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"*Depressed*" caudate and ventral striatum dopamine transporter availability in de novo *Depressed* Parkinson's disease

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ABSTRACT

Depression can occur before the onset of motor symptoms in Parkinson's disease (PD) patients. The pathophysiology of depression in PD involves various brain regions and relevant functional circuits. This study investigated whether there exist distinctive patterns of presynaptic monoamine transporter densities in the basal ganglia depending on the degree of depression in patients with PD. A total of 123 early and drug-naïve PD patients were enrolled. Their affective status was evaluated by the Montgomery–Asberg Depression Rating Scale (MADRS), and subjects were subgrouped into one of the following three groups according to their MADRS scores: no depression, mild depression, and moderate-to-severe depression. All patients underwent positron emission tomography (PET) using ^{18}F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane. The PET images were normalized, and differences in the regional standardized uptake value ratios (SUVRs) for each side of the caudate, putamen, globus pallidus, thalamus, and ventral striatum were analyzed and compared between the three groups. A trend analysis was performed across the groups to discern any associations between SUVR values of the basal ganglia and depression severity. The SUVR values of the caudate, anterior caudate nuclei, and ventral striatum declined as MADRS increased. The SUVR values of the striatum showed an inverse dose-dependent trend of antero- and ventroposterior gradient across the groups. This result indirectly revealed the involvement of the associative and limbic circuitry of the brain that are modulated by monoamines in early PD with depression. This might suggest an *in vivo* causal relationship between the ventral striatum, caudate and depression.

1. Introduction

Mood disturbances, such as depression, are known to occur even before the onset of motor symptoms in patients with Parkinson's disease (PD) (Pont-Sunyer et al., 2015). The prevalence of depression in PD is estimated to be 30–35%; the mild depressive mood often persists during disease progression and is a risk factor for moderate to severe depression (Aarsland et al., 2011).

Depression involves different sets of regional brain circuitry, such as the limbic and associative loops, and information processing through these circuits is mediated by distinctive monoamines, such as dopamine, serotonin, and noradrenaline, relevant to the particular brain areas (Aarsland et al., 2011; Stahl, 2013; Tremblay et al., 2015). When these connections are disrupted, depression occurs. It has been known that PD pathology encroaches upon these circuits, evoking mood disorders (Aarsland et al., 2011; Frisina et al., 2009).

^{18}F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane (^{18}F-FP-CIT) and positron emission tomography (PET) can assess the functional integrity of the presynaptic nigrostriatal system. It has now become an important, albeit not essential, tool in diagnosing idiopathic PD (Kägi et al., 2010; Postuma et al., 2015). Not only does it reflect PD severity, it also implicates the interactions of different monoaminergic systems, such as the dopaminergic, noradrenergic, and serotonergic systems (Hesse et al., 2009; Remy et al., 2005).

In PD, the posterior and dorsal striatum (sensorimotor territory) is more affected than the anterior and ventral parts of the striatum (associative and limbic territories) (Tremblay et al., 2015). Depending on the distinctive brain circuits, a different threshold of dopaminergic

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availability exists to elicit specific symptoms relevant to particular areas of the basal ganglia (Tremblay et al., 2015). The hypothesis tested in this study is that distinctive patterns of presynaptic monoamine transporter densities in the basal ganglia may exist depending on the degree of depression in patients with PD. We investigated which areas of the brain are related to depression in early PD patients and how the affected regions correlate to the severity of depression.

2. Methods

2.1. Patients

The study protocol was approved by the Institutional Review Board at Seoul St. Mary's Hospital, and all subjects provided written informed consent to participate. All experiments were performed in accordance with relevant guidelines and regulations.

One hundred and twenty-three, early and drug-naïve PD patients were evaluated between May 2015 and March 2018. Subjects were diagnosed as having PD according to the criteria of UK PD Society Brain Bank (Gibb and Lees, 1988). The clinical diagnosis was supported by ^{18}F-FP-CIT PET imaging, which revealed that all patients had decreased dopamine transporter uptake in the striatum, mainly in the posterior putamen on visual analysis (Postuma et al., 2015). All enrolled patients were PD naïve and had not taken any dopaminergic agents or antidepressants.

Clinical information was obtained, including age, sex, disease duration, body mass index, education status, history of hypertension and diabetes mellitus, and smoking status. Parkinsonian motor symptoms were measured using the Unified Parkinson's Disease Rating Scale (UPDRS) part III and the modified Hoehn and Yahr (H&Y) stage scores. The UPDRS score was divided into two sub scores: tremor score and akinetic-rigid score (Schiess et al., 2000). The presence of rest tremor was defined by ≥ 1 in the UPDRS item 20. General cognitive status was examined by the Mini-Mental State Examination (MMSE), and comprehensive neuropsychiatric tests (Ahn et al., 2010). Each participant's affective status was screened by the Montgomery–Asberg Depression Rating Scale (MADRS) (Ahn et al., 2005; Schrag et al., 2007). The MADRS scores ranged from zero to sixty, and each patient was stratified into one of the following three groups according to the level of clinical suspicion based on the MADRS score: Group 1, 0–6, no depression; Group 2, 7–19, mild depression; and Group 3, scores of ≥ 20, moderate-to-severe depression (the moderate and severe depression severity subjects were grouped together due to the small sample number) (Herrmann et al., 1998).

Subjects were excluded for the following reasons: (1) normal dopamine transporter scan based on the Movement Disorder Society Clinical Diagnostic Criteria for PD (Postuma et al., 2015); (2) with dementia according to the clinical diagnostic criteria of the Movement Disorder Society (Emre et al., 2007); (3) neurological abnormalities related to atypical or secondary parkinsonism; (4) structural or space-occupying lesions on the basal ganglia; and (5) those who were taking medications at the time of diagnosis known to influence central dopaminergic, noradrenergic, and/or serotonergic systems.

2.2. Imaging acquisition and processing

Brain computed tomography (CT) and ^{18}F-FP-CIT PET images were acquired using a Discovery STE PET/CT scanner (GE Healthcare, Milwaukee, WI, USA). After 3 h of intravenous injection of an average of 3.7 MBq/kg of ^{18}F-FP-CIT, brain CT scans were obtained for attenuation correction followed by a 10 min ^{18}F-FP-CIT PET scan. PET images were reconstructed with a $512 \times 512 \times 110$ matrix using an ordered-subsets expectation maximization algorithm. The voxel size was $0.668 \times 0.668 \times 2$ mm. Axial T1-weighted brain magnetic resonance images with 3D-spoiled gradient-recalled sequences (512×512 matrix, voxel spacing $0.469 \times 0.469 \times 1$ mm) were also acquired with a 3.0-T scanner (Magnetom Verio, Siemens, Erlangen, Germany).

Statistical Parametric Mapping 8 software (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB 2015a (MathWorks, Natick, MA) were utilized for co-registration and spatial normalization of the images and voxel-based comparisons (Kim et al., 2015; Oh et al., 2018). Briefly, ^{18}F-FP-CIT PET were co-registered to individual MR images and spatially normalized to the Montreal Neurological Institute space with parameter-normalizing skull-stripped MR images. Subject-specific striatal volume of interest (VOI) templates derived from FreeSurfer 5.1 (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu), which is regarded as the gold standard for comparing striatal ^{18}F-FP-CIT PET binding values, were used. T1-weighted MR images were resliced to 1 mm isovoxel space, corrected for inhomogeneity, skull-stripped, and segmented into gray and white matter. To measure the striatal subregional and cerebellar binding values in spatially-normalized PET images, we created VOI templates for the caudate, putamen, and cerebellum. Then, the striatal and cerebellar segments were spatially normalized to the skull-stripped MR template within 1 mm-sized isovoxel space. Using the VOI template, we measured the regional standardized uptake value (SUV) of the cerebellum and each side of the caudate, putamen, globus pallidus, thalamus, and ventral striatum in the PET images. We also used an in-house MATLAB program for simple arithmetic operations on images and measuring the regional uptake values. Mean SUV ratios (SUVRs) were calculated as the target SUV divided by the cerebellum SUV.

2.3. Statistical analysis

All statistical analyses were executed with the Statistical Package for the Social Sciences, version 24.0 for Mac (IBM Corporation, Armonk, NY, USA). Pearson's $\chi 2$ tests were used to compare frequencies for categorical variables, and one-way analysis of variance (ANOVA) tests were used to compare mean differences among the groups. Group differences of the regional SUVR values were analyzed by analysis of covariance (ANCOVA), adjusted for age, disease duration and UPDRS part III score. In a sub-analysis of the striatum, within-group gradient vector differences by subtracting the SUVR value of posterior putamen (a preset reference in PD) from the SUVR values of caudate nuclei, anterior caudate nuclei, posterior caudate nuclei, anterior putamen, ventral putamen and ventral striatum, were analyzed by paired t-test. Those gradient values were examined for trend between groups using the Jonckheere-Terpstra method. A family-wise type I error was set at a two-tailed p value $< .05$, and the Bonferroni correction was applied in cases of multiple comparisons.

3. Results

The clinical characteristics of the studied participants are summarized in Table 1. The mean age ($\pm$ SD) was 68.6 $\pm$ 9.1 years, and 62 subjects (50.4%) were male. The mean disease duration was 1.1 $\pm$ 1.6 years, and the modified H&Y stage score was 1.5 $\pm$ 0.5. The mean MMSE score was 27.0 $\pm$ 2.7, and there were not any between-group differences. Of 123 early PD patients, 68 (55.3%) were found to have depressive moods, and the mean MADRS score was 9.0 $\pm$ 7.6. Subjects in the PD-no depression group were younger than the other two groups with depression. Indices of disease severity measured by the UPDRS part III and modified H&Y stage scores showed that subjects without depression had a milder PD severity than PD subjects with depression. The frequencies of rest tremor and tremor scores were not different among the groups.

Between-group analyses of regional SUVR values showed significant differences in the anterior caudate nucleus and ventral striatum as depression became worse (Table 2 and Fig. 1). The moderate-to-severe depression group achieved lower SUVR values in both the caudate

Table 1
Participant clinical characteristics.

	All (n = 123)	Group 1[a] (n = 55)	Group 2[b] (n = 54)	Group 3[c] (n = 14)	p value	Post-hoc test[d]
Age, years	68.6 ± 9.1	65.6 ± 9.2	71.0 ± 8.7	71.4 ± 6.9	0.003	a < b**
Sex, Male, n (%)	62 (50.4%)	30 (54.5%)	26 (48.1%)	6 (42.9%)	0.668	a = b = c
Disease duration, years	1.1 ± 1.6	1.1 ± 1.3	1.2 ± 1.9	1.2 ± 1.5	0.900	a = b = c
Body mass index, kg/m^2	23.8 ± 3.3	24.0 ± 3.2	24.0 ± 3.6	22.5 ± 2.1	0.290	a = b = c
Education, years	11.2 ± 4.7	12.2 ± 4.7	10.7 ± 4.8	9.4 ± 4.2	0.081	a = b = c
Hypertension, n (%)	52 (42.3%)	20 (36.4%)	24 (44.4%)	8 (57.1%)	0.340	a = b = c
Diabetes mellitus, n (%)	16 (13.0%)	5 (9.1%)	9 (16.7%)	2 (14.3%)	0.495	a = b = c
Never-smoker, n (%)	88 (71.5%)	39 (70.9%)	38 (70.4%)	11 (78.6%)	0.824	a = b = c
MMSE	27.0 ± 2.7	27.6 ± 2.4	26.5 ± 2.5	26.7 ± 3.9	0.128	a = b = c
UPDRS, total score	22.6 ± 10.8	18.1 ± 10.1	25.7 ± 10.3	28.0 ± 9.0	< 0.001	a < b**, a < c**
Part I	1.6 ± 1.6	0.9 ± 1.0	2.2 ± 1.8	2.2 ± 1.4	< 0.001	a < b**, a < c**
Part II	6.4 ± 4.0	4.7 ± 3.1	7.6 ± 3.8	8.6 ± 4.9	< 0.001	a < b**, a < c**
Part III	14.6 ± 7.5	12.5 ± 7.7	16.0 ± 7.3	17.6 ± 5.4	0.014	a < b*
Rest tremor, n (%)	73 (59.3%)	32 (58.2%)	34 (63.0%)	7 (50.0%)	0.660	a = b = c
Tremor score	4.0 ± 3.1	4.0 ± 3.0	3.9 ± 3.0	4.4 ± 3.6	0.888	a = b = c
Akinetic rigid score	8.1 ± 4.7	6.7 ± 4.7	9.1 ± 4.6	10.3 ± 4.1	0.006	a < b = c*
Modified H&Y stage	1.5 ± 0.5	1.3 ± 0.5	1.6 ± 0.4	1.8 ± 0.4	< 0.001	a < b**, a < c**
MADRS	9.0 ± 7.6	2.1 ± 1.9	12.4 ± 3.6	23.0 ± 3.3	< 0.001	a < b < c**

All patients were stratified into three groups by the Montgomery–Asberg Depression Rating Scale (MADRS). Group 1[a], 0–6, no depression; Group 2[b], 7–19, mild depression; and Group 3[c], scores of ≥20, moderate-to-severe depression; [d] Multiple comparisons were adjusted by the Bonferroni method.
Abbreviations: MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr, MADRS, Montgomery–Asberg Depression Rating Scale (MADRS).
Data is shown as mean ± standard deviation for continuous variables and number with percentage in parenthesis for categorical variable.
One-way analysis of variance was performed for continuous variables and $\chi 2$ test for categorical variables to compare between-group differences.
* $p < .05$.
** $p < .01$.

Table 2
Regional standardized uptake ratio (SUVR) differences between groups.

	Group 1[a] (n = 55)	Group 2[b] (n = 54)	Group 3[c] (n = 14)	p value	Post-hoc test
Caudate	4.2 ± 1.4	3.6 ± 1.3	2.7 ± 0.9	0.012	a > c*, b > c*
Right	4.2 ± 1.3	3.8 ± 1.4	2.7 ± 0.9	0.008	a > c*, b > c**
Left	4.1 ± 1.5	3.5 ± 1.3	2.6 ± 1.1	0.030	a > c*
Anterior caudate	4.5 ± 1.5	3.8 ± 1.5	2.7 ± 1.1	0.010	a > c*, b > c*
Right	4.5 ± 1.5	4.0 ± 1.5	2.7 ± 1.0	0.007	a > c*, b > c**
Left	4.5 ± 1.7	3.7 ± 1.5	2.7 ± 1.3	0.029	a > c*
Posterior caudate	3.4 ± 1.2	3.0 ± 1.1	2.3 ± 0.8	0.054	a = b = c
Right	3.7 ± 1.3	3.3 ± 1.2	2.4 ± 0.9	0.030	a > c*, b > c*
Left	3.2 ± 1.2	2.7 ± 1.1	2.1 ± 0.8	0.126	a = b = c
Putamen	4.2 ± 1.1	4.1 ± 1.3	3.3 ± 1.0	0.069	a = b = c
Right	4.1 ± 1.4	4.2 ± 1.4	3.2 ± 1.0	0.067	a = b = c
Left	4.2 ± 1.2	4.0 ± 1.4	3.3 ± 1.2	0.136	a = b = c
Anterior putamen	4.3 ± 1.3	4.2 ± 1.5	3.2 ± 1.2	0.046	a = b = c
Right	4.3 ± 1.5	4.4 ± 1.6	3.2 ± 1.1	0.046	a = b = c
Left	4.4 ± 1.4	4.1 ± 1.6	3.2 ± 1.5	0.115	a = b = c
Posterior putamen	3.2 ± 1.2	3.3 ± 1.5	2.7 ± 1.0	0.381	a = b = c
Right	3.3 ± 1.6	3.5 ± 1.7	2.8 ± 1.1	0.350	a = b = c
Left	3.2 ± 1.2	3.1 ± 1.5	2.7 ± 1.1	0.536	a = b = c
Ventral putamen	4.0 ± 1.0	3.8 ± 0.9	3.4 ± 0.7	0.245	a = b = c
Right	4.0 ± 1.1	3.9 ± 1.1	3.3 ± 0.6	0.119	a = b = c
Left	4.0 ± 0.9	3.8 ± 0.9	3.6 ± 0.8	0.442	a = b = c
Globus pallidus	3.4 ± 1.0	3.5 ± 0.9	3.5 ± 1.2	0.935	a = b = c
Right	3.4 ± 1.0	3.5 ± 0.9	3.6 ± 1.4	0.926	a = b = c
Left	3.4 ± 1.1	3.4 ± 0.9	3.3 ± 1.1	0.757	a = b = c
Thalamus	1.5 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	0.150	a = b = c
Right	1.5 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	0.173	a = b = c
Left	1.4 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	0.167	a = b = c
Ventral striatum	5.0 ± 1.1	4.9 ± 1.2	3.8 ± 1.0	0.008	a > c*, b > c*
Right	4.7 ± 1.2	4.7 ± 1.2	3.5 ± 1.0	0.010	a > c*, b > c**
Left	5.4 ± 1.2	5.0 ± 1.3	4.0 ± 1.0	0.012	a > c*, b > c*

All patients were stratified into three groups by the Montgomery–Asberg Depression Rating Scale (MADRS). Group 1[a], 0–6, no depression; Group 2[b], 7–19, mild depression; and Group 3[c], scores of ≥20, moderate-to-severe depression.
Data is shown as mean ± standard deviation.
Analyses were performed by one-way analysis of variance (ANCOVA) test with Bonferroni post-hoc tests controlling for age, disease duration, and Unified Parkinson's Disease Rating Scale part III scores.
* $p < .05$.
** $p < .01$.

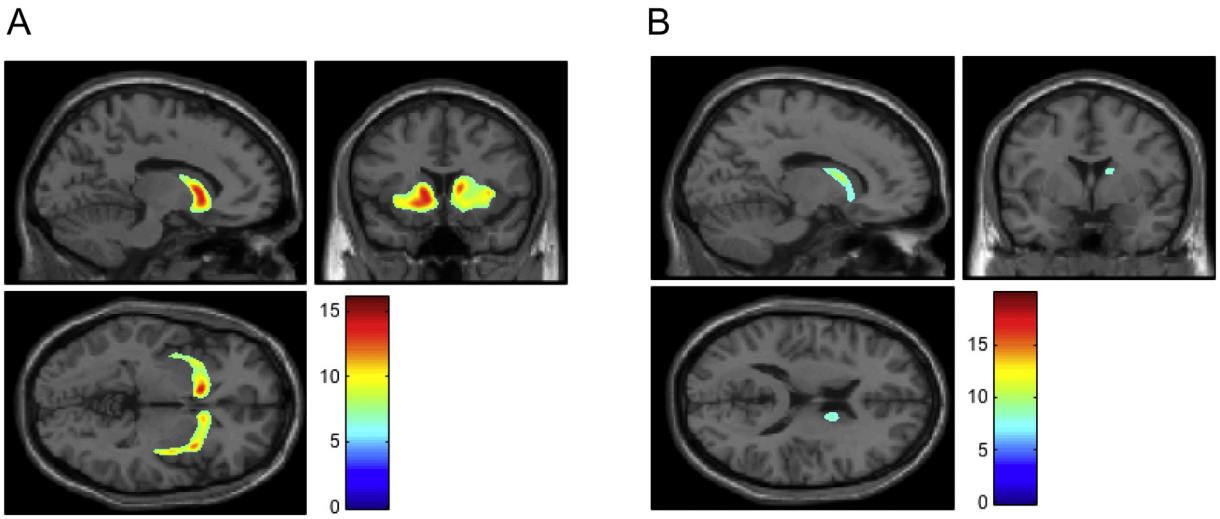

Fig. 1. Voxel-based comparison of ^{18}F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane positron emission tomography (^{18}F-FP-CIT PET) controlling for age, disease duration, and Unified Parkinson's Disease Rating Scale part III scores. (A) no depression vs. moderate-to-severe depression, (B) mild depression vs. moderate-to-severe depression. The differences of the standardized uptake value ratios (SUVRs) between groups were demonstrated in the colored region. T values are indicated by the color bar.

nuclei and ventral striatum than the PD-no depression group. When the mild depression group and the moderate-to-severe depression group were compared, the latter group also had lower SUVR values in the both anterior caudate, the right posterior caudate, and both ventral striatum. However, no significant differences were observed upon comparison of the SUVR values between the no depression group and the mild depression group.

Table 3 summarizes the within-group differences of SUVR values between the antero- and ventral regions of the striatum with a reference posterior putamen area. Antero- and ventroposterior gradient of SUVR value was found within each group. Interestingly, the anteroposterior gradient between the anterior caudate nucleus and posterior putamen disappeared as the severity of depression increased (Group 1, $p < .001$; Group 2, $p = .029$; Group 3, $p = .934$). A strong significance of ventroposterior gradient remained across the groups. Inverse dose-dependent associations were found between within-group sub-region differences as depression worsened (Fig. 2).

4. Discussion

The participants of this study exhibited distinctive regional dopamine transporter uptake patterns depending on the degree of depression in early PD. In a subgroup analysis of the striatum, an antero- and ventroposterior gradient of SUVR values was found when the posterior putamen was defined as a reference area. The gradient also manifested an inverse dose-dependent relationship with worsening depression.

In previous studies, the caudate (Koerts et al., 2007; Vriend et al., 2014) and ventral striatum (Remy et al., 2005) with dopaminergic deficits were related to depression in PD. Similar results were observed in this study, but with more details which were compatible with the established neurocircuitry of mood. Caudate nuclei, especially the anterior part and ventral striatum, are key substructures within distinctive basal ganglia circuits that are associated with affect and psychomotor fatigue (Price and Drevets, 2010; Stahl, 2013; Tremblay et al., 2015). The findings of this study substantiate this *in vivo*.

The caudate (with more anterior part) and the ventral striatum were inversely associated with MADRS total score, signifying that the severity of depression is related to the amount of disrupted monoaminergic systems in subregions relevant to mood (Frisina et al., 2009; Hesse et al., 2009; Price and Drevets, 2010; Remy et al., 2005). However, the dopamine transporter uptakes were not different between the no depression group and the mild depression group in this study. The MADRS scores of the mild depressive group were 12.4 ± 3.6, meeting the subthreshold for clinically relevant depression (Schrag et al., 2007). The SUVR value change reached a critical point in the moderate-to-severe group, surpassing the symptomatic threshold. Substructural changes that correspond to depression may occur after a greater loss of nigro-putamen projection in an independent process; different thresholds for each of the limbic, associative and sensorimotor functional parallels seem to exist (Brooks and Piccini, 2006; Price and Drevets, 2010; Tremblay et al., 2015). This argument explains for such disparity in the between-group differences.

In this study, we analyzed gradient patterns within basal ganglia, an approach which had been used before with a different methodology

Table 3
Within-group standardized uptake ratio (SUVR) gradients by subtracting the SUVR value of the posterior putamen from each anterior subregion.

Sub-region	Group 1 (n = 55)	*p* value	Group 2 (n = 54)	*p* value	Group 3 (n = 14))	*p* value
Caudate	0.9 ± 1.6	< 0.001	0.4 ± 1.7	0.120	−0.1 ± 1.4	0.830
Anterior caudate	1.2 ± 1.7	< 0.001	0.6 ± 1.8	0.029	−0.03 ± 1.5	0.934
Posterior caudate	0.2 ± 1.5	0.462	−0.3 ± 1.6	0.131	−0.5 ± 1.4	0.214
Anterior putamen	1.1 ± 0.6	< 0.001	0.9 ± 0.8	< 0.001	0.5 ± 0.5	0.004
Ventral putamen	0.7 ± 0.7	< 0.001	0.5 ± 1.0	< 0.001	0.7 ± 0.8	0.005
Ventral striatum	1.8 ± 0.9	< 0.001	1.6 ± 1.2	< 0.001	1.0 ± 0.9	0.001

All patients were stratified into three groups by the Montgomery–Asberg Depression Rating Scale (MADRS). Group 1, 0–6, no depression; Group 2, 7–19, mild depression; and Group 3, scores of ≥20, moderate-to-severe depression.
Data is shown as mean ± standard deviation.
Analysis was performed paired t-test to find within-group differences between areas of interest and posterior putamen.

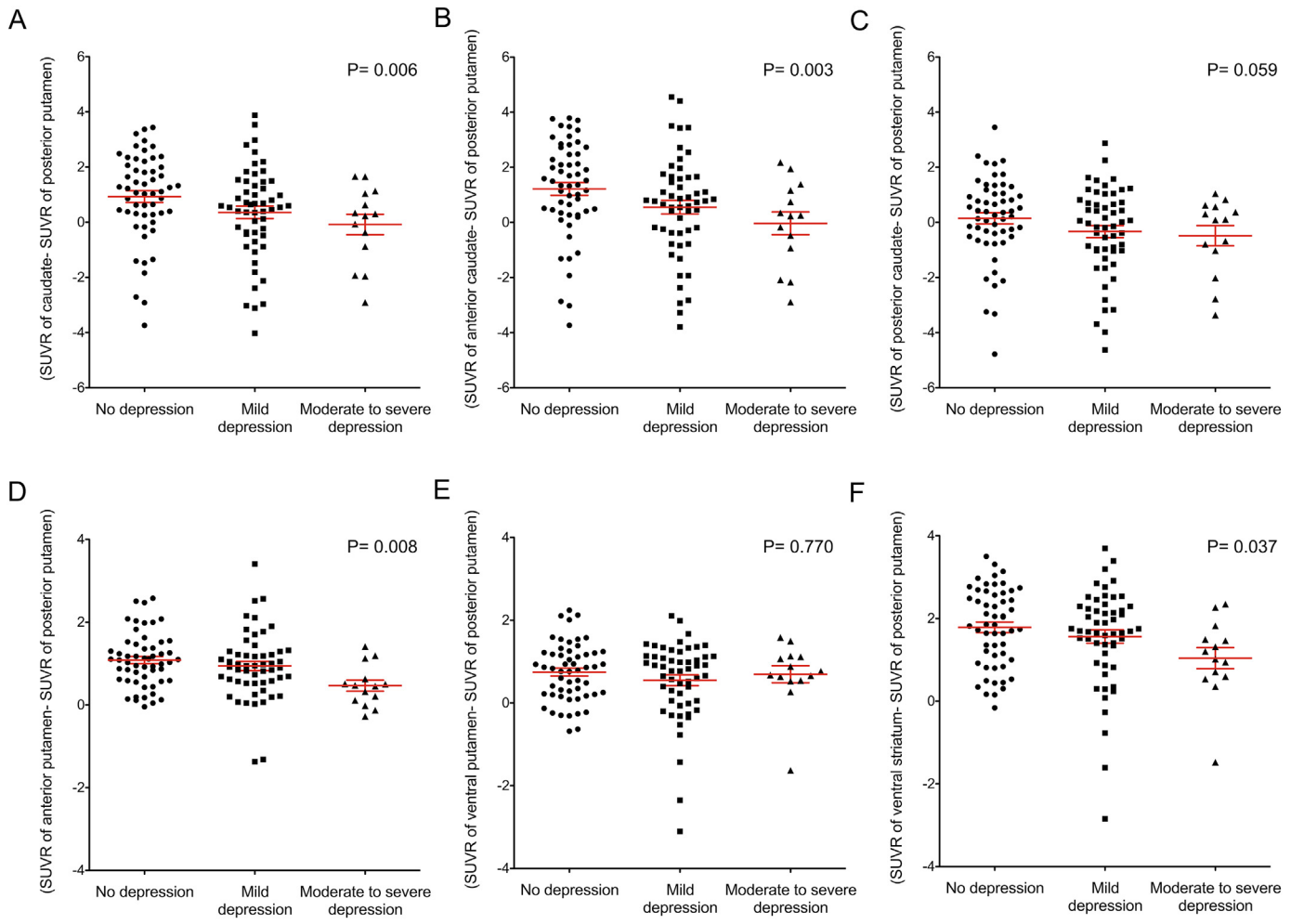

Fig. 2. Dose-dependent relationships of antero- and ventroposterior gradient of standardized uptake value ratio (SUVR) values with increasing depression severity.

(Oh et al., 2012). This study's method is plausible if we consider the gradient as a vector with a fixed point. Vector is a term that includes magnitude and direction. Simple subtraction between SUVR values of substructures does not cancel out the ratio of the cerebellum, thus rendering it suitable for analysis. In a subanalysis of the striatum, forward and ventral gradients of SUVR values with posterior putamen possessing the lowest reference values were observed. In PD, the posterior putamen, where the sensorimotor loop is located, becomes predominantly and preferentially affected in ^{18}FP-CIT PET images (Brooks and Piccini, 2006; Tremblay et al., 2015). Its lower dopamine transporter uptake reflects the selective neuropathological process in PD (Braak et al., 2003). With disease progression, the posterior putamen dopamine transporter uptake falls further while the ventral and anterior putamen and the dorsal caudate integrity become involved (Brooks and Piccini, 2006). The ventral striatum remains spared until the late stage (Brooks and Piccini, 2006; Oh et al., 2012; Tremblay et al., 2015). Within each group, the posterior putamen displayed the lowest uptake, forming antero- and ventroposterior gradients between substructures. This trend was found across the subgroups with increasing severity of depression, except that the caudate-putamen gradient lost its significance. This corresponds with the accepted predominant role of the ventral striatum in the limbic system, whereas the caudate is more associated with cognition despite its participation in depression (Tremblay et al., 2015; Vriend et al., 2014). Subregional gradients within a group and negative dose-dependent associations across groups in early PD can be explained by its independent process and lower threshold than sensorimotor territory. This analysis might suggest *in vivo* causal relationship between dopaminergic modulation of the ventral striatum and depression in early PD.

^{18}F-FP-CIT is a radioligand that has differential monoaminergic binding affinity relevant to anatomical structures. It is known to strongly reflect dopamine transporter in the striatum whereas it almost exclusively represents serotonergic transporter in thalamus (Hesse et al., 2009; Koch et al., 2014). This further enhances the argument of this study that disrupted dopaminergic modulation of the striatum is relevant to the depression severity.

This study has a few advantages compared to other studies. First, this study utilized the MADRS which has been validated in PD. It is accepted as suitable because it has relatively few somatic items (Schrag et al., 2007). The Beck Depression Inventory (BDI) is also validated in PD, but it contains several somatic symptoms (Schrag et al., 2007). A study using BDI as an assessment tool showed that mood was unrelated to striatal dopaminergic deficits (Broussolle et al., 1999), but such a result might have been confounded by the somatic effects of the scale. Second, we utilized a methodology that allowed spatial normalization of the PET images to quantify presynaptic monoamine transporter densities in a relatively large number of subjects. PET is a more advantageous method of quantitative instrumentation than single photon emission computed tomography (SPECT) (Oh et al., 2012; Rektorova et al., 2008). Visual and semi-quantitative analyses can be biased due to image noise and sampling errors. The MR-guided spatial-normalization method is considered more accurate and works independently from receptor density (Ashburner and Friston, 1999; Gispert et al., 2003; Kim et al., 2015).

However, our study has limitations, including its cross-sectional design. First, depression was investigated at the time of PD diagnosis. The MADRS assessment at diagnosis can be associated with the five stages for illness, death, and transition (Kübler-Ross, 1969), affecting the depression assessment scale. In addition, motor disability is known to affect depression in PD (Aarsland et al., 2011). In this study, we only enrolled patients at an early disease stage with short disease duration. Such selection of study subjects can abate the confounding influence of motor disability. Furthermore, motor disability was statistically adjusted to minimize its influence on the association between striatal ^{18}F-FP-CIT uptake and depression. A long-term cohort that studies the influence, treatment response, and interaction of depression with motor and other non-motor burdens could clarify such clinical implications. Second, the number of subjects in the moderate-to-severe depressive group was relatively small compared to the other groups. In early PD patients, non-medicated moderate-to-severe depressive patients were extremely rare; most patients with severe depression were on antidepressants. Third, because ^{18}FP-CIT ligand has preferential binding affinity to different monoamine transporters according to its anatomical substrates, possible contributions of other neurotransmitters associated with noradrenergic and serotonergic systems to depression in PD cannot be neglected. Lastly, the results would be more empiric if the study included comprehensive cognitive examinations. Cognitive symptoms in PD could influence the results of MADRS as "concentration difficulties," and "lassitude" subscales may be related to cognition in relevance to striatal dopaminergic deficits (Koerts et al., 2007). Mild cognitive impairment is also known to occur in the early stage of PD (Litvan et al., 2012). and its relation to mood, including depression and apathy, would enhance the clinical implications (Rektorova et al., 2008).

In conclusion, depression in early PD is related to dopaminergic modulation in the caudate, especially the anterior part, and the ventral striatum. This study might contribute to unveiling the causal relationship between mood and basal ganglia functional sub-territories *in vivo*.

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Disclosures

The authors report no disclosures relevant to the manuscript.

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