

Cognitive Profile and Markers of Alzheimer Disease–Type Pathology in Patients With Lewy Body Dementias

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Abstract

Objective

To determine whether patients with Lewy body dementia (LBD) with likely Alzheimer disease (AD)–type copathology are more impaired on confrontation naming than those without likely AD-type copathology.

Methods

We selected 57 patients with LBD (dementia with Lewy bodies [DLB], $n = 38$; Parkinson disease dementia [PDD], $n = 19$) with available AD CSF biomarkers and neuropsychological data. CSF β -amyloid₁₋₄₂ ($A\beta_{42}$), phosphorylated-tau (p-tau), and total-tau (t-tau) concentrations were measured. We used an autopsy-validated CSF cut point (t-tau: $A\beta_{42}$ ratio > 0.3 , $n = 43$), or autopsy data when available ($n = 14$), to categorize patients as having LBD with (LBD + AD, $n = 26$) and without (LBD – AD, $n = 31$) likely AD-type copathology. Analysis of covariance tested between-group comparisons across biologically defined groups (LBD + AD, LBD – AD) and clinical phenotypes (DLB, PDD) on confrontation naming (30-item Boston Naming Test [BNT]), executive abilities (letter fluency [LF], reverse digit span [RDS]), and global cognition (Mini-Mental State Examination [MMSE]), with adjustment for age at dementia onset, time from dementia onset to test date, and time from CSF to test date. Spearman correlation related cognitive performance to CSF analytes.

Results

Patients with LBD + AD performed worse on BNT than patients with LBD – AD ($F = 4.80$, $p = 0.03$); both groups performed similarly on LF, RDS, and MMSE (all $p > 0.1$). Clinically defined PDD and DLB groups did not differ in performance on any of these measures (all $p > 0.05$). A correlation across all patients showed that BNT score was negatively associated with CSF t-tau ($\rho = -0.28$, $p < 0.05$) and p-tau ($\rho = -0.26$, $p = 0.05$) but not $A\beta_{42}$ ($p > 0.1$).

Conclusion

Markers of AD-type copathology are implicated in impaired language performance in LBD. Biologically based classification of LBD may be advantageous over clinically defined syndromes to elucidate clinical heterogeneity.

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Glossary

$A\beta$ = β -amyloid₁₋₄₂; AChEI = acetylcholinesterase inhibitor; AD = Alzheimer disease; ANCOVA = analysis of covariance; BNT = Boston Naming Test; DLB = dementia with Lewy bodies; LBD = Lewy body dementia; LF = letter fluency; MMSE = Mini-Mental State Examination; p-tau = phosphorylated tau; PD = Parkinson disease; PDD = PD dementia; RDS = reverse digit span; t-tau = total tau.

Parkinson disease (PD) dementia (PDD) and dementia with Lewy bodies (DLB) are Lewy body dementias (LBDs) characterized by progressive cognitive and motor deficits.^{1,2} Historically, LBD has been partitioned into PDD or DLB on the basis of relative onset of cognitive and motor features,³ but this approach is not well supported in large autopsy studies.⁴ Other work has attempted to distinguish clinically defined PDD and DLB by neuropsychological profiles.^{5,6} However, findings are inconsistent, with some emphasizing memory and language difficulties in DLB,^{7,8} while others show these deficits in PDD.^{9,10}

One important source of heterogeneity in LBD may be differences in underlying neuropathology.^{4,11,12} LBD is defined by the aggregation of pathologic α -synuclein protein; however, \approx 50% of LBD autopsy cases have additional plaque and tangle pathology consistent with a secondary diagnosis of Alzheimer disease (AD),^{12,13} which has been linked to worse prognosis.^{4,14-16} Few studies have examined directly the specific cognitive impairments associated with AD-type copathology in LBD, but recent postmortem work has found evidence of greater temporal lobe tau burden¹⁷ associated with antemortem confrontation naming deficits in patients with LBD with AD-type copathology.¹⁷⁻¹⁹

This study compares neuropsychological profiles between patients with LBD with (LBD + AD) and without (LBD - AD) likely AD-type copathology, using CSF biomarkers or autopsy data to biologically define groups. We hypothesize that patients with LBD + AD will be more impaired on temporal lobe-mediated confrontation naming than patients with LBD - AD and that this deficit will be linked to markers of tau pathology. We do not expect biologically defined groups to differ on frontal lobe-mediated executive functioning or clinically defined groups (PDD/DLB) to have differentiated neuropsychological profiles.

Methods

Patients

Figure 1 outlines the inclusion criteria for 57 patients with LBD retrospectively selected from the University of Pennsylvania Integrated Neurodegenerative Disease Database²⁰ as of October 7, 2019. Patients were followed up and evaluated at the University of Pennsylvania's Frontotemporal Degeneration Center, Parkinson's Disease and Movement Disorders Clinic, or Alzheimer's Disease Core Center. To investigate the effects of AD-type copathology in LBD, with a

specific emphasis on the temporal lobe-mediated task of confrontation naming, patients were included according to clinical diagnosis of cognitively impaired LBD (DLB or PDD)^{1,2} and availability of CSF biomarkers or autopsy diagnosis and Boston Naming Test (BNT) data collected after the onset of dementia. We performed a chart review of medical records of patients with DLB to ensure that they met current clinical criteria, using the 1-year interval between parkinsonism motor symptoms and dementia onset to differentiate PDD from DLB,² and to confirm the year of dementia onset on the basis of the year of earliest noted cognitive symptom with a functional deficit in the record. Clinical diagnoses of PDD and DLB were rendered in a manner blinded to CSF data. Of our final cohort of patients, 14 (24.6%) had autopsy data and confirmed LBD neuropathologic diagnosis. Exclusion criteria included PD without cognitive impairment and autopsy or genetic evidence²¹ of nonsynucleinopathy neuropathologic diagnoses. Thirty-eight patients with a clinical diagnosis of DLB and 19 patients with a clinical diagnosis of PDD fulfilled these criteria (figure 1). Because these data are retrospective, a subset of patients with BNT scores ($n = 4$) were included in a previous autopsy study of LBD.¹⁷

Biological Classification

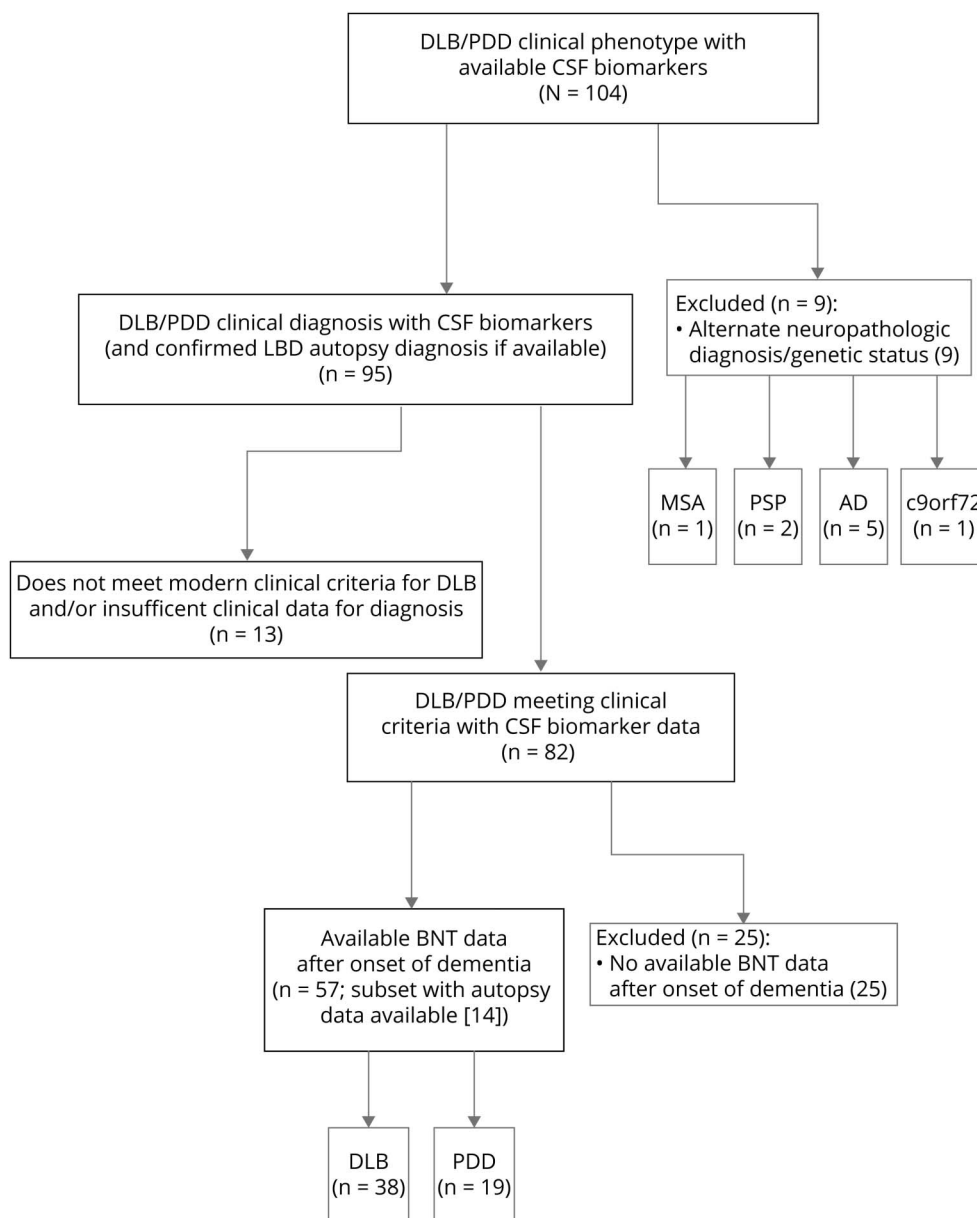
CSF was collected for AD biomarkers, including total tau (t-tau), phosphorylated tau (p-tau), and β -amyloid₁₋₄₂ ($A\beta_{42}$), and measured with the Luminex xMAP immunoassay platform (Luminex Corp, Austin, TX) as described.²² To establish biologically defined groups, we used an autopsy-validated CSF cut point as a biomarker of concomitant AD-type pathology in LBD (t-tau: $A\beta_{42}$ ratio >0.3)²³ to categorize patients as having LBD + AD ($n = 19$) or LBD - AD ($n = 24$). For the small subset of patients with autopsy data available ($n = 14$), we used neuropathologic criteria²⁴ to define patients with LBD with concomitant AD. Patients with LBD with intermediate or high AD neuropathologic change were considered to have LBD + AD ($n = 7$), and patients with LBD with no or low AD neuropathologic change were considered to be LBD - AD ($n = 7$). We note that 3 of the 31 total patients with LBD - AD (9.68%) had a CSF collection date before the onset of dementia (maximum interval 1.4 years); these patients were included in our main analysis because accumulation of AD-type pathology is thought to precede cognitive impairment,²⁵ and longitudinal AD CSF biomarker data in LBD show minimal change over this time interval of <2 years.²⁶ Even so, because we cannot be certain that the biological status of these 3 patients with CSF collection before dementia onset fully reflected their underlying disease state at the time of testing, we also repeated all analyses excluding these 3 cases.

Neuropsychological Testing

To test the association between AD-type copathology in LBD and confrontation naming early in the symptomatic course of dementia, we retrospectively selected available neuropsychological data collected at the earliest time point after the onset of dementia. The 30-item BNT and 32-item Multi-Lingual Naming Test were used to assess confrontation naming. Correct responses given after semantic cues were included in the total score. For patients given the Multi-Lingual Naming Test, we used a previously normed conversion developed by the National Alzheimer's Coordinating Center to make these scores comparable to BNT scores.²⁷ To test the specificity of AD-type copathology in LBD to deficits in language, we included other neuropsychological tests

assessing global cognition and executive functioning collected within a year of BNT. The majority (97.24%) were restricted to a 9-month interval; to maximize available data, a small number (2.76%) had a slightly longer 12-month interval. Neuropsychological tasks in which <50% of our main cohort completed the task were excluded from analysis; thus, available data included letter fluency (LF), reverse digit span (RDS), and Mini-Mental State Examination (MMSE).²⁸ LF, or the number of unique words beginning with the letter F named in a minute, and RDS, or the longest span of digits that can be reproduced in reverse order, were used to measure executive functioning. The MMSE total score was used as a measure of global cognition; all MMSE scores were collected within 3 months of BNT. All standardized instructions for

Figure 1 Flowchart of Inclusion/Exclusion Criteria Used to Select Our Cohort



AD = Alzheimer disease; BNT = Boston Naming Test; c9orf72 = chromosome 9 open reading frame 72 mutation; DLB = dementia with Lewy bodies; LBD = Lewy body disease; MSA = multiple system atrophy; PDD = Parkinson disease dementia; PSP = progressive supranuclear palsy.

Table 1 Patient Clinical and Demographic Characteristics

	LBD + AD (n = 26)	LBD – AD (n = 31)	p Value
Clinical phenotype, n^{a,c}			
DLB	17 (65)	21 (68)	1.00
PDD	9 (35)	10 (32)	
Sex, n^{a,c}			
Male	17 (65)	26 (84)	0.2
Female	9 (35)	5 (16)	
APOE status, n^{a,c,e}			
0 ε4 alleles	5 (25)	22 (78.5)	0.001
1 ε4 allele	13 (65)	5 (18)	
2 ε4 alleles	2 (10)	1 (3.5)	
Core clinical features, n^f			
Parkinsonism ^{a,c}	23 (88.5)	23 (77)	0.4
Hallucinations ^{a,c}	14 (54)	17 (57)	1.00
Cognitive fluctuations ^{a,c}	12 (46)	15 (50)	1.00
RSBD ^{a,c}	10 (38)	17 (57)	0.3
AChEI medication use, n ^{a,c}	14 (54)	16 (52)	1.00
Education, y ^{b,d}	14.0 (6.0)	16.0 (2.5)	0.5
Age at test, y ^{b,d}	71.5 (15.3)	68.0 (12.0)	0.05
Age at dementia onset, y ^{b,d}	69.0 (16.3)	64.0 (13.0)	0.009
Onset-to-CSF, y ^{b,d}	2.2 (2.8)	3.0 (3.6)	0.1
Onset-to-test, y ^{b,d}	2.3 (2.2)	3.2 (2.7)	0.01
CSF-to-test, y ^{b,d}	-0.04 (0.4)	0.07 (1.5)	0.3

Abbreviations: AChEI = acetylcholinesterase inhibitor; AD = Alzheimer disease; CSF-to-test = interval from CSF collection date to Boston Naming Test date; DLB = dementia with Lewy bodies; LBD = Lewy body disease; onset-to-CSF = interval from dementia onset to CSF collection date; onset-to-test = interval from dementia onset to Boston Naming Test date; PDD = Parkinson disease dementia; RSBD = REM sleep behavior disorder.

^a Data reported as number (percent).

^b Data reported as median (interquartile range).

^c p Value reflects χ^2 test estimate.

^d p Value reflects *U* test estimate.

^e Nine patients (n = 6 LBD + AD, n = 3 LBD – AD) did not have available genetic data.

^f One patient (LBD – AD) did not have itemized clinical data available.

neuropsychological examinations were administered to participants by trained research personnel. Of note, these standardized research neuropsychological assessments were distinct from clinical examinations used for diagnosis.

Statistical Analyses

Demographic variables, neuropsychological scores, and CSF analytes were not normally distributed according to the Shapiro-Wilk test. Mann-Whitney *U* tests compared education, age at dementia onset, and the intervals from dementia onset to CSF collection date (onset-to-CSF), from CSF collection date to cognitive test date (CSF-to-test), and from dementia onset to cognitive test date (onset-to-test) between the LBD + AD and LBD – AD groups (table 1). The χ^2 tests

compared categorical variables of sex, phenotype, *APOE* genetic status, core clinical features, and acetylcholinesterase inhibitor (AChEI) medication use across groups. Analysis of covariance (ANCOVA) performed between-group comparisons on all neuropsychological tests across biologically defined groups (LBD + AD, LBD – AD). To test whether phenotype could explain the neuropsychological differences observed, ANCOVAs were repeated across clinical phenotype (DLB, PDD). To perform nonparametric comparisons, we rank-transformed the neuropsychological data before performing these analyses.²⁹ Covariates in each model included age at dementia onset, the interval from onset-to-test, and education (formula = test ~ group + age + onset-to-test + education). In addition, because CSF used to determine

Table 2 Neuropsychological Testing Data for Biologically Defined and Clinically Defined Groups

	LBD + AD	LBD – AD	<i>p</i> Value	DLB	PDD	<i>p</i> Value
MMSE score (maximum = 30)	N = 26	N = 30	0.8	N = 38	N = 18	0.06
	26.0 (4.0)	26.0 (5.8)		26.0 (5.0)	26.5 (3.8)	
BNT score (maximum = 30)	N = 26	N = 31	0.02	N = 38	N = 19	0.5
	24.5 (4.5)	27.0 (4.0)		25.0 (4.0)	26.0 (5.5)	
RDS score (maximum = 8)	N = 20	N = 28	0.5	N = 31	N = 17	0.2
	3.5 (1.0)	3.5 (1.3)		3.0 (1.0)	3.8 (2.0)	
LF score (word count)	N = 17	N = 24	0.6	N = 32	N = 9	0.3
	6.0 (8.0)	9.5 (8.3)		9.5 (8.3)	8.0 (7.0)	

Abbreviations: AD = Alzheimer disease; BNT = Boston Naming Test; LBD = Lewy body disease; LF = letter fluency; MMSE = Mini-Mental State Examination; RDS = reverse digit span. Data reported as median (interquartile range). All *p* values reflect analysis of covariance test between groups (LBD + AD vs LBD – AD and DLB vs PDD), with age at onset and onset-to-test and CSF-to-test intervals included as covariates.

biologically defined groups was not necessarily acquired at the same time as cognitive test data, we included the CSF-to-test interval in biologically defined models.

Spearman correlation tested associations between CSF analytes (t-tau, p-tau, $A\beta_{42}$) and BNT, as well as other neuropsychological measures, within the whole patient cohort. We retested associations after removing high leverage data points to ensure robustness. Mann-Whitney *U* test compared BNT performance between *APOE* $\epsilon 4$ carriers (1 or 2 alleles) and *APOE* $\epsilon 4$ noncarriers (0 alleles).

All analyses were performed with R programming (version 1.2.5033; R Foundation for Statistical Computing, Vienna, Austria) and used a 2-tailed test with $\alpha = 0.05$.

Standard Protocol Approvals, Registrations, and Patient Consents

All procedures were performed with written informed consent from all patients under guidelines established and approved by the Institutional Review Board at the University of Pennsylvania.

Data Availability

Anonymized data will be shared with qualified investigators who have Institutional Review Board approval and a Material Transfer Agreement on request.

Results

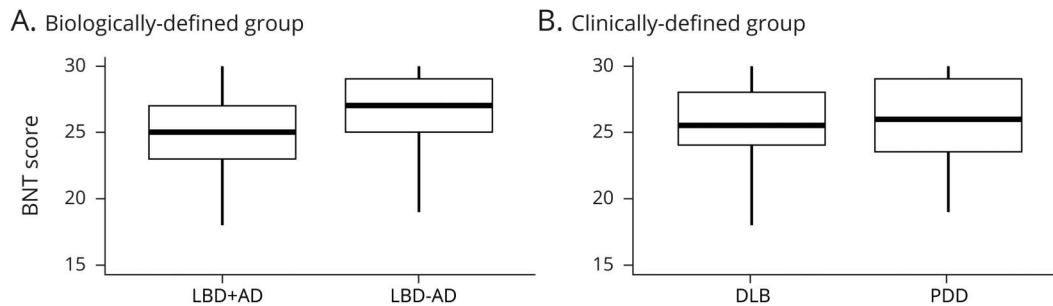
Demographic and clinical characteristics are described in table 1. The LBD + AD group was older at the time of dementia onset, while the LBD – AD group had a longer time interval between dementia onset and test date. The LBD + AD group also had a greater frequency of *APOE* $\epsilon 4$ alleles, indicating a heightened risk of AD. The LBD + AD group otherwise did

not differ from the LBD – AD group in clinical features or AChEI use. When our cohort was compared by clinical phenotype, the PDD group was older at the time of dementia onset and test date, and the DLB group had a longer time interval between dementia onset and test date (both $p < 0.01$). Clinical groups also differed in core clinical features: the PDD group had more parkinsonism motor symptoms, whereas the DLB group had a greater frequency of hallucinations, cognitive fluctuations, and REM sleep behavior disorder (all $p < 0.05$). The PDD and DLB groups did not significantly differ in sex, education, *APOE* genetic status, or AChEI use. There was no clear association between clinical phenotype (DLB, PDD) and biologically based grouping (LBD + AD, LBD – AD) in this cohort.

Table 2 summarizes neuropsychological data and ANCOVA comparisons across biologically based (LBD + AD, LBD – AD) and clinical (DLB, PDD) subgroups. Patients with LBD + AD performed worse than patients with LBD – AD on confrontation naming (BNT: $F = 4.80$, $p = 0.03$) (figure 2). There was no difference between the performance of patients with LBD + AD and LBD – AD on measures of global cognition (MMSE) or executive (RDS, LF) functioning (all $p > 0.1$). When our cohort was divided by phenotype, the PDD and DLB groups performed similarly on all neuropsychological tasks (all $p > 0.05$).

Covariates examined additional factors that might contribute to confrontation naming performance in LBD + AD and LBD – AD. Education was significantly associated with BNT performance between biologically defined groups ($F = 7.62$, $p = 0.008$). Despite a positive correlation between BNT score and education ($\rho = 0.36$, $p = 0.007$), the groupwise difference between patients with LBD + AD and those with LBD – AD seen in BNT score remained robust. Age and the onset-to-test and CSF-to-test intervals had no effect on BNT performance

Figure 2 Confrontation Naming Performance Across Biologically and Clinically Defined Groups



Patients with Lewy body dementia (LBD) + Alzheimer disease pathology (AD) perform worse than patients with LBD – AD on the Boston Naming Test (BNT) (A), but the dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD) groups perform similarly (B). Boxplots illustrate the median, interquartile range, and range of scores for each group independently.

(all $p > 0.1$). Mann-Whitney U test showed no difference in BNT score according to $APOE \epsilon 4$ status ($p > 0.1$).

Spearman correlation tested the relationship between CSF analyte concentrations and BNT score impairments across all patients with LBD. We found an inverse correlation between BNT score and CSF t-tau ($\rho = -0.28, p = 0.04$) and p-tau ($\rho = -0.26, p = 0.05$) levels. To ensure robustness of this observation, we repeated this correlation after removing high leverage points according to the Cook distance³⁰; the correlation remained for both t-tau ($\rho = -0.34, p = 0.01$) and p-tau ($\rho = -0.33, p = 0.01$) (figure 3). There was no correlation between BNT score and $A\beta_{42}$ ($p > 0.1$). Finally, we tested whether the t-tau and p-tau associations were specific to BNT score and found no correlation between CSF tau measures and the remaining neuropsychological measures (MMSE, RDS, LF; all $p > 0.1$).

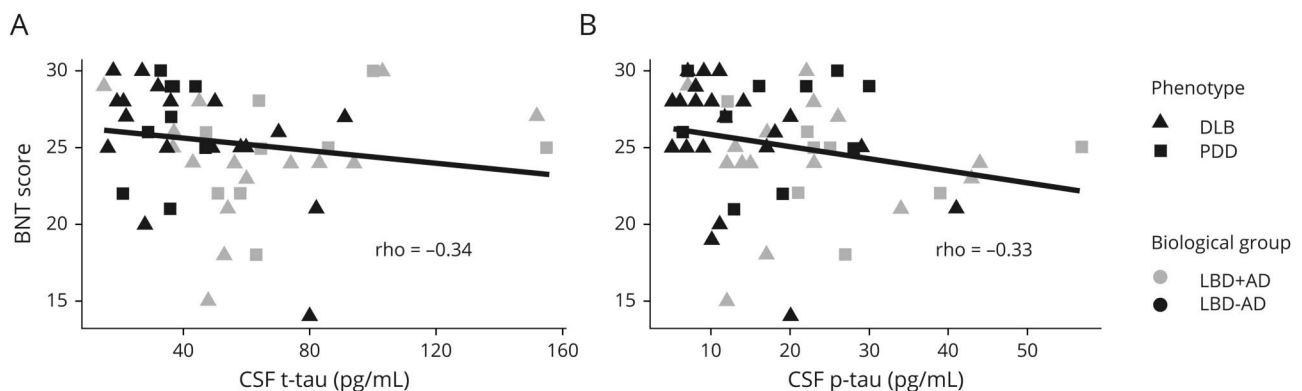
When analyses excluding the 3 patients with CSF collection before dementia onset were repeated, our main findings were consistent, showing that BNT performance was significantly different between the LBD + AD and LBD – AD groups ($F =$

$5.50, p = 0.02$) but not between clinical phenotypes ($p = 0.4$). No other group-wise comparisons were significant (all $p > 0.05$). Although the trend of the correlation between BNT and t-tau was nonsignificant when these 3 patients were removed, the correlation between BNT score and p-tau ($\rho = -0.29, p = 0.03$) remained. When we omitted high leverage points, similar to our main analyses, BNT was significantly associated with both t-tau ($\rho = -0.31, p = 0.03$) and p-tau ($\rho = -0.39, p = 0.005$) but not $A\beta_{42}$.

Discussion

There is considerable evidence that AD-type copathology presents in up to one-half of patients with LBD at autopsy^{12,13} and markedly affects disease in LBD.¹⁴ While biologically based in vivo diagnostic strategies are emerging that use CSF biomarkers to identify AD,³¹ these approaches are seldom explored to address clinical heterogeneity in the context of LBD. Here, we use a biologically based approach, partitioning LBD into subgroups with and without likely AD-type

Figure 3 Confrontation Naming Correlates With CSF t-Tau and p-Tau Levels



Scatterplots depict individual patients' CSF total tau (t-tau) (A) and phosphorylated tau (p-tau) (B) measurements plotted against Boston Naming Test (BNT) score value with a line of best fit. High leverage points are excluded. BNT score tends to decrease as t-tau and p-tau accumulation in the brain increases.

copathology based on CSF biomarkers and autopsy data when available, to examine cognitive impairment in the full spectrum of LBD. We compare these biological groupings to a clinically based approach and examine the same patients partitioned according to PDD and DLB clinical diagnostic criteria.^{1,2} We find evidence of a selective, domain-specific cognitive impairment in language in patients with LBD with markers of likely AD-type copathology compared to those lacking significant markers of AD-type copathology. This finding is consistent with autopsy data demonstrating relatively greater tau burden in the temporal lobe of patients with LBD with AD-type copathology.¹⁷ In contrast, classic clinical groupings of PDD and DLB do not reveal robust differences in cognitive performance. These observations may have important implications for the clinical utility of stratifying LBD patient cohorts on the basis of biomarkers of AD-type copathology, leading to more biologically meaningful patient groupings compared to clinically based syndromic diagnoses such as PDD and DLB.

Both retrospective autopsy series^{4,14} and prospective studies using CSF biomarkers as a surrogate marker for AD-type copathology^{15,16} relate the increasing severity of plaque and tangle pathology to faster cognitive decline and reduced survival during life. Despite this growing body of evidence that AD-type copathology is associated with detrimental outcomes and clinical heterogeneity in LBD,^{11,16} there are limited data on the specific neuropsychological features associated with AD-type copathology in LBD. This is due in part to the infrequent harmonization of clinical evaluations coordinated with biomarker or autopsy data across cognitive and movement disorders centers³² needed to effectively study the full spectrum of LBD.^{3,5} Indeed, the clinical criteria for both PDD¹ and DLB² are largely overlapping and acknowledge heterogeneity of cognitive impairment with frequent attentional and executive deficits. Moreover, there is ongoing debate about whether these syndromes are distinct clinicopathologic entities^{1,3,33} and whether therapeutic trials should include both PDD and DLB due to heterogeneous underlying biology and partially overlapping symptomatology.^{3,34} To address this issue, we use a unique approach of biologically based stratification in a cohort of patients with PDD and DLB to directly examine clinically and biologically based groupings of LBD.

We hypothesize that the impaired confrontation naming observed in LBD + AD may be related to increased pathologic burden in the temporal lobe, grounded in anatomic data from previous histology and neuroimaging. Confrontation naming is a cognitive task that relies heavily on temporal lobe resources to recognize and retrieve the name of a line drawing.³⁵ Indeed, recent autopsy studies have linked confrontation naming to AD-type copathology in LBD.^{18,19} In vivo molecular tracer studies in LBD have also found tau^{36,37} and amyloid³⁸ tracer uptake largely in temporoparietal regions, often implicated in confrontation naming tasks, and our recent PET study associated tau tracer uptake in the temporal lobe with naming difficulty in LBD.³⁹

MRI data comparing LBD + AD and LBD – AD directly are rare, and the few existing studies have focused on medial temporal lobe atrophy^{40,41} associated with tau tangles and episodic memory difficulty.⁴¹ Nonetheless, we recently found greater antemortem MRI neocortical temporal lobe atrophy in LBD + AD vs LBD – AD cohorts.⁴² Moreover, our group's previous autopsy study showed that antemortem naming deficits in LBD + AD were related to regional tau pathologic burden in the temporal neocortex.¹⁷ In the current study, we extend these findings using a largely independent dataset, suggesting that a relative predominance of AD-type tau pathology in the temporal neocortex may indeed play a role in impaired BNT performance seen in patients with LBD + AD. Future work is needed to examine the relationship of other neocortical temporal lobe-mediated domains such as ideomotor apraxia and other features of language impairment associated with frontal disease in LBD such as narrative organization,⁴³ which have been related to AD biomarkers in LBD.

In addition to group-wise comparisons using dichotomized CSF biomarker cut points of AD-type pathology, we test continuous measures of CSF A β ₄₂, p-tau, and t-tau. We find a significant, negative correlation between BNT scores and CSF t-tau and p-tau levels (figure 3), which have been shown to have a direct linear relationship with postmortem tau pathology in LBD.²³ These findings further link confrontation naming with tau pathology in LBD. While amyloid pathology is also implicated in LBD + AD, the association of cognitive difficulty with tau pathology appears to be relatively specific because we find no correlations with CSF A β ₄₂. These findings are in accordance with our postmortem work that did not find an association of BNT scores with amyloid-plaque pathology¹⁷ and others' work showing that tau correlates more closely with cognitive functioning.^{36,39,44} Still, others have found that CSF A β ₄₂ is also linked to atrophy patterns and cognitive deficits in LBD.^{15,40,45} The reasons for these discrepancies remain unclear and could be due in part to the fact that it is difficult to determine the impact of α -synuclein⁴⁶ and other copathologies in a clinical LBD cohort defined on the basis of CSF biomarkers.^{12,13,47} Additional work is needed to investigate the relative contributions of tau, amyloid, α -synuclein, and other copathologies to cognitive impairment and clinical heterogeneity seen in LBD.

Aside from confrontation naming, our analysis finds no differences in performance on measures of executive functioning (RDS, LF) or global cognition (MMSE) between the LBD + AD and LBD – AD patient groups. There is also no correlation between these measures and continuous CSF analytes, further suggesting a relatively specific cognitive association of confrontation naming with tau pathology in LBD. These findings are in contrast to previous studies that show that low CSF A β ₄₂ relates to executive performance in PD.⁴⁸ The reasons for these discrepancies are unclear and may be related in part to differences in patient cohorts; we focus on dementia in PDD and DLB, while the previous study focused on PD without dementia. One interpretation is that executive

dysfunction may be an earlier phenomenon in LBD more closely linked to amyloidosis, α -synuclein, or another pathology. Nonetheless, future prospective work is needed to study longitudinal changes from presymptomatic to end-stage LBD with autopsy.

In this study, we find no evidence for cognitive domain-specific distinctions across clinically defined groups of PDD and DLB. These data contrast with a recent autopsy-confirmed study that found greater decline in memory and language domains in DLB vs PDD⁷; however, the authors found that when a subgroup of DLB with relative pure α -synuclein pathology was examined, the cognitive profile was more similar to PDD. Thus, it is not entirely clear how the clinical diagnoses of PDD and DLB correspond to LBD subgroups defined on the basis of biomarkers and pathology. Our study supports the consideration of AD-type pathology in LBD and the use of AD CSF biomarker profiles to help define LBD patient cohorts.³⁴ In the setting of LBD, a disease-modifying treatment focused on coexistent AD-type pathology could potentially benefit from the ability to identify a biologically defined subgroup such as LBD + AD.³¹ Future prospective work following patients to autopsy should explore these and other biological influences on clinical heterogeneity in LBD such as genetic factors⁴⁹ to better address these complex issues.

Limitations of this study include the retrospective nature of available neuropsychological data and limited testing in specific cognitive domains. While these data reflect a unique effort to harmonize clinical assessments across cognitive and movement disorders researchers³² that facilitates comprehensive study of the full LBD spectrum rather than focused study of clinically defined subgroups alone, lack of completely harmonized data prevented testing of other domains such as episodic memory recall and visuo-construction. Some comparisons were unbalanced and may have lacked power to observe existing group differences, with small numbers of patients with PDD with LF score. Future efforts should focus on collecting prospective, harmonized, complete datasets with molecular imaging for anatomic localization. A second important caveat to consider is our definition of groups. While our study supports the use of CSF cut points²³ to provide a biologically meaningful diagnosis in LBD, CSF samples in autopsy-confirmed cases are rare and need further replication before widespread clinical use of AD CSF biomarkers in LBD. Moreover, most patients in this study lacked autopsy data, so we could not assess for other copathologies, such as TAR DNA-binding protein 43, which may influence cognitive performance in the aging brain.⁵⁰ Third, LBD and AD-type pathology may exist along more of a spectrum⁵ that is not represented by our CSF-based dichotomization of groups. To test this possibility, we also examined CSF measures as continuous biomarker variables and found an association between CSF tau and BNT performance. Fourth, we could not study the potential contribution of α -synuclein pathology to differences seen in confrontation naming performance between

groups because most of our participants had only CSF biomarkers. AD-type pathology may co-occur with greater α -synuclein⁴⁶ and overall pathologic burden,^{12,17} but this can be determined only in an autopsy cohort, and validated CSF biomarkers to directly measure α -synuclein in CSF-defined cohorts are lacking. Finally, the greater impairment seen in LBD + AD could have been attributed to more general impairment from a more advanced stage of disease compared to LBD – AD. Although we saw no evidence for differences in global cognition between groups, we included measures of disease severity in our analyses to account for this potential confound. Future studies should investigate longitudinal cognitive data in autopsy- or biomarker-defined cohorts to explore potential effects of AD-type copathology in patients with PD without dementia.

We show that biological markers of AD-type copathology in LBD have a relatively specific association with cognition in the language domain, where reduced confrontation naming appears to be related in part to markers of AD-type copathology and the burden of tau in particular. While cognition in clinically defined LBD syndromes (DLB, PDD) remains heterogeneous, we observe more interpretable cognitive profiles in biologically defined cohorts. Defining LBD by markers of AD-type copathology may have advantages over solely clinically defined syndromes (DLB, PDD) because the antemortem identification of both AD-type and synuclein pathologies appears to have a strong impact on prognosis and treatment. Incorporating biomarker stratification of LBD + AD vs LBD – AD into clinical trials will allow the development of more targeted, disease-modifying drug therapies.

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David J. Irwin, MD	University of Pennsylvania, Philadelphia	Design and conceptualized study; acquisition and interpretation of data; drafting and revision of manuscript
Katya Rascovsky, PhD	University of Pennsylvania, Philadelphia	Acquisition and collection of data; revision of manuscript

Appendix (continued)

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Meredith Spindler, MD	University of Pennsylvania, Philadelphia	Revision of manuscript; major role in acquisition of data
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Alice Chen-Plotkin, MD	University of Pennsylvania, Philadelphia	Revision of manuscript; major role in acquisition of data
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John Q. Trojanowski, MD, PhD	University of Pennsylvania, Philadelphia	Revision of manuscript; major role in acquisition of data; provided funding
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Katheryn A.Q. Cousins, PhD	University of Pennsylvania, Philadelphia	Conceptualized study; analyzed the data; performed statistical analysis; drafting and revision for intellectual content

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