SUPPLEMENTARY MATERIAL

SECTION 1 – PPMI cognitive categorization

The following cognitive tests assessing memory, visuospatial function, processing speed-attention, executive function and semantic fluency were administered to each patient as part of the PPMI study: Hopkins Verbal Learning Test-Revised (HLVT-R), Benton Judgment of Line Orientation (JOLO) 15-item (split-half) version, Symbol-Digit Modalities Test (SDMT), Letter-Number Sequencing (LNS) and semantic fluency tests (animals, vegetables and fruits).

The Cognitive Categorization assessment was used to make a determination of Parkinson Disease Dementia (PDD) and PD with mild cognitive impairment (PD-MCI). Information for this assessment was provided through a combination of responses from the subject or other informant, the Investigator's judgment, and results from the cognitive testing covering the four cognitive domains mentioned above.

The determination of PDD was made on the following factors: (i) History of cognitive decline determined by the investigator based on information from the patient, other informant (spouse, family member or friend) and the investigator's judgment (The investigator reports the presence of cognitive decline [Yes/No] based on clinical evaluation of attention, memory, orientation, executive abilities, praxis and language and the presence of functional impairment compared to premorbid state; this determination is made prior to or independent from review of neuropsychological test scores/results); (ii) Cognitive impairment defined as at least 1 test score (out of 6 scores) from at least 2 domains (out of 4 domains) >1.5 SD below the standardized mean; (iii) Functional limitation as a result of cognitive impairment (IADLs).

The determination of PD-MCI was made based on the following factors: (i) Cognitive complaint by either the patient or informant (spouse, family member or friend); (ii) Cognitive impairment defined as at least 2 test scores (out of 6 scores) from at least 1 domain (out of 4 domains) >1.0 SD below the standardized mean; (iii) No functional impairment as a result of cognitive impairment (IADLs).

SECTION 2 – PPMI DAT imaging protocol

Imaging site set up. All PPMI imaging centres were visited for technical site evaluation and set up which involved performing a SPECT acquisition on an anthropomorphic striatal phantom filled with ^{123}Ioflupane on the same camera with the same parameters and collimators as the subsequent patients imaged in the study. This procedure was used to optimize and standardize the reconstruction and filtration of the SPECT images across the different imaging centers.

^{123}I-FP-CIT SPECT procedure. Before the ^{123}I-FP-CIT injection, subjects were pre-treated with stable iodine (10 drops of a saturated solution of potassium iodide) to reduce the uptake of ^{123}I-FP-

CIT by the thyroid. Subjects were injected with 3-5 mCi (111–185 MBq) of ^{123}I-FP-CIT. Within a 4 hour (+/- 30 minute) window following the injection, subjects underwent SPECT imaging on the camera. Raw SPECT data were acquired into a 128x128 matrix stepping each 3° for a total of 120 (or 4° for a total of 90) projections in a window centred on 159±10 KeV with a total scan duration of 30-45 min.

Processing and analysis. ^{123}I-FP-CIT SPECT imaging acquired at each PPMI imaging center were sent to Institute for Neurodegenerative Disorders, New Haven, Connecticut for processing and calculation of SBRs. SPECT raw projection data were imported to a HERMES (Hermes Medical Solutions, Skeppsbron 44, 111 30 Stockholm, Sweden) system for iterative (HOSEM) reconstruction. This was done for all imaging centers to ensure consistency of the reconstructions. Iterative reconstruction was done without any filtering applied. The HOSEM reconstructed files were then transferred to PMOD (PMOD Technologies, Zurich, Switzerland) for subsequent processing. Attenuation correction ellipses where drawn on the images and a Chang 0 attenuation correction was applied utilizing a site specific mu that was empirically derived from phantom data acquired during site initiation for the trial. Once attenuation correction was completed, a standard Gaussian 3D 6.0 mm filter was applied. These files were then normalized to standard Montreal Neurologic Institute (MNI) space so that all scans were in the same anatomical alignment. Next the transaxial slice with the highest striatal uptake was identified and the 8 hottest striatal slices around it were averaged in to generate a single slice image. Regions of interest (ROI) were then placed on the of left and right caudate, the left and right putamen, and the occipital cortex (reference tissue). Count densities for each region were extracted and used to calculate striatal binding ratios (SBRs) for each of the 4 striatal regions. SBR were calculated as (target region/reference region)-1.

SUPPLEMENTARY TABLES

Supplementary table 1. Distribution of caudate and putamen ^{123}I-FP-CIT binding across PD patients compared to the controls' mean (caudate: mean ± SD = 2.56 ± 0.60; putamen: mean ± SD = 2.14 ± 0.55).

	Within -2 SD	**Unilateral reduction**	**Bilataral reduction**
Caudate, n	205	103	89
Putamen, n	25*	120	252

Unilateral reduction: one side < -2 SDs of the controls' mean. Bilateral reduction: both sides < -2 SDs of the controls' mean.

Supplementary table 2. Reciprocal distribution of caudate and putamen ^{123}I-FP-CIT binding across PD patients as classified in comparison to the controls' mean (caudate: mean ± SD = 2.56 ± 0.59; putamen: mean ± SD = 2.14 ± 0.55).

		Caudate, SDs with respect to HCs' mean		
		Within -2 SD, n	Unilateral reduction, < -2 SDs, n	Bilateral reduction, < - 2 SDs, n
Putamen, SDs with respect to HCs' mean	Within -2 SD, n	25*	0	0
	Unilateral reduction < -2 SDs, n	91	28	1
	Bilateral reduction < - 2 SDs, n	89	75	88

* All these patients had an abnormal pattern of putaminal uptake on DAT SPECT visual assessment compatible with the presence of nigrostriatal hypofunction. Their mean ± SD reduction in the most affected putamen compared to healthy controls [((mean putamen in HCs – most affected putamen PD) / mean putamen in HCs)*100] was 63.61 ± 30.64%.

Supplementary Table 3. Comparison of baseline clinical variables between patients with and without available data at follow up.

	Available (n = 323)	**Not available** (n =74)	**P-value**
Age (years, mean ± SD)	61.26 ± 9.88	63.49 ± 8.87	0.075
Gender (M/F)	212/111	46/28	0.591
MoCA score (mean ± SD)	27.28 ± 2.31	27.34 ± 2.46	0.852
GDS score (mean ± SD)	2.26 ± 2.40	2.76 ± 2.81	0.121
RBDSQ score (mean ± SD)	4.43 ± 2.79	4.75 ± 3.16	0.437
Caudate SBR (mean ± SD)	1.99 ± 0.52 (n=267)	2.00 ± 0.64 (n=130)	0.934

An independent t-test was used in order to assess differences between groups in age, MoCA score, GDS score, RBDSQ score and caudate SBR. A Fisher exact chi-square test was used in order to assess differences in gender between groups.
MoCA: Montreal Cognitive Assessment
GDS: geriatric depression scale
RBDSQ: REM sleep behavior disorder questionnaire
SBR: specific binding ratio