Reproducibility of ^{99m}Tc-TRODAT-1 SPECT Measurement of Dopamine Transporters in Parkinson's Disease

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Functional brain imaging targeting the presynaptic dopamine nerve terminal of the nigrostriatal system has been used for monitoring disease progression and evaluating therapeutic effectiveness in patients with Parkinson's disease (PD). ^{99m}Tc-TRODAT-1 binds with high selectivity to the dopamine transporters in the striatum and can be imaged with SPECT 4 h after injection. We studied the test and retest reproducibility of ^{99m}Tc-TRODAT-1 SPECT measures in patients with PD to assess the reliability of ^{99m}Tc-TRODAT-1 for longitudinal evaluation of the nigrostriatal dopaminergic function. **Methods:** Each of 20 patients with PD underwent 2 ^{99m}Tc-TRODAT-1 SPECT scans at an interval of 2–3 wk. Patients were imaged 4 h after injection of 925 MBq ^{99m}Tc-TRODAT-1. Two imaging outcome measures were evaluated: the ratio of specific-striatal-to-nonspecific uptake and the striatal asymmetry index. For both measures, the test/retest variability was calculated. Reproducibility of the 2 outcome measures was evaluated in terms of intraclass correlation coefficient (ICC) and 95% limits of agreement. **Results:** The mean ratio of specific-striatal-to-nonspecific uptake showed excellent test/retest reproducibility with a mean variability of 10.20%, an ICC of 0.95 (95% confidence interval = 0.88–0.98), and 95% limits of agreement, ranging from −0.19 to 0.19. The striatal asymmetry index had larger test/retest variability (60.41%), a slightly smaller ICC of 0.86 (95% confidence interval = 0.65–0.95), and a wider range of 95% limits of agreement (−16.09 to 15.19). In addition, there was a significant negative correlation between the mean ratio of specific-striatal-to-nonspecific uptake and the motor subscore of the Unified Parkinson's Disease Rating Scale in both test and retest conditions. **Conclusion:** Our data indicate that the imaging outcome expressed by the mean ratio of specific-striatal-to-nonspecific uptake has an excellent test/retest reproducibility and correlates with disease severity. These findings suggest that ^{99m}Tc-TRODAT-1 SPECT imaging is useful and feasible for measuring disease progression in PD.

Key Words: dopamine transporter; SPECT; Parkinson's disease; ^{99m}Tc-TRODAT-1

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Symptomatic medical treatment has been the mainstay of Parkinson's disease (PD) management for decades. The development of neuroprotective or neurorestorative strategies to stop or slow down the progression of PD has become increasingly important. However, the identification of neuroprotective therapies for PD has been hampered by a lack of biologic markers that can reliably parallel the extent or pace of nigral degeneration. Although some clinical rating scales (e.g., Unified Parkinson's Disease Rating Scale [UPDRS]) have been used to evaluate the disease progression, they have been criticized for considerable interrater variability and possible confounding factors (e.g., medication, stress, and fatigue) (*1,2*).

Searching for a valid and reliable disease progression marker may start with an understanding of PD pathology. The primary deficit of PD is a decrease of presynaptic dopaminergic neurons in the substantia nigra. The dopamine transporter (DAT) is located on the functioning dopamine nerve terminal and maintains dopamine homeostasis by actively pumping synaptic dopamine back into the nerve terminal. Because the DAT is heavily expressed in the terminals of dopamine neurons that are lost in PD, it is not surprising that striatal binding of various radioligands targeting the DAT site is reduced in PD patients (*3–11*).

SPECT with ^{123}I-based ligands and PET using ^{11}C-based DAT ligands or 6-^{18}F-fluoro-L-dopa (^{18}F-DOPA) may serve as surrogate markers for measuring the severity and progression of PD and have been used with excellent reproducibility to improve clinical diagnosis, monitor the rate of disease progression, and evaluate the effectiveness of putative neuroprotective therapies (*2,12–15*). However, ^{11}C, ^{18}F, and ^{123}I are cyclotron produced, which limits the widespread use of these agents in the clinical setting.

^{99m}Tc-TRODAT-1, developed by Kung et al. (*16,17*), has shown promise as a tracer for the imaging of DAT. Animal studies and SPECT images in healthy volunteers have shown that ^{99m}Tc-TRODAT-1 has high affinity and selectivity for DAT sites in the striatum (Ki = 14.1 nmol; dopamine:serotonin transporter selectivity = 26:1) and has

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good in vivo stability and low toxicity (*10,16–19*). In addition, a ^{99m}Tc-based tracer for DAT has several advantages: ^{99m}Tc has a convenient half-life (6 h) for in vivo imaging, it is less expensive compared with cyclotron-produced ^{123}I, it can be readily produced by a commercially available ^{99}Mo/^{99m}Tc generator, and the medium γ-ray energy emitted by ^{99m}Tc (140 keV) is suitable for γ-camera detection (*16*). The development of a ^{99m}Tc-based tracer for DAT with comparable binding and in vivo localization properties has greatly enhanced ease of use and availability for routine clinical study in humans (*20*).

The demonstration of reproducible ^{99m}Tc-TRODAT-1 SPECT outcome measures, including longitudinal monitoring of progressive neurologic disorders, is important and critical for clinical applications. Therefore, the purpose of this study was to examine the test/retest reproducibility of 2 SPECT outcome measures—the ratio of specific-striatal-to-nonspecific uptake and the striatal asymmetry index—to assess the feasibility of ^{99m}Tc-TRODAT-1 SPECT imaging as a potential tool for evaluating disease progression in patients with PD.

MATERIALS AND METHODS

Patients

Twenty patients in the early stage of PD were recruited in this study (13 men, 7 women; mean age, 62.1 ± 10.8 y [range, 42–79 y]). Inclusion criteria were the presence of at least 2 of the following signs: resting tremor, rigidity, bradykinesia, or postural reflex impairment, at least 1 of which had to be either resting tremor or bradykinesia. In addition, the parkinsonism could not have been caused by trauma, brain tumor, infection, cerebrovascular disease, other known neurologic disease, or known drugs, chemicals, or toxins; there had to be an absence of prominent oculomotor palsy, cerebellar signs, vocal cord paresis, orthostatic hypotension, pyramidal signs, or amyotrophy; and improvement had to have been shown with levodopa therapy (*21*). Table 1 summarizes the demographic data, clinical motor status, and side of symptom onset for each patient. The interval between the 2 scans was 2 wk in 18 patients and 3 wk in the 2 remaining patients. Fourteen patients took no antiparkinsonian medications before or during the scans. Five patients stopped their standard levodopa/benserazide for at least 1 d, and the remaining patient stopped bromocriptine for 5 d before the scans. All the patients denied the use of methylphenidate, cocaine, amphetamine, benztropine, or other chemicals known to act as competitors for binding of ^{99m}Tc-TRODAT-1 to DAT. No blood or urine screens were performed to verify the drug-free status of the patients. Three patients (patients 8, 12, and 20) continued to use tobacco during the study period. All patients had a standard low-protein breakfast and lunch on the days of the scanning. This study was authorized by our hospital's Institutional Review Board. All patients gave written informed consent before each scan.

Radiopharmaceutical Preparation

^{99m}Tc-TRODAT-1 was prepared from a preformulated lyophilized kit provided by the Institute of Nuclear Energy Research (Lung-Tan, Taiwan) (*22*). The kit was reconstituted with 1,110 MBq (30 mCi) freshly eluted ^{99m}Tc-sodium pertechnetate in 5 mL normal saline solution and was autoclaved at 121°C for 30 min to complete the labeling. After cooling to room temperature, ^{99m}Tc-TRODAT-1 with a radiochemical purity of >90% (determined by a dual-strip instant thin-layer chromatography method) was obtained in a neutral solution (pH 7.0–7.5) (*23*).

TABLE 1
Patient Demographics

Patient no.	Age (y)	Sex	Modified H & Y stage	UPDRS motor subscore*	Symptom onset side
1	71	M	2	37	L
2	47	M	1	19	L
3	65	F	1	6	R
4	79	M	1.5	19	L
5	54	M	2.5	34	L
6	71	M	2	28	R
7	71	M	2.5	27	R
8	61	M	2.5	44	L
9	49	F	1	8	R
10	71	M	2	21	R
11	74	M	1	9	R
12	63	M	2	20	R
13	74	M	2.5	23	R
14	57	F	2	28	R
15	54	F	2	23	R
16	51	F	1	9	R
17	66	F	1.5	18	R
18	71	M	2	38	R
19	42	F	2	25	R
20	51	M	2	25	R

*Maximum score = 108.
H & Y = Hoehn & Yahr.

Image Acquisition and Analysis

The dose of ^{99m}Tc-TRODAT-1 was 1,003.3 ± 21.8 MBq (range, 965.7–1,054.5 MBq) for the test condition, and 1,005.5 ± 28.8 MBq (range, 943.5–1,054.5 MBq) for the retest condition. ^{99m}TcTRODAT-1 in normal saline solution was injected intravenously into each patient soon after preparation. The binding to dopamine transporter was assessed with SPECT (γ-camera, 140 keV) 232.6 ± 18.6 and 236.6 ± 15.1 min after injection for the test and retest conditions, respectively. Patients were examined in the supine position with a head holder to avoid motion artifacts. A rotating triple-head γ-camera with fanbeam collimators (MultiSPECT 3; Siemens) and a commercially available computer system were used for data acquisition and processing. The patient was positioned with the image plane parallel to the orbitomeatal line. Data were collected over a circular 360° rotation (3°/projection) in a 128 × 128 × 16 matrix. The acquisition time was 50 s per projection. Reconstruction was performed by filtered backprojection using a Butterworth filter (cutoff frequency, 0.4 Nyquist; power factor, 7). Attenuation correction was performed in selected transverse slices according to Chang's method (*24*). In-plane resolution of the reconstructed images was 8.5 mm in full width at half maximum, and slice thickness was approximately 2.89 mm. Six consecutive transverse slices (17.34 mm in thickness in total) representing the most intense striatal uptake were summed. Based on individual MR images, the regions of interest (ROIs; 776 ± 33 mm^2) were manually placed over the left and right striatum. The reference background ROI (2,864 ± 60 mm^2) was placed on the occipital cortex of the same summed image. Two outcome measures were computed. The specific striatal uptake was measured 4 h after injection and was calculated for both the left and the right striatum as:

$$\frac{ST - OC}{OC}, \qquad \text{Eq. 1}$$

where ST = striatum and OC = occiptal cortex, and then averaged. In addition, a striatal asymmetry index (AI) was calculated as:

$$\frac{|\text{ipsilateral} - \text{contralateral}|}{(\text{ipsilateral} + \text{contralateral})/2} \times 100\%, \qquad \text{Eq. 2}$$

where contralateral was defined as the side opposite the side of symptom onset.

Each patient also underwent brain MRI (1.5 T; Siemens) with 3-mm thin cuts at the level of the basal ganglia. The MRI study was performed to exclude rare causes of parkinsonian syndrome and to provide a reference for the determination of ROIs for ^{99m}Tc-TRODAT-1 SPECT.

Statistical Analysis

The test/retest variability (*15*) was calculated as:

$$\frac{|\text{retest} - \text{test}|}{(\text{retest} + \text{test})/2} \times 100\%. \qquad \text{Eq. 3}$$

The reliability was estimated by intraclass correlation coefficient (ICC) and 95% limits of agreement. The ICC ranged from 0.00 (no reliability) to 1.00 (high reliability was defined as test score = retest score). To calculate ICC, repeated-measures ANOVA was performed to obtain variance between and within subjects. The ICC was expressed as:

$$ICC = \frac{MSBS - MSWS}{MSBS + (k - 1)MSWS}, \qquad \text{Eq. 4}$$

where MSBS and MSWS are the mean sum of squares between and within subjects, respectively, and k is the number of within-subject measurements.

For the 95% limits of agreement, the difference scores between the retest and the test conditions were plotted against mean scores for each patient. We examined the agreement between the 2 conditions by looking at the spread of the difference scores around the center line representing 0 difference.

RESULTS

Table 2 shows the ratio of specific-striatal-to-nonspecific uptake ([ST − OC]/OC) of ^{99m}Tc-TRODAT-1 for each patient in the test and retest conditions. Figure 1 shows a close correlation ($r = 0.91$, $P = 2.35 \times 10^{-8}$) and agreement of the mean (ST − OC)/OC between the test and retest conditions. The mean (ST − OC)/OC showed excellent test/retest reproducibility with a mean variability of 10.20% ± 6.17% (range, 1.87%–22.22%), an ICC of 0.95 (95% confidence interval [CI] = 0.88–0.98), and 95% limits of agreement ranging from −0.19 to 0.19 (Fig. 2).

Figure 3 shows a statistically significant correlation ($r = 0.76$, $P = 0.0001$) and agreement of the striatal AI between the test and retest conditions. There was a reduced correlation of striatal AI ($r = 0.56$, $P = 0.012$) if one outlier represented in Figure 3 was removed and only the other 19 patients were considered. The striatal AI had a larger test/retest variability (60.41% ± 48.64%; range, 6.08%–160.61%; Table 3), a slightly smaller ICC of 0.86 (95% CI = 0.65–0.95), and a wider range of 95% limits of agreement (−16.09 to 15.19; Fig. 4). Ten of twenty patients had test/retest AI variability of >50%, and 5 of 20 had AI variability of >100%. It was noted that the smaller the striatal AI, the greater AI variability tended to be. This may be expected from the formula used for calculating AI variability. Figure 4 indicates that the absolute value of the difference of AI on repeated measures was around 15. Both the ICC and the 95% limits of agreement suggested that the mean (ST − OC)/OC had a higher reproducibility than the striatal AI.

For the test condition, (ST − OC)/OC in the contralateral striatum was lower in 16 patients and higher in 4 patients (Table 2). For the retest condition, (ST − OC)/OC in the contralateral striatum was lower in 12 patients and higher in 8 patients. Lower (ST − OC)/OC values were on opposite sides in the test and retest conditions for 6 patients (patients 6, 10, 13, 17, 19, and 20).

Figure 5 shows a moderately negative correlation between the mean (ST − OC)/OC and the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore for both the test ($r = -0.53$, $P = 0.017$) and the retest ($r = -0.48$, $P = 0.031$) conditions. This means that patients with more severe clinical symptoms and signs were associated with a lower mean specific striatal uptake of DAT tracer on a

TABLE 2
Test/Retest Variability for the Ratio of Specific-Striatal-to-Nonspecific Uptake

Patient no.	Test (ST − OC)/OC			Retest (ST − OC)/OC			Variability of the mean (ST − OC)/OC (%)
	Ipsilateral side	Contralateral side	Mean	Ipsilateral side	Contralateral side	Mean	
1	0.82	0.74	0.78	0.84	0.77	0.81	3.15
2	1.17	1.00	1.09	1.13	0.90	1.02	6.67
3	1.18	1.26	1.22	1.11	1.21	1.16	5.04
4	1.11	1.24	1.18	0.97	1.06	1.02	14.61
5	0.49	0.47	0.48	0.63	0.51	0.57	17.14
6	0.98	0.89	0.94	0.94	0.98	0.96	2.64
7	0.80	0.61	0.71	0.96	0.76	0.86	19.81
8	0.67	0.48	0.58	0.50	0.42	0.46	22.22
9	1.15	0.90	1.03	1.02	0.81	0.92	11.34
10	0.53	0.44	0.49	0.54	0.57	0.56	13.46
11	0.87	0.72	0.80	0.91	0.82	0.87	8.43
12	1.00	0.65	0.83	0.85	0.51	0.68	19.27
13	0.70	0.71	0.71	0.82	0.72	0.77	8.81
14	1.16	1.07	1.12	1.25	1.13	1.19	6.51
15	0.76	0.78	0.77	0.86	0.92	0.89	14.46
16	1.28	1.24	1.26	1.40	1.31	1.36	7.27
17	1.05	1.02	1.04	0.91	0.94	0.93	11.22
18	0.99	0.93	0.96	1.04	1.02	1.03	7.04
19	0.84	0.78	0.81	0.79	0.80	0.80	1.87
20	1.05	0.97	1.01	0.95	1.01	0.98	3.02
Mean±SD	0.93 ± 0.23	0.85 ± 0.25	0.89 ± 0.23	0.92 ± 0.22	0.86 ± 0.24	0.89 ± 0.22	10.20 ± 6.17

(ST − OC)/OC = (striatum − occipital cortex)/occipital cortex.

population basis. However, this may not be true for individual patients.

DISCUSSION

This study showed that the ratio of specific-striatal-to-nonspecific uptake had excellent test/retest reproducibility in patients with PD. The ICC for mean (ST − OC)/OC was 0.95, and the 95% limits of agreement ($\bar{X} \pm 2$ SD) were 0.00 ± 0.19 (Fig. 2). The striatal AI had a larger variability and a less satisfactory reproducibility. The ICC for striatal AI was 0.86, and the 95% limits of agreement were −0.44 ± 15.63 (Fig. 4). Overall, the mean specific striatal uptake test/retest variability for ^{99m}Tc-TRODAT-1 was 10.20% ± 6.17% (Table 2) and for ^{123}I-β-carboxymethoxy-3β-(4-fluorophenyl)tropane (^{123}I-βCIT) and ^{123}I-fluoropropyl-CIT (^{123}I-FP-CIT) was reported to be 16.80% ± 13.30% and 7.90% ± 6.89%, respectively (*14*,*25*). This suggests that ^{99m}Tc-TRODAT-1 can be a good alternative to the more commonly used ^{123}I-β-CIT as a DAT imaging ligand with SPECT.

Theoretically, the specific striatal uptake is expected to be lower on the contralateral striatum. In this study, the contralateral striatal uptake ratio was higher in 4 of 20 patients (20%) for the test condition and in 8 patients (40%) for the retest condition. Previous studies with ^{123}I-β-CIT also showed a higher contralateral striatal (or putaminal) uptake ratio in about 30% of patients (*14*,*26*). One study with ^{123}I-FP-CIT showed a higher contralateral striatal uptake in 1 of 6 (17%) patients with PD (*26*). We also noted that the side of lower specific striatal uptake changed in 6 patients with the same measurement techniques. The reasons for these findings are unclear. Although some of the variability might be the result of technical factors, such as head position, operator error, and instrumental instability, some might represent true biologic variability within individuals. A comparison with variability on the clinical rating scale, the UPDRS, may be helpful to understand the variability of the SPECT outcome measure. We suggest that the mean (ST − OC)/OC, rather than only the contralateral (ST − OC)/OC, could be a better index for measuring and monitoring dopaminergic degeneration.

PD usually has an asymmetric onset and maintains asymmetry during the chronic progressive course (*27*). Parkinsonian syndromes (e.g., progressive supranuclear palsy, multiple-system atrophy) other than PD usually have a relatively symmetric onset and clinical manifestations (*27*). Our study and another previous study showed a large variability of striatal AI (>50%) in about 50% of PD patients studied (*14*). The 95% limits of agreement showed that the difference of AI can vary between −16.09 and 15.19 in repeated measures. On a population basis, it appears as if the striatal AI might be a useful diagnostic tool. Our findings, however, may not support the idea that striatal AI can be used to make potentially important diagnostic decisions

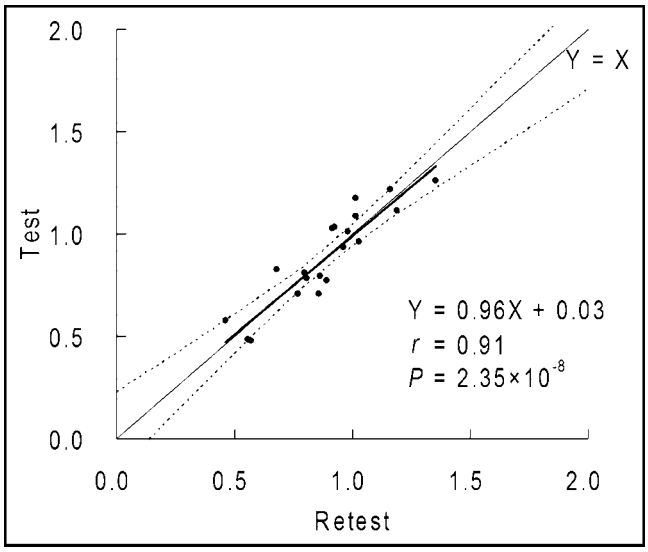

FIGURE 1. Agreement between the test and retest conditions for measuring the mean ratio of specific-striatal-to-nonspecific uptake ([striatum − occipital cortex]/occipital cortex). The line of identity (Y = X) emerging from the origin (0,0) indicates complete agreement between the 2 conditions. The dashed lines represent 95% confidence curves. The 95% CI for the observed correlation of 0.91 is 0.78–0.97.

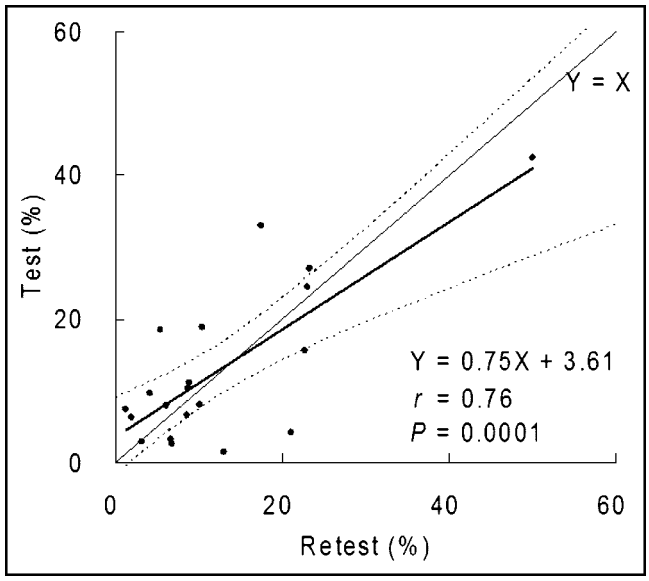

FIGURE 3. Agreement between the test and retest conditions for measuring the striatal AI. The line of identity (Y = X) emerging from the origin (0,0) indicates complete agreement between the 2 conditions. The dashed lines represent 95% confidence curves. The 95% CI for the observed correlation of 0.76 is 0.48–0.90.

in parkinsonian disorders, primarily because of the large variability in individual patients and because our sample was too small. The potential usefulness of AI in differentiation of PD from parkinsonian syndromes at early disease stages needs to be studied further.

The specific striatal binding of ^{99m}Tc-TRODAT-1 shows a moderately negative correlation with the UPDRS motor subscore. This finding is similar to that for ^{123}I-β-CIT (*6*) and suggests that ^{99m}Tc-TRODAT-1 may be a useful marker of disease severity in PD with potential utility for serially monitoring disease progression.

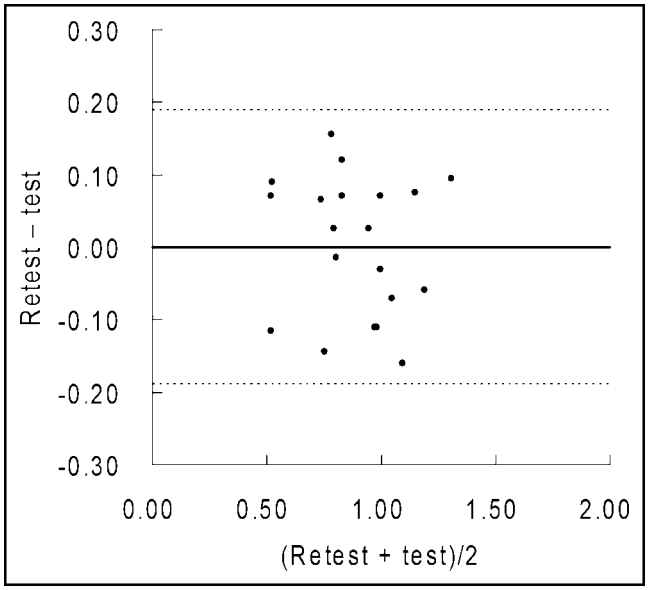

FIGURE 2. Ratio of specific-striatal-to-nonspecific uptake. Solid line shows the mean difference score (0.00). The 95% limits of agreement represent 2 SDs above and below the mean difference score ($\bar{X}$ ± 2 SDs = 0.00 ± 0.19 = −0.19 to 0.19).

The decision to place an ROI on the total striatum or only on the putamen depends on the purpose of evaluation. For longitudinal prospective studies that evaluate disease progression or the effectiveness of medication, an ROI placed on the total striatum, rather than only on the putamen, may result in higher reliability, because variation in the emission counts, differences in repositioning, and degradation of data by subject movement will be less affected with larger ROIs (*14*,*28*). However, because PD is initially and most severely affected at the posterior putamen, the placement of a smaller ROI on the posterior putamen may be the best method for differentiating preclinical or early PD patients from healthy controls in cross-sectional studies (*28*). Several studies have shown that DAT SPECT imaging has a discriminative ability similar to that of ^{18}F-DOPA PET in distinguishing patients with PD from age-matched healthy controls (*6*,*8*,*9*,*26*,*29*,*30*).

Previous studies on neuroprotection using ^{123}I-β-CIT SPECT or ^{18}F-DOPA PET (*12*,*13*,*31*,*32*) had the following limitations: lack of a placebo group, imaging outcomes of disease progression that may have been confounded by pharmacologic effects of the study drug, imaging results that may not have clearly reflected changes in clinical disability, incomplete information about reliability and validity of the scans, and potential compensatory downregulation of DAT expression or binding sites in the face of the disease process (*19*,*33*). ^{99m}Tc-TRODAT-1 SPECT has the

TABLE 3
Test/Retest Variability for Striatal AI

Patient no.	Test AI (%)	Retest AI (%)	Within-subject test/retest AI variability (%)
1	10.26	8.70	16.47
2	15.67	22.66	36.48
3	6.56	8.62	27.19
4	11.06	8.87	22.04
5	4.17	21.05	133.91
6	9.63	4.17	79.16
7	26.95	23.26	14.72
8	33.04	17.39	62.07
9	24.39	22.95	6.08
10	18.56	5.41	109.77
11	18.87	10.40	57.82
12	42.42	50.00	16.39
13	1.42	12.99	160.61
14	8.07	10.08	22.17
15	2.60	6.74	88.75
16	3.17	6.64	70.64
17	2.90	3.24	11.22
18	6.25	1.94	105.19
19	7.41	1.26	141.94
20	7.92	6.12	25.61
Mean ± SD	13.07 ± 11.18	12.62 ± 11.32	60.41 ± 48.64

same limitations and problems. Further exploration of these issues is mandatory if ^{99m}Tc-TRODAT-1 SPECT is to become an important and valuable clinical tool. Studies on nonhuman primates are crucial for validating and establishing the relationship between DAT binding of ^{99m}Tc-TRODAT-1 and loss of nigral neurons or striatal dopamine levels.

This study showed that ^{99m}Tc-TRODAT-1 SPECT has excellent reproducibility and may thus provide a reliable objective measurement of the nigrostriatal system. Our findings indicate that ^{99m}Tc-TRODAT-1 SPECT produces an outcome measure that is probably good enough for use in

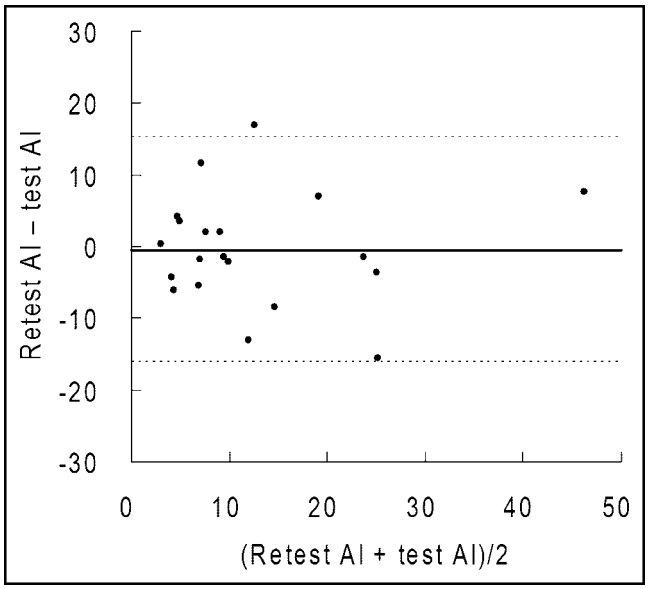

FIGURE 4. Striatal AI. Solid line shows the mean difference score (−0.44). The 95% limits of agreement represent 2 SDs above and below the mean difference score ($\bar{X}$ ± 2 SDs = −0.44 ± 15.63 = −16.09 to 15.19).

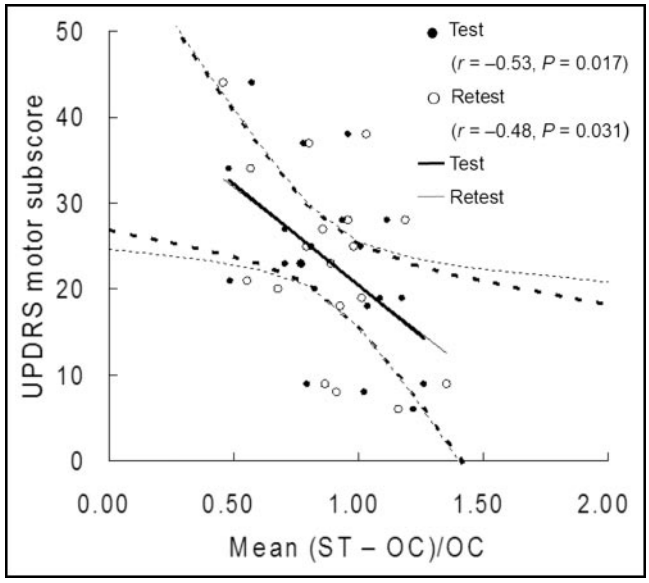

FIGURE 5. The correlation between UPDRS motor subscore and the mean ratio of specific-striatal-to-nonspecific uptake ([ST − OC]/OC) of the test and retest conditions. The dashed lines represent 95% confidence curves. The 95% CI for the observed correlation of −0.53 is −0.05 to −0.79 (test condition) and that for the observed correlation of −0.48 is −0.05 to −0.76 (retest condition).

designs that require repeated measures within subjects. In addition, its relatively short equilibration phase between injection and imaging (4 h), as compared with that of ^{123}I-β-CIT (24 h), increases the feasibility of withholding medications sufficiently long to eliminate the drug effect on DAT binding (*19*). The lower costs and greater availability of ^{99m}Tc-based tracer and SPECT cameras greatly enhance the ease of use for routine clinical practice in humans.

CONCLUSION

This study showed that ^{99m}Tc-TRODAT-1 SPECT is a safe, convenient, and reliable tool for measuring dopamine transporters and for evaluating and monitoring nigrostriatal degeneration. Although the clinical rating scales and DAT SPECT imaging have some limitations, the complementary measurements of clinical disability by UPDRS and the mean ratio of specific-striatal-to-nonspecific uptake of ^{99m}Tc-TRODAT-1 by SPECT should provide adequate monitoring of disease progression and evaluation of potential neuroprotective effects. Slowing the loss of imaging outcomes is meaningful only if these imaging changes result in improved clinical function and quality of life in patients with PD.

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