Age-Related Decline in Dopamine Transporters

Analysis of Striatal Subregions, Nonlinear Effects, and Hemispheric Asymmetries

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*Neuroimaging studies have documented an age-related decline in striatal dopamine transporters (DATs) as a marker of dopaminergic neurodegeneration. The authors further elucidated the effects on this neural system in healthy aging, in contrast to Parkinson disease (PD). The effects of age on striatal DAT availability were examined in a large, healthy subject sample (*N = *126) with [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT) and single photon emission computed tomography (SPECT). Striatal DAT availability (V_3'') showed a significant inverse correlation with age, declining in a nearly linear manner by 46% over the age range 18 to 88 years, or 6.6% per decade. Rates of decline were comparable for caudate (48%) and putamen (45%), with only minimal increase in left–right asymmetry with age. Hemispheric asymmetries were unrelated to the handedness of subjects. These results demonstrate that aging is associated with a relatively symmetric loss of DATs in the caudate and putamen in both hemispheres. These findings have implications not only for healthy aging but also for neurodegenerative disorders such as PD.* (Am J Geriatr Psychiatry 2002; 10:36–43)

The decline in motor performance that accompanies advanced age almost certainly affects activities of daily living in older adults[1] and may contribute to the increased risk of a damaging fall by age 80.[2] Aging is associated with a higher frequency of dyskinesias[3] and mild parkinson-like changes such as slowed reaction time and motor speed.[4,5] Many of these motoric changes have been attributed to an age-related degeneration in the nigrostriatal dopamine system.[6]

In recent years, both postsynaptic and presynaptic elements of this neural system have been probed for age-related changes. Most studies of dopamine-receptor

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binding with aging have been conducted with D_1 and D_2 receptors whose location is primarily postsynaptic.[7–10] Presynaptic markers are uniquely valuable, however, because they provide direct information about the nigrostriatal cells. In vitro studies of presynaptic elements have shown various signs of deterioration with age, including reduction in the number of neurons in the substantia nigra[6] and striatal dopamine content,[11,12] both of which demonstrate an age-dependent reduction of approximately 50% over the adult lifespan. Another presynaptic marker located on the terminals of dopaminergic neuronal projections is the dopamine transporter (DAT), which functions to remove dopamine from the synapse back into the terminal for storage or metabolism. The concentration of striatal DATs shows a decline with age of 65% to 75% over the adult lifespan, or approximately 9% per decade.[10,13,14]

With the advent of functional neuroimaging, it has become possible to study the aging of neural systems in living subjects. The DAT has served as a particularly useful target for imaging modalities, including positron emission tomography (PET) and single photon emission computed tomography (SPECT). Previous studies using the radioligands [^{11}C]nomifensine,[15] [^{11}C]cocaine,[16] [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT),[17] [^{123}I]IPT,[18] [^{123}I]βCIT-FP,[19] and [^{11}C]*d-threo*-methylphenidate[20] have reported decreases in DATs with age, although one small study using [^{11}C]WIN 35 428[21] found no aging effect. Collectively, PET and SPECT studies have confirmed postmortem reports, with the majority of studies documenting a robust decline with age (of 6.6% to 8% per decade).

Among the issues left unresolved by previous imaging studies is how the pattern of DAT losses with normal aging differs from that of idiopathic Parkinson disease (PD). PD has been hypothesized by some to involve either rapidly accelerated aging of the nigrostriatal dopaminergic neurons[22] or aging superimposed on endogenous or exogenous neurotoxicity.[23] Previous postmortem data in PD have shown reduced DAT concentrations in the striatum, with relatively greater reductions in the putamen than in the caudate.[24,25] Neuroimaging studies of the DAT in PD have confirmed postmortem findings, showing markedly abnormal striatal uptake, more pronounced in the putamen than caudate,[26–28] and have also demonstrated significantly greater hemispheric asymmetry than in healthy control subjects.[28]

If age-related changes (either normal or accelerated) actually play an important role in the etiology of PD, then the subregional patterns of striatal DAT loss in aging should be similar to those previously observed in PD.[29] On the basis of this premise, we used [^{123}I]β-CIT and SPECT to examine the influence of normal aging on the subregional and hemispheric DAT losses in the striatum of 126 normal control subjects ranging in age from 18 to 88 years. We also explored another emerging question: whether aging effects on DATs are linear, or better characterized by nonlinear functions.[18] Previous imaging studies of DAT losses with age have rarely used subject samples of sufficient size to address these important issues.

METHODS

Subjects

The study population consisted of 126 healthy volunteers (70 male, 56 female) who ranged in age from 18 to 88 (46 ± 19 years; 104 white, 10 black, 8 Asian, 4 Hispanic). Subjects underwent a clinical examination by a research psychiatrist to exclude any neurological or psychiatric disease, or alcohol or substance abuse. Screening procedures included a physical and neurological examination, ECG, serum chemistries, thyroid-function studies, CBC, urinalysis, and urine toxicology screen. Female subjects of childbearing potential were required to have a negative pregnancy test (serum at screening; urine immediately before tracer injection). Those subjects ≥55 years of age ($n = 31$) were also required to have no significant evidence of cognitive impairment, as indicated by a Folstein Mini-Mental State Exam (MMSE)[30] score ≥27. Those subjects ≥68 ($n = 25$) were required to have a normal brain MRI scan. No subject was taking medication known to affect the brain dopamine system. Handedness was assessed in a subset of subjects ($n = 114$) by use of the Edinburgh Handedness Inventory.[31] All subjects gave written informed consent for the study after the procedures had been fully explained. The present subject sample is identical to the sample ($N = 126$) in which we previously reported an age-related decline in serotonin transporters in the midbrain-diencephalon,[32] using the same [^{123}I]β-CIT SPECT scans. However, it is independent of the sample ($N = 28$) in which we previously analyzed aging effects on the DAT with a different SPECT camera.[17]

SPECT Imaging

All subjects received 0.6 g potassium iodide (SSKI solution) in the 24 hours before the SPECT scan. They then received an injection of [^{123}I]β-CIT (6.0 ± 0.8 mCi; specific activity >5,000 Ci/mmol) on Day 1, followed 23.1 ± 1.9 hour later by a 24-minute scan with a Picker (Cleveland, OH) PRISM 3000 (n = 89) or 3000XP (n = 37) SPECT camera equipped with a low-energy, high-resolution (LEHR) fanbeam collimator (128 × 128 matrix, 120° angular range, 3° angular step, 40 steps, 36 seconds per step, 15.5-cm radius of rotation). In this configuration, the PRISM 3000 acquires images at a reconstructed full width at half-maximum resolution of 12.3 mm, as determined by an ^{123}I point-source in water. Comparability of the two cameras was confirmed by imaging 26 subjects on both cameras from a single [^{123}I]β-CIT injection and finding no significant difference in V_3'' in the striatum (PRISM 3000: 5.0 ± 1.1; 3000XP: 5.0 ± 0.8; $t_{[25]}$ = 0.04; p = 0.97, paired t-test; intraclass correlation coefficient[33] = 0.85). Previous studies have demonstrated that [^{123}I]β-CIT reaches equilibrium binding in the brain by 18 to 24 hours,[34] yielding a simple unitless ratio of regional radioactivities (V_3'' = specific/nondisplaceable binding = [striatal — occipital]/occipital) in estimating DAT number (i.e., B_{max}). Before scanning, four or five fiducial markers filled with 5 μCi of $Na^{99m}TcO_4$ were attached to the skin along the canthomeatal plane to identify this plane during image analysis.

Images were reconstructed from photopeak counts (159 ± 16 keV), by use of standard filtered back-projection methods (Butterworth, Power 10, cutoff 0.24 cm^{-1}) and displayed as a 128 × 128 × 64 matrix with a voxel size of 2.07 × 2.07 × 3.56 mm (15.25 mm^3). Subsequent image analysis was performed by an operator who was unaware of subject demographics. SPECT data were reoriented to correct for deviations from the canthomeatal plane, as identified by the fiducial markers. Eight contiguous transaxial slices with the highest uptakes in striatum were identified from a reconstructed midsagittal image and digitally summed to yield a transaxial slice 28.5 mm thick. Attenuation correction was performed using a Chang zero-order method (attenuation coefficient μ = 0.15 cm^{-1}), within an ellipse drawn around the skull. Standard region of interest (ROI) templates for left and right caudate (424 voxels or 6.5 mL each), left and right putamen (824 voxels or 12.6 mL each), and occipital cortex (7,912 voxels or 120.6 mL; similar to those previously published[17]) were positioned on the summed slice. No attempt was made to correct for scatter or partial volume effects.

Statistical Analysis

V_3'' for the striatum and striatal subregions (caudate and putamen) was computed without conversion of SPECT counts per minute (cpm) to absolute units of radioactivity as $[(cpm/voxel)_{striatum} - (cpm/voxel)_{occipital})] / (cpm/voxel)_{occipital}$. The effect of age on V_3'' for all structures was examined by linear-regression analysis and Pearson product-moment correlation coefficient (r). Also, several nonlinear functions (including 2nd-order polynomial, exponential, logarithmic, and power) were examined, using Kaleidagraph 3.5 (Synergy Software; Reading, PA) to see if they provided a better fit for the relationship between V_3'' (for striatum, caudate, and putamen) and age. Five models were considered.

1. $y = a + bx$
2. $y = a + bx + cx^2$
3. $y = ae^{bx}$
4. $y = a * \log x + b$
5. $y = ax^b$

where Model 1 describes a linear function with a slope of b and a y-intercept of a, Model 2 is a 2nd-order polynomial (quadratic) that reduces to a linear equation when c = 0; Model 3 is a monoexponential function; Model 4 is a common (base 10) logarithmic function; and Model 5 is a power function. Models 2–5 were considered as alternatives to the linear relationship represented by Model 1. The quality of fit of these functions was evaluated by use of nonlinear regression and correlation coefficients (r).

Differences in V_3'' between left and right caudate and left and right putamen were tested with paired Student t-tests. A hemispheric asymmetry index was also derived for the striatum, caudate, and putamen, using the following formula.

$$\text{Asymmetry Index (AI)} = \frac{\text{right} - \text{left}}{(\text{right} + \text{left})/2} \times 100$$

The effect of age on AI, as well as on the absolute value of AI, was then examined by linear-regression analysis and Pearson r. The relationship between handedness

(using the Edinburgh Handedness Score, or laterality quotient, a continuous variable ranging from –1: strongly left-handed, to +1: strongly right-handed)[31] and the striatal AI was examined by Spearman's rank-order correlation (r_s). The striatal AI was also compared between right- and left-handers by two-sample Student *t*-test.

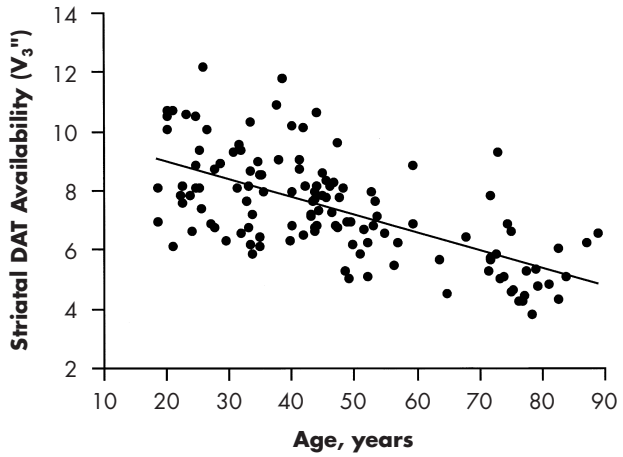
RESULTS

Effect of Age on Dopamine Transporters in Striatum and Striatal Subregions

The values for DAT availability (V_3'') in the striatum ranged from 3.9 to 12.2 (7.4 ± 1.8) for this healthy subject sample. There was an age-dependent decline in striatal V_3'' values ($r_{[124]}$ = –0.64; p <0.0001 ([Figure 1]). Linear-regression analysis revealed that V_3'' declined by 46% over the age range 18 to 88, or approximately 6.6% per decade. Rates of decline were similar for V_3'' in the caudate ($r_{[124]}$ = –0.65; p <0.0001; 48% decline, or 6.8% per decade) and putamen ($r_{[124]}$ = –0.63; p <0.0001; 45% decline, or 6.5% per decade [Figure 2]).

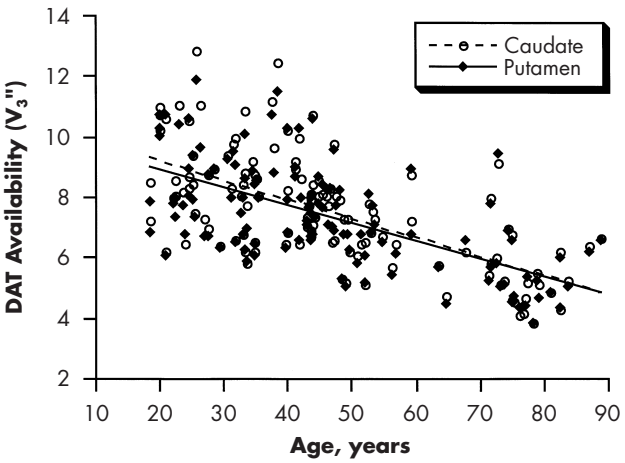
Table 1 displays the results of nonlinear curve-fit-

FIGURE 1. Striatal dopamine transporter (DAT) availability (V_3'') by age as measured by [^{123}I]β-CIT SPECT in 126 healthy subjects.



Note: Striatal V_3'' = –0.0604 × age + 10.225; $r_{[124]}$ = –0.64; p <0.0001 (Pearson's test). Linear-regression analysis revealed that V_3'' declined by 46% over the age range 18 to 88, or approximately 6.6% per decade

FIGURE 2. Dopamine transporter (DAT) availability (V_3'') by age for caudate and putamen, as measured by [^{123}I]β-CIT SPECT in 126 healthy subjects



Note: Caudate V_3'' = –0.0637 × age + 10.497; $r_{[124]}$ = –0.65; p <0.0001 (Pearson's test). Putamen V_3'' = –0.0587 × age + 10.085; $r_{[124]}$ = –0.63; p <0.0001. Linear-regression analysis revealed similar rates of decline for V_3'' in the caudate (48% decline, or 6.8% per decade) and putamen (45% decline, or 6.5% per decade).

TABLE 1. Linear and nonlinear effects of normal aging on striatal dopamine transporters (DATs) with [^{123}I]β-CIT SPECT

Model	Best-Fitting Equation	*r*
Striatal curve fits		
Linear	$y = 10.225 - 0.0604x$	0.63859
Polynomial	$y = 9.973 - 0.049x - 0.000111x^2$	0.63896
Monoexponential	$y = 10.811 * e^{-0.00872x}$	0.63443
Logarithmic	$y = 17.355 - 6.089 * \log x$	0.61651
Power	$y = 29.672 * x^{-0.377}$	0.59976
Caudate curve fits		
Linear	$y = 10.497 - 0.0637x$	0.64609
Polynomial	$y = 10.453 - 0.0617x - 0.0000193x^2$	0.64610
Monoexponential	$y = 11.123 * e^{-0.00902x}$	0.64313
Logarithmic	$y = 18.077 - 6.460 * \log x$	0.62716
Power	$y = 31.865 * x^{-0.392}$	0.61065
Putamen curve fits		
Linear	$y = 10.085 - 0.0587x$	0.63118
Polynomial	$y = 9.726 - 0.0424x - 0.000158x^2$	0.63196
Monoexponential	$y = 10.648 * e^{-0.00856x}$	0.62641
Logarithmic	$y = 16.984 - 5.899 * \log x$	0.60749
Power	$y = 28.569 * x^{-0.369}$	0.59071

Note: Best-fitting equation = equation of given model yielding largest linear or nonlinear correlation coefficient (*r*); polynomial = 2nd-order polynomial (i.e., quadratic); logarithmic = common (base 10) logarithmic function.

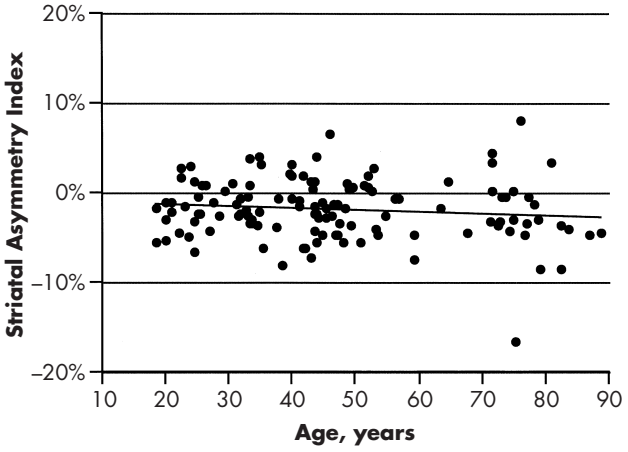
ting for the relationship between V_3'' and age. For the striatum, caudate, and putamen, the best-fitting equation was a 2nd-order polynomial. However, for each structure, the quality of fit (as measured by the correlation coefficient *r*) was only incrementally superior to a linear fit. In each case, the 2nd-order polynomial approached a linear equation (as values of *c* approached 0). Other nonlinear functions (monoexponential, logarithmic, and power) provided fits that were inferior to that of the linear model (Table 1).

Effect of Age on Hemispheric Asymmetry of Striatal Dopamine Transporters

Comparisons between left and right striatal regions showed significantly higher values for DAT availability (V_3'') in the left (7.61 ± 1.88) than in the right (7.49 ± 1.82) caudate ($t_{[125]} = 3.43$; p = 0.0008; paired *t*-test); and in the left (7.44 ± 1.76) than in the right (7.30 ± 1.73) putamen ($t_{[125]} = 4.81$; p < 0.0001; paired *t*-test).

The striatal AI is displayed as a function of age in Figure 3. The striatal AI was unrelated to age ($r_{[124]} = -0.11$; p = 0.19), as were the caudate AI ($r_{[124]} = 0.03$; p = 0.71) and putamen AI ($r_{[124]} = 0.10$; p = 0.27). However, the absolute value of the striatal AI was weakly correlated with age ($r_{[124]} = 0.23$; p = 0.01), increasing from a mean of 2.2% at age 18 to 4.2% at age 88 (Figure 3). When a single outlier (striatal AI = –17%) was removed from the analysis, this weak effect of age persisted ($r_{[123]} = 0.18$; p = 0.04). There was no correlation between age and the absolute value of either the caudate AI ($r_{[124]} = 0.13$; p = 0.13) or putamen AI ($r_{[124]} = -0.11$; p = 0.24). Those subjects for whom handedness data were available ($n = 114$) comprised 101 right-handers and 13 left-handers. The Edinburgh Handedness Scores (laterality quotients) were not normally distributed and were examined by nonparametric statistical tests. The striatal AI was unrelated to the Edinburgh Handedness Score ($r_s = -0.0726$; (df = 112); p = 0.44; see Figure 4). When handedness was instead considered as a dichotomous variable, the striatal AI did not differ between right- and left-handers ($t_{[112]} = 0.15$; p = 0.88).

FIGURE 3. The Asymmetry Index (AI) for striatal dopamine transporter (DAT) availability versus age, as measured by [^{123}I]β-CIT SPECT in 126 healthy subjects

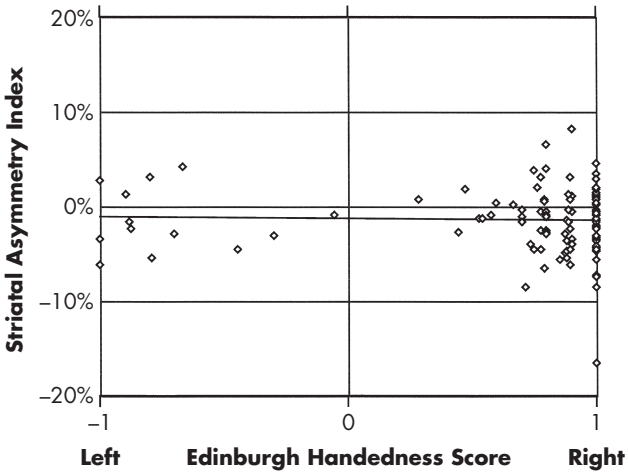


Note: The striatal AI was unrelated to age ($r_{[124]} = -0.11$, p = 0.19); however the absolute value of the striatal AI was weakly correlated with age ($r_{[124]} = 0.23$, p = 0.01), increasing from a mean of 2.2% at age 18 to 4.2% at age 88.

DISCUSSION

We investigated aging effects in DAT availability in the largest healthy subject sample analyzed to date. The overall rate of decline in DATs we observed with [^{123}I]β-CIT is very comparable to that reported in previous PET and SPECT studies using a variety of radioligands (Table

FIGURE 4. The Asymmetry Index (AI) for striatal dopamine transporter (DAT) availability in relation to handedness in 114 subjects for whom handedness information was available



Note: Handedness was determined by the Edinburgh Handedness Score or laterality quotient. The regression line shows the best linear fit. Striatal AI was unrelated to the handedness of subjects (Spearman's $r_s = -0.0726$, df = 112; p = 0.44).

2). The measured 6.6% decline per decade is identical to the figure reported by Volkow et al. using PET and [^{11}C]*d-threo*-methylphenidate[20] and within the range documented by other studies,[16] including our previous investigation with [^{123}I]β-CIT SPECT, using a different SPECT camera.[17] Collectively, imaging studies of aging effects on DATs are consistent with earlier postmortem reports using in vitro homogenate binding with the DAT radioligand [^{3}H]GBR-12935.[10,13,14]

We also found comparable rates of decline between the caudate (6.8% per decade) and putamen (6.5% per decade). Previous in vivo and in vitro studies of aging effects on the DAT have only minimally addressed differential aging effects in striatal subregions. Mozley et al.[18] compared seven volunteers less than age 30 years with five volunteers over 60 years old and reported that specific uptake of [^{123}I]IPT SPECT was reduced by 49% in the caudate and 53% in the putamen in the older group. Volkow et al.[20] compared 13 volunteers less than 40 years old with 10 volunteers over 40 and observed that B_{max}/K_D using [^{11}C]*d-threo*-methylphenidate and PET was reduced by 34% for the caudate and 25% for the putamen in the older group. Given the spatial resolution of SPECT (and even PET) instruments, in vivo imaging studies have inherently limited ability to detect differential aging effects in striatal subregions. Postmortem reports show similar effects of age (approximately 9% per decade) on DAT concentrations in the caudate[14] vs. putamen.[10,13] However, no postmortem report has examined aging effects in striatal subregions in the same specimens.

Our results lend support to the common practice of approximating age-related losses of DATs by a linear model. One previous study with [^{123}I]IPT SPECT[18] has suggested that age-related DAT losses may be nonlinear, with rapid decline during young adulthood, followed by less rapid decline throughout middle age. These investigators reported that several nonlinear functions (including 2nd-order polynomial and stick functions) provided a better fit for aging effects seen in a much smaller sample of healthy volunteers ($N = 18$). Our data certainly leave open the possibility that nonlinear functions (e.g., 2nd-order polynomial) may provide a slightly more optimal description of DAT losses with age. However, they strongly suggest that the appropriate function is *nearly* linear over the age range 18–88 and that linear models may provide a reasonable age-correction for clinical studies, for example, of PD. Longitudinal imaging studies of PD are emerging, documenting a precipitous fall in striatal DATs during the course of the disease (11.2% to 13% per year, vs. 0.8% to 2.5% per year in control subjects[35,36]), although the precise shape of longitudinal losses in PD remains to be defined.

The reduction in DATs with age as measured by [^{123}I]β-CIT SPECT is likely related in part to an age-related shrinkage in the corpus striatum. Quantitative MRI studies have demonstrated that striatal volume declines by anywhere from 20% to 50% over the adult age range.[37–40] Given that our analysis uses standard ROIs of preset area and shape, it may be sensitive to such changes in striatal volume. Future studies with MRI coregistration, segmentation, and image-blurring[41,42] may correct for these "partial volume" effects.[43] Nonetheless, the impact of aging may be better appreciated by an uncorrected outcome measure that is sensitive to absolute reduction in DAT number.

Our findings of greater left than right putamen and caudate DAT availability (also noted in our previous study[28] and noted for putamen-only by Volkow et al.[20]), however, are apparently not due to volume differences.

TABLE 2. Imaging studies of aging effects on striatal dopamine transporters (DATs)

Modality	Tracer	Reference	Subjects	Age Range	Decline per Decade
PET	[^{11}C]nomifensine	Tedroff, 1988[15]	7 (6M, 1F)	24–81	NR
PET	[^{11}C]WIN 35428	Wong, 1993[21]	10 (5M, 5F)	19–81	none
PET	[^{11}C]cocaine	Volkow, 1994[16]	27 (27M)	21–63	7%
SPECT	[^{123}I]β-CIT	van Dyck, 1995[17]	28 (14M, 14F)	18–83	8%
SPECT	[^{123}I]IPT	Mozley, 1996[18]	18 (12M, 6F)	19–67	NR
SPECT	[^{123}I]β-CIT-FP	Ishikawa, 1996[19]	15 (11M, 4F)	21–79	3.3%
PET	[^{11}C]*d-threo*-methylphenidate	Volkow, 1996[20]	23 (14M, 9F)	20–74	6.6%
SPECT	[^{123}I]β-CIT		126 (70M, 56F)	18–88	6.6%

Note: PET = positron emission tomography; SPECT = single photon emission computed tomography; NR = not reported; however, both studies documented an age-related decline in DATs.

Most MR volumetric studies have found no significant hemispheric differences in the volumes of putamen[38,40] or caudate.[39,40] Interestingly, Peterson et al.[43] have reported significantly larger left total basal ganglia volume and left putamen volume in right-handed healthy control subjects, raising the possibility that increased left-striatal DAT binding in PET and SPECT studies could accrue from a preponderance of right-handed subjects. Previous healthy control groups in DAT imaging studies have been poorly characterized with regard to cerebral dominance. However, the absence of a correlation in the present study between striatal AI and Edinburgh Handedness Score argues that greater left-striatal DAT availability is not simply a function of cerebral dominance.

Although we found a small, statistically significant increase with age in absolute left–right asymmetry of striatal DAT availability with [^{123}I]β-CIT, the magnitude of this asymmetry is quite small (4.2% at age 88) in comparison to the degree of asymmetry we previously observed in PD (40.1% for the putamen, 23.1% for caudate, using a somewhat different ROI template).[28] In other studies, focused on early hemi-parkinsonian patients, at the threshold of their illness, [^{123}I]β-CIT imaging demonstrated a 50% reduction in DATs in the putamen contralateral to the symptomatic side.[44]

Our findings suggest that the pattern of DAT loss in normal aging is not typical of the pattern observed in idiopathic PD. In PD, the magnitude of DAT loss in the putamen is much more severe than in the caudate both in postmortem[24,25] and in vivo imaging[26–28] studies. In healthy aging, by contrast, the magnitude of DAT loss is similar in both neostriatal nuclei. Moreover, PD is characterized by marked hemispheric asymmetry of DAT losses,[28] whereas DAT losses in normal aging are relatively symmetrical. These divergent patterns of striatal DAT losses in aging and PD argue against an etiological relationship between the two conditions. The nigrostriatal degeneration that occurs in normal aging may be associated with mild "parkinsonian" signs. But PD, unlike aging, must involve a mechanism producing a regionally specific (putamen) dopaminergic loss.[29]

Limitations of the present study include the absence of MRI coregistration with SPECT for identification of striatal subregions, the relative paucity of subjects age 60 to 70 for characterization of aging-curve fits, and the small number of left-handed subjects ($n = 13$) for analysis of cerebral dominance in relation to DAT asymmetries.

In conclusion, healthy aging appears to be associated with a relatively symmetrical loss of DATs in the caudate and putamen and in both hemispheres. This pattern differs from that of idiopathic PD, which involves a much more marked loss of DATs in the putamen and greater hemispheric asymmetry.

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