Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000201269

Association Between White Matter Networks and the Pattern of Striatal Dopamine Depletion in Patients With Parkinson Disease

Author(s):
Seok Jong Chung, MD1, 2; Yae Ji Kim, BS3, 4; Yun Joong Kim, MD, PHD1, 2; Hye Sun Lee, PhD3; Seong Ho Jeong, MD6; JI-MAN HONG, MD, PhD1, 2; Young H. Sohn, MD, PhD3; Mijin Yun, MD, PhD3; Yong Jeong, MD, PhD3, 4, 8; Phil Hyu Lee, MD, PhD1, 9

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Corresponding Author: Phil Hyu Lee, phlee@yuhs.ac

Affiliation Information for All Authors: 1. Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea; 2. Department of Neurology, Yongin Severance Hospital, Yonsei University Health System, Yongin, South Korea; 3. Program of Brain and Cognitive Engineering, Korea Advanced Institute of Science and Technology, Daejeon, South Korea; 4. KI for Health Science and Technology, Korea Advanced Institute of Science and Technology, Daejeon, South Korea; 5. Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, South Korea; 6. Department of Neurology, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, South Korea; 7. Department of Nuclear Medicine, Yonsei University College of Medicine, Seoul, South Korea; 8. Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology, Daejeon, South Korea; 9. Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, South Korea

Equal Author Contribution:
Drs. Chung and Yae J. Kim contributed equally to this work as co-first authors. Drs. Y. Jeong and P.H. Lee contributed equally to this work as co-senior authors.

Contributions:
Seok Jong Chung: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Yae Ji Kim: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Yun Joong Kim: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Hye Sun Lee: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Seong Ho Jeong: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
JI-MAN HONG: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Young H. Sohn: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Mijin Yun: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or
Abstract

Objectives: Individual variability in nigrostriatal dopaminergic denervation is an important factor underlying clinical heterogeneity in Parkinson’s disease (PD). This study aimed to explore whether the pattern of striatal dopamine depletion was associated with white matter (WM) networks in PD.

Methods: A total of 240 newly diagnosed PD patients who underwent $^{18}$F-FP-CIT PET scans and brain diffusion tensor imaging at initial assessment were enrolled in this study. We measured $^{18}$F-FP-CIT tracer uptake as an indirect marker for striatal dopamine depletion. Factor analysis-derived striatal dopamine loss patterns were estimated in each patient to calculate the composite scores of four striatal subregion factors (caudate, more- and less-affected sensorimotor striata, and anterior putamen) based on the availability of striatal dopamine transporter. The WM structural networks that were correlated with the composite scores of each striatal subregion factor were identified using a network-based statistic analysis.

Results: A higher composite score of caudate (i.e., relatively preserved dopaminergic innervation in the caudate) was associated with a strong structural connectivity in a single subnetwork comprising the left caudate and left frontal gyri. Selective dopamine loss in the caudate was associated with strong connectivity in the structural subnetwork whose hub nodes were bilateral thalami and left insula, which were connected to the anterior cingulum. However, no subnetworks were correlated with the composite scores of other striatal subregion factors. The connectivity strength of
the network with a positive correlation with the composite score of caudate affected the frontal/executive function either directly or indirectly through the mediation of dopamine depletion in the caudate.

Conclusions: Our findings indicate that different patterns of striatal dopamine depletion are closely associated with WM structural alterations, which may contribute to heterogeneous cognitive profiles in individuals with PD.

Parkinson’s disease (PD) is a heterogeneous neurodegenerative disorder with individual variability in the clinical phenotype and rate of disease progression. This clinical heterogeneity suggests the existence of different subtypes of PD, and several studies have attempted to define the subtypes of PD based on clinical manifestations and biomarkers. The patterns of nigrostriatal dopaminergic denervation, which vary among individuals with PD and persist throughout the disease course, have been proposed as possible markers to delineate PD subtypes in both postmortem and in vivo PET imaging studies. Recently, we demonstrated that the patterns of striatal dopamine depletion (i.e., which striatal subregions are selectively involved or relatively preserved) could provide information on the long-term prognosis, including the development of motor complications and dementia in patients with early-stage PD.

Growing evidence indicates that dopamine depletion impairs neuronal processing in the striatum, which subsequently affects the cortical-striatal connections. Various clinical features of PD may result from functional and structural alterations not only in the striatal subregions, but also in the corresponding cortico-striatal networks. This indicates that approaching PD as a disease of striatal network dysfunction is essential in understanding its pathophysiology. Therefore, in the present study, we
hypothesized that structural brain networks that are closely associated with the pattern of striatal dopamine depletion would exist, and that alterations in these structural networks may contribute to the clinical heterogeneity of PD. To test this, we explored whether the pattern of striatal dopamine depletion is closely associated with white matter (WM) structural connectivity in drug-naïve PD patients. We also investigated the clinical relevance of the identified WM connectivity networks in PD, particularly their relationship with cognitive function.

Methods

Participants

We retrospectively reviewed the medical records of patients in the Yonsei Parkinson Center database who visited the Movement Disorders outpatient clinic at Severance Hospital between January 2015 and April 2018, and were newly diagnosed as PD according to the clinical diagnostic criteria of the UK PD Society Brain Bank. All study participants had never been exposed to PD drugs prior to being diagnosed with PD, and underwent \(^{18}\text{F}\) N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane positron emission tomography \((^{18}\text{F}-\text{FP-CIT PET})\) and brain magnetic resonance imaging (MRI) scans available for diffusion tensor imaging (DTI) analyses at initial assessment. All patients did not exhibit additional atypical features during the follow-up period (> 3 years). Parkinsonian motor symptoms were assessed using the Unified Parkinson’s Disease Rating Scale Part III (UPDRS- III). The Korean version of the Mini-Mental State Examination (K-MMSE) was used to assess general cognition. Olfactory function and depression were evaluated using the cross-cultural smell identification test and the Beck Depression Inventory, respectively. The severity of white matter hyperintensity was rated on fluid-attenuated inversion
recovery images using the Scheltens scale.\textsuperscript{17}

**Standard Protocol Approvals, Registration, and Patient Consents**

This study was approved by the Yonsei University Severance Hospital institutional review board (9-2020-0101). The need for informed consent was waived because of the retrospective nature of the study.

**Quantitative analyses of $^{18}$F-FP-CIT PET**

$^{18}$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 (FWHM). After a 6-hour fast, the patients were intravenously injected with 5 mCi (185 MBq) of $^{18}$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.\textsuperscript{18}

Image processing was performed using MATLAB (The MathWorks, Inc, Natick, MA, USA) software for statistical parametric mapping\textsuperscript{8} (http://www.fil.ion/uc.ac.uk/spm) and ITK-SNAP (http://www.itksnap.org). All reconstructed $^{18}$F-FP-CIT PET images were spatially normalized to the $^{18}$F-FP-CIT PET template, which was made using the $^{18}$F-FP-CIT PET images and T1-weighted MR images of 40 healthy controls (mean age, 61.6 ± 8.0 years, 22 females) as described previously to remove inter-subject anatomic variability.\textsuperscript{19} Briefly, all of the healthy controls from which the $^{18}$F-FP-CIT PET 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 $^{18}$F-FP-CIT PET. Using a 12-parameter affine transformation, $^{18}$F-FP-CIT PET images of healthy controls were co-registered to T1-
weighted MR images of those individuals. Ten volumes of interest (VOI) for bilateral striatal subregions and one occipital VOI were drawn on the co-registered $^{18}$F-FP-CIT PET template. The striatum was divided into the anterior caudate, posterior caudate, anterior putamen, posterior putamen, and ventral putamen. The ventral striatum was excluded from the analysis given that the ventral tegmental area, which projects the dopaminergic fibers to the ventral striatum and other limbic structures, is much less damaged than other nigral areas in PD. The outer boundaries of the striatal subregions were visually determined by characteristic dense gray signal of the striatum. The VOI for the ventral putamen was defined using the anterior-posterior commissure line on the transverse plane. The other striatal subregions were divided into the following anterior and posterior subregions along the coronal anterior commissure plane: the anterior caudate, posterior caudate, anterior putamen, and posterior putamen. The occipital VOI, namely calcarine fissure and surrounding cortex (V1), was selected from AAL atlas. Manual adjustment of VOI was then performed to minimize possible mis-registration occasionally occurring in the automated VOI analysis. Dopamine transporter (DAT) availability in each striatal subregion was estimated using the specific/nonspecific binding ratio as a surrogate, which was defined as follows: (mean uptake value of the striatal subregion VOI – mean uptake value of the occipital VOI) / (mean uptake value of the occipital VOI). We used striatal DAT availability as an indirect marker for striatal dopamine depletion.

**Estimation of striatal dopamine depletion pattern in each subject**

We previously conducted a factor analysis to identify the patterns of striatal dopamine depletion based on the DAT availability in 10 striatal sub-regions (eMethods and eTables 1 and 2). The factor analysis yielded four striatal subregion
factors, which indicated the degree of dopaminergic denervation in the striatal subregions or sectors compared to that of the whole striatum. The four factors were named according to the striatal subregions which constituted each factor with a strong factor loading: Factor 1 (caudate), Factor 2 (more-affected sensorimotor striatum), Factor 3 (less-affected sensorimotor striatum), and Factor 4 (anterior putamen). For example, a high composite score of Factor 1 (caudate) indicated that the subject’s dopaminergic innervation in the caudate was relatively preserved, considering the degree of dopaminergic denervation in the whole striatum. In this study, we applied the same formula to calculate the composite scores of each striatal subregion factor in each subject.

White matter structural connectivity analyses

*Imaging pre-processing*

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.\textsuperscript{23–25} The high-resolution axial T1-weighted MRI data were obtained using a 3D T1-TFE sequence with the following parameters: 224 × 224 axial acquisition matrix; 256 × 256 reconstructed matrix with 170 slices; voxel size, 0.859 × 0.859 × 1 mm\textsuperscript{3}; 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-collinear, non-coplanar diffusion-encoded gradient directions; 128 × 128 acquisition matrix with 70 slices; voxel size, 1.75 × 1.75 × 2 mm\textsuperscript{3}; field of view, 220 mm; b-factor, 600 s/mm\textsuperscript{2}; echo time, 70 msec; repetition time, 7.663 sec; flip angle, 90°.

Each subject’s MR scans was visually inspected to check for the presence of any
signal dropouts or artifacts before pre-processing the data. After the inspection, the DTI data were pre-processed using the FMRIB Software Library (FSL version 5.0.9; fmrib.ox.ac.uk/fsl/). To correct artifacts induced by eddy currents and head motion, data were pre-processed by affine registration to the first b0 image using the “eddy_current” function in FSL. Individual skull-stripped binary brain masks using Brain Extraction Tool (BET) were created with a fractional intensity threshold of 0.2. Then, the T1-weighted data of each subject was co-registered to the corresponding b0 image and transformed to native DTI space using linear registration.

_Fiber tracking analysis and network construction_

From the pre-processed DTI data, whole-brain deterministic tractography was performed using Euler’s method in DSI Studio to identify anatomical connections following the parameters: a fractional anisotropy (FA) threshold of 0.15, maximum turning angular threshold of 45°, step size of 1.0 mm, and four iterations of a pruning count to automatically remove false connections using Topology-Informed Pruning. Tracts shorter than 30 or longer than 300 mm were discarded. The fiber trajectories were smoothed by averaging the propagation direction with a random percentage from 0% to 95% of the previous direction. The fiber tracking was executive until a total of 100,000 seeds were placed in the seeding regions. For structural network construction, the brain was automatically parcellated using automated anatomical labeling (AAL) atlas, which consists of 116 cortical and subcortical regions. AAL atlas in MNI space was inversely warped to the native DTI space to preserve the individual’s anatomical information. With AAL ROIs as nodes of the constructed network, an edge between the nodes was identified to be presented if connections start and end within the two regions. The weights of each edge were computed by the
average FA values of all generated fiber tracts within trajectories $i$ and $j$.

*Network-based statistic (NBS) analysis*

We conducted a NBS analysis to identify the associated structural networks with striatal dopamine depletion pattern in patients with PD. The advantage of the NBS is that increases the statistical power for nodal analyses that have become underpowered after multiple comparisons correction by controlling type I error. First, we performed a general linear regression with the composite score of each striatal subregion factor as a dependent variable and the structural connectivity as a predictor, while adjusting for age at brain MRI scans, sex, disease duration of PD (i.e., time from symptom onset to diagnosis or study enrollment), and UPDRS-III score. After that, a primary cluster forming threshold ($t = 3.6$) was initially applied to calculate the statistical value at each edge of the network to identify the set of supra-threshold edges. To estimate the statistical significance of all interconnected components presented in the edges, $K$ numbers of nonparametric permutation test ($K = 5,000$) was performed. After a number of random permutations, the subnetworks were determined to be significant at $p < 0.05$ (family-wise error [FWE]-corrected). Within the identified networks, we calculated the connectivity strengths of the significant networks as the sum of the weights of connections between the network components. Moreover, we identified the hub regions of the significant subnetworks from NBS. Hubs play a crucial role in the fast segregation and efficient integration of information within a whole network. Hub nodes were defined as nodes with nodal properties of betweenness centrality (Bc) exceeding one standard deviation above the mean Bc value of all nodes in the subnetworks.
Neuropsychological assessment

The Seoul Neuropsychological Screening Battery (SNSB), a comprehensive Korean language neuropsychological test battery, covers five cognitive domains consisting of 14 scorable tests: 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). We previously conducted a factor analysis to collapse the neuropsychological subtests into four cognitive function domains (visual memory/visuospatial, verbal memory, frontal/executive, and attention/working memory/language function) in patients with PD. In the present study, we calculated the composite scores of each cognitive function domain by applying the same formula described in our previous work.

Statistical analyses

The Pearson’s correlation coefficient was calculated to assess the relationship between the composite scores of each striatal subregion factor and cognitive domain. The relationship between the connectivity strength of identified subnetworks and cognitive composite scores was also assessed using Pearson’s correlation analyses. A Bonferroni correction was used for multiple testing correction. Moreover, mediation analyses were performed to evaluate whether the network strength mediated the
association between striatal dopamine deficits and cognitive function. Age, sex, and years of education were entered as covariates. We used a bootstrapping method with 1000 resamples to derive the 95% confidence intervals and standard errors using the “lavaan” package for the R program. The statistical analyses were performed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA) and R software package (version 4.1.1; http://www.r-project.org). Results with a two-tailed \( p \)-value < 0.05 were considered statistically significant.

Data availability

For purposes of replicating procedures and results, any qualified investigator can request anonymized data after ethics clearance and approval by the corresponding authors.

Results

Baseline clinical characteristics of patients with PD

Of the 264 subjects who met the inclusion criteria, 24 were excluded as their data included extensive focal brain damage, artifacts, and image distortions. Therefore, a total of 240 patients with early-stage drug-naïve PD were included for neuroimaging analyses. Table 1 shows the baseline clinical characteristics of patients with PD included in this study. The mean age at PD symptom onset was 69.1 ± 9.0 years and the mean disease duration was 17.9 ± 15.1 months. The mean UPDRS-III score at the time of diagnosis was 22.5 ± 9.7. The composite scores of four striatal subregion factors (caudate, more- and less-affected sensorimotor striata, and anterior putamen) and four cognitive function domains (visual memory/visuospatial, verbal memory, frontal/executive, and attention/working memory/language function) are shown in
Table 1.

**Subnetworks correlated with subregion factors**

A single subnetwork whose structural connectivity positively correlated with the composite score of striatal subregion Factor 1 (caudate) was identified (FWE-corrected $p = 0.011$). The subnetwork consisted of 3 edges that were connected to 4 nodes (left caudate, left middle frontal gyrus, left middle frontal gyrus [orbital part], and left inferior frontal gyrus [orbital part]), while the hub node was the left caudate (Figure 1A; Table 2).

There was a single subnetwork that was negatively correlated with the composite score of striatal subregion Factor 1 (caudate) (FWE-corrected $p < 0.001$). It consisted of 13 edges that were connected to 14 nodes (right anterior cingulate and paracingulate gyri, left anterior cingulate and paracingulate gyri, right median cingulate and paracingulate gyri, left median cingulate and paracingulate gyri, left putamen, right pallidum, left pallidum, right thalamus, left thalamus, left inferior frontal gyrus [.opercular part], left Rolandic operculum, left insula, lobule IX of left cerebellar hemisphere, and lobule I, II of vermis) The bilateral thalami and left insula were hub nodes (Figure 1B; Table 2).

Meanwhile, there were no subnetworks whose structural connectivity was correlated with the composite scores of other striatal subregion factors, including Factor 2 (more-affected sensorimotor striatum), Factor 3 (less-affected sensorimotor striatum), and Factor 4 (anterior putamen).

**Correlation analyses with cognitive composite scores**

Correlation analyses demonstrated that the composite score of striatal subregion Factor 1 (caudate) positively correlated with the composite score of frontal/executive
function domain ($\gamma = 0.355, p < 0.001$). Meanwhile, there were no significant associations between the composite scores of other striatal subregion factors and cognitive function domains (Table 3).

The connectivity strength of the subnetwork that exhibited a positive correlation with the composite score of caudate was also significantly correlated with the composite scores of frontal/executive function domain ($\gamma = 0.300, p = 0.001$), but not with those of other cognitive domains (visual memory/visuospatial function domain, $\gamma = 0.199, p = 0.087$; verbal memory function domain, $\gamma = 0.132, p = 0.752$; attention/working memory/language function domain; $\gamma = 0.118, p > 0.999$).

Additionally, there were no significant correlations between the cognitive composite scores and the connectivity strength of the subnetwork that had a negative correlation with the composite score of caudate (Table 4).

**Mediation analysis**

Based on the results of correlation analyses, the composite score of striatal subregion Factor 1 (caudate) and the connectivity strength of the network that showed positive correlation with the composite score of caudate were entered as a predictor or mediator in the mediation analyses for the composite score of frontal/executive function domain (Figure 2 and Table 5). The composite score of frontal/executive function domain was directly affected by selective dopamine loss in the caudate ($\beta = 0.292$, bootstrapping standard error [BootSE] = 0.108, $p = 0.007$), but the effect of dopamine deficits in the caudate on frontal/executive function was not indirectly mediated by the connectivity strength of the caudate structural network ($\beta = 0.068$, BootSE = 0.039, $p = 0.082$; Figure 2A). Meanwhile, network strength affected frontal/executive function either directly ($\beta = 1.101$, BootSE = 0.541, $p = 0.042$) or indirectly through the mediation of dopamine depletion in the caudate ($\beta = 0.576$, BootSE = 0.245, $p = 0.019$; Figure 2B).
Discussion

In the present study, we explored the WM structural connectivity networks that were associated with the pattern of nigrostriatal dopamine depletion in patients with PD. The major findings were as follows: (1) We identified the structural brain networks whose WM structural connectivity correlated with the composite scores of caudate. (2) Relatively preserved dopaminergic innervation in the caudate (i.e., a higher composite score of caudate) was associated with strong connections within a single brain network composed of the left caudate and left middle frontal gyri. (3) Relatively severe dopamine loss in the caudate (i.e., a lower composite score of caudate) was associated with strong connections within a single brain network composed of the insula, thalamus, and anterior cingulum, as well as the putamen, pallidum, inferior frontal gyrus, and cerebellum. (4) The connectivity strength of the subnetwork whose structural connectivity was positively correlated with the composite score of caudate, affected the frontal/executive function directly or indirectly through the mediation of dopamine depletion in the caudate. These findings suggested that different patterns of striatal dopamine depletion are closely associated with WM structural alterations, which may contribute to heterogeneous cognitive profiles in individuals with PD.

It is well-recognized that dopaminergic neurons in the substantia nigra are not uniformly degenerated in PD. There is a regional selectivity of dopaminergic denervation in the striatal subregions, which occurs most severely in the posterior putamen. Furthermore, dopaminergic neuronal loss occurs asymmetrically, leading to parkinsonian motor symptoms with unilateral onset and persistent asymmetry.
throughout the course of the illness. Although the mechanisms underlying these spatial patterns of striatal dopamine depletion remain unclear, several factors have been proposed to explain the anteroposterior gradient and side-to-side asymmetry of dopamine loss in PD, including the axonal arborization size, metabolic stress, defense mechanisms, gene expression, the integrity of blood-brain barrier, and an inborn number of nigral dopaminergic neurons. Furthermore, the degree of unevenness or asymmetry of the striatal dopamine loss varies among individuals with PD, which may be specific to each individual and thus closely linked to the clinical heterogeneity of PD.

Previously, we conducted a factor analysis to yield four striatal subregion factors, which represented the degree of dopaminergic denervation in the striatal subregions or sectors compared to that of the whole striatum. The composite scores of these striatal subregion factors were associated with the risk for developing levodopa-induced dyskinesia, wearing-off, and dementia, suggesting that the patterns of striatal dopamine depletion have a prognostic implication in patients with PD. In the present study, we applied the same factor analysis-derived formula to calculate the composite scores of striatal subregion factors of each subject, and explored the WM structural networks which were correlated to the composite scores of each striatal subregion factor. This approach has an advantage that the estimated composite scores indicate the spatial pattern of striatal dopamine deficits, rather than the absolute value of the striatal DAT binding, thus avoiding the possibility that WM structural disruption were simply related to an advanced disease state at initial assessment. Furthermore, the composite scores of striatal subregion factors did not correlate with each other, thereby reducing the redundancy of striatal subregions in the analyses.

Several lines of evidence have suggested that striatal dopamine depletion in PD leads to a remapping of cerebral connectivity via alterations of structural and
synaptic plasticity and subsequent axonal disconnection. In this study, NBS analysis identified two subnetworks whose connectivity strength either positively or negatively correlated with the extent of dopamine depletion in the caudate. As expected, subjects with relatively spared dopaminergic innervation in the caudate had strong connections within the corresponding cortico-striatal network comprising the caudate and frontal region, consistent with previous observations that the caudate receives massive projections from the prefrontal cortex. In particular, the identified structural network was found only in the left hemisphere, which might be ascribed to the inherent hemispheric asymmetry: the dominant hemisphere (left hemisphere in most individuals) has more profuse interconnections and greater use-dependent facilitation of motor-evoked potentials than the non-dominant hemisphere. Meanwhile, subjects with a preferential dopamine loss in the caudate exhibited a stronger connection within the WM structural network where the insula and thalamus were hub nodes, implying that there may be a trade-off between dopamine degeneration in the caudate and WM structural connections to complement the role of the caudate, such as cognitive function in PD. Indeed, the insula is highly interconnected with several cortical regions involved in cognitive processes and has been reported to be associated with executive and memory function in patients with PD. The thalamus is traditionally characterized as the central motor and sensory relay station of the brain, but also supports cognitive function by serving as a triage center for information to determine what information would be passed on to higher cortical regions for processing. Aside from the hub nodes, several nodes constituting the WM structural network are also involved in the cognitive process. For example, the anterior cingulate cortex is a key component of the salience network which modulates the activation of the default mode network and central executive network.
putamen acts as an integrative hub via the convergence of multiple distal cortical inputs and appears to be associated with a higher risk for developing dementia in PD. In this regard, dopamine loss in the caudate would be closely linked to altered structural connections in different cortico-striatal loops depending on the level of depletion relative to other striatal subregions. Moreover, the connectivity strength of the identified white matter structural networks would be useful for delineating PD subtypes according to the patterns of striatal dopamine depletion (e.g., PD subgroup with diffuse dopamine loss throughout the striatum versus PD subgroup with selective dopaminergic loss in the putamen). Conversely, no subnetworks whose structural connectivity was well-correlated to the composite scores of other striatal subregion factors were found. Although the exact reasons are unclear, it is plausible that dopamine depletion in the putamen may affect the cortico-striatal networks through functional dedifferentiation rather than structural alterations in early stages of PD.

In this study, we found that frontal/executive function was correlated with the connectivity strength of the subnetwork composed of the left caudate and left frontal regions, as well as dopamine depletion in the caudate. Furthermore, the effect of network strength on frontal/executive function was direct or indirectly mediated by dopaminergic innervation in the caudate. These findings suggest that alterations in the cortico-striatal network, including striatal dopamine depletion and disruption of the corresponding cortico-striatal circuit, can affect the frontostriatal-based cognitive deficits in PD. Indeed, it has long been known that the basal ganglia interact closely with the frontal cortex, and some circuits that originate in the frontal cortex and engage specific striatal subregions are involved in non-motor aspects of behavior. In particular, the dorsolateral prefrontal circuit, which arises in the Brodmann’s area 9 and 10 and projects to the caudate nucleus, has been implicated in frontal/executive
function. The caudate nucleus in turn projects to the dorsomedial internal pallidum, the rostral substantia nigra pars reticulata and the ventral anterior and medial dorsal thalamic nuclei, and then returns bilaterally to the dorsolateral prefrontal area.\textsuperscript{47} Furthermore, the basal ganglia play a central role in reward-based learning, where reward processing engages the basal ganglia bilaterally.\textsuperscript{48} Our findings that only the network composed of nodes in the left hemisphere was associated with frontal/executive function might be attributed to the fact that the neuropsychological assessment is mainly delivered through verbal way and has a strong verbal bias. The results of our study also support the view that PD is a disease of striatal network dysfunction.\textsuperscript{16} Further studies to be conducted in this perspective (i.e., the concept of network degeneration hypothesis) would provide important insights into the pathophysiology of PD and account for the clinical heterogeneity in patients with PD. Meanwhile, the connectivity strength of the subnetwork that was negatively correlated with the composite score of caudate was not associated with the cognitive composite scores. It might be because the nodes constituting the subnetwork are involved in various cognitive processes that are not limited to a specific cognitive function domain. Accordingly, along with the patterns of striatal dopamine depletion acting as a determinant of PD subtypes, our data indicate that structural brain networks closely associated with the patterns of striatal dopamine depletion would exist. Alterations in the structural connectivity within these brain networks at the extranigral level may contribute to the clinical heterogeneity of PD and additionally define PD subtypes.

Our study had some limitations. First, DAT binding may not be an ideal measure for the nigrostriatal dopaminergic nerve terminal density or striatal dopamine depletion. Nevertheless, $^{18}$F-FP-CIT PET scan is a widely used imaging modality to assess the dopaminergic neuronal loss in the clinical practice, and other reliable
surrogate markers that can replace it are not yet available. Additionally, further studies measuring the serotonin transporter level in the midbrain using $^{18}$F-FP-CIT PET images may provide additional information on the nigral neuronal loss. Second, the equations used to estimate the composite scores of either the striatal subregion factors or cognitive function domains can be derived differently depending on the dataset. Third, AAL atlas, which was used for automated parcellation of the brain, does not contain some important structures that are closely related to cognitive dysfunction or psychiatric symptoms of PD, such as the lower part of basal forebrain. Finally, a comprehensive evaluation of the non-motor symptoms other than cognitive impairment was not available in our cohort. Although a number of non-motor symptoms in PD appear to have a non-dopaminergic basis, the overall burden of non-motor symptoms may be associated with distinct patterns of striatal dopamine loss, further highlighting the clinical significance of the identified WM connectivity networks. Additionally, the fact that only two-thirds of study participants underwent a detailed neuropsychological test could introduce bias. However, there were no significant differences in clinical characteristics and striatal DAT availability between patients who underwent cognitive testing at initial assessment and who did not (eTable 3).

In conclusion, we identified the structural brain networks whose structural connectivity was associated with the patterns of striatal dopamine depletion, particularly in the caudate, in patients with PD. These findings suggest that clinical heterogeneity according to the striatal dopamine depletion pattern can be explained not only in the functional aspect, but also in the aspect of WM structural connectivity in patients with PD.
### Appendix 1. Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seok Jong Chung, MD, PhD</td>
<td>Yonsei University College of Medicine</td>
<td>Design and conceptualized study; analyzed data; major role in the acquisition of data; interpreted the data; drafted the manuscript for intellectual content</td>
</tr>
<tr>
<td>Yae Ji Kim, BS</td>
<td>Korea Advanced Institute of Science and Technology</td>
<td>Analyzed data; interpreted the data; drafted the manuscript for intellectual content</td>
</tr>
<tr>
<td>Yung Joong Kim, MD, PhD</td>
<td>Yonsei University College of Medicine</td>
<td>Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Hye Sun Lee, PhD</td>
<td>Yonsei University College of Medicine</td>
<td>Analyzed data; interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Seong Ho Jeong, MD</td>
<td>Inje University College of Medicine</td>
<td>Analyzed data; interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Ji-Man Hong, MD, PhD</td>
<td>Yonsei University College of Medicine</td>
<td>Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Young H. Sohn, MD, PhD</td>
<td>Yonsei University College of Medicine</td>
<td>Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Mijin Yun, MD, PhD</td>
<td>Yonsei University College of Medicine</td>
<td>Analyzed data; interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Yong Jeong, MD, PhD</td>
<td>Korea Advanced Institute of Science and Technology</td>
<td>Design and conceptualized study; interpreted data; drafted the manuscript for intellectual content</td>
</tr>
<tr>
<td>Phil Hyu Lee, MD, PhD</td>
<td>Yonsei University College of Medicine</td>
<td>Design and conceptualized study; interpreted data; drafted the manuscript for intellectual content</td>
</tr>
</tbody>
</table>

WNL-2022-201174_emth1 --http://links.lww.com/WNL/C372

WNL-2022-201174_etab1 --http://links.lww.com/WNL/C373

WNL-2022-201174_etab2 --http://links.lww.com/WNL/C374
References


8. Jellinger KA. Post mortem studies in Parkinson's disease--is it possible to


16. He BJ, Shulman GL, Snyder AZ, Corbetta M. The role of impaired neuronal


34. Lee CS, Schulzer M, Mak E, Hammerstad JP, Calne S, Calne DB. Patterns of


Table 1. Baseline clinical characteristics, striatal dopamine transporter availability, and level of cognitive performance of the study participants

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Patients with PD (n = 240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (year)</td>
<td>70.58 ± 8.90</td>
</tr>
<tr>
<td>Onset age (year)</td>
<td>69.11 ± 8.99</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>125 (52.1%)</td>
</tr>
<tr>
<td>PD duration (months)</td>
<td>17.94 ± 15.12</td>
</tr>
<tr>
<td>UPDRS-III</td>
<td>22.47 ± 9.68</td>
</tr>
<tr>
<td>K-MMSE (/30)</td>
<td>26.45 ± 3.50</td>
</tr>
<tr>
<td>CDR-SOB</td>
<td>1.04 ± 1.36</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.17 ± 5.14</td>
</tr>
<tr>
<td>CCSIT</td>
<td>6.88 ± 2.56</td>
</tr>
<tr>
<td>BDI</td>
<td>12.44 ± 9.72</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>106 (44.2%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>59 (24.6%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>56 (23.3%)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.82 ± 3.13</td>
</tr>
<tr>
<td>Total WMH burden ‡</td>
<td>11.25 ± 7.73</td>
</tr>
</tbody>
</table>

Striatal dopamine transporter availability
<table>
<thead>
<tr>
<th>Striatal Subregion</th>
<th>Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior caudate</td>
<td>2.62 ± 0.68</td>
</tr>
<tr>
<td>Anterior putamen</td>
<td>2.58 ± 0.68</td>
</tr>
<tr>
<td>Posterior caudate</td>
<td>1.70 ± 0.49</td>
</tr>
<tr>
<td>Posterior putamen</td>
<td>1.77 ± 0.63</td>
</tr>
<tr>
<td>Ventral putamen</td>
<td>1.84 ± 0.47</td>
</tr>
</tbody>
</table>

Composite score of striatal subregion factors \(^b\)

- **Caudate**  
  \[0.40 ± 0.91\]
- **More-affected sensorimotor striatum**  
  \[1.74 ± 1.57\]
- **Less-affected sensorimotor striatum**  
  \[-0.15 ± 0.77\]
- **Anterior putamen**  
  \[-0.29 ± 0.82\]

Level of cognitive performance \(^c\)

- **Visual memory/visuospatial**  
  \[-0.15 ± 1.01\]
- **Verbal memory**  
  \[0.23 ± 0.94\]
- **Frontal/executive**  
  \[-0.21 ± 0.93\]
- **Attention/working memory/language**  
  \[-0.21 ± 0.93\]

Values are expressed as mean ± standard deviation or number (percentage).

Abbreviations: PD, Parkinson’s disease; UPDRS-III, Unified PD Rating Scale Part III; K-MMSE, the Korean version of the Mini-Mental State Examination; CDR-SOB, Clinical Dementia Rating Scale Sum of Boxes; CCSIT, the cross-cultural smell identification test; BDI, Beck Depression Inventory; WMH, white matter hyperintensity.

\(^a\) The WMH severity was rated on FLAIR images using the Scheltens scale (Journal of the Neurological Sciences 1993;114:7-12).

\(^b\) The composite scores for each striatal subregion to identify the patterns of striatal dopamine depletion were calculated using the formula described in our previous work.
Of the 240 patients with PD, 163 (67.9%) underwent the Seoul Neuropsychological Screening Battery, a comprehensive Korean language neuropsychological test battery, at initial assessment. The composite scores of each cognitive function domain were calculated according to the formula described previously (Neurology 2020;95:e1650-e1659).

Table 2. Subnetworks whose white matter structural connectivity correlated with the composite score of striatal subregion Factor 1 (Caudate)

<table>
<thead>
<tr>
<th>Hub nodes</th>
<th>Connection between nodes</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate_L</td>
<td>Frontal_Mid_L – Caudate_L</td>
<td>5.19</td>
</tr>
<tr>
<td></td>
<td>Frontal_Mid_Orib_L – Caudate_L</td>
<td>3.69</td>
</tr>
<tr>
<td></td>
<td>Frontal_Inf_Orb_L – Caudate_L</td>
<td>3.93</td>
</tr>
<tr>
<td>Insula_L</td>
<td>Frontal_Inf_Oper_L – Cingulum_Ant_R</td>
<td>3.79</td>
</tr>
<tr>
<td>Thalamus_L</td>
<td>Insula_L – Cingulum_Ant_R</td>
<td>3.83</td>
</tr>
<tr>
<td>Thalamus_R</td>
<td>Rolandic_Oper_L – Cingulum_Mid_R</td>
<td>4.62</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Ant_R – Putamen_L</td>
<td>4.23</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Mid_R – Putamen_L</td>
<td>3.61</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Mid_L – Pallidum_L</td>
<td>3.81</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Ant_L – Pallidum_R</td>
<td>4.56</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Ant_R – Thalamus_L</td>
<td>4.69</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Ant_L – Thalamus_R</td>
<td>3.73</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Ant_R – Thalamus_R</td>
<td>3.86</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Mid_L – Cerebellum_9_L</td>
<td>3.98</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Ant_L – Vermis_1_2</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Cingulum_Mid_L – Vermis_1_2</td>
<td>3.67</td>
</tr>
</tbody>
</table>
Abbreviations: Caudate_L = left caudate; Cerebellum_9_L = lobule IX of left cerebellar hemisphere; Cingulum_Ant_L = left anterior cingulate and paracingulate gyri; Cingulum_Ant_R = right anterior cingulate and paracingulate gyri; Cingulum_Mid_L = left median cingulate and paracingulate gyri; Cingulum_Mid_R = right median cingulate and paracingulate gyri; Frontal_Inf_Oper_L = left inferior frontal gyrus, opercular part; Frontal_Inf_Orb_L = left inferior frontal gyrus, orbital part; Frontal_Mid_L = left middle frontal gyrus; Frontal_Mid_Orb_L = left middle frontal gyrus, orbital part; Insula_L = left insula; Pallidum_L = left pallidum; Pallidum_R = right pallidum; Putamen_L = left putamen; Rolandic_Oper_L = left Rolandic operculum; Thalamus_L = left thalamus; Thalamus_R = right thalamus; Vermis_1_2 = lobule I, II of vermis.
### Table 3. Correlation analyses between the composite scores of striatal subregion factors and cognitive domains

<table>
<thead>
<tr>
<th></th>
<th>Caudate (^a)</th>
<th>more-affected sensorimotor striatum (^b)</th>
<th>less-affected sensorimotor striatum (^b)</th>
<th>anterior putamen (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\gamma)</td>
<td>(P)</td>
<td>(Q^*)</td>
<td>(\gamma)</td>
</tr>
<tr>
<td>Visual memory/visuospatial (^b)</td>
<td>0.190</td>
<td>0.015</td>
<td>0.238</td>
<td>0.008</td>
</tr>
<tr>
<td>Verbal memory (^b)</td>
<td>0.113</td>
<td>0.150</td>
<td>NS</td>
<td>-0.075</td>
</tr>
<tr>
<td>Frontal/executive (^b)</td>
<td>0.355</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-0.106</td>
</tr>
<tr>
<td>Attention/working memory/language (^b)</td>
<td>0.041</td>
<td>0.606</td>
<td>NS</td>
<td>-0.059</td>
</tr>
</tbody>
</table>

Abbreviations: PD, Parkinson’s disease;

\(^a\) The composite scores for each striatal subregion to identify the patterns of striatal dopamine depletion were calculated using the formula described in our previous work (Neurology 2020;95:e280-e290).

\(^b\) The composite scores for each cognitive function domain were calculated using the formula described in our previous work (Neurology 2020;95:e1650-e1659).

\(^c\) **Bonferroni**-corrected \(p\)-value to correct multiple testing (\(n = 16\)) in correlation analyses.

Abbreviation: NS, not significant (\(p > 0.999\)).
Table 4. Correlation analyses between the composite scores of cognitive domains and the connectivity strength of identified subnetworks

<table>
<thead>
<tr>
<th>Subnetwork 1</th>
<th>Subnetwork 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>γ</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td><strong>Visual memory/visuospatial</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.199</td>
</tr>
<tr>
<td><strong>Verbal memory</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.132</td>
</tr>
<tr>
<td><strong>Frontal/executive</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.300</td>
</tr>
<tr>
<td><strong>Attention/working memory/language</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.118</td>
</tr>
</tbody>
</table>

<sup>a</sup> Subnetwork 1 = the subnetwork whose structural connectivity positively correlated with the composite score of caudate; Subnetwork 2 = the subnetwork whose structural connectivity negatively correlated with the composite score of caudate

<sup>b</sup> The composite scores for each cognitive function domain were calculated using the formula described in our previous work (Neurology 2020;95:e1650-e1659).

<sup>c</sup> Bonferroni-corrected p-value to correct multiple testing (n = 8) in correlation analyses.

Abbreviation: NS, not significant (p > 0.999).
Table 5. Relationship between dopamine loss in the caudate, the network strength, and the frontal/executive function

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Outcome (Frontal/executive)</th>
<th>Goodness of fit model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predictor: Caudate Dopamine</td>
<td>0.061</td>
<td>0.014</td>
</tr>
<tr>
<td>Mediator: Network Strength</td>
<td>1.101</td>
<td>0.541</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predictor: Network Strength</td>
<td>1.971</td>
<td>0.434</td>
</tr>
<tr>
<td>Mediator: Caudate Dopamine</td>
<td>0.292</td>
<td>0.108</td>
</tr>
</tbody>
</table>

Mediation analyses for the composite score of frontal/executive function domain were performed to evaluate the association between dopamine loss in the caudate, structural connectivity strength of the identified network, and frontal/executive function, while adjusting for age, sex, and years of education. All models showed a good fit to the composite score of frontal/executive function domain based on CFI and RMSEA. Abbreviations: CFI = confirmatory fit index; RMSEA = root mean square error of approximation; \( \beta \) = unstandardized regression coefficient; SE = standard error.
Figure legends

Figure 1. Subnetworks associated with striatal dopamine depletion pattern in patients with Parkinson’s disease. (A) A subnetwork whose structural connectivity is positively correlated with the composite score of striatal subregion Factor 1 (caudate) (FWE-corrected $p = 0.011$). (B) A subnetwork whose structural connectivity is negatively correlated with the composite score of striatal subregion Factor 1 (caudate) (FWE-corrected $p < 0.001$). The large size of nodes indicates hub nodes of each identified subnetwork. Abbreviations: A = anterior; P = posterior; L = left hemisphere; R = right hemisphere; ACG.L = left anterior cingulate and paracingulate gyri; ACG.R = right anterior cingulate and paracingulate gyri; CAU.L = left caudate; Cerebelum_9.L = lobule IX of left cerebellar hemisphere; DCG.L = left median cingulate and paracingulate gyri; DCG.R = right median cingulate and paracingulate gyri; IFGoperc.L = left inferior frontal gyrus, opercular part; INS.L = left insula; MFG.L = left middle frontal gyrus; ORBinf.L = left inferior frontal gyrus, orbital part; ORBmid.L = left middle frontal gyrus, orbital part; PAL.L = left pallidum; PAL.R = right pallidum; PUT.L = left putamen; ROL.L = left Rolandoic operculum; THA.L = left thalamus; THA.R = right thalamus; Vermis_1_2 = lobule I, II of vermis.
Figure 2. Mediation analyses for frontal/executive function in early-stage Parkinson’s disease. The composite score of striatal subregion Factor 1 (caudate) and structural connectivity strength of the network with positive correlation with the composite score of caudate were entered as a predictor or mediator in the mediation analyses for the composite score of frontal/executive function domain. Paths that were statistically significant are displayed with unstandardized regression coefficients (β) and standard error (SE) on solid lines. Abbreviations: BootSE = bootstrapping standard error.

\[ \beta = 0.292, SE = 0.108 \]

\[ \beta = 0.360, SE = 0.095, p = 0.001 \]
Association Between White Matter Networks and the Pattern of Striatal Dopamine Depletion in Patients With Parkinson Disease

Seok Jong Chung, Yae Ji Kim, Yun Joong Kim, et al.

Neurology published online October 4, 2022
DOI 10.1212/WNL.0000000000201269

This information is current as of October 4, 2022