

## Supplementary Material

### METHODS

#### Quantitative analyses of $^{18}\text{F}$ -FP-CIT PET

$^{18}\text{F}$ -FP-CIT PET was performed using a Discovery 600 (GE Healthcare, Milwaukee, WI, USA) device, which acquires images with a three-dimensional resolution of 2.3-mm full-width at half-maximum. After a 6-hour fast, the patients were intravenously injected with 5 mCi (185 MBq) of  $^{18}\text{F}$ -FP-CIT. Ninety minutes after the injection, PET images were acquired for 20 minutes in three-dimensional mode at a power of 120 kVp and a current of 200 mA.<sup>1</sup>

Image processing was performed using MATLAB (The MathWorks, Inc, Natick, MA, USA) software for statistical parametric mapping (SPM) 8 (<https://www.fil.ion.ucl.ac.uk/spm/>) and ITK-SNAP (<http://www.itksnap.org>). All reconstructed  $^{18}\text{F}$ -FP-CIT images were normalized to the  $^{18}\text{F}$ -FP-CIT template, which was made using the  $^{18}\text{F}$ -FP-CIT PET images and T1-weighted MR images of 40 healthy controls, as described previously.<sup>2</sup> Briefly, all of the healthy controls from which the  $^{18}\text{F}$ -FP-CIT template was derived had no previous history of neurologic or psychiatric illness. They showed normal cognitive function on all neuropsychological tests, and exhibited normal findings on neurologic examination, structural MRI, and  $^{18}\text{F}$ -FP-CIT PET. The volumes of interest (VOI) for the bilateral posterior putamen and one occipital VOI were drawn on the  $^{18}\text{F}$ -FP-CIT template.<sup>3</sup> Dopamine transporter (DAT) availability in the posterior putamen was estimated using the specific/nonspecific binding ratio as a surrogate, which was defined as follows: (mean standardized uptake value of the posterior putamen VOIs – mean standardized uptake value of the occipital VOI) / (mean standardized uptake value of the occipital VOI).

#### Neuropsychological assessment

The Seoul Neuropsychological Screening Battery covers five cognitive domains consisting of 14 scorable tests<sup>4</sup>: attention (forward/backward digit span task); language and related functions (the Korean version of the Boston Naming Test); visuospatial function (the Rey Complex Figure Test [RCFT] copy), verbal and visual memory (immediate recall/delayed recall/recognition test using the Seoul Verbal Learning Test for verbal memory; immediate recall/delayed recall/recognition test using the RCFT for visual memory); and frontal/executive function (the Controlled Oral Word Association Test [COWAT] animal, COWAT supermarket, COWAT phonemic, and the Stroop color reading test).

#### Diffusion tensor imaging data acquisition

MRI scans were acquired using a 3.0 T scanner (Achieva; Philips Medical Systema, Best, The Netherlands) with a 32-channel receiver array head coil as described in our previous work.<sup>5-10</sup> The high-resolution axial T1-weighted MRI data were obtained using a 3D T1-TFE sequence with the following parameters:  $224 \times 224$  axial acquisition matrix;  $256 \times 256$  reconstructed matrix with 170 slices; voxel size,  $0.859 \times 0.859 \times 1$  mm<sup>3</sup>; field of view, 220 mm; echo time, 4.6 msec; repetition time, 9.8 msec; flip angle, 8°. The diffusion-weighted MRI data were acquired using a single-shot echo-planar acquisition with the following parameters: 45 non-coplanar, non-coplanar diffusion-encoded gradient directions;  $128 \times 128$  acquisition matrix with 70 slices; voxel size,  $1.75 \times 1.75 \times 2$  mm<sup>3</sup>; field of view, 220 mm; b-factor, 600 s/mm<sup>2</sup>; echo time, 70 msec; repetition time, 7.663 sec; flip angle, 90°.

#### Mediation analysis

We performed a mediation analysis to evaluate whether white matter changes in the left fornix mediated the association between striatal dopamine deficits and parkinsonian motor symptoms (i.e., motor reserve). The natural logarithm of DAT availability in the posterior putamen and fractional anisotropy values of the left fornix were entered as a predictor and mediator, respectively, in the mediation analysis for Unified Parkinson's Disease Rating Scale Part III scores. Age, sex, and disease duration were entered as covariates. We used a bootstrapping method with 1,000 resamples to derive the 95% confidence intervals and standard errors using the “lavaan” package for the R program. The statistical analysis was performed using R software package (version 4.1.1; <http://www.r-project.org>).

#### References

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