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Neuropsychological Comparison of Patients With Alzheimer's Disease and Dementia With Lewy Bodies

Sungwoo Kang[a]
So Hoon Yoon[a]
Han Kyu Na[a]
Young-gun Lee[a]
Seun Jeon[a,b]
Kyoungwon Baik[a]
Young H Sohn[a]
Byoung Seok Ye[a]

Departments of [a]Neurology and [b]Brain Research Institute, Yonsei University College of Medicine, Seoul, Korea

Background and Purpose This study aimed to determine the neuropsychological differences between patients with early-stage Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) with a Clinical Dementia Rating (CDR) score of ≤1.

Methods We examined 168 patients with AD (126 with CDR score=0.5, 42 with CDR score=1) and 169 patients with DLB (104 with CDR score=0.5, 65 with CDR score=1) whose diagnoses were supported by ^{18}F-flobetaben positron-emission tomography (PET) and ^{18}F-N-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane PET. Neuropsychological test scores were compared after controlling for age, sex, and education duration. Using a cut-off motor score on the Unified Parkinson's Disease Rating Scale of 20, patients with AD were further divided into AD with parkinsonism (AD^{P+}, n=86) and AD without parkinsonism (AD^{P-}, n=82).

Results At CDR scores of both 0.5 and 1, the DLB group had lower scores on the attention (digit-span forward at CDR score=0.5 and backward at CDR score=1), visuospatial, and executive (color reading Stroop test at CDR score=0.5 and phonemic fluency test, Stroop tests, and digit symbol coding at CDR score=1) tests than the AD group, but higher scores on the memory tests. The AD^{P-} and AD^{P+} subgroups had comparable scores on most neuropsychological tests, but the AD^{P+} subgroup had lower scores on the color reading Stroop test.

Conclusions Patients with DLB had worse attention, visuospatial, and executive functions but better memory function than patients with AD. Parkinsonism was not uncommon in the patients with AD and could be related to attention and executive dysfunction.

Keywords Alzheimer disease; dementia with Lewy bodies; neuropsychological assessment.

INTRODUCTION

Alzheimer's disease (AD)[1] and dementia with Lewy bodies (DLB)[2] are the two most common neurodegenerative causes of dementia. AD is characterized by progressive memory decline with the pathological hallmarks of β-amyloid plaque and tau neurofibrillary tangle accumulation.[3] DLB features progressive cognitive decline, fluctuating cognition, visual hallucination, and motor parkinsonism with neuropathological hallmarks of α-synuclein aggregates in the form of Lewy bodies.[4] Although the two diseases have distinct clinical and neuropathological features, they frequently co-occur[5-7] and tend to have overlapping clinical presentations. Memory impairment is a symptom that commonly presents in DLB,[8] and parkinsonism is not uncommon in mild AD.[9] The overlapping of neuropathological and clinical symptoms between the two diseases makes it difficult to perform precise clinical diagnoses of dementia in patients.

The differential diagnosis of AD and DLB is important not only for neuroleptic hypersensitivity in patients with DLB[10] but also for accurately determining the effectiveness of disease-

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Correspondence
Byoung Seok Ye, MD, PhD
Department of Neurology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel +82-2-2228-1609
Fax +82-2-393-0705
E-mail romel79@gmail.com

modifying treatments for patients with AD. Although amyloid positron-emission tomography (PET) is used to identify patients with AD for whom disease-modifying treatments are suitable, it cannot sufficiently differentiate AD from DLB due to approximately 60% of patients with DLB exhibiting significant β-amyloid deposition.[11] Considering the high accessibility of neuropsychological tests in clinical settings, neuropsychological profiling for AD and DLB can help clinicians to effectively distinguish between them. Although several autopsy studies have compared the neuropsychological patterns of patients with AD and DLB,[12-15] they had the inevitable limitations of long intervals between neuropsychological evaluation and autopsy as well as small samples.

The present study examined the neuropsychological characteristics of patients who were clinically diagnosed with AD or DLB supported by amyloid PET and dopamine transporter (DAT) PET, respectively. Based on the results of neurological examinations for parkinsonism, patients with AD were further divided into AD with parkinsonism (AD^{P+}) and AD without parkinsonism (AD^{P-}), and their neuropsychological performances were compared. We hypothesized that patients with AD and DLB have different neuropsychological profiles, and patients with AD^{P+} have neuropsychological features intermediate between AD^{P-} and DLB. Our findings could provide clinical guidance for identifying patients with Lewy-body-related cognitive impairment, especially in the mixed form with AD in which further biomarker validation is needed for DLB.

METHODS

Participants

This study recruited 337 patients with cognitive impairments due to AD (*n*=168) and DLB (*n*=169) with a Clinical Dementia Rating (CDR) score of 0.5 or 1 at the dementia clinic of Yonsei University Severance Hospital, Seoul, South Korea from January 2018 to June 2022. All participants underwent neurological examinations including the Unified Parkinson's Disease Rating Scale (UPDRS) motor score and detailed neuropsychological tests. The clinical features of patients with DLB, including parkinsonism, rapid-eye-movement sleep behavior disorder (RBD), visual hallucinations, and cognitive fluctuation, were evaluated by the caregivers using semistructured questionnaires. All participants also underwent brain metabolism imaging using ^{18}F-fluorodeoxyglucose (FDG) PET or brain perfusion imaging using early-phase ^{18}F-N-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) PET.[16]

All patients with AD met the 2011 National Institute on Aging and Alzheimer's Association's diagnostic guidelines for AD dementia[1] and mild cognitive impairment due to AD.[17] Specifically, all patients with AD presented evidence of cerebral β-amyloid deposition on ^{18}F-flobetaben (FBB) PET and neurodegeneration on FDG PET or early-phase FP-CIT PET predominantly in the entorhinal cortex. All patients with DLB satisfied the criteria for probable DLB criteria based on the fourth consensus report of the DLB Consortium published in 2012,[2] or the research criteria for prodromal DLB.[18] All of the patients with DLB who underwent FP-CIT PET presented evidence of DAT depletion in the striatum. However, although the patients presented cognitive impairment, parkinsonism, and DAT depletion, they were not considered to have DLB if they did not experience cognitive fluctuation or visual hallucination.

The patients with AD were further divided based on a UPDRS motor-score cutoff into AD^{P+} (UPDRS motor score ≥20, *n*=86) and AD^{P-} (UPDRS motor score <20, *n*=82) groups. Among the 86 patients with AD^{P+}, 50 underwent FDG PET, 3 underwent FP-CIP PET, and 33 underwent both types of PET. The 83 patients with AD^{P+} who underwent FDG-PET presented a Parkinson's-disease-related pattern (PDRP),[19] and increased metabolic activity in the posterior putamen on FDG PET. Among the 36 patients with AD^{P+} who underwent FP-CIT PET, 7 presented moderate DAT depletion in the striatum, while 29 presented suspected DAT depletion in the striatum with prominent PDRP and increased perfusion in the posterior putamen.[16]

The exclusion criteria were as follows: 1) other degenerative causes of dementia including frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy, 2) drug-induced cognitive impairment, 3) presence of vascular parkinsonism indicated by decreased DAT uptake with a simultaneous decrease in metabolism or perfusion in the striatum, 4) presence of other causes of cognitive impairment such as epilepsy, psychiatric disorder, normal-pressure hydrocephalus, or structural brain lesions (e.g., tumor or hemorrhage), or 5) mixed disease of AD with DLB.

Standard protocol approval, registration, and patient consent

This study was approved by the Institutional Review Board of the Yonsei University Medical Center (IRB No. 4-2021-0759). Informed consent was waived because this study based on retrospective chart review.

Neuropsychological evaluation and clinical assessment

All participants completed the standardized Seoul Neuropsychological Screening Battery (SNSB),[20] which contains attention, language, visuospatial, memory, and frontal/ex-

ecutive function tests. Specifically, digit-span forward and backward tasks were used to assess attention function; the Korean version of the Boston Naming Test (K-BNT) was used to assess language function; the copying item of the Rey-Osterrieth Complex Figure Test (RCFT) was used to assess visuospatial function; the immediate-recall, 20-min delayed recall, and recognition items of the Seoul Verbal Learning Test (SVLT) were used to assess verbal memory, and RCFT was used for visual memory; and finally frontal/executive function was assessed using the contrasting program, go-no-go test, fist-edge-palm task, alternating hand movement, alternating square and triangle task, Luria loop task, phonemic and semantic (animal and supermarket) items of the Controlled Oral Word Association Test (COWAT), Korean version of the color-word Stroop test (K-CWST), digit symbol coding (DSC), and the Korean version of the Trail-Making Test for the Elderly (K-TMT-E) part B. The findings of motor control and perseveration tests (contrasting program, go-no-go test, fist-edge-palm task, alternating hand movement, alternating square and triangle task, and Luria loop task) were divided into normal and abnormal based on the SNSB criteria. In addition to frontal/executive function, the K-CWST color reading test can also measure selective attention function,[21] and the COWAT can measure language-related function including semantic and phonemic fluency. Standardized z scores were available based on age- and education-matched norms for all tests with scores.[22]

Statistical analyses

The baseline demographic and clinical characteristics were compared using the independent *t*-test, analysis of variance, and chi-square test, as appropriate. Groupwise comparisons of neuropsychological test scores were performed using general linear models (GLMs) with age, sex, and education duration as covariates. Since the CDR score distribution differed between the AD and DLB groups, the GLMs for neuropsychological test scores were conducted after further controlling for CDR score or separately for patients with CDR scores of 0.5 and 1. The proportions of patients with standardized neuropsychological z scores less than -1.0 or -1.5 standard deviations (SDs) from the mean were compared using a chi-square test to capture the cognitive dysfunction patterns in the AD and DLB groups. We used the false discovery rate (FDR) method to correct for multiple comparisons in all statistical analyses. FDR correction was performed for 17 cognitive tests to compare their scores between the AD and DLB groups. FDR correction was performed for 51 comparisons among the AD^{P-}, AD^{P+}, and DLB groups (i.e., 17 cognitive tests for each group).

RESULTS

Demographics and clinical characteristics of the study participants

The demographic and clinical characteristics of the study participants are listed in Table 1. Compared with the patients in the AD group, those in the DLB group were older, had a shorter education duration, and comprised a larger proportion of males. There was a higher proportion of patients with core clinical features including cognitive fluctuation, RBD, visual hallucination, and higher mean UPDRS motor scores in the DLB group. The scores on the Korean version of the Mini Mental State Examination (K-MMSE) and CDR Sum of Boxes (SOB) were comparable between the AD and DLB groups, but the DLB group had a larger proportion of patients with CDR score=1.

Comparisons of neuropsychological test scores between AD and DLB groups

The patients with AD and a CDR score of 0.5 performed worse than patients with DLB and a CDR score of 0.5 on the immediate-recall, delayed-recall, and recognition items of the SVLT (p=0.019, p<0.001, and p<0.001, respectively) and RCFT (p<0.001, p<0.001, and p<0.001), while those with DLB and a CDR score of 0.5 performed worse on the digit-span forward task (p=0.016), RCFT copy (p=0.029), and K-CWST color reading test (p=0.048) (Table 2). The patients with AD and a CDR score of 1 performed worse than those

Table 1. Comparison of demographic data between the AD and DLB groups

	AD (n=168)	DLB (n=169)	p
Age, years	73.63±8.00	76.67±6.00	<0.001
Education duration, years	10.45±5.02	9.02±5.65	0.015
Sex, female	119 (70.8)	79 (46.7)	<0.001
Cognitive fluctuation	0 (0)	147 (87.0)	<0.001
RBD	11 (6.5)	63 (37.3)	<0.001
Visual hallucination	0 (0)	44 (26.0)	<0.001
UPDRS motor score	17.15±12.18	32.01±11.49	<0.001
UPDRS motor score >20	86 (51.2)	162 (95.9)	<0.001
K-MMSE	21.93±3.94	22.00±4.26	0.884
CDR score			0.011
0.5	126 (75.0)	104 (61.5)	
1	42 (25.0)	65 (38.5)	
CDR-SOB score	3.15±2.09	3.28±2.05	0.540

Data are mean±SD or number (%) values. Group comparisons were performed using chi-square tests or independent *t*-tests.
AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CDR-SOB, Clinical Dementia Rating Sum of Boxes; DLB, dementia with Lewy bodies; K-MMSE, Korean version of Mini Mental State Examination; RBD, rapid-eye-movement sleep behavior disorder; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 2. Comparison of neuropsychological test scores between the AD and DLB groups according to CDR score

	CDR score=0.5			CDR score=1			Total		
	AD (*n*=126)	DLB (*n*=104)	*p**	AD (*n*=42)	DLB (*n*=65)	*p**	AD (*n*=168)	DLB (*n*=169)	*p*†
Attention									
Digit-span forward	5.80±1.33	5.11±1.39	0.016	5.05±1.17	4.77±1.16	0.072	5.61±1.33	4.98±1.31	<0.001
Digit-span backward	3.56±1.16	2.99±1.29	0.122	3.00±0.88	2.55±1.02	0.011	3.42±1.12	2.82±1.21	0.001
Language									
K-BNT	40.24±9.95	40.51±10.56	0.162	34.05±12.88	31.29±11.75	0.500	38.69±11.05	36.96±11.88	0.836
Visuospatial function									
RCFT copy	29.02±6.58	25.31±7.88	0.029	23.83±9.89	18.13±9.94	0.002	27.72±7.84	22.55±9.38	<0.001
Verbal memory									
SVLT immediate recall	14.20±4.26	14.40±4.71	0.019	10.88±3.96	10.86±3.68	0.549	13.37±4.41	13.04±4.66	0.150
SVLT delayed recall	1.59±2.25	3.42±2.90	<0.001	0.33±0.79	1.35±1.79	0.001	1.27±2.06	2.63±2.72	<0.001
SVLT recognition	17.29±2.64	18.91±2.76	<0.001	15.52±2.76	16.25±2.73	0.169	16.85±2.77	17.89±3.03	<0.001
Visual memory									
RCFT immediate recall	4.94±4.38	8.11±6.53	<0.001	2.23±2.47	3.12±2.83	0.169	4.26±4.15	6.19±5.92	0.002
RCFT delayed recall	4.16±4.76	7.61±6.17	<0.001	1.04±2.04	2.40±2.87	0.016	3.38±4.45	5.60±5.74	<0.001
RCFT recognition	16.76±2.80	18.08±2.50	<0.001	15.07±2.58	16.49±2.57	0.011	16.34±2.84	17.47±2.64	<0.001
Executive function									
COWAT animal	11.77±3.74	11.28±4.35	0.693	8.43±3.90	7.72±3.39	0.211	10.93±4.04	9.91±4.36	0.195
COWAT supermarket	12.04±4.74	10.17±4.25	0.181	8.81±5.38	6.92±3.61	0.169	11.23±5.09	8.92±4.31	0.007
COWAT phonemic	20.50±9.61	15.06±9.68	0.061	15.52±10.22	9.29±7.34	0.002	19.24±9.97	12.84±9.27	<0.001
K-CWST word reading	108.78±10.07	98.78±30.69	0.099	105.95±12.85	79.26±37.81	<0.001	108.08±10.86	91.27±34.82	<0.001
K-CWST color reading	64.17±28.67	48.73±27.26	0.048	38.12±24.56	17.51±16.97	<0.001	57.70±29.85	36.72±28.24	<0.001
DSC	38.81±17.40	30.61±17.60	0.181	27.38±14.32	16.79±13.51	0.001	35.99±17.36	25.68±17.52	0.001
K-TMT-E part B	124.16±99.52	158.21±112.00	0.329	226.62±107.42	264.67±72.95	0.169	148.83±110.27	198.05±111.63	0.010

Data are mean±standard deviation values.

**p* values from general linear models for neuropsychological test scores after controlling for age, sex, and education duration; †*p* values after controlling for age, sex, education duration, and CDR score. *p* values were corrected for multiple comparisons across 17 neuropsychological tests using the false discovery method.

AD, Alzheimer's disease; CDR, Clinical Dementia Rating; COWAT, Controlled Oral Word Association Test; DLB, dementia with Lewy bodies; DSC, digit symbol coding; K-BNT, Korean version of the Boston Naming Test; K-CWST, Korean version of the color-word Stroop test; K-TMT-E, Korean version of the Trail-Making Test for the Elderly; RCFT, Rey-Osterrieth Complex Figure Test; SVLT, Seoul Verbal Learning Test.

with DLB and a CDR score of 1 on the delayed-recall item of the SVLT (p=0.001) and delayed-recall and recognition items of the RCFT (p=0.016 and p=0.011, respectively), while the patients with DLB and a CDR score of 1 performed worse on the digit-span backward task (p=0.011), RCFT copy (p=0.002), COWAT phonemic items (p=0.002), K-CWST word (p<0.001) and color (p<0.001) reading, and DSC (p=0.001) tests. Comparing all of the patients with AD and DLB revealed that those with AD performed worse than those with DLB on the delayed-recall and recognition items of the SVLT and RCFT (all p<0.001) and on the immediate-recall item of the RCFT (p=0.002), while those with DLB performed worse than those with AD on the digit-span forward (p<0.001) and digit-span backward (p=0.001) tasks, RCFT copy (p<0.001), COWAT supermarket items (p=0.007), COWAT phonemic items (p< 0.001), K-CWST word (p<0.001) and color (p<0.001) reading, DSC (p=0.001), and K-TMT-E part B (p=0.010). In terms of motor control and perseveration tests (Supplementary Table 1 in the online-only Data Supplement), the proportions of patients with abnormal performance in alternating hand movement, alternating square and triangle task, Luria loop, and fist-edge-palm task were higher in the DLB than the AD group. The proportion of patients who exhibited more than three abnormal performances among six motor control and perseveration tests was higher in the DLB group (p=0.005). At a CDR score of 0.5, the proportion of patients with abnormal performance in the alternating square and triangle task, Luria loop, and fist-edge-palm task was higher in the prodromal DLB group. At a CDR score of 1, the proportion of patients with abnormal performance in the Luria loop was higher in the DLB group. The proportion of patients with a CDR score of 0.5 who had more than three abnormal performances among six motor control and perseveration tests did not differ significantly between the AD and prodromal DLB groups (p=0.256), but that proportion among those with a CDR score of 1 was higher in the DLB

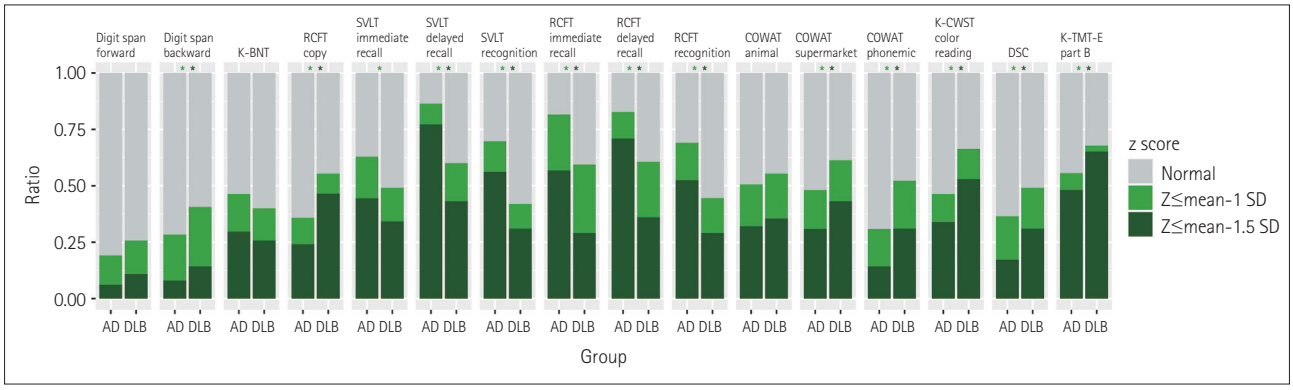

Fig. 1. Comparisons of the proportion of cognitive impairment between the AD and DLB groups. Stacked bar graph illustrating the proportions of subjects with cognitive impairment according to each neuropsychological test. The proportion of subjects with z scores less than mean-1.0×SD for age- and education-matched norms are shown in bright green, while that of subjects with z scores less than mean-1.5×SD are in dark green. Stars denote significant differences (p<0.05) in the comparisons between the AD and DLB groups after corrections for multiple comparisons across 16 neuropsychological tests using the false discovery rate method. Bright stars represent significant difference in the proportion of subjects with z scores less than mean-1.0×SD, and dark stars represent z scores less than mean-1.5×SD. AD, Alzheimer's disease; COWAT, Controlled Oral Word Association Test; DLB, dementia with Lewy bodies; DSC, digit symbol coding; K-BNT, Korean version of the Boston Naming Test; K-CWST, Korean version of the color-word Stroop test; K-TMT-E, Korean version of the Trail-Making Test for the Elderly; RCFT, Rey-Osterrieth Complex Figure Test; SD, standard deviation; SVLT, Seoul Verbal Learning Test.

group (p=0.045).

To determine whether the prevalence of cognitive dysfunction according to specific cognitive tests differed between the AD and DLB groups, we created stacked bar graphs of the percentage of patients with cognitive impairment on each neuropsychological test (Fig. 1). As per the scores for the delayed-recall and recognition items of the SVLT and RCFT (z score less than mean-1.0×SD and less than mean -1.5×SD, respectively) and SVLT immediate recall (z score less than mean-1.0×SD), the AD group had a larger proportion of patients with cognitive impairment. In contrast, according to the scores for the digit-span backward task, RCFT copy, COWAT supermarket item, COWAT phonemic item, K-CWST color reading, DSC, and K-TMT-E part B (z score less than mean-1.0×SD and less than mean-1.5×SD for the AD and DLB groups, respectively), the DLB group had a larger proportion of patients with cognitive impairment. When we illustrated the neuropsychological impairment patterns for each group (Supplementary Fig. 1 in the online-only Data Supplement), >80% of those in the AD group presented cognitive impairment (z score less than mean-1.0×SD) with poor scores on the delayed-recall items of the SVLT and RCFT, and the DLB group had poor scores across widespread neuropsychological tests, especially for RCFT copy, COWAT semantic items, K-CWST color reading, and T-TMT-E part B.

Comparison of neuropsychological test scores among the AD^{P-}, AD^{P+}, and DLB groups

Among the 168 patients with AD, 86 (51.2%) had UPDRS motor scores ≥20 and so were classified as having AD^{P+}. The demographic and clinical characteristics of the patients with AD^{P-}, AD^{P+}, and DLB are listed in Supplementary Table 2 (in the online-only Data Supplement). The patients in the AD^{P+} subgroup were older and comprised a larger proportion of those with CDR score=1 than the patients in the AD^{P-} subgroup. The patients in the AD^{P-} and AD^{P+} groups had comparable neuropsychological test scores, except for those for K-CWST color reading (Table 3), in which patients with AD^{P+} performed worse (p=0.014). Both the AD^{P-} and AD^{P+} subgroups performed worse than the DLB group on the delayed-recall and recognition items of the SVLT and RCFT, but performed better on the digit-span forward task, RCFT copy, COWAT phonemic item, and K-CWST tests. The AD^{P-} subgroup performed better than the DLB group on the digit-span backward task, immediate-recall item of the SVLT, DSC, and K-TMT-E part B.

DISCUSSION

We found that patients with AD and probable DLB who were carefully evaluated and diagnosed using FBB, FDG, and FP-CIT PET presented different levels of neuropsychological performance during the early stages of their respective diseases (with CDR scores ≤1). Our major findings were as follows: first, the patients with AD had worse verbal- and visual-memory functions than the patients with DLB, while the latter had worse attention, visuospatial, and executive functions. Second, compared with the age- and education-matched norms, more than half of the patients with AD performed

Table 3. Comparison of neuropsychological test scores among the AD^{P+}, AD^{P-}, and DLB groupss

	AD^{P-} (*n*=82)	AD^{P+} (*n*=86)	DLB (*n*=169)	pAD^{P-} vs. AD^{P+}	pAD^{P-} vs. DLB	pAD^{P+} vs. DLB
Attention						
Digit-span forward	5.72±1.27	5.51±1.38	4.98±1.31	0.736	0.010	0.016
Digit-span backward	3.61±1.16	3.23±1.05	2.82±1.21	0.345	0.008	0.082
Language						
K-BNT	40.76±10.97	36.72±10.83	36.96±11.88	0.648	0.885	0.461
Visuospatial function						
RCFT copy	28.72±7.61	26.77±7.98	22.55±9.38	0.781	0.003	0.003
Verbal memory						
SVLT immediate recall	13.93±4.34	12.84±4.44	13.04±4.66	0.648	0.035	0.091
SVLT delayed recall	1.37±2.33	1.19±1.77	2.63±2.72	0.345	<0.001	<0.001
SVLT recognition	16.89±2.90	16.81±2.65	17.89±3.03	0.198	<0.001	0.001
Visual memory						
RCFT immediate recall	4.34±4.25	4.20±4.08	6.19±5.92	0.483	0.001	0.003
RCFT delayed recall	3.43±4.81	3.33±4.11	5.60±5.74	0.345	<0.001	0.001
RCFT recognition	16.52±2.82	16.16±2.86	17.47±2.64	0.834	0.001	<0.001
Executive function						
COWAT animal	11.88±3.79	10.03±4.09	9.91±4.36	0.208	0.318	0.756
COWAT supermarket	12.06±5.20	10.44±4.88	8.92±4.31	0.699	0.091	0.192
COWAT phonemic	21.31±10.03	17.31±9.59	12.84±9.27	0.326	0.002	0.022
K-CWST word reading	109.75±9.53	106.51±11.81	91.27±4.82	0.986	0.003	0.001
K-CWST color reading	67.30±28.66	48.66±28.22	36.72±28.24	0.014	<0.001	0.025
DSC	40.94±18.19	31.28±15.20	25.68±17.52	0.092	0.001	0.122
K-TMT-E part B	114.77±96.27	181.24±113.48	198.05±111.63	0.068	0.019	0.718

Data are mean±standard deviation values.
p values were from general linear models for neuropsychological test scores after controlling for age, sex, education duration, and CDR score. *p* values after 51 corrections for multiple comparisons across 17 neuropsychological tests and three groups using the false discovery rate method.
AD, Alzheimer's disease; AD^{P+}, AD without parkinsonism; AD^{P-}, AD with parkinsonism; CDR, Clinical Dementia Rating; COWAT, Controlled Oral Word Association Test; DLB, dementia with Lewy bodies; DSC, digit symbol coding; K-BNT, Korean version of the Boston Naming Test; K-CWST, Korean version of the color-word Stroop test; K-TMT-E, Korean version of the Trail-Making Test for the Elderly; RCFT, Rey-Osterrieth Complex Figure Test; SD, standard deviation; SVLT, Seoul Verbal Learning Test.

poorly on all of the memory-related tests and more than half of those with DLB performed poorly on the RCFT copy, COWAT semantic items, K-CWST color reading, and K-TMT-E part B tests. Third, about half of the patients with AD had significant motor parkinsonism (AD^{P+}) and performed worse than the AD^{P-} group on the K-CWST color reading test, but had comparable scores for most other neuropsychological tests. The DLB group performed worse on the digit-span backward task, immediate-recall item of the SVLT, DSC, and K-TMT-part B than the AD^{P-} subgroup, but comparably to the AD^{P+} subgroup. These findings suggest that DLB is characterized by attention, visuospatial, and executive dysfunctions while AD is characterized by memory dysfunction. AD^{P+} share some neuropsychological features with AD^{P-} and DLB. Motor parkinsonism in AD could be a phenomenon related to Lewy bodies, which are related to attention and executive dysfunction.

Our first major finding was that the patients with AD had worse memory function than those with DLB, and the latter had worse attention, visuospatial, and executive functions. This was consistent with previous studies finding that patients with DLB developed more-severe attention,[13,14] visuospatial,[12,15,23,24] and executive[13,14,23] dysfunctions earlier than the patients with AD, while the latter were found to develop more-severe memory dysfunction earlier than those with DLB.[12,13,15,23] However, some studies found that the levels of memory,[24] visuospatial,[13] and executive[12,15,24] dysfunctions were comparable between patients with AD and DLB. There could be several explanations for these discrepancies. First, there can be discrepancies between clinical and neuropathological diagnoses. Previous autopsy studies found that 12%–23%[25,26] of patients clinically diagnosed with AD and 50%[27] of those with DLB had other pathological diagnoses. Second, mixed AD+DLB pathologies are common in patients with sporadic AD[2,28] and DLB.[7,29] Third, clinical symptoms that overlap between DLB and AD make accurate clinical diagnoses difficult, especially in the early or late stages. To overcome these obstacles, our evaluation incorporated imaging biomarkers of synaptic dysfunction (FDG PET and early-phase

FP-CIT PET), cerebral β-amyloid deposition (FBB PET), and DAT depletion (FP-CIT PET) to increase the validity of the clinical diagnoses of AD and DLB. We also excluded patients with both AD and DLB and restricted our study to patients with a CDR score of ≤1.

Our second finding was that compared with the age- and education-matched norms, more than half of the patients with AD performed poorly in all memory-related tests and more than half of the patients with DLB performed poorly in the RCFT copy, COWAT semantic items, K-CWST color reading, and K-TMT-E part B tests. The cognitive dysfunction patterns based on age- and education-matched norms (Fig. 1) were similar to the results of the comparison between the continuous neuropsychological test scores for the AD and DLB groups. However, fewer than 50% of patients in the DLB group had attention dysfunction, and more than half of the patients in that group presented memory dysfunction according to the scores for the immediate- and delayed-recall items of the SVLT and RCFT. Further, more than half of the patients in each of the AD and DLB groups had poor scores for the COWAT animal items and K-TMT-E part B. Impaired semantic fluency in AD and DLB could be explained by different mechanisms. Degradation in the structure or content of semantic knowledge could explain impaired semantic fluency in AD,[30] while a breakdown in the executive control mechanism that is responsible for effortful retrieval could explain impaired semantic fluency in DLB.[31] These results suggest that AD could be characterized by prominent memory dysfunction with additional semantic fluency dysfunction, and DLB by heterogeneous and diffuse cognitive dysfunction, with markedly worse performance on visuospatial, semantic fluency, and executive functions.

The difference in cognitive dysfunction between AD and DLB groups changed according to the CDR scores, indicating a different disease progression pattern. The patients with AD with CDR scores of either 0.5 or 1 performed worse than the patients with DLB on the delayed-recall item of the SVLT and delayed-recall and recognition items of the RCFT, while the patients with DLB performed worse on the RCFT copy and K-CWST color reading tests. However, the patients with DLB with a CDR score of 1 but not 0.5 performed worse on the digit-span backward task, COWAT phonemic items, K-CWST word reading, and DSC. Further, the patients with DLB with a CDR score of 0.5 but not 1 performed better than those with AD on the immediate-recall item of the SVLT and RCFT. The RCFT copy test actually requires not only visuospatial perception but also sufficient attention and concentration, and planning and organizational abilities, which aid in executive function.[32] The backward task requires more executive control than the forward task of the digit-span test,[33] and the COWAT phonemic items and DSC are regarded as frontal-lobe-related function tests.[34,35] Further, the immediate-recall item is related to both attention and memory functions.[21,36] These results could therefore be related to more-prominent decline in frontal/executive function and attentions in the patients with DLB than in those with AD.

According to our third major finding, patients with AD^{P+} comprised about half of the AD group, and they performed worse on the K-CWST color reading test than those with AD^{P-}. The performances of the patients with DLB in the digit-span backward task, SVLT immediate recall, DSC, and K-TMT-E part B were worse than those of the patients with AD^{P-}, but comparable to those with AD^{P+}. These results suggest that motor parkinsonism is not uncommon in patients with AD and is related to attention and executive dysfunction. Although previous studies found that parkinsonism may occur in patients with AD without nigral degeneration,[37-39] they also found that half of the patients with AD^{P+} were confirmed as having concomitant Parkinson's Disease (PD) postmortem.[39] Moreover, in the patients with AD^{P+}, compensatory processes that involve mRNA changes have been observed in the dopaminergic neurons of the midbrain, similar to those observed in patients with PD.[39] Likewise, although a significant proportion of our patients with AD^{P+} only presented suspicious DAT depletion on FP-CIT PET, some of them may have had LB-related degeneration. This point of view is supported by our finding that the neuropsychological tests in which the patients with DLB most commonly exhibited dysfunction were the K-CWST color reading and K-TMT-E part B tests (Fig. 1). K-WCST color reading and K-TMT-E part B are believed to reflect selective attention[21,40] and executive function,[41,42] and previous studies found that dopaminergic dysfunction in patients with PD is related to poor scores on these tests.[43-45]

Our study had some strengths, in that our diagnoses of AD^{P-}, AD^{P+}, and DLB were supported by PET imaging biomarkers; we also performed standardized PET, MRI, and neuropsychological evaluations. However, there were several limitations. First, the underlying causes of cognitive impairment were not confirmed through pathological examinations. Although we excluded patients with DLB who presented metabolic activity or perfusion patterns that suggested the coexistence of AD, the possibility of the patients having coexisting AD could not be ruled out. Second, the cross-sectional design restricted the ability to determine causal and temporal relationships. Third, the single-center setting of our study could have induced selection bias. Multicenter studies are therefore needed to validate the concept of AD^{P+}. Fourth, patients with AD were younger and had longer education duration than did those with DLB. We could not exclude the possibility that lower cognitive performance in DLB had orig-

inated from higher age or shorter education duration, although age and education duration were adjusted for in the analysis. Fifth, the patients with parkinsonism and AD might have been diagnosed as possible DLB if abnormalities were observed on FP-CIT PET. However, AD diagnoses in this study were based on both amyloid positivity on FBB PET and AD-related synaptic dysfunction on FDG PET. Longitudinal studies are required to determine whether the clinical trajectory of patients with AD and parkinsonism differs from that of patients with DLB. Sixth, the difference between the AD^{P+} and AD^{P-} groups could have originated from the difference in dementia stages, in that the AD^{P+} group had higher CDR or CDR-SOB scores and lower K-MMSE scores than the AD^{P-} group. However, the AD^{P+} group had lower K-CWST color reading scores after further controlling for MMSE, CDR, or CDR-SOB scores. Despite these limitations, this study has provided clinical clues for the diagnosis of the two most common neurodegenerative causes of dementia, especially in its early stages.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.0358.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

ORCID iDs

Sungwoo Kang	https://orcid.org/0000-0001-9791-6899
So Hoon Yoon	https://orcid.org/0000-0003-3265-3965
Han Kyu Na	https://orcid.org/0000-0002-2093-1641
Young-gun Lee	https://orcid.org/0000-0003-0460-455X
Seun Jeon	https://orcid.org/0000-0003-2817-3352
Kyoungwon Baik	https://orcid.org/0000-0001-7215-375X
Young H Sohn	https://orcid.org/0000-0001-6533-2610
Byoung Seok Ye	https://orcid.org/0000-0003-0187-8440

Author Contributions

Conceptualization: Byoung Seok Ye. Data curation: Sungwoo Kang, So Hoon Yoon, Han Kyu Na, Young-gun Lee, Seun Jeon, Kyoungwon Baik. Formal analysis: Sungwoo Kang. Funding acquisition: Byoung Seok Ye. Investigation: Sungwoo Kang, Young-gun Lee, Byoung Seok Ye. Methodology: Sungwoo Kang, Seun Jeon, Byoung Seok Ye. Project administration: Young H Sohn, Byoung Seok Ye. Resources: Young H Shon, Byoung Seok Ye. Supervision: Byoung Seok Ye. Validation: Byoung Seok Ye. Visualization: Sungwoo Kang. Writing—original draft: Sungwoo Kang. Writing—review & editing: Byoung Seok Ye.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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