ORIGINAL ARTICLE

Striatal Size and Relative Glucose Metabolic Rate in Schizotypal Personality Disorder and Schizophrenia

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Background: Schizotypal personality disorder (SPD) shares social deficits and cognitive impairment with schizophrenia, but is not typically characterized by frank psychosis. Because striatal size and functional activity have both been shown to be associated with psychotic symptoms, we carried out the first study of SPD to assess the caudate and putamen for comparison with findings in schizophrenia.

Methods: Patients with SPD (n=16), schizophrenic patients (n=42), and age- and sex-matched normal control subjects (n=47) were assessed with magnetic resonance imaging. All of the patients with SPD and subsamples of the schizophrenic patients (n=27) and control subjects (n=32) were also assessed with positron emission tomography using fluorodeoxyglucose F-18.

Results: The relative size of the putamen in controls was significantly larger than in patients with SPD and significantly smaller than in schizophrenic patients, while the relative size of the caudate was similar in all 3 groups. Compared with control values, relative glucose metabolic rate in the ventral putamen was significantly elevated in patients with SPD and reduced in schizophrenic patients. When subsamples of schizophrenic patients (n=10) and patients with SPD (n=10) both of whom never received medication were compared, this pattern was more marked, with the highest value for the putamen being found in patients with SPD for the ventral slice and the lowest value for the right dorsal putamen.

Conclusions: Patients with SPD showed reduced volume and elevated relative glucose metabolic rate of the putamen compared with both schizophrenic patients and controls. These alterations in volume and activity may be related to the sparing of patients with SPD from frank psychosis.

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SCHIZOTYPAL personality disorder (SPD) shares many of the social deficits and cognitive peculiarities of schizophrenia,[1-8] but not its chronic, active psychotic symptoms. A critical question is what shields SPD from the florid symptoms associated with much of the extensive morbidity of schizophrenia. One possible explanation for the lack of frank psychosis in SPD, despite its strong genetic-phenomenological links to schizophrenia, could be better regulation of dopamine activity in contrast to the dopaminergic hyperactivity that is hypothetically linked to schizophrenic psychosis.

Although both striatal size, assessed with magnetic resonance imaging (MRI), and functional activity, assessed with positron emission tomography (PET), have been extensively studied in schizophrenia, few neuroimaging studies have been carried out in SPD. There are distinct advantages to the study of SPD, notably a comparative freedom from artifacts of long-term hospitalization and maintenance neuroleptic agents. Striatal volume is usually increased in patients with schizophrenia who were medicated[9] but decreased in those who never received medical therapy (hereafter referred to as "never-medicated schizophrenia"or "never-medicated schizophrenic patients").[10,11] The increased striatal volume in medicated patients could reflect increased dopaminergic innervation, perhaps secondary to neuroleptic exposure or an interaction between neuroleptic agents and pathophysiologic conditions. Two longitudinal MRI studies found progressive enlargement in striatal volume after neuroleptic treatment.[12,13] In our own study, comparisons with control subjects revealed reduced caudate volume in never-medicated patients, and increased dorsal putamen volume in currently drug-free but previously medicated schizophrenic patients.[10] Similar findings have been reported by others,[14,15] including greater

SUBJECTS AND METHODS

MRI SAMPLE

Sixteen patients with SPD (15 men and 1 woman; mean [SD] age, 43.3 [12.7] years) were recruited from outpatient clinics of Mount Sinai Hospital, New York, NY, and the Bronx Veterans Affairs Medical Center, Bronx, NY, through community referrals and advertisements. All patients were medication-free for 2 weeks or longer, and 10 of them had never been exposed to neuroleptic agents. Diagnoses of SPD were made by 2 trained PhD-level interviewers (confirmed in consensus meeting with J.S.) with the Schedule for Affective Disorders and Schizophrenia[17] and the Structured Interview for *DSM-III-R* Personality.[18] Patients who met criteria for bipolar I disorder were excluded from this study. Diagnostic reliability was assessed on 56 individuals with a total of 4 raters (2 per subject); κ values ranged from 0.86 for magical thinking to 0.60 for suspiciousness (average, $\kappa=0.73$); and for SPD vs other personality disorders, $\kappa=0.90$. Illness onset was gradual and not precisely determined.

Forty-two schizophrenic patients (30 men and 12 women; mean [SD] age, 37.8 [12.4] years), who were recruited from the inpatient and outpatient units of Mount Sinai Hospital, Bronx Veterans Affairs Medical Center, and Elmhurst Hospital Center, Elmhurst, NY, were evaluated with the Comprehensive Assessment of Symptoms and History[19] and diagnosed as having *DSM-IV* schizophrenia (n=38) or schizoaffective disorder (n=4). Patients were never-medicated (n=10) or neuroleptic-free (median, 3 weeks; shortest washout, 12 days; reference range, 12 days to 1 year).

Forty-seven healthy volunteers (35 men and 12 women; mean [SD] age, 38.3 [12.6] years), all screened with the Comprehensive Assessment of Symptoms and History, were recruited by advertisement and word of mouth. All subjects received a physical examination and underwent laboratory tests, including substance abuse screening, and signed an institutional review board–approved written consent form. Subjects with unstable medical illness, history of substance abuse dependence in the last 6 months, neurological disorders, or head trauma were excluded from this study. Data on 18 of the 42 schizophrenic patients and 24 of the 47 normal volunteers have been reported.[10]

PET SUBSAMPLE

All 16 patients with SPD, 27 of the 42 schizophrenic patients (20 men and 7 women; mean age, 38.3 [14.3] years), and 32 of the 47 controls (25 men and 7 women; mean age, 41.8 [12.2] years) underwent PET. On the day of the PET scan, 25 schizophrenic patients and all 16 patients with SPD were assessed with the 18-item Brief Psychiatric Rating Scale[20]; 2 schizophrenic patients were rated on another day (Brief Psychiatric Rating Scale psychopathology score=54.4 [SD=12.1]); reference range, 30-85, minimum possible score, 18). Ten patients with SPD and 7 schizophrenic patients were neuroleptic naive. Some data on 18 of the 27 schizophrenic patients and 24 of the 47 volunteers, but none of the striatal data on the 16 patients with SPD, have been reported.[10]

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 in a 50-mm circle in plane center) and 5.0 mm axially. Magnetic resonance imaging parameters (Signa 5x system; GE Medical Systems) were as follows: repetition time, 24 milliseconds; echo time, 5 milliseconds; flip angle, 40°; and slice thickness, 1.2 mm. The PET/MRI coregistration was performed as described previously.[10] Brain edges were outlined without the knowledge of the diagnosis on an MRI axial slice at a midstriatal level and at an approximately matching PET slice using a semiautomated thresholding algorithm. Intertracer edging reliability, assessed by intraclass correlation on 27 individuals for slice area, was 0.99. Brain volumes

increases in putamen than caudate in previously medicated patients.[14]

Studies of relative glucose metabolic rate (rGMR) have tended to find increases in previously medicated schizophrenic patients and decreases in never-medicated schizophrenic patients relative to controls.[16] We found decreased rGMR in the right ventral putamen of drug-free patients compared with controls, especially in never-medicated schizophrenic patients.[10] Decreased rGMR may reflect an increased dopaminergic inhibitory influence on the D2 dopamine receptor–rich putamen. Thus, findings that striatal metabolism is markedly increased after receipt of neuroleptic agents[16] are consistent with D2 receptor blockade. Given that patients with SPD are less likely to require neuroleptic agents—possibly reflecting a more optimally controlled level of dopamine activity than in schizophrenia—we hypothesized that (1) striatal rGMR would be higher and (2) striatal volume would be smaller in patients with SPD than in schizophrenic patients or controls. Because SPD is characterized by varying degrees of associated psychoticlike symptoms, we further hypothesized that the magnitude of the rGMR increase and the volumetric reduction in striatum would be correlated with reduced levels of psychoticlike symptoms.

RESULTS

STRIATAL SIZE

Unmedicated Patients

Compared with control values (mean±SD, 0.251±0.043), the relative size of the putamen was significantly smaller in patients with SPD (0.243±0.071) and larger in schizophrenic patients (0.265±0.052), while the size of the caudate nucleus was similar in all 3 groups (0.129, 0.128, 0.128, respectively; 3-group ANOVA, group×brain structure interaction, $F_{2,102}=3.74$; $P=.02$; follow-up post hoc ANOVA on putamen only, $F_{2,102}=3.15$; $P=.047$). Follow-up post hoc ANOVA comparing SPD and schizophrenia was also significant ($F_{1,56}=4.23$, $P=.044$).

(intraclass correlation=0.98) were obtained by summing all axial oval edges at 6.5-mm intervals from the top of the brain to the level at which frontal and temporal lobes separate and form 3 separate circular masses (Talairach-Tournoux,[21] z=–24).

PET UPTAKE TASK

The task, based on the California Verbal Learning Test,[22] consisted of five 16-word lists, each presented 5 times; free recall was required and responses were recorded. The task was chosen for its suitability to the 30-minute uptake period, psychometric stability associated with high trial numbers, and activation of prefrontal regions.[23] For each subject, 2 slices resembling Talairach-Tournoux[21] levels 12 and –4 (approximately Matsui and Hirano[24] slices 8 and 9 at 34% and 41% of head height) were chosen. These slices are characterized by the full appearance of both caudate and putamen separated by the internal capsule and lying 6 axial MRI slices apart; PET slices 6.5 mm thick, and 1 axial full width at half maximum apart and centered on these MRI slices were used for analysis. For convenient reference, levels 12 and –4 were termed "dorsal" and "ventral", respectively.

AUTOMATED EDGE FINDING

An automated boundary-finding method based on the Sobel-gradient filter provides a reproducible structure edge, with little operator variability.[10] Independent tracings by 2 tracers in 10 subjects yielded an intraclass correlation of 0.92 for the caudate and 0.98 for the putamen. The average outline across the 24 controls was calculated, and each subject's caudate or putamen was stretched radially (from the centroid) to conform to that shape using 360 radial positions and oversampling. To survey both caudate and putamen and provide a conventional region of interest (ROI)–based analysis of variance (ANOVA), a complementary analysis was done on 2 MRI slices selected, without knowledge of diagnosis, to match Talairach-Tournoux[21] levels z=12 and z=–4, corresponding to dorsal and ventral levels previously reported.[10]

STATISTICAL ANALYSIS

Repeated-measures ANOVA or multivariate analysis of variance was used in diagnostic group comparisons. Groups had independent dimensions for the whole population (SPD, schizophrenia, and control) and for never-medicated and previously medicated subgroups. Repeated measures were region (caudate, putamen), hemisphere (right, left), and slice level (z=–4, 12). Group×region and higher-order interactions were examined to establish regional differences. Follow-up simple interactions were performed to identify the strongest sources of group interactions. Analysis of relative data (striatal region/whole brain metabolic rate and striatal size/whole brain volume) removed "global scaling factors" or the constant individual differences in whole brain metabolic rate or size.

In addition to ANOVA and multivariate analysis of variance, exploratory statistical probability mapping was performed. Coregistered MR/PET images were standardized[23] and t tests comparing groups computed.[25] To standardize the entire image, we identified 9 midline points on the 12 and –4 planes (located along the midline at the anterior tip of the frontal lobe, cingulate sulcus, anteroposterior edge of the genu of the corpus callosum, posterior tip of the anterior horn of the lateral ventricle, anteroposterior edge of the posterior corpus callosum, posterior cingulate sulcus, and posterior tip of the occipital lobe). The mean anteroposterior length of each of the 9 segments was calculated. Coregistered MR/PET images were adjusted so that each subject had the same number of pixel rows between each of the 9 landmarks and each horizontal row was of the average length of the entire normal group. Every image had the same number of pixels, and every pixel on the edge was aligned. This method is similar to other standardization methods[26,27] with lower, more uniform variance compared with bounding-box methods.[27]

Never-Medicated vs Previously Medicated Patients

Never-medicated patients with SPD had a smaller relative size of the putamen (mean±SD, 0.234±0.079) than either never-medicated schizophrenic patients (0.251±0.044) or controls (0.251±0.043). Although the absolute difference between never-medicated patients with SPD and controls was greater than in the total group, the difference did not reach statistical significance because of reduced power when the sample size was restricted (**Table 1**, **Figure 1**A). No significant differences were found for the caudate. When absolute size (millimeters square) was examined for both caudate and putamen in never-medicated schizophrenic patients and never-medicated patients with SPD, neither main group effects nor group×structure interactions were significant.

Previously medicated (but currently unmedicated) patients with SPD had significantly smaller putamen size (0.245±0.057) than previously medicated schizophrenic patients (0.269±0.054) and controls (0.251±0.043) (Region×Group interaction, $F_{2,82}$=3.81; P=.02). Size of the putamen in previously medicated schizophrenic patients was significantly larger than in controls ($F_{1,77}$=6.33, P=.01). No significant differences were found for the caudate nucleus. While the putamen was larger in previously medicated (mean [SD], 0.269[0.057]) than in never-medicated schizophrenic patients (0.252[0.053]; $F_{1,40}$=1.39; P=.24), the difference was not statistically significant, and the size of the caudate nucleus was similar in the 2 groups. The difference in size of the caudate and the putamen between never-medicated schizophrenic patients and previously medicated patients with SPD was not statistically significant.

STRIATAL rGMR

Unmedicated Patients

Schizophrenic patients, patients with SPD, and controls showed significantly different patterns of rGMR in superior and inferior parts of the dorsal striatum (**Table 2**),

Table 1. Relative Size of Caudate and Putamen

Location	Normal Control Subjects (n = 32)	Schizophrenic Patients			Patients With SPD		
		All (N = 27)	Never Medicated (n = 7)	Previously Medicated (n = 20)	All (N = 16)	Never Medicated (n = 10)	Previously Medicated (n = 6)
Caudate 34%*							
Left	0.122 (0.020)	0.118 (0.022)	0.104 (0.026)	0.120 (0.020)	0.120 (0.022)	0.121 (0.017)	0.118 (0.031)
Right	0.120 (0.025)	0.122 (0.024)	0.126 (0.029)	0.121 (0.023)	0.119 (0.021)	0.123 (0.022)	0.112 (0.019)
Caudate 41%*							
Left	0.135 (0.019)	0.131 (0.021)	0.134 (0.022)	0.134 (0.021)	0.137 (0.030)	0.132 (0.026)	0.145 (0.037)
Right	0.140 (0.023)	0.140 (0.019)	0.140 (0.018)	0.140 (0.019)	0.137 (0.030)	0.133 (0.033)	0.143 (0.024)
Caudate							
34%	0.121 (0.022)	0.120 (0.023)	0.115 (0.028)	0.121 (0.022)	0.119 (0.022)	0.122 (0.020)	0.115 (0.025)
41%	0.138 (0.022)	0.135 (0.020)	0.137 (0.020)	0.135 (0.020)	0.137 (0.030)	0.133 (0.030)	0.144 (0.025)
Combined	0.129 (0.022)	0.128 (0.022)	0.126 (0.024)	0.128 (0.021)	0.128 (0.012)	0.127 (0.025)	0.130 (0.025)
Putamen 34%							
Left	0.271 (0.035)	0.282 (0.058)	0.270 (0.042)	0.286 (0.063)	0.259 (0.076)	0.251 (0.088)	0.272 (0.057)
Right	0.277 (0.039)	0.292 (0.047)	0.291 (0.028)	0.292 (0.052)	0.271 (0.053)	0.270 (0.063)	0.272 (0.035)
Putamen 41%							
Left	0.227 (0.053)	0.246 (0.052)	0.299 (0.050)	0.252 (0.051)	0.200 (0.083)	0.200 (0.088)	0.199 (0.081)
Right	0.227 (0.045)	0.240 (0.054)	0.217 (0.057)	0.247 (0.051)	0.255 (0.070)	0.217 (0.078)	0.238 (0.056)
Putamen							
34%	0.274 (0.037)	0.287 (0.053)	0.280 (0.035)	0.289 (0.057)	0.265 (0.065)	0.260 (0.075)	0.272 (0.046)
41%	0.227 (0.049)	0.243 (0.053)	0.223 (0.054)	0.250 (0.051)	0.222 (0.078)	0.209 (0.083)	0.218 (0.069)
Combined	0.251 (0.043)	0.265 (0.053)	0.252 (0.044)	0.269 (0.054)	0.244 (0.071)	0.235 (0.079)	0.245 (0.057)
Striatum	0.190 (0.032)	0.196 (0.037)	0.189 (0.034)	0.199 (0.038)	0.186 (0.049)	0.181 (0.052)	0.187 (0.041)

*Percentage of head height from Matsui and Hirano atlas,[24] 1978. 34% is equivalent to $z=-4$ and 41% is equivalent to $z=12$ in Talairach and Tournoux atlas.[21]

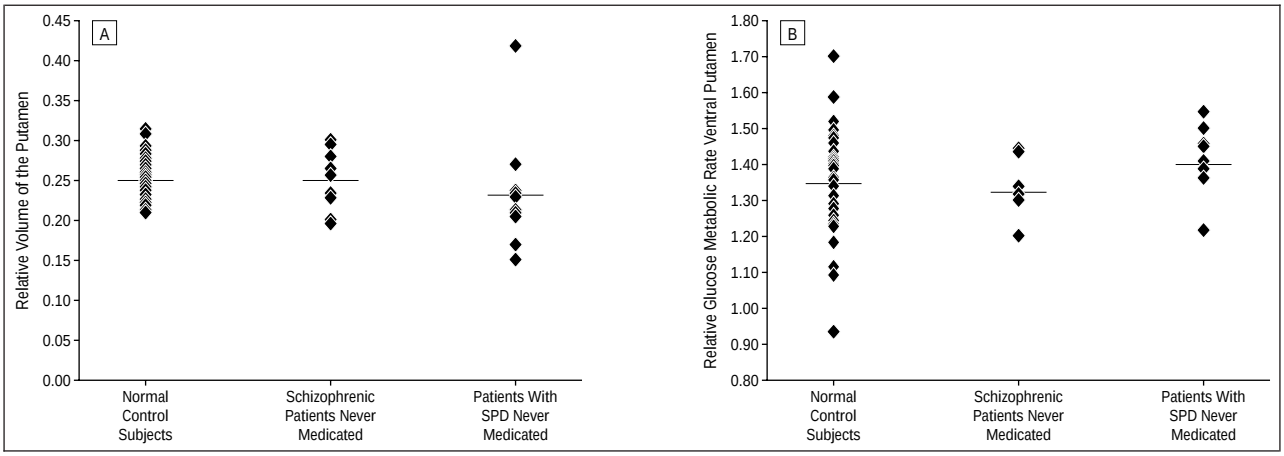

Figure 1. A, Relative size of the putamen. Normal control subjects, patients with schizophrenia who never received medication (ie, never-medicated schizophrenic patients), and never-medicated patients with schizotypal personality disorder (SPD). For statistical contrasts, see the "Striatal Size" subsection of the "Results" section, and Table 1. B, Relative glucose metabolic rate in ventral putamen. Normal control subjects, never-medicated schizophrenic patients, and never-medicated patients with SPD. For statistical contrasts, see the "Striatal rGMR" subsection of the "Results" section and Table 2.

a pattern that still held in analyses confined to never-medicated subsamples. The rGMR in the ventral putamen was significantly elevated, confirmed by ANOVA in a group (healthy volunteers, patients with SPD, schizophrenic patients)×level (dorsal, ventral)×region (caudate, putamen) interaction ($F_{2,72}=3.44$; $P=.03$), in the group with SPD (1.395±0.130) vs the control (1.350±0.16) and schizophrenic groups (1.353±0.164), which were similar to each other (Table 2).

Never-Medicated Patients

When never-medicated schizophrenic patients and never-medicated patients with SPD were compared, this pattern was more marked (Table 2, Figure 1B), with the largest difference being found for the ventral right putamen, which had higher values in never-medicated patients with SPD than in never-medicated schizophrenic patients (effect size=0.84, up from 0.34 in all patients) (**Figure 2**). This was confirmed with a 2-group contrast of never-medicated patients with SPD vs never-medicated schizophrenic patients (Region×Group interaction, $F_{1,15}=5.56$; $P=.03$) and provided support for the hypothesized elevation of striatal metabolism in SPD. The rGMR in the caudate nucleus, however, tended to be lower in patients with SPD. Exploratory statistical probability mapping was consistent with ANOVA in showing elevated rGMR in the anterior ventral putamen in patients with SPD and

Table 2. Relative Glucose Metabolic Rate in Caudate and Putamen

Location	Normal Control Subjects (n = 32)	Schizophrenic Patients			Patients With SPD		
		All (N = 27)	Never Medicated (n = 7)	Previously Medicated (n = 20)	All (N = 16)	Never Medicated (n = 10)	Previously Medicated (n = 6)
Caudate 34%*							
Left	1.211 (0.137)	1.190 (0.135)	1.216 (0.129)	1.180 (0.140)	1.228 (0.154)	1.121 (0.121)	1.305 (0.184)
Right	1.139 (0.193)	1.119 (0.149)	1.181 (0.074)	1.097 (0.164)	1.105 (0.094)	1.105 (0.094)	1.112 (0.117)
Caudate 41%*							
Left	1.227 (0.123)	1.226 (0.134)	1.237 (0.099)	1.222 (0.147)	1.194 (0.116)	0.193 (0.030)	1.195 (0.090)
Right	1.170 (0.139)	1.147 (0.132)	1.209 (0.125)	1.125 (0.130)	1.149 (0.100)	1.151 (0.086)	1.145 (0.131)
Caudate							
34%	1.175 (0.165)	1.150 (0.142)	1.199 (0.101)	1.138 (0.152)	1.168 (0.127)	1.113 (0.108)	1.208 (0.150)
Slice 41%	1.198 (0.131)	1.186 (0.133)	1.222 (0.111)	1.174 (0.139)	1.171 (0.108)	1.172 (0.110)	1.170 (0.110)
Combined	1.187 (0.149)	1.168 (0.137)	1.211 (0.107)	1.156 (0.145)	1.170 (0.118)	1.143 (0.109)	1.189 (0.130)
Putamen 34%							
Left	1.361 (0.177)	1.377 (0.177)	1.383 (0.122)	1.372 (0.195)	1.409 (0.144)	1.405 (0.154)	1.415 (0.139)
Right	1.339 (0.148)	1.328 (0.152)	1.293 (0.082)	1.341 (0.169)	1.381 (0.116)	1.374 (0.109)	1.392 (0.136)
Putamen 41%							
Left	1.250 (0.189)	1.320 (0.200)	1.259 (0.238)	1.342 (0.186)	1.174 (0.262)	1.177 (0.254)	1.168 (0.300)
Right	1.182 (0.192)	1.264 (0.236)	1.120 (0.208)	1.314 (0.228)	1.204 (0.151)	1.196 (0.150)	1.217 (0.165)
Putamen							
Slice 34%	1.350 (0.163)	1.353 (0.164)	1.338 (0.102)	1.356 (0.182)	1.395 (0.130)	1.390 (0.132)	1.403 (0.138)
Slice 41%	1.216 (0.191)	1.292 (0.218)	1.189 (0.223)	1.328 (0.207)	1.189 (0.206)	1.187 (0.193)	1.193 (0.233)
Combined	1.283 (0.162)	1.323 (0.190)	1.263 (0.163)	1.342 (0.195)	1.291 (0.168)	1.288 (0.162)	1.298 (0.185)
Striatum	1.235 (0.162)	1.245 (0.164)	1.237 (0.135)	1.450 (0.170)	1.230 (0.143)	1.215 (0.136)	1.244 (0.158)

*Percentage of head height from Matsui and Hirano atlas,[24] 1978. 34% is equivalent to $z=-4$ and 41% is equivalent to $z=12$ in Talairach and Tournoux atlas.[21]

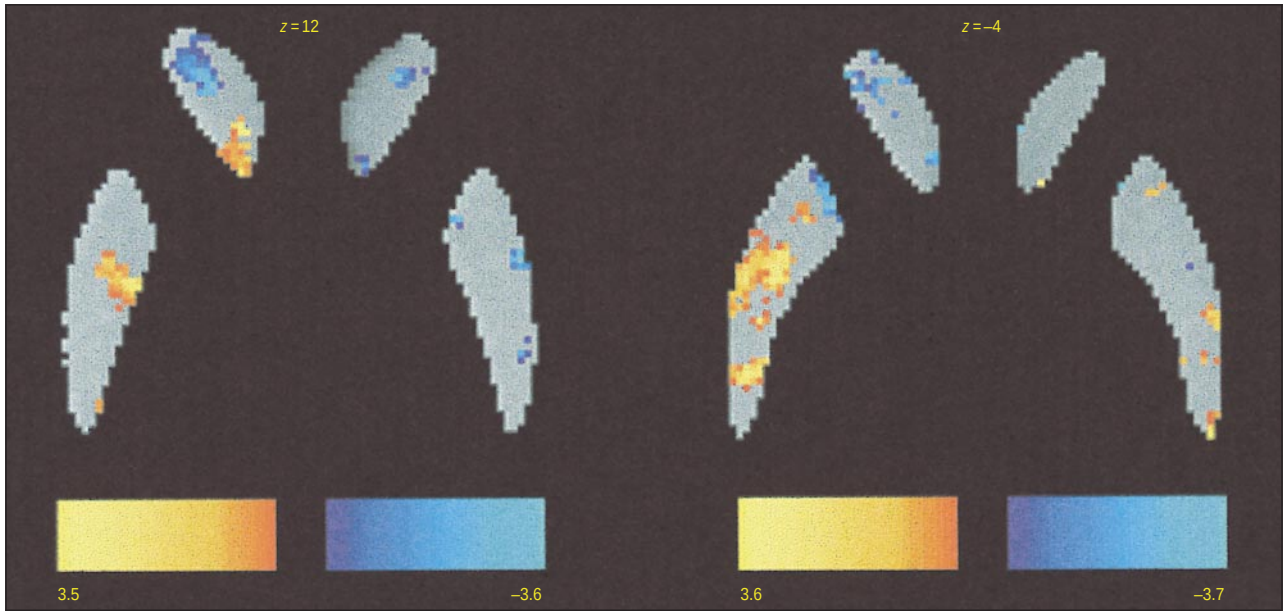

Figure 2. Caudate and putamen relative metabolic rate in patients with schizotypal personality disorder and schizophrenic patients who never received medications (ie, never-medicated patients). The dorsal ($z=12$[21]) and ventral ($z=-4$) caudate and putamen are shown on a background of the mean shape-standardized magnetic resonance image on which they were traced. The color bar represents *t* values comparing relative metabolic rate in patients with schizotypal personality disorder and schizophrenic patients. The red-orange-yellow color bar extends from red ($t_{16}=2.12$, $P=.05$, 2-tailed) to the maximum light yellow value at 3.5 to 3.6 ($P<.003$). Red represents the significantly higher metabolic rate in the patients with schizotypal personality disorder than in the schizophrenic patients and is consistent with the analysis of variance (see "Results" section and Table 2). The violet-purple–light blue bar is similarly arranged for the schizophrenic patients and is greater than for the patients with schizotypal personality disorder. Left side of the brain is on the right side of the image.

diminished rGMR in the caudate nucleus, especially in the contrast of the never-medicated patients with SPD vs the never-medicated schizophrenic patients (**Figure 3**).

The rGMR in the ventral striatum was lowest in previously medicated patients with SPD (mean±SD, 1.215±0.162) in a 3-way ANOVA comparing them with previously medicated schizophrenic patients (1.249±0.169) and normal subjects (1.234±0.162) (group, $F_{1,24}=4.40$; $P=.04$). The rGMR in the previously medicated patients with SPD (1.244±0.19) was nonsig-

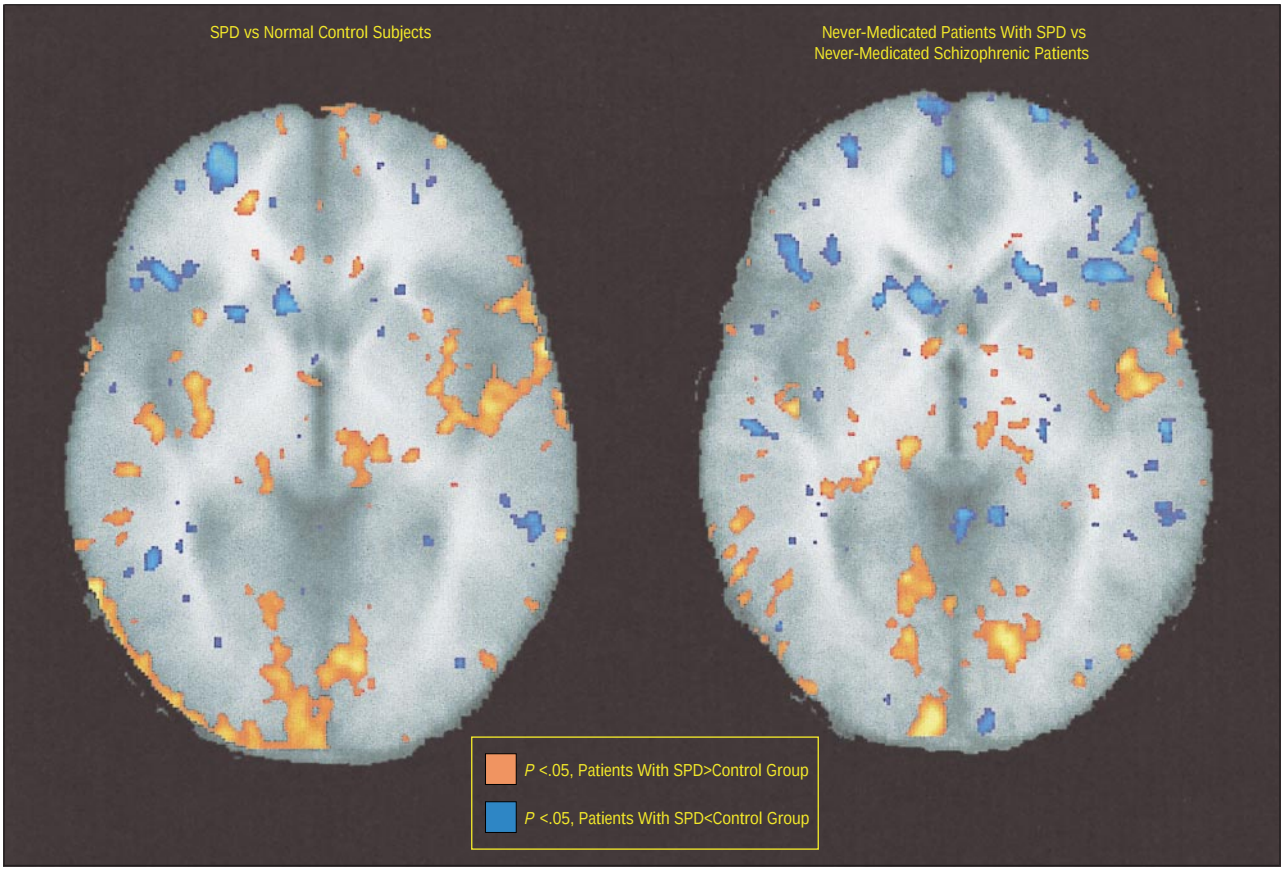

Figure 3. Significance probability maps contrasting patients with schizotypal personality disorder (SPD) who never received medication (ie, the never-medicated patients) with normal control subjects and never-medicated schizophrenic patients. *t* Tests comparing relative metabolic rate are presented on the background of the coregistered average standardized magnetic resonance image ($z=-4^{21}$). Note that the patients with SPD show the same caudate decrease and putamen increases observed with individual putamen templates (Figure 2) and multivariate analysis of variance on the entire striatal area in Table 1, indicating agreement between the 3 statistical methods. Left side of the brain is on the right side of the image.

nificantly higher than in the never-medicated patients with SPD (1.215±0.17). The rGMR was higher in the putamen in previously medicated schizophrenic patients (mean [SD], 1.342 [0.194]) than in never-medicated schizophrenic patients ((mean [SD], 1.264 [0.191]; group×region interaction, $F_{1,25}=5.56$; $P=.03$), while rGMR in the caudate nucleus was similar in previously medicated and never-medicated subgroups.

CLINICAL CORRELATIONS IN SPD

The number of SPD psychoticlike symptoms (*DSM-III-R*) and size of the caudate nucleus (right side, $r=0.81$, $P<.001$; age partialed out, $r=0.73$, $P<.001$) were positively correlated; patients with SPD with the fewest psychoticlike symptoms had smaller caudates. There was a negative correlation with rGMR in the ventral putamen, the area where rGMR was lowest in schizophrenia, and psychoticlike symptoms in SPD (right side, $r=-0.47$, $P=.03$, 1-tailed; age partialed out, $r=0.29$, $P=.28$), consistent with the hypothesized relationship between reduced psychoticlike symptoms and increased metabolism. There were no correlations between caudate or putamen size or rGMR and age, depressive symptoms, or sporadic substance abuse in patients with SPD. There were also no correlations between caudate or putamen size and rGMR in patients with SPD.

COMMENT

The abnormalities in MRI-assessed putamen size and rGMR that characterized SPD were distinctly different from findings in schizophrenia. Patients with SPD had smaller putamens than either controls or schizophrenic patients (whereas putamen size was increased in schizophrenic patients relative to controls). Patients with SPD also had higher rGMR in the putamen than did schizophrenic patients. The findings in SPD of reduced size and increased rGMR in the putamen are consistent with reduced dopaminergic activity in the putamen or lower susceptibility to dopaminergic up-regulation, hypothetically protective against full-blown psychotic symptoms.

Increased dopaminergic activity has been linked to psychosis based on the D_2 dopamine receptor–blocking potency of neuroleptic agents.[28] Postmortem findings[29-31] are not definitive, partly because of the unknown degree to which they may reflect prior medication exposure, and in vivo brain-imaging findings suggest "some, but not all schizophrenic patients have elevated levels of striatal D_2 receptors."[32(p609)] Amphetamine-stimulated dopamine release in schizophrenic patients is greater than in controls and, moreover, is proportional to the amphetamine-induced increase in psychosis.[33-34] In contrast, amphetamine does not exacerbate psychoticlike symptoms in SPD.[35-36] Our finding of a greater

difference in putamen than caudate is consistent with the distribution of D2 dopamine receptors in man. Postmortem studies show greater D2 dopamine receptor densities in putamen than caudate,[37,38] especially anterior putamen,[39] where we observed our greatest effects with statistical probability mapping.

While our data provide no direct information about dopaminergic activity in striatum, volumetric increases in caudate or putamen occur after treatment with neuroleptic agents in schizophrenia.[10,12,13] Enlarged volume may reflect increased presynaptic dopaminergic activity, perhaps through increased size of the dendritic trees or the actual neurons or the intracellular neuronal structures.[12,40] Long-term treatment with haloperidol can lead to increased striatal size in rats,[40] in contrast with decreased size after long-term treatment with clozapine.[41] Thus, the smaller size of the putamen in SPD could reflect decreased dendritic branching, possibly on a developmental basis, and diminished dopamine responsiveness, although other interpretations are possible. Increased striatal size in schizophrenic patients compared with controls could stem from direct medication effects or an interaction between pathophysiology and medication exposure. Higher levels of dopaminergic activity in schizophrenic patients might lead to greater medication exposure, leading in turn to dopaminergic proliferation and striatal size increases. The smaller size of the putamen in never-medicated schizophrenic patients than in previously medicated patients may reflect past medication exposure in the latter or, again, an interaction between the disease process and such exposure. Smaller size of the putamen in previously medicated patients with SPD than in previously medicated schizophrenic patients could reflect lesser exposure to neuroleptic agents in SPD. The reduced size of the putamen in previously medicated patients with SPD relative to controls, however, cannot be attributed to neuroleptic exposure (minimal in SPD and nonexistent in controls) and is consistent with a deficit in the sensitivity of some mechanisms to changes in dopamine. Indeed, neuroleptic exposure would have been expected to increase rather than decrease striatal volumes in patients with SPD. Decreases in striatal size have also been reported in affective disorder, where neuroleptic exposure is minimal.[42] Further, our finding of a significant decrease in the size of the putamen but not in the caudate in patients with SPD is consistent with the smaller size of the putamen, but not of the caudate, found in the relatives of schizophrenic patients.[43]

Our study's limitations include small sample size in a heterogeneous disorder, patient-selection bias, and examination of whole-putamen volumes. While we previously found never-medicated and previously medicated schizophrenic patients differed significantly in caudate size,[10] the difference was not statistically significant here. The largest differences remained in the putamen, with effect sizes in the range of 0.6 for the dorsal right putamen in schizophrenic patients, our strongest region previously[10]; effect size in patients with SPD was 0.3. Further studies of striatal volume using more detailed anatomical analysis[26] to examine anterior and posterior putamen separately and to contrast both globus pallidus and nucleus accumbens with the putamen in larger numbers of patients may prove informative. It is also possible that laterality and gender effects with greater right hemisphere change (Figure 2) also seen with D2 dopamine receptor binding[44] may contribute to group differences but require larger samples to fully demonstrate.

The relationship between rGMR, size of the putamen, and psychoticlike symptoms in patients with SPD was strongest in the ventral striatum, the area thought to receive dopaminergic projections from the mesolimbic pathway.[45] This area is also thought to be the richest in D2 dopamine receptors[46] and most affected in schizophrenia.[10] The posterior ventral putamen (Figure 2 and Figure 3) was relatively unaffected, a result similar to that observed in fluorodopa F 18 scans in Parkinson disease.[47]

Increased rGMR in patients with SPD, whether currently unmedicated or never-medicated, compared with both schizophrenic patients, whether currently unmedicated or never-medicated, and controls could suggest reduced dopaminergic inhibitory tone in SPD. A linear correlation between D2 dopamine receptor availability and rGMR in 37 healthy subjects[48] is also consistent with this hypothesis. Three statistical methods—ANOVA on rGMR in MRI-template regions, pixel-by-pixel analysis of standardized putamens, and statistical probability mapping—showed consistent results. Diminished putamen function in patients with SPD relative to schizophrenic patients, reflected by the smaller size of the putamen and higher rGMR, would be consistent with the hypothesis of a relatively low level of dopamine activity in SPD. According to this hypothesis, dopaminergic activity in the putamen might be lower in patients with SPD than schizophrenic patients, leading to smaller volumes and greater rGMR, and possibly serving a protective function against the development of frank psychosis. Confirmation of this hypothesis would require more detailed anatomical studies, carried out in concert with functional studies using both fluorodeoxyglucose F-18 and dopamine-receptor ligands, in larger samples of both never-medicated patients with SPD and schizophrenic patients.

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REFERENCES

1. Siever LJ, Silverman JM, Horvath TB, Klarr H, Coccaro E, Keefe RS, Pinkham L, Rinaldi P, Mohs RC, Kavis KL. Increased morbid risk for schizophrenia-related disorders in relatives of schizotypal personality disordered patients. *Arch Gen Psychiatry.* 1990;47:634-640.
2. Buchsbaum MS, Yang S, Hazlett E, Siegel BV Jr, Germans M, Haznedar MM, O'Flaithbheartaigh S, Wei T, Silverman J, Siever LJ. Ventricular volume and asymmetry in schizotypal personality disorder and schizophrenia assessed with magnetic resonance imaging. *Schizophr Res.* 1997;27:45-53.
3. Trestman RL, Keefe RS, Mitropoulou V, Harvey PD, deVegvar ML, Lees-Roitman S, Davidson M, Aronson A, Silverman J, Siever LJ. Cognitive function and biological correlates of cognitive performance in schizotypal personality disorder. *Psychiatry Res.* 1995;59:127-136.
4. Siever L, Friedman L, Moskowitz J, Mitropoulou V, Keefe R, Roitman SL, Merhige D, Trestman R, Silverman J, Mohs R. Eye movement impairment and schizotypal psychopathology. *Am J Psychiatry.* 1994;151:1209-1215.
5. Braff DL, Geyer MA. Sensorimotor gating and schizophrenia: human and animal model studies [review]. *Arch Gen Psychiatry.* 1990;47:181-188.
6. Siever LJ, Amin F, Coccaro EF, Bernstein D, Kavoussi RJ, Kalus O, Horvath TB, Warne P, Davidson M, Davis KL. Plasma homovanillic acid in schizotypal personality disorder patients and controls. *Am J Psychiatry.* 1991;148:1246-1248.
7. Siever LJ, Kalus OF, Keefe RF. The boundaries of schizophrenia [review]. *Psychiatr Clin North Am.* 1993;15:217-244.
8. Dickey CC, McCarley RW, Voglmaier MM, Niznikiewicz MA, Seidman LJ, Hirayasu Y, Fischer I, Teh EK, Van Rhoads R, Jakab M, Kikinis R, Jolesz FA, Shenton ME. Schizotypal personality disorder and MRI abnormalities of temporal lobe gray matter. *Biol Psychiatry.* 1999;45:1393-1402.
9. Hokama H, Shenton ME, Nestor PG, Kikinis R, Levitt JJ, Metcalf D, Wible CG, O'Donnell BF, Jolesz FA, McCarley RW. Caudate, putamen, and globus pallidus volume in schizophrenia: a quantitative MRI study. *Psychiatry Res.* 1995;61:209-229.
10. Shihabuddin L, Buchsbaum MS, Hazlett EA, Haznedar MM, Harvey PD, Newman A, Schnur DB, Spiegel-Cohen J, Wei, T, Machac J, Knesaurek K, Vallabhajosula S, Biren MA, Ciaravolo, T, Luu-Hsia C. Dorsal striatal size, shape, and metabolic rate in neuroleptic-naive and previously medicated schizphrenic patients performing a verbal learning task. *Arch Gen Psychiatry.* 1998;55:235-243.
11. McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA, Shenton ME. MRI anatomy of schizophrenia [review]. *Biol Psychiatry.* 1999;45:1099-1119.
12. Chakos MH, Lieberman JA, Bilder RM, Borenstein M, Lerner G, Bogerts B, Wu H, Kinon B, Ashtari M. Increase in caudate nuclei volume of first-episode schizophrenic patients taking antipsychotic drugs. *Am J Psychiatry.* 1994;151: 1430-1436.
13. Keshavan MS, Bagwell WW, Haas GL, Sweeney JA, Schooler NR, Pettegrew JW. Changes in caudate volume with neuroleptic treatment [letter]. *Lancet.* 1994; 344:1434.
14. Gur RE, Maany V, Mozley PD, Swanson C, Bilker W, Gur RC. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. *Am J Psychiatry.* 1998;155:1711-1717.
15. Corson PW, Nopoulos P, Miller DD, Arndt S, Andreasen NC. Change in basal ganglia volume over 2 years in patients with schizophrenia: typical versus atypical neuroleptics. *Am J Psychiatry.* 1999;156:1200-1204.
16. Buchsbaum MS, Hazlett EA. Positron emission tomography studies of abnormal glucose metabolism in schizophrenia [review]. *Schizophr Bull.* 1998;24: 343-364.
17. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry.* 1978;35:837-844.
18. Stangl D, Pfohl B, Zimmerman M, Bowers W, Corenthal C. A structured interview for *DSM-III* personality disorders: a preliminary report. *Arch Gen Psychiatry.* 1985;42:591-596.
19. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry.* 1992;49:615-623.
20. Overall J, Gorham D. The Brief Psychiatric Rating Scale. *Psychol Rep.* 1962;10: 799-812.
21. Talairach J, Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain.* Stuttgart, West Germany: Georg Thieme Verlag; 1988.
22. Delis DC, Kramer JH, Kaplan E, Ober BA. *The California Verbal Learning Test.* San Antonio, Tex: Psychological Corp; 1987.
23. Hazlett EA, Buchsbaum MS, Mohs RC, Spiegel-Cohen J, Wei TC, Azueta R, Haznedar MM, Singer MB, Shihabuddin L, Luu-Hsia C, Harvey PD. Age-related shift in brain region activity during successful memory performance. *Neurobiol Aging.* 1998;19:437-445.
24. Matsui T, Hirano A. *An Atlas of the Human Brain for Computerized Tomography.* Tokyo, Japan: Igaku-Shoin Ltd; 1978.
25. Bartels P, Subach J. Significance probability mappings and automated interpretation of complex pictorial scenes. In: Preston E, Onoe M, eds. *Digital Processing of Biomedical Imagery.* New York, NY: Academic Press Inc; 1976:101-114.
26. Buchsbaum MS, Fallon JH, Wei TC, Guich S, Spiegel-Cohen J, Hamilton M, Tang C. A method of basal forebrain anatomical standardization for functional image analysis. *Psychiatry Res.* 1998;84:113-125.
27. Buchsbaum MS. Neuroimaging, VII: PET and the averaging of brain images. *Am J Psychiatry.* 1996;153:456.
28. Creese I, Hess EJ. Biochemical characteristics of D1 dopamine receptors: relationship to behavior and schizophrenia. *Clin Neuropharmacol.* 1986;9(suppl 4): 14-16.
29. Mackay AV, Iversen LL, Rossor M, Spokes E, Bird E, Arregui A, Creese I, Snyder SS. Increased brain dopamine and dopamine receptors in schizophrenia. *Arch Gen Psychiatry.* 1982;39:991-997.
30. Lee T, Seeman P, Rajput A, Farley IJ, Hornykiewicz O. Receptor basis for dopaminergic supersensitivity in Parkinson's disease. *Nature.* 1978;273:59-61.
31. Joyce JN, Meador-Woodruff JH. Linking the family of D2 receptors to neuronal circuits in human brain: insights into schizophrenia [review]. *Neuropsychopharmacology.* 1997;16:375-384.
32. Soares JC, Innis RB. Neurochemical brain imaging investigations of schizophrenia. *Biol Psychiatry.* 1999;46:600-615.
33. Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci U S A.* 1996;93:9235-9240.
34. Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, van Dyck CH, Charney DS, Innis RB, Laruelle M. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry.* 1998;155:761-767.
35. Siegel BV Jr, Trestman RL, O'Flaithbhertaigh S, Mitropoulou V, Amin F, Kirrane R, Silverman J, Schmeidler J, Keefe RS, Siever LJ. D-amphetamine challenge effects on Wisconsin Card Sort Test: performance in schizotypal personality disorder. *Schizophr Res.* 1996;20:29-32.
36. Kirrane RM, Mitropoulou V, Nunn M, New AS, Harvey PD, Schopick F, Silverman J, Siever LJ. Effects of amphetamine on visuospatial working memory performance in schizophrenia spectrum personality disorder. *Neuropsychopharmacology.* 2000;22:14-18.
37. Boyson SJ, Adams CE. D1 and D2 dopamine receptors in perinatal and adult basal ganglia. *Pediatr Res.* 1997;41:822-831.
38. Joyce JN, Gurevich EV. D3 receptors and the actions of neuroleptics in the ventral striatopallidal system of schizophrenics [review]. *Ann N Y Acad Sci.* 1999; 877:595-613.
39. Piggott MA, Marshall EF, Thomas N, Lloyd S, Court JA, Jaros E, Costa D, Perry RH, Perry EK. Dopaminergic activities in the human striatum: rostrocaudal gradients of uptake sites and of D1 and D2 but not of D3 receptor binding or dopamine. *Neuroscience.* 1999;90:433- 445.
40. Chakos MH, Shirakawa O, Lieberman J, Lee H, Bilder R, Tamminga CA. Striatal enlargement in rats chronically treated with neuroleptics. *Biol Psychiatry.* 1998; 44:675-684.
41. Lee H, Tarazi FI, Chakos M, Wu H, Redmond M, Alvir JM, Kinon BJ, Bilder R, Creese I, Lieberman JA. Effects of chronic treatment with typical and atypical antipsychotic drugs on the rat striatum. *Life Sci.* 1999;64:1595-1602.
42. Parashos IA, Tupler LA, Blitchington T, Krishnan KR. Magnetic-resonance morphometry in patients with major depression. *Psychiatry Res.* 1998;84:7-15.
43. Seidman LJ, Faraone SV, Goldstein JM, Goodman JM, Kremen WS, Matsuda G. Hoge EA, Kennedy D, Makris N, Caviness VS, Tsuang MT. Reduced subcortical brain volumes in nonpsychotic siblings of schizophrenic patients: a pilot magnetic resonance imaging study. *Am J Med Genet.* 1997;74:507-514.
44. Schröder J, Bubeck B, Silvestri S, Demisch S, Sauer H. Gender differences in D2 dopamine receptor binding in drug-naive patients with schizophrenia: an [^{123}I]iodobenzamide single photon emission computed tomography study. *Psychiatry Res.* 1997;75:115-123.
45. Mello LE, Villares J. Neuroanatomy of the basal ganglia [review]. *Psychiatr Clin North Am.* 1997;20:691-704.
46. Farde L, Wiesel FA, Stone-Elander S, Halldin C, Nordström AL, Hall H, Sedvall G. D2 dopamine receptors in neuroleptic-naive schizophrenic patients: a positron emission tomography study with [^{11}C]raclopride. *Arch Gen Psychiatry.* 1990;47: 213-219.
47. Morrish PK, Sawle GV, Brooks DJ. Regional changes in [^{18}F]dopa metabolism in the striatum in Parkinson's disease. *Brain.* 1996;119:2097-2103.
48. Volkow ND, Logan J, Fowler JS, Wang GJ, Gur RC, Wong C, Felder C, Gatley SJ, Ding YS, Hitzemann R, Pappas N. Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. *Am J Psychiatry.* 2000;157:75-80.