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Phenotypic differences based on staging of Alzheimer's neuropathology in autopsy-confirmed dementia with Lewy bodies

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Abstract

Introduction—The goal was to compare subgroups of dementia with Lewy Bodies (DLB) using neuropathological measures to differentiate 'pure' Lewy body (LB) dementia from 'mixed' DLB [co-occurring LB and Alzheimer's disease (AD) pathology] to facilitate diagnostic decision-making and future development of interventions based on predicted type(s) of neuropathology. Studies comparing these groups are rare relative to those differentiating 'pure' AD and all-cause DLB, and are limited by insufficient sample size, brief cognitive batteries, and/or absence of autopsy confirmation. To address these limitations, we assessed cognition and other features in a large, autopsy-confirmed DLB sample using an extensive neuropsychological battery.

Methods—Subjects from an AD research center autopsy series satisfying DLB pathology criteria were divided by an AD neuropathology index into DLB-LB (Braak stage 0–3) (n = 38) and DLB-AD (Braak stage 4–6) (n = 41) and compared on baseline variables from chart reviews and standardized measures.

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Author contributions to manuscript

Dr. Peavy drafted, revised, and gave final approval for the manuscript.
Dr. Edland conducted statistical analyses, and drafted, revised and gave final approval.
Dr. Toole provided suggestions for revising the manuscript and gave final approval.
Dr. Hansen drafted portions of the manuscript, provided suggestions for revision, and gave final approval.
Dr. Galasko revised the manuscript and gave final approval.
Dr. Mayo obtained funding, drafted and revised the manuscript, and gave final approval.

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Results—DLB-LB subjects were more impaired on visuospatial constructions, visual conceptual reasoning, and speed of processing, but less impaired on verbal memory and confrontation naming. All-type hallucinations occurred more frequently in DLB-LB, while delusions were common in both groups. Groups were similar in education and age at onset, and in baseline age, dementia severity, and functional capacity.

Conclusion—Salient findings included greater impairment on visual tasks and speed of processing and more frequent reports of all-type hallucinations in DLB-LB compared to DLB-AD. Relatively intact confrontation naming in DLB-LB and no differences in reported delusions were of note. Identifying differences in phenotypic features can improve prediction of underlying neuropathology.

Keywords

Dementia with Lewy bodies; Parkinsonism; Alzheimer's disease; Neuropsychology; Behavior; Delusions; Hallucinations

1. Introduction

Pathological heterogeneity of late life dementia makes linking neuropathological changes with phenotypic features challenging. The diagnostic classification of dementia with Lewy bodies (DLB) is a prime example given its prevalence and the frequent co-occurrence of Lewy body (LB) and Alzheimer's disease (AD) neuropathology. Most clinico-pathologic studies have compared DLB regardless of AD burden with ‘pure’ AD (pAD), noting better episodic memory [1,2], and poorer visuospatial abilities [1,3,4] and executive functions [1,4] in DLB, and mixed results on measures of confrontation naming [3–6].

Contributions of LB and AD neuropathology may be more clearly assessed by dividing, based on measures of AD pathology (e.g., Braak stage), broadly categorized DLB into ‘pure’ DLB (DLB-LB) and ‘mixed’ LB/AD pathology (DLB-AD) and comparing on phenotypic variables. One study of subjects with mild dementia administered a brief battery of tests and found poorer visuospatial abilities and better delayed memory in DLB-LB (n = 12) (Braak ≤ 3) than DLB-AD (Braak ≥ 4), but no differences in other areas of cognitive functioning [7]. Previous studies addressing differences in visual hallucinations [7–10], delusions [7,8,11], and extrapyramidal signs (EPS) [7–9,11] in these groups have yielded mixed results.

For the few studies that have compared ‘pure’ and ‘mixed’ DLB, small sample sizes, brief cognitive assessments, and lack of autopsy confirmation have limited interpretation of the findings. Our objective was to capitalize on a cohort of extensively characterized subjects who had prospective clinical assessments and standardized autopsy evaluations to define more clearly phenotypic features of ‘pure’ DLB in relation to DLB subjects with concomitant AD burden.

2. Methods

2.1. Participants

Subjects (n = 104) received a baseline clinical assessment at the time of enrollment into the University of California, San Diego (UCSD), Shiley-Marcos Alzheimer's Disease Research Center (ADRC) and satisfied criteria for DLB at autopsy [12]. Subjects with severe cognitive impairment (n = 18), defined as a baseline score less than 90 on the Mattis Dementia Rating Scale (DRS) [13], and subjects with a baseline diagnosis of Normal Control (n = 7) were excluded, leaving 79 participants. Braak stage, a widely employed method to determine burden of AD pathology [14], was used to compare DLBLB (minimal AD load; Braak 0–3) (n = 38) and DLB-AD (significant AD pathology; Braak 4–6) (n = 41). The decision to designate subjects with Braak stage 0–3 as one group and Braak stage 4–6 as a second group was made because, in our experience, it is typical for individuals age 70 and older who are “normal controls” to have neuropathology consistent with Braak stages 1 or 2. Those few with stage 3 typically have no clinically detectable dementia or MCI. However, every case with a Braak stage 4 or higher has a diagnosis of dementia, or at least MCI. We, therefore, made a decision to separate subjects into groups of Braak stage 0–3 versus 4–6.

2.2. General procedure

All data were retrieved from the first (baseline) visit; these took place between 1985 and 2010. All participants received neuropsychological, medical, neurological, and neuropsychiatric evaluations through the ADRC longitudinal cohort study. We examined two sources of data: 1) a structured nursing/neurology evaluation, and 2) neuropsychological tests. A nurse practitioner obtained medical history and reviewed outside medical records and medication use, and a neurologist performed a neurological exam that included standardized motor ratings. Nurses and neurologists obtained information through standardized ratings and structured questionnaires about neuropsychiatric symptoms and daily activities from the subject and a study partner who knew the subject well. A trained psychometrist administered a 2–3 h neuropsychological battery.

The subject and study partner provided written informed consent for the ADRC longitudinal cohort study prior to the initial evaluation. Consent for autopsy was obtained from subjects prior to death or from next of kin at the time of death. Study oversight was provided by the UCSD Human Research Protections Program.

2.3. Measures

2.3.1. Nursing/neurology chart review—Data were systematically abstracted from baseline Nursing and Neurology charts, medical records, and narrative records from examining nurses and neurologists. Prior to reviewing the charts, a list of specific behavioral, psychiatric, and other features associated with DLB was generated from the scientific literature and clinical experience. Symptoms of fluctuations, delusions, and hallucinations were located in standardized rating scales {Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) [15] and Diagnostic Interview Schedule (DIS) [16] prior to 2005, Neuropsychiatric Inventory (NPI) [17] 2005 and after} as well as in

thoroughly reviewed medical records. Responses concerning sleep and ‘acting out dreams’ were reviewed to produce a composite measure for REM Sleep Behavior Disorder (RBD). Blind to Braak stage, two investigators (AMM, GMP) and three trained graduate nursing students completed chart reviews. Items were coded as either present or absent. To determine inter-rater reliability, eight randomly selected charts originally reviewed by nursing students were reviewed by one of two investigators (AMM, GMP) blinded to the original review. The Cohen's Kappa statisticwas substantial/good at 0.65 [18,19]. Percent agreement was 84%.

2.3.2. Standardized neuropsychological battery—The ADRC neuropsychological battery included measures of global cognition, psychomotor skills, and premorbid intellectual functioning, as well as two or more tests within each of five domains: attention, language, memory, executive functions, and visuospatial abilities. The Mattis DRS measured global cognition. Digit Span Forward and Backward (Wechsler Adult Intelligence Scale, Psychological Corporation) targeted basic attention and working memory, respectively. Trail-making, Part A [20] was considered a measure of basic visual attention and speed. Visuospatial abilities were assessed through simple and complex copies, as well as construction of Block Designs (Wechsler Intelligence Scale for Children-Revised, Psychological Corporation). Measures of executive functioning included a modification of the Wisconsin Card Sorting Test (WCST) [21], Trail-Making, Part B [20], and clock drawing to command. The Boston Naming Test (BNT) [22] and letter and category fluency assessed language. Memory tests included Visual Reproduction and Logical Memory subtests of the Wechsler Memory Scale-Revised (WMS-R; Psychological Corporation) and the California Verbal Learning Test, first edition (CVLT) [23]. Timed tests across several domains (e.g., Trail-Making, WMS-R Digit Symbol) informed speed of processing.

2.3.3. Other measures—Motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS) is composed of 27 movement tasks or features, each rated from 0 (absent, normal, or none) to 4 (markedly abnormal). For this study, ratings were dichotomized as absent or present (any rating other than absent, normal, or none).

Pfeffer Outpatient Disability Scale (PODS) [24] was administered to the subject's study partner through 2004 and includes ten items (e.g., finances, shopping) reflecting level of dependence in instrumental daily activities. The Functional Assessment Questionnaire (FAQ) [25], composed of the same items, but scored differently, was administered to informants from 2005 through 2010. Both the FAQ and PODS provided a “not applicable” choice, but for the FAQ, the respondent could choose ‘normal’ (0 points), ‘has difficulty but does by self’ (1 point), ‘requires assistance’ (2 points), or ‘dependent’ (3 points). The PODS allowed responses of ‘does without any assistance or advice’ (0 points), ‘needs frequent advice or assistance’ (1 point), and ‘someone has recently taken over this activity completely or nearly completely’ (2 points). In order to re-calculate FAQ scores to match PODS scoring rules, the 1- and 2-point FAQ choices (difficulty, requires assistance) were combined and counted as 1 point, corresponding to the PODS 1- point choice, ‘needs frequent advice or assistance’.

2.3.4. Neuropathology—The UCSD ADRC has an autopsy rate of 90%. Each autopsy was performed within 24 h of death using a standard protocol. The brain was divided sagittally, then the left hemibrain fixed by immersion in 10% formalin for 10–14 days. Paraffin embedded blocks from midfrontal (MF, rostral superior temporal (ST) and inferior parietal (IP) neocortex, hippocampus, entorhinal cortex, basal ganglia/substantia innominata, mesencephalon, and pons were cut at 7 μm thickness for hematoxylin-eosin (H & E) and thioflavin-S counts. The midfrontal block is primarily from Brodmann area 46, the middle frontal area roughly corresponding to the dorsolateral prefrontal cortex. Depending on the cut, portions of Brodmann areas 9 and 45 may be included. The same examiner (LAH) using the same criteria determined total plaques, neuritic plaques, and neurofibrillary tangles (NFT). A modified Braak stage, a method that requires counting NFTs in at least five neuron clusters in layer two of the entorhinal cortex and averaging the results, was obtained for each case. Cases with Braak stage I to IV have fewer than 18 tangles on average in layer two of the entorhinal cortex and sparse neocortical tangles. Braak stage V required at least two neocortical sections (MF, ST, or IP) with some high magnification fields containing 3 or more neurofibrillary tangles each, while brains with 3 or more tangles in single high magnification fields in all three neocortical sections (MF,ST, and IP) were classified as Braak stage VI.

The DLB cases met consensus criteria for the pathologic diagnosis of DLB based on H & E staining, antiubiquitin immunostaining, and anti-α-synuclein immunostaining. Cases were only construed as DLB if Lewy bodies were found in the locus coeruleus, substantia nigra, and/or nucleus basalis of Meynert, as well as in the neocortex. Because all cases categorized as DLB had neocortical as well as brainstem Lewy bodies, all fell into either the limbic (transitional) or neocortical categories proposed in the 1996 consensus guidelines for the pathologic diagnosis of DLB. Cases were not classified as DLB if Lewy bodies were found only in the amygdala.

2.4. Statistical analyses

Items included in the retrospective nursing/neurology chart review were categorized as present or absent. Composite variables, rated as present if one or more items were acknowledged, included hallucinations of any type (i.e., visual, tactile, auditory), EPS (i.e., hypophonic speech, masked facies, resting tremor, rigidity, stooped posture, Parkinsonian gait, postural instability, bradykinesia), and behaviors associated with RBD (i.e., vivid dreams, acting out dreams, movements associated with dreams, flailing arms or legs, hitting, kicking). Ratings of presence or absence of falls, syncope, and hypotension were derived from a combination of structured questionnaires and outside medical records.

Due in part to floor effects and possible final common pathways for differing types of dementia [26,27], we excluded 18 severely demented (DRS < 90) participants as uninformative of early stage phenotype. We also excluded 7 subjects who had a diagnosis of normal control at baseline, leaving 38 DLB-LB and 41 DLB-AD for data analyses.

We used non-parametric Wilcoxon rank-sum test to compare groups on continuous variables and the non-parametric Fisher's exact test to compare categorical variables. Level of significancewas set at $p < 0.05$, with trending statistics defined as $0.05 < p < 0.10$.

Assumptions of all parametric tests (symmetry, approximate normality, absence of outlier values) were assessed by visual inspection of histograms and relevant bivariate scatterplots.

3. Results

3.1. Demographic/clinical features

Means and standard deviations for demographic and general clinical features for the entire group (n = 79) and for subjects divided by Braak stage are presented in Table 1. The DLB-LB and DLB-AD groups were similar at baseline in age and education, and on measures of global cognition and activities of daily living (ADLs).

3.2. Nursing/neurology chart review

Of the items from the nursing/neurology chart review, memory deficits were reported most frequently but did not differentiate DLB-LB and DLB-AD groups (see Table 2). Similarly, groups did not differ on reports of attention, visuospatial abilities, cognitive fluctuations, and vision, or on reported occurrence of delusions, apathy, depression, anxiety, and agitation. Hearing deficits were reported more often for DLB-LB than DLB-AD subjects, as were stooped posture and bradykinesia. Visual, auditory, and tactile hallucinations were acknowledged more frequently by the DLB-LB group. There were no significant group differences in autonomic symptoms including syncope, constipation, and hypotension. Although composite components targeting movements during sleep (e.g., acting out dreams) were reported infrequently, RBD features were more common in the DLB-LB group. Occurrence of falls was of interest given few DLB studies targeting this variable and its importance as a primary safety issue in older adults. Falls were more common in DLB-LB (32%) than DLB-AD (12%), a difference that was marginally significant (Fisher exact test: $p = 0.054$).

3.3. Standardized neuropsychological battery

The DLB-LB group performed worse on completion times for both conditions A (Wilcoxon; $p = 0.006$) and B (Wilcoxon; $p = 0.028$) of the Trail Making Test (see Table 3), but did not differ on the computed difference between completion times for A and B ($t = 1.18$; $p = 0.244$). The DLB-LB group performed worse than the DLB-AD group on one measure of executive functions (WCST) and on tests of simple and complex visuospatial processing (Visual Reproduction Copy, Clock Copy, Block Design). In contrast, the DLB-AD group performed worse on a language test that required naming visually-presented pictures. There was a notable discrepancy in scores on a test of delayed story recall, with performance significantly worse for the DLB-AD group. The majority of timed tests that included speed of processing as one component (i.e., Digit Symbol, Trail Making, Block Design, letter fluency) provided evidence of greater slowing in the DLB-LB than the DLB-AD group.

3.4. Other variables

UPDRS motor ratings identified a greater frequency of masked facies, Parkinsonian gait, postural instability, and bradykinesia in DLB-LB compared to DLB-AD (see Table 4), showing a trend toward significance ($p = 0.051$). Ratings on these factors were reflected in a significant group difference in the composite EPS measure ($p = 0.003$).

Mean brain weight was lower in the DLB-AD than DLB-LB group by sex, but the difference only reached statistical significance within women. While mean reported age at onset was 1.8 years older for the DLB-LB subjects, mean duration of illness onset to death was 2.4 (95% CI, 4.04 to 0.66) years shorter ($t = -3.2$; $p = 0.002$), and net age at death was comparable across the two groups. The percentage of subjects with at least one Apolipoprotein E (APOE)-e4 allele was significantly greater for the DLB-AD group. Finally, there were more men in the DLB-LB group, although the difference was not statistically significant (Fisher exact test; $p = 0.24$).

4. Discussion

This study compared groups of autopsy-confirmed DLB subjects divided by Braak stage in a relatively large cohort with mild to moderate dementia at baseline. The DLB-LB group performed worse than the DLB-AD group on visuospatial constructions, but better on indices of memory. Visual hallucinations, EPS and symptoms associated with RBD were detected more often in the DLB-LB than DLB-AD group. Symptoms typically associated with DLB [27] were generally more severe in the pure DLB-LB group. We interpret this to mean that the DLB-LB group had more LB pathology, an amount sufficient to lead to clinical dementia without concomitant AD pathology, as compared to the DLB-AD group.

Subjective reports of cognitive symptoms from subjects and informants were not sensitive to group membership, with subjective memory impairment reported for approximately 80% of both groups. Results revealed a notable discrepancy in scores on tests of story recall, with performance significantly worse for the DLB-AD group. Similar to the results of Yoshizawa et al. [7], we found minimal evidence of group differences in basic attention; the DLB-AD group completed Trails A more quickly than the DLB-LB subjects, but while this task reflects attentional capacity, it also requires visual scanning and speed of processing. Tests of attention that are more difficult or reflect fluctuating attention may be more sensitive to differences in DLB groups. On a second visual sequencing task (Trail Making B), commonly identified as a test of executive function due to a requirement to shift attention, we found better performance by the DLB-AD than DLB-LB group. Trails B, however, also measures attention, visual processing speed, and initiation. The two groups did not differ significantly on the normally distributed difference between A and B in time to completion ($t = 1.18$; $p = 0.244$), suggesting that the differences in the individual conditions is related, at least in part, to speed of processing, although there also may be an aspect of executive function (shifting from one line of thinking to another) that contributes to performance in both groups.

On measures of language, in contrast to findings by Yoshizawa et al. [7], the DLB-LB group in our study had greater difficulty on a test of letter fluency, but performed significantly better than DLB-AD subjects on a test of confrontation naming. While both are considered tests of language, fluency also measures initiation and speed of processing. Significantly better performance on confrontation naming by the DLB-LB group has not been reported in previous studies with autopsy confirmation and is not included in the most recent consensus criteria. It may, however, be a useful feature for discriminating pure DLB from DLB-AD and pAD.

A number of studies [10,11,28] have found that delusions are reported more frequently by DLB than pAD subjects. However, consistent with two studies addressing DLB-LB and DLB-AD [7,11], we found delusions occurring frequently in both groups (44% and 54% respectively). In addition to visual hallucinations, the DLB-LB group reported auditory and tactile hallucinations more frequently than the DLB-AD group, based largely on rare reports of these “other” hallucinations in DLB-AD. There have been very few, if any, studies of auditory and tactile hallucinations within subgroups of DLB. Multiple studies [28–31] have found more frequent reports of auditory hallucinations in DLB when compared to pAD.

Criteria for the clinical diagnosis of DLB list spontaneous parkinsonism as a core feature but do not identify specific signs. We observed increased occurrence of masked facies, Parkinsonian gait, postural instability, and bradykinesia in DLB-LB, observations consistent with the supposition that the DLB-LB group have a greater LB burden or greater effects on the nigrostriatal system.

Comparison of DLB-LB and DLB-AD on several additional variables revealed results similar to those of previous studies. There was a greater frequency of the APOE-e4 allele in the DLB-AD than DLB-LB group [11,32]. Interestingly, in our study, brain weight was greater in the DLB-LB than DLB-AD group, but only for women [8,33]. Duration of illness was significantly shorter in the DLB-LB group [8], but there were no significant differences between groups in age at onset and age at death [11,32].

Limitations of the study include reliance on multiple scales to obtain neuropsychiatric data and behavioral reports, identification of RBD only on the basis of these data and reports (polysomnography unavailable), the lack of a systematic questionnaire to assess fluctuating cognition, and subjective data alone from the nursing/neurological chart review to assess dysautonomic features. In addition, both the PODS and FAQ were used to assess ADLs; the rescoring of the FAQ to match PODS scores may have underestimated slightly the independence level in those subjects who could perform an activity with difficulty but without help or advice. Finally, bias may have resulted from the fact that the study sample was not population-based, and, therefore, may not have been representative of the population at large.

The availability of autopsy information that included quantification and categorization of AD-associated neuropathology and DLB diagnostic confirmation was a strength of the study. We addressed a wide range of variables, particularly those from objective neuropsychological testing, with multiple measures within each domain. The small number of studies comparing DLB-LB and DLB-AD groups have generally used samples without autopsy confirmation or small autopsy-confirmed samples. The significantly larger number of subjects in our study increases confidence in both confirmatory and novel findings.

In summary, the frequent co-occurrence of neuropathological changes associated with DLB and AD and persisting difficulties encountered in the clinical diagnosis of DLB highlight the importance of studying clinical features of autopsy-confirmed DLB. Inconsistences in the literature may be explained by variability in the extent of AD pathology, sample size, level of diagnostic certainty, stage of disease progression, and type and validity of selected

measures. Our findings, derived from a relatively large, autopsy-confirmed DLB cohort with detailed characterization at initial presentation, confirm and expand results from previous studies. We found many of the central and core features listed in the revised consensus criteria for the clinical diagnosis of DLB to differentiate DLB-LB and DLB-AD subjects, although these criteria are based largely on studies that have compared DLB-AD and pAD. In our study, performance on easily administered tests of confrontation naming may be clinically relevant to diagnoses within the broader DLB category. Greater cognitive impairment in DLB-LB than DLB-AD was identified exclusively on tasks that involved performance on visual tasks and/or speed of processing, leaving questions concerning primary contributions of basic attention and executive functions. Similarly, the literature provides limited data or inconsistent results concerning auditory and tactile hallucinations, delusions, and falls, despite consideration of these symptoms as supportive features of DLB. We propose systematic assessment of these features to improve diagnostic accuracy and understanding of neuropathological processes underlying pure and mixed DLB. More precise clinical measures, imaging techniques, and biomarkers within DLB will allow progress toward understanding phenotypic variability and developing targeted interventions.

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Table 1

Means and standard deviations (SD) of demographic and clinical features for all subjects (n = 79) and subjects divided into low (n = 38) and high (n = 41) Braak stage.

	Braak stage						
	All subjects		Low		High		*t*-test
	Mean	SD	Mean	SD	Mean	SD	p-value
Age, years	73.7	6.7	74.7	6.0	72.8	7.2	0.201
Education, years	14.9	2.9	15.4	2.8	14.4	2.9	0.124
Mattis DRS total score	113.0	11.1	112.6	10.9	113.4	11.5	0.763
PODS, total/(items included × 2)*	0.6	0.3	0.6	0.2	0.6	0.3	0.549

DRS = Dementia Rating Scale; higher score reflects better cognitive performance.
PODS = Pfeffer Outpatient Disability Scale.

*Score calculation (total divided by # items included × 2) controlled for activities never performed. Higher score reflects greater dependence in instrumental activities of daily living.

Table 2

Nursing/neurology chart review results for all (n = 79), low Braak (n = 38) and high Braak (n = 41) subjects.

Symptom	Percentage reporting symptom			p-value
	Braak stage			
	All subjects	Low	High	Fisher's exact test
Cognitive				
Attention	15.2	18.4	12.2	0.537
Memory	83.5	86.8	80.5	0.550
Visuospatial Abilities	24.1	28.9	19.5	0.431
Fluctuations	11.4	15.8	7.3	0.300
Sensory				
Hearing loss	50.6	63.2	39.0	0.043
Visual problems	29.1	28.9	29.3	1.00
Psychiatric				
Hallucinations, any type	31.6	50.0	14.6	0.001
Visual Hallucinations e People	24.1	36.8	12.2	0.017
Auditory Hallucinations	11.4	21.1	2.4	0.012
Tactile Hallucinations	7.6	15.8	0.0	0.010
Delusions, any type	48.1	39.5	56.1	0.178
Apathy	38.0	42.1	34.1	0.495
Depression	53.2	50.0	56.1	0.655
Anxiety	22.8	31.6	14.6	0.107
Agitation	7.6	10.5	4.9	0.420
Motor				
Hypophonic Speech	11.4	15.8	7.3	0.300
Masked Facies	31.6	42.1	22.0	0.089
Resting Tremor	16.5	21.1	12.2	0.368
Rigidity	25.3	34.2	17.1	0.120
Stooped Posture	41.8	60.5	24.4	0.002
Parkinsonian Gait	32.9	36.8	29.3	0.632
Postural Instability	17.7	23.7	12.2	0.242
Bradykinesia	32.9	47.4	19.5	0.016
EPS Composite	75.9	92.1	61.0	0.001
Activities of Daily Living				
Getting lost	73.4	81.6	65.9	0.133
Falls	21.5	31.6	12.2	0.054
Sleep				
Composite RBD	13.9	26.3	2.4	0.003
Other				
Hypotension	7.6	13.2	2.4	0.100
Syncope	12.7	13.2	12.2	1.00

Symptom	Percentage reporting symptom			p-value
	Braak stage			
	All subjects	Low	High	Fisher's exact test
Constipation	21.5	26.3	17.1	0.414

DLB = Lewy body dementia.
RBD = REM Sleep Behavior Disorder.
Hallucinations, any type includes visual, auditory, and olfactory hallucinations.
RBD composite includes vivid dreams, acting out dreams, movements associated with dreams, flailing arms or legs, hitting, kicking.
EPS composite includes hypophonic speech, masked facies, resting tremor, rigidity, stooped posture, Parkinsonian gait, postural instability, and bradykinesia.

Table 3

Means and standard deviations (SD) for DLB subjects with low (n = 38) or high (n = 41) Braak stage on tests from the standardized neuropsychological battery.

	Braak stage				
	Low		High		Wilcoxon rank-sum test
	Mean	SD	Mean	SD	p-value
Mattis DRS Subscale Scores					
Attention	33.6	2.5	34.9	2.0	0.009
Initiation	24.0	5.8	26.6	6.0	0.063
Construction	3.6	1.4	4.6	1.3	0.003
Conceptualization	32.3	4.3	32.6	4.1	0.702
Memory	19.0	3.4	14.8	4.2	<0.0001
Attention					
Digit Span Total	11.3	3.3	12.1	3.3	0.236
Digit Span Forward length	5.9	1.1	6.2	1.1	0.247
Digit Span Backward length	3.5	1.0	3.7	1.0	0.421
Trails A (time, seconds)	116.4	37.5	88.2	42.4	0.006
Trails A errors	4.2	5.8	2.2	4.8	0.126
Executive Functions					
Modified WCS –# categories	1.3	1.1	2.3	1.8	0.013
Trails B (time, seconds)	278.6	53.8	231.1	84.4	0.028
Trails B errors	13.6	8.7	6.7	7.6	0.004
Clock Command	1.5	0.8	1.8	0.8	0.128
Speed of Processing					
Digit Symbol	14.6	9.7	22.3	12.1	0.014
Visuospatial Ability					
Visual Reproduction Copy	9.6	5.0	14.3	3.9	<0.0001
Clock Copy	1.8	1.0	2.4	0.8	0.020
Block Design	8.9	9.4	19.1	13.6	<0.001
Language					

	Braak stage				
	Low		High		Wilcoxon rank-sum test
	Mean	SD	Mean	SD	p-value
Boston Naming Test	23.4	4.6	21.1	5.6	0.044
Letter Fluency	19.3	11.1	24.6	11.1	0.007
Category Fluency	20.5	7.6	22.1	8.3	0.456
Memory					
CVLT Learning 1–5, scaled	22.1	12.7	20.7	10.3	0.958
CVLT Long Delay Free Recall	2.2	2.6	1.4	2.1	0.134
CVLT Discriminability	72.9	10.9	67.6	14.2	0.151
Logical Memory Immediate	13.2	8.0	8.5	4.6	0.054
Logical Memory Delay	9.5	7.3	2.8	3.0	<0.0001
Visual Reproduction Immediate	3.7	2.7	4.7	2.4	0.072
Visual Reproduction Delay	1.6	2.1	1.3	2.0	0.532

CVLT = California Verbal Learning Test.
WCS = Wisconsin Card Sort, Nelson version.
Note: For all tests except times to completion and error scores associated with Trail Making A and B, higher scores reflect better performance.

Table 4

Results for all (n = 79), low Braak (n = 38) and high Braak (n = 41) subjects on dichotomized ratings of items from the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS).

	Percentage with impaired rating			p-value
	All subjects	Low Braak	High Braak	Fisher's exact test
Hypophonic Speech	24.1	31.6	17.1	0.188
Masked Facies	41.8	57.9	26.8	0.007
Resting Tremor	8.9	15.8	2.4	0.051
Rigidity	31.6	42.1	22.0	0.089
Stooped Posture	20.3	28.9	12.2	0.093
Parkinsonian Gait	31.6	47.4	17.1	0.007
Postural Instability	44.3	63.2	26.8	0.002
Bradykinesia	35.4	47.4	24.4	0.037
EPS Composite	58.2	76.3	41.5	0.003