Verbal and visuospatial deficits in dementia with Lewy bodies

David K. Johnson, PhD; John C. Morris, MD; and James E. Galvin, MD, MPH

Abstract—*Objective:* To investigate the cognitive decline in dementia with Lewy bodies (DLBs) and characterize the contribution of Lewy bodies (LBs) to cognitive impairment in the presence of concurrent Alzheimer disease (AD). *Methods:* Cognitive deficits and rates of progression attributable to DLB and AD neuropathology were investigated in three groups of participants from the longitudinal cohort of the Alzheimer Disease Research Center at Washington University with autopsy-confirmed diagnoses of pure DLB (n = 9), mixed DLB/AD (n = 57), and pure AD (n = 66). Factor analysis was used to recover latent constructs in a comprehensive psychometric test battery, analysis of variance was used to test group differences on the observed dimensions, and random effects models were used to test longitudinal rates of cognitive decline. *Results:* Patients with AD pathology performed worse on the verbal memory dimension. Patients with LB pathology performed worse on the visuospatial dimension. Combined pathology affected visuospatial performance but not verbal memory. The rate of cognitive decline in the DLB, DLB/AD combined, and the pure AD groups was equivalent. *Conclusions:* The comorbid presence of DLB and AD alters the cognitive presentation of visuospatial deficits in dementia but does not alter dementia progression. Both visuospatial and verbal abilities declined at similar rates across the three patient groups. DLB diagnosis may be improved, particularly when there is comorbid AD, by using domain-specific testing.

NEUROLOGY 2005;65:1232–1238

In contrast to the neuritic plaques and neurofibrillary tangles of Alzheimer disease (AD), dementia with Lewy bodies (DLB) is characterized by α-synuclein inclusions (i.e., Lewy bodies [LBs]) in neocortical, limbic, and subcortical regions. DLB and associated disorders of α-synuclein aggregation (synucleinopathies) are the second most common cause of neurodegenerative dementia after AD.[1] Although a minority of DLB cases have only LBs at autopsy ("pure" DLB), the more common finding is a mixture of LBs with sufficient burden of neuritic plaques and neurofibrillary tangles to also diagnose AD (mixed DLB/AD). The reverse is also true, as LBs are observed frequently in AD. A review of autopsied cases from the Washington University Alzheimer Disease Research Center (ADRC) suggests that as many as 25% of autopsied AD cases have cortical/limbic LBs in sufficient quantity to be classified as mixed DLB/AD, although most did not clinically manifest the distinctive symptoms of DLB.[2,3] Other autopsy series confirm the high co-occurrence of DLB and AD.[4,5]

Although there are published criteria for the clinical features of DLB,[3] these criteria appear to best capture the "pure" DLB cases. It is unclear how well the criteria capture the more common mixed DLB/AD group, many of whom may be misclassified clinically as probable AD.[1] Diagnostic criteria for DLB include progressive cognitive decline plus at least two of the following: parkinsonism, visual hallucinations, or cognitive fluctuation.[3] Because neuropsychological studies of well-characterized samples with confirmed neuropathology are lacking, the specific cognitive features of DLB and its rate of progression remains unclear.[6-9] Some studies suggest that DLB is marked by specific declines in executive function[10,11] and visuospatial ability,[12-17] but others find a visuospatial deficit alone.[18-20] Interpretation of these findings is limited by failure to test across multiple cognitive domains, small sample sizes, and contamination of the DLB patient groups with varying levels of AD pathology.

This report describes cross-sectional and longitudinal performance on a battery of cognitive tests in people with autopsy-confirmed pure DLB, pure AD, and mixed DLB/AD. Our goals were to determine which tests differed among the groups, whether rates of cognitive decline varied, and whether differences could be attributed to either verbal, visuospatial, or executive domains. Analyses with autopsy-confirmed diagnoses, irrespective of antemortem clinical diagnosis, are an important first step in defining the

From the Alzheimer's Disease Research Center (Drs. Johnson, Morris, Galvin) and Departments of Neurology (Drs. Johnson, Morris, Galvin), Pathology and Immunology (Dr. Morris), and Anatomy and Neurobiology (Dr. Galvin), Washington University School of Medicine, St. Louis, MO.

Supported by grants from the National Institute on Aging (AG20764 [J.E.G.], AG03991 [J.C.M.], and AG05681 [J.C.M.]) and the American Federation for Aging Research [JEG]. Dr. Galvin is a recipient of the Paul Beeson Physician Faculty Scholar Award in Aging Research. This project was also supported by generous gifts from the Alan A. and Edith L. Wolff Charitable Trust and the Blue Gator Foundation to the ADRC and Dr. Galvin.

Disclosure: The authors report no conflicts of interest.

Received February 12, 2005. Accepted in final form July 8, 2005.

Address correspondence and reprint requests to Dr. James E. Galvin, Alzheimer Disease Research Center, Washington University School of Medicine, 4488 Forest Park, Suite 130, St. Louis, MO 63108; e-mail: galvinj@neuro.wustl.edu

Table 1 *Sample demographics*

	Pure AD, n = 66	DLB/AD, n = 57	Pure DLB, n = 9	*F*(2,129)
Age	77.0 (8.1)	75.2 (9.7)	72.6 (5.7)	1.34
Age at death	83.5 (7.5)[a]	80.0 (8.9)[b]	77.2 (5.8)[b]	4.41*
Years before death	6.6 (3.7)[a]	4.7 (3.5)[b]	4.6 (2.4)[b]	4.44*
Years of education	13.3 (3.7)	12.9 (3.9)	12.9 (2.4)	0.14
Gender (M/F)	39/27	31/26	8/1	4.44†
Visual hallucinations	4	11	4	6.94*†
Hearing voices	1	7	3	8.75*†
Smelling odors	1	0	1	3.82†
Feelings of being spied on	10	15	3	1.13†
Controlled by others	1	0	1	3.82†
Sent special messages	1	1	0	0.38†
CDR 0.5	21	17	4	
CDR 1.0	29	25	4	
CDR 2.0	13	12	1	
CDR 3.0	3	3	0	
Sum of boxes	6.4 (4.3)	6.6 (3.9)	4.6 (2.7)	1.06
Blessed Dementia Scale‡	14.5 (7.8)[a]	15.1 (8.9)[a]	6.1 (4.9)[b]	4.19*

Means within the same row sharing the same superscript (a or b) are equivalent. Bonferroni correction was applied to all paired comparisons.

* $p < 0.05$.
† Likelihood ratio (2, n = 132).
‡ Number of participants vary due to incomplete data (pure Alzheimer disease [AD] = 48, dementia with Lewy bodies [DMB]/AD = 52, and pure DLB = 8; *F*[2,105]).

cognitive deficits associated with the synucleinopathies and hence to improve clinical diagnostic criteria.

Methods. *Case selection.* Cases were selected from volunteers who enrolled in a longitudinal study of healthy aging and dementia. Initiated in 1979, a total of 2,716 individuals have been enrolled and 842 have come to autopsy.[21,22] Demographic data and diagnoses at expiration are reported in tables 1 and 2. The pure and mixed DLB samples included all available cases. Pure AD cases were selected to be similar in age, education, and dementia severity to the combined pure DLB and DLB/AD groups and drawn at random from a total of 483 available AD-confirmed autopsies. The combined data reported here span 23 years and thus include only the available clinical and psychometric scores common to all participants. Although previous research from our center has indicated that depression, a common comorbidity of dementia, does not worsen performance on the battery of psychometric tests used here[23] and that other comorbidities do not influence the rate of progression of dementia of the Alzheimer type,[24] autopsied cases with other comorbid disorders that could potentially cause dementia (e.g., cerebrovascular disease) were excluded from this sample. The Washington University Human Studies Committee approved all procedures

Table 2 *Clinical diagnoses at expiration*

	Pure AD	DLB/AD	Pure DLB
Dementia of the Alzheimer type (pure)	60	36	3
Dementia of the Alzheimer type with secondary parkinsonism or DLB	4	10	2
Pure DLB	0	5	2
Uncertain dementia	1	2	1
Other forms of dementia (e.g., vascular, frontotemporal)	1	4	1

AD = Alzheimer disease; DLB = dementia with Lewy bodies.

Clinical assessment. Experienced clinicians conducted independent semistructured interviews with the participant and a knowledgeable collateral source at the initial visit and annually thereafter. The Clinical Dementia Rating (CDR),[21,22,25] was used to determine the presence or absence of dementia and, if present, stage its severity.[26] The CDR rates cognitive function in each of six categories (memory, orientation, judgment, problem solving, performance in community affairs, and home and hobbies and personal care). Scores are derived from information gathered at the clinical assessment but without reference to psychometric performance. Two scores result. The global CDR synthesizes the six categories. CDR 0 indicates no dementia and CDR 0.5, 1, 2, or 3 correspond to very mild, mild, moderate, or severe dementia. The second score is "sum of boxes" that refers to the sum of the scores in all six categories and provides a quantitative expansion of the CDR ranging from 0 (no impairment) to 18 (maximum impairment).[27] The diagnostic criteria for AD used for this study are consistent with "probable AD" according to the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[28] Published criteria were used for DLB.[3] The CDR has been validated in studies of all forms of dementia, is sensitive to clinical progression, and correlates highly with autopsy-confirmed AD.[22,26,29] The criteria used to diagnose DLB have been evolving since the inception of the McKeith criteria, and many of the participants with pure DLB and DLB/AD enrolled in the current study before their implementation. As a result, diagnostic criteria for AD has been historically more accurate and prevalent, as shown in table 2. Table 1 also presents an aggregated report of psychiatric symptoms experienced by the participant at any time during the re-

Table 3 *Means and SDs*

	Pure AD	DLB/AD	Pure DLB	$F(2,129)$
Visuospatial factor	0.51 ± 0.92[a]	−0.52 ± 0.83[b]	−0.42 ± 0.70[b]	22.69*
Trailmaking A (s†)	87.41 ± 50.07[a]	145.81 ± 47.54[b]	121.89 ± 50.49[ab]	21.81*
WAIS Block Design	16.65 ± 10.76[a]	7.44 ± 8.97[b]	10.56 ± 10.78[ab]	13.06*
WAIS Digit Symbol	22.12 ± 14.37[a]	9.07 ± 11.14[b]	18.11 ± 8.67[ab]	16.14*
Benton Recall Correct	2.68 ± 2.00[a]	1.39 ± 1.52[b]	2.33 ± 1.50[ab]	8.21*
Benton Copy Correct	7.64 ± 3.29[a]	5.51 ± 3.82[b]	6.67 ± 3.04[ab]	5.60‡
Crossing Off	124.08 ± 50.49[a]	90.65 ± 57.90[b]	116.89 ± 46.64[ab]	6.04‡
Verbal factor	−0.16 ± 0.86[a]	0.01 ± 1.10[a]	1.09 ± 0.67[b]	6.73‡
WMS Logical Memory (immediate recall)	2.20 ± 2.02[a]	2.02 ± 2.59[a]	5.28 ± 3.35[b]	7.53*
Boston Naming Test	34.92 ± 17.08[a]	31.86 ± 17.59[a]	51.67 ± 5.34[b]	5.40‡
WAIS Information	11.41 ± 6.62[a]	10.54 ± 6.75[a]	17.00 ± 5.68[b]	3.70§
Word Fluency	18.03 ± 10.65[a]	12.68 ± 10.90[b]	16.22 ± 8.24[ab]	3.90§
WMS Associate Learning	5.88 ± 3.27	5.61 ± 3.69	7.78 ± 4.76	1.44
WMS Digits Forward	5.68 ± 1.76	4.98 ± 1.92	6.33 ± 1.32	3.50
WMS Digits Backward	3.45 ± 1.70	2.74 ± 1.63	3.22 ± 0.83	2.98

Means within the same row sharing the same superscript (a or b) are equivalent. Bonferroni correction was applied to all paired comparisons.

* $p < 0.001$.
† High scores indicate worse performance.
‡ $p < 0.01$.
§ $p < 0.05$.

AD = Alzheimer disease; DLB = dementia with Lewy bodies; WMS = Wechsler Memory Scale; WAIS = Wechsler Adult Intelligence Scale.

ported longitudinal course of study (answered in a yes/no format by an informant).[30]

Psychometric assessment. A 90-minute psychometric battery was administered annually to all participants approximately 2 weeks after of the clinical assessment to assess multiple cognitive domains: primary memory (Wechsler Memory Scale [WMS] Digits Forward),[31] working memory (WMS Digits Backward),[31] episodic memory (WMS Logical Memory and Associate Learning,[31] Benton Visual Retention Test: Form C-Recall),[32] semantic memory (Word Fluency,[33] Boston Naming Test),[34] and visuospatial/constructive (Wechsler Adult Intelligence Scale [WAIS] Digit Symbol and Block Design,[35] Benton Visual Retention Test: Form D-Copy,[32] Trailmaking A),[36] and a simple test of motor speed (Crossing Off).[37] Although these data originally were collected to investigate the clinical features of AD, the assessment protocol is sufficiently broad to test aspects of concentration and visuospatial domains as well as different aspects of memory. Psychometric data from the final time of assessment with fewer than three missing data points was used for the cross-sectional analyses; this final assessment averaged 5.7 years before death. Longitudinal analyses included all times of psychometric assessment and ranged from two to 20 assessments.

Neuropathologic assessment. All brains were examined with a standard protocol.[22,38] Following fixation in neutral buffered 10% formalin, tissue blocks were taken from 30 brain regions. Sections (6 μm) from paraffin-embedded tissue blocks were stained with hematoxylin-eosin, Gallyas, and modified Bielchowsky silver stains and immunohistochemical methods.[22,38] Two separate criteria for AD were used. One was based on quantification of diffuse and neuritic amyloid deposition in ten cortical regions.[22,38] In addition, National Institute on Aging-Reagan neuropathologic probability estimates of AD were calculated for each case.[39] The two sets of criteria have nearly complete diagnostic agreement. DLB pathologic diagnoses were made according to published criteria[3] using α-synuclein to screen for LBs. In this study, only cases with both neocortical and limbic LBs were included in the analyses. Terminal cases of AD (CDR 3) with LBs present limited to amygdala were not included.[40]

Statistical analyses. Factor analysis (Varimax rotation) was completed on psychometric raw scores. Factor extraction was based on both the Kaiser-Guttman rule of retaining components with eigenvalues >1 and inspection of screen plots of eigenvalues vs their ordinal positions. Although the sample size does not satisfy more conservative rules of factor analysis,[41,42] this sample size satisfies the subject-to-variable ratio rule of thumb (10:1) as cited by Nunnally and Bernstein[43], which has been supported by recent Monte Carlo studies findings, indicating that these ratios are sufficiently powerful to establish preliminary clinical results when the total sample size is >100.[44] Between-group comparisons of quantitative measures were conducted using analysis of variance (ANOVA) followed by Bonferroni corrected post hoc comparisons. The χ^2 test of independence was used for nominal variables. Longitudinal rates of cognitive decline on the psychometric measures were compared for the three groups using a random effects mixed model (PROC Mixed in SAS). This method was chosen because it is least susceptible to premorbid cognitive ability biases (intercept effects) by comparing average slopes of cognitive decline between groups.

Results. *Cross-sectional analyses.* Factor analysis on raw scores from the current sample confirmed a two-factor solution that replicates established indices of verbal memory and visuospatial ability found previously by our group using psychometric data from volunteers with pure AD.[45] Group means and SDs of the psychometric tests and factor scores are reported in table 3 (rotated eigenvalues = 4.99 and 4.14, 70% of variance explained;tables 3 and 4).

ANOVAs indicated group differences on both factors ($F(2,129) = 23.00$, $p < 0.001$; $F(2,129) = 6.82$, $p < 0.01$). Bonferroni corrected paired comparisons indicated that the pure DLB and DLB/AD did not differ on the visuospatial factor but that both groups scored significantly worse on

Table 4 *Rotated component matrix*

Psychometric test	Factor 1 visuospatial	Factor 2 verbal
Visuospatial factor		
WAIS Digit Symbol	0.88	0.26
Trailmaking A (s)	−0.87	−0.24
WAIS Block Design	0.87	0.21
Benton Recall Correct	0.78	0.32
Benton Copy Correct	0.77	0.34
Crossing Off	0.68	0.29
Verbal Factor		
WAIS Information	0.25	0.85
WMS Logical Memory	0.17	0.82
WMS Associate Memory	0.22	0.82
Boston Naming Test	0.33	0.75
WMS Digits Forward	0.38	0.64
WMS Digits Backward	0.54	0.58
Word Fluency	0.59	0.56
% Explained variance	38	32

WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale.

this factor than the pure AD group. The pure AD and DLB/AD groups did not differ on the verbal factor, but both groups scored significantly worse than the pure DLB group. Further, multivariate F tests indicated that the patterns of scores on the component subtests that made up each factor differed ($F(12,250) = 3.53$, $p < 0.001$; $F(14,248) = 2.85$, $p < 0.001$).

To determine which measures contributed to the observed group differences, univariate ANOVAs of the individual psychometric tests were also conducted (table 3). There were significant group differences on all visuospatial tests. The pattern of means was similar on all measures. The pure AD group performed best, followed by the pure DLB group, and then the mixed DLB/AD. Because many of these tests are speeded, group differences on the visuospatial tasks were reexamined using Crossing Off to control for motor slowing due to Parkinsonism and sum of boxes to control for dementia severity. The results remained unchanged. Although better motor scales exist in the literature to assess motor slowing (e.g., Unified PD Rating Scale),[46] Crossing Off was the only measure available for the entire sample.

There were also significant group differences on four of the seven measures of verbal memory: WMS Logical Memory, Boston Naming Test, WAIS Information, and Word Fluency. The pure DLB group performed best on all but one measure (Word Fluency) followed by the pure AD group and then the mixed DLB/AD group. Although the level of dementia was slightly lower for the pure DLB group, results remained unchanged if the CDR sum of boxes was used as a statistical control for dementia severity. Because of the small pure DLB group size in all post hoc, comparisons were repeated using the Mann–Whitney U nonparametric test. Results remained essentially unchanged (pure AD and pure DLB group differences become significant on one additional measure in each the visuospatial and verbal domains: Trailmaking and Associate Learning). In terms of behavioral manifestations, participants with pure DLB and DLB/AD experienced significantly more visual and auditory hallucinations than did the pure AD participants (table 1).

Longitudinal analyses. As expected, analyses of the longitudinal factors scores and individual psychometric tests indicated the presence of a main effect of time; progressive cognitive impairment was noted across both visuospatial and memory domains in all three groups (all F values >24.92, all p values <0.001). In contrast, none of the group $\times$ time interactions were significant (all F values <1.63, all p values >0.23). Thus, the rate of longitudinal cognitive decline for the pure DLB, DLB/AD, and AD groups were equivalent.

Discussion. Using data from a well–characterized longitudinal sample with neuropathologic confirmation, the current findings indicate that unlike other comorbidities of AD,[23,24] the presence of LB neuropathology significantly changes the cognitive presentation of AD but does not affect rates of cognitive decline once dementia is present.

First, results indicate that the presence of LB pathology alone is not associated with the *verbal memory* deficits witnessed in AD. These findings are consistent with other preliminary reports in the literature.[47] Pure DLB participants performed significantly better on all tests of verbal memory than did pure AD or mixed DLB/AD participants. Further, the DLB/AD performance was roughly equivalent to the AD participants on the verbal composite score and its subtests, indicating that LB and AD neuropathologic burden did not produce worse verbal memory in the combined group. The relative preservation of verbal skills in DLB may be an important feature of DLB that can aid in its clinical diagnosis in life.

Second, the pure AD and pure DLB groups were statistically equivalent on all tests of visuospatial ability, although individual subtest scores of the pure DLB group were generally lower than the scores of the pure AD group. This finding was surprising because current diagnostic criteria and findings of others[12-17] predict that those with pure DLB should perform much worse than those with pure AD in visuospatial ability. Only when a composite score of the individual tests was computed based on factor analysis did the groups differ significantly. Given the relatively low number of subjects in the pure DLB group, the purer measure of visual spatial ability was needed to attenuate error and increase sensitivity to detect the visuospatial decrement. Although a larger sample of pure DLB participants may increase the sensitivity of statistical tests for individual subtests, the composite scoring method is a more sensitive index than any single test. Given the rarity of pure DLB and the intensiveness of longitudinal study, the composite score is an efficient index of visuospatial deficits in DLB.

In contrast to the pure DLB participants, the com-

bined DLB/AD participants performed significantly worse on the visuospatial composite score and all its component subtests. Thus, the presence of both diseases produced poorer visuospatial performance than either pathologic burden alone. Unlike the verbal memory factor, the co-occurrence of the two diseases appears to interact, as evidenced by the significantly lower visuospatial scores, both composite and individual test scores.

Finally, the three groups were equivalent in the longitudinal analyses, indicating that the rate of decline was comparable across all three groups in both the visuospatial and verbal memory domains. Somewhat surprisingly, the presence of both LB and AD neuropathologies did not change the rate of dementia progression over the 4.5-year course measured. This suggests that LBs in the presence of AD plaques and tangles adds a selective visuospatial cognitive deficit but does not accelerate the dementing process in either the visuospatial or verbal memory domains. Further, the significant main effects in the longitudinal analyses indicate that the observed differences at the selected cross-sectional moment were present at enrollment (presumably before the clinical detection of the dementia) and persisted throughout the course of the disease. These longitudinal results extend the findings reported by others investigators.[48,49]

As a retrospective study, these findings have several limitations. First, volunteers who complete brain donation may not represent the population at large. Diagnosis of DLB in life is difficult (table 2), and the neuropathologic confirmed cases presented here may represent a sampling bias. Until diagnostic criteria for DLB are refined and the clinicopathologic features of the disease are known, this potential limitation will continue to be an issue in clinical DLB research.

Second, a valid criticism of the cross-sectional design of this study is that the observed lack of differences between the pure DLB and AD groups on the individual visuospatial subtests may have been due to the fact that the pure DLB participants were not matched well to the other groups. The pure DLB group contains more men, became demented at a younger age, and died earlier, which may have resulted in their relatively lower dementia ratings (see CDR and Blessed Dementia Scale[30] scores in table 1). The pure DLB group represents a convenience sample of those individuals presenting for evaluation; however, every attempt was made to match the overall sample at the cross-sectional moment on gender and dementia rating. The gender distribution of our sample is consistent with other reports of male predominance in DLB.[50] Further, the longitudinal analyses used a random effects mixed linear model because it is less susceptible to premorbid cognitive ability biases (intercept effects) by comparing average slopes of cognitive decline between groups. Thus, every individual serves as his or her own control reducing any biases that may occur with poor matching of the samples. Finally, all analyses were run with the dementia level statistically controlled. This did not substantially change any of the current findings. Ultimately, this clinical sample used all available participants who had come to postmortem examination, and one must judge the reliability of the test results by weighing the homogeneity of the sample (i.e., the pure DLB group were uniquely burdened by LB pathology) vs the statistical sensitivity of the tests and the effect sizes noted in table 3.

Third, variables selected for these analyses may not optimally capture the all clinical differences between the DLB and AD. For example, the pattern of visuospatial and verbal test scores across the psychometric battery suggests that there may be an important attention/executive function component to the cognitive deficits associated in mixed DLB/AD. Although an executive functioning factor was not indicated by this factor analysis, three visuospatial tasks with significant attention demands were significantly impaired in the mixed dementia group (Trailmaking A, Block Design, and Digit Symbol). Further, the verbal tasks that did not load very highly on the verbal factor have significant executive components as part of successful test performance. Several reports in the literature site attentional deficits,[12-17] but the tasks used are often speeded, thus confounding true cognitive impairment with motor slowing due to parkinsonism. Notably, all visuospatial differences remained significant even after motor slowing was statistically controlled.

Unfortunately, to test the attentional hypothesis robustly, a battery of more difficult visual attention tests is needed. For example, Trailmaking B may be a better test of executive function in the visuospatial domain, but it has not been consistently included in the ADRC longitudinal battery and thus data were not available for most of the participants in this report. Other tasks testing specific attentional modalities (e.g., Stroop task)[51] are not part of the standard ADRC battery and therefore may have precluded us from replicating the attention deficits previously described.[13] With a wider sampling of tests of visual attention and executive functioning domains, other cognitive changes associated with DLB might be detected and an executive factor may be indicated. Other tasks that have been used to discriminate DLB from AD include both unspeeded tasks (Wisconsin Card Sort,[52] Ravens Progressive Matrices,[53] Embedded Figures Test,[54] and Clock Drawing)[34] and speeded tasks (Trailmaking A and B, Stroop task, and select WAIS subtests[55,56] Block Design, Digit Symbol, Picture Arrangement, and Object Assembly).

Overall, these cross-sectional and longitudinal analyses are encouraging because they indicate that LB pathology in the presence of AD results in dissociable deficits that may be used to identify participants with either or both dementia pathologies. The visuospatial/verbal memory differences observed here were consistent across groups, persisted across time, and occurred very early in the dementing pro-

cess. Further, these data suggest that the presence of LBs alone may not produce the verbal memory deficits seen in AD or the frank visuospatial deficits suspected by current clinical criteria. When both diseases are present, the effect of LB and AD pathologies appear to be additive, wherein visuospatial performance suffers more in the presence of combined pathologies than with AD or LB pathologies alone. In contrast, there was no evidence that the combined pathologies accelerate the course of decline. Importantly, the combined longitudinal and cross-sectional results present an integrated snapshot of a broad set of findings from other cross-sectional clinical research.[20,57-59] Domain-specific testing may be one way to distinguish clinically the two types of dementia in life. Future investigations of cognitive impairment due to neuropathologic confirmed LB and AD pathology may help to refine the diagnostic criteria to discriminate better patients with pure DLB vs the more common mixed AD/DLB presentation. The application of quantitative pathology burden counts instead of categorical diagnostic groups may also add to future investigations of the impact that LBs have on cognitive function.

Acknowledgment

The authors thank Drs. Martha Storandt, Dan McKeel, Chengjie Xiong, and Elizabeth Grant of Washington University for assistance with manuscript preparation. They also thank the Clinical and Neuropathology cores of the Alzheimer Disease Research Center for providing diagnostic data.

References

1. Galvin JE, Lee VMY, Trojanowski JQ. Synucleinopathies—clinical and pathological implications. Arch Neurol 2001;58:186–190.
2. McKeith IG, Burn DJ, Ballard CG, et al. Dementia with Lewy bodies. Semin Clin Neuropsychiatry 2003;8:46–57.
3. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113–1124.
4. Dickson DW. Alpha-synuclein and the Lewy body disorders. Curr Opin Neurol 2001;14:423–432.
5. Hohl U, Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. Diagnostic accuracy of dementia with Lewy bodies. Arch Neurol 2000;57:347–351.
6. Lopez OL, Becher JT, Kaufer DI, et al. Research evaluation and prospective diagnosis of dementia with Lewy bodies. Arch Neurol 2002;59: 43–46.
7. Merdes AR, Hansen LA, Jeste DV, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. Neurology 2003;60:1586–1590.
8. Richard IH, Papka M, Rubio A, Kurlan R. Parkinson's disease and dementia with Lewy bodies: one disease or two? Mov Disord 2002;17: 1161–1165.
9. Stern Y, Jacobs D, Goldman J, et al. An investigation of clinical correlates of Lewy bodies in autopsy-proven Alzheimer disease. Arch Neurol 2001;58:460–465.
10. Calderon J, Perry RJ, Erzinclioglu SW, Berrios GE, Dening TR, Hodges JR. Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001;70:157–164.
11. Doubleday EK, Snowden JS, Varma AR, Neary D. Qualitative performance characteristics differentiate dementia with Lewy bodies and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002;72:602–607.
12. Armstrong TP, Hansen LA, Salmon DP, Masliah E. Rapidly progressive dementia in a patient with the Lewy body variant of Alzheimer's disease. Neurology 1991;41: 1180.
13. Collerton D, Burn D, McKeith I, O'Brien, J. Systematic review and meta-analysis show that dementia with Lewy bodies is a visual-perceptual and attentional-executive dementia. Dement Geriatr Cogn Disord 2003;16:229–237.
14. Galasko D, Katzman R, Salmon DP, Hansen L. Clinical and neuropathological findings in Lewy body dementias. Brain Cogn 1996;31: 166–175.
15. Hansen L, Salmon D, Galasko D, et al. The Lewy body variant of Alzheimer's disease—a clinical and pathological entity. Neurology 1990; 40:1–8.
16. Salmon DP, Galasko D, Hansen LA, Masliah E. Neuropsychological deficits associated with diffuse Lewy body disease. Brain Cogn 1996;31: 148–165.
17. Simard M, van Reekum, R, Cohen T. A review of the cognitive and behavioral symptoms in dementia with Lewy bodies. J Neuropsychiatry Clin Neurosci 2000;12:425–450.
18. Mosimann UP, Mather G, Wesnes KA, O'Brien, JT, Burn DJ, McKeith IG. Visual perception in Parkinson disease dementia and dementia with Lewy bodies. Neurology 2004;63:2091–2096.
19. Ralph MAL, Powell J, Howard D, Whitworth AB, Garrard P, Hodges JR. Semantic memory is impaired in both dementia with Lewy bodies and dementia of Alzheimer's type: a comparative neuropsychological study and literature review. J Neurol Neurosurg Psychiatry 2001;70: 149–156.
20. Shimomura T, Mori E, Yamashita H, et al. Cognitive loss in dementia with Lewy bodies and Alzheimer disease. Arch Neurol 1998;55:1547–1552.
21. Rubin EH, Storandt M, Miller JP, et al. A prospective study of cognitive function and onset of dementia in cognitively healthy elders. Arch Neurol 1998;55:395–401.
22. Berg L, McKeel DW Jr, Miller, JP, Baty J, Morris JC. Neuropathological indices of Alzheimer's disease in demented and nondemented persons aged 80 years and older. Arch Neurol 1993;50:349–358.
23. Powlishta KK, Storandt M, Mandernach TA, Hogan E, Grant EA, Morris JC. Absence of effect of depression on cognitive performance in early-stage Alzheimer disease. Arch Neurol 2004;61:1265–1268.
24. Villareal DT, Grant E, Miller JP, Storandt M, McKeel D, Morris JC. Clinical outcomes of possible versus probable Alzheimer's disease. Neurology 2003;61:661–667.
25. Berg L, McKeel DW Jr, Miller, JP, et al. Clinicopathologic studies in cognitively healthy aging and Alzheimer disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Arch Neurol 1998;55:326–335.
26. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414.
27. Berg L, McKeel DW, Miller JP, et al. Clinicopathologic studies in cognitively healthy aging and Alzheimer disease—relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Arch Neurol 1998;55:326–335.
28. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34: 939–944.
29. Berg L, Morris JC Diagnosis. In: Terry RD, Katzman R, Bick K, eds. Alzheimer disease. New York: Raven Press, 1994:9–25.
30. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of the elderly subjects. Br J Psychiatry 1968;114:797–811.
31. Wechsler D, Stone CP. Manual: Wechsler Memory Scale. New York: Psychological Corporation, 1973.
32. Benton AL. The revised visual retention test: clinical and experimental applications. New York: Psychological Corporation, 1963.
33. Thurstone LL, Thurstone LG. Examiner Manual for the SRA Primary Mental Abilities Test. Chicago: Science Research Associates, 1949.
34. Goodglass H, Kaplan E. The assessment of aphasia and related disorders, 2nd ed. Philadelphia: Lea & Febiger, 1983.
35. Wechsler D. Manual: Wechsler Adult Intelligence Scale. New York: Psychological Corporation, 1955.
36. Armitage SG. An analysis of certain psychological tests used in the evaluation of brain injury. Psych Monogr 1946;60:1–48.
37. Botwinick J, Storandt M. Speed functions, vocabulary ability, and age. Percept Mot Skills 1973;36:1123–1128.
38. McKeel DW Jr, Ball, MJ, Price JL, et al. Interlaboratory histopathologic assessment of Alzheimer neuropathology: different methodologies yield comparable diagnostic results. Alzheimer Dis Assoc Disord 1993; 7:136–151.
39. National Institute on Aging, Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiol Aging 1997;18:S1-S2.
40. Lippa CF, Fujiwara H, Mann DMA, et al. Lewy bodies contain altered alpha-synuclein in brains of many familiar Alzheimer's disease patients with mutations in presenilin and amyloid precursor protein genes. Am J Pathol 1998;153:1365–1370.
41. Fidell LS, Tabachnick BGA. California State. Preparatory data analysis. New York: USs, Inc., 2003: xxiii,711:141.
42. Comrey AL, Lee HB. A first course in factor analysis, 2nd ed., 1992.
43. Nunnally JC, Bernstein IH. Psychometric theory, 3rd ed. New York: McGraw-Hill, 1994.
44. Osborne JW, Costello AB. Sample size and subject to item ratio in principal components analysis. *Practical Assess Res Eval* 2004;9.
45. Kanne SM, Balota DA, Storandt M, McKeel DW, Morris JC. Relating anatomy to function in Alzheimer's disease. Neuropsychological profiles

predict regional neuropathology five years later. Neurology 1998;50: 979–985.
46. Movement Disorder Society. The Unified Parkinson's Disease Rating Scale (UPDRS): Status and recommendations. Mov Disord 2003;18: 738–750.
47. Hamilton JM, Salmon DP, Galasko D, et al. A comparison of episodic memory deficits in neuropathologically-confirmed dementia with Lewy bodies and Alzheimer's disease. J Int Neuropsychol Soc 2004;10:689–697.
48. Ballard C, Patel A, Oyebode F, Wilcock G. Cognitive decline in patients with Alzheimer's disease, vascular dementia and senile dementia of Lewy body type. Age Ageing 1996;25:209–213.
49. Walker Z, Allen RL, Shergill S, Mullan E, Katona CL. Three years survival in patients with a clinical diagnosis of dementia with Lewy bodies. Int J Geriatr Psychiatry 2000;15:267–273.
50. Rosenberg CK, Cumming TJ, Saunders AM, Widico C, McIntyre LM, Hullette CM. Dementia with Lewy bodies and Alzheimer's disease. Acta Neuropathol 2001;102:621–626.
51. Stroop JR. Studies of interference in serial verbal reaction. J Exp Psychol 1935;18:643–662.
52. Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtis G. Wisconsin Card Sorting Test Manual: revised and expanded. Odessa, FL: Psychological Assessment Resources, 1993.
53. Raven JC, Court JH, Raven J. Manual for Raven's Progressive Matrices. London: H.K. Lewis, 1976.
54. Spreen O, Strauss E. Compendium of neuropsychological tests. New York: Oxford University Press, 1991.
55. Wechsler DA. Manual: Wechsler Memory Scale-III. New York: Psychological Corporation, 1991.
56. Wechsler DA. Manual: Wechsler Adult Intelligence Scale, third edition. New York: Psychological Corporation, 1998.
57. Galasko D, Katzman R, Salmon DP, Hansen L. Clinical and neuropathological findings in Lewy body dementias. Brain Cogn 1996;31: 166–175.
58. Salmon DP, Galasko D, Hansen LA, et al. Neuropsychological deficits associated with diffuse Lewy body disease. Brain Cogn 1996;31:148–165.
59. Walker Z, Allen RL, Shergill S, Katona CL. Neuropsychological performance in Lewy body dementia and Alzheimer's disease. Br J Psychiatry 1997;170:156–158.