Research article

Neuropsychological and clinical indicators of Lewy body and Alzheimer's pathology

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Abstract

Background: Clinical distinction between Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) poses significant challenges due to pathological comorbidity. Similar ages of onset and overlapping cognitive and psychiatric symptoms can lead to diagnostic inaccuracy and inappropriate treatment recommendations.

Objective: Identify the best combination of clinical and neuropsychological predictors of AD, DLB, and mixed DLB/AD neuropathology in dementia patients.

Methods: Using the National Alzheimer's Coordinating Center dataset, we selected either pure AD ($n = 189$), DLB ($n = 21$), or mixed DLB/AD ($n = 42$) patients on autopsy. Neuropsychological and clinical predictors, including core clinical features of DLB, were entered into multivariable logistic regressions.

Results: Gait disturbances (odds ratio (OR) = 19.32; p = 0.01), visual-spatial complaints (OR = 6.06; p = 0.03), and visual hallucinations (OR = 31.06; p = 0.002) predicted DLB compared to AD, along with better memory (OR = 3.42; p = 0.003), naming (OR = 3.35; p = 0.002), and worse processing speed (OR = 0.51; p = 0.01). When comparing DLB to DLB/AD, gait disturbances (OR = 6.33; p = 0.01), increased depressive symptoms (OR = 1.44; p = 0.03), and better memory (OR = 3.01; p = 0.004) predicted DLB. Finally, rapid eye movement sleep behavior disorder (RBD) (OR = 6.44; p = 0.004), parkinsonism severity (OR = 1.07; p = 0.02), and lower depressive symptoms (OR = 0.70; p = 0.006) and memory impairment (OR = 0.57; p = 0.02) distinguished DLB/AD from AD.

Conclusions: Our study converges with prior research suggesting specific neuropsychological and clinical features can help distinguish DLB from AD. Neuropsychological differentiation becomes more challenging among mixed pathologies and in advanced cognitive impairment, although the presence of RBD and parkinsonism distinguished DLB. Earlier clinical assessment and incorporation of in vivo and postmortem biomarkers should enhance diagnostic accuracy and understanding of disease characteristics, offering significant relevance for disease-modifying treatments.

Keywords

Alzheimer's disease, cognition, dementia, diagnosis, Lewy body disease, neuropathology, neuropsychology

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Introduction

Dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia following Alzheimer's disease (AD), comprising up to 5% of all dementia patients.[1,2] Diagnosis of probable DLB requires the presence of dementia with at least two of the following core features: parkinsonism, visual hallucinations, cognitive fluctuations, and rapid eye movement (REM) sleep behavior disorder (RBD).[3] Clinically, DLB is diagnosed when dementia occurs before or concurrently with parkinsonism (before or within one year after the onset of parkinsonism

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in research settings), whereas the term Parkinson's disease dementia is given when dementia occurs in the context of well-established Parkinson's disease.[4] Diagnostic features of AD include insidious onset, clear-cut history of gradual cognitive decline (by report or observation), and deficits in at least two cognitive domains (e.g., memory, language, executive functioning, etc.).[5] While both AD and DLB are diagnosed clinically, definitive diagnosis is only achieved with neuropathological examination.

The primary underlying neuropathology in AD consists of intracellular neurofibrillary tangles (NFT), composed of tau, and extracellular amyloid-β (Aβ) plaques, while DLB involves abnormal accumulations of a-synuclein (αSyn) proteins (i.e., Lewy bodies [LB] in neurons, Lewy neurites [LN] in axons and dendrites). While pathologically distinct, AD and DLB commonly overlap in varying degrees of cellular density and distribution, with studies indicating over 50 percent of DLB patients also manifest AD neuropathology.[6–8] Not surprisingly, pathologic heterogeneity can make diagnostic differentiation challenging for clinicians, especially in the later disease stages when considerable overlap in cognitive, psychiatric, and motor presentations exists.[3] Indeed, the diagnostic accuracy of DLB is especially low in cases with high levels of NFT.[9] As a result, DLB is often misdiagnosed, with many mixed DLB/AD cases misclassified as probable AD and vice versa.[10] Diagnostic accuracy is also important for prognosis, as mixed DLB/AD patients tend to progress more rapidly compared to pure DLB or AD patients,[11,12] and experience significantly more functional decline.[13] Further, improving clinical differentiation will help facilitate the accuracy of disease-modifying agents (e.g., targeting Aβ, tau, and/or αSyn) and inform safety considerations, as some patients with DLB can experience adverse reactions to antipsychotic medication (i.e., neuroleptic sensitivity).[14] From a research standpoint, findings may be confounded if subjects are placed into inappropriate groups due to misclassification.

Neuropsychological evaluation can provide valuable diagnostic information when distinguishing DLB from AD. For instance, relatively greater neurocognitive deficits in attention, processing speed, executive function, and visuospatial ability have been documented in DLB, while more pronounced verbal memory and naming deficits may suggest AD.[15–18,19–21] However, the vast majority of prior investigations have used clinical diagnostic cohorts without neuropathological verification,[18,19,22,23] and the relatively small number of autopsy-confirmed studies have revealed some inconsistent neuropsychological findings, especially in mixed pathologies (e.g., DLB/AD). For example, some studies have found worse visuospatial ability in DLB compared to AD,[20,21,24,25] with relatively intact memory and naming abilities;[15,24,26] while others have failed to find any differences in memory, naming, or executive functioning,[27,28] and in some cases, visuospatial abilities.[26]

Neuropsychiatric and motor features can also enhance diagnosis accuracy and inform treatment; for example, higher rates of visual hallucinations, delusions, depression, and extrapyramidal symptoms (EPS) have been observed in DLB compared to AD patients,[20,21,24,27,29,30] with associated worse functional impairment, likely due to a combination of cognitive, motor, and behavioral deficits in DLB.[31] Unfortunately, the majority of autopsy studies examined either neuropsychological *or* clinical (e.g., motor, neuropsychiatric) symptoms, but have failed to include both.[15,17] Moreover, most work combining clinical and neuropsychological variables were done prior to the updated 2017 DLB Consortium criteria, which added RBD as a core clinical feature,[20,21] which is especially important given that RBD is highly associated with synuclein pathology.[32] Additional methodological limitations from prior clinicopathological studies include not accounting for varying levels of neuropathology (e.g., not including a pure DLB or mixed DLB/AD group), small sample sizes, and using brief neuropsychological protocols.[11,12,22,23,27,33–35]

The current study utilized a large autopsy-confirmed dementia sample of patients with three different levels of neuropathology: pure AD, pure DLB, or mixed DLB/AD. Our primary objective was to investigate the predictive value of several key neuropsychological, motor, *and* clinical features that have empirically shown to enhance differentiation of DLB and AD, including the most recent core DLB criteria (visual hallucinations, cognitive fluctuations, EPS, and RBD).[3]

Methods

Data set and participants

Data from this study were obtained from The National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS) and Neuropathology Data Set (NP) through the Alzheimer's Disease Research Centers Program (ADRC), which is funded by the National Institute on Aging. Patient and collateral information is collected by trained physicians, neuropsychologists, and ADRC research personnel, and diagnosis is made by either the examining physician or consensus team.[36] Consent is obtained at individual ADRCs and approved by individual institutional review boards.[37] Institutional Review Board (IRB) approval was granted 4/27/20 (Pacific University IRB Reference # 052-20).

Since 2005, data from the UDS have been supplemented by the NP for participants who had autopsy. These data are linked to the UDS and include information on demographics, date of death, and presence or absence of neuropathological features of most major dementias such as AD, DLB, and frontotemporal lobar degeneration (FTLD). Data collected from NACC Versions 1 and 2 (September 2005 to April 2014) were included in this study.

Neuropathological examination

All participants underwent standardized autopsy examinations.[38] The inclusion criteria for the current study were: (a) clinical diagnosis of dementia (b) neuropathological confirmation of AD and/or LB pathology (described in detail below) and (c) completed UDS forms, including demographics (age, sex, education, race); specific clinical variables (clinical diagnosis, age of death, disease duration); neuropsychological test scores; motor symptoms (Unified Parkinson's Disease Rating Scale; UPDRS-III); Neuropsychiatric Inventory Questionnaire (NPI-Q); self-reported depressive symptoms (Geriatric Depression Scale - Short Version, [GDS-15]); and other cognitive/behavioral symptoms (Clinician Judgment of Symptoms). Exclusion criteria for the current study were: (a) a diagnosis of PD or other dementia subtypes (e.g., FTLD, vascular dementia), and (b) neuropathological evidence of hippocampal sclerosis, TDP-43, or other pathological diagnoses (e.g., neoplasm, abscess, multiple sclerosis, large arterial infarcts, lacunes, or hemorrhages). Figure 1 includes a summary of the inclusion/exclusion criteria for the current study. Data from the first ADRC visit with a dementia diagnosis were analyzed in this study.

All AD cases were rated by ADRC staff according to the National Institute on Aging-Alzheimer's Association (NIA-AA)[39] criteria. Among the variables available in NACC, the NACC utilizes the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[40] semi-quantitative grading scale for both neuritic and diffuse Aβ plaques (as opposed to Thal phase) and Braak staging[41] for NFTs.

Neuritic plaques are considered argyrophilic, thioflavin-S-positive or tau-positive dystrophic neuritis with or without amyloid cores. Aβ plaques are considered plaques with non-compact amyloid and no dystrophic neurites. The CERAD criteria for both types of plaques are rated accordingly: 0 = none; 1 = sparse; 2 = moderate; 3 = frequent. Braak staging for NFTs was rated according to stages of neurofibrillary degeneration: 0 (none), 1–2 (trans-entorhinal/entorhinal region); 3–4 (hippocampus and

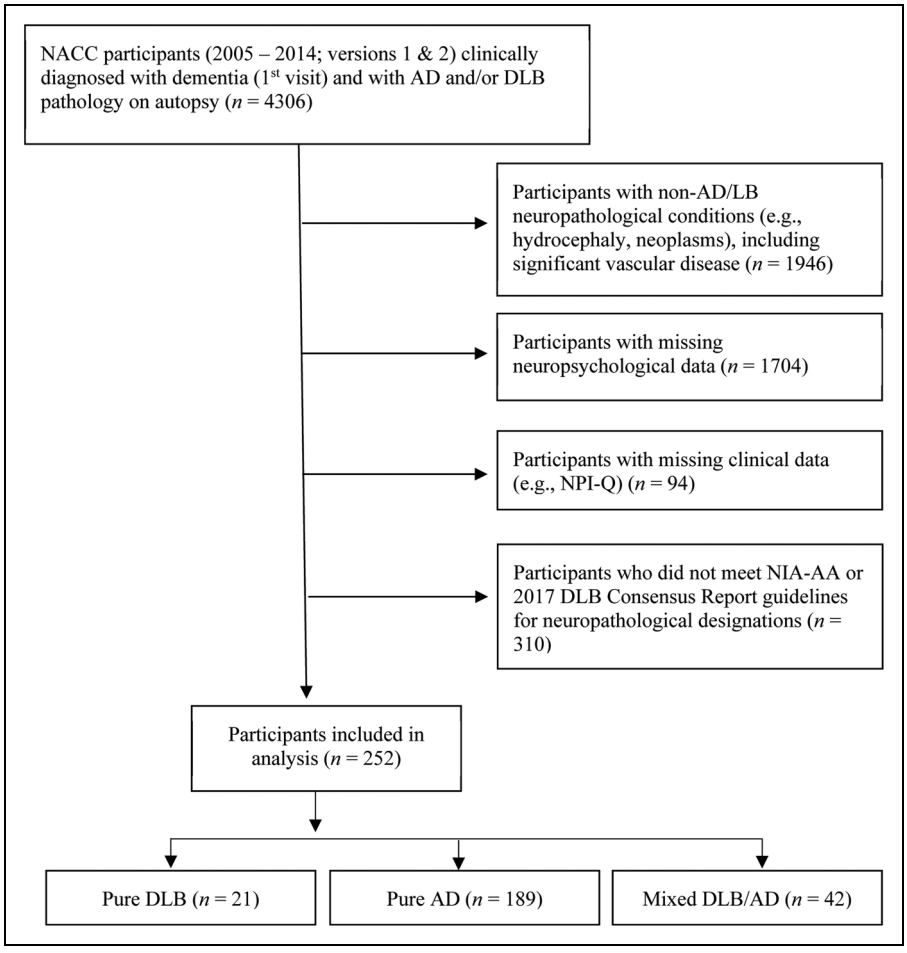

Figure 1. Flow diagram of exclusion/inclusion process for selection of NACC participants. NACC: National Alzheimer's Coordinating Center; AD: Alzheimer's disease; DLB: dementia with Lewy bodies; NIA-AA: National Institute on Aging-Alzheimer's Association; NPI-Q: Neuropsychiatric Inventory Questionnaire.

amygdala extending slightly to association areas); 5–6 (widely distributed throughout neocortex). The NIA-AA combines the three types of AD neuropathological change into an "ABC" score, rated as "No," "Low," Intermediate," and "High," representing the likelihood that neuropathological findings are associated with the AD clinical syndrome.

All DLB cases were characterized according to the fourth consensus report of the DLB consortium,[3] according to 5 stages: (1) no LB pathology, (2) brainstem predominant (medulla, pons, or midbrain), (3) limbic/transitional (cingulate or entorhinal cortex, typically with brainstem involvement) or amygdala predominant, (4) neocortical/diffuse (frontal, temporal, or parietal cortices, usually brainstem or limbic involvement, which may include the amygdala, and (5) LB present, but region unspecified or found in the olfactory bulb. The fourth consensus report developed a classification system determining the likelihood - "Low," "Intermediate," or "High" - of the DLB clinical syndrome based on LB neuropathology as well as taking into account the degree of concomitant AD pathology (based on NIA-AA guidelines). All DLB participants underwent αSyn immunohistochemistry staining, as recommended by the DLB consensus guidelines.

All participants received an antemortem diagnosis of dementia at their first visit. Participants were assigned to one of three neuropathological groups: pure DLB, AD, and mixed DLB/AD. Pure DLB participants met the consensus guidelines for "High" likelihood DLB (neocortex areas) and NIA-AA "Low" likelihood AD neuropathological change (Braak stages 0–3). Pure AD participants met criteria for NIA-AA "High" likelihood AD (Braak stages 5–6, moderate/frequent neuritic plaques, and frequent Aβ plaques) and "Low" likelihood DLB (no LB). Mixed DLB/AD participants met "High" likelihood for both AD and DLB. Of the 4306 autopsy subjects initially received from NACC, a total of 252 participants were retained after applying inclusion/exclusion criteria: pure AD = 189; pure DLB = 21; mixed DLB/AD = 42. A vast number of subjects were excluded for either missing data or co-occurring non-DLB or AD neurological conditions (see Figure 1 for a breakdown of inclusion/exclusion process).

Neuropsychological assessment

All participants were administered the neuropsychological tests listed in Table 1, which included measures of global cognition, attention, processing speed, visuospatial ability, learning, memory, language (semantic fluency and naming), and executive functioning. Demographic adjusted (age, gender, and education) z-scores were calculated for neuropsychological measures when available using a web-based calculator.[42] Normative data for pentagon copy and number of errors on the Trail-Making Test – B (TMT-B) were not available. To limit the number of analyses, z-scores for Trail Making Test – A (TMT-A) and Digit Symbol Substitution Test (DSST) were averaged to create a composite z-score for processing speed. Likewise, verbal fluency tests (animals and vegetables) were averaged to form a composite z-score for semantic fluency. Unfortunately, data for phonemic fluency were unavailable in the current data set.

Table 1. Description of neuropsychological measures.

Measure	Cognitive functions
MMSE	Global cognition
MMSE Intersecting Pentagons Copy	Visuospatial ability
WMS-R Digit Forward	Simple auditory attention
WMS-R Digit Backward	Working memory
WAIS-R Digit Symbol Substitution Test	Visuomotor processing speed, fine motor control of the hands, and sustained attention
Trail Making Test - A	Visuomotor processing speed, fine motor control of the hands, and sustained attention
Trail Making Test – B	Executive functioning
Trail Making Test – B Errors	Executive functioning
WMS-R Logical Memory Story A part 1	Immediate recall
WMS-R Logical Memory Story A part 2	Delayed recall
Boston Naming Test (30-odd numbered items)	Confrontation naming
Category Fluency (Animals and Vegetables)	Word generation and semantic fluency

WMS-R: Wechsler Memory Scale – Revised; WAIS-R: Wechsler Adult Intelligence Scale – Revised; MMSE: Mini-Mental State Examination.

Clinical and motor assessment

Clinician judgment of symptoms. Clinician judgment of symptoms includes information obtained from the patient, collateral informant, medical records, and/or observation. The NACC protocol includes questions about the presence of cognitive, behavioral, and motor symptoms, course of decline, predominant cognitive domain affected, and whether the patient is a candidate for further DLB or FTLD screening.[43] Information retained from this form includes the presence or absence of fluctuating cognition, apathy/withdrawal, anxiety, irritability, motor impairment (gait disorder, falls, tremor, and bradykinesia), visual and auditory hallucinations, delusions, subjective reporting of visual-spatial impairment, and RBD.

The Geriatric Depression Scale (GDS – 15; short version). The GDS-15 was used to assess depressive symptomatology; recommended cutoff scores are: 0–4 = Normal; 5–8 Mild; 9–11 Moderate; and 12–15 = Severe.[44]

Unified Parkinson's Disease Rating Scale – Motor Examination (UPDRS-III). The UPDRS-III includes 27 items related to severity of movement impairment.[43] Questions are rated from 0 (absent, normal, or none) to 4 (markedly abnormal). Motor domains assessed include speech, facial mobility, tremor (resting and action), finger taps, hand movements, rapid alternating movements (pronation and supination), leg agility, arising from a chair, posture, gait, postural stability, and body bradykinesia/hypokinesia.

Neuropsychiatric Inventory Questionnaire (NPI-Q). The NPI-Q is a brief informant-based instrument that measures neuropsychiatric symptoms of the participant over the last month.[45] The NPI-Q contains 12 neuropsychiatric domains (i.e., hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, nighttime behavioral disturbances, and appetite/eating disturbances) and there is one question per domain that reflects the cardinal symptoms of that domain. Each question is rated either "Yes" (present), "No" (absent), or "Unknown." If the response is "Yes" the interviewer then rates the severity of the symptoms over the last month on a 3-point scale (1 – mild, 2 – moderate, 3 – severe).

Statistical analyses

Three separate binary logistic regressions were performed to identify all potential neuropsychological and clinical predictors for differentiation of pure DLB versus pure AD, pure DLB versus mixed DLB/AD, and mixed DLB/AD versus pure AD. For each comparison, univariable analyses were first conducted. A popular variable selection approach is to select variables from a univariable analysis for candidate predictor variables for the multivariable model based on the univariable p values (e.g., $p < 0.05$ or perhaps $p < 0.20$). Since nearly all variables met that criterion (Supplemental Table 1), we simply considered all variables to be candidate predictors. We then used a forward variable selection, with $p < 0.05$ as the criterion for inclusion in the model and interactively chose between collinear variables to achieve model stability. In addition, due to the fact that using a long list of candidate predictor variables in a multivariable model can increase likelihood of finding false positive predictors (possibly due to overfitting), a bootstrap inclusion fraction (*BIF*) was computed for each predictor variable. This represents the percentage of times the variable remains in the final multivariable model in a large number of bootstrap resamples in which the variable selection is repeated.[46,47] Predictors with $BIFs < 50\%$ were dropped from the final model as unreliable, as these would not likely remain as significant predictors in future datasets. To assess the performance of the three multivariable models, we discovered the optimal cut point of the predicted probabilities from the three models to create a binary predictor. Then we computed the sensitivity and specificity and area under the receiver operating characteristic curve (ROC). Of note, we made no attempt to validate model performance as providing a prediction equation is not a goal of the paper. We simply identified some potential candidates that could be used to come up with a prediction equation. All reported p values are two-sided comparisons. It is also important to note that while many variables had significant associations in the univariable model, including core DLB symptoms,[3] some were not retained in the final multivariable models. This is very common in multivariable modeling as variables by themselves can be predictive of the outcome but once combined with other variables they drop out of the model as being non-significant because another variable or combination of variables explains the outcome more completely.[48] Statistical analysis was performed using the Stata version 17.0- statistical software (StataCorp, College Station, TX, USA).

Results

Descriptive demographic, clinical, and neuropsychological data are presented in Tables 2 and 3, including the p values obtained from each of the three univariable logistic regressions, which are reported in Supplemental Table 1. Table 2 shows that for demographic data, only sex was significant; however, the vast majority of neuropsychological scores were previously demographically adjusted (i.e., age, education, and sex). Importantly, disease characteristics (age of death and disease duration) did not significantly predict group membership.

Multivariable logistic regressions

Pure DLB versus pure AD. Table 4 lists the results and indicates that 6 variables were retained in the final model: gait disturbance, delayed recall (Logical Memory – II [LM-II]), processing speed (composite score; DSST and TMT – A), Boston Naming Test (BNT, odd-numbered items), visual hallucinations, and visual-spatial complaints. For clinical symptoms, presenting with visual hallucinations, gait disturbances, and visual-spatial complaints increases the odds of having pure DLB by about 31- ($p = 0.002$), 19- ($p = 0.01$), and 6-fold ($p = 0.03$), respectively, compared to pure AD. For neuropsychological variables, for every one-unit z-score increase in LM-II and BNT, the odds of having pure DLB were about 3-fold (i.e., a relative 200% greater odds; $p = 0.003$, .002) compared to pure AD. Conversely, for every z-score unit increase in processing speed, the odds of having pure DLB decreased (i.e., a relative 51% lesser odds; $p = 0.01$) compared to pure AD. No

Table 2. Demographic and clinical characteristics.

	(A) pure DLB ($n=21$)	(B) pure AD ($n=189$)	(C) mixed DLB/AD ($n=42$)	p from univariable logistic regressions		
Demographics				A/B	C/B	A/C
Age (y)	73.2 (9.4)	76.1 (9.1)	74.3 (8.9)	–	–	–
Education (y)	16.1 (3.5)	15.6 (2.7)	15.5 (2.3)	–	–	–
Sex (% male)	76	53	83	*	**	–
Race (% white)	90	95	95	–	–	–
Age of Death (y)	77.6 (9.1)	81.3 (8.9)	79 (9)	–	–	–
Disease Duration (y)	4.4 (1.8)	5.2 (2.3)	4.7 (1.9)	–	–	–
Clinical Symptoms (%)						
Gait Disturbances	61.9	9	16.7	***	–	**
Tremors	38.1	7.4	19.1	***	*	–
Bradykinesia	61.9	12.2	21.4	***	–	**
Falls	23.8	5.8	4.8	*	–	*
Apathy/Withdrawal	52.4	32.3	52.4	–	*	–
Anxiety	42.9	38.6	33.3	–	–	–
Cognitive Fluctuations	23.8	7.4	19.1	*	*	–
REM Sleep Behavior	42.9	3.2	23.8	***	***	–
Visual-Spatial Complaints	71.4	38.6	38.1	*	–	*
Visual Hallucinations	42.9	2.1	16.7	***	**	*
Auditory Hallucinations	9.5	1.6	2.4	–	–	–
Delusions	14.3	10.1	9.5	–	–	–
Irritability	14.3	24.3	26.2	–	–	–

Values are presented as Mean (SD) unless otherwise specified. The p values are from univariable logistic regressions shown in Supplemental Table 1. *$p <$ 0.05, **$p < 0.01$***$p < 0.001$.

Table 3. Neuropsychological and clinical assessment data of the neuropathologically-defined participant groups.

	(A) pure DLB ($n=21$)	(B) pure AD ($n=189$)	(C) mixed DLB/AD ($n=42$)	p from univariable logistic regression		
Neuropsychological Measures				A/B	C/B	A/C
MMSE [b]	−2.5 (2.5)	−4.1 (2.9)	−4.5 (3.3)	*	–	*
Semantic Fluency [a, b]	−1.3 (0.7)	−1.2 (0.9)	−1.5 (0.9)	–	*	–
Processing Speed [a, b]	−2.8 (1.4)	−1.4 (1.5)	−2.2(1.4)	***	**	–
DSF [b]	−0.9 (0.8)	−0.7 (1)	−0.6 (0.9)	–	–	–
DSB [b]	−0.8 (0.8)	−0.7 (1)	−1.1 (0.8)	–	*	–
LM-I [b]	−1.5 (1)	−2 (0.9)	−2.5 (0.8)	*	*	**
LM-II [b]	−1.3 (1.1)	−2.1 (0.8)	−2.4 (0.7)	***	–	**
TMT-B [b]	−3.9 (1.5)	−2.5 (2)	−3.3 (2)	*	*	–
TMT-B Errors	2 (1.9)	1.9 (2.3)	1.8 (1.6)	–	–	–
BNT [b]	−0.7 (1.1)	−1.9 (1.9)	−1.8 (2.3)	*	–	*
MMSE Pentagons	0.4 (0.5)	0.7 (0.5)	0.7 (0.5)	*	–	–
Clinical Measures						
GDS-15	3.4 (3.3)	2.3 (2.2)	1.6 (1.6)	–	*	*
UPDRS-III	14.6 (11.6)	2.9 (5.3)	6.6 (9.2)	***	**	*
NPI-Q Total	76.5 (11.5)	79.4 (12.4)	81.8 (11.5)	–	–	–

Values are presented as Mean (SD) unless otherwise specified. The p values are from univariable logistic regressions shown in Supplemental Table 1. DLB: dementia with Lewy bodies; AD: Alzheimer's disease; DSF: Digit Span Forward; DSB: Digit Span Backward; LM-I: Logical Memory-I; LM-2: Logical Memory-II; BNT: Boston Naming Test; GDS-15: Geriatric Depression Scale (Short Form); MMSE: Mini-Mental State Examination; NPI-Q: Neuropsychiatric Inventory Questionnaire; TMT-B: Trail Making Test B; UPDRS-III: Unified Parkinson's Disease Rating Scale - Motor Examination. *$p <$ 0.05, **$p < 0.01$***$p < 0.001$, composite score [a]; z-scores are adjusted for age, education, and sex [b], otherwise raw scores are provided (due to z-scores being unavailable).

variables were removed after bootstrapping was applied, suggesting that the predictors can be deemed as reliable.

Pure DLB versus mixed DLB/AD. Table 5 lists the results and indicates that 3 variables were retained in the final model: gait disturbance, LM-II, and self-reported depressive symptoms (GDS-15). Presenting with gait disturbances significantly increased the odds of pure DLB by about 6-fold ($p = 0.01$), as well as higher scores of self-reported

Table 4. Final multivariable logistic regression: pure DLB versus pure AD.

Predictors	Odds Ratio	95% CI	p
Gait Disturbance [b]	19.32	2.02–185.23	0.01
LM-II [c]	3.42	1.52–7.67	0.003
Processing Speed [a, c]	0.51	0.31–0.86	0.01
BNT [c]	3.35	1.55–7.24	0.002
Visual Hallucinations [b]	31.06	3.50–277.31	0.002
Visual-Spatial Complaints [b]	6.06	1.16–31.77	0.03
Model Performance			
Sensitivity: 91%, 95% CI (70%, 99%)			
Specificity: 92%, 95% CI (88%, 95%)			
ROC area: 91%, 95% CI (85%, 98%)			

ROC: Receiver Operating Characteristics Curve; DLB: dementia with Lewy bodies; AD: Alzheimer's disease; CI: confidence interval; LM-II: Logical Memory-II; BNT: Boston Naming Test; GDS-15: Geriatric Depression Scale (Short Form), composite score [a]; present versus absent [b]; per 1 point increase [c].

Table 5. Final multivariable logistic regression: pure DLB versus DLB/AD.

Predictors	Odds Ratio	95% CI	p
Gait Disturbance [a]	6.33	1.50–6.42	0.01
LM-II [b]	3.01	1.41–6.42	0.004
GDS-15 [b]	1.44	1.04–1.99	0.03
Model Performance			
Sensitivity: 95%, 95% CI (76%, 99%)			
Specificity: 90%, 95% CI (85%, 93%)			
ROC area: 92%, 95% CI (87%, 98%)			

ROC: Receiver Operating Characteristics Curve; DLB: dementia with Lewy bodies; AD: Alzheimer's disease; CI: confidence interval; LM-II: Logical Memory-II; GDS-15: Geriatric Depression Scale (Short Form); present versus absent [a]; per 1 point increase [b].

depressive symptoms (i.e., about 1.5-fold; $p = 0.03$) compared to mixed DLB/AD. Only 1 neuropsychological predictor remained in the model, LM-II, which indicated that better memory performance increased the odds of pure DLB by about 3-fold ($p = 0.004$) compared to mixed DLB/AD. No variables were removed after bootstrapping was applied, suggesting that the predictors can be deemed as reliable.

Mixed DLB/AD versus pure AD. Table 6 lists the results and indicates that 4 variables were retained in the final model: RBD, UPDRS-III, GDS-15, and LM-II. RBD had a large positive odds ratio, suggesting that the presence of RBD increases the odds of having mixed DLB/AD by about 6-fold ($p = 0.004$) compared to pure AD. In addition, higher scores on the UPDRS-III increased the odds of having mixed DLB/AD by 1.07-fold (a relative 7% greater odds; $p = 0.02$) of having pure AD. Higher scores of self-reported depressive symptoms (GDS-15) decreased the odds of having mixed DLB/AD by 0.70 fold (i.e., relative 30% lesser odds; $p = 0.006$) as well as better delayed memory (LM-II) performance (i.e., relative 40% lesser odds; $p = 0.02$). The variable, apathy, was removed after bootstrapping (deeming that variable as unreliable), and bradykinesia was also removed due to collinearity.

Table 6. Final multivariable logistic regression: DLB/AD versus pure AD.

Predictors	Odds Ratio	95% CI	p
RBD [a]	6.44	1.81–22.93	0.004
GDS-15 [b]	0.70	0.54–0.90	0.006
LM-II [b]	0.57	0.37–0.89	0.02
UPDRS-III [b]	1.07	1.01–1.13	0.02
Model Performance			
Sensitivity: 69%, 95% CI (53%, 82%)			
Specificity: 60%, 95% CI (53%, 67%)			
ROC area: 65%, 95% CI (57%, 72%)			

ROC: Receiver Operating Characteristics Curve; DLB: dementia with Lewy bodies; AD: Alzheimer's disease; CI: confidence interval; LM-II: Logical Memory-II; GDS-15: Geriatric Depression Scale (Short Form); UPDRS-III: Unified Parkinson's Disease Rating Scale - Motor Examination; RBD: REM Sleep Behavior Disorder; present versus absent [a]; per 1 point increase [b].

Discussion

The current study investigated the predictive ability of neuropsychological and clinical assessment in a large autopsy sample of dementia patients harboring DLB and/or AD neuropathology. While univariate logistic models demonstrated several significant cognitive and clinical predictors across the three comparisons, we were particularly interested in identifying the best *combination* of measures to distinguish DLB from AD, mixed DLB/AD from AD, and DLB from mixed DLB/AD. The final multivariable logistic regression models indicated that relatively better performance in memory and confrontation naming robustly differentiated pure DLB from AD, as well as worse processing speed. This is largely in line with prior literature on DLB.[21,24,26,49] In our study, neuropsychological differentiation was less useful in cases with mixed pathology. For example, memory was the only cognitive variable that distinguished the pure pathological groups from the mixed group. That is, pure DLB subjects had better memory than the DLB/AD group, but when comparing the pure AD to the DLB/AD group, the mixed group performed better than the pure AD group in memory performance. Although this has been demonstrated in previous studies,[33,34] the reason for this is unclear. Some have suggested that the extent of DLB neurodegeneration and clinical symptoms may be primarily driven by αSyn in patients with co-pathology.[50] A recent large autopsy study examined cognitive profiles based on LB stages of progression (brainstem, limbic, cortical) in individuals with co-occurring AD pathology and found later (but not earlier) stage LB spread was associated with poor

executive/visuospatial functioning, suggesting a unique impact on this cognitive domain. However, global cognitive and memory deficits were more severe in mixed pathology regardless of LB disease distribution (i.e., across all stages), but no greater than those with pure AD, suggesting memory deficits in particular may be more driven by AD pathology.[15] In our current study, it is also important to highlight that the pure AD and mixed DLB/AD groups were significantly, and equally, more globally impaired compared to the pure DLB group as measured by the Mini-Mental State Examination (MMSE) (e.g., ~ 4 standard deviations below the mean; see Table 3), which may help explain the reduced ability to identify neuropsychological patterns in those with marked generalized impairment.

Importantly, we did not find that attention, executive, or visuospatial deficits predicted underlying DLB pathology among patients with dementia. While prior work has demonstrated more severe visuospatial and/or attentional-executive deficits in DLB compared to AD,[15,20,21,24,26,28] the literature has not entirely been consistent, especially in mixed DLB/AD cohorts. For example, one study found that only worse processing speed, phonemic fluency, and visuoconstruction predicted mixed DLB/AD versus pure AD in a mild dementia cohort, but no significant differences in memory, semantic fluency, or executive functioning (set-shifting) were found.[28] Other studies have also failed to show any meaningful differences between pure AD and mixed DLB/AD on neuropsychological assessment measures.[21,27] In the present study, one reason for our lack of significant predictors in visuospatial/executive domains may be related to the limited number of respective measures in the current cognitive battery. For example, our dataset only included one single, rather limited measure of visuospatial ability (MMSE pentagon copy) and one measure of executive functioning (TMT-B total time and number of errors) which may have limited our predictive ability. Note that although we did not observe objective evidence of visuospatial dysfunction, subjective reporting of visual-spatial complaints strongly predicted DLB pathology.

Univariable analyses revealed more preserved MMSE scores in the pure DLB group compared to the pure AD and mixed DLB/AD group, which is consistent with a previous NACC autopsy study[51] and other work demonstrating subjects with mixed pathology tend to have worse global cognitive impairment compared to pure pathologic groups.[11,12,26,51] The underlying pathophysiological mechanism explaining this finding is largely unknown, but some have suggested αSyn and AD pathology trigger synergistic processes that make additional networks of neurons more vulnerable to abnormal protein deposition.[4,52–54] However, in the current study, the MMSE was not retained in the final models, suggesting that it was not a potent predictor when combined with other variables. Moreover, the MMSE may not be the most appropriate proxy for global cognitive impairment given that it heavily relies on memory and orientation which could explain why the pure DLB group, with more preserved memory, performed better than AD participants. Furthermore, the MMSE fails to capture key cognitive domains commonly impacted in DLB, namely executive dysfunction and processing speed. This is why we chose to include a comprehensive battery of measures in an effort to capture the diverse cognitive phenotypes of AD and DLB.

We also assessed the extent to which clinical and behavioral features distinguished AD and DLB, including core DLB symptoms. Aligned with our expectations, visual hallucinations was a potent predictor of pure DLB versus AD pathology, which is largely consistent with prior studies[9,20,21,24,29] and is often a hallmark feature of DLB.[3] Interestingly, despite being significant in univariable modeling, visual hallucinations were not predictive in either of the multivariable models comparing pure AD or DLB to mixed DLB/AD. It has been shown that up to 20% of AD patients experience visual hallucinations in their lifetime[55] (which was similar to our mixed DLB/AD group) and thus group differences may have been obfuscated in our sample. Regarding other core DLB criteria, EPS (UPDRS-III) and RBD were useful at discriminating mixed DLB/AD from AD, suggesting EPS and RBD may help identify LB pathology in the context of AD, as has been previously demonstrated.[24,27,56] Our study also suggests that gait disturbances may be a useful indicator of DLB, which is included as a supportive feature rather than a core feature in the consensus criteria. In contrast, classic features of parkinsonism including rest tremor and bradykinesia did not inform the presence of LB pathology *in the multivariable models*, which could be related to the difficulty of identifying these features in the context of established dementia (where reliable clinical information can be difficult to obtain). It also may be related to the NACC database only assessing these symptoms on a dichotomous rating scale (i.e., yes/no), potentially reducing diagnostic sensitivity.

Current findings did not identify cognitive fluctuations as predictive of DLB (listed as a core feature), though measuring cognitive fluctuations through the clinical interview has historically been particularly challenging[57] and future studies may increase sensitivity by incorporating standardized questionnaires (e.g., The Mayo Fluctuations Scale[58]). Finally, although participants in the pure DLB and AD groups had somewhat higher GDS-15 scores compared to the mixed pathology group, mean GDS-15 scores were within the average range for all groups making this finding of questionable clinical significance. Studies comparing rates of depressive symptomatology between AD and DLB have demonstrated inconsistent results, as some have failed to find differences,[59,60] while others have shown that depression is more common in DLB.[61–63]

It is important to highlight criteria for both DLB and AD include specific biomarkers[3,64] and the field is shifting to

biological definitions of DLB[65] and AD.[64] The NIA-AA convened a workgroup and developed a biological diagnostic and staging framework for AD, which was recently updated and remains largely intended for research purposes only (with formal clinical practice guidelines set to follow).[64] While progress in biomarkers is a promising area of development and can assist with detecting AD pathology, at the present time they do not definitively rule in or out the presence of underlying LB pathology.[3,66] Further, amyloid positron emission tomography (PET) presents a particular challenge differentiating DLB from AD given approximately 60% of DLB patients have amyloid deposition.[66]

To date, no clinical biomarkers exist for reliably identifying αSyn pathology underlying DLB, though some initial studies using αSyn cerebrospinal fluid (CSF) assays have demonstrated good sensitivity but are less useful in quantifying disease progression and in mixed dementia pathologies.[67,68] Recent preliminary efforts were undertaken in developing a conceptual framework for biological staging system, which included αSyn aggregation, dopaminergic neuronal dysfunction, and clinical symptomatology.[65] Unfortunately, synucleinopathies are often very heterogeneous in pathological distribution and clinical symptomatology, which presents challenges regarding accuracy and sensitivity of various biomarkers.[65,67,68] Despite promising areas of research, access to fluid or imaging biomarkers may be limited in non-academic settings.[5] In fact, a recent survey of DLB experts in the United States indicates that structural MRI and neuropsychological assessment are the most frequently utilized biomarkers, even when clinicians have access to a wide variety of tests.[69] The current study attempts to combine clinical and neuropsychological data to identify predictors of pure DLB, mixed AD/DLB, and pure AD pathology and assist in treatment planning.

This study has several limitations. First, the NACC neuropathological classification system at the time of this dataset did not differentiate LBs in limbic versus amygdala regions, with the former (depending on level of NFT involvement) considered high likelihood DLB and the latter group now considered low likelihood by the current consensus report.[3] Therefore, cases were only classified as DLB if there was diffuse neocortical involvement, which specifically reduced the size of the pure DLB group due to the lack of these patients with minimal concurrent NFT burden. Further, in order to increase sample size, the pure DLB group included subjects with Braak stage ≤ 3, allowing the possibility of some subjects to have stage 3 NFT entorhinal regional burden. This is an important consideration and may have reduced our ability to detect unique neuropsychological differences. Recent research indicates the location of pathology appears to be related to the severity of DLB symptoms.[50]

Second, versions 1 and 2 of the NACC neuropsychological battery did not include a comprehensive assessment of visuospatial/visuoconstructional abilities (e.g., Rey Complex Figure, Block Design) and additional key executive measures (e.g., Stroop Color and Word Test, phonemic fluency), which could have compromised our ability to detect differences in those respective domains. This is notable considering that visuospatial and executive impairment is often a key discriminator in DLB versus AD neuropathology[20,21,24,49] and future work should ensure test protocols include empirically validated visuospatial and/or executive functioning measures.

Third, NACC subjects are predominantly Caucasian and well-educated, which may limit the generalizability of our findings. Recent studies highlight differences in pathology and co-pathology among individuals from different racial and ethnic backgrounds[70] and co-pathology appears to be more prevalent among women compared to men.[71] Fourth, while we selected subjects who were diagnosed with dementia on their first visit in order to identify patients earlier in the dementia process, patients were more impaired at their first visit than we expected (as measured by the MMSE), potentially obfuscating group differences that may be present earlier in the disease process.

Neurodegenerative pathology has also been found in some patients in the absence of overt clinical impairment. In our study, we only examined patients with a clinical diagnosis of dementia who were clearly symptomatic, which may not have been fully representative of those who harbor pathology and are in subclinical or preclinical phases. Fifth, selecting subjects diagnosed with dementia at their first visit also raises the concern that the clinical picture may not accurately reflect the underlying pathology at autopsy. Although disease duration and age of death were not significantly different among groups suggesting roughly equivalent trajectories, the mean interval time was nearly five years, providing sufficient time for disease progression and altered symptom presentation, especially for the mixed DLB/AD group. This is a common limitation in cross-sectional neuropathological studies, which is not informative for when the pathology appeared and the interaction with other pathologies during the disease course. Finally, the NACC database set did not contain in vivo biomarker assessment data for DLB or AD (e.g., CSF tau, amyloid PET) and thus we were unable to compare the effectiveness of such methods with clinical/neuropsychological assessment, as well as examine in vivo disease characteristics at the time of clinical assessment

Despite those limitations, this study has several strengths. First, this study utilized a neuropathological rather than a clinical diagnosis, the latter being shown to have poor diagnostic accuracy, especially in DLB,[9,10] although the accuracy has improved with the addition of RBD to the clinical criteria.[72] The majority of prior investigations have either lacked pathological verification or utilized smaller autopsy samples, and did not include a pure DLB group.[18,19,22,23] Second, while it may have contributed to the reduced

sample size for the DLB group, our rigorous neuropathological selection criteria (according to DLB Consortium[3] and the NIAA-AA[39]) and exclusion of other disease processes was indeed a significant strength of our study, allowing the potential to eliminate confounding pathologies and identify true disease characteristics. Indeed, most studies have not controlled for significant vascular burden, which is surprising considering 30–70% of AD patients have co-occurring vascular pathologies.[73–75] In contrast, the current study excluded individuals with significant cerebrovascular disease. Between 11–13% of samples have identified overlap with significant cerebrovascular disease and LB pathology,[76,77] which can impact the clinical phenotype, limiting some of the generalizability of this study. Third, the NACC contains a breadth of empirically validated clinical and neuropsychological measures, many of which are used clinically and when combined, can provide a rich amount of information regarding cognitive, psychiatric, and motor presentations.

In summary, our results indicate that differentiating DLB and AD remains a considerable challenge, especially in cases with mixed pathology. Nonetheless, neuropsychological assessment remains critically important in identifying DLB pathology, as our study showed that better memory and naming performance (and worse processing speed) helped distinguish DLB from AD pathology. Clinically, visual hallucinations, visuospatial complaints, and gait disturbances strongly indicated the presence of DLB alone and EPS dysfunction and the presence of RBD suggests LB pathology in the context of AD. This is in line with research demonstrating the presence of RBD increased diagnostic accuracy among patients with LB pathology.[78] Unfortunately, differentiating the pure AD or DLB group from the mixed group was relatively unsuccessful based on neuropsychological assessment.

As mentioned, some of our inconsistencies with what has been demonstrated in the literature may be related to the overall degree of cognitive impairment in our sample and/or type of measures used. Future research may investigate DLB and AD earlier in the disease process (e.g., prodromal stages or mild cognitive impairment) to better detect more subtle differences, which will hopefully enable earlier intervention—both pharmacological and non-pharmacological—while neuropathological burden is more confined and clinical symptoms are less severe. Our study emphasizes the need to examine clinical features of AD and DLB in conjunction with cognitive testing to better identify the constellation of symptoms that best differentiates between AD and DLB. Future work incorporating measures of autonomic dysfunction may be particularly helpful with identifying LB pathology in the context of AD, especially earlier in the disease process, which has been previously documented.[79–81] Furthermore, examining sex differences may lend itself to better diagnostic accuracy given data suggesting different DLB phenotypes of men and women, including a recent review[82] showing women with DLB may exhibit greater cognitive impairment than men, as well as experience earlier and more frequent visual hallucinations, while RBD and parkinsonism may occur earlier and more often in men. Another large DLB cohort study found women had more severe co-occurring AD neuropathological burden and cognitive impairment compared to men, and were more likely to be diagnosed with AD.[71] Finally, autopsy studies incorporating in-vivo biomarker assessment (e.g., CSF analysis, dopamine transporter imaging) along with systematic and comprehensive clinical/neuropsychological protocols will enable better understanding of the phenotypic differences and underlying neuroanatomic mechanisms of AD and DLB. As disease-modifying treatments for these conditions emerge, the need to improve diagnostic accuracy using clinical tools will be increasingly more relevant.

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Statements and declarations

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Data availability

The data in this study were obtained from the NACC (https://naccdata.org), which is available free of charge for researchers who submit a research proposal.

Supplemental material

Supplemental material for this article is available online.

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