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^{99m}Tc-TRODAT-1 SPECT Revealed That Striatal Dopamine Transport Availability Significantly Decreases in Late Mid-Aged Healthy Taiwanese and Then Remains Stable

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Objectives: Neuroimaging studies in the past 20 years have documented an age-related decline in striatal dopamine transporters (DATs), which is a marker of dopaminergic neurodegeneration; however, concerns about ethnic variations in the decline in DAT with age have not been addressed. The purpose of this study was to assess the rate of striatal DAT loss in healthy Taiwanese adults using kit-based ^{99m}Tc-TRODAT-1, a radioligand for DAT SPECT.

Patients and Methods: Fifty healthy subjects (mean age ± SD, 63 ± 12 years; range, 30–80 years) were studied. ^{99m}Tc-TRODAT-1 was prepared from a lyophilized kit. Brain DAT SPECT imaging was acquired between 165 and 195 minutes postinjection (~740 MBq or 20 mCi) using a dual-head camera equipped with fan-beam collimators (Helix SPX; GE). Specific uptake in the striatum (ST), caudate nucleus (CA), and putamen (PU) were calculated from reconstructed transaxial slices at the level of maximal striatal activity. Occipital cortices were used as reference areas. Data were presented as specific binding ratios.

Results: Age had a significant moderate to large negative effect on striatal DAT, which declined by $-25.7\% \pm 6.10\%$ between the ages of 30 and 80 years, equivalent to 6.4% loss per decade. The rates of decline in the CA and PU were 6.9% and 7.3% per decade, respectively.

Conclusions: This study suggests ethnic variations may not significantly affect the age-related decline in DAT. The data generated in this study could also be used as a reference to estimate DAT loss/occupancy in patients with DAT-related diseases.

Key Words: aging, ^{99m}Tc-TRODAT-1, DAT SPECT, ethnical

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Ageing is associated with changes in multiple components of the brain's dopamine system,¹ which is linked to complex cognitive functions such as working memory, cognitive flexibility,² language and thought, motor planning, abstract representation, temporal analysis or sequencing, and generativity. Therefore, dopamine represents a prime target for investigating the neurochemical basis of variability in executive function during aging.³ Declines in multiple components of the dopamine system with age have been well documented, including loss of dopamine-producing neurons in the substantia nigra,⁴ and reduced D₁/D₂ receptor^{4–6} and dopamine transporter (DAT) densities,^{7,8} although a parallel decline in dopamine synthesis is not evident.

The advent of functional neuroimaging techniques, such as PET and SPECT, has enabled measurement of changes in various dopamine parameters as a function of age in living human subjects.⁹ In this respect, DATs play a crucial role in regulation of the dopamine concentration in the synaptic cleft by dopamine reuptake, and the DAT density is considered as a marker of presynaptic function.^{10,11} A number of radioligands for imaging DAT have been developed, such as ¹¹C-cocaine,¹² ¹¹C-CFT,¹³ ¹¹C-β-CIT,¹⁴ ¹¹C-MP,¹⁵ ¹⁸F-CFT,¹⁶ ¹⁸F-FPCIT,¹⁷ and ¹⁸F-FE-PE2I¹⁸ for PET, and ^{99m}Tc-TRODAT,¹⁹ ¹²³I-β-CIT,²⁰ ¹²³I-IPT,²¹ and ¹²³I-FP-CIT²² for SPECT. Furthermore, over 33 in vivo PET or SPECT studies have consistently demonstrated a significant age-related decrease in DAT in the striatum (ST) or its subregions.²³ Mozley et al²⁴ used ^{99m}Tc-TRODAT SPECT and found the effects of aging on DAT in the central nervous system were nonlinear, with most loss occurring before the age of 40 years. van Dyck et al²⁵ showed that striatal DAT declines in a nearly linear manner by 46% between the ages of 18 and 88 years. The majority of empirical studies have demonstrated a linear correlation between DAT decline and age. The rates of DAT decline in the ST, with group mean values of ~6.2% to 10% per decade for the whole sample (ST and subregions) and approximately 11% per decade for younger adults, are consistent with several previous estimates that used DAT imaging agents.^{7,18,25–27}

Changes in the density and function of DAT, a key component of the DA system, in the living human brain have been reported in PET studies of patients with various neuropsychiatric disorders, such as Parkinson disease (PD),²⁸ Huntington disease,²⁹ attention-deficit/hyperactivity disorder,³⁰ autism,³¹ and schizophrenia.³² Health inequalities related to ethnicity/lifestyle are well recognized in clinical medicine and health care settings. Much of our understanding of medicine and scientific research on chronic diseases are based on clinical studies of White patient groups. Ethnic inequality in terms of inclusion in genome-wide association studies is particularly stark.³³ For example, the global prevalence of PD is increasing, yet the characteristics, risk factors, and genetics of PD in Black, Asian, and Hispanic populations are poorly understood.

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The systematic analysis of clinical variations in the symptoms and signs of PD and responses to treatment in different ethnic groups by Ben-Joseph et al³⁴ concluded that geographic and ethnic differences in the clinical manifestations, epidemiology, and mortality rates of PD are highly likely to be there. However, there are few published evidences for ethnic variation in the clinical features of PD, and there are substantial limitations and gaps in the current literature.

Taken together, these issues raise concerns about whether ethnic variations affect the DAT decline during age, and there is very limited published literature focusing on healthy Asian subjects. Furthermore, both PET and SPECT have been widely used to non-invasively assess the changes in DAT in DAT-related diseases. PET provides a higher resolution and better quantitative capacity than SPECT; however, the availability of DAT PET radiotracers is still limited. Altoprane SPECT has been proven as an alternative for the evaluation of presynaptic neuronal function in clinical settings.³⁵ ¹²³I-labeled altoprane derivatives for DAT SPECT have been recognized to effectively identify individuals who will develop dopaminergic pathology before the onset of motor symptoms.^{20,22} In addition, due to the limited availability and relatively higher cost of ¹²³I, few ¹²³I-labeled DAT ligands have been used for clinical DAT imaging on a large scale.^{19,99mTc} is the most common tracer used in clinical nuclear medicine departments. Their suitable energies and half-lives for imaging, as well as relatively low cost and ready availability, make ^{99m}Tc-labeled ligands more practical for imaging on a routine basis. ^{99m}Tc-TRODAT-1, a radioligand that selectively binds DAT, has been validated as an in vivo marker for evaluation of idiopathic PD^{19,36,37} and possibly other parkinsonism disorders.³⁸ Measuring the changes in ST and its subregional uptake with age may potentially clarify the effects of aging on ^{99m}Tc-TRODAT-1 binding and may also help to interpret these disorders more precisely.

Therefore, the purpose of this study was to assess the relationship between DAT function in the ST, caudate nucleus (CA), and putamen (PU) with age using ^{99m}Tc-TRODAT SPECT in healthy Taiwanese subjects. Moreover, the parameters describing the aging curves were discussed in the context of previous reports.

PATIENTS AND METHODS

Healthy Subjects

This study was approved by the ethical committees and review board of Tri-Service General Hospital, Taipei, Taiwan.

Case Setting

Taiwan Health Insurance data were retrieved for the subjects recruited to this study, including National Identification Card code, date of birth, place of birth, race, sex, and zip code of residence. The study population consisted of individuals in the Taiwan Health Insurance system living in Taiwan at any time between 1995 and 2015. Sex and ethnicity were identified using standard Medicare sex and race codes. The race declarations for race-specific data in Taiwan Health Insurance were “Asian/Taiwan” for all subjects. Age was determined using the subject's date of birth. Commonly used age strata, that is, 31 to 40 years, 41 to 50 years, and so on, were used to classify the age groups. During this study, neurologists used as Tri-Service General Hospital physicians provided the neurologic tests/care.

Fifty healthy subjects (31 women, 19 men; mean age \pm SD, 63 \pm 12 years; age range, 33.9–79.5 years) were recruited in this study. Written informed consent was obtained from all subjects. All participants underwent physical and neurological examinations (ie, tandem walking, Romberg sign, finger tapping, muscle strength test) and showed no signs of any neuropsychiatric disorders, including

drug or alcohol abuse, and had not taken any medications for at least 3 months. None of the subjects had a current or past history of neuropsychiatric disorders or a family history of movement disorders, as determined by a screening interview. Race, sex, and age data for the eligible cases were obtained from direct interviews as part of the study. Table 1 summarizes the demographic data for all subjects.

Radiopharmaceutical

The preparation of ^{99m}Tc-TRODAT-1 was conducted using a modified version of the method described. Briefly, ^{99m}Tc-TRODAT-1 was prepared from a freeze-dried kit by adding 1110 MBq of freshly eluted ^{99m}TcO₄ to 5 mL of saline preparation.³⁶ The ^{99m}Tc-TRODAT-1 was obtained over 6 hours as a neutral solution (pH = 7.0–7.5) with greater than 90% radiochemical purity, as determined by high-performance liquid chromatography. The shelf life of the lyophilized kit was over 2 months when stored at room temperature.

Image Acquisition

The imaging procedure was conducted using a modified version of the dopaminergic imaging in parkinsonian syndromes 1.0 published in the European Association of Nuclear Medicine guidelines.³⁹

Brain ^{99m}Tc-TRODAT-1 SPECT imaging was performed 3 hours after IV injection of 740 \pm 43 MBq (20 \pm 1.16 mCi) of ^{99m}Tc-TRODAT-1. Subjects were placed in the supine position and fixed with a head-holder. SPECT images were acquired using a dual-headed camera equipped with ultra-high-resolution fan-beam collimators (Helix SPX; Elscint, Haifa, Israel). Data were acquired in a 128 \times 128 matrix with a 1.4 zoom through 360 degrees (180 degrees for each head) rotation at 3 degrees intervals, for 30 seconds per angle step. Images were reconstructed using a back projection method with a Metz filter. Attenuation correction was performed using Chang's first-order method.

Data Analysis

To avoid interreader and intrareader variability in the region of interest (ROI) analysis, the entire task was carried out by an experienced technologist. Regions of interest were drawn manually on overlaid summed SPECT⁴⁰ and coregistered MRIs for each subject using PMOD 4.0 software (PMOD Technologies Ltd, Zurich, Switzerland). As differences in the size and sharpness of the ROIs directly affect the results, the technologist drew the almost same shape and size of ROIs in all subjects to contain the most intense activity in each slice on the summed SPECT images. Our previous study showed a good test-retest reproducibility of the striatal specific uptake ratios (SURs) of ^{99m}Tc-TRODAT-1 in healthy young

TABLE 1. Demographic Data for All Subjects

	Female	Male	Total
Age (years)/sex			
30–40	2	1	3
41–50	8	1	9
51–60	2	4	6
61–70	9	5	14
71–80	10	8	18
Mean \pm SD	62.0 \pm 13.5		
Race/ethnicity			
Asian	31	19	50
Place of birth			
Taiwan	31	19	50

men using the SUR method. The mean variability of the striatal SURs between test and retest of ^{99m}Tc -TRODAT-1 in healthy young men was $7.63\% \pm 5.01\%$.⁴⁰

The SPECT images were analyzed along the level of the canthometal line. Regions of interest were marked for the ST, CA, and PU in each hemisphere, with reference to the corresponding MRI, on composite images of the 3 highest basal ganglia activity slices. The occipital cortices (OCs) were also drawn in the same manner and served as background areas. Specific uptake ratios were calculated by subtracting the mean counts per pixel in the OC from the mean counts per pixel in the whole ST, PU, or CA regions, and dividing the result by the mean counts per pixel in the background, that is, (ST-OC)/OC, (PU-OC)/OC, or (CA-OC)/OC.

Statistics

Linear regression analysis was performed to assess the relationship between specific uptake in the ST and its subregions and age. Multiple analysis of variance was used for multigroup comparisons in different age groups with GraphPad Prism 9 (GraphPad Software, La Jolla, CA). A *P* value less than 0.05 was considered statistically significant for both the multiple-comparison test and the correlation analysis. All data are presented as the mean \pm 95% CI.

Sex differences were not considered in this study as the sex and age distribution of this study population were not balanced.

RESULTS

Quantification of DAT Availability by Age

Figure 1 shows examples of SPECT images of the ST region of 45- and 75-year-old subjects obtained 3 hours postinjection of ^{99m}Tc -TRODAT-1. The mean ^{99m}Tc -TRODAT-1 SURs for all age groups were 1.90 ± 0.24 , 1.97 ± 0.27 , and 1.77 ± 0.28 for the ST, CA, and PU, respectively (Table 1). The distribution of ^{99m}Tc -TRODAT-1 uptake in the ST and its subregions in each age group is presented in Figure 1. The highest ^{99m}Tc -TRODAT-1 uptake in the ST was observed in 30- to 40-year-old subjects, then uptake progressively decreased with age and was lowest in 80-year-old subjects. Similar patterns were observed in the CA and PU. Notably, uptake was significantly lower in the ST and PU of 50- to 60-year-old subjects compared with 40- to 50-year-old subjects ($P < 0.05$ – 0.005),

whereas there was no such trend in the CA (Fig. 2). Detailed results are summarized in Table 2.

DAT Availability Correlates Negatively With Age

In linear regression analysis, the regression coefficient between ^{99m}Tc -TRODAT-1 uptake in the striatal region and age was -0.0145 ($r = 0.5955$, $P < 0.0001$), with a decline of $-25.7\% \pm 6.10\%$ over the age range from 36 to 80 years, equivalent to a loss of 6.4% per decade (Fig. 3; ST, solid blue line). The rates of decline in the CA and PU were 6.9% ($r = 0.2578$, $P < 0.0011$) and 7.3% ($r = 0.5344$, $P < 0.0001$), respectively (Fig. 3; CA and PU, solid blue line).

As shown in Fig. 3, 2-line fitting fitted the current data better than a single straight line. In the ST, a significant reduction of DAT binding was observed in aged 50 to 60 years. The regression coefficient for subjects younger than 60 years was -0.0243 ($r = 0.5617$, $P < 0.0001$) compared with -0.0061 ($r = 0.0644$, $P < 0.0001$) for subjects older than 60 years (green dot line). A similar pattern was observed in the PU: the regression coefficient for subjects younger than 60 years was ~ 1.8 -fold lower than that for subjects older than 60 years (-0.0271 vs 0.0148). In the CA, the regression coefficient for subjects younger than 50 years was ~ 5.0 -fold lower than the regression coefficient for subjects older than 50 years (-0.0279 vs -0.0047). Detailed results are summarized in Table 3.

More Than 20% of Striatal DAT Loss Occurs Between the Ages of 40 and 50

Next, we normalized the SURs of all subjects to the average of subjects in the 30- to 40-year-old age group to estimate the percentage of DAT loss. The rate of decline in the ST was $\sim 8.0\%$ per decade at age 40 to 50 years, significantly increased to $\sim 20.2\%$ at 50 to 60 years, and then reduced to $\sim 2\%$ to 3% per decade in subjects older than 60 years (Fig. 4). A similar trend was observed in the PU, and a large decline was observed in the CA of 40- to 50-year-old subjects. Detailed results are summarized in Table 4.

DISCUSSION

To the best of our knowledge, this is the largest study to systematically evaluate striatal binding of the commercially available DAT tracer ^{99m}Tc -TRODAT-1 in a cohort of healthy Taiwanese/Asian controls with a wide age range and well-defined criteria of

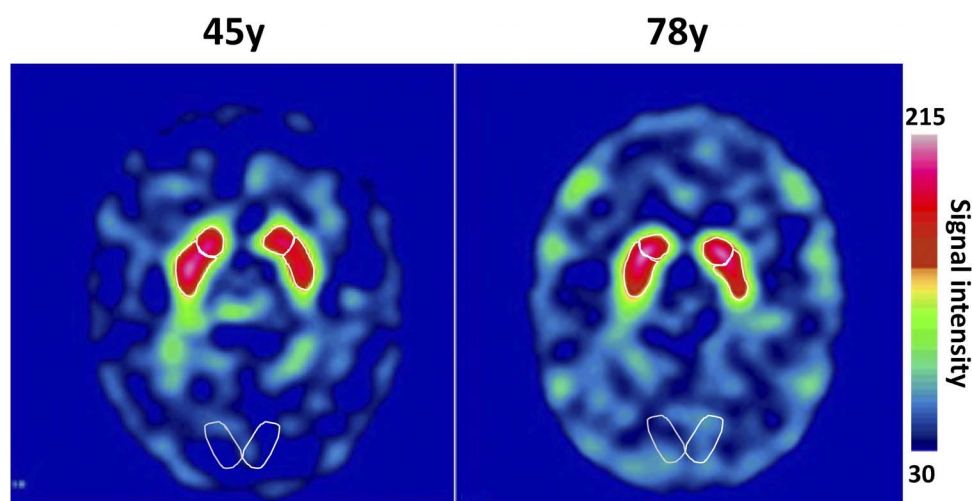


FIGURE 1. Transverse ^{99m}Tc -TRODAT-1 DAT SPECT images of healthy (A) 45- and (B) 78-year-old subjects. Example ROIs are shown in white. Relative ^{99m}Tc -TRODAT-1 DAT uptake in the striatal regions of both sides was lower in the older subject than the younger subject.

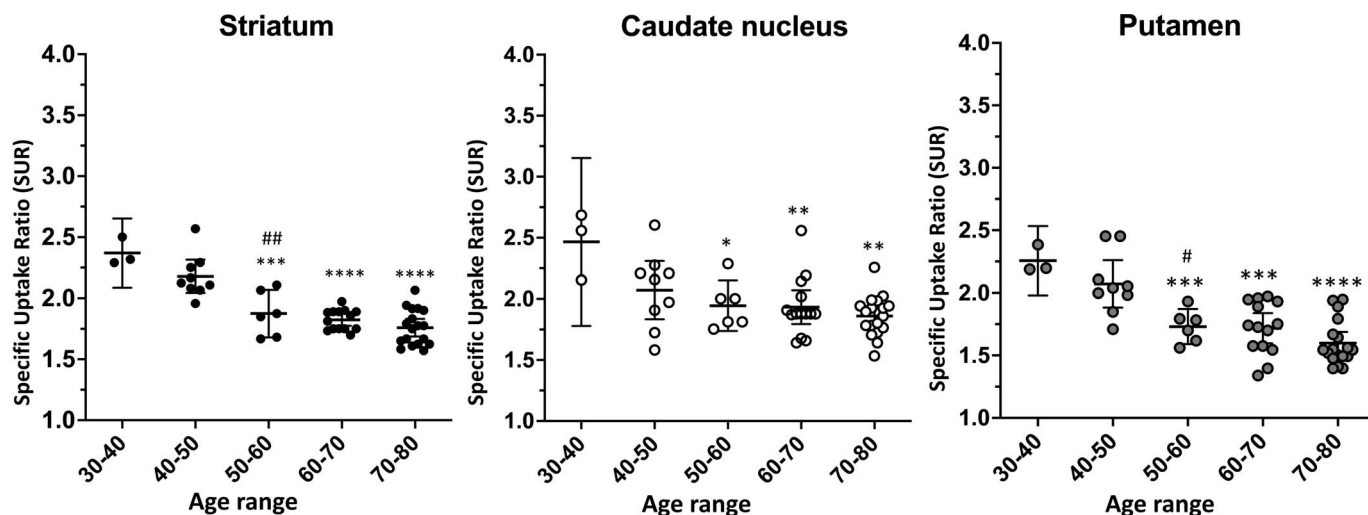


FIGURE 2. Dopamine transporter availability (specific binding ratios) by age for the ST, CA, and PU as measured by ^{99m}Tc-TRODAT-1 SPECT in 50 healthy subjects. Data are presented as mean ± 95% confidence interval; **P* < 0.05, ***P* < 0.005, ****P* < 0.0005, *****P* < 0.0001.

normality. We aimed to investigate the effect of aging on DAT in healthy Taiwanese subjects. Linear regression analysis revealed ^{99m}Tc-TRODAT-1 uptake in the ST and its subregions declined by -23.87% to -29.1% in the healthy subjects between the ages of 30 to 80 years, which is equivalent to yearly loss of -0.48% to -0.58% during this age range. These results are consistent with previous postmortem and imaging studies conducted in the United States or Europe,^{6,20,26,41-46} suggesting that the loss of DAT with age is not affected by ethnic variation.

Although we observed similar age-related declines in the ST and its subregions, the rate of decline was higher in the PU than in the CA. The results of this study are in good agreement with previous DAT imaging studies that observed age-related declines in DAT and reported comparable^{26,47} or a slightly higher¹⁷ rates of decline in the PU than the CA. Mozley et al²⁴ even observed an increase in DAT uptake in the CA in healthy subjects older than 40 years compared with younger subjects. Shingai et al¹⁸ reported similar declines in DAT in the caudate and PU and further demonstrated the rate of decline was lower in the substantia nigra than caudate or PU, whereas DAT uptake in the thalamus remained relatively stable with age. Koch et al⁴⁸ observed varied rates of DAT decline in the thalamus, pons, and PU. Therefore, the varied rates of DAT decline in the PU and CA imply that regional-specific degeneration of DAT in the ST and its subregions may occur during aging.^{24,48,49} However, it should be noted that a large number of DAT imaging agents based on cocaine or its closely related congener tropane derivatives have been reported as useful PET and SPECT imaging agents, as described previously. The variations between the results of the studies described previously could be due to the use of different radioligands, measuring techniques, and age groups. For example, in the line of DAT-SPECT imaging agents, ^{99m}Tc-TRODAT-1 is an analog of tropane that selectively binds the presynaptic DATs and can be visualized by SPECT imaging. Therefore, when assessing the correlation between striatal binding ratios and age (even in healthy subjects), the binding characteristics and pharmacologic specificity of various DAT ligands for DAT should be considered to avoid obtaining mixed results in different studies.

Profound loss of striatal DAT and presynaptic dopamine neurons in early or even asymptomatic PD were observed in previous SPECT DAT imaging studies^{20,50} or pathological studies.^{51,52} Our group previously reported that the losses of DAT in the ST

and PU with aging are relatively minor in healthy subjects compared with age-matched patients with PD.³⁶ Moreover, patients with PD did not show a remarkable decline in DAT with age.^{27,53,54} However, similar DAT loss was observed in older healthy subjects and patients with early-stage PD; thus, it is crucial to clinically discriminate motor dysfunction in the elderly from early PD.^{6,53} This issue has practical importance because, in contrast to patients with early PD, L-dopa does not seem to improve extrapyramidal motor impairment and induces adverse effects in elderly subjects without PD.⁵⁵ Although decreased dopa-decarboxylase activity and enhanced dopamine catabolism are proposed to occur in elderly subjects,⁵⁶ the

TABLE 2. DAT Availability (Specific Binding Ratios) by Age for the ST, CA, and PU Measured by ^{99m}Tc-TRODAT-1 SPECT

Groups	Age Range	n	SUR	<i>VS</i> _{30-40y}	<i>VS</i> _{last decade}
ST					
1	30-40	3	2.37 ± 0.11		
2	40-50	9	2.18 ± 0.18		
3	50-60	6	1.89 ± 0.21	***	##
4	60-70	14	1.82 ± 0.08	****	
5	70-80	18	1.76 ± 0.15	****	
Total/mean	63.0 ± 12.5	50	1.90 ± 0.23		
CA					
1	30-40	3	2.47 ± 0.28		
2	40-50	9	2.07 ± 0.31		
3	50-60	6	1.95 ± 0.20	*	
4	60-70	14	1.93 ± 0.24	**	
5	70-80	18	1.86 ± 0.16	**	
Total/mean	63.0 ± 12.5	50	1.97 ± 0.26		
PU					
1	30-40	3	2.26 ± 0.11		
2	40-50	9	2.07 ± 0.25		
3	50-60	6	1.73 ± 0.13	***	#
4	60-70	14	1.72 ± 0.21	***	
5	70-80	18	1.60 ± 0.18	****	
Total/mean	63.0 ± 12.5	50	1.77 ± 0.28		

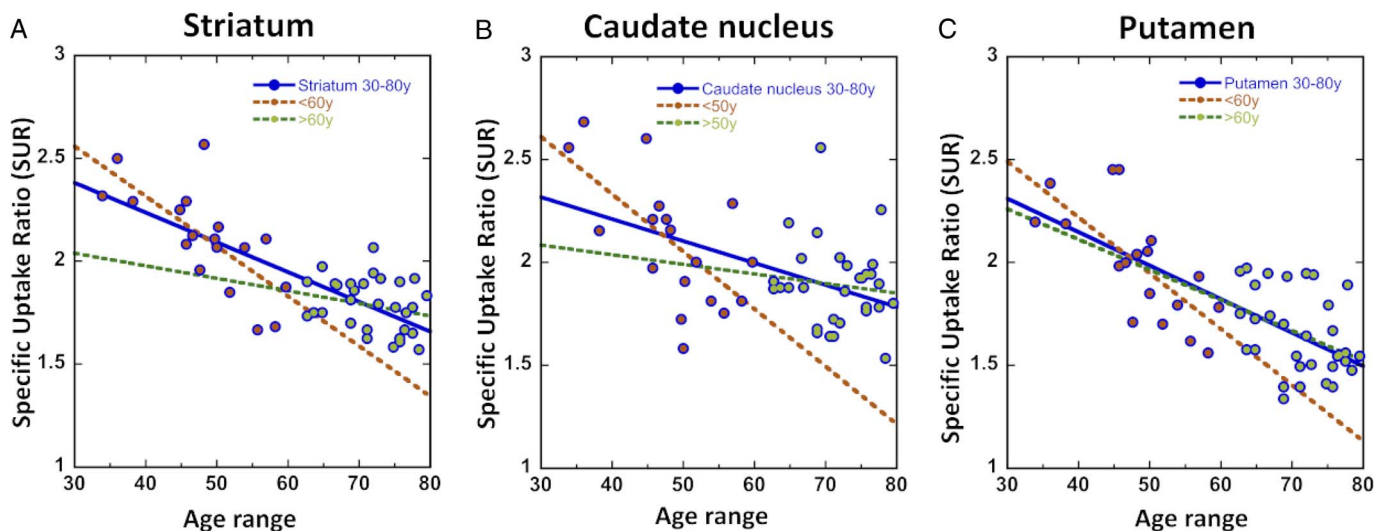


FIGURE 3. Relationships between age and the SUR of ^{99m}Tc-TRODAT-1 in the (A) ST, (B) CA, and (C) PU. Blue line, 30- to 80-year olds; orange dotted line <50 or <60 years; green dotted line, >50 or >60 years. DAT loss rapidly declined during young adulthood, followed by a less rapid decline throughout middle age.

nature of the aging-related decline in DAT density and the effect of such decline on the functional capacity of remaining cells remain under debate.^{27,57}

Although it is generally agreed that DAT binding significantly decreases with age, the reported patterns and rates of decline vary. Reeves et al²⁷ summarized the in vivo imaging literature and identified 2 types of decline: linear and nonlinear. In reports of linear decline, the rate of DAT loss ranged from 3.3% to 10% per decade,^{7,17,25,47,49,53,58} whereas studies suggesting a nonlinear pattern reported rates of decline ranging from 10.9% and 2.9% per decade between the ages of 20 and 40 years, followed by a less rapid decline throughout middle age.^{27,49} In our subjects ranging in age from 30 to 80 years, a 2-linear model provided the best fit: the turning point was aged 40 to 50 years for the ST and PU and 30 to

40 years for the CA. Our results are slightly different to those of a previous study, which reported greater DAT loss in the ST of subjects younger than 36 years.²⁴ To sum up, the decline values obtained in this study (6.4% per decade in the ST, 5.95% per decade in the CA, and 7.28% per decade in the PU) lie in a similar range as the aforementioned studies with sample sizes of over 50 subjects.^{25,48,59,60}

Sex differences were not considered in this study. Zelnik et al and Muller et al demonstrated there was no significant difference in the B_{max} values for specific DAT binding in age-matched women and men based on analysis of postmortem brain tissue⁴¹ and SPECT imaging.⁶¹ In contrast, Nobili et al⁶⁰ reported sex differences in the age-related decline in DAT in a large sample of healthy subjects (n = 122), and a subsequent study by Koch et al⁴⁸ also indicated sex affects DAT binding in the thalamus (n = 103). Moreover, based

TABLE 3. Two-Linear Effect of Aging on Striatal Dopamine Transporters as Measured by ^{99m}Tc-TRODAT-1 SPECT

Groups	Age Range	Normalized to 30–40y	V/S _{30–40y}	V/S _{last decade}	Total Percentage Decrease	Decline Per Decade
ST						
1	30–40	100%			0%	0%
2	40–50	92.0% ± 7.4%			-8.0% ± 7.4%	-8.0% ± 7.4%
3	50–60	79.8% ± 8.8%	***	##	-20.2% ± 8.84%	-12.2% ± 8.8%
4	60–70	77.0% ± 3.6%	****		-22.3% ± 3.20%	-2.2% ± 3.2%
5	70–80	74.3% ± 6.1%	****		-25.7% ± 6.13%	-3.4% ± 6.1%
CA						
1	30–40	100%			0%	0%
2	40–50	84.0% ± 12.6%			-17.0% ± 10.9%	-17.0% ± 10.9%
3	50–60	78.9% ± 8.0%	*	##	-21.1% ± 8.0%	-4.2% ± 8.0%
4	60–70	76.3% ± 0.5%	**		-20.5% ± 12.3%	0.6% ± 12.3%
5	70–80	75.5% ± 6.7%	***		-23.8% ± 8.0%	-3.3% ± 8.0%
PU						
1	30–40	100%			0%	0%
2	40–50	91.8% ± 10.9%			-8.2% ± 10.9%	-8.2% ± 10.9%
3	50–60	76.7% ± 5.9%	**	##	-23.3% ± 5.9%	-15.1% ± 5.9%
4	60–70	78.0% ± 7.8%	****		-23.9% ± 9.3%	-0.6% ± 9.3%
5	70–80	70.9% ± 7.9%	****		-29.1% ± 7.9%	-5.3% ± 7.9%

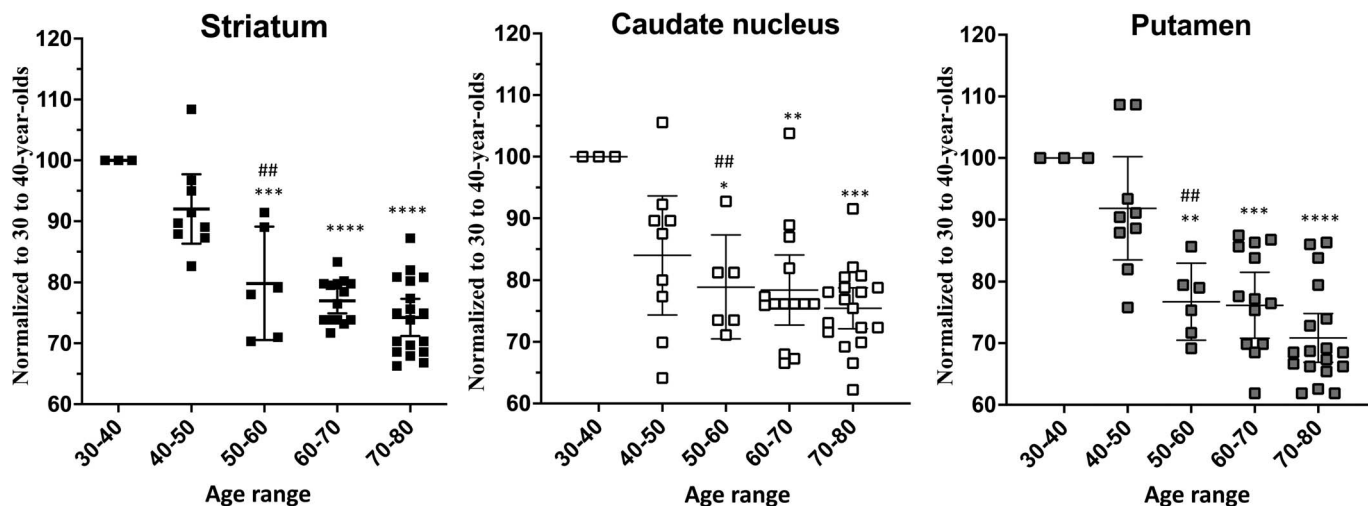


FIGURE 4. Age-related percentage changes in DAT per decade in the ST, CA, and PU. Data are presented as mean ± 95% confidence interval; **P* < 0.05, ***P* < 0.005, ****P* < 0.0005, *****P* < 0.0001.

on this evidence, some researchers suggest that DAT loss with age and sex differences should be taken into consideration when evaluating the severity of PD.^{7,26}

Further, asymmetric striatal uptake from a single transverse SPECT image was not uncommon in our aged subjects and could represent normal variation²⁵ or the use of different cutoff levels on each side of the ST. Reading sequential image planes of the whole ST or calculating SURs from composite images of the 3 or more highest basal ganglia activity slices could minimize the latter artifact.

Moreover, the present results obtained using kit-based ^{99m}Tc-labeled TRODAT-1 combined with conventional cameras are compatible with the results of PET or SPECT DAT imaging studies using cyclotron-produced tracers, such as ¹¹C or ¹²³I, as described previously. In conjunction with a previous report,²⁴ our results suggest that ^{99m}Tc-labeled TRODAT-1 can be used to detect the effects of aging on DAT. Other studies that used ^{99m}Tc-TRODAT-1 SPECT in subjects with PD,^{19,36} movement disorders,^{38,62,63} and depression⁶⁴ imply that ^{99m}Tc-TRODAT-1 could serve as an ideal tracer for routine clinical application.

This study has some limitations. Although the SURs are relative values based on the OC as a reference area, different values are obtained when using different imaging parameters such as a fan beam collimator versus an all-purpose parallel collimator or a Butterworth filter versus a Metz filter. In practice, we prefer to use cameras equipped with a fan beam collimator and Metz filter for ^{99m}Tc-TRODAT-1 SPECT, as this combination provides improved imaging contrast (ie, higher signal to noise ratios) that enables easier interpretation of the images by visual assessment from clinicians' point of view. Some researchers have argued semiquantitative

assessment using a Metz filter results in a nonlinear correlation with the authentic striatal activity in time-activity curves.⁶⁵ Our previous report showed that the nonlinear phenomenon only occurs at extremely high SURs, far beyond the normal ranges of human striatal uptake; in other words, acceptable linearity is obtained for the range observed in clinical practice. Another limitation of the present study is the imbalanced sex distribution (39 males vs 11 females).

After over 30 years of research and more than 35 published studies, it is well established that DAT declines with age; however, the evidence for an age effect on dopamine synthesis capacity remains unclear.²³ Karrer et al²³ suggested that the combination of large losses in DAT and the lack of age effects on dopamine synthesis capacity may together partially compensate for the lower density of DA receptors in older age. The observed reduction of DAT should lead to a lower rate of DA reuptake into presynaptic neurons. Hence, DA may remain active in the synaptic cleft for a prolonged time and may be able to modulate signal transmission for a lengthier period in older age.^{66,67} In fact, others have suggested that upregulated DA synthesis capacity may represent a compensatory mechanism for a reduction in the density of DA receptors.⁶⁴ If we assume retained DA synthesis, capacity may also be associated with the potential for at least partially spared DA release; this—together with reduced DAT density—may imply that dopaminergic functionality is potentially retained with age. Future studies are required to focus on the age-related correlations with DA targets, including dopaminergic function (ie, using ¹⁸F-fluorodopa: 3,4-dihydroxy-6-[¹⁸F]fluoro-L-phenylalanine PET for dopamine synthesis or ¹²³I-IBZM: (S)-3-[¹²³I]iodo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6-methoxybenzamide that targets the D₂ receptor) and cognitive performance.²

TABLE 4. Effects of Aging (Percentage Change Per Decade Normalized to 30- to 40-Year Olds)

Region	Most Related-Divide Age Range (MRDAR)	Slope Before MRDAR	<i>r</i>	Slope After MRDAR	<i>r</i>	Slope in All Age	<i>r</i>
ST	50–60	−0.0243 ± 0.0059	0.5167	−0.0061 ± 0.0042	0.0644	−0.0145 ± 0.0017	0.5955
CA	40–50	−0.0279 ± 0.0082	0.4196	−0.0047 ± 0.0070	0.0145	−0.0107 ± 0.0026	0.2578
PU	50–60	−0.0271 ± 0.0065	0.5187	−0.0148 ± 0.0064	0.1492	−0.0163 ± 0.0022	0.5344

MRDAR, most related-divide age range.

In conclusion, imaging with the kit-based radioligand ^{99m}Tc-TRODAT-1 lends supports to the common practice of approximating age-related DAT losses using a 2-linear model, suggesting that age-related DAT losses may be not be linear, but are characterized by a rapid decline during early adulthood, followed by a less rapid decline throughout middle age. The decline rates of DAT loss in the ST, CA, and PU with age are in line with previous postmortem and DAT imaging studies of subjects from the United States or Europe. Thus, our data suggest that ethnic variations may not represent a significant consideration in DAT studies, and our data could also be served as a reference to estimate DAT loss/occupancy in patients with DAT-related diseases.

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