(1,81) = 12.7$, $p = .001$; partial eta squared = .14] and sensorimotor [$F(1,81) = 4.7$, $p = .03$; partial eta squared = .06] but not in the limbic [$F(1,81) = 2.1$,

Table 3. Results of the Previous and Present Studies of Striatal Presynaptic Dopamine Function in Healthy Control Versus Subjects at Ultra-High Risk of Psychosis

	Control			UHR				
Study	*n*	Mean	SD	*n*	Mean	SD	Significance	*d*
Whole Striatum								
Previous	12	.0142	.0012	24	.0151	.0012	$t(34) = 2.2$; $p = .04$	.75
Present	20	.0128	.0009	26	.0135	.0009	$t(44) = 2.6$; $p = .01$	.81
Associative Striatum								
Previous	12	.0137	.0012	24	.0147	.0011	$t(34) = 2.5$; $p = .02$	.83
Present	20	.0123	.0008	26	.0129	.0009	$t(44) = 2.6$; $p = .01$	.73
Limbic Striatum								
Previous	12	.0140	.0027	24	.0152	.0013	$t(34) = 1.9$; $p = .06$	.72
Present	20	.0134	.0014	26	.0134	.0013	$t(44) = .05$; $p < 1.0$	.00
Sensorimotor Striatum								
Previous	12	.0154	.0018	24	.0162	.0019	$t(34) = 1.2$; $p = .2$	.45
Present	20	.0131	.0010	26	.0138	.0012	$t(44) = 2.0$; $p = .05$	.65

For each study, the table presents the number of subjects per group (*n*), mean and SD k_i^{cer} (min−1) values (^{18}F-DOPA influx rate constant, indexing presynaptic dopamine synthesis capacity), and the statistical significance of the group comparison and effect size (*d*).

k_i^{cer}, uptake; UHR, ultra-high risk.

$p = .2$; partial eta squared = .03] striatal subdivision. There were no significant scanner by group interactions. Analysis showed that the combined data were associated with a power to detect significant group difference in k_i^{cer} (at alpha = .05) of .9 in the whole and associative striatum and .6 in the sensorimotor striatum but only .3 in the limbic striatum. After combining the two cohorts and excluding individuals with schizotypal personality disorder ($n = 11$), individuals on antipsychotic medication ($n = 3$), and individuals reporting any recreational drug use (except nicotine or alcohol) ($n = 27$) to obtain a cleaner sample of 23 control subjects and 23 UHR subjects, the group differences in k_i^{cer} reached significance in the whole [$F(1,45) = 7.4$, $p = .01$; partial eta squared = .15] and associative [$F(1,45) = 8.9$, $p = .005$; partial eta squared = .17] striatum but not in the sensorimotor [$F(1,45) = 1.9$, $p = .17$; partial eta squared = .04] or limbic [$F(1,45) = 3.3$, $p = .8$; partial eta squared = .07] striatum.

Discussion

The main finding of this study is an elevation in striatal dopamine synthesis capacity (as estimated by ^{18}F-DOPA uptake, k_i^{cer}) in individuals at UHR for psychosis relative to matched healthy volunteers. This difference remained significant after exclusion of UHR subjects who were currently taking antipsychotic medication or had a diagnosis of schizotypal personality disorder and after exclusion of UHR and control subjects who reported recreational drug use. This finding replicates and extends our previous study by showing a large and similar effect size for the elevation in striatal dopamine synthesis capacity in an entirely new cohort of UHR individuals, scanned on a different PET scanner. While replication by an independent research group is awaited, our reports of increased striatal dopamine synthesis capacity in the UHR state are consistent with the recent report of increased stress-induced striatal dopamine release in UHR individuals (43). Together, these findings provide robust evidence that striatal dopaminergic abnormalities precede the onset of psychosis.

As in the first cohort, elevations in dopamine synthesis capacity were significant across the whole striatum but were particularly marked in the associative striatal subdivision. In patients with schizophrenia, elevations in both dopamine synthesis capacity (5) and in estimated synaptic dopamine levels (16) were particularly apparent in the associative striatum. The preferential localization of dopaminergic abnormalities to the associative striatum in psychosis has been related to cognitive dysfunction (5,16) in accordance with associative striatal-prefrontal cortical connectivity (44). Our analysis combining both cohorts found that there was evidence of an elevation in the sensorimotor striatum as well, where longitudinal changes have been seen in the progression from UHR to the first psychotic episode (26). In contrast, no group differences in dopamine synthesis capacity were apparent in the limbic striatum. However, while ^{18}F-DOPA k_i^{cer} shows good reproducibility and reliability across all striatal areas, estimates in the ventral (limbic) striatum have somewhat greater within-subject variability and lower reliability than those in dorsal aspects, as smaller volumes are more susceptible to motion artifacts and effects of resolution constraints (39). Even in the combined sample, the observed limbic values were only associated with a power of .3 to detect a significant group difference in ^{18}F-DOPA k_i^{cer}. Therefore, elevations in presynaptic dopamine synthesis capacity are consistently observed in the dorsal striatum, but we cannot be confident in excluding an effect in the limbic striatum on the basis of these data.

As noted previously (5), it is unlikely that elevated striatal dopamine synthesis capacity is a nonspecific indicator of being unwell, as striatal dopamine synthesis capacity is not elevated in patients with other psychiatric disorders, such as nonpsychotic bipolar disorder or depression (see [45] and review [24]). The results are also unlikely to be due to abnormalities in the cerebellar reference region, as similar findings have been reported in schizophrenia using other reference regions (3,4,7). Striatal dopamine synthesis capacity was significantly lower in the six individuals (two control and four UHR subjects) who reported previously taking amphetamine. This is consistent with studies in monkeys that show decreases in striatal ^{18}F-DOPA uptake following amphetamine or methamphetamine administration, interpreted as neurotoxic effects on dopaminergic terminals (46), but the reliability of this observation in our sample is questionable, given the small number of subjects with a history of amphetamine use. The elevation in striatal presynaptic dopamine synthesis capacity in the UHR compared with control group remained when volunteers who had previously taken amphetamine or any other recreational drug were excluded from the analysis and we did not detect any further influence of recreational drug use.

One caveat is that while the ^{18}F-DOPA reference region approach affords greater practicability by avoiding the need for arterial sampling over a 95-minute scan acquisition period, this method does not allow separation of the rate of dopamine synthesis from the capacity to store synthesized dopamine in presynaptic vesicles. A previous study has shown that schizophrenia is associated with an increased capacity for dopamine synthesis together with a reduction in the ability to store synthesized dopamine (47). At present, it is unknown whether elevations in ^{18}F-DOPA k_i^{cer} in the UHR state are primarily driven by abnormalities in dopamine synthesis or storage. A further limitation is that the method used to classify the striatum to sensorimotor, associative, and limbic regions does not take into account subtle anatomic points or regional overlap in striatal functional circuits (36). Finally, although we cannot exclude the presence of group differences in striatal volume in this sample, striatal volumetric abnormalities are not a feature of the UHR state (48).

The positive relationships between striatal dopamine synthesis capacity and symptom severity in the UHR observed in our first cohort (5) were not replicated in the new sample. However, subsequent clinical follow-up of the first cohort showed that the relationships between striatal dopamine synthesis capacity and symptoms were most marked in the individuals who developed a frank psychotic illness in the following 3 years (25), and longitudinal imaging has shown that there is a progressive increase in striatal dopamine synthesis capacity with the onset of psychosis (26). Thus, the relationship between striatal dopamine synthesis capacity and symptoms may only become apparent in subjects later in the trajectory to psychosis, when the dopaminergic dysregulation has progressed. This interpretation will be tested once clinical follow-up of the present cohort has been completed. While dopamine dysfunction is centrally implicated in psychosis, the development and onset of psychosis has also been associated with abnormalities in glutamatergic neurotransmission, brain structure, and function (49–52). Interactions between these abnormalities, as revealed by multimodal imaging studies (e.g. [53]), may clarify the neurobiology of psychosis risk.

In conclusion, this study confirms that striatal dopamine synthesis capacity, as indexed by ^{18}F-DOPA uptake (k_i^{cer}), is elevated in people at ultra-high risk for psychosis. The presence of elevated

dopamine synthesis capacity before the onset of psychosis suggests that dopaminergic interventions may be useful in this phase of the disorder (21). Furthermore, clinical follow-up of our first cohort found that those UHR subjects with the highest levels of striatal ^{18}F-DOPA uptake at presentation were the most likely to develop a psychotic disorder over the next 3 years (25). Clinical follow-up of this second cohort will confirm whether the extent of dopaminergic elevation at baseline is predictive of subsequent onset of psychosis.

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