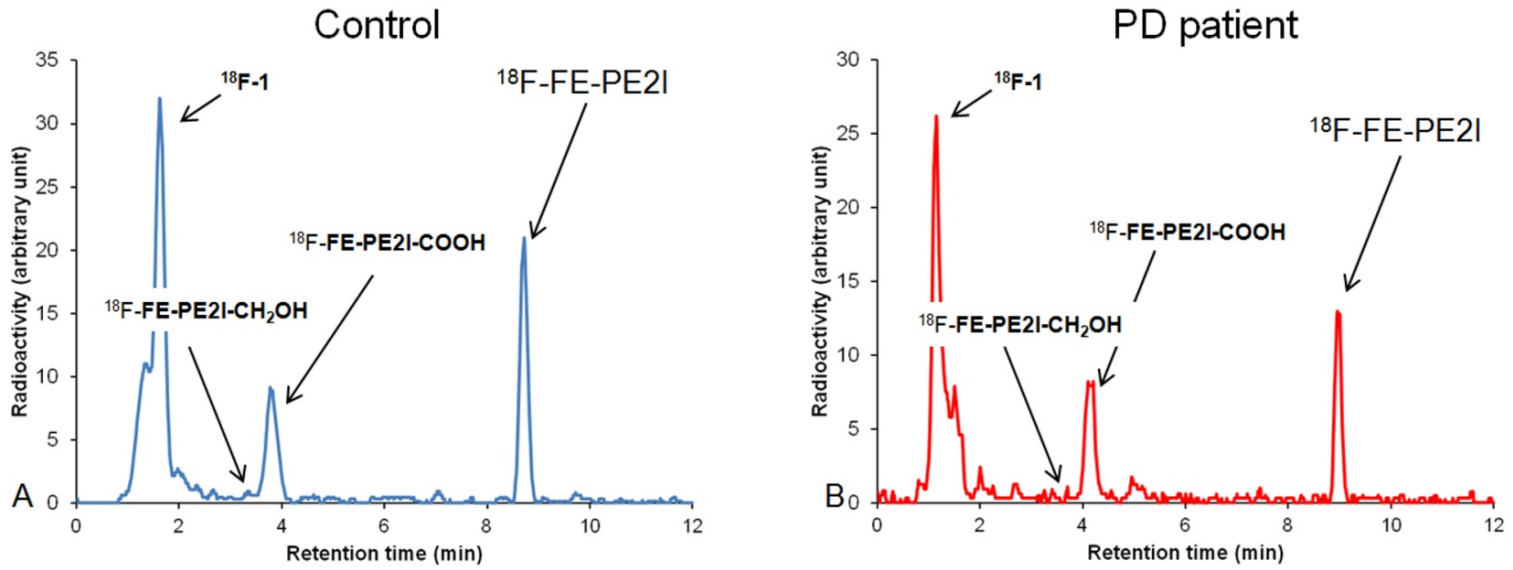
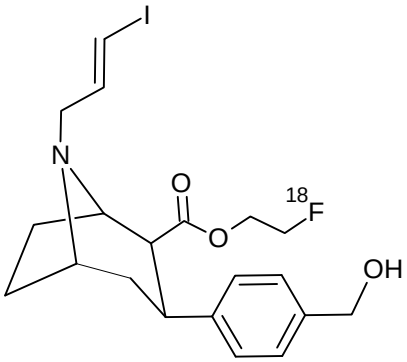
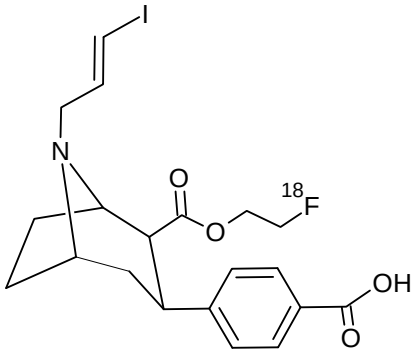


Supplemental Figure 1 (A-B). In vivo metabolism of ^{18}F-FE-PE2I. Representative high-performance liquid chromatography (HPLC) analysis of plasma in one control subject (A) and one patient with Parkinson's disease (B) following injection of ^{18}F-FE-PE2I. Different radioactive species were observed among which two were identified, ^{18}F-FE-PE2I-CH_2OH and ^{18}F-FE-PE2I-CHOOH. The radiometabolite peak ^{18}F-1 was the most abundant and the least lipophilic, as judged by the retention time < 2 min.

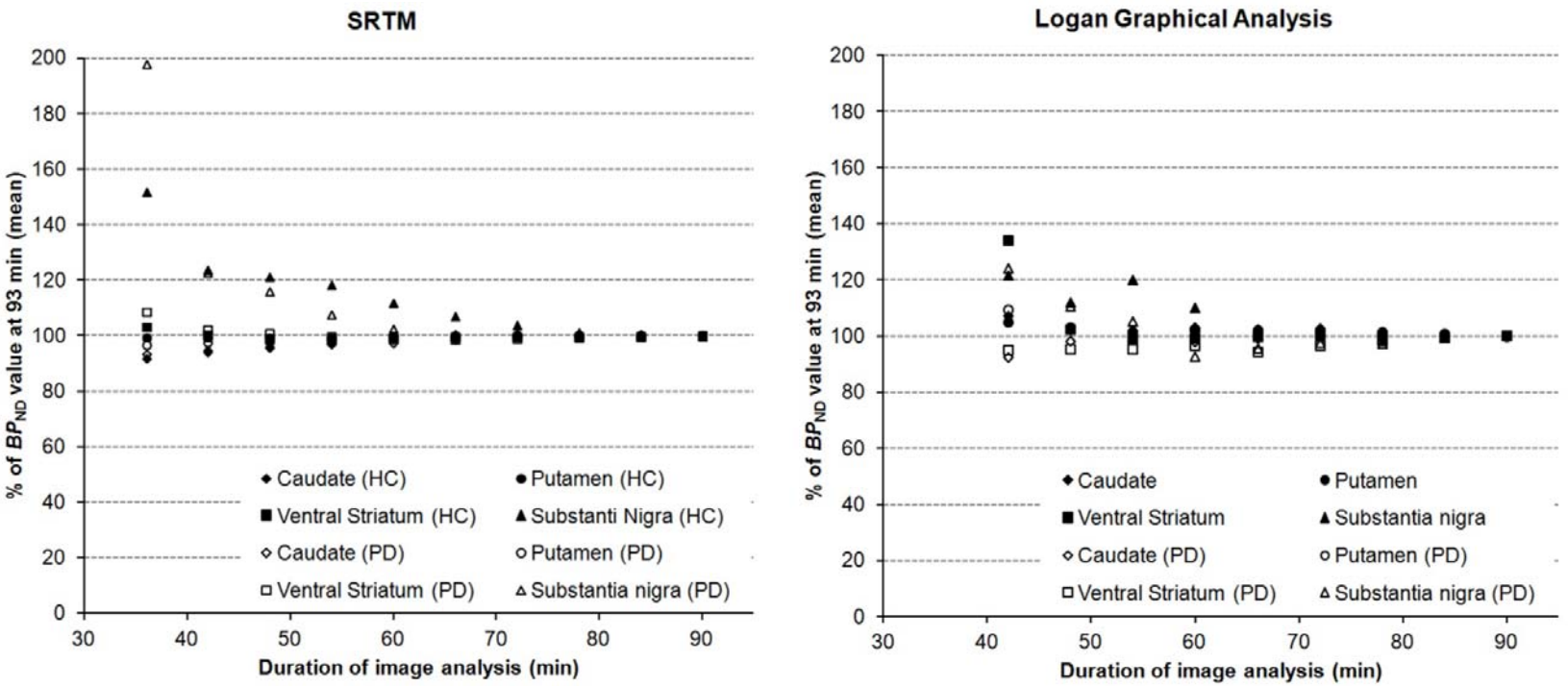


^{18}F-FE-PE2I- CH_2OH

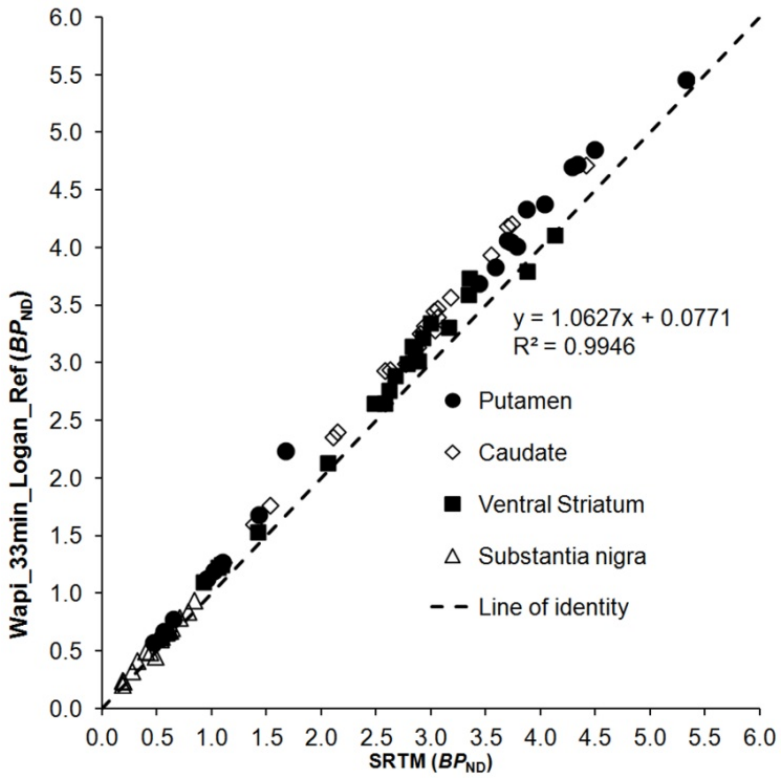


^{18}F-FE-PE2I-COOH

Supplemental Figure 2: The two identified radioactive metabolites ^{18}F-FE-PE2I-CH_2OH and ^{18}F-FE-PE2I-OH and their relative chemical structures.



Supplemental Figure 3: Time stability of binding potential (BP_{ND}) estimated with the simplified reference tissue model (SRTM) and Logan graphical analysis (LoganRef) expressed as % of BP_{ND} value (mean) at 93 minute.



Supplemental Figure 4: Correlation of binding potential (BP_{ND}) estimated with Logan graphical analysis based on Wavelet-aided parametric imaging (Wapi_33min_Logan Ref) and BP_{ND} estimated with the simplified reference tissue model (SRTM) based on manually delineated regions of interest. Each data point represents BP_{ND} values of each subject.

Supplemental Table 1: Binding Potential Values (BP_{ND}) of ^{18}F-FE-PE2I using the quantification with the simplified reference tissue model (SRTM) and Logan Graphical Analysis (LoganGA) in patients with Parkinson's disease (PD) and control subjects (CS) in the different regions of interest. Values are mean ± 1 SD.

Regions	SRTM		LoganGA	
	CS	**PD**	**CS**	**PD**
Caudate	*3.32±0.5*	*2.25±0.7*	*3.36±0.5*	*2.29±0.7*
Putamen	*4.08±0.6*	*1.21±1*	*4.1±0.6*	*1.21±1*
Ventral Striatum	*3.12±0.5*	*2.08±0.9*	*3.13±0.5*	*2.06±0.9*
Substantia nigra	*0.61±0.1*	*0.38±0.2*	*0.56±0.1*	*0.35±0.2*

Supplemental Appendix

Methods

Patients with Parkinson's disease

At the time of imaging, two of the patients were drug-naïve; three had been treated with levodopa and dopamine agonist medication, one was in treatment with L-dopa, dopamine agonists, and monoamine oxidase B inhibitors and four with dopamine agonists only. PET measurements were performed during a drug off-state (twelve hours without antiparkinsonian medication). Ratings of present cognitive functioning and mood-related symptoms included the Mini-Mental State Examination, the Beck Depression Inventory (BDI-II) (*1*) and the Montgomery-Åsberg Depression Ratings Scale (MADRS) (*2*). The MADRS and BDI-II scales are typically used to diagnose depression or to assess the effects of treatment with antidepressant drugs. In this study, the scales were used as part of the screening procedure in patients with Parkinson's disease (PD) to rule out the diagnosis of depression and were also administered to control subjects for comparative purposes.

PET experimental procedures

To prevent head motion during the PET measurement, an individual plaster helmet was made for each subject (*3*). A 6-minute transmission scan using a ^{137}Cs source was first acquired for attenuation correction. Emission data were acquired in list mode for a period of 93 minutes after i.v. bolus injection of the radioligand within 10 sec. After injection, the i.v. line was flushed with 10 mL NaCl. Dynamic images were reconstructed in a series of 37 frames of increasing duration (8 x 10 sec, 5 x 20 sec, 4 x 30 sec, 4 x 60 sec, 4 x 180 sec, 12 x 360 sec) using three-dimensional ordinary Poisson ordered subset expectation maximization (OP-3D-OSEM) including modeling of the system's point spread function (PSF). The in-plane resolution with this reconstruction method has been estimated to 1.5 mm in full width at

half maximum in the center of the field of view (*4*). Images were corrected for motion with a post-reconstruction frame-to-frame correction realignment as previously described (*5*). In one case (P11) a modified procedure was applied to correct for head movements larger than 2 mm, using a frame-specific attenuation-data.

Region-of-interest analysis

3D T1-weighted MRI images were first realigned along the plane connecting the anterior and the posterior commissures and then coregistered to the summed PET images using SPM5 (Statistical parametric mapping, Wellcome Trust Centre for Neuroimaging, U.K.). Regions of interest (ROIs) were manually delineated on subject's MRI on caudate, putamen, ventral striatum, SN and cerebellum using the software Human brain atlas (Hba). ROIs were then applied to the dynamic PET images using the MRI-PET transformation matrix to obtain regional time activity curves (TACs). In PD patients, the contralateral striatum was defined as the striatum opposite to the clinically most affected side.

Measurement of Protein binding

Plasma (500 µL) or phosphate buffered saline solution (500 µL) as a control were mixed with the formulation (50 µL, ~1 MBq) and incubated at room temperature for 10 minutes. After the incubation, 200 µL portions of the incubation mixtures were pipetted into ultrafiltration tubes (Centrifree YM-30, molecular weight cutoff, 30,000; Millipore: Billerica, USA) and centrifuged at 1,500g for 15 min. Equal aliquots (20 µL) of the ultrafiltrate (C_{free}) and of the plasma (C_{total}) were counted for their radioactivity using a NaI well-counter. Each determination was performed in duplicate. The free fraction was then calculated as $f_P=C_{free}/C_{total}$, and the results were corrected for the membrane binding measured with the control samples.

Results

Asymmetry Index

In PD patients, the asymmetry index (A.I. %) of the binding potential (BP_{ND}) was measured as: (Ipsi-Contra)/(average Ipsi and Contra)*100. The A.I. (mean±SD) of BP_{ND} in Caudate, Putamen, Ventral Striatum and SN were respectively 19.6±19%, 39.2±35.9%, 13.7±11.2% and -1.31±35.8%.

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