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Striatal Dopaminergic Loss and Dysphagia in Parkinson Disease

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Purpose: To better understand the development of dysphagia in patients with Parkinson disease (PD) and to identify possible neuromodulatory target regions of dysphagia, we studied the striatal dopamine transporter (DAT) availability distribution by subtype of dysphagia.

Methods: In this retrospective cross-sectional study, patients with PD who underwent videofluoroscopic swallowing study and *N*-(3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) PET at intervals of less than 1 month were analyzed. The 14 binarized subitem scores of the Videofluoroscopic Dysphagia Scale were analyzed using a voxel-wise Firth's penalized binary logistic regression model, adjusting for age and disease duration at videofluoroscopic swallowing study.

Results: Sixty-five patients with PD were finally included. Striatal mapping showed association of decreased DAT availability with 5 subitems with 1 or more clusters surviving the statistical threshold: 1 oral phase and 4 pharyngeal phase subitems. The overlap maps created by superimposing clusters for all 5 statistically significant subitems revealed associations of dysphagia in PD with decreased DAT availability in the bilateral ventral striatum. Of these, 4 subitems belonging to the pharyngeal phase-specific dysphagia were additionally found to be related to dopaminergic degeneration of the bilateral anterior-to-posterior caudate and ventral striatum.

Conclusions: These findings suggest that subitem/phase-specific striatal subregional dopaminergic depletion may explain the dysphagia of PD. This dopaminergic degeneration of striatal subregions specific to the phases of dysphagia may serve as a potential target for neuromodulatory brain stimulation through stimulation of cortices functionally connected.

Key Words: Parkinson disease, dysphagia, dopamine transporter, striatum

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Gastrointestinal system disorders are common dysfunctions in Parkinson disease (PD) and are important factors for reduced quality of life and increased mortality.[1] Of these, dysphagia can cause malnutrition and aspiration pneumonia, posing a serious threat to health and maintenance of life, and up to 90% of patients with PD eventually develop dysphagia.[2]

Experiments using task-specific functional MRI and PET have shown that the swallowing process in human recruits the cerebellum, thalamus, insula, lateral precentral and postcentral gyri, superior temporal gyrus, middle and inferior frontal gyri, frontal operculum, occipital gyrus, precuneus, and anterior cingulate gyrus.[3,4] Furthermore, lesions in areas other than the neuroanatomical area of the brain involved in the normal swallowing process can also cause dysphagia, and in the case of dysphagia in stroke, lesions of putamen and globus pallidus have already been reported to induce dysphagia.[5,6]

In PD, nigrostriatal dopaminergic degeneration is a hallmark of its pathogenesis, and many motor and nonmotor symptoms related thereto have been described using functional neuroimaging[7]; however, despite the significant debilitating effects of dysphagia in patients with PD, the relationship between the striatal distribution of dopaminergic loss and dysphagia has not yet been elucidated. When the distribution of dopaminergic degeneration related to each subitem of dysphagia in PD is identified, the indirect effects of targeted transcranial stimulation on dysphagia symptoms can be tested through stimulating functionally connected cortical area, similar to that of noninvasive neuromodulatory stimulation targeted to other motor symptoms in PD.[8]

In the present study, we hypothesized that there may be distributions of striatal dopaminergic degeneration specific to each dysphagia phase. We, therefore, implemented a case-control analyses of the distribution of striatal dopamine transporter (DAT) availability and the clinical parameters indicative of phase-specific dysphagia.

PATIENTS AND METHODS

Study Design and Participants

This study was conducted on patients who visited our hospital between January 2015 and October 2021. We retrospectively reviewed the database of patients who met the following criteria. The inclusion criteria were as follows: (1) diagnosis of PD by a neurologist according to clinical diagnostic criteria of the UK PD Society Brain Bank[9]; (2) underwent T2-weighted MRI, *N*-(3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane PET, and videofluoroscopic swallowing study (VFSS) at our hospital; and (3) Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr staging performed within 1 month from the VFSS.[10] The exclusion criteria were as follows: (1) degenerative neurological disease other than PD such as atypical parkinsonism is suspected; (2) more than 1 month between VFSS and ^{18}F-FP-CIT PET; (3) comorbid conditions involving the central nervous system other than PD such as cerebrovascular insults; (4) evidence of old cerebral lesions >3 mm in diameter on MRI[11]; (5) ventriculomegaly with Evans' index >0.4[12]; (6) white matter hyperintensities with Fazekas scale >2[13]; and (7) a history

of major trauma or surgery in the laryngopharynx. This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement, and the study protocol was approved by the institutional review board of our hospital (2021-11-018). The need for informed consent was waived due to the retrospective nature of the study.

For all patients, the following demographic and clinical information were collected: sex; age at the time of VFSS; more involved side of the body as judged by the UPDRS part III total scores, chewing and swallowing scores, and total scores of the UPDRS part II; Hoehn and Yahr stages; and period from the first diagnosis of PD to the date of VFSS.

Protocol and Scoring of Videofluoroscopic Swallowing Study

All VFSSs were performed by the rehabilitation physician using standard Logemann's protocol.[14] For stabilization of the anatomical postures, real-time lateral radiographs of the head, neck, and upper chest were taken in a sitting position with the patient's head fixed. Each patient was asked to swallow each of the following items twice consecutively: 2 mL of water-diluted barium (35% weight/volume), 2 mL of barium (35% weight/volume) mixed with curd yogurt, sliced bananas, boiled rice, and cookies (3 cubes with dimensions of 1 cm).

We used the Videofluoroscopic Dysphagia Scale (VDS) as scoring system, which is a standardized and validated tool to rate 14 swallowing subitems (each of the oral and pharyngeal phase consists of 7 subitems) that are scored during the VFSS.[15] The 7 subitems of oral phase consist of lip closure, bolus formation, mastication, swallowing apraxia, tongue-to-palate contact, premature bolus loss, and oral transit time. For pharyngeal phase, the 7 subitems include vallecular residue, triggering of pharyngeal swallow, laryngeal elevation, pyriform sinus residue, coating of pharyngeal wall, pharyngeal transit time, and food aspiration into airways. Interrater reliability of the VDS has been validated, and this measure has been demonstrated to be statistically relevant with other etiologies as well.[16] The worst performance score across the 10 swallows (2 swallows for each bolus and 5 types of bolus) for each bolus-type was then determined as the overall impression score for each of the 14 subitems and used as the primary dependent variables.[5] All recorded VFSSs were analyzed according to the VDS by 2 rehabilitation specialists who had more than 10 years of VFSS reading experience and were regular members of the Korean Dysphagia Society. When multiple VFSSs were performed, we analyzed the results for the date closest to the date of the PET scan.

PET Image Acquisition

For ^{18}F-FP-CIT PET, all patients fasted for at least 6 hours, and all antiparkinsonian medications were discontinued for at least 12 hours before the scan. The patients were injected intravenously with a mean of 5 mCi (185 MBq) of ^{18}F-FP-CIT, and PET images were obtained for 20 minutes in the 3D mode at 120 kVp 30 mAs, using a Biograph 20 mCT PET/CT scanner (Siemens Medical Systems, Milwaukee, WI) 3 hours after the injection. The time-averaged PET scans were reconstructed using the ordered subsets expectation maximization (2 iterations and 21 subsets) and postfiltered with an isotropic full-width at half-maximum Gaussian kernel of 3 mm. The reconstructed PET image consisted of $400 \times 400 \times 110$ voxels in 3 dimensions, and the size of each voxel was $1 \times 1 \times 1.5$ mm^3.

PET Image Preprocessing and Quantitative Analysis

Preprocessing was performed using Statistical Parametric Mapping 12 (Wellcome Trust Centre for Neuroimaging; https://www.fil.ion.ucl.ac.uk/spm/) and in-house scripts with MATLAB 2020b (MathWorks Inc; https://www.mathworks.com). First, reorientation was implemented according to the anterior commissure of each raw PET image, and to consider minimal brain atrophy observed in patients, all PET scans of each patient were spatially normalized to the standard template in the Montreal Neurological Institute (MNI)-152 space ($2 \times 2 \times 2$ mm^3 per voxel).[17] All PET scans were then smoothed using an 8-mm full-width at half-maximum isotropic Gaussian kernel to improve the signal-to-noise ratio. After preprocessing, all PET images were confirmed to be registered in the MNI-152 space by a nuclear medicine specialist. Using the Oxford-Imanova Striatal Structural Atlas for the spatial definition of the striatum, voxel-wise DAT availability was calculated by the nondisplaceable binding potential defined as follows: (uptake value of the striatal voxels − mean uptake of the calcarine fissure and surrounding cortex [V1])/(mean uptake of the V1) where the V1 was defined according to the automated anatomical labeling atlas 3.[18]

For the voxel-wise analysis, preprocessed PET images of each patient were masked with the striatal volume, and all values of the voxels belonging to this volume were used as independent variables. Labeling of the neuroanatomical regions of voxels was performed according to the definition of striatal 12 subregions (6 on each side) in previous studies.[19] In summary, the striatum was divided into dorsal and ventral parts along the transaxial anteroposterior commissure line. The ventral part consists of 2 subregions: the ventral putamen and the ventral striatum. Thereafter, the dorsal part was divided by the coronal plane of the anterior commissure, resulting in 4 subregions, which are the anterior/posterior caudate and putamen.

Statistical Analyses

The normality of all variables was tested using the Shapiro-Wilk test and visual data inspection with histograms. For the binary dependent variables and the ordinal dependent variables that were dichotomized because normality was rejected, we coded "intact" or "none" as 1 and "impaired," "present," or "delayed" as 0, so that higher scores indicate better performance. Scores for each VFSS subitem were taken as primary dependent variables, and the secondary dependent variables were summative scores of dichotomized 7 oral and 7 pharyngeal phases, respectively (0 for "totally impaired phase" to 7 for "intact phase").[20]

For voxel-wise analyses of striatal DAT availability for dysphagia, voxel-wise Firth's penalized binary logistic regression analyses were implemented adjusting for age and disease duration at VFSS, valid negative predictors of swallowing,[21] with dichotomized scores for each VFSS subitem. Here, we found that the case-to-control ratio of each of the 14 subitems of the patients varied, and because some subitems had less than 10 events per group, we reduced the bias of maximum likelihood estimates due to rare events by using the Firth's correction, a robust technique that can be used to reduce rare event induced bias by assigning penalties.[22] For ordinal logistic regression with the summative scores of oral and pharyngeal phases, respectively, as dependent variables, the assumption of proportionality was tested using the score test.[23] In the case of a violated assumption, the phase-specific overlaps of the clusters that survived the threshold in binary logistic regression for each subitems was overlapped to delineate the common regions associated with each of the oral, pharyngeal, and total phases of dysphagia.[24] The significant regions were labeled using the peak beta values in the clusters that survived the threshold.

A 2-tailed P value <0.05 was considered statistically significant. To avoid type I errors inflated by multiple comparisons, a Benjamini-Hochberg false discovery rate of 0.05 was applied to the voxel-wise statistics for each subitem variable.[25] Threshold-free cluster enhancement could not be applied because the dependent variables were not continuous; therefore, among the clusters that survived

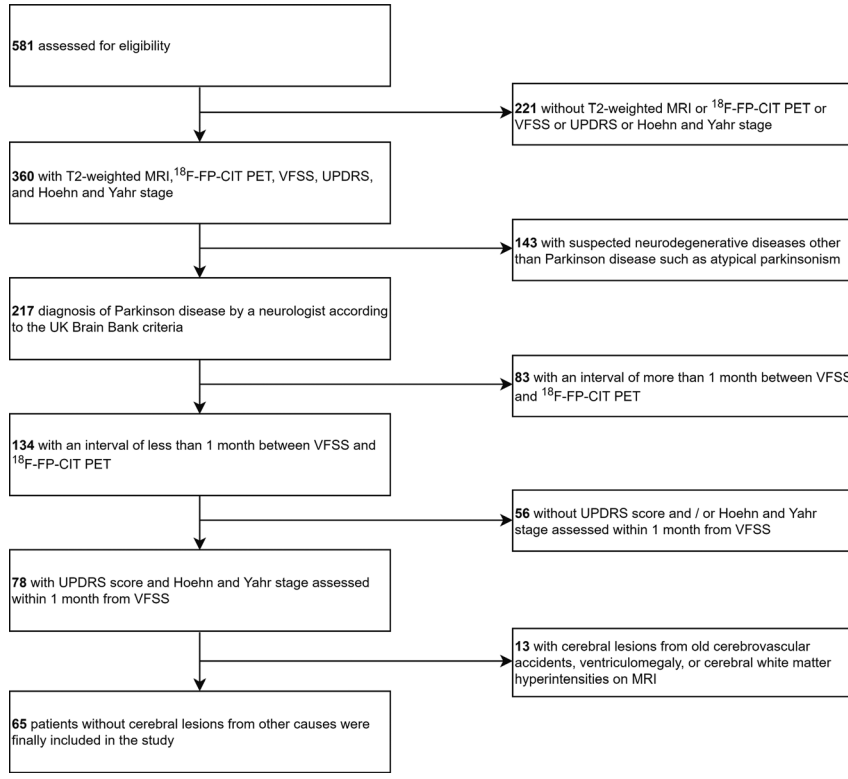

FIGURE 1. Flowchart of subject inclusion. ^{18}F-FP-CIT PET, *N*-(3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane PET.

multiple comparison correction in voxel-wise analyses, only clusters consisting of 50 or more contiguous voxels were considered valid clusters.[26] Statistical analyses of the PET images and clinical variables were implemented using in-house MATLAB scripts and "logistf" package of R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Data Availability

Deidentified data will be shared on request through personal correspondence.

RESULTS

Demographic and Clinical Characteristics

Figure 1 depicts the study inclusion flowchart. Among 581 patients with PD during the study period, 65 patients who met the inclusion criteria were included in the analyses (Table 1). The mean (standard deviation) of age at the time of VFSS was 74.9 (5.4) years, and 64 (98.5%) were male. None of the included patients had any missing data for the variables of interest.

Association of Striatal DAT Availability With Each of the Dysphagia Subitems

All subitem dependent variables in the VFSS were dichotomized as the normality of the distribution was rejected (Table 2, see online Supplementary Table for dichotomization of the subitem scores, http://links.lww.com/CNM/A413). Among the 14 dysphagia subitems as the dependent variable, 1 oral (presence of premature bolus loss) and 4 pharyngeal (impaired triggering of pharyngeal swallow, impaired laryngeal elevation, delayed pharyngeal transit time, and presence of aspiration of food into airway) phase subitems showed statistically significant clusters composed of striatal voxels (Table 3).

First, the presence of premature bolus loss, the only surviving variable of the oral subitems, was associated with decreased DAT availability in the anterior-to-ventral aspect of the bilateral striatum, especially with the highest beta values in the bilateral posterior and ventral putamen (Fig. 2A).

Second, the impaired triggering of pharyngeal swallow, one of the subitems in the pharyngeal phase, was associated with decreased

TABLE 1. Subject Characteristics

Parameter	Total (n = 65)
Age at VFSS, mean (SD), y	74.9 (5.4)
Sex, n (%)	
Male	64 (98.5)
Female	1 (1.5)
Clinical characteristics	
PD duration, mean (SD), y	13.5 (6.4)
Hoehn and Yahr stage, median (IQR)	4 (1)
Chewing and swallowing scores, median (IQR)*	3 (1.5)
Side of the body more involved, n (%)†	
Right	28 (43.1)
Left	36 (55.4)
Equal	1 (1.5)

*Judged by the UPDRS part II.
†Judged by the UPDRS part III.
IQR, interquartile range; SD, standard deviation.

TABLE 2. Case-to-Control Distribution by Subitem Score of Dysphagia for Voxel-Wise Analyses

Subitem*	Intact (Control) n (%)	Impaired (Case) n (%)
Oral phase		
Lip closure	62 (95.4)	3 (4.6)
Bolus formation	61 (93.8)	4 (6.2)
Mastication	60 (92.3)	5 (7.7)
Swallowing apraxia	57 (87.7)	8 (12.3)
Tongue-to-palate contact	63 (96.9)	2 (3.1)
Premature bolus loss	37 (56.9)	28 (43.1)
Oral transit time	44 (67.7)	21 (32.3)
Pharyngeal phase		
Vallecular residue	22 (33.8)	43 (66.2)
Triggering of pharyngeal swallow	37 (56.9)	28 (43.1)
Laryngeal elevation	24 (36.9)	41 (63.1)
Pyriform sinus residue	28 (43.1)	37 (56.9)
Coating of pharyngeal wall	48 (73.8)	17 (26.2)
Pharyngeal transit time	57 (87.7)	8 (12.3)
Food aspiration into airways	21 (32.3)	44 (67.7)

*Assessed based on the VDS.

DAT availability in most of the bilateral striatum except the posterior putamen (Fig. 2B). Of these, the highest beta values were observed in the bilateral posterior caudate to posteromedial aspect of anterior caudate. Third, the impaired laryngeal elevation was associated with decreased DAT availability of the bilateral posteroventral putamen, caudate, and ventral striatum (Fig. 2C), and the location showing the highest beta value was concentrated in the bilateral posterior putamen. Fourth, the delayed pharyngeal transit time was associated with DAT availability decrement in the bilateral ventral striatum and caudate, and parts of the left ventral putamen (Fig. 2D). Of these, the bilateral posterior caudate showed the highest beta value for the delayed transit time. Fifth, the presence of aspiration of food into the airway was associated with decreased DAT availability in the bilateral striatum except for the bilateral posterior aspects of the caudate and putamen, and the bilateral posteromedial aspects of the anterior caudate showed the highest beta value for this subitem (Fig. 2E).

Association of Striatal DAT Availability With Phase-Specific Dysphagia

The voxel-wise proportional odds model for summative scores of oral and pharyngeal phases violated the assumption of proportionality, so the subitem clusters that survived the thresholds in oral and pharyngeal phase were overlapped for each phase. The thresholded and binarized striatal DAT availability maps of the 4 statistically significant pharyngeal phase subitems were superimposed because only the dependent variable of the pharyngeal phase had more than one threshold-surviving subitem (Fig. 3A). The overlap of clusters that survived the thresholds of the pharyngeal phase-specific subitems showed that the neuroanatomical striatal subregions commonly associated with disorder of this phase were concentrated in the bilateral ventral striatum and anterior-to-posterior caudate (except for the posterior-most region among the bilateral posterior caudates).

An additional overlay map was generated for all 5 surviving subitems from both phases (Fig. 3B). Compared with overlapping only the pharyngeal subitems, the number of overlaps was relatively

TABLE 3. Striatal Subregions With Statistically Significant Correlations Between Decreased DAT Availability and Dysphagia Subitem Scores

Subitem of Dysphagia	Total	No. Significant Voxels, n (%)										Critical *P* of FDR	Striatal Subregion With Peak Beta Values
		Anterior Caudate		Posterior Caudate		Anterior Putamen		Posterior Putamen		Ventral Putamen		Ventral Striatum			
		R	L	R	L	R	L	R	L	R	L	R	L		
Oral phase															
Presence of premature bolus loss	1723 (100.0)	100 (5.8)	90 (5.2)	0 (0.0)	0 (0.0)	420 (24.4)	412 (23.9)	203 (11.8)	216 (12.5)	34 (2.0)	29 (1.7)	81 (4.7)	138 (8.0)	0.030	L posterior putamen
Pharyngeal phase															
Impaired triggering of pharyngeal swallow	2353 (100.0)	383 (16.3)	401 (17.0)	91 (3.9)	96 (4.1)	404 (17.2)	396 (16.8)	76 (3.2)	47 (2.0)	49 (2.1)	57 (2.4)	174 (7.4)	179 (7.6)	0.041	R anterior caudate
Impaired laryngeal elevation	1634 (100.0)	383 (23.4)	401 (24.5)	21 (1.3)	83 (5.1)	153 (9.4)	92 (5.6)	10 (0.6)	40 (2.4)	38 (2.3)	60 (3.7)	174 (10.6)	179 (11.0)	0.029	R posterior putamen
Delayed pharyngeal transit time	1200 (100.0)	281 (23.4)	376 (31.3)	79 (6.6)	96 (8.0)	60 (5.0)	34 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	10 (0.8)	104 (8.7)	160 (13.3)	0.021	R posterior caudate
Presence of aspiration of food into airway	2474 (100.0)	383 (15.5)	401 (16.2)	66 (2.7)	63 (2.5)	419 (16.9)	415 (16.8)	100 (4.0)	195 (7.9)	28 (1.1)	51 (2.1)	174 (7.0)	179 (7.2)	0.043	R anterior caudate

FDR, false discovery rate; L, left; R, right.

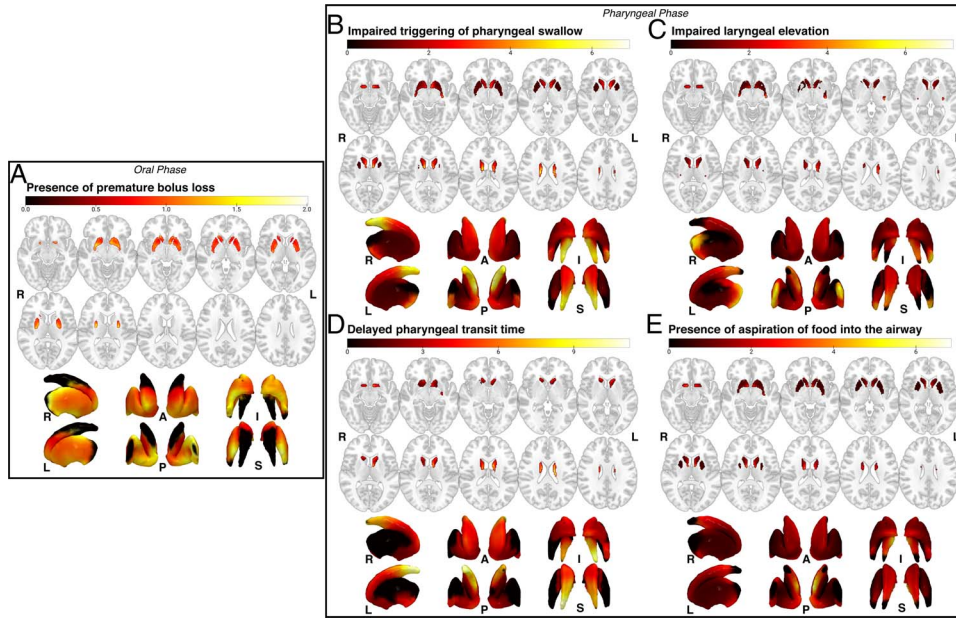

FIGURE 2. Statistical maps of decreased striatal DAT availability associated with each dysphagia subitem. **A**, Presence of premature bolus loss. **B**, Impaired triggering of pharyngeal swallow. **C**, Impaired laryngeal elevation. **D**, Delayed pharyngeal transit time. **E**, Presence of aspiration of food into the airway. Only voxels contained in the surviving clusters are displayed. Beta values of Firth's penalized binary logistic regression were computed using voxel-wise striatal DAT availability values and each binarized subitem score of dysphagia, where age and disease duration at videofluoroscopic swallowing study were controlled as a covariate. The color bar shows beta values: the larger the positive beta values the greater the likelihood of impairment of the corresponding subitems per the same voxel-wise decrement of DAT availability. The MNI-152 z-coordinates for each row of the slices were –14, –12, –10, –8, –6, –4, –2; 0, 2, 4, 6, 8, 10, 12; and 14, 16, 18, 20, 22, 24, 26 in ventrodorsal orders, respectively. A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior.

reduced in the bilateral caudate, and the region with highest number of overlaps was in the bilateral ventral striatum.

DISCUSSION

We present, for the first time, the striatal subregional dopaminergic loss associated with the development of dysphagia in PD that may facilitate a shift from a neurophysiological basis to symptom-targeted neuromodulation. The topological distribution presented by the number of overlaps of surviving clusters indicated that all the significant subitems commonly resulted from a decreased DAT availability in the ventral striatum, and of these, pharyngeal phase-specific dysphagia was also associated with the dopaminergic degeneration of anterior-to-posterior caudate. Despite slight differences in terms of spatial laterality, all subitem-related significant regional distributions showed bilateral symmetry.

Of the 7 subitems in the oral phase, only the premature bolus loss showed at least one cluster composed of statistically significant voxels, and the dysfunction was strongly associated with decreased DAT availability of the bilateral posterior-to-ventral putamen. Premature bolus loss is a dysfunction in which the food bolus falls prematurely before triggering of pharyngeal swallowing reflex from the base of the tongue into the pharynx, whereas the preparation in the oral phase is still being processed.[27] For the timely downward movement of the food bolus, sequential anteroposterior movement of the tongue muscles with flexibility is essential, and it is known that the dysfunction occurs because bradykinesia and rigidity adversely affect the motor function of the tongue in PD.[28] Dopaminergic depletion of the posterior putamen is a representative pathophysiology of PD, and it is known that a decrease in ^{18}F-FP-CIT uptake in that region is directly related to UPDRS akinesia-rigidity scores.[29] Also, in our study, the decreased DAT availability of the bilateral posterior putamen was significantly associated with impaired laryngeal elevation, which is a pharyngeal phase subitems. Laryngeal elevation serves to prevent food aspiration into the airway through the closure of the laryngeal vestibule following the approximation of the arytenoid cartilages and the epiglottis.[30] Taken together, these findings suggest that a dysfunction of the process in which the flexibility of the oropharyngeal muscles plays a key role, such as premature loss of the bolus and impairment of laryngeal elevation, may have occurred due to the deterioration of sequential movement of the muscles due to parkinsonian bradykinesia and rigidity.

Impaired triggering of the pharyngeal swallow and the delayed pharyngeal transit time, all of which belong to pharyngeal phase subitems, showed a strong association with decreased DAT availability in the bilateral posterior caudate to the posteromedial aspect of the anterior caudate. In a study conducted using the VFSS outcomes of stroke patients, the caudate nucleus lesion was reported to have a strong positive correlation with the prolonged laryngopharyngeal response duration.[31] Because the duration of the laryngopharyngeal response is a response variable directly associated with the triggering of pharyngeal swallow and pharyngeal bolus transit,[32] the detrimental effect of decreased DAT availability in the caudate nucleus on this variable in our study was in line with the results of previous reports. Triggering of the pharyngeal swallow and initiation of the transit of the pharyngeal bolus require afferent sensory inputs via the trigeminal, glossopharyngeal, internal branch of the superior laryngeal nerves, and other branches of the vagus nerve, and are completed by voluntary and involuntary efferent motor output through pharyngeal muscles.[33] Because the caudate nucleus contributes significantly to the accuracy and initiation of directed movements,[34] the impaired triggering of pharyngeal swallow and delayed pharyngeal

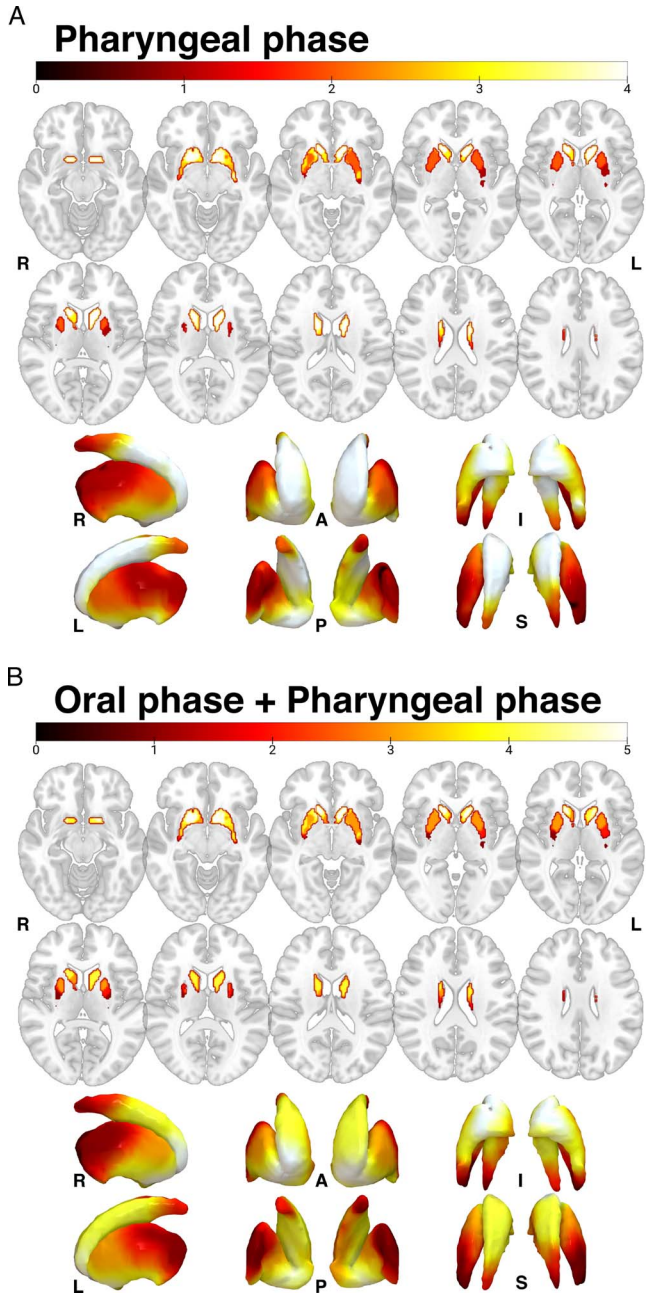

FIGURE 3. Overlay maps showing association of decreased striatal DAT availability with swallowing phase-specific dysphagia subitems. **A**, Overlay of the 4 pharyngeal phase-specific subitems. **B**, Overlay of the 5 subitems in both oral and pharyngeal phases. Integers in the colorbar indicates the phase-specific overlaps of the clusters surviving the threshold in Firth's penalized binary logistic regression for each subitem controlling the age and disease duration at the time of the videofluoroscopic swallowing study. The higher the number of overlaps, the higher the likelihood that the corresponding phase will be impaired by the same decrement of DAT availability. The MNI-152 z-coordinates of each row of the slices were –14, –12, –10, –8, –6, –4, –2; 0, 2, 4, 6, 8, 10, 12; and 14, 16, 18, 20, 22, 24, 26 in ventrodorsal orders, respectively. A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior.

bolus transit might have occurred. Furthermore, a previous study using ^{18}F-FDG PET showed that the difficulty in initiating swallowing in PD was associated with reduced metabolism in the anterior cingulate cortex,[35] a region functionally connected to the caudate nucleus.[36]

Aspiration of food into the airway, the most clinically debilitating factor of dysphagia in PD, is strongly associated with dopaminergic degradation in the medial aspects of the bilateral posteromedial aspect of the anterior caudate. Im et al[31] reported that caudate nucleus lesions in stroke patients were significantly associated with an increased risk of food aspiration into the airway, and this is consistent with our findings. However, aspiration of food into the airway may reflect dyssynergia of the other 13 subitems,[37] and thus may be due to a combination of impairment in other subitems rather than a direct causality by depletion of dopaminergic neurons in the caudate nucleus.

In the overlay map derived from overlapping clusters of significant subitems of the pharyngeal phase dysfunctions associated with decreased DAT availability, the highest degree of overlap was detected in the bilateral ventral striatum and anterior-to-posterior caudate. In a study that analyzed the swallowing process of healthy volunteers using task-specific functional MRI, the caudate nucleus and putamen were activated during swallowing in humans,[38] and this can be considered as physiological evidence to support our findings. However, adding significant clusters from impaired triggering of pharyngeal swallowing, the only surviving subitem of the oral phase-dependent variables, to the 4 significant pharyngeal phase subitems, the highest overlap of 5 was found in only in the ventral striatum. In an experiment to induce swallowing reflex by electrical and chemical stimulation in anesthetized adult cats, the ventral striatum was identified as a neuroanatomical area responsible for inducing swallowing reflex through electrical stimulation,[39] and an injection of dopamine and apomorphine into this region facilitated the swallowing reflex, which, taken together, support our report that dopamine depletion in the ventral striatum is associated with the entire domain of dysphagia.

Our presentation has several limitations. First, because the institution where the study was conducted was a hospital for veterans, the demographic characteristics of patients visiting the hospital were biased toward male sex (98.5%), making it difficult to consider sex-related factors. Second, the statistical power of some dependent variables may have decreased because the case-control ratios were different for each subitem dependent variable (Table 2). Although we used Firth's correction to reduce the bias of maximum likelihood estimates due to rare events, 6 of 14 dependent variables showed 10 or less cases of abnormality, so statistically significant striatal neuroanatomical regions may not have been detected due to the unbalanced case-control ratio per group. Third, administration of antiparkinsonian medications was discontinued at least 12 hours before the ^{18}F-FP-CIT PET scans, but for VFSS, it was not possible to confirm whether each patient was in the on- or off-state at the time of the evaluation, so it could not be entered as a nuisance variable. Fourth, the method of overlapping the binarized clusters that survived thresholds for each subitem in this study was based on a lesion network mapping approach using resting-state functional MRI[24]; however, this technique has debate about the arbitrary threshold values.[40] We tried to perform the ordinal logistic regression using the summative scores of each phase, but the proportional odds assumption was violated, leading to the suboptimal choice of the overlapping methodology.

In conclusion, the current study revealed, for the first time, distinct distributions of decreased striatal DAT availability associated with dysphagia in patients with PD. Although the distribution pattern was different for each subitem, dopaminergic depletion of the bilateral ventral striatum and anterior-to-posterior caudate was

commonly related to pharyngeal-phase dysphagia. Determining a relationship between oral dysphagia and DAT availability in PD will depend on future work with balanced case-control ratios for each subitem. In addition, as a potential target of neuromodulation in PD, it is necessary to identify the cerebral cortices functionally connected to the striatal region revealed in this study through methods such as seed-based connectivity analysis and to confirm whether phase-specific dysphagia is alleviated through extracranial stimulation of the corresponding cortical region.

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