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Paired Studies Comparing Clinical Profiles of Lewy Body Dementia with Alzheimer's and Parkinson's Diseases

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Abstract. Limited data compares clinical profiles of Lewy Body Dementia (LBD) with Alzheimer's disease (AD) and Parkinson's disease (PD). Twenty-one mildly demented ambulatory LBD subjects were individually matched by MMSE score with 21 AD subjects and by UPDRS motor score with 21 PD subjects. Matched by age, gender, education, and race, pairs were compared using cognitive, functional, behavioral, and motor measures. LBD group performed worse than PD on axial motor, gait, and balance measures. AD had more amnesia and orientation impairments, but less executive and visuospatial deficits than LBD subjects. LBD group had more sleepiness, cognitive/behavioral fluctuations, hallucinations, and sleep apnea than AD or PD. Axial motor, gait, and balance disturbances correlated with executive, visuospatial, and global cognition deficits. LBD is differentiated from AD and PD by retrieval memory, visuospatial, and executive deficits; axial motor, gait and balance impairments; sleepiness, cognitive/behavioral fluctuations, hallucinations, and sleep apnea.

Keywords: Alzheimer's disease, dementia, Lewy body dementia, Parkinson disease, Parkinsonian disorders

INTRODUCTION

Research on the diagnosis and management of dementia with Lewy bodies (DLB) has increased greatly in the past decade [1–11]. Currently it is thought that DLB represents about 10–15% of all dementia cases [12]. Postmortem immunohistochemical staining for alpha-synuclein easily distinguishes DLB from Alzheimer's disease (AD). However, there are complexities in clinicopathological correlates, with multiple neuropathologies contributing to dementia and many cases with Lewy body neuropathology without dementia or Parkinsonism [13–15]. Furthermore, clinically we find that DLB is often diagnosed as AD, PD, or Parkinson's disease dementia (PDD) as there are many overlapping clinical features, dual diagnoses, or atypical presentations. It is therefore not surprising that the literature shows that the sensitivity of the clinical criteria is very low for the accurate clinical diagnosis of DLB conditions [16]. Additionally, distinctions between DLB and PDD, both forms of Lewy Body Dementia (LBD), are still being explored [12, 17–20]. Since the use of amyloid PET and other biomarkers for the diagnosis of AD, PD, and LBD are limited in clinical practice and since prognosis and management are distinct for each of these conditions, improved clinical methods in differentiating these groups to achieve accurate diagnoses are critically needed.

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While motor abnormalities are the hallmark of Parkinsonian conditions, it is becoming apparent that there may be distinct differences regarding the motor phenotype of PD and those of other Parkinsonian disorders (DLB or PDD) [2]. Additionally in recent years, non-motor symptoms of PD, including impaired cognition, excessive daytime sleepiness, depression, and other neuropsychiatric symptoms, have received increased medical attention [21]. Cognitive impairment is common and the prevalence of frank dementia occurring later in the course of PD, i.e., PDD, is around 30% [22]. The pattern of cognitive deficits in PDD and DLB, however, appears to differ in significant ways from that of AD [4–7, 9, 10, 23]. Furthermore, evidence suggests that there are specific relationships between motor and gait impairment patterns and the type of cognitive impairment or dementia condition present [1, 2, 24–30].

We conducted two paired comparison studies in an attempt to clinically distinguish LBD (DLB and PDD) from PD or AD by comparing similarities and differences of motor impairments, cognitive profiles, autonomic features, behavior profiles, and sleep issues among these subjects. This careful matching allowed comparisons between groups similar in their motor impairments and groups similar in their cognitive impairments. We used cognitive and motor/gait assessment tools not often applied to these groups and not previously employed, and the matched pair design where age, gender, education, and race were used to create close matching of subjects. Our goal was to see if these measures could be used to clinically differentiate LBD from PD or AD to improve the accuracy and timeliness of diagnosis. This approach should guide management and treatment decisions and lead to improved outcomes and quality of life for patients and caregivers [31].

MATERIAL AND METHODS

Study population

The research complied with the Declaration of Helsinki and was approved by the Ohio State University's Biomedical Sciences Human Subject Institutional Review Board. The study used a matched-pair cross-sectional design.

Participants

All subjects met clinical diagnostic criteria for their specific neurodegenerative condition. Inclusion criteria included vision and English sufficient for compliance with testing, Mini-Mental State Examination (MMSE) score greater or equal to 15, and the ability to ambulate 15 feet independently or with the use of an assistive device (i.e., walker or cane). Subjects were excluded if they had additional conditions (other than the diagnoses of interest) that in the opinion of the investigators might contribute to dementia, gait, or balance impairment or complicate their assessment.

Individuals meeting inclusion and exclusion criteria and with an informed consent, or assent through a legally authorized representative consent, were enrolled. Permission from the subject was obtained to be able to interview a study partner who knew the subject well. Subjects were recruited from the Memory Disorder and Movement Disorder Clinics at The Ohio State University Wexner Medical Center. Subjects with LBD met standard clinical criteria for either DLB or PDD as established by McKeith or Emre, respectively [17, 32]. All AD subjects met clinical diagnosis of probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association and DSM-IV TR criteria [33]. PD subjects met clinical diagnostic criteria according to the UK Parkinson's Disease Society Brain Bank [34]. Strict adherence to clinical criteria for diagnosis was maintained and all subjects were carefully assessed and diagnosed as typical cases by both movement and cognitive experts.

Each DLB and PDD subject was matched by age, gender, education, race, and MMSE [35] score with one subject with AD. They were also matched by age, gender, education, race and Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS III) [36] score with one subject with PD.

Outcome measures

Study subjects underwent a medical evaluation including a medical history, physical examination, orthostatic vital signs, and neurological examination including UPDRS III and Hoehn and Yahr (H&Y) staging [37]. We designated specific components of the UPDRS III into the following subsections that have been reported commonly in the literature: axial Postural Instability and Gait Difficulty (PIGD; arising from chair, posture, gait, and postural stability), axial bulbar (speech, facial expression), and bradykinesia (hand movement, rapid alternating movements of hands, leg agility, body bradykine-

sia) [25]. Each subject underwent cognitive, gait, and mobility evaluations. Cognitive assessment consisted of Self-Administered Gerocognitive Examination (SAGE), MMSE, FAS verbal fluency task (the sum of the number of words in one minute starting with "F", then "A", then "S"), Consortium to Establish a Registry for Alzheimer's Disease (CERAD), modified (15-word) Boston Naming Test, Wisconsin Card Sort Task-64 (WCST-64), forward digit span, and Alzheimer's Disease Assessment Scale (ADAS) constructional task [38–40]. Motor measurements included Berg Balance Scale (BBS), Tinetti Mobility Test (TMT), Figure of 8 (FO8), and nine hole Pegboard Test (9HP) [41–44]. Study partners were interviewed for assessments of subject behavior and function using the following: Epworth Sleepiness Scale (ESS), Mayo Sleep Questionnaire-Informant (MSQ), Mayo Fluctuations Scale (MFS), Neuropsychiatric Inventory (NPI), and Activities of Daily Living (ADLs) interview [45–47]. Study partners and subjects were queried about duration of cognitive impairment (if any), prior diagnosis of sleep apnea, duration of Parkinsonism (if any) and falls history (if any). Subjects were asked to take all regularly scheduled medications during the study visit.

Statistical analyses

Summary statistics for continuous data are given by mean ± SD, and the range, min-max. Paired differences were computed and tested for normality using Shapiro-Wilk test with a p-value of 0.10 as a threshold for normality. For normal data paired t-test was used and Wilcoxon signed rank test was used otherwise. For paired nominal data McNemar test and 95% confidence intervals (CI) were used. Level of significance was set at 0.05 and appropriate Bonferroni corrections were implemented to adjust for multiple tests. Spearman's correlation coefficient was used to express the strength of association. Statistical software SAS JMP 11.0 was used for statistical analyses.

RESULTS

Subject exclusions

Seventy-two (72) subjects were screened and sixty-three (63) subjects, all Caucasian, meeting inclusion and exclusion criteria were enrolled for the study. Nine subjects were excluded due to low score MMSE ($n = 2$), uncertain diagnosis ($n = 3$), diabetic neuropathy affecting ambulation ($n = 1$), and severe knee pain affecting ambulation ($n = 1$). Two subjects could not be matched: one subject with 10 years of education and one subject with a low UPDRS III score. Twenty-one subjects met clinical criteria for either DLB ($n = 11$) or PDD ($n = 10$), were pooled into one group designated as LBD, and were individually matched with 21 subjects who met clinical criteria for AD and 21 subjects who met clinical criteria for PD.

Demographics (Table 1)

Demographic data and clinical characteristics for the three groups are presented in Table 1. As expected, there were significant differences between LBD and PD subjects for MMSE (mean difference (MD): -5.24 ± 3.48, $p < 0.0001$), SAGE (MD: -7.19 ± 5.33, $p < 0.0001$), and CERAD (MD: -13.91 ± 11.0, $p < 0.0001$). PD subjects had lower H&Y scores (MD: -0.31 ± 0.46, $p = 0.0112$) and longer duration in years of motor symptoms than LBD subjects (MD: -4.13 ± 7.82, $p = 0.025$). Also as expected, there were significant differences between LBD and AD for UPDRS III scores (MD: 22.05 ± 7.10, $p < 0.0001$) and H&Y scores ($p < 0.0001$). Eighty-one percent of LBD group used anti-Parkinsonian medication (95% CI = 60%–92%).

Motor comparisons between LBD versus PD and AD (Table 2)

Despite being matched by total UPDRS III scores, PD subjects performed significantly better than LBD subjects on the following measures of motor function: UPDRS III sum of axial subscores (PIGD; arising from chair, posture, gait, postural stability), BBS, TMT, non-dominant hand 9HP score, and number of missteps in FO8 after accounting for multiple tests. No significant differences were found between the groups in the other UPDRS III subscores. LBD subjects demonstrated more motor impairment than AD subjects on all measures (p-values not reported).

Cognitive comparisons between LBD versus AD and LBD versus PD (Table 3)

Despite being matched by MMSE score, AD subjects were significantly more impaired than LBD subjects with orientation questions of MMSE. AD subjects also had significantly worse delayed recall, more false positive intrusions and poorer recognition discrimination memory on the CERAD memory list.

Table 1
Subject demographics and clinical characteristics

Characteristics	PD ($n=21$)	LBD ($n=21$)	AD ($n=21$)
Male : Female	13 : 8	13 : 8	13 : 8
	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)
Age	72.38 ± 4.72 (63–78)	73.95 ± 4.78 (65–82)	75.05 ± 4.96 (66–85)
Education (y)	14.86 ± 2.31 (12–18)	15.57 ± 2.58 (12–20)	14.67 ± 2.13 (12–19)
MMSE	27.81 ± 1.36 (25–30)*	22.57 ± 3.57 (16–28)	22.43 ± 4.25 (15–28)
CERAD	64.57 ± 7.94 (47–80)*	50.67 ± 11.01(29–73)	50.81 ± 14.32(24–74)
SAGE	17.29 ± 3.45 (8–21)*	10.10 ± 5.64 (0–20)	11.43 ± 5.52 (2–22)
UPDRS III (motor)	25.52 ± 5.89 (13–36)	25.95 ± 5.82 (14–38)	3.90 ± 3.62 (0–11)*
H&Y score	2.21 ± 0.34 (2–3)**	2.52 ± 0.46 (1.5–3)	0**
Cognitive impairment duration (y)	Not applicable	4.74 ± 3.19 (0.5–13)	3.75 ± 2.29 (0.8–8)
Parkinsonism duration (y)	10.16 ± 6.26 (0.3–24)*	6.02 ± 3.00 (1–13)	Not applicable
Anti-Parkinsonian medication use (n)	100%***	81%	0***

PD, Parkinson's disease; LBD, Lewy body dementia; AD, Alzheimer's disease; SD, standard deviation; MMSE, Mini-Mental State Examination; SAGE, Self-Administered Gerocognitive Examination; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr. *Significantly different from LBD group by t-test ($p<0.05$). **Significantly different from LBD group by Wilcoxon signed rank test ($p<0.05$). ***Significant difference established using 95% confidence interval (CI) = 60–92% for proportion using medication in LBD group.

Table 2
Motor comparisons

	PD Mean ± SD	LBD Mean ± SD	AD Mean ± SD	LBD versus PD p value*
UPDRS III Motor Subscales(k = 6)**				
Axial PIGD Items† (max score = 16)	2.62 ± 2.11	4.48 ± 2.34	0.71 ± 1.19	0.0073[1]
Axial Bulbar score§ (max score = 8)	3.29 ± 1.15	3.05 ± 1.20	0.29 ± 0.56	0.5939^
Total Tremor (Resting + Action) (max score 28)	3.19 ± 2.32	2.05 ± 1.77	0.67 ± 1.24	0.0898
Rigidity (max score = 20)	4.71 ± 2.41	4.62 ± 3.11	0.10 ± 0.44	0.8781
Bradykinesia¶ (max score = 28)	8.81 ± 2.11	9.05 ± 2.67	1.24 ± 1.64	0.7540
Finger Taps (max score = 8)	2.90 ± 0.89	2.67 ± 0.91	0.91 ± 1.22	0.3972
Other Motor Tasks (k = 4)				
Berg Balance Scale (max score = 56)#	49.86 ± 6.14	41.76 ± 9.87	52.57 ± 4.21	0.0059[1]
Tinetti Mobility Test (max score = 28)#	23.14 ± 3.05	19.10 ± 4.81	25.48 ± 1.54	0.0065[1]
Non-dominant 9 Hole Pegboard (s)**	37.77 ± 11.09	49.14 ± 16.47	30.92 ± 8.90	<0.0001^[1]
Missteps in Figure of 8 (steps)**	6.43 ± 6.49	11.60 ± 6.51	5.62 ± 6.00	0.0098[1]

PD, Parkinson's disease; LBD, Lewy body dementia; AD, Alzheimer's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; PIGD, postural instability and gait difficulty. *Based on a t test or Wilcoxon signed rank test (marked ^); [1]significant P values after using Bonferroni correction; those under 0.05/k are considered significant while testing k hypotheses; k = 6 for UPDRS subscores, and k = 4 for other motor tasks. **Lower scores better. †UPDRS III Axial PIGD Items = Arise from chair + Posture + Gait + Postural stability. §UPDRS III Axial Bulbar Items = Speech + Facial Expression. ¶UPDRS III Bradykinesia = Hand Move. + Rap. Alt Mov. Hands + Leg agility + Body Bradykinesia. #Higher scores better.

This implies a retrieval memory disturbance for LBD subjects and an amnestic memory impairment for AD subjects.

On the other hand, LBD subjects showed significantly more deficits compared to AD subjects on the executive domain tasks of SAGE, FAS verbal fluency, and the ADAS constructional task, with near significance on the visuospatial domain tasks of SAGE, and the MMSE interlocking pentagon construction task.

There were no significant differences noted between LBD and AD subjects on CERAD word list learning or intrusions, forward digit span, modified Boston Naming Test, WCST, or the language, memory, or reasoning/computation domains of SAGE. LBD subjects demonstrated more cognitive impairment than PD subjects on all measures.

Autonomic, behavioral, and other comparisons between LBD and PD and between LBD and AD (Table 3)

Compared to either PD or AD subjects, LBD subjects were significantly more impaired in ADLs and had significantly more daytime sleepiness (ESS score), decreased level of alertness (question 8 of the MSQ), cognitive/behavioral fluctuations (MFS composite total score), hallucinations (NPI subscore), and increased incidence of sleep apnea (prior diagnosis). Compared with AD subjects, LBD subjects had significantly more symptoms of orthostatic hypotension (vital signs on study visit), falls, and marginally significantly more restless leg syndrome (question 3 of the MSQ) but there was no significant increase in the

Table 3
Cognitive, autonomic, and behavioral comparisons

	PD Mean ± SD or % present	LBD Mean ± SD or % present	AD Mean ± SD or % present	LBD versus PD (p value)*	LBD versus AD (p value)*
SAGE ** **(k = 4)**					
Orientation = month/date/year	3.71 ± 0.64	2.57 ± 1.47	1.62 ± 1.50	0.0020^[1]	0.0176
Visuospatial = 3-D + Clock	2.86 ± 0.91	1.29 ± 1.31	2.19 ± 1.17	0.0002[1]	0.0161
Verbal Fluency	1.86 ± 0.36	1.05 ± 0.87	1.38 ± 0.87	0.0029^[1]	0.1279^
Executive = modified Trails B + Problem Solving	2.48 ± 1.72	0.81 ± 1.25	1.81 ± 1.63	0.0006^[1]	0.0039^[1]
CERAD ** **(k = 8)**					
Word List Learning	15.24 ± 4.17	12.24 ± 4.43	10.71 ± 5.61	0.0191	0.1792
False Positive	0.10 ± 0.30	0.48 ± 0.68	2.67 ± 2.39	0.0547^	0.0006[1]
True Positive	8.86 ± 1.59	8.19 ± 1.91	6.48 ± 2.68	0.1201^	0.0047[1]
Recognition Discrimination	8.76 ± 1.61	7.71 ± 2.31	3.81 ± 3.30	0.0146^	<0.0001[1]
Delayed Recall	3.76 ± 2.12	2.29 ± 2.37	0.43 ± 1.36	0.0208^	0.0013^[1]
Boston Naming (max score = 15)	14.48 ± 0.75	13.81 ± 1.21	13.05 ± 1.77	0.0255^	0.0533
FAS (replaces animal fluency)	13.24 ± 4.24	8.33 ± 3.90	14.24 ± 7.75	0.0013[1]	0.0036[1]
ADAS Construction	9.10 ± 2.05	6.52 ± 1.78	8.57 ± 2.25	0.0010^[1]	0.0039^[1]
MMSE ** **(k = 4)**					
Orientation = month/date/day/year	3.81 ± 0.40	2.90 ± 1.14	1.95 ± 1.36	0.0005^[1]	0.0027^[1]
Serial 7	4.29 ± 0.90	1.81 ± 1.78	3.10 ± 2.10	<0.0001^[1]	0.0239
Recall	2.43 ± 0.81	1.76 ± 1.04	1.10 ± 1.18	0.0179^	0.0269^
Pentagon correctly copied	76.2%	23.8%	66.7%	0.0023‡[1]	0.0126‡
Attention					
Digit forward span (max = 6 digits)	6.00 ± 0.00	5.71 ± 0.56	5.52 ± 0.81	0.0625^	0.5557^
ADLs**	60.48 ± 7.37	43.00 ± 12.81	52.29 ± 10.47	<0.0001[1]	0.0040^[1]
ESS Total Score	9.00 ± 4.72	13.14 ± 5.17	9.48 ± 5.52	0.0144[1]	0.0373[1]
Orthostatic Hypotension	47.62%	66.67%	19%	0.2059‡	0.0039‡[1]
Sleep Apnea	4.76%	33.33%	4.76%	0.0339‡[1]	0.0039‡[1]
Number of Falls in 6 months	1.57 ± 3.40	2.00 ± 1.92	0.76 ± 2.66	0.2651^	0.0220^[1]
MSQ (k = 3)					
MSQ 1 dream enactment behaviors	66.67%	66.67%	47.62%	1.0000‡	0.2482‡
MSQ 3 restless leg syndrome	19.05%	38.10%	4.76%	0.1573‡	0.0196‡
MSQ 8 alertness (scale: 0–10)	8.43 ± 1.75	6.14 ± 1.96	8.10 ± 1.48	0.0002[1]	0.0033[1]
MFS					
MFS 1–19 composite total score	3.05 ± 4.01	11.05 ± 2.88	7.00 ± 4.79	<0.0001^[1]	0.0003[1]
NPI (k = 4)					
Depression	0.76 ± 1.95	1.62 ± 1.77	1.05 ± 1.07	0.0242^	0.2391
Hallucination	0.095 ± 0.30	2.57 ± 3.46	0.29 ± 0.96	0.0002^[1]	0.0042^[1]
Irritability	0.19 ± 0.68	0.33 ± 0.91	1.91 ± 3.27	0.6563^	0.0408^
NPI Total Score (max = 144)	5.38 ± 7.70	15.10 ± 13.82	14.09 ± 15.55	0.0132	0.8294

PD, Parkinson's disease; LBD, Lewy body dementia; AD, Alzheimer's disease; SD, standard deviation; SAGE, Self-Administered Gerocognitive Examination; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MMSE, Mini-Mental State Examination; ADL, Activities of Daily Living; ESS, Epworth Sleepiness Scale; MSQ, Mayo Sleep Questionnaire-Informant; MFS, Mayo Fluctuations Scale; NPI, Neuropsychiatric Inventory. *Based on a t test or Wilcoxon signed rank test (marked †), or McNemar's test (marked ^); [1]significant P values after using Bonferroni correction; those under 0.05/k are considered significant while testing k hypotheses. **Higher scores better. §Lower scores better.

presence of dream enactment behaviors (question 1 of MSQ).

Correlations between motor and cognitive performance in subjects with LBD and PD (Table 4)

We examined the Spearman correlations between seven cognitive scores (SAGE total, SAGE executive, SAGE visuospatial, MMSE total, CERAD total, CERAD memory, and FAS verbal fluency) and nine motor tasks (Berg Balance Scale, Tinetti Mobility Test, missteps in the FO8, non-dominant 9HP, and the following five subscores of the UPDRS III: axial PIGD items, axial bulbar items, rigidity, tremor (resting & action), and bradykinesia) for the LBD and PD subjects. Except for the axial PIGD items, correlations between the seven cognitive scores and UPDRS III subscores were small (under 0.29, p-value >0.05) and are not reported in Table 4. However, accounting for the 63 correlations considered and using the Bonferroni correction, only the seven with p-values under

Table 4
Spearman correlations between motor features and cognition (LBD and PD)

Motor Tasks	SAGE Total Total	SAGE Executive	SAGE Visuospatial	MMSE Total score	CERAD Total score	CERAD memory score	FAS Verbal fluency
Berg Balance Scale	0.5737[1]	0.5820[1]	0.4198	0.4355	0.5032[1]	0.3416	0.4268
Tinetti Mobility Test	0.4919	0.5199[1]	0.3963	0.3932	0.4430	0.2777	0.4297
Missteps in Figure of 8	–0.4952	–0.5279[1]	–0.5044[1]	–0.3164	–0.3221	–0.1162	–0.1936
Non-dominant 9 Hole Pegboard	–0.4980[1]	–0.4498	–0.4777	–0.3326	–0.4334	–0.2412	–0.3943
Axial PIGD Items (UPDRS III Motor) [§]	–0.4009	–0.3766	–0.2195	–0.2960	–0.3440	–0.2402	–0.3516

LBD, Lewy body dementia; PD, Parkinson's disease; SAGE, Self-Administered Gerocognitive Examination; MMSE, Mini-Mental State Examination; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; UPDRS, Unified Parkinson's Disease Rating Scale; PIGD, Postural Instability and Gait Difficulty; SAGE Visual Spatial, 3-D +Clock; SAGE Executive, Modified Trail + Problem Solving; FAS, Sum of number of words/ one minute starting with "F", then "A", then "S" (test of verbal fluency). [1] Significant correlations with $p < 0.000793$ upon the implementation of the Bonferroni correction with a total Type I error rate of 0.05 that accounts for 63 tests for correlations. [§] Axial PIGD Items = Arise from chair + Posture + Gait + Postural stability.

0.000793 are taken to be significant. These are numerically high as well (ranging from 0.498 to 0.582) representing a strong clinical association between the concerned variables.

Table 4 shows strong associations, many statistically significant, between SAGE total, executive, and visuospatial scores and motor tasks. Among other cognition test scores, only the CERAD total score correlates with the BBS total score significantly.

DISCUSSION

Method and design

Currently accepted diagnostic criteria for DLB and PDD are based on having one year or less between onset of dementia and parkinsonism for DLB diagnosis, the so called "one year rule". Identifying the onset of dementia is subjective and often suspect in its accuracy [12, 17–20]. Therefore, we decided to combine our DLB and PDD subjects into one group, called LBD.

Our average MMSE of 22.6 allowed us to investigate early cognitive pattern differences and more accurately differentiate and diagnose these disorders. As dementia conditions become more severe, differences in cognitive profiles are harder to evaluate due to floor effects of cognitive tests.

Our inclusion criteria also required our study subjects to be able to ambulate 15 feet. Comparing ambulatory subjects defines early gait pattern differences and provides clues to more accurately differentiate and diagnose these disorders. As Parkinsonian symptoms become more severe, patients become non-ambulatory and gait differences can no longer be assessed.

The standard clinical criteria for DLB considers whether the participant has fluctuating attention, REM sleep behavior disorder, and visual hallucinations. These features are not required as part of the standard clinical criteria to diagnose PDD. In our study we had 11 DLB subjects and 10 PDD subjects that were pooled together to make up our LBD group. Therefore, our comparisons of cognitive/behavioral fluctuations, REM sleep behavior disorder, and visual hallucinations between the LBD group and the AD and PD groups may reflect in large part the impact of the diagnostic clinical criteria used for our 11 DLB subjects.

Unlike many studies using only group comparison or age matched samples, the strength of our method is the gender, age, education, race, and MMSE or UPDRS III scores matched comparison.

Differentiation of PD and LBD subjects based on motor characteristics

The items of the UPDRS III that include arising from a chair, posture, gait, and postural stability have been referred to as axial PIGD items [25]. Some investigators include speech and facial expression (bulbar features) or neck rigidity as additional axial motor items [25–27]. In our study, LBD subjects, while matched for UPDRS III total score, did significantly worse than the PD subjects on only PIGD items (Table 2). LBD subjects also had significantly worse gait and balance compared to PD subjects, who tended to have more resting tremor. Our results are consistent with other studies showing that patients presenting with more prominent resting tremor compared to PIGD and balance disturbances are more likely to have PD, while those with more prominent PIGD and balance issues compared to resting tremor

may be more likely developing a LBD condition [1, 2, 24–30].

The prominent non-dominant hand 9HP score differences between LBD and PD subjects likely reflect the more impaired visuospatial impairments seen in our LBD group [48].

Differentiation of AD and LBD subjects based on cognitive characteristics

Despite being matched for MMSE (global cognitive) scores, LBD subjects were significantly more impaired than AD subjects in executive and visuospatial domains and significantly less impaired in orientation, delayed memory recall, and recognition discrimination memory. The progression of pathology in LBD starts in the brainstem and deep grey matter before spreading to limbic regions and parietal-occipital, posterior temporal-occipital and frontal cortical regions. This corresponds to more retrieval memory (frontal-subcortical pathways), executive (frontal), and visual processing (parietal-temporal-occipital) deficits [49]. The progression of pathology in AD starts in the mesial temporal lobe before spreading to frontal and parietal cortical regions resulting in an amnestic pattern of memory loss (hippocampus), orientation impairments due to memory deficits, and eventually aphasia (peri-Sylvian), visuospatial (parietal), and executive (frontal) deficits [50]. The timing of the cognitive deficits is distinctly different in AD and LBD and therefore can be very useful in differentiating those conditions.

Although our LBD subjects did significantly worse than our AD subjects on the executive measures we employed, the pattern of dysfunction in LBD and AD subjects appear to be similar, involving more dorsolateral frontal (verbal fluency, problem solving, modified Trails B) and less orbitofrontal (disinhibition or impulsivity) impairments. Visual processing and executive planning impairments in our LBD subjects combine to create more constructional deficits than in our AD subjects matched to the same MMSE score.

Differentiation of PD and AD from LBD subjects based on autonomic, behavioral, and other characteristics

Since some ADLs require both cognitive and physical skills it is not surprising that our LBD subjects with both physical and mental impairments did worse than matched AD (predominantly cognitive disabilities) or matched PD (predominantly physical disabilities) subjects. Alpha-synuclein aggregates are commonly found in the peripheral autonomic nervous system in both non-demented PD and LBD patients [51], which may explain why orthostatic hypotension was more commonly seen in our PD and LBD subjects than in the AD subjects. Orthostatic hypotension likely contributes to increased falls. Central autonomic control pathways outside the hypothalamus or brain stem structures are differentially impacted by cortical Lewy bodies in LBD patients compared to PD patients [52]. While further study is warranted, the alterations in those pathways in LBD subjects might be correlated to the excessive daytime somnolence, impaired alertness, cognitive/behavioral fluctuations, and sleep apnea seen significantly more often in our LBD subjects than either our matched PD or AD subjects [52–54]. Other autonomic-influenced sleep impairments including symptoms of restless leg syndrome and REM sleep behavioral disorder were seen similarly in PD and LBD subjects and more commonly than in our matched AD subjects [53, 54]. Visual hallucinations occurred in 62% of our LBD subjects but only in 9.5% of our PD and AD subjects. Visual hallucinations are thought to be more common in LBD subjects due to alpha-synuclein proteinopathy involving the visual processing posterior cortical regions and the limbic areas [55]. More research is required to fully understand the pathophysiology of the behavioral disturbances.

Correlations between motor and cognitive features

SAGE scores were significantly correlated with BBS, TMT, missteps in the FO8, and non-dominant 9HP scores (Table 4). Some of these high correlations may be due to the strong association between the four motor tasks (the correlations between them ranged from 0.45 to 0.81). Among other cognitive tests performed, only CERAD total score exhibited strong association with BBS. Executive and visuospatial cognitive domains had higher correlations than temporal (memory) domains. Frontal and parietal cognitive deficits might predictably correlate with the motor tasks and spatial processing involved in balance, walking in FO8, and performing spatial tasks utilizing a pegboard. Walking and balance relies on several cognitive skills, particularly executive and visuospatial abilities. Intact attentional skills may also play a role, and in our study, PD subjects per-

formed better than matched LBD subjects on serial 7 subtractions.

The PIGD features did not reach significance but correlated the best with global cognitive results (CERAD and SAGE) and executive domain assessments (SAGE and FAS verbal fluency), and correlated less well to memory (CERAD) or visuospatial (SAGE) domain scores. Therefore, frontal more than temporal or parietal cognitive deficits correlate with axial motor impairments. It is interesting to note that the cognitive deficits and the axial motor impairments that correlated the best are both associated with frontal regional impairments. Those cognitive findings prominently involve frontally located executive domain deficits and those axial motor findings suggest impairments in the supplementary motor area, also located in the frontal lobes. The supplementary motor area is thought to be involved in control of postural stability with standing or walking, initiation of internally generated motor activities like arising from a chair, and coordinating temporal sequences of action like walking [25–28].

The non-PIGD items that contribute to 85% of the UPDRS III score, i.e., axial bulbar items of facial expression and speech, tremor, rigidity, bradykinesia, and finger taps, did not correlate with cognitive measures. These motor measures also did not differentiate PD from LBD subjects. This suggests that these motor findings are more related to damage in subcortical and brainstem regions than from cortical regions [25–28]. Therefore, patients presenting with subtle evidence of PIGD and cognitive impairment might alert clinicians to possible LBD.

Limitations of the research

Limitations include small sample size, particularly with the PDD and DLB subjects, diminishing meaningful comparisons between these groups. In order to reduce the chance of having subjects with the pathological features of both AD and dementia with Lewy bodies (the Lewy body variant of AD), strict adherence to clinical criteria for diagnosis was maintained and all subjects were carefully assessed and diagnosed as typical cases by both movement and cognitive experts. By these methods, subjects with atypical symptoms at the onset of their condition and those with uncharacteristic clinical courses were avoided. Nevertheless, this clinical study did not include the use of DaTscan, amyloid PET imaging, cerebrospinal fluid analysis, polysomnography, or pathology to substantiate or negate the clinical diagnoses given. Going forward, more research in establishing the criteria of when to use these other biomarker oriented techniques and which combinations are most useful and cost effective will be a great help in aiding the diagnosis of these neurodegenerative conditions.

Our cognitive tool for matching, the MMSE, exhibits ceiling effects in more educated patients and is not sensitive for mild cognitive impairment or executive deficits. LBD subjects have prominent executive impairment so the MMSE may not accurately reflect their global cognitive impairments. Despite its shortcomings, we used the MMSE due to its familiarity and long tradition as a brief global cognitive assessment instrument. Our motor tool for matching, the UPDRS III, has floor effects that may limit sensitivity in early disease, concealing important differences between PD and LBD subjects.

While the milder cognitive impairment (average MMSE = 22.6) and mild motor dysfunction (requirement for ambulating 15 feet) of our subjects limits its generalizability, our focus was on distinguishing characteristics in early disease. Our LBD subjects also had more falls than our matched PD subjects in the last 6 months but significance was not achieved. This trend might become significant if more subjects were evaluated or if we had subjects with more severe cognitive impairments. Some studies have shown that falls may predict cognitive decline [30]. We excluded subjects who had undergone deep brain stimulation, which may have inadvertently excluded PD subjects with severe tremor.

CONCLUSION

Our findings suggest that subjects with LBD are differentiated from PD by having more axial motor, gait, and balance impairments. Compared to AD, LBD subjects have more executive and visuospatial deficits and less amnesia and disorientation. LBD subjects also show more daytime sleepiness, cognitive/behavioral fluctuations, hallucinations, and obstructive sleep apnea than either AD or PD subjects. Significant correlations were noted between axial motor, balance and gait disturbances, and executive functioning, visuospatial abilities, and global cognitive deficits.

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