Annals of Nuclear Medicine Vol. 18, No. 7, 609–616, 2004

Reproducibility of dopamine transporter density measured with ^{123}I-FPCIT SPECT in normal control and Parkinson's disease patients

Tatsuro TSUCHIDA,[*1,*3,*7] James R. BALLINGER,[*1,*3,*5] Douglass VINES,[*1,*4] Yun J. KIM,[*2,*3] Keita UTSUNOMIYA,[*1,*3,*6] Anthony E. LANG[*2,*3] and Masanori ICHISE[*1,*3,*4]

[*1]*Division of Nuclear Medicine, Department of Medical Imaging, Mount Sinai Hospital,*
[*2]*Morton and Gloria Shulman Movement Disorders Center,* [*3]*University of Toronto,*
[*4]*Molecular Imaging Branch, National Institute of Mental Health,* [*5]*Department of Nuclear Medicine, Guy's and St. Thomas' Hospital,* [*6]*Department of Radiology, Osaka Medical College, and* [*7]*Department of Radiology, University of Fukui*

The objective of this study was to evaluate the reproducibility of ^{123}I-FPCIT SPECT by using whole striatal region of interest (ROI) and subdivided ROI in normal controls (NC) and Parkinson's disease (PD) patients. ***Methods:*** Ten NC and 6 PD received a SPECT scan for 6 hours postinjection of FPCIT. The distribution volume ratio (R_V) and specific-nonspecific tissue activity ratio (R_T) were measured as an outcome measure. The test/retest reproducibility of R_V and R_T was evaluated by calculating the test/retest difference, variability, and reliability. ***Results:*** There were no significant test/retest differences for any regions in either the NC or PD. The test/retest variability/reliability of R_V was 5.53 ± 4.12%/0.89 in NC, 4.50 ± 5.31%/0.99 in PD with whole striatal ROI, 4.29 ± 0.78%/0.94 ± 0.03 in NC, and 6.87 ± 1.23 %/0.98 ± 0.01 in PD with subdivided ROI. The test/retest variability/reliability of R_T was 11.1 ± 10.4%/0.59 in NC, 7.84 ± 8.94%/0.95 in PD with whole striatal ROI, 11.9 ± 1.22%/0.65 ± 0.06 in NC, and 12.2 ± 4.00%/0.95 ± 0.03 in PD with subdivided ROI. ***Conclusion:*** R_V is highly reproducible and reliable compared with R_T in both NC and PD as an outcome measure.

Key words: ^{123}I-FPCIT, reproducibility, distribution volume ratio

INTRODUCTION

THE IMAGING of dopamine transporters using positron emission tomography (PET) or single photon emission computed tomography (SPECT) has been introduced as a valuable tool to evaluate patients with movement disorders like Parkinson's disease (PD).[1,2] PET with ^{11}C-nomifensine or ^{11}C-labeled cocaine analogs showed a loss of striatal dopamine transporters in PD patients.[3,4]

SPECT, which is more widely available than PET, with ^{123}I-labeled cocaine analogs, ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT), also showed a dramatic loss of striatal dopamine transporters in patients with PD with high signal-to-noise ratios.[2,5–8] However, the slow kinetics of ^{123}I-β-CIT is a serious drawback. A stable level of radioactivity in the striatum is only reached between 20 and 30 hr postinjection.[9] This indicates that optimal image acquisition can be performed only the day following the injection of [^{123}I]β-CIT (2-day protocol), which is highly inconvenient for outpatient evaluations. Moreover, due to the half-life of ^{123}I (13.2 hr), the counting statistics are considerably diminished at that time by physical decay.

^{123}I-*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (FPCIT) is a new cocaine analog with a high affinity for dopamine transporter.[10–12] Previous studies have revealed that FPCIT SPECT allows the use of a 1-day protocol for imaging of dopamine transporters, due to the fast kinetics.[7,8,11,13,14]

The demonstration of a reproducible SPECT outcome measure is critical and preliminary to the extension of FPCIT to clinical populations, including the serial monitoring of progressive disorders like PD, as has been revealed by other radiopharmaceuticals in normal

Received May 12, 2004, revision accepted July 8, 2004.

For reprint contact: Tatsuro Tsuchida, M.D., Department of Radiology, University of Fukui, 23–3 Shimoaizuki, Matsuoka, Fukui 910–1193, JAPAN.

Table 1 Demographic characteristics of PD patients

Patient no.	Sex	Age, y	Disease duration, y	Hoehn & Yahr stage	UPDRS*		Medication (total daily dose in mg)
					Total	Motor (contralateral/ ipsilateral)	
1	M	59	14	2	52	31.5 (11.5/9)	Sinemet (600), deprenyl (20), Bromocriptine (7.5)
2	F	50	7	2	26.5	18.5 (13.5/1.5)	None
3	M	40	0.75	1	4	3 (3/0)	None
4	F	69	5	2	33.5	19.5 (7/4)	Sinemet (500), Requip (5)
5	M	71	11	2	21	11 (5/3)	Sinemet CR (1200), Tolcapone (100)
6	M	59	10	2	55.5	32 (13/11)	Sinemet (200), Sinemet CR (1300)
Mean		58.0	8.0	1.8	32.1	19.3 (8.8/4.8)	Permax (6), Amantadine (200)
SD		11.7	4.7	0.4	19.4	11.4 (4.4/4.3)	

* Unified Parkinson's Disease Rating Scale (Total: maximum possible score = 176; Motor: maximum possible score = 108; contralateral/ipsilateral motor; maximum possible score = 36)

controls (NC) or PD.[15–19] Therefore, we undertook to evaluate the test/retest reproducibility of FPCIT SPECT imaging.

MATERIALS AND METHODS

Subjects

We studied 10 NC subjects (6 men, 4 women; mean age 36.4 ± 15.9 y, range 25 to 70 y) with no current or past history of neuropsychiatric disorders or family history of movement disorders, and 6 PD patients (4 men, 2 women; mean age 58.0 ± 11.7 y, range 40 to 71 y), who were recruited from the Movement Disorder Clinic at The Toronto Hospital. The patients' characteristics are described in detail in Table 1. The patients had mild PD, as assessed by the Hoehn and Yahr Scale[20] (1 stage I patient, and 5 stage II patients), and the Unified Parkinson's Disease Rating Scale (UPDRS)[21] (mean total UPDRS, score 32.1 ± 19.4, range 4 to 55.5). The diagnosis of PD was made according to the UK Parkinson's Disease Brain Bank clinical diagnosis criteria.[22] Four of the 6 patients took antiparkinsonian medication, which included L-dopa or dopamine agonists. Patients who were on treatment discontinued their drugs for at least 12 hours before the commencement of the SPECT studies and until their completion. All UPDRS scores were obtained before the SPECT studies, when the drug-treated patients had been off medication for at least 12 hours. All patients and controls gave written informed consent. The project was approved by the Human Subjects Review Committee of the University of Toronto.

Preparation of ^{123}I-FPCIT

FPCIT was prepared by a modification of the method of Zea-Ponce et al.[23]

Fifty μg of the trimethylstannyl precursor supplied by Nihon Medi-Physics Co., Ltd. (Tokyo, Japan) was dissolved in 50 μl ethanol, and added to a vial containing ^{123}I sodium iodide (supplied by Nordion International, Ltd., Vancouver, BC, Canada) in 0.1 N NaOH (460–720 MBq in 40–850 μl). To the reaction mixture were added 50 μl 1 M phosphoric acid and 50 μl freshly-diluted 2.6% peracetic acid. After incubation for 30 minutes at room temperature, the reaction was quenched with 50 μl sodium metabisulfite (300 mg/ml) and 500 μl sodium bicarbonate (100 mg/ml), diluted with 5 ml sterile water and passed through a C-18 solid-phase extraction cartridge (Sep-Pak Classic). The cartridge was eluted with four fractions of 0.5 ml absolute ethanol. The hottest fractions were pooled, and diluted with 5 volumes of saline. After the addition of 100 μl ascorbic acid (1 mg/ml), the solution was sterilized through a low-protein-binding 0.22-microm membrane filter into a sterile 10 ml multidose vial. The radiochemical purity was checked using a C-18 extraction cartridge eluted with water. Retrospective sterility testing was negative. In 32 preparations, the yield was 68.5 ± 10.4% and the radiochemical purity was 99.2 ± 0.6%.

SPECT imaging

Imaging was performed using a triple-headed SPECT system (Prism 3000XP, Picker International, Inc., Cleveland, OH) equipped with ultra-high resolution fan beam collimators and interfaced to a dedicated computer (Odyssey VP; Picker International, Inc., Cleveland, OH). The NC subjects had a test/retest SPECT examination 1 wk apart, and the PD patients had it within 3 wks apart (13 ± 5 days). The FPCIT SPECT scans were acquired every 5 minutes at 0–120, 150–210, 240–300, and 330–360 minutes postinjection. The injected doses of FPCIT were 351 ± 56 MBq for NC, and 365 ± 26 MBq for PD. For each scan, 120–7.5 second projection images were obtained using 3 degree angle intervals on a 128 × 128 matrix over 360 degrees by rotating each head 120 degrees. The radius of rotation was fixed at 13.5 cm. To identify the canthomeatal line (CML), fiducial markers containing 55.5 MBq of ^{99m}Tc were taped on the outer canthus of the eye and over the external auditory meatus

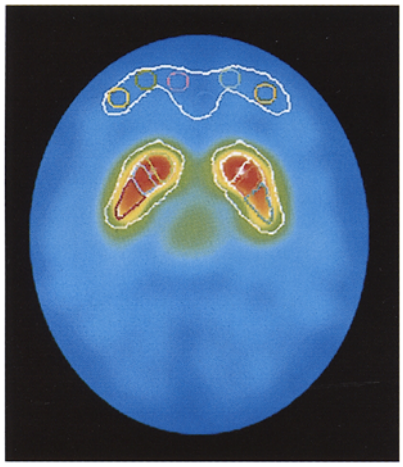
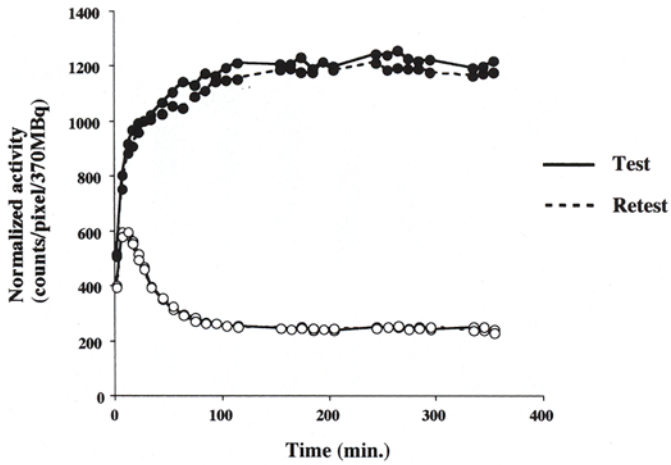
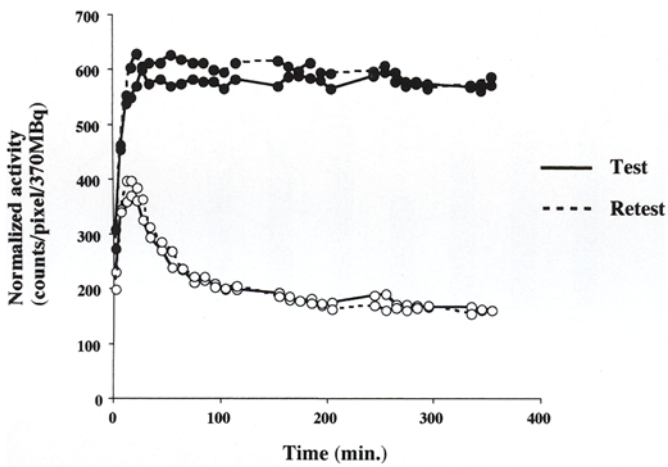


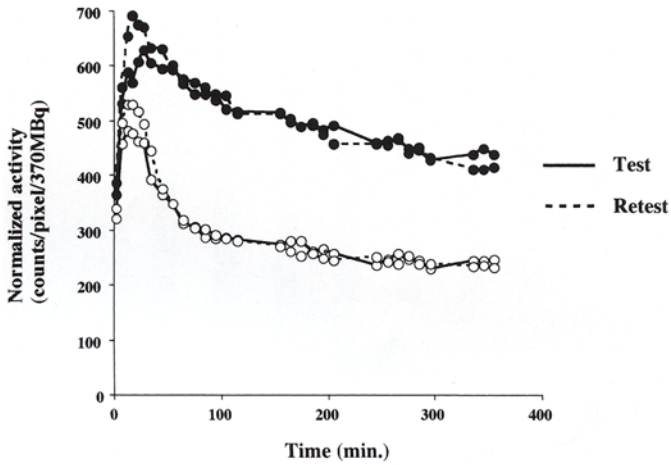
Fig. 1 ROI template image.



2a



2b



2c

Fig. 2 Test/retest time-activity curve (TAC) in representative cases in NC and PD. Six subdivided ROIs were averaged in each study, and their activities were normalized by an injected dose of 370 MBq in each study. Neither NC (2a, 23-year-old female) nor stage I PD (2b, 40-year-old male) show any apparent decline of striatal uptake. In contrast, in stage II PD (2c, 69-year-old female), a decline of the uptake in both striatum (*closed circle*) and the frontal cortex (*open circle*) was observed.

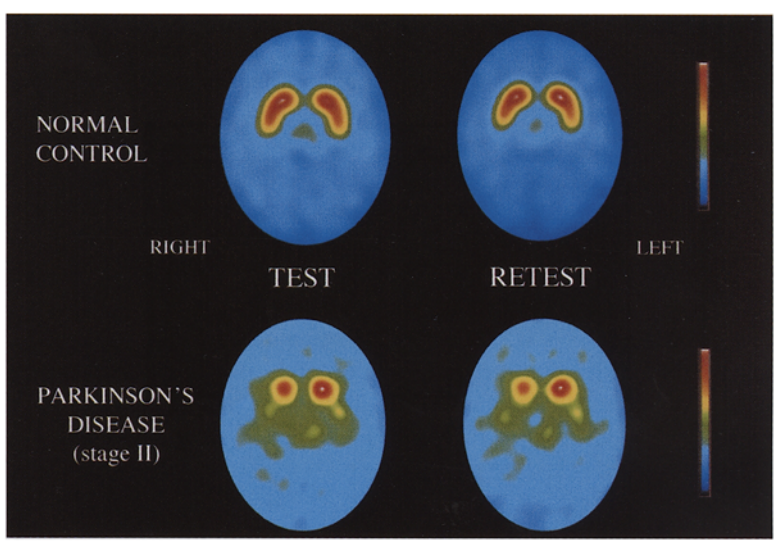


Fig. 3 Test/retest FPCIT SPECT images in NC (53-year-old male, *left*) and PD (59-year-old male, *right*). The averaged variability of R_V was 3.05 ± 2.46% in NC and 9.03 ± 1.86% in PD. The image intensity was adjusted so that the striatal uptake would reflect the mean striatal values of R_V.

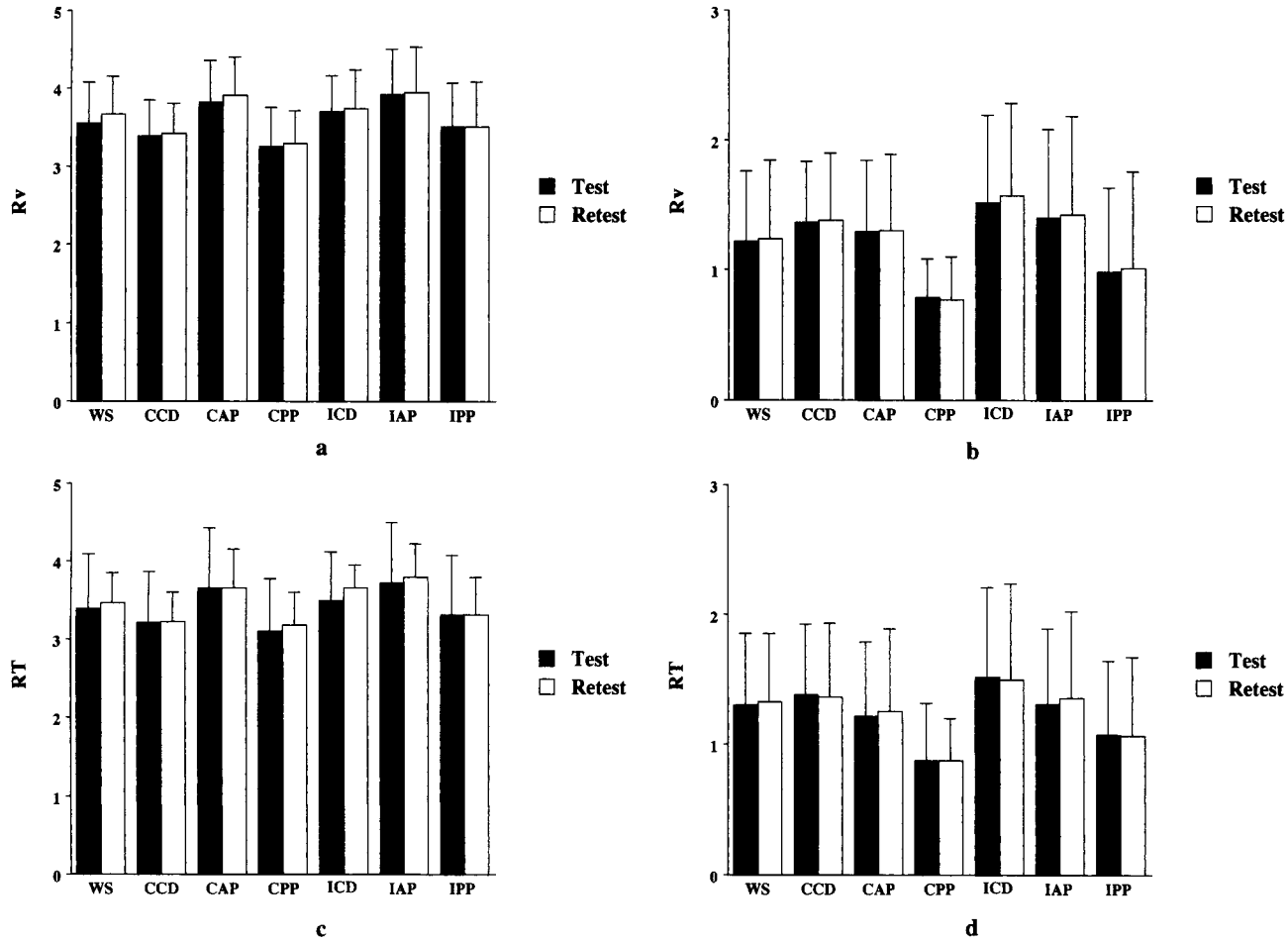


Fig. 4 The test/retest difference of R_V in NC (a) and PD (b) and R_T in NC (c) and PD (d). No significant difference was observed in any regions. WS; whole striatum, CCD; contralateral caudate head, CAP; contralateral anterior putamen, CPP; contralateral posterior putamen, ICD; ipsilateral caudate head, IAP; ipsilateral anterior putamen, IPP; ipsilateral posterior putamen.

bilaterally throughout the imaging experiment.[24] Full width with half-maximum of this system was 9.1 mm in water at the center of the field of view. Before the SPECT study, each subject took 400 mg of potassium perchlorate orally for thyroid blocking.

The SPECT images were reconstructed every 5 minutes for the first 30-minute data. Otherwise, they were reconstructed every 10 minutes. To obtain the template image of regions of interest (ROIs), the first 15-minute data were summed and used for reconstruction. One-pixel-thick transaxial slices from the vertex of the brain to the level of the CML, as identified by the fiducial markers, were reconstructed parallel to the CML using a three-dimensional Butterworth postreconstruction filter (order 10, cutoff frequency 0.25 cycles/pixel) after applying a ramp back projection filter. Attenuation correction was performed ($\mu = 0.12\ cm^{-1}$) within an ellipse drawn around the skull, as identified by the fiducial markers.

Data analysis

For NC, the contralateral side was assigned to the left side. For PD, the contralateral side was defined as the side contralateral to the most affected limbs. The ROIs used were three striatal subregions (subdivided ROI)—caudate head (volume, 1.10 cm^3) anterior putamen (0.89 cm^3) and posterior putamen (1.23 cm^3)—and six circular frontal cortex ROIs (total volume, 3.93 cm^3) shown in Figure 1. The ROIs placement depended on the visual identification of anatomic regions aided by the stereotaxic atlas and the early (first 15-minute) FPCIT image, which reflects mostly regional perfusion. In PD, as striatal perfusion is intact, this strategy facilitated placing striatal ROIs on the FPCIT images even after a long time postinjection. All ROIs were applied by one operator to eliminate interoperator variation. To obtain the whole striatal ROI value, six subdivided ROIs in each subject were averaged.

For assessment of the time-activity curve (TAC), whole striatal ROI was used. The time-to-peak uptake in the striatum, the frontal cortex, and specific binding (striatum-frontal cortex) was quantified after fitting a sum of three exponentials to the regional time-activity data. The

time-to-peak uptake in the striatum and specific binding were used to evaluate the reproducibility of the TAC.

The dopamine transporter binding was quantified as the distribution volume ratio (R_V) by using the multilinear regression technique[19] and the specific-nonspecific tissue activity ratio (R_T). The multilinear regression technique permits measurement of the binding potential, $R_V = V_3/V_2$, without blood data, according to the following equation:

$$\frac{\int_0^t C_{ST}(t)dt}{C_{ST}(t)} = \left(\frac{a}{a'}\right)\frac{\int_0^t C_{ST}(t)dt}{C_{ST}(t)} + \left(-\frac{ab'}{a'}\right)\frac{C_{FC}(t)}{C_{ST}(t)} + b \quad (1)$$

where $C_{ST}(t)$ represents the time-activity measurements in the striatum and $C_{FC}(t)$ represents the time-activity measurements in the frontal cortex, and a, a', b and b' are constants. R_V is related to the partial regression coefficient a/a' in equation 1, as follows:

$$R_V = V_3/V_2 = a/a' - 1$$

R_T was calculated as follows;

$$R_T = (ST - FC)/FC - 1$$

where ST and FC represent the measured activity in the striatum and the frontal cortex. In this study, R_T at 3-hour postinjection, which was reported to be a simple outcome measure by Booij et al.,[14] was compared with R_V in terms of variability and reliability.

Statistical analysis

All statistical analyses, including multilinear regression analysis, were implemented in STATISTICA (StatSoft, Inc., Tulsa, OK).

For the assessment of the test/retest reproducibility of R_V and R_T in NC and PD, the test/retest differences, variability, and reliability were applied. Wilcoxon Matched-Pairs Signed Rank test was used for comparison between the test and retest measures. The test/retest variability in R_V and R_T was calculated as the absolute value of the difference between the two measurements, expressed as a percentage of the mean value of both measurements, and the rest/retest variability of R_V and R_T was also compared between the corresponding subdivided ROIs by means of Wilcoxon Matched-Pairs Signed Rank test. The reliability of the two measurements between the test and retest was assessed by calculating the intraclass correlation coefficient, according to the following equation.[25]

$$\rho = \frac{MSBS - MSWS}{MSBS + (k-1)MSWS} \quad (3)$$

where MSBS and MSWS are the mean sum of squares between and within subjects, respectively, and k is the number of within-subject measurements, being 2 in the present study. This coefficient is an estimate of the reliability of the two sets of measurements, and varies from 0 (no reliability) to 1 (total reliability). Statistical significance was defined as $p < 0.05$. The summaries of study variables were expressed as mean ± s.d.

Table 2 Test/retest measures of R_V

	Test	Retest	p
NC			
WS	3.56 ± 0.52	3.68 ± 0.47	0.12
CCD	3.39 ± 0.47	3.42 ± 0.40	0.64
CAP	3.83 ± 0.54	3.91 ± 0.50	0.20
CPP	3.25 ± 0.52	3.29 ± 0.42	0.42
ICD	3.70 ± 0.48	3.74 ± 0.50	0.48
IAP	3.94 ± 0.59	3.96 ± 0.59	0.69
IPP	3.51 ± 0.57	3.50 ± 0.60	0.83
PD			
WS	1.22 ± 0.54	1.24 ± 0.61	0.62
CCD	1.36 ± 0.47	1.38 ± 0.51	0.54
CAP	1.29 ± 0.55	1.30 ± 0.59	0.89
CPP	0.79 ± 0.30	0.77 ± 0.33	0.70
ICD	1.52 ± 0.67	1.57 ± 0.71	0.27
IAP	1.41 ± 0.68	1.43 ± 0.76	0.73
IPP	0.99 ± 0.65	1.02 ± 0.75	0.66

WS; whole striatum, CCD; contralateral caudate head, CAP; contralateral anterior putamen, CPP; contralateral posterior putamen, ICD; ipsilateral caudate head, IAP; ipsilateral anterior putamen, IPP; ipsilateral posterior putamen

Table 3 Test/retest measures of R_T

	Test	Retest	p
NC			
WS	3.67 ± 0.57	3.68 ± 0.53	0.50
CCD	3.53 ± 0.52	3.47 ± 0.43	0.42
CAP	3.89 ± 0.56	3.97 ± 0.50	0.27
CPP	3.34 ± 0.52	3.33 ± 0.51	0.93
ICD	3.82 ± 0.56	3.75 ± 0.47	0.28
IAP	3.95 ± 0.59	4.00 ± 0.62	0.62
IPP	3.50 ± 0.69	3.54 ± 0.65	0.49
PD			
WS	1.24 ± 0.69	1.22 ± 0.74	0.78
CCD	1.28 ± 0.57	1.26 ± 0.63	0.86
CAP	1.33 ± 0.66	1.33 ± 0.75	0.98
CPP	0.83 ± 0.37	0.82 ± 0.43	0.80
ICD	1.60 ± 0.80	1.55 ± 0.77	0.51
IAP	1.40 ± 0.87	1.38 ± 0.96	0.81
IPP	1.02 ± 0.87	1.00 ± 0.91	0.70

RESULTS

Of 20 SPECT studies in NC, the peak time of striatal uptake was not observed during a 6 hr scan in 1 study, and that of specific binding was not observed in 5 studies. In these studies, the peak time was assumed to be 6 hr postinjection for the convenience of statistical analysis. In PD, all studies showed the peak of striatal uptake and

Table 4 Test/retest variability (%) and reliability (ρ) between R_V and R_T

	R_V		R_T		p for variability
	Variability	ρ	Variability	ρ	
NC					
WS	5.53 ± 4.12	0.89	11.1 ± 10.4	0.59	0.049
CCD	5.08 ± 3.41	0.90	11.7 ± 10.3	0.59	0.12
CAP	4.17 ± 3.69	0.93	12.5 ± 1.38	0.63	0.025
CPP	4.15 ± 2.93	0.95	13.7 ± 9.89	0.66	0.03
ICD	4.09 ± 2.94	0.92	11.2 ± 7.49	0.59	0.004
IAP	5.18 ± 2.08	0.93	10.0 ± 8.37	0.71	0.16
IPP	3.04 ± 1.96	0.97	12.2 ± 8.51	0.73	0.002
PD					
WS	4.50 ± 5.31	0.99	7.84 ± 8.94	0.95	0.84
CCD	4.86 ± 2.70	0.99	8.35 ± 9.09	0.95	0.56
CAP	7.03 ± 3.86	0.98	11.9 ± 6.72	0.95	0.09
CPP	7.98 ± 5.86	0.97	17.7 ± 12.3	0.89	0.22
ICD	6.49 ± 2.03	0.99	15.0 ± 10.5	0.94	0.15
IAP	6.53 ± 4.42	0.98	7.11 ± 3.97	0.96	0.69
IPP	8.30 ± 4.30	0.98	13.3 ± 9.65	0.98	0.44
NC + PD					
WS	5.08 ± 4.09	0.93	9.42 ± 8.60	0.73	0.06
CCD	5.00 ± 3.07	0.93	10.4 ± 9.69	0.73	0.03
CAP	5.25 ± 3.90	0.95	12.3 ± 6.96	0.75	0.006
CPP	5.59 ± 4.50	0.96	15.2 ± 10.6	0.75	0.01
ICD	4.99 ± 2.83	0.95	12.6 ± 8.59	0.72	0.002
IAP	5.69 ± 3.10	0.95	8.95 ± 7.03	0.80	0.13
IPP	5.01 ± 3.92	0.97	12.6 ± 8.64	0.82	0.007

specific binding within the end of the scan. The mean peak time of the striatal uptake in NC (222 ± 56 min) came later than that in PD (31 ± 30 min). The variability/reliability of the peak time of striatal uptake were 22.5 ± 12.9%/0.54 in NC and 16.4 ± 17.5%/0.29 in PD. The mean peak time of specific binding in NC (271 ± 57 min) was also reached later than in PD (123 ± 68 min). The variability/reliability of the peak time of specific binding were 18.9 ± 18.6%/0.50 in NC and 12.9 ± 14.5%/0.84 in PD. The test/retest TAC in NC, stage I PD (Patient 3), and stage II PD (Patient 4) are shown in Figures 2a, 2b, and 2c. The test/retest FPCIT SPECT images in NC and stage II PD (Patient 6) are shown in Figure 3.

Figures 4a, 4b, 4c, and 4d show the test/retest differences of R_V and R_T in NC and PD. Test/retest measures are shown in Tables 2 and 3. There were no significant test/retest differences of R_V or R_T in either NC or PD ($p > 0.1$).

The test/retest variability and reliability of R_V and R_T in the whole striatal and subdivided ROI are shown in Table 4. A significant difference of variability between R_V and R_T was observed in the WS, CAP, CPP, ICD, and IPP of NC. When NC and PD data were combined, a significant difference was observed in all regions except WS and IAP.

DISCUSSION

In this study, the averaged variability and reliability of R_V with FPCIT SPECT was 4.29%/0.94 in NC, and 6.87%/0.98 in PD when subdivided ROIs were used. In the previous reports,[26] the averaged variability/reliability of FPCIT SPECT was estimated as 7.25%/0.99 in NC and 7.9%/1.00 in PD. The averaged test/retest variability (%) and reliability in NC and PD on other PET/SPECT ligands are as follows: NC; 6.8/0.96 in ^{123}I β-CIT,[18] and 3.3/0.73 in ^{18}F DOPA,[16] PD; 3/0.76 in ^{18}F DOPA.[17] In our study, we used both whole striatal and subdivided ROI to evaluate the test/retest reproducibility. In contrast, only whole striatal ROI was used for all other reproducibility studies. We used the subdivided ROI to determine if the reproducibility of FPCIT SPECT would be preserved or not in small or low count regions. The importance of estimating transporter binding in subdivided regions arises from the intrastriatal differences of dopaminergic function in PD.[27] In PD, the ventral portion of the substantia nigra pars compacta appears more susceptible to degeneration than the dorsal tier,[28] and more severe reduction in radiotracer binding can be observed in the posterior putamen. The uneven dopamine transporter deficit within the putamen is also known from postmortem findings, and from recent PET studies.[4,29] On the one hand, if whole striatal ROI is applied to estimate the dopamine transporter binding in

PD, the regional differences of the transporter binding might be obscured, and the sensitivity to detect subtle differences in the transporter density might decrease. On the other hand, if using subdivided ROI results in larger variability and lower reliability compared to using whole striatal ROI, the method would be of no use. Our results are thought to be comparable or superior to those of previous reports with respect to the values of variability and reliability, even though we used subdivided ROIs. Therefore, we think R_V values are available for the estimation of transporter binding in subdivided regions.

We speculated that our data showed excellent reproducibility because we used R_V as outcome measures. Compared to R_V which is estimated from multilinear regression analysis with multi point data, the specific to non-specific ratio (R_T), widely used for the estimation of transporter/receptor binding,[7,8,11,14,26,30–32] is obtained from one time point data. The variability reported by Booij et al.[26] is larger than that of our study, despite the fact that they used whole striatal ROI. This may mean that R_T itself presents a risk of causing large variability. In our study, the larger variability of R_T was observed in all subdivided ROIs. R_T is a very simple index to calculate, and because of this, it might be suitable to use for routine study, but not of course if the index is unreliable. We think the selection of outcome measures depends on the situation in which they are used.

For the discrimination of NC and PD, R_T would be available, because PD shows a marked decrease of transporter density from the very early stage. Gutmann et al.[4] reported that even in very early PD, a 56% reduction of the transporter binding in the contralateral posterior putamen was observed with ^{11}C-RTI-32, and Marek et al.[33] reported a 53% reduction of contralateral striatal uptake with ^{123}I-β-CIT in patients with hemi-Parkinson's disease. In contrast, to estimate the disease progression, a more reproducible method should be applied. Vingerhoets et al.[34] reported that the decline of striatal dopaminergic metabolic function in PD is 7.8% per decade, while an annual decline of 7% was reported by Morrish et al.[35] These changes are apparently smaller than the difference between NC and PD. Therefore, we think R_V, rather than R_T, should be applied for the estimation of disease progression, although R_T is sufficient for diagnosing PD.

The disadvantage to obtaining R_V is that a dynamic scan is required. This is extremely inconvenient for the subjects. To make it easier for the subjects, the simplified method proposed by Ichise et al.[36] can be used.

In conclusion, we reported the excellent reproducibility of R_V in FPCIT SPECT with whole striatal and subdivided ROI.

REFERENCES

1. Leenders KL, Salmon EP, Tyrrell P, Perani D, Brooks DJ, Sager H, et al. The nigrostriatal dopaminergic system assessed *in vivo* by positron emission tomography in healthy volunteer subjects and patients with Parkinson's disease. *Arch Neurol* 1990; 47: 1290–1298.
2. Innis RB, Seibyl JP, Scanley BE, Laruelle M, Abi-Dargham A, Wallece E, et al. Single photon emission computed tomographic imaging demonstrates loss of striatal dopamine transporters in Parkinson disease. *Proc Natl Acad Sci USA* 1993; 90: 11965–11969.
3. Frost JJ, Rosier AJ, Reich SG, Smith JS, Ehlers MD, Snyder SH, et al. Positron emission tomographic imaging of the dopamine transporters with ^{11}C-WIN 35,428 reveals marked declines in mild Parkinson's disease. *Ann Neurol* 1993; 34: 423–431.
4. Guttman M, Burkholder J, Kish SJ, Hussey D, Wilson A, DaSilva J, et al. [^{11}C]RTI-32 PET studies of the dopamine transporters in early dopa-naive Parkinson's disease: implications for the symptomatic threshold. *Neurology* 1997; 48: 1578–1583.
5. Brücke T, Kohnhuber J, Angelberger P, Asenbaum S, Frassine H, Podreka I. SPECT imaging of dopamine and serotonin transporters with [^{123}I]β-CIT binding kinetics in human brain. *J Neural Transm [GenSect]* 1993; 94: 137–146.
6. Seibyl JP, Marek KL, Quinlan D, Sheff K, Zoghbi S, Zea-Ponce Y, et al. Decreased single-photon emission computed tomographic [^{123}I]β-CIT striatal uptake correlates with symptom severity in Parkinson's disease. *Ann Neurol* 1995; 38: 589–598.
7. Booij J, Tissingh G, Boer GJ, Speelman JD, Stoof JC, Janssen AGM, et al. [^{123}I]FP-CIT SPECT shows a pronounced decline of striatal dopamine transporter labelling in early and advanced Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; 62: 133–140.
8. Booij J, Tissingh G, Winogrodzka A, Boer GJ, Stoof JC, Wolters EC, et al. Practical benefit of [^{123}I]FP-CIT SPET in the demonstration of the dopaminergic deficit in Parkinson's disease. *Eur J Nucl Med* 1997; 24: 68–71.
9. Laruelle M, Wallace E, Seibyl JP, Baldwin RM, Zea-Ponce Y, Zoghbi S, et al. Graphical, kinetic, and equilibrium analysis of *in vivo* [^{123}I]β-CIT binding to dopamine transporters in healthy human subjects. *J Cereb Blood Flow Metab* 1994; 14: 982–994.
10. Neumeyer JL, Wang S, Gao Y, Milius RA, Kula NS, Campbell A, et al. *N*-ω-fluoroalkyl analogs of (1*R*)-2β-carbomethoxy-3β-(4-iodophenyl)-tropane (β-CIT): radiotracers for positron emission tomography and single photon emission computed tomography imaging of dopamine transporters. *J Med Chem* 1994; 37: 1558–1561.
11. Abi-Dargham A, Gandelman MS, DeErausquin GA, Zea-Ponce Y, Zoghbi SS, Baldwin RM, et al. SPECT imaging of dopamine transporters in human brain with iodine-123-fluoroalkyl analogs of β-CIT. *J Nucl Med* 1996; 37: 1129–1133.
12. Scheffel U, Lever JR, Abraham P, Parham KR, Mathews WB, Kopajtic T, et al. *N*-substituted phenyltropanes as *in vivo* binding ligands for rapid imaging studies of the dopamine transporter. *Synapse* 1997; 25: 345–349.
13. Kuikka JT, Bergström KA, Ahonen A, Hiltunen J, Haukka J, Lansimies E, et al. Comparison of iodine-123 labelled 2β-carbomethoxy-3β-(4-iodophenyl)tropane and 2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)

nortropane for imaging of the dopamine transporter in the living human brain. *Eur J Nucl Med* 1995; 22: 356–360.
14. Booij J, Hamelaar JTGM, Speelman JD, de Bruin K, Janssen AGM, van Royen EA. One-day protocol for imaging of the nigrostriatal dopaminergic pathway in Parkinson's disease by [^{123}I]FPCIT SPECT. *J Nucl Med* 1999; 40: 753–761.
15. Volkow ND, Fowler JS, Wang GJ, Dewey SL, Schlyer D, MacGregor R, et al. Reproducibility of repeated measures of carbon-11-raclopride binding in the human brain. *J Nucl Med* 1993; 34: 609–613.
16. Vingerhoets FJG, Snow BJ, Schulzer M, Morrison S, Ruth TJ, Holden JE, et al. Reproducibility of fluorine-18-6-fluorodopa positron emission tomography in normal human subjects. *J Nucl Med* 1994; 35: 18–24.
17. Vingerhoets FJG, Schulzer M, Ruth TJ, Holden JE, Snow BJ. Reproducibility and discriminating ability of fluorine-18-6-fluoro-L-dopa PET in Parkinson's disease. *J Nucl Med* 1996; 37: 421–426.
18. Seibyl JP, Laruelle M, van Dyck CH, Wallace E, Baldwin RM, Zoghbi S, et al. Reproducibility of iodine-123-β-CIT SPECT brain measurement of dopamine transporters. *J Nucl Med* 1996; 37: 222–228.
19. Ichise M, Ballinger JR, Vines D, Tsai S, Kung HF. Simplified quantification and reproducibility studies of dopamine D2-receptor binding with iodine-123-IBF SPECT in healthy subjects. *J Nucl Med* 1997; 38: 31–37.
20. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology* 1967; 17: 427–442.
21. Lang AE, Fahn S. Assessment of Parkinson's disease. In: Munsat TL, ed. *Quantification of Neurologic Deficit*. Boston; Butterworths, 1989: 285–309.
22. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; 55: 181–184.
23. Zea-Ponce Y, Baldwin RM, Laruelle M, Wang S, Neumeyer JL, Innis RB. Simplified multidose preparation of iodine-123-β-CIT: a marker for dopamine transporters. *J Nucl Med* 1995; 36: 525–529.
24. Vines DC, Ivo BD, Ballinger JR, Ichise M. External radioactive reference markers in SPECT imaging of the dopamine system. *J Nucl Med Technol* 1999; 27: 112–116.
25. Snedecor GW, Cochran WG. Specific indices of interater reliability. In: Snedecor GW, Cochran WG, eds. *Statistical Methods, 6th ed.* Ames, IO; Iowa State University Press, 1989: 147–156.
26. Booij J, Habraken JBA, Bergmans P, Tissingh G, Winogrodzka A, Wolters EC, et al. Imaging of dopamine transporters with iodine-123-FP-CIT SPECT in healthy controls and patients with Parkinson's disease. *J Nucl Med* 1998; 39: 1879–1884.
27. Brooks DJ, Ibanez V, Sawle GV, Quinn N, Lees AJ, Mathias CJ, et al. Differing patterns of striatal ^{18}F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Ann Neurol* 1990; 28: 547–555.
28. Gibb WR. Neuropathology of Parkinson's disease and related syndromes. *Neurol Clin* 1992; 10: 361–376.
29. Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease: pathophysiologic and clinical implications. *N Engl J Med* 1988; 318: 876–880.
30. Ishikawa T, Dhawan V, Kazumata K, Chaly T, Mandel F, Meumeyer J, et al. Comparative nigrostriatal dopaminergic imaging with iodine-123-βCIT-FP/SPECT and fluorine-18-FDOPA/PET. *J Nucl Med* 1996; 37: 1760–1765.
31. Seibyl JP, Marek K, Sheff K, Zoghbi S, Baldwin RM, Charney DS, et al. Iodine-123-β-CIT and iodine-123-FPCIT SPECT measurement of dopamine transporters in healthy subjects and Parkinson's patients. *J Nucl Med* 1998; 39: 1500–1508.
32. Tissingh G, Booij J, Bergmans P, Winogrodzka A, Janssen AGM, van Royen EA, et al. Iodine-123-*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane SPECT in healthy controls and early-stage, drug-naive Parkinson's disease. *J Nucl Med* 1998; 39: 1143–1148.
33. Marek KL, Seibyl JP, Zoghbi SS, Zea-Ponce Y, Baldwin RM, Fussell B, et al. [^{123}I]β-CIT/SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. *Neurology* 1996; 46: 231–237.
34. Vingerhoets FJG, Snow BJ, Lee CS, Schulzer M, Mak E, Calne DB. Longitudinal fluorodopa positron emission tomographic studies of the evolution of idiopathic parkinsonism. *Ann Neurol* 1994; 36: 759–764.
35. Morrish PK, Sawle GV, Brooks DJ. An [^{18}F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. *Brain* 1996; 119: 585–591.
36. Ichise M, Ballinger JR, Golan H, Vines D, Luong A, Tsai S, Kung HF. Noninvasive quantification of dopamine D2 receptors with iodine-123-IBF SPECT. *J Nucl Med* 1996; 37: 513–520.