Analysis of neurocognitive and cortical thinning patterns between early onset and late onset Parkinson's disease dementia

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Analysis of neurocognitive and cortical thinning patterns between early onset and late onset Parkinson's disease dementia

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ABSTRACT

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Cognitive dysfunction in Parkinson's disease (PD) is one of the most disabling features and occurs mainly in old age. Although aging is a risk factor of dementia in PD, the early onset form of Parkinson's disease dementia (PDD) had not been researched. The present study included 116 patients with PDD and 121 patients with normal cognition, The subjects were divided into two groups based on a cutoff value of 70 years; 39 patients with onset age younger than 70 years (Early-onset PDD, EOPDD) and 77 patients with onset after 70 years of age (Late-onset PDD, LOPDD). All of these patients were assessed with a neuropsychological battery. Among the patients, 65 underwent three-dimensional T1-weighted MRI scans and analyses of cortical thickness. In addition, volumetry of substantia innominata (SI) was performed. The effects of diagnosis and age and their interaction on neuropsychological tests, cortical thickness, and volume of SI were assessed using analysis of covariance. The EOPDD group exhibited poorer performance in backward span ($p=0.011$) and visual recognition tests ($p=0.002$) after adjusting for the effect of aging. In cortical thickness

analysis, the LOPDD group showed widespread cortical thickness. After adjusting for age, the EOPDD group exhibited greater cortical thinning in the left anterior cingulate gyrus and right mesial temporal area, with a lower threshold of uncorrected $p<0.001$. The normalized SI volume was decreased in the EOPDD group after adjusting for aging effects in volumetric analysis. Our data suggest that EOPDD may be a distinct phenotype different from LOPDD. EOPDD had a greater pathological burden in key structures responsible for PD-related cognitive decline, whereas LOPDD had a widespread pathological burden related to aging.

Key words : Parkinson's disease dementia, Age at onset, Neuropsychological test, Cortical thickness

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I. INTRODUCTION

Cognitive dysfunction in Parkinson's disease (PD) is one of the most disabling non-motor features leading to poorer performances of daily living and increase in caregiver burden. Clinical risk factors and neuroimaging predictor for ongoing cognitive decline in patients with PD have been suggested. Neuropsychological predictions of dementia in PD (PDD) in longitudinal studies suggested that cognitive performance associated with posterior cortical areas, such as semantic fluency and visuoconstructional ability seems to be an important determinant for ongoing cognitive decline of PD,[1] although frontal executive functions are also considered a significant predictor of PDD.[2] Additionally, poor performance at baseline is an independent predictor of cognitive decline in PD.[3] In aspects of functional neuroimaging, the status of cerebral glucose metabolism in posterior visual association cortical areas and posterior cingulate areas was a significant predictor of dementia in patients with PD.[4] Moreover, the cholinergic system arising from the nucleus basalis of Meynert located in the substantia innominata (SI) of the basal forebrain was suggested as an important neural system responsible for cognitive dysfunctions and ongoing cognitive decline in PD patients.[5,6]

Ample evidence has showed that aging is the most important risk factor of development of PDD[7,8] and thus, there has been amount of efforts to evaluate

chronological changes of PD pathologies in PD patients. It was well known that early-onset PD patients showed slower disease progression and lower rates of dementia.[9] However, one longitudinal study showed age itself, rather than age at motor symptom onset is associated with incident dementia in subjects with PD.[10] One prospective study also showed a relationship between age and cognitive decline, with particular susceptibility above 70 years of age.[1] Another clinico-pathologic study comparing PD patient groups showed that PD patients reached a common pathological endpoint at a similar average age irrespective of age of onset or disease duration, suggesting that aging might accelerate progression after the age of 70 years.[11]

However, despite lower incidence, early onset PD patient experienced dementia like other neurodegenerative disease. In Alzheimer's disease, ample evidence pointed out that early-onset AD and late onset AD had different phenotype. Early-onset AD presented with more diverse cognitive impairment,[12] faster cognitive decline,[13] more temporo-parietal defects in perfusion,[14] more cortical thinning[15] and more pathologic burdens.[16] These findings suggest the causal mechanisms underlying the two forms of disease might be different, and thus therapeutic strategies should be specifically considered for early-onset AD. In this regard, it is reasonable to postulate that clinical and pathological phenotype in patients with PDD might differ depending on onset age. However, early onset form of PDD had not been focused yet clinically.

In the present study, we analyzed neuropsychological profiles and radiological patterns of cortical thinning and measured the SI volumes in patients with early-onset and late-onset PDD to examine whether patients with PDD represent clinical and radiological heterogeneity depending on age at onset.

II. MATERIALS AND METHODS

1. Subjects

The study included 116 patients with PDD recruited from the Movement Disorders and Dementia outpatient clinic at Yonsei University Severance Hospital from March 2007 to December 2014. PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank.[17] PDD was diagnosed based on the Movement Disorder Society consensus criteria for dementia associated with PD.[18] To ensure sufficient clinical diagnosis of PDD, we enrolled patients showing decreased dopamine transporter uptake in the posterior putamen on [18F]FP-CIT PET scans. Motor symptoms were assessed using the Unified PD Rating Scale Part Ⅲ (UPDRS-Ⅲ).

Depending on the age at PDD diagnosis, the patients were divided into early-onset PDD (EOPDD < 70 years of age, n= 39) and late-onset PDD (LOPDD ≥ 70 years of age, n=77). Each patient underwent history taking, laboratory examinations, physical and neurological examinations and conventional brain magnetic resonance imaging (MRI) scans. Disease duration and memory complaints in each patient were based on interviews with patients and caregivers living with patients. We also used the caregiver-based structured interview of the Neuropsychiatric Inventory (NPI),[19] which was administered by a trained neuropsychologist. History of hypertension was defined as prior physician-diagnosed hypertension with or without the use of antihypertensive agents, and history of diabetes or dyslipidemia was defined based on self-report or the use of hypoglycemic or lipid-lowering agents.

All patients participated in the Seoul Neuropsychological Screening Battery (SNSB), consisting of the following cognitive subsets: attention (forward and backward digit span), language and related functions (Korean version of the Boston Naming Test and calculation), visuospatial function (Rey Complex Figure Test; RCFT), verbal memory (three-word registration and recall and the Seoul Verbal Learning Test), visual memory (RCFT, immediate recall, 20-minute delayed recall, and recognition), and frontal/executive function (contrasting program, go-no-go test, phonemic and

semantic fluency test, and Stroop test). The scores of these quantifiable cognitive tests were classified as abnormal when they were below the 16th percentile of the norms for the age-, gender- and education-matched normal subjects.

We recruited 121 healthy age- and sex-matched normal controls who had no history of neurological disease and no abnormalities on neurologic examinations. The normal controls exhibited no objective cognitive dysfunction on the mini-mental state examination (MMSE) and neuropsychological tests (SNSB). The normal controls were divided into the young control group (< 70 years of age) and the old control group (≥ 70 years of age) and were compared with the respective age-matched PDD group; 49 were allotted to the young controls and 72 to the old controls.

Among study subjects, three-dimensional T1-weighted MRI scans used for cortical thickness analysis were available in 65 patients with PDD. Of these 65 patients, 25 were classified as EOPDD and 40 patients as LOPDD. We excluded patients with focal neurological deficits, evidence of focal brain lesions, diffuse white matter intensities, multiple lacunae in the basal ganglia based on MRI, or other past medical comorbidities that could contribute to cognitive decline. Possible medical comorbidities were excluded using laboratory tests, including thyroid function test, vitamin B12 and folic acid levels, and VDRL test.

This study was approved by the Yonsei University Severance Hospital ethical standards committee on human experimentation for experiments using human subjects. Written informed consent was obtained from all subjects participating in this study.

2. MRI acquisition

All scans were acquired using a Philips 3.0-T scanner (Philips Intera; Philips Medical System, Best, The Netherlands) with a SENSE head coil (SENSE factor=2). A high-resolution T1-weighted MRI volume data set was obtained from all subjects using a 3D T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224 × 256 matrix; 256 × 256 reconstructed matrix with 182

slices; 220 mm field of view; 0.98 × 0.98 × 1.2 mm^3 voxels; TE, 4.6 ms; TR, 9.6 ms; flip angle, 8°; slice gap, 0 mm.

3. Image processing for cortical thickness

We corrected intensity inhomogeneity caused by magnetic field inhomogeneity by varying the signal intensity slowly over the image. The N3 algorithm was used to correct images for intensity non-uniformities resulting from inhomogeneities in the magnetic field.[20] Skull stripping was performed using a Brain Extraction Tool (BET) with a deformable model fitted to the brain surface and optimized parameters.[21] Each brain was transformed separately into a standardized stereotaxic space (an ICBM 152 template) and resampled on a 1 mm^3 voxel grid to account for inter-individual differences in absolute brain size.[22] An artificial neural network classifier was applied to identify gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF).[23] Partial volume level and MRI intensity mixing at the tissue interfaces due to the finite resolution of the imaging device were estimated and corrected using a trimmed minimum covariance determinant method.[24] A cortical surface was extracted automatically from each MR volume using the Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm.[25] Cortical thickness was defined as the Euclidean distance between linked vertices or the inner and outer surfaces. The inner surface was defined by the WM/GM boundary surfaces and the outer surface by GM/CSF boundary surfaces. Diffusion smoothing, which generalizes Gaussian kernel smoothing, with 20-mm full width half maximum (FWHM) was used to increase the signal to noise ratio and adequately detect population changes. To assess group differences in cortical thickness, a general linear model was constructed with age, sex, and intracranial volume as independent variables and each of the vertices of thickness as a dependent variable. For multiple comparisons, the results were thresholded at a false discovery rate (FDR)-corrected p-value of 0.05 and cluster of 100. In addition, the effect of diagnosis (PDD *versus* control), age (< 70 years *versus* ≥ 70 years), and their interaction with cortical thinning was assessed using analysis of covariance

(ANCOVA) with a threshold of uncorrected $p<0.001$ and cluster of 100, controlling for educational level, hypertension, diabetes mellitus, and hyperlipidemia.

4. Volumetric determination of SI

The analysis was performed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK, available at http://www.fil.ion.ucl.ac.uk/spm). Each structural MRI scan was bias-corrected, segmented into SPM default tissue probability maps, and then normalized with VBM8 DARTEL templates for registration to MNI space using linear (12-parameter affine) and nonlinear transformations within a unified model. According to a previous study,[26] the ROI of SI was defined for the left and right hemispheres based on the location of the anterior commissure, which forms the boundary of the superior part of the end of the anterior third of the substantia innominata. The ROI extended 25 mm lateral from the midline, 13 mm ventral from the superior edge of the anterior commissure at the midline, and 3 mm anterior and 9 mm posterior from the middle of the anterior commissure (Figure 1). The masks were created using the WFU PickAtlas 2.4 software,[27] and volumetry of GM within a selected ROI was performed automatically. The total SI volume calculated included both the right and left hemispheres. To correct for individual brain size, volumes were normalized by dividing by total intracranial volume derived from the masks covering the entire brain. Normalized SI volume was defined by the following formula: total SI volume (mL)/total intracranial volume (mL) X 10,000.

5. Statistical analysis

The χ^2 and Mann-Whitney U tests were used for categorical and continuous variables, respectively. The effect of diagnosis (PDD versus control) and age (<70 versus ≥ 70), and their interaction on neuropsychological tests and volumes of SI were assessed with analysis of covariance (ANCOVA), controlling for educational years, hypertension, diabetes mellitus, and hyperlipidemia. The significance of the interaction was tested in a full factorial model including the two main effects of

diagnosis and age, and their interaction. As both PDD groups had test scores poorer and brain volumes lower than the pertinent control group, significance of the interaction denoted a relatively poorer performance or relatively lower volumes in one of the two patient groups. Statistical analyses were performed using commercially available software (SPSS, version 18.0), and a two- tailed $P < 0.05$ was considered significant.

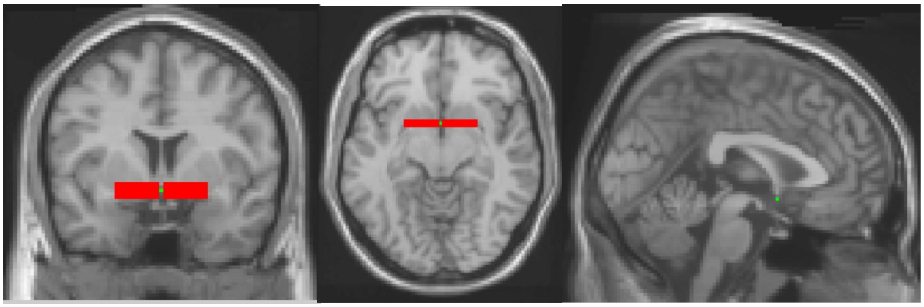

Figure 1. Mask image for ROI of substantia innominata. A region of interest is placed on the PD scan in MNI space starting at the middle (anterior–posterior) rostral level of the anterior commissure in the midline and extending 25, 13 and 12 mm in x, y and z directions, respectively.

III. RESULTS

1. Demographic characteristics of the EOPDD and LOPDD

The demographic characteristics of patients with PDD are shown in Table 1. Mean age at onset was 64.6 years in EOPDD and 75.5 years in LOPDD. There were significant differences in sex, educational level, duration of Parkinsonism, and duration of cognitive impairment between the EOPDD and LOPDD groups. K-MMSE score tended to be higher in the EOPDD group (19.9) than the LOPDD group (18.5), which may be due to the difference in age. Levodopa equivalent dose and vascular risk factors, such as hypertension, diabetes mellitus, or dyslipidemia, did not differ between the EOPDD and LOPDD groups. The UPDRS motor score was higher in patients with LOPDD (35.5) than EOPDD (28.8, p=0.005).

The demographic characteristics of 65 patients with available MRI data were similar to those of patients with PDD (Table 2). Mean age at onset in these 65 patients was 64.6 years in the EOPDD group and 75.3 years in the LOPDD group. No significant differences in sex, MMSE, educational level, PD duration, levodopa equivalent dose, UPDRS motor score, or duration of memory complaints were observed between the EOPDD and LOPDD groups. Total intracranial volume was not statistically different between the two patient groups (p=0.596).

Table 1. Demographic characteristics between patients with EOPDD and LOPDD

Variables	EOPDD (n=39)	LOPDD (n=77)	p-value
Age(years)	64.6(4.3)	75.5(4.2)	< 0.001
Sex (number of men, %)	18(46.2%)	37(48%)	0.847
K-MMSE	19.9(3.9)	18.5(4.8)	0.135
Education (years)	6.6(4.1)	7.8(5.5)	0.297
Parkinsonism duration(months)	73.5(51.8)	64.9(49.2)	0.351
Cognitive impairment duration (months)	6.6(4.1)	7.8(5.5)	0.209
UPDRS part III	28.8(13.5)	35.5(14.1)	0.005
Levodopa equivalent dose (mg)	658.8(422.0)	650.8(442.9)	0.710
Hypertension	13(33.3%)	33(42.9%)	0.322
Diabetes mellitus	5(12.8%)	16(20.8%)	0.293
Dyslipidemia	2(5.1%)	2(2.6%)	0.480

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

EOPDD: Early onset Parkinson's disease dementia, LOPDD: Late onset Parkinson's disease dementia, K-MMSE: Korean version of the Mini Mental State Examination, UPDRS: unified PD rating scale.

Table 2. Demographic characteristics between patients with EOPDD and LOPDD (with MRI)

Variables	EOPDD (n=25)	LOPDD (n=40)	p-value
Age(years)	64.5(4.0)	74.7(4.5)	< 0.001
Sex (number of men, %)	10 (40.0%)	20 (50.0%)	0.431
K-MMSE	20.0(3.7)	18.3(4.4)	0.098
Education (years)	5.6(3.7)	7.1(5.5)	0.180
Parkinsonism duration(months)	55.3(33.9)	57.8(44.3)	0.814
Cognitive impairment duration (months)	16.4(14.5)	22.6(19.2)	0.176
UPDRS part III	31.8(13.2)	33.9(13.0)	0.545
Levodopa equivalent dose (mg)	610.1(481.4)	723.6(385.7)	0.299
Hypertension	9(36.0%)	13(32.5%)	0.772
Diabetes mellitus	3(12.0%)	9(22.5%)	0.288
Dyslipidemia	0(0%)	0(0%)	1.0
Total intracranial volume(ml)	1670.3(58.5)	1670.6(63.8)	0.596

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

EOPDD: Early onset Parkinson's disease dementia, LOPDD: Late onset Parkinson's disease dementia, K-MMSE: Korean version of the Mini Mental State Examination, UPDRS: unified PD rating scale.

2. Neuropsychological features of the YOPDD and LOPDD

The NPI score in patients with PDD is shown in Table 3. The total NPI scores and the subitem scores did not differ significantly between the EOPDD and LOPDD groups. The neuropsychological test results of patients with EOPDD and LOPDD are shown in Table 4. Compared with the young control group, EOPDD patients showed significantly poorer performances in all domains of attention, language, visuospatial, and memory functions. Additionally, the LOPDD group showed a lower score in all cognitive subdomains compared with the old control group. The results of a direct comparison between the EOPDD and LOPDD groups in terms of an interaction between diagnosis and age are illustrated in Table 5. Significant group-by-age interaction effects were observed for backward and forward digit span test ($p=0.05$ and 0.011, respectively) and visual recognition memory function ($p=0.02$) in EOPDD patients compared with LOPDD patients. In addition, EOPDD patients tended to show poorer performance in phonemic generative naming, contrasting program, and verbal memory tests ($p=0.095$, 0.078, and 0.118, respectively) than the LOPDD patients, although the difference was not statistically significant. No significant interaction effects between EOPDD and LOPDD groups were observed in language, visuospatial function, or other frontal-executive functions.

The group-by-age interaction effects in the PDD subpopulation with available MRI data are illustrated in Table 6. Similar to the overall PDD patients, significant group-by-age interaction effects were observed for backward digit span and visual recognition memory tests ($p=0.006$ and 0.005, respectively) in EOPDD patients compared with LOPDD patients.

Table 3. Analysis of neuropsychiatric inventory between patients with EOPDD and LOPDD

	EOPDD(n=24)	LOPDD(n=48)	p-value
Delusion	1.1(2.5)	1.2(2.8)	0.86
Hallucination	0.8(2.5)	1.7(3.0)	0.22
Agitation/Aggression	1.2(2.9)	1.8(2.6)	0.39
Depression/Dysphoria	2.8(2.0)	2.0(2.7)	0.25
Anxiety	1.7(2.8)	2.0(3.2)	0.64
Elution/euphoria	0.3(1.2)	0.3(1.7)	0.95
Apathy/indifference	3.0(3.6)	3.7(4.0)	0.49
Disinhibition	0.5(1.4)	0.5(1.7)	0.88
Irritability/lability	2.2(3.8)	2.2(3.8)	0.99
Aberrant behavior	2.0(3.5)	1.5(3.2)	0.60
Sleep behavior	2.7(4.4)	2.9(3.9)	0.85
Appetite/eating change	1.8(3.3)	2.2(3.2)	0.58
Total score	20(22.1)	22.1(21.7)	0.70

Values expressed as mean (standard deviation)

EOPDD: Early onset Parkinson's disease dementia LOPDD: Late onset Parkinson's disease dementia

Table 4. Neuropsychological characteristics between patients with EOPDD and LOPDD

Domain	Test		EOPDD			LOPDD		
			Patients (n=39)	Control (n=49)	p	Patients (n=77)	Control (n=72)	p
Attention	Forward digit span		4.9(1.2)	6.8(1.5)	<0.001	5.0(1.2)	6.0(1.2)	<0.001
	Backward digit span		2.1(1.1)	4.3(1.4)	<0.001	2.2(1.3)	3.4(1.0)	<0.001
	Letter cancellation (error, %)		18(46.1%)	0(0%)	<0.001	37(48.0%)	3(4.2%)	<0.001
Language	K-BNT		31.6(8.4)	50.0(5.9)	<0.001	27.4(10.8)	43.6(8.7)	<0.001
Visuospatial functions	Interlocking pentagon (error, %)		23(59.0%)	1(2.0%)	<0.001	51(66.2%)	8(11.1%)	<0.001
	RCFT		16.0(9.2)	34.4(2.7)	<0.001	13.6(10.3)	32.5(4.8)	<0.001
Memory	Verbal memory	SVLT (Delayed recall)	1.4(1.6)	7.0(1.7)	<0.001	1.1(1.6)	5.6(1.7)	<0.001
		SVLT (recognition)	16.7(3.0)	21.4(1.5)	<0.001	15.7(3.1)	20.9(1.6)	<0.001
	Visual memory	RCFT (delayed recall)	4.1(3.9)	17.0(5.1)	<0.001	2.6(3.7)	14.0(6.1)	<0.001
		RCFT (recognition)	16.8(2.6)	20.1(1.7)	<0.001	15.2(2.6)	20.0(2.7)	<0.001
Frontal executive functions	Phonemic generative		6.3(6.2)	29.8(11.7)	<0.001	6.1(6.4)	24.0(9.5)	<0.001
	Semantic generative		17.0(8.3)	35.6(8.0)	<0.001	14.8(7.2)	31.2(7.8)	<0.001
	Contrasting program		13.9(7.5)	20.0(0.2)	<0.001	10.8(8.4)	19.5(1.2)	<0.001
	Go-no-Go		10.2(6.8)	19.5(1.8)	<0.001	8.7(7.9)	18.9(2.7)	<0.001
	Color stroop		31.9(27.3)	93.9(18.2)	<0.001	28.4(26.4)	80.9(19.0)	<0.001

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

K-BNT: Korea version of the Boston Naming Test; RCFT: Rey Complex Figure Test; SVLT: Seoul Verbal Learning Test

Table 5. Comparison of neuropsychological test between EOPDD and LOPDD patients using the group-by-age interaction effects

Domain	Test		P of interaction on ANCOVA
Attention	Forward digit span		0.050
	Backward digit span		0.011
	Letter cancellation		0.554
Language	K-BNT		0.950
Visuospatial	Interlocking pentagon		0.653
	RCFT		0.211
Memory	Verbal memory	SVLT (Delayed recall)	0.118
		SVLT (recognition)	0.315
	Visual memory	RCFT (delayed recall)	0.722
		RCFT (recognition)	0.002
Frontal-Executive	Phonemic generative		0.095
	Semantic generative		0.524
	Contrasting program		0.078
	Go-no-Go		0.436
	Color stroop		0.326

K-BNT: Korea version of the Boston Naming Test; RCFT: Rey Complex Figure Test; SVLT: Seoul Verbal Learning Test

Table 6. Comparison of neuropsychological test between EOPDD and LOPDD patients using the group-by-age interaction effects(with MRI)

Domain	Test		P of interaction on ANCOVA
Attention	Forward digit span		0.172
	Backward digit span		0.009
	Letter cancellation		0.150
Language	K-BNT		0.540
Visuospatial	Interlocking pentagon		0.842
	Rey copy test		0.072
Memory	Verbal memory	HVLT (Delayed recall)	0.599
		HVLT (recognition)	0.140
	Visual memory	REY (delayed recall)	0.802
		REY (recognition)	0.006
Frontal-Executive	COWAT(A)		0.403
	COWAT(S)		0.658
	Phonemic generative		0.892
	Semantic generative		0.470
	Contrasting program		0.153
	Go-no-Go		0.509
	Color stroop		0.614

K-BNT: Korea version of the Boston Naming Test; RCFT: Rey Complex Figure Test; SVLT: Seoul Verbal Learning Test

3. Cortical thickness analysis between the EOPDD and LOPDD groups

A comparison of EOPDD patients and age-matched controls is shown in Figure 1. As expected, patients with EOPDD exhibited a cortical thinning in extensive cortical areas, involving frontal, temporal, and parietal areas. A comparison of LOPDD and age-matched controls is shown in Figure 2. The LOPDD group showed significant cortical thinning in widespread cortical areas of frontal, temporal, and parietal areas, with prominent cortical thinning in bilateral prefrontal areas. Notably, the areas of cortical thinning were more extensive in LOPDD than EOPDD patients. A direct comparison of cortical thickness between the EOPDD and LOPDD groups based on interaction effect demonstrated that, compared with LOPDD patients, EOPDD patients exhibited cortical thinning in the left anterior cingulate gyrus and a small area of the right mesial temporal lobe when adjusting for age with a threshold of uncorrected $p<0.001$ (Figure 3).

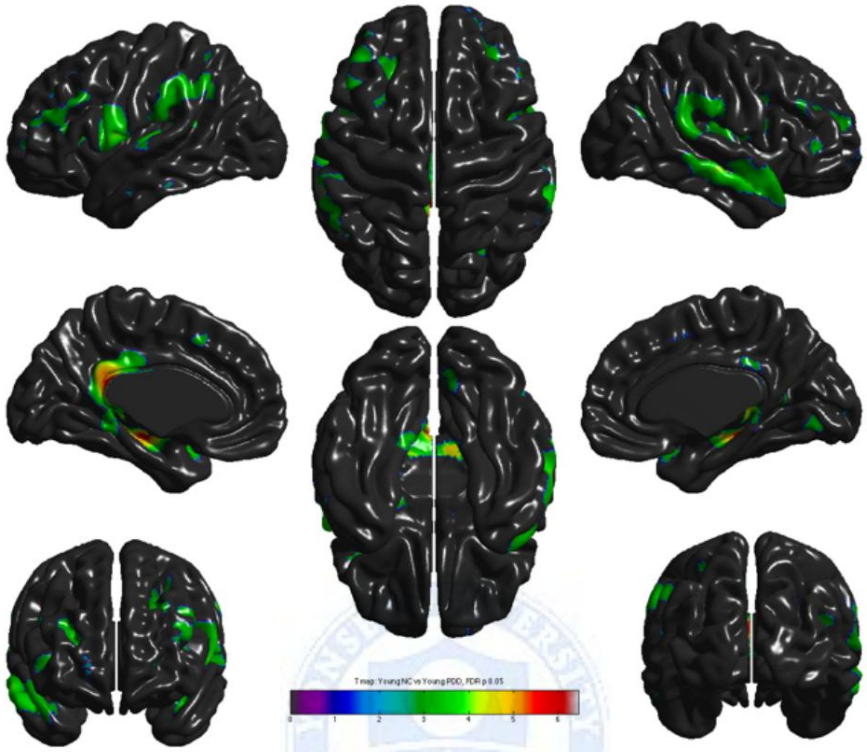

Figure 2. Analysis of cortical thickness between EOPDD patients and age-matched controls. The EOPDD group showed significant cortical thinning in the left frontoparietal and right parietotemporal areas. Additionally, cortical thinning was observed in the bilateral mesial temporal and left posterior cingulate areas. The colored areas indicate statistically significant cortical thinning in EOPDD patients compared with controls (FDR $p<0.05$).

EOPDD, early-onset Parkinson's disease dementia; FDR, false discovery rate

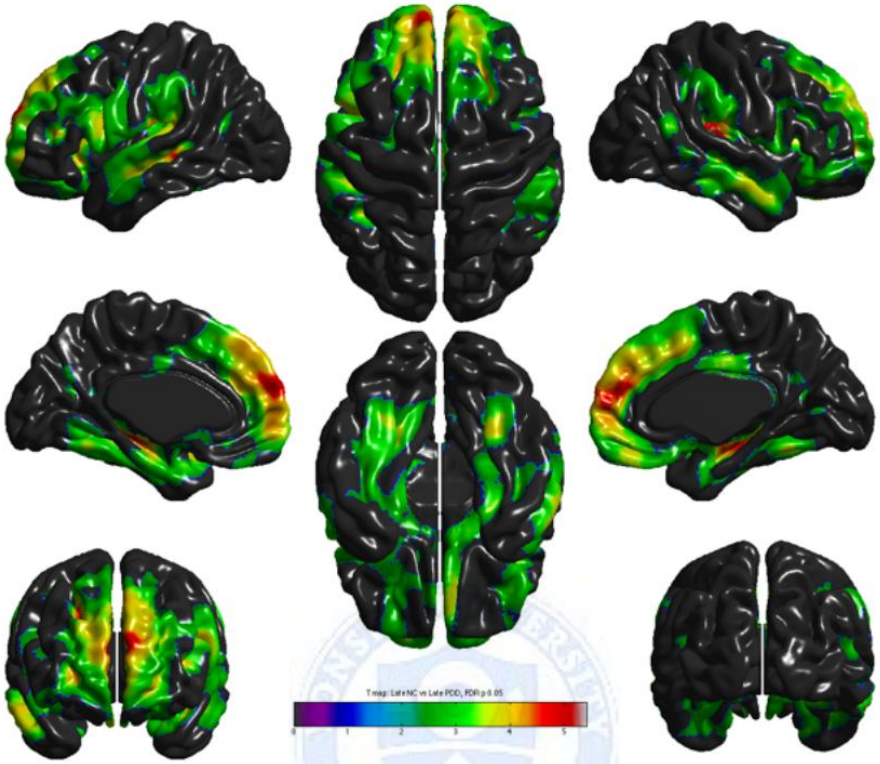

Figure 3. Analysis of cortical thickness between LOPDD patients and age-matched controls. The LOPDD group showed significantly widespread cortical thinning in the bilateral frontotemporal area, particularly in the bilateral prefrontal cortex. The colored areas indicate statistically significant cortical thinning in LOPDD patients compared with controls (FDR $p<0.05$).

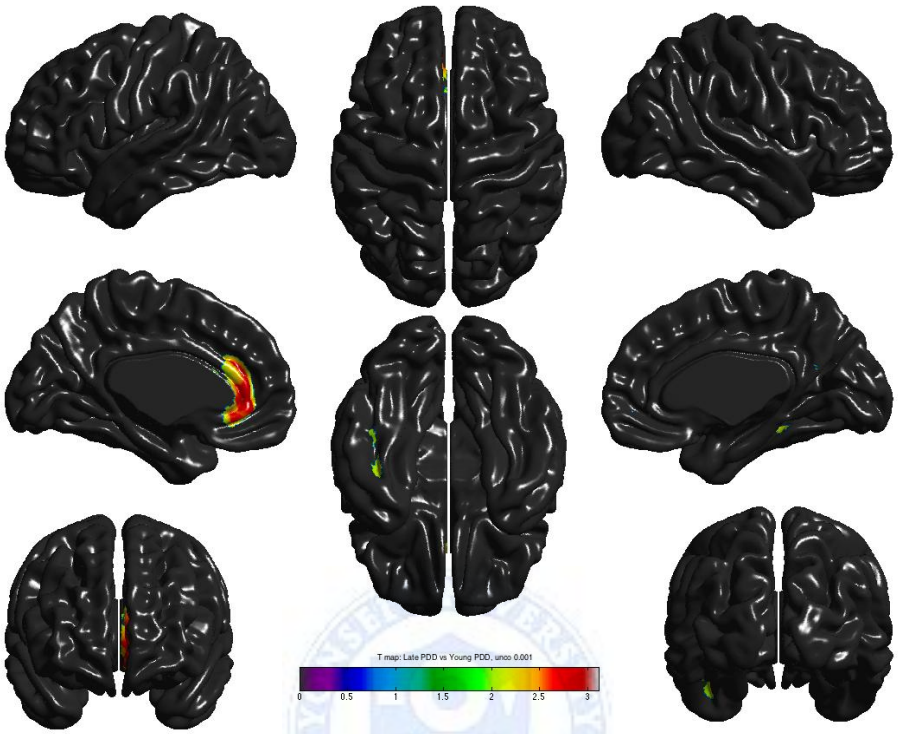

Figure 4. Analysis of cortical thickness using ANCOVA between EOPDD and LOPDD groups after adjusting for age. Colored areas indicate statistical significance. Significant group-by-age interaction was observed in the left anterior cingulate gyrus and right medial temporal lobe.

4**. Comparison of SI volume between the EOPDD and LOPDD groups**

The mean normalized SI volumes among groups are shown in Table 7. Compared with the young control group, the mean normalized SI volume (nSI) was significantly decreased in EOPDD patients ($p<0.001$). In LOPDD patients, nSI was decreased compared to the control group, although the difference was not statistically significant. A significant group-by-age interaction effect was observed, suggesting that SI volume was decreased in the EOPDD group after adjusting for the aging effect ($p=0.044$).

Table 7. Comparison of volumes of substantia innominata between EOPDD and LOPDD patients using the group-by-age interaction effects

	EOPDD			LOPDD			P of interaction
	Patients (n=25)	Control (n=39)	p-value	Patients (n=40)	Control (n=52)	p-value	
Normalized SI volume	6.76 (1.11)	7.81 (0.79)	<0.001	6.47 (1.58)	6.80 (0.90)	0.212	0.044

Values expressed as mean (standard deviation).

EOPDD: Early onset Parkinson's disease dementia, LOPDD: Late onset Parkinson's disease dementia

IV. DISCUSSION

The present study demonstrated for the first time that EOPDD patients had a poorer cognitive performance on attention and visual recognition memory tests after adjusting for aging effects compared with LOPDD patients. In addition, an analysis of cortical thickness and SI volume between the EOPDD and LOPDD groups based on interaction effect showed that EOPDD patients exhibited cortical thinning in the left anterior cingulate gyrus and a small area of the right mesial temporal lobe as well as a smaller SI volume than the LOPDD patients. Our data suggest that EOPDD patients exhibit poorer cognitive performance and more severe atrophy in the cortex and SI compared with LOPDD patients, implying that pathological burden responsible for dementia in PD patients is greater in EOPDD patients.

A comprehensive neuropsychological test showed that EOPDD patients had poorer performance on attention tests compared with LOPDD patients. Importantly, attention is a hallmark of PD-related cognitive dysfunction; thus, underlying impaired attention in PD is a key factor contributing to the development of cognitive fluctuation, visual hallucinating, frontal executive dysfunction, or visuospatial dysfunction.[3,28] Impaired attention has also been associated with a more rapid cognitive decline in patients with PD.[3] In terms of neuroanatomical correlates, the cholinergic system arising from the SI is closely associated with attention in patients with PD.[29,30] Results have shown that the SI undergoes degeneration in the early stages of PD,[31] with its volume being a significant predictor of PDD,[32] and patients with PDD have a profound cholinergic deficit compared with PD patients without cognitive deficits.[5] In the present study, the EOPDD group showed a significant volume reduction in the SI compared with the LOPDD group, which may be associated with attention deficits in the EOPDD patients.

In addition, patients with EOPDD demonstrated cortical thinning in the anterior cingulate gyrus compared with LOPDD patients. Neural substrates of attention control are extensive networks of regions that include prefrontal and parietal cortices,[33] superior colliculus,[34] posterior parietal cortex,[35] and cingulate cortex.[36] Of

those, the anterior cingulate gyrus is reciprocally connected with frontoparietal regions implicated in cognitive control and maintenance of goals.[37] [37] Particularly, the anterior cingulate gyrus plays a role in identifying the motivational relevance of extrapersonal events and in sustaining the level of effort needed for execution of attentional tasks,[38,39] thus being a critical component of an integrated network for modulation of directed attention. Taken together, these results suggest that greater atrophy in the SI and the anterior cingulate gyrus is possibly due to increased pathological burden in EOPDD compared with LOPDD and may lead to attention deficits in EOPDD patients.

We also found that EOPDD patients showed poorer performance on visual recognition memory tests. The mesial temporal structures are required to recognize previously encountered items.[40] Additionally, recent studies highlights the role of striatum and prefrontal cortex on memory retrieval.[41] In patients with Alzheimer's disease, a neuroimaging study showed that poor retrieval performance is related to decreased connectivity between parahippocampal regions and frontal areas.[42] In terms of neuroanatomical correlates, the present study results suggest that cortical thinning patterns involving the right temporal area observed in patients with EOPDD compared with LOPDD may be attributed to visual recognition memory dysfunction.

In cortical thickness analysis, the EOPDD and LOPDD groups showed cortical thinning in bilateral frontotemporoparietal areas compared with controls; however, the LOPDD group showed more widespread cortical thinning involving entire cortical areas, more significantly in the prefrontal cortex. Considering the extent of cortical thinning in the LOPDD group compared with controls, the major contributor of cortical thinning between the EOPDD and LOPDD patients is the aging process. This is consistent with a previous study of cortical thinning in aging, showing prominent prefrontal thinning and relative sparing of temporal and parahippocampal cortices.[43]

When adjusting aging effect, our analysis revealed that the EOPDD group exhibited a significant cortical thinning in left anterior cingulate gyrus and right

medial temporal areas as well as smaller SI volume relative to the LOPDD group. Interestingly, these areas seem to be one of key areas vulnerable to the development of dementia in PD. Previous neuroimaging study showed non-demented patients with PD showed more accelerated rate of cortical thinning in bilateral fronto-temporal areas compared to controls, which represent early PD-related degenerative changes.[44] Hanganu et al showed PD-mild cognitive impairment(MCI) group exhibited increased atrophy and changes of local surface area in the bilateral occipital, left temporal, and frontal cortices; whereas the PD non-MCI group exhibited only unilateral thinning and decreased surface area in the occipital lobe and in the frontal cortex.[45] Functional neuroimaging study also showed demented PD patients showed significant perfusion decrements in all cortical areas, whereas non-demented PD cohorts showed reductions limited to the frontal lobe area.[46] Accordingly, these results imply that pathologic substrate related to cognitive decline in PDD may exhibit a unique spreading of cortical thinning pattern involving fronto-temporal areas.

Moreover, a longitudinal neuroimaging study demonstrated that cortical thinning in anterior cingulate areas and the superior frontal area is a significant baseline predictor of development of dementia.[47] Additionally, our previous study demonstrated that the baseline volume of the SI is a significant predictor of PDD.[6] Accordingly, these results imply that anatomical correlates related to development of dementia in patients with PD may exhibit a similar contribution to the development of EOPDD. However, considering that posterior cortical atrophy or hypometabolism is also an important factor in PDD,[1,4] posterior cortical lobe-based pathologies may exert minimal influence on EOPDD.

Many pathologic studies investigated chronological changes of PD-related pathologies. Braak and colleagues proposed that caudorostral progression of Lewy body/Lewy neurites are linked to cognitive dysfunction in subset of patients with PDD.[48,49] According to this scheme, the development of dementia is inevitable in final stage of PD. However, recent studies showed that the incidence and the severity of PDD are largely variable among the patients, and a portion of PD

patients even remain non-demented.[50] Pathologic heterogeneity among the patients with PDD may contribute to the clinical heterogeneity of PDD in terms of chronological aspects. Majority of pathologic studies pointed out that cortical Lewy bodies are the best pathological correlates of dementia in PD.[51,52] On the other hand, other investigators argued that only small portion of patients with cortical Lewy body showed clinical symptoms of dementia, suggesting alpha-synuclein-positive structures are not definite markers of neuronal dysfunction.[53] Especially, concurrent Alzheimer's disease (AD) pathology appears to be significantly correlated with moderate to severe dementia and negatively correlated with survival.[54] Moreover, combination of Lewy body pathology and AD pathology was suggested to be a better neuropathological correlate of PDD than any of the pathologies in isolation,[55] and combined AD pathology was closely associated with faster progression to dementia in PD.[56] Importantly, Irwin et al,[52] recently showed that a large number of PDD patients demonstrated AD pathologies at a higher correlation with older age in PD, suggesting that LOPDD patients are at greater risk of comorbid AD. Subsequently, comorbid AD in EOPDD patients may be less of a risk and not solely a consequence of PD pathological burden. A future study using clinicopathological correlation in patients with earlier cognitive dysfunction would advance the understanding of pathobiology of cognitive decline in PD patients.

This study had several limitations. First, this study was not based on autopsy-proven data; thus, we cannot draw a solid conclusion regarding pathological substrates responsible for EOPDD. Second, in cortical thickness analysis, significant clusters were observed using a relatively liberal threshold; therefore, we could not exclude the possibility of false positives. This might be partly due to the small sample size of EOPDD patients, and other imaging analyses used to evaluate microstructural abnormality or functional network changes with a large sample size are warranted to resolve this issue. Third, due to this study's cross-sectional design, a longitudinal change in cognitive performance between the EOPDD and LOPDD groups is lacking.

V. CONCLUSION

Our data showed that EOPDD patients had severe cognitive deficit on attention and visual cognitive memory tests and cortical thinning in anterior cingulate and temporal areas compared with LOPDD patients. Additionally, SI volume was significantly decreased in the EOPDD group, which is correlated with attentional and cognitive deficits in this patient group. These results imply that PD-related pathological burden responsible for dementia in PD patients may be greater in EOPDD patients.

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ABSTRACT(IN KOREAN)

조발성 파킨슨병치매와 만발성 파킨슨병치매 환자에서의 신경인지검사 및 대뇌피질 두께 변화에 대한 후향적 비교연구

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김영광

파킨슨병 환자에서의 치매 발생에 있어 고령이 위험인자임은 잘 알려져 있으나, 연령에 따른 변화가 파킨슨병치매 환자들에서 신경인지검사 소견 및 병리학적 소견에 어떤 영향을 미치는지는 아직도 불확실하다. 본 저자들은 116명의 파킨슨병치매 환자와 121명의 정상인지기능을 가진 대조군을 70세를 기준으로 2개의 군으로 나누어 후향적 비교연구를 실시하였다. 39명의 환자는 70세 미만이었으며(조발성 파킨슨병치매 군), 77명의 환자는 70세 이상이었다. (만발성 파킨슨병치매 군) 모든 환자에서 신경인지검사를 시행하였다. 65명의 환자에서 3차원 고해상도 T1 강조 자기공명영상을 시행하였으며, 상기 환자군에서 대뇌피질두께에 대한 비교분석 및 대뇌 무명질에 대한 부피분석을 시행하였다. 통계분석을 위하여 연령 및 성별보정을 시행한 121명의 정상 인지기능인 대조군을 구하였다. 신경인지검사 결과와 대뇌피질두께, 무명질 부피는 질병 여부와 연령, 그리고 두 변수간의 상호작용이 있는지를 공분산분석으로 분석하였으며, 교육 수준과 고혈압, 당뇨, 고지혈증의 변수를 공변량으로 설정하였다. 두 군 사이에서 성별, 간이인지기능검사 점수, 교육 수준, 파킨슨병 유병기간, 레보도파 용량 및 기억력 감소 증상의 기간에 있어서 통계적으로 유의한 차이는 없었으며, 만발성 파킨슨병 치매 환자에서 통합된 파킨슨병 평가 점수는 유의하게 낮은 수치를 보였다. 신경인지검사상에서 언어 능력, 시공간 능력, 전두엽 집행기능 영역에서 두 군 사이의 유의한 차이는 없었다. 그러나 나이를 보정하였을 때 거꾸로 따라 외우기 (p=0.011), 시각재인검사에서 (p=0.002) 조발성파킨슨병치매 환자군이 유의하게 낮은 수행능력을 보임을 알 수

있었다. 대뇌피질두께 분석상에서 좌측 전대상피질과 우측 중앙 측두엽에서 나이를 보정했을 때 조발성파킨슨병치매에서 대뇌피질의 두께가 얇아졌음을 알 수 있었다. 또한 나이를 보정하였을 때 조발성파킨슨병치매 환자에서 무명질 부피의 감소가 관찰되었다. 이러한 결과는 조발성파킨슨병치매 군에서 인지기능의 악화와 관련된 영역의 병리학적 변화가 더 심하다는 것을 시사하며, 만발성파킨슨병치매 군에서는 연령변화와 관련된 비교적 광범위한 병리학적 변화를 보임을 시사한다. 본 연구는 두 질병군에서 다른 치료적 접근이 필요함을 보여주는 결과로 사료된다.

핵심되는 말 : 파킨슨병치매, 발생연령, 신경인지검사, 대뇌피질두께