Supplementary Materials

Supplementary Method S1. Quantitative analyses of ^{18}F-FP-CIT PET

The ^{18}F-FP-CIT PET images were acquired using a GE PET-CT DSTe scanner (GE Discovery STE; GE Healthcare; Milwaukee, WI, USA), which obtains images with a three-dimensional resolution of 2.3-mm full width at half maximum. After the subjects fasted for at least 6 h, they were intravenously injected with 5 mCi (185 MBq) of ^{18}F-FP-CIT. 90 min after the injection, PET images were acquired for 20 min in the three-dimensional mode at 12 kVp and 380 mA. Image processing was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) with Matlab 2013a for Windows (Math Works, Natick, MA, USA). Quantitative analyses were based on volumes of interests (VOIs), which were defined on the basis of a template in standard space. All reconstructed PET images were spatially normalized to the Montreal Neurology Institute (MNI) template space using a standard ^{18}F-FP-CIT PET template which was generated in-house from ^{18}F-FP-CIT PET and T1-weighted MRI scans of 13 normal controls (four men and nine women, mean age 55.2 ± 9.2 years) as described previously to remove intersubject anatomic variability (1). All healthy controls had no previous history of psychiatric or neurologic illness and showed normal cognition on all neuropsychological items. First, we co-registered individual ^{18}F-FP-CIT PET images onto corresponding T1-weighted MRI images. Second, each individual T1-weighted MRI image was spatially normalized onto the MNI T1 template. Third, the deformation fields, which are used to map the individual MRI images to the MNI T1 template, were applied to the corresponding ^{18}F-FP-CIT PET images. Finally, the ^{18}F-FP-CIT PET template was defined by averaging the spatially normalized ^{18}F-FP-CIT PET images.

Twelve VOIs of bilateral striatal subregions and one occipital VOI were drawn on a co-registered spatially normalized single T1-weighted magnetic resonance and ^{18}F-FP-CIT PET template image on MRIcro version 1.37 (Chris Rorden, Columbia, SC, USA) (2). To describe briefly, the striatum was divided along the anterior-posterior commissure line on the transverse plane into dorsal and ventral portions. The ventral portion comprises two subregions: the ventral putamen and ventral

striatum. Subsequently, the dorsal portion was divided along the coronal anterior commissure plane into the following anterior and posterior subregions: the anterior caudate, posterior caudate, anterior putamen, and posterior putamen. The positions of the automatically defined template VOIs were adjusted manually by our in-house VOI editing software called ANIQUE (AMC NM Image Quantification Toolkit of Excellence) to ensure registration accuracy (3). Our manual adjustment of VOI is a step that may minimize possible mis-registration occasionally occurring in the automated VOI analysis. DAT availability was calculated using the non-displaceable binding potential, which was defined as follows: (mean standardized uptake value of the striatal subregions VOI–mean standardized uptake value of the occipital VOI)/(mean standardized uptake of the occipital VOI) (4).

Supplementary Method S2. MRI acquisition

All scans were acquired with a Philips 3.0T scanner (Philips Intera; Philips Medical System, Best, The Netherlands) with a SENSE head coil (SENSE factor=2). A high-resolution, T1-weighted MRI volume data set was obtained from all subjects with a 3-dimensional T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224 × 256 matrix; 256 × 256 reconstructed matrix with 182 slices; 220-mm field of view; 0.98 × 0.98 × 1.2mm^3 voxels; 4.6 ms echo time; 9.6 ms repetition time; 8° flip angle; and 0mm slice gap.

Supplementary Method S3. The detailed step of choroid plexus (CP) segmentation

Automated segmentation of brain regions and each region's cortical thickness values were extracted using Freesurfer software package Version 7.2. Freesurfer volume-based segmentation preprocessing stream has been fully documented in a freesurfer online link (*http://surfer.nmr.mgh.harvard.edu/*). Briefly, Freesurfer conducts volume-based segmentation preprocessing methods which includes skull-stripping, bias field correction and MNI305 space registration. Freesurfer then generates segmentation of gyral based regions of interest (ROI), also known as Desikan-Killiany cortical atlas (5), and cortical thickness values of each ROI. As a result, brain regions including the intracranial volume (ICV), CP volume (CPV), lateral ventricle volume (LVV), gray matter volume (GMV), white matter

hyperintensities volume (WMHV), and hippocampal volume were obtained.

After that, we performed additional automated segmentation of CP in the lateral ventricles according to the Gaussian Mixture Models (GMM) segmentation method (6) for more accurate choroid plexus segmentation. The pipeline for GMM segmentation can be divided into three parts: (1) A first Bayesian GMM with two components to all within the mask to differentiate between a CSF voxels cluster and a lateral ventricular wall voxels cluster. (2) 3D Susan smoothing algorithm implemented in FSL software (sigma = 1mm) smooths the lateral ventricular wall voxels cluster. (3) A second Bayesian GMM with fourth components detects the CP voxels which belongs to the cluster with the highest average voxel intensity. Unlike previous study that used three components in a second Bayesian GMM (6), we applied a Bayesian GMM with three components to all the within the mask for reducing the false positive ratio.

Supplementary Table S1. Demographic characteristics and dopamine transporter availability in patients with Parkinson's disease

	Low-tertile (n = 107)	Middel-tertile (n = 108)	High-tertile (n = 107)	*p* value
Demographic characteristics				
Age at symptom onset, y	60.47 ± 8.53	63.14 ± 8.55	68.83 ± 10.14	<0.001[b,c]
Female,	71 (66.36%)	50 (46.30%)	49 (45.79%)	0.003[a,b]
Disease duration, m	15.20 ± 12.21	18.23 ± 16.24	17.96 ± 17.08	0.277
UPDRS-III	20.82 ± 8.83	22.44 ± 10.47	26.51 ± 11.32	<0.001[b,c]
Clinical phenotype				0.397
TD	57 (53.27%)	52 (48.15%)	52 (48.60%)	
PIGD	38 (35.51%)	50 (46.30%)	44 (41.12%)	
Intermediate	12 (11.21%)	6 (5.56%)	11 (10.28%)	
Vascular risk factors				
Hypertension	37 (34.58%)	48 (44.44%)	42 (39.25%)	0.334
Diabetes mellitus	14 (13.08%)	19 (17.59%)	21 (19.63%)	0.423
Dyslipidemia	20 (18.69%)	21 (19.44%)	17 (15.89%)	0.775
BMI, kg/m^2	23.34 ± 2.70	23.60 ± 2.81	23.26 ± 2.83	0.637
Volumetric MRI measures				
CP volume, ratio of ICV × 10^3	0.90 ± 0.18	1.29 ± 0.11	2.05 ± 0.57	<0.001
GM volume, ratio of ICV × 10^3	258.17 ± 48.81	263.53 ± 29.38	258.72 ± 61.07	0.669
hippocampal volume, ratio of ICV × 10^3	11.87 ± 5.27	18.04 ± 5.94	25.53 ± 8.74	<0.001[a,b,c]
LV volume, ratio of ICV × 10^3	5.14 ± 1.28	5.18 ± 0.74	4.88 ± 0.77	0.045
WMH volume, ratio of ICV × 10^3	0.35 ± 0.62	0.36 ± 0.49	0.70 ± 1.55	0.016[b,c]
ICV, mL	1655.00 ± 510.96	1540.10 ± 184.77	1559.37 ± 247.84	0.034[b,c]

Values are expressed as mean ± standard deviation or number (percentage). *p* values are the results of analysis of variance or χ^2 tests as appropriate.

[a] Significantly different in comparison between the low-tertile and middle-tertile groups

[b] Significantly different in comparison between the low-tertile and high-tertile groups

[c] Significantly different in comparison between the middle-tertile and high-tertile groups

CP = choroid plexus; GM = gray matter; ICV = intracranial volume; LV = lateral ventricle; PIGD = postural instability/gait difficulty; TD = tremor dominant; UPDRS = Unified Parkinson's Disease Rating Scale; WMH = white matter hyperintensity.

Supplementary Table S2. Multivariate linear regression analysis of UPDRS-III score

	UPDRS-III score (F = 7.808, P <0.001)	
Variables	*Beta*	*P*
Age at symptom onset	0.180	0.001
Female	0.029	0.587
Disease duration	0.178	<0.001
Motor subtype		
TD	Ref.	
PIGD/indeterminate	0.027	0.610
DAT availability in the posterior putamen	-0.221	<0.001
BMI	-0.008	0.879
WMH volume	0.069	0.200
CPV	**0.121**	**0.035**

Results of multivariate linear regression analysis for the striatal subgroup after controlling for age at symptom onset, sex, disease duration, motor subtype, BMI, WMH volume, and DAT availability in the posterior putamen.

Beta = standardized beta coefficient; BMI = body mass index; CPV = choroid plexus volume; PIGD = postural instability and gait difficulty; TD = tremor dominant; UPDRS = Unified Parkinson's Disease Ratings Scale; WMH = white matter hyperintensity

Supplementary Table S3. Multivariate linear regression analysis of dopamine transporter availability in each striatal subgroup

Striatal subgroup	Anterior caudate		Posterior caudate		Anterior putamen		Posterior putamen		Ventral putamen		Ventral striatum	
	F = 16.16, *P* <0.001		*F* = 15.21, *P* <0.001		*F* = 5.148, *P* <0.001		*F* = 2.406, *P* = 0.021		*F* = 4.316, *P* <0.001		*F* = 7.784, *P* <0.001	
	Beta	*P*	*Beta*	*P*	*Beta*	*P*	*Beta*	*P*	*Beta*	*P*	*Beta*	*P*
Age at symptom onset	-0.344	<0.001	-0.324	<0.001	-0.126	0.032	0.024	0.689	-0.112	0.060	-0.249	<0.001
Female,	0.249	<0.001	0.236	<0.001	0.154	0.005	0.090	0.108	0.123	0.026	0.119	0.027
Disease duration	-0.079	0.108	-0.029	0.564	-0.026	0.633	-0.008	0.878	-0.064	0.240	-0.098	0.065
Motor subtype												
TD	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
PIGD/intermediate	-0.039	0.427	-0.082	0.096	-0.138	0.011	-0.142	0.010	-0.115	0.035	-0.126	0.017
BMI	0.020	0.686	-0.007	0.892	-0.002	0.976	-0.006	0.919	0.012	0.822	0.014	0.788
WMH volume	-0.064	0.203	-0.051	0.312	-0.015	0.791	0.004	0.948	-0.054	0.328	-0.093	0.085
CPV group												
Low-tertile	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Middle-tertile	-0.068	0.240	-0.106	0.071	-0.143	0.025	-0.192	0.003*	-0.158	0.014*	-0.048	0.439
High-tertile	-0.164	0.008*	-0.175	0.005*	-0.172	0.012*	-0.178	0.011*	-0.162	0.018*	-0.095	0.152

Results of multivariate linear regression analysis for the striatal subgroup after controlling for age at symptom onset, sex, disease duration, motor subtype, BMI, and WMH volume.

* $P < 0.05$ after correction for multiple comparisons using the FDR method

Beta = standardized beta coefficient; BMI = body mass index; CPV = choroid plexus volume; PIGD = postural instability and gait difficulty; TD = tremor dominant; WMHs = white matter hyperintensity.

Supplementary Table S4. Relationship between CPV, DAT availability in the posterior putamen, and UPDRS-III score

	Mediator			Outcome (UPDRS-III)			Goodness of fit model		
	β	SE	*P*	*β*	SE	*P*	χ^2 (*df*); *P value*	CFI	RMSEA
Predictor: CPV	**-0.107**	**0.033**	**0.001**	**2.137**	**1.001**	**0.033**	3.895 (5); 0.565	1.000	<0.001
Mediator: DAT availability in the posterior putamen	-	-	-	**-5.016**	**1.217**	**<0.001**			

The model showed a good fit to the UPDRS-III scores based on χ^2 statistics, CFI, and RMSEA. Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; df = degree of freedom; *β* = regression coefficient; CFI = confirmatory fit index; CPV = choroid plexus volume; DAT = dopamine transporter; RMSEA = root mean square error of approximation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

Supplementary Table S5. Cox regression models for prediction of the development of FOG according to the tertile groups of CPV

Variables	FOG development	
	Hazard ratio (95% CI)	*P*
Age at symptom onset	0.993 (0.966-1.020)	0.583
Female	1.279 (0.766-2.134)	0.347
Disease duration	1.001 (0.983-1.018)	0.954
Motor subtype		
TD	Ref.	
PIGD/intermediate	2.044 (1.206-3.463)	0.008
DAT availability in the posterior putamen	0.780 (0.442-1.377)	0.392
BMI	0.988 (0.904-1.081)	0.796
LED	1.001 (1.001-1.002)	0.001
WMH volume	0.883 (0.586-1.331)	0.552
CPV group		
Low-tertile	Ref.	
Middle-tertile	1.382 (0.732-2.607)	0.318
High-tertile	**2.172 (1.156-4.081)**	**0.016**

Results of Cox regression analyses for the development of FOG after controlling for age at symptom onset, sex, disease duration, motor subtype, DAT availability in the posterior putamen, BMI, LED, and WMH volume. BMI = body mass index; CPV = choroid plexus volume; DAT = dopamine transporter; FOG = freezing of gait; LED = levodopa-equivalent dose; PIGD = postural instability and gait difficulty; TD = tremor dominant; WMH = white matter hyperintensity.

Supplementary Table S6. Longitudinal changes of levodopa-equivalent doses according to the tertile groups of CPV for 2 years

Variables	*Estimates (SE)*	*P*
Intercept	-202.03 (84.13)	0.017
Age at symptom onset	5.30 (0.73)	<0.001
Female,	-5.62 (13.27)	0.673
Disease duration	0.97 (0.44)	0.027
Motor subtype		
TD		
PIGD/intermediate	23.61 (13.17)	0.074
DAT availability in the posterior putamen	-67.45 (14.33)	<0.001
BMI	3.26 (2.36)	0.168
WMH volume	6.07 (6.50)	0.352
CPV group		
Low-tertile × Time		
Middle-tertile	-6.85 (21.05)	0.745
High-tertile	-34.44 (22.35)	0.124
Time, y	184.29 (9.67)	<0.001
CPV group × Time		
Low-tertile × Time		
Middle-tertile × Time	20.37 (13.52)	0.132
High-tertile × Time	**40.27 (14.04)**	**0.004**

Results of linear mixed models for LED after controlling for age of symptom onset, sex, disease duration, motor subtype, DAT availability in the posterior putamen, BMI, WMH volume, CPV, time, and CPV × time.

BMI = body mass index; CPV = choroid plexus volume; DAT = dopamine transporter; PIGD = postural instability and gait difficulty; TD = tremor dominant; WMH = white matter hyperintensity.

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