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Striatal and extrastriatal dopamine D₂/D₃ receptors in schizophrenia evaluated with [¹⁸F]fallypride PET

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Abstract

Background—Alterations in dopamine D₂/D₃ receptor binding have been reported in schizophrenia, and a meta-analysis of imaging studies has shown a modest elevation in striatum. Newer radioligands now allow the assessment of these receptors in extrastriatal regions. We used PET with [¹⁸F]fallypride to evaluate D₂/D₃ receptors in both striatal and extrastriatal regions in schizophrenia.

Methods—Twenty-one patients with schizophrenia and 22 matched healthy controls were scanned with an HR+ camera. Two-tissue compartment modeling (2TCM) and the reference tissue method gave binding potentials BP_{ND}, BP_P, and BP_F which were compared between groups in five striatal and 8 extrastriatal regions. Several regional volumes were lower in the patient group, and PET data were corrected for partial volume effects.

Results—BP values differed in three regions between groups. BP_{ND} values from 2TCM in patients and controls respectively were 28.7 ± 6.8 and 25.3 ± 4.3 in post-commissural caudate, 2.9 ± 0.7 and 2.6 ± 0.4 in thalamus, and 1.8 ± 0.5 and 2.1 ± 0.7 in uncus. Loss of D₂/D₃ receptors with age was found in striatal and extrastriatal regions and was greater in neocortex.

Conclusions—Our study found selective alterations in D₂/D₃ receptors in striatal and extrastriatal regions, consistent with some but not all previously published reports. As previously shown for the striatum, a more sensitive imaging approach for studying the role of dopamine in the pathophysiology of schizophrenia might be assessment of neurotransmitter levels rather than D₂/D₃ receptor levels in extrastriatal regions.

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Keywords

schizophrenia; positron emission tomography; dopamine D₂/D₃ receptor; fallypride; extrastriatal regions; partial volume correction; age-related D₂/D₃ receptor loss

INTRODUCTION

Alterations in dopamine D₂/D₃ receptor binding have been reported in many studies in schizophrenia. A meta-analysis of imaging studies comparing D₂/D₃ receptor parameters in patients with schizophrenia revealed a small (12%) but significant elevation of these receptors in striatum (1). Excessive activity at striatal D₂/D₃ receptors in schizophrenia is thought to be related to the positive symptoms of the illness (2).

Imaging studies have mainly focused on striatal D₂/D₃ receptors in part because the first generation of D₂/D₃ receptor ligands ([¹¹C]NMSP, [¹¹C]raclopride, [¹²³I]IBZM) allowed imaging only in the striatum. More recently a new generation of D₂/D₃ receptor radiotracers has allowed visualization of extrastriatal receptors. Because of the low density of extrastriatal D₂/D₃ receptors (3–7), and therefore the low signal to noise ratio, radiotracers with high affinity and/or low nonspecific binding are required, such as [¹¹C]FLB 457 (K_D = 0.018 nM) (8) and [¹⁸F]fallypride (K_D = 0.030 nM in vitro, 0.2 nM in vivo) (9;10). Using [¹⁸F]fallypride, these receptors have been quantified in thalamus, midbrain, amygdala, insula, hippocampus, uncus, entorhinal cortex, and temporal neocortex. These extrastriatal structures are important to the pathophysiology of schizophrenia, as many reports have suggested alterations in structure or function of limbic and cortical regions. Postmortem studies in schizophrenia have indicated increased tissue levels of dopamine in the amygdala (11) and decreased dopaminergic innervation in the dorsolateral prefrontal cortex and the entorhinal cortex (12;13). In order to generate a fuller picture of dopaminergic alterations in these circuits, we chose to use [¹⁸F]fallypride, which is labeled with the relatively slowly decaying isotope F-18 and allows measurement of D₂/D₃ receptor binding in both striatal and extrastriatal areas (14;15). In contrast, [¹¹C]FLB 457 is labeled with the rapidly decaying isotope C-11, has slower kinetics of uptake, and can be used for quantification of D₂/D₃ receptor parameters in extrastriatal areas only. Furthermore, we measured D₂/D₃ receptors in striatal substructures as previously described (16), in order to discriminate possible pathology in dopaminergic D₂/D₃ receptor density in limbic versus associative or sensorimotor loops.

Recent studies from other centers have already reported alterations in extrastriatal regions but no conclusive picture has yet emerged. We used [¹⁸F]fallypride and a relatively large sample of unmedicated patients with schizophrenia to further explore alterations in D₂/D₃ receptors in subregions of the striatum as well as the extrastriatal regions that can be quantified and are relevant to the pathophysiology of schizophrenia.

METHODS

Subjects

Twenty-one patients and 22 matched healthy control subjects underwent a total of 43 [¹⁸F]fallypride scans (see Table 1 for clinical and demographic characteristics that include matching for age, gender, ethnicity, smoking status, and parental but not subject socioeconomic status (17)). Patients were medically healthy and met inclusion criteria for schizophrenia or schizoaffective disorder but no other DSM-IV (18) Axis I diagnosis, no substance abuse by history confirmed with negative urine drug screens, and were free of any psychotropic medication for at least 18 days before scanning (with the exception of lorazepam, which was allowed at a maximal dose of 3 mg per day no later than 24 h before the study). There were no

occurrences of relapse during the medication-free period. Patients were recruited from the Schizophrenia Research Unit, the New York State Psychiatric Institute (NYSPI) or the affiliated outpatient research clinic. The protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute and Columbia University Medical Center and after complete description of the study to the subjects, written informed consent was obtained. Capacity to provide informed consent was evaluated by a psychiatrist not associated with the study. Assent from involved family members was obtained. The PET scan data for 8 of the patients were published previously as baseline scans in a medication occupancy study (19).

Radiochemistry

[¹⁸F]fallypride was prepared by reacting the starting material tosylate (2–3 mg) (20) with resolubilized K[¹⁸F]F/K222 in acetonitrile (1 ml) at 80° C for 15 min. The crude reaction mixture was mixed with water (20 ml) and passed through a C-18 Sep-Pak. The Sep-Pak was washed with 20 ml of 20% aqueous ethanol and the crude product was recovered with 1.5 ml of ethanol, which was then purified by a semipreparative HPLC method. The HPLC product fraction was mixed with 100 ml of water and passed through a C-18 Sep-Pak. After 20% ethanol (10 ml) and water (10 ml) wash, the tracer was recovered from the Sep-Pak using 1 ml of absolute ethanol. The average radiochemical yield was about 30% at the end of bombardment (EOB) or about 15% at the end of synthesis (EOS). A small sample from the ethanol solution was removed for determination of specific activity, radiochemical purity and chemical purity. The rest of the ethanol solution was diluted with saline (9 ml) and passed through a sterile membrane filter into a vented sterile sample vial. The injected mass was $1.01 \pm 0.19 \mu\text{g}$, specific activity was $1163 \pm 542 \text{ Ci/mmol}$, and activity dose was $3.02 \pm 1.01 \text{ mCi}$ at time of injection (n=43) (Table S1 in the Supplement).

PET scanning

PET imaging was performed in 3D mode with an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN) (21). Ten-minute transmission scans were obtained as detailed below. [¹⁸F]fallypride was injected i.v. over 30s. Emission data were acquired over 240 min as 24 frames of increasing duration (3 * 20 s, 3 * 1 min, 3 * 2 min, 2 * 5 min, and 13 * 10 min, totaling 150 min of acquisition time). During the 240 min there were two breaks out of the camera as follows: at 50 min, a 10-min transmission scan was followed by a 20-min break; and at 140 min, a 10-min transmission scan was followed by a 40-min break followed by a final 10-min transmission scan preceding the final acquisitions. Thus, emission data were obtained in 3 successive blocks of 50 min, 60 min, and 40 min. PET emission data were attenuation-corrected using the transmission scans, and frames were reconstructed using a Shepp filter (cutoff 0.5 cycles/projection ray).

Input function measurement

Arterial access was available for n=42 of the 43 scans (all healthy control subjects and n=20 of the 21 patients). Following radiotracer injection, arterial samples were collected every 10–20 s with an automated sampling system for the first four minutes, and manually thereafter at longer intervals. Following centrifugation (10 min at 1,100g), plasma was collected in 0.2 ml aliquots and radioactivity was measured in a gamma counter calibrated with the PET camera (Wallac 1480 Wizard 3M Automatic, Perkin-Elmer). Five plasma samples (collected at 2, 20, 40, 80, and 120 min) were processed by HPLC to measure the fraction of plasma radioactivity representing unmetabolized parent tracer. The eluent was fraction-collected as 1-min fractions over 12 min. For each sample, the fraction parent was estimated by the ratio of decay-corrected radioactivity measured by gamma counter in fractions 8–10 to the radioactivity of the total collection. A control blood sample with standard [¹⁸F]fallypride solution was similarly

processed with each experiment. A biexponential function was fitted to the five measured parent fractions and used to interpolate and extrapolate values. The smallest exponential rate constant of the fraction parent curve was constrained to the difference between the terminal rate of washout of cerebellar activity, and the smallest elimination rate constant of the total plasma. The product of total counts times the biexponential function was computed, and the resulting “empirical” input function was fitted to a sum of three exponentials from the time of peak plasma activity. These fitted values were used as input for the kinetic analyses (22).

PET data analysis

Each subject underwent a high-resolution T1-weighted magnetic resonance imaging (MRI) scan on a GE-Signa system. For each PET scan, frame to frame registration, followed by co-registration to the subject’s MRI using mutual information maximization, was implemented in the SPM2 software environment (23).

Regions of interest (ROIs) were drawn on each subject’s MRI using MEDx software (Sensor Systems, Inc., Sterling, Virginia): the cerebellum (reference region); 5 striatal subregions (pre-commissural dorsal caudate, post-commissural caudate, pre-commissural dorsal putamen, post-commissural putamen, ventral striatum) (16), and 8 extrastriatal regions (thalamus, amygdala, insula, midbrain, hippocampus, uncus, temporal cortex, entorhinal cortex). Delineation of ROIs was as previously described for striatal subregions (16) and as described here for extrastriatal regions of particular interest. The uncus was defined as the superior medial temporal lobe gray matter region extending anteriorly from the anterior commissure to the coronal level at which the temporal lobe white matter becomes discontinuous from that of the cerebral hemisphere. The uncus is anterior to the entorhinal cortex, which extends posteriorly from the anterior commissure at a level inferior to the uncus. The midbrain extends anteriorly to the coronal level of the superior junction of the pons and brainstem, and its inferior boundary is the axial level of the junction. The region is delineated with superior boundary inferior to the third ventricle, and the lateral and posterior boundaries defined by visualizing the signal intensity of the midbrain region. Additional cortical regions were examined but exhibited very low binding and were considered unreliable for comparison purposes and excluded from analysis. Right and left regions were averaged.

Outcome measures were calculated using two modeling methods. The first of these was the simplified reference tissue model (SRTM) (24), yielding BP_{ND} ($n=43$), a binding potential measure denoting the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue (25). The second method was the two tissue compartment model (2TCM) with arterial input function ($n=42$; one subject lacked arterial access), yielding binding potential measures BP_{ND} , BP_P , and BP_F (25). In each region, total distribution volume (VT , mL/cm^3 defined as the ratio of total radioligand concentration in the ROI to unmetabolized tracer concentration in arterial plasma at equilibrium) was computed by nonlinear least squares fitting. Outcome measures were then computed as $BPP(ROI) = VT(ROI) - VT(cerebellum)$, $BP_{ND} = BPP(ROI)/VT(cerebellum)$ and $BP_F(ROI) = BPP(ROI)/fp$ where fp is the fraction of radioligand in arterial plasma not bound to protein. For SRTM analysis, the cerebellum time activity curve was used as input.

In several brain regions, volumetric measurements from individual subjects’ MRI scans were lower in patients than in healthy control subjects. A hybrid partial volume effect correction was performed for all regions, utilizing a voxel-based approach in cortical regions (26), and a modified ROI-based method in striatum, thalamus and midbrain (16;27;28).

Clinical ratings

Patients were evaluated while unmedicated near the time of PET scanning with the PANSS rating scale (29) (a comprehensive instrument incorporating the BPRS (30) and additional positive and negative symptom items) to assess symptoms, and with the n-back test (31) to evaluate working memory. Ratings were examined for correlations with regional binding potential.

Statistical tests

Group means are presented as average $\pm$ standard deviation.

ANCOVA with age as covariate, or repeated measures ANCOVA as appropriate, was used to compare ROI-based and voxelwise BP values between patient and control groups since the patients were older than the controls at trend level (Table 1). Regression analysis with the Pearson correlation coefficient was used for comparison of D₂/D₃ receptor binding levels to age and to clinical ratings, as well as comparison of plasma free fraction of radioligand to body mass index.

RESULTS

Emission data were stable and continuous across the blocks of acquisition time in both patient and healthy control groups (Figure S1 in the Supplement). Injected doses, masses, and specific activities of [¹⁸F]fallypride did not differ between the patient and healthy control groups (Table S1 in the Supplement).

Effect of partial volume correction

Partial volume correction of the PET regional data resulted in from 30% to over 100% increases in BP values. For example, increases were 30% in controls and 33% in schizophrenia in thalamus, 94% and 103% in post-commissural caudate and 109% and 88% in uncus, respectively and were comparable across BP measures. These regions showed trends toward group differences in the uncorrected data that became significant after partial volume correction (see Tables 2, 3, and 4 for comparisons of data prior to and post correction; all BP data in Figures S2-S5 (in the Supplement) are partial volume corrected).

D₂/D₃ receptor binding

Regional differences between patients and controls in D₂/D₃ receptor binding emerged for some BP outcome measures, and for 3 regions these differences were consistent across at least 2 of the outcome measures. All ROIs included in the analysis met a criterion of BP_{ND} > 0.5 prior to partial volume correction, which excluded seven additional cortical regions initially examined.

BP_{ND} from 2TCM—The 2TCM outcome measures represent the patient group reduced by one (n=20) because of the lack of arterial access in one patient.

Comparison with ANCOVA showed significant elevations of BP_{ND} from 2TCM in the patients in two regions, the post-commissural caudate and the thalamus (Table 2; Figure S2 in the Supplement). The post-commissural caudate, a component of the associative striatum, lies medial and superior to the post-commissural putamen, which is the sensorimotor portion of the striatum (16).

BP_{ND} from SRTM—ROI comparisons of BP_{ND} from SRTM showed a significant elevation in the post-commissural caudate and a trend-level elevation in the thalamus (p = .07 by

ANCOVA) in the patients, as well as a decrease in the patients in the uncus (Table 3; Figure S3 in the Supplement).

BP_P from 2TCM—BP_P from 2TCM showed a tendency for lower values in patients than controls, with 7 regions significantly lower by ANCOVA (Figure S4 in the Supplement, left panels; see Table 4 for uncorrected values). The tendency toward lower values in the patients suggested a difference in plasma concentration of ligand, the new element in this outcome measure compared to BP_{ND}. The plasma free fraction of radioligand, f_p , was in fact lower in the patients at trend level ($f_p = 0.056 \pm 0.013$ for patients and $f_p = 0.065 \pm 0.022$ for controls, $p = 0.10$ by t test). The outcome measure, BP_F, that corrects for f_p was therefore evaluated to assess the impact of f_p on BP_P.

BP_F from 2TCM—The outcome measure BP_F, the specifically bound radioligand concentration relative to the plasma free fraction, corrects for f_p by dividing BP_P by f_p , according to

$$BP_F = BP_P / f_p = B_{MAX} / K_D.$$

As expected, the group means differed less for BP_F than for BP_P, leaving only 3 regions, the amygdala, uncus, and temporal neocortex significantly lower by ANCOVA (Figure S4 in the Supplement, right panels; see Table 4 for uncorrected values).

Effect of antipsychotic medication

This study enrolled both drug-naïve patients ($n = 5$) and previously treated, unmedicated patients ($n = 16$). While the small size of the drug-naïve subgroup may have made the comparison underpowered to detect a difference, striatal and extrastriatal BP measures were not significantly different between drug-naïve and unmedicated, previously treated patients.

Clinical ratings

There were no regions of significant correlation of BP_{ND} from SRTM with either the negative or the positive symptom subscales of the PANSS. Working memory performance on the 2-back test showed a significant decline with BP_{ND} from SRTM in the hippocampus in patients ($p = 0.017$, $n = 14$, $R = 0.62$), but not in healthy controls nor in any other region.

Reduced plasma free fraction (f_p) in patients

With the goal of understanding why f_p of [¹⁸F]fallypride was lower in patients than controls, we considered the metabolic syndrome. This condition can develop with administration of second-generation antipsychotic medications and may involve alterations in circulating levels of lipids and glucose in the blood (32;33) accompanied by excessive weight and increased body mass index (BMI). We evaluated f_p in relation to BMI and found a significant relationship, especially in the patients ($R = 0.66$, $p = .004$, $n = 17$). The relationship was weaker in the controls, partly because of the absence of heavier control subjects, but remained significant in the pooled sample of all subjects ($R = 0.39$, $p = .014$, $n = 39$).

Age dependence of D₂/D₃ receptor binding

A decline with age in D₂/D₃ receptors has previously been reported in striatum (34–36), both in patients and in healthy subjects. Our data replicated the striatal relationship, and showed an even stronger decline in cortex (Figure S5 in the Supplement). We found 6% decline of SRTM BP_{ND} per decade in striatum, 7% in other subcortical regions including thalamus, and 10% in cortex for the whole sample, with slightly higher rates in the patients (7%, 8%, and 10%

respectively). These rates of decline were reduced by partial volume correction from apparent rates of decline of 7%, 9%, and 20% respectively in the patients prior to correction. The more marked effect of partial volume correction in cortex suggested greater cortical volume loss, hence greater correction, in the older subjects, which was confirmed by the significant relationship between age and percent increase in BP_{ND} generated by partial volume correction ($r = .59$, $p < .0001$ for temporal cortex in the whole sample).

DISCUSSION

We found baseline abnormalities in D_2/D_3 receptor binding in particular striatal and extrastriatal regions in this study. Increases in BP in thalamus and post-commissural caudate and a decrease in uncus were each detected with more than one outcome measure. Our finding in post-commissural caudate is consistent with prior literature showing a moderate increase in striatal D_2/D_3 receptor binding in schizophrenia (1;37). The increase we found in thalamus does not replicate recent reports, and D_2/D_3 receptor alterations in uncus have not previously been reported. However, all three regions have been implicated in a recent meta-analysis of the anatomy of gray matter changes in voxel-based MRI studies in first-episode and chronic schizophrenia (38). Six recent studies in drug-naïve patients with schizophrenia measuring extrastriatal D_2/D_3 receptors have reported mixed regional findings (Table S2 in the Supplement). All six studies used BP_{ND} as outcome measure, which was derived from reference tissue modeling in the four PET studies and from ratio methods in the two SPECT studies.

Of these prior studies, the first (39) used PET with the radioligand [^{11}C]FLB 457 to study 11 patients and 18 healthy controls and found a decrease in the anterior cingulate cortex not seen in any of the subsequent studies.

Two of the six reports (40;41) found decreases in temporal cortex. The study by Tuppurainen et al. (40) used SPECT with [^{123}I]epidepride and included 7 patients and 7 healthy controls, while the study of Buchsbaum et al. (41) enrolled 15 patients and 15 controls and used PET with [^{18}F]fallypride.

Two reports found thalamic deficits more pronounced in medial subregions: the study of Buchsbaum et al. (41) and another by Yasuno et al. (42) that scanned 10 patients and 19 healthy subjects with [^{11}C]FLB 457. In addition, two studies (43;44) reported (contrasting) lateralized thalamic changes. Talvik et al. (43) used [^{11}C]FLB 457 and found lower BP on the right in patients ($n = 9$) relative to controls ($n = 8$) but no group difference at the level of the whole thalamus, while Glenthøj et al. (44) used [^{123}I]epidepride SPECT and found thalamic BP higher on the right side than the left within the patients ($n = 25$), again with no group differences.

The largest study (44) included 25 patients and 20 healthy controls and found no differences between the patients and controls.

A seventh study, which used [^{18}F]fallypride with SRTM BP_{ND} as outcome measure and included 11 patients (4 of them drug-naïve) and 11 controls, is the only prior study that reported on both striatal and extrastriatal D_2/D_3 receptors (45). This study found no changes in the striatum, but reported a decrease in left medial thalamus and an increase in substantia nigra (Table S2 in the Supplement).

Our study is the only one using kinetic modeling with arterial input function, as well as the only one reporting partial volume correction. For brain regions with volume deficit such as the thalamus (46–48) the partial volume correction is potentially important, since decreases in PET signal can arise in part from this effect. This correction may contribute to the difference between our finding of BP elevation and prior reports of thalamic deficits. Other factors potentially

distinguishing our sample from prior reports might be clinical characteristics. While we saw no relation between positive or negative symptom ratings and BP, we found a relationship between working memory performance and hippocampal SRTM BP_{ND} consistent with a possible role of this structure in working memory (49;50). A potential limitation of our study was its inclusion of a majority (16 of 21) of patients who had been previously medicated, while six of the seven prior studies enrolled only medication-naïve patients. However, comparison of our medication-naïve and unmedicated previously treated patients showed no differences in BP outcome measures between these patient subgroups.

A difference in plasma free fraction f_p of radioligand is rarely found in psychiatric illness, and is not detectable with quantification methods that avoid plasma measurements such as SRTM. The quantity f_p is generally regarded as the fraction of radioligand in blood unbound to plasma proteins, but plasma protein binding measurement methods may not adequately distinguish protein from lipid binding. The relationship found here to BMI might be related to greater lipid binding with higher BMI, leaving less free radioligand in plasma and thus less free to cross the blood-brain barrier, leading to lower BP_p. This observation may have potential clinical implications for the availability of other drugs in patients with abnormally elevated BMIs, affecting drug response. This interpretation is speculative and would require testing of lipid versus protein binding across a range of drugs to assess its clinical relevance.

Age-related decline in extrastriatal D₂/D₃ receptor binding was previously reported in healthy subjects using [¹¹C]FLB457, showing 6% loss per decade in thalamus and 11–14% in cortical regions (51;52). Here we found rates that are comparable but 3 to 6 percentage points greater in patients (prior to partial volume correction). Cortical rates of decline were previously reported in patients as 10% per decade in frontal and temporal cortex but not significant in thalamus or anterior cingulate (43). Higher cortical rates of decline found in our study are consistent with the combination of the patterns of cortical exceeding subcortical rates previously seen within controls (51;52), and with rates in patients exceeding those in controls previously seen within striatum (34–36).

It should be emphasized that baseline binding potential measured with [¹⁸F]fallypride is affected by different factors: receptor density, the affinity of these receptors for the radiotracer, and endogenous dopamine concentration in the vicinity of the receptors. An individual baseline scan cannot distinguish among these three components. Separate measurement of the binding potential components affinity and receptor density would require saturation scans, which were not done here and are generally not performed in clinical PET studies. As shown previously in striatum using two D₂/D₃ receptor scans per subject (baseline state and following dopamine depletion (53)), a modest elevation of striatal D₂/D₃ receptor density in schizophrenia was masked by higher endogenous dopamine levels. [¹⁸F]Fallypride has been shown to be susceptible to amphetamine-induced DA release in striatal and extrastriatal regions (54;55). It is possible that, similarly to the striatum, alterations may exist in extrastriatal regions both in receptor density and in endogenous dopamine activity, which may mask each other and not become evident until PET imaging with a two-scan dopamine release or depletion paradigm is utilized. As for changes in affinity of receptors for the radiotracer, we believe that these are unlikely, considering the negative findings in a number of regions.

Summary

Differences were seen in D₂/D₃ receptor binding between patients and controls in specific striatal and extrastriatal regions in this study. Plasma free fraction of radioligand was lower in patients and declined with body mass index, which emphasizes a caveat for plasma-based binding measures but also shows their power to uncover information that reference-region based methods cannot. Binding potential declined with age in extrastriatal regions, as previously shown both in healthy subjects and in striatum in patients. In conclusion, the absence

of widespread alteration in levels of extrastriatal D₂/D₃ receptors does not necessarily indicate normal dopaminergic transmission in these regions. Studies of dopamine release capacity or baseline occupancy to assess levels of the transmitter are needed to obtain a more comprehensive assessment of the level of D₂/D₃ signaling in these regions, as done previously for the striatum.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical variables of the study sample

	Healthy Controls	SCZ	p
n	22	21	
Age (y)	26 ± 6	31 ± 12	0.09
Gender	5F/17M	7F/14M	ns
Ethnicity	8AA/4AS/8C/2H	5AA/3AS/10C/3H	ns
Smoking status	3S/19N	5S/16N	ns
Drug naïve/drug free	-	5/16	-
Days med-free (n=16)	-	191 ± 516 (18d, 5y)	-
Subject SES [†]	38 ± 14	20 ± 6	< 0.001
Parental SES	47 ± 15	43 ± 18	ns
PANSS Total	-	64 ± 15	-
BMI	23.9 ± 3.6	27.1 ± 5.7 (n = 17)	0.04

SCZ, patients with schizophrenia; F, Female; M, male; AA, African-American; AS, Asian; C, Caucasian; H, Hispanic; S, Smoker; N, Nonsmoker; BMI, Body mass index

[†] Socioeconomic status (17)

Table 2

BP_{ND} (unitless) from two tissue compartment model (2TCM), comparing values uncorrected and corrected for partial volume effect

	Region	uncorrected			corrected		
		SCZ*	Controls**	P=	SCZ*	Controls**	P=
Striatal	POST-PU	24.58 ± 5.72	23.17 ± 3.47	ns	42.43 ± 9.29	39.08 ± 6.96	ns
	PRE-DPU	22.00 ± 4.70	21.65 ± 3.01	ns	31.11 ± 7.48	29.55 ± 4.71	ns
	VST	17.92 ± 3.82	18.10 ± 3.15	ns	29.94 ± 8.20	28.68 ± 5.84	ns
	PRE-DCA	18.69 ± 4.09	18.21 ± 2.67	ns	28.62 ± 6.58	26.74 ± 4.41	ns
	POST-CA	13.92 ± 3.51	12.97 ± 2.14	0.03	28.69 ± 6.77	25.34 ± 4.32	0.04
Extra-striatal	thalamus	2.14 ± 0.51	1.99 ± 0.26	ns	2.90 ± 0.70	2.59 ± 0.37	0.03
	amygdala	1.89 ± 0.66	1.95 ± 0.32	ns	2.73 ± 0.94	2.81 ± 0.50	ns
	insula	1.42 ± 0.67	1.35 ± 0.37	ns	2.40 ± 0.70	2.11 ± 0.62	ns
	uncus	0.94 ± 0.36	0.98 ± 0.25	ns	1.76 ± 0.45	2.06 ± 0.67	ns
	midbrain (SN)	1.26 ± 0.30	1.21 ± 0.21	ns	1.83 ± 0.48	1.67 ± 0.28	ns
	hippocampus	1.04 ± 0.36	1.00 ± 0.26	ns	1.67 ± 0.52	1.68 ± 0.55	ns
	temporal cortex	0.68 ± 0.44	0.77 ± 0.29	ns	1.54 ± 0.43	1.68 ± 0.48	ns
	entorhinal cortex	0.64 ± 0.36	0.67 ± 0.18	ns	1.28 ± 0.34	1.23 ± 0.31	ns

POST-PU = post-commissural putamen, PRE-DPU = pre-commissural dorsal putamen, VST = ventral striatum, PRE-DCA = pre-commissural dorsal caudate, POST-CA = post-commissural caudate, SN = substantia nigra,

* n = 20;

** n = 22;

= ANCOVA with age as covariate

Table 3

BP_{ND} (unitless) from simplified reference tissue model (SRTM), comparing values uncorrected and corrected for partial volume effect

	Region	uncorrected			corrected		
		SCZ [*]	Controls ^{**}	P ⁼	SCZ [*]	Controls ^{**}	P ⁼
Striatal	POST-PU	19.50 ± 2.40	19.69 ± 2.08	ns	32.97 ± 4.21	32.57 ± 4.15	ns
	PRE-DPU	17.68 ± 2.11	18.51 ± 2.01	ns	24.39 ± 3.82	25.02 ± 3.18	ns
	VST	14.58 ± 2.57	15.48 ± 1.92	ns	23.90 ± 5.70	24.11 ± 3.98	ns
	PRE-DCA	15.28 ± 2.39	15.58 ± 1.65	ns	22.63 ± 3.67	22.54 ± 2.74	ns
Extra-striatal	POST-CA	11.40 ± 1.90	11.18 ± 1.76	ns	22.31 ± 3.97	21.10 ± 3.25	0.04
	thalamus	1.84 ± 0.36	1.79 ± 0.21	ns	2.42 ± 0.51	2.31 ± 0.28	0.07
	amygdala	1.64 ± 0.47	1.77 ± 0.36	ns	2.31 ± 0.63	2.53 ± 0.49	ns
	insula	1.23 ± 0.48	1.23 ± 0.29	ns	2.05 ± 0.42	1.89 ± 0.46	ns
	uncus	0.82 ± 0.26	0.89 ± 0.20	ns	1.50 ± 0.33	1.82 ± 0.51	0.03
	midbrain (SN)	1.10 ± 0.19	1.10 ± 0.17	ns	1.57 ± 0.50	1.49 ± 0.25	ns
	hippocampus	0.91 ± 0.29	0.93 ± 0.22	ns	1.43 ± 0.36	1.51 ± 0.36	ns
	temporal cortex	0.59 ± 0.38	0.70 ± 0.23	ns	1.36 ± 0.33	1.50 ± 0.33	ns
	entorhinal cortex	0.58 ± 0.30	0.62 ± 0.15	ns	1.12 ± 0.25	1.11 ± 0.23	ns

Abbreviations as in Table 2;

* n = 21;

** n = 22;

= ANCOVA with age as covariate

BP_P and BP_F from two tissue compartment model (2TCM), showing values uncorrected for partial volume effect (corrected values are displayed in Figure S4 in the Supplement)

Table 4

	Region	BP _P (mL/cm ³)			BP _F (mL/cm ³)		
		SCZ*	Controls**	P=	SCZ*	Controls**	P=
Striatal	POST-PU	13.49 ± 4.10	16.34 ± 4.39	ns	249.84 ± 87.18	266.63 ± 84.49	ns
	PRE-DPU	12.10 ± 3.72	15.18 ± 3.62	0.03	225.01 ± 82.07	249.38 ± 79.08	ns
	VST	9.85 ± 2.83	12.66 ± 3.15	< 0.01	182.44 ± 60.91	209.43 ± 72.76	0.045
	PRE-DCA	10.33 ± 3.32	12.75 ± 3.02	0.02	190.06 ± 63.23	209.79 ± 65.90	ns
Extra-striatal	POST-CA	7.65 ± 2.42	9.18 ± 2.73	ns	139.64 ± 41.26	147.65 ± 39.51	ns
	thalamus	1.19 ± 0.39	1.40 ± 0.36	ns	21.72 ± 7.23	22.53 ± 4.99	ns
	amygdala	1.02 ± 0.30	1.36 ± 0.32	0.01	18.80 ± 5.98	22.31 ± 6.68	ns
	insula	0.78 ± 0.39	0.96 ± 0.38	ns	15.03 ± 8.91	15.14 ± 4.29	ns
	uncus	0.50 ± 0.19	0.68 ± 0.17	0.02	9.37 ± 3.87	11.21 ± 4.07	ns
	midbrain (SN)	0.69 ± 0.21	0.85 ± 0.24	ns	12.82 ± 4.67	13.76 ± 4.02	ns
	hippocampus	0.56 ± 0.18	0.70 ± 0.21	0.08	10.33 ± 3.59	11.47 ± 4.16	ns
	temporal cortex	0.37 ± 0.25	0.53 ± 0.22	ns	7.05 ± 4.77	8.61 ± 3.52	ns
	entorhinal cortex	0.35 ± 0.20	0.47 ± 0.15	ns	6.51 ± 3.38	7.57 ± 2.61	ns

Abbreviations as in Table 2;

* n = 20;

** n = 22;

= ANCOVA with age as covariate