Radiotracer Imaging in PD
Eshuis, Sietske Aleida

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Comparison of FP-CIT SPECT and F-DOPA PET in patients with de novo and advanced Parkinson’s disease


Abstract

Purpose: Diagnosis of Parkinson’s disease (PD) can be difficult. F-DOPA PET is able to quantify striatal dopa decarboxylase activity and storage capacity of F-dopamine, but is expensive and not generally available. FP-CIT binds to the dopamine transporter, and FP-CIT SPECT is cheaper and more widely available, but has a lower resolution. The aim of this study was to compare these two methods in the same patients with different stages of PD to assess their power in demonstrating deficits of the striatal dopaminergic system.

Thirteen patients with de novo PD and 17 patients with advanced PD underwent FP-CIT SPECT and static F-DOPA PET. After data transfer to standard stereotactic space, a template with regions of interest was used to sample values of the caudate, putamen and an occipital reference region. The outcome value was striato-occipital ratios. Patients were clinically examined in the “off state” (UPDRSIII and H&Y stage).

Good correlations were found between striatal F-DOPA uptake and striatal FP-CIT uptake (r=0.78) and between putaminal F-DOPA uptake and putaminal FP-CIT uptake (r=0.84, both p<0.0001). Both striatal uptake of FP-CIT and that of F-DOPA correlated moderately with H&Y stage (\(\rho=-0.52\) for both techniques), UPDRS-III (\(\rho=-0.38\) for F-DOPA; \(\rho=-0.45\) for FP-CIT) and disease duration (\(\rho=-0.59\) for F-DOPA; \(\rho=-0.49\) for FP-CIT, all p<0.05).

FP-CIT values correlate well with F-DOPA values. Both methods correlate moderately with motor scores and are equally able to distinguish patients with advanced PD from patients with de novo PD.

Keywords: F-DOPA PET – FP-CIT SPECT – Parkinson’s disease – Dopamine transporter
Introduction

Parkinson’s disease (PD) is a slowly progressive disorder, characterised by progressive degeneration of dopaminergic neurones in the substantia nigra. The classic triad of clinical symptoms of PD consists of bradykinesia, rigidity and resting tremor. In the early phases of disease, these signs may be subtle. Also, PD may present heterogeneously and may also be confused with parkinsonism caused by other disorders like multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration or essential tremor. Assessment of the severity and progression of PD can be done by examination of motor symptoms and application of standardised rating scales. However, the clinical heterogeneity of PD, inter-rater variability and the influence of symptomatic medication may complicate the clinical evaluation. Examining the patient in the “off state”, i.e. after 12 h without any symptomatic antiparkinsonian medication, may only partially overcome the masking effect of antiparkinsonian treatment.

The difficulties in primary diagnosis and assessment of disease progression are illustrated by findings from autopsy studies, where the diagnosis of PD before death was found to be incorrect in about a quarter of cases. In addition, even neurologists associated with a clinic specialising in movement disorders incorrectly diagnose PD in about 10% of cases. Against this background, objective in vivo markers of dopaminergic degeneration, such as neuroimaging studies, are important for the detection of PD, especially in the early stages of disease, for the assessment of disease severity, and for the monitoring of disease progression.

Neuroimaging techniques as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) enable visualisation and measurement of striatal dopaminergic functioning. PET scans with 6-[18F]-fluoro-L-3,4-dihydroxyphenylalanine (F-DOPA) allow quantification of striatal dopa decarboxylase activity and storage capacity of F-dopamine. However, high costs, restricted availability of PET instruments and the difficult production of F-DOPA limit its use.

Another neuro-imaging technique is SPECT using [123I] N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT). This tracer belongs to a group of compounds derived from cocaine, which has a high affinity for the dopamine transporter (DAT). SPECT scans using the ligand FP-CIT (DaTscan) are cheaper and much more widely available. FP-CIT is a selective and potent DAT imaging agent with a high target to background ratio and rapid clearance from the cerebellum and cortical brain regions. Several studies have shown a reduction in striatal FP-CIT uptake in PD compared with healthy controls. Although the uptake mechanism of the two tracers is quite different, FP-CIT SPECT may be a good alternative to F-DOPA PET. To the best of our knowledge, only one study has compared these two imaging modalities in the same subjects. Ishikawa et al. performed
both FP-CIT SPECT and F-DOPA PET scans in healthy controls and patients with mild PD, but not in patients with an advanced stage of disease\(^\text{15}\).

Therefore, the aim of this study was to compare FP-CIT SPECT with F-DOPA PET in the same group of patients with different stages of PD, in order to study the degree of correlation of the two methods, the feasibility of separating de novo from advanced disease stage, and the relation between tracer uptake and clinical parameters such as motor scores.

**Materials and methods**

**Patients**

A total of 30 consecutive PD patients were recruited between 2002 and 2003 from the Movement Disorders outpatient clinic of the University Hospital of Groningen, which has a tertiary referral function. Patients were recruited based on their clinical inclusion requirements.

The subjects were divided into two distinct groups: de novo PD patients (n=13) and patients in an advanced stage of disease. The de novo group included patients with strong diagnostic evidence of PD based on two of the three cardinal symptoms (rest tremor, bradykinesia and rigidity), a disease duration of less than 3 years, no use of antiparkinsonian medication and a Hoehn and Yahr (H&Y) stage of less than 2.0. The advanced group consisted of PD patients with two of the three cardinal symptoms, with disease duration of 5–15 years, use of antiparkinsonian medication and a H&Y stage of 2.0–4.0.

Patients with atypical signs, psychiatric disorders, signs of severe cognitive deterioration or severe cardiovascular co-morbidity, or on medication known to interfere with the dopamine transporter, were excluded from participation.

The motor score of patients was determined in the “off” state (after 12 h without any symptomatic antiparkinsonian medication) to avoid confounding effects on the clinical examination. Clinical examination included the motor score of the Unified Parkinson’s Disease Rating Scale (UPDRS-III), which is composed of subscores for speech, facial expression, tremor, rigidity, bradykinesia and axial symptoms (total motor score ranges from 0 to 108). H&Y stage was also determined, which includes several stages of disease severity varying from ‘no signs of disease’ to ‘wheelchair bound or bedridden unless aided’ (1– 5).

Each subject underwent a [\(^{123}\)I]FP-CIT SPECT and an [\(^{18}\)F]F-DOPA PET scan at a mean interval of 61 days (±35 days). Written informed consent was obtained according to the Helsinki convention and the study was approved by the local medical ethics committee.
F-DOPA PET
Patients fasted for at least 4 h before the start of the scan. Patients were allowed to continue their antiparkinsonian medication. Patients taking other medication potentially affecting the dopaminergic system were excluded (see above). On arrival, patients were given carbidopa (2.5 mg/kg) orally. Sixty minutes after the carbidopa dose, 200 MBq of \[^{18}F\]F-DOPA was administered intravenously. \[^{18}F\]F-DOPA was prepared in the radiochemical laboratory of the University Hospital Groningen as described elsewhere. Ninety minutes after administration of the tracer, the subject was positioned in the PET camera in a comfortable head holder, with their orbito-meatal line in a transverse plane. One static 3D acquisition of 6 min was performed with a Siemens HR+PET camera (Siemens, Erlangen, Germany), according to the standard operating procedures protocol of the University Hospital Groningen. In daily clinical practice, static scans are preferred to dynamic scans in patients with PD as dynamic scans take a very long time to perform and are therefore too inconvenient. For estimation of the diagnostic value in this patient group, it was therefore decided to perform static and not dynamic scans. Furthermore, it is strongly suggested that the striatal–occipital ratio (SOR) determined from a static scan can be as accurate as kinetic parameters (such as binding constant \(K_{\text{occ}}\)) from a dynamic scan10. Scan data were reconstructed using iterative methods (ordered subsets expectation maximisation) and were corrected for attenuation using a separate ellipse algorithm. An example of an F-DOPA PET scan is shown in Fig. 1a.

FP-CIT SPECT
Patients were allowed to continue all medication, including antiparkinsonian medication. Patients were injected with 185 MBq FP-CIT (DaTscan, commercially obtained from Amersham Health, Eindhoven, The Netherlands). No thyroid blocking was given, according to our local operating procedure, as thyroid blocking will not interfere with striatal uptake. After 180 min a SPECT acquisition was performed using a dual-headed gamma camera (Multispect 2, Siemens, Hoffman Estates, IL, USA) with a low-energy high-resolution collimator, 128x128 image matrix, zoom factor 1.23, 40 s per view and 2x64 views. Data acquisition was in agreement with the Dutch National Guidelines and with the guidelines from the manufacturer. Acquisition time was approximately 45 min. Images were acquired in a symmetrical 15% energy window around the photopeak of \(^{123}\)I at 159 keV. System resolution was 12mm full-width at half-maximum at 10 cm. Patients had been carefully positioned in the gamma camera, with their meato-orbito axis in a transverse plane to avoid reorientation during reconstruction, in a special head-holder that allowed a minimal rotation distance. Image data were reconstructed using filtered back-projection and a Butterworth (0.50/6) filter. No attenuation correction was performed (as advised by the manufacturer at the time of the study). An example of an FP-CIT SPECT scan is shown in Fig. 1b.
Figure 1: Transaxial slices through the striatum in a patient with advanced PD.
Upper row: F-DOPA PET
Lower row: FP-CIT SPECT
Images show comparable activity, but the ipsilateral dysfunction (left) is slightly more severe on SPECT than on PET.

**Image analysis**
Reconstructed PET and SPECT data were both realigned to the common co-ordinate system of the stereotactic brain atlas of Talairach and Tournoux. This realignment was performed using standard linear brain normalisation algorithms (SPM software, FIL London, UK). An image analysis algorithm was used to remove skin uptake. A standard set of regions of interest (ROIs) was used to sample both the caudate and putamen and a non-specific reference region in the occipital cortex. Occipital activity was assumed to represent non-specific radioactivity. Ratios of specific to non-specific binding (SORs) were calculated by dividing striatal count density by occipital count density. ROI size-weighted average uptake values of caudate and putamen were used to calculate mean whole striatal binding. Uptake values on the same half of the body as the dominant (and generally initial) side of motor symptoms were called ipsilateral uptake values and those opposite to that side were called contralateral uptake values. Asymmetry indices were used to quantify the degree of asymmetry. These indices were calculated by subtraction of ipsilateral values from contralateral values, divided by the sum of the values of both sides: (contralateral−ipsilateral)/(contralateral+ipsilateral). The two groups of patients were lumped for correlation of clinical scores with uptake values.
Statistical analysis

Parametric or non-parametric correlation coefficients were calculated for all correlations of SPECT SOR vs PET SOR as appropriate. The Shapiro-Wilk test was used to examine the presence of a normal distribution of datasets. Sensitivity and specificity values were calculated for PET and SPECT, after performing receiver operator characteristic (ROC) analysis of both SPECT and PET data in both groups. The optimal cut-off levels were derived from the ROC data. If data were not normally distributed, Spearman’s rho was used for correlations. In addition to correlation, linear regression analysis was performed and Bland-Altman plots were constructed. Spearman’s rho was also used to correlate the SOR values of the PET and SPECT studies with the UPDRS-III and H&Y scores and disease duration. SPECT and PET values were entered into separate ANOVA analysis to determine whether there is a significant difference between the distinct clinical stages using each method.

Results

Patients

Thirteen patients with de novo PD and 17 patients with advanced stage of disease were included. Table 1 shows the clinical profile of all patients included in the study. More male than female patients participated, but the male to female ratio was similar in both groups (chi-square p=0.41). Mean age in the de novo PD group was 54 years [standard deviation (SD) =11] years, with mean disease duration of 1.3 (SD=0.5) years. Mean UPDRS-III score was 20 (SD=8) and the median H&Y stage was 1.5. In the group with advanced stage of disease, mean age was 64 (SD=6) years and mean disease duration was 9.4 (SD=3.1) years. In this group, mean UPDRS-III score was 33 (SD=11) and median H&Y stage was 2.5. One de novo PD patient and one patient with advanced stage of disease refused clinical examination in the “off state”. As might have been expected, H&Y stage, UPDRS-III score and disease duration were significantly lower in the de novo PD group than in the advanced PD group (p=0.003 for mean age; p<0.0001 for H&Y stage, p=0.002 for UPDRS-III and p<0.0001 for disease duration).
Table 1: Clinical profile of all patients

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M = male  
F = female  
NA = not available

Correlation of F-DOPA PET and FP-CIT SPECT

Striatal SORFP-CIT ranged from 1.32 to 2.50 and striatal SORF-DOPA ranged from 1.66 to 2.51. Mean striatal SORFP-CIT was 1.95 for the total group, 2.12 for the de novo patients and 1.81 for the patients with an advanced stage of disease. The area under the ROC curve for FP-CIT SPECT was 0.79, and the optimal cut-off SOR to separate the groups was determined to be 1.95. Mean striatal SORF-DOPA of the total group was 2.05. For the de novo patients, striatal SORF-DOPA was 2.20 and for the advanced patients it was
The area under the ROC curve for F-DOPA PET was 0.86, and the optimal cut-off SOR to separate the groups was determined to be 2.05. In general, uptake values of FP-CIT show a greater variability than uptake values of F-DOPA. Striatal SOR\textsubscript{F-DOPA} in healthy volunteers has previously been reported as above 2.4\textsuperscript{1,22}. Normal values for striatal SOR\textsubscript{FP-CIT} are less well known, but appear to vary around 3–3.5, also depending on the method of acquisition and processing. For the whole group together and for the whole striatum, SOR\textsubscript{F-DOPA} correlated well with SOR\textsubscript{FP-CIT} (Fig. 2): r=0.78, p<0.0001. Also SOR\textsubscript{F-DOPA} and SOR\textsubscript{FP-CIT} for putamen and caudate separately were highly correlated (r=0.84, p<0.0001 for putaminal uptake and r=0.74, p<0.0001 for caudate uptake).

Also, in the subgroups of de novo and advanced PD patients, whole striatal uptake on the two scans correlated significantly (r=0.77, p=0.0009 for de novo PD patients and r=0.57, p=0.016 for advanced PD patients). When comparing ipsilateral and contralateral striatal SORs of the two scanning methods we found good correlations (r=0.77, p<0.0001 for ipsilateral uptake values and r=0.76, p<0.0001 for contralateral uptake values).

The mean difference between SOR\textsubscript{F-DOPA} and SOR\textsubscript{FP-CIT} was 0.11. However, the difference between F-DOPA uptake and corresponding FP-CIT uptake was not constant across the range of measured values, but decreased as F-DOPA uptake and FP-CIT uptake increased (Bland-Altman plot: Fig. 3).

![Figure 2: Correlation between striatal FP-CIT uptake and striatal F-DOPA uptake in all 30 patients (r = 0.78, p < 0.0001).
Regression line: F-Dopa mean striatum = 1.13 + 0.48 FP-CIT mean striatum]
Correlation of SOR and disease severity

**H&Y stage**
Both striatal uptake of F-DOPA and striatal uptake of FP-CIT correlated moderately with H&Y stage (Fig. 4a,b): Spearman’s rho=0.52, p=0.004 for both scanning methods. Putaminal and caudate uptake showed a significant relationship with H&Y stage, although caudate SOR correlated less closely with H&Y stage than did putaminal SOR.

**UPDRS-III**
UPDRS-III score correlated moderately with striatal uptake of F-DOPA and FP-CIT (Fig. 4c,d): Spearman’s rho=−0.38 for F-DOPA, p=0.05 and Spearman’s rho=−0.45 for FP-CIT, p=0.02.

Subanalyses of putaminal and caudate uptake of F-DOPA and FP-CIT showed similar results to whole striatal uptake for correlation between uptake and UPDRS-III scores. Both correlation and significance level increased slightly when using asymmetry indices: for correlation between asymmetry index UPDRS-III and asymmetry index striatal F-DOPA uptake, Spearman’s rho=−0.58, p=0.002 and for correlation between asymmetry index UPDRS-III and asymmetry index striatal FP-CIT uptake, Spearman’s rho=−0.49, p=0.012.
Comparison of FP-CIT and F-DOPA in patients with de novo and advanced PD

Figure 4: Correlation between motor scores (H&Y stage and UPDRS-III) and putaminal uptake for PET and SPECT in all 30 PD patients. Ellipses form the 95% confidence interval.

Figure 4a: H&Y stage vs F-DOPA uptake: Spearman’s rho = -0.52, p = 0.004

Figure 4b: H&Y stage vs FP-CIT uptake: Spearman’s rho = -0.52, p = 0.004

Figure 4c: UPDRS-III vs F-DOPA uptake: Spearman’s rho = -0.38, p = 0.05

Figure 4d: UPDRS-III vs FP-CIT uptake: Spearman’s rho = -0.45, p = 0.02

**Disease duration**

Significant but moderate correlations were found between disease duration and striatal F-DOPA uptake (Spearman’s rho = -0.59, p = 0.001) and between disease duration and striatal FP-CIT uptake (Spearman’s rho = -0.49, p = 0.01) (Fig. 5). From the whole dataset, we calculated a mean annual decrease in uptake, which proved equal for striatum, putamen and caudate and for both F-DOPA and FP-CIT values at a value of 3% decrease per year. The results are also presented in Table 2.
Figure 5: Correlation between disease duration and striatal uptake. Ellipses form the 95% confidence interval.

Figure 5a: disease duration vs striatal F-DOPA uptake: Spearman’s rho $\rho = -0.59$, $p = 0.001$

Figure 5b: disease duration vs striatal FP-CIT uptake: Spearman’s rho $\rho = -0.49$, $p = 0.01$
Comparison of FP-CIT and F-DOPA in patients with de novo and advanced PD

Table 2: Overview of relationship between motor scores and uptake values

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<th>Scan method</th>
<th>ROI</th>
<th>Motor evaluation</th>
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<th>Disease duration (p)</th>
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<td></td>
<td>UPDRS-III (p)</td>
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<td></td>
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<tr>
<td>FP-CIT</td>
<td>Striatum</td>
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<td>−0.52 (0.004)</td>
<td>−0.49 (0.01)</td>
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<td>Putamen</td>
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<td>−0.51 (0.004)</td>
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<td>Caudate</td>
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<td>Striatum ipsilateral</td>
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<td></td>
<td>Putamen contralateral</td>
<td>−0.26 (0.18)</td>
<td>−0.34 (0.07)</td>
<td>−0.38 (0.04)</td>
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<td>Caudate ipsilateral</td>
<td>−0.43 (0.02)</td>
<td>−0.51 (0.005)</td>
<td>−0.45 (0.020)</td>
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<td>−0.54 (0.003)</td>
<td>−0.70 (0.0003)</td>
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<td>−0.15 (0.44)</td>
<td>−0.25 (0.18)</td>
<td>−0.38 (0.04)</td>
</tr>
</tbody>
</table>

ROI = region of interest

Discrimination between patients with de novo and patients with advanced PD

Patients with de novo PD could be discriminated from patients with more severe stages of the disease with both methods (p=0.0002 for F-DOPA and p=0.01 for FP-CIT) (Fig. 6). Sensitivity of FP-CIT SPECT for discrimination between de novo and advanced PD patients was 0.88, while specificity was 0.70. For F-DOPA PET, sensitivity for discrimination between the two patient groups was 0.88 and specificity, 0.77. The differences between PET and SPECT were not significant. When putaminal values were used instead of striatal values, sensitivity and specificity of both methods remained approximately the same (sensitivity and specificity for FP-CIT=0.77 and 0.71 respectively and sensitivity and specificity for F-DOPA=0.76 and 0.85 respectively).
Chapter 5

Figure 6: Discrimination between the two groups of patients by means of F-DOPA PET and FP-CIT SPECT

Figure 6a: ANOVA analysis: F-DOPA PET

Figure 6b: ANOVA analysis: FP-CIT SPECT
Discussion

In this study, we have compared FP-CIT SPECT and F-DOPA PET in terms of their ability to quantify the activity of the striatal dopaminergic system in patients with different stages of PD. We found that FP-CIT uptake and F-DOPA uptake correlate highly with each other and that both scanning methods correlate reasonably with motor scores and disease duration. The two tracers were equally able to discriminate de novo from advanced PD patients with a high sensitivity and specificity.

Both tracers are in vivo markers of the presynaptic dopaminergic system. However, the two scanning methods are based on different biochemical processes. F-DOPA PET uptake reflects the activity of the decarboxylating enzyme AADC and the storage capacity of F-dopamine in the nerve terminals, whereas FP-CIT SPECT measures the activity of DAT. This results in a different approach to assessment of the functioning of the presynaptic dopaminergic system, and the question arises as to whether it is permissible to compare these methods with each other. Lee et al. applied three tracer methods in vivo in patients with PD. In that study, they compared striatal PET measurements using [11C]dihydrotetrabenazine (labelling the vesicular monoamine transporter type 2), [11C]methylphenidate (labelling the plasma membrane DA transporter, in a similar way to FP-CIT) and [18F]DOPA in patients with PD. Striatal F-DOPA uptake was higher in parkinsonian patients than the uptake of methylphenidate. It was postulated that this difference in tracer uptake may be due to an upregulation of AADC and thereby of F-DOPA uptake, and a downregulation of DAT and thus of FP-CIT uptake, although no direct proof was provided for this. Experimental animal studies support this contention and suggest that loss of DA neurones is functionally compensated by an increase in dopamine release and by downregulation of DA reuptake in an attempt to maintain dopamine levels. Also, β-CIT binding and L-DOPA uptake decrease in parallel with decrease in dopamine neurones in several stages of PD. However, the decrease in β-CIT binding mirrors more closely the reduction in dopaminergic neurones than does the decrease in L-DOPA uptake, suggesting that β-CIT binding is a superior indicator of dopaminergic neurone loss. These different reactions of the two tracers in response to a reduction in dopamine imply a different degree of decrease in striatal uptake of the two tracers, as striatal FP-CIT uptake will be reduced in an earlier phase of disease than will F-DOPA uptake. This is also suggested by our findings. Our results are also in agreement with the results described by Ishikawa et al., who found a correlation coefficient of 0.77 (p<0.0001) for the correlation between striatal FP-CIT uptake and striatal F-DOPA uptake. Although our study demonstrates a significant correlation between F-DOPA PET measures and corresponding FP-CIT SPECT measures, differences are still observed between the uptake values. Striatal FP-CIT shows a greater variability in uptake than does striatal F-DOPA (Fig. 1). As indicated by the Bland-Altman plot (Fig. 1)},
2), at low values of FP-CIT uptake, F-DOPA values are higher than FP-CIT uptake values, whereas at high values of FP-CIT uptake, F-DOPA uptake values are lower than those of FP-CIT. Furthermore, when specific uptake of FP-CIT equals aspecific uptake (SOR=1), F-DOPA still shows specific uptake. These findings may be due to technical problems such as lower resolution of SPECT scans compared with PET scans, differences in signal to noise ratio and scattered radiation, but they may also be the result of the above-mentioned different biochemical mechanisms of the two tracer uptake methods.

This study demonstrates that the uptake values for the two tracers show a similar but moderate correlation with UPDRS motor scores (Fig. 4c,d). After reducing interindividual variability by calculating asymmetry indices, this correlation increases but remains moderate. Many others have found a statistically significant correlation between UPDRS motor scores and SOR_F-DOPA and SOR_FP-CIT, but with higher correlation coefficients varying from 0.51 to 0.812, 4, 10, 15, 26, 29, 36, 41. However, other investigators did not find any statistically significant correlation between UPDRS-III and striatal uptake of CIT7, 37. This discrepancy in findings may be due to methodological differences in data processing. Patients were clinically examined 12 h after withdrawal of antiparkinsonian medication. It is assumed that any therapeutic effect of the medication is washed out at that time. Nevertheless, long-lasting effects of antiparkinsonian therapy on motor signs should not be ignored, and it is possible that such effects, and their interindividual variation, also partially explain the differences in correlation between clinical measures and striatal uptake. The moderate correlation between motor scores and tracer uptake further underlines the difficulties in clinical assessment even when it is standardised. This increases the value of imaging studies in general. We did find a good correlation between H&Y stage and striatal uptake, with a higher correlation coefficient than for the correlation between SOR and the motor part of the UPDRS. This was also found by others7, 26, 33. Our data show that the uptake values of the two tracers correlated well in a similar way with disease duration (Fig. 5) and that the different patient groups could be discriminated with both methods (Fig. 6). In addition, correlation coefficients were highest for ipsilateral SOR values, as expected because the disease starts on the ipsilateral side.

Many studies suggest a significant age-dependent decline in SOR_FP-CIT 15, 17, 19, 35, 38, 40. On the other hand, it has been suggested that adjusting SOR_FP-CIT for age barely alters accuracy in the assessment of nigrostriatal functioning in PD. Decline with age in SOR_FP-CIT is therefore not sufficiently large as to require a specific correction in the assessment of parkinsonism15, 27, or such correction may result in only a minimal improvement in the correlation of striatal DAT binding with UPDRS-III26. A few authors mention an ageing effect with F-DOPA uptake as well29, but many others have not been able to confirm this11, 15, 31. The absence of an ageing effect on striatal F-DOPA uptake may be explained by up regulation of AADC activity as dopaminergic neurones decline in normal ageing. This is
Comparison of FP-CIT and F-DOPA in patients with de novo and advanced PD

supported by post-mortem studies showing little or no decrease in striatal AADC activity in normal senescence\(^\text{18}\). Some studies suggest gender effects, as striatal FP-CIT binding ratios have been found to be significantly higher in females than in males. We also looked for a gender effect in our data, but, due to the small number of women participating in the study, we were not able to find any significant effect.

The annual decrease in uptake in PD patients is, according to our data, 3% per year. This is in line with the results of others\(^\text{15, 28, 30}\). Morrish et al. reported a progression rate of 4.7% of the normal mean per year in a group of patients with PD with a mean disease duration of 39 months, using F-DOPA PET scans\(^\text{22}\). An annual decrease of 11.2% was found by Marek et al. using \(\beta\)-CIT SPECT scans\(^\text{33}\). Pirker and co-workers reported an annual reduction of striatal \(\beta\)-CIT SPECT binding of 3–4.5%\(^\text{37}\). An annual decline of 3% in striatal \(123^\text{I}\)-IPT binding was found in 11 PD cases followed over 12 months by Tatsch et al\(^\text{34}\). It has been suggested that progression will be faster in those regions which are less affected in the beginning, like the caudate nucleus\(^\text{8}\). We were not able to confirm this, as annual decrease was equal in caudate and putamen.

Our data show that FP-CIT SPECT scans have a high sensitivity and specificity for discriminating de novo parkinsonian patients from patients with advanced stage of disease. Sensitivity and specificity are at levels comparable to those of F-DOPA PET scans, based on our method of separation of patients into the de novo and advanced groups on clinical grounds, which is notoriously difficult. In this study we used the H\&Y stage as well as the duration of symptoms. However, it cannot be concluded from our data whether it is also possible to discriminate parkinsonian patients from healthy persons. This is important for early detection of patients with PD. Several studies have demonstrated the utility of FP-CIT SPECT scans for discriminating patients with PD from healthy controls\(^\text{5, 24, 32, 33, 36, 37}\). Ishikawa et al. showed that FP-CIT SPECT scans and F-DOPA PET scans were able to discriminate PD patients from healthy controls with comparable accuracy, even when the analysis was restricted to patients with H\&Y stage 1\(^\text{15}\). Although it has been widely demonstrated that parkinsonian patients can be discriminated from healthy controls with either of these scanning methods, this has only been investigated in patients with an obvious clinical diagnosis, and no studies have been performed in patients with a questionable diagnosis of PD. In daily clinical practice, helping to differentiate between PD and a healthy state will be especially interesting in patients with debatable clinical symptoms. The high sensitivity and specificity of FP-CIT SPECT scans in discriminating between different stages of PD justify extension of the study to include healthy controls in order to allow comparison of the ability of the two scanning methods to discriminate patients with PD from patients with suspicious symptoms but without PD.
Conclusion

Both FP-CIT SPECT and F-DOPA PET can be used to measure the presynaptic dopaminergic system in vivo, and they show equally good ability to separate the early from the advanced stage of PD. In our study the good correlation between F-DOPA uptake values and FP-CIT uptake values, as well as the moderate correlation between striatal uptake and clinical findings, underscores this conclusion. It remains to be seen whether, in daily clinical practice, either method will allow similarly good discrimination between patients with early PD and patients with suspicious symptoms but without PD.

Acknowledgements

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The experiments comply with the current laws of the Netherlands, including approval of the local medical ethics committee.

Reference List


