ORIGINAL ARTICLE

Dorsal Striatal Size, Shape, and Metabolic Rate in Never-Medicated and Previously Medicated Schizophrenics Performing a Verbal Learning Task

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Background: Magnetic resonance imaging and positron emission tomography were used to study the size and metabolic rate of the caudate and the putamen in 18 patients with schizophrenia (n=16) or schizo-affective disorder (n=2) and 24 age- and sex-matched control subjects.

Methods: The patients were either never medicated (n=7) or drug free (n=11) for a median of 3 weeks. During uptake of fludeoxyglucose F 18, all patients performed a serial verbal learning test. Positron emission tomographic and magnetic resonance imaging scans were coregistered, and the caudate and the putamen were traced on the magnetic resonance image.

Results: The striatum had a significantly lower relative metabolic rate in schizophrenics than in controls. Never-medicated patients had lower metabolic rates in the right putamen (ventral part of the dorsal striatum) than previously medicated patients. The caudate was significantly smaller in never-medicated patients than in controls and largest in previously medicated patients. Patients with higher relative metabolic rates in the putamen scored higher on the Abnormal Involuntary Movements Scale.

Conclusions: The findings are consistent with reports of striatal enlargement in previously medicated patients and size increases after neuroleptic treatment. Never-medicated patients, in contrast, had ventral striatal structures that were smaller and less active than those observed in controls and previously medicated patients.

Arch Gen Psychiatry. 1998;55:235-243

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THE EFFICACY of neuroleptics in the treatment of schizophrenics has been linked to dopamine D_2 receptors, which are highly concentrated in the striatum.[1-3] Because brain tissue studies have not revealed consistent histopathological changes in striatal structures, quantitative differences in size and activity have been sought in morphometric and functional imaging studies. No significant difference in basal ganglia size was found between 13 schizophrenics and 9 control subjects in a postmortem morphometric study.[4] However, a similar study of 23 schizophrenics found increased volume of the basal ganglia in both hemispheres (statistically significant on the right).[5]

Findings from magnetic resonance imaging (MRI) studies of striatal size in normal vs schizophrenic patients have been inconsistent. The first report[6] of hand-traced MRI measurements of the caudate and lenticular nucleus revealed no significant differences. Later, results of a sophisticated automated thresholding procedure[7] demonstrated a larger volume of the lenticular nucleus, especially on the left. Another study[8] found the left putamen significantly enlarged and a trend toward bilateral enlargement in the caudate, while 2 others[9,10] found left caudate enlargement. A larger right caudate was observed in patients with deficit schizophrenia than in patients with nondeficit schizophrenia.[10] Most recently, a group[11] reported enlargement of the caudate and the putamen in medicated patients, whereas another[12] did not find caudate differences in schizophrenics and controls. None of these studies considered previous neuroleptic exposure, but the importance of this factor is underlined by reports[13-15] of increased caudate volume after neuroleptic treatment.

Since the first positron emission tomography (PET) report of reduced basal ganglia metabolism in schizophrenics,[16] 4 additional studies reported decreased metabolic rates in the basal ganglia of drug-free[17-19] or never-medicated patients[20]; 5 studies[21-25] did not confirm significant patient-control difference; and 2 studies[26,27] observed an increase in relative metabolic rate. Reports of greater right- than left-sided neuroleptic effects suggest the importance of lateralization.[25] Except for

PATIENTS AND METHODS

PATIENTS

Eighteen patients (12 men and 6 women; mean±SD age, 38.5±14.8 years; median age, 39 years; age range, 18-65 years; mean education, 12.3 years) were recruited from Mount Sinai Hospital, New York, NY; Elmhurst Hospital Center, Elmhurst, NY; and Department of Veterans Affairs Medical Center, Bronx, NY . Fifteen patients were right-handed, 1 patient was left-handed, and 2 patients were ambidextrous.[37] Two diagnosticians (E.A.H. and P.D.H.) independently evaluated patients with the Comprehensive Assessment of Symptoms and History.[38] The diagnostic breakdown was as follows: schizophrenia, n=16; schizo-affective disorder, n=2. Patients were also assessed with the Scale for the Assessment of Thought, Language, and Communication[39] and the Clinical Global Impressions.[40] Patients were either never medicated (n=7; 5 men and 2 women) or free of neuroleptics for a median of 3 weeks (n=11; 7 men and 4 women; shortest period of washout, 12 days; next shortest, 14 days; longest, 2 years; no patients were taking long-acting neuroleptics). On the day of PET scanning, patients were assessed with the Brief Psychiatric Rating Scale (BPRS)[41] (score: mean, 61.5; median, 57.5; range, 41-126) and the Abnormal Involuntary Movements Scale (AIMS)[42] (mean±SD score, 4.64±6.68). Two of the 18 patients did not undergo any of these evaluations. Compared with previously medicated patients, never-medicated patients were younger (mean±SD, 24.4±6.1 vs 44.9±13.1 years; t=3.29; P=.005) and had lower AIMS scores (mean±SD, 0.75±1.50 vs 7.62±7.60; t=2.45; P=.03), but they differed on BPRS negative symptoms (mean±SD, 9.0±4.3 vs 10.9±1,7; t=0.73; P=.24), educational level (mean±SD, 12.0±3.2 vs 13.0±2.0 years; t=0.63; P=.28), age at onset (mean±SD, 21.2±3.6 vs 24.4±3.4 years; t=1.66; P<.12), Clinical Global Impressions score (mean±SD, 4.8±0.5 vs 5.0±0.8; t=0.63; P=.28), or Scale for the Assessment of Thought, Language, and Communication score (mean±SD, 9.8±4.3 vs 9.6±5.2; t=0.09; P<.94).

Twenty-four right-handed controls (15 men and 9 women; mean±SD age, 37.0±13.1; median age, 30 years; age range, 21-52 years; mean education, 16.1 years), all screened with the Comprehensive Assessment of Symptoms and History, were recruited by advertisement and word of mouth.

All patients were screened with a physical examination and laboratory tests. Patients with a history of substance abuse or dependence, neurologic disorders, and head trauma were excluded from the study. All patients provided informed consent.

IMAGING

Positron emission tomographic scans were obtained with a head-dedicated scanner (model 2048, GE Medical Systems, Milwaukee, Wis), with measured resolution of 4.5 mm in plane (4.2-4.5 mm across 15 planes) and 5.0 mm axially. Magnetic resonance image acquisition used the Signa 5x system (GE Medical Systems), with repetition time of 24 milliseconds, echo time of 5 milliseconds, flip angle of 40°, and slice thickness of 1.2 mm. Our version of the surface-fitting method of Pelizzari et al[43] was used for PET and MRI coregistration. Brain edges were outlined without knowledge of diagnosis on an MRI axial slice at a midstriatal level and on an approximately matching PET slice using a semiautomated thresholding algorithm. Intertracer MRI edging reliability on 27 individuals for slice area was high (intraclass correlation coefficient, 0.99). Positron emission tomography volume was translated (x,y) and rotated on the center of mass to minimize root-mean-square difference in edges. After resectioning, sagittal PET and MRI edges were similarly generated. Positron emission tomography volume was translated and rotated in the sagittal plane, with the atlas bone as the rotation point. The coronal plane was treated similarly, and the axial plane was redone as the fourth step. This method was tested by scanning a patient with capillary tubes fastened to the face filled with a mixture of copper sulfate (0.5 mol/L) and fludeoxyglucose F 18; the resulting distance between the 2 marker centers (fludeoxyglucose F 18 and copper sulfate outside and independent of the traced edges) was 1.79 vs 1.83 mm reported by Pelizzari et al.[43] Greater accuracy of MRI-based templates than stereotaxic ROI placement has been reported.[44]

AUTOMATED EDGE FINDING

For the caudate and the putamen, an automated boundary-finding method based on the Sobel gradient filter provides

1 report of never-medicated patients,[20] all metabolic PET studies of the basal ganglia were confined to previously medicated patients. Only 2 studies[25,28] used an MRI template to locate these small, variably shaped structures.

Memory impairments are among the most salient deficits in schizophrenics.[29,30] Significantly reduced learning and recall have been reported in schizophrenics performing such tasks as word-list learning.[31,32] Diminished performance on serial word-list learning also has been found in patients with striatal dysfunction (eg, Parkinson and Huntington disease).[33,34] Whereas controls used a semantic organization strategy, possibly frontal in execution, patients with Parkinson disease treated with levodopa[34] depended more on serial sequence, a pattern resembling that in never-medicated schizophrenics during the Continuous Performance Task.[20] Beatty et al[35] found schizophrenics to be impaired on tasks "sensitive to dysfunction in frontostriatal circuitry." Thus, word-list learning seemed to be an appropriate task for imaging of the frontostriatal circuit.

Magnetic resonance imaging and PET were combined to provide accurate anatomical identification of the basal ganglia for metabolic quantification and size assessment. Findings of a neuroleptic-related increase in metabolism in the right basal ganglia[36] led us to hypothesize a lower right-sided metabolic rate in unmedicated patients. Assuming that larger structures might be more or less active per unit area, we tested this hypothesis for mean metabolic rate per average region of interest (ROI) pixel and for total striatal metabolic rate.

RESULTS

STRIATAL METABOLIC RATE

Relative metabolic rate in the caudate and the ventral putamen was lower in all schizophrenics than in controls, while the rate in the dorsal putamen (41%) was higher

a reproducible edge, with little operator variability (**Figure 1**). After the contour is applied to the PET image, pixels within the edge can be extracted and mean metabolic rate calculated. For structures like the caudate nucleus, metabolic rate can be measured per unit area (average rate in each pixel from equation of Sokoloff et al[45]), relative metabolic rate (rate in each pixel per average rate in all pixels within the brain) and weighted structure metabolic rate (average rate in each pixel from equation of Sokoloff et al by number of pixels in area), and size in square millimeters.

The gradient filter structure outlines had relative metabolic rate averaged for every pixel within the MRI outline for entry into multivariate analysis of variance (MANOVA). Then the average outline across the group of 24 controls was calculated, and each patient's caudate or putamen was stretched radially from the centroid to conform to that shape (**Figure 2**). Because right caudate activity has been related to medication response, the right caudate was outlined on consecutive MRI slices from the top to the ventral boundary of the dorsal striatum, where it merged with the putamen, and the morphed metabolic volume was examined statistically, as described below. To survey the caudate and the putamen and provide a conventional ROI-based analysis of variance (ANOVA), a complementary analysis was performed on 2 MRI slices, selected without knowledge of diagnosis, by matching levels 8 and 9 of the Matsui-Hirano atlas[46]; slice 8 is typically the first slice superiorly on which the caudate and the putamen, separated by the internal capsule, can be clearly outlined bilaterally (termed "dorsal"), and slice 9 was chosen 6.5 mm inferiorly (termed "ventral").

UPTAKE TASK

The uptake task, developed for PET scanning and based on the California Verbal Learning Test,[47] consisted of five 16-word lists, each comprising 4 words in 4 conceptual categories. Categories were chosen for concreteness, and words were selected based on norms for levels of "associability."[48]

Each list was presented 5 times in a fixed random order on a computer monitor at a 1.5/s rate. After presentation of each list, free recall was required and responses were recorded. Patients could remember words in semantic categories, temporal order, or without organization. Scores were averaged across trials. Semantic categorization was defined as the number of contiguously recalled items from the same category, correcting for chance, which yielded a score of up to 12 clustered words per list.

STATISTICAL ANALYSIS

Repeated-measures ANOVA or MANOVA[49] was used in group comparisons. Groups were independent dimensions for the whole population (schizophrenics and controls) and for never-medicated and previously medicated subgroups. Repeated measures were region (caudate and putamen), hemisphere (right and left), and slice level (41% and 34% of head height). Group by region and higher-order interactions were examined to establish regional differences. Simple follow-up interactions were performed to identify the strongest sources of group interactions. Analysis of relative data (striatal region/whole brain metabolic rate) removed "global scaling factors" or the constant individual differences in whole brain metabolic rate.

Pixel-by-pixel statistical mapping was also performed. In an adaptation of the cluster-counting approach,[50,51] a resampling method with actual PET scan data from 76 normal individuals (rather than theoretical simulations) determined significance levels. To establish the threshold for significance in a t test analysis of 24 controls and 18 schizophrenics, samples of n_1=18 and n_2=24 were drawn randomly from a pool of 76 normal patients. For each random sample, pixel-by-pixel t tests were performed. In each cluster of pixels above the threshold level of $P<.05$ ($t[40]=2.02$), the number of contiguous pixels was counted, and the volume of the largest cluster (number of contiguous pixels by average t value height above $t=2.02$, $P<.05$) was determined (ie, 100 pixels with a mean t of 2.52 yield a volume of 50). An empirical table of cluster volume was derived by generating 5000 such random samples of 18 and 24 patients and obtaining the largest cluster for each random draw. Volumes for 95%, 97.5%, and 99% levels were obtained, permitting a test of whether any given pixel cluster volume might occur by chance if schizophrenic groups differed no more than random sets of controls.

(**Table 1**). A nearly identical result emerged when relative metabolic rate was calculated per slice instead of for whole brain (ANOVA: $F_{1,40}$=10.8; P=.002). No ANOVA interaction test with hemisphere and group reached statistical significance when all patients entered the analysis. However, because lower glucose metabolic rate in the right putamen previously predicted favorable haloperidol response,[36] and because of a significant main effect of hemisphere in the present data (striatum mean values: left, 1.29; right, 1.25; $F_{1,37}$; P=.02), simple-interaction analyses were performed for each hemisphere (**Table 2**). Significantly lower glucose metabolic rates were found in the ventral (34%) right putamen in never-medicated patients (1.30) than in controls (1.37).

The right caudate nucleus had a significant region of decrease (area of statistically significant contiguous pixels, 70; mean t=2.76; cluster volume >2.02=52; P=.02) (Figure 2).

MEDICATION HISTORY AND METABOLIC RATE

Previously medicated patients tended to have higher metabolic rates than never-medicated patients. The correlation coefficient between medication history (previously medicated, 2; never medicated, 1) and metabolic rate in the caudate and the putamen (both hemispheres, both slice levels) revealed 1 significant positive correlation (right putamen at 41% level; r=0.40, $P<.05$, 1-tailed). Because the greatest medication effect had previously been found in the putamen,[36] a 4-way ANOVA (medication group by hemisphere by slice level by structure) was performed on the relative metabolic rate data; significant region by medication group and region by slice level by group interactions were confirmed (Table 1). Controls showed much lower values in the dorsal (1.21) than the ventral (1.38) putamen; never-medicated patients showed a more modest mean (±SD) dorsal-ventral gradient for the putamen (dorsal, 1.26±0.16; ventral, 1.33±0.09), and

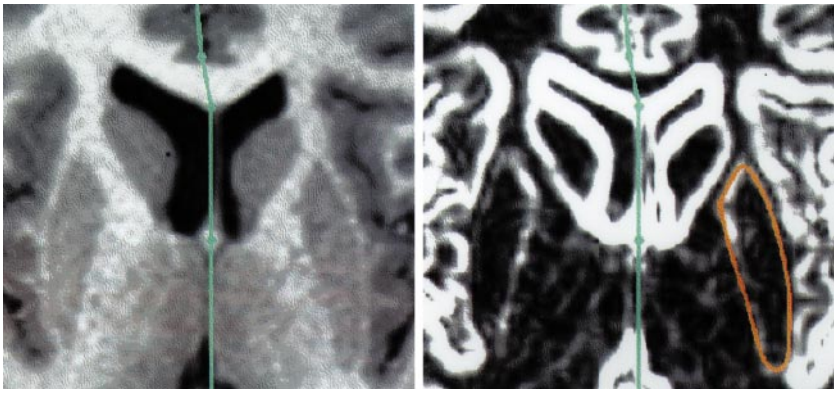

Figure 1. *Edge enhancement improves magnetic resonance image tracing of the putamen. Left, Enlarged striatal region with the caudate and the putamen, midline points, and brain outline. Right, Same image with gradient filter applied showing enhanced outline of the putamen as outlined by placing pointer on or near white line and computer searching for local maximum. Intertracer reliability assessed by intraclass correlation coefficient for the right caudate was 0.856 for area and 0.987 for relative metabolic rate. The concordance or average percentage of pixels within the outline common to both tracers' caudate outlines was 94.8%; this represents about one fourth of the circumferential pixels displaced by 1 row.*

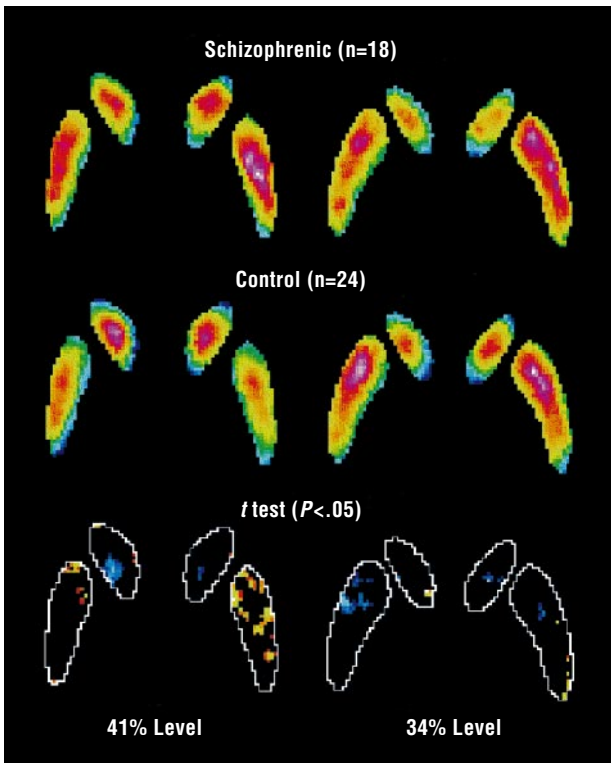

Figure 2. *Coregistered striatum relative metabolic rate. Top, Metabolic rate in schizophrenics (n=18) and controls (n=24). Magnetic resonance imaging coregistered positron emission tomography metabolic rate areas from all patients are stretched to the outline of the average contour derived from the control magnetic resonance imaging scan. Bottom,* t *tests are calculated on this morphed image for each pixel. This process produced sets of congruent regions of interest for pixel-by-pixel* t *tests to define the within-caudate variation. These coregistered average templates are displayed with each structure centered on the group mean centroid location with respect to the brain bounding box. Metabolic rate is scaled so that the highest relative area is white and the lowest area is purple;* t *images are colored so that* P<*.05 is purple and* P<*.01 is blue when patients have significantly lower relative metabolic rates than controls. Areas of the lateral caudate and the lateral putamen (ventral or 34% level) that are densest dopamine in* D_2 *receptors seem to be the greatest contributors to differences between schizophrenics and controls.*

previously medicated patients showed almost no gradient (dorsal, 1.34±0.20; ventral, 1.36±0.16).

Differences between schizophrenics and controls involved interactions with slice level and the caudate and the putamen but not hemisphere (Table 1). Differences between controls and never-medicated patients were confirmed by simple interactions that involved hemisphere, ventral slice, and the putamen (Table 2). Low values in the right but not the left putamen characterized never-medicated patients compared with the more symmetrical pattern in controls. Left-minus-right difference scores for the whole putamen were 0.01 for controls, 0.04 for previously medicated patients, and 0.12 for never-medicated patients (simple interaction: hemisphere by group for the putamen, never-medicated patients vs controls, $F_{1,27}$=6.40; P=.01) (Table 1). Previously medicated patients were older (mean age, 44.9 years) than never-medicated patients (mean age, 24.4 years), but the relative metabolic rate in striatal components was negatively correlated with age (–0.39 to 0.53), thus not providing an explanation of the lower metabolic rates in the younger subgroup.

STRIATAL SIZE AND METABOLIC RATE

Compared with controls, schizophrenics had smaller caudates (mean±SD, 149±37 vs 165±28 mm^2) and larger putamens (mean±SD, 314±57 vs 304±72 mm^2; group by structure interaction: $F_{1,40}$=4.33; P=.04; simple interaction for the caudate: $F_{1,40}$=10.2; P=.003).

Comparison of striatal size in never-medicated vs previously medicated patients revealed a significant group by level by structure interaction (**Table 3** and **Figure 3**). The largest difference was between mean size of the dorsal putamen (41% level) in previously medicated patients (291±62 mm^2) vs controls (270±71 mm^2). There was no significant difference in brain volume or volume variability (controls: mean±SD, 1300±149 cm^3; patients: mean±SD, 1252±129 cm^3; t=1.16; variance comparison, $F_{17,32}$=1.33). When relative metabolic rate weighted for size ([structure size/brain volume] by [relative metabolic rate]) was examined, schizophrenics continued to have significantly lower values than controls (**Table 4** and **Figure 4**). The difference was more pronounced in the caudate than in the putamen.

TASK PERFORMANCE

Although schizophrenics recalled significantly fewer words than did controls, 15 of 18 schizophrenics completed all 5 sets of words. Across the 5 trials, these 15 patients recalled an average of 7.41±2.94 (mean±SD) words per 16-word list, and controls recalled 13.0±1.84

Table 1. Relative Metabolic Rate*

	Controls (n=24)	Schizophrenic Patients		
		All (N=18)	Never Medicated (n=7)	Previously Medicated (n=11)
Caudate				
Slice 41%	1.24 (0.13)	1.22 (0.19)	1.29 (0.06)	1.20 (0.24)
Slice 34%	1.22 (0.17)	1.20 (0.17)	1.25 (0.11)	1.18 (0.20)
Combined	1.23 (0.15)	1.21 (0.18)	1.27 (0.09)	1.18 (0.21)
Putamen				
Slice 41%	1.21 (0.20)	1.31 (0.19)	1.26 (0.16)	1.34 (0.20)
Slice 34%	1.38 (0.10)	1.35 (0.13)	1.33 (0.09)	1.36 (0.16)
Combined	1.30 (0.18)	1.33 (0.17)	1.30 (0.13)	1.34 (0.18)

**Data are given as mean (SD). Controls vs all patients with schizophrenia, ANOVA (analysis of variance): region by group by slice level interaction, $F_{1,40}=10.45$; P=.003. Simple-interaction, ANOVA: region by group at 41% level, $F_{1,40}=6.96$; P=.01. Controls vs never-medicated vs previously medicated patients, ANOVA: region by group interaction, $F_{2,37}=3.76$; P=.03; region by slice by group interaction, $F_{2,37}=5.76$; P=.007. Simple interaction at 41% level, region by group, $F_{2,37}=8.23$; P=.001. Simple interaction, previously medicated patients vs controls, region by slice by group interaction, $F_{1,33}=10.93$; P=.002. Percent head height is percentage of distance from canthomeatal line to top of skull, as given in the Matsui-Hirano atlas.[46]*

Table 2. Hemisphere and Relative Metabolic Rate*

	Controls (n=24)	Schizophrenic Patients		
		All (N=18)	Never Medicated (n=7)	Previously Medicated (n=11)
Caudate slice 34%				
Left	1.26 (0.14)	1.21 (0.21)	1.24 (0.14)	1.20 (0.26)
Right	1.18 (0.20)	1.20 (0.13)	1.26 (0.08)	1.15 (0.11)
Caudate slice 41%				
Left	1.25 (0.12)	1.24 (0.24)	1.31 (0.04)	1.21 (0.31)
Right	1.22 (0.18)	1.20 (0.14)	1.27 (0.08)	1.18 (0.14)
Putamen slice 34%				
Left	1.38 (0.10)	1.39 (0.13)	1.37 (0.10)	1.40 (0.15)
Right	1.37 (0.11)	1.32 (0.13)	1.30 (0.07)	1.32 (0.16)
Putamen slice 41%				
Left	1.22 (0.23)	1.33 (0.15)	1.34 (0.10)	1.32 (0.19)
Right	1.21 (0.17)	1.28 (0.23)	1.18 (0.19)	1.36 (0.21)

**Data are given as mean (SD). Controls vs all patients with schizophrenia, ANOVA (analysis of variance): simple interaction for right side, $F_{1,40}=8.15$; P=.007. Controls vs never-medicated vs previously medicated patients, ANOVA: simple interaction for right side, region by slice level by group interaction, $F_{2,37}=5.04$; P=.01. Region by group on the right side: $F_{2,37}=4.31$; P=.02. Never-medicated patients vs controls, ANOVA: region by hemisphere by group ANOVA: $F_{1,27}=6.69$; P=.02. Simple interaction for putamen, hemisphere by group, $F_{1,27}=6.40$; P=.01; simple interaction for 34% slice (ventral), region by hemisphere interaction, $F_{1,27}=5.60$; P=.02.*

(mean±SD; $t[40]=6.6$; $P<.05$). Use of semantic categories was significantly lower in schizophrenics than in controls (mean±SD score, 2.44±1.33 vs 7.49±3.37; $t_{40}=2.11$; $P<.05$). The correlation between word recall and total BPRS score was 0.16 ($P=.32$). Only the BPRS disorientation subscale score was significantly correlated with word recall ($r=-0.58$, $P<.01$) or semantic categorization ($r=-0.48$, $P<.05$).

No significant correlations were found between total correct or semantic category scores and medication status, striatal size, or striatal metabolic rate in the patients.

STRIATAL METABOLIC RATE AND SIZE: EXPLORATORY ANALYSES WITH AIMS AND SEX

Patients with higher relative metabolism in the dorsal putamen had higher AIMS scores ($r=0.40$, $P<.05$, 1-tailed), but caudate correlations did not reach significance. Clinical diagnosis of tardive dyskinesia (in 5 patients) showed a significant positive correlation with metabolic rate in the caudate (**Figure 5**). A significant correlation ($r=0.48$, $P<.05$) was found between medication exposure and current AIMS score but not between striatal size and AIMS score. No metabolic rate variable correlated significantly with medication duration. Neither metabolic rate nor structure size correlated significantly with sex.

COMMENT

Most PET studies[28,36,52-59] have found significant elevations in striatal metabolism after neuroleptic administration. The present findings of lower striatal metabolism in never-medicated vs previously medicated schizophrenics suggest that neuroleptic-related metabolic increases may persist for 2 to 3 weeks after treatment. A report of striatal haloperidol therapy effects in PET studies performed 12 hours after neuroleptic administration, but not in studies performed after 2 hours, suggests that metabolic changes reflect adaptation to receptor blockade.[56]

Our results are partly consistent with those of a study[13] showing that use of neuroleptics enlarges cau-

date size. In another study,[60] neuroleptic-treated patients showed less decrease in caudate size in 4 years than did controls, also suggestive of treatment-related enlargement. We observed larger ventral putamen size in previously medicated than never-medicated patients, but caudate size was actually smaller in the previously medicated subgroup. Posttreatment enlargement might be of longer duration for the putamen than for the caudate, reflecting a higher density of dopamine D_2 receptors.[61] Greater putamen than caudate shrinkage also has been reported in patients with mild Huntington disease,[62] and increases in neuronal size and larger dendrite calibers were observed in rat striatum after haloperidol therapy.[63] Results of animal studies suggest that D_1 and D_2 receptors are localized in separate populations of medium spiny neurons and that D_2 receptors are largely inhibitory. Haloperidol, which primarily blocks D_2 receptors, might have a disinhibitory effect. Disinhibition could increase firing, structural proteins, size, and metabolic rate. In contrast to the right dorsal caudate, an area in which controls had relatively lower metabolism than did schizophrenics, the right medial ventral putamen showed

Table 3. Striatal Size*

	Schizophrenic Patients		
	Never Medicated	Previously Medicated	Controls
Caudate head height, %			
34%	136 (36)	133 (32)	156 (25)
41%	162 (21)	149 (23)	174 (29)
Combined	149 (37)	141 (28)	165 (28)
Putamen head height, %			
34%	352 (53)	333 (60)	337 (55)
41%	275 (29)	291 (62)	270 (71)
Combined	314 (57)	312 (64)	304 (72)

*Data are given as mean (SD) in square millimeters. Simple interaction: caudate, $F_{2,37}=5.34$; $P<.01$.

Table 4. Relative Size by Relative Glucose Metabolic Rate*

	Controls	Schizophrenic Patients	
		Never Medicated	Previously Medicated
Caudate			
34%	0.15 (0.03)	0.13 (0.03)	0.13 (0.03)
41%	0.17 (0.03)	0.17 (0.02)	0.15 (0.04)
Combined	0.16 (0.03)	0.15 (0.03)	0.14 (0.04)
Putamen			
34%	0.36 (0.07)	0.37 (0.01)	0.38 (0.10)
41%	0.26 (0.09)	0.26 (0.02)	0.33 (0.12)
Combined	0.31 (0.09)	0.32 (0.08)	0.35 (0.11)

*Data are given as mean (SD). Group (control or schizophrenic) by structure interaction: $F_{1,40}=4.42$; $P=.04$. Simple effect for caudate, group (control or schizophrenic): $F_{1,40}=4.37$; $P=.04$. Region by group interaction: $F_{2,37}=3.34$; $P=.04$.

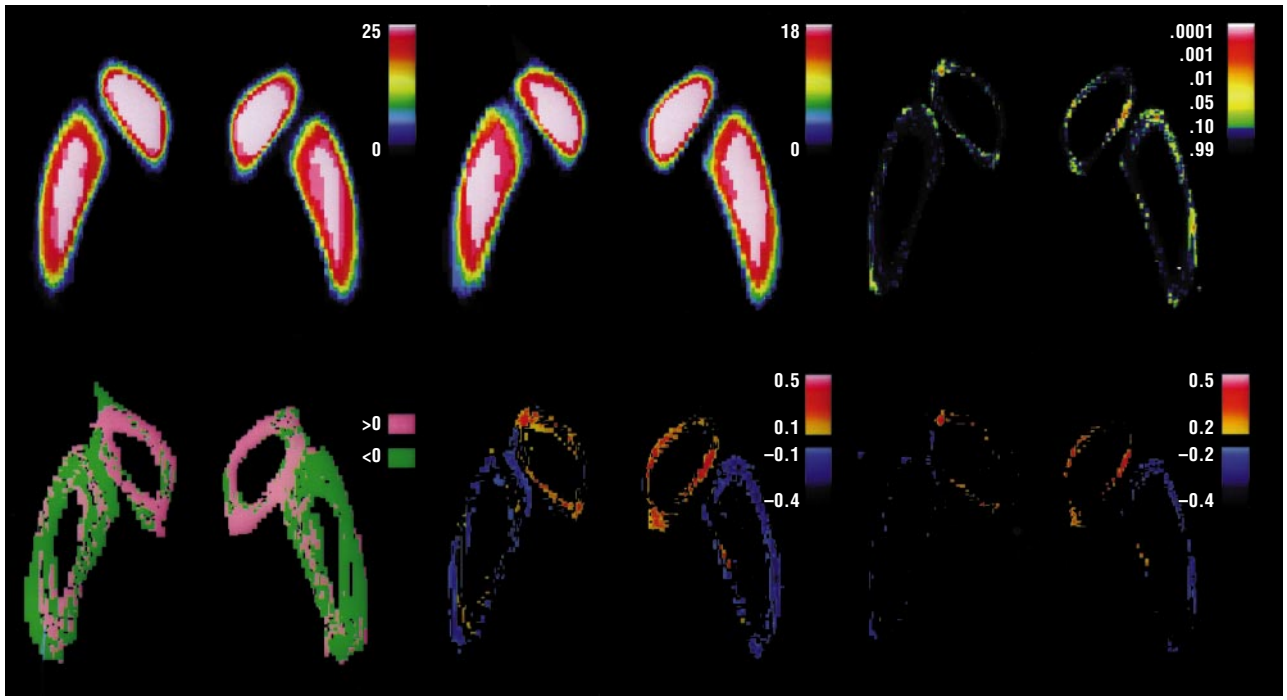

Figure 3. *Caudate and putamen contour differences between controls and schizophrenics. Tally plots are applied to the striatal outlines of controls and never-medicated schizophrenics at the 41% level to assess shape. The left side of the picture is the patient's left. The color bar shows the number of patients for each pixel position whose striatal outline is outside this x,y location. Thus, the center of the structure is light pink, indicating that at this position, all patients' outlines were outside this area (all patients have pixels in this area). Striatal outlines tallied for controls (top left) and never-medicated schizophrenics (top middle). The difference plots (bottom row) show the difference in percentage at each pixel location between controls and schizophrenics. The color bar shows areas where a larger percentage of controls than schizophrenics have a pixel inside the striatal outline in red, pink, and orange. Areas in which a larger percentage of patients have a pixel inside the outline than controls are shown in green, blue, or purple. For example, the green (bottom left) and blue (bottom middle) areas along the caudate margin suggest a smaller width and posterior pole in schizophrenics; the χ^2 tests (top right) are consistent with this difference. The χ^2 plot (top left) is a 2×2 test for each pixel. The number of controls for whom the pixel is inside and outside their own striatal outline is contrasted with the number of schizophrenics for whom the pixel is inside or outside their outline. Yellow areas (χ^2 color bar, top right) indicate a $\chi^2>3.84$, $P<.05$. For example, at x=120, y=57, if 20 controls have the pixel inside the outline and 4 outside, whereas 8 schizophrenics have it inside and 10 outside, then $\chi^2=7.0$, $P<.01$.*

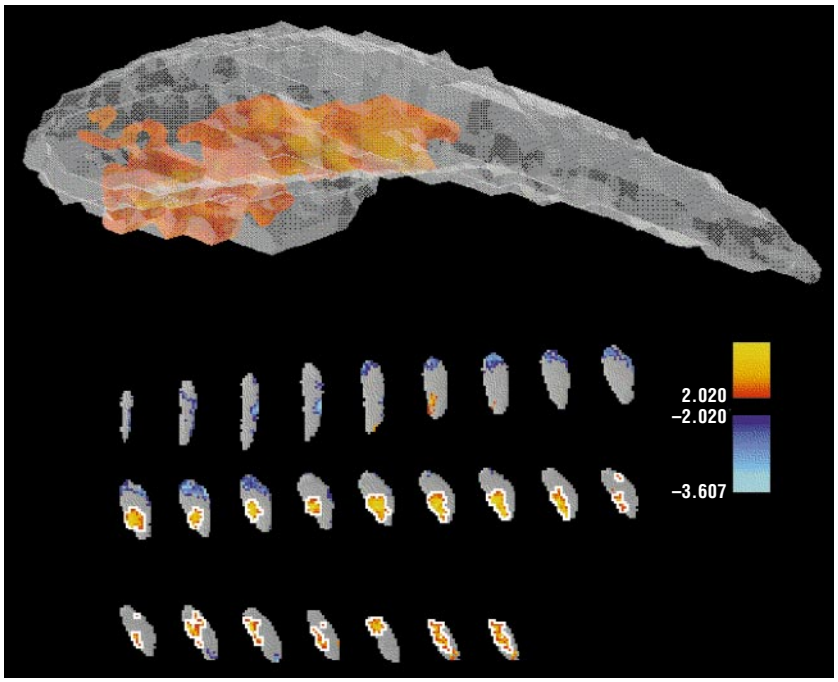

Figure 4. *Right caudate nucleus metabolic rate comparison of schizophrenics and controls (an average of 25 slices). Caudate outlines were interpolated to the average of 25, and outlines and metabolic activity images for each patient were stretched to the average normal outline. The resulting caudates entered a 3-dimensional interpolation program, and* t *tests were performed on every level. The gray surface is the 3-dimensional average magnetic resonance imaging caudate contour from the normal subjects. The red solid is the cluster of* P<*.05* t *tests comparing relative metabolic rate in controls and schizophrenics. Below are the* t *tests from the 25 level tracings; red areas outlined in white are the contiguous pixels that reached the* P<*.05 threshold. A cluster with this volume would not occur in the caudate more than once in 20 random drawings of groups of 18 and 25 normal individuals from our large pool of patients. Note the longitudinal orientation of the significant pixel cluster.*

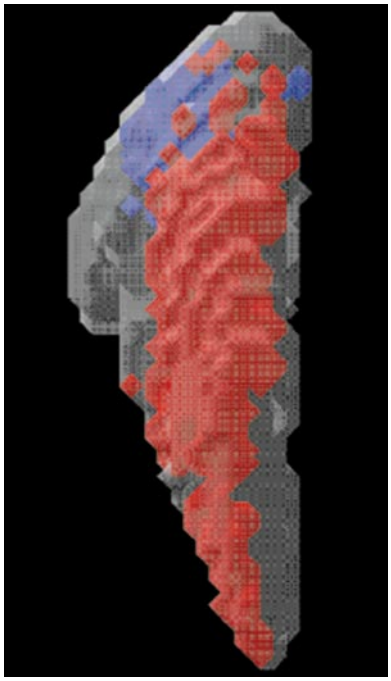

Figure 5. *Diagnosis of tardive dyskinesia and glucose metabolic rate in the right caudate. The view of the caudate is from the top looking down on the structure, with the lateral side on the left and the medial side on the right. Red volume indicates* P<*.05 correlation between tardive dyskinesia and relative metabolic rate.*

relatively decreased activity in schizophrenics. This decrease may have reflected changed activity in the adjacent globus pallidus externa, which abuts the putamen and receives inhibitory input from D_2-containing striatal neurons. Lesions in the ventromedial mesencephalic tegmentum in primates were associated with hypertrophy of dopamine neurons in the caudate and the putamen.[64] The ventral region, unlike the dorsal region, is richer in D_3 than D_2 receptors.[65]

Magnetic resonance imaging coregistration permitted ROI tracing entirely independent of the PET scan. Regions of interest were used to explore metabolic patterns within the striatum and to compare them with the topography of cortical connections in the elegant anterograde tracing studies of Selemon and Goldman-Rakic.[66] They illustrate the dorsal prefrontal cortex terminal fields occupying a large central area in the anterior portion of the head of the caudate, with more terminals in the dorsal caudate and on the lateral edge; this dorsal and lateral pattern was also observed for the putamen (see their Figure 11). Our area of greatest statistical difference between schizophrenics and controls is in the lateral region of the right caudate (light blue area in Figure 2 and red cluster in Figure 4). The area of statistical significance also extends along the lateral and dorsal edge of the putamen. A methodological study of ROI size effects found that smaller ROIs, down to 2 mm, were more powerful in identifying patients with early Huntington disease.[67]

Although some imaging studies with radioligands have examined D_2 receptors in unmedicated and never-medicated schizophrenics, no consensus has emerged.[1,68] Farde et al[61] reported higher levels of D_2 receptor density in the putamen than in the caudate (significantly higher values in the left than the right putamen) in never-medicated patients. The asymmetry was present only in schizophrenics, not in controls (similar to our finding of metabolic asymmetry in the putamen). Pilowsky et al[69] found a left lateralized increase in striatal D_2 receptor binding in schizophrenic men but no overall increase in D_2 receptor binding relative to controls.

Differences in metabolic asymmetry between schizophrenics and controls have been more widely studied. In 18 never-medicated patients,[20] the right posterior putamen had a lower relative metabolic rate (1.09) than any hemisphere, group (controls or schizophrenics), or structure (caudate or putamen) examined. The present study replicates these findings in a new sample of never-medicated patients scanned with higher PET and MRI resolution and MRI coregistration templates. In previously published studies, metabolic rate in the right putamen was a better predictor of medication response than that in other areas of the striatum,[36] and a greater neuroleptic effect was observed for the right than the left putamen.[19] Also consistent with a pattern of right-sided dopaminergic hyperactivity in schizophrenics were postmortem findings of 19% greater receptor density in the right than the left putamen in schizophrenic but not

in control brains.[70] The current data suggest that the residual effects of chronic medication exposure may lessen striatal asymmetry, so that previously medicated patients are more similar to controls in the symmetry of striatal metabolism than are never-medicated patients.

Although some consistency in striatal lateralization in schizophrenics has been observed, the interpretation is not without difficulty. The asymmetry may result from corticostriatal projections and left-greater-than-right functional asymmetry differences between controls and schizophrenics.[25] The intrinsic lateralization of subcortical structures may also have been underestimated; the extensive connections between association areas and the anterior striatum[71] may represent lateralized pathways subserving specific cognitive functions.

Although schizophrenics performed more poorly than controls on the verbal learning test used in our study, they were significantly engaged in the task, and no significant differences between previously and never-medicated patients emerged. Moreover, performance deficits did not merely reflect illness severity because total BPRS score and total number of words remembered were not correlated. No correlations emerged between task performance and positive symptoms. Although the correlational pattern is not inconsistent with striatal dysfunction being related to memory deficits, no significant relationship was found between performance and striatal metabolic rate in either controls or schizophrenics. Larger sample sizes would reduce the risk of type II statistical error. However, a factor-analytic study[72] did not relate a frontostriatal factor to disorganization in 70 unmedicated patients; instead, cortical hypofrontality was related to disorganization. Thus, a purely striatal abnormality in schizophrenics does not seem as closely related to memory deficits as to medication sensitivity and medication effects.

Although we have attributed differences in striatal metabolism and size between never-medicated and previously medicated patients to persisting effects of past medication exposure, other explanations should be considered. Not surprisingly, never-medicated patients were younger and less severely ill than previously medicated patients. However, basal ganglia size decreased with age in normal individuals, whereas the older, previously medicated patients showed a size increase. Moreover, functional abnormalities (lower metabolic rate and greater asymmetry) were more prominent in the younger, less severely ill, never-medicated patients than in the older, sicker, previously medicated patients. The differences between the 2 schizophrenic subgroups therefore seemed most likely to reflect never-medicated vs previously medicated status than age or illness severity. Future studies, with larger samples and a prospective design, should enhance our understanding of the striatal changes that appear to occur as a result of neuroleptic exposure.

Accepted for publication April 8, 1997.

This work was supported by grant MH-40071 from the National Institute of Mental Health, Bethesda, Md (Dr Buchsbaum).

We thank Rami Kaminski, MD; Jack Hirschowitz, MB, ChB, FFPsych; and John Edgar, MD, for help with patient recruitment.

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