Simple Ratio Analysis of ^{18}F-Fluorodopa Uptake in Striatal Subregions Separates Patients with Early Parkinson Disease from Healthy Controls

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6-^{18}F-fluoro-L-dopa (^{18}F-FDOPA) is widely used to investigate dopaminergic hypofunction, for instance, in Parkinson disease (PD). Conventionally, a 90-min scan with either a graphical or a metabolite-purified plasma input approach has been used for quantification. In the clinical setting, to increase compliance, especially in patients with more advanced disease, and to increase the efficacy of tracer and scanner time use, a shorter acquisition and a simple quantitative analysis are desirable. Taking into account the asymmetry of clinical symptoms and the uneven distribution of striatal dopaminergic hypofunction may also improve the use of ^{18}F-FDOPA PET in early disease detection. Therefore, we compared subregional striatal ^{18}F-FDOPA PET data from a large group of nonmedicated patients with early PD and a set of healthy elderly volunteers to find out whether a simple ratio approach would reliably separate PD patients from healthy controls. **Methods:** A total of 89 nonmedicated patients with early PD and 21 healthy volunteers were studied with ^{18}F-FDOPA PET, and both a region-to-reference (striatal-to-occipital) ratio (SOR) calculated from 75 to 90 min after injection and a graphical analysis of data calculated from 15 to 90 min after ^{18}F-FDOPA injection (yielding the influx constant [K_i^{ref}]) were used. **Results:** Both SOR and K_i^{ref} values in the PD patients were lowest, relative to those in the healthy controls, in the posterior putamen contralateral to the side with predominant clinical symptoms. The contralateral posterior putamen showed the largest areas under the receiver operating characteristic (ROC) curve—0.994 for SOR and 0.998 for K_i^{ref}—indicating excellent separation of the PD and control groups. The caudate nucleus and the ventral striatum were less impressive in this respect. **Conclusion:** A single 15-min scan 75 min after tracer injection seems to be sufficient for separating patients with PD from healthy controls in a clinical research environment. This method represents a powerful and economical alternative for research on the disease mechanism and differential diagnosis.

Key Words: ^{18}F-FDOPA; quantification; Parkinson disease; PET

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PET, especially with 6-^{18}F-fluoro-L-dopa (^{18}F-FDOPA) as the tracer, has been used to demonstrate and to quantify presynaptic dopaminergic function. Decreased ^{18}F-FDOPA uptake has been reported in the striatum in Parkinson disease (PD) (*1–3*). Postmortem studies have shown that there is an uneven pattern of dopamine loss in the striatum in PD. The depletion is more severe in the putamen than in the caudate nucleus and is most prominent in the caudal parts of the putamen because of the topographic organization of the nigrostriatal projection (*4*).

Accordingly, subregional analysis of striatal ^{18}F-FDOPA uptake in PD has revealed predominately posterior putamen impairment (*5–7*). The posterior putamen receives dopaminergic projections especially from the ventrolateral part of the substantia nigra, which is the most severely degenerated nigral subregion (*8*).

A variety of analytic methods have been developed to quantify ^{18}F-FDOPA PET images for the purpose of reliably discriminating patients with PD from healthy controls. The striatal-to-occipital ratio (SOR) and the influx constant calculated with a graphical tissue reference approach (K_i^{ref}) are commonly used as quantitative parameters in ^{18}F-FDOPA PET studies. They have been measured noninvasively in the dynamic mode with region-of-interest (ROI)–based approaches (*9–12*). Both SOR and K_i have been used to quantify regional dopamine metabolism and to reflect disease severity in PD (*5,13–16*).

Determining K_i^{ref} requires dynamic scans over a longer time than determining SOR, which can be determined with a shorter static data acquisition. A long study poses a compliance issue, may increase potential bias because of subject movement, and may diminish the cost-effectiveness of the cameras and tracers used. SOR may offer a practical advantage because it is a simple measure and would be the easiest to apply in clinical studies quantifying nigrostriatal dopamine function in PD and related disorders. SOR also does not require any plasma measurements.

It has been observed that both SOR and K_i^{ref} successfully discriminate patients with moderate PD from healthy subjects and are equally sensitive as descriptors of disease severity (*17*). In that study, the average for the left and right sides of the putamen and the caudate was used to establish a conservative estimate. PD is characterized by the unilateral appearance of symptoms that can be visualized with ^{18}F-FDOPA as well. Patients in the early stage of PD have at least a 30% loss of ^{18}F-FDOPA uptake in the putamen contralateral to the side with clinical symptoms (*7,18*). Examining ^{18}F-FDOPA uptake contralateral to the more affected body side would probably better discriminate healthy subjects from patients with PD. Because dopaminergic deficiency is seen predominantly in the posterior putamen (*4*), the discrimination of healthy subjects from patients with PD might also improve if SOR and K_i^{ref} analyses were performed separately on the anterior and posterior parts of the putamen.

Our aim was to evaluate whether a simple scanning and analysis protocol is feasible for distinguishing patients with early PD from healthy controls. Therefore, we compared subregional striatal ^{18}F-FDOPA PET data from a larger set of nonmedicated patients with early PD and a set of healthy elderly volunteers.

MATERIALS AND METHODS

Study Population

The patient sample consisted of 89 patients (32 women and 57 men; mean [SD] age, 63.8 [8.6] y) with idiopathic PD. The patients were diagnosed at the Department of Neurology, University of Turku, and they had at least 2 of the main symptoms of PD: tremor, rigidity, and hypokinesia. None of the patients exhibited atypical symptoms (*19*). All patients had a brain MRI showing no findings incompatible with the diagnosis of PD. None of the PD patients were taking antiparkinsonian medication at the time of the PET scan. The severity of the motor symptoms was rated with the Unified PD Rating Scale (UPDRS). The mean motor UPDRS score was 29.6 (SD, 9.8; range, 8–49). Six patients were at Hoehn and Yahr stage 1, 28 were at stage 1.5, and 55 were at stage 2. The mean (SD) duration of symptoms was 1.26 (0.67) y (range, 0.3–2 y). The controls were 21 healthy volunteers (10 women and 11 men), and none had a history of neurologic or psychiatric diseases. The mean (SD) age was 60.3 (6.0) y; the age of the healthy controls was statistically significantly different ($P = 0.03$) from that of the PD patients. There was no significant difference in sex distribution between the PD patients and the healthy controls ($P = 0.24$).

All patients and controls gave written consent. The study protocol was approved by the Joint Ethics Committee of Turku University and Turku University Hospital.

Methods

PET. All patients and controls underwent a 90-min dynamic PET scan with a GE Advance PET scanner (GE Healthcare) in the 3-dimensional scanning mode. Attenuation was corrected by use of a 10-min transmission scan with ^{68}Ge rod sources. ^{18}F-FDOPA was used as the tracer to examine presynaptic dopaminergic function; it was synthesized by previously described methods (*20*). The radiochemical purity exceeded 95%. All subjects were given 150 mg of carbidopa before the scan to block the peripheral decarboxylation of ^{18}F-FDOPA. The average intravenously injected dose of ^{18}F-FDOPA was 172 MBq (range, 105–213 MBq).

Image Analysis. The MRI scans were matched with the PET images by use of the surface fitting method (*21*) and resliced according to the PET scans using trilinear interpolation. The ROIs were drawn on the MR images and copied to the PET images. The ROIs were located bilaterally at the head of the caudate nucleus, the putamen (divided into the anterior and posterior parts along the longitudinal axis of the transaxial plane), the ventral striatum, and the occipital cortex. The occipital cortex ROI was used as a reference. The average of the radioactivity concentrations of the ROIs in 2 planes was calculated before statistical analysis. The uptake of ^{18}F-FDOPA was calculated by use of a graphical analysis method with data from 15 to 90 min after ^{18}F-FDOPA injection (*22*). This method (Patlak method) yields the K_i^{ref}, which mainly represents the decarboxylation of ^{18}F-FDOPA to and storage as fluorodopamine, reflecting presynaptic dopaminergic function. SORs were generated for each structure from (bilaterally averaged) occipital ROI data. SORs were calculated for a 15-min time frame 75 min after injection.

Statistical Analysis. The data were characterized by calculating the mean and SD. Comparisons of the mean values for the PD and control groups were done with a 2-sample *t* test. The eligibility of SOR and Ki^{ref} measurements for the diagnosis of PD were studied with a logistic regression analysis. In this analysis, the dichotomic variable indicating PD or control group was the response variable, and the SOR or K_i^{ref} measurement was the predictor. The strength of the association in the logistic regression analysis was quantified by calculating odds ratios (ORs) with 95% confidence intervals (95% CIs). For each variable, the OR, corresponding to the change equal to the coefficient of variation (CV) (calculated as SD/mean) of the variable, was calculated. ORs calculated in this way are comparable among different variables because the differences in the original measurement units do not confuse the comparisons. Exact tests and CIs for ORs were used in the logistic regression analysis. The estimated logistic regression models were illustrated by graphs of prediction probabilities (*23*). The diagnostic ability to predict PD with SOR or Ki^{ref} measurements was also studied with an analysis of receiver operating characteristic (ROC) curves. The area under the curve was used to quantify the results of the ROC analysis. The diagnostic abilities of different measurements were compared by testing the differences in the areas under the empiric ROC curves with nonparametric techniques (*24*). A value of 0.05 was used as a cutoff for statistical significance. Statistical analysis was performed with the SAS System for Windows, release 9.2/2007 (SAS Institute Inc.).

RESULTS

All of the results were calculated separately for brain regions ipsilateral and contralateral to the side with predominant symptoms. The between-group analysis showed that the mean striatal SOR and K_i^{ref} values in the PD group were significantly smaller than those in the control group. The decrease was most severe in the putamen and more intense on the contralateral side than on the ipsilateral side. The decreases in the putamen, expressed as a percentage of

the control mean, varied from 18% to 31% for SOR and from 33% to 64% for K_i^{ref}. The magnitudes of reduction in the caudate nucleus ranged from 9% to 13% for SOR and from 9% to 18% for K_i^{ref}. The decrease in the ventral striatum was approximately 10% for both SOR and K_i^{ref} (Table 1).

We performed an ROC analysis of both SOR and K_i^{ref} to evaluate how well these measures could separate PD patients from healthy controls. An ROC curve is a plot of the sensitivity of a measurement against one minus specificity. The overall accuracy of the measurement can be described as the area under the ROC curve: the larger the area, the better the tool. An area under the ROC curve of 1.00 indicates a perfect diagnostic tool. The contralateral posterior putamen showed the largest areas under the ROC curve: 0.994 for SOR and 0.998 for K_i^{ref}; these values indicated excellent diagnostic accuracy. The ROC curves for the ipsilateral and contralateral SOR and K_i^{ref} values in each striatal subregion are shown in Figure 1. For each subregion, the area under the ROC curve for the contralateral side was larger than that for the ipsilateral side. In addition, the ROC analysis revealed that the SOR and K_i^{ref} values in the caudate nucleus and the ventral striatum, both ipsilateral and contralateral, had lower diagnostic accuracy than the values in the putamen.

We also applied a logistic regression model to calculate the prediction probabilities of SOR and K_i^{ref} for PD in ipsilateral and contralateral striatal regions. In addition to the analysis of the association between binary outcome (i.e., PD patient or control) and continuous predictor variables (i.e., SOR or K_i^{ref}), the logistic regression model provided estimates of outcome probability at various levels of the predictor variable. It has been suggested that the logistic regression model is a useful method for determining the decision level with less ambiguity than ROC curves (*25*). The ORs, corresponding to the change equal to the CV (SD/mean) of the variable, were calculated for SOR and Ki^{ref} in the substriatal structures. ORs calculated in this way are comparable among different variables because the differences in the original measurement units do not confuse the comparisons.

Almost identical prediction probability curves were obtained for K_i^{ref} and SOR. Curves were dependent on both striatal subregions and the laterality of the predominant symptoms. Figure 2 shows that for the contralateral subregions of the putamen, the curves were steep, indicating that when a certain threshold was reached, the probability of being a PD patient rose dramatically. A change of one CV for SOR and Ki^{ref} in the contralateral posterior putamen increased the risk of being a PD patient approximately 30- and 4-fold, respectively ($P < 0.0001$) (Table 2). Five patients (5.6%) with PD had ^{18}F-FDOPA uptake within the control range on both the contralateral and the ipsilateral sides.

DISCUSSION

In the present study, we investigated and compared the abilities of SOR and K_i^{ref} of ^{18}F-FDOPA uptake to differentiate patients with PD from healthy subjects. We found that the values for the contralateral posterior putamen showed the largest area under the ROC curve: 0.994 for SOR and 0.998 for K_i^{ref}; these values indicated excellent separation of the groups. The results for the caudate nucleus and the ventral striatum were not as impressive in this respect. The probability curves were steepest for the contralateral putamen, indicating that when a certain threshold was reached, the probability of being a PD patient rose

TABLE 1. Mean SOR and K_i^{ref} Values for Healthy Controls and PD Patients

	SOR				K_i^{ref} (1/min)			
	Mean (SD)				Mean (SD)			
Region	PD patients	Controls	*P*	Δ%	PD patients	Controls	*P*	Δ%
Anterior putamen								
Ipsilateral	2.12 (0.26)	2.59 (0.18)	<0.0001	18	0.008 (0.002)	0.012 (0.001)	<0.0001	33
Contralateral	1.93 (0.23)	2.62 (0.20)	<0.0001	27	0.006 (0.002)	0.012 (0.001)	<0.0001	50
Posterior putamen								
Ipsilateral	1.91 (0.27)	2.43 (0.22)	<0.0001	21	0.006 (0.002)	0.010 (0.002)	<0.0001	40
Contralateral	1.71 (0.21)	2.47 (0.19)	<0.0001	31	0.005 (0.002)	0.011 (0.001)	<0.0001	55
Putamen								
Ipsilateral	1.89 (0.25)	2.46 (0.19)	<0.0001	23	0.006 (0.002)	0.011 (0.002)	<0.0001	45
Contralateral	1.68 (0.21)	2.44 (0.22)	<0.0001	31	0.004 (0.002)	0.011 (0.002)	<0.0001	64
Caudate								
Ipsilateral	2.05 (0.21)	2.26 (0.14)	<0.0001	9	0.010 (0.002)	0.011 (0.001)	<0.0001	9
Contralateral	1.96 (0.21)	2.26 (0.15)	<0.0001	13	0.009 (0.002)	0.011 (0.001)	<0.0001	18
Ventral striatum								
Ipsilateral	2.03 (0.24)	2.20 (0.27)	0.003	8	0.009 (0.002)	0.010 (0.003)	0.02	10
Contralateral	1.96 (0.20)	2.19 (0.22)	<0.0001	10	0.009 (0.002)	0.010 (0.002)	<0.0001	1

Δ% = percentage decrease in PD patients relative to controls.

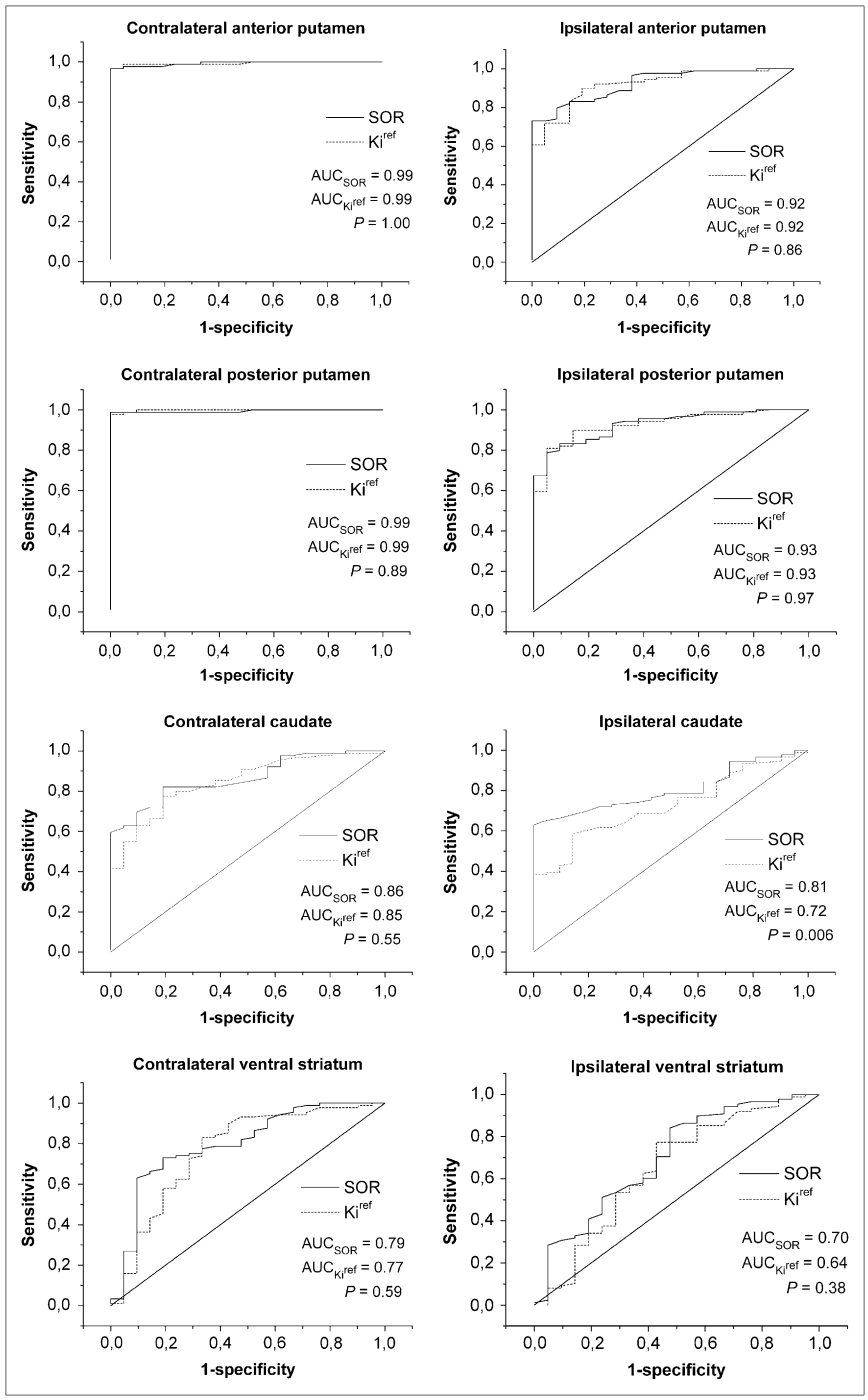

FIGURE 1. ROC curves for SOR and Ki^{ref} in substriatal structures. The larger the *P* value, the smaller the difference between SOR and Ki^{ref}. AUC = area under curve.

dramatically. Thus, a simple 15-min SOR performed as well as a dynamic 90-min scan with graphical analysis (K_i^{ref}) in separating patients with PD from healthy controls.

In a previous study with 21 PD patients, both SOR and K_i^{ref} of ^{18}F-FDOPA uptake completely separated PD patients from healthy controls (*17*). This result may have been partially attributable to the fact that patients in that study were at the moderate stage of PD, with half of them being at Hoehn and Yahr stage 3 or 4. In contrast, the patients in the present study were nonmedicated patients at the early stage of the disease (mean duration of symptoms, 1.26 y). The highest Hoehn and Yahr stage was 2. Thus, the patients in the present study represented the situation at a time close to the clinical diagnosis.

In addition, as an extension of the previous study (*17*), we investigated regions contralateral and ipsilateral to the side with predominant symptoms separately and divided the striatum into subregions. The decreased striatal ^{18}F-FDOPA uptake observed in patients with PD was more pronounced in the putamen than in any other striatal subregion. This finding is consistent with the results of the PD imaging studies, which suggested that the dopamine depletion began

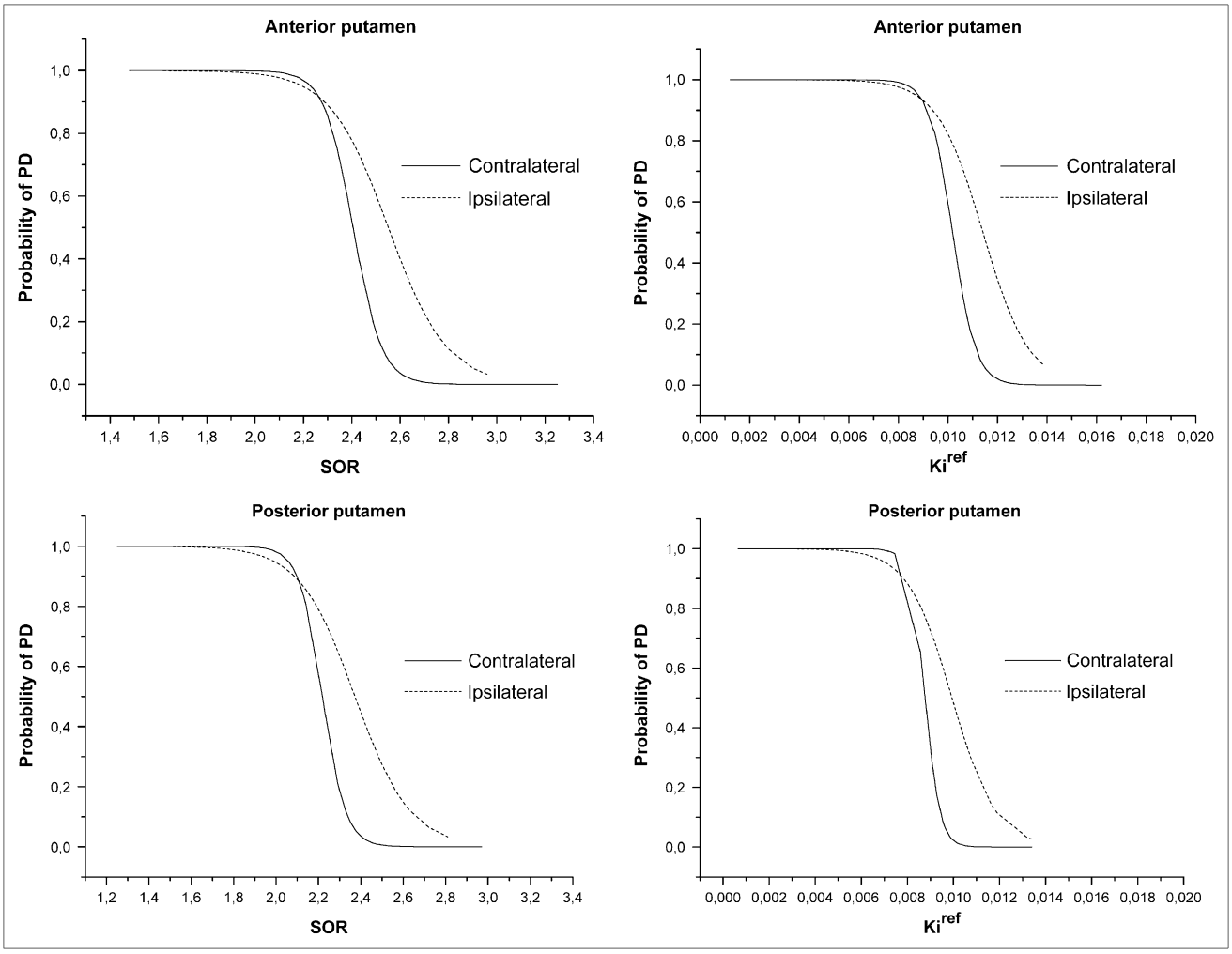

FIGURE 2. Probability of receiving positive diagnosis (PD) at given substriatal SOR and K_i^{ref} ipsilateral and contralateral to side with predominant symptoms.

in the posterior parts of the putamen and proceeded during the disease to the caudate nucleus and other parts of the dopaminergic system (*5,6,26,27*). The decrease in ^{18}F-FDOPA uptake in the present study was larger in the contralateral striatum, a result that is understandable given that motor symptoms have been shown to be more severe on the side contralateral to the striatum with lower dopaminergic activity. Accordingly, we found that the separation of PD patients from healthy controls was most obvious with ^{18}F-FDOPA uptake in striatal structures contralateral to the side with predominant symptoms, especially those of the posterior putamen. Furthermore, the probability plot was steepest in the contralateral posterior putamen, a result also indicating the good discriminatory ability of ^{18}F-FDOPA

TABLE 2. OR in Subregions of Putamen for SOR and K_i^{ref} Evaluated with Logistic Regression Model

	SOR			K_i^{ref}		
Region	CV	OR (95% CI)	*P*	CV	OR (95% CI)	*P*
Anterior putamen						
Ipsilateral	0.1	2.3 (1.6–3.4)	<0.0001	0.3	1.4 (1.2–1.6)	<0.0001
Contralateral	0.2	24.2 (6.2–175.9)	<0.0001	0.4	2.3 (1.6–4.1)	<0.0001
Posterior putamen						
Ipsilateral	0.2	4.5 (2.5–9.2)	<0.0001	0.4	1.5 (1.3–1.9)	<0.0001
Contralateral	0.2	29.6 (5.9–495.5)	<0.0001	0.5	4.0 (1.8–26.9)	<0.0001

For each variable, OR, corresponding to change equal to CV (SD/mean) of variable, was calculated.

uptake. Actually, the probability curves for SOR and K_i^{ref} were comparable, indicating that the probability of being a PD patient can be equally accurately estimated by either analytic method. Different slopes in probability curves may indicate different diagnostic patterns for PD; a steep curve, like that found in both the anterior putamen and the posterior putamen, would indicate a PD diagnosis easily linked to low SOR or K_i^{ref} values. A flatter curve, in contrast, would indicate difficulty linking even very low SOR or K_i^{ref} values to a PD diagnosis, as was seen in the caudate nucleus and the ventral striatum in the present study.

It has been suggested that the logistic regression model is a useful method for determining the decision level with less ambiguity than ROC curves as well as for providing measures of dispersion for the decision level (*25*). We emphasize, however, that we are not implying that the diagnosis of PD can be based on ^{18}F-FDOPA imaging alone. ^{18}F-FDOPA PET can be used to support the clinical diagnosis, but its appropriate role in the diagnosis and management of PD should be studied further.

The PD patients in the present study were, on average, 3.5 y younger than the healthy controls, a difference that became statistically significant in this large population. This difference in mean age could theoretically enhance the difference in ^{18}F-FDOPA uptake between patients and controls. However, ^{18}F-FDOPA uptake shows no or only a minimal decrease during aging (*15,28–30*); therefore, it is unlikely that the small difference in the ages of the PD patients and the healthy controls in the present study would have affected the results.

For 5 patients (5.6%) with a clinical diagnosis of PD, ^{18}F-FDOPA uptake was within the control range. Such results are sometimes referred to as "SWEDDs" (scans without evidence of "dopaminergic deficit") (*31*). In large clinical series, individuals with such results represented about 11%−15% of patients with PD (*32–34*). Clinical follow-up showed that the final diagnoses for these patients were diverse and included secondary forms of parkinsonism as well as psychogenic conditions (*32,35*). Four of the PD patients with normal ^{18}F-FDOPA uptake in the present study still had a diagnosis of PD, and they were all taking levodopa. In 3 of them, the clinical progression has been very slow. In one patient, the disease has progressed to the severe stage, and the patient has had a subthalamic nucleus stimulator inserted. One patient was later thought to have vascular PD because MRI showed widespread vascular lesions and "lower-body parkinsonism" with prominent gait impairment.

Two earlier studies reported K_i^{ref} to be more powerful than SOR in differentiating PD patients from healthy controls and in detecting the rate of disease progression (*10,11*). Possible explanations for this discrepancy are differences in acquisition (2 dimensional (*10*) vs. 3 dimensional (present study)) and the time of the SOR determination. Indeed, it has been shown that inclusion of the early scanning phase in calculation of the SOR decreases the sensitivity of the measure (*17*). In addition, we investigated patients at the early phase of the disease; thus, it is possible that the performance of SOR might differ from that of K_i^{ref} in a long-term evaluation of disease progression. However, at least in evaluating longitudinal changes in ^{18}F-FDOPA uptake in patients with a fetal transplant, SOR was superior to K_i (calculated with metabolic-corrected arterial plasma as the input) (*16*).

The strength of the present study is the large number of PD patients ($n = 89$) who were all recently diagnosed and nonmedicated at the time of the PET scan. In addition, analyzing regions contralateral and ipsilateral to the side with predominant symptoms separately and dividing the striatum into its subregions provided us with the possibility of finding the most sensitive striatal subregions for differentiating PD patients from healthy controls. One minor limitation of the present study was that the relationship between the clinical state (UPDRS) and the 2 parameters (SOR and K_i^{ref}) could not be examined. Although striatal ^{18}F-FDOPA uptake correlates well with motor disability in patients with advanced PD (*36*), the correlation is often weak in early PD because of the narrow range of motor disability in the patient sample.

A limitation of studies evaluating the diagnostic value of various imaging technologies in PD is the lack of a gold standard for diagnosis in living patients. Drawbacks of the present study are the lack of clinical follow-up in all patients and, of course, the lack of neuropathologic confirmation of the diagnosis. Underdiagnosis and misdiagnosis of PD are common because of the variety of syndromes with parkinsonism (*37*), although it has been shown that with the current clinical criteria, an accuracy of 90% can be obtained in the clinical diagnosis of PD (*38*). Neuropathologic examination at autopsy is currently the definitive diagnostic gold standard. Biomarkers could improve diagnostic accuracy. Even though PD is still diagnosed clinically, imaging techniques such as ^{18}F-FDOPA PET with SOR and K_i^{ref} as analytic parameters could be unique aids in the diagnosis and differential diagnosis of PD. In daily clinical practice, helping to differentiate between PD and a healthy state is especially useful in patients with mild or debatable clinical symptoms. Verification of dopaminergic hypofunction may warrant early treatment initiation, as recently suggested (*39*), although contradictory views are equally justified (*40*). Early detection of dopaminergic hypofunction and early treatment initiation will become important when disease-modifying therapies become available.

CONCLUSION

The present study showed that both SOR and K_i^{ref} can be used to measure presynaptic dopaminergic function in vivo and have equal abilities to distinguish PD patients from healthy controls. The contralateral anterior and posterior putamen had the greatest ability to distinguish PD patients from healthy controls. A single 15-min scan 75 min after

tracer injection seems to be sufficient in a clinical research environment for patients with PD. This method provides a powerful and economical alternative for research on the disease mechanism and differential diagnosis.

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