

# Cognitive Dysfunction in Drug-induced Parkinsonism Caused by Prokinetics and Antiemetics

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The use of prokinetics/antiemetics is one of the leading causes of drug-induced parkinsonism (DIP) observed in neurology clinics. Cognitive dysfunction in DIP has recently been recognized, but pathologies related with cognitive dysfunction is unknown. Among our retrospective cohort of 385 consecutive parkinsonian patients enrolled in our parkinsonism registry, 14 patients were identified who satisfied our inclusion criteria: parkinsonism caused by prokinetics/antiemetics, existing T1-weighted 3D volumetric MR images, and normal [<sup>18</sup>F]-N-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-iodophenyl) nortropane PET scan images. For the comparison of volumetric MR data, 30 age- and sex-matched healthy individuals were included in this study. Among 14 patients with DIP, 4 patients were diagnosed with dementia, and all other patients had mild cognitive impairment (MCI). Comparisons of MR volumetric data between DIP patients with MCI and controls show that cortical gray matter volumes are reduced bilaterally in DIP ( $P = 0.041$ ) without changes in either total white matter volume or total intracranial volume. Among subcortical structures, the volume of the right hippocampus is reduced in DIP patients compared with controls ( $P = 0.011$ , uncorrected). In DIP, cortical thickness is reduced in the bilateral lingual ( $P = 0.002$ ), right fusiform ( $P = 0.032$ ) and part of the left lateral occipital gyri ( $P = 0.007$ ). Our results suggests that cognitive dysfunction in DIP caused by prokinetics/antiemetics is common. Structural changes in the brain by 3D MRI may be associated with cognitive decline in DIP.

**Keywords:** Drug-induced Parkinsonism; Magnetic Resonance Imaging; Prokinetics; Volumetry; Cortical Thickness; SWEDD (Scans without Evidence of Dopaminergic Deficit)

## INTRODUCTION

Drug-induced parkinsonism (DIP) is the second most common form of parkinsonism (1) after Parkinson's disease (PD) and constitutes 15%-60% of all parkinsonism cases (2) in the elderly. In the past, most cases of DIP were caused by classical antipsychotics, whereas more recently, a wider range of classes of drugs have been reported as responsible for DIP cases. Classes of drugs known to cause DIP include atypical antipsychotics, benzamide derivatives used to control nausea and vomiting, phenothiazine derivatives used to treat vertigo, drugs that interfere with vesicular storage of monoamines, calcium channel blockers, antidepressants and others. Among the drugs known to cause DIP, prokinetics/antiemetics such as levosulpiride, metoclopramide, and clebopride are leading causes of DIP, especially among the elderly in Korea (3, 4).

Most previous studies of cognitive dysfunction in DIP have investigated patients with schizophrenia taking typical or atypical antipsychotics. Studies on cognitive changes in DIP in the setting of a neurology clinic are rare (5-7). In a previous report on cognitive dysfunction in DIP, the study subjects were a het-

erogeneous population in terms of their underlying diseases and the drugs responsible for their DIP; because these drugs possessed varying degrees of dopamine-blocking potency, the interpretation of the results of this study is difficult (8). Because the age of onset of DIP is late in life (3, 4, 8), it is difficult to determine whether cognitive change in DIP is due to normal aging or to pathological processes underlying or accompanying DIP. Moreover, some DIP patients are in a prodromal stage of a neurodegenerative disease, which is associated with cognitive dysfunction (9-12).

To investigate whether DIP is associated with cognitive dysfunction and to explore the mechanisms underlying cognitive dysfunction in DIP, we analyzed clinical and neuropsychological test results together with T1-weighted 3D volumetric MR images of patients with prokinetic/antiemetic-induced parkinsonism. The subjects of our study were consecutively enrolled from our retrospective cohorts and showed no evidence of pre-synaptic dopaminergic deficits in [<sup>18</sup>F]-fluorinated N-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-iodophenyl) nortropane positron emission tomography ([<sup>18</sup>F]-FP-CIT PET) scans.

## MATERIALS AND METHODS

### Subjects

We analyzed magnetic resonance images and neuropsychological test results from a retrospective cohort of 14 DIP patients recruited from the movement disorders clinic at Hallym University Sacred Heart Hospital. A flow diagram illustrating the patient recruitment process is shown in Fig. 1. Briefly, among 385 consecutive parkinsonian patients who were enrolled in our standardized parkinsonism registry and had undergone a standardized protocol of history taking, neurological examination, neuropsychological evaluation and magnetic resonance imaging (MRI) from May 2011 to August 2013, we identified 61 DIP patients who had been diagnosed with parkinsonism according to the criteria used in our previous publication (3). T1-weighted 3D volumetric MR images included in our MR protocol were available for only 38 patients because MRI had been performed at a referred hospital in the other patients ( $n = 23$ ). Among the remaining 38 DIP patients, the drugs responsible for DIP in 21 patients were prokinetics/antiemetics such as levosulpiride, metoclopramide, or clebopride. [ $^{18}\text{F}$ ]-FP-CIT PET scans were normal in 14, abnormal in 3 and not available in 4 patients. Our routine MRI protocol included T1-weighted 3D volumetric MRI. Neuropsychological evaluations were conducted using the Seoul Neuropsychological Screening Battery (SNSB) (13) at least 24 hr after discontinuing the drugs responsible for the patient's DIP. Thirty healthy age- and gender-matched controls with no past or present neurological or psychiatric illnesses were also included in the study. All patients and con-

trols underwent neurologic examinations and were evaluated using the Unified Parkinson disease rating scale (UPDRS) and the Mini Mental State Examination (MMSE). No study subject in the control group had parkinsonian symptoms or signs, and the mean MMSE score was 27.4 (range 25-30).

### Magnetic resonance image acquisition and processing

We used a multisequence 3T MRI scanner (Achieva, Philips, Best, The Netherlands) to acquire MR images. T1-weighted 3D MPRAGE image ( $1 \times 1 \times 1 \mu\text{L}$  resolution) files in DICOM format were analyzed using FreeSurfer software (v5.0, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA). FreeSurfer is a semi-automated brain morphometry tool. The details of the postprocessing sequence implemented by FreeFurfer used in this study have been described elsewhere (14-17). Briefly, the processing included skull stripping, Talairach transformation, optimization of the grey matter-white matter and grey matter-CSF boundaries, and segmentation (16, 17). The cortical thickness was individually assessed at each vertex (16). All images were aligned to a common surface template using a high-resolution surface-based averaging technique that aligned cortical folding patterns (14). Finally, before further analysis, the cortical thickness maps were smoothed with a 10 mm full width at half maximum 2-dimensional Gaussian kernel to reduce local variations in the measurements.

### [ $^{18}\text{F}$ ]-FP-CIT PET scan

[ $^{18}\text{F}$ ]-FP-CIT PET was performed using a PET/CT scanner (Gemini TF; Phillips-ADAC Medical Systems, Cleveland, OH, USA) that provides an in-plane spatial resolution of 2.0 mm full width at half maximum at the center of the field of view. The drugs that were responsible for patients' DIP were discontinued by all patients at least 24 hr before the scans were obtained. Image acquisition was started 90 min after intravenous injection of [ $^{18}\text{F}$ ]-FP-CIT (185 MBq). Emission PET data were acquired for 10 min in the 3-dimensional mode after brain CT, which was performed in the spiral mode at 120 kVp and 150 mAs. [ $^{18}\text{F}$ ]-FP-CIT PET images were reconstructed from CT data after attenuation correction using the ordered-subset expectation maximization (OSEM) algorithm and an all-pass filter with a  $128 \times 128$  matrix.

### Statistical analysis

Statistical analyses were performed using SPSS Statistics V21. Independent *t*-tests were used to assess differences between groups for all demographic variables, brain volumetric measurements and subcortical volume measurements. Variations in regional cortical thickness and volume between DIP patients and the control group were estimated using a general linear model (GLM) at each vertex across the cortical surface, with group (DIP, control) as the dependent variable and age as a nuisance vari-

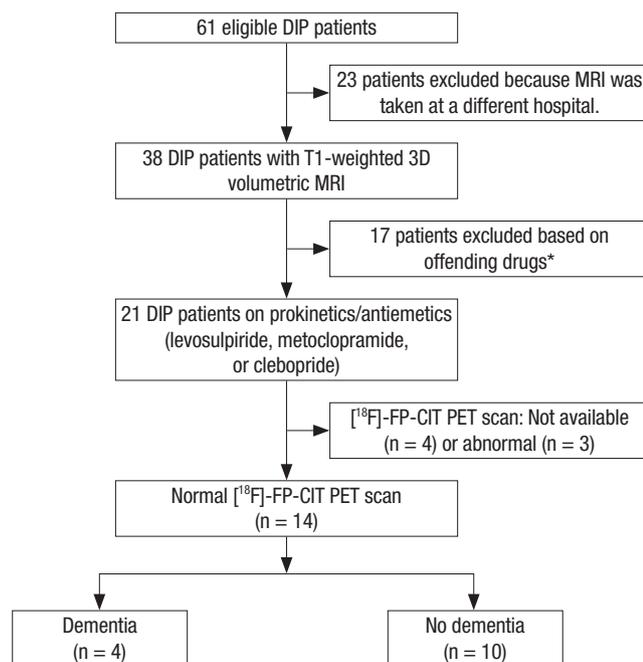


Fig. 1. Flow diagram of the patient recruitment process.

able, using Qdec implemented in FreeSurfer software. The cortical surfaces of the left and right hemispheres were analyzed separately. The maps generated by this analysis show the distribution of *P* values for pairwise comparisons between DIP patients and healthy controls. Clusters of vertices for which the *P* values for thickness-group and volume-group regression coefficients exceeded a predetermined threshold were identified, and cluster-wise statistical significances were calculated via 10,000 Monte Carlo simulations implemented in Qdec ( $P < 0.05$ ) (18). Subsequently, region-of-interest (ROI) analyses were performed by creating labels for gyral regions of interest and calculating the mean cortical thicknesses for each labeled ROI. Results of the neuropsychological tests for all individuals were transformed into Z-scores adjusted for age, sex, and education. Correlations between the average subcortical volume and the motor UPDRS score or between cortical thickness and neuropsychological test scores were analyzed using Kendal correlation analysis. In all analyses, the threshold for statistical significance was set at  $P < 0.05$ .

### Ethics statement

This study was approved by the institutional review board of Sacred Heart Hospital, Hallym University College of Medicine (IRB number 2014-1014). Informed consents were waived by the board. In case of control group, informed consent was obtained from all participant.

## RESULTS

Demographic data for 14 patients with DIP are summarized in Table 1. Motor disability in DIP patients was of mild to moderate severity according to Hoehn and Yahr staging criteria (1.5 to 3) with the exception of one patient who also suffered from de-

mentia and tuberculous spondylitis. Based on extensive neuropsychological evaluations, 4 out of 14 patients (28.6%) were diagnosed with dementia, and the remaining 10 patients had mild cognitive impairment (MCI). Two DIP patients had non-amnesic MCI, and the other patients with MCI had amnesic MCI. A history of rapid eye movement behavior disorder was present in 2 patients.

To explore whether cognitive dysfunction in DIP patients was related with underlying structural changes in the brain, we compared 3D volumetric MRI data between patients with DIP and control subjects. In a group comparison, DIP patients exhibited decreased cortical gray matter volumes in both hemispheres ( $P = 0.041$ ). However, cortical white matter and total intracranial volumes were not significantly different between the two groups (Table 2). When subcortical structures were examined, it was found that the volume of the right hippocampus was smaller in DIP patients ( $P = 0.011$ , uncorrected), whereas the volume of the cerebellum ( $P = 0.022$ , uncorrected) and the volume of the right amygdala ( $P = 0.038$ , uncorrected) were larger in DIP patients compared with the control group (Table 3). The volume of the right hippocampus was inversely correlated with the Seoul Verbal learning test (SVLT) recognition score ( $r = -0.614$ ,  $P = 0.015$ ),

**Table 2.** Mean volumetric measurements of the brain

Volume (mL)	DIP (n = 10)	Control (n = 30)	P value
	Mean (SD)	Mean (SD)	
Total cortical gray matter	301.46 (16.52)	319.99 (25.75)	0.041*
Left cortical gray matter	150.03 (8.03)	159.89 (13.69)	0.046*
Right cortical gray matter	151.37 (8.75)	160.10 (12.24)	0.039*
Left cortical white matter	201.12 (23.54)	208.64 (24.12)	0.331
Right cortical white matter	203.05 (25.59)	208.74 (22.53)	0.428
Intracranial volume	1383.34 (163.78)	1301.29 (159.39)	0.316

\*Significant difference ( $P < 0.05$ , independent *t*-test) between the DIP and control groups. DIP, drug-induced parkinsonism; SD, standard deviation.

**Table 1.** Demographic data for all drug-induced parkinsonism patients

Patient No.	Patient		Onset age (yr)	DIP-causing drugs	Dose mg/day	Duration of motor symptoms (yr)	H&Y stage	Motor UPDRS	MMSE z-score	Cognitive diagnosis	RBD
	Sex										
1	F		67.0	LVSP	75	4.99	3	36	-1.63	Amnesic multiple-domain MCI	-
2	F		78.0	CLBP	2.04	1.00	3	30	-0.12	Amnesic single-domain MCI	-
3	M		81.7	LVSP	75	0.33	3	45	-3.87	Dementia	-
4	F		72.4	LVSP	75	0.56	3	43	-1.57	Amnesic single-domain MCI	-
5	F		75.0	MCP+LVSP	11.52+50	0.01	3	29	-0.96	Amnesic multiple-domain MCI	-
6	F		74.5	LVSP	75	0.48	3	21	-1.22	Non-amnesic multiple-domain MCI	-
7	F		71.8	LVSP	75	0.18	2.5	20	0.56	Amnesic multiple-domain MCI	-
8	F		81.0	LVSP	75	0.04	3	30	-1.57	Amnesic single-domain MCI	-
9	F		64.3	LVSP	75	0.70	3	29	-4.36	Dementia	+
10	F		75.0	LVSP	50	2.97	1.5	13	-0.97	Amnesic multiple-domain MCI	-
11	M		73.9	LVSP	75	6.09	2.5	32	-2.84	Dementia	+
12	F		77.7	LVSP	75	0.28	5	68	-2.65	Dementia	-
13	M		76.0	LVSP	75	2.01	2.5	20	1.13	Non-amnesic single-domain MCI	-
14	F		74.3	LVSP	75	0.71	3	22	-1.37	Amnesic multiple-domain MCI	-

LVSP, levosulpiride; MCP, metoclopramide; CLBP, clebopride; MCI, mild cognitive impairment; H & Y stage, Hoehn & Yahr stage; UPDRS, Unified Parkinson's Disease Rating Scale score; MMSE, mini mental state examination; RBD, rapid eye movement behavior disorder.

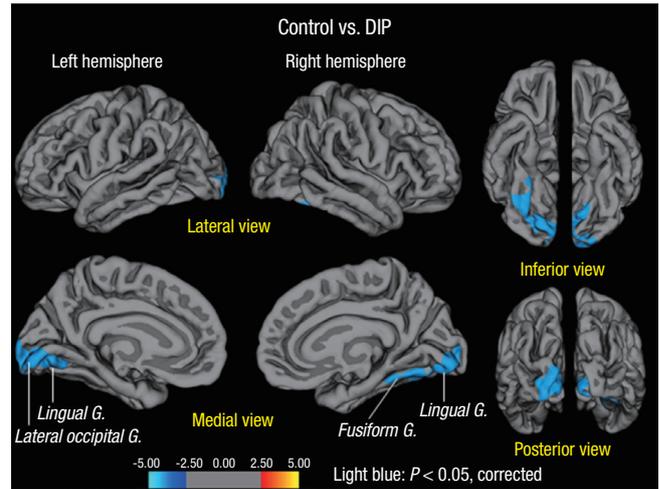
and the volume of the right amygdala was correlated with the SVLT immediate recall score ( $r = 0.600, P = 0.016$ ) (Table 4). We did not observe a correlation between volumes of subcortical structures and motor UPDRS scores (data not shown). Cortical

thickness was significantly decreased in the bilateral lingual gyrus ( $P = 0.002$ , corrected), the right fusiform gyrus ( $P = 0.032$ , corrected) and part of the left lateral occipital gyrus ( $P = 0.07$ , corrected) (Table 5 and Fig. 2) in DIP patients compared with control subjects. Cortical thickness in the left lingual gyrus was correlated with recognition scores on the Rey complex figure

**Table 3.** Comparison of subcortical volume measurements between DIP patients and control subjects

Volume (mL)	DIP (n = 10)		Control (n = 30)		P value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
L Cerebellar cortex	52.12 (1.15)	51.12 (2.09)	51.12 (2.09)	51.12 (2.09)	0.162
L Thalamus	83.10 (4.18)	83.07 (4.13)	83.07 (4.13)	83.07 (4.13)	0.984
L Caudate	68.08 (4.61)	69.22 (4.29)	69.22 (4.29)	69.22 (4.29)	0.480
L Putamen	78.47 (5.12)	78.42 (5.60)	78.42 (5.60)	78.42 (5.60)	0.979
L Pallidum	96.96 (3.91)	99.89 (4.91)	99.89 (4.91)	99.89 (4.91)	0.095
L Hippocampus	55.96 (2.34)	54.95 (2.74)	54.95 (2.74)	54.95 (2.74)	0.304
L Amygdala	58.47 (2.78)	57.72 (2.65)	57.72 (2.65)	57.72 (2.65)	0.452
L Accumbens	66.34 (3.94)	66.39 (3.41)	66.39 (3.41)	66.39 (3.41)	0.968
R Cerebellar cortex	53.40 (1.15)	51.65 (2.20)	51.65 (2.20)	51.65 (2.20)	0.022*
R Thalamus	84.20 (2.50)	82.63 (4.21)	82.63 (4.21)	82.63 (4.21)	0.271
R Caudate	66.34 (3.94)	66.39 (3.41)	66.39 (3.41)	66.39 (3.41)	0.782
R Putamen	77.02 (4.38)	75.85 (4.47)	75.85 (4.47)	75.85 (4.47)	0.472
R Pallidum	98.44 (3.71)	98.86 (5.21)	98.86 (5.21)	98.86 (5.21)	0.816
R Hippocampus	56.41 (2.76)	53.82 (2.63)	53.82 (2.63)	53.82 (2.63)	0.011*
R Amygdala	57.57 (3.58)	55.49 (2.30)	55.49 (2.30)	55.49 (2.30)	0.038*
R Accumbens	68.92 (3.78)	67.56 (3.86)	67.56 (3.86)	67.56 (3.86)	0.336

\*Significant difference ( $P < 0.05$ , uncorrected) between the DIP and Control groups. DIP, drug-induced parkinsonism; R, right hemisphere; L, left hemisphere; SD, standard deviation.



**Fig. 2.** Maps of differences in cortical thickness between the controls ( $n = 30$ ) and DIP patients ( $n = 10$ ;  $P < 0.05$  corrected for multiple comparisons). Monte Carlo simulations consisted of 10,000 iterations. The color-coding for P values is on a logarithmic scale of 1-5. Blue color represents cortical thinning.

**Table 4.** Correlations between cortical thickness and neuropsychological test scores in DIP

Brain location	Digit span forward	Digit span backward	Naming K-BNT	RCFT copy score	RCFT copy time	SVLT immediate recall	SVLT delayed recall	SVLT recognition	RCFT immediate recall	RCFT delayed recall	RCFT recognition	COWAT animal	COWAT supermarket	K-MMSE
L hippo-campus	$r$ squared 0.230 $P$ values 0.365	-0.092 0.717	0.289 0.245	0.111 0.655	-0.244 0.325	0.067 0.788	0.180 0.472	-0.296 0.241	-0.022 0.929	-0.333 0.180	-0.225 0.369	0.477 0.058	0.090 0.719	-0.360 0.151
R hippo-campus	$r$ squared 0.322 $P$ values 0.205	-0.138 0.586	0.289 0.245	0.289 0.245	-0.422 0.089	0.156 0.531	0.360 0.151	-0.614 0.015	0.067 0.788	-0.156 0.531	-0.180 0.472	0.205 0.417	0.045 0.857	0.270 0.281
R amygdala	$r$ squared 0.276 $P$ values 0.277	-0.046 0.856	-0.244 0.325	0.467 0.060	0.111 0.655	0.600 0.016	0.360 0.151	-0.386 0.125	0.067 0.788	-0.156 0.531	-0.315 0.209	0.159 0.528	0.225 0.369	0.045 0.857
L lingual gyrus	$r$ squared 0.414 $P$ values 0.103	0.046 0.856	0.333 0.180	-0.022 0.929	-0.200 0.421	-0.333 0.180	-0.225 0.369	-0.159 0.528	-0.156 0.531	-0.111 0.655	0.674 0.007	-0.068 0.787	0.000 1.000	0.315 0.209
R lingual gyrus	$r$ squared -0.276 $P$ values 0.277	0.276 0.276	0.022 0.929	0.111 0.655	-0.333 0.180	0.067 0.788	0.045 0.857	0.114 0.652	0.333 0.180	0.378 0.128	0.090 0.719	-0.159 0.528	-0.270 0.281	0.180 0.472
R fusiform gyrus	$r$ squared 0.046 $P$ values 0.856	0.322 0.204	0.067 0.788	0.244 0.325	0.156 0.531	-0.511 0.040	-0.405 0.106	0.477 0.058	0.022 0.929	-0.111 0.655	0.180 0.472	-0.068 0.787	-0.449 0.072	-0.315 0.209

Values are Kendall's tau-b correlation coefficients and P values. L, left hemisphere; R, right hemisphere; K-BNT, Boston naming test; RCFT, Rey complex figure test; SVLT, Seoul verbal learning test; COWAT, Controlled oral word association test; K-MMSE, Korean version of mini mental state examination.

**Table 5.** Comparison of cortical thickness measurements between DIP patients and control subjects

Cortical thickness (mm)	DIP (n = 10)		CON (n = 30)		TalX	TalY	TalZ	CWP
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)				
R lingual gyrus	1.52 (0.07)	1.64 (0.09)	-32.28	29.02	13.58	0.0001		
R fusiform gyrus	2.03 (0.11)	2.14 (0.12)	-21.31	2.95	-15.15	0.0001		
L lingual gyrus	1.47 (0.07)	1.61 (0.01)	-21.31	2.95	-15.15	0.0001		
L Lateral occipital gyrus	1.45 (0.11)	1.75 (0.11)	-1.50	-99.09	-5.29	0.0001		

Vertex cluster-wise statistic determined by Monte Carlo simulation. Values for DIP and CON are means and standard deviations in parentheses. CWP, The cluster-wise P value; DIP, drug-induced parkinsonism; CON, control; TalX, TalY, TalZ, Talairach x, y, and z coordinates; R, right hemisphere; L, left hemisphere; SD, standard deviation.

test ( $r = 0.674, P < 0.007$ ) (Table 4). SVLT immediate recall scores were inversely correlated with cortical thickness in the right fusiform gyrus ( $r = -0.511, P = 0.040$ ).

## DISCUSSION

The analysis of our retrospective cohort of patients with DIP caused by prokinetics/antiemetics showed that cognitive dysfunction was present in all patients that were studied. Analysis of 3D MR brain volumetry in DIP with MCI demonstrated that DIP patients have cortical gray matter atrophy and that the cortical thickness is significantly reduced in specific brain regions, including the bilateral lingual, right fusiform and part of the left lateral occipital gyri. To our knowledge, this is the first study to show structural changes in the brain that are associated with cognitive dysfunction in DIP. Although the number of cases in our retrospective cohort of DIP caused by prokinetic/antiemetics is relatively small, we believe that our data is not biased for several reasons. First, we enrolled consecutive parkinsonian patients based strictly on clinical criteria for the diagnosis of DIP, and neuropsychological test results and MRI data were not considered in the diagnosis. Second, we studied only patients with DIP caused by prokinetics/antiemetics, excluding those on classical or atypical antipsychotics to exclude heterogeneous underlying neurological or psychiatric disorders such as dementia, depression or schizophrenia, which may be associated with structural changes in the brain. Third, by studying only parkinsonian patients with normal [ $^{18}$ F]-FP-CIT PET scans, we excluded the possibility of enrolling patients with Parkinson's disease or other Parkinson plus syndromes in preclinical stages to avoid including subjects in whom parkinsonian symptoms could be aggravated by dopamine antagonists. In our study, all patients had cognitive dysfunction to varying degrees ranging from MCI in a single domain to dementia. Recently, cognitive dysfunction was reported in DIP patients recruited from a neurology outpatient clinic (8). Because the DIP patients investigated in that study were drawn from a mixed population that had developed DIP as a result of taking drugs with diverse dopamine receptor-blocking capabilities and that also suffered from underlying central nervous system disorders, direct comparison of our results with the results of that study is difficult. Nevertheless, a higher prevalence of cognitive dysfunction in both studies suggests that cognitive dysfunction may be a risk factor for DIP. Kim et al. (8) observed that cognitive dysfunction was reversible in some of their patients and suggested toxic or metabolic effects as a mechanism of DIP. However, given the structural changes observed in the brains of our DIP patients, our results strongly suggest that underlying pathological processes were resulting in anatomical changes in patients with DIP caused by prokinetic drugs, although we do not know the extent to which these processes may be reversible. The possibil-

ity that underlying pathological processes may exist in DIP has been raised in a number of previous studies, although we do not know whether such pathological processes represent a distinctive pathology or a prodromal stage of known neurodegenerative disorders (10-12). The cause of increased right cerebellar volume is not clear. Increased right cerebellar cortical volume could be related to the compensatory changes of the cortical thickness in the occipital cortex for adapting the lack of sensorial inputs. Our finding of volumetric changes and areas of cortical thinning in subcortical structures in our DIP patients may offer clues to increase our understanding of the pathological processes underlying DIP induced by prokinetics. Although hippocampal volumes were smaller in DIP, the brain regions in which changes in cortical thickness were observed in DIP differ from those observed in Alzheimer's disease (AD) or frontotemporal dementia (19). In AD, cortical thinning predominantly involves the temporal and parietal areas extending into the frontal lobes. In amnesic MCI, which may represent a transitional stage between a healthy, normal state and Alzheimer's disease, cortical thinning involves the left medial temporal lobe, the precuneus, and anterior and inferior basal temporal, insular, and temporal association cortices (20). In dementia with Lewy bodies (DLB), a reduction in cortical thickness was reported in the pericalcarine and lingual gyri, cuneus, precuneus, and superior parietal gyrus bilaterally (21). Interestingly, areas of cortical thinning in PD patients with cognitive dysfunction are similar to those observed in our DIP patients (22). Taken together, these results suggest that the pathology underlying DIP may be heterogeneous.

Our investigation of correlations between volumetric changes or changes in cortical thickness and neuropsychological test results for the corresponding cognitive domains also suggest that anatomical changes underlie cognitive dysfunction in our DIP patients. However, verbal and visual function showed false lateralization in our results of correlation analysis. To rule out a possible coding error, we reviewed our analysis repeatedly and confirmed our results. Currently, we do not have a clear explanation for this observation; it is possible that compensatory changes or brain plasticity may have led to these changes. However, we cannot exclude the possibility that neuropsychological test results may have been confounded by the residual effects of a DIP-causing drug. Beyond these considerations, two additional potential limitations to our study should be recognized. First, we considered only patients with DIP due to prokinetics/antiemetics. Thus, the DIP patients in this study may not truly represent the whole DIP patient population. Finally, the results of this study concerned only the early stages of DIP, without long-term follow up. The examination of SNSB was done within 1 week after the discontinuation of an offending drug. Validation of our observations in a larger cohort and longitudinal studies by other groups would be useful to increase our understanding

of DIP.

In conclusion, 3D volumetric MRI finds structural changes in the brains of patients with DIP caused by prokinetics/antiemetics, which may be associated with cognitive dysfunction. Whether cognitive dysfunction is a risk factor for DIP should be validated in larger studies.

## DISCLOSURE

All authors have no potential conflicts of interest.

## AUTHOR CONTRIBUTION

Research concept: Ma HI, Kim YJ. Data collection: Ahn HJ, Yoo WK, Park J. Writing: Ahn HJ, Ma HI. Statistical analysis: Kim YJ. Revision: Yoo WK, Park J, Kim YJ, Ma HI. Manuscript approval: all authors.

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