J Neurol (1998) 245 : 14–20

ORIGINAL COMMUNICATION

G. Tissingh
P. Bergmans
J. Booij
A. Winogrodzka
E. A. van Royen
J. C. Stoof
E. C. Wolters

Drug-naive patients with Parkinson's disease in Hoehn and Yahr stages I and II show a bilateral decrease in striatal dopamine transporters as revealed by [^{123}I]β-CIT SPECT

Received: 12 February 1997
Received in revised form:
12 September 1997
Accepted: 16 September 1997

G. Tissingh (✉) · P. Bergmans
A. Winogrodzka · J. C. Stoof
E. C. Wolters
Academisch Ziekenhuis Vrije Universiteit,
Department of Neurology,
De Boelelaan 1117,
1081 HV Amsterdam, The Netherlands
Tel.: +31-20 4442997,
Fax: +31-20 4442800

J. Booij · E. A. van Royen
Graduate School
for Neurosciences Amsterdam,
Department of Nuclear Medicine,
Academic Medical Centre,
University of Amsterdam, The Netherlands

Abstract Ten healthy subjects and 16 patients with early Parkinson's disease (PD) were examined with single photon emission computed tomography (SPECT) and [^{123}I]β-CIT, a ligand for the dopamine (DA) transporter. Only drug-naive patients were examined since the expression of and binding to DA transporters may be influenced by dopaminergic medication. The main finding was a significant reduction in [^{123}I]β-CIT binding in the ipsi- and contralateral striatal regions, especially in the putamen, which showed a mean reduction of 65% of the control mean. Discriminant function analysis of the putaminal [^{123}I]β-CIT binding measures classified 100% of the cases in the correct group. Disease severity correlated negatively and highly significantly with the binding measures. Tremor ratings did not correlate with the SPECT measures, whereas rigidity, and to a lesser extent bradykinesia, did. Patients with unilateral PD showed a bilateral loss of striatal DA transporters. Our findings indicate that with [^{123}I]β-CIT SPECT it is possible to diagnose PD in subjects with very mild symptoms and signs. Moreover, finding a bilateral loss of striatal DA transporters in patients with unilateral PD also suggests that it may be possible to identify subjects in the preclinical phase of the disease.

Key words Parkinson's disease · SPECT · Dopamine transporter · Cocaine analogues

Introduction

Parkinson's disease (PD) is a severe and progressive neurodegenerative disease with an insidious onset. The predominant neuropathological feature is a loss of dopaminergic cells in the substantia nigra, pars compacta and the ventral tegmental area. This results in a marked deficiency of striatal dopamine (DA) [2]. The main motor signs are bradykinesia, tremor, rigidity and postural instability. Postmortem studies have shown that the loss of DA cells in PD is accompanied by a decline in the striatal, presynaptic DA transporter, located on the nerve terminals of DA neurons projecting from the substantia nigra to the striatum [20]. Recently, ligands derived from cocaine have become available for imaging these presynaptic DA transporters in vivo by single photon emission computed tomography (SPECT) [6, 17, 28, 29]. One of these compounds, [^{123}I]β-CIT (2β-carbomethoxy-3β-(4-iodophenyl) tropane, has been shown to be especially useful in monitoring the dopaminergic degeneration of the nigrostriatal pathway in PD patients [17]. Although [^{123}I]β-CIT binds in vitro to DA transporters and to serotonin transporters with approximately equivalent affinity, Laruelle et al. [25] showed in primate studies that the in vivo striatal [^{123}I]β-CIT binding is specific for the DA transporter. This finding is consistent with the known relative density of DA to serotonin transporters in the striatum of > 10:1 [17].

Initial SPECT studies imaging the DA transporter with [^{123}I]β-CIT showed a severe loss of striatal DA transporters in PD, more pronounced in the putamen than in the caudate nucleus, compared with healthy human sub-

Table 1 Summary of [123I]β-CIT SPECT studies performed in Parkinson's disease (*Med* medication, *HY* Hoehn and Yahr Staging Scale, *UPDRS-mot* motor section of Unified Parkinson's Disease Rating Scale)

[a] Number of patients using levodopa, dopamine agonists or selegiline
[b] 18 patients stopped therapy 24 h before administration of the ligand or were untreated
[c] Total UPDRS score
[d] Mean age

Authors	Controls	Patients	Med	Age (years)	HY	UPDRS-mot
Asenbaum et al. [1]	13	47	–[b]	66 (median)	2.5	–
Brücke et al. [5]	4	2	2[a]	73.5[d]	4.5	–
Innis et al. [18]	5	5	5	56	2.1	21
Kuikka et al. [24]	2	2	0	76.5	–	–
Marek et al. [26]	8	8	3	61.8	1.2	14
Rinne et al. [30]	6	18	11	55.3	2.8	–
Seibyl et al. [31]	27	28	23	63	2.3	44[c]
Vermeulen et al. [33]	2	4	4	53	2.5	–
Present study	10	16	0	51.6	1.6	16.3

jects [5, 17, 18, 24]. More recent studies [1, 26, 30, 31, 33] have confirmed these findings.

Most patients included in these recent studies were showing a wide range of disease severity, with varying disease stages (Table 1). More importantly however, the patients examined in these studies were often receiving drugs acting on the dopaminergic system. This may lead to a change in the number of DA transporters as a result of alterations in the concentration of DA in the synaptic cleft and to a competition of endogenous DA or the active drug with the radioligand for the DA transporters.

The function of the DA transporter is to remove DA from the synaptic cleft, which is an important mechanism for the termination of dopaminergic neurotransmission. Therefore, the number of these DA transporters may be regulated by the level of synaptic DA, which would be consistent with the concept of synaptic homeostasis [36]. For instance, it has been reported that subchronic treatment with reserpine caused a significant decrease in the binding of the widely used dopamine transporter ligand GBR 12935 in rat and mouse striatum [12, 21]. Gordon et al. [12] also showed that amantadine caused a significant increase in GBR 12935 binding sites. Ikawa et al. [16] reported an up-regulation of [3H]mazindol binding sites in rat striatum after chronic levodopa treatment, whereas Gnanalingham and Robertson [11] found a decrease in [3H]mazindol binding after continuous, but not intermittent, infusion of levodopa. Others found no effect of levodopa treatment on DA transporter binding in rats or in mice [12, 27, 32].

Laruelle et al. [25] found an inhibitory effect upon acute administration of selegiline on the [3H] GBR 12935 binding in rat striatal slices, whereas infusion of high doses of levodopa failed to displace striatal [123I]β-CIT binding in non-human primates. It has also been shown that chronic administration of L-deprenyl induced an up-regulation of the [3H]mazindol-associated dopamine uptake carrier, probably partly being mediated directly by binding to the DA transporter [8, 34].

Thus, taking these data together, it is not unlikely that the expression of the DA transporter may be influenced by drugs modulating the synaptic DA level and that direct interactions between the dopaminergic drugs and the DA transporter occur. The use of these drugs may therefore be a considerable confounding factor when studying in vivo the number of DA transporters in humans and by inference the number of DA cells in the substantia nigra. Therefore, in the present study only drug-naive patients with PD were examined with [123I]β-CIT SPECT. The purpose was: (1) to examine the ability of [123I]β-CIT SPECT to discriminate patients with early PD from healthy controls and (2) to investigate the relationship between the binding measures and the nature and severity of the extrapyrimidal signs in early PD. In this way, we hoped to improve our understanding of the pathophysiology of PD and to define the value of this technique in diagnosing early PD.

Subjects and methods

Subjects

Sixteen early and drug-naive PD patients (8 men, 8 women) and ten healthy controls (4 men, 6 women) were examined, ranging in age from 32 to 64 years (mean 51.6, SD 9.5) and 20 to 65 years (mean 44.7, SD 16.9), respectively (Table 2). The patients were recruited from the Movement Disorders Unit of our outpatient clinic. PD was diagnosed according to the criteria of the UK Parkinson's Disease Society Brain Bank [15]. The patients were examined with the Hoehn and Yahr Staging Scale (HY) [13] and the Unified Parkinson's Disease Rating Scale (UPDRS) [7] to assess the stage and severity of illness. All patients showed a positive apomorphine challenge test (subcutaneously injected dose of 3 mg), defined as 20% reduction or more in the UPDRS motor score, strenghthening the diagnosis of PD [14]. The healthy volunteers were free of any neurological or psychiatric disease, and they were not taking drugs known to affect the dopaminergic system. All subjects gave written informed consent to the research protocol, which was approved by the Medical Ethical Committee of the hospital.

Methods

UPDRS

To study the relationship between the nature of the motor signs and the SPECT binding measures, we used the UPDRS motor

Table 2 Clinical data of 16 de novo patients with Parkinson's disease [*PD* Parkinson's disease, *Trem* tremor (maximum score = 16), *Rig* rigidity (maximum score = 20), *Brad* bradykinesia (maximum-score = 44)]

Patient	Age (years)	Sex	Duration PD (years)	HY	UPDRS	UPDRS-mot	Trem	Rig	Brad
1	54	M	0.5	1	21	13	1	2	8
2	53	F	2.5	1	13	8	0	1	7
3	34	M	3	1	25	17	1	5	10
4	32	M	2	1	31	15	0	4	10
5	51	F	4	2	46	27	0	3	21
6	64	F	3	2	36	17	3	3	9
7	53	M	4	2	38	22	0	4	17
8	48	M	2	2	25	17	0	4	11
9	44	F	2	2	40	22	0	6	12
10	58	F	6	1	35	20	0	4	13
11	61	M	3	2	29	20	1	5	12
12	45	F	5	2.5	21	13	1	4	7
13	48	M	2	1	27	20	1	4	14
14	61	M	3	2.5	21	12	1	3	5
15	57	F	1	1	17	11	3	0	8
16	62	F	0.5	1	9	6	0	1	5
Mean	51.6		2.7	1.6	27.1	16.3	0.75	3.3	10.6

scores on the three main extrapyramidal signs of PD: *bradykinesia* (the summed score of facial expression, finger taps, hand movements, pronation-supination of the hands, leg agility, arising from a chair and body bradykinesia); *rigidity* (rigidity of extremities and neck); and *tremor* (tremor of extremities).

SPECT procedure

For SPECT studies, a brain-dedicated SPECT system, the Strichman Medical Equipment 810X system, linked to a MacIntosh II (Apple) computer, was used. The Strichman camera consists of 12 individual crystals, each equipped with a focusing collimator. The transaxial resolution of this camera is 7.6 mm full-width at half-maximum (FWHM) of a line source in air [33]. The energy window was set at 135–190 keV. The subjects received potassium iodide before imaging in order to block thyroid uptake of free radioactive iodine. [^{123}I]β-CIT (specific activity of > 185 MBq/nmol; radiochemical purity of > 99%) was injected intravenously at an approximate dose of 110 MBq. ^{123}I labelling of β-CIT was performed by Amersham Cygne BV (Technical University Eindhoven, The Netherlands), using the trimethylstannyl precursor of β-CIT obtained from Research Biochemicals International (Natick, Mass., USA). SPECT image acquisition was performed 24 h after injection [18]. Slices were acquired during 300-s periods from the orbitomeatal line to the vertex with an interslice distance of 10 mm. Data acquisition took place in a 128 × 128 matrix. Attenuation, correction and reconstruction of the images were performed as earlier described [3, 4]. The measured concentration of radioactivity was expressed as Strichman Medical Units (SMUs; 1 SMU = 100 Bq/ml as specified by Strichman Medical Equipment Inc., Medfield, Mass., USA).

Data processing

For analysis of striatal [^{123}I]β-CIT binding, the ratio of specific to non-specific binding was calculated by summing two transversal slices representing the most intense striatal binding. The analyses were performed blind to the clinical data. A standard region of interest (ROI) template, constructed according to a stereotactic atlas and including regions for putamen, caudate nucleus and occipital cortex, and additional ROIs for the entire striatum, was placed bilaterally on the summed image, as earlier described [3]. Estimates of specific striatal binding were made by subtracting occipital counts from striatal counts. The ratio of specific to non-specific striatal [^{123}I]β-CIT binding was then calculated by dividing specific striatal uptake by occipital binding [31].

The binding measures were used:

1. To calculate ipsilateral to contralateral asymmetry of [^{123}I]β-CIT binding in putamen, caudate nucleus and striatum:
Asymmetry-index AI = (ipsilateral – contralateral)/(ipsilateral + contralateral)

2. To express the (ipsilateral and contralateral) relation between [^{123}I]β-CIT binding in putamen and caudate nucleus with the following index:
Putamen-caudate index (Pcidx) = (putamen – caudate)/(putamen + caudate)

Contralateral refers to the side opposite that of initial presentation of motor signs.

Statistics

Relationships between variables were measured with Spearman's rho. Analysis of variance (ANOVA), with age as a covariate, was used to compare the regional SPECT data in the PD patients and healthy controls. For healthy subjects, the mean striatal binding of left and right was used for all analyses. Multiple regression analysis was used to examine the relation between the [^{123}I]β-CIT binding measures and age, UPDRS motor score, bradykinesia, rigidity and tremor. The discriminative power of the binding measures was analysed with discriminant function analysis. All analyses were carried out with statistical software (SPSS version 5.0). Significance was assessed at the $P < 0.05$ level.

Results

There was no significant difference in age and gender between patients and controls. Within the PD group, 12 pa-

Table 3 [^{123}I]β-CIT SPECT measures of de novo patients with Parkinson's disease and healthy controls [*ipsi* ipsilateral, *contra* contralateral (side opposite that of initial presentation of motor signs), *AI* asymmetry-index, *Pcidx* putamen-caudate index]

SPECT data are expressed as follows: (binding in region of interest – binding in occipital cortex)/(binding in occipital cortex). Data are shown as mean (minimum-maximum). In the control group, ipsilateral is arbitrarily assigned to the left region.
* Significant difference compared with controls (all *P* values < 0.01). Bonferroni correction was used to allow for multiple testing

	Controls	PD group		
			HY = 1	HY = 2–2.5
	n = 10	*n* = 16	*n* = 8	*n* = 8
Putamen				
Ipsi	6.13 (3.67– 9.83)	2.43 (1.29–4.20)*	3.02 (1.88–4.20)*	1.84 (1.29–2.47)*
Contra	5.99 (3.67– 8.50)	1.82 (1.00–3.40)*	2.15 (1.13–3.40)*	1.48 (1.00–1.84)*
AI	0.01 (–0.05– 0.07)	0.14 (–0.03–0.29)*	0.18 (0.11–0.29)*	0.11 (–0.03–0.21)*
Caudate				
Ipsi	6.93 (4.78–10.17)	4.60 (2.48–7.93)*	5.54 (3.25–7.93)	3.66 (2.48–5.53)*
Contra	6.91 (5.25–10.33)	3.98 (2.04–6.87)*	4.86 (2.38–6.87)	3.10 (2.04–4.68)*
AI	0.00 (–0.09– 0.07)	0.08 (0.00–0.21)*	0.07 (0.02–0.21)*	0.09 (0.00–0.15)*
Striatum				
Ipsi	6.28 (4.11– 9.50)	3.08 (1.70–5.40)*	3.83 (2.38–5.40)*	2.33 (1.70–3.32)*
Contra	6.18 (4.11– 8.83)	2.51 (1.35–4.20)*	3.04 (1.50–4.20)*	1.99 (1.35–3.00)*
AI	0.00 (–0.04– 0.05)	0.10 (0.02–0.25)*	0.12 (0.05–0.25)*	0.08 (0.02–0.12)*
Pcidx				
Ipsi	–0.07 (–0.16– 0.01)	–0.31 (–0.45–0.22)*	–0.30 (–0.40–0.22)*	–0.33 (–0.45–0.24)*
Contra	–0.08 (–0.21– 0.02)	–0.36 (–0.55–0.21)*	–0.39 (–0.55–0.28)*	–0.34 (–0.44–0.21)*

Table 4 Results of discriminant function analyses in 16 de novo patients with Parkinson's disease and 10 healthy controls

	Predictors	λ	*F* ratio	*P* value	Classified correct
1	Putamen contra	0.24	74.4	< 0.0001	92%
2	Putamen ipsi	0.34	47.5	< 0.0001	100%
	Putamen contra	0.24	74.4	< 0.001	
3	Caudate contra	0.51	22.7	< 0.001	85%
4	Caudate ipsi	0.64	13.7	< 0.01	92%
	Caudate contra	0.51	22.7	< 0.01	
5	Striatum contra	0.30	55.1	0.0001	92%
6	Striatum ipsi	0.42	33.6	< 0.0001	100%
	Striatum contra	0.30	55.1	< 0.0001	

tients had initial right-sided motor signs and 4 patients left-sided onset (patients 1, 2, 11 and 13; Table 2).

SPECT data: patients versus controls

Three patients showed overlap with the control subjects on the SPECT data of the ipsilateral putamen, seven (ipsilateral) and four (contralateral) patients on the SPECT data of the caudate nucleus, and four (ipsilateral) and one (contralateral) patient(s) on the data of the entire striatum. The ratios of specific to non-specific [^{123}I]β-CIT binding in all studied regions are shown in Table 3. The mean ratios in these 6 regions were significantly lower in the patient compared with the control group [all *P* values < 0.01 (ANOVA with age as covariate)], being lower at the contralateral side (*P* values < 0.001, Wilcoxon Signed Rank test). The reduction of [^{123}I]β-CIT binding in the putamen was ipsilateral 60% and contralateral 70%, whereas the decrease in the caudate nucleus was lower, being 34% and 42% of the control mean, respectively. When only the patients with unilateral PD (HY = 1, *n* = 8) were compared with the healthy controls, the striatal binding measures were significantly reduced bilaterally in the patient compared with the control group (ipsilateral: $P = < 0.001$, $r^2 = 0.75$; contralateral: $P < 0.001$, $r^2 = 0.80$). When the putamen and caudate nucleus were considered as two distinct striatal regions, the ipsi- and contralateral caudate nuclei were not significantly decreased in the patients compared with the controls.

The AI's for putamen, caudate, and striatum were significantly higher in the patient group compared with the controls (putamen: $P < 0.001$, $r^2 = 0.61$; caudate: $P < 0.001$, $r^2 = 0.50$; striatum: $P < 0.001$, $r^2 = 0.57$). The putamen-caudate indices were higher on the ipsi- as well as on the contralateral sides in the control group ($P < 0.001$, $r^2 = 0.80$ and 0.78, respectively).

Discriminant analysis

The results of the discriminant function analysis, utilizing the SPECT data of the studied brain regions, are shown in Table 4 and Fig. 1. Classification was 100% correct with the contra- and ipsilateral putamen or striatum as predictors as well as with the overall putamen-caudate index (*F* ratio = 87.2, Wilks' lambda = 0.22, $P < 0.0001$). The AI for putamen and caudate nuclei predicted group membership in 92% of the cases.

Disease severity and SPECT

A clear and significant negative correlation was found between the UPDRS total[a] and motor[b] scores and the [^{123}I]β-

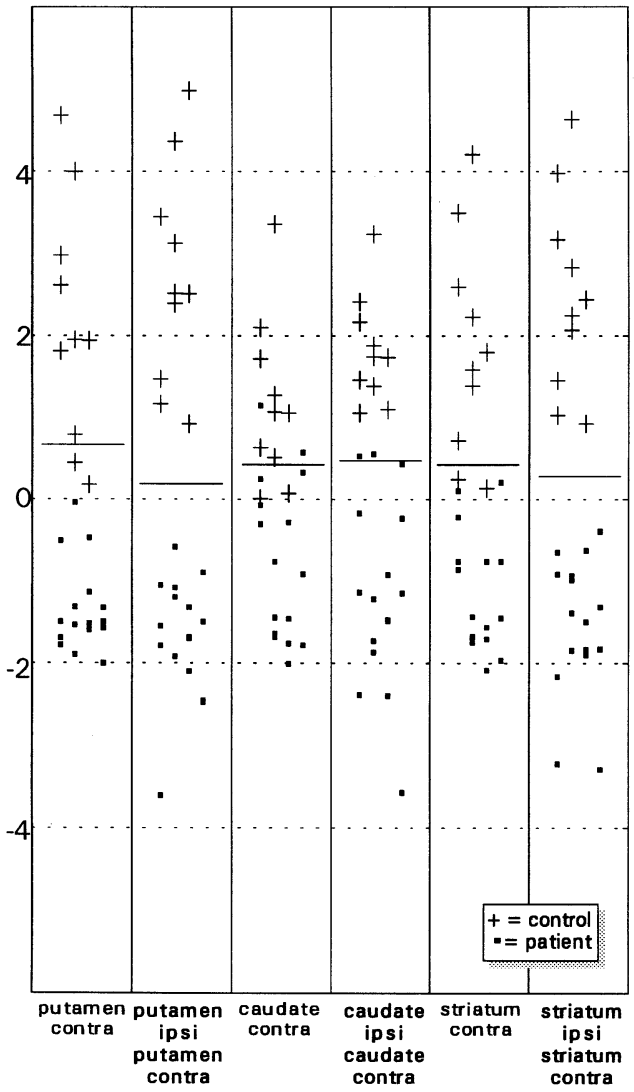

Fig. 1 Application of discriminant analyses to 16 de novo patients with PD and 10 healthy controls, with different predictors. Individual discriminant scores are shown

CIT binding in the entire putamen [[a]: $r = -0.69$ ($P = 0.001$), [b]: $r = -0.71$ ($P < 0.01$)], caudate nucleus ([a]: $r = -0.81$ ($P < 0.001$), [b]: $r = -0.89$ ($P < 0.001$)] and striatum ([a]: $r = -0.79$ ($P < 0.001$), [b]: $r = -0.81$ ($P < 0.001$)]. No significant correlations could be detected between age and disease duration, and UPDRS motor score (Table 5). Multiple regression analysis was performed with the binding measures of the putamen, caudate nucleus and striatum as dependent variables, and with age and UPDRS motor score as independent variables. Disease severity accounted for a great and highly significant part of the variance in the studied regions (*putamen*: r^2: 0.51; β-age: nonsign; β-UPDRS: –0.66; *caudate nucleus*: r^2: 0.81; β-age: –0.34; β-UPDRS: –0.90; *striatum*: r^2: 0.70; β-age: –0.39; β-UPDRS: –0.82).

Patients with unilateral signs showed significantly higher [^{123}I]β-CIT binding ratios for all studied striatal regions (except the contralateral putamen) than subjects in a more advanced stage of PD with bilateral extrapyramidal signs, being comparable in age and UPDRS motor scores (Table 3).

Nature of motor signs and SPECT

The correlations between the main motor signs and the striatal [^{123}I]β-CIT binding measures are shown in Table 5. Tremor, in contrast to bradykinesia and rigidity, is not correlated with the UPDRS motor score and the SPECT measures. Multiple regression analysis was performed with the striatal [^{123}I]β-CIT binding (ipsi- and contralateral) as dependent variable, and with age, bradykinesia, rigidity and tremor as independent variables (Table 6).

It appeared that the majority of the variability in striatal [^{123}I]β-CIT binding can be explained by variation in rigidity, age and bradykinesia, the last of these accounting for the smallest part. Adding tremor as an independent variable did not change the proportion of the total variation explained (r^2) by the regression model. The residuals and all variables used in the model did show normal distribution.

Discussion

This is the first reported extensive study in early PD examining only drug-naive patients with [^{123}I]β-CIT SPECT. By doing this, we have excluded the possible confounding influence of dopaminergic drugs on the striatal [^{123}I]β-CIT binding. We have shown that early and drug-naive patients with PD can be clearly distinguished from healthy controls with [^{123}I]β-CIT SPECT. The reduction in [^{123}I]β-CIT binding was more pronounced in the putamen than in the caudate nucleus, and greater in

Table 5 Correlation coefficients between age, disease variables and striatal (*Str*) [^{123}I] β-CIT binding

	Str ipsi	Str contra	Age	Brad	Rig	Trem
Age	–0.14	0.01				
Brad	–0.61*	–0.72**	–0.29			
Rig	–0.46	–0.58*	–0.52**	0.54**		
Trem	0.11	0.13	0.30	–0.31	–0.16	
UPDRS-mot	–0.79**	–0.86**	–0.27	0.94**	0.66**	–0.25

* $P < 0.05$; ** $P < 0.01$

Table 6 Data of multiple regression analysis in patients

Dependent variable	Independent variables	Adjusted r^2 ($P <$)	Sign F	Beta ($P <$)	Sign t
Striatum ipsi		0.75	0.001		
	Age			–0.68	0.001
	Brad			–0.33	0.05
	Rig			–0.76	0.001
Striatum contra		0.81	0.0001		
	Age			–0.62	0.001
	Brad			–0.33	0.05
	Rig			–0.82	0.001

the regions contralateral to that of initial presentation of motor signs, which confirms postmortem [9, 10, 22] and in vivo findings by others [1, 26, 31]. Our data show a decrease in putaminal [^{123}I]β-CIT binding of 60% and 70% of the control mean, and in the caudate nucleus of 34% and 42%, ipsi- and contralateral, respectively. These percentages are somewhat different from those found by Seibyl et al. [31] (putamen: 65% and 75%; caudate nucleus: 49% and 59%), and Innis et al. [18] (putamen: 76%; caudate nucleus: 58%), probably because of a difference in disease severity and possibly also owing to alterations in the number of DA transporters after prolonged treatment with dopaminergic drugs.

It appeared that discriminant function analysis of the binding measures of the ipsi- and contralateral putamen classified 100% of the cases in the correct group. The contralateral putamen did show the greatest discriminative power. Thus, our findings indicate that it is possible to discriminate healthy subjects from PD patients very well in the earliest stage of the disease using only the SPECT measures of the putamen.

Interestingly, the striatal binding measures of the patients with unilateral PD (HY = 1) were significantly reduced bilaterally compared with those of the controls. We found a significant reduction in striatal binding amounting to 39% on the ipsilateral side. Finding an ipsilateral loss of striatal DA transporters in unilateral, drug-naive PD strongly indicates that with [^{123}I]β-CIT SPECT it is possible to identify patients in the preclinical phase of the disease, which may be a long period [23]. Others have reported similar findings in unilateral PD patients, who were, however, not all drug-naive [1, 26]. Their findings and ours emphasize the importance of investigations aimed at the discovery of preclinical signs that can help to identify subpopulations having an increased risk of the development of PD.

In the present study, highly significant, negative correlations were found between disease severity and the binding measures of the studied regions. We also found significantly higher ratios in patients with HY stage 1 compared with patients with HY stage 2 or 2.5. These findings support the results of earlier studies demonstrating significant correlations between [^{123}I]β-CIT SPECT binding measures and symptom severity [1, 31], and the disability stage of PD [30]. Of interest is the lack of correlation between tremor scores and SPECT, whereas rigidity, and to a lesser extent bradykinesia, explained a significant part of the variability in striatal [^{123}I]β-CIT SPECT binding. With respect to tremor, 8 out of 16 patients have a tremor score equivalent to 0 (Table 2), producing a distribution which is skewed to the right. Seibyl et al. [31] also found no correlation between [^{123}I]β-CIT SPECT binding and tremor ratings. This, and the absence of a correlation of tremor with the other motor signs, raises the question of whether the neuropathological and biochemical basis of tremor is different from that of rigidity and bradykinesia, which has been suggested earlier [2, 19, 35].

In summary, with [^{123}I]β-CIT SPECT it is now possible to discriminate drug-naive patients with early PD from healthy subjects very well, the putamenal binding measures showing the greatest discriminative power. Subjects with very mild motor symptoms and signs that do not yet fulfill the criteria for PD, but who are suspected of having the disease may be diagnosed earlier with [^{123}I]β-CIT SPECT. Disease severity correlated negatively and highly significantly with the binding measures of the putamen, caudate nucleus and the striatum. Tremor ratings did not correlate with the SPECT measures, whereas rigidity and bradykinesia did. A bilateral loss of striatal [^{123}I]β-CIT binding was found in patients with unilateral motor symptoms and signs, indicating that in the future it may be possible to detect the dopaminergic deficit in preclinical PD, offering many opportunities regarding new neuropharmacological therapy.

Acknowledgements A. Winogrodzka was supported by a grant from NWO-MW, Den Haag, The Netherlands (number 49–093).

References

1. Asenbaum S, Brücke T, Pirker W, et al (1997) Imaging of dopamine transporters with iodine-123-β-CIT and SPECT in Parkinson's Disease. J Nucl Med 38:1–6
2. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F (1973) Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J Neurol Sci 20:415–455
3. Booij J, Tissingh G, Winogrodzka A, et al (1997) Practical benefit of [^{123}I]FP-CIT SPECT in the demonstration of the dopaminergic deficit in Parkinson's disease. Eur J Nucl Med 24:68–71

4. Booij J, Tissingh G, Boer GJ, et al (1997) [^{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 62: 133–140
5. Brücke T, Kornhuber J, Angelberger P, Asenbaum S, Frassine H, Podreka I (1993) SPECT imaging of dopamine and serotonin transporters with [^{123}I]β-CIT. Binding kinetics in the human brain. J Neural Transm Gen Sect 94: 137–146
6. Carroll FI, Scheffel U, Dannals RF, Boja JW, Kuhar MJ (1995) Development of imaging agents for the dopamine transporter. Med Res Rev 15: 419–444
7. Fahn S, Elton RL, and members of the UPDRS Development Committee (1987) Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M (eds) Recent developments in Parkinson's disease. Macmillan Healthcare Information, Florham Park, N.J., pp 153–163
8. Fang J, Yu PH (1994) Effect of L-deprenyl, its structural analogues and some mono-amine oxidase inhibitors on dopamine uptake. Neuropharmacology 33: 763–768
9. Fearnley JM, Lees AJ (1991) Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114: 2283–2301
10. Gibb WRG, Lees AJ (1991) Anatomy, pigmentation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in Parkinson's disease. J Neurol Neurosurg Psychiatry 54: 388–396
11. Gnanalingham KK, Robertson RG (1994) The effects of chronic continuous versus intermittent levodopa treatments on striatal and extrastriatal D_1 and D_2 dopamine receptors and dopamine uptake sites in the 6-hydroxydopamine lesioned rat – an autoradiography study. Brain Res 640: 185–194
12. Gordon I, Weizman R, Rehavi M (1996) Modulatory effect of agents active in the presynaptic dopaminergic system on the striatal dopamine transporter. Eur J Pharmacol 298: 27–30
13. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression, and mortality. Neurology 17: 427–442
14. Hughes A, Lees AJ, Stern GM (1990) Apomorphine test to predict dopaminergic responsiveness in parkinsonian syndromes. Lancet 336: 32–34
15. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55: 181–184
16. Ikawa K, Watanabe A, Kaneno S, Toru M (1993) Modulation of [^{3}H]mazindol binding sites in rat striatum by dopaminergic agents. Eur J Pharmacol 250: 261–266
17. Innis RB (1994) Single-photon emission tomography imaging of dopamine terminal innervation: a potential clinical tool in Parkinson's disease. Eur J Nucl Med 21: 1–5
18. Innis RB, Seibyl JP, Scanley BE, et al (1993) Single photon emission computed tomographic imaging demonstrates loss of striatal dopamine transporters in Parkinson's disease. Proc Natl Acad Sci USA 90: 11965–11969
19. Jankovic J, McDermott M, Carter J, et al (1990) Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. Neurology 40: 1529–1534
20. Kaufman MJ, Madras BK (1991) Severe depletion of cocaine recognition sites associated with the dopamine transporter in Parkinson's disease striatum. Synapse 9: 43–49
21. Kilbourn MR, Sherman PS, Pisani T (1992) Repeated reserpine administration reduces in vivo [^{18}F]GBR 13119 binding to the dopamine uptake site. Eur J Pharmacol 216: 109–112
22. Kish SJ, Shannak K, Hornykiewics O (1988) Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. N Engl J Med 318: 876–880
23. Koller WC, Langston JW, Hubble JP, et al (1991) Does a long preclinical period occur in Parkinson's disease? Neurology 41 [Suppl 2]: 8–13
24. Kuikka JT, Bergström KA, Vanninen E, Laulumaa V, Hartikainen P, Länsimies E (1993) Initial experience with single-photon emission tomography using iodine-123-labelled 2β-carbomethoxy-3β-(4-iodophenyl)tropane in human brain. Eur J Nucl Med 20: 783–786
25. Laruelle M, Baldwin RM, Malison RT, et al (1993) SPECT imaging of dopamine and serotonin transporters with [^{123}I]β-CIT: pharmacological characterization of brain uptake in nonhuman primates. Synapse 13: 295–309
26. Marek KL, Seibyl JP, Zoghbi SS, et al (1996) [^{123}I]β-CIT/SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. Neurology 46: 231–237
27. Moody CA, Granneman JG, Bannon MJ (1996) Dopamine transporter binding in rat striatum and nucleus accumbens is unaltered following chronic changes in dopamine levels. Neurosci Lett 217: 55–57
28. Neumeyer JL, Wang S, Millius RA, et al (1991) [^{123}I]-2β-Carbomethoxy-3β-(4-iodophenyl)tropane: high-affinity SPECT radiotracer of monoamine reuptake sites in brain. J Med Chem 34: 3144–3146
29. Neumeyer JL, Wang S, Gao Y, et al (1994) N-Ω-Fluoroalkyl analogs of (1R)-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 37: 1558–1561
30. Rinne JO, Kuikka JT, Bergström KA, Rinne UK (1995) Striatal dopamine transporter in different disability stages of Parkinson's disease studied with [^{123}I]β-CIT SPECT. Parkinsonism Rel Disord 1: 47–51
31. Seibyl JP, Marek KL, Quinlan D, et al (1995) Decreased single-photon emission computed tomographic [^{123}I]β-CIT striatal uptake correlates with symptom severity in Parkinson's disease. Ann Neurol 38: 589–598
32. Vaugeois J-M, Bonnet J-J, Costentin J (1990) Relationship between the effects of dexamphetamine on locomotion and on striatal [^{3}H]GBR 12783 binding in vivo. Eur J Pharmacol 178: 221–227
33. Vermeulen RJ, Wolters ECh, Tissingh G, et al (1995) Evaluation of [^{123}I]β-CIT Binding with SPECT in controls, early and late Parkinson's disease. Nucl Med Biol 22: 985–991
34. Wiener HL, Hashim A, Lajtha A, Sershen H (1989) Chronic L-deprenyl- induced up-regulation of the dopamine uptake carrier. Eur J Pharmacol 163: 191–194
35. Zetusky WJ, Jankovic J, Pirozzolo FJ (1985) The heterogeneity of Parkinson's disease: clinical and prognostic implications. Neurology 35: 522–526
36. Zigmond MJ, Abercrombie ED, Berger TW, Grace AA, Stricker EM (1990) Compensations after lesions of central dopaminergic neurons: some clinical and basic implications. Trends Neurosci 13: 290–296