Neuroanatomic basis of amnestic MCI differs in patients with and without Parkinson disease

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ABSTRACT

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We investigated the cognitive profiles and neuroimaging characteristics using voxel-based morphometry (VBM) to explore the neuroanatomic basis of amnestic mild cognitive impairment (aMCI) in patients with Parkinson disease (PD; aMCI–PD^{+}) and without PD (aMCI–PD^{-}). A total of 119 patients with aMCI (aMCI–PD^{-}, $n=78$ and aMCI–PD^{+}, $n=41$) underwent T1-weighted MRI, and the image data were analyzed using VBM. No significant differences in demographic characteristics or general cognition were found between patients with aMCI–PD^{-} and aMCI–PD^{+}. Comparisons of neuropsychological tests between groups revealed that aMCI–PD^{-} patients had lower scores in delayed verbal and visual recognition memory, whereas visuospatial dysfunction was more severe in patients with aMCI–PD^{+}. Gray matter (GM) density in the right temporal and posterior cingular cortices was significantly lower in the aMCI–PD^{-} group compared with controls. In contrast, GM density in the aMCI–PD^{+} group was significantly lower in the precuneus and left prefrontal

and primary motor areas relative to controls. A direct comparison between groups showed that decreased GM density in aMCI–PD^{-} relative to aMCI–PD^{+} was localized in the right temporal and anterior prefrontal areas, whereas decreased GM density in aMCI–PD^{+} relative to aMCI–PD^{-} was involved in the bilateral precuneus, left primary motor, and right parietal areas. Memory decline was correlated with temporal area atrophy in aMCI–PD^{-} patients and with posterior cingulate cortex atrophy in aMCI–PD^{+} patients. Our data suggest that different neuroanatomic systems underlie memory dysfunction in patients with aMCI–PD^{-} and aMCI–PD^{+}.

Key words: amnestic mild cognitive impairment, Parkinson's disease.

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I. INTRODUCTION

Mild cognitive impairment (MCI) is a transitional state between normal aging and dementia that has been used for earlier detection and treatment of dementia.[1] Although several studies have shown that MCI is composed of heterogeneous subtypes and etiologies, amnestic MCI (aMCI) is generally regarded as a pathological precursor to Alzheimer's disease (AD).[2] Recently, several studies have demonstrated that a substantial portion of patients with Parkinson Disease (PD) have quantifiable cognitive deficits that do not meet the criteria for dementia even in the early course of disease; these patients have been categorized as having mild cognitive impairment (PD-MCI).[3, 4] One epidemiologic study showed that about 19% of patients with untreated early PD were classified as MCI.[5] As in AD, patients with PD-MCI have a higher risk of developing dementia.[4]

aMCI is the most common MCI subtype in the general population and also frequently observed in patients with PD, being composed with about 30-50% of

PD-MCI.[3, 6, 7] Furthermore, parkinsonism is more common in people who have MCI than in healthy subjects and aMCI is accompanied by parkinsonism more frequently than the nonamnestic type of MCI,[8, 9] suggesting that parkinsonism and aMCI share a similar pathogenesis. However, whether neuroanatomic basis of memory dysfunction in patients with PD-MCI represent AD type pathology or Lewy bodies is not determined. In this study, with a hypothesis that different pathologies contribute to aMCI in patients with PD and patients without PD, we investigated the cognitive profiles and neuroimaging characteristics using voxel-based morphometry (VBM) to explore the neuroanatomic basis of memory dysfunction in patients having aMCI with (aMCI–PD^{+}) and without PD (aMCI–PD^{-}).

II. MATERIALS AND METHODS

Subjects

Participants were 119 patients with aMCI recruited consecutively from the movement disorders and dementia outpatient clinic at a university hospital. Based on the diagnostic criteria for aMCI and PD,[2,10] patients with aMCI were classified into aMCI–PD^- (n=78) and aMCI–PD^+ (n=41) depending on the presence of PD. Information concerning memory problems and other subjective cognitive deficits was obtained by care giver–based interviews. To determine cognitive subsets in the diagnosis of MCI, we used the Seoul Neuropsychological Screening Battery (SNSB).[11, 12] The SNSB covers the following cognitive subsets: attention (forward and backward digit span and letter-cancellation tests); language and related functions (the Korean version of the Boston Naming Test (K-BNT)[13] and calculation); visuospatial function (drawing an interlocking pentagon and the Rey Complex Figure Test (RCFT)); verbal memory (three-word registration and recall, and the Seoul Verbal Learning Test (SVLT)); visual memory (the RCFT, immediate recall, 20-minnute delayed recall, and recognition); and frontal executive function (motor impersistence, contrasting program, go-no-go test, fist-edge-palm, alternating hand movement, alternating square and triangle, Luria loop, phonemic and semantic Controlled Oral Word Association Test (COWAT), and Stroop test). We considered attention function to be abnormal if at least 2 of the 3 items were abnormal. Abnormal memory function was defined as a score below the 16th percentile of the norm for the delayed recall on the SVLT or RCFT. Language function was considered abnormal if the score on the K-BNT was below the 16th percentile of the norm, and abnormal visuospatial function was defined as a RCFT copying score below the 16th percentile of the norm. The frontal/executive function tests were classified into three groups: motor executive function, COWAT, and the Stroop test. Frontal/executive function was

considered to be abnormal when at least 2 of 3 tests were abnormal. Based on these criteria, the patients were categorized as having single domain (SD) aMCI with only isolated abnormal memory function or multiple domain (MD) aMCI with abnormal memory function and one or more additional cognitive dysfunctions. All patients had scores of Korean version of MMSE (K-MMSE) above the 16th percentile for age and educational appropriate norm. Participants also showed no evidence of abnormal activities of daily living (ADL), judged clinically and by an ADL scale.[14]

Parkinsonian motor symptoms were assessed using the Unified Parkinson`s Disease Rating Scale Part Ⅲ (UPDRS-Ⅲ). Total medication dosages were calculated in levodopa equivalents.[15] Patients having history of offending drugs causing parkinsonism (antipsychotics, gastrointestinal kinetics, antiepileptic drugs, or L-type calcium channel blockers) were excluded. An [^{18}F]FP-CIT PET scan was performed on 30 of aMCI-PD^{+} patients, and all showed decreased dopamine transporter uptake in the posterior putamen.

Exclusion criteria included evidence of focal brain lesions, diffuse white matter hyperintensities, or multiple lacunes in the basal ganglia by MRI. Possible medical comorbidities were excluded by laboratory tests, including thyroid function test, vitamin B12 and folic acid levels, and VDRL test. Healthy age- and gender-matched elderly volunteers were used as controls for VBM analysis (n = 21, age = 70.7 ± 2.7 years). The control subjects had no active neurological disorders, no cognitive complaints, and a minimum score of 28 on the K-MMSE. We received approval from 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.

MRI acquisition

All scans of healthy controls and patients 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). Head motion was minimized with restraining foam pads provided by the manufacturer. A high-resolution T1-weighted MRI volume data set was obtained from all subjects using 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 mm3 voxels; TE, 4.6 ms; TR, 9.6 ms; flip angle, 8°; slice gap, 0 mm.

VBM of Gray Matter

VBM was conducted using DARTEL[16] in SPM8 software (Institute of Neurology, University College London, UK). A group of gray matter (GM) templates was generated from control groups, to which all individual GM was spatially normalized. Spatially normalized GM maps were modulated by the Jacobian determinant of the deformation field to adjust volume changes during nonlinear transformation.[17] These modulated GM maps were smoothed using a 6-mm full-width half-maximum isotropic Gaussian kernel. Regional volume differences were determined using one-way analysis of variance at every voxel in the GM from patients with aMCI–PD^- and MCI–PD^+ and healthy controls where age and K-MMSE were included as covariates in analysis of covariance. The total volume of GM did not differ among groups (controls, 597 ± 59 mL; aMCI–PD^-, 602 ± 68 mL; and aMCI–PD^+, 592 ± 67 mL). Additionally, we searched for significant brain areas in which GM density correlated with memory functions (SVLT or RCFT) using multiple regression model covariated with age and K-MMSE. Statistical significance was determined at uncorrected P <0.001 with cluster size> 50 mm^3.

Statistical analysis

The χ^2 and *t* tests were used for categorical and continuous variables, respectively. Statistical analyses were performed using commercially available software (SPSS, version 13.0), and a two- tailed $P < 0.05$ was considered significant.

III. RESULTS

Comparison of whole patients with aMCI–PD$^-$ and aMCI–PD$^+$

The demographic characteristics of the patients are shown in table 1. No significant differences in age, gender, education level, duration of memory complaints, K-MMSE scores, clinical dementia rating (CDR) scores, or the sum of boxes score of the CDR (SOB) were found between patients with aMCI–PD$^-$ and those with aMCI–PD$^+$. The mean duration of parkinsonism, UPDRS Ⅲ score, and levodopa equivalents dose in patients with aMCI–PD$^+$ were 43.3 months, 19.9, and 205.9 mg. No patients were receiving cholinesterase inhibitors. Comparison of neuropsychological tests between groups showed that aMCI–PD$^-$ patients had lower scores in delayed verbal and visual recognition memory (each p=0.04), whereas visuospatial dysfunction was more severe in the aMCI–PD$^+$ group (p=0.02). Additionally, impairments in alternating square and triangle test were more prevalent in patients with aMCI–PD$^+$ than in those with aMCI–PD$^-$ (table 2). No other significant differences in cognitive function were found between groups.

VBM analysis demonstrated that patients with aMCI–PD$^-$ had significantly decreased GM density in the right temporal, left posterior cingulate, and right paracentral areas compared to controls (figure 1A). In patients with aMCI–PD$^+$, the GM density was significantly lower in the precuneus, left prefrontal, and left primary motor cortex relative to that of controls (figure 1B). On a direct comparison between groups, decreased GM density in aMCI–PD$^-$ relative to aMCI–PD$^+$ was localized in the right temporal and anterior prefrontal areas (figure 1C), whereas decreased GM density in aMCI–PD$^+$ relative to aMCI–PD$^-$ was observed in the bilateral precuneus, left primary motor, and right parietal areas (figure 1D). Anatomic location of areas showing a significant difference in GM density is listed in table 3.

Table 1. Demographic characteristics between amnestic mild cognitive impairment patients with PD (aMCI-PD$^+$) and without PD (aMCI-PD$^-$)

	aMCI-PD$^+$ (n=41)	aMCI-PD$^-$ (n=78)	*p*-value
Age (yr)	71.3 (6.3)	70.5 (8.0)	NS
Gender (number of men)	21	32	NS
Education durations (yrs)	8.9 (4.7)	9.4 (4.9)	NS
Memory impairment duration (months)	20.4 (19.4)	23.1 (18.9)	NS
K-MMSE	25.4 (3.4)	25.1 (2.4)	NS
CDR	0.5 (0.0)	0.5 (0.0)	NS
SOB	1.7 (0.9)	1.7 (0.9)	NS

Values are expressed as mean (standard deviation).

K-MMSE=the Korean version of the Mini-Mental State Examination;

CDR=Clinical Dementia Rating Scale;

SOB=the sum of boxes score of the CDR; NS=not significant

Table 2. Neuropsychological data in patients with amnestic mild cognitive impairment with PD (aMCI-PD$^+$) and without PD (aMCI-PD$^-$)

Test	aMCI-PD$^+$ (n=41)	aMCI-PD$^-$ (n=78)	*p*-value
Attention			
Digit span (forward)	5.4 (1.3)	5.4 (1.4)	NS
Digit span (backward)	3.2 (0.8)	3.4 (1.0)	NS
Digit span total	8.6 (1.8)	8.7 (2.1)	NS
Letter cancellation*	12	16	NS
Language and related function			
K-BNT	42.6 (8.8)	40.6 (10.9)	NS

Repetition	14.1 (1.0)	14.2 (1.4)	NS
Calculation	10.0 (2.4)	10.0 (2.3)	NS
Interlocking pentagon*	11	15	NS
Visuospatial function			
RCFT	28.4 (9.3)	32.2 (6.2)	0.02
Verbal memory function			
3 words registration	3.0 (0.2)	3.0 (0.0)	NS
3 words recall	1.6 (1.2)	1.2 (1.1)	NS
SVLT			
Immediate recall	15.4 (4.3)	15.1 (4.8)	NS
Delayed recall	3.2 (2.3)	2.3 (2.3)	0.04
Recognition	18.6 (2.2)	18.3 (2.6)	NS
Visual memory function (RCFT)			
Immediate recall	8.4 (6.8)	8.9 (6.5)	NS
Delayed recall	8.9 (6.8)	8.2 (6.5)	NS
Recognition	18.2 (1.8)	17.4 (2.2)	0.04
Frontal executive function			
Contrasting program	19.1 (1.8)	19.1 (3.1)	NS
Go-no-go	17.6 (4.2)	17.6 (3.9)	NS
Phonemic generative naming	22.3 (10.2)	22.9 (10.0)	NS
COWAT (Animal)	12.7 (3.3)	12.7 (4.2)	NS
COWAT (supermarket)	14.3 (4.4)	14.4 (4.1)	NS
Word stroop test	104.2 (12.7)	107.4 (11.0)	NS
Color stroop test	59.8 (26.5)	63.2 (26.9)	NS
Motor impersistence*	2	1	NS
Fist-edge-palm *	8	9	NS

Alternating hand movement*	4	19	NS
Alternating square and triangle*	14	8	0.001
Luria loop*	6	7	NS

Values are expressed as mean (standard deviation). *Data were represented by the number of patients with abnormal score. K-BNT= the Korean version of Boston Naming Test; RCFT= Rey Complex Figure Test; SVLT= Seoul Verbal Learning Test; COWAT= the Controlled Oral Word Association Test; NS= not significant.

Table 3. Anatomic location of areas showing significant difference in gray matter density among controls, amnestic mild cognitive impairment patients with PD (aMCI-PD$^+$), and without PD (aMCI-PD$^-$)

Talairach Coordinates				Anatomical location	Cluster size (κ)	Z score
X	Y	Z	Side			
Control > aMCI-PD$^-$						
26	-6	-23	Right	Hippocampus	116	3.40
48	-18	-10	Right	Superior temporal gyrus	264	3.85
-7	-33	45	Left	Posterior cingulate gyrus	177	3.75
1	-31	60	Right	Paracentral lobule	72	3.47
Control > aMCI-PD$^+$						
-49	33	15	Left	Middle frontal gyrus	70	4.04
-59	-3	22	Left	Precentral gyrus	81	3.37
6	-66	28	Right	Precuneus	271	4.76
aMCI-PD$^+$ > aMCI-PD$^-$						
34	3	-25	Right	Parahippocampal gyrus	99	3.61
-36	8	-14	Left	Inferior frontal gyrus	55	3.34
37	10	-12	Right	Inferior frontal gyrus	81	3.54
-27	55	-12	Left	Superior frontal gyrus	410	4.19
-37	61	-11	Left	Middle frontal gyrus	410	5.00
9	70	3	Right	Superior frontal gyrus	295	3.94
aMCI-PD$^-$> aMCI-PD$^+$						
4	-60	21	Right	Precuneus	392	3.64
-1	-64	24	Left	Precuneus	392	4.11
6	-66	30	Right	Cuneus	392	4.54
40	-59	35	Right	Angular gyrus	62	4.10
-53	-7	38	Left	Precentral gyrus	201	3.67

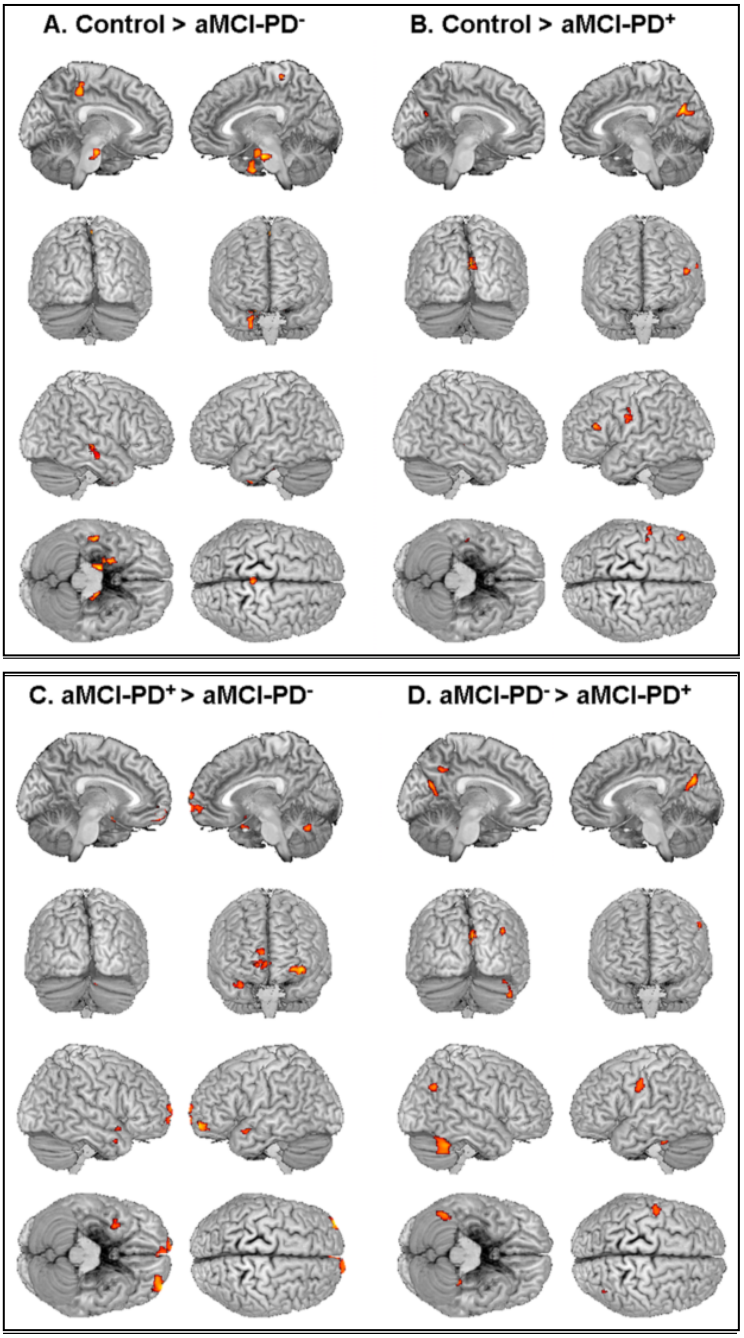

Figure 1. VBM analysis in patients with amnestic mild cognitive impairment patients with PD (aMCI-PD^{+}) and without PD (aMCI-PD^{-}). Areas of decreased

gray matter density in patients with aMCI-PD$^-$ (A) and aMCI-PD$^+$ (B), compared with healthy subjects. A direct comparison between the two groups revealed that decreased gray matter density in aMCI–PD$^-$ relative to aMCI–PD$^+$ was localized in the right temporal and anterior prefrontal areas (C), whereas decreased gray matter density in aMCI–PD$^+$ relative to aMCI–PD$^-$ was involved in the bilateral precuneus, left primary motor, and right parietal areas (D).

Comparison of patients with single domain aMCI–PD$^-$ and aMCI–PD$^+$

Of the 119 patients with aMCI, 44 with aMCI–PD$^-$ and 15 with aMCI–PD$^+$ were subclassified into single domain aMCI. No significant differences in demographic characteristics were found between groups. The neuropsychological tests between groups showed that verbal and visual recognition were more severely impaired in patients with single domain aMCI–PD$^-$ than in those with single domain aMCI–PD$^+$ (table 4).

VBM analysis demonstrated that compared to the controls, patients with single domain aMCI–PD$^-$ had significantly decreased GM density in the right temporal and posterior cingulate areas extending into paracentral areas, whereas patients with single domain aMCI–PD$^+$ had significantly decreased GM density in the paracentral lobule extending into posterior cingulate and right prefrontal areas (figure 2). On a direct comparison between the groups, single domain aMCI–PD$^-$ showed decreased GM density in the right prefrontal areas and posterior and middle cingulate areas relative to single domain aMCI–PD$^+$, whereas decreased GM density in single domain aMCI–PD$^+$ relative to single domain aMCI–PD$^-$ was localized in the left posterior cingulate and left primary motor areas (figure 2).

Table 4. Neuropsychological data in patients with single domain amnestic mild cognitive impairment with PD (SD aMCI-PD^{+}) and without PD (SD aMCI-PD^{-})

Test	SD aMCI-PD^{+} (n=15)	SD aMCI-PD^{-} (n=45)	*p*-value
Attention			
Digit span (forward)	5.7 (1.1)	5.7 (1.5)	NS
Digit span (backward)	3.3 (0.9)	3.4 (1.1)	NS
digit span total	8.9 (1.6)	9.1 (2.2)	NS
Language and related function			
K-BNT	46.1 (5.5)	45.3 (7.7)	NS
Repetition	14.5 (0.7)	14.3 (1.5)	NS
Calculation	10.7 (1.5)	10.0 (2.4)	NS
Visuospatial function			
RCFT	32.8 (4.6)	32.4 (4.6)	NS
Verbal memory function			
3 words registration	3.0 (0.0)	3.0 (0.0)	NS
3 words recall	1.9 (1.1)	1.5 (1.1)	NS
SVLT			
Free recall	17.8 (4.1)	15.6 (5.1)	NS
Delayed recall	3.7 (2.5)	2.8 (2.7)	NS
Recognition	19.7 (2.0)	18.1 (2.7)	0.04
Visual memory function (RCFT)			
Immediate recall	6.9 (6.2)	9.8 (6.9)	NS

Delayed recall	7.2 (6.1)	8.7 (6.8)	NS
Recognition	19.1 (1.2)	17.5 (2.4)	0.01
Frontal executive function			
Contrasting program	19.7 (1.0)	19.5 (2.2)	NS
Go-no-go test	18.7 (2.8)	17.8 (3.5)	NS
Phonemic generative naming	28.5 (8.8)	25.3 (11.1)	NS
COWAT (Animal)	13.4 (4.0)	13.8 (4.5)	NS
COWAT (supermarket)	16.1 (4.7)	15.7 (3.9)	NS
Word stroop test	106.9 (10.0)	107.0 (12.9)	NS
Color stroop test	69.9 (22.5)	65.5 (27.9)	NS

K-BNT: the Korean version of Boston Naming Test, RCFT: Rey Complex Figure Test, SVLT: Seoul Verbal Learning Test, COWAT: the Controlled Oral Word Association Test.

Values are expressed as mean (standard deviation), NS: not significant.

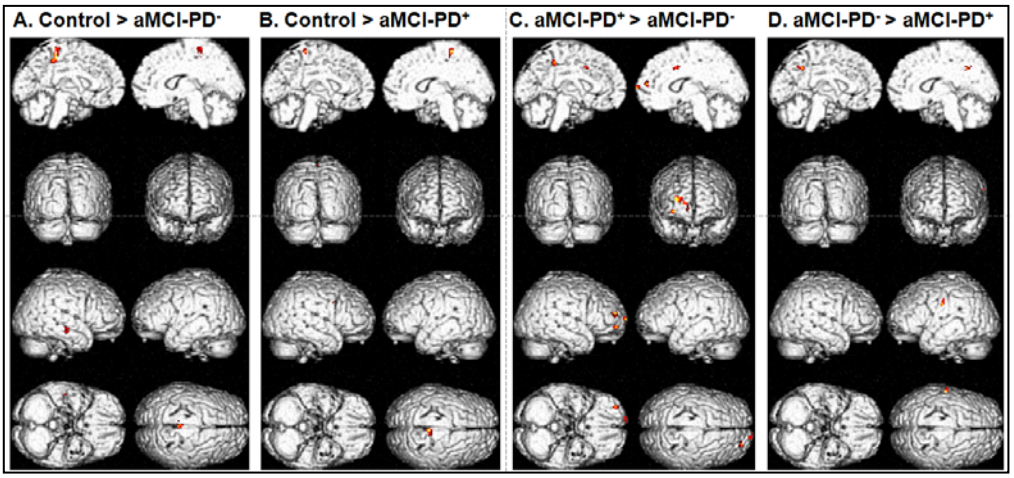

Figure 2. VBM analysis in patients with single domain amnestic mild cognitive impairment patients with PD (SD aMCI-PD^{+}) and without PD (SD aMCI-PD^{-}). Areas of decreased gray matter density in patients with SD aMCI-PD^{-} (A) and

SD aMCI-PD^{+} (B), compared with healthy subjects. A direct comparison between the two groups revealed that decreased gray matter density in SD aMCI–PD^{-} was localized in the right prefrontal areas and posterior and middle cingulate areas relative to SD aMCI–PD^{+}, whereas decreased GM density in SD aMCI–PD^{+} relative to SD aMCI–PD^{-} was localized in the left posterior cingulate and left parietal areas (C and D).

Comparison of patients with multiple domain aMCI–PD^{-} and aMCI–PD^{+}

Sixty patients with aMCI (34 with aMCI–PD^{-} and 26 with aMCI–PD^{+}) were subclassified as having multiple domain aMCI. No other significant differences in demographic characteristics were found between the groups. The neuropsychological tests between groups revealed that aMCI–PD^{-} patients had lower scores in delayed verbal memory and the K-BNT, whereas multiple domain aMCI–PD^{+} patients showed a worse performance in visuospatial function (table 5).

Compared to the controls, patients with MD aMCI–PD^{-} had significantly decreased GM density in the bilateral temporal, left orbitofrontal, and right lingual areas, whereas decreased GM density in patients with MD aMCI–PD^{+} was localized in the posterior and anterior cingulate areas (figure 3). A direct comparison between the groups revealed that MD aMCI–PD^{-} showed decreased GM density in the bilateral temporal and right parietal areas relative to MD aMCI–PD^{+}, whereas decreased GM density in MD aMCI–PD^{+} relative to MD aMCI–PD^{-} was localized in the posterior and anterior cingulate, occipital, left motor and left insular areas (figure 3).

Table 5. Neuropsychological data in multiple domain amnestic mild cognitive impairment patients with PD (MD aMCI-PD^{+}) and without PD (MD aMCI-PD^{-})

Test	MD aMCI-PD^{+} (n=26)	MD aMCI-PD^{-} (n=43)	*p*-value
Attention			
Digit span (forward)	5.3 (1.4)	4.8 (1.4)	NS
Digit span (backward)	3.1 (0.7)	3.1 (1.1)	NS
digit span total	8.4 (1.9)	7.9 (2.2)	NS
Language and related function			
K-BNT	40.6 (9.7)	34.1 (11.0)	0.02
Repetition	13.9 (1.1)	13.6 (1.6)	NS
Calculation	9.4 (2.7)	9.1 (3.2)	NS
Visuospatial function			
RCFT	25.9 (10.4)	29.7 (9.0)	NS
Verbal memory function			
3 words registration	3.0 (0.3)	3.0 (0.2)	NS
3 words recall	1.4 (1.2)	0.8 (1.0)	0.04
SVLT			
Free recall	14.0 (3.8)	13.8 (4.6)	NS
Delayed recall	2.9 (2.2)	1.6 (2.0)	0.01
Recognition	17.9 (2.1)	18.1 (2.7)	NS
Visual memory function (RCFT)			
Immediate recall	9.4 (7.1)	6.7 (5.5)	0.09

Delayed recall	9.8 (7.1)	6.7 (5.8)	0.05
Recognition	17.7 (1.9)	16.8 (2.3)	NS
Frontal executive function			
Contrasting program	18.8 (2.1)	18.0 (4.8)	NS
Go-no-go test	16.9 (4.7)	15.6 (6.1)	NS
Phonemic generative naming	18.8 (9.4)	19.1 (10.0)	NS
COWAT (Animal)	12.4 (2.9)	11.6 (4.3)	NS
COWAT (supermarket)	13.2 (3.9)	12.3 (4.1)	NS
Word stroop test	102.8 (14.0)	103.4 (19.0)	NS
Color stroop test	54.4 (27.2)	56.9 (27.8)	NS

K-BNT: the Korean version of Boston Naming Test, RCFT: Rey Complex Figure Test, SVLT: Seoul Verbal Learning Test, COWAT: the Controlled Oral Word Association Test.

Values are expressed as mean (standard deviation), NS: not significant.

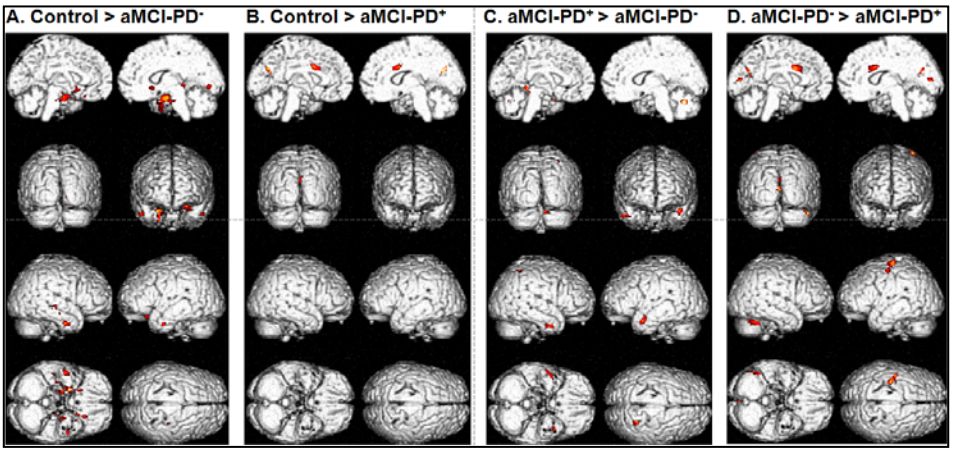

Figure 3. VBM analysis in patients with multiple domain amnestic mild cognitive impairment with PD (MD aMCI-PD+) and without PD (MD aMCI-PD-). Areas of decreased gray matter density in patients with MD

aMCI-PD- (A) and MD aMCI-PD+ (B), compared with healthy subjects. A direct comparison between the two groups revealed that decreased GM density in MD aMCI–PD- was localized in the bilateral temporal and right parietal areas relative to MD aMCI–PD+, whereas decreased GM density in MD aMCI–PD+ relative to MD aMCI–PD- was localized in the posterior and anterior cingulate, occipital, left motor and left insular areas (D and D).

Correlation of cortical atrophy and memory dysfunction in patients with aMCI–PD$^-$ and aMCI–PD$^+$

In patients with aMCI–PD$^-$, a decline in verbal memory was positively correlated with cortical atrophy in the bilateral temporal and parietal areas, and visual memory decline was positively correlated with the bilateral temporal, right prefrontal, and right insular areas (figure 4A). In patients with aMCI–PD$^+$, verbal memory decline was positively correlated with cortical atrophy in the posterior cingulate area (figure 4B); however, we did not detect a correlation between visual memory and cortical atrophy at this discrimination threshold.

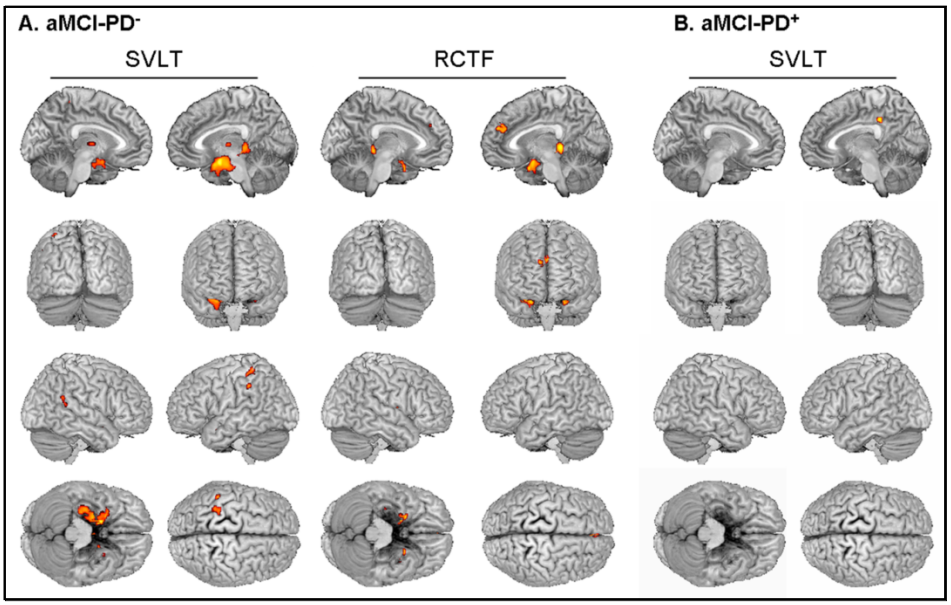

Figure 4. Correlation between gray matter density and memory dysfunction in patients with amnestic mild cognitive impairment with PD (aMCI-PD^{+}) and without PD (aMCI-PD^{-}). In patients with aMCI-PD, a decline in verbal memory (Seoul Verbal Learning Test, SVLT) was positively correlated with cortical atrophy in the bilateral temporal and parietal areas, and visual memory (Rey Complex Figure Test, RCFT) decline was positively correlated with the bilateral temporal, right prefrontal, and right insular areas (A). In patients with aMCI–PD^{+}, verbal memory decline was positively correlated with cortical atrophy in the posterior cingulate area (B).

IV. DISCUSSION

Our study showed that the pattern of cortical atrophy differed between patients with aMCI–PD$^-$ and aMCI–PD$^+$. Cortical atrophy in the aMCI–PD$^-$ group was mainly localized in the temporal area, whereas atrophy in the posteromedial cortical areas including the posterior cingulate and precuneus was primarily involved in the aMCI–PD$^+$ group. Furthermore, a distinct pattern of cortical atrophy was correlated with memory dysfunction in each group, demonstrating the temporal areas in the aMCI–PD$^-$ group and the posterior cingulate area in the aMCI–PD$^+$. These data suggest that while memory dysfunction as assessed by detailed neuropsychological evaluation was similar in these patients, aMCI–PD$^-$ and aMCI–PD$^+$ may have different neuroanatomic basis of memory dysfunction.

As expected, cortical atrophy in patients with aMCI–PD$^-$ was observed in the temporal and posterior cingulate areas because most aMCIs share AD pathology as a precursor of AD.[18, 19] In contrast, the pattern of decreased GM density in patients with aMCI–PD$^+$ was mainly localized in the posteromedial cortical areas with no evidence of temporal area involvement. The different patterns of cortical atrophy between aMCI–PD$^-$ and aMCI–PD$^+$ were more evident on a direct comparative analysis of GM density, where more widespread cortical involvement in the temporal and prefrontal areas was exhibited in patients with aMCI–PD$^-$, and relative localization of cortical atrophy in the posteromedial areas within the left motor and right parietal areas was evident in those with aMCI–PD$^+$. The memory domains on the neuropsychological tests were more severely impaired in patients with aMCI–PD$^-$ than in those with aMCI–PD$^+$, which may be in accordance with the different patterns of cortical atrophy between groups, especially with respect to involvement of the temporal areas. Nevertheless, the atrophy in the posteromedial cortical areas was greater in aMCI–PD$^+$ relative to aMCI–PD$^-$ although memory function in the patients with

aMCI–PD^{+} was less impaired. This may suggest that neuroanatomic basis of memory dysfunction is different between the two groups; in patients with aMCI–PD^{-}, temporal and posterior cingulate areas or their circuit play an important role, whereas posteromedial cortical areas including the posterior cingulate or precuneus appear to be key mediators of memory in patients with aMCI–PD^{+}.

Along with the temporal cortex, posteromedial cortical areas are known to be functionally connected with entorhinal cortex and to play a key role in memory function.[20, 21] Pathology and neuroimaging studies have shown that these areas act as induction sites for AD pathologies,[22, 23] and recent in vivo imaging studies have also demonstrated a significant increase in the binding of β-amyloid ligand in the temporal and posterior cingulate regions in aMCI-PD^{-}.[24, 25] In contrast, little is known about pathologic substrates involved in aMCI-PD^{+}, although recent pathological studies demonstrated that α-synuclein-positive Lewy bodies rather than AD pathologies play an important role in dementia in patients with PD.[26, 27] Despite limited data, one pathological study argued that the number of Lewy bodies in the cingulate cortex was mostly associated with the cognitive impairment in PD.[28] Additionally, a recent functional neuroimaging study demonstrated that cerebral perfusion in patients with aMCI-PD^{+} decreased significantly in the posterior cortical regions, including the parietal and occipital areas, compared to that of controls or patients with aMCI-PD^{-}.[29] Interestingly, Griffith el al.[30] reported that the brain magnetic resonance spectroscopy profiles of the posterior cingulate cortex were distinctly different between patients with AD and those with PD-dementia; despite similar impairment in neuronal integrity between groups, patient with PD-dementia showed decreased glutamate, whereas AD patients showed an increased in a marker of gliosis. They argued that this difference might potentially reflect different underlying neuropathology. Taken together with our finding that the atrophy in the

posteromedial cortical areas is greater in aMCI–PD^{-} than in aMCI–PD^{+}, this may suggest that the pathological burden in these areas is greater in aMCI–PD^{-} than in aMCI–PD^{+}. Accordingly, it is inferred that posteromedial cortical areas may act as a pathological induction site for aMCI in patients with PD without involvement of the temporal cortex, which may underlie the difference in atrophic patterns and cognitive profiles between aMCI–PD^{-} and aMCI–PD^{+}.

The overall patterns of cortical atrophy in the single domain and multiple domain aMCI subgroups were similar to atrophic patterns observed in aMCI patients. In patients with single domain aMCI, cortical atrophy was largely localized in the temporal and posteromedial areas in aMCI–PD^{-} and in the posteromedial areas in aMCI–PD^{+}. Cortical atrophy was more extensive in multiple domain aMCI, involving the entire temporal, lingual, and orbitofrontal areas in the aMCI–PD^{-} subgroup and extending into the anterior cingulate cortex in the aMCI–PD^{+} subgroup. On analyzing correlation between cortical atrophy and memory dysfunction, temporal atrophy was mainly associated with memory decline in patients with aMCI–PD^{-} as previously reported,[31, 32] whereas atrophy in extratemporal areas involving the posterior cingulate was correlated with memory declines in patients with aMCI–PD^{+}. Accordingly, the temporal area is not involved in the memory dysfunction of patients with aMCI–PD^{+}, further supporting the argument that different anatomic substrates underlie aMCI in patients with PD and those without PD.

In this study, the primary motor area was one of the areas showing different atrophic patterns between the aMCI–PD^{-} and aMCI–PD^{+} groups. The motor cortex and supplementary motor areas, along with basal ganglia circuits, play important roles as output factors during the movement process, and parkinsonian motor symptoms are known to be associated with dysfunction in these areas.[33] Thus, cortical atrophy in the motor cortex observed in aMCI–PD^{+} patients seems to be a reflection of parkinsonian motor symptoms rather than

cognitive status.

The strengths and limitations of the present study need to be addressed. With a relatively large case series, dopamine transporter imaging was used to determine the underlying PD pathology in 30 subjects with aMCI–PD^{+}. Nevertheless, this study is not autopsy-proven data; thus, we could not exclude the influence of AD-like pathology in our aMCI–PD^{+} group because some proportion of aMCI is known to accompany parkinsonism, and parkinsonism in aMCI is known to be a risk for development of AD.[8, 9] Second, this study was not longitudinal, and our results should be interpreted with caution, especially with respect to whether patients with aMCI-PD^{-} and aMCI-PD^{+} will develop AD and PD-dementia. Third, the pathologic substrates leading to the different neuroanatomical bases for memory dysfunction in the two groups were not determined, and future studies using functional imaging with FDG and PiB PET should address this issue. Finally, the low educational level of the current elderly Korean population, which is associated with the sociopolitical circumstances of their upbringing, may have led to the rather lower mean MMSE score relative to MCI studies in Western populations.

V. CONCLUSION

Our data suggest that neuroanatomic basis for memory dysfunction might differ between aMCI–PD^{-} and aMCI–PD^{+}, exhibiting mainly involvement in the temporal area with posteromedial cortex in the former and in the posteromedial areas in the latter.

REFERENCES

1. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. Arch Neurol 2009;66:1447-55.

2. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985-92.

3. Caviness JN, Driver-Dunckley E, Connor DJ, et al. Defining mild cognitive impairment in Parkinson's disease. Mov Disord 2007;22:1272-7.

4. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord 2006;21:1343-9.

5. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology 2009;72:1121-6.

6. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Stern MB. Evidence for impaired encoding and retrieval memory profiles in Parkinson disease. Cogn Behav Neurol 2004;17:195-200.

7. Sollinger AB, Goldstein FC, Lah JJ, Levey AI, Factor SA. Mild cognitive impairment in Parkinson's disease: subtypes and motor characteristics. Parkinsonism Relat Disord 2010;16:177-80.

8. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer disease. Arch Neurol 2006;63:1763-9.

9. Louis ED, Schupf N, Manly J, Marder K, Tang MX, Mayeux R. Association between mild parkinsonian signs and mild cognitive impairment in a community. Neurology 2005;64:1157-61.

10. Hughes AJ, Ben-Shlomo Y, Daniel SE, et al. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology 1992;42:1142-6.

11. Kang Y, Na DL. Seoul Neuropsychological Screening Battery. Incheon: Human Brain Research & Consulting Co, 2003
12. Lee JE, Park HJ, Park B, et al. A comparative analysis of cognitive profiles and white-matter alterations using voxel-based diffusion tensor imaging between patients with Parkinson's disease dementia and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2010;81:320-6.
13. Kim H, Na DL. Normative data on the Korean version of the Boston Naming Test. J Clin Exp Neuropsychol 1999;21:127-33.
14. Cho H, Yang DW, Shon YM, et al. Abnormal integrity of corticocortical tracts in mild cognitive impairment: a diffusion tensor imaging study. J Korean Med Sci 2008;23:477-83.
15. Esselink RA, de Bie RM, de Haan RJ, et al. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial. Neurology 2004;62:201-7.
16. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95-113.
17. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21-36.
18. Whitwell JL, Petersen RC, Negash S, et al. Patterns of atrophy differ among specific subtypes of mild cognitive impairment. Arch Neurol 2007;64:1130-8.
19. Jicha GA, Parisi JE, Dickson DW, et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. Arch Neurol 2006;63:674-81.
20. Vogt BA, Vogt L, Laureys S. Cytology and functionally correlated circuits of human posterior cingulate areas. Neuroimage 2006;29:452-66.
21. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006;129:564-83.

22. Choo IH, Lee DY, Oh JS, et al. Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2010;31:772-9.
23. Trivedi MA, Wichmann AK, Torgerson BM, et al. Structural MRI discriminates individuals with Mild Cognitive Impairment from age-matched controls: a combined neuropsychological and voxel based morphometry study. Alzheimers Dement 2006;2:296-302.
24. Kemppainen NM, Aalto S, Wilson IA, et al. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. Neurology 2007;68:1603-6.
25. Li Y, Rinne JO, Mosconi L, et al. Regional analysis of FDG and PIB-PET images in normal aging, mild cognitive impairment, and Alzheimer's disease. Eur J Nucl Med Mol Imaging 2008;35:2169-81.
26. Hurtig HI, Trojanowski JQ, Galvin J, et al. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology 2000;54:1916-21.
27. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Ann Neurol 2005;58:773-6.
28. Mattila PM, Rinne JO, Helenius H, Dickson DW, Roytta M. Alpha-synuclein-immunoreactive cortical Lewy bodies are associated with cognitive impairment in Parkinson's disease. Acta Neuropathol 2000;100:285-90.
29. Nobili F, Abbruzzese G, Morbelli S, et al. Amnestic mild cognitive impairment in Parkinson's disease: a brain perfusion SPECT study. Mov Disord 2009;24:414-21.
30. Griffith HR, den Hollander JA, Okonkwo OC, O'Brien T, Watts RL, Marson DC. Brain metabolism differs in Alzheimer's disease and Parkinson's disease dementia. Alzheimers Dement 2008;4:421-7.

31. Schmidt-Wilcke T, Poljansky S, Hierlmeier S, Hausner J, Ibach B. Memory performance correlates with gray matter density in the ento-/perirhinal cortex and posterior hippocampus in patients with mild cognitive impairment and healthy controls--a voxel based morphometry study. Neuroimage 2009;47:1914-20.
32. Leube DT, Weis S, Freymann K, et al. Neural correlates of verbal episodic memory in patients with MCI and Alzheimer's disease--a VBM study. Int J Geriatr Psychiatry 2008;23:1114-8.
33. Nagano-Saito A, Kato T, Arahata Y, et al. Cognitive- and motor-related regions in Parkinson's disease: FDOPA and FDG PET studies. Neuroimage 2004;22:553-61.

ABSTRACT(IN KOREAN)

기억상실성 경도 인지장애 환자에서 파킨슨 병 동반유무에 따른 신경구조학적 차이

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기억 상실 성 경도 인지장애 환자에서 파킨슨병 동반유무에 따른 신경구조학적 차이를 보기 위해서 인지적 특징과 복셀 기준 형태 계측 법을 이용한 뇌 영상 특징을 연구했다. 기억 상실 성 경도 인지장애 환자 총 119명 환자(파킨슨병이 동반되지 않은 기억 상실 성 경도 인지장애 환자 78 명, 파킨슨병이 동반된 기억 상실 성 경도 인지장애 환자 41 명)들이 T1-강조 뇌 자기공명영상을 시행하였고 이 영상을 복셀 기준 형태 계측 법을 이용하여 분석 하였다. 파킨슨병이 동반되지 않은 기억 상실 성 경도 인지장애 환자와 파킨슨병이 동반된 기억 상실 성 경도 인지장애 환자 사이에서 통계적으로 의미 있는 임상 특징의 차이나 일반적인 인지 기능의 차이는 보이지 않았다. 두 집단에서의 신경인지검사를 비교해보면 파킨슨병이 동반되지 않은 기억 상실 성 경도 인지장애 환자가 언어지연회상 검사 및 시각적 재인기억 검사에서 더 낮은 수행을 보였으나 시공간

기능은 파킨슨병이 동반된 기억 상실 성 경도 인지장애 환자에서 더 심한 장애를 보였다. 정상 대조군에 비해 파킨슨병이 동반되지 않은 기억 상실 성 경도 인지장애 환자에서 오른쪽 측두엽과 후 허면 결절 피질 (posterior cingular cortex) 의 회백질의 위축이 심했지만 파킨슨병이 동반 된 기억 상실 성 경도 인지장애 환자에서는 정상 대조군에 비해 쐐기 앞부분, 왼쪽 이마앞엽, 일차운동피질에서 회백질의 위축이 통계적으로 의미 있게 있었다. 두 환자 군을 직접 비교한 결과에서는 파킨슨병이 동반되지 않은 기억 상실 성 경도 인지장애 환자에서 파킨슨병이 동반 된 기억 상실 성 경도 인지장애 환자에 비해 오른쪽 측두엽과 전전두엽 피질에서 회백질의 위축이 있었다. 반면에 파킨슨병이 동반되지 않은 기억 상실 성 경도 인지장애 환자보다 파킨슨병이 동반 된 기억 상실 성 경도 인지장애 환자에서 양쪽 이마앞엽, 왼쪽 일차운동피질, 오른쪽 두정엽의 회백질의 위축을 보였다. 기억의 감소 정도는 파킨슨병이 동반 되지 않은 기억 상실 성 경도 인지장애 환자에서 측두엽의 위축 정도와 상관관계를 보였으며 파킨슨병이 동반 된 기억 상실 성 경도 인지장애 환자에서의 기억의 감소 정도는 허면 결절 피질 (posterior cingular cortex)의 회백질의 위축 정도와 상관 관계가 있었다. 우리의 연구는 파킨슨병이 동반 된 기억 상실 성 경도 인지장애 환자와 파킨슨병이 동반 되지 않은 기억 상실 성 경도 인지장애 환자에서의 기억의 장애는 서로 다른 신경구조학적 체계를 갖는 다는 것을 보여주었다.

핵심 되는 말 : 기억 상실 성 경도인지 장애, 파킨슨병, 복셀 기준 형태 계측 법,