

Supplementary Online Content

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eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Methods

SPM Analysis

Voxel-wise analysis was performed by SPM5 in Matlab 2010a (MathWorks Inc., Natick, MA). In PD patients, the ipsilateral striatum was flipped to right side for statistical parametric mapping analysis. Spatially normalized SUR images were smoothed using an isotropic Gaussian kernel of 8 mm FWHM. Voxel-wise two-sample t-test for group comparison between HC and each PD group was computed in ^{18}F -FP-(+)-DTBZ SUR images. SPM *t*-maps were examined using a threshold of $P < 0.05$ with false discovery rate (FDR) correction and an extent threshold of 50 voxels.

Correlations of nigrostriatal VMAT2 Activity to Clinical Characteristics

The correlations between nigrostriatal SURs and clinical characteristics of PD patients were calculated by an exponential regression model. The exponential regression model was calculated by the following equation: $\text{SUR} = A * \exp(B * \text{clinical score})$. The SUR was the SUR value extraction from each nigrostriatal VOI, and the clinical score was the scores of clinical characteristics including mH-Y stage, disease duration, UPDRS III, PIGD (posture instability and gait disturbance), akinesia, rigidity, and tremor. Both A and B were the fitting constants.

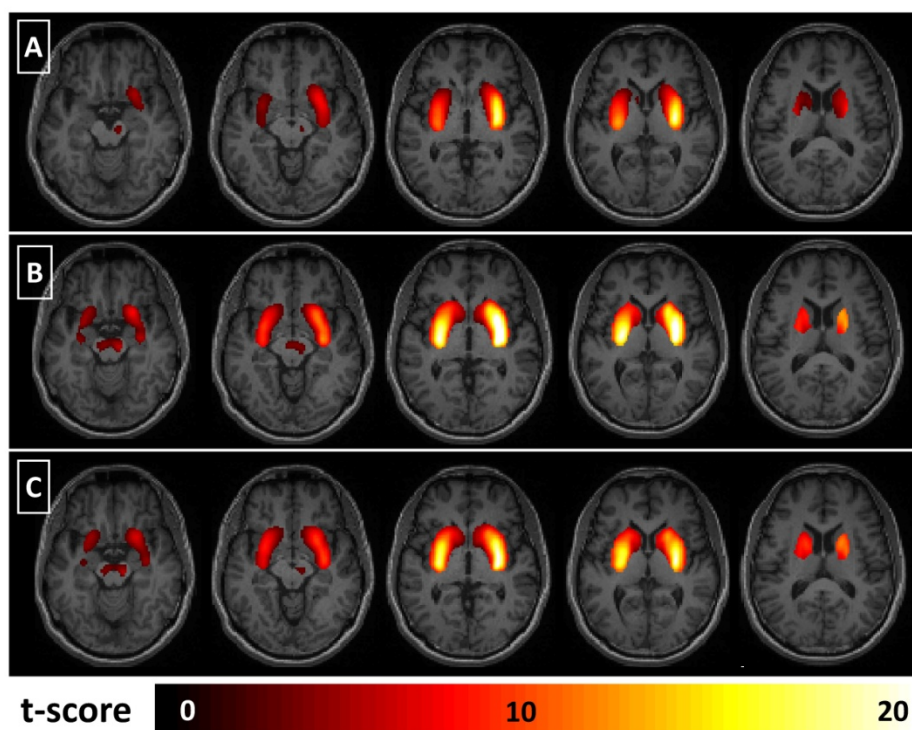
Asymmetry Index

The asymmetry index ASI was calculated as $\text{ASI} = [2 \times (\text{ipsilateral SUR} - \text{contralateral SUR}) / (\text{ipsilateral SUR} + \text{contralateral SUR})] \times 100\%$ ¹ for evaluating the asymmetry of the SUR in each VOI for PD patients.

eAppendix 2. Results

SPM Analysis

Results of voxel-wise analysis from statistical parametric mapping for discriminating three different PD groups from HCs were shown in eFigure 1. Asymmetric SUR reduction in nigrostriatal is obvious in mild PD, less visible in moderate PD, and prominent symmetric deficits in advanced PD. In the mild PD group, the SPM result exhibited statistically significant reduction of ^{18}F -FP-(+)-DTBZ uptake in the contralateral SN and Cau, as well as bilateral putamen. The decrease was greatest in the contralateral putamen. While the continuous and apparent SUR decrease of all VOIs including striatum and SN was observed in the moderate PD, the asymmetric VMAT2 decline pattern became less discernible in this stage. Both moderate and advanced PDs were with prominently higher level and larger area of SUR reduction in the nigrostriatal region. Though, due to a smaller sample size in advanced PD group, a slightly higher difference was observed in eFigure 1B than in eFigure 1C.



eFigure. Statistical Parametric Maps of Decreased Nigrostriatal VMAT2 Binding in Mild PD (A), Moderate PD (B), and Advanced PD (C) as Compared With HCs

Exponential Correlation of Nigrostriatal VMAT2 Activity to Clinical Measurements

As shown in eTable 1, the correlations between nigrostriatal SURs and clinical characteristics of PD patients were explored in terms of an exponential regression model. The SURs of bilateral striatum exhibited significant correlations to mH-Y stage, disease duration, UPDRS III, PIGD, akinesia, rigidity, and tremor scores, while SUR in SN displayed significant correlation only to stage, disease duration, UPDRS III, and PIGD scores (eTable 1). No statistically significant correlation between quantitative values and clinical characteristics in Hip, Am, and Rap was observed. In both moderate and to advanced PD stages (mHY ≥ 3), the uptake in bilateral Ppu was similar. In addition, SURs in bilateral nigrostriatal regions were exponentially correlated to disease stages with a statistical significance of $P < 0.05$, and that indicated two-phase decline: rapid decline (mild stage) and slower decline (moderate and advanced stages).

eTable 1. Correlation of Bilateral Nigrastriatal SURs to Disease Severity and Clinical Measures in Parkinson Disease

| | Contralateral | | | | Ipsilateral | | | |
|-------------------------|---------------|--------|-------|---------|-------------|--------|-------|---------|
| | A | B | r | P value | A | B | r | P value |
| Stage | | | | | | | | |
| Substantia Nigra | 0.753 | -0.089 | 0.243 | .079 | 0.968 | -0.124 | 0.376 | .005 |
| Caudate | 1.920 | -0.286 | 0.572 | <.001 | 2.199 | -0.265 | 0.554 | <.001 |
| | Contralateral | | | | Ipsilateral | | | |
| | A | B | r | P value | A | B | r | P value |
| Anterior Putamen | 1.551 | -0.273 | 0.656 | <.001 | 2.015 | -0.288 | 0.652 | <.001 |
| Posterior Putamen | 0.714 | -0.297 | 0.566 | <.001 | 1.013 | -0.391 | 0.360 | .008 |
| Disease duration | | | | | | | | |
| Substantia Nigra | 0.655 | -0.008 | 0.111 | .431 | 0.857 | -0.018 | 0.280 | .042 |
| Caudate | 1.556 | -0.047 | 0.496 | <.001 | 1.863 | -0.047 | 0.510 | <.001 |
| Anterior Putamen | 1.239 | -0.043 | 0.540 | <.001 | 1.627 | -0.047 | 0.562 | <.001 |
| Posterior Putamen | 0.558 | -0.046 | 0.464 | <.001 | 0.804 | -0.070 | 0.338 | .013 |
| UPDRS III | | | | | | | | |
| Substantia Nigra | 0.734 | -0.008 | 0.303 | .027 | 0.865 | -0.008 | 0.337 | .013 |
| Caudate | 1.547 | -0.021 | 0.561 | <.001 | 1.758 | -0.019 | 0.516 | <.001 |
| Anterior Putamen | 1.256 | -0.020 | 0.635 | <.001 | 1.546 | -0.019 | 0.579 | <.001 |
| Posterior Putamen | 0.564 | -0.021 | 0.541 | <.001 | 0.667 | -0.024 | 0.289 | .036 |
| PIGD | | | | | | | | |
| Substantia Nigra | 0.683 | -0.025 | 0.221 | .113 | 0.830 | -0.031 | 0.305 | .026 |
| Caudate | 1.391 | -0.079 | 0.505 | <.001 | 1.583 | -0.067 | 0.448 | .001 |
| Anterior Putamen | 1.135 | -0.074 | 0.570 | <.001 | 1.424 | -0.074 | 0.542 | <.001 |
| Posterior Putamen | 0.508 | -0.080 | 0.490 | <.001 | 0.598 | -0.090 | 0.266 | .055 |
| Akinesia | | | | | | | | |
| Substantia Nigra | 0.695 | -0.015 | 0.246 | .076 | 0.798 | -0.012 | 0.225 | .106 |
| Caudate | 1.304 | -0.034 | 0.415 | .002 | 1.469 | -0.027 | 0.342 | .012 |
| Anterior Putamen | 1.089 | -0.034 | 0.499 | <.001 | 1.329 | -0.032 | 0.435 | .001 |
| Posterior Putamen | 0.475 | -0.035 | 0.402 | .003 | 0.522 | -0.033 | 0.183 | .190 |
| Rigidity | | | | | | | | |
| Substantia Nigra | 0.655 | -0.024 | 0.165 | .239 | 0.770 | -0.024 | 0.178 | .202 |
| Caudate | 1.184 | -0.068 | 0.336 | .014 | 1.372 | -0.056 | 0.289 | .036 |

| | | | | | | | | |
|-------------------|-------|--------|-------|------|-------|--------|-------|------|
| Anterior Putamen | 0.971 | -0.062 | 0.370 | .006 | 1.217 | -0.063 | 0.354 | .009 |
| Posterior Putamen | 0.456 | -0.086 | 0.403 | .003 | 0.600 | -0.133 | 0.303 | .027 |
| Tremor | | | | | | | | |
| Substantia Nigra | 0.627 | -0.016 | 0.115 | .414 | 0.748 | -0.021 | 0.173 | .216 |
| Caudate | 1.068 | -0.052 | 0.279 | .043 | 1.256 | -0.042 | 0.233 | .094 |
| Anterior Putamen | 0.880 | -0.047 | 0.299 | .030 | 1.101 | -0.047 | 0.282 | .041 |
| Posterior Putamen | 0.380 | -0.045 | 0.229 | .099 | 0.414 | -0.033 | 0.081 | .564 |

Values represent constants from regression analyses based on an exponential model of $SUR=A*\exp(B*Clinical\ score)$ using data from all PD for each VOI. r: correlation coefficient; PIGD: posture instability and gait disturbance

Asymmetry Index

As shown in eTable 2, a significant asymmetry (ASI > 15%) was shown in NAc and nigrostriatal regions for the three different PD stages, except in SN (7.97%) and Ppu (3.20%) of advanced PD. These asymmetry results measured by ^{18}F -FP(+)-DTBZ imaging were consistent with the previous imaging studies using ^{11}C -DTBZ PET and ^{99m}Tc -TRODAT SPECT^{2,3}. Furthermore, the asymmetric ^{18}F -FP(+)-DTBZ binding among the three different PD groups in our study was negatively in accordance with the disease severity measured by mH-Y stages (i.e. the unilateral symptom in stage 1.0-1.5, mild bilateral characteristic in stage 2.0-3, and severe disability in stage 4-5)⁴. In contrast to these hallmarks of asymmetric nigrostriatal uptake patterns in PD patients, a more symmetric property in striatal dopaminergic neuron loss was observed in patients with Parkinsonism, including multiple system atrophy and progressive supranuclear palsy⁵⁻⁸

eTable 2. Asymmetry Index (ASI) Calculated From Bilateral Regional SURs in Each PD Group

| | Mild PD | Moderate PD | Advanced PD |
|-------------------|-------------|-------------|-------------|
| Caudate | 15.9 (13.8) | 17.4 (12.2) | 26.2 (20.6) |
| Anterior putamen | 24.3 (17.4) | 19.9 (17.8) | 20.7 (19.1) |
| Posterior putamen | 26.7 (73.0) | 17.0 (27.6) | 3.2 (41.1) |
| Accumbens | 24.1 (44.6) | 17.3 (59.9) | 40.2 (36.2) |
| Substantia Nigra | 21.5 (14.1) | 14.8 (30.4) | 8.0 (19.9) |
| Hippocampus | 1.1 (21.5) | 3.5 (35.2) | 12.3 (39.5) |
| Amygdala | 1.8 (25.7) | -9.2 (29.3) | 0.2 (19.3) |

Asymmetry index (ASI) was calculated as $ASI = [2 \times (\text{ipsilateral SUR} - \text{contralateral SUR}) / (\text{ipsilateral SUR} + \text{contralateral SUR})] \times 100\%$

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