[^{123}I]FP-CIT SPECT shows a pronounced decline of striatal dopamine transporter labelling in early and advanced Parkinson's disease

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Abstract

Objectives—The main neuropathological feature in Parkinson's disease is a severe degeneration of the dopaminergic neurons in the substantia nigra resulting in a loss of dopamine (DA) transporters in the striatum. [^{123}I]β-CIT single photon emission computed tomography (SPECT) studies have demonstrated this loss of striatal DA transporter content in Parkinson's disease in vivo. However, studies with this radioligand also showed that an adequate imaging of the striatal DA transporter content could only be performed on the day after the injection of radioligand, which is not convenient for outpatient evaluations. Recently, a new radioligand [^{123}I]FP-CIT, with faster kinetics than β-CIT, became available for imaging of the DA transporter with SPECT, and the applicability of this ligand was tested in patients with early and advanced Parkinson's disease, using a one day protocol.

Methods—[^{123}I]FP-CIT SPECT was performed in six patients with early and 12 patients with advanced Parkinson's disease, and in six age matched healthy volunteers.

Results—Compared with an age matched control group striatal [^{123}I]FP-CIT uptake in patients with Parkinson's disease was decreased, and this result was measurable three hours after injection of the radioligand. In the Parkinson's disease group the uptake in the putamen was reduced more than in the caudate nucleus. The contralateral striatal uptake of [^{123}I]FP-CIT was significantly lower than the ipsilateral striatal uptake in the Parkinson's disease group. Specific to non-specific striatal uptake ratios correlated with the Hoehn and Yahr stage. A subgroup of patients with early Parkinson's disease also showed significantly lower uptake in the putamen and lower putamen:caudate ratios than controls.

Conclusion—[^{123}I]FP-CIT SPECT allows a significant discrimination between patients with Parkinson's disease and age matched controls with a one day protocol, which will be to great advantage in outpatient evaluations.

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Parkinson's disease is a severe, progressive neurodegenerative disorder which is neuropathologically characterised by a degeneration of the dopamine (DA) containing cells in the substantia nigra.[1] As a result of this cell loss, there is a substantial decrease in the DA content of the striatum, and a corresponding loss of DA transporters.[2][3] The striatum is the main output region of the substantia nigra.[3]

Single photon emission computed tomography (SPECT) and PET provide unique opportunities of examining DAergic systems in the human brain in vivo. Visualisation of the DA transporter with various ligands in SPECT and PET imaging has been introduced as a valuable tool for the in vivo evaluation of the integrity of the nigrostriatal DAergic pathway in Parkinson's disease. PET studies with ^{11}C-labelled nomifensine have discriminated between groups of patients with Parkinson's disease and healthy volunteers.[4-6] Recently, radiolabelled cocaine-like ligands for in vivo imaging of the DA transporter were introduced. In particular, SPECT with the ^{123}I-labelled cocaine analogue β-CIT (or RTI-55) showed a dramatic loss of striatal DA transporters in patients with Parkinson's disease with high signal to noise ratios.[7-10] PET in Parkinson's disease, using the ^{11}C-labelled cocaine analogue WIN 35 428 (or β-CFT), showed much lower signal to noise ratios, although patients could clearly be discriminated from controls.[11][12] The use of [^{11}C]β-CIT in PET imaging failed to significantly discriminate between small groups of patients with early Parkinson's disease and healthy controls.[12]

Uptake of [^{123}I]β-CIT in the human striatum is characterised by very slow kinetics, which is a serious drawback. Radioactivity in the striatum increases for 20 hours after injection of this radioligand, and stabilises thereafter up to 30 hours. The stable level of radioactivity between 20 and 30 hours satisfies conditions of prolonged equilibrium.[13] However, this indicates that an image acquisition should be performed on the day after the injection, which is not convenient for outpatient evaluation. Moreover, it is not optimal for counting statistics as the half life of ^{123}I is about 13 hours.

N-ω-fluoroalkyl analogues of β-CIT have

recently been synthesised in an effort to produce ligands for the DA transporter with faster kinetics than for β-CIT.[14-16] This may provide the ability to perform an adequate image acquisition on the day of the injection of the radioligand. One of these new compounds, N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane)(FP-CIT), has been labelled with ^{123}I for SPECT or with ^{11}C for PET.[15 17] [^{123}I]FP-CIT (or β-CIT-FP) has been tested in baboons and humans as a tracer for the DA transporter.[14 15 18 19] These studies showed high brain uptake, faster kinetics than for β-CIT, an early peak in striatal specific activity (several hours postinjection), and high striatal to occipital cortex ratios (high target to non-target ratios). In addition, in vivo displacement studies in the monkey showed that striatal uptake of [^{11}C]FP-CIT was primarily due to DA transporter labelling.[17] Thus [^{123}I]FP-CIT is a promising SPECT probe for measuring DA transporters in living human brain non-invasively.

The aim of the present study was to investigate if the striatal DA deficiency of Parkinson's disease could be demonstrated using [^{123}I]FP-CIT, and whether this new radioligand is able to discriminate presynaptic DAergic hypofunction in patients with early Parkinson's disease from that in age matched healthy controls by using a one day protocol.

Subjects and methods

SUBJECTS

Six healthy controls and 18 patients with clinically established Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank criteria,[20] were selected (table 1). The controls were healthy volunteers with no evidence of a neurological or a psychiatric disease. The controls were age matched (mean age 57·5, range 44–83 years) with the group of patients with Parkinson's disease (mean age 60·8, range 40–77 years) because [^{123}I]β-CIT

SPECT investigations in healthy human subjects showed reductions of tracer uptake with increasing age, compatible with postmortem findings of DA transporter loss.[21 22]

A neurological examination of the patients was performed (by GT and JDS) to assess the severity of motor signs according to the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS),[23] and the scores ranged from 8 to 55. The stage of illness was determined from the Hoehn and Yahr staging scale,[24] and ranged from I to IV. In patients with severe on/off fluctuations, the motor signs were scored during the worst off period (defined according to Langston *et al*[25]; table 1). The highest values, both for the Hoehn and Yahr scale and the UPDRS, were found in five patients with Parkinson's disease with on/off fluctuations. At the time of the SPECT experiments the patients under DAergic medication used either only levodopa or both levodopa and DA receptor agonists (table 1).

The medical ethics committee gave permission for the study. All participants gave written informed consent.

METHODS

SPECT camera and reconstruction

For the SPECT a brain dedicated SPECT system, the Strichman Medical Equipment 810X 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 of a line source in air (FWHM), and the axial resolution is 13·5 mm FWHM. The energy window was set at 135–190 keV. Data acquisition took place in a 128 × 128 matrix. A linear attenuation correction, based on an absorption length of 95 mm, was applied in all studies. The attenuation elliptic contour corresponded to the diameter of the skull, as automatically estimated by the software. The images were automatically reconstructed with a variable fil-

Table 1 Details of patients and controls

No	Sex	Age (y)	Duration of PD (y)	Onset L/R	Hoehn and Yahr stage	Motor UPDRS	Drugs (mg/day) D	P	B
				Controls					
1–6	2M; 4F	Mean 58 Range (44–83)	—	—	—	—	—	—	—
				Patients with PD					
7	F	65	4	R	1·5	19	200	0·75	—
8	M	76	2	L	1·5	11	50	—	—
9	M	68	4·5	R	2	17	400	2	—
10	F	68	3	R	1·5	19	150	1·5	—
11	M	57	5	R	2	10	300	1·5	—
12	F	64	2·5	R	2	14	—	—	—
13	M	69	2	L	2·5	32	—	—	—
14	F	45	3	R	1	8	—	—	—
15	F	46	2	R	1	15	—	—	—
16	M	54	13	L	2	28	150	15†	3
17	F	58	5	R	2	18	75	—	—
18	M	46	2	R	1	10	—	—	—
19	M	40	5	R	3	39	—	—	—
20	M	71	21	L	4‡	31‡	1250	4	—
21	M	77	23	L	4‡	51‡	700	4·5	—
22	F	63	15	R	4‡	40‡	300	3·5	—
23	M	71	25	L	4‡	39‡	375	2·25	—
24	M	57	17	L	4‡	55‡	1400	4·5	—

PD = Parkinson's disease; Motor UPDRS = motor section of the unified Parkinson's disease rating scale; L = left; R = right; D = levodopa; P = pergolide; B = biperideen.
*Retrospectively determined onset of parkinsonian signs.
†This subject received bromocriptine instead of pergolide.
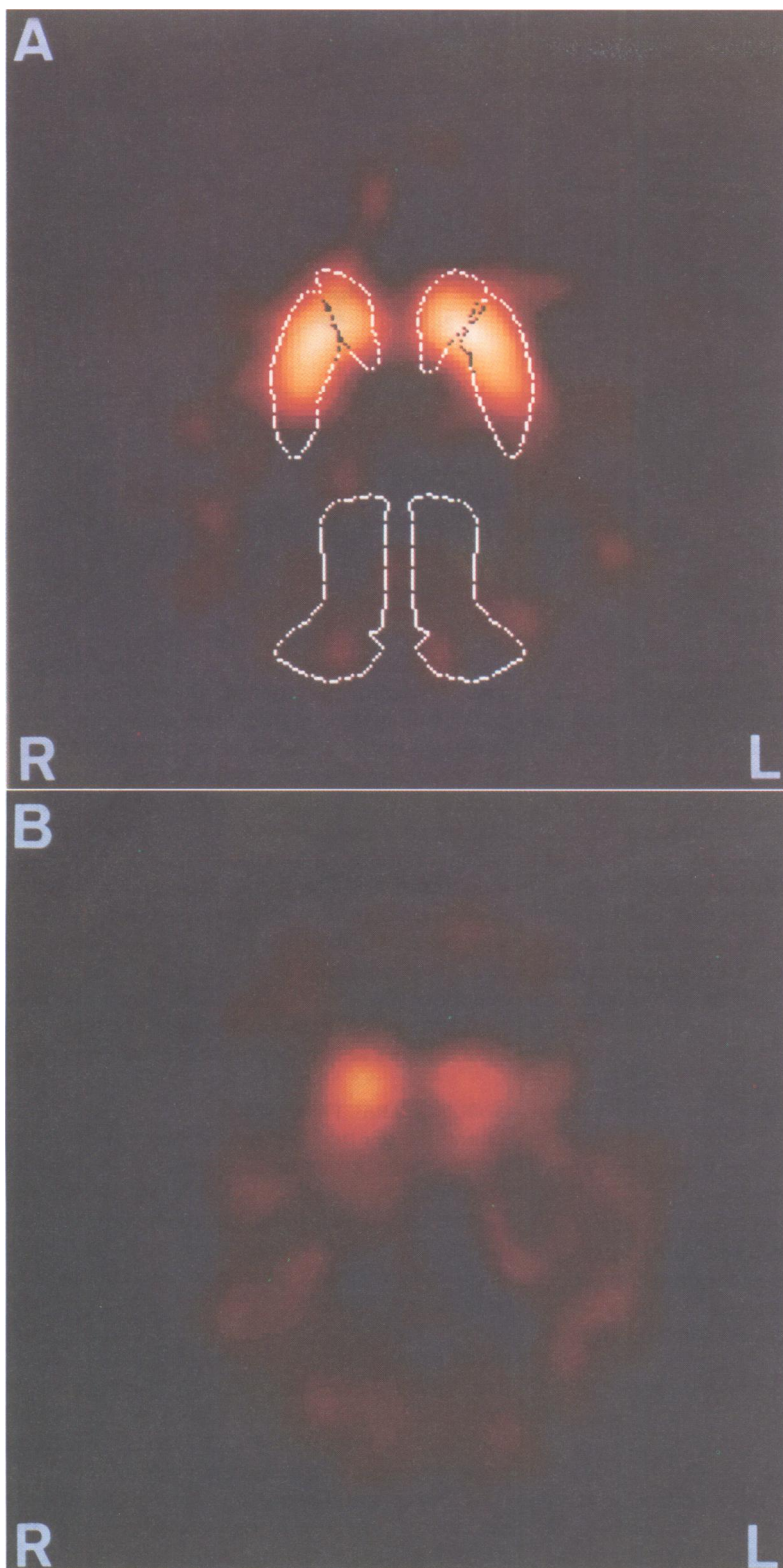‡Worst off values.

Figure 1   [¹²³I]FP-CIT   SPECT images of a healthy volunteer (A) and a patient with Parkinson's disease (B). Transverse slices from the brain at the level of the striatum (about 3 cm above the orbitomeatal line) (L = left side and R = right side). In both images the level of [¹²³I]FP-CIT activity is colour encoded from low (black) via medium (yellow) to high (white) and scaled (corrected for injected dose/kg) to the maximum in the slice of the control person (maximum is 116 SMU). (A) 66 year old healthy woman, regions of interest placed in right and left caudate and putamen and occipital cortex; (B) 64 year old woman with Parkinson's disease, Hoehn and Yahr stage II (patient 12, table 1).

ter, according to the level of counts per slice. The measured concentration of radioactivity was expressed as Strichman Medical Units (SMUs; 1 SMU = 100 Bq/ml as specified by Strichman Medical Equipment Inc).

SPECT experiments

All subjects received potassium iodide (total about 266 mg) orally to block thyroid uptake of free radioactive iodine. After intravenous injection of 71–126 MBq [¹²³I]FP-CIT, tomographic SPECT studies were performed (specific activity > 93 MBq/nmol; radiochemical purity > 99%; ¹²³I labelling by Amersham Cygne BV, Technical University Eindhoven, The Netherlands, using the trimethylstannyl precursor of FP-CIT obtained from Research Biochemicals International, Natick, USA). On the basis of dosimetry studies performed in humans, the effective dose equivalent of [¹²³I]FP-CIT was estimated to be 0·03 mSv/MBq.[19]

Pilot time course study

A pilot time course study, in one healthy volunteer and in two patients with Parkinson's disease, was performed to determine the optimal time postinjection for in vivo DA transporter imaging with ¹²³I FP-CIT. For this purpose single slice dynamic SPECT (150–180 s/slice) was performed at the level of the basal ganglia (orbitomeatal line + 30 mm dorsally) between 0–60 minutes after injection This was followed by multislice SPECT at two, three, and four hours postinjection (for the volunteer also at five hours postinjection) starting at and parallel to the orbitomeatal line (300 s/slice; interslice distance 10 mm; 12 slices or less). The optimum time of acquisition was defined as the time at which specific radioactivity in the striatum (total striatal counts minus counts in the occipital cortex) was at a stable level. The activity in the occipital cortex was defined as non-specific activity, as the occipital cortex is a region nearly devoid of DA transporters.[26] On the basis of this pilot study (see results) further tomographic acquisitions were taken at three hours after the injection of [¹²³I]FP-CIT. For the groups of healthy volunteers and patients with Parkinson's disease, 12 slices or less, starting at and parallel to the orbitomeatal line were acquired (one slice at a time; 300 s/slice) with an interslice distance of 10 mm.

Data processing

For analysis of striatal [¹²³I]FP-CIT binding, the slice with the highest activity was selected and a standard template, with regions of interest constructed manually according to a stereotactic atlas,[27] was applied (fig 1). Small variations of individual brains required movement of the fixed regions of interest, without changing size and shape, within the template for optimal fitting. Specific to non-specific [¹²³I]FP-CIT binding was then calculated as

$$[^{123}\text{I}]\text{FP-CIT Binding} = \frac{(\text{ROI} - \text{OCC})}{\text{OCC}}$$

in which ROI represents the mean radioactivity (in SMU) in the region of interest (striatum, putamen, or caudate nucleus) and OCC depicts the mean radioactivity in the occipital cortex. This method assumes equal non-specific uptake in the striatum and occipital cortex. In previous studies this binding ratio

Figure 2 Radioactivity in the striatum (▼), occipital cortex (▲), and specific striatal radioactivity (◆) from 0–240 minutes after injection of [^{123}I]FP-CIT. (A) healthy volunteer (data 300 minutes after injection not shown); (B) patient with Parkinson's disease.
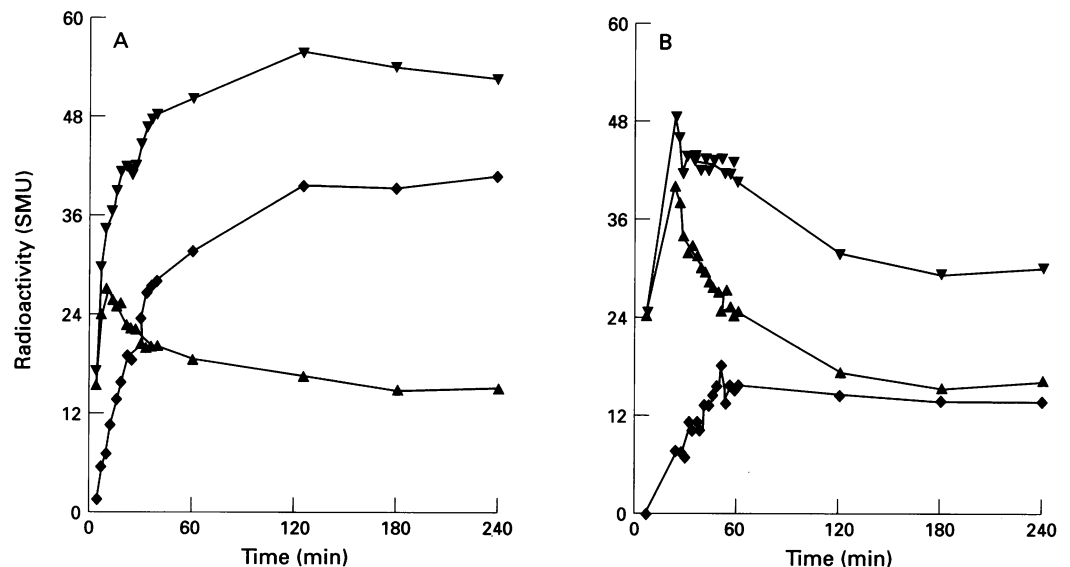
proved to be a reliable estimate of the so-called binding potential (B_{max}/K_D).[13 28 29] These binding values were also used to calculate putamen:caudate nucleus ratios for the ipsilateral and contralateral striatum.

In the patients with Parkinson's disease, the contralateral striatum was defined as the side opposite that of initial presentation of motor signs. For the control subjects, contralateral was arbitrarily assigned to the left striatum. The binding values were used to calculate relative ipsilateral to contralateral asymmetry of tracer uptake based on the following formula:

$$\text{Asymmetry index} = \frac{\text{ipsilateral} - \text{contralateral}}{(\text{ipsilateral} - \text{contralateral})/2} \times 100$$

For statistical analysis the non-parametric Mann-Whitney rank sum test (IN-STAT™) was used. For analysis of the difference in uptake ratios between ipsilateral and contralateral sides within groups the non-parametric Wilcoxon paired test was used. All tests were two tailed with the accepted level of significance at $P \leqslant 0.05$.

Results

PILOT TIME COURSE STUDY

There were no subjective or objective adverse reactions in any subject after injection of [^{123}I]FP-CIT. The time course of uptake in the brain of the healthy volunteer showed a gradual accumulation of radioactivity in the striatum during the first two hours after injection, with a stable level of activity until the end of the study. Radioactivity in the occipital cortex accumulated rapidly but started to decline after 15 minutes, with a stable level of activity 60 minutes after injection until the end of the study (fig 2). Specific striatal radioactivity reached a plateau at about two hours after injection and remained stable until four hours after injection. The time period between two and four hours after injection was therefore considered as a period of pseudoequilibrium.

The striatal uptake in the brain of the patients with Parkinson's disease showed an initial peak, but also a stable level of radioactivity from two hours after injection onwards (fig 2). Radioactivity in the occipital cortex started to decline after 15 minutes, with a stable level of activity after two hours until end of the study. A similar pattern of specific striatal radioactivity was found for the patients with Parkinson's disease compared with the volunteer: a plateau was reached about 60 minutes after injection and remained stable until four hours after injection (fig 2). Therefore, the optimal time for in vivo DA transporter imaging with ^{123}I-FP-CIT was set at three hours after injection.

GROUP CHARACTERISTICS

There were no significant age differences between the controls and groups of patients with Parkinson's disease (table 1). Within the Parkinson's disease group, seven patients had initial left sided motor signs, 11 had right sided onset (mean duration of disease 8·6; range 2 to 25 years).

SPECT MEASURES

For all six regions measured (ipsilateral striatum, contralateral striatum, ipsilateral caudate, contralateral caudate, ipsilateral putamen, and contralateral putamen) significant lower uptake ratios were found for the Parkinson's disease group compared with the control group (P < 0·01, table 2, fig 1). Within the control group there were no significant differences between the ipsilateral and contralateral uptake ratios for the striatum, caudate nucleus, and putamen. However, within the Parkinson's disease group the contralateral uptake ratios were significantly lower than the ipsilateral uptake ratios for the same three regions (table 2). Overall average of the asymmetry index was higher in Parkinson's disease compared with controls for the putamen ((mean (SEM)) 19·1 (2·4) and 5·6 (1·3) respectively) and caudate (16·8 (3·4) and 8·6 (2·5) respectively), although it reached significance only for the putamen.

Table 2   Mean (range) of [¹²³I]PF-CIT SPECT measures in healthy volunteers and patients with Parkinson's disease

	Controls n = 6	All patients with PD n = 18	Patients with early PD n = 6	Patients with non-early PD n = 12
Striatum:				
Contralateral	2·73 (1·87–4·75)	0·98 (0·48–1·82)*	1·29 (1·00–1·82)*	0·83 (0·48–1·81)*†
Ipsilateral	2·62 (1·72–3·92)	1·11 (0·53–2·32)*‡	1·44 (0·92–2·32)*	0·94 (0·53–1·88)*†‡
Caudate:				
Contralateral	2·82 (1·92–5·17)	1·38 (0·62–2·55)*	1·84 (1·31–2·55)	1·16 (0·62–2·38)*†
Ipsilateral	2·76 (1·87–4·33)	1·55 (0·53–2·86)*‡	2·06 (1·45–2·86)‡	1·30 (0·53–2·29)*†‡
Putamen:				
Contralateral	2·51 (1·51–3·92)	0·77 (0·40–1·50)*	1·02 (0·79–1·50)*	0·65 (0·40–1·38)*†
Ipsilateral	2·61 (1·46–4·42)	0·90 (0·35–2·05)*‡	1·20 (0·80–2·05)*	0·74 (0·35–1·63)*†‡
Putamen/caudate ratio:				
Contralateral	0·92 (0·79–1·11)	0·58 (0·34–0·93)*	0·57 (0·35–0·74)*	0·59 (0·34–0·93)*
Ipsilateral	0·93 (0·78–1·02)	0·61 (0·39–1·00)*	0·59 (0·39–0·71)*	0·61 (0·40–1·00)*

PD = Parkinson's disease; contralateral is the side opposite that of initial presentation of motor signs. For healthy subjects contralateral is arbitrarily assigned to the left striatum. All SPECT values are expressed as (region of interest – occipital cortex)/occipital cortex (range).
*P < 0·05 v controls.
†P < 0·05 v patients with early Parkinson's disease.
‡P < 0·05 v contralateral side.

Table 3   Correlation coefficient (Spearman rank correlation) for [¹²³I]FP-CIT SPECT measures and motor disability scores in patients with Parkinson's disease

	Hoehn and Yahr ranking	P value	Motor UPDRS rating	P value
Striatum:				
Contralateral	−0·59	0·01	−0·40	0·10
Ipsilateral	−0·50	0·03	−0·30	0·23
Caudate:				
Contralateral	−0·58	0·01	−0·40	0·10
Ipsilateral	−0·49	0·04	−0·27	0·28
Putamen:				
Contralateral	−0·52	0·03	−0·31	0·22
Ipsilateral	−0·48	0·04	−0·29	0·24
Putamen/caudate ratio:				
Contralateral	−0·02	0·56	−0·03	0·89
Ipsilateral	−0·01	0·97	−0·12	0·63

In patients with Parkinson's disease binding of the ligand was decreased more in the putamen than in the caudate nucleus, as seen from the decreased putamen:caudate ratios of binding values, both for the ipsilateral and the contralateral side compared with those of the controls. There were no differences in these ratios between ipsilateral and contralateral sides within either the control or Parkinson's disease group (P = 0·84 and P = 0·61 respectively; table 2).

SPECT MEASURES IN EARLY PARKINSON'S DISEASE

If only a subgroup of six patients with early Parkinson's disease (defined as patients with Hoehn and Yahr stage 1 or 1·5 and duration of disease less than five years; table 1) was considered for comparison with controls, significant differences were still found in four out of the six binding measures (both ipsilateral and contralateral for striatum, putamen, and caudate) presented for all 18 patients with Parkinson's disease together (table 2). Only ipsilateral and contralateral caudate uptake showed no significant difference (P = 0·18 and P = 0·09, for ipsilateral and contralateral caudate respectively; table 2). In patients with early Parkinson's disease binding of the ligand was also decreased more in the putamen than in the caudate nucleus, as measured by the putamen:caudate ratio of binding values, both for the ipsilateral and the contralateral side compared with controls (table 2). For the entire Parkinson's disease group and the early Parkinson's disease group the contralateral

binding ratio in the caudate nucleus was significantly lower than the ipsilateral ratio (table 2).

Moreover, the value of [¹²³I]FP-CIT binding in the putamen was lower contralateral to the side where the motor signs started in five out of the six patients with early Parkinson's disease. Overall average of the asymmetry index was higher in early Parkinson's disease than controls for the putamen ((mean (SEM) 16·1 (4·3)) and 5·6 (1·3) respectively) and caudate (10·6 (1·7) and 8·6 (2·5) respec-
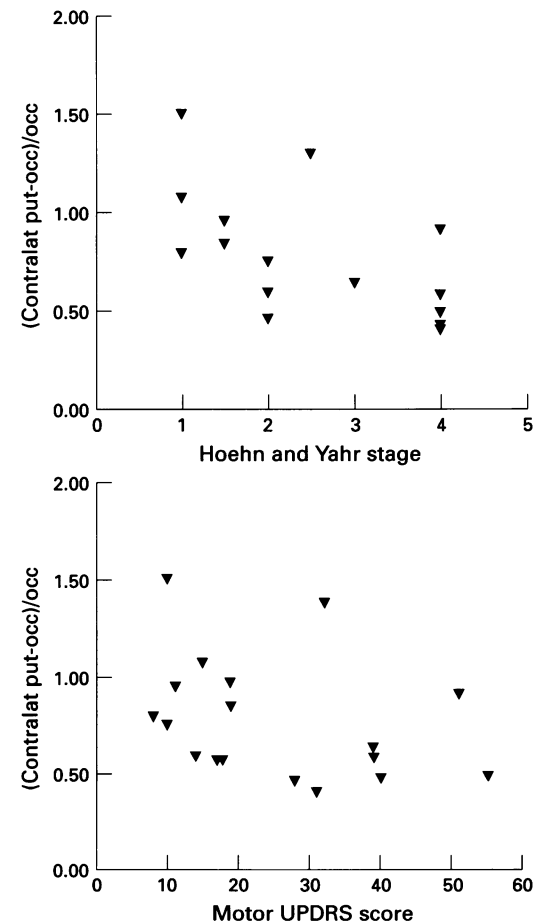

Figure 3   Correlation (Spearman rank correlation) of Hoehn and Yahr stage and motor UPDRS score with specific to non-specific binding in the contralateral putamen for individual patients with Parkinson's disease.

tively), although the difference was not significant.

The non-early Parkinson's disease group (all patients with Parkinson's disease studied minus the six patients with early Parkinson's disease) had significantly lower binding than the early Parkinson's disease group for all six regions measured (table 2). Finally, there was no significant difference in age between the early Parkinson's disease, non-early Parkinson's disease, and control groups.

CORRELATION OF SPECT SIGNAL WITH HOEHN
AND YAHR STAGE AND UPDRS SCORE
Hoehn and Yahr stage of the patients with Parkinson's disease was significantly correlated (Spearman rank correlation) with all six binding measurements (both ipsilateral and contralateral for the striatum, putamen, and caudate; table 3, fig 3), whereas putamen:caudate ratios were not significantly correlated with Hoehn and Yahr stage.

Motor UPDRS score had no significant correlation with uptake variables although a tendency for an inverse correlation was noticeable (table 3, fig 3). Putamen:caudate ratios were also not significantly correlated with motor UPDRS score.

Discussion
A major finding of this study is that [^{123}I]FP-CIT binding in both the caudate nucleus and putamen (ipsilateral as well as contralateral) of patients with Parkinson's disease was significantly lower compared with age matched controls. The second important finding was the low ipsilateral and contralateral putamen:caudate ratios in patients with Parkinson's disease. Finally, a subgroup of patients with early Parkinson's disease showed significantly lower ipsilateral and contralateral binding in the putamen, and lower putamen:caudate binding ratios. The loss of [^{123}I]FP-CIT uptake in both the putamen and caudate nucleus in patients with Parkinson's disease as well as the preferential loss in the putamen is in agreement with results from necropsy studies, which disclosed a more severe depletion of DA in the putamen than in the caudate nucleus.[30] It, moreover, confirms the recent findings with [^{123}I]β-CIT SPECT.[10] This finding is likely due to the more extensive degeneration in Parkinson's disease of subpopulations of substantia nigra cells that project primarily to the putamen than other nigral cell bodies.[1 30–32] The fact that the decreases of striatal [^{123}I]FP-CIT reflects this differential loss in Parkinson's disease probably indicates the power of brain imaging with this new radioligand.

In the present study, the time point for in vivo imaging of the DA transporter with [^{123}I]FP-CIT was chosen at three hours after injection—that is, in the period of pseudoequilibrium. This is in agreement with two other studies in healthy volunteers, which found peak uptake of [^{123}I]FP-CIT into the basal ganglia three to four hours after injection,[19] or 90% level of the initial peak value of specific striatal uptake between 80 and 220 minutes

after injection[18] respectively. This one day protocol seems therefore to allow identification of DAergic nigrostriatal loss by non-invasive visualisation of striatal DA transporter content. This offers a great advantage compared with the SPECT studies with [^{123}I]β-CIT, which require imaging acquisition 24 hours after injection.

Estimation of specific to non-specific binding ratios gives information about the binding potential. For [^{123}I]β-CIT it has been suggested that metabolism of this ligand may have a significant influence on measurement of the DA transporter with SPECT.[33] The metabolic fate of [^{123}I]FP-CIT has only been studied in primates.[14] In that study, the major metabolite of [^{123}I]FP-CIT seemed to be found in the polar fraction, and the major lipophilic fraction consisted mostly of parent tracer up to five hours after injection. It is unlikely that the polar fraction will cross the blood-brain barrier and subsequently influence the measurement. However, more accurate measurement of [^{123}I]FP-CIT uptake in future studies still requires the investigation of its metabolism in humans.

The present study shows for the first time that on application of [^{123}I]FP-CIT a pronounced reduction of striatal DA transporter binding in patients with Parkinson's disease can be seen using SPECT. Although this lower signal most likely reflects degeneration of the DAergic nigrostriatal neurons (see above) it should be kept in mind that a possible down regulation of DA transporter on the remaining DAergic terminals could perhaps contribute to the reduction. Compensatory mechanisms linked to DA cell loss in Parkinson's disease and animal models of Parkinson's disease have been described.[34] For example, depletion of tissue DA by chronic treatment with reserpine in rodents decreased DA transporter levels.[35] So, as the loss of DA transporters reaches a critical value, it may perhaps be possible that the remaining DAergic cells maintain synaptic DA concentrations in part by decreasing the available DA transporters per terminal. Additionally, the extent to which the density of DA transporters reflects that of DA terminals is also uncertain. The transporter-terminal relation may be altered in patients with Parkinson's disease compared with controls, as DA transporters are known to be modulated by concentrations of endogenous DA.

Until recently most research on the DAergic deficit in Parkinson's disease in vivo has been performed with [^{18}F]DOPA PET.[4 36 37] Even more recently, a PET study showed declines of [^{18}F]DOPA uptake in early Parkinson's disease.[38] Interestingly, in that study most contralateral putamen K_i-values of 11 patients with hemi-Parkinson's disease of recent onset fell outside the range of normal values. However, most ipsilateral putamen [^{18}F]DOPA uptake values fell within the normal range. The authors concluded that either the patients with early hemi-Parkinson's disease do not have the disease ipsilaterally, or it is not identifiable with the [^{18}F]DOPA PET technique. In

the present study, the range of individual data of [¹²³I]FP-CIT binding in the contralateral putamen, obtained in a group of patients with recent onset of hemi-Parkinson's disease, did not overlap with data obtained from age matched controls. However, the present study showed minimal overlap between individual data of [¹²³I]FP-CIT binding in the ipsilateral putamen of the patients with early Parkinson's disease compared with that of healthy volunteers ([¹²³I]FP-CIT binding in the ipsilateral putamen of only one patient in the early Parkinson's disease group fell within the normal range; table 2 does not show individual data). Importantly, very recently a [¹²³I]β-CIT SPECT study also showed bilateral loss of dopamine transporters in hemi-Parkinson's disease.[39] Based on the results of our study, the [¹²³I]FP-CIT SPECT technique may be sensitive enough to detect the preclinical period of Parkinson's disease.

[¹⁸F]DOPA PET mainly reflects decarboxylation activity of the presynaptic DAergic terminals, whereas imaging of the presynaptic DA transporters of the DAergic terminals is the target for the new PET and SPECT ligands. SPECT studies using [¹²³I]β-CIT, and the present study with [¹²³I]FP-CIT, are consistent with PET [¹⁸F]DOPA studies including the demonstration of greater abnormality of the putamen compared with the caudate nucleus, asymmetric uptake, and correlation with symptom severity.[10 36] However, SPECT studies with the DA transporter ligands showed high target to non-target ratios resulting in nearly no overlap for the data between controls and patients with Parkinson's disease. It is therefore very intriguing to see what PET studies using these transporter ligands in patients with Parkinson's disease will show.[11 12] Preliminary studies with [¹¹C]FP-CIT have already shown a very high striatal uptake ratio in healthy volunteers, with an equilibrium in the striatum attained within the acquisition time.[17] However, studies in patients with Parkinson's disease have not been performed with this new PET ligand.

A source of possible confounding in the data of the present study lies in the fact that most of the patients with Parkinson's disease received DAergic medication. It is possible that direct or indirect effects of this medication could have interfered with binding measurements of the DA transporter. However, Laruelle *et al*[39] showed in baboons that acute administration of a large dose of levodopa (50 mg/kg intravenously) had no influence on specific striatal β-CIT binding. In the present study, comparison of striatal [¹²³I]FP-CIT binding still showed significantly lower binding in the six unmedicated patients compared with the six healthy controls, even though the average age of the patients was lower. None the less, the effects of medication were not considered in this study and should be in the future.

In conclusion, the present results indicate that the [¹²³I]FP-CIT SPECT procedure is very sensitive in discriminating patients with Parkinson's disease from healthy age matched

volunteers. By contrast with [¹²³I]β-CIT SPECT, in which an adequate image acquisition could only be obtained 24 hours after injection, SPECT with FP-CIT can give the required information by three hours after injection

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NEUROLOGICAL STAMP

Carl Zeiss (1816–88)

Carl Zeiss studied medicine and was also apprenticed to various instrument makers in Weimar, Stutgart, and Vienna. In 1846 he opened a shop in Jena in Germany which produced and repaired optical equipment. Initially he specialised in the manufacture of microscopes. In 1866, with Otto Schott and Ernst Abbe, a German mathematician and physicist, he worked on the microscope, perfecting the homogeneous immersion lens in 1878. The Zeiss workshop soon acquired a world wide reputation for the manufacture of high quality optical equipment, embracing every kind of optic instrument but especially cameras and microscopes.

He was honoured philatelically by East Germany in 1956 on a stamp issued to commemorate the founding of the 110th Anniversary of the Zeiss Optical Works in Jena. (Stanley Gibbons E283, Scott 313). Abbe was also honoured on a stamp issued in the same series.

L F HAAS