Gray Matter Correlates of Dopaminergic Degeneration in Parkinson's Disease: A Hybrid PET/MR Study Using ^{18}F -FP-CIT

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Abstract: Dopaminergic degeneration is a hallmark of Parkinson's disease (PD), which causes various symptoms affected by corticostriatal circuits. So far, the relationship between cortical changes and dopamine loss in the striatum is unclear. Here, we evaluate the gray matter (GM) changes in accordance with striatal dopaminergic degeneration in PD using hybrid PET/MR. Sixteen patients with idiopathic PD underwent ^{18}F -FP-CIT PET/MR. To measure dopaminergic degeneration in PD, binding ratio (BR) of dopamine transporter in striatum was evaluated by ^{18}F -FP-CIT. Voxel-based morphometry (VBM) was used to evaluate GM density. We obtained voxelwise correlation maps of GM density according to the striatal BR. Voxel-by-voxel correlation between BR maps and GM density maps was done to evaluate region-specific correlation of striatal dopaminergic degeneration. There was a trend of positive correlation between striatal BR and GM density in the cerebellum, parahippocampal gyri, and frontal cortex. A trend of negative correlation between striatal BR and GM density in the medial occipital cortex was found. Voxel-by-voxel correlation revealed that the positive correlation was mainly dependent on anterior striatal BR, while posterior striatal BR mostly showed negative correlation with GM density in occipital and temporal cortices. Decreased GM density related to anterior striatal dopa-

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: Intramural Research Grant of Seoul National University; Contract grant number: 0420130670; Contract grant sponsor: SNU Research Fund and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea; Contract grant number: HI14C1072

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Received for publication 5 November 2015; Revised 14 January 2016; Accepted 20 January 2016.

DOI: 10.1002/hbm.23130

Published online 5 February 2016 in Wiley Online Library (wileyonlinelibrary.com).

minergic degeneration might demonstrate degeneration of dopaminergic nonmotor circuits. Furthermore, the negative correlation could be related to the motor circuits of posterior striatum. Our integrated PET/MR study suggests that the widespread structural progressive changes in PD could denote the cortical functional correlates of the degeneration of striatal dopaminergic circuits. *Hum Brain Mapp* 37:1710–1721, 2016. © 2016 Wiley Periodicals, Inc.

Key words: ^{18}F -FP-CIT; PET/MR; Parkinson's disease; voxel-based morphometry; basal ganglia

INTRODUCTION

Neuroimaging studies have contributed to understanding the pathophysiology of Parkinson's disease (PD). The hallmark of the disease is the progressive degeneration of dopaminergic neurons in the substantia nigra combined with decreased dopamine level in the striatum [Lotharius and Brundin, 2002]. The dopaminergic degeneration can be assessed by positron emission tomography (PET) or single-photon emission computed tomography (SPECT) using radiotracers such as ^{18}F -fluoropropyl-carbomethoxyiodophenyl-nortropane (^{18}F -FP-CIT) [Ravina et al., 2005]. Although dopaminergic degeneration is the important pathologic marker of PD, it is followed by various types of functional progressive degeneration in the whole brain involving limbic system and neocortex [Del Tredici et al., 2002]. These abnormalities have been investigated by magnetic resonance imaging (MRI) or ^{18}F -fluorodeoxyglucose (FDG) PET studies mostly focusing on cortical gray matter (GM) or metabolic changes [Brooks, 2010; Stoessl, 2009].

Among MRI studies investigating structural changes in PD, voxel-based morphometry (VBM) approach have showed GM density changes in PD. GM density changes in PD were varied in accordance with clinical symptoms or disease duration [Brenneis et al., 2003; Camicioli et al., 2009; Summerfield et al., 2005; Wattendorf et al., 2009]. In particular, the various GM changes in PD included atrophy in the left caudate nucleus [Brenneis et al., 2003], right hippocampus, olfactory bulbs [Summerfield et al., 2005; Wattendorf et al., 2009] and cerebellum [Camicioli et al., 2009]. Several studies reported that nonmotor symptoms such as cognitive dysfunction in PD were related to widespread cortical atrophy in frontoparietal, limbic areas, and cerebellum [Beyer et al., 2007; Camicioli et al., 2009; Nishio et al., 2010]. Furthermore, structural changes are not only related to disease specific symptoms but affected by secondary compensatory mechanisms [Lee et al., 2013; Obeso et al., 2004; Reetz et al., 2009]. In addition to the structural changes in PD, the pattern of dopaminergic degeneration is also related to the clinical symptoms. Dopaminergic degeneration in PD is mostly found in posterior putamen which is involved in dopaminergic motor circuits [Jokinen et al., 2009; Wang et al., 2007]. Several studies have reported that anterior striatal dopamine system is associated with cognitive functions [Carbon et al., 2004; Polito et al., 2012].

Given dopaminergic loss as the cardinal sign of neurodegeneration of PD followed by structural and functional changes in the cortex, their relationship could be important in the pathophysiology of PD. However, to our knowledge, there has been no study regarding the association between dopaminergic degeneration and cortical change as measured by MRI. The correlation between them could reveal whether specific structural changes are functionally related to patterns of dopaminergic loss in PD. Here, we investigate voxelwise correlation of GM changes with dopamine transporter (DAT) loss measured by ^{18}F -FP-CIT PET in patients with PD using hybrid PET/MR. Recently developed hybrid PET/MR system can provide functional and structural information simultaneously. Thus, it can overcome the limitation of previous neuroimaging studies that functional and structural information is spatially and temporally separated. In this study, we aimed to find the structural changes functionally related to dopaminergic neurons in the striatum. Furthermore, we hypothesized that these structural changes would be dependent on either motor or nonmotor dopaminergic circuits. More specifically, structural changes in frontal, limbic cortices and cerebellum associated with nonmotor symptoms in PD as well as motor cortex involved in corticostriatal circuits could be functionally related to the dopaminergic degeneration. The relationship between dopamine system and structural changes could provide an insight into the interconnectivity of neurotransmitter and cortical structure of PD-related brain networks.

MATERIALS AND METHODS

Subjects

Thirty patients (15 male, 15 female; mean age 60.8 years, range: 39–77 years) who were initially suspected of PD were prospectively enrolled for ^{18}F -FP-CIT PET/MR study from November 2013 to March 2014. Specifically, patients were referred to movement disorder clinic due to tremor, rigidity, hypokinesia, or postural instability and planned dopamine transporter imaging. This study included a larger cohort than a previous ^{18}F -FP-CIT PET/MR study regarding attenuation correction [Choi et al., 2014]. This study was approved by the Institutional Review Board of our institute. All study participants signed an informed consent form. Clinical severity of the disease was assessed

TABLE I. Demographic data

		Parkinson's disease (<i>n</i> = 16)	Non-Parkinsonian tremor (<i>n</i> = 7)
Age (yrs)		59 ± 8 (39-71)	64 ± 11 (40-74)
Sex		9 males, 7 females	3 males, 4 females
UPDRS III score		7.6 ± 4.5	-
Subscores	Tremor	2.1 ± 1.4	-
	Rigidity	1.7 ± 1.8	-
	Bradykinesia	2.6 ± 2.5	-
Hoehn & Yahr score		1.4 ± 0.5	-

with Hoehn & Yahr (H&Y) scale and the motor part (III) of the Unified Parkinson's Disease Rating Scale (UPDRS) which included subscores for speech, facial expression, tremor, rigidity, bradykinesia, and axial symptoms. Subscores of UPDRS were calculated for tremor, rigidity and bradykinesia. Tremor score was a sum of scores of resting tremor (head, upper and lower extremities, respectively) and action or postural tremor of hands. Rigidity score included scores of rigidity of neck, upper and lower extremities. Bradykinesia score included scores of finger taps, hand movements, rapid alternating movement of hands and leg agility. The motor part of UPDRS was assessed in the "off" state, after at least 24 h without any antiparkinsonian medication. Clinical assessment was conducted by a movement disorder specialist at 18 months follow-up. Video-recording for motor testing was performed and reviewed for UPDRS and the subscores. Sixteen patients (9 males and 7 females; age: 59 ± 8 years; H&Y score: 1.4 ± 0.5 ; UPDRS III score 7.6 ± 4.5) were diagnosed as idiopathic PD according to UK PD Brain Bank criteria [Gibb and Lees, 1988]. Six patients were atypical Parkinsonism and eight patients were no presynaptic dopaminergic deficit. Among them, seven patients without presynaptic dopaminergic deficit were clinically non-Parkinsonian tremor in the follow-up diagnosis. Images of 16 PD patients and 7 patients with non-Parkinsonian tremor were analyzed (Table I).

PET/MR Acquisition

Patients underwent PET/MR after 185 MBq (5 mCi) of ^{18}F -FP-CIT injection. Antiparkinsonian and psychiatric medication was stopped at least 24 h before the image acquisition. Emission scans were acquired 110 min after the injection using a dedicated PET/MR scanner (Biograph mMR, Siemens Healthcare, Erlangen, Germany) for 10 min. PET images were reconstructed by an iterative algorithm (ordered-subset expectation maximization, OSEM) with 24 subsets and 5 iterations. Images were post-filtered with 4 mm Gaussian filter. Image matrix size was 256×256 , voxel size was $1.4 \times 1.4 \times 2.0$ mm. Segmentation-based attenuation correction was performed using three-tissue segmentation maps acquired by ultrashort echo time (UTE) sequence (TR 11.9/TE1 0.07/TE2 2.46 ms, flip angle 10° , 192×192 matrix sizes). The reconstruction process

was performed by Biograph mMR software as the manufacturer's recommendation.

MR images were also acquired on the integrated PET/MR scanner using a T1-weighted 3-D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR = 1,670 ms; TE = 1.89 ms; FOV 250 mm, flip angle 9° , image matrix 256×256 , voxel size $1.0 \times 1.0 \times 1.0$ mm).

Image Preprocessing

PET data preprocessing and quantification of dopaminergic degeneration

Image processing procedures for ^{18}F -FP-CIT PET/MR images were summarized in Figure 1. First, we calculated DAT specific-to-nonspecific binding ratio (BR) of putamen to evaluate dopaminergic degeneration in PD. For automated quantification, all the PET images were spatially normalized into an in-house ^{18}F -FP-CIT PET template [Kim et al., 2012; Lee and Lee, 2005]. PET counts of putamen and cerebellum were calculated using statistical probabilistic anatomical mapping. BR was defined as $\text{BR} = (C_{\text{specific}} - C_{\text{nonspecific}}) / C_{\text{nonspecific}}$, where C represented PET counts. Note that the counts of cerebellum were regarded as nonspecific binding, $C_{\text{nonspecific}}$. In addition, to compare the effects of anatomical difference, BR of anterior, and posterior putamen was calculated. The anatomical boundary was determined by a coronal plane including anterior commissure [Oh et al., 2012].

For voxel-by-voxel correlation analyses between ^{18}F -FP-CIT PET and VBM, PET images were normalized to Montreal Neurological Institute (MNI) space using the in-house ^{18}F -FP-CIT template. To generate BR maps, voxel values of the images were scaled to BR using the cerebellar counts. Finally, BR maps were smoothed by Gaussian filter of 12 mm full width at half maximum (FWHM). The voxel size of spatially normalized BR maps was $2.0 \times 2.0 \times 2.0$ mm.

MRI data preprocessing

We performed MRI data analyses using the VBM8 toolbox based on statistical parametric mapping software (SPM8, University College of London, London, UK). T1-weighted images were automatically segmented into GM,

Figure 1.

Image processing procedures for ^{18}F -FP-CIT hybrid PET/MR images. **(A)** To generate correlation maps between GM density and striatal dopamine transporter (DAT) binding ratio (BR), DAT BR of putamen was obtained by statistical probabilistic anatomical mapping. T1-weighted MR images were segmented to obtain GM tissues. The GM density maps were spatially normalized using DARTel algorithm. Voxelwise GM density maps were generated by calculating correlation coefficient with the putami-

nal DAT BR. **(B)** Voxel-by-voxel correlation analysis between DAT BR maps and GM density maps were performed to evaluate anatomical difference of the correlation. The BR values of each voxel and GM density values were correlated across subjects. To visualize significant correlations, uncorrected values of $P < 0.0001$ were set as the threshold. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

white matter (WM), and cerebrospinal fluid (CSF) after image-intensity nonuniformity correction. These segmented images were spatially normalized to the custom-

ized template in the standardized anatomic space using the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTel) algorithm [Ashburner,

2007]. The specific template was created from patients with idiopathic PD ($n = 16$). DARTEL-based deformations were iteratively applied to the tissue segments for good alignment of GM morphology of subjects. The GM tissue segments were then normalized to MNI space using the DARTEL transformations and the volume scale acquired by the Jacobian determinants. The normalized GM volumes were smoothed by Gaussian filter of 8 mm FWHM. The voxel size of normalized GM volumes was $1.5 \times 1.5 \times 1.5$ mm.

Image Analysis

The PET/MR imaging analysis was designed to assess regional GM density that correlates with dopaminergic degeneration measured by ^{18}F -FP-CIT PET in idiopathic PD patients (16 patients) who assessed at 18 months follow-up clinical diagnosis. To compare with patients without dopaminergic degeneration, the imaging analysis was also performed in patients who revealed non-Parkinsonian tremor in follow-up diagnosis. Voxelwise correlation between GM density and BR was assessed in a multiple regression analysis including patients' age and total intracranial volume (TIV) as nuisance covariates. TIV was calculated as the sum of the volumes of GM, WM, and CSF. The analysis was performed using SPM8. To point out which specific GM regions have strong association with dopaminergic degeneration, uncorrected values of $P < 0.001$ were set as the significance threshold and extent threshold of 50 contiguous voxels was applied. In addition, as a post-hoc volume-of-interests (VOIs) analysis, mean GM density of significant clusters was extracted. To confirm the correlation, mean GM density value of the clusters were correlated with DAT BR. In addition, the GM density of the clusters was correlated with subscores of UPDRS including tremor, rigidity, and bradykinesia using Pearson's correlation coefficient.

We showed global patterns of correlation using two different ways. First, to represent overall association pattern, the voxelwise correlation maps were generated using overall putaminal DAT BR and GM density maps. GM density was correlated with right and left putaminal DAT BR, respectively. To specify whether the correlation map were related to symptom laterality of PD, GM volumes of patients with left-side symptom dominant PD were flipped and correlated with the severely affected putaminal BR. The correlation maps were also generated from DAT BR calculated by anterior and posterior putamen. We selected more severe side of motor symptoms scored by UPDRS and calculated anterior and posterior putaminal DAT BR contralateral to the side of severe motor symptoms. The correlation maps were visualized by BrainNet Viewer [Xia et al., 2013]. The correlation maps were also generated in patients with non-Parkinsonian tremor with intact striatal dopamine transporter. They were compared with the correlation maps of idiopathic PD group. Correlation coefficients

of the correlation maps were transformed to z-value using Fisher transformation and extracted mean z-scores of brain regions segmented by automated anatomical labeling (AAL). z-Scores of each brain region were compared between the two groups using Pearson's correlation across the segmented brain regions.

Second, we carried out voxel-by-voxel correlation analyses to find whether GM changes were associated with anatomical patterns of dopaminergic degeneration in striatum (Fig. 1B). The voxels of BR maps and those of GM density maps were correlated across the subjects. Preprocessed BR maps and GM density maps were spatially normalized to MNI space, thus, the preprocessed maps were coregistered. Size of VBM data was reduced for voxel-by-voxel computation, which voxel size of resliced GM maps was $3 \times 3 \times 3$ mm. Pearson correlation coefficient and p-values of voxel-by-voxel correlation matrices were generated. Thus, a component of matrices represents the correlation coefficient between BR of a voxel and GM density of another voxel. To find significant pairs between DAT BR and GM density, uncorrected values of $P < 0.0001$ were set as the threshold. Finally, for 3-D visualization of connections between DAT BR and GM density, a tenth of the significant connections were selected and visualized.

RESULTS

Among 30 patients who initially suspected of Parkinsonism, 16 patients were diagnosed as idiopathic PD at 18 months follow-up and these patients were included in the analysis. The diagnosis of the remaining 14 patients were; atypical Parkinsonism in six and no presynaptic dopaminergic deficit in eight.

Voxelwise correlation between DAT BR in putamen and GM density in the patients with idiopathic PD was performed. It revealed positive correlation between right putaminal DAT BR and GM density in right cerebellum crus ($Z_{\max} = 4.08$, $r = 0.86$; Pearson correlation obtained from a posthoc VOI analysis), left parahippocampal gyrus ($Z_{\max} = 3.71$, $r = 0.64$), right superior frontal gyrus ($Z_{\max} = 4.42$, $r = 0.91$), left middle temporal gyrus ($Z_{\max} = 3.85$, $r = 0.87$) and right precentral gyrus ($Z_{\max} = 3.70$, $r = 0.71$). Positive correlation between left putaminal DAT BR and GM density was also found in right cerebellum crus ($Z_{\max} = 4.35$, $r = 0.74$), left parahippocampal gyrus ($Z_{\max} = 3.51$, $r = 0.62$) and right middle frontal gyrus ($Z_{\max} = 4.13$, $r = 0.84$). The analysis showed a trend of negative correlation between right putaminal DAT BR and GM density in left calcarine ($Z_{\max} = 3.65$, $r = -0.75$) and both middle cingulum ($Z_{\max} = 3.62$, $r = -0.48$ for left side and $Z_{\max} = 3.73$, $r = -0.70$ for right side). There was also a trend of negative correlation between left putaminal DAT BR and GM density in left calcarine ($Z_{\max} = 3.81$, $r = -0.80$) (Table II). There was no significant correlation between subscores of UPDRS including tremor, rigidity and bradykinesia and mean GM density of those significant clusters, though a trend of negative

TABLE II. Clusters of the most significant correlations between binding ratio (BR) and GM density

	Anatomical Region	Cluster Size (Size of a cluster is $1.5 \times 1.5 \times 1.5$ mm)	Coordinates (mm)			Z
			x	y	z	
Right putaminal BR, positive correlation	Right cerebellum crus I/II	72	9	-73	-27	4.08
	Left parahippocampal gyrus	51	-24	-21	-23	3.71
	Right superior/middle frontal gyrus	83	29	17	54	4.42
	Left middle temporal gyrus	52	-48	-64	12	3.85
	Right precentral gyrus	61	59	8	31	3.70
Left putaminal BR, positive correlation	Right cerebellum crus I/II	159	10	-73	-30	4.35
	Left superior temporal pole/ parahippocampal gyrus	113	-26	8	-21	3.51
	Right superior/middle frontal gyrus	89	32	17	52	4.13
Right putaminal BR, negative correlation	Left calcarine	69	-15	-51	10	3.65
	Left middle cingulum	65	-14	-25	42	3.62
	Right middle cingulum	111	12	21	33	3.73
Left putaminal BR, negative correlation	Left calcarine	144	-16	-54	9	3.81

correlation was found between bradykinesia and GM density of right cerebellar crus ($r = -0.45$, $P = 0.08$) and left parahippocampal gyrus ($r = -0.45$, $P = 0.09$) (Supporting Information, Table S1).

Global correlation maps placed on brain surface were displayed in Figure 2. They showed a trend of a positive correlation between DAT BR and GM density in cerebellum, parahippocampal gyri, and medial frontal cortex. They also showed a trend of negative correlation in medial occipital cortex, precuneus and neocortex of temporal lobes. The global correlation maps obtained from severely-affected DAT BR were similar with those obtained from right and left DAT BR, although patients have symptom-laterality. Note that the positive correlation suggests GM atrophy correlated with dopaminergic degeneration. Voxelwise correlation between DAT BR and GM density was also analyzed in patients with non-Parkinsonian tremor who did not show dopaminergic degeneration on ^{18}F -FP-CIT PET. Global correlation maps showed a trend of positive correlation between DAT BR and GM density in parahippocampal gyri and medial frontal cortex. GM in medial occipital cortex, precuneus and neocortex of temporal lobes also showed trends of negative correlation with DAT BR as in patients with idiopathic PD (Supporting Information, Fig. S1). Two correlation maps of idiopathic PD and patients with non-Parkinsonian tremor were compared. The two maps were significantly correlated to each other, which suggested the similar structural-dopaminergic correlation pattern in PD and non-PD group ($r = 0.30$, $P = 0.001$ for right putamen and $r = 0.22$, $P = 0.02$ for left putamen) (Supporting Information, Fig. S2).

We additionally performed voxel-by-voxel correlation analysis between DAT BR and GM density to recognize region-specific correlation in idiopathic PD patients. Positive correlation was mainly found between anterior striatal DAT BR and GM density in cerebellum crus, left parahippocampal gyrus, and left middle temporal gyrus. Negative correlation was mainly found between posterior striatal DAT BR and GM density in both occipito-temporal cortices (Fig. 3). The analysis suggested that GM atrophy associated with dopaminergic degeneration was mostly dependent on anterior striatum and GM hypertrophy associated with dopaminergic degeneration was mostly dependent on posterior striatum. The difference between voxelwise correlation maps of the anterior and posterior putaminal BR was found (Fig. 4). The correlation of GM density with posterior putaminal DAT BR of the most affected side showed widespread negative correlation in occipito-temporal cortices. Besides, the correlation map of anterior putaminal DAT BR was similar to that of whole putaminal DAT BR.

DISCUSSION

In this study, we investigated the relationship between dopaminergic degeneration in striatum and GM density using ^{18}F -FP-CIT PET/MR in idiopathic PD. Voxelwise correlation analysis showed putaminal DAT BR was positively correlated with GM density in the cerebellum, parahippocampal gyrus, and frontal cortices. Putaminal DAT BR showed a trend of negative correlation with GM density in calcarine, precuneus and both middle cingulum.

Gray matter density correlates of right putaminal BR

Gray matter density correlates of left putaminal BR

Contralateral *Ipsilateral to symptom*

Gray matter density correlates of putaminal BR of severe side

Figure 2.

GM density correlates of putaminal dopaminergic degeneration. Global correlation maps of GM density were generated by GM volumes correlated with right and left DAT BR. In addition, GM volumes of patients with left-side symptom dominant PD were flipped and correlated with putaminal BR of the severely affected side. Three types of correlation maps showed similar pattern. Note red color represents positive correlation which means

GM atrophy correlated with striatal dopaminergic degeneration. A trend of a positive correlation was mostly found in the cerebellum and parahippocampal gyri while a trend of negative correlation was found in occipital and temporal cortices. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Voxel-by-voxel correlation analysis revealed region-specific correlation patterns. Anterior putaminal DAT BR mostly showed positive correlation with GM density in the cerebel-

lum, parahippocampal gyri and frontal cortices, while posterior putaminal DAT BR mostly showed negative correlation with GM density in the temporal and occipital cortices.

Figure 3.

Anatomical difference of the correlation between GM density and DAT BR. Positive (**A**) and negative (**B**) voxel-by-voxel correlation was calculated and significant pairs of voxels are represented. Note that red color means GM correlates of anterior striatal BR and blue color means those of posterior striatal BR.

Anterior striatal BR mainly shows positive correlation with GM in the cerebellum and left parahippocampal gyrus, while posterior striatal BR mainly shows negative correlation with occipito-temporal GM. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

To our knowledge, this study is the first study that evaluated structural and neurochemical abnormalities simultaneously using hybrid PET/MR. We evaluated GM changes in accordance with the dopaminergic degeneration in the striatum in patients with PD. Recent hybrid PET/MR neuroimaging studies have focused on the functional relationship between metabolism and hemodynamic signals reflecting neuronal activity [Aiello et al., 2015; Riedl et al., 2014; Wehrl et al., 2013], however, the relationship between structural and functional information obtained by PET/MRI has not yet been studied. Since structural change in the brain detected by MR is a rapid and dynamic process [May et al., 2007], simultaneously acquired neurochemical (PET) and structural (MRI) data are crucial for investigating the relationship between them.

The cerebellum crus was one of the significant GM regions positively correlated with putaminal DAT BR.

Because motor, cognitive and behavioral circuits are widely affected by cerebellum as well as basal ganglia in PD [Middleton and Strick, 2000], the findings corresponded to functional relationship of these structures. Furthermore, the cerebellum and striatum is anatomically connected to process motor and nonmotor information [Hoshi et al., 2005]. The trend of positive correlation between dopaminergic degeneration and cortical atrophy in the cerebellum supports functional relationship of basal ganglia and the cerebellum. Several neuroimaging studies which compared PD patients with healthy controls also showed cerebellar atrophy [Benninger et al., 2009; Camicioli et al., 2009; Nishio et al., 2010; Pereira et al., 2009]. Furthermore, Parkinsonian tremor is related to the interaction between basal ganglia and cerebello-thalamo-cortical circuit [Helmich et al., 2011], though we could not find the relationship between severity

Figure 4.

GM density correlates of anterior and posterior putaminal DAT BR. According to the voxel-by-voxel correlation, anatomical patterns of the correlation between GM density and DAT BR were found. Specifically, voxelwise correlation maps of GM density with anterior and posterior putaminal BR were gen-

erated. A trend of negative correlation between left posterior putaminal BR and widespread occipito-temporal cortices were found, which was different from the correlation map of anterior putaminal BR. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of tremor which measured by subscores of the motor part of UPDRS and cerebellar GM density. Rather, a trend of negative correlation between GM density of cerebellum crus and subscores of bradykinesia in our study partly corresponded to previously reported cerebellar volume changes associated with bradykinesia [Lee et al., 2014]. The finding, correlation of DAT BR and cerebellar GM density, suggests that cerebellar atrophic changes could be associated with dopaminergic degeneration via striatum-cerebellar connections.

The positive correlation between DAT BR and GM density was mainly found in anterior striatum. Anterior striatal dopaminergic denervation is related to nonmotor symptoms including sensory, neuropsychiatric and cognitive functions [Cao et al., 2011; Carbon et al., 2004; Polito et al., 2012; Rektorova et al., 2008; Weintraub et al., 2005]. In this study, the brain regions with reduced GM density correlated with anterior striatal dopaminergic degeneration included the cerebellum, parahippocampal gyri and medial frontal lobes. The regions are considerably consistent with previously reported cortical atrophy associated with cognitive impairment in PD [Beyer et al., 2007; Camicioli et al., 2009; Nishio et al., 2010]. Furthermore, the cerebellum crus are closely associated with nonmotor functions including working memory, executive functions, and spatial tasks [Stoodley and Schmahmann, 2009; Stood-

ley et al., 2012]. Anterior striatal dopaminergic degeneration is connected to neocortical associative and limbic loops, which may cause cognitive symptoms in PD. FDG PET studies also showed that anterior striatal dopaminergic degeneration was closely related to PD-related cognitive patterns [Berti et al., 2010; Holtbernd et al., 2015; Polito et al., 2012]. Our results are in accordance with these previous results. The finding of the relationship between anterior striatal dopaminergic degeneration and reduced GM regions might be demonstrated by abnormality of nonmotor circuits in PD. Various nonmotor features of PD might be caused by progressive and widespread cortical degeneration depending on dopaminergic loss in anterior striatal nonmotor area.

Posterior striatal dopaminergic loss was mostly associated with increased GM density in occipital and temporal cortices. Posterior striatal dopaminergic loss is a characteristic degeneration of PD. Dopaminergic degeneration detected by DAT imaging is mainly found in posterior putamen [Jokinen et al., 2009; Oh et al., 2012]. Furthermore, spatial covariance pattern approach based on principal component analysis revealed PD-related patterns [Eckert et al., 2007] were associated with posterior striatal dopaminergic degeneration [Holtbernd et al., 2015]. Since posterior striatal dopaminergic degeneration is functionally different from

anterior striatum and they are related to motor circuits of PD [Jokinen et al., 2009], the GM changes according to the posterior striatal DAT BR might be related to dysfunctional cortico-striatal motor circuit. In spite of decreased DAT density in posterior putamen, GM density changes were more likely to be increased particularly in the temporal and occipital cortices. Though the cause of opposite changes is uncertain, they could be demonstrated by compensatory functions in PD [Lee et al., 2013; Obeso et al., 2004; Reetz et al., 2009]. A possible explanation for the opposite changes is that increased GM density in the widespread temporo-occipital cortices might compensate for dysfunctional cortico-striatal connectivity. The finding was partly consistent with previous reports which showed functional compensatory activation for altered dorsal premotor activity in PD [Helmich et al., 2007; van Nuenen et al., 2012]. Structural hypertrophic changes in occipito-temporal cortices in PD were also reported in cortical thickness analysis which suggested compensatory neuroplasticity [Biundo et al., 2013]. Overall, though reduced metabolic activity in dorsal premotor area accompanied with dopaminergic degeneration in PD [Berti et al., 2010; Polito et al., 2012], structural changes of cortico-striatal circuits were indistinct while the increased GM in temporo-occipital areas was dominant. Furthermore, structural changes of the basal ganglia correlated with dopaminergic degeneration were not found though MR signal changes related to iron content in substantia nigra were previously reported [Gorell et al., 1995; Schwarz et al., 2011]. Because VBM has limitations in segmentation focusing on these subcortical structures, further studies using various MR signals will be required to analyze functional interconnections of dopaminergic degeneration and subcortical structures. In the future, to clarify the dopaminergic-structural link in PD, comprehensive multimodal approaches with clinical symptom follow-up will be needed.

In this study, the GM regions correlated with severely affected DAT BR were similar with those correlated with right and left DAT BR (Fig. 2). This result could be due to bilaterally decreased DAT BR though the patients have symptom laterality. In early PD with unilateral symptoms, DAT loss can be found bilaterally [Filippi et al., 2005]. Because dopaminergic loss detected by DAT imaging is a prodromal biomarker for PD, decreased DAT BR in the striatum could affect the both sides of cortical structures regardless of symptom laterality [Jennings et al., 2014]. Our finding suggests that PD-related dopaminergic degeneration and structural changes related to DAT BR could be bilaterally progressed before the manifestation of bilateral symptoms in early PD.

In this study, the subjects were limited to the patients with PD and healthy controls were not included. Because PD shows not only regional changes in the brain but abnormal connectivity [Helmich et al., 2010; Wu et al., 2009], brain networks associated with the striatum are disrupted in PD. Therefore, the GM changes that correlated

with dopaminergic degeneration in PD could not mean direct structural connections of dopaminergic circuits in the normal brain. Nevertheless, we also performed the correlation analysis between GM and DAT BR in patients with non-Parkinsonian tremor who showed intact striatal dopaminergic system. The patterns of positive and negative correlation in this group were considerably similar with those of the patients with idiopathic PD. More specifically, positive correlation in parahippocampal and medial frontal cortex and negative correlation in medial occipital cortex were similar. Furthermore, the correlation maps of the two groups were significantly correlated to each other across the brain regions, which meant that they had similar correlation pattern. It implied the functional relationship of structural and dopaminergic systems in idiopathic PD as well as in normal subjects though the patients with non-Parkinsonian tremor were not healthy subjects. Structural and functional connectivity analyses in PD and healthy controls would provide further information of striatal dopaminergic networks as well as distinctive degeneration patterns in PD. Despite small number of subjects in this study to find GM changes according to striatal circuits, PD patients group revealed crucially affected cortical regions by the striatal dopaminergic degeneration. In the future, a larger cohort study including comprehensive motor and cognitive evaluation and healthy control groups will promise understanding of neuronal circuits of PD related to clinical features as well as detection of definite GM changes.

CONCLUSION

We showed GM changes according to the striatal dopaminergic degeneration using simultaneously acquired PET and MRI data. A trend of positive correlation was found in the cerebellum and parahippocampal gyri and a trend of negative correlation was found in the medial occipital cortex. Positive correlation was mostly dependent on anterior striatal dopaminergic degeneration, which might be associated with nonmotor circuits of basal ganglia. Besides, posterior striatal dopaminergic degeneration mostly showed negative correlation with GM density in temporal and occipital cortices. Our integrated ¹⁸F-FP-CIT PET/MR study could demonstrate the close relationship between global structural changes and the degeneration of striatal dopaminergic circuits in PD.

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